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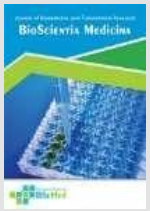

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Concomitant Erythema Nodosum Leprosum and Bullous Dapsone Hypersensitivity Syndrome in Relapsed Multibacillary Leprosy: Pathophysiological Insights and Therapeutic Strategy

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A B S T R A C T

Background: Multibacillary leprosy management is frequently complicated by severe immunological reactions and adverse drug events. Erythema nodosum leprosum is an immune-complex-mediated complication, while dapsone hypersensitivity syndrome is an idiosyncratic, potentially life-threatening drug reaction. The concomitant presentation of these distinct entities, especially with bullous eruptions, creates a profound diagnostic and therapeutic dilemma. **Case presentation:** A 42-year-old male with a history of relapsed borderline lepromatous leprosy and rheumatoid arthritis presented with exquisitely painful erythematous nodules, high-grade fever, and bullous eruptions exactly 72 hours after the re-initiation of multidrug therapy. Physical examination recorded a Visual Analog Scale pain score of 9. Expanded histopathological evaluation confirmed a dual pathology: extensive dermal neutrophilic infiltration characteristic of Erythema Nodosum Leprosum, occurring alongside pronounced subepidermal blistering and marked eosinophilic exocytosis indicative of a dapsone-induced bullous eruption. Standard multidrug therapy was immediately discontinued. A modified regimen comprising rifampicin, clarithromycin, and carefully titrated immunosuppressants (methylprednisolone and azathioprine) was initiated. **Conclusion:** The substitution of dapsone with clarithromycin facilitated rapid clinical resolution of both the bullous eruptions and recurrent immune reactions. This case underscores the critical need for precise temporal tracking, individualized therapeutic modifications, and comprehensive histopathological evaluation in leprosy patients demonstrating complex, overlapping hypersensitivity syndromes.

1. Introduction

Morbus Hansen, universally recognized as leprosy, remains a chronic granulomatous infectious disease of profound global health concern and significant historical weight. Caused by the obligate intracellular bacterium *Mycobacterium leprae*, this insidious pathogen exhibits a unique and highly specialized affinity for the Schwann cells of the peripheral nervous system and the mononuclear phagocytes of the reticuloendothelial system. The pathogenesis of leprosy is not strictly dictated by the virulence of the bacterium itself, but rather by the highly variable and intricate spectrum of the host's cellular immune response. This immunological continuum, classically described by the Ridley-Jopling classification, ranges from the tuberculoid pole, characterized by a robust cell-mediated immunity that successfully restricts bacillary proliferation at the cost of localized tissue damage, to the lepromatous pole.[1] At the lepromatous end of the spectrum, patients exhibit a specific T-cell anergy towards *Mycobacterium leprae* antigens, permitting unchecked bacillary multiplication and

widespread dissemination throughout the skin, peripheral nerves, and cooler regions of the body.

To combat this complex pathogen, the World Health Organization advocates for a standardized multidrug therapy regimen, which has fundamentally transformed the epidemiological landscape of the disease since its global implementation. For multibacillary leprosy—the more severe and highly infectious form of the disease—the gold standard regimen consists of a tripartite combination of rifampicin, dapsone, and clofazimine. Rifampicin serves as the highly potent bactericidal backbone of the regimen, rapidly eliminating viable bacilli. Clofazimine provides a dual action, acting as a slow-acting bacteriostatic agent that binds to mycobacterial DNA while simultaneously exerting significant anti-inflammatory properties. Dapsone, a diamino-diphenyl sulfone, functions primarily as a bacteriostatic agent by competitively inhibiting the synthesis of dihydrofolic acid, while also modulating the host immune response.[2]

While this multidrug therapy regimen is highly efficacious in halting active infection and curing the disease bacteriologically, the clinical course of multibacillary leprosy is rarely linear. It is frequently punctuated by severe, acute inflammatory episodes universally termed as leprosy reactions.[3] These reactions are not indications of treatment failure or disease relapse, but rather represent dynamic immunological perturbations resulting from the massive release of antigens from dead and fragmenting bacilli as the multidrug therapy exerts its antimicrobial effects. These immunological storms can erupt spontaneously before the initiation of therapy, during the course of active treatment, or even years after the successful completion of the multidrug regimen, posing a persistent threat to nerve function and patient well-being.

Among these reactions, erythema nodosum leprosum, classified as a Type 2 reaction, stands out as a severe, systemic immune-complex-mediated complication. erythema nodosum leprosum predominantly afflicts patients situated near the lepromatous pole of the disease spectrum, specifically those diagnosed with borderline lepromatous and polar lepromatous leprosy. These patients carry a massive bacillary load; as the bacilli are slowly degraded, massive quantities of mycobacterial antigens are released into the systemic circulation. Pathophysiologically, erythema nodosum leprosum is classically understood as an Arthus-type, Type III hypersensitivity reaction.[4] The circulating antigens bind to pre-existing host antibodies, forming high molecular weight immune complexes. These complexes subsequently deposit within the walls of small blood vessels in the dermis, subcutaneous tissue, and occasionally internal organs. This deposition triggers the classical complement cascade, leading to the generation of potent chemotactic factors that provoke an aggressive and rapid influx of neutrophils into the surrounding tissue.

Clinically, this intense localized and systemic inflammation manifests as recurrent, exquisitely painful, and tender erythematous nodules typically distributed across the extensor surfaces of the extremities and the face. The localized cutaneous inflammation is frequently accompanied by a profound systemic inflammatory response syndrome.[5] Patients routinely present with high-grade, spiking fevers, severe arthralgia, myalgia, lymphadenopathy, and varying degrees of visceral involvement, including iridocyclitis, orchitis, and glomerulonephritis. Most critically, the inflammatory infiltrate frequently extends into the perineural tissue, resulting in acute, agonizing neuritis that, if not rapidly suppressed, rapidly progresses to irreversible peripheral nerve damage, paralysis, and permanent physical deformity. The management of erythema nodosum leprosum requires prolonged, carefully titrated courses of systemic corticosteroids or thalidomide to suppress the erratic immune response while maintaining the underlying multidrug therapy to ensure bacterial eradication.

