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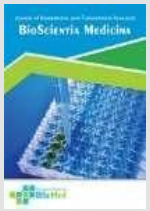

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The Silent Saboteur: Chronic Refractory Erythema Nodosum Leprosum Perpetuated by Neglected Odontogenic Foci in a Post-RFT Borderline Lepromatous Patient

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A B S T R A C T

Background: Erythema nodosum leprosum (ENL) is a severe, immune-complex mediated complication of lepromatous leprosy that can manifest before, during, or after multidrug therapy (MDT). While the primary etiology involves the release of *Mycobacterium leprae* antigens, the chronicity of ENL is frequently driven by secondary, often occult, triggers. Focal infections, particularly of odontogenic origin, are frequently overlooked in standard dermatological assessments, leading to refractory clinical courses. **Case presentation:** We report the case of a 32-year-old male with a history of borderline lepromatous (BL) leprosy who had achieved release from treatment (RFT). The patient presented with severe, chronic, and recurrent ENL characterized by painful erythematous nodules, high-grade fever, and acute neuritis, occurring more than one year post-RFT. Laboratory evaluation revealed significant inflammatory markers, including a C-Reactive Protein level of 172.7 mg/L and leukocytosis. Crucially, intraoral examination identified neglected chronic dental caries (gangrene radix) and generalized periodontal inflammation. Despite medical advice, the patient refused dental intervention. The reactional state was managed with a combination of intravenous methylprednisolone and high-dose oral clofazimine. While cutaneous symptoms improved, the persistence of the focal infection poses a substantial risk for further recurrence. **Conclusion:** This case highlights the critical and often underestimated role of odontogenic focal infections as perpetuating factors in chronic ENL. It underscores the necessity for a multidisciplinary approach integrating dentistry and dermatology. We propose that recalcitrant ENL in post-RFT patients should trigger mandatory screening for occult dental infections to disrupt the cycle of systemic inflammation.

1. Introduction

Leprosy, historically known as Morbus Hansen, remains one of humanity's oldest and most enigmatic afflictions.[1] Despite the success of the World Health Organization's (WHO) global elimination campaigns and the widespread implementation of multidrug therapy (MDT) since the 1980s, the disease has not been relegated to the pages of history. Instead, it persists as a complex chronic granulomatous infection caused by *Mycobacterium leprae*, an obligate intracellular acid-fast bacillus with a unique predilection for the skin and peripheral nerves. While the bacteriological cure is achievable, the disease burden remains paradoxically high in specific endemic regions.[2] Recent epidemiological data indicates that over 200,000 new cases are detected annually, with the vast majority concentrated in India, Brazil, and Indonesia. In 2021 alone, nearly 140,594 new cases were reported globally, a statistic that underscores the limitations of current control strategies which focus primarily on antimicrobial coverage rather than the interruption of transmission or the management of

long-term immunological sequelae.[3]

The clinical spectrum of leprosy is dictated by the host's cell-mediated immune response, ranging from the localized tuberculoid (TT) form to the disseminated lepromatous (LL) form. It is within the multibacillary (MB) spectrum—specifically borderline lepromatous (BL) and lepromatous (LL) types—that the disease manifests its most volatile characteristics.[4] In these patients, the high bacterial load does not merely cause tissue damage through direct invasion; it sets the stage for turbulent immunological complications known as leprosy reactions. These reactions are the primary cause of irreversible nerve damage and permanent disability, transforming a curable infection into a lifelong burden of morbidity.

