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Case Series

Role of Phosphodiesterase-4 Inhibitor Apremilast in Patients of Chronic Recurrent Erythema Nodosum Leprosum: A Prospective Observational Study

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Erythema nodosum leprosum (ENL), or Type 2 lepra reaction, is a severe immune complex-mediated complication caused by the deposition of antigen-antibody complexes in these patients. If untreated, recurrent ENL episodes can lead to nerve damage, deformities, and severe disability. Corticosteroids remain the mainstay of treatment, but their prolonged use leads to significant side effects. Apremilast, a phosphodiesterase-4 (PDE-4) inhibitor with anti-inflammatory properties, is being explored as a steroid-sparing alternative for managing ENL. This study included seven patients with chronic or recurrent ENL. They received apremilast 30 mg twice daily along with tapering corticosteroids over six months. Disease severity was assessed monthly using ENLIST scores, focusing on nodules, neuritis, arthritis, orchitis, and systemic symptoms. Five patients showed significant improvement, as measured by ENLIST scores, which reduced to 0-2 by 6th month. Four patients showed complete remission, one had partial significant improvement. Symptoms such as fever, eruption of nodules, joint pain, and neuritis resolved in responsive cases. Two patients required alternative therapies due to persistent symptoms, and in one patient residual symptoms remained after a follow-up of 6 months study period. Apremilast was well-tolerated, with no major immediate side effects, and steroid-related toxicities were minimized. During the 12 months of follow-up, remission of ENL episodes was maintained in four cases. To conclude, apremilast, as an adjunct to corticosteroids, demonstrated significant potential for managing ENL by reducing ENL severity, addressing systemic symptoms, and minimizing steroid dependency**.** Apremilast thus**,** demonstrates potential as an adjunct in managing moderate ENL, reducing long-term steroid dependency**.** Its favorable safety profile and ability to improve clinical outcomes make it a promising adjunct in ENL management. Further studies with larger cohorts and follow-up are needed to validate these findings.

Introduction

Leprosy, caused by *Mycobacterium leprae*, is a chronic granulomatous infection with subtle symptoms, non-fatal that primarily affects the skin and peripheral nervous system. Among its complications, episodes of inflammation termed as lepra reactions, continue to be important clinical problem (Kumar et al 2004). Erythema nodosum leprosum (ENL), or type 2 lepra reaction, is observed in some multibacillary (MB) patients before, during, or even after release from treatment. It is a systemic immune

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complex-mediated condition characterized by the occurrence of painful erythematous nodules/ papules plaques which are evanescent. It appears in crops over the body, as painful nodules over the extensor surface of the body accompanied by fever. It usually heals in the next few days but in some cases more cases it can exacerbate as bulla, pustule/ ulcerative, or erythematous. urticarial like lesions. It may also be associated with systemic symptoms like acute neuritis, arthritis, orchitis, fever, weight loss, generalized fatigue, joint pain, and lymphadenopathy. ENL predominantly affects patients with the lepromatous form of leprosy and is associated with high bacterial load. Repeated ENL episodes can lead to nerve damage, deformities such as claw hand or foot drop, and disabilities, significantly impairing the patient's quality of life.

Corticosteroids remain the cornerstone of treatment, but long-term use is associated with severe side effects, including hyperglycemia, osteoporosis, and hypertension. Thalidomide is effective in refractory cases but is limited by its teratogenic risks and adverse effect profile, highlighting the need for safer, long-term alternatives.

Apremilast, a selective phosphodiesterase-4 (PDE-4) inhibitor, is a promising steroid-sparing agent. It works by increasing intracellular cyclic AMP (cAMP), reducing pro-inflammatory cytokines like TNF-α and IL-17, and enhancing the anti-inflammatory cytokine IL-10. After oral administration, apremilast achieves peak plasma concentration within 2-3 hours, has a bioavailability of 73%, and is primarily metabolized by CYP3A4. Its metabolites are excreted via renal and fecal routes, with a half-life of 6-9 hours, making it suitable for twice-daily dosing. Apremilast is approved by the Central Drugs Standard Control Organization (CDSCO) in India for psoriasis and psoriatic arthritis. Though off-label for ENL, its anti-inflammatory properties (Schafer et al 2010) and favorable safety profile make it an attractive alternative/adjunct to corticosteroids. Common side effects to it, include vomiting, diarrhea, and headache, these are typically mild, and no steroid-like toxicities have been reported when used in psoriasis and psoriatic arthritis (Torres & Puig 2018).

Apremilast is emerging as an anti-reaction drug in leprosy and has been found to be promising in the management of ENL (Narang et al 2020, 2021, Patil & Bubna 2023). This study evaluates the role of apremilast in managing chronic recurrent ENL, focusing on its efficacy in reducing reaction severity, alleviating systemic symptoms, and minimizing steroid dependency. This study aims at investigating the role of apremilast that can be given to patients having chronic recurrent ENL and to reduce the toxicity due to systemic corticosteroids and other treatment modalities. This may improve the treatment outcome and well-being of the patient.

Materials and Methods

This is a single-center prospective observational study conducted in the Department of DVL, Government Stanley Medical College and Hospital, North Chennai, in leprosy patients presenting with chronic and recurrent ENL reaction. This one- year -observational- study was conducted on seven patients who fulfilled the following inclusion criteria:

1. Chronic and recurrent/ recalcitrant ENL cases of leprosy of all ages, both genders and of all treatment statuses with MDT.
2. Patients who gave a valid written informed consent after proper explanation of the study.
3. Willing for monthly follow-up visits for at least 1 year.

Following category of patients were excluded**:**

1. Pregnant and lactating mothers.
2. Patients with CKD and severe renal dysfunction.
3. Patients suffering from HIV, hepatitis B and hepatitis C.
4. Those who cannot provide informed consent for the study.
5. Known case of any psychiatric disease.
6. Allergic to drugs under study.
7. Patients with sepsis, active bacterial infections, including tuberculosis; active herpes. zoster infection, or active invasive fungal infections. Patients were screened with chest X-ray, Sputum AFB and pulmonologist opinion to rule out tuberculosis.

