Review Article

What is New in the Pathogenesis and Management of Erythema Nodosum Leprosum

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Abstract

Erythema nodosum leprosum (ENL) is a manifestation of type II lepra reaction, seen in lepromatous or borderline lepromatous leprosy. Although it is a common reaction encountered in clinical practice, there are an increasingly large number of newer updates in the pathophysiology and management of this condition.The treatment options have expanded far beyond just thalidomide and steroids and now extends to TNF-α inhibitors, thalidomide analogs, tenidap, cyclosporine A, plasma exchange, and even IVIG amongst others. These updates and the current knowledge of ENL are summarized in this review.

Keywords: *Erythema nodosum leprosum, erythema nodosum leprosum, lepra reaction, thalidomide*

Introduction

Reactions in leprosy may be classified into three different types,[1] namely, "type I reaction," or "reversal" or "upgrading" reaction, seen typically in borderline leprosy, categorized by an increase in cell-mediated immunity and a shift towards the tuberculoid spectrum, type II reaction seen in the lepromatous or borderline lepromatous types that includes a spectrum of three variants: erythema nodosum leprosum, erythema polymorphous-like reaction, and Lucio phenomenon. Besides, the Lucio phenomenon has at times been designated as a type III reaction, although usually included in type II reactions.

Erythema nodosum leprosum (ENL) is a type II lepra reaction, an immune-mediated inflammatory complication.[2] ENL affects about 50% of patients with lepromatous leprosy (LL) and 10% of borderline lepromatous (BL) patients.[2] In terms of incidence per person-years at risk (PYAR), the incidence varied from 1–8 per 100 PYAR.[3,4]

A systematic review by Voorend *et al*. compared ENL incidence across a number of studies, predominantly from India and Brazil. They found different incidences in field-based and hospital-based studies. Amongst the field-based studies, the incidence of ENL was at an average of 1.2% among all leprosy patients, and at 4.5% among MB patients. Among the hospital-based studies, an average of 13.7% of MB cases developed ENL.The incidence of ENL in LL leprosy as deduced by Voorend *et al*. is 15.4% and 4.1% in BL leprosy.[5]

Risk Factors

The risk factors for developing ENL include LL type and a high-bacillary index. The relative risk of developing ENL with an LL spectrum is 3.6, and with a bacillary index of 6 is 8.6.[4] Nery *et al*. found that ENL predominated in patients with BI >3.[6] A study by Manandhar *et al*. claims a higher incidence of multiple ENL episodes than single episodes in LL cases.[7] It is widely believed that owing to the ENL suppressive and preventive effect of clofazimine, the risk of developing ENL has significantly decreased after the institution of MDT.[8,9]

Age and gender are not riskfactors for ENL, as has been corroborated in various studies.[2,4,10] Pregnancy and lactation are proven precipitating factors for ENL, with a significantly higher incidence in pregnant and lactating females.[9,11] Minimal evidence implicating psychological stress, puberty, intercurrent infection, vaccination, HIV,

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malaria, andtuberculosis as triggering factors has been found but is not yet sufficient to be conclusive.[4,9,12,13]

Multiple episodes of ENL were seen in 39%[14] to 77%.[15] Of all ENL cases, 15.1% have more than 4 episodes.[16]Saunderson *et al*. found that almost a third of ENL patients suffer from ENL for more than 2 years in Ethiopia.[4] In India, it was found to last for about 18.5 months.[2] Various studies have shown vast differences in the duration of each episode, ranging from a period of 14 days[17] to 26 weeks.[18] Manandhar *et al*. identified five risk factors for multiple episodes of ENL. They were an LL subtype, a smear >4+, more than five nerves enlarged, the presence of skin nodules or infiltration.[7]

A moderate-to-severe intensity was found in 30–50% of all ENL cases.[5] A shorter MDT duration of just 12 months was found to have increased the incidence of moderate and severe ENL.[10,18] The onset of ENL was found to be highest during the first year of MDT in most studies,[15,19-21] although a few studies claim the incidence to be highest in the second and third years after starting MDT.[3,16]

A few recent studies have reported patients presenting with recurrent or chronic ENL, who have been subsequently found to have relapse owing to drug-resistant strains of *Mycobacterium leprae*.[22]

Pathogenesis

(i) Role of neutrophils in ENL

Neutrophils have long been considered the histological hallmark of ENL, although their presence greatly depends on the timing of biopsy. A study of skin biopsies of ENL lesions showed the presence of neutrophils in only 30% of biopsies within 72 h, and in only 1.6% in biopsies between 9 to 12 days on onset of ENL.[23]