Concurrently, the pharmacological management of multibacillary leprosy carries its own inherent and potentially devastating risks of adverse drug reactions,

creating a precarious balancing act for clinicians. Dapsone, while serving as a fundamental bacteriostatic and anti-inflammatory pillar of the multidrug therapy regimen, is widely recognized in dermatological and infectious disease medicine for its potential to induce severe systemic toxicity. Beyond its predictable, dose-dependent hematological side effects such as methemoglobinemia and hemolytic anemia, dapsone is notorious for triggering Dapsone hypersensitivity syndrome. Dapsone hypersensitivity syndrome is a severe, idiosyncratic, and potentially life-threatening delayed-type drug hypersensitivity reaction.[6] Unlike the immune-complex pathology of erythema nodosum leprosum, Dapsone hypersensitivity syndrome is driven by a distinct cell-mediated mechanism. The pathogenesis is primarily attributed to the hepatic metabolism of dapsone via the cytochrome P450 system, which generates a highly reactive and toxic metabolite known as dapsone hydroxylamine. In individuals with specific, largely genetically determined susceptibilities, this hydroxylamine metabolite fails to be adequately detoxified. Instead, it acts as a potent hapten, covalently binding to host cellular proteins to form neoantigens. These neoantigens are presented to the immune system, precipitating a massive, uncontrolled activation of cytotoxic CD8+ and helper CD4+ T-cells.

This profound T-cell-mediated immune dysregulation manifests clinically with a classic diagnostic triad: a high-grade persistent fever, severe cutaneous eruptions, and significant internal organ involvement. The cutaneous manifestations of Dapsone hypersensitivity syndrome are highly variable but typically begin as an intensely pruritic, widespread maculopapular or morbilliform exanthem. In severe cases, this exanthem can rapidly progress to exfoliative dermatitis, toxic epidermal necrolysis, or severe bullous eruptions characterized by widespread subepidermal cleavage and blistering.[7] The systemic component is equally aggressive, most commonly presenting as a severe, acute toxic hepatitis accompanied by jaundice, tender hepatomegaly, and significantly elevated transaminases. Lymphadenopathy is a nearly universal finding, and other organ systems may be implicated, leading to pneumonitis, nephropathy, or myocarditis. Given the idiosyncratic nature of this syndrome, recognizing the temporal relationship to drug initiation—typically between two to six weeks—and executing the immediate, permanent cessation of dapsone are the absolute mandates of clinical management.

The intersection of recurrent erythema nodosum leprosum and Dapsone hypersensitivity syndrome in a single patient presents a formidable and deeply complex clinical challenge. Both conditions represent explosive, systemic immunological emergencies characterized by sudden onset, high fevers, intense systemic inflammation, and severe cutaneous manifestations. In their early evolutionary stages, the cutaneous eruptions of a severe, necrotizing erythema nodosum leprosum flare can be clinically indistinguishable from the progressive bullous transformations seen in Dapsone Hypersensitivity Syndrome. The development of fluid-filled bullae overlying deeply inflamed skin serves as a terrifying clinical crossroad.[8]

This overlapping presentation creates a profound diagnostic and therapeutic dilemma. To misdiagnose Dapsone hypersensitivity syndrome as a severe erythema nodosum leprosum reaction and subsequently maintain the patient on the offending drug, dapsone, while merely escalating corticosteroids, invariably leads to progressive, fatal multiorgan failure driven by continuous T-cell activation. Conversely, misdiagnosing an erythema nodosum leprosum reaction as a drug hypersensitivity and prematurely aborting the multidrug therapy regimen severely compromises the antimicrobial treatment plan, exposing the patient to the grave risks of unchecked bacillary multiplication, clinical relapse, and the development of antimicrobial resistance. The clinician is forced to decipher whether the blistering skin and failing liver are the result of massive mycobacterial immune complex deposition or an aberrant, cytotoxic reaction to the very medication prescribed to cure the infection.[9]

This diagnostic complexity is exponentially magnified in patients who harbor pre-existing autoimmune conditions. An underlying state of autoimmune dysregulation intrinsically alters the host's immunological baseline, creating a highly volatile environment pre-primed for exaggerated inflammatory responses. Conditions characterized by a loss of regulatory T-cell suppression and a chronic overproduction of pro-inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6, act as powerful catalysts. In such a skewed immunological landscape, the host immune system is highly sensitized. The massive antigen release associated with mycobacterial death synergizes destructively with the haptenization of the dapsone metabolite. The shared cytokine milieu acts as a bidirectional amplifier, blurring the pathophysiological boundaries between infection-induced hypersensitivity and drug-induced hypersensitivity, and accelerating the progression toward severe tissue necrosis and organ dysfunction.[10]

Understanding this intricate cross-talk between infectious antigen load, idiosyncratic pharmacological toxicity, and host autoimmune status is paramount for advancing the clinical management of severe, complex leprosy cases. Therefore, the primary aim of this study is to elucidate the complex pathophysiological interplay between a chronic infectious antigen load, idiosyncratic drug hypersensitivity, and underlying autoimmune dysregulation within a single host. The novelty of this research lies in the detailed methodological deconstruction of a rare, simultaneous presentation of bullous dapsone hypersensitivity syndrome and severe erythema nodosum leprosum, providing a rigorously validated clinical timeline that differentiates the overlapping syndromes, and outlining the clinical rationale and therapeutic efficacy of a clarithromycin-based salvage regimen in a resource-limited setting.

