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The diagnostic dilemma of erythema nodosum leprosum - a clinicohistological study

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Summary
Background: Erythema nodosum leprosum (ENL) is a common complication among leprosy patients. It is diagnosed based on clinical findings and biopsy is performed only in patients with atypical presentation or doubtful diagnosis. This study was undertaken to describe the key clinical and pathological features in doubtful and severe cases of ENL.
Materials and methods: Biopsies of all diagnosed ENL cases over the past 10 years (January 2005 to July 2014) were reviewed along with the related clinical features.
Results: A total of 1195 leprosy patients were registered in the leprosy clinic of our institute over this period, amongst whom 233 cases of ENL (19·5%) were diagnosed; a biopsy was performed in 37 cases (15·8%). Of these 37 cases, the diagnosis of ENL was doubtful in 32 cases with the absence of typical erythematous nodules. Frequent histological findings in doubtful cases included stromal neutrophilic infiltrate (31/32, 97%), panniculitis (81%) and vasculitis of varying degree (24/32, 75%). Neutrophilic infiltration within the granuloma and eosinophilic infiltrate (nine cases each, 27%) were relatively less common. Among five cases with severe presentation, four had suppurative ENL with neutrophilic abscess within the dermis and one presented with ulcers and epidermal necrosis.
Conclusion: Besides vasculitis, panniculitis and varying degrees of neutrophilic infiltrate, which are diagnostic features of ENL, eosinophilic infiltrate and stromal oedema are reliable early diagnostic clues for ENL on histopathology. As ENL can be the initial presentation of leprosy, an adequate biopsy including subcutaneous fat is required for a definite diagnosis, in the absence classical clinical features.

Keywords: erythema nodosum leprosum, vasculitis, panniculitis, suppurative ENL

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Introduction

Leprosy is one of the oldest infectious diseases known to man. Leprosy is also an important cause of permanent disability in the world and poses a major social and economic burden on the patients and health care system of the country.[1–2] Leprosy is further complicated by its reactions, which are immune mediated. Leprosy reactions are of two major types - Type 1 (Type IV hypersensitivity reaction) and Type 2 or erythema nodosum leprosum (ENL), which is due to a Type III hypersensitivity reaction.[3] Lepra reaction can occur before, during and even after multi-drug therapy for leprosy. ENL is more commonly seen in lepromatous (LL) and borderline lepromatous (BL) patients. There may be wide variations in the clinical and histological appearance of Type 2 lepra reactions.[1] Usually the diagnosis of ENL is based on the clinical findings of evanescent, erythematous nodules or papules often associated with constitutional symptoms and painful enlargement of a nerve in a patient with leprosy, and a skin biopsy is generally not requiring.[4] However, in the absence of a classical presentation, including small nodules, papular lesions, pustules and sometimes plaques without any systemic manifestation, it is difficult to make a diagnosis of ENL clinically. These cases probably represent a milder or early form of ENL which are clinically challenging. However, an early and accurate recognition of Type 2 lepra reaction is essential since delay in diagnosis and treatment initiation can lead to significant morbidity. The treatment of ENL is equally challenging and early treatment with corticosteroids may be helpful.[5]

Thus skin biopsy is performed only in early/atypical cases of ENL and/or severe unusual forms, with a doubtful clinical diagnosis. The present study was undertaken to describe the histological and clinical features of atypical and severe cases of ENL with diagnostic difficulties.

Materials and Methods

All cases of ENL diagnosed clinically or on biopsy over the past 10 years were retrieved from the database. The clinical presentation and treatment history were noted from the records. Biopsies of all the confirmed cases were included in the study and reviewed. The biopsies were evaluated with emphasis on the following findings: epidermal changes, presence of granuloma, nature of infiltrate, stromal oedema, presence of vasculitis and panniculitis. The inflammation and vasculitis were graded as absent, mild, moderate and severe. Modified Ziehl- Neelsen (ZN) stain for leprosy bacilli using 0·5% acid alcohol was performed in all cases. The Elastic van Giesen (EVG) was performed in cases with suspected or definite vasculitis to evaluate and grade the vascular changes.

