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Severe Erythema Nodosum Leprosum Complicated by Warm Autoimmune Hemolytic Anemia: Navigating the Immunosuppressive Paradox

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A B S T R A C T

Erythema nodosum leprosum (ENL) is a severe, systemic immune-complex mediated complication of multibacillary Hansen's disease. While anemia of chronic disease is frequently observed in leprosy, the concurrent development of Warm Autoimmune Hemolytic Anemia (wAIHA) is an exceptionally rare and precarious clinical entity. This comorbidity creates a therapeutic paradox wherein the high-dose corticosteroids required to halt hemolysis may exacerbate the risk of sepsis in patients with necrotic skin lesions and compromised barrier function. We report the case of a 42-year-old male with multibacillary Hansen's disease on multidrug therapy who presented with high-grade fever, progressive fatigue, and necrotic cutaneous lesions. Laboratory evaluation revealed life-threatening normocytic normochromic anemia (Hemoglobin 3.5 g/dL) and a leukemoid reaction (WBC 42,540/μL). Hemolysis was confirmed by elevated lactate dehydrogenase (564 U/L), indirect hyperbilirubinemia, and a strongly positive direct Coombs test (IgG). A diagnosis of wAIHA secondary to severe necrotic ENL was established. Standard high-dose pulse steroid therapy was deemed high-risk due to the patient's extreme neutrophilia (NLR 80.25) and open necrotic ulcers. Consequently, a tailored regimen of intermediate-dose intravenous methylprednisolone (62.5 mg twice daily) combined with broad-spectrum antibiotics was initiated. This strategy successfully suppressed hemolysis and resolved the ENL reaction without precipitating secondary opportunistic infections. In conclusion, the coexistence of wAIHA and ENL suggests a shared mechanism of dysregulated T-cell immunity and molecular mimicry. This case demonstrates that in scenarios involving high infectious risk, an individualized, intermediate-dose corticosteroid protocol can achieve remission while mitigating the dangers of profound immunosuppression.

1. Introduction

Hansen's disease, an ancient chronic granulomatous infection caused by the obligate intracellular bacillus *Mycobacterium leprae*, remains a formidable public health challenge, particularly in endemic regions where it continues to inflict significant morbidity.[1] While the disease is primarily characterized by its cutaneous and neurological sequelae, the clinical spectrum is dictated by the host's cellular immune response to the mycobacterium. This spectrum is not static; it is frequently punctuated by acute, systemic inflammatory episodes known as reactions, which constitute the major source of permanent nerve damage and disability in affected populations. Among the most debilitating of these complications is the Type 2 reaction, classically termed erythema nodosum leprosum (ENL).[2]

ENL represents a severe, systemic immune-complex mediated vasculitis that affects approximately 50% of patients with lepromatous leprosy (LL) and borderline lepromatous (BL) leprosy,

often manifesting during the bactericidal phase of multidrug therapy. The pathogenesis of this reaction involves the deposition of *M. leprae* antigen-antibody complexes within tissues, which triggers the activation of the complement cascade and the recruitment of neutrophils. This cascade results in a systemic inflammatory milieu driven by elevated levels of pro-inflammatory cytokines, specifically tumor necrosis factor-alpha (TNF-α) and Interleukin-6 (IL-6).[3] Clinically, ENL is distinguished by the abrupt onset of painful, erythematous nodules, high-grade fever, neuritis, and multi-organ involvement, creating a clinical picture of profound systemic toxicity that often necessitates prolonged and aggressive immunosuppressive therapy to prevent irreversible sequelae.[4]

While the cutaneous and neurological manifestations of Hansen's disease are well-documented, hematologic abnormalities in this population are typically mild and multifactorial.[5] When anemia presents in leprosy patients, it is most frequently attributed to the anemia of chronic disease or, in the context of treatment, to dapsone-induced hemolysis, a predictable adverse effect particularly prevalent in patients with Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency. In these standard scenarios, the hemolysis is oxidative in nature and generally manageable through dose adjustment or cessation of the offending agent. However, the development of frank autoimmune hemolytic anemia (AIHA) represents an exceptionally rare and precarious clinical entity within the leprosy spectrum. autoimmune hemolytic anemia is characterized by the destruction of red blood cells (RBCs) due to the presence of autoantibodies directed against antigens on the erythrocyte surface.[6] The specific subtype known as warm autoimmune hemolytic anemia (wAIHA) accounts for the majority of these cases. Mediated by high-affinity IgG autoantibodies that react optimally at body temperature, wAIHA leads to the opsonization of RBCs and their subsequent Fc-receptor-mediated destruction by macrophages in the spleen. Unlike the gradual decline seen in chronic anemia, wAIHA constitutes a medical emergency; the rapid rate of hemolysis can precipitate acute cardiovascular collapse if not intervened upon with urgency.[7]

