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CASE REPORT

Familial clustering of severe atypical variants of erythema nodosum leprosum in immunocompetent siblings

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Summary The clinical picture of leprosy is very varied, with familial clustering of the disease being rare. Erythema nodosum leprosum (ENL) is a common manifestation of Type 2 reaction in leprosy. We present here two immunocompetent siblings who presented simultaneously with pustular, ulceronecrotic, bullous and impetigo like erythema nodosum leprosum.

Keywords: Leprosy, Hansens, reaction, erythema nodosum leprosum, ulcerative, bullous

Introduction

Erythema nodosum leprosum is characterised by brightly erythematous tender nodules or plaques usually in bilateral symmetrical distribution.[1] ENL can also present in several atypical presentations like pustular, erythema multiform like, ulcerative, necrotic, panniculitic and bullous forms. Various precipitating factors for ENL include stress, pregnancy, surgery, lactation, menstruation, infections and sometimes therapy.[2] We report two rare varities of ENL - pustular ENL and bullous variant manifesting simultaneously in 2 siblings of a family.

Case report

Two siblings aged 23 years and 19 years reported to our emergency department with the complaints of multiple pus filled lesions and ulcerations over the body for 2 months. They were apparently well 2 months previously when they developed multiple painful red nodules associated with fever, joint pains and myalgia. These nodules were more over the upper and lower limbs. Fever was moderate to severe, associated with chills and rigors and joint pains were associated with joint swelling restricting mobility on occasions. The patients took some

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undocumented ayurvedic medications which led to some improvement in fever, however they started developing numerous pustular lesions which ruptured and coalesced to form large ulcero-necrotic plaques with deep punched out ulcers. There was no history of neuritis, numb white lesions, peripheral anesthesia, difficulty in buttoning or unbuttoning, nasal epistaxis, slippage of chappals or contact with any leprosy patient.

On examination, both brothers were thin built, showed pallor, cervical and submandibualr lymphadenopathy in elder sibling while only submandibualr lymphadenopathy in the younger sibling. Both were febrile with tachycardia and pedal edema was noted in the elder sibling. Cutaneous examination of the elder sibling showed multiple eythematous tender nodules, along with pustules, impetigo like lesions and pus filled bullae of size varying from 0·5 cm × 0·5 cm to 1 cm × 1 cm over upper and lower limbs (Figures 1, 2).

Large erosio-crustive, haemorrhagic and necrotic plaques were also present (Figure 3).

At places, deep punched out ulcers were seen. Face showed multiple nodules over eyebrows. The younger sibling showed lesions of similar morphology but being less severe and fewer in number (Figure 4).

Both showed mild infiltration over the ears and face. Nasal, oral, genital mucosa and nail examination were normal. Ulnar nerve was thickened in the elder sibling, while the younger one showed thickening of ulnar, radial cutaneous and common peroneal nerves. Sensory and motor examination revealed no abnormality in both the siblings. Slit skin smear (SSS) examination from the ear lobes revealed bacteriological index (BI) of 6+ in both, while that from the bullous lesions gave BI of 6+ but with fragmented bacilli. Skin biopsy of the nodular and pustular lesions in both brothers showed diffuse infiltration of dermis with foamy macrophages and neutrophils and vasculitis at places (Figure 5). Fite staining revealed fragmented bacilli which was suggestive of ENL.

Hematological investigation revealed low hemoglobin in both brothers, with raised ESR and leucocytosis (Table 1).

