Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Spl Issue [4] 2022 : 168-173

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

Erythema Nodosum Necroticans : Review Article and A Case Report

***Sakshi Aggarwal[1] , Saurav Bhagat[2] , Sudipta Satpathi[1] , Saloni Mahajan[1], Nalini Bansal[1] , Rajeev Sen[1]**

1 Department of Pathology, FMHS, SGT University, Gurugram
2 Department of Radiology, SMSR, Sharda University, Greater Noida
*Corresponding Author's Email : sakshi.aggarwal94@gmail.com

ABSTRACT

Erythema Nodosum Necroticans (ENN) is a severe and rare variant of Erythema nodosum leprosum (ENL) first described in 1993. ENL is an immune complex mediated reaction of multibacillary leprosy during or after completing multidrug therapy. In severe ENL the lesions can become vesiculobullous, ulcerative and necrotic termed as Erythema Nodosum Necroticans (ENN). A 40 years old female presented with 4 years history of numerous bullous turbid fluid filled lesions with ulceration over extremities, trunk and face. Biopsy showed grenz zone in patchy areas and dense diffuse infiltrate of foamy histiocytes along with leukocytoclastic vasculitis. Focal aggregates of polymorphs were noted in subepithelial region. Leprae stain showed scattered bacilli. Slit skin smear examination revealed a Bacteriological Index of 4+. These rare variants of Erythema nodosum leprosum are usually misdiagnosed especially in those patients who do not have any prior history of previously diagnosed leprosy. Therefore, a high index of suspicion is required in such cases to avoid delay in the diagnosis and resulting morbidity.

Keywords: *Erythema nodosum necroticans, Erythema nodosum leprosum, Type 2 lepra reaction*

Received 04.10.2022 Revised 18.10.2022 Accepted 28.11.2022

INTRODUCTION

Leprosy is a slowly developing disease that presents with wide spectrum of clinical, immunological and histopathological characterization. Erythema nodosum leprosum (ENL) occurs in cases of high bacillary load and hence Lepromatous Leprosy (LL) and Borderline Lepromatous Leprosy (BL) cases mostly suffer from these episodes. It is an immune complex-mediated disease. ENL often involves capillary rich organs such as nerves, testes, joints, kidneys, eyes and lymph nodes. It commonly present during or after antimycobacterial treatment and characterized by the appearance of highly inflamed skin nodules in crops which in severe cases become oustule and may even ulcerate.. Severe ENL can become vesicular, pustular , bullous and necrotic and break down to produce ulceration called as Erythema Nodosum Necroticans(ENN). We herein present a case of Erythema Nodosum Necroticans (ENN).

CASE REPORT

A 40 years old female, farmer by occupation presented to the hospital with a 4 years history of multiple painful pus filled elevated skin lesion present all over the body and from past 1 year multiple painful raw crusted areas all over the body. Upon arrival her vitals are stable except for the mild hyperthermia. She was conscious, well oriented to time, place and person. Patient was apparently well 4 years back then she developed red elevated skin lesions over right forearm and both lower extremities. These lesions were not associated with any pain or itching. It was associated with fever and myalgia which used to relieve after taking medication. Patient developed a second flare of lesions one year back when she developed painful fluid filled lesions over left thigh, which progress to involve both lower and upper extremities .These lesions ruptured by itself leaving painful raw areas behind. There was no history of any drug intake prior to the appearance of lesion .On examination, multiple turbid fluid filled vesicles and bullae of size varying from 0.5 x 0.5 cm to 3 x 4 cms, generalized in distribution present over face , chest , lower abdomen, both extremities including palm and sparing soles .Some of them are ruptured leaving behind erosions and crustation. Some bullae have black pigmentation in the centre of the lesion. Also multiple well defined ulcers (punched out) with red granulation tissue over floor and indurated base of varying size from 1 x1 cm to 3 x 3 cms present over both forearm, legs, abdomen and buttocks. Some ulcers were

covered with eschar. Multiple erythematous papules and plaques present over back extending towards buttocks. There was no significant loss of sensation or nerve thickening. Infiltration present over face and left earlobe along with lateral madarosis is noted. Hyperpigmentation of buccal mucosa also present. Scalp and genitals are healthy. Nickolsky sign negative. Asboe Hansen sign negative.