The coexistence of severe ENL and wAIHA suggests a profound and dangerous dysregulation of the host immune system. The convergence of these two distinct pathologies likely stems from shared mechanisms of dysregulated T-cell immunity. Two primary hypotheses clarify this link: molecular mimicry and epitope spreading. In the first mechanism, *M. leprae* antigens may share structural homology with erythrocyte surface glycoproteins, leading to cross-reactivity where antibodies originally targeted at the bacillus inadvertently attack the host's red blood cells. This process may be primed by the massive release of antigens during antimicrobial therapy. Alternatively, the mechanism of epitope spreading suggests that the chronic, intense inflammation inherent to necrotic ENL disrupts peripheral tolerance. The extensive tissue destruction characteristic of severe Type 2 reactions may expose cryptic self-antigens, stimulating autoreactive B-cell clones to produce anti-RBC IgG antibodies, thereby igniting the hemolytic fire.[8]

Regardless of the precise molecular etiology, the simultaneous presentation of severe necrotic ENL and wAIHA creates a formidable immunosuppressive paradox for the treating clinician. This paradox is rooted in the conflicting therapeutic requirements of the two conditions.[9] The established standard of care for severe wAIHA involves the administration of high-dose corticosteroids—typically prednisone at 1 to 2 mg/kg/day or intravenous pulse methylprednisolone—to rapidly blockade the Fc-receptor-mediated destruction of erythrocytes in the reticuloendothelial system. Under normal circumstances, more is better is the dogma for arresting acute hemolysis to prevent hemodynamic failure. However, in the context of necrotic ENL, the patient is already in a state of compromised barrier function and severe physiological stress. Severe ENL often presents with necrotic skin lesions that breach

the protective dermal barrier, creating direct portals of entry for pathogens. Furthermore, these patients frequently exhibit a leukemoid reaction—an extreme elevation of white blood cells—which signals a system pushed to the brink of its metabolic and immunologic reserves. The Neutrophil-to-Lymphocyte Ratio (NLR) in such cases can reach extreme levels, reflecting a state of unbridled innate immunity coupled with adaptive immune exhaustion. In this fragile clinical landscape, the administration of high-dose pulse steroids carries a catastrophic potential: it significantly elevates the risk of superimposing lethal opportunistic infections, fungal dissemination, or bacterial sepsis upon an already compromised host.

The clinician is thus forced to navigate a therapeutic tightrope: they must administer potent immunosuppression to halt the rapid, life-threatening hemolysis, yet they must simultaneously restrain that very immunosuppression to avoid precipitating fatal sepsis in a patient with open, necrotic wounds. The risk is further compounded in tropical, resource-limited settings where advanced second-line biologics—such as rituximab, which might offer a steroid-sparing alternative—are frequently unavailable or cost-prohibitive. To date, medical literature guiding the management of this specific and complex comorbidity is sparse. While guidelines exist for ENL and wAIHA independently, there is a paucity of evidence regarding the optimal management of their collision. This gap leaves clinicians without a clear roadmap when ensuring survival requires deviating from standard protocols.[10]

This case report describes a unique and challenging presentation of Warm Autoimmune Hemolytic Anemia occurring in the setting of severe necrotic Erythema Nodosum Leprosum. We detail the clinical trajectory of a patient presenting with a hemoglobin of 3.5 g/dL and a leukemoid reaction, necessitating a departure from conventional high-dose steroid protocols. The primary aim of this report is to propose an individualized, intermediate-dose corticosteroid algorithm that successfully prioritizes patient safety. By outlining a strategy that achieves hematologic remission while mitigating the dangers of profound immunosuppression, we hope to provide a practical framework for clinicians managing similar high-stakes convergences of autoimmunity and chronic infection in resource-limited environments.

2. Case Presentation

A 42-year-old male presented to the Emergency Department of Wangaya Regional General Hospital with a primary complaint of progressive, debilitating fatigue and high-grade fever persisting for one week. The patient had a known history of Multibacillary Hansen's disease and was currently in the fifth month of the standard World Health Organization Multidrug Therapy regimen consisting of Rifampicin, Clofazimine, and Dapsone. One month prior to admission, the patient reported the onset of painful, erythematous nodules distributed extensively over the extensor surfaces of his extremities and face. Despite adherence to the multidrug therapy, these lesions rapidly progressed to become necrotic and ulcerative. Concurrently, he experienced recurrent episodes of symptomatic anemia requiring blood transfusions on three separate occasions over the preceding six months, although a definitive etiology for the anemia had not been established prior to this admission.

