Indian J Lepr 2021, 93 : 211-220
© Hind Kusht Nivaran Sangh, New Delhi
http://www.ijl.org.in

Case Report

Deep Vein Thrombosis in Refractory Erythema Nodosum Leprosum: A Report of Two Cases

RS Mahajan[1], KR Ninama[2], AR Shah[3], YS Marfatia[4]

Received : 21.07.2020 Accepted : 09.02.2021

Hansen's disease is a chronic granulomatous disease caused by *Mycobacterium leprae*. Acute exacerbations termed as lepra reactions often mark the course of the disease. These are of two types - Type 1 or Reversal Reaction and Type 2 or Erythema Nodosum Leprosum (ENL). Chronic recurrent ENL is a frequently encountered, difficult to treat condition which is usually managed with systemic corticosteroids, increasing the dose of clofazimine, non-steroidal anti-inflammatory drugs, cyclosporine A, azathioprine, pentoxyphylline, mycophenolate mofetil, methotrexate and intravenous immunoglobulin (IVIG). Thalidomide is the drug of choice in most instances. Thrombo-embolism is a rare but known complication of thalidomide therapy especially when combined with corticosteroids or chemotherapeutic agents. Herein we report 2 cases of refractory ENL developing Deep Vein Thrombosis (DVT) while on concomitant therapy with thalidomide and corticosteroids for the control of ENL.

Keywords : Deep Vein Thrombosis (DVT), Thalidomide, Erythema Nodosum Leprosum (ENL)

Introduction

Acute exacerbations or reactions are frequently seen in the course of leprosy, which may be of two types Type 1 or Reversal Reaction and Type 2 or Erythema Nodosum Leprosum (ENL) (Pôrto et al 2019, Prabhu et al 2009). ENL is an immune-mediated complication of lepromatous leprosy (LL) and borderline lepromatous leprosy (BL). Transient painful erythematous nodules are seen on the trunk, extremities and face with systemic manifestations like fever, arthritis, myositis, lymphadenitis, iridocyclitis and painful neuritis (Kahawita & Lockwood 2008, Teo et al 2002, Rea & Levan 1975). In severe and recurrent type 2 reactions, thalidomide is the treatment of choice (Pôrto et al 2019, Meyerson 1996) owing to its anti-inflammatory properties due to inhibition of inflammatory cytokines, tumour necrosis factor-alpha (TNF-α), vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (b FGF) in RNA processing. Deep vein thrombosis (DVT) is a known complication of thalidomide, albeit rare

[1] Dr RS Mahajan, Professor & Head
[2] Dr KR Ninama, Professor
[3] Dr AR Shah, 3rd Year Resident
[4] Dr YS Marfatia, Professor
Department of Skin & VD, Dhiraj Hospital, SBKS Medical Institute & Research Centre, Sumandeep Vidyapeeth Deemed to be University, Piparia, Waghodia, District Vadodara – 391760, Gujarat, India.
Corresponding Author: Dr Atmakalyani Shah, **Email**: juishah13@gmail.com

with a higher incidence in patients receiving it for multiple myeloma and renal cell carcinoma (Jew & Middleton 1990, Eisen et al 2000, Stebbing et al 2001, Sharma et al 2004). Herein we report two cases of DVT in patients with chronic ENL on concomitant thalidomide and systemic corticosteroids.

Case Reports

Case 1

A 35 year old male patient presented with a history of recurrent episodes of joint pain, fever and erythematous nodules since one year. He was on treatment with multibacillary multidrug therapy (MBMDT) and prednisolone (40 mg/day), the dose of which had to be repeatedly altered due to frequent remissions and exacerbations.

On examination, the patient had cushingoid habitus with multiple necrotic lesions and healed scars over the trunk, gluteal region and extremities (Figs. 1A, 1B, 1C). His bilateral ulnar and lateral popliteal nerves were uniformly thick, tender with cord like in consistency. Glove and stocking anaesthesia was present over extremities. Other findings included lateral superciliary madarosis and nodular infiltration over bilateral pinnae. The above findings were suggestive of lepromatous leprosy (LL) with Erythema Nodosum Necroticans.

