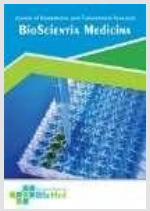
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

The Steel-Blue Peppering and Systemic Eosinophilia: Dermoscopic-Histopathological Correspondence of the Tyndall Effect in Generalized Fixed Drug Eruption

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ARTICLE INFO

Keywords:
Dermoscopy
Eosinophilia
Generalized fixed drug eruption
Steel-blue peppering
Tyndall effect

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v10i3.1538

A B S T R A C T

Background: Generalized fixed drug eruption (GFDE) represents a severe and distinctive variant of delayed-type hypersensitivity, characterized by widespread, recurrent pigmentary lesions involving at least three anatomical sites. Its clinical presentation often mimics extensive lichenoid dermatoses or infectious conditions such as Hansen's disease, leading to significant diagnostic delays, particularly in geriatric populations with polypharmacy. While dermoscopy offers a non-invasive bridge to histopathology, specific correlative studies in generalized cases remain scarce. **Case presentation:** We report the case of a 69-year-old male presenting with diffuse, well-demarcated, violaceous plaques affecting the face, trunk, extremities, and genitalia. The eruption demonstrated a pathognomonic acute latency, recurring at identical anatomical sites within six hours of re-exposure to an unprescribed analgesic cocktail. High-definition non-contact polarized dermoscopy identified two distinct morphological patterns: a brown starburst pattern with central clearing on the extremities and diffuse steel-blue peppering on femoral lesions. Notably, the patient exhibited a mixed immunophenotype characterized by marked eosinophilia (2,080 cells per microliter) and elevated total immunoglobulin E (2,295 IU per milliliter). Parasitic infection was rigorously excluded via negative stool examination and serology, and a Naranjo probability score of 10 confirmed a definite adverse drug reaction. Histopathological examination confirmed interface dermatitis with necrotic keratinocytes and marked pigment incontinence. **Conclusion:** This study illustrates that steel-blue peppering is a reliable dermoscopic surrogate for deep dermal pigment incontinence via the Tyndall effect. The discrepancy between high systemic eosinophilia and low tissue eosinophilia suggests a complex, potentially mixed-hypersensitivity phenotype in generalized cases, distinct from classic localized fixed drug eruption.

1. Introduction

Cutaneous adverse drug reactions (cADRs) represent one of the most pervasive and complex challenges in modern dermatology and pharmacovigilance, imposing a substantial burden on global healthcare systems.[1] As pharmaceutical access expands and polypharmacy becomes the norm in aging populations, the incidence of these iatrogenic eruptions continues to rise, manifesting in a diverse clinical spectrum that ranges from benign, transient exanthems to catastrophic, life-threatening emergencies such as toxic epidermal necrolysis (TEN).[2] Within this vast nosological landscape, fixed drug eruption (FDE) occupies a unique and clinically fascinating niche. Unlike other hypersensitivity reactions that strike indiscriminately, FDE is

distinguished by its pathognomonic anatomical memory—the phenomenon where lesions recur at the exact same cutaneous or mucosal sites upon re-exposure to the causative hapten. This site-specific recurrence is not merely a clinical curiosity but a reflection of a distinct immunological mechanism involving the persistence of memory T cells in the localized tissue microenvironment.[3]

While the classic textbook presentation of FDE is often described as a solitary, well-demarcated, erythematous or violaceous patch that resolves with hyperpigmentation, this reductionist view fails to capture the full severity of the condition.[4] The generalized fixed drug eruption (GFDE) variant represents the severe end of this spectrum and poses a formidable diagnostic challenge for clinicians. Defined by the involvement of at least three distinct anatomical sites—and often covering a significant percentage of the body surface area—GFDE blurs the clinical boundaries between benign drug eruptions and severe cutaneous adverse reactions (SCARs). In its acute phase, extensive GFDE can present with widespread dusky violaceous plaques that may be indistinguishable from the early stages of Stevens-Johnson syndrome (SJS) or TEN, particularly when blistering occurs. Conversely, in its subacute or pigmentary phase, the condition manifests as widespread, slate-gray to brown hyperpigmentation. This presentation frequently masquerades as acquired pigmentary disorders such as lichen planus pigmentosus (LPP), erythema dyschromicum perstans (EDP), or even extensive post-inflammatory hyperpigmentation, leading to diagnostic confusion and therapeutic delays.[5]

