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Research Article

The Multifaceted Manifestations of Type 2 Lepra reaction: A Series of Four Cases

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A B S T R A C T

Type 2 lepra reaction is a Th2-mediated type III hypersensitivity reaction in leprosy, with a characteristic cutaneous manifestation in the form of erythema nodosum leprosum (ENL). Chronic ENL is described as recurrent or persistent nodules existing for more than 6 months' duration. Reaction hand manifests with oedemaof the dorsum of the hands, arthritis, and functional incapacity during type 2 lepra reaction. The diagnosis of ENL is quite challenging because of its heterogeneous clinical presentations and prolonged incubation period. A 36-year-old female developed recurrent painful nodules with fever all over the body two years ago. She was also treated for rheumatoid arthritis 7 years back. She was subsequently treated with steroids, clofazimine, and thalidomide. A 19-year-old male presented with a recurrent history of fever, joint pain, and erythematous painful nodules over extremities after completing a course of MDT (Multi Drug Therapy). He was on treatment with steroids, due to which he developed avascular necrosis of the left hip joint and was later shifted to thalidomide. A 45-year-old female having completed 2 years of MDT developed erythema and oedema of palms and soles with myalgiafor which she was given steroids, methotrexate, and clofazimine thrice daily. A 27-year-old male having completed the course of MDT developed swelling and pain in his fingers, for which he was treated with steroids, hydroxychloroquine, and methotrexate. We report these four cases due to the unusual manifestations of type 2 lepra reactions, such as chronic ENL and reaction hand.

Keywords: Chronic, ENL, Erythema Nodosum Leprosum, Reaction hand, Type 2 Lepra Reaction

Introduction

Leprosy is a chronic granulomatous infection caused by Mycobacterium leprae, targeting mucosal tissues and peripheral nerves, leading to decreased skin sensation and increased disability over time. [1] There are three types of leprosy reactions, each of which manifests with diverse clinical presentations. A Type II reaction occurs in borderline leprosy during the first six months of MDT due to an increased cell-mediated immune response. Type II reaction, on the other hand, is observed in lepromatous or borderline lepromatous forms of leprosy after completion of MDT. It encompasses three variants: erythema nodosum leprosum, erythematous polymorphous-like reaction, and Lucio phenomenon. Sometimes the Lucio phenomenon is categorised as a type III reaction. [2] Type 2 lepra reaction is a Th2-mediated type III hypersensitivity reaction due to immune complex deposits in the tissue against Mycobacterium leprae. [3,4] The hallmark feature of type 2 reaction is erythema nodosum leprosum (ENL), which presents as crops of tender erythematous, subcutaneous nodules on seemingly unaffected skin. It may be accompanied by fever, neuritis, orchitis, and osseous pain.[5] Acute ENL is defined as episodes lasting below 24 weeks during corticosteroid treatment, with no recurrence after the drug withdrawal. [6] Chronic ENL is referred to as nodules occurring for more than 24 weeks in which the patient needs continuous treatment or recurrence within 27 days of stopping treatment. [5] Recurrent ENL is defined as an episode wherein there is a succeeding episode that occurs in 28 days or above. [6] Histopathologically, ENL lesions exhibit the presence of Mycobacterium leprae along with neutrophils, vasculitis, and panniculitis. Chronic lesions demonstrate an increased number of bacilli along with T cells, histiocytes, and plasma cells. One notable clinical manifestation is reaction hand, which is defined as oedema of the dorsum of hands, arthritis, and functional debilitation. [7] Understanding these various presentations of ENL is imperative for timely intervention, mitigating complications, and reducing mortality. Herein, we describe four such interesting presentations of type 2 leprosy reactions