A critical challenge in contemporary leprosy management is not merely the clearance of bacilli, but the stabilization of the host's immune system. Among the complications encountered, erythema nodosum leprosum (ENL), or Type 2 reaction, stands out as a debilitating, immune-complex-mediated systemic vasculitis. ENL typically strikes patients with a high bacterial index, occurring in up to 50% of LL cases and 10-30% of BL cases. Unlike the slow progression of the primary disease, ENL is clinically explosive. It is characterized by the sudden eruption of crops of tender, erythematous nodules that may ulcerate or become necrotic, frequently accompanied by profound systemic symptoms including high-grade fever, malaise, arthralgia, acute neuritis, and iridocyclitis.[5]

While acute ENL may be self-limiting or responsive to short courses of corticosteroids, the natural history of the condition is often far more treacherous. A significant subset of patients transitions into a state of chronic or recurrent ENL. Chronic ENL is rigorously defined as reactional episodes occurring continuously for more than 24 weeks or requiring continuous immunosuppressive therapy to prevent relapse.[6] This chronicity creates a therapeutic entrapment for the clinician and patient alike. The management of chronic ENL necessitates the prolonged use of high-dose corticosteroids or thalidomide, exposing the patient to severe adverse effects ranging from hypertension and osteoporosis to potentially teratogenic consequences. The impact on quality of life is devastating; patients are often cured of the bacterial infection (Release from treatment, or RFT) yet remain shackled to a cycle of pain and immunosuppression that can last for years.

To understand the persistence of ENL, one must look closely at its immunopathogenesis. Classically, ENL is described as a Type III hypersensitivity reaction (Coombs and Gel classification). The abundance of *M. leprae* antigens in lepromatous patients leads to the formation of antigen-antibody immune complexes. These complexes deposit in the vascular endothelium of the skin, nerves, and visceral organs, triggering the complement cascade and recruiting neutrophils. The resulting release of lysosomal enzymes and reactive oxygen species causes the fibrinoid necrosis and vasculitis seen histopathologically.[7]

However, the immune complex theory alone does not fully explain the prolonged, chronic course of the disease observed in some individuals. Recent immunological research suggests a breakdown in the established Th1/Th2 paradigm. While lepromatous leprosy is traditionally associated with T-cell anergy (Th2 dominance), ENL episodes are marked by a sudden, transient restoration of cell-mediated immunity (Th1) and a surge in Th17 cell activity. This immunological shift results in a cytokine storm, characterized by elevated levels of tumor necrosis factor-alpha (TNF-α), Interleukin-6 (IL-6), and IL-1β. TNF-α, in particular, is the master regulator of this inflammatory cascade, driving the systemic toxicity and tissue damage. The question that plagues researchers and clinicians is: what sustains this cytokine storm long after the administration of effective multidrug therapy?

The transition from an acute, manageable reaction to a refractory, chronic condition suggests the presence of a perpetuating factor—a continuous source of antigenic stimulation or systemic inflammation. This has revitalized interest in the concept of focal infection within dermatology. The

focal infection theory posits that a localized, often asymptomatic, chronic infection in one part of the body can sustain systemic pathology elsewhere. In the context of ENL, if the primary load of *M. leprae* is being reduced by antibiotics, the persistence of inflammation may be driven by secondary triggers. Known triggers include physiological stress, pregnancy, and intercurrent infections such as malaria or helminthiasis. However, one anatomical site remains significantly under-investigated in routine leprosy care: the oral cavity.

The oral cavity is a complex ecosystem and a potential reservoir for systemic pathogens.[8] Odontogenic infections, comprising dental caries, pulpitis, chronic apical abscesses, and periodontitis, are potent sources of gram-negative anaerobic bacteria and pro-inflammatory mediators. The connection between oral health and leprosy is multifaceted. First, *Mycobacterium leprae* has a known biological affinity for the cooler regions of the body. The nasal and oral mucosae, particularly the hard palate (where temperatures average 27.4°C), are preferred sites for bacillary colonization and survival. Consequently, the oral cavity may act as a sanctuary site where antigens persist despite systemic therapy.