In tropical and subtropical regions, the diagnostic landscape is further complicated by the prevalence of infectious mimics. In countries like Indonesia, where Hansen's disease (leprosy) remains endemic, the widespread, hypopigmented or erythematous plaques of atypical GFDE can easily be misdiagnosed as multibacillary leprosy. This mimicry is particularly dangerous; mislabeling a drug eruption as an infectious disease not only subjects the patient to unnecessary and potentially toxic multidrug therapy but also leads to inappropriate public health interventions and stigmatization.[6] This diagnostic dilemma is most acute in the geriatric population, a demographic often plagued by undifferentiated musculoskeletal pain and a reliance on unregulated, over-the-counter analgesic cocktails. In these patients, the combination of immune senescence, altered drug metabolism, and complex polypharmacy creates a perfect storm for atypical and severe drug reactions, necessitating a high index of suspicion and precise diagnostic tools.

The pathophysiology underpinning this site-specific aggression is a subject of intense immunological interest. FDE is classically categorized as a Type IVc hypersensitivity reaction, mediated primarily by CD8+ cytotoxic T cells that act as tissue-resident memory T cells (Trm).[7] These specialized immune sentinels reside in a quiescent state within the basal layer of the epidermis at the site of the previous lesion. They are the sleeping enemy within the skin. Upon systemic re-exposure to the offending drug, these Trm cells are rapidly activated, releasing a potent cocktail of cytotoxic granules, including granulysin, perforin, and granzyme B. This release triggers the Fas-Fas Ligand apoptotic pathway, inducing localized necrosis of keratinocytes. The subsequent destruction of the basal cell layer leads to the hallmark pigment incontinence, where melanin pigment drops from the damaged epidermis into the dermis, where it is phagocytized by melanophages, resulting in the long-lasting, slate-gray hyperpigmentation characteristic of the resolved lesion.[8]

However, the immunological mechanisms driving the generalization of lesions—the shift from a solitary patch to a widespread eruption—remain an area of active investigation and debate. Why do some patients develop a single spot while others experience a generalized breakout? Emerging evidence suggests that severe or generalized cases may involve a broader and more complex cytokine milieu than previously understood. While the localized destruction is

undoubtedly driven by Th1/Tc1 cytokines (such as IFN-gamma), there is a hypothetical potential for immunological overlap in extensive cases. The mixed phenotype hypothesis suggests that in generalized eruptions, the massive surface area of inflammation may recruit Type IVb (Th2-driven) pathways, characterized by the release of IL-4, IL-5, and IL-13, and the subsequent recruitment of eosinophils. This overlap is under-characterized in the literature but could explain the systemic symptoms and peripheral eosinophilia observed in some severe GFDE cases, which confusingly mimic drug reaction with eosinophilia and systemic symptoms (DRESS).[9]

Given the diagnostic complexities and the invasive nature of skin biopsy—which is often delayed by logistical hurdles or patient reluctance—there is a critical need for rapid, non-invasive diagnostic surrogates. Dermoscopy has evolved from a tool reserved for melanocytic tumors to a vital instrument in general dermatology (inflammoscopy). The physics of light interaction with skin—specifically the Tyndall effect—allows dermoscopy to visualize pathological changes invisible to the naked eye. While the pigment network of melanoma is well-described, the specific dermoscopic patterns of drug eruptions are less standardized. There is a scarcity of detailed correlation studies linking specific chromatic patterns, such as steel-blue peppering or starburst patterns, to their precise histopathological substrates (such as depth of pigment incontinence or interface dermatitis) specifically in the context of generalized fixed drug eruption.[10]

This study aims to bridge this significant diagnostic and pathophysiological gap by providing a high-resolution, multi-modal analysis of an atypical case of generalized fixed drug eruption. Unlike previous reports that focus solely on clinical features, this study offers three key novel contributions to the literature: (1) Dermoscopic-Pathological Mapping: We establish a direct structural correlation between specific dermoscopic patterns—specifically the steel-blue peppering and starburst signs—and their exact histopathological counterparts (deep dermal melanophagy and interface dermatitis), validating dermoscopy as a reliable optical biopsy for GFDE; (2) The immunological paradox: We investigate a novel immunophenotype characterized by massive systemic eosinophilia (mimicking DRESS) in the presence of classic FDE morphology, proposing a mixed-hypersensitivity mechanism that challenges the rigid classification of FDE as a pure Type IVc reaction; (3) Causality in the unknown context: We demonstrate the utility of the Naranjo Probability Scale in establishing definitive causality in rural, resource-limited settings where the culprit agent is an unidentified street analgesic cocktail, providing a methodological framework for clinicians working in similar environments.