Case 1: Lepromatous Leprosy with Chronic Enl

A 36-year-old female, diagnosed with lepromatous leprosy (LL), had completed MB-MDT (multibacillary multidrug therapy) 2 years back. She was also treated for rheumatoid arthritis 7 years back. She gave a history of recurrent painful lesions over both arms, hands, and thighs for the past 2 years, accompanied by fever, malaise, and bilateral knee joint pain. She was mismanaged outside with analgesics and steroids on and off by physicians without a proper diagnosis, following which she also developed an extensive dermatophytosis infection. On examination, there were multiple erythematous tender nodules present over face, bilateral arms, forearms, and thighs. (Figure 1) Histopathological examination of a nodule showed periadnexal lymphoplasmocytic and neutrophilic infiltrate, with positive Fite-Faraco staining showing numerous fragmented bacilli indicating an inactive disease. After being confirmed as chronic ENL, the patient was given initial treatment with oral methylprednisolone 40 mg and oral clofazimine 100 mg TID, which was later discontinued due to gastric intolerance. She was also prescribed oral itraconazole130 mg (supra bioavailable dose) at night for dermatophytosis. The patient developed new nodules with fever despite being on steroids, and once the dose of steroids was tapered. Hence, she was put on oral thalidomide 200 mg BD along with steroids. An excellent response with cessation of new lesions was achieved after starting on thalidomide, which was subsequently tapered to 100 mg OD and alternate days over 6 months. Methylprednisolone 40 mg was tapered slowly over a period of 6 months, and the patient did not develop any recurrences.

Figure 1.Lepromatous leprosy with ENL nodules present over the face

Case 2: Lepromatous Leprosy with Chronic Enl

A 19-year-old male presented to us with recurrent widespread painful eruptions over his hands, back, and thighs for the past 1 year, accompanied by fever and joint pain. He was a previously diagnosed case of lepromatous leprosy who completed MB-MDT 2 years ago. The patient also developed avascular necrosis (AVN) of the left hip joint after erratic and prolonged use of steroids for ENL and underwent surgery for the same. On examination, multiple erythematous tender nodules were seen over bilateral arms, trunk, and thighs. (Figure 2A & B) Slit skin smear was positive, which showed numerous fragmented and granular acid-fast bacilli. Histopathological examination revealed radial histiocytic aggregations, giant cells, bacilli, and fibrinoid necrosis. Hence, a diagnosis of chronic ENL was made, and the patient was given a low dose of prednisolone (20 mg) to prevent steroid withdrawal symptoms and oral

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thalidomide (100 mg TID). There was a significant response seen with the resolution of lesions, and thalidomide was tapered to twice and once daily every 3 months.

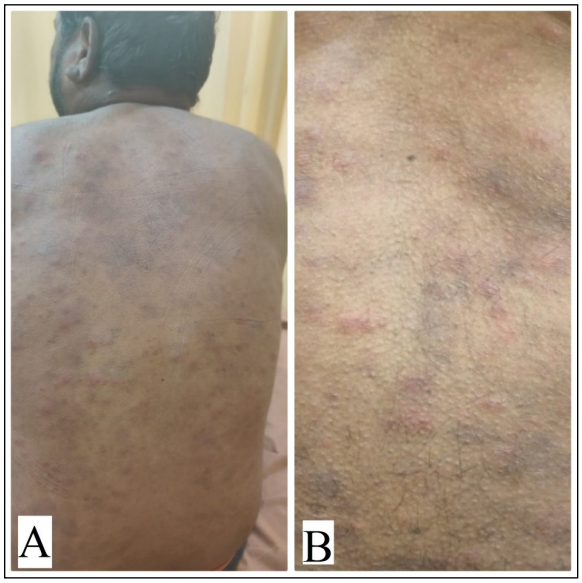

Figure 2.(A) Chronic ENL with multiple nodules seen over the back.(B) Multiple nodules seen over the abdomen