Second, chronic dental infections act as continuous cytokine factories. Inflamed periodontal tissues release significant quantities of TNF-α, IL-1β, and IL-6 into the systemic circulation. In a patient with lepromatous leprosy, whose immune system is already primed for reactivity, this additional cytokine load can lower the threshold for developing ENL. Recent studies have demonstrated a statistically significant correlation between the severity of dental caries and the occurrence of ENL, suggesting that patients with poor oral hygiene are predisposed to more severe and recalcitrant reactions. Furthermore, transient bacteremia resulting from chewing or oral hygiene practices in patients with oral infections can introduce bacterial antigens (from *Streptococcus mutans*) that may share molecular mimicry with *M. leprae* proteins, further confusing the immune system and perpetuating the hypersensitivity response.[9]

Despite the biological plausibility and emerging evidence linking oral health to leprosy reactions, dental screening is rarely integrated into the standard protocol for investigating refractory ENL in dermatological settings. The management of leprosy often occurs in silos; dermatologists focus on the cutaneous and neurological manifestations, while the oral cavity is neglected unless the patient complains of acute toothache. This clinical blind spot is critical. Patients with ENL often suffer from neglect and low socioeconomic status, factors that simultaneously predispose them to poor oral hygiene and delayed dental treatment. Consequently, a vicious cycle is established: the neglected tooth fuels the systemic reaction, the reaction necessitates steroids, and the steroids further suppress immunity and mask dental symptoms, leading to severe decay and chronic inflammation.[10]

Against this backdrop of immunological complexity and clinical compartmentalization, this manuscript presents a sophisticated investigation of a specific clinical phenotype: severe, chronic erythema nodosum leprosum in a borderline lepromatous patient who had already achieved release from treatment (RFT). The novelty of this study lies in its identification of a distinct, modifiable maintenance factor for chronic ENL in the post-MDT era. While most literature focuses on ENL during active treatment, this case highlights the silent saboteur of neglected odontogenic infection as the primary driver of recalcitrant symptoms in a cured patient. By detailing the clinical trajectory, the failure of standard immunosuppression in the face of focal infection, and the subsequent response to a combined regimen of methylprednisolone and clofazimine, we aim to bridge the gap between dermatology and dentistry. This study seeks to elucidate the mechanism of dental-associated ENL and provides a compelling argument for the mandatory inclusion of dental eradication protocols in the management of refractory leprosy reactions, ultimately proposing a paradigm shift towards a more holistic, multidisciplinary approach to this ancient disease.

2. Case Presentation

A 32-year-old male, of Javanese ethnicity and Indonesian nationality, presented to the Emergency Department of Prof. Dr. I.G.N.G. Ngoerah General Hospital on December 2024. The patient reported a chief complaint of multiple painful, reddish subcutaneous nodules scattered diffusely across his body.

The patient's medical history was significant for a diagnosis of borderline lepromatous (BL) leprosy established in September 2022. The initial presentation involved hypopigmented and erythematous plaques with anesthesia on the extremities. He was treated with the standard World Health Organization (WHO) Multidrug Therapy (MDT) for Multibacillary (MB) leprosy for 12 months and was declared Release from Treatment (RFT) in October 2023. The clinical course was complicated by recurrent episodes of ENL beginning in May 2023, during the MDT course, and persisting post-RFT. These episodes were managed intermittently with oral methylprednisolone and analgesics at peripheral health centers, often resulting in temporary symptomatic relief followed by rapid recurrence.

Four days prior to admission, the patient experienced an acute exacerbation of symptoms. He reported the sudden appearance of new, intensely painful nodules, accompanied by high-grade fever and localized swelling of the hands and feet. The pain was described as debilitating and throbbing, particularly over the distributions of the ulnar and tibial nerves. Systemic review was positive for fevers, malaise, and decreased appetite. Musculoskeletal review indicated arthralgia involving the left knee and ankle. Neurologically, the patient reported numbness persisting on the soles of the feet and occasional paresthesia in the hands. Notably, the patient reported a history of chronic dental pain and admitted to the presence of untreated dental caries (Table 1a).