2. Case Presentation

In strict adherence to the principles of the Declaration of Helsinki regarding medical research involving human subjects, written informed consent was obtained from the patient prior to the drafting of this manuscript. This consent explicitly covered the publication of the case details, clinical chronology, and all accompanying imagery, including potentially sensitive clinical photographs of the genitalia and high-definition dermoscopic findings. The patient was fully briefed on the scientific value of his case, particularly regarding the atypical presentation and the use of dermoscopy, and he agreed to the dissemination of this data for educational purposes.

The patient is a 69-year-old male belonging to the Sangihe ethnic group, a demographic detail that provides essential genetic and geographic context. He is employed as a traditional cassava farmer, an occupation that implies chronic exposure to soil-transmitted pathogens and intense ultraviolet radiation, factors that can complicate the dermatological baseline. He resides in a rural setting within the Siau Tagulandang Biaro Regency, an archipelago in North Sulawesi. This geographic isolation is clinically significant; the region is endemic for several neglected tropical diseases, including filariasis and leprosy (Hansen's disease), necessitating

a broader differential diagnosis than might be required in an urban setting.

The patient presented to the Department of Dermatology, Venereology, and Aesthetic Medicine with a chief complaint of progressive, widespread dark brown to blackish patches. These pigmentary lesions affected multiple body surface areas, causing significant cosmetic concern and psychological distress. His medical history was notable for a chronic, two-year struggle with gout arthritis. Crucially, his management of this condition reflects a common public health challenge in the region: the reliance on self-medication. The patient reported the intermittent use of various pharmacological agents purchased from unlicensed vendors (locally known as *warung* or street stalls). This unregulated consumption of shop-bought medication often involves analgesic cocktails—unlabeled mixtures of potent non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids—which are notorious triggers for severe cutaneous adverse reactions.

A detailed anamnesis was conducted to reconstruct the precise timeline of the eruption, revealing a clinical narrative that perfectly mirrors the immunological phases of a fixed drug eruption (FDE): sensitization, resting, and elicitation. The patient's initial dermatological event occurred approximately four months prior to the current consultation. The primary lesion, a solitary patch, manifested on the left calf exactly seven days following the ingestion of an unidentified analgesic cocktail. This seven-day latency is consistent with the primary immune response, where naïve T cells require time to recognize the hapten, proliferate, and migrate to the skin to establish a population of tissue-resident memory T cells (Trm).

Over the subsequent months, the eruption did not remain static. It progressively increased in distribution, a phenomenon known as generalization. The inflammatory process recruited new anatomical sites, spreading from the lower extremities to the face, bilateral auricular regions (ears), forearms, posterior thorax, penile shaft, crural regions (groin), and the dorsum of both feet. This stepwise recruitment suggests a widening of the immunological field, potentially due to repeated sub-clinical exposures or the persistence of the drug allergen.

Seven days prior to hospital admission, the patient experienced an acute gout flare and ingested the same specific over-the-counter analgesic packet. This event served as an unintentional but definitive re-challenge. Crucially, the lesions recurred and flared at the identical anatomical sites involved in previous episodes. Most significantly, the latency period—the time between ingestion and symptom onset—shortened dramatically from seven days to an acute latency of approximately six hours. This accelerated response is pathognomonic for FDE and represents the rapid activation of the resident Trm cells, which, unlike naïve T cells, do not require migration time; they are already positioned in the epidermis, ready to release cytotoxic granules immediately upon antigen recognition. Regarding symptomatology, the patient reported persistent pruritus and a distinct sensation of heaviness in the affected skin. Importantly, he explicitly denied the burning or stinging sensation often associated with acute epidermal necrosis seen in Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). This subjective report helps clinically differentiate the widespread plaques of GFDE from the early stages of SJS.