General physical examination (GPE) revealed mild pallor while the systemic examination was normal. Complete blood count revealed hemoglobin 10.7 gm% with leucocytosis 13,400/ mm^3. Biochemical parameters, electrocardiography

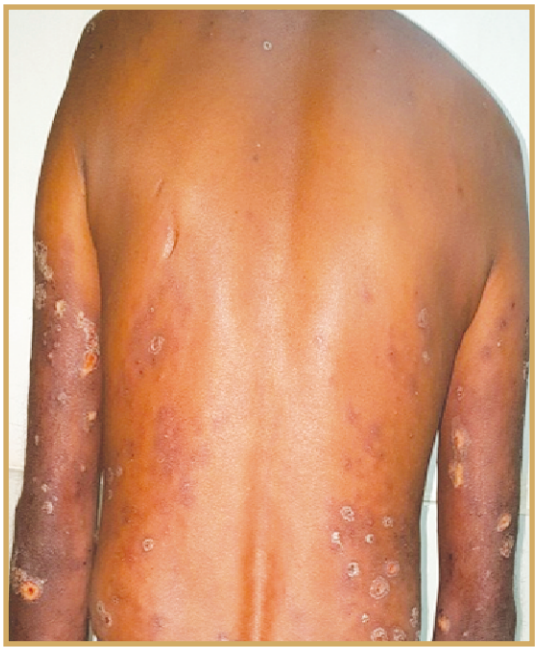

Fig. 1A : Multiple necrotic lesions, healed scars and post inflammatory hyperpigmentation seen over back, bilateral arms and elbows

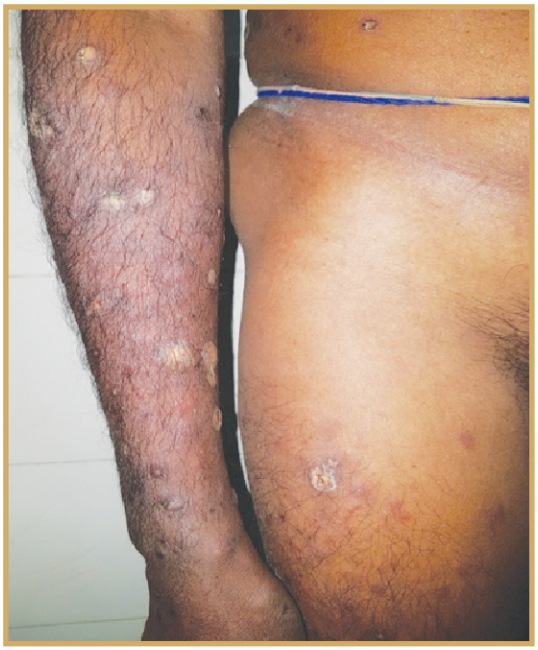

Fig. 1B : Few nodular lesions, multiple necrotic lesions and healed scars over lower abdomen, right forearm and thigh.

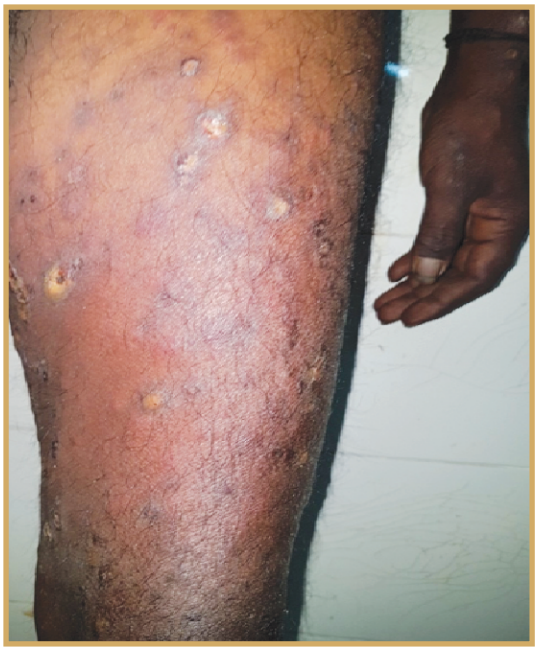

Fig. 1C : Multiple necrotic lesions, healed scars and post inflammatory hyperpigmentation seen over left thigh.

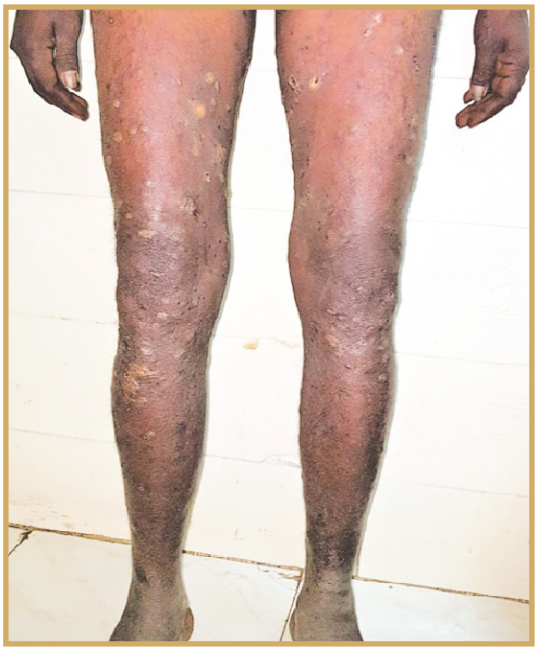

Fig. 1E : Left lower limb edema with bilateral lower limbs showing necrotic lesions, healed scars and ichthyotic changes.