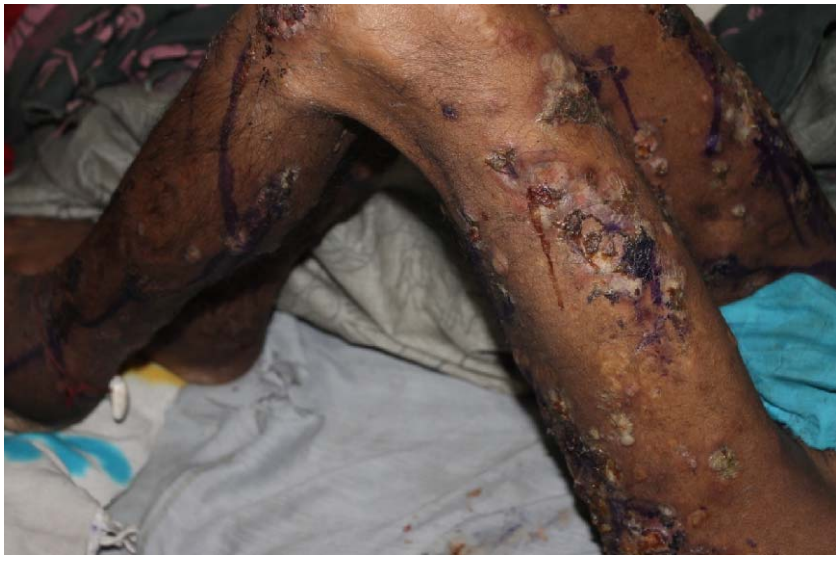

Figure 1. Large erosio-crustive plaques over both lower limbs in elder sibling.

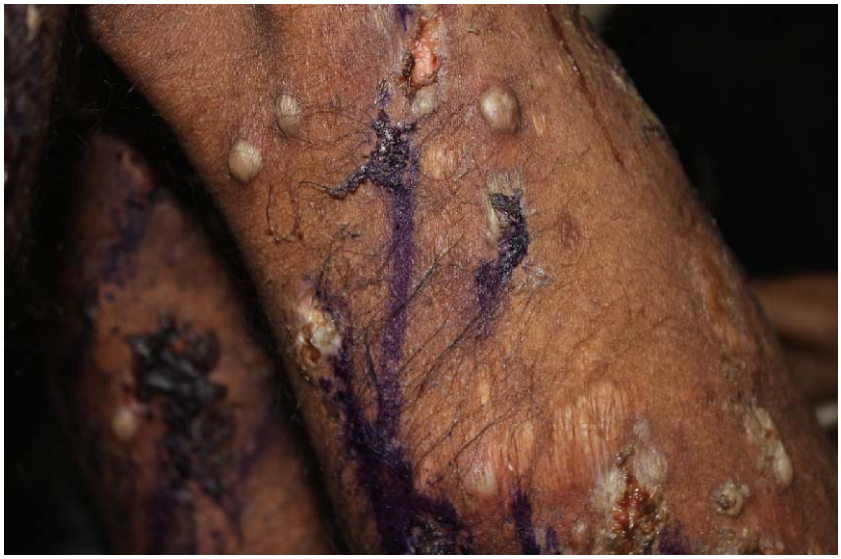

Figure 2. Impetigo-like bullous ENL in elder sibling.

G6PD showed no deficiency and VCTC was non-reactive. Multi-bacillary multi-drug therapy (MBMDT) was started along with prednisolone 40 mg in both. In the 4 weeks of treatment, the hemoglobin gradually fell and reached to very low levels and hence dapsone was withheld in the first sibling. They continued to get multiple new tender lesions and hence thalidomide (100 mg tds) was started after sensory nerve action potential test. After 4 weeks, they still continued to get new nodular and pustular lesions. Some form of improvement was seen only after 10 weeks, after which the dose of prednisolone and thalidomide was gradually