On admission, the patient appeared severely ill with a Visual Analog Scale (VAS) pain score of 7/10. Vital signs revealed tachycardia (Pulse 100 bpm) and pyrexia (Temperature 38.3°C). Blood pressure was 120/70 mmHg and respiratory rate was 18 breaths per minute. On dermatological examination, inspection revealed a generalized distribution of lesions involving the face, anterior and posterior trunk, and bilateral upper and lower extremities. The morphology consisted of multiple erythematous, tender nodules, well-demarcated, varying in diameter from 1.0 to 1.5 cm. Several older lesions exhibited hyperpigmentation, indicating the chronicity of the condition. A solitary ulcer was noted on the left lateral malleolus, measuring 1x1x0.5 cm, presenting with a clean granular base, likely secondary to trauma on anesthetic skin or a ruptured ENL nodule. Bilateral pitting edema of the hands and feet was observed, consistent with severe ENL-associated acral edema. On neurological examination, palpation revealed thickening of the right and left Ulnar nerves and Tibial Posterior nerves. Tenderness on palpation was positive for the Tibial Posterior nerve, indicating active neuritis. Sensory function assessment via monofilament testing confirmed glove and stocking anesthesia. On dental examination, intraoral inspection revealed poor oral hygiene. Multiple deep caries compatible with gangrene radix were observed involving the mandibular molars. The gingival tissues appeared erythematous and edematous, consistent with chronic generalized gingivitis. Despite the clear presence of odontogenic infection, the patient expressed reluctance regarding dental extraction or intervention.

Laboratory investigations demonstrated a robust systemic inflammatory response. The Complete Blood Count showed leukocytosis (8.32 x 10^3/µL) with a neutrophilic shift (83%). Hemoglobin was decreased at 11.5 g/dL, with normocytic normochromic indices, suggestive of anemia of chronic disease. Biochemical analysis revealed a markedly elevated C-reactive protein (CRP) level of 172.7 mg/L (Reference <5 mg/L), confirming severe active inflammation. Albumin was slightly low at 3.0 g/dL.

Table 1a. Patient Profile and Physical Examination (Systemic & Cutaneous)

1. PATIENT PROFILE & HISTORY		
Demographics	32-year-old Male, Javanese, Married	*Endemic demographic context*
Leprosy Status	Borderline Lepromatous (BL); Release from Treatment (RFT) Oct 2023	*Post-MDT recurrence*
Chief Complaint	Multiple painful erythematous nodules, 4 days duration	*Acute exacerbation of ENL*
2. VITAL SIGNS		
Systemic State	Severely ill	*Systemic toxicity*
Temperature	**38.3°C** (Febrile)	*Active systemic inflammation*
Hemodynamics	HR: **100 bpm**; BP: 120/70 mmHg	*Tachycardia secondary to pain/fever*
3. DERMATOLOGICAL STATUS		
Lesion Morphology	Multiple erythematous, tender nodules (1–1.5 cm); Hyperpigmented macules	*Polymorphous ENL (Acute & Chronic)*
Distribution	Generalized (Face, Trunk, Extremities)	*Disseminated reaction*
Specific Lesions	Solitary ulcer (Left Lateral Malleolus); Bilateral Pitting Edema	*Vasculitic edema & trauma sequelae*

Table 1b. Specialized Examination (Neurological, Dental) and Laboratory Workup

1. NEUROLOGICAL STATUS		
Nerve Involvement	Thickening: **N. Ulnaris & N. Tibialis Posterior** (Bilateral)	*Peripheral nerve damage*
Neuritis	Tenderness (+) on N. Tibialis Posterior	*Active Neuritis*
Sensory Deficit	Glove and Stocking Anesthesia	*Advanced sensory neuropathy*
2. ODONTOGENIC SCREENING (FOCAL INFECTION)		
Oral Pathology	**Gangrene Radix** (Deep Caries); Chronic Gingivitis	*Potential cytokine reservoir*
Patient Behavior	Refusal of dental intervention	*Persistent trigger maintenance*
3. LABORATORY PROFILE		
Inflammatory Markers	CRP: **172.7 mg/L** (Normal <5)	*Severe immune activation*
Hematology	Leukocytes: 8.32 x 10^3/µL (Neutrophils 83%); Hb: 11.5 g/dL	*Neutrophilia & Anemia of Chronic Disease*
Bacteriology	Slit Skin Smear: Negative (0)	*Paucibacillary phase of reaction*

Abbreviations: RFT: Release from Treatment; ENL: Erythema Nodosum Leprosum; CRP: C-Reactive Protein; HR: Heart Rate; BP: Blood Pressure; Hb: Hemoglobin.