A study done by Lee *et al*.with immunohistochemistry demonstrated that E-selectin was expressed in a vascular pattern and at higher levels in ENL skin lesions than in LL, although this was not quantified. They showed that activation of TLR2/Fc induced interleukin (IL)-1β which subsequently along with interferon (IFN)-γ, induced E-selectin expression on endothelial cells, and promoted migration of neutrophils and their adhesion to endothelial cells. Thalidomide inhibited this neutrophil pathway which explains its role in the treatment of ENL.[24]

CD64 (FcγRI) is a surface receptor on neutrophils, showing low expression in resting neutrophils but high expression with stressors such as gram-negative bacterial infections, sepsis, disseminated intravascular coagulation, etc.[25] CD64 upregulation is seen in ENL which may occur due to the release of fragmented intracellular components of *M. leprae* which are released after initiating MDT. The upregulation of CD64 leads to increased pro-inflammatory cytokines which further plays a role in the pathogenesis of ENL. This explains the higher incidence of ENL after initiation of MDT.[26]

On stimulation with lipopolysaccharide (LPS) of *M. leprae*, neutrophils in ENL or BL/LL patients released TNF-α and IL-8.[27]However, the exact role of neutrophils in ENL is still unclear. Whether neutrophils have a role in initiating ENL, or if they are just recruited to the site of ENL due to chemokines like IL-8, has yet to be determined.[28]

(ii) Role of immune complexes

One of the oldest theories regarding the pathogenesis of ENL is the immune complex theory, involving a type III hypersensitivity reaction with deposition of immune complexes in vessel walls, serosa, and glomeruli. This theory gets credence by the histopathological features of vasculitis with a neutrophilic inflammatory infiltrate.[29]

Rojas *et al*. found circulating immune complexes against phenolic glycolipid-1 (PGL-1) and major cytosolic protein of *M. leprae* (MCP-I). This supports the immune complex theory but similar complexes were also found in leprosy controls (BT/BL/LL). Thus, immune complexes may not be specific to ENL.[30]

To implicate immune complexes in the causation of ENL, the deposition of immune complexes in tissues, the presence of bacterial antigens in the immune complexes, and interaction of immune complexes with complement and phagocytic cells is required. Polycarpou *et al*. conducted a systematic review on immunological studies in ENL and found that immune complexes maybe just an epiphenomenon in ENL, and their role in the pathogenesis is still uncertain.[28]

(iii) Role of T cells in ENL

Newer studies believe ENL to be a primarily T cell-mediated response.[28,31] There is an increase in CD4+ T cells, a decrease in CD8+ T cells, and a subsequent increase in the CD4+/CD8+ ratio in patients of ENL, as compared to LL controls.[32,33]

Recent studies have found lowered numbers and proportion of regulatory T cells (Tregs) in ENL.[34]Tregs suppress effector T cells, which might explain the higher proportion of T cells in ENL.[35]

(iv) Role of cytokines in ENL

Tumour necrosis factor (TNF)-α: Several studies have been performed on TNF-α levels in ENL with highly variable results. Most studies showed very high levels of TNF-α during ENL, which may suggest an inflammatory role for TNF-α in ENL.[36,37] The efficacy of TNF-α inhibitors such as etanercept and infliximab in ENL helps to corroborate this role.[38,39]

The production of TNF-α may be induced by stimulation of cells with *M. leprae* or its components such as lipoarabinomannan (the mycobacteria

"lipopolysaccharide-" like component), a mycolyl-arabinogalactan-peptidoglycan complex of *Mycobacterium* species, the protein-peptidoglycan complex, and muramyl dipeptide.[40,41]

Interferon (IFN)-γ: Elevated levels of IFN-γ are seen in ENL, more consistently than those of TNF-α. In a clinical trial by Sampaio *et al*., IFN-γ-induced ENL was seen in a significant number of patients after 7 months of repeated intradermal injections of IFN-γ along with MDT.[42]

Interleukin (IL)-1β: Most studies suggest a prognostic role of IL-1β in developing ENL,[43,44] although some studies dispute any association between the two.[37]

The role of IL-2 and IL-6 is disputable, with conflicting studies on the topic.[28,37] Consistent levels of TNF-α and IL-6, with low levels of IL-4 suggest a Th-1 response.[45]

Various studies have shown raised levels of IL-6 in cases of both type 1 as well as type 2 reactions as compared to leprosy controls. Sousa *et al*. showed strikingly higher levels in type 2 reactions rather than type 1 reactions. They also showed that certain SNPs such as SNP rs1800795 were associated with type 2 reaction. They also found that the expression of certain alleles in these SNPs contributed to increased susceptibility (allele C on either rs1800795 or rs2069840) or protection (allele G of rs2069840) from type 2 reaction.[46]

(v) Role of innate immunity

In a study conducted in Bangladesh, a non-synonymous polymorphism ofToll-like receptor 1 (*TLR1),* rs4833095, which causes a substitution of asparagine to serine (N248S) in the external recognition site of the protein, was shown to be associated with LR susceptibility. This allele was described as a protective factor against T2R.[47]

