

## CASE OF THE MONTH

# Erythema Nodosum Leprosum as a Rare and Challenging Cause of Pyrexia of Unknown Origin

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## Abstract

A 30-year old male presented with fever for last 1 year. There were associated multiple painful skin eruptions with hyperpigmentation and scaling over whole body which had been progressively increasing. He also had anasarca along with generalized weakness. He presented to us in shock after an acute episode of gastroenteritis. After stabilization, he was evaluated for cause of fever. Routine fever workup (for typhoid, syphilis, malaria, filariasis, HIV, scrub typhus, leishmaniasis) was negative. CECT chest and abdomen revealed hepatosplenomegaly. There was no response to intravenous (IV) antibiotics and anti-fungal medications. Slit skin smears revealed 3+ acid fast bacilli (AFB). Skin biopsy revealed fragmented acid-fast bacilli with dense collection of neutrophils and foamy histiocytes in upper and middle dermis suggestive of Erythema Nodosum Leprosum (ENL). A diagnosis of ENL with lepromatous leprosy was made and patient started on steroids and thalidomide and subsequently on multidrug therapy (MDT). On therapy, patient's symptoms improved, and skin lesions resolved. Though Leprosy itself is a well-known common cause of PUO in India, its first presentation as ENL is rare and needs good index of suspicion and timely management.

## Case Report

A 30-year old male, resident of western UP, shopkeeper by profession, presented with complaints of fever for more than a year. Fever was intermittent, high grade (up to 103-degree F) that lasted for 2-3 days, then resolved spontaneously only to recur after 7-8 days. It was associated with multiple painful skin eruptions over whole body (Figures 1-4). These lesions used to resolve with some unknown medication. This continued for 6 months, when patient started developing non-pitting edema of bilateral lower limbs. Around a month before presentation, patient developed hyperpigmentation of face (Figure 1), abdomen (Figure 2) and extremities along with swelling of bilateral upper limbs. He also developed severe generalized weakness so much so that he could not walk out of house without support. Patient presented to us with acute gastroenteritis and shock.

On presentation, patient was in

congestion was present. There was no pallor, icterus or any lymphadenopathy.



**Fig. 1:** Induration in ear lobe [white arrowhead] and forehead [black arrow], along with patchy hyperpigmentation over neck [black arrowhead]. Slit skin smear was taken from earlobes and forehead



**Fig. 2:** Generalized abdominal distension with patchy hyperpigmentation [black arrow] involving whole abdomen

shock with a blood pressure (BP) of 65/36 milli-meter of mercury (mm Hg), with a heart rate of 140/min and a respiratory rate of 20/min. His shock responded to IV fluids and BP improved to 90/50 mm Hg and heart rate was 110/min after fluid resuscitation. General physical examination revealed anasarca, with multiple erythematous to hyperpigmented skin eruptions involving trunk and extremities. Some lesions were thin and atrophic with presence of scaling. Induration was present in forehead and bilateral ear lobes. Left ulnar nerve was thickened, non-tender. Bilateral common peroneal nerves were tender. Mild focal hyperalgesia was present over trunk and extremities. However, there were no motor deficits. Nails in bilateral hands and feet had features suggestive of onychomycosis. Conjunctival



**Fig. 3: Lower limbs had non-pitting edema with extensive scaling [black arrow] and patchy hyperpigmentation [white arrow]**