Bacteriological examination via slit skin smear from the earlobes performed on November 22nd, 2024, was negative for Acid-Fast Bacilli (AFB), consistent with the RFT status and the paucibacillary nature of the reactional phase (Table 1b). Based on the comprehensive clinical evaluation and the established criteria by Naafs et al., the patient's condition was categorized as a severe, chronic manifestation of erythema nodosum leprosum (ENL) superimposed on a background of Borderline Lepromatous (BL) leprosy. The diagnosis of severity was predicated on the presence of widespread, ulcerating erythematous nodules, high-grade fever, and acute neuritis affecting multiple peripheral nerves. Furthermore, the classification of chronic ENL was substantiated by the patient's history of recurrent reactional episodes persisting for more than 24 weeks, a clinical trajectory that is notoriously difficult to manage. Crucially, the diagnostic workup identified a significant comorbidity: chronic odontogenic infection manifesting as gangrene radix and chronic gingivitis. This finding was pivotal, as it represented a probable reservoir of systemic inflammation and a perpetuating trigger for the recalcitrant leprosy reaction.

The therapeutic strategy employed was a robust, dual-modality approach designed to rapidly suppress the acute cytokine storm while establishing a long-term maintenance regimen to prevent relapse. Upon admission, the immediate priority was stabilization. The patient was initiated on intravenous methylprednisolone at a dose of 62.5 mg every 24 hours for three days. This pulsed corticosteroid therapy was selected to achieve rapid downregulation of pro-inflammatory mediators. Following this acute stabilization phase, the regimen was transitioned to an oral tapering schedule. To address the chronic and relapsing nature of the disease, and to mitigate the risks associated with prolonged steroid monotherapy, Clofazimine was introduced as a steroid-sparing agent. A high-dose regimen of 100 mg orally every 8 hours (totaling 300 mg daily) was prescribed for a duration of two months. This strategy leverages Clofazimine's unique anti-inflammatory properties, which are distinct from its antibacterial action, making it highly effective for chronic ENL.

Supportive care was equally comprehensive, adopting a holistic approach to symptom management. Gastric protection was secured with Omeprazole 20 mg twice daily. The debilitating neuropathic pain stemming from neuritis was managed with a combination of Gabapentin 100 mg twice daily and Mecobalamin 500 mcg daily, aiming to support nerve regeneration and modulate pain signaling. Localized care for the malleolar ulcer included saline compresses and sodium fusidate cream to promote granulation and prevent secondary bacterial infection. Despite strong medical advice advocating for the extraction of the carious teeth to eliminate the suspected antigenic trigger, the patient refused invasive dental procedures, presenting a significant barrier to complete immunological resolution.

The clinical outcome at the follow-up visit on February 2025 (Day 64), demonstrated the efficacy of the pharmacological intervention. The patient exhibited a marked reduction in systemic toxicity; the fever had resolved, and the acute phase reactants had likely normalized. Dermatologically, no new nodules were observed, and the previous extensive lesions had resolved into hyperpigmented macules, a hallmark of healing ENL. Acral edema had subsided, and while nerve tenderness was significantly reduced, some sensory loss persisted, reflecting the chronicity of the neural damage. Consequently, the treatment was de-escalated to a maintenance phase comprising Methylprednisolone 8 mg twice daily and Clofazimine 100 mg twice daily. However, the persistence of the untreated odontogenic infection remains a critical concern, serving as a dormant threat for future reactivation of the disease (Table 2).