Histologically, ENL was diagnosed by the presence of a neutrophilic infiltrate within the stroma or within granulomas, vasculitis and panniculitis in variable combinations and severity.

As this was a retrospective study and the biopsy was taken from the patient as a part of routine care, no formal ethical clearance was required. Formal written consent was obtained from the patients before the biopsy.

Results

Over the 10 year study period, a total of 1195 leprosy patients were registered in the leprosy clinic at our institute, of which 233 patients were diagnosed as ENL (19·5%), based on clinical criteria (Figure 1a).

Biopsies were performed in 37 cases (3·1%) where the clinical diagnosis was doubtful or because of an atypical presentation or overlapping between Type 1 and Type 2 reaction (in five cases). None of the patients received steroid therapy or any other form of immunosuppressant before the biopsy. The patients' age range was 32 to 70 years (mean 42 years) and there was a male preponderance (M:F = 2·7:1). Of these 37 ENL biopsies, the diagnosis was doubtful or the presentation was atypical in 32 cases (86·5%) and in the remaining five cases (13·5%) the presentation was severe (four pustular and one ulcerated/ necrotic).

In the first group (doubtful diagnosis or atypical presentation, $n = 32$), patients had small, non-erythematous nodules in the extremities without any significant systemic manifestations (Figure 1b); ENL was suspected clinically in 20 cases and five cases had overlapping clinical feature of Type 1 and Type 2 lepra reaction. In the remaining seven cases the diagnosis of ENL was suggested on biopsy. Only eight patients (25%) were on multidrug therapy (MDT) and the remaining were fresh cases (75%). The majority of cases were lepromatous type (LL- 24 cases, 75%) and the rest were borderline lepromatous type (BL- 8 cases, 25%). The bacillary index (BI) in these cases ranged from 3+ to 6+. The detailed results are shown in Table 1.

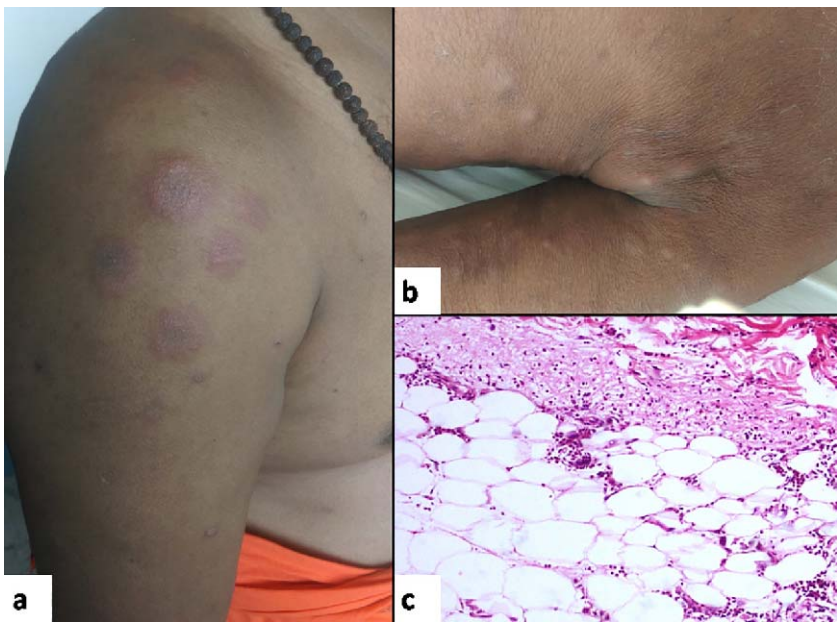

Figure 1. (a) A case of classical erythema nodosum leprosum (ENL) presenting with raised, erythematous nodule. (b) A case of early ENL with small nodules restricted in the hands. (c) Histology of the same case showing presence of panniculitis (HE, X100).