Case 3: Lepromatous Leprosy with Reaction Hand

A 45-year-old female, post- MB-MDT for LL, 2 years prior, presented with episodic painful swelling in both palms and soles for the past 18 months associated with fever, muscle pain, and arthralgia. Cutaneous examination revealed diffuse erythema, oedema with tender plaques and nodules over bilateral palms and soles, and ill-defined hypopigmented patches over the trunk. (Figure 3A & B) Serological tests such as ANA and rheumatoid factor were negative. A presumptive diagnosis of reaction hand was considered, and a biopsy was performed to confirm the condition. Histopathological examination of the nodule revealed neutrophilic dermal infiltrate, numerous bacilli in clusters, vasculitis, and septal panniculitis consistent with ENL, and the radiographic exam showed reduced joint space, mild osteopenia, and periarticular oedema of soft tissue. The patient was administered oral prednisolone 30 mg OD, oral clofazimine 100 mg TID, and oral methotrexate 10 mg weekly once, after which her condition responded very well. She is currently on maintenance with prednisolone 15 mg OD along with other drugs.

Case 4: Lepromatous Leprosy with Enl with Dactylitis

A 27-year-old male with a history of MB-MDT for LL, who completed ityear back, presented with chief complaints of pain and swelling over the fingers of both hands on and off with concomitant fever for the past 8 months. There was no history of any other joint pain. On examination, banana-shaped swelling and erythema of fingers with arthritis and a few tender nodules were present over bilateral forearms and earlobes. (Figure 4) Acid-fast staining was positive for lepra bacilli. Serology for RF and ANA was negative, ruling out rheumatoid arthritis and connective tissue disease. Histopathological examination showed neutrophilic infiltration in the dermis and fibrinoid necrosis with fragmented bacilli, which confirmed the diagnosis as ENL with dactylitis. The patient was treated with oral methylprednisolone 24 mg OD, tapered to 4 mg OD for 6 months, along with oral methotrexate 10 mg weekly once and oral hydroxychloroquine 200 mg OD. The patient showed complete resolution of pain and swelling of fingers within 6 months of treatment. The summary of all cases is shown in Table 1.

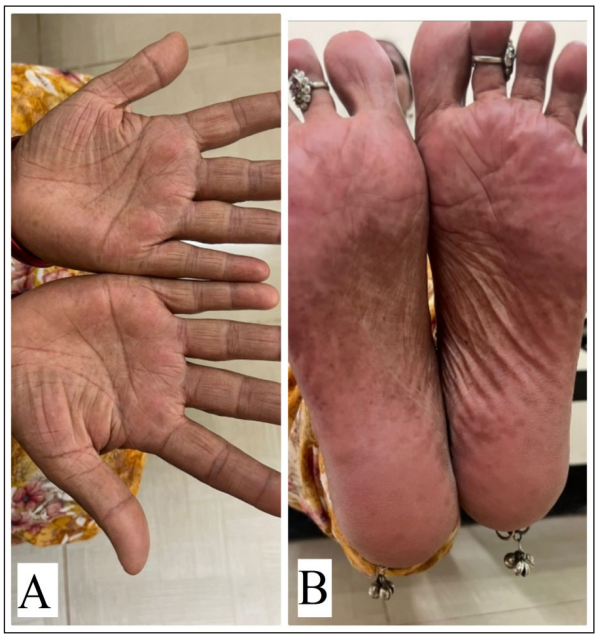

Figure 3.(A) Reaction hand showing diffuse erythema and nodules over both palms (B) Diffuse erythema over both soles

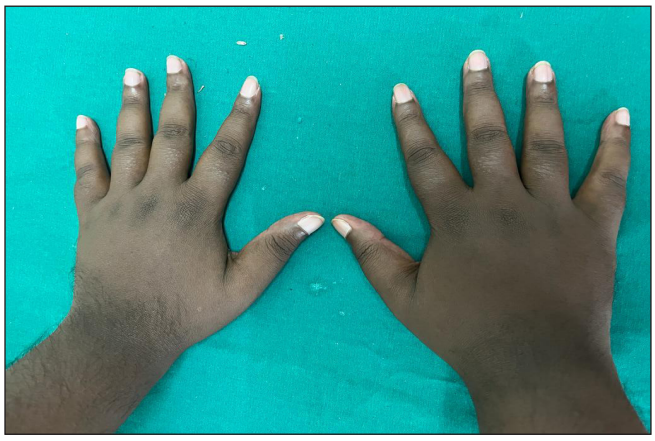

Figure 4.ENL with swelling of fingers (dactylitis)