Pus fluid (cytology)- Tzank smear submitted show mainly degenerated inflammatory cells comprising of predominantly neutrophils along with few lymphocytes , macrophages . Clusters of squamous cells also noted .No significant acantholytic cells/ RBC seen. Slit skin smear examination for acid fast bacilli from representative sites showed a Bacteriological Index of 4+, Morphological Index being 40%. Routine investigations done included complete blood count , renal and liver function tests, all these were within normal limits, except for a low hemoglobin level of 9.1 mg percent. Viral markers are negative. A biopsy was taken from the lesion for histopathological examination which revealed the following features. Skin biopsy done from one of the lesions showed tissue lined by epidermis. There is presence of grenz zone in patch areas. Beneath the zone superficial dermis show dense diffuse infiltrate of foamy histiocytes along with presence of inflammatory cells. In other areas there is presence of superficial and deep perivascular and periadnexal infiltrates of foam cells along with leukocytoclastic vasculitis. Focally aggregates of polymorphs noted in subepithelial region. Repeat stain of leprae bacilli showed presence of scattered fragmented granular bacilli within foam cells.

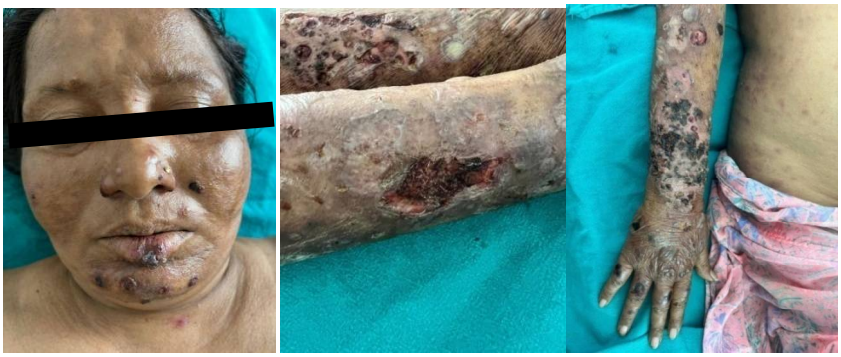

Figure 1:
(a) Frontal photograph of the patient showing lateral madarosis.
(b - c) Ulceronecrotic lesions present over extremities.

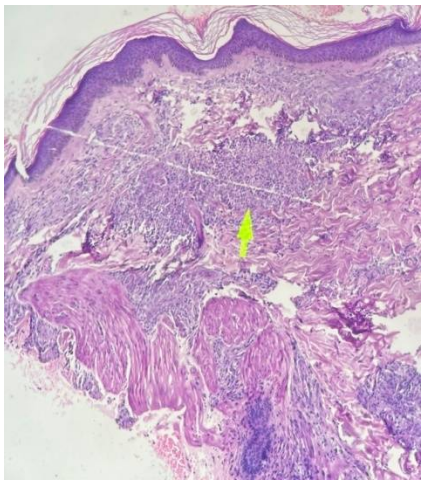

Figure 2: (a) Presence of grenz zone in patchy areas (H and E, X10).

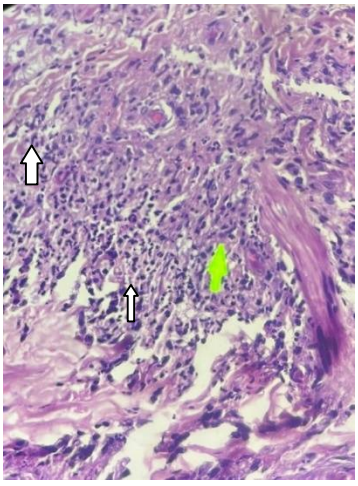

Figure 2: (b) Leukocytoclastic vasculitis (marked by red arrow), Clusters of Polymorphs (marked by green arrow)(H and E, X10).
(H and E, X 10).

DISCUSSION AND REVIEW OF LITERATURE

Type 2 reactions or erythema nodosum leprosum (ENL) is a Type III immunological reaction characterized generally by crops of evanescent, coppery tender nodules, and plaques with the involvement of other organ systems such as the eyes, testes, nerves, liver, and kidney. ENL occurs most

commonly in the lepromatous pole and can present before initiation, during or after completion of multidrug therapy (MDT).

Morphology of nodules should be studied carefully:

- Persistent, asymptomatic erythematous/coppery/normal skin-coloured nodules, firm on palpation of variable size, with sloping edges on to the surrounding infiltrated skin are seen in lepromatous spectrum of the disease (BL/LL).
- Well defined, succulent, hemispherical glistening nodules, with or without umblication, present on apparently normal appearing skin may suggest histoid leprosy.
- Recurrent erythematous , evanescent , tender nodules on the skin , commonly distributed over face , arms and thigh unrelated to preexisting lesions and healing with post inflammatory hyperpigmentation are suggestive of ENL, a feature of type 2 leprosy reaction.