2. Case Presentation

Ethical consideration

This case report was conducted in strict adherence to the fundamental ethical principles outlined in the Declaration of Helsinki regarding medical research involving human subjects. Written informed consent was formally obtained from the patient prior to the drafting and submission of this manuscript. The patient was comprehensively briefed regarding the objectives of this publication, and explicit permission was granted for the reproduction of anonymized clinical data, including laboratory results, chronological disease progression, and therapeutic outcomes, for educational and academic dissemination. To guarantee absolute patient confidentiality and privacy, all personally identifiable information has been thoroughly redacted from this document. Furthermore, due to the retrospective and observational nature of this single-case presentation, formal approval from the institutional ethics committee was waived in accordance with standard institutional policies. The authors ensure that the integrity of the clinical narrative remains intact while unequivocally protecting the patient's anonymity throughout the publication process.

Patient history and clinical course

A 42-year-old male was referred to the Dermatology and Venereology outpatient clinic with a chief complaint of recurrent, exquisitely painful nodular lesions on his bilateral upper and lower extremities. The patient reported that these lesions systematically worsened, accompanied by high-grade fevers, severe arthralgia, and the sudden emergence of large, fluid-filled bullae on his limbs. A rigorous review of the patient's medical history revealed a diagnosis of multibacillary Hansen's disease, Borderline Lepromatous type, established two years prior and complicated by initial episodes of erythema nodosum leprosum. He had completed a standard 12-month multidrug therapy regimen while concurrently receiving systemic methylprednisolone. One year following the completion of therapy, he experienced a

confirmed clinical relapse characterized by the reappearance of painful nodules. The patient was re-prescribed the standard multibacillary multidrug therapy regimen at a primary care facility. Crucially, exact temporal tracking established that exactly 72 hours following the re-initiation of dapsone, the patient developed acute, blistering eruptions on his extremities, leading to subsequent ulceration and hemorrhagic crusting. Additionally, the patient has a confirmed comorbidity of Rheumatoid Arthritis and was maintained on azathioprine 50 mg/day. He denied any history of hypertension, malignancy, atopy, or familial history of similar dermatological conditions.

Physical and neurological examination

Upon admission, the patient appeared severely ill but was fully conscious (Glasgow Coma Scale 15). Vital signs revealed a blood pressure of 139/82 mmHg, heart rate of 98 beats/min, respiratory rate of 22 breaths/min, and an elevated temperature of 39.1 degrees Celsius. Validating the qualitative description of his symptoms, the patient recorded a Visual Analog Scale pain score of 9, indicating severe, debilitating pain. His Body Mass Index was 22.7 kg/m^2. Dermatological examination was striking. The facial region exhibited a prominent saddle nose deformity. Examination of the bilateral dorsum manus and inferior extremities revealed multiple, discrete, intensely erythematous nodules. Interspersed among these nodules were numerous intact tense bullae, ranging from 1 to 4 centimeters in diameter, alongside extensive erosions and thick hemorrhagic crusts. Neurological assessment yielded intact sensory functions; however, motor evaluation demonstrated notable deficits, specifically a reduction in strength innervated by the left radial nerve and bilateral common peroneal nerves (Table 1).

Laboratory and histopathological investigations

A comprehensive diagnostic workup was initiated. Routine hematology and chemistry panels revealed severe systemic inflammation and hepatic stress: Hemoglobin 11.2 g/dL, Hematocrit 34 percent, significant leukocytosis at 21,300/uL with prominent peripheral eosinophilia (12 percent), Platelets 185,000/uL, and Erythrocytes 4.17 million/uL. Liver function tests indicated notable transaminitis with SGOT at 145 U/L and SGPT at 162 U/L, while renal parameters remained within normal limits (Creatinine 0.9 mg/dL, Urea 29 mg/dL). A chest CT-scan was performed to rule out pulmonary opportunistic infections, revealing no acute cardiopulmonary abnormalities. Acute phase reactants revealed a significantly elevated C-reactive protein at 95 mg/L.

A slit-skin smear examination demonstrated a Bacteriological Index of +2 with a Morphological Index of 0 percent, confirming the presence of persistent, fragmented bacilli consistent with a relapse state. To establish a definitive diagnostic framework for the dual pathology, a cutaneous punch biopsy was obtained from a fresh bullous lesion overlying an erythematous nodule. Histopathological evaluation via Hematoxylin and Eosin staining revealed a highly complex dual morphology. The deep dermis and subcutaneous adipose tissue exhibited extensive necrosis accompanied by a dense, destructive inflammatory infiltrate composed predominantly of neutrophils, histiocytes, and evidence of leukocytoclasia, which strictly aligns with the criteria for erythema nodosum leprosum (Figure 2). Concurrently, the upper dermis and dermo-epidermal junction displayed distinct features of a severe drug eruption: pronounced subepidermal blistering, basal layer vacuolization, and massive eosinophilic exocytosis extending into the blister cavity. Fite-Faraco staining confirmed the presence of Acid-Fast Bacilli within the deep dermal macrophages, yielding a logarithmic Bacteriological Index of 3 (Figure 3).

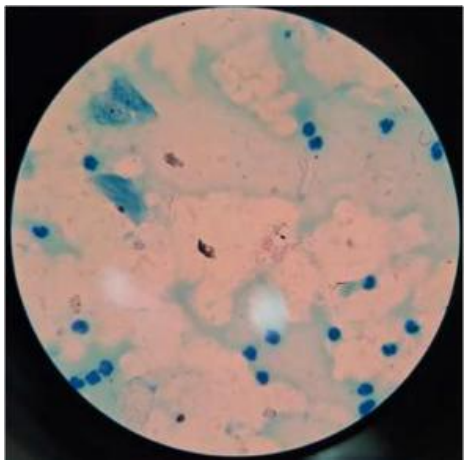

Figure 1. Slit-skin smear examination.