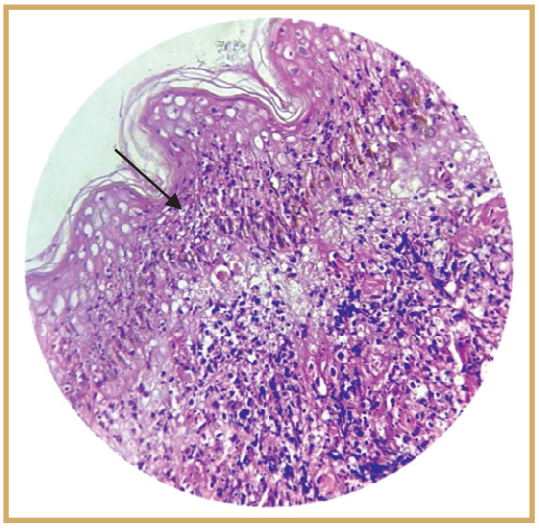

Fig. 1D : Skin biopsy showing thinning of epidermis with atrophic rete pegs. Focal aggregates of foamy hitiocytes and macrophages seen in upper dermis (H&E stain, 40X magnification)

(ECG) and chest x-ray were normal. Anti Nuclear Antibody (ANA) and Rheumatoid Factor (RA) were Negative. VDRL test was non reactive.

Slit skin smear (SSS) done from bilateral earlobes and eyebrows showed bacillary index (BI) 3+. Skin biopsy from a nodular lesion over the right thigh showed thinning of the epidermis with atrophic rete pegs. The upper dermis showed focal aggregates of foamy histiocytes and macrophages (Fig. 1D). Fite-Faraco staining was positive (BI 4+).

A diagnosis of LL with chronic ENL with neuritis was made. (Chronic ENL is ENL occurring for 24 weeks or more during which a patient has required treatment either continuously or where the treatment free period had been 27 days or less).

Injectable dexamethasone (8 mg) was started and

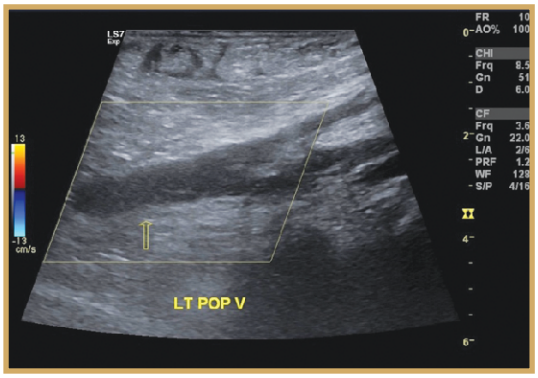

Fig. 1F : Doppler ultrasonography showing left DVT of the popliteal vein.

gradually tapered based on clinical improvement. After 10 days, the patient was discharged on tablet prednisolone 60 mg/day tapered by 5 mg every week. After 6 weeks, new ENL lesions cropped up once the patient reached a dose of prednisolone 30 mg per day. Hence, tablet thalidomide was started in a dose of 100 mg thrice daily. He responded dramatically by the 4th day and dose of prednisolone was further reduced and maintained at 10 mg (Table 1). 2 months later, the patient developed asymptomatic swelling of left leg (Fig. 1E). Doppler ultrasonography revealed left DVT of the common femoral vein, superficial femoral vein and popliteal vein as they appeared non compressible and showed echogenic material within (Fig. 1F). Blood investigations revealed neutrophilic leucocytosis and International Normalised Ratio (INR) 4.13. Tablet Prednisolone was stopped, and Tablet Thalidomide was reduced to 100 mg twice daily. Anticoagulant therapy was initiated with subcutaneous (SC) low molecular weight heparin (LMWH) 5000 international units (IU) thrice daily and tablet warfarin 3 mg and later maintained on tablet warfarin 2 mg with INR in the target range of 2 and 3. Patient was free from

Table 1 : Schedule of tapering of oral prednisolone in case 1

Week 0 – Tab. Prednisolone 60mg
↓
Week 1 – Tab. Prednisolone 55mg
↓
Week 2 – Tab. Prednisolone 50mg
↓
Week 3 – Tab. Prednisolone 45mg
↓
Week 4 – Tab. Prednisolone 40mg
↓
Week 5 – Tab. Prednisolone 35mg
↓
Week 6 – Tab. Prednisolone 30mg [recurrent ENL]
↓
Tab. Thalidomide 100mg TDS started
↓
Week 7 – Tab. Prednisolone 25mg
↓
Week 8 – Tab. Prednisolone 20mg
↓
Week 9 – Tab. Prednisolone 15mg
↓
Week 10 onwards Tab. Prednisolone maintained at 10mg

lesions of ENL, but 2 months later, asymptomatic swelling with DVT was detected in the right leg, for which dose adjustment of anticoagulant therapy was done. Tablet thalidomide was continued concomitantly at 100 mg twice daily.