***Assessment criteria*:**

Patients were categorized based on the 10-item ENLIST ENL severity scale as described in Table 1 (Walker et al 2016). Patients were graded as "inactive" or "mild" / "moderate" / "severe".

The Visual Analog Scale (VAS), a validated, subjective measure, was used to assess pain intensity. It consists of a 10 cm horizontal or vertical line, with endpoints representing the extremes of pain perception. The left end (0 cm) indicates "no pain", while the right end (10 cm) represents "worst imaginable pain." Patients are instructed to mark a point along the line that best corresponds to their pain intensity at a given moment. The measured distance (in cm) from the left end provides a numerical pain score, facilitating the quantification of pain severity. The scoring interpretation is as follows:

- 0 cm – No pain
- 1–3 cm – Mild pain
- 4–6 cm – Moderate pain
- 7–10 cm – Severe pain

Besides classifying the ENL patients, this scale was also used to capture, measure and record the responsiveness of patients to treatment.

Methodology:

After obtaining approval from IEC, these seven chronic, mild to moderate recurrent ENL cases fulfilling the inclusion criteria who attended the Dermatology Department of our hospital were assessed and included in the study.

After obtaining written informed consent from the patients, a detailed history of the reaction was elicited and recorded. Dermatological & neurological examination was done, slit skin smears (SSS) were taken and stained with Ziehl-Neelsen (ZN) stain, biopsy from the lesion was taken and slides were cut and stained with Fite-Faraco stain. The BI was noted both from the SSS and biopsy sections, complete blood count, ESR, CRP, LFT, RFT, HIV, HbsAg, Anti HCV tests were performed and recorded, Complete urine analysis, Chest Xray, ultrasound abdomen was done and results were recorded. Complete hemogram, liver function test (LFT), and renal function test (RFT) were performed and recorded every 2nd month.

Based on the ENLIST score, noted during examination, Mild to moderate ENL cases with scores less than or equal to 8 were included in the study and are being reported. All patients included were started on the tablet apremilast along with a low dose of oral corticosteroids (Prednisolone 30mg)

Starter Pack -- Apremilast

Day 1 - 10 mg in the morning; Placebo at night

Day 2 - 10 mg in the morning and 10 mg at night

Day 3 - 10 mg in the morning; 20 mg at night

Day 4 - 20 mg in the morning; 20 mg at night

Day 5 - 20 mg in the morning; 30 mg at night

Day 6 - 30 mg in the morning; 30 mg at night

Day 7 - 30 mg in the morning; 30 mg at night

After the patient completed the starter pack, apremilast 30mg twice daily was administered along with tapering corticosteroids was given for 6 months. Steroids were stopped for all the patients at the end of 6 months. During the follow-up period apremilast dose was tapered as follows:

7th month- Apremilast 20mg BD

8th month- Apremilast 20mg OD

9th month- Apremilast 10mg OD

10th month- Apremilast 10mg on alternative days

11th and 12th month- Apremilast stopped.

Tapering schedule used for steroids (Prednisolone): Steroids were tapered based on each patient's response and stopped after 6 months.

Month 1 : Prednisolone 30mg OD

Month 2 : Prednisolone 20mg OD

Month 3 : Prednisolone 10mg OD

Month 4 onwards: Prednisolone 5 mg OD

Whenever there was an exacerbation of ENL lesions, steroid dose was increased to 30 mg and tapered every 2-4 weeks.

ENLIST score was recorded at the time of presentation and the severity score was assessed and recorded every 15 days using the same scoring system.

Results

Among the 7 patients being reported 6 were males and 1 was a female patient. Their age ranged from 20 years to 62 years. The female patient presented with bullous & pustular type of ENL, while one male patient presented with ENL abscess. All other patients presented with typical erythematous, evanescent, tender nodules and papules. All the patients were associated with constitutional symptoms including fever, joint pain, and malaise.

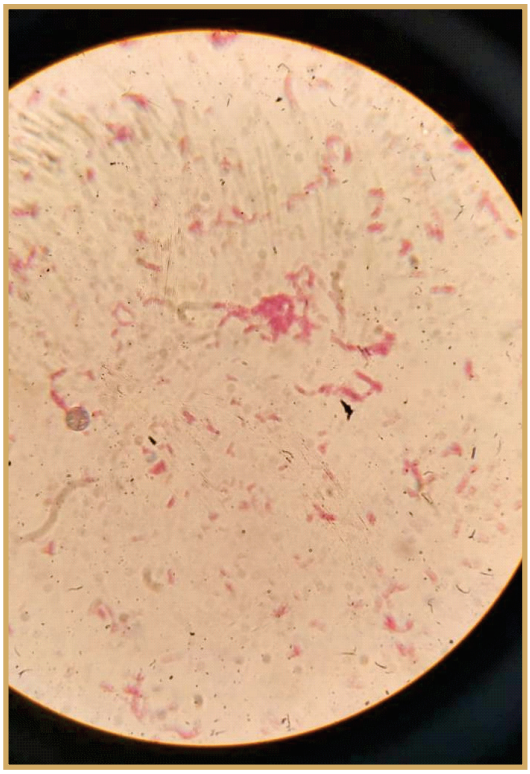

Fig. 1: Figure showing acid-fast lepra bacilli in slit skin smear of a patient included in the study (ZN staining under oil immersion).

Five patients were on the MB spectrum showing SSS positivity on ZN staining (Fig. 1) and biopsy showing macrophage granuloma, with Fite Ferraco stain with numerous bacilli. All patients were on MB multi-drug therapy.

Out of the 7 patients, 2 patients presented with ENL at the time of coming to the clinic, and the other 5 patients developed ENL after 3 months of multi-bacillary multi-drug therapy (Fig. 2). Clinical details of each patient are presented separately.