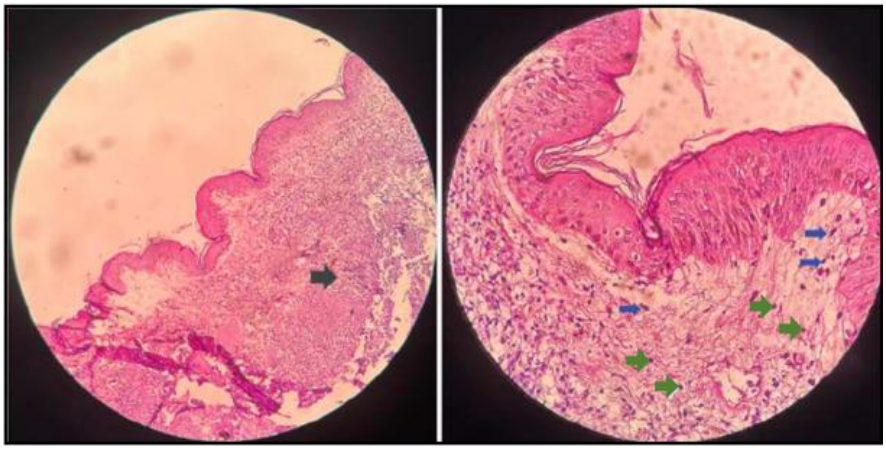

Figure 2. Histopathological evaluation via hematoxylin and eosin staining. Deep dermis and subcutaneous adipose tissue exhibited extensive necrosis (black arrow), accompanied by an inflammatory infiltrate composed predominantly of neutrophils (blue arrows) and histiocytes (green arrows).

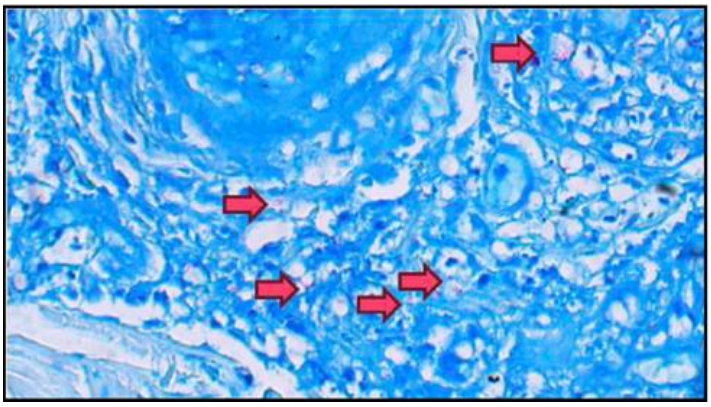

Figure 3. Fite-Faraco staining. Red arrows point to the presence of acid-fast bacilli.

Table 1

Summary of Clinical Findings on Admission

Clinical Category	Parameter	Observation / Value
General Status & Vital Signs	**General Appearance**	Severely ill, fully conscious (GCS 15)
	Pain Score	Visual Analog Scale (VAS) 9 (Severe)
	Blood Pressure	139/82 mmHg
	Heart / Respiratory Rate	98 beats/min / 22 breaths/min
	Body Temperature	**39.1 °C**
	Body Mass Index (BMI)	22.7 kg/m²
Physical & Neurological Examination	**Facial Region**	Prominent saddle nose deformity
	Dermatological (Extremities)	Multiple, discrete, intensely erythematous nodules. Intact tense bullae (1-4 cm), extensive erosions, thick hemorrhagic crusts.
	Neurological (Motor Function)	Reduced strength innervated by left radial nerve and bilateral common peroneal nerves (Sensory function intact).
Laboratory & Radiology Investigations	**Hematology**	Hb: 11.2 g/dL, Hct: 34%, Platelets: 185,000/uL, RBC: 4.17 million/uL
	Leukocytes & Differential	21,300/uL with prominent peripheral eosinophilia (12%)
	Liver Function Tests	SGOT: 145 U/L, SGPT: 162 U/L
	Acute Phase Reactants	C-Reactive Protein (CRP): 95 mg/L
	Radiology (CT-scan)	Chest CT-scan: No acute cardiopulmonary abnormalities
Microbiology & Histopathology	**Slit-Skin Smear**	Bacteriological Index (BI): +2, Morphological Index (MI): 0%
	Cutaneous Biopsy (H&E Stain)	Deep dermis/subcutaneous: extensive necrosis, dense neutrophilic infiltrate (leukocytoclasia). Upper dermis/epidermis: subepidermal blistering, basal layer vacuolization, massive eosinophilic exocytosis.
	Fite-Faraco Stain	Acid-Fast Bacilli present in deep dermal macrophages (Logarithmic BI: 3)

Therapeutic intervention and follow-up

Based on the synthesis of the precise 72-hour temporal relationship to drug ingestion, the severely elevated VAS pain score, and the expanded histopathological evidence demonstrating both neutrophilic panniculitis and eosinophilic subepidermal cleavage, a definitive diagnosis of relapsed multibacillary Hansen's disease with recurrent erythema nodosum leprosum and concomitant bullous Dapsone hypersensitivity syndrome was established (Table 2). Standard multidrug therapy was immediately revoked. A pharmacologically tailored, clarithromycin-based modified regimen was instituted: Rifampicin 600

mg/month and Clarithromycin 500 mg/day. To manage the intense immunological cascade driven by the overlapping hypersensitivity syndromes and the patient's baseline Rheumatoid Arthritis, immunosuppression was optimized using Methylprednisolone 32 mg/day and Azathioprine 50 mg/day, alongside Gabapentin 300 mg/day for neuropathic pain control. Local wound care comprised normal saline compresses, mupirocin 2 percent ointment, and intra-site hydrogel application. During comprehensive follow-up evaluations over the subsequent four weeks, the patient demonstrated profound clinical improvement. The febrile episodes ceased entirely within 48 hours of dapsone cessation. No novel bullous eruptions were observed, the prominent peripheral eosinophilia normalized, hepatic transaminases returned to baseline, and the existing necrotizing ulcerative lesions showed excellent granulation and re-epithelialization.