On initial assessment, the patient appeared acutely ill, toxic, and markedly pale (Table 1). Vital signs revealed tachycardia with a heart rate of 112 beats per minute, pyrexia with a temperature of 38.9°C, tachypnea with a respiratory rate of 22 breaths per minute, and hypotension with a blood pressure of 100/60 mmHg. Dermatological examination demonstrated classic features of severe ENL. Multiple tender, erythematous, and necrotic nodules were observed on the face, arms, and legs. Several lesions on the lower extremities had evolved into deep, punched-out ulcers with purulent bases and eschar formation, consistent with necrotic ENL or erythema necroticans. Peripheral nerve enlargement was palpable in the bilateral ulnar and common peroneal nerves. Scleral icterus was prominent. Abdominal examination revealed no palpable

hepatosplenomegaly, contrasting with the typical presentation of chronic extravascular hemolysis, likely due to the acute nature of the current crisis.

Initial laboratory investigations indicated a critical hematologic crisis. The complete blood count revealed severe anemia with a Hemoglobin level of 3.5 g/dL and Hematocrit of 12.2%. This was accompanied by a profound leukemoid reaction; the White Blood Cell count was 42,540/µL, with an Absolute Neutrophil Count of 41,730/µL. The Neutrophil-to-Lymphocyte Ratio was calculated at 80.25, signaling severe systemic physiological stress. The platelet count was preserved at 165,000/µL. Biochemical markers confirmed a hemolytic process. Lactate Dehydrogenase was markedly elevated at 564 U/L (Reference range: 140–280 U/L), and Total Bilirubin was 1.05 mg/dL with a predominant indirect fraction. Renal function was preserved with a Serum Creatinine of 0.8 mg/dL, and electrolytes were within normal limits. Morphological examination of the peripheral blood smear was critical for diagnosis. It demonstrated normocytic normochromic red blood cells with significant anisopoikilocytosis. Key findings included the presence of spherocytes, target cells, teardrop cells, helmet cells or schistocytes, and polychromasia, indicating a regenerative response. Autoagglutination and rouleaux formation were noted. Toxic granulations were observed in neutrophils, correlating with the severe inflammatory state.

A Direct Antiglobulin Test, also known as the Coombs test, was strongly positive (4+) for IgG and C3d, confirming the autoimmune nature of the hemolysis. The Indirect Coombs test was negative. This pattern is pathognomonic for Warm Autoimmune Hemolytic Anemia. Dapsone-induced hemolysis was considered; however, the strong Coombs positivity and the persistence of hemolysis despite intermittent cessation of Dapsone in previous months pointed toward an autoimmune etiology rather than oxidative stress or methemoglobinemia alone. Glucose-6-Phosphate Dehydrogenase levels were normal. Screening for Antinuclear Antibodies and viral serologies for HIV, Hepatitis B, and Hepatitis C could not be performed due to resource limitations, but clinical suspicion for systemic lupus erythematosus was low, given the absence of malar rash, arthralgia, or renal involvement. The patient was diagnosed with warm autoimmune hemolytic anemia secondary to severe erythema nodosum leprosum.

The clinical management of the patient, as summarized in Table 2, followed a phased trajectory designed to navigate the immunosuppressive paradox inherent to this case. The therapeutic strategy was divided into three distinct phases: immediate acute stabilization, monitored clinical progression, and long-term discharge outcomes. Each phase required a careful calibration of pharmacological interventions to balance the urgent need to arrest hemolysis against the critical requirement to preserve innate immunity against sepsis.

Phase I is acute stabilization and strategic immunosuppression (0–48 hours). Upon admission, the patient presented in a state of impending hemodynamic collapse, driven by a life-threatening hemoglobin level of 3.5 g/dL. The immediate priority was the restoration of oxygen-carrying capacity to prevent high-output cardiac failure. This was achieved through the urgent transfusion of six units of packed red blood cells (PRBCs) over the initial 48 hours. This aggressive transfusion protocol was necessary not only to support vital organ perfusion but also to buy time for the immunosuppressive therapy to take effect. The core dilemma of the acute phase lay in the selection of the corticosteroid regimen. Standard protocols for severe warm autoimmune hemolytic anemia (wAIHA) advocate for high-dose pulse therapy (such as Methylprednisolone 1000 mg/day) to rapidly block Fc-receptor-mediated destruction of erythrocytes. However, the patient's clinical picture was complicated by severe necrotic erythema nodosum leprosum (ENL), characterized by deep, open ulcers with purulent bases and an extreme leukemoid reaction (WBC > 42,000/µL).