A recent study from Brazil documented upregulated Toll-like receptor (TLR)-9 levels. TLR-9 agonist stimulation led to higher levels of TNF-α, IL-6, and IL-1β. The use of a TLR-9 antagonist inhibited the secretion of pro-inflammatory cytokines. This may give way to a therapeutic option for ENL.[48]

Variations in the nucleotide-binding oligomerization domain-2 (*NOD-2*) gene wasstudied, and two single nucleotide polymorphisms (SNPs) in the *NOD-2* gene, (rs2287195 and rs8044354) were found to have a strong association with general cases of leprosy, type 1 reaction as well as type 2 reaction. It was found that the risk allele for T2R is the protective allele for T1R and*vice versa*for both SNPs. This may suggest an association between the SNPs and the leprosy type.[49,50]

Natural resistance-associated macrophage protein 1(NRAMP1) - NRAMP1, also known asSCL11A1, is a multi-pass membrane protein that mediates the transport/ transition of divalent metals (iron and manganese).The SNP 274C/T ofNRAMP1 was found to be associated with LR.The presence of the "C" allele on this SNP was a risk factor for T1R while being protective for T2R.[51]

An association between HLA-DRB1 and leprosy has been proven, with both protective as well as risk alleles being described. HLA-DR expression is characteristic in leprosy reactions and is an important marker on biopsy.[52]

(vi) Role of humoral immunity

Although B cells are not believed to have a significant role in the pathogenesis of ENL, there is an increase in IgG1 secreting B cells, with lower concentrations of *M. leprae* specific IgG1 and IgG3.[53,54]

(vii) Newer developments

CCL-5 (Chemokine [C-C motif] ligand 5), followed by IFN-γ is the most important upstream regulator of ENL.[55] CCL-2, CCL-3, and superoxide dismutase (SOD)-2 may be potential biomarkers for ENL.[55] Keratinocyte 1a and intercellular adhesion molecule-1 (ICAM-1) have been found in the epidermis, suggesting a cell-mediated immune response.[45]

Thus, ENL appears to be a complex interaction of various aspects of the immune system and systems biology approach using various technologies such as genomics, epigenomics, transcriptomics, and proteomics on cohorts of patients will help in better understanding of this condition.[28]

A schematic and simple representation of the pathogenesis of ENL has been presented in Figure 1.

Clinical features

Type II lepra reaction usually occurs at the lepromatous end of the spectrum. It presents with various presentations, including the classical erythema nodosum leprosum, erythema polymorphous-like reaction, and Lucio's phenomenon.[1]

The classical ENL consists of multiple crops of evanescent, erythematous, tender nodules, and plaques all over the body, as seen in Figure 2. Some rare types include bullous, pustular, ulcerated, hemorrhagic, and erythema multiforme like lesions, as seen in Figure 3.[56-58] Lesions are commonly found on the extensor surface of the limbs or the face. As lesions fade, they may appear as brawny induration on the forearms and thighs.[59]

Vasculonecrotic erythema nodosum presents with severe, deep, painful ulcers that heal with atrophic scarring, as seen in Figure 4a and b. This is usually accompanied by systemic symptoms, visceral involvement, and neuritis.[60] Lucio phenomenon although designated as type III lepra reaction is usually considered a variant of type II lepra reaction. It is an ulceronecrotic reaction with angular infarcts occurring