Table 1. Clinical features of doubtful and severe ENL patients

Feature	Doubtful/atypical ENL ($n = 32$)	Severe ENL ($n = 5$)
Average Age in years (range)	42 (8–78)	37 (27–48)
M:F	3:1	4:1
Type of leprosy	LL-24, BL-8	LL-4, BL-1
Received MDT	Yes- 8, No- 24	4 on MDT, one completed MDT
Steroid/immunosuppressant	None	None
Clinical diagnosis	Suspected early ENL- 20, Overlapping features of type 1 and type 2 lepra reaction- 5, Not suspected ENL- 7	Ulcerated ENL-1, Pustular ENL- 4
Extrecutaneous manifestation	None	Fever- 5, Arthralgia- 4
Bacillary index (at the onset of treatment)	3+ to 6+	4+ to 6+

ENL - erythema nodosum leprosum, MDT - multidrug therapy, LL - lepromatous leprosy, BL - borderline lepromatous leprosy.

Histologically, foam cells and histiocytic collection with ill-defined granuloma formation was seen in 12 cases and none showed well-formed granuloma (Table 2).

The inflammation was mild to moderate, comprising of lymphocytes (100%), followed by neutrophils (96·9%) and eosinophils (28·2%) (Figures 2c and d).

The majority of cases with neutrophilic infiltrate had stromal oedema and only nine had associated granulomas (28·2%). More than half of the cases had loss of adnexal structures (53·1%) and leprosy bacilli could be demonstrated in 27 cases (84·3%). All the cases negative for leprosy bacilli had already received MDT. In addition perineural inflammation was seen in 84·4% of cases. Out of eight cases of BL leprosy, five had presented with overlapping

Table 2. Histological features of early and severe cases of erythemaa nodosum leprosum (ENL)

Features	Early ENL ($n = 32$)	Severe ENL ($n = 5$)
Neutrophilic infiltrate	31 (96·9%)	5 (100%)
None	1 (3·1 %)	0 (0%)
Mild	14 (43·8%)	0 (0%)
Moderate	15 (46·9%)	0 (0%)
Severe	2 (6·3%)	5 (100%)
Eosinophilic infiltrate	9 (28·2%)	5 (100%)
None	23 (71·9%)	0 (0%)
Mild	6 (18·8%)	2 (40%)
Moderate	3 (9·4%)	3 (60%)
Severe	0 (0%)	0 (0%)
Lymphocytic infiltrate	32 (100%)	5 (100%)
None	0 (0%)	0 (0%)
Mild	14 (43·8%)	0 (0%)
Moderate	15 (46·9%)	3 (60%)
Severe	3 (9·4%)	2 (40%)
Vasculitis	24 (75%)	5 (100%)
Panniculiis	13 (81·25%)*	5 (100%)
Leprosy bacilli present	27 (84·4%)	5 (100%)

*Subcutaneous fat was included in 16 biopsies of early ENL.