Follow-up scores of these patients included in the series are summarised in Table 2.

Case 1:

A female patient presented to the OPD with

Table 1: Table showing the ENLIST SCORE as used in the Study.

S.No	Item	Score 0	Score1	Score 2	Score 3
1	VAS – Pain scoring (mm)	0	1-39	40-69	70-100
2	Fever (in °C)	None (37.5 °C degrees or less)	No fever now but history of fever in last 7 days	37.6-38.5°C	38.6 °C or higher
3	Number of ENL skin lesions	None	1-10	11-20	21 or more
4	Inflammation of ENL skin lesions	Nontender	Redness	Painful	Complex
5	Extent of ENL skin lesions	0	1-2 regions	3-4 regions	5-7 regions
6	Peripheral oedema	None	1 site of Hands or Feet or Face	2 sites	All three sites (hands and feet and face)
7	Bone pain	None	Present on examination but does not limit activity	Present in sleep and restricts activity	Incapacitating
8	Inflammation of Joints and/or digits due to ENL	None	Present on examination but does not limit activity	Present, disturbs sleep and restricts activity	disturbed Incapacitating
9	Lymphadenopathy due to ENL	None	Enlarged	Pain or tenderness in 1 group	Pain or tenderness in 2 or more groups
10	Nerve tenderness due to ENL	None	Absent if attention distracted	Present even if attention distracted	Patient withdraws limb on examination

Table 2: ENL ENLIST SCORE at presentation and during the subsequent 6 months of treatment.

Case	Month 0	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
1	7	6	6	3	1	0	0
2	7	5	5	3	2	2	2
3	7	4	2	0	0	0	0
4	8	6	7	8	8	6	3
5	8	8	9	9	6	2	1
6	6	4	2	0	0	0	0
7	8	5	7	4	2	0	0

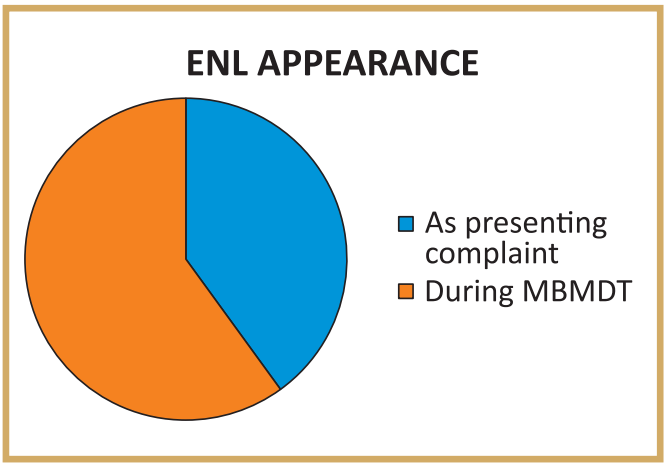

Fig. 2: Graph showing the appearance of ENL in patients in relation to treatment (MDT) intake.

painful pustules, bullae, and ulcerating nodules over infiltrated skin. She had a fever, joint pain, grade 1 nerve tenderness over the right and left ulnar nerve, right and left common peroneal nerve, and bilateral pedal edema. Her slit skin smear (SSS) was positive. She was diagnosed with lepromatous leprosy with erythema nodosum leprosum (ENL), The ENLIST score at the time of recruitment was 7 (Table 1). She was started on MB-MDT along with steroids. Prednisolone 40 mg was initiated, and she showed mild improvement. However, whenever the steroids were tapered to 20 mg, the patient experienced exacerbation and recurrence of ENL. Thalidomide was added at the end of the third month and continued for four months. However, she developed giddiness and sensory neuropathy, leading to discontinuation of thalidomide. Subsequently, she was started on apremilast while she was on her 8th MB-MDT dose. As shown in Table 2 and Fig. 3 (a and b) she gradually improved and steroids could be stopped after 4 months.

Briefly, the clinical response to the treatment of ENL for this case was as follows:

- Baseline (Month 0): ENLIST score 7. Moderate ENL with active tender nodules. Prednisolone started at 30 mg/day alongside apremilast 30 mg twice daily.
- Month 1: ENLIST score reduced to 6. Ulcerated lesions healed significantly. Prednisolone was tapered to 20 mg/day.
- Month 2: ENLIST score remained at 6. Stable condition with no new lesions. Prednisolone is maintained at 20 mg/day.
- Month 3: ENLIST score reduced to 3. Significant improvement; lesion count decreased. Prednisolone tapered to 10 mg/day.
- Month 4: ENLIST score reduced to 1. Almost all lesions resolved. Prednisolone was further tapered to 5 mg/day.
- Month 5: ENLIST score 0. Complete resolution achieved; steroids discontinued. Apremilast was continued at 30 mg twice daily.
- Month 6: ENLIST score 0. Remission was maintained with apremilast monotherapy.

