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Case Series

ENL Necroticans at a Tertiary Care Centre – A Case Series

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Lepra reactions particularly the severe forms constitute a great concern of mortality and morbidity, and the severe forms like ENL necroticans is underestimated. We hereby report four cases of ENL necroticans. The first case was a 45-year-old male patient presented with multiple erythematous nodules on the trunk and extremities along with ulceration of nodules for 15 days. He had a history of ENL without ulceration 5 year back. Our second case was a 40-year-old male presented with a 15 days history of multiple ulceration along with nodular lesion over extremities. He also has a history of ENL on and off since the last 1 year. Third case was a forty-year male on MB-MDT 1st pack presented with ulceration with ENL lesions for 1 month; he had a history of on and off ENL without ulceration since the last 6 months; and fourth one was a 35-year-old male presented with similar nodular and ulcerated lesions since 4 days, and he was on the 12th pack of MB MDT. Fever was present in all the patients. Turbid bullae/pustules were noted in three patients. Neuritis was present in one, and Grade 2 disability was seen in three patients. All the cases were treated with systemic corticosteroid, thalidomide and clofazimine, and they responded well to therapy. Necrotic ENL cases are reporting to hospitals more frequently than reported earlier; some of them had an uncommon presentation.

Keywords : ENL Necroticans, Lepra Reactions, Severe Forms, Varying Presentations

Introduction

Leprosy is a chronic granulomatous infectious disease known to man since ancient times, caused by *Mycobacterium leprae*, which mainly affects the skin and the nerves, resulting in various skin lesions as well as neuropathy. Lepra reactions play a major role in the morbidity associated with this disease. They are immune-mediated complications, seen in approximately 50% of patients. Two types of reactions are known: type 1 and type 2 reactions (erythema nodosum leprosum, ENL) (Britton & Lockwood 2004).

ENL are immune complex-mediated reactions characterized by painful, erythematous sub-cutaneous nodules occurring with systemic features including fever, lymphadenitis, arthritis, neuritis, iridocyclitis or orchitis (Jopling & McDogall 1996). Seen in patients of lepromatous pole, ENL can occur before initiation, during or

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after completion of multidrug therapy (MDT) (Sharma et al 2004). In mild reaction, the subcutaneous nodules are small in number and spontaneously resolve leaving behind hyperpigmented macules but in severe reactions (around 8%), these nodules tend to increase in size, ulcerate and heal with scarring (Gomathy et al 2002, Barman et al 2005).

Leprosy is considered to be eliminated from India but lepra reactions and it's severe forms constitute a great concern of mortality and morbidity in patients and the incidence of such cases and their severe forms like ENL necroticans is underestimated (Van Veen et al 2009).

We hereby report four cases of ENL necroticans who presented to us in a short span of 2 months from July 2019 - September 2019. Consent was taken from these patients for publishing their data and figures.

Case Reports

Case 1 :

A 40 year old male labourer presented with acute onset multiple ulcers over the painful, red raised evanescent tender nodules over his buttocks, upper and lower limbs along with fever and arthralgia since past 15 days. There was no history of sharp shooting pain along the nerves, tenderness in the scrotal region, joint pain, painful swelling at the site of lymph nodes, decreased urine output, hematuria, pain abdomen, pain or watering in the eyes or decreased vision. Past history revealed similar 3 episodes in 1 year. He had completed his full course of MB-MDT 5 months back from a dispensary in Uttar Pradesh. Before reporting to us he was on oral corticosteroids and clofazimine for 2 weeks with mild improvement. There was no comorbidity.

On examination, he had generalized hyperpigmentation, bilateral pitting pedal oedema and cervical and inguinal lymphadenopathy. Bilateral testes were enlarged and tender. On examination, eight tender necrotic well defined ulcers covered by black eschar and oozing yellowish purulent discharge over the extensor surface of his bilateral upper limb (Fig. 1), buttocks and thighs overlying tender nodules. Four well to ill-defined tender erythematous nodules of size about 2x2 cm were present over the left thigh and buttocks. On investigations, haemoglobin was 9.1gm/dl and total leukocyte count was 15,500 (out of which 90% were neutrophils). Slit skin smear showed 5+ solid staining and fragmented bacilli from lesional skin (ear lobe) and 3+ fragmented bacilli from non-lesional uninvolved skin. Histopathology from the ENL lesion showed subepidermal grenz zone, marked neutrophilic infiltrate in the lower dermis, periadnexal and perivascular lymphocytic infiltrate, vasculitis, obliteration of the lumen of few blood vessels and lobular panniculitis. Investigations for multidrug resistance were done from skin smear, and bacilli was found to be resistant to dapsone. For his