Table 2

Diagnosis, Treatment, Follow-up, and Outcome

Phase	Component	Clinical Details
1. Definitive Diagnosis	**Primary Infection**	Relapsed Multibacillary Hansen's Disease (Borderline Lepromatous type)
	Immunological Complication	Recurrent Erythema Nodosum Leprosum (Type 2 Reaction)
	Adverse Drug Reaction	**Concomitant Bullous Dapsone Hypersensitivity Syndrome**
	Underlying Comorbidity	Rheumatoid Arthritis
2. Therapeutic Intervention	**Discontinued Medication**	**Immediate cessation of Dapsone**
	Modified Antimicrobial Regimen	Rifampicin 600 mg/month Clarithromycin 500 mg/day
	Immunosuppression	Methylprednisolone 32 mg/day Azathioprine 50 mg/day
	Neuropathic Protection	Gabapentin 300 mg/day
	Local Wound Care	Normal saline compresses, mupirocin 2 percent ointment, and intra-site hydrogel application
3. Follow-up (Over 4 Weeks)	**Systemic Symptoms**	Febrile episodes ceased entirely within 48 hours of dapsone cessation
	Laboratory Parameters	Prominent peripheral eosinophilia normalized; Hepatic transaminases (SGOT/SGPT) returned to baseline
	Cutaneous Evaluation	No novel bullous eruptions observed during the bi-weekly evaluation periods
4. Final Outcome	**Lesion Resolution**	Existing necrotizing ulcerative lesions demonstrated excellent granulation and re-epithelialization
	Overall Clinical Status	**Profound clinical improvement with successful extinguishing of both the immune reaction and drug hypersensitivity flare**

3. Discussion

The simultaneous clinical manifestation of severe Type 2 leprosy reactions and bullous Dapsone hypersensitivity syndrome within a single patient represents a profoundly complex immunological conundrum that demands an exhaustive and precise pathophysiological deconstruction. To fully comprehend the catastrophic tissue destruction observed in this case, one must independently analyze the underlying mechanisms of each syndrome before examining their synergistic convergence. Erythema nodosum leprosum is classically defined in the immunological literature as an Arthus-type, or Type III, hypersensitivity reaction. This severe complication is fundamentally triggered by the sudden and massive release of mycobacterial antigens into the systemic circulation.[11] In multibacillary leprosy, particularly within the borderline lepromatous and polar lepromatous spectrums, the host harbors an extraordinarily high bacterial load. As the antimicrobial agents of the multidrug therapy regimen begin to exert their bactericidal and bacteriostatic effects, the *Mycobacterium leprae* bacilli undergo fragmentation and degradation. This process liberates vast quantities of highly immunogenic structural components, including lipoarabinomannan and phenolic glycolipid-I. In a patient with an established humoral immune response, these newly released antigens rapidly encounter high titers of circulating IgG and IgM antibodies. The subsequent binding results in the formation of large, circulating extravascular immune complexes. Due to their molecular weight and the hemodynamic properties of the microvasculature, these immune complexes preferentially precipitate and deposit within the endothelial walls of small blood vessels in the deep dermis, subcutaneous adipose tissue, and occasionally within peripheral nerves and internal organs. This physical deposition is the critical initiating event that triggers the classical complement pathway. The cleavage of complement proteins generates potent anaphylatoxins and chemotactic factors, most notably C3a and C5a, which provoke an intense, rapid, and unrelenting influx of polymorphonuclear neutrophils. The localized degranulation of these neutrophils results in the deep dermal and subcutaneous nodular inflammation, clinically pathognomonic for Erythema Nodosum Leprosum, driving the severe pain and systemic febrile response observed in this patient.[12]

In stark contrast to the immune-complex-mediated pathology of erythema nodosum leprosum, Dapsone hypersensitivity syndrome is governed by a delayed-type, cell-mediated, or Type IV hypersensitivity reaction. The pathogenesis of this potentially fatal syndrome is inextricably linked to the hepatic pharmacokinetics of dapsone.[13] While dapsone is primarily metabolized via N-acetylation, an alternative oxidative pathway mediated by the cytochrome P450 enzyme system—specifically the CYP2C9 and CYP2E1 isoenzymes—generates a highly reactive and toxic hydroxylamine metabolite known as dapsone hydroxylamine. In individuals harboring specific, yet not fully elucidated, genetic susceptibilities or those lacking adequate glutathione-dependent detoxification reserves, this hydroxylamine metabolite accumulates. Rather than being safely excreted, the metabolite acts as a potent hapten. It covalently binds to intrinsic host cellular proteins, thereby altering their structural conformation and creating novel, non-self antigens or neoantigens. These neoantigens are subsequently engulfed, processed, and presented by professional antigen-presenting cells via Human Leukocyte Antigen molecules to the host's adaptive immune system. This presentation triggers a robust, uncontrolled, and systemic activation of both helper CD4+ T-cells and cytotoxic CD8+ T-cells.