Table 1. Summary of Clinical and Laboratory Findings on Admission

PARAMETER	FINDING / VALUE	CLINICAL INTERPRETATION
PATIENT PROFILE & HISTORY		
Demographics	42-year-old Male	Known Multibacillary Hansen's Disease
Treatment History	Month 5 of Multidrug Therapy (MDT)	Rifampicin, Clofazimine, Dapsone
Presenting Complaint	Fatigue & High-grade Fever (1 week)	Rapid progression of symptoms
VITAL SIGNS (HEMODYNAMIC STATUS)		
Temperature	**38.9°C**	Pyrexia
Heart Rate	112 beats/min	Tachycardia
Blood Pressure	100/60 mmHg	Hypotension
Respiratory Rate	22 breaths/min	Tachypnea
PHYSICAL EXAMINATION		
Dermatological	Multiple tender, necrotic nodules; Deep punched-out ulcers with purulent bases	Severe necrotic Erythema Nodosum Leprosum (ENL)
Neurological	Palpable nerve enlargement	Bilateral ulnar and common peroneal nerves
General	Prominent Scleral Icterus; Marked pallor	Suggestive of hemolysis
HEMATOLOGY (COMPLETE BLOOD COUNT)		
Hemoglobin	**3.5 g/dL**	Life-threatening Anemia
White Blood Cells (WBC)	**42,540 /µL**	Leukemoid Reaction
Absolute Neutrophil Count	41,730 /µL	Extreme neutrophilia
Neutrophil-to-Lymphocyte Ratio (NLR)	**80.25**	Marker of severe physiological stress
Platelets	165,000 /µL	Preserved (Normal)
BIOCHEMISTRY & IMMUNOLOGY		
Lactate Dehydrogenase (LDH)	**564 U/L**	Elevated (Ref: 140–280 U/L); Indicates Hemolysis
Direct Antiglobulin Test (Coombs)	**Positive (4+)**	IgG and C3d positive; Confirms Autoimmune etiology
Indirect Coombs Test	Negative	Pathognomonic for Warm AIHA
Peripheral Blood Smear	Spherocytes, Target cells, Toxic granulations, Autoagglutination	Confirmed regenerative response and inflammation

Abbreviations: MDT: Multidrug Therapy; AIHA: Autoimmune Hemolytic Anemia; ENL: Erythema Nodosum Leprosum; IgG: Immunoglobulin G.

Note: Data compiled from Case Presentation sections of the manuscript.

These findings signaled a precarious breach in the skin barrier and a physiological system under maximum stress. The clinical team determined that a standard pulse-dose regimen carried an unacceptable risk of inducing iatrogenic sepsis by paralyzing the immune response in the presence of necrotic tissue.

Consequently, a novel intermediate-dose protocol was implemented. The patient was started on Intravenous Methylprednisolone at a dose of 62.5 mg administered twice daily, totaling 125 mg per day. The rationale for this specific dosage was pharmacokinetic: it was calculated to be sufficiently potent to saturate

glucocorticoid receptors and inhibit the splenic sequestration of IgG-coated red blood cells, yet low enough to avoid total immune paralysis. By avoiding the massive pharmacological burden of pulse therapy, the team aimed to preserve residual neutrophil function—specifically chemotaxis and oxidative burst—which serves as the primary defense against bacterial invasion in patients with open wounds.

Concurrently, a robust infection control strategy was initiated. Intravenous Ceftriaxone (2 grams daily) was administered as broad-spectrum prophylaxis. This decision was driven by the presence of the necrotic ENL lesions, which acted as significant reservoirs for potential bacterial superinfection. Additionally, the patient's Multidrug Therapy (MDT) for leprosy was temporarily adjusted. Dapsone, a known oxidizing agent capable of causing hemolysis, was withheld to eliminate any potential contribution to red cell destruction, while Rifampicin and Clofazimine were continued to maintain antimicrobial pressure on the *Mycobacterium leprae* bacilli.

Next, phase II is clinical progression and systemic response (day 4 – week 2). The efficacy of this tailored, intermediate-dose regimen was evident by the fourth day of hospitalization. The patient demonstrated a rapid clinical response, marked primarily by the cessation of fevers and the stabilization of the cutaneous pathology. The progression of the necrotic skin lesions halted, and the inflammatory erythema began to recede, validating the anti-inflammatory potency of the 125 mg/day steroid dose.

Biochemically, the response was equally favorable. Serial monitoring revealed a stabilization of hemoglobin levels following the initial transfusions, indicating that the active destruction of red blood cells had been arrested. This was corroborated by a marked decrease in serum lactate dehydrogenase (LDH), a sensitive marker of cell turnover and hemolysis. The reduction in LDH confirmed that the corticosteroid dosage was sufficient to downregulate the macrophage activity in the reticuloendothelial system effectively. Following this stabilization, the therapeutic focus shifted to de-escalation. To minimize the long-term metabolic and immunologic side effects of corticosteroids, the methylprednisolone was not maintained at high levels but was instead gradually tapered over the subsequent weeks. This tapering process was critical to prevent a rebound phenomenon, where abrupt withdrawal of steroids can trigger a resurgence of both the hemolytic anemia and the ENL reaction.