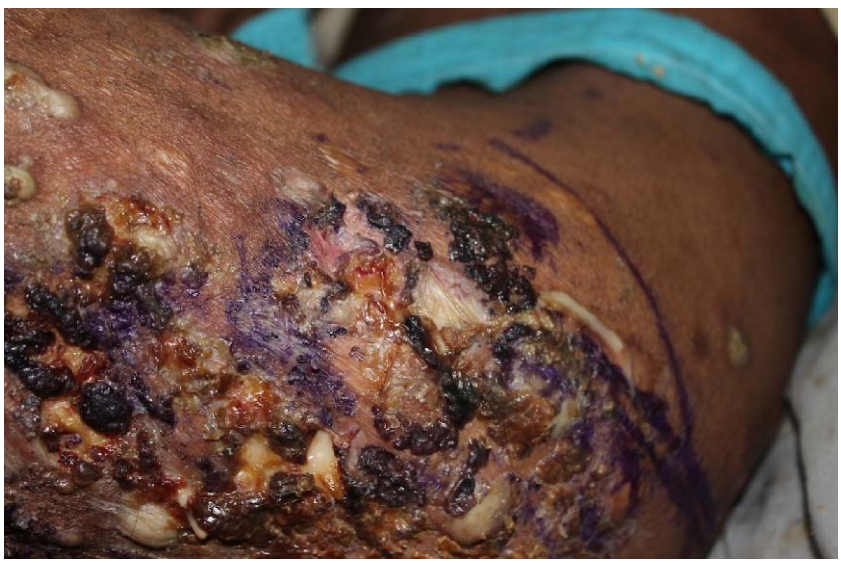

Figure 3. Hemorrhagic ulcer-necrotic plaques.

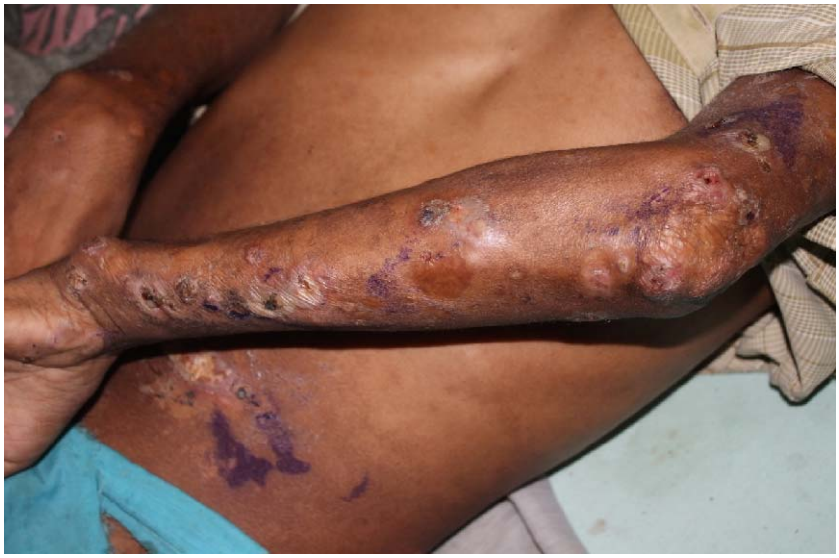

Figure 4. Bullous and necrotic ENL in a milder form in younger sibling.

tapered. The number of ENL crops decreased gradually after 10th week, however four to five crops developed every alternate day till 18 to 20 weeks, after which the ENL crops stopped erupting. The younger sibling responded earlier than the elder. After 20th week, thalidomide 100 mg daily and prednisolone 20 mg were continued for another 2 months and then the prednisolone was tapered and stopped. MBMDT was continued.