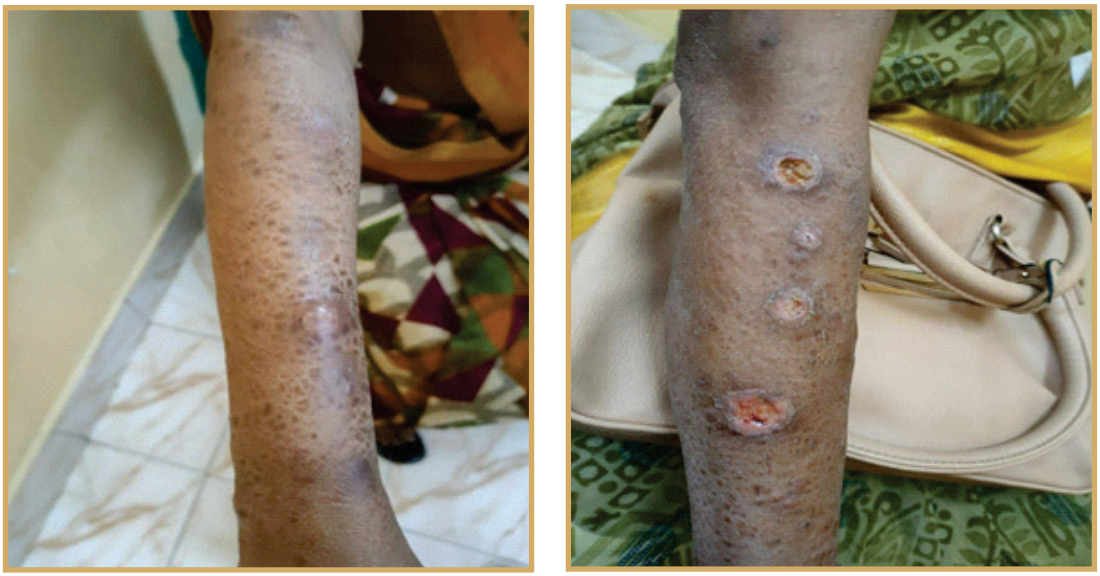

Fig. 3 (a): Case 1 – Lepromatous leprosy with bullous/pustular ENL showing multiple ulcerated nodules and bullae at baseline (ENLIST score 7).

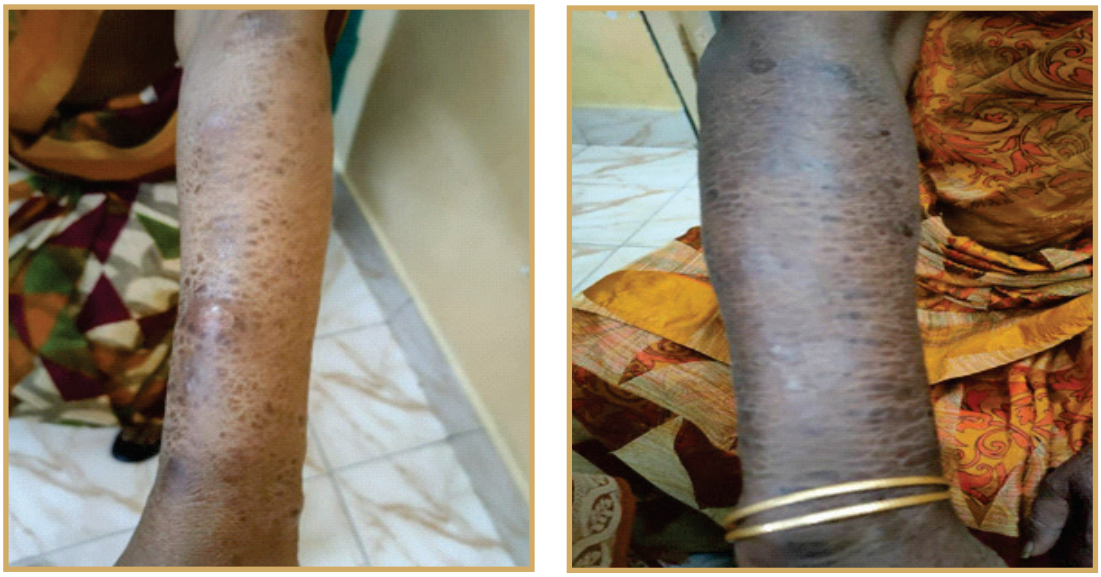

Fig. 3 (b): Case 1 – Same patient after 5 months of apremilast therapy, showing complete resolution of lesions with residual post-inflammatory pigmentation (ENLIST score 0).

- Patient follow-up for 6 months: Only apremilast tapering dose for 4 months and no anti-reaction drug for 2 months.

Case 2:

This patient was a young male patient, diagnosed with lepromatous leprosy and on MB-MDT. He

developed ENL lesions at the end of the 2nd month of treatment. He presented with fever, 10 tender papules over his body, fever, and grade 1nerve tenderness over the bilateral ulnar nerve and posterior tibial nerve. his ENLIST score was 7 (Table 2). He was started on steroids, with prednisolone 30 mg. This was slowly tapered but over the next 10 months, he experienced four exacerbations while tapering off the steroids. To manage the recurrent ENL lesions, he was started on hydroxychloroquine along with prednisolone. However, the lesions continued to recur, he was administered clofazimine 100 mg three times a day for 3 months, then twice daily for 3 months, and finally once daily for 3 months. After completing MB-MDT for 12 months, he still had a high BI both on slit skin smear (SSS) and on histopathology. There was a Grade 1 disability involving a sensory loss in both extremities Consequently, MDT was continued for another year. Apremilast was introduced when he was on his 17th MB-MDT drug schedule due to recurrent ENL. He showed improvement in the subsequent months but he had residual symptoms and is being continued on apremilast low dose till date.

Briefly, the clinical response to the treatment of ENL for this case was as follows:

- Baseline (Month 0): ENLIST score 7. Moderate ENL with systemic symptoms (fever, joint pain). Prednisolone started at 30 mg/day and apremilast 30 mg twice daily.
- Month 1: ENLIST score reduced to 5. Initial improvement with fewer lesions, constitutional symptoms improved. Prednisolone was tapered to 20 mg/day.
- Month 2: ENLIST score remained at 5. Stable response. Prednisolone is maintained at 20 mg/day.
- Month 3: ENLIST score reduced to 3. Marked improvement noted. Prednisolone was tapered to 10 mg/day.
- Month 4: ENLIST score reduced to 2. Residual lesions persisted. Prednisolone was reduced to 5 mg/day.
- Month 5: ENLIST score remained at 2. Plateau phase reached. Prednisolone was discontinued; Apremilast was continued at 30 mg twice daily.
- Month 6: ENLIST score remained at 2. No recurrence was observed.
- Patient follow-up for 6 months: Only Apremilast tapering dose for 4 months and no drug for 2 months.

