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Case Report

De-Novo Erythema Nodosum Leprosum Necroticans Mimicking Cutaneous Necrotizing Vasculitis

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Abstract

Lepra reactions are events with acute intense tissue damage in an otherwise chronic course of leprosy. Type 2 lepra reaction can present with cutaneous features, classical lesions being erythema nodosum leprosum (ENL) and its variants, and/or rheumatological features with polyarthralgia and arthritis along with systemic involvement. The ulceronecrotic variant of ENL is a marker of severe reaction and can mimic other etiologies of cutaneous vasculitides. We present a case of a young female presenting with diffuse scarring ulcers with severe constitutional symptoms, raised cytoplasmic-antineutrophil cytoplasmic antibodies (c-ANCA), mimicking necrotizing vasculitis in the absence of overt cutaneous features of leprosy, later diagnosed as ENL necroticans by a slit skin smear.

Keywords: Necrotic erythema nodosum leprosum, immune complex, vasculitis, immunopathogenesis, ANCA

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Introduction

Leprosy is a neglected tropical disease caused by *Mycobacterium leprae*. The course of this disease is often punctuated by reactions which occur due to the interplay between the bacilli and host immunity.[1] Delays in the identification of cases of leprosy and lepra reactions can accelerate dermatological, neurological, and systemic complications.

Case Presentation

A 29-year-old para-2 female with no known comorbidity presented with recurrent episodes of high-grade fever, painful red-raised lesions over the body, multiple joint pains, and swelling of hands and feet of 5 months duration. A diurnal pattern of fever was noted predominantly with an evening rise of temperature, accompanied by crops of red-raised painful lesions that used to rupture spontaneously, forming painful ulcers that healed with scarring over 3 to 4 weeks. There was no history of cough, hemoptysis, weight loss, early morning stiffness in joints, deformities, oral ulcers, photosensitivity, Raynaud's phenomenon, epistaxis, neurological deficit, oliguria, frothy urine, or hematuria. On clinical examination, she had tachycardia (124 beats per minute), fever (103^{0}F), pallor, pitting edema of the hands and feet, and bilateral axillary and inguinal lymphadenopathy. Systemic examination was normal. Dermatological examination revealed generalized involvement of the body with multiple polysized ulcers with thick-adherent-yellow to black necrotic crusts, as well as atrophic and hypertrophic scars with relative sparing of the scalp, palms, soles, and intertriginous sites (Figure 1A-C). There were no thickened or tender peripheral nerve trunks, sensory-motor neurological deficits, or deformities. Our clinical differentials were medium-vessel vasculitis, papulo-necrotic tuberculosis, lues maligna (secondary syphilis), ulcerative conditions in leprosy—necrotic ENL, Lazarine leprosy, and Lucio phenomenon—systemic lupus erythematosus (SLE), and sarcoidosis. Investigations revealed microcytic hypochromic anemia (Hb-6.5 g/dL), neutrophilic leukocytosis (15 900/mm^3 with 85% polymorphs), raised ESR (60 mm in 1st hour), and trace proteinuria. Peripheral blood smear revealed a microcytic hypochromic anemia with no evidence of hemolysis. Direct Coombs test was negative. Serum iron studies confirmed an iron deficiency anemia. A 24-hour urine sample showed subnephrotic proteinuria. However, urea, creatinine, serum bilirubin were within normal limits. ELISA for HIV, HBsAg, Anti HCV, VDRL, TPHA, serum angiotensin-converting enzyme (ACE), alkaline phosphatase, and electrolytes were within normal limits. Induced sputum for acid-fast bacilli, Mantoux test, and CBNAAT (Genexpert) were negative. Autoimmune workup revealed negative anti-nuclear antibody (ANA) by indirect immunofluorescence and rheumatoid factor, but a raised CRP (54 mg/dL), raised c-ANCA level at

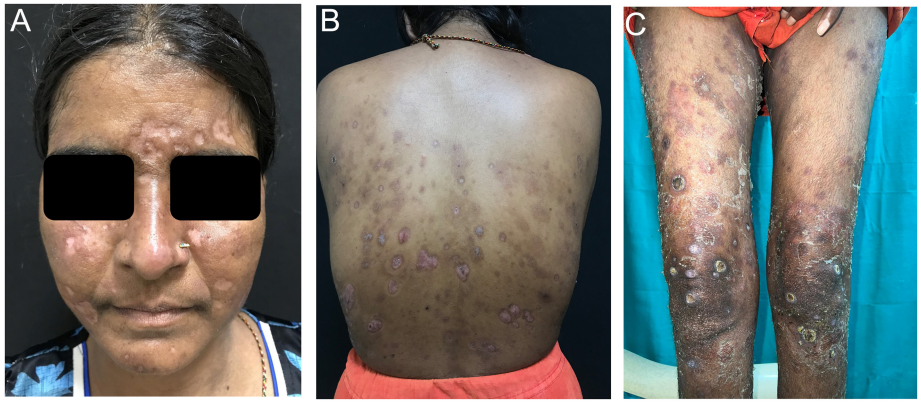

Figure 1. A-C: Generalized involvement of the body with numerous polysized crusted ulcers in various stages of evolution, with most showing atrophic scarring.