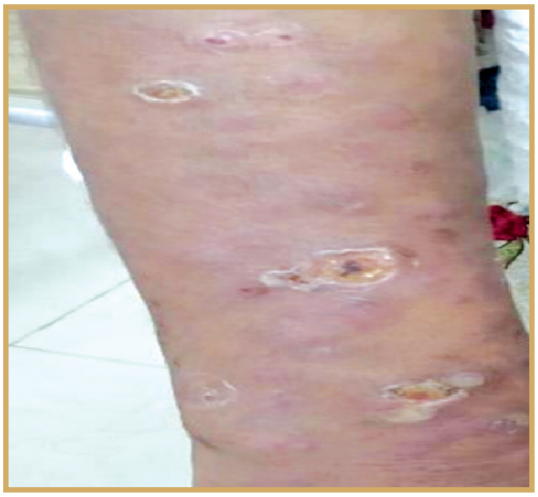

Fig. 1 : Ulcers covered by black eschar and oozing yellowish purulent discharge over the extensor surface of his bilateral upper limb.

episode of ENL necroticans, the patient was started on oral prednisolone 60mg per day and was tapered to 40mg, 30mg, 20mg, 15mg, 10mg, 5 mg after 15 days along with thalidomide 100 mg TDS and showed improvement in 10 days. Thalidomide was gradually tapered in a week to 100mg BD, and this dose was continued for another 4 weeks, after which it was tapered to 100mg OD alternate days and patient is still under follow-up. MB-MDT without dapsone was restarted for him for another year due to the presence of solid staining bacilli after which his lesions healed.

Case 2

A 45 year old male labourer, known case of leprosy, presented with the complaints of painful red raised evanescent skin lesions over his body, with few of them having overlying ulcers associated with fever, malaise and arthralgia since past 15 days. There was no history of sharp shooting pain along the nerves, tenderness in the scrotal region, joint pain, painful swelling at the site of lymph nodes, decreased urine output, hematuria, pain abdomen, pain or watering in the eyes or decreased vision. There is a history of one similar episode but without ulceration four and a half years back while he was on multidrug therapy. He had completed full course of anti-leprosy therapy 4 years back from our hospital. There was no comorbidity.

On general physical examination, he had bilateral pedal pitting oedema. On mucocutaneous examination, multiple erythematous tender nodules were present all over his body predominantly on bilateral extensor of both the extremities (Fig. 2), sparing the axilla, face, groin, scalp, palms and soles. Few of those present over lateral thigh and buttocks had overlying necrotic ulcers and pustules covered with yellowish dirty slough. On investigation, haemoglobin was 10.4 gm%. Slit skin smear did not reveal any bacilli from lesional as well as non-lesional skin. Histopathology revealed atrophic epidermis, numerous neutrophils and macrophages in dermis, lobular panniculitis and vasculitis; however, Fite Faraco stain was negative for acid fast bacilli.

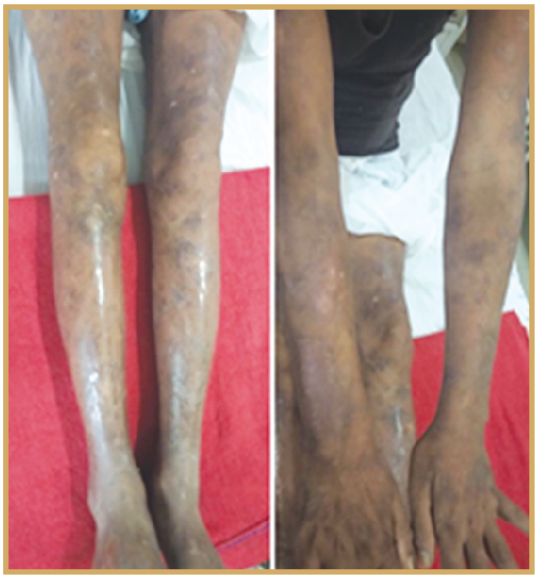

Fig. 2 : Erythematous tender nodules were present all over his body predominantly on bilateral extensor of both the extremities.