Case 2

A 42 year old male patient presented with tender skin lesions, fever and joint pain since 10 months. On enquiry, it was found that he was on MBMDT for leprosy since 10 months and had recurrent

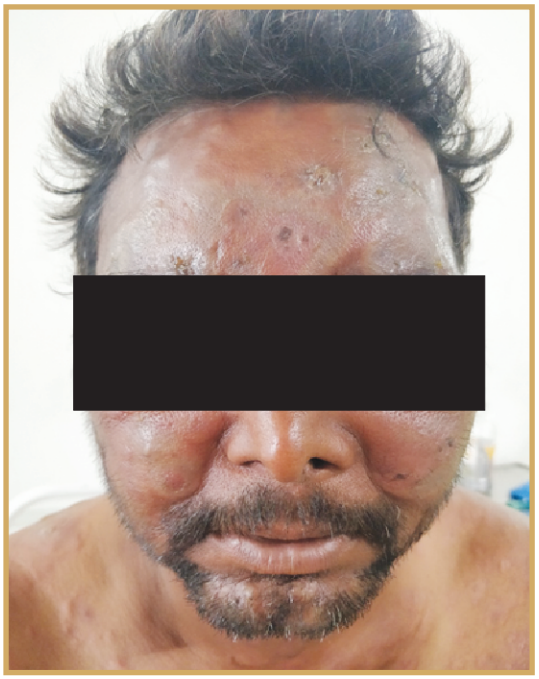

Fig. 2A : Facial edema, tender erythematous nodules and few necrotic lesions over the face.

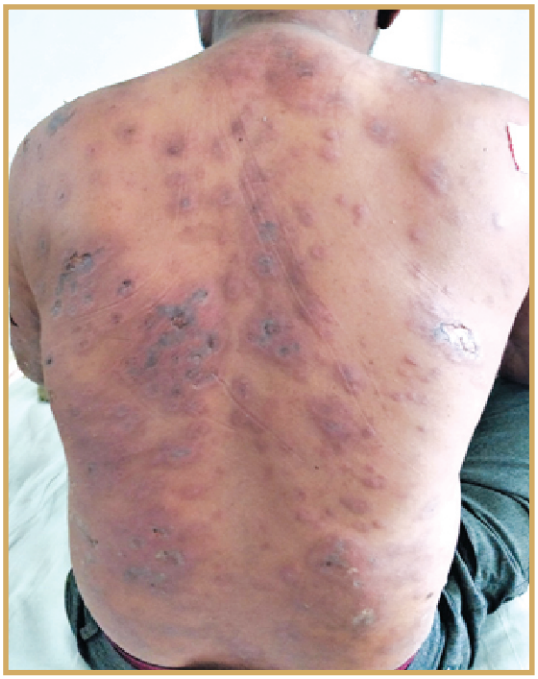

Fig. 2C : Multiple erythematous nodules, plaques and necrotic lesions seen over back.

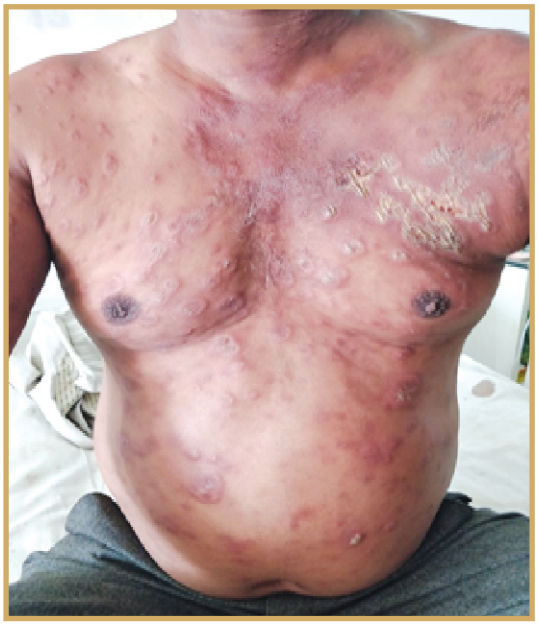

Fig. 2B : Cushingoid habitus with multiple erythematous nodules, plaques and few flaccid bullae seen over chest and abdomen.