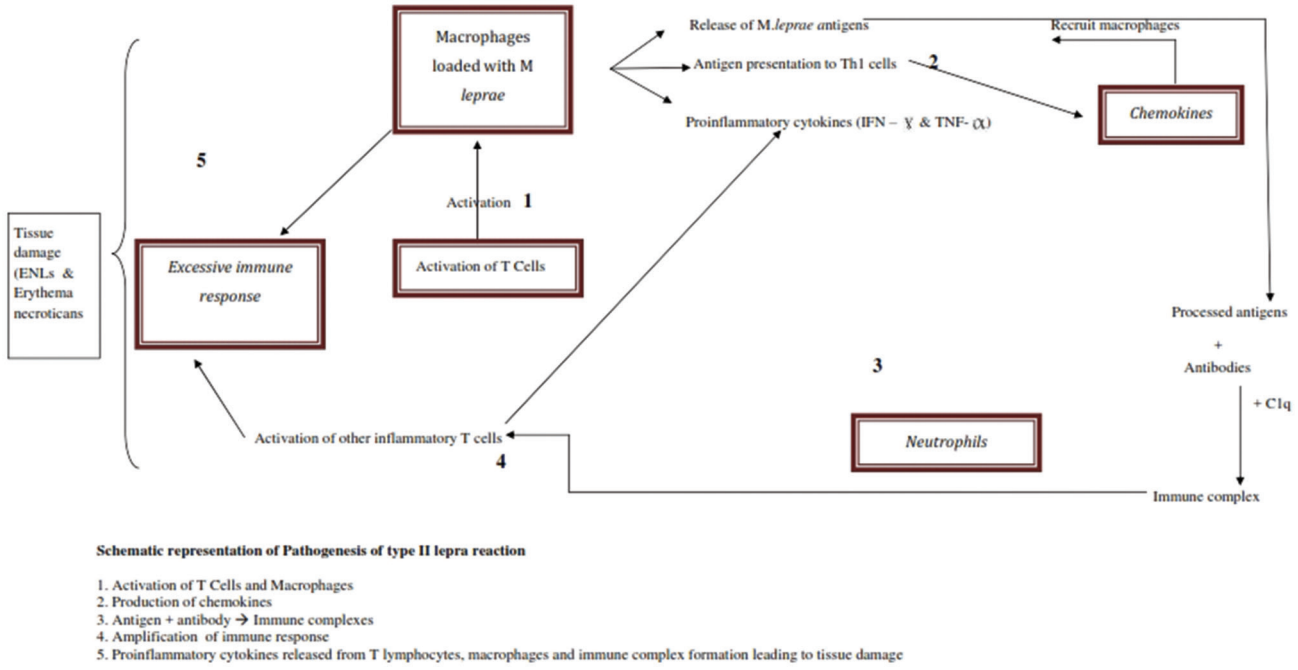

Figure 1: Pathogenesis of type II lepra reaction

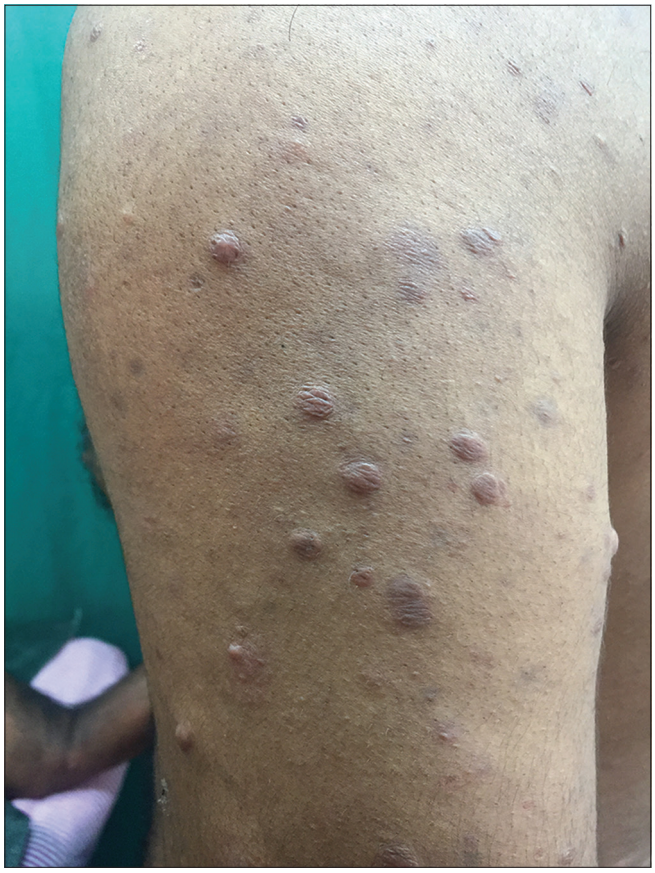

Figure 2: Classical ENL lesions, with crops of erythematous, tender nodules all over the body

in a diffuse, non-nodular form of leprosy known as Lucio leprosy [Figure 5]. It has been classically described in Mexico by Lucio and Alvarado but a few cases have also been reported from India.

The onset of ENL may be of the cutaneous, rheumatoid, or mixed types. The rheumatoid type presents with symmetrical arthritis affecting the small joints of the hands and feet, in the so-called "rheumatoid distribution."[61] This has an incidence of more than 57%.[62] The cutaneous onset is characterized by the classical skin lesions which precede systemic involvement.[63,64]

Neuritis although more common and more severe in type 1 reaction, may also occur in ENL. It presents as painful, enlarged nerves, with or without accompanying functional impairment. It is imperative to diagnose neuritis early to prevent permanent loss of function.[45]

Systemic involvement may occur as a result of immune complex-mediated damage such as lymphadenitis, neuritis, iridocyclitis, arthritis, synovitis, myositis, epididymo-orchitis, glomerulonephritis, etc.[56] Arthritis in ENL is usually acute in onset, involving the small joints of the hands and feet, along with the knees and elbows. Arthritis lasts for a few weeks, and in most cases, resolves completely with treatment.[57,58]

The natural course of untreated ENL is of 1 to 2 weeks but the reaction may be recurrent and may last upto many months.[59]

ENL may be classified as acute, recurrent or chronic, as follows:[65]

Acute ENL is defined as a single episode lasting less than 24 weeks.