Case 3:

This young male patient was diagnosed with lepromatous leprosy and started on MB-MDT. After 3 months, he developed ENL, presenting with erythematous nodules and plaques, fever, lymphadenopathy, neuritis, and pedal edema. His ENLIST score was 7. He was started on steroids. During the second episode of ENL, he developed an ulcerative type of ENL, thalidomide was initiated and maintained along with low-dose steroids for 9 months. However, as the patient was planning for pregnancy, thalidomide was discontinued. He was subsequently started on anti-reaction dosage of clofazimine 100mg three times a day. Subsequently, over two months period, the patient experienced two severe exacerbations, requiring injection dexamethasone for management. Due to the persistence of nodules, positive slit skin smear (SSS), MB-MDT was extended for another year. Apremilast was introduced when he was on his 20th MB-MDT drug schedule. Patient ENLIST score steadily decreased.

Briefly, the clinical response to the treatment of ENL for this case was as follows:

- Baseline (Month 0): ENLIST score 7. Moderate ENL with extensive papules and

nodules (Fig. 4a). Prednisolone started at 30 mg/day and Apremilast 30 mg twice daily.

- Month 1: ENLIST score reduced to 4. The rapid response was noted. Prednisolone was tapered to 20 mg/day.
- Month 2: ENLIST score reduced to 2. Significant improvement. Prednisolone was reduced to 10 mg/day.
- Month 3: ENLIST score reduced to 0. Complete resolution was achieved (Fig. 4b). Prednisolone was reduced to 5 mg/day.
- Month 4: ENLIST score 0. No recurrence was observed. Steroids were discontinued; Apremilast continued.
- Month 5: ENLIST score 0. Stable remission maintained.
- Month 6: ENLIST score 0. No recurrence was noted.
- Patient follow-up for a further 6 months: Only apremilast tapering dose for 4 months and no drug for 2 months.

Case 4:

This middle-aged male patient presented with erythematous, tender nodules and papules, accompanied by fever and lymphadenopathy, resembling Sweet's syndrome. Following slit skin smear (SSS) examination and histopathology, he was diagnosed as borderline lepromatous (BL) with erythema nodosum leprosum (ENL) and started on MB-MDT along with steroids. His ENLIST score was 8 (Table 2). After showing initial improvement for 2 months, he developed severe ENL with neuritis and orchitis while his steroids were being tapered. He was hospitalized and started on cyclosporine 100 mg twice daily for a month. However, he experienced exacerbations when the

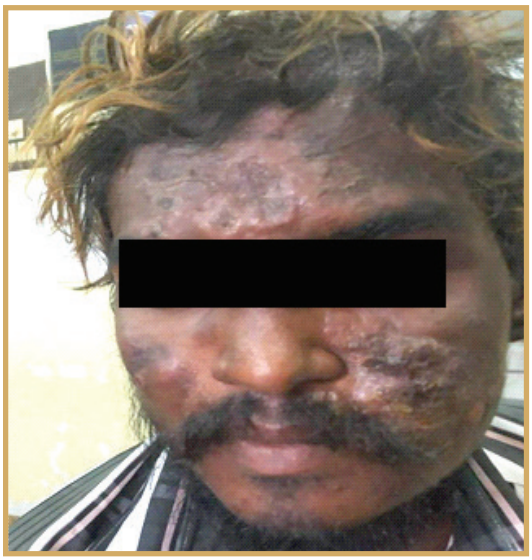

Fig. 4 (a): Case 3 – Lepromatous leprosy with ulcerative ENL presenting with erythematous nodules and ulcerating plaques at baseline (ENLIST score 7).

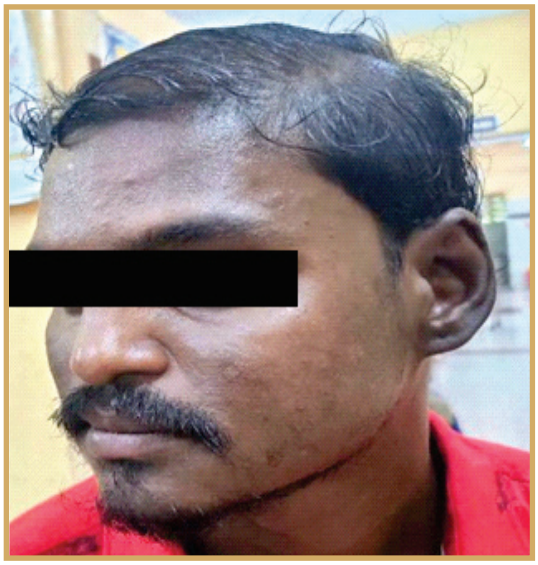

Fig. 4 (b): Case 3 – After 3 months of therapy, showing complete clearance of lesions with no active ENL (ENLIST score 0).

Cyclosporine dose was tapered. Thalidomide was subsequently initiated, leading to clinical improvement. After 4 months, his neuritis became severe involving the bilateral common peroneal nerve, posterior tibial nerve, and sural nerve of Grade 2 along with sensory loss in the bilateral lower limb. There was no motor disability. Apremilast was introduced when he was on his 13th MB-MDT drug. No response to apremilast at the end of 3rd month. Hence patient switched to an injection etarnacept 50mg subcutaneously biweekly for 12 weeks. ENLIST score improved.

Briefly, the clinical response to the treatment of ENL for this case was as follows:

- Baseline (Month 0): ENLIST score 8. Severe ENL with neuritis, arthritis, tender lymphadenopathy, and epididymo-orchitis. Prednisolone was started at 40 mg/day and apremilast 30 mg twice daily.
- Month 1: ENLIST score reduced to 6. Partial improvement with fewer lesions. Prednisolone was tapered to 30 mg/day.
- Month 2: ENLIST score increased to 7. Recurrence was noted during steroid tapering. Prednisolone was reduced to 20 mg/day.
- Month 3: ENLIST score worsened to 8. Poor response, neuritis, and lymphadenopathy was present; the patient was classified as unresponsive. Prednisolone is maintained at 20 mg/day.
- Month 4: ENLIST score remained at 8. Treatment switched to injection etarnacept (due to lack of improvement. Apremilast was stopped.
- Month 5: No further follow-up data available due to treatment change.
- Month 6: No further follow-up data available.