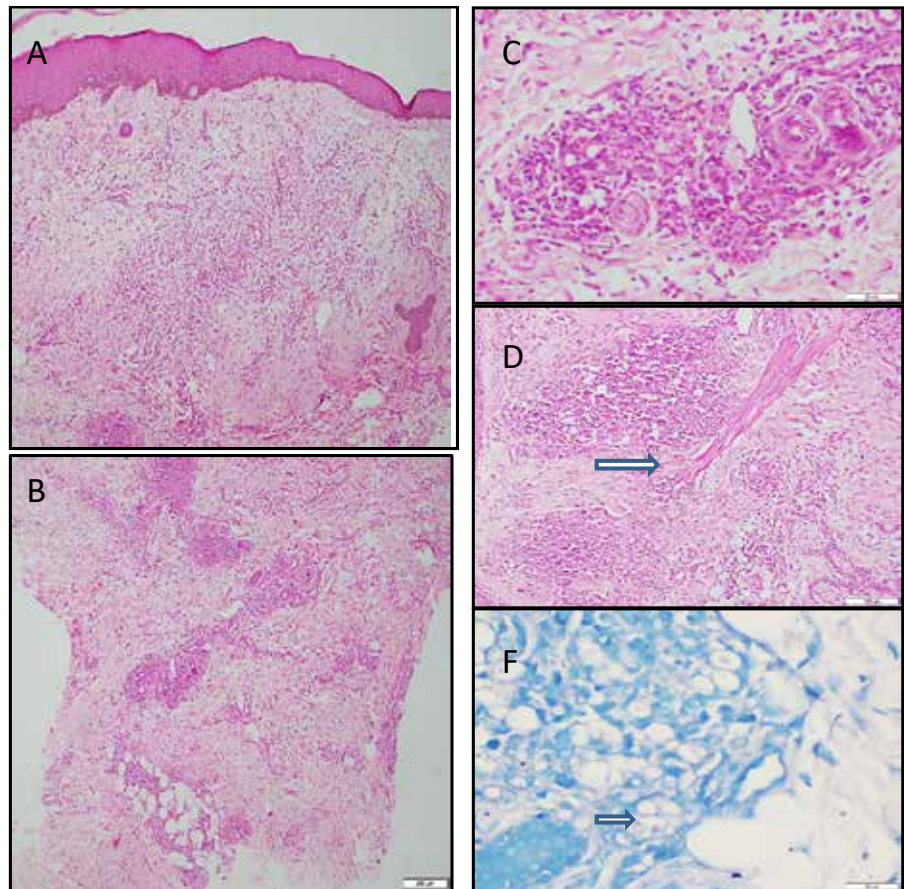


**Fig. 4: Gross swelling of upper extremity with scaling and induration of skin [black arrow]. Features suggestive of severe onychomycosis involving all nails were also present [white arrow]**

**Table 1: Investigations**

Test	At admission	At follow up
Hb (gm/dl)	8.8 (Normocytic normochromic)	12.1
Platelet count (per ml)	3,23,000	2,88,000
TLC (per ml)	18,000	6,700
ESR (mm/1 <sup>st</sup> hr)	60	28
Urea (mg/dl)	29	21
Cr (mg/dl)	4.0	1.1
Calcium (mg/dl)	9.6	9
Phosphate (mg/dl)	4.6	4.5
Uric acid (mL/dl)	8.1	7.3
Na <sup>+</sup> (meq/dL)	119	144
K <sup>+</sup> (meq/dL)	3.2	4.2
Total Bilirubin (mg/dl)	1.6	1.1
AST (IU/mL)	19	30
ALT (IU/mL)	10	26
ALP (IU/mL)	255	128
Total protein (g/dl) -	4.5	6
Albumin (g/dl)	2.2	3.4

Abbreviations: \*cells/ml-cells per millimeter cube (milliliter); \*mg/dL- milli gram per deciliter; \*g/dL- gram per deciliter; \*meq/dL- milliequivalents per deciliter; \*IU/mL- international units per millilitre, TLC -Total Leucocyte Count, AST - Aspartate transaminase, ALT - Alanine transaminase



**Fig. 5: Erythema nodosum leprosum reaction: (A) Upper dermal mixed inflammatory infiltrate with dermal edema. (B) The inflammation is extending in to the subcutaneous fat. (C) Prominent peri-neural and peri-adnexal inflammation rich in neutrophils. (D) Inflammation is involving the erector pili muscle [Arrow]. (E) Acid fast stain, reveals few fragmented bacilli within the macrophages [Arrow]**

Abdominal examination revealed mild splenomegaly. Rest of the systemic examination was unremarkable.

Lab findings revealed microcytic hypochromic anemia with a haemoglobin of 8.8 g/dl, along with leukocytosis with TLC of 18000/cu mm with presence of toxic granules (Table 1). Erythrocyte Sedimentation Rate (ESR) was raised. Patient had acute kidney injury (AKI) on presentation with a serum creatinine of 4.0 mg/dl which came back to normal in 3 days. However, patient had persistent hyponatremia along with borderline hypokalaemia. Hypoalbuminemia (2.2 gm/dl) was also present. Blood and urine cultures were sterile. Serum procalcitonin was raised to 41ng/mL. Chest X-ray was normal. Contrast Enhanced Computed Tomography (CECT) chest and abdomen revealed hepatosplenomegaly but no other abnormality (Table 2).