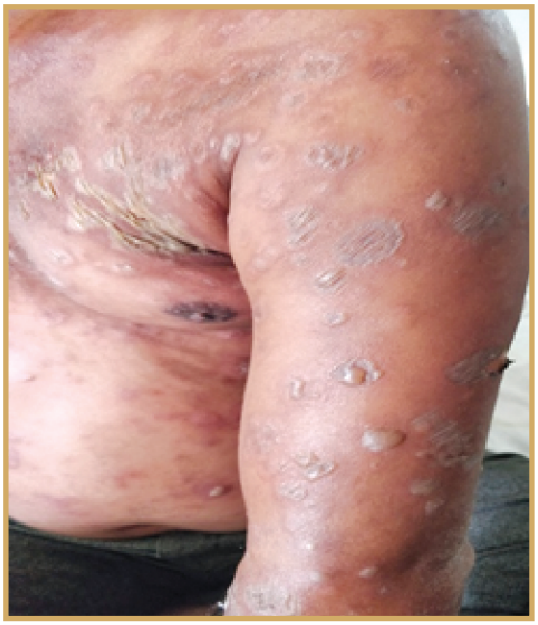

Fig. 2D : Erythematous nodules and bullous lesions seen over left arm and chest.

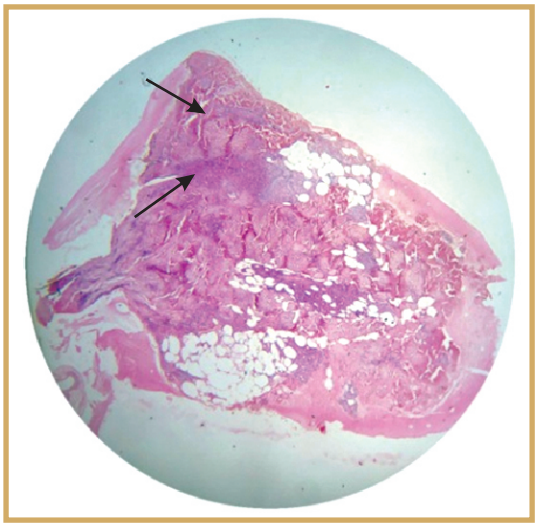

Fig 2E : Thin epidermis with atrophic rete pegs. Focal aggregates of lymphocytes and macrophages seen in upper dermis and surrounding the dermal appendages along with septal panniculitis. (H&E stain, 40X magnification)

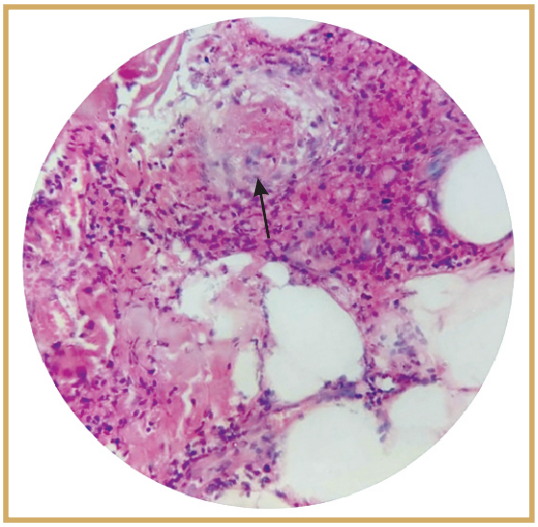

Fig. 2F : Focal aggregates of lymphocytes and macrophages in upper dermis and surrounding the dermal appendages with perineural infiltration. (H&E stain, 40X magnification)

episodes of fever, skin lesions and joint pain on and off since 3 months. He was on tablet prednisolone 40 mg/day with inadequate control.

On examination, the patient had cushingoid habitus, tender erythematous nodules, atypical targetoid lesions (suggestive of erythema multiforme) and bullous lesions over the face, back, upper and lower limbs, bilateral earlobe infiltration, ichthyotic changes over extremities (Fig. 2A, 2B, 2C, 2D) with glove and stocking anaesthesia. Bilateral ulnar nerves were uniformly thickened, cord like and tender. GPE revealed mild pallor, bilateral tender inguinal lymphadenopathy and facial edema. Systemic examination was normal. Hemoglobin was 9.6 gm% with leucocytosis 14,100 / mm^3. Biochemical parameters, ECG and chest x-ray were normal. ANA and RA Factor were Negative. VDRL test was non reactive.

Slit Skin Smear (SSS) done from bilateral earlobes and eyebrows showed BI 4+. Two serial biopsies were taken for this patient. First punch biopsy taken at the presentation from nodular lesion over the right arm revealed a thin epidermis with atrophic rete pegs. Focal aggregates of lymphocytes and macrophages were seen in the upper dermis and surrounding the dermal appendages. Perineural infiltration and septal panniculitis were also appreciated (Fig. 2E, 2F, 2G).

Second punch biopsy taken from the nodular lesion over the back showed a thin epidermis. The dermis was diffusely infiltrated with polymorphs. Abortive granulomas with epitheloid cells, macrophages and multinucleated giant cells were seen. The adnexal structures were also surrounded by polymorphs and epitheloid cells (Fig. 2H).