He was treated with tab clofazimine 100 mg TDS with oral prednisolone 80mg per day and responded to treatment in a span of 7 days. Clofazimine was given for a total period of 12 months, i.e. 100mg TDS and BD for 12 weeks each and 100mg OD for another 24 weeks, whereas tab prednisolone was tapered to 60mg, 40mg, 30mg, 20mg, 15mg, 10mg, 5mg at 15 days each. Patient is still under follow up.

Case 3

A 45 year old male, also a labourer presented to us with chief complaints of multiple crops of red raised evanescent tender nodules over his body associated with fever since the past 1 month.

There was no history of sharp shooting pain along the nerves, tenderness in the scrotal region, joint pain, painful swelling at the site of lymph nodes, decreased urine output, hematuria, pain abdomen, pain or watering in the eyes or decreased vision. He had a history of a similar episode around 5 months back. He had no comorbidity. There was no history of previous MB-MDT intake.

On mucocutaneous examination, 5 erythematous tender round to oval nodules about 4x4 cm in size were present over bilateral arms, forearm and thighs with some of them showing overlying turbid bullae filled with purulent fluid and necrotic ulcers. Slit skin smear revealed 5+ fragmented bacilli in lesional and 3+fragmented bacilli in non lesional skin. Skin biopsy was sent for histopathology and it showed numerous foamy macrophages and neutrophils in lower dermis, grenz zone and lymphocytic infiltration in perineural and periadnexal region along with evidence of lobular panniculitis and vasculitis. He was started on MB-MDT for 12 months along with clofazimine 100mg TDS since no new lesions were developing during hospital stay. He showed improvement in a span of 3 weeks. After 12 weeks, clofazimine was tapered to 100mg BD for 12 weeks. However, the patient was lost to follow up after 5 months.

Case 4

A 35 year old male, farmer by occupation presented with chief complaints of painful red raised lesions with overlying ulceration associated with fever, swelling of bilateral hands and feet, arthralgia, malaise since past 4 days. There was no history of sharp shooting pain along the nerves, tenderness in the scrotal region, painful swelling at the site of lymph nodes, decreased urine output, hematuria, pain abdomen, pain or watering in the eyes or decreased vision. He had no comorbidity. He also had history of similar episode but without ulceration, 7 months back and currently he was on 12th pack of MB-MDT from our hospital. He had pallor, generalized lymphadenopathy, edema of bilateral hands and feet. On mucocutaneous examination, he had multiple necrotic ulcers over these red raised tender nodules. The nodules were erythematous, tender of size about 4x4cm, present over bilateral upper and lower limbs (predominantly over extensor surface), back, buttocks, face. The overlying ulcers ranged in size from 2x2 cm to 5x5cm, well defined, having sloping edge, covered with yellowish dirty slough and exuding purulent discharge. He had partial clawing in left hand, which was fixed. Slit skin smear showed globi 6+ in lesional skin and 5+ solid and fragmented bacilli in non lesional skin. On investigation, haemoglobin was 7.8gm%, total leukocyte count was 37,000 with 90% neutrophils. Peripheral smear showed toxic granules, which were indicative of sepsis. Histopathology revealed superficial and deep perivascular infiltrate of lymphohistiocytes with ill-defined granulomas and evidence of endothelial damage and fibrin deposition along with panniculitis and neutrophilic infiltrate. Fite stain showed numerous solid staining and fragmented bacilli. FNAC from submandibular lymph nodes showed histiocytes with lepra bacilli and plenty of neutrophils suggestive of ENL. He was started on prednisolone 60 mg per kg per day tapered to 40 mg in 15 days, along with thalidomide 100mg TDS which was tapered to 100mg BD for 4 weeks in tapering doses after which he showed healing of ulcers. Injection piperacillin and tazobactam was given in view of sepsis along with injection vancomycin after which total leukocyte count normalized. He showed improvement in a span of 12 days after which he was discharged and advised to follow up in OPD. However, the treatment could not be continued regularly due to irregular follow-up.