In a standard clinical scenario, the sensitization and clonal expansion of these T-cells dictate that dapsone hypersensitivity syndrome typically manifests two to six weeks following the initial administration of the drug (Figure 4). However, in patients burdened with recurrent Erythema Nodosum Leprosum, the immunological landscape is drastically altered. Chronic erythema nodosum leprosum creates

a state of sustained, systemic immune activation. The patient's serum is chronically saturated with high levels of pro-inflammatory cytokines, specifically tumor necrosis factor-alpha and interleukin-6.[14] Furthermore, this chronic inflammatory state induces a profound and inherent imbalance between Regulatory T cells, which normally suppress aberrant immune responses, and Transforming Growth Factor-beta. This pre-existing state of immunological hyper-responsiveness dramatically lowers the threshold required to trigger a secondary hypersensitivity event. Consequently, when this specific patient was re-exposed to the dapsone hydroxylamine metabolite upon the re-initiation of multidrug therapy, his inherently primed and hyper-vigilant immune system bypassed the standard sensitization phase. Instead, it launched an exaggerated, accelerated, and overwhelmingly cytotoxic anamnestic response, which perfectly explains the unusually rapid 72-hour clinical onset observed in this case.[15]

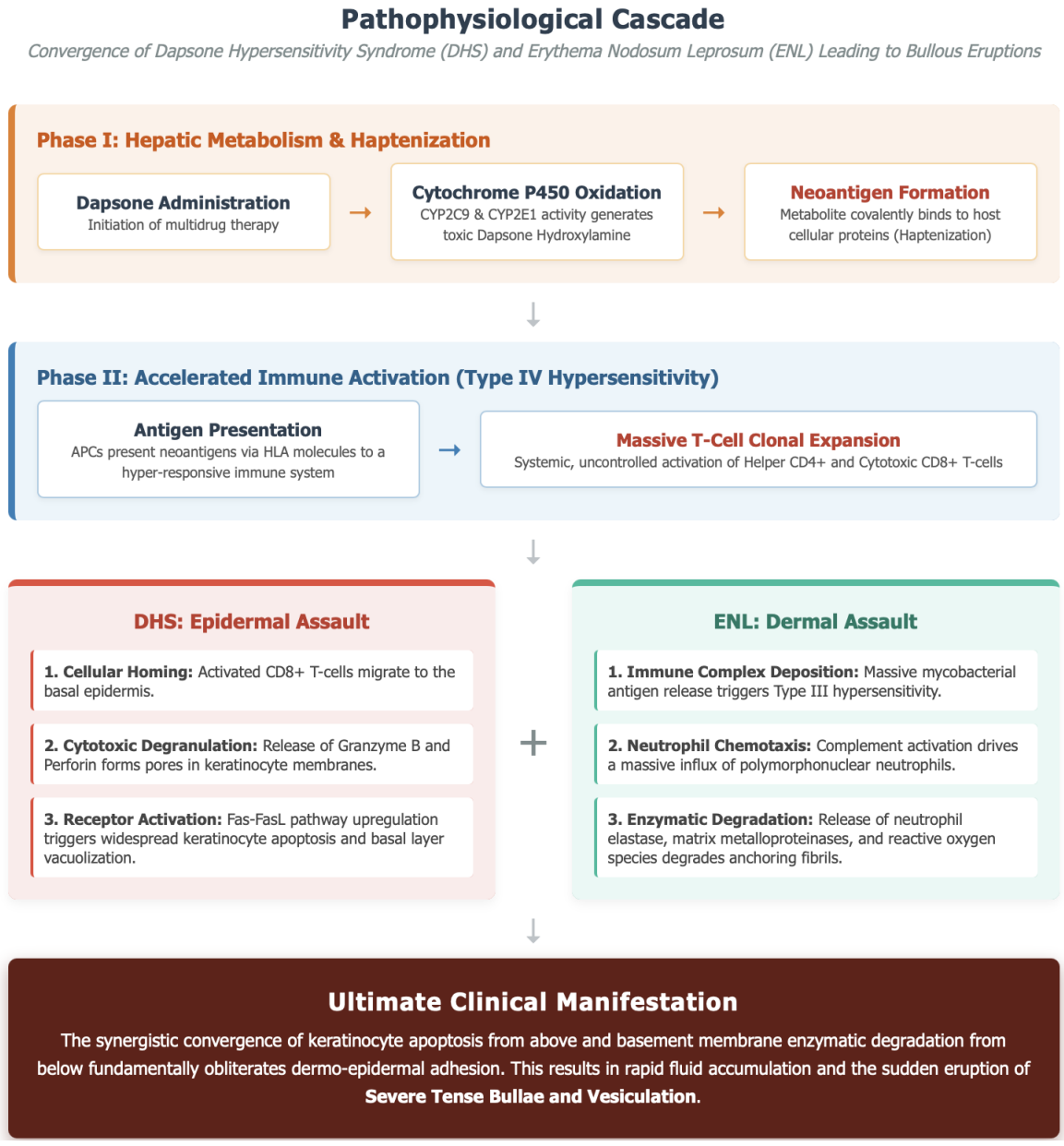

Figure 4. Pathophysiological cascade of dapsone hypersensitivity syndrome.

The subsequent development of widespread bullous eruptions in this specific clinical context is not merely a symptom, but rather the visible result of a catastrophic convergence of these two independent immunological pathways occurring simultaneously within the skin. The structural integrity of the skin relies heavily on the dermo-epidermal junction, a complex matrix of hemidesmosomes, anchoring fibrils, and glycoproteins that bind the epidermis to the underlying dermis. The severe bullae observed in Dapsone Hypersensitivity Syndrome are directly precipitated by the massive, systemic activation of cytotoxic CD8+ T cells. Homing to the skin, these highly active CD8+ T cells target the basal keratinocytes. Upon recognition of the haptenized proteins on the keratinocyte surface, the T cells release lytic granules containing granzyme B and perforin.[16] Perforin creates pores in the target cell membrane, allowing granzyme B to enter and initiate the caspase cascade, leading to programmed cell death. Simultaneously, the T cells upregulate Fas ligand, which binds to the Fas receptor on the keratinocytes, further driving widespread cellular apoptosis. This massive wave of keratinocyte death was histopathologically evident in the biopsy as severe basal layer vacuolization and distinct subepidermal cleavage.