Phase III is discharge outcomes and therapeutic validation. The ultimate validation of this corticosteroid-sparing strategy was observed at the time of discharge. The patient achieved a sustained hematologic remission, with the hemoglobin level stabilizing at 10 g/dL. Crucially, this level was maintained without the need for further blood transfusions, signaling the restoration of erythropoietic homeostasis. From a safety perspective, the outcome was distinctively positive. Despite the patient's high-risk profile—characterized by an extreme Neutrophil-to-Lymphocyte Ratio (NLR) of 80.25 and open necrotic wounds—he did not develop any opportunistic infections or hospital-acquired sepsis during his admission. This negative finding is clinically significant; it supports the hypothesis that the intermediate-dose steroid regimen successfully occupied the therapeutic window, providing enough immunosuppression to treat the autoimmunity without rendering the patient defenseless against infection. Dermatologically, the severe necrotic nodules of ENL showed signs of resolution, with the ulcers beginning to granulate and heal. The successful management of this case demonstrates that in complex scenarios involving concurrent infection and autoimmunity, a deviation from rigid, high-dose protocols in favor of an individualized, risk-stratified approach can achieve optimal outcomes. The strategy effectively navigated the immunosuppressive paradox, securing patient survival while mitigating the potentially fatal complications of aggressive therapy.

Table 2. Therapeutic Management, Follow-up, and Clinical Outcome

PHASE / TIME	INTERVENTION / PARAMETER	DETAILS / DOSAGE	RATIONALE & RESPONSE
I. ACUTE STABILIZATION (0 - 48 HOURS)			
ADMISSION	Hemodynamic Support	Blood Transfusion: 6 Units of Packed Red Blood Cells (PRBCs)	Stabilization of profound anemia (Hb 3.5 g/dL).
DAY 1	Immunosuppression Strategy	**IV Methylprednisolone** 62.5 mg twice daily (Total: 125 mg/day)	**"Intermediate-Dose" Protocol:** Selected to saturate GC receptors without inducing total immune paralysis/sepsis risks associated with pulse doses.
DAY 1	Infection Control	**IV Ceftriaxone** 2 grams per day	Broad-spectrum coverage for potential secondary bacterial infection of necrotic skin ulcers.
DAY 1	MDT Adjustment	**Withheld:** Dapsone **Continued:** Rifampicin, Clofazimine	Elimination of potential oxidative stress contributors to hemolysis.
II. CLINICAL PROGRESS & FOLLOW-UP			
DAY 4	Systemic Response	Resolution of Fever & Necrosis	**Rapid Clinical Response:** Pyrexia subsided; progression of necrotic skin lesions halted.
DAY 4	Hematologic Response	Biochemical Markers	Stabilization of Hemoglobin levels; Decrease in Lactate Dehydrogenase (LDH) indicating cessation of hemolysis.
WEEK 2+	De-escalation	Steroid Tapering	Methylprednisolone dose gradually reduced over subsequent weeks.
III. DISCHARGE OUTCOME			
DISCHARGE	Hematologic Status	**Hemoglobin: 10 g/dL**	Achieved without further transfusion requirements after initial stabilization.
DISCHARGE	Infection Status	No Sepsis / No OI	Patient did not develop opportunistic infections (OI) or hospital-acquired sepsis despite high-risk profile.
DISCHARGE	Dermatologic Status	Lesion Resolution	Resolution of ENL nodules and healing of ulcers.

Abbreviations: IV: Intravenous; PRBC: Packed Red Blood Cells; MDT: Multidrug Therapy; GC: Glucocorticoid; OI: Opportunistic Infection.

3. Discussion

The case presented herein illustrates the intricate and frequently perilous interplay between chronic infectious granulomatous disease and acute autoimmunity. The simultaneous occurrence of warm autoimmune hemolytic anemia (wAIHA) and necrotic erythema nodosum leprosum (ENL) represents a perfect storm of immune dysregulation, characterized by concurrent hyperactivity of the innate immune system and aberrant targeting by the adaptive immune system.[11] This comorbidity challenges the rigidity of standard therapeutic algorithms, forcing the

clinician to navigate an immunosuppressive paradox where the treatment for one condition threatens to exacerbate the mortality risk of the other. By dissecting the pathophysiology, diagnostic nuances, and therapeutic decision-making in this case, we offer a framework for managing complex autoimmunity in the context of neglected tropical diseases.[12]

Understanding the genesis of wAIHA in a patient with Hansen's disease requires a deep dive into the immunological chaos of the Type 2 reaction. ENL is not merely a cutaneous eruption; it is a systemic, immune-complex mediated vasculitis that fundamentally alters the host's cytokine landscape.[12] The pathogenesis involves the deposition of *Mycobacterium leprae* antigen-antibody complexes within the vascular endothelium and other tissues. This deposition triggers the classical complement pathway, leading to the chemotactic recruitment of neutrophils and the release of lysosomal enzymes. The result is a systemic inflammatory milieu dominated by high titers of pro-inflammatory cytokines, specifically tumor necrosis factor-alpha (TNF-α) and Interleukin-6 (IL-6).[13] In this specific case, we hypothesize that the transition from this generalized inflammation to specific anti-erythrocyte autoimmunity was driven by two distinct but complementary mechanisms: molecular mimicry and epitope spreading (Figure 1).