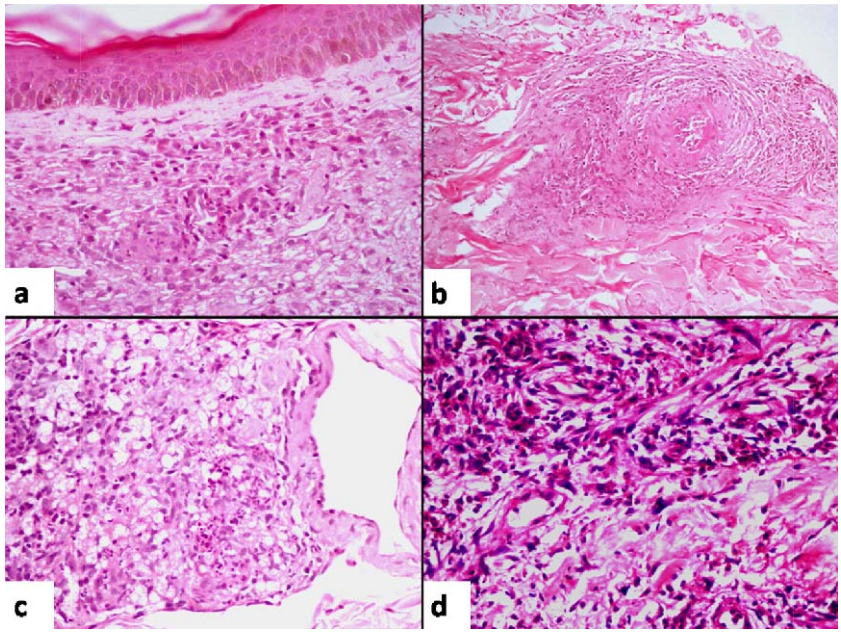

Figure 2. Cases of early ENL showing (a) focal vasculitis involving capillary (HE, X200), (b) arteriolar involvement with fibrinoid necrosis and endothelitis (HE, X200), (c) collection of foam cells infiltrated by neutrophils (HE, X200) and (d) eosinophilic infiltrate admixed with neutrophils (HE, X200).

clinical features of Type 1 (reversal reaction) and Type 2 (ENL) lepra reactions. The biopsy examination of all these cases showed features of ENL. In addition, three cases showed the presence of dermal oedema and a lymphocytic infiltrate in the upper dermis in the adjacent areas. Thus in these three cases, there was a clinical and histological overlap of Type 1 and Type 2 lepra reactions.

Subcutaneous fat was included in 16 biopsies, of which 13 (81%) showed evidence of panniculitis (Figure 1c). Vasculitis was a common finding, seen in 75% of cases involving mainly capillaries (21 cases, 65·6%) and in three cases it involved arterioles and venules as well; only one case showed involvement of a small artery. The most common vasculitic finding observed was leukocytoclastic type, with neutrophilic infiltrate and fibrinoid necrosis of the vessel wall. Fibrin thrombi formation was seen in only four cases (12·5%) and none showed fibrointimal proliferation or endarteritic changes. There was evidence of endothelitis or endothelial cell damage in the majority of cases (19/21, 80%). There were six cases which had focal vasculitis (Figures 2a and b) and the diagnosis of ENL was confirmed by examination of multiple levels as clinical suspicion of ENL was raised.

Among those presenting with severe disease ($n = 5$), four patients had pustular lesions, while one had ulcerated skin lesions with systemic manifestations in the form of fever and arthralgia. The lesions in these cases were multiple, and present over the trunk and extremities (Figure 3a) with a history of receiving treatment for leprosy; one patient had already completed therapy 6 months previously.

Histologically, all cases showed extensive inflammatory infiltrate composed predominantly of neutrophils, eosinophils admixed with histiocytes and areas of necrosis in the upper dermis (Figures 3b and c). There was evidence of vasculitis involving capillaries. Four cases