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Table 1.Summary of all 4 cases

	CASE 1	CASE 2	CASE 3	CASE 4
Age and sex	36 years, female	19 years, male	45 years, female	27 years, male
Complaints	Painful nodules all over the body for 2 years.	Painful nodules all over the body for 1 year.	Painful swelling of palms and soles for 18 months.	Pain and swelling of fingers for 8 months.
Clinical features	Multiple erythematous tender nodules over arms, forearms and thighs	Multiple Erythematous tender nodules over B/L arms, trunk and thighs	Diffuse Erythema with tender plaques and nodules over palms and soles Ill-defined hypopigmented patches over trunk	Banana shaped swelling and erythema of fingers Few tender nodules over B/L forearms and earlobes
Associated features	Rheumatoid arthritis (treated 6 years back) Fever Bilateral knee joint pain Recurrent Dermatophytosis	Fever, Arthralgia Avascular necrosis of left hip joint (outside treatment on long-term steroids)	Fever, arthralgia Myalgia	Fever, arthritis of small joints of hand
Histopathology	Numerous fragmented bacilli with periadnexal lymphoplasmocytic and neutrophilic infiltrate	Small histiocytes radially around central cleft, giant cells, bacilli and fibrinoid necrosis	Neutrophilic infiltrate, numerous bacilli in clusters vasculitis and septal panniculitis	Neutrophilic infiltration in the dermis and blood vessels, few bacilli and fibrinoid necrosis
Diagnosis	Lepromatous leprosy with chronic ENL	Lepromatous leprosy with chronic ENL	Lepromatous leprosy with ENL with reaction hand	Lepromatous leprosy with ENL with dactylitis
Completion of MDT	Completed 2 years back	Completed 2 years back	Completed 2 years back	Completed 1 year back
Treatment given	Steroids- T. Methylprednisolone 40mg tapered and stopped over 6 months Clofazimine 100 mg tds T.Thalidomide 200 mg BD to T.thalidomide 100 mg OD to 100 mg alternate days, C.Itraconazole 130 mg HS	Low dose steroids –T. Prednisolone 20 mg tapered and stopped over 3 months Thalidomide 100mg TDS to 100mg BD to 100mg OD	Steroids – T.Prednisolone 30 mg OD tapered to 15 mg OD Clofazimine 100 mg TDS T. Methotrexate 10 mg weekly once	Steroids- T. Methylprednisolone 24 mg OD tapered to 4 mg OD T. Methotrexate 10 mg weekly once T.HCQ 200 mg OD

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Discussion

Leprosy-associated immune reactions occur in about 30-50% of all cases. [8] They are broadly categorised into Type 1 reactions (upgrading/reversal and downgrading reactions) and Type 2 reactions (ENL). ENL is a type III hypersensitivity reaction noticed in 15.4% of LL patients and 4.1% of BL patients. [7] The mechanisms driving this reaction are not fully understood. Yet, they are closely linked to the formation of immune complexes. When an excess of antigen is present, it provokes a robust production of antibodies, resulting in significant inflammation. This highlights the critical role of immune responses in mediating inflammatory reactions. [1,8] It is characterised by the invasion of neutrophils, immune complex deposition, pro-inflammatory cytokine release, and T-cell -mediated response contributing to both cutaneous and systemic manifestations .BL and LL spectra could be risk factors for ENL, as higher concentrations of M. leprae antigens in tissues can result in increased production of IgM and IgG antibodies. [1] In the present study, all four patients diagnosed with ENL were LL cases showing the high prevalence rate of ENL among the LL spectrum, which is in concordance with Manandhar et al. [9] study.