Simultaneously, the massive influx of neutrophils, aggressively driven by the concomitant Erythema Nodosum Leprosum reaction, invades the lower and mid-dermis. As these hyperactive neutrophils degranulate, they release vast quantities of proteolytic enzymes, most notably neutrophil elastase and various matrix metalloproteinases, alongside highly destructive reactive oxygen species into the dermal extracellular matrix. While the CD8+ T cells are systematically destroying the basal layer of the epidermis from above, the neutrophil-derived enzymes are chemically degrading the basement membrane zone and the anchoring fibrils from below. This combined, synergistic assault of targeted cellular apoptosis and indiscriminate enzymatic degradation fundamentally obliterates dermo-epidermal adhesion.[17] The loss of structural integrity results in rapid, massive fluid accumulation within the cleavage planes, presenting clinically as severe, tense, and widespread vesiculation and bulla formation.

The profound severity of this pathological cascade is intrinsically amplified by the patient's comorbid rheumatoid arthritis. Rheumatoid arthritis is fundamentally defined by profound, chronic systemic immune dysregulation. It is dominated by the continuous production of autoantibodies, such as rheumatoid factor and anti-cyclic citrullinated peptide, and a persistent overexpression of a specific triad of pro-inflammatory cytokines: tumor necrosis factor-alpha, interleukin-6, and interleukin-17.[18] The shared pathophysiological foundation interlinking rheumatoid arthritis, erythema nodosum leprosum, and Dapsone hypersensitivity syndrome rests upon the critical loss of functional Regulatory T cells. Regulatory T cells, heavily dependent on the transcription factor FOXP3, are essential for maintaining peripheral tolerance and dampening hyperactive inflammatory responses. In the context of active rheumatoid arthritis, regulatory T cell function is notably impaired, allowing autoreactive T cells and B cells to proliferate unchecked. This shared cytokine milieu acts as a bidirectional, compounding amplifier. The baseline systemic inflammation emanating from the autoimmune arthritis essentially primes the patient's entire reticuloendothelial system, making the host highly susceptible to more severe, refractory, and recurrent leprosy reactions. Conversely, the chronic, sustained antigen load provided by the persistent *Mycobacterium leprae* infection, coupled with the haptenization of the dapsone metabolite, continuously stimulates and triggers the autoreactive pathways associated with Rheumatoid Arthritis, creating a vicious, self-sustaining cycle of inflammation and tissue destruction.

Faced with this immunological storm, the immediate and permanent cessation of dapsone is the absolute, non-negotiable clinical mandate upon the initial suspicion of a drug-induced hypersensitivity syndrome. Continuing the offending agent in the

presence of an active T-cell-mediated cytotoxic reaction invariably leads to progressive, fatal multiorgan failure, typically culminating in fulminant hepatic necrosis. However, discontinuing a cornerstone bacteriostatic agent in the treatment of multibacillary leprosy presents a secondary therapeutic dilemma. A robust, highly effective antimicrobial substitute must be immediately deployed to prevent unchecked bacillary multiplication, the risk of disease dissemination, and the potential development of rifampicin resistance.[19]

In this highly complex scenario, clarithromycin, a semi-synthetic macrolide antibiotic, was strategically selected as the optimal substitute. Clarithromycin acts primarily by penetrating the bacterial cell wall and reversibly binding to the 50S ribosomal subunit of the mycobacterium, thereby effectively inhibiting RNA-dependent protein synthesis. Beyond its well-established and potent antimicrobial efficacy against *Mycobacterium leprae*, clarithromycin was chosen for this specific patient due to its thoroughly documented intrinsic immunomodulatory properties. Macrolides possess a unique ability to downregulate the production of pro-inflammatory cytokines, decrease neutrophil chemotaxis, and reduce oxidative burst activity independent of their antimicrobial action. This makes clarithromycin uniquely suited to help manage the neutrophil-driven pathology of Erythema Nodosum Leprosum. Most critically, from a pharmacological safety perspective, clarithromycin features a completely distinct molecular structure compared to dapsone. It lacks the arylamine structure and does not undergo the specific N-hydroxylation metabolic pathways that trigger dapsone hypersensitivity, thereby eliminating the risk of cross-reactivity or exacerbation of the existing hypersensitivity syndrome. Furthermore, its concurrent administration with azathioprine—utilized to manage the underlying Rheumatoid Arthritis—provided a carefully calibrated, stabilized immunosuppressive blanket. This dual approach successfully extinguished the intense inflammatory flares of both the Type III and Type IV hypersensitivity reactions simultaneously, promoting rapid cutaneous healing and systemic recovery without precipitating any further drug-induced toxicity or organ strain.

A notable limitation of this case study involves the diagnostic constraints inherent to a resource-limited healthcare setting. This environment precluded the performance of advanced molecular diagnostics and comprehensive transcriptomic profiling that would have further characterized the patient's intricate baseline. The inability to perform high-resolution genetic sequencing restricted the identification of specific human leukocyte antigen alleles that may have predisposed this individual to such a severe adverse drug event.[20] Future research endeavors must prioritize large-scale, prospective cohort studies utilizing real-time transcriptomic profiling and pharmacogenomic mapping to elucidate the precise genetic overlaps between leprosy hypersensitivity states, underlying autoimmune diseases, and idiosyncratic drug reactions. Such advancements are imperative, paving the way for targeted genetic risk stratification and highly personalized therapeutic modifications prior to the initiation of multidrug therapy in endemic regions.

4. Conclusion

The concomitant presentation of Erythema Nodosum Leprosum and bullous Dapsone Hypersensitivity Syndrome constitutes a profound, life-threatening dermatological and immunological emergency. This case powerfully illustrates that persistent, rapidly accelerating inflammatory flares accompanied by sudden bullous transformations following the re-initiation of multidrug therapy must immediately raise the highest clinical index of suspicion for an overlapping, drug-induced hypersensitivity reaction, rather than being dismissed as a merely recalcitrant leprosy reaction. The rapid 72-hour onset observed in this patient underscores the dangerous reality of anamnestic immune responses in hosts primed by chronic infection and underlying autoimmunity.