Case 5:

A young 25-year-old male patient presented with multiple patches and nerve thickening. He was diagnosed with borderline lepromatous Hansen's disease based on his clinical presentation, Slit Skin Smear (SSS) results, and histopathology findings and was started on MB-MDT. After 4 months of MB-MDT, he developed ENL with multiple crops of nodules, fever, neuritis, and watering of the eyes. His ENLIST score was 8. This episode subsided with 40 mg of prednisolone and pentoxifylline. However, he experienced an exacerbation 2 weeks later when the prednisolone dose was tapered to 30 mg. Apremilast was added when he was on his 8th MB-MDT schedule to control his recurrent ENL. At the end of 3rd month patient's ENLIST score increased. Hence patient switched to capsule thalidomide 400mg OD for 3 days along with IV steroids. As the patient improved clinically thalidomide dose was tapered to 100mg every month and maintained at 50mg OD for 3 months. The steroid dose was also tapered and stopped in 3 months subsequently.

Briefly, the clinical response to the treatment of ENL for this case was as follows:

- Baseline (Month 0): ENLIST score 8. Severe ENL with widespread lesions. Prednisolone was started at 40 mg/day and apremilast 30 mg twice daily.
- Month 1: ENLIST score remained at 8. No response was observed. Prednisolone was maintained at 40 mg/day.
- Month 2: ENLIST score increased to 9. Symptoms, mainly neuritis worsened despite treatment. Steroids are maintained at 40 mg/day.
- Month 3: ENLIST score remained at 9. Treatment switched to thalidomide and IV steroids.

- Month 4: No follow-up data available due to treatment change.
- Month 5: No follow-up data is available.
- Month 6: No follow-up data is available.

Case 6:

A young male 20-year-old patient, diagnosed with borderline lepromatous Hansen's disease, was started on MB-MDT. After 3 months of treatment, he developed ENL and was started on steroids and hydroxychloroquine His ENLIST ENL score was 6. He presented with tender nodules, fever, and joint pain with an ENLIST score of 6. Despite treatment, he experienced three exacerbations. Apremilast was introduced when he was on his 10th MB-MDT drug treatment schedule.

Briefly, the clinical response to the treatment of ENL for this case was as follows:

- Baseline (Month 0): ENLIST score 6. Mild ENL with localized lesions. Prednisolone was started at 20 mg/day and apremilast 30 mg twice daily.
- Month 1: ENLIST score reduced to 4. Gradual improvement observed. Prednisolone tapered to 15 mg/day.
- Month 2: ENLIST score reduced to 2. Continued improvement. Prednisolone was reduced to 10 mg/day.
- Month 3: ENLIST score reduced to 0. Complete resolution was achieved. Prednisolone was reduced to 5 mg/day.
- Month 4: ENLIST score 0. No recurrence was observed. Steroids were discontinued; Apremilast was continued.
- Month 5: ENLIST score 0. Stable remission maintained.
- Month 6: ENLIST score 0. No recurrence was noted.
- Maintenance 6: Only apremilast tapering dose for 4 months and no drug for 2 months.

Case 7:

A 62-year-old male patient, diagnosed with histoid Hansen's disease, was started on MB-

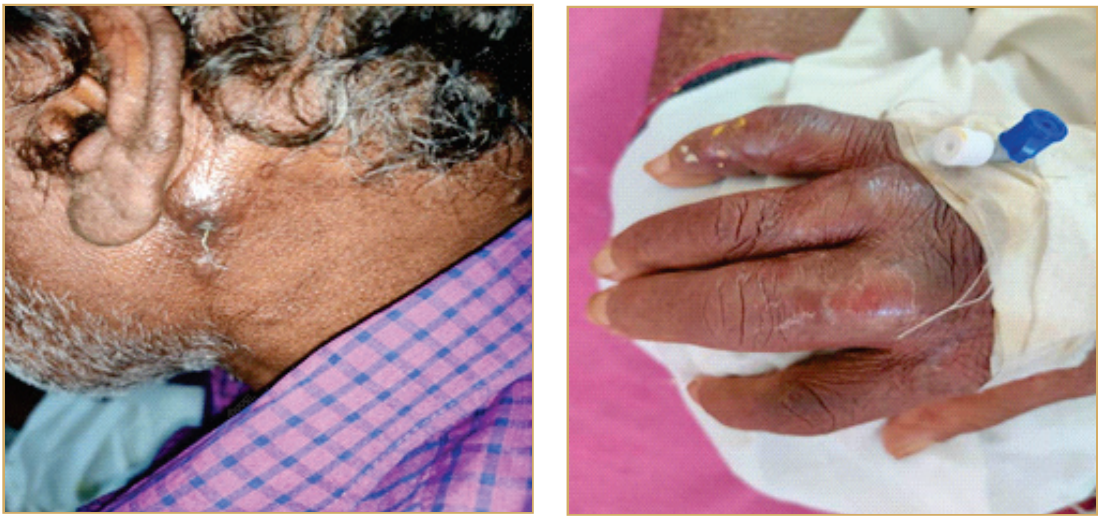

Fig. 5(a): Case 7 – Histoid Hansen's with ENL presenting with multiple tender nodules and a subcutaneous abscess at baseline (ENLIST score 8).

MDT. After 8 months of treatment, he presented with fever, neuritis, and tender nodules, and was started on steroids. Despite treatment, he experienced recurrent exacerbations, including an episode with orchitis, for which cyclosporine 100 mg twice daily was added to his regimen alongside steroids. During the last exacerbation, he presented with fever, joint pain, lymphadenopathy, and a subcutaneous abscess. Apremilast was initiated when he was on his 18th MB-MDT treatment schedule.