According to previous studies, ENL onset post-MDT was most likely acute, which could be due to the fragmentation of bacilli by MDT, whereas in our study we observed chronicity during ENL. There has been a rise in the trend of chronic ENL cases in the current era. This trend may be linked to increased autoimmunity post-COVID, age-related immune modulation, or increased susceptibility in younger individuals due to higher occupational stress and physical or mental fatigue exacerbating severe health and economic issues for the patients and their families. In our study, there was a notable downturn in the prevalence of ENL with an advance in age, which is consistent with the study done by Manandhar et al. [9] They also reported various risk factors for ENL, such as bacteriological index > 4+, upper respiratory tract infection, diabetes mellitus, dermatophytosis, anaemia, and stress, which aligned with our study, where one of the patients had a dermatophytosis infection.

ENL is also characterised by an impressive array of morphological presentations, which can encompass distinct nodules, bullae, ulcers, necrotic lesions, pustules, and even haemorrhagic and erythema multiforme-like manifestations. [7] We observed 2 cases (1 & 2) of chronic ENL that had a nodular presentation. This diversity highlights the complex nature of ENL and underscores the need for careful observation and tailored treatment approaches. Moreover, a range of significant systemic manifestations can occur, including neuritis, arthritis, synovitis, lymphadenitis, iritis, uveitis, orchitis, and glomerulonephritis, which again underscores the complexity and seriousness of the condition. [7] Musculoskeletal involvement stands as the third most common presentation of leprosy, following skin and nerve involvement, and it can sometimes be the sole manifestation or appear before other symptoms. [10]

Chauhan et al. [11] categorised arthritis in leprosy into distinct forms: Charcot's arthropathy, which arises as a consequence of peripheral sensory neuropathy; the swollen hands and feet syndrome; acute polyarthritis linked to lepra reactions; and chronic arthritis caused by the direct infiltration of the synovium by lepra bacilli. [4,10] The pathophysiology of arthritis in type 2 reactions closely mirrors that of ENL observed in the skin. The synovial membrane gets infiltrated by collections of Virchow cells, which activate a powerful antigen-antibody-complement reaction, forming insoluble complexes that ignite a robust inflammatory response in the synovial tissue. The most affected joints include the knees, proximal interphalangeal joints, metacarpophalangeal joints, wrists, ankles, metatarsophalangeal joints, and elbows.[12] This can mimic the presentations of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). RF and ANA can sometimes be detected in type 2 reactions, also making it difficult to differentiate from these conditions. However, there are several other clues, such as the absence of rheumatoid nodules, ENL lesions involving the face and upper limbs as opposed to the involvement of lower extremities in erythema nodosum, and the presence of anaesthetic patches or glove-and-stocking anaesthesia. Moreover, systemic lupus erythematosus and antiphospholipid syndrome have other key features, such as malar rash and photosensitivity, which were absent in our cases. Additionally, acid-fast bacilli (AFB) were detected on slit-skin smears, which pointed towards ENL. This led us to conclude that the arthritis of metacarpophalangeal and interphalangeal joints in our cases (3 & 4) was likely due to tenosynovitis caused by M. leprae, similar to the study by Pathania et al. [10] The comparison of our study with similar studies reported elsewhere is shown in Table 2.

Table 2.Summary of similar cases reported elsewhere

Study	Year	Age & sex	Initial presentation	Diagnosis	Onset after MDT	Treatment given
I.M.B. Goulart et al [12]	2022	57Y, M	Right knee pain, erythematous nodules all over the body	Type 2 lepra reaction with monoarthritis (Right knee)	4 months after completion	Thalidomide400 mg/day, Prednisolone60mg/day, Clofazimine300mg/day