41.92 U/mL (normal <20) and normal p-ANCA (0.8 U/mL). C3 and C4 were low C3 (23 and 9 mg/dL, respectively). Contrast-enhanced chest and abdomen computed tomography (CT) showed splenomegaly with enlarged necrotic bilateral axillary, inguinal, external iliac, left obturator, and right common iliac lymph nodes. (Figure 2A-C) Nerve conduction studies recorded an axonal sensorimotor neuropathy involving bilateral ulnar nerves. The diagnosis was clinched by a slit skin smear (SSS) which showed numerous rod-shaped acid-fast bacilli with a bacillary index of 6+. Histopathological examination of the lesional biopsy was consistent with Hansen's disease with type 2 lepra reaction with findings of epidermal atrophy, grenz zone, moderate perivascular and peri-adnexal mixed inflammatory infiltrate comprising numerous neutrophils, lymphocytes, and monocytes with focal vasculitis (Figure 3A). Axillary lymph node biopsy showed features of necrotizing granulomatous lymphadenitis. (Figure 3B) Based on the above findings, our patient was diagnosed as a case of Hansen's disease lepromatous leprosy in type 2 reaction manifesting as severe necrotic ENL reaction. For anemia, she was administered packed RBC transfusion. She was started on multibacillary multi-drug therapy (MDT) consisting of dapsone, clofazimine, and rifampicin with tapering doses of prednisolone 1.5 mg/kg/day, thalidomide 100 mg QID for type 2 lepra reaction. Fever and appearance of new skin lesions subsided in 3 days. Lymphadenopathy and proteinuria resolved over a fortnight. Prednisolone and thalidomide were tapered over next 4 months and MDT was continued for a year. The patient is on regular follow-up and is asymptomatic with no recurrence of type 2 lepra reaction.

Written informed consent was obtained from the patient who participated in this study.

Discussion

Three types of hypersensitivity reactions are described in leprosy: type 1 or reversal reaction presenting in the borderline spectrum of the Ridley Jopling classification, type 2 (also known as ENL), and type 3 (Lucio phenomenon) lepra reactions occurring in the anergic lepromatous spectrum.[2] The classical cutaneous lesions in type 2 Lepra reactions (T2LR)/ENL were first described by a Japanese

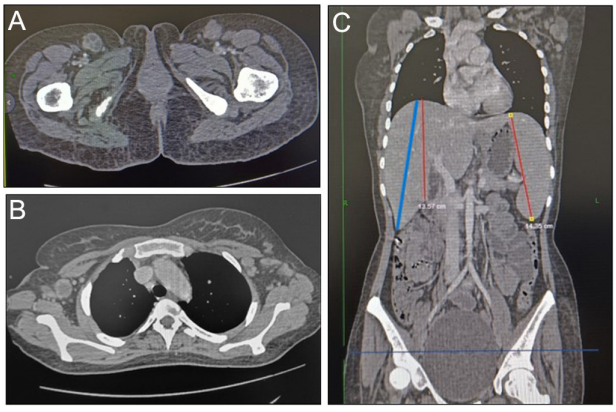

Figure 2. A: Axial section on contrast-enhanced computed tomography of the chest show bilateral enlarged necrotic axillary lymph nodes measuring 17 mm on the right and 20 mm on the left side; B: Bilateral inguinal necrotic lymph nodes are seen largest measuring 17 mm on the right side; C: Coronal section shows splenomegaly of 14 cm.

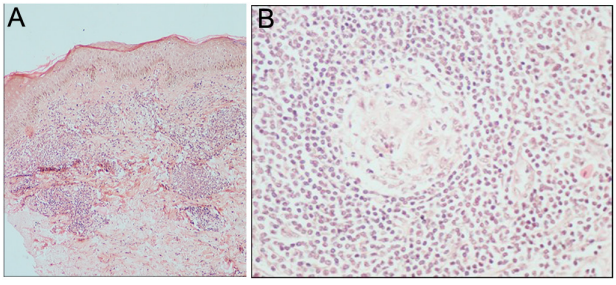

Figure 3. A: Histopathology on the skin specimen from the ulcers show epidermal atrophy, blunting of rete ridges, dermal grenz zone, dermal peri adnexal and perivascular mixed infiltrate, focal vasculitis (×20; H&E). B: Section from left axillary lymph node shows effacement of architecture, numerous non-confluent well-formed epithelioid cell granulomas, numerous foci of necrosis and multinucleated giant cells suggestive of granulomatous vasculitis of the lymph nodes (×40; H&E).