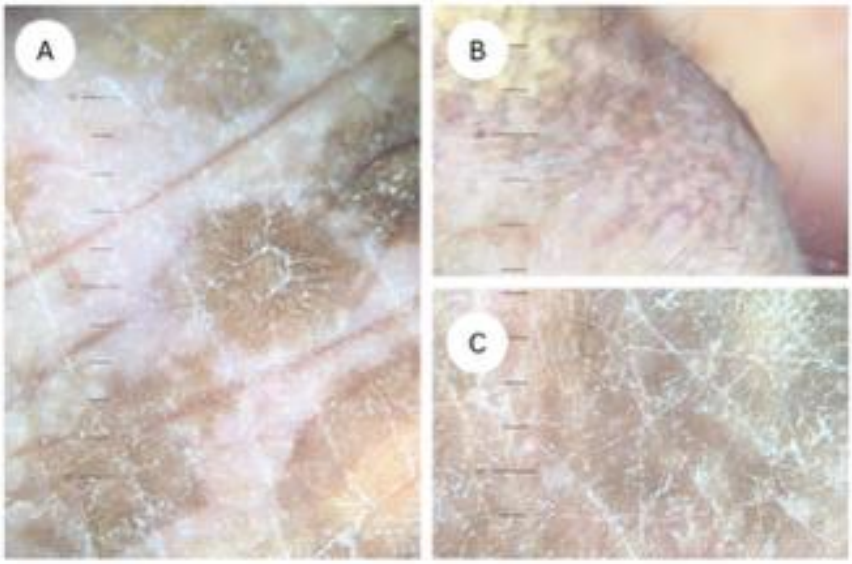
One of the most significant challenges in this case was the unlabeled nature of the causative agent. In resource-limited settings, patients frequently consume loose pills without packaging. However, a forensic approach was utilized. Based on the remnant packaging retrieved from the patient and local pharmacological surveillance data, the cocktail was identified as a likely combination of Phenylbutazone and Dexamethasone. Phenylbutazone is a potent NSAID largely withdrawn from Western markets due to hematological toxicity, but it remains available in unregulated Asian markets; it is a high-risk trigger for FDE. To scientifically validate the

diagnosis of a drug eruption despite the lack of a chemical assay, the Naranjo Adverse Drug Reaction Probability Scale was applied. This algorithm assigns a quantitative score to the likelihood of a drug causation. The patient's case received a total score of 10, categorized as follows: +1 for conclusive previous reports on this reaction (Phenylbutazone is a known cause); +2 for the appearance of the adverse event after the suspected drug was administered (the temporal correlation is strong); +1 for improvement when the drug was discontinued (de-challenge was positive); +2 for reappearance when the drug was re-administered (the inadvertent re-challenge was positive); +2 for the absence of alternative causes (infectious and autoimmune causes were ruled out); +1 for a similar reaction in a previous exposure (the history of the initial lesion); +1 for confirmation by objective evidence (biopsy and dermoscopy results). A Naranjo score of 9 or greater indicates a definite adverse drug reaction. This methodological step provided the statistical confidence necessary to confirm the diagnosis of drug-induced GFDE, bridging the gap left by the unidentified chemical agent. The general physical examination revealed a patient in good general condition with stable vital signs, ruling out impending cardiovascular collapse or sepsis often seen in severe drug reactions. There was no lymphadenopathy or hepatosplenomegaly, which helps exclude systemic hypersensitivity syndromes like DRESS at the clinical level.

Dermatological inspection revealed a symmetrical, generalized eruption involving approximately 15 to 20 percent of the body surface area (BSA). This extent of involvement classifies the case as generalized FDE. The primary lesions were characterized as multiple, well-demarcated violaceous to hyperpigmented macules and plaques. The term violaceous (purple-hued) is critical; it implies inflammation at the dermo-epidermal junction and pigment incontinence, distinguishing it from the bright red erythema of urticaria or the scaly plaques of psoriasis. The lesions ranged in size from nummular (coin-sized) to palm-sized dimensions. Three specific findings on the physical exam were pivotal for the differential diagnosis: (1) Distribution: The involvement of the face, genitalia (penile shaft), and extremities is a classic acral and central distribution for FDE; (2) Mucosal Status: The oral and genital mucosae were intact. This negative finding is the primary clinical discriminator against Stevens-Johnson syndrome (SJS), which almost invariably involves mucosal ulceration; (3) Neurological Exam: Given the endemicity of leprosy in the region, a neurological assessment was mandatory. No peripheral nerve thickening (e.g., greater auricular or ulnar nerves) or anesthesia was noted. This effectively reduced the likelihood of Hansen's disease, which can present with similar widespread plaques.

Dermoscopy served as a non-invasive bridge between clinical inspection and histopathology. Imaging was performed using a handheld dermatoscope employing both non-polarized and non-contact polarized light modes. This distinction is vital: non-polarized light reflects off the stratum corneum, visualizing the surface, while polarized light eliminates surface glare, allowing visualization of deeper dermal structures (Figure 1); (1) Lesion A (lower extremity): examination of the initial lesion revealed a brown starburst-like structure. This pattern consisted of a hyperpigmented rim and a central clearing. In the context of FDE, the central clearing represents the eye of the storm—an area where the inflammatory process has peaked and is now regressing or re-epithelializing. The peripheral starburst represents the active firing of CD8+ T cells at the expanding margin of the lesion, driving the centrifugal spread of the plaque; (B) Lesion C (femoral region): Under polarized light, the most distinct and clinically significant finding was a diffuse distribution of steel-blue to slate-gray peppering. This is not merely a color; it is an optical phenomenon. According to the Tyndall effect, melanin pigment appears black in the superficial epidermis, brown at the dermo-epidermal junction, and blue-gray when it drops deep into the dermis. The shorter wavelengths of blue light

are scattered by the collagen in the dermis, while longer wavelengths are absorbed by the deep melanin. Therefore, the presence of steel-blue peppering serves as an optical surrogate for deep pigment incontinence, indicating that the basal layer has been breached and melanin has fallen into the reticular dermis.