Rarely few ulcerated lesion may be present in patients with untreated LL Leprosy, histoid leprosy and ENL lesion or over the lesions of type 1 reaction. Such ulcers are usually present onthe dorsa of the fingers and toes, instep of the soles or other nonweight bearing areas, Sometimes in severe type 2 reaction , ENL lesions may become vesicular and bullous and break down to produce ulcers known as **erythema nodosum necroticans (ENN)**

ENL can be graded as mild and severe. Severe ENL includes necrotic ENL or **erythema nodosum necroticans (ENN)**, which is a rare presentation seen in around 8% of patients [1].

ENN is characterized by the vesicular, bullous, or pustular lesions which become necrotic and break down to produce ulcers. It was first reported by Verma and Pandhi in 1993[2].

ENN heal with fibrotic, hypertrophic, or radiating scars. On histopathology, ENN is characterized by pan vasculitis starting in the hypodermis [3].

AUTHOR	AGE/ SEX	PRESENTING COMPLAINTS	PAST HISTORY	PHYSICAL EXAMINATION AND INVESTIGATIONS	MICROSCOPIC EXAMINATION	DIAGNOSIS AND TREATMENT	FOLLOW UP
Deepika Pandhi et al. [4]	9 Years/ Male	c/o various erythematous , elevated tendor lesions on face starting from chin and limbs for past 4 months which subsided with scaling and hyperpigmentation. Few lesions rupture and pus is discharged associated with episodic fever with each crop of lesions.	No H/O leprosy, tuberculosis, or any chronic illness in past or in any family member.	-Febrile -Multiple large and discrete submandibular lymphadenopathy. -Multiple redish tender nodules and plaques and their size varying from 0.7 cm to 2cm, few lesions also had irregular ulcers with necrotic base. -Bilateral ulnar, posterior tibial and lateral popleteal nerves were thickened. -Low Hb, neutrophilic leukocytosis with raised ESR. -Mantoux test - Negative.	-Slit skin smear showed a morphological index of 10% and bacteriological index of 5+. -Neutrophilic infiltration along with diffuse infiltrate of plasma cells and foamy macrophages. - Leucocytoclastic vasculitis present. -Fite's stain – Positive for acid-fast bacilli (AFB).	DIAGNOSIS-Erythema Nodosum Necroticans TREATMENT-Multibacillary (MB) multi-drug therapy.	-Lesions subsided in next two months after initiation of treatment. - Recurrence not seen during follow up.
Nazeeha Al Hayki et al. [5]	44 Years/ Male	c/o severe tendor skin lesions in whole body including face , hyperthermia along with postinflammatory hyperpigmentation ,bony tenderness, myalgia, arthralgia and malaise.	-H/o Diabetes(+) -No H/O any neurological defecit or chronic skin lesions in past. - Misdiagnosed as Sweet's	-Numerous red painful nodules and necrosed lesions of various sizes. -Mostly showed flaccid blisters and sometimes bleed or discharge pus.	-Slit skin smear from the lesion showed Bacteriological index of 3. -Illdefined epithelioid granulomas along with few lepra cells also	DIAGNOSIS-Erythema Nodosum Necroticans TREATMENT-Multibacillary (MB) multi-drug therapy , prednisolone, Thalidomide, Azathioprine	-Lesions subsided and no evidence of recurrence.

			syndrome in past and received steroids.	-Mildly swollen and painful joints -Nerves thickening (+) -ESR and CRP raised.	seen . -Diffuse inflammatory cells mainly neutrophils and lymphocytes along with few eosinophils around blood vessels. -Fite stain shows numerous acid fast organisms		
Dhillon K S et al. [6]	36 Years/ Female	c/o various erythematous , elevated tendor lesions all over body from past 8 months along with hyperthermia, arthralgia	No H/O leprosy, tuberculosis, or any chronic illness in past or in any family member.	-Multiple erythematous tender nodules and plaques varying sizes(+). -Temperature sensation was lost -Nerves thickening (+) -Low Hb, neutrophilic leukocytosis with raised ESR and CRP.	-Slit skin smear from the lesion showed Bacteriological index of 5+. Illdefined epithelioid granulomas along with lepra cells . -Diffuse inflammatory cells mainly neutrophils.	DIAGNOSIS-Erythema Nodosum Necroticans TREATMENT-Multibacillary (MB) multi-drug therapy , prednisolone, clofazimine	Lesions subsided
Anila Sunandini et al. [7]	40 Years/ Male	c/o numerous ulcers on both extremities for last 10 days.	-H/O MB-MDT treatment from past 2 years. -H/O recurrent episodes of evelated erythematous nodular lesions associated with hyperthermia.	-Numerous well defined superficial ulcers, varying from 1-4 cm with dry necrotic floor and mobile base. - Hyperpigmentation (+) -Decreased sensations, bilateral nerve thickening and tenderness (+) - Low Hb, neutrophilic leukocytosis with raised ESR	-Slit skin smear from the lesion showed Bacili in granular form. -Biopsy revealed orthokeratosis, flattened rete ridges, dermis showed numerous infiltrate of neutrophils, lymphocytes and rarely histiocytes.	DIAGNOSIS-Erythema Nodosum Necroticans TREATMENT-Chloroquine,Thalidomide and oral prednisolone	-Ulcers healed. -No evidence of recurrence.
Mehta N et al. [8]	27 Years/ Male	Numerous erythematous papules and ulcerative nodules along with hyperthermia, pedal edema and athralgia.	-	-	-Slit skin smear from the lesion showed Bacili in granular form. -Biopsy showed superficial dermis showing dense focal perivascular infiltrate of macrophages , lymphocytes and few neutrophils with edema	DIAGNOSIS-Erythema Nodosum Necroticans TREATMENT-Thalidomide and oral prednisolone	Ulcers healed.
Aggarwal S et al. {Index patient }	40 Years/ Female	c/o -multiple painful pus filled elevated skin lesion X 1 year	-No H/O leprosy, tuberculosis, or any	-Multiple turbid fluid filled vesicles and bullae of size varying from 0.5 x	-Pus fluid (cytology)-Tzank smear showed mainly	DIAGNOSIS-Erythema Nodosum Necroticans TREATMENT-	Currenly on treatment