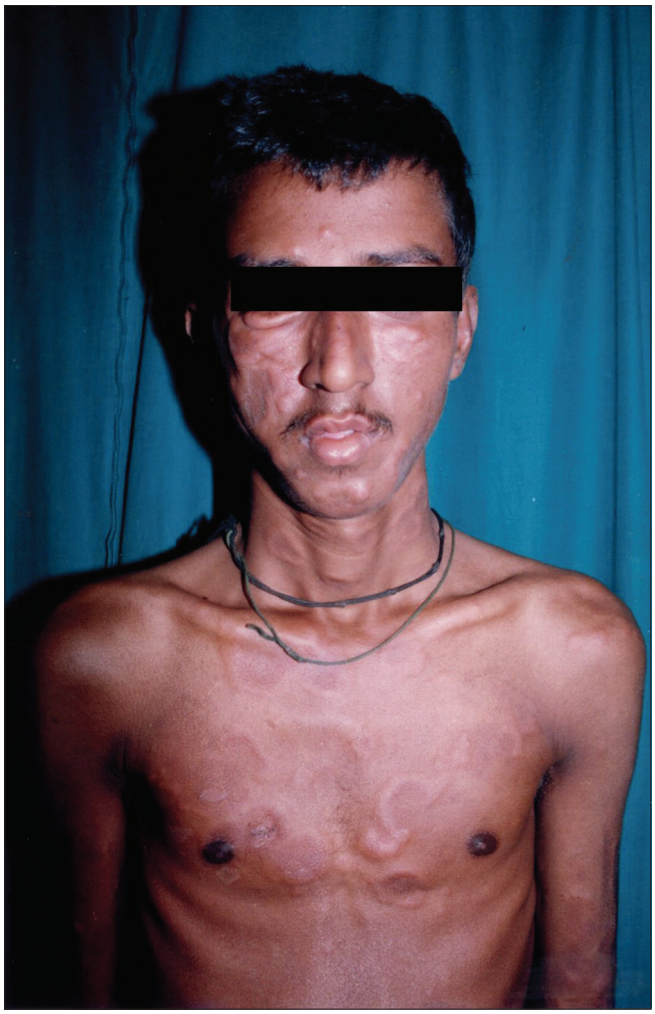

Figure 3: Erythema multiforme-like ENL

Recurrent ENL is characterized by repeated episodes of ENL occurring after 28 days of stopping treatment for ENL.

Chronic ENL is defined as ENL occurring for 24 weeks or more, wherein a patient has required continuous treatment, or any treatment-free period has been 27 days or less.

A 16 point scoring system called the ENLIST ENL Severity Scale (EESS) was put forth by Walker *et al*. in 2016,[67] which was subsequently modified by them into a 10 point severity scale in 2017.[66] This EESS is the latest scoring system developed to assess the severity of ENL [Table 1].

Diagnosis

The diagnosis of ENL is predominantly clinical.Naafs *et al*. proposed their criteria to diagnose a type II (ENL) reaction [Table 2].[68]

The Ryrie test is performed by stroking a blunt instrument like the handle of a reflex hammer over the sole with light pressure (as in the Babinski reflex test). The test is positive

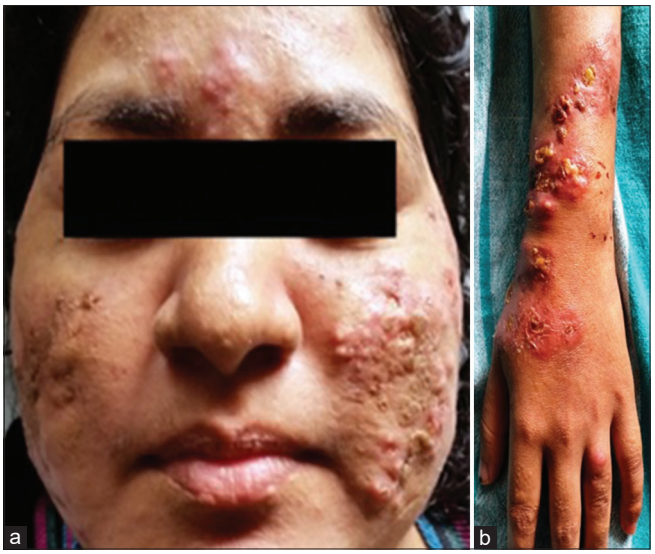

Figure 4: (a) Vasculonecrotic ENL lesions over the face. (b) Vasculonecrotic ENL lesions with ulceration seen over the forearm

if the patient expresses pain by wincing.[69] The Ellis test is performed by squeezing the forearm of the patient just above the wrist gently with both hands. As in the Ryrie test, it is considered positive if the patient's wincing face indicates pain.[69] However, these tests are now obsolete and of historical significance only.