Figures 1. Dermoscopic examination of lesions on the lower limb (A), ear lesion (B), and femoral lesion (C).

The laboratory workup revealed a startling and distinct inflammatory signature. The patient exhibited a massive absolute eosinophil count of 2,080 cells per microliter (reference range < 500). Concurrently, the Total IgE was significantly elevated at 2,295 IU per milliliter. This finding presented a diagnostic dilemma. Such profound eosinophilia is typically associated with parasitic infections or DRESS syndrome, not classic FDE. Given the patient's occupation as a cassava farmer in a tropical rural area, he is at high risk for soil-transmitted helminths. Therefore, a rigorous exclusion of helminthic infection was mandated to validate the drug-induced nature of the eosinophilia. The workup was comprehensive: (1) Stool Examination: Three consecutive stool samples were collected and found negative for ova, cysts, and parasites, ruling out common intestinal worms like *Ascaris lumbricoides*, *Hookworm*, and *Trichuris trichiura*; (2) Serology: IgG serology for *Strongyloides stercoralis* and *Toxocara canis* yielded negative results, ruling out occult or tissue-invasive parasitic infections; (3) Infectious Disease: A slit-skin smear for Acid-Fast Bacilli was negative, definitively excluding lepromatous leprosy. This exhaustive exclusion confirmed that the massive eosinophilia was not an incidental finding of rural life but a systemic manifestation of the drug hypersensitivity itself. This suggests that Generalized FDE may possess a mixed immunophenotype, recruiting Th2 (eosinophilic) pathways alongside the classic Th1 (cytotoxic) pathways due to the widespread nature of the inflammation.

A 4-mm punch biopsy was obtained from the posterior femoral lesion, specifically targeting the area of steel-blue dermoscopic change. The microscopic findings provided the structural correlate to the clinical picture: (1) Epidermis: The hallmark of FDE, focal vacuolar degeneration of the basal layer, was evident. This was accompanied by scattered necrotic keratinocytes (also known as apoptotic or Civatte bodies). These dead cells are the direct victims of the CD8+ Trm cell attack; (2)

Dermis: A superficial perivascular inflammatory infiltrate was observed, composed primarily of lymphocytes; (3) The Eosinophil Disconnect: A fascinating discrepancy was noted. Despite the massive peripheral blood eosinophilia (2,080/µL), the tissue eosinophils were sparse, numbering only one to two per high-power field. This disconnect implies that while the systemic immune system was churning out eosinophils (perhaps due to cytokine spillover like IL-5), the specific chemokines required to recruit them into the skin (like Eotaxin) were absent in the FDE lesion. This reinforces the unique pathophysiology of FDE compared to DRESS; (4) Pigmentary Abnormalities: The dominant feature was marked pigment incontinence. Free melanin granules and coarse melanophages (macrophages that have eaten pigment) were abundant in the papillary and upper reticular dermis. This histological finding is the direct physical cause of the steel-blue peppering seen on dermoscopy, validating the utility of the dermatoscope as a non-invasive diagnostic tool.

TABLE 1A. SUMMARY OF PATIENT PROFILE AND CLINICAL FINDINGS

1. PATIENT PROFILE & DEMOGRAPHICS	
Demographics	69-year-old Male | Sangihe Ethnicity
Occupation & Residence	Traditional Cassava Farmer | Rural Siau Tagulandang Biaro (Endemic area for neglected tropical diseases)
Comorbidities	Chronic Gout Arthritis (2-year duration)
2. CLINICAL HISTORY & EXPOSURE	
Suspected Agent	Phenylbutazone Dexamethasone (Unprescribed Analgesic Cocktail)
Reaction Chronology	**Sensitization:** Initial lesion 4 months prior (7-day latency). **Generalization:** Progressive recruitment of new anatomical sites. **Elicitation (Current):** Re-exposure 7 days prior.
Latency Period	**Acute (6 hours post-ingestion)**
Symptomatology	Pruritus, sensation of heaviness. **Negative:** No burning/stinging sensation.
3. PHYSICAL EXAMINATION FINDINGS	
Morphology	Multiple well-demarcated violaceous to hyperpigmented macules and plaques; Nummular to palm-sized.
Extent	Generalized (15–20% Body Surface Area)
Distribution	Face, bilateral ears, posterior thorax, penile shaft, forearms, crural regions, dorsum of feet.
Crucial Exclusions	**Mucosa Intact:** Rules out Stevens-Johnson Syndrome (SJS). **Nerves Normal:** No thickening/anesthesia (Rules out Hansen's disease).