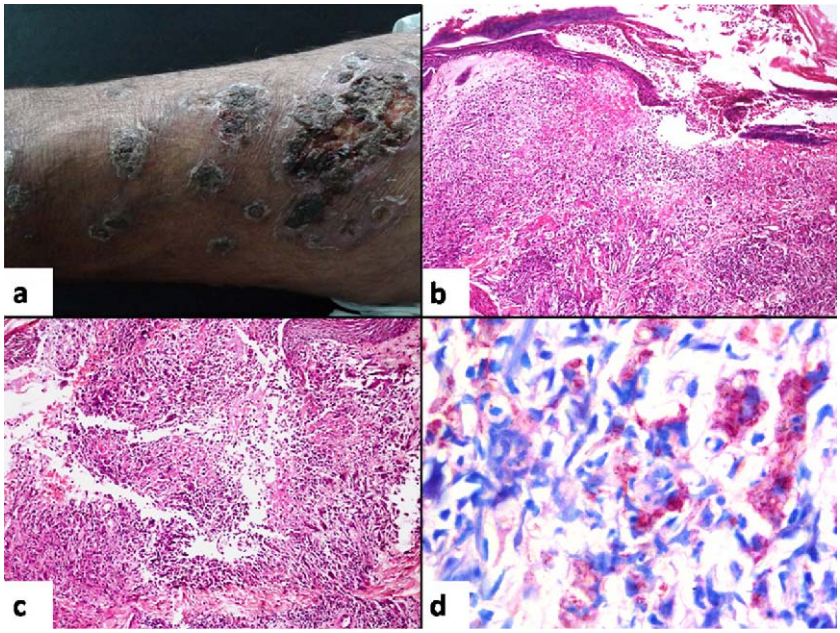

Figure 3. (a) A case of severe ENL with ulcerated lesions. Histology showing (b) epidermal ulceration along with necrosis (HE, X100) and (c) central necrosis, surrounded by dense neutrophilic infiltrate and many giant cells in a case of pustular ENL (HE, X200). (d) Strong positivity for leprosy bacilli (modified Ziehl-Neelsen, X1000).

showed pustule formation, and one showed complete epidermal ulceration. Histologically, these cases resembled pyoderma gangrenosum (PG) and/or acute neutrophilic dermatosis. One case was initially diagnosed as suppurative inflammation, however a modified ZN stain was performed in view of previous history of leprosy and showed strong positivity. In other cases, two were strongly positive for leprosy bacilli (Figure 3d) and in one case positivity was also seen in endothelial cells.

Discussion

Erythema nodosum leprosum (ENL) or Type 2 leprosy reaction is an immune-mediated complication of leprosy occurring in LL or BL leprosy patients. It is a Type III hypersensitivity reaction, due to the formation of circulating immune complexes and thus can show systemic manifestations as well. It causes an acute inflammatory reaction which can occur in any organ or tissue invaded by the leprosy bacillus.[6] However, recent evidence suggests some role of cell mediate immunity in the pathogenesis of ENL.[7] The skin lesions can be seen at any place, but are more common over the extremities and are present in varying sizes; they may be superficial or deep seated, erythematous, tender papules or nodules. The diagnosis of ENL can usually be made by thorough clinical evaluation and a slit skin smear, hence a biopsy confirmation is often not required. A biopsy is only required to confirm the diagnosis in atypical/early cases of ENL in which the diagnostic is uncertain. Severe ENL is rare and the skin lesions may become vesiculo-bullous, ulcerated or even necrotic[8] and may resemble pyoderma gangrenosum (PG), so that a biopsy becomes essential in order to make a definitive diagnosis and provide appropriate treatment. We had such lesions in five of our

patients who were misdiagnosed as PG or neutrophilic dermatosis at first, and only later was the diagnosis revised to a severe form of ENL.

The ENL reaction is usually accompanied by a systemic signs including high fever, systemic upset, oedema of face, hands and feet, and proteinuria, although the same was not seen in any of our patients. Other systemic manifestations include iritis, episcleritis, arthritis, arthralgia, dactylitis, lymphadenopathy, organomegaly and orchitis.[6] However, these were observed only in patients with late ENL in our study who had fever and arthropathy at presentation, while none of the early ENL patients had these features. In a minority of patients, there may be co-existence of Type 1 and Type 2 lepra reactions. In cases of BL leprosy, the reversal reaction can present as small patches, which can be very difficult to distinguish from ENL without a biopsy. In our series, five cases clinically had overlapping features of Type 1 and 2 reactions. Among these, two showed features of pure ENL on histology, while three patients had features of both Type 1 and 2 reactions. This further emphasises the importance of a careful histological evaluation.