Laboratory tests show low hemoglobin, raised total count and hematocrit. Deranged liver function tests and C-reactive protein may also be seen.[59]

On histopathological examination, neutrophils within the granulomas are considered the hallmark of ENL.[23] There is an intense neutrophilic perivascular infiltrate in the dermis and subcutis. However, this, not a rule, and many cases of ENL present without this classical neutrophilic infiltrate.[70] Other histopathological features seen include leukocytoclasia, dermal edema, neutrophilic panniculitis, fibrin in vessel walls, and granulomas and folliculotropism.[71]

The smears obtained from fine-needle aspiration from the enlarged lymph nodes andstained with Papaniculaou, May-grünwald-Giemsa (MGG) stain, and modified ZN stainshowed cellular smears with a good number of foamy macrophages interspersed with reactive lymphoid cells with plenty of neutrophils in the background. Modified ZN stained smears showed foamy histiocytes containing lepra bacilli.[72]

Biomarkers of ENL:

1. Pentraxin-3 (PTX3):
   Mendes *et al*. demonstrated the role of PTX3, a protein present in the secondary neutrophilic granule as a potential biomarker of ENL. They found higher levels of PTX3 in multibacillary patients before the onset of ENL, and these levels were found to persist during the reaction. Treatment with thalidomide showed a reduction in PTX3 levels within 7 days of initiating

treatment. PTX3 can be used to differentiate an episode of ENL from a reversal reaction.[73]

2. a1-Acid glycoprotein (AGP)
   Gupta *et al*. demonstrated raised AGP levels in patients of ENL as compared to healthy controls as well as other leprosy patients without ENL. AGP may induce ENL due to increased secretion of TNF-alpha or due to a physiological feedback inhibition mechanism for inflammation by increased sLex -rich AGP glycoforms, which compete with leukocytes for binding to E-selectin and decrease/inhibit inflammation. AGP binds to thalidomide, and thalidomide may inhibit AGP induced TNF-alpha secretion.[74]
3. CD64 (FcγRI)
   CD64 is an early biomarker as well as a predictor of severity in ENL. Circulating and lesional neutrophils in ENL exclusively express CD64 which is not the case in leprosy patients without reaction.[26,75]
4. Complement C1q:
   Patients with active ENL reactions show a low circulating C1q, with greater gene expression of C1q. This may suggest the consumption of C1q in the formation of immune complexes in ENL. Thus, C1q may be used as a diagnostic marker, as well as for monitoring therapy.[76]
5. IL-6:
   Higher levels of IL-6 were found in cases of ENL, as well as in the lepromatous rather than a tuberculoid spectrum.[77]
6. IL-7:
   Stefani *et al*. found higher levels of IL-7 in cases of ENL, which suggests the role of both B and T cells in the pathogenesis of ENL.[37]
7. PDGF-BB and VEGF:
   PDGF-BB and VEGF, both known stimulators of angiogenesis were found to be elevated in ENL. This has significance as ENL is often associated with vasculitis.[37]
8. Anti-LID-1 antibody
   LID-1 is a fusion protein of ML2331 and ML0405. It is recognized by *M. leprae* specific antibodies and

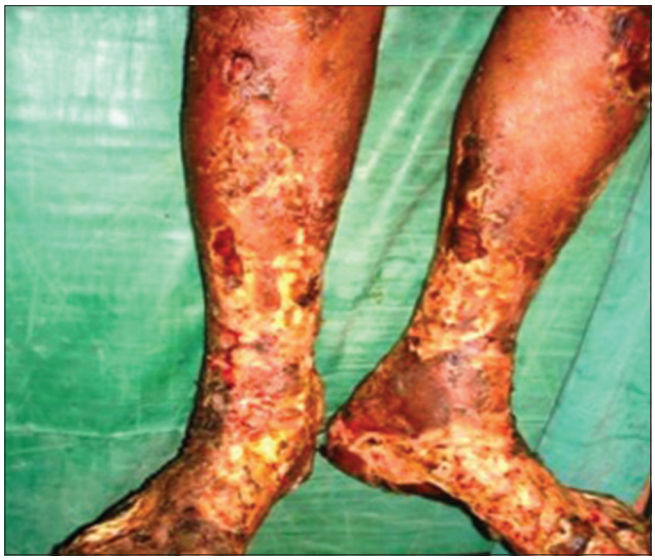

Figure 5: A case of Lucio leprosy, with ulceronecrotic lesions over the lower legs

Table 1: ENLIST ENL severity score[66]

Pain Rating - Visual Analog Scale (Ensure line is 100 mm long)

How severe is your pain today? Mark the line below with an X to indicate how bad you feel your pain is today