TABLE 1B. SUMMARY OF DERMOSCOPIC, LABORATORY, AND HISTOPATHOLOGICAL FINDINGS

4. DERMOSCOPIC EVALUATION (POLARIZED LIGHT)	
Lesion A (Extremity)	Starburst Pattern Hyperpigmented rim with central clearing (post-inflammatory regression).
Lesion C (Femoral)	Steel-Blue Peppering Diffuse slate-gray dots indicating deep dermal pigment incontinence (Tyndall Effect).
5. LABORATORY & IMMUNOLOGICAL PROFILE	
Peripheral Blood	**Eosinophils:** 2,080 /µL (Marked Eosinophilia) **Total IgE:** 2,295 IU/mL (Significantly Elevated)
Parasitic Workup (Exclusion)	**Negative:** Stool Exam (Ascaris, Hookworm, Trichuris) **Negative:** Serology (Strongyloides, Toxocara)
Causality Assessment	**Naranjo Score: 10** (**Definite Adverse Drug Reaction**)
6. HISTOPATHOLOGICAL ANALYSIS (4MM PUNCH BIOPSY)	
Epidermal Findings	Focal vacuolar degeneration of basal layer; Scattered necrotic keratinocytes (Civatte bodies).
Dermal Findings	Superficial perivascular lymphocytic infiltrate; **Marked pigment incontinence** (melanophages).
The "Disconnect"	**Tissue Eosinophils:** Sparse (1–2 per HPF) despite high blood counts.

Table 2 delineates the comprehensive clinical management pathway, establishing a definitive diagnosis of generalized fixed drug eruption (GFDE). This diagnostic conclusion was achieved through a rigorous process of exclusion, distinguishing the presentation from severe cutaneous adverse reactions like Stevens-Johnson syndrome (SJS) due to the absence of mucosal involvement, and from Hansen's disease based on intact peripheral nerve function and negative slit-skin smears. The therapeutic intervention prioritized the immediate cessation of the suspected offending agent—an unprescribed analgesic cocktail likely containing Phenylbutazone. The pharmacological strategy utilized a dual modality: systemic H1-receptor blockade via Cetirizine 10 mg to modulate pruritus and histamine-mediated vasodilation, combined with high-potency topical Clobetasol propionate 0.05% to arrest the cytotoxic interface dermatitis and accelerate epidermal barrier repair.

Longitudinal follow-up at days 7 and 20 confirmed therapeutic efficacy, evidencing a transition from active violaceous inflammation to quiescent post-inflammatory hyperpigmentation. A pivotal prognostic indicator was the biological response; the massive admission eosinophilia (2,080 cells/µL) significantly

trended downward to 650 cells/μL following drug withdrawal. This objective laboratory decay validates the non-parasitic, drug-induced etiology of the systemic eosinophilia, confirming an excellent prognosis provided strict avoidance of pyrazolone derivatives is maintained.

TABLE 2. DIAGNOSIS, THERAPEUTIC MANAGEMENT, AND CLINICAL OUTCOME

1. FINAL DIAGNOSIS & RATIONALE	
Primary Diagnosis	**Generalized Fixed Drug Eruption (GFDE)**
Differentials Excluded	• **Stevens-Johnson Syndrome:** Excluded due to **intact mucosa**. • **Hansen's Disease:** Excluded due to **negative slit-skin smear** and lack of neuropathy. • **Parasitic Infection:** Excluded due to **negative stool/serology** (despite eosinophilia).
2. THERAPEUTIC INTERVENTION	
Trigger Management	**Strict Cessation and Avoidance:** Immediate discontinuation of unprescribed analgesic cocktails (suspected Phenylbutazone/Dexamethasone).
Systemic Therapy	**Oral Cetirizine:** 10 mg once daily (to control pruritus and histamine release).
Topical Therapy	• **Clobetasol Propionate 0.05% Ointment:** Applied twice daily to active plaques (anti-inflammatory). • **Emollients:** Petrolatum jelly for epidermal barrier repair.
3. FOLLOW-UP AND MONITORING	
Day 7 Follow-Up	**Stabilization Phase** • No new lesions appeared. • Pruritus reduced from persistent to intermittent.
Day 20 Follow-Up	**Resolution Phase** • **Clinical:** Violaceous plaques faded to post-inflammatory hyperpigmentation; significant thinning of plaques. • **Symptomatic:** Complete resolution of pruritus. • **Wound Care:** Biopsy site fully healed with healthy granulation.
4. PROGNOSIS & LABORATORY TRENDS	
Eosinophil Trend	**Admission:** 2,080 cells/μL (Severe) **Day 20:** **650 cells/μL** (Significant reduction following drug cessation).
Final Prognosis	Excellent prognosis for current episode. **High risk of recurrence** upon re-exposure to Phenylbutazone or Pyrazolone derivatives.