Seven of the early ENL cases were not suspected clinically. These patients presented with mildly raised skin lesions without any other clinical features to suggest leprosy. Biopsy in these cases showed features of leprosy with early ENL changes. All of these seven cases showed leprosy bacilli positivity on histology. On follow up, they all showed slit skin smear positivity (BI 3+ to 5+). The presence of early ENL in these cases was probably responsible for masking the clinical features of leprosy. Thus an experienced dermato-pathologist can pick up the early changes of ENL and guide the adequate treatment of patients.

It is relatively difficult to predict which patient would develop ENL though LL cases and a BI ≥ 4 are significant risk factors for the development of ENL.[9–11] We also observed a high BI of 3+ to 6+ in all our cases diagnosed as ENL in the background of BL or LL leprosy. Five of the doubtful ENL cases were negative for leprosy bacilli, all of whom had received MDT. Although ENL can be seen in leprosy patients after receiving therapy, MDT is not essential for the development of ENL, which can be seen after, during or even before therapy.[1] We observed that 75% of the doubtful ENL cases did not receive MDT, indicating ENL can be the first manifestation of leprosy. In our setting, the majority of the patients develop ENL during the course or after finishing MDT. However, the cases included in this series are early cases and constituted only 3·1% of the total ENL cases seen within this period. The clinical features were very mild, which were recognised by the dermatologists and a biopsy was performed to exclude the possibility of early ENL. Thus an experienced clinician can recognise the early manifestations of ENL, which is essential for early treatment of this condition.

The classical changes described in the histopathology of acute ENL include neutrophil rich inflammatory infiltrate classically in the deeper dermis, infiltrating within pre-existing lepromatous lesions, granulomas and extending into the subcutaneous fat, producing panniculitis and often associated with vasculitis.[12] Accompanying stromal oedema of the dermis is another frequent finding.[13] The constituent cells in the infiltrate vary according to the duration of the lesion.[12] In acute lesions (duration <72 hours), neutrophils dominate the infiltrate, sometimes even leading to microabscess formation. Hussain *et al*. described neutrophils as the dominant inflammatory infiltrate in only 64% of biopsies performed within 7 days of the appearance of lesions.[14] As the duration of the lesion progresses, the number of ploymorphonuclear leukocytes (PMNL) reduces and gradually chronic inflammatory cells appear. In our study, in biopsies performed within 72–96 hours, the infiltrate consisted of approximately equal numbers of PMNLs, lymphocytes, plasma cells and mast cells, whereas the biopsy in chronic lesions (>9 days) had a predominant population of chronic

inflammatory cells comprising of lymphocytes, plasma cells and histiocytes.[12] The majority of our cases were biopsied early (within 4 days), thus showing neutrophilic infiltrate admixed with a variable amount of lymphomononuclear cells and prominent stromal oedema.

This transition from the acute phase to the regressing chronic phase of the reaction highlights the importance of the timing of the skin biopsy in ENL, as skin biopsies taken later in the course of disease may not demonstrate the classical neutrophilic infiltrate. Adhe *et al*. observed neutrophilic spongiosis in 19% of ENL patients.[15] There is very limited data on early histological changes in ENL as it is difficult to recognise clinically and hence requires a biopsy for definite diagnosis. It is very important to recognise the histological changes in early and atypical cases of ENL as early treatment in these patients may avoid complications and deformity. Although neutrophilic infiltrate within the granuloma has been reported as a uniform feature of ENL by Adhe *et al.*,[15] we observed it in only 28·2%. We found neutrophilic infiltration/nuclear debris in 97% of our cases in the stroma with accompanied oedema. In some cases, the neutrophilic infiltrate was very scanty possibly an early stage lesion was biopsied. In addition we found eosinophils in 28·2% our cases which have not been widely described. However, a few authors have observed varying numbers of eosinophils and mast cell infiltration in ENL.[12–13] Thus finding eosinophils in the biopsy of a leprosy patient without an overt neutrophilic infiltrate can indicate the development of early ENL. Though we do not have a definite clinical correlate in cases with eosinophilic infiltrate since the patients were already started on treatment, a diligent search of clinical clues may be helpful in identifying such cases.