Table 2. Diagnosis, Treatment Regimen, Follow-up, and Outcomes

1. ESTABLISHED DIAGNOSIS		
Primary Diagnosis	Severe, Chronic Erythema Nodosum Leprosum (ENL)	*Duration > 24 weeks; Recurrent*
Leprosy Classification	Morbus Hansen Type Borderline Lepromatous (BL) - Release from Treatment (RFT)	*Post-MDT status*
Comorbidities	1. Chronic Odontogenic Infection (Gangrene Radix) 2. Peripheral Neuropathy (Polineuropathy)	*Focal infection trigger identified*
2. THERAPEUTIC INTERVENTION		
Acute Phase (Induction)	**Methylprednisolone IV:** 62.5 mg every 24 hours (3 days)	*Rapid suppression of cytokine storm*
Chronic Phase (Maintenance)	**Clofazimine Oral:** 100 mg every 8 hours (Total 300 mg/day) for 2 months **Methylprednisolone Oral:** Tapering dose	*High-dose Clofazimine for anti-inflammatory & steroid-sparing effect*
Neuropathic Management	Gabapentin 100 mg BID Mecobalamin 500 mcg OD	*Targeting active neuritis*
Focal Infection Control	Dental Extraction Advised	***Patient Refused*** *intervention*
3. FOLLOW-UP ASSESSMENT (DAY 64 - FEB 2025)		
Dermatological Outcome	No new nodules; Old lesions resolved to hyperpigmented macules; Ulcer healed	***Remission Achieved***
Systemic Symptoms	Fever resolved; Joint pain resolved; Acral edema subsided	***Systemic Control***
Neurological Outcome	Nerve tenderness significantly reduced	***Sensory Loss Persists***
Current Regimen	Methylprednisolone 8 mg BID Clofazimine 100 mg BID	*De-escalation phase*

Notes: Treatment strategy focused on dual-pathway inhibition (Steroid + Clofazimine) due to chronicity. Odontogenic infection remains a persistent risk factor for relapse.

3. Discussion

The case presented illustrates a classic yet often mismanaged scenario in modern leprosy care: the waxing and waning course of chronic erythema nodosum leprosum (ENL) in a patient who is bacteriologically cured but remains immunologically volatile.[11] While the patient had achieved release from treatment (RFT), his clinical reality was far from a cure, defined instead by debilitating cycles of inflammation. This discordance between bacteriological clearance and clinical morbidity compels us to look beyond the standard paradigms of leprosy management. This discussion will delve deep into the immunopathogenesis of chronic ENL, the mechanistic links between neglected odontogenic infections and systemic reactions, and the

pharmacological rationale for combined immunosuppressive regimens.[12]

To understand the persistence of ENL in a post-RFT patient, one must first deconstruct the immunological storm that defines the condition. Classically, ENL is categorized as a Type III hypersensitivity reaction. In patients with lepromatous leprosy (LL) and borderline lepromatous (BL) leprosy, the host harbors a massive load of *Mycobacterium leprae* antigens.[13] Even after multidrug therapy (MDT) kills the bacilli, the clearance of dead bacterial debris is slow. These fragmented antigens bind with high titers of circulating antibodies (IgG and IgM) to form insoluble antigen-antibody immune complexes (ICs). These complexes deposit preferentially in the vascular endothelium of the skin, peripheral nerves, and visceral organs like the eyes and testes. Upon deposition, they trigger the classical complement pathway. The resulting anaphylatoxins, specifically C3a and C5a, serve as potent chemotactic signals, recruiting neutrophils to the site. The massive influx of neutrophils and their subsequent degranulation release lysosomal enzymes, reactive oxygen species, and myeloperoxidase, causing the fibrinoid necrosis and leukocytoclastic vasculitis seen histopathologically. However, the immune complex theory alone is insufficient to explain the chronicity seen in our patient, where reactions persist for more than 24 weeks and occur long after the bulk of the bacterial load should have been reduced. The transition from an acute, self-limiting episode to a chronic, refractory state involves a more complex shift in cell-mediated immunity. Recent immunological studies suggest a breakdown in the traditional Th1/Th2 paradigm. While lepromatous leprosy is characterized by Th2 dominance (humoral immunity) and T-cell anergy, ENL episodes witness a transient, chaotic restoration of Th1 immunity (Figure 1).