Briefly, the clinical response to the treatment of ENL for this case was as follows:

- Baseline (Month 0): ENLIST score 8. Severe ENL in Histoid Hansen's with abscess formation (Fig. 5a). Prednisolone started at 40 mg/day and apremilast 30 mg twice daily.
- Month 1: ENLIST score reduced to 5. Significant improvement was observed, abscess subsided (Fig. 5b). Prednisolone tapered to 30 mg/day.
- Month 2: ENLIST score increased to 7. Recurrence was noted during steroid tapering. Prednisolone was maintained at 30 mg/day.
- Month 3: ENLIST score reduced to 4. Adjusted steroid dose to control recurrence.
- Month 4: ENLIST score reduced to 2. The abscess resolved with fewer lesions.
- Month 5: ENLIST score 0. Complete remission achieved (Fig. 5c). Prednisolone was discontinued.
- Month 6: ENLIST score 0. Stable remission was maintained with apremilast.
- Maintenance 6 months: Only apremilast tapering dose for 4 months and no drug for 2 months.

***Other important observations*:**

In case 4, no response to apremialst at the end of 3rd month was observed. Hence patient was switched to an injection etarnacept 50mg subcutaneously biweekly for 12 weeks. ENLIST score improved.

In case 5, at the end of 3rd month patient's ENLIST score increased. Hence patient was switched to

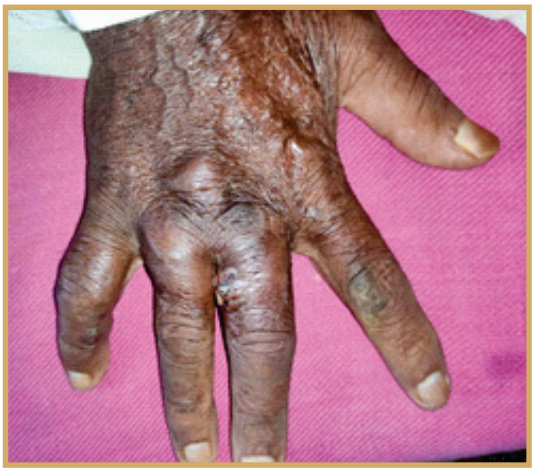

Fig. 5b: Case 7 – At 4 weeks of apremilast therapy: Marked reduction in nodules and partial resolution of abscess, ENLIST score decreased to 5.

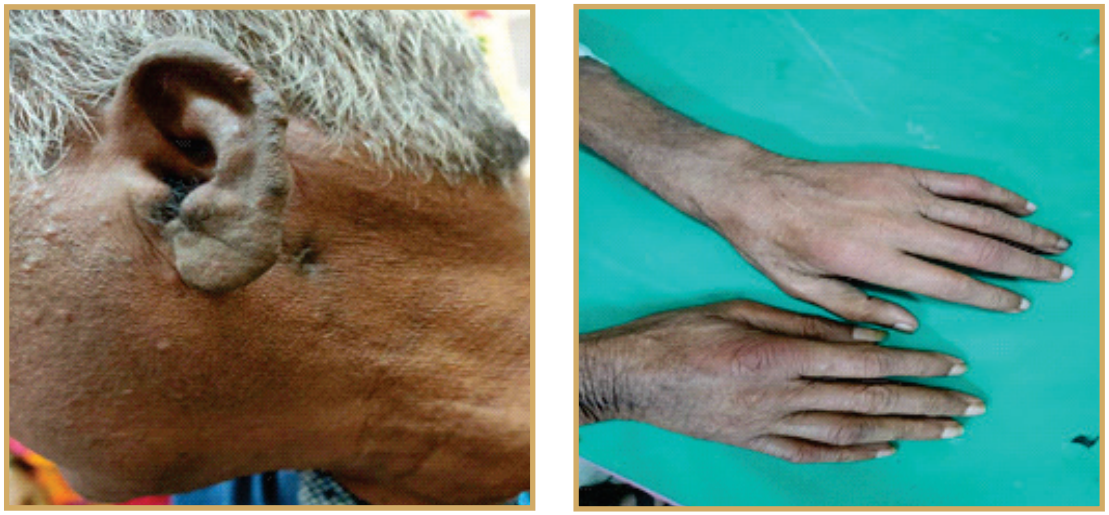

Fig. 5c: Case 7 – After 5 months of apremilast therapy: Complete remission with clearance of nodules and resolution of abscess (ENLIST score 0).

capsule thalidomide 400mg OD for 3 days along with IV steroids. As the patient improved clinically thalidomide dose was tapered to 100mg every month and maintained at 50mg OD for 3 months. The steroid dose also tapered and stopped in 3 months subsequently.

In total, 7 patients were treated with apremilast. Of these, 4 patients achieved complete remission, 1 had partial improvement, and 2 did not respond and were shifted to alternative therapy. All 7 patients are included in this case series.

None of the patients developed any side effects pertaining to apremilast and responded well to the treatment. The frequently encountered gastrointestinal side effects were also not observed in our series. The repeated blood investigations were found to be normal. During the follow-up period all the patients didn't experience any new disability or nerve damage.

Discussion

Leprosy reactions, particularly erythema nodosum leprosum (ENL), pose significant morbidity risks due to multi-organ involvement, chronicity, recurrence and residual effects. It is an immunological reaction and is usually treated effectively with systemic corticosteroids. ENL reactions can profoundly affect patients' mental and physical well-being, occasionally resulting in lifelong disabilities and fatal outcomes. ENL manifests with a spectrum of clinical features including skin lesions, neuritis, arthritis, dactylitis, eye inflammation, osteitis, orchitis, lymphadenitis, and nephritis (Cuevas et al 2007). These reactions can occur before initiating treatment, during treatment, and also after stopping MDT after release from treatment. They are usually acute episodes but may present intermittently and persist for months or even years. The diagnosis is typically based on the history of the disease and the clinical picture of characteristic lesions, associated constitutional symptoms, and painful nerve thickening. LL type of disease and high bacteriological index are recognized as risk factors for ENL. Immunologically, ENL is an antigen-antibody

reaction and deposition of immune complexes in various tissues which are responsible for this clinical picture and involves the elevation of pro-inflammatory mediators, particularly tumor necrosis factor α (TNF-α), interferon-γ (IFN-γ), and interleukins (IL-2, IL-6, IL-12).