		- multiple painful raw crusted areas all over the body X 1 year	chronic illness in past or in any family member.	0.5 cm to 3 x 4 cms, generalized in distribution. -No significant loss of sensation or nerve thickening. -Low hemoglobin	degenerated inflammatory cells, predominantly neutrophils. -Slit skin smear examination for acid fast bacilli showed a Bacteriological Index of 4+, Morphological Index being 40%. -Biopsy showed presence of grenz zone in patch areas. Beneath the zone superficial dermis show dense diffuse infiltrate of foamy histiocytes. -Presence of superficial and deep perivascular and periadnexal infiltrates of foam cells along with leukocytoclastic vasculitis. Repeat stain of leprae bacilli showed presence of scattered fragmented granular bacilli within foam cells	Multibacillary (MB) multi-drug therapy.	

CONCLUSION

The diagnosis of Erythema Nodosum Necroticans can be challenging in cases presenting for the first time. This case emphasizes on the role of histopathology and histochemistry in reaching the final diagnosis. An early diagnosis is essential for optimal management of the underlying disease, thus a detailed medical history, physical examination, laboratory tests , imaging studies and microscopic evaluation must be performed to avoid delay in the diagnosis and resulting morbidity.

REFERENCES

1. Sharma N, Koranne RV, Mendiratta V, Sharma RC. (2004): A study of leprosy reactions in a tertiary hospital in Delhi. The Journal of dermatology. 2004 Nov;31(11):898-903.
2. Verma KK, Pandhi RK. Necrotic erythema nodosum leprosum; a presenting manifestation of lepromatous leprosy. INTERNATIONAL JOURNAL OF LEPROSY AND OTHER MYCOBACTERIAL DISEASES. 1993 Jun 1;61:293-.
3. Kumar B, Kar HK. IAL textbook of leprosy. Jaypee Brothers Medical Publishers; 2015.
4. Pandhi D, Mehta S, Agrawal S, Singal A. Erythema nodosum leprosum necroticans in a child-an unusual manifestation. International journal of leprosy and other mycobacterial diseases. 2005 Jun 1;73(2):122.
5. Al Hayki N, Al-Mahmoud B. Erythema necroticans: a presenting manifestation of silent leprosy. Journal of the Saudi Society of Dermatology & Dermatologic Surgery. 2011 Jul 1;15(2):63-6.
6. DHILLON, K S et al. Erythema necroticans: a rare reaction pattern in leprosy. **International Journal of Advances in Medicine**, [S.l.], v. 2, n. 2, p. 185-187, feb. 2017. ISSN 2349-3933.
7. Sunandini A. Type 2 lepra reaction with ulceration (erythema necroticans) a case report. Journal of Evolution of Medical and Dental Sciences. 2015 Feb 19;4(15):2630-5.
8. Mehta N, Ramachandran R, Srikanth S. Erythema Necroticans-A Case Report. Indian Journal of Leprosy. 2016 Sep 1;87(4):255-7.

9. Nur Z, Mohammed FR, Chowdhury MH, Shams MZ, Alam MB, Ahasan HN. Steroid dependent ulcerated erythema nodosum leprosum 16 years after successful treatment of leprosy. Journal of Medicine. 2009;10(1):31-3.

CITATION OF THIS ARTICLE

S Aggarwal , S Bhagat , S Satpathi , S Mahajan, N Bansal , R Sen. Erythema Nodosum Necroticans : Review Article and A Case Report. Bull. Env.Pharmacol. Life Sci., Spl Issue [4]: 2022: 168-173