More critically, contemporary research implicates the Th17 pathway. During ENL, there is a surge in IL-17-producing T-cells. Interleukin-17 (IL-17) is a pro-inflammatory cytokine that acts as a bridge between adaptive and innate immunity, further recruiting neutrophils and preventing their apoptosis, thereby perpetuating the inflammatory cycle. In our patient, the persistence of symptoms post-RFT suggests that this immunological switch has become stuck. While the viable bacilli are eliminated, the immune system remains in a hyper-responsive state, driven likely by persistent fragmented antigens or, more insidiously, by secondary triggers that mimic the original antigenic stimulation.[14]

The most salient and clinically actionable feature of this case is the presence of severe, untreated dental caries (gangrene radix) and chronic gingivitis.[15] The concept of focal infection posits that a localized, often asymptomatic infection can induce systemic pathology in distant organs. In the context of ENL, the oral cavity is a significant, yet frequently ignored, reservoir of inflammation. The mechanisms linking oral health to leprosy reactions are multifaceted, involving both direct bacteriological and indirect immunological pathways. The first mechanism involves transient bacteremia. The oral cavity in patients with poor hygiene harbors a complex microbiome, including gram-negative anaerobes like *Porphyromonas gingivalis* and gram-positive cocci like *Streptococcus mutans*. In the presence of caries and periodontal disease, the epithelial barrier is breached. Simple acts such as mastication or tooth brushing can force these bacteria into the bloodstream.[16] Once systemic, these oral pathogens may trigger molecular mimicry. Certain heat shock proteins (HSPs) found in oral bacteria share significant structural homology with the HSP-65 of *Mycobacterium leprae*. The immune system, already primed to attack *M. leprae*, cross-reacts with these new bacterial antigens, effectively reigniting the Type III hypersensitivity reaction even in the absence of live leprosy bacilli.

The second, and perhaps more potent mechanism, is the cytokine spillover effect. Chronic dental infections act as a continuous biological factory for pro-inflammatory cytokines. Periodontal tissues in patients with dental disease constitutively release

tumor necrosis factor-alpha (TNF-α), Interleukin-1β (IL-1β), and Interleukin-6 (IL-6) into the systemic circulation. TNF-α is recognized as the master regulator of ENL. It is responsible for the fever, malaise, and tissue necrosis associated with the reaction. In a healthy individual, the systemic load of cytokines from a tooth infection might be negligible.[17] However, in a post-RFT leprosy patient, the immune system exists at a delicate threshold. The additional systemic load of TNF-α from odontogenic sources can tip the balance, lowering the threshold for a reactional episode. This converts what might have been a subclinical immune fluctuation into a severe, refractory condition.

Our case mirrors findings in the literature. Previous study demonstrated a statistically significant correlation between the severity of dental caries (measured by the DMF-T index) and the severity of ENL, suggesting that patients with poor oral hygiene are predisposed to severe reactions. Additionally, another study reported that ENL recurrence is strongly associated with oral chronic infections and elevated serum markers of IL-1 and TNF-α. In our patient, the refusal to treat the dental infection creates a vicious cycle: the focal infection maintains high cytokine levels, fueling the ENL; the ENL necessitates high-dose steroids; and the steroids, in turn, suppress local oral immunity, exacerbating the dental pathology and allowing the bacterial reservoir to expand.[18]

Figure 1. Pathogenesis of chronic ENL in the presented case.

The management of this patient utilized a combination of high-dose corticosteroids and clofazimine, a strategy dictated by the chronicity and severity of the presentation. Intravenous Methylprednisolone was chosen as the induction therapy. Corticosteroids are the first line of defense for acute ENL due to their rapid onset. They work by inhibiting the NF-κB pathway, which blocks the transcription of pro-inflammatory genes, and by inhibiting phospholipase A2, thereby halting the arachidonic acid cascade. This results in an immediate reduction in neutrophil chemotaxis and vascular permeability. However, their utility in chronic ENL is limited by toxicity. Long-term use is associated with Cushingoid features, osteoporosis, hypertension, glucose intolerance, and susceptibility to secondary infections—a particular risk in a patient with an open oral infection source.[19]