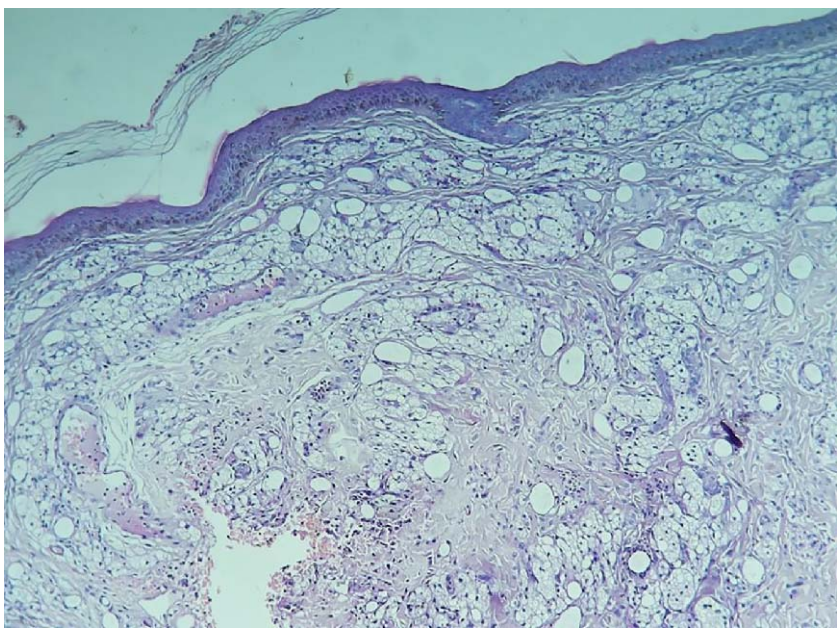

Figure 5. Dermis showing diffuse infiltration of foamy macrophages and neutrophils. (H and E, 40X).

Table 1. Laboratory profile of the siblings

BASELINE	Elder Sibling	Younger Sibling
Hemoglobin	8·4 mg/dl	9·2 mg/dl
Total leucocyte count	24,400	22,600
ESR	65	48
Chest x ray	Normal	Normal
24 hour urinary protein	3·38 mg/l	Normal
HIV test	Non reactive	Non reactive
G6PD levels	No deficiency	No deficiency
Total protein/albumin	5·6/2·4 mg/dl	6·7/3·2 mg/dl
AFTER 2 WEEKS OF TREATMENT WITH DAPSONE		
Hemoglobin	7·2	8·4
AFTER 4 WEEKS OF TREATMENT		
Hemoglobin	5·4	7·6

Discussion

Type 2 leprosy reaction is a Type 3 coomb's and gell hypersensitivity reaction seen in lepromatous and borderline lepromatous patients. It occurs during course of treatment or longstanding untreated patients. Although bullous and pustular lesions are reported, such severe ulcero-necrotic lesion along with pustular and bullous lesions in the same family is rare. The mechanism of bullous lesions described is dermal edema or leuco-cytoclastic vasculitis.[3] Familial clustering of leprosy is known. But both the brothers, presenting simultaneously with such florid ENL is unusual. Evidence supports the role of several human genetic determinants as risk factors for leprosy reactions.[4] Genome wide scans have revealed several HLA and non-HLA variants as risk factors for disease per-se, its clinical variants and reactions. Studies on genetics of leprosy reactions have implicated variants of NOD2 and IL6 as risk factors for developing Type 2 reaction.[5] However, such genetic studies could not be performed on our patients due to lack of resources.

De-novo ENL without taking MBMDT is rare, in the absence of certain triggering factors like stress pregnancy, lactation, concurrent illness and medications. The precipitation of reaction in our patients could be attributed to ayurvedic drugs which are known to aggravate the reaction.

Another interesting fact in our case was the rapid fall of hemoglobin in the first sibling, inspite of his G6PD levels being normal. It is said that, patients with increased creatinine and lower body weight are at higher risks of hemolysis and require dose adjustment while on dapsone. This could explain the rapid fall of hemoglobin in our patient. Alternatively, mutations in hexose mono-phosphate shunt pathway and glutathione metabolism may also lead to hemolysis in G6PD normal patients.[6] Also, the oxidative action of dapsone is so potent that it can cause damage to even G6PD-normal erythrocytes.

Lucio phenomena needs to be excluded in such ulcerative cases. The points that went against this in our patients was the absence of diffuse infiltration of the skin, presence of discrete nodules, ulceration and necrosis developing over nodular lesions rather than spontaneously on normal skin, fragmented bacilli on slit skin smear and evidence of vasculitis on histology.[7]

Usually ENL responds very well to thalidomide. But our cases showed severe and prolonged reactions in-spite of being on steroids, thalidomide and clofazimine, and thus posed a challenge to clinical management.

The major point of interests in our cases was the de novo presentation of multiple atypical forms of ENL like bullous, pustular, impetigo like, ulcerative and necrotic type simultaneously in two immunocompetent siblings. These presentations of ENL are rare, and this would be first report showing atypical severe ENL with familial clustering.

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