No Pain _____ Worst possible Pain

Item		Scores				Score
		0	1	2	3	
1	VAS-Pain (mm)	0	1-39	40-69	70-100	
2	Fever (in °C)	None (37.5 or less)	No fever now but history of fever in last 7 days	37.6-38.5	38.6 or higher	
3	Number of ENL skin lesions	None	1-10	11-20	21 or more	
4	Inflammation of ENL skin lesions	Non tender	Redness	Painful	Complex	
5	Extent of ENL skin lesions	0	1-2 regions	3-4 regions	5-7 regions	
6	Peripheral edema	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	Sleep or activity disturbed	Incapacitating	
8	Inflammation of joints and/or digits due to ENL	None	Present on examination but does not limit activity	Sleep or 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	
	TOTAL					

The score for each item should be added together to obtain the ENLIST ENL Severity Scale score. Mild ENL is categorized as an ENLIST ENL Severity Scale score of 8 or less. The Minimal Important Difference inthe ENLIST ENL Severity Scale is 5

induces cell-mediated immunity. Anti-LID-1 antibodies were found to be elevated in patients with a high bacillary index who subsequently developed ENL. Thus anti-LID-1 serology may be used as a predictive marker for the development of ENL, with a sensitivity of 71% and a specificity of 80%.[78]

9. CCL-11

   CCL-11, produced by monocytes, is a known chemoattractant for eosinophils and Th2 lymphocytes. It has been found to be a potential plasma marker for ENL.[52]

   Table 3 shows a list of the basic investigations that may be performed to work up a case of ENL.

Treatment

The goals of treatment are to control inflammation, relieve pain, and prevent further episodes.Rest and anti-inflammatory medications are the treatment of choice for mild ENL. Aspirin is the most commonly used anti-inflammatory drug. Other drugs such as NSAIDs, colchicine, oral zinc, pentoxifylline, and chloroquine have also been used.[79-82]However, all the treatment options available come with their limitations and drawbacks and have to be carefully selected to suit every individual case.[83]

Table 2: Naafs criteria to diagnose ENL[68]

Naafs criteria:[68] A patient is considered to have a type II reaction if he has the major criterion or at least three minor criteria	
Major:	A sudden eruption of tender (red) papules, nodules or plaques, which may ulcerate
Minor	Mild fever, the patient is unwell.
	Tender enlarged nerves.
	Increased loss of sensation or strength.
	Arthritis.
	Lymphadenitis.
	Epididymo-orchitis.
	Iridocyclitis or episcleritis.
	Edema of extremities or face.
	Positive Ryrie or Ellis test.

Table 3: Workup for a case of ENL

Clinical tests	Thorough cutaneous and systemic examination Ryrie test and Ellis test (Obsolete)
Hematological parameters	Complete blood count Liver function tests CRP (C- Reactive Protein)
Histopathological examination	Neutrophils within granulomas Intense perivascular neutrophilic infiltrate in dermis and subcutis Foamy macrophages containing lepra bacilli Special stains: Papaniculaou, May-grünwald-Giemsa (MGG) stain, and modified ZN stain
Biomarkers	Pentraxin-3 (PTX-3) a1-Acid glycoprotein (AGP) CD- 64 Complement C1q Interleukin- 6 and 7 PDGF-BB and VEGF Anti-LID-1 antibody CCL-2,3,5 and 11

Corticosteroids: Corticosteroids such as prednisolone offer rapid control, and are considered as the first line of treatment of ENL. They rapidly control inflammation and relieve pain. They are usually started at the lowest possible dose required to keep ENL under control, and then they are gradually tapered as per the course of the disease.[80] High doses of prednisolone are usually required, which may increase the risk of adverse effects such as raised blood sugars, hypertension, and steroid dependency.[79]

Steroids should not be used to prevent a new reaction as it may induce steroid dependence. The combination of low-dose steroids with low-dose thalidomide is counterproductive.[84] The combination also increases the risk of associated deep vein thrombosis by nearly 10%.[85]

Thalidomide: The use of thalidomide in ENL provides an effective alternative to steroid therapy. It provides a rapid anti-inflammatory effect by acting on TNF, which is a pro-inflammatory cytokine. However, its use is limited by its teratogenic effects, cost, and poor availability.[84] It is now recommended to only be administered to males and post-menopausal females. In women in the childbearing age group, it should only be given when effective contraception is ensured.[86]

Clofazimine: Clofazimine is a useful and inexpensive anti-inflammatory drug used in ENL. When used at a dose of 300 mg/day, the serum concentration doubles. It exerts an anti-neutrophilic effect and inhibits prostaglandins. It is particularly useful in managing recurrent and chronic type II reactions, where its steroid-sparing effect comes into great use.[87] The disadvantage is that it is very slow in action, and takes 4–6 weeks to exert its effects. It also produces significant gastrointestinal side effects and dark discoloration of the skin.[79]

Azathioprine and methotrexate have been used along with prednisolone and as steroid-sparing agents in the treatment of ENL.[88,89]