Clofazimine was pivotal in breaking the cycle of recurrence in this case. Originally developed as an anti-leprosy antibiotic, its role in ENL is primarily immunomodulatory. Unlike steroids, which broadly suppress the immune system, clofazimine has specific mechanisms of action that make it ideal for maintenance: (1) Lysosomal stabilization: Clofazimine accumulates in macrophages and stabilizes lysosomal membranes. This enhances the phagocytes' ability to clear immune complexes and bacterial debris without releasing their cytotoxic enzymes into the surrounding tissue, thereby limiting tissue damage; (2) T-Cell modulation: It inhibits the Kv1.3 potassium channels in T-lymphocytes. This channel is crucial for the activation of effector memory T-cells (TEM), which are heavily implicated in the pathogenesis of chronic autoimmune disorders. By blocking this channel, clofazimine effectively dampens the specific T-cell activation that drives the chronic phase of ENL; (3) Steroid-sparing effect: Clinical studies confirm that adding Clofazimine (300 mg/day initially) allows for a faster and safer tapering of corticosteroids. This is crucial for chronic patients to avoid steroid dependency. As observed in the follow-up, the patient showed significant improvement after two months of this combined regimen. The skin lesions resolved, and the neuritis subsided. However, it is important to note that the full anti-inflammatory effect of Clofazimine is not immediate; it often takes 4 to 6 weeks to reach peak therapeutic efficacy due to its high lipophilicity and slow tissue accumulation. Therefore, it must be continued for up to 12 months in chronic cases to prevent relapse.

While this case offers compelling evidence for the link between oral health and ENL, it is not without limitations. The primary limitation was the inability to demonstrate the resolution of ENL contingent upon dental extraction, due to the patient's persistent refusal of invasive dental treatment. This reflects a real-world barrier in leprosy management: the complex interplay of psychosocial fear, stigma, and educational gaps that prevents comprehensive care.[20] We could not definitive prove causation, only a strong clinical and biological association. Future research must move beyond observational case reports. We need prospective, interventional trials where ENL patients with dental disease are randomized to receive comprehensive dental eradication versus standard care. Such studies could quantify the impact of focal infection treatment on the frequency and severity of ENL episodes. Furthermore, advanced molecular studies are needed to analyze the microbiome of periodontal pockets in ENL patients compared to non-reactional leprosy patients. Identifying specific oral pathogens (e.g., via 16S rRNA sequencing) that share antigenic mimicry with *M. leprae* could lead to targeted antibiotic prophylaxes or probiotic interventions to prevent reactions.

4. Conclusion

This case report underscores a critical evolution in our understanding of Erythema Nodosum Leprosum: it is not merely a dermatological event triggered by a dying bacillus, but a systemic crisis often perpetuated by occult, secondary triggers. The 32-year-old patient presented with severe, chronic ENL more than a year after being declared cured (Release from Treatment). His condition was driven by a convergence of residual

immunopathology and a neglected, active odontogenic focal infection. The successful management of this patient relied on recognizing the limitations of monotherapy. While the pharmacological combination of Methylprednisolone and high-dose Clofazimine successfully induced remission and controlled the immediate symptoms, the clinical victory remains fragile. The persistence of the untreated dental caries leaves the patient with a loaded gun—a persistent reservoir of cytokines and antigens that places him at high risk of future relapse.

Based on this case and the supporting literature, we advocate for a paradigm shift in the management of leprosy reactions: (1) Mandatory Screening: Dental evaluation should be elevated from an optional consultation to a mandatory component of the workup for any patient presenting with chronic or recurrent ENL; (2) Holistic Eradication: The eradication of focal infections (dental, urinary, or respiratory) should be considered a cornerstone of ENL therapy, equal in importance to pharmacological immunosuppression; (3) Multidisciplinary Care: Effective leprosy care requires breaking down the silos between dermatology and dentistry. A collaborative approach is essential to interrupt the cycle of inflammation. Ultimately, curing leprosy requires more than just distributing MDT blister packs; it demands a vigilant, holistic commitment to the patient's general health, ensuring that hidden infections do not undermine the success of leprosy elimination efforts. By addressing the silent saboteurs like odontogenic infections, we can offer patients not just a release from treatment, but a true release from suffering.

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