3. Discussion

The diagnosis of generalized fixed drug eruption (GFDE) in the present case serves as a paradigm for the evolving understanding of cutaneous adverse drug reactions (cADRs). Historically, the diagnosis of FDE was predicated almost exclusively on clinical intuition—the recognition of pathognomonic round patches recurring at identical sites.[11] However, as this

case demonstrates, the modern dermatological approach must transition from a purely morphological diagnosis to one underpinned by precise optical, histopathological, and immunological parameters. This shift is particularly crucial in complex, generalized presentations where the classical clinical boundaries blur with other severe cutaneous adverse reactions (SCARs) or chronic pigmentary disorders. By integrating high-definition dermoscopy with a nuanced understanding of immunophenotypes, clinicians can navigate the diagnostic ambiguity that often plagues geriatric and complex dermatology cases.[12]

This study highlights the critical, non-invasive diagnostic utility of colorimetry via dermoscopy, transforming the dermatoscope from a tool for neoplasm screening into an instrument for optical biopsy in inflammatory dermatoses. The central dermoscopic finding in this case—the steel-blue peppering—is not merely a chromatic curiosity but a direct manifestation of the optical physics governing light interaction with biological tissues, specifically the Tyndall effect. The Tyndall effect describes the preferential scattering of shorter wavelengths of light (blue spectrum) by colloidal particles suspended in a medium, while longer wavelengths (red spectrum) are transmitted or absorbed. In the context of the skin, the perceived color of melanin is strictly dictated by its depth.[13] Melanin residing in the stratum corneum appears black due to minimal scattering. When located at the dermo-epidermal junction (DEJ), it appears brown. However, when melanin is displaced into the reticular dermis, the collagen bundles scatter the blue light back to the observer's eye while absorbing the red light, creating a slate-gray or steel-blue hue (Figure 2).