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Mishra et al [13]	2024	60Y, F	Multiple painful nodules, ulcers with purulent discharge, severe joint pain, headache	Chronic steroid-dependent erythema necroticans	2 months after completion	Low dose steroids, Thalidomide, clofazimine, Apremilast 30mg BD
P. Arora et al [15]	2019	22Y, M	Multiple reddish painful lesions, glove and stocking anesthesia	Chronic steroid-dependent ENL	6 months after completion	Prednisolone 1mg/kg/day slowly tapered, Clofazimine 100mg TDS Thalidomide 100 mg TDS, Methotrexate, colchicine, Minocycline 100mg OD, Ofloxacin 400 mg OD, clofazimine 50 mg OD
Gupta et al [16]	2021	24 Y, F	Swelling of bilateral hands, interphalangeal joint pain, painful rash over the arms and leg fever, morning stiffness	ENL with dactylitis and hand swelling	Initial presentation	Minocycline, Moxifloxacin, Rifampicin once a month
Deo et al[4]	2024	52Y, F	Joint pain, fever, crops of reddish raised papules nodules and digital ulcers	Chronic ENL with polyarthritis.	Initial presentation	High dose of steroids, MB-MDT
Youssef et al[17]	2023	68Y, M	Erythematous plaques over bilateral legs, Non healing ulcer, paresthesia over extremities, diffuse joint pain	ENL with polyarthritis	Initial presentation	Prednisone (20 mg/day) and Hydroxychloroquine (400mg/day) Mycophenolate (2000 mg/day), Minocycline, Rifampicin

Clofazimine, an integral component of MB-MDT, reduces the frequency and severity of ENL lesions because patients who had been treated without clofazimine presented with multiple episodes, as per the Manandhar et al. study. [9] Our study supports this, in which one patient demonstrated significant clinical improvement following clofazimine. In another report, clofazimine and apremilast were strategically introduced as effective steroid-sparing agents in the management of ENL, offering a promising alternative to reduce dependency on steroids. [13] V. V. Pai et al. [14] showed that all four cases in their study successfully completed 12 months of a high-dose Clofazimine and prednisolone regimen, with significant resolution of ENL. Clofazimine at doses of 100 mg/day or higher has been widely utilised to alleviate the severity and recurrence of ENL. [14] The WHO guidelines for managing ENL recommend a regimen of 300 mg/day for 12 weeks, followed by 200 mg/day for 12 weeks, and then 100 mg/day for 12-24 weeks.

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However, strong clinical trial evidence does not support this approach. Hence, there is a need for a more tailored approach to prevent the recurrence of ENL. Tables 3 & 4 depict the treatment algorithm for the management of acute and chronic ENL.

Corticosteroids used for managing chronic or recurrent ENL are associated with numerous adverse effects, and there is no proof that preventive steroid therapy delays the onset of the first ENL episode. This highlights the urgent need for alternative therapies beyond thalidomide. [14] Extended corticosteroid therapy in ENL patients causes immune suppression, leading to threatening complications like shock, pneumonia, and diabetic ketoacidosis. [13] One patient in our case series developed avascular necrosis of the femur as a complication following prolonged use of steroids.

Table 3.Management of Acute ENL

MILD	NSAIDs (Aspirin 600 mg every 6 hours) Or Colchicine 0.5 mg TDS
SEVERE	Prednisolone(1mg/kg/day) in tapering doses with Clofazimine Or Thalidomide (400 mg/day in tapering doses)

Table 4.Management of Chronic and Recurrent ENL

First Line of Management	Prednisolone(1mg/kg/day) in tapering doses with Clofazimine Or Thalidomide
Second Line of Management	Pentoxifylline Or Cyclosporine Or Minocycline
Third Line of Management	Experimental therapies: Apremilast Or IV corticosteroid pulse Or Methotrexate Or TNF-α blockers or Immunotherapy.

Conclusion

Though there are various eradication programmes, leprosy still seems to persist with unusual presentations. The diagnosis of ENL remains a big challenge because of its heterogenous clinical presentations and prolonged incubation period. This case series was presented to highlight the atypical scenarios of ENL, such as chronic ENL and reaction hand, which may lead to diagnostic delays unless one is aware of this entity. Serious systemic complications may arise if ENL is left untreated. Hence, prompt identification of the condition and adequate intervention are vital for optimising patient outcomes and preventing long-term disability.

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