Discussion

Leprosy is a chronic infectious disease whose course is interrupted by acute immunologically mediated events called lepra reactions. The presence of ulceration along with constitutional and systemic manifestations is indicative of severe ENL and can manifest as recurrent or chronic episodes, not responding promptly to conventional therapy (Kar & Chauhan 2010, Rees & Young 1994, Manandhar et al 1999). Its pathogenesis is type 3 type of hypersensitivity reaction (Gel and Coombs) which is an antibody-antigen reaction.

Histopathologically, the necrotic ENL lesions show necrotizing vasculitis affecting arterioles, venules, and capillaries. Foamy macrophages containing fragmented bacilli are usual (Lucas 2008).

For mild ENL NSAIDs followed by corticosteroids if needed are preferred. NSAIDS inhibits cyclo-oxygenase and prostaglandin synthesis; suppresses antigen-antibody aggregation and reaction, besides stabilizing the capillary permeability and inhibition of neutrophil activation (Grosser et al 2011), the common side effects seen are stomach upset, increase in blood pressure (except aspirin), increase in bleeding tendency, swelling of ankles by fluid retention. Glucocorticoids act by glucocorticoid / glucocorticoid receptor complex to glucocorticoid responsive elements in the promoter region of genes, or by an interaction of this complex with other transcription factors, in particular activating protein-1 or nuclear factor-kappaB. Glucocorticoids inhibit many inflammation-associated molecules such as cytokines, chemokines, arachidonic acid metabolites, and adhesion molecules. Common Side Effects seen with glucocorticoids are increase in blood pressure, triglycerides, cholesterol, or glucose level, Water retention, including swelling in the feet, ankles, lower legs, or hands, Increased appetite and weight gain, Unwanted hair growth, Headache, Dizziness, and Vertigo, Mood Swings, Osteoporosis, Broken Bones, Thrush (Fungus) in Mouth, Thin Skin, Cataracts, Glaucoma, Acne.

For severe ENL, oral prednisolone and clofazimine are the most commonly used drugs. Clofazimine is an anti-inflammatory drug by exerting anti-neutrophillic effects and inhibition of prostaglandins used when corticosteroids are contraindicated or need to be reduced, but it takes 4 to 6 weeks to show response. Continuous high doses of clofazimine can lead to gastrointestinal side effects and dark discoloration of the skin (Lockwood 1996). Another drug used to treat ENL is thalidomide, a TNF alpha inhibitor and also acts on T-cells, reducing the CD4 cells and increasing the CD8 cell counts (Walker et al 2007). Though considered as a drug of choice for severe ENL, it may cause serious birth defects and potential neurotoxicity when taken in early pregnancy.

In this case series, two of these 4 patients with ulceronecrotic ENL presented to us after completion of MDT therapy, whereas one patient was on the 12th pack of MB-MDT. One patient had recurrent ENL, whereas in the other three patients, it was the second episode of ENL. Precipitating factor could be identified in any patient. All patients were in the lepromatous pole and showed typical features of ENL on histopathology. All the patients were males, anemic falling in lepromatous pole. No coinfections like TB, hepatitis B/C, HIV were found nor were there any comorbidities like DM, Asthma, HTN. No precipitating factors like vaccinations, infection, drug intake (potassium iodide), mental stress, change in weather were found. It is known that reactions are more common in women (Shale 2000) but in our study, all patients were males. Age ranged from 35 to 45 years, but three out of these 4 patients were above the age of 40 years, whereas literature mentions that age less than 40 years is a risk factor for type 2 lepra reactions (Manandhar et al 1999). Our study concluded

that ENL in its severe form is not an uncommon presentation of leprosy.

Vasculonecrotic reactions presenting as bullae and ulcers usually occur in BL and LL patients, either as Lucio Phenomenon (LP) or Erythema Nodosum Leprosum (ENL). LP usually appears in untreated or inadequately treated non-nodular lepromatous leprosy patients after a median of 1 to 3 years after the first manifestations of the disease and presents with erythematous mildly painful areas over the extremities, which evolve into necrotic, geometric-shaped or jagged-edged ulcers of 0.5 to 1 cm in size. There is usually no associated fever, constitutional symptoms, visceral involvement or neuritis. LP is endemic in Mexico although cases have been reported from USA, Spain, South and Central America, including Brazil (Furtado 1959) and Asia (Moschella 1967). While reasons for increase in occurrence of such cases need in depth investigations, it would be important to build adequate expertise and develop standardized guidelines usable by specialists as well as leprologists handling such cases in the field.

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