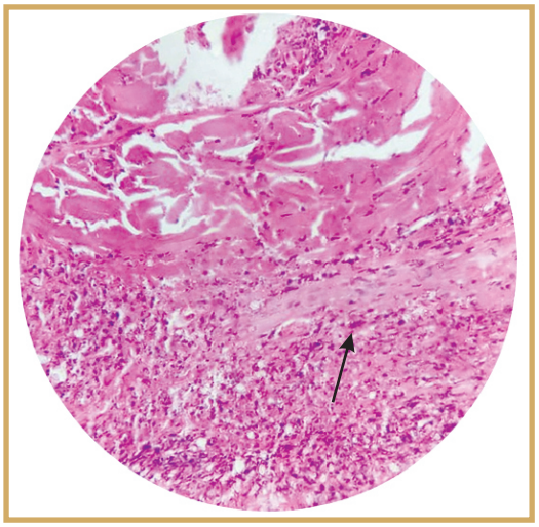

Fig. 2G: Focal aggregates of lymphocytes and macrophages in upper dermis and surrounding the dermal appendages with perineural infiltration. (H&E stain, 40X magnification)

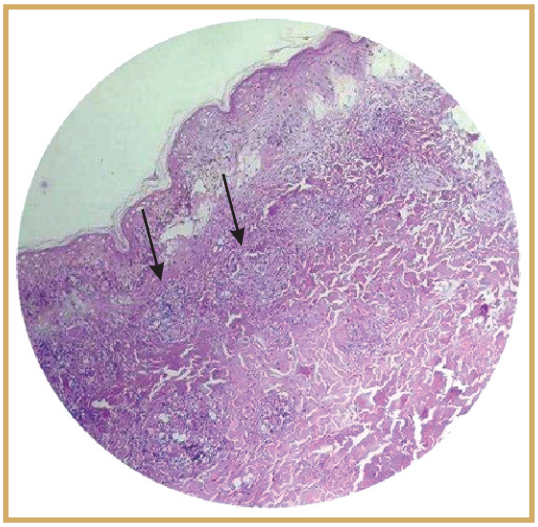

Fig. 2H : Skin biopsy showing thin epidermis. The dermis is diffusely infiltrated with polymorphs. Abortive granulomas with epitheloid cells, macrophages and multinucleated giant cells are also seen. (H&E stain, 40X magnification)

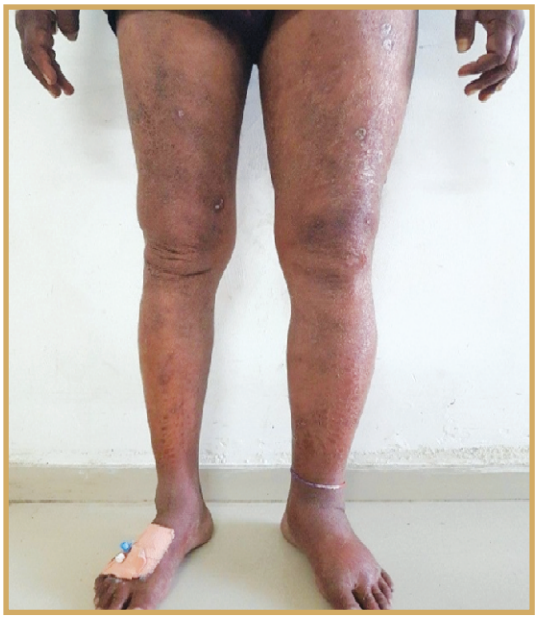

Fig. 2I : Left limb edema with necrotic lesions, healed scars and ichthyotic changes seen over bilateral lower limbs.

A diagnosis of LL with chronic ENL with neuritis was made.

He was started on injectable dexamethasone (8 mg) and later shifted to tablet prednisolone at a dose of 60 mg/day, gradually tapered by 5 mg weekly to 40 mg/day after the control of symptoms. There was a severe exacerbation of the symptoms after reducing the prednisolone dose to 40 mg/day; hence, thalidomide was added in the dose of 100 mg thrice daily. Gradual improvement was observed on follow up (Table 2). However, in the eighth week (Tab Prednisolone 20 mg) the patient developed swelling and severe pain in his left leg (Fig. 2I).

Doppler ultrasonography of left lower limb showed diffuse hypoechoic thrombus distension up to inferior vena cava bifurcation; of the common femoral vein and superficial femoral vein contiguous into popliteal vein also involving the short saphenous vein and its tributaries

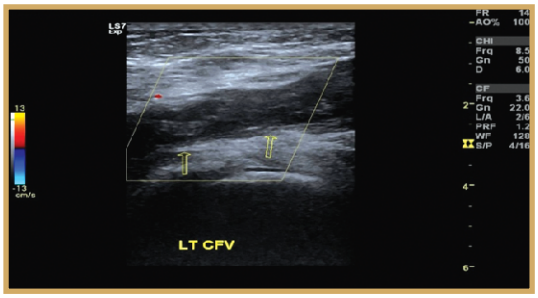

Fig. 2J : Doppler ultrasonography showing left lower limb extensive DVT of common femoral vein with diffuse subcutaneous edema of the left lower limb.