Vascular changes are common in ENL and it has been hypothesised that vasculitis is the major pathological event in ENL and depends on the duration of the lesion and timing of biopsy.[15] Classical features of acute necrotising vasculitis and thrombus formation have been demonstrated in the acute stage.[13,16] Late lesions show features of healing including proliferative or obliterative changes.[12] The index study revealed 75% of early ENL cases had vasculitis in the form of leukocytoclastic vasculitis involving the capillary, without formation of fibrin thrombi though arteriolar involvement was rare. There was evidence of endothelial cell damage and swelling, along with evidence of endothelitis, indicating the endothelial cells to be the primary target of immunological damage. Either the antigen-antibody complex may get deposited in the endothelial cells[3] or the other possibility could be endothelial cells carrying the antigen, and thus leprosy bacilli could reside there. We could demonstrate leprosy bacilli within endothelial cells in one of our cases, which supports this conclusion. Other mycobacterial infections, especially tuberculosis, can also produce vasculitis. However, in comparison to ENL, vasculitis in tuberculosis is due to the extension of inflammation from the adventitial aspect of vessels, and is thus restricted to the site of infection. The vasculitis in ENL may be very subtle as six cases of early ENL in our study showed focal leukocyoclastic vasculitis which was more evident on multiple level examination. This indicates the importance of examination of multiple levels in cases where ENL is suspected clinically, but histological changes are not diagnostic. In such cases, a clinico-pathological correlation becomes essential, as these patients have more tender nodular lesions.

The inflammatory infiltrate of ENL can involve the subcutaneous fat producing panniculitis.[12] Panniculitis in ENL is variable, and may be seen in 60–70% of cases.[15] However, in our study we observed a relatively high percentage of panniculitis, in 81% of the biopsies. The presence of panniculitis in an appropriate background is almost diagnostic of ENL. Thus an adequate biopsy containing subcutaneous fat is very helpful to confirm the diagnosis of ENL.

Diagnosis of early cases of ENL thus is very challenging and histological changes may be very subtle. In six cases the changes were brought out by examination of multiple levels of sections in view of clinical suspicion of ENL. Similarly, seven cases were not suspected clinically and the diagnosis of ENL was suggested by the dermato-pathologists. These cases responded well to steroid therapy subsequently. This further emphasises the difficulty in diagnosing early cases of ENL, both clinically as well as histologically, and highlights the importance of clinico-pathological correlation.

The dermato-pathologist must be aware of the histological changes that can be seen in the early phase of ENL to offer a correct diagnosis to institute early therapy, which could reduce morbidity in these patients.

Rarely, ENL may become severe, namely - ulcerated, necrotic, pustular and bullous[4] which can pose a significant clinico-pathological diagnostic challenge and can clinically resemble pyoderma gangrenosum or erythema multiforme.[7] We found four pustular and one ulcerated form of ENL which were initially suggested to be suppurative inflammation with a PG like picture. However, strong positivity for leprosy bacilli helped in clinching the diagnosis, along with the appropriate history. Thus an adequate history is essential for proper diagnosis.

In conclusion, early cases of ENL without any systemic manifestations are a diagnostic challenge both clinically and histologically. The changes may be subtle in problematic cases thus clinicohistological correlation with examination of multiple levels of skin biopsy is necessary. Histologically, stromal neutrophilic infiltrate or nuclear debris with panniculitis and leukocytoclastic vasculitis may indicate the diagnosis. In the absence of neutrophils, stromal eosinophilic infiltrate with accompanying oedema, can give a diagnostic clue for early lesions of ENL. Severe cases of ENL may resemble pyoderma gangrenosum or abscess where leprosy bacilli positivity and clinical correlation is essential.

Contributorship

DC analysed the cases and prepared the manuscript. UNS conceived the idea, analysed the cases and critically reviewed the manuscript. TN and SD provided the clinical detail and critically reviewed the manuscript.

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