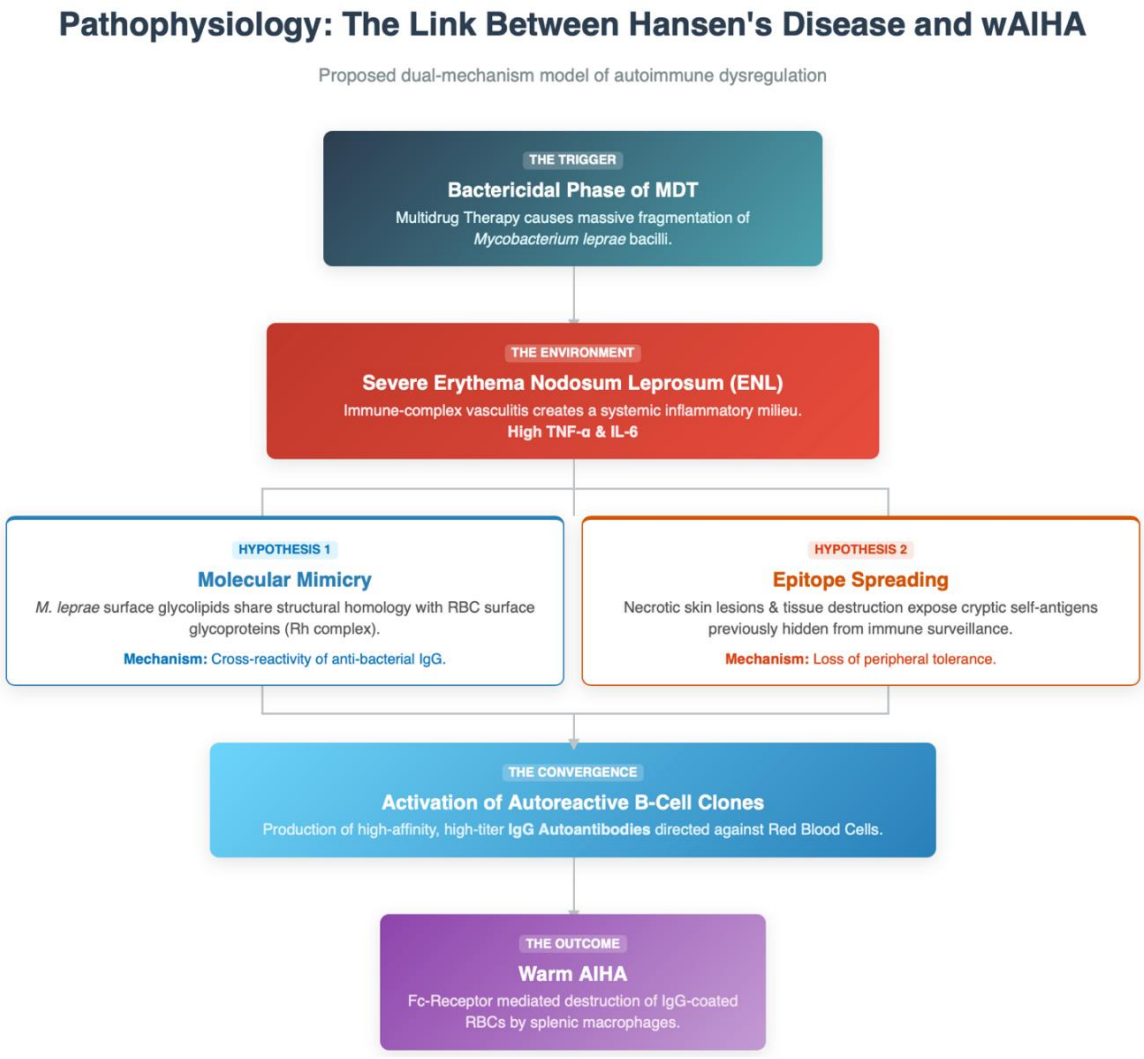

Figure 1. The link between Hansen's disease and wAIHA.