Routine fever workup (for typhoid,

syphilis, chronic malaria, filariasis, HIV, scrub typhus, leishmaniasis) was negative. Patient was empirically started on broad spectrum antibiotics with a possibility of gastrointestinal sepsis. Even after resolution of gastroenteritis, fever persisted with no improvement in skin lesions. Blood for fungal cultures was sterile. Serology for aspergillus and histoplasma were also negative. Serum galactomannan was positive (1.36). Despite rK39 antigen being negative, in view of long duration of fever associated with hyperpigmentation and hepatosplenomegaly, kala azar was kept a strong possibility. In view of this, patient was started empirically on injection liposomal amphotericin B, but there was neither any symptomatic improvement, nor resolution of skin lesions.

Fundus examination revealed bilateral steroid induced posterior subcapsular cataract, further strengthening our suspicion of chronic steroid use. Due to the presence





**Figs. 6,7,8: Follow up images showing resolution of skin lesions post treatment**

of hyperpigmentation along with hyponatremia in a chronic diseased state, with presentation in shock, adrenal insufficiency was suspected; however, serum cortisol and ACTH levels came out to be normal. Anemia workup was suggestive of anemia of chronic disease.

Slit skin smears were prepared from ear lobules, forehead and back, which revealed 3+ acid fast bacilli. Skin biopsy (Figure 5) revealed fragmented AFB with dense collection of neutrophils and foamy histiocytes in upper and middle dermis suggestive of Erythema Nodosum Leprosum (ENL).

A final diagnosis of ENL with lepromatous leprosy was made and patient was started on steroids and thalidomide followed by multidrug therapy (MDT) for leprosy comprising rifampicin, clofazimine and dapsone, on which his skin lesions improved. His fever completely resolved, and anasarca markedly decreased, along with an improvement in general well-being within a week of onset of therapy. Hyponatremia and hypokalaemia also improved with treatment. At 2-month follow-up, skin lesions had resolved completely (Figures 6, 7, 8).

## Discussion

Since pyrexia of unknown origin (PUO) was first defined by Petersdorf and Beeson more than 5 decades ago, the definition has subsequently evolved with advancement in medicine as well as greater availability of resources. PUO was initially defined as an illness of more than 3-week duration with fever > 38.3-degree C (101° F) documented on at least 2 occasions, whose diagnosis could not be determined despite 1 week of extensive in-patient evaluation. However, the current definition of PUO further includes ruling out immunocompromised state

and performing general microbiological and imaging investigations before classifying any fever as PUO.<sup>1</sup>

Erythema nodosum leprosum is a Type 2 lepra reaction, seen in patients with lepromatous end of spectrum of leprosy. It is characterised by crops of painful erythematous nodules on limbs but may involve whole body. Other features include neuritis, anemia, fever, lymphadenopathy, orchitis, uveitis and glomerulonephritis.

As per official estimates, prevalence of leprosy in India is 0.66/10,000 population, with an Annual New Case Detection Rate (ANCDR) of 9.71 per 100,000 population.<sup>2</sup> ENL is known to occur in 5% of BL cases and 26% of LL cases.<sup>3</sup>

Leprosy (Hansen's disease) is a chronic infectious disease caused by the AFB, *Mycobacterium leprae*. It mainly affects skin and peripheral nerves, however, can also involve eyes, bones, testes and internal organs. The disease manifestation has a broad spectrum depending on host's immune status, varying from tuberculoid at one end to lepromatous at the other end of the spectrum.

Erythema nodosum leprosum, aka Type 2 lepra reaction, is an immune complex reaction usually seen in patients with lepromatous end of the spectrum. It is characterized by crops of multiple painful erythematous lesions that may last for a few days, but frequently recur. Systemic manifestations include fever, malaise, neuritis, arthritis, orchitis and lymphadenitis.<sup>4</sup> Hepatosplenomegaly may be present. Skin biopsy reveals an infiltrate of polymorphonuclear leukocytes over a background of chronic inflammation and dense collection of acid fast bacilli (*M. leprae*).

In our patient, clinical presentation was different from classic ENL presentation in that fever and skin

lesions were of very long duration. Also, skin lesions were not similar to those seen in classical ENL. There was patchy hyperpigmentation along with scaling over whole body. This could be attributable to chronic topical steroid use. Possibility of chronic fungal skin infection was also there which was supported by the presence of hyperpigmentation and severe onychomycosis in nails of both hands and feet. Nail changes are frequently encountered in patients with leprosy. Kaur et al and others have observed that onychomycosis is associated in 5 percent of these patients.<sup>5,6</sup> The fungal infection of nails might be due to spread of superficial dermatophytic infection, or caused by another fungus, like *Candida albicans*. Serum precipitins for aspergillus was negative on initial evaluation. However, serum galactomannan had come back positive. This might be due to false positivity of serum galactomannan assay. With regards to the long duration of fever, it is highly likely that this patient would have received antibiotics like amoxicillin-clavulanate which can explain the positive galactomannan assay.<sup>7</sup> Also, systemic fungal infection would have responded to amphotericin B that the patient had initially received. Patient's anemia was attributable to the presence of chronic diseased state. The generalized weakness is explained by anemia, and the fact that malaise is a known feature of ENL. His acute worsening in weakness might be attributable to borderline hypokalemia, which also got corrected with therapy.