Treatment primarily focuses on pain alleviation, prevention of nerve damage,–and identification of aggravating factors before initiating specific therapies. ENL severity is categorized as mild, moderate, or severe based on symptoms, with mild episodes often responding to rest and oral aspirin, while severe cases require corticosteroids (e.g., Prednisolone) and/or thalidomide therapy. Treatment options to manage ENL are expanding (Bhat & Vaidya 2020). However, prolonged use of high-dose prednisolone poses risks of steroid toxicity. Thalidomide is a category X drug (unsafe in pregnancy), not freely available, has cost limitations, and has few severe side effects like irreversible sensory neuropathy (Bastuji-Garin et al 2002). Other drugs like clofazimine and minocycline are also effective in the treatment of ENL Clofazimine requires higher doses, and takes 4 to 6 weeks to be effective. The high dosage produces gastrointestinal side effects in some patients and skin discoloration. Minocycline itself precipitates ENL in some patients. Pentoxifylline, and other immunosuppressants like cyclosporine, cyclophosphamide, methotrexate, and azathioprine have also been used can be used as treatment options (Girdhar 1990). All these immunosuppressant drugs need meticulous monitoring for their side effects. Alongside conventional treatments, immunomodulators like zinc and levamisole have also been given with beneficial effects. However, refractory cases may experience severe morbidity or mortality, necessitating the exploration of alternative agents like apremilast (Narang et al 2020, 2021; Patil & Bubna 2023).

The patients described in this study had similar recurrent ENL with repeated exacerbations whenever the steroid dose tapered. Three patients had received hydroxychloroquine 200mg HS for 6-8 months; 1 patient had received pentoxiphylline 800mg TDS; two patients had received cyclosporine 100mg BD & one patient had received clofazimine 300mg TDS along with steroids. Although the disease activity had reduced whenever prednisolone was tapered, these patients had exacerbation suggesting steroid dependence and risk of development of side effects due to continued steroid intake. Common side effects seen with long-term steroid intake include acneiform eruptions, early cataracts, weight gain, cushingoid facies, peptic ulcers and precipitation of diabetes mellitus.

Apremilast, a phosphodiesterase-4 inhibitor, has shown promise in chronic recurrent ENL. It is FDA-approved for conditions like plaque psoriasis and psoriatic arthritis. Apremilast is a PDE-4 inhibition, it increases intracellular cAMP which in turn downregulates inflammatory response by modulating expression of TNF-α, IL 23, IL 17 & other inflammatory cytokines (Serezani et al 2008). It is also used in other conditions like atopic dermatitis, alopecia areata, lupus erythematosus, lichen planus, LMDF, and chronic aphthous stomatitis. Most reported adverse effects are pertaining to the gastrointestinal system – nausea, vomiting & diarrohea. Other side effects include upper respiratory infection, headache, backache, urticaria & rarely insomnia, depression, and suicidal ideation. PDE-4 isoenzymes are the predominant cAMP-degrading enzymes in most immune cells. Apremilast appears to be a promising drug in ENL (Narang et al 2020, 2021; Patil & Bubna 2023). This drug doesn't need any specific pre-monitoring guidelines (Schafer et al 2010).

In our study, apremilast 30 mg twice daily was initiated in all 7 enrolled ENL patients along with tapering doses of corticosteroids, and ENL severity was assessed every 2 weeks using the ENLIST ENL severity scale. Apremilast demonstrated encouraging outcomes, with 4 patients achieving complete remission (ENLIST scores 0–2 by 6 months), 1 patient showing partial improvement, while 2 did not respond and required alternative therapies. No major side effects of apremilast were observed.

In our study, seven ENL patients meeting inclusion/exclusion criteria were included, predominantly young males, with most falling within the lepromatous spectrum of Hansen's disease and two patients had presented with histoid nodules. Histopathology in all cases showed features consistent with ENL, including macrophage granulomas, dermal oedema, neutrophilic infiltration, and vasculitis. Fite-Faraco staining revealed numerous lepra bacilli, with a bacteriological index ranging from 3+ to 6+ across the cases. The findings were similar to those reported by Lockwood et al (2012. Six of our cases were on Drug card MBMDT when ENL was diagnosed. All patients were started on Apremilast along with low dose steroids. All were followed once in 15 days with ENLIST score. Five of these 7 cases had excellent response to study protocol. Among them two patients with pustular type of histoid Hansen's who presented with ENL had dramatic response to our treatment. Histoid Hansen's cases have been reported to suffer from ENL (Vasavi & Reddy 2012), thus, apremilast will be useful to treat such cases as well.

Patil & Bubna (2023) concluded that apremilast may not be a standalone steroid-sparing agent in ENL. Our study demonstrated its effectiveness as an adjunct treatment in over 70% of our cases. In their study, low-dose apremilast (30 mg BD) was administered after stopping prednisolone for a month, followed by 30 mg on alternate days for 2 months before discontinuation. Further, our study employed apremilast at 30 mg BD for 6 months alongside tapering steroids, followed by maintenance with apremilast in tapering doses for an additional 6 months. This regimen proved effective in managing moderate and pustular ENL.

Conclusions

Apremilast, used in combination with corticosteroids, showed significant potential in managing chronic recurrent ENL by reducing disease severity, addressing systemic symptoms, and can help in minimizing long-term steroid dependency. Its favourable safety profile and steroid-sparing benefits highlight its role as an adjunctive therapy, particularly in moderate ENL. However, a longer follow-up is required and more cases need to be studied in reaching a definitive conclusion.

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