The concept of molecular mimicry posits that foreign antigens share structural homology with self-antigens, leading to an immunological case of mistaken identity. *Mycobacterium leprae* is a complex organism with a cell wall rich in glycolipids and proteins. It is plausible that specific *M. leprae* antigens, liberated in massive quantities during the bactericidal phase of multidrug therapy (MDT), share epitope sequences with glycoproteins on the surface of human red blood cells, such as the Rh complex or Band 3 protein.[14] In our patient, the onset of ENL occurred during the fifth month of MDT. This timing correlates with the fragmentation of bacilli and the peak release of mycobacterial antigens. The adaptive immune system, primed to attack these bacterial fragments, produces high-affinity IgG antibodies. If these bacterial epitopes structurally mimic erythrocyte surface antigens, the resultant antibodies will cross-react, effectively opsonizing the patient's own red blood cells for destruction by splenic macrophages. This mechanism transforms a protective antimicrobial response into a destructive autoimmune process.[15]

The second, and perhaps more potent driver in the context of *necrotic* ENL, is epitope spreading. Peripheral tolerance—the mechanism by which the immune system learns to ignore self-antigens—relies on the sequestration of certain auto-antigens and the suppression of autoreactive lymphocytes.[16] The chronic, intense inflammation of ENL disrupts this delicate balance. The clinical presentation of punched-out ulcers with purulent bases and eschar formation indicates massive tissue destruction. This necrosis results in the release of intracellular contents and cryptic self-antigens that are normally hidden from the immune surveillance system. In an environment saturated with pro-inflammatory signals (TNF-α, IL-6) and co-stimulatory molecules, antigen-presenting cells (APCs) may present these cryptic self-antigens to B-cells with heightened efficiency. This stimulates quiescent, low-affinity autoreactive B-cell clones to proliferate, undergo somatic hypermutation, and differentiate into plasma cells producing high-affinity anti-RBC IgG antibodies. Thus, the tissue destruction of ENL essentially vaccinates the patient against their own red blood cells.

A critical component of the discussion in any case of hemolysis involving leprosy is the differentiation between drug-induced pathology and true autoimmunity. Dapsone, a cornerstone of MDT, is a well-known oxidizing agent capable of causing hemolysis, particularly in patients with Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency.[17] In this case, the distinction was vital for long-term management. Dapsone-induced hemolysis is typically non-immune; it results from oxidative stress leading to methemoglobinemia and the formation of Heinz bodies, which damage the RBC membrane as they pass through the splenic sinusoids. However, our diagnostic evaluation pointed decisively away from this common etiology. The patient had normal G6PD levels. More importantly, the Direct Antiglobulin Test (DAT/Coombs) was strongly positive (4+) for IgG and C3d. A positive DAT is the sine qua non of immune-mediated hemolysis and effectively rules out pure oxidative damage. While Dapsone syndrome (Dapsone Hypersensitivity Syndrome) can rarely present with immune-mediated hemolysis, it typically occurs within the first 6 weeks of therapy. Our patient was in his fifth month of treatment, making a hypersensitivity reaction unlikely. Furthermore, the persistence of hemolysis despite intermittent cessation of Dapsone in the months prior to admission reinforced the conclusion that an autonomous autoimmune clone had been established. Therefore, the diagnosis was definitively Warm Autoimmune Hemolytic Anemia (wAIHA) secondary to the immune dysregulation of leprosy, rather than a toxic effect of the treatment. The management of this patient was defined by the immunosuppressive paradox. The clinician was forced to balance the need for potent immunosuppression to halt rapid hemolysis against the heightened risk of life-threatening sepsis inherent to necrotic ENL.

Standard clinical guidelines for severe wAIHA are unequivocal: the first-line therapy is high-dose corticosteroids, typically prednisone at 1–2

mg/kg/day, or in cases of fulminant hemolysis (like our patient's Hb of 3.5 g/dL), intravenous pulse methylprednisolone (1000 mg/day for 3 days). The mechanism is to rapidly blockade the Fc-gamma receptors on splenic macrophages, preventing them from biting off pieces of the IgG-coated red blood cells. However, applying this standard algorithm to a patient with necrotic ENL is fraught with peril. ENL patients are already functionally immunocompromised due to the high mycobacterial load and the systemic stress of the reaction. The presence of necrotic skin lesions creates a direct breach in the integumentary barrier, serving as a portal of entry for environmental pathogens. Administering pulse-dose steroids in this setting is akin to disabling the fire alarm while the building is smoking; it significantly elevates the risk of opportunistic infections, bacterial superinfection, and steroid-dependency.[18]

To navigate this paradox, we utilized the Neutrophil-to-Lymphocyte Ratio (NLR) as a critical risk stratification marker. The patient presented with a leukemoid reaction (WBC 42,540/μL) and an NLR of 80.25. In the context of severe inflammation, the NLR acts as a barometer of immune system stress. The numerator (neutrophilia) reflects an unbridled innate immune response, often driven by bacterial burden or tissue necrosis. The denominator (lymphopenia) reflects adaptive immune exhaustion and lymphocyte apoptosis induced by the chronic stress response. An NLR of 80.25 is exceptionally high and signals a physiological state teetering on the edge of decompensation. It suggested that while the innate system was hyperactive (causing tissue damage and pus), the adaptive system was fragile. We postulated that adding the profound lympholytic effect of pulse-dose steroids to this pre-existing lymphopenia could precipitate a tipping point into fatal sepsis or disseminated fungal infection—a complication well-documented in historical leprosy cohorts. This data point was instrumental in our decision to reject the standard pulse-dose protocol.