Voorend et al have shown that ENL most commonly occurs during first year of MDT. However, Kumar et al have analysed Indian data and found that here ENL has maximum incidence during second year of MDT. ENL is rarely the presenting feature of leprosy. ENL presenting as PUO is an even rarer

**Table 2: Fever Work-up**

Investigations	Patient Value
X-ray Chest	Normal
Ultrasound abdomen	Mild hepatosplenomegaly
HIV 4 <sup>th</sup> Generation assay- rK39	Non-reactive Negative
Blood Cultures	Negative
CECT Chest and abdomen	Mild hepatosplenomegaly
HBsAg	Negative
Anti-HCV	Negative

entity. ENL is known to present in myriad atypical clinical manifestations. These include necrotic, hemorrhagic, pustular and bullous lesions.<sup>8,9</sup> Histopathological examination and detection of acid fast bacilli in skin lesions leads to definitive diagnosis and rules out other clinical mimics. These findings also highlight the need to have strong clinical suspicion for this disease, failing which a delay in diagnosis is likely, as was the case with our patient.

### Conclusion

This case was a diagnostic challenge because of rarity of erythema nodosum leprosum presenting as PUO. On searching “Erythema nodosum leprosum” and “pyrexia of unknown origin” in PubMed database, only 2 case reports were found.<sup>10,11</sup> Definite cause is found in only 50% of PUO cases. Rest remain undiagnosed with only symptomatic treatment being prescribed. Routine fever or fever with hepatosplenomegaly workup usually does not include leprosy/lepra reaction because of its low prevalence as well as classical clinical features of skin and nerve involvement. This case reinforces the need to consider leprosy and its reactions in cases of PUO with skin lesions that may not be like those as mentioned in classical teachings.

### References

1. Kasper D, Fauci A, Hauser S. Harrison's principles of internal medicine. 19th ed. New York: McGraw Hill Education; 2015.

135 p.

2. National Leprosy Eradication Programme - Annual Report 2015-2016. Directorate General of Health Services Ministry of Health and Family Welfare Government of India.
3. Voorend CGN, Post EB. A systematic review on the epidemiological data of erythema nodosumleprosum, a type 2 leprosy reaction. *PLoS Negl Trop Dis* 2013;7(10):e2440.
4. Meyerson MS. Erythema nodosumleprosum. *Int J Dermatol* 1996; 35:389-92.
5. Kaur I, Chakrabarti A, Dogra S, Rai R, Kumar B. Nail involvement in leprosy: a study of 300 patients. *Int J Lepr Mycobact Dis Off Organ Int Lepr Assoc* 2003; 71:320-7.
6. Ramesh V, Misra RS. Nail changes in leprosy and recognition of fungal nail infection. *Indian J Lepr* 1987; 59:360-1.
7. Ansorg R, van den Boom R, Rath PM. Detection of Aspergillusgalactomannan antigen in foods and antibiotics. *Mycoses* 1997; 40:353-7.
8. Vijendran P, Verma R, Vasudevan B, Mitra D, Badad A, Neema S. Rare atypical presentations in Type 2 lepra reaction: a case series. *Int J Dermatol* 2014; 53:323-6.
9. Bakshi N, Rao S, Batra R. Bullous ErythemaNodosumLeprosom as the First Manifestation of Multibacillary Leprosy: A Rare Phenomenon. *Am J Dermatopathol* 2017; 39:857-9.
10. Reghukumar A, Gurudas A, Kumar V, Ravi R. Erythema nodosumleprosum presenting as pyrexia of unknown origin. *BMC Infect Dis* 2014; 14(Suppl 3):P69.
11. Vinod KV, Chandramohan R, Dutta TK, Rajesh NG, Basu D. Type 2 lepra reaction as a cause of pyrexia of unknown origin. *J Assoc Physicians India* 2012; 60:70-2.