Table 2 : Schedule of tapering of oral prednisolone in case 2

Week 0 – Tab. Prednisolone 60mg
↓
Week 1 – Tab. Prednisolone 55mg
↓
Week 2 – Tab. Prednisolone 50mg
↓
Week 3 – Tab. Prednisolone 45mg
↓
Week 4 – Tab. Prednisolone 40mg [recurrent ENL]
↓
Tab. Thalidomide 100mg TDS started
↓
Week 5 – Tab. Prednisolone 35mg
↓
Week 6 – Tab. Prednisolone 30mg
↓
Week 7 – Tab. Prednisolone 25mg
↓
Week 8 – Tab. Prednisolone 20mg [Left Lower Limb DVT]
↓
Week 9 – Tab. Prednisolone 15mg
↓
Week 10 onwards Tab. Prednisolone maintained at 10mg

with diffuse subcutaneous edema of the left lower limb suggestive of DVT (Fig. 2J). Various laboratory parameters were within normal limits. Thalidomide was discontinued immediately. The patient was given SC LMWH 5000 IU eighth hourly with tablet warfarin 2 mg for seven days; later maintained on oral warfarin 3 mg. The target INR was between 2 to 3. Limb elevation with crepe bandage application was done.

Patient's leg pain and swelling improved considerably, after which he was restarted on 100 mg thalidomide. Prednisolone dosage was also tapered. After 24 MBMDT, the patient is asymptomatic. Currently, he is on tablet warfarin 2 mg on alternate days with monitoring of INR.

Discussion

Chronic recurrent ENL is a grave and niggling complication of leprosy. It is frequently challenging to control (Sharma et al 2004). Thalidomide, oral corticosteroids, clofazimine, cyclosporine A, azathioprine, pentoxyphylline, mycophenolate mofetil, methotrexate and IVIG are the medications used in the treatment of ENL (Moschella 2004, Scollard et al 2006).

The clinical features of ENL are ascribed to higher levels of TNF-α and interferon-γ (INF-γ). This phenomenon is reversed by thalidomide through its immunomodulatory properties, including down-regulation of cell-surface adhesion molecules ICAM-1 on epidermal keratinocytes involved in leukocyte migration, decreasing circulating helper T-cell to suppressor T-cell ratio, inhibition of IFN-γ and reduction in neutrophils, TNF-α, MHC class-II antigens hence managing ENL efficiently (Sharma et al 2004, Matthews & McCoy 2003).

The teratogenic effect of thalidomide came into light when over 10,000 cases of phocomelia were detected in children of mothers who had been prescribed the same as an antiemetic, leading

to its withdrawal in the early 1960s (Kim & Scialli 2011). Sheskin & Convit (1969) used it for treating ENL and reported a quick and dramatic clinical response. Verified in a double-blind clinical trial by World Health Organization (Iyer et al 1971), the Federal Drug Authority first approved it for the treatment of ENL in 1992 (Ahamed et al 2011).

Thalidomide is approved for therapeutic use in multiple myeloma and as an off-label drug in various diseases such as Crohn's disease, lupus erythematosus and solid organ malignancies of kidney, brain and breast (Ahamed et al 2011) along with dermatological indications including aphthous stomatitis, Behcet syndrome, Sjogren's syndrome, nodular prurigo, actinic prurigo, graft versus host disease, sarcoidosis, pyoderma gangrenosum, Jessner's lymphocytic infiltrate, adult Langerhans cell histiocytosis, toxic epidermal necrolysis, lichen planus, Kaposi's sarcoma, uremic pruritus, rheumatoid arthritis, post herpetic neuralgia, erythema multiforme, Waldenstroms macroglobulinemia, malignant melanoma, pemphigoid disorders, HIV infection, brachioradial pruritus, scleromyxodema, polymorphic light eruptions, oral precancerous and cancerous conditions (Hassan et al 2015).

Apart from teratogenic side effects and peripheral neuropathy, thrombogenic potential of thalidomide, especially when concurrently used with corticosteroids is emerging as an unrecognized complication. Thrombocytopenia, somnolence, dizziness, fatigue, constipation and skin rash are among the other frequently observed side effects of thalidomide therapy (Ahamed et al 2011, Hassan et al 2015).