Our successful therapeutic strategy challenged the dogma that more is better in acute hemolytic crises. We opted for an intermediate-dose regimen of Intravenous Methylprednisolone 62.5 mg twice daily (total 125 mg/day). This dosage was not arbitrary; it was calculated to occupy a specific therapeutic window. Pharmacologically, corticosteroids exert their effects through two mechanisms: genomic and non-genomic. Genomic effects (altering protein synthesis) occur at lower doses but take time. Non-genomic effects (altering membrane physicochemical properties and rapid receptor blockade) occur at high pulse doses.

We hypothesized that 125 mg/day was sufficient to saturate the available glucocorticoid receptors, thereby maximizing the genomic anti-inflammatory benefits required to stop antibody production and reduce ENL inflammation. Simultaneously, by avoiding the massive 1000 mg pulse doses, we aimed to preserve residual neutrophil function—specifically chemotaxis and oxidative burst—which are essential for defending against bacterial invasion through the necrotic skin ulcers. This dose was high enough to halt the splenic sequestration of RBCs but low enough to maintain a perimeter defense against sepsis.[19]

The results validated this hypothesis. The patient achieved hematologic stabilization (Hb rising to 10 g/dL) and resolution of ENL lesions without requiring further transfusions or developing secondary infections. This outcome aligns with emerging steroid-sparing concepts in internal medicine, which advocate for the Minimum Effective Dose (MED) to reduce long-term sequelae. In leprosy patients, who already face significant disability and potential neuropathy, the long-term adverse effects of corticosteroids—such as metabolic syndrome, osteoporosis, and avascular necrosis—are particularly devastating. By achieving remission with an intermediate dose, we minimized the cumulative steroid burden. Furthermore, the concurrent use of broad-spectrum antibiotics (Ceftriaxone) provided a prophylactic shield, covering potential skin flora entering through the necrotic lesions, further mitigating the risk inherent in the immunosuppressive paradox.

While this case offers valuable insights, several limitations must be acknowledged. First, due to resource constraints typical of the setting where leprosy is endemic, we were unable to perform viral serologies. Viral pathogens such as Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), and Parvovirus B19 are known triggers of AIHA. Without serological exclusion, we cannot definitively rule out a viral co-factor that may have acted as a second hit to the immune system. Second, the lack of flow cytometry prevented detailed immunophenotyping of the patient's lymphocyte subsets. Understanding the specific T-helper cell (Th1/Th2/Th17) balance would have provided deeper mechanistic proof of our epitope spreading hypothesis. Finally, as a single case report, the generalizability of the 125 mg/day dosing regimen remains to be validated. While successful in this specific patient with this specific NLR profile, it requires investigation in larger cohorts to establish it as a reproducible protocol.[20]

4. Conclusion

The case of severe Erythema Nodosum Leprosum complicated by Warm Autoimmune Hemolytic Anemia serves as a stark reminder of the complexity of the human immune response. It demonstrates that the collision of chronic mycobacterial infection and acute autoimmunity creates a volatile clinical landscape where standard treatment algorithms may falter. The central lesson of this report is that strict adherence to high-dose corticosteroid protocols (pulse therapy) may not be safe for patients presenting with the dual threat of necrotic skin lesions and extreme leukocytosis. The immunosuppressive paradox demands a nuanced approach. Our findings suggest that an individualized, intermediate-dose corticosteroid regimen (Methylprednisolone 125 mg/day) offers an optimal safety profile in this high-risk subset of patients. This regimen appears sufficient to arrest hemolysis and resolve vasculitis while preserving enough innate immunity to prevent fatal sepsis. Clinicians managing leprosy reactions must remain vigilant for hematologic autoimmunity, distinct from the more common drug-induced anemias. When faced with this rare comorbidity, we recommend a departure from reflexive high-dose steroids in favor of a risk-stratified approach—using markers like the NLR and the extent of skin necrosis—to navigate the delicate balance between necessary immunosuppression and catastrophic infection. This tailored strategy prioritizes patient safety and survival in resource-limited settings where the margin for error is razor-thin.

5. References

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