Main Points

- Type 2 reactions in leprosy is seen in heavily infected cases (lepromatous pole) and is characterized by fever, joint pains (arthralgia) or arthritis, myalgia with crops of recurrent nodular eruptions over body known as erythema nodosum leprosum (ENL)
- Rarely in severe type 2 reactions, the ENL lesions can be necrotic or bullous.
- Patients in type 2 reactions can mimic vasculitis and can be rheumatoid factor, ANA, cANCA and pANCA positive leading to misdiagnosis of connective tissue disease and vasculitides.
- A simple slit skin smear for Ziehl Neelsen stain for acid fast bacilli (Mycobacterium leprae) cab clinch the diagnosis of Leprosy.

leprologist, Murrata in 1912.[3] In severe forms of the reaction, variants of ENL—bullous, hemorrhagic, pustular, erythema-multiforme-like, Sweet syndrome-like, and ulceronecrotic (Verma and Pandhi, 1993)—can be seen.[4] Type 2 Lepra reactions usually present around 6 months after starting MDT, but may be the presenting feature in one-third of the patients as in our patient, or even years after completion of MDT due to the persistence of antigens. Here, since the immunity targets bacillary antigens infiltrating multiple organs, a systemic response in the form of prominent constitutional symptoms is seen. Basic underlying mechanisms include immune complex deposition and a shift of immunity from a TH2 to TH1 and TH17 response. Multiple immune axes are at play, including genetic determinants (protective role of TLR1 and susceptibility conferred by NOD 2 genes), upregulation of CD64 and IL-10R1-positive neutrophils, basophils, increased CD4: CD8 ratio, elevated IgG1-secreting B cells, increased circulating IFN-γ, TNF-α, IL-1β, IL-6, IL-7, IL-17, and chemokines such as CCL2, 3, 5, and 11.[5] Due to probable cross-reactivity between mycobacterial antigens and human DNA and polyclonal B cell activation, various autoantibodies can be expressed in leprosy: rheumatoid factor (RF) (most common), ANA (speckled pattern, present in ~30% of patients), anti-SS-B, antimitochondrial, antithyroglobulin, and p-ANCA >> c-ANCA.[6] There are some plausible theories explaining the presence of serological autoantibodies in leprosy. *M. leprae* infects hosts through the mucosa of upper respiratory tract and then binds to the G domain in Schwann cells. Schwann cells can then process and present the antigen to antigen-specific T lymphocytes and trigger immune responses. A similar case was reported by Yu *et al* where the patient presented with recurrent nodules associated with fever and was associated with p-ANCA.[7] Manoj *et al* reported a case presenting with symmetrical polyarthritis of small and large joints with correctable swan-neck deformities, rheumatoid factor positive mimicking rheumatoid vasculitis but turned out to be leprosy.[8] Other authors have reported leprosy presenting as leukocytoclastic vasculitis and cryoglobulinemic vasculitis.[9,10] The overlapping clinical presentation between different autoimmune and infectious conditions, especially in the presence of autoantibodies, can pose a diagnostic challenge. The recurrent ulceronecrotic lesions with fever and constitutional symptoms in the absence of cardinal cutaneous and neurological features of leprosy with c-ANCA positivity proved to be the red herring in our case, which was resolved by a test as simple as ZN stain on an SSS specimen. Delays in diagnosis and treatment can accelerate neuronal damage and systemic involvement and lead to complications such as chronic kidney disease leading to end-stage renal disease (the most common cause of mortality), secondary infections, and sepsis leading to death. Despite the atypical presentation, we could diagnose this patient due to strong clinical suspicion preventing further delay and potential complications by early institution of therapy.

Infections are a vasculitic mimic. Infectious etiologies of vasculitic lesions should always be looked for, especially in tropical countries.

Data Availability Statement: The data that support the findings of this study are openly available in [repository name] at http://doi.org/[doi], reference number [reference number].

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – P.D., S.S., A.W.K., B.V., V.K., A.B., K.L.P., V.G., R.T., N.B., A.M., N.K.D., Data Collection and/or Processing – P.D., S.S., A.W.K., N.B., A.M., N.K.D., Writing Manuscript – P.D., S.S., A.B., K.L.P., V.G., R.T., N.B., A.M., N.K.D., Critical Review – A.W.K., B.V., V.K., A.B., K.L.P., V.G., R.T.

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Declaration of Interests: The authors have no conflict of interest to declare.

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