The combination of thalidomide and corticosteroids produces modifications in endothelial cell function, alters the cellular response of Th-1 and increases INF-γ and interleukin-2 secretion. Thrombotic events are related to a fibrinolytic system imbalance and are associated with risk factors such as smoking, immobility, cancer, heart disease, inflammatory bowel disease, past history of thrombosis, drug usage and alteration of pro- or anticoagulant factors (Pôrto et al 2019).

DVT risk is linked to genetic factors, being greater in blacks, moderate in Caucasians and lower in Asians. Its incidence and prevalence are closely related to age, rising nearly 90-fold from age 15 to 80 with no conclusive data on frequency between genders. Also, its incidence is higher with contraceptive use and HIV infection (Pôrto et al 2019).

The rise in thromboembolic events in ENL patients' concomitantly receiving thalidomide and corticosteroid therapy is not linked to genetic events of thrombophilia but a combination of the two drugs (Pôrto et al 2019).

Conclusion

Patients who are on concomitant systemic steroids and thalidomide treatment for a long duration may develop DVT that manifests as edema of the affected limb, which may be symptomatic or asymptomatic. A high index of suspicion will prevent life-threatening complications in such patients.

References

1. Ahamed R, Bandula W, Chamara R (2011). An unexpected case of venous and pulmonary thrombo-embolism in a patient treated with thalidomide for refractory erythema nodosum leprosum: A case report. *Thrombosis J*. **9(1)**: 1-4.
2. Eisen T, Boshoff C, Mak I et al (2000). Continuous low dose thalidomide: a phase II study in advanced melanoma, renal cell, ovarian and breast cancer. *Br J Cancer*. **82(4)**: 812-817.
3. Hassan I, Dorjay K, Anwar P (2015). Thalidomide in dermatology: revisited. *Indian J Dermatol*. **60(2)**: 213.
4. Iyer CG, Languillon J, Ramanujam K et al (1971). WHO co-ordinated short-term double-blind trial with thalidomide in the treatment of acute lepra

reactions in male lepromatous patients. *Bull World Heal Organ*. **45(6)**: 719-732.

5. Jew LJ, Middleton RK (1990). Thalidomide in erythema nodosum leprosum. *DICP (Cincinnati, Ohio)*. **24(5)**: 482-483.
6. Kahawita IP, Lockwood DN (2008). Towards understanding the pathology of erythema nodosum leprosum. *Trans R Soc Trop Med Hyg*. **102(4)**: 329-337.
7. Kim JH, Scialli AR (2011). Thalidomide: the tragedy of birth defects and the effective treatment of disease. *Toxicol Sci*. **122(1)**: 1-6.
8. Matthews SJ, McCoy C (2003). Thalidomide: a review of approved and investigational uses. *Clin Ther*. **25(2)**: 342-395.
9. Meyerson MS (1996). Erythema nodosum leprosum. *Int J Dermatol*. **35(6)**: 389-392.
10. Moschella SL (2004). An update on the diagnosis and treatment of leprosy. *J Am Acad Dermatol*. **51(3)**: 417-426.
11. Pôrto LA, Grossi MA, Alecrim ES et al (2019). Deep venous thrombosis in patients with erythema nodosum leprosum in the use of thalidomide and systemic corticosteroid in reference service in Belo Horizonte, Minas Gerais. *Case Rep Dermatol Med*. 2019. Article ID : 8181507; https://doi.org/10.1155/2019/8181507.
12. Prabhu S, Shenoi SD, Pai SB et al (2009). Erythema nodosum leprosum as the presenting feature in multibacillary leprosy. *Dermatol Online J*. **15(6)**: 15.
13. Rea TH, Levan NE (1975). Erythema nodosum leprosum in a general hospital. *Arch Dermatol*. **111(12)**: 1575-1580.
14. Scollard DM, Adams LB, Gillis TP et al (2006). The continuing challenges of leprosy. *Clin Microbiol Rev*. **19(2)**: 338-381.
15. Sharma NL, Sharma V, Shanker AK et al (2004). Deep vein thrombosis: a rare complication of thalidomide therapy in recurrent erythema nodosum leprosum. *Int J Lepr*. **72**: 483-485.
16. Sheskin J, Convit J (1969). Results of a double blind study of the influence of thalidomide on the lepra reaction. *Int J Lepr*. **37(2)**: 135-146.
17. Stebbing J, Benson C, Eisen T et al (2001). The treatment of advanced renal cell cancer with high-dose oral thalidomide. *Br J Cancer*. **85(7)**: 953-958.
18. Teo SK, Resztak KE, Scheffler MA et al (2002). Thalidomide in the treatment of leprosy. *Microbes Infect*. **4(11)**: 1193-1202.

How to cite this article : Mahajan RS, Ninama KR, Shah AR et al (2021). Deep Vein Thrombosis in Refractory Erythema Nodosum Leprosum: A Report of Two Cases. *Indian J Lepr.* **93**: 211-220.