The successful implementation of a clarithromycin-substituted, multi-disciplinary regimen highlights the absolute necessity of agile, highly individualized pharmacotherapy when navigating the dangerous intersection of infectious disease and clinical immunology. Rigorous, minute-by-minute temporal tracking of symptom onset relative to drug administration, combined with deeply comprehensive, multi-layered histopathological evaluation, remains the most essential diagnostic tool for frontline clinicians. Ultimately, navigating complex, overlapping hypersensitivity syndromes in patients harboring intrinsic autoimmune comorbidities requires a paradigm shift away from rigid, standardized treatment protocols toward a highly vigilant, personalized approach to leprosy management, ensuring that the pursuit of a microbiological cure does not come at the cost of catastrophic iatrogenic harm.

5. References

1. Chiramel MJ, George R, Daniel D, Sam Arul Das R, Mani V, Antonisamy B, et al. Case-control study measuring the association between HLA-B*13:01 and Dapsone hypersensitivity syndrome in Indian patients. Lepr Rev. 2019; 90(4): 371–7.
2. Agrawal S, Borkar M, Deoke S. A rare case of pure neuritic leprosy with hereditary spherocytosis: implications for Dapsone use. Lepr Rev. 2024; 95(3).
3. Spałek MM, Jałowska M, Welc N, Bowszyc-Dmochowska M, Dmochowski M. Dapsone as a current option for the treatment of autoimmune bullous diseases with autoimmunity to non-enzymes: a retrospective study from a single Central European referral center. Medicina (Kaunas). 2024; 60(8): 1324.
4. Sinha A, Dangwal V, R. Mallick A, Singh A, Sinha A. Conundrum of recurrent erythema nodosum leprosum and dapsone hypersensitivity syndrome complicating pediatric leprosy. Ind J Paediatr Derm. 2021; 22(4): 352.
5. Craig J, MacRae C, Melvin RG, Boggild AK. Case report: a case of Type 1 leprosy reaction and dapsone hypersensitivity syndrome complicating the clinical course of multibacillary leprosy. Am J Trop Med Hyg. 2019; 100(5): 1145–8.
6. You J, Sun L, Zhao Q, Zhang H, Huai P, Yu G, et al. Dynamic cytokine profiles combined with enzyme-linked immunospot assay are useful for immunologically confirming the dapsone hypersensitivity syndrome. J Am Acad Dermatol. 2021; 84(3):
7. Pahadiya HR, Lakhotia M. Dapsone hypersensitivity syndrome with leukemoid reaction and severe thrombocytosis. Cureus. 2021; 13(3): e14026.
8. Babu T, Panachiyil GM, Ramesh S, Vasudev PH, Ravi MD, Chandrashekhar C. A rare case of dapsone hypersensitivity syndrome and leukemoid reaction with coexisting hepatitis E in a pediatric patient. Hosp Pharm. 2021; 56(4): 347–9.
9. Weerasekara SPN, Abeynayake C, Abeywardana S, Akarawita J, Senadheera N. A case report of Dapsone hypersensitivity syndrome in a child with Lepromatous Leprosy and potential genetic element. Kandy Med J. 2022; 31(1): 122–5.
10. Ansah R, Arkoh EA, Quao BO, Groger M. Lack of suspicion of dapsone hypersensitivity syndrome in a leprosy patient: case report with fatal outcome. Res Rep Trop Med. 2023; 14: 135–9.
11. Dev A, Narang T, Thakur V, Dogra S. The dapsone conundrum: Understanding implications of adverse reactions to dapsone including dapsone hypersensitivity syndrome in leprosy patients treated with multidrug therapy. Int J Dermatol. 2025; 64(10): 1862–9.

12. Palaniappan V, Sadhasivamohan A, Karthikeyan K. Dapsone hypersensitivity syndrome skin rash exhibiting anatopic phenomenon. Indian Dermatol Online J. 2025; 16(1): 143–5.
13. Rana DR, Shakya J, Baral S, Shrestha R, Koju K, Joshi J, et al. Clinico-epidemiological and molecular evidences for reactivation of herpesviruses in dapsone-induced hypersensitivity reactions in Nepalese leprosy patients: an observational study. Immun Inflamm Dis. 2026; 14(2): e70385.
14. Choudhary SR, Bhatnagar A, Chalise S, Bajaj V, Das P, Priya L, et al. Dapsone-induced hypersensitivity pneumonitis in borderline tuberculoid leprosy. Int J Dermatol. 2026; 65(3): 674–6.
15. Mrigpuri P, Sarma M, Spalgais S, Menon B. When treatment imitates tuberculosis: Dapsone induced hypersensitivity pneumonitis in a patient with Hansen's disease. Indian J Tuberc. 2026.
16. Jindal A, Alam R, Goel S, Chaudhary AF. Dapsone hypersensitivity syndrome with multisystem involvement in a case of borderline tuberculoid Hansen's disease. Lepr Rev. 2025; 96(4).
17. Sagar HK. Dapsone hypersensitivity syndrome in leprosy. Am J Trop Med Hyg. 2025; 113(6): 1167–8.
18. Zhu H-Q, Jiang S-H, Song G-L. Non-leprosy related dapsone hypersensitivity syndrome: a case report and literature review. Medicine (Baltimore). 2025; 104(27): e43073.
19. Linuwih Menaldi S, Rahayu T, Gibran K, Widaty S, Handaru Priyanto M, Friska D, et al. The role of the HLA-B*13:01 allele in leprosy patients with Dapsone hypersensitivity syndrome (DHS): a systematic review and meta-analysis. Lepr Rev. 2025; 96(3).
20. Liu H, Wang Z, Bao F, Wang C, Sun L, Zhang H, et al. Evaluation of prospective HLA-B*13:01 screening to prevent dapsone hypersensitivity syndrome in patients with leprosy. JAMA Dermatol. 2019; 155(6): 666–72.