Cyclosporine A: Cyclosporine A was first used in ENL by Mshana in 1982, with good results in chronic steroid-dependent ENL which had failed to respond to thalidomide. Cyclosporine A provides a beneficial effect in ENL by increasing the number of T suppressor cells in lesions.[90]

Tenidap: Tenidap is a newer nonsteroidal anti-inflammatory drug with disease-modifying properties in rheumatoid arthritis comparable to hydroxychloroquine. It inhibits

neutrophil-mediated damage and has significant anti-TNF-α properties, which can play an important role in its activity against ENL.[79,80]

Thalidomide analogs: Non-teratogenic analogs of thalidomide such as supidimide have been tried for the treatment of ENL with success. A study by Celgene Corporation, USA found two groups of thalidomide analogs. The first group, like thalidomide, inhibited TNF-α and phosphodiesterase-IV (PDE-IV) and stimulated the production of IL-8 and IL-10. The other group inhibited TNF-α, IL-6, and IL-8, strongly stimulated IL-10but did not inhibit PDE-IV. PDE-IV inhibition resulted in increased T cell stimulation. Thus the analogs of thalidomide that do not inhibit PDE-IV, subsequently do not cause T-cell activation. Thalidomide cannot be used in reversal reactions owing to this T-cell activation. Thus, its analogs that do not cause inhibition of PDE-IV may be used even in reversal reactions. Celgene Corporation has developed two thalidomide analogs, Revlimid, and Actimid which are effective as anti-myeloma agents, and may also be used in the treatment of ENL.[91]

TNF-α inhibitors: TNF-α plays a key role in the pathogenesis of ENL, as has been previously explained which provides the rationale for use of TNF-α inhibitors in ENL. Infliximab is a human-murine chimeric monoclonal antibody against TNF-α, and etanercept is a dimeric fusion protein of the extracellular portion of the p75 TNF receptor coupled to IgG1.[92] Both of these effectively reduce TNF-α levels and have been found to have impressive clinical responses in ENL.[38,93] The disadvantage with their use, however, is an increased risk of reactivation of latent tuberculosis infection (more so with infliximab as compared to etanercept).[94]

Minocycline: A single study reports the use of minocycline in the treatment of ENL. Narang *et al*. report 10 cases of chronic or recurrent ENL who were treated with oral minocycline at a dose of 100 mg daily for 3 months, with gradual tapering of the prednisolone regimen to discontinuation. A good response was observed in 80% of the cases.[95] Minocycline along with its antibacterial properties also exhibits good anti-inflammatory and antiapoptotic activity, which may explain its efficacy in ENL.[96] It also inhibits microglial activation, which confers upon it a neuroprotective function. This may help in leprosy neuritis.[96]

Apremilast: Apremilast is an oral phosphodiesterase-IV inhibitor with strong anti-inflammatory action, and is commonly used in psoriasis, psoriatic arthritis, atopic dermatitis, alopecia areata, etc.[97] A single case report in 2019 reports the use of Apremilast in two cases of poorly controlled chronic ENL, with significant clinical improvement and no adverse events.[98]

Plasma exchange: Plasma exchange helps clear immune complexes, which are considered pathogenic in ENL.It has been used successfully in four cases of ENL who had failed to respond to conventional therapy. However, plasma exchange is expensive, and may not be feasible in most leprosy endemic countries.[79]

Intravenous immunoglobulins (IVIG): IVIG has anti-inflammatory and immunoregulatory effects, down-regulating both the cellular and humoral responses and thus, may show promise in the treatment of ENL.[79]

Immunotherapy: Immunotherapy using *Mycobacterium w* vaccine in patients of multibacillary leprosy has been found to decrease the incidence and severity of type 2 reactions in these patients. The rapid fall in the bacteriological index with the use of this vaccine may explain the lower incidence of type 2 reactions, as well as the occurrence of these reactions, earlier in the course of the disease as compared to the control group.[99]However, Deo *et al*. found an increase in type 2 reactions following the use of the ICRC vaccine, which may be attributed to large quantities of *M. leprae* antigens being broken down and released following the use of this vaccine.[100]

Conclusion

Advances have been made in the understanding of the etiopathogenesis of ENL. The role of neutrophils and immune complexes which have been considered critical in the pathophysiology of ENL, is now increasingly disputed. This pathophysiology is now considered to be more complex, caused by a multitude of factors such as pro-inflammatory cytokines, Treg cells, TLR-9, CCL-5, IFN-γ, and even possibly B cells, bringing humoral immunity into the picture. More studies using advanced techniques are required to elucidate the pathogenesis.The ENLIST ENL severity scale is the latest scale to assess the severity of ENL and to prognosticate it. Numerous treatment options are now available other than the conventional NSAIDs, corticosteroids, and thalidomide, ranging from tenidap, TNF-α inhibitors (biologics) to IVIG.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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