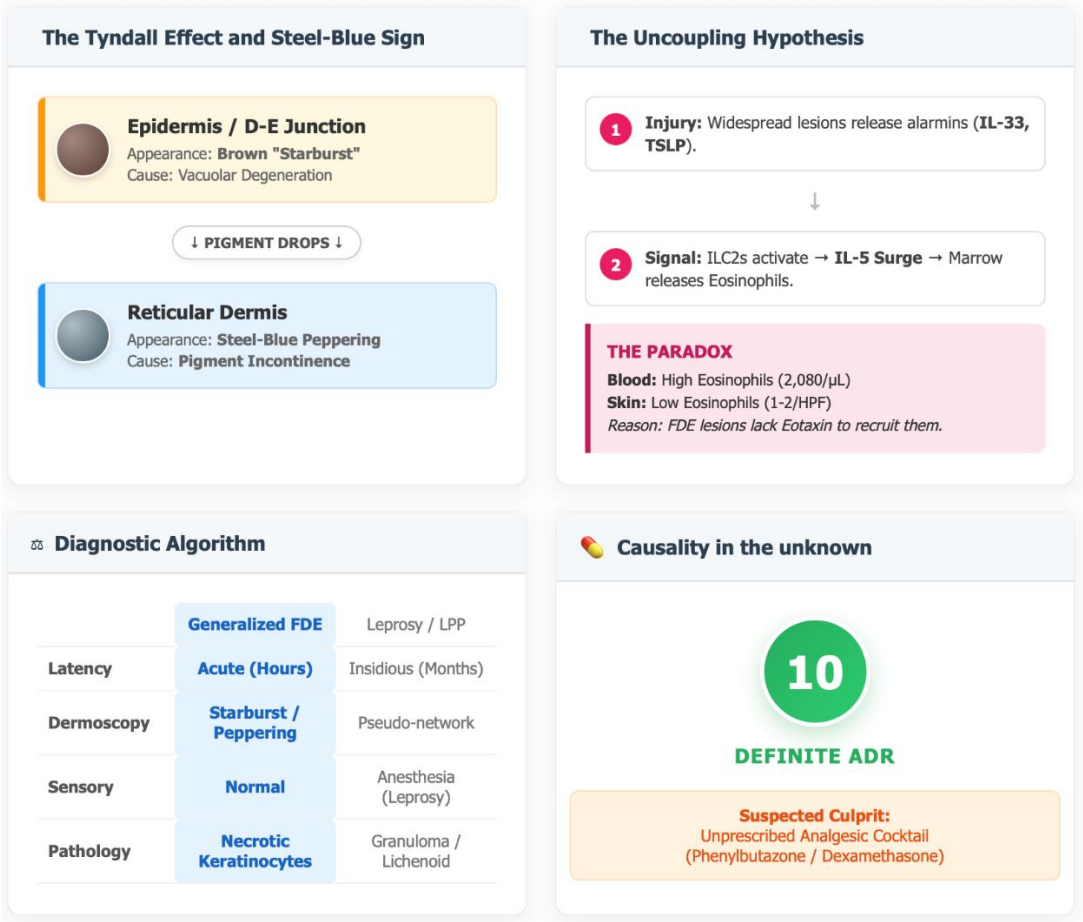


Figure 2. Pathophysiological mechanism of this case.

In our patient, the diffuse steel-blue peppering observed on the femoral lesions under non-contact polarized light correlated precisely with the histopathological finding of marked pigment incontinence. The peppering corresponds to aggregates of melanin-laden macrophages (melanophages) trapped between collagen fibers. Consequently, this blue hue serves as an in vivo confirmation of a specific sequence of pathological events: the cytotoxic attack on the basal layer was severe enough to cause vacuolar degeneration, disrupting the integrity of the DEJ and allowing melanin to drop deep into the dermis. This optical distinction provides a robust framework for distinguishing GFDE from its primary clinical mimic, lichen planus pigmentosus (LPP). Both conditions share the histological feature of pigment incontinence, leading to diagnostic confusion. However, their dermoscopic signatures diverge based on the tempo and architecture of inflammation. LPP, characterized by a chronic, insidious, lichenoid interface dermatitis, typically presents with a pseudo-network or diffuse, exaggerated slate-gray dots that follow the skin markings. In contrast, FDE is an explosive, localized event. This results in the starburst pattern (observed on the extremities) or clustered peppering (observed on the thighs), reflecting the centrifugal spread of cytotoxic granules from a central nidus of resident memory T cells. Recognizing this explosive versus insidious optical pattern allows the clinician to favor GFDE over LPP even before biopsy confirmation.[14]

A significant challenge highlighted by this case is the unknown nature of the causative agent, a scenario emblematic of the public health landscape in many developing nations. The widespread availability of loose, unlabeled medications sold in unregulated stalls (often referred to as *warung* in Indonesia) creates a formidable barrier to specific drug identification.[15] In such environments, analgesic cocktails frequently contain potent non-steroidal anti-inflammatory drugs (NSAIDs) such as Phenylbutazone or Metampyrone, often combined with corticosteroids like Dexamethasone. Phenylbutazone, a pyrazolone derivative, has been withdrawn from many Western markets due to risks of agranulocytosis and severe cutaneous reactions, yet it remains a covert but ubiquitous trigger for FDE in the tropics.

In the absence of a chemical assay or labeled packaging, the establishment of medical causality can be fraught with uncertainty. This study demonstrates the indispensability of the Naranjo Adverse Drug Reaction Probability Scale in such resource-limited settings. By rigorously scoring clinical parameters—specifically the temporal sequence, the recurrence upon inadvertent re-challenge, and the exclusion of alternative causes—we achieved a score of 10, indicating a definite causal relationship. This validates the use of algorithmic pharmacovigilance tools as a substitute for definitive chemical identification. It underscores that a diagnosis of drug-induced FDE can, and should, be legally and medically sustained by the strength of the clinical timeline (re-challenge phenomenon) even when the specific molecule remains chemically anonymous.[16]

Perhaps the most scientifically pivotal finding in this case is the immunological paradox: the dissociation between the systemic immune profile and the local tissue pathology.[17] The patient exhibited massive peripheral eosinophilia (2,080 cells/μL) and elevated IgE, hallmarks of a Type IVb (Th2-driven) hypersensitivity reaction. Yet, the biopsy revealed a classic Type IVc (Th1/Cytotoxic) interface dermatitis with sparse to absent tissue eosinophils. Classically, FDE is mediated by CD8+ tissue-resident memory T cells (Trm) located in the basal layer of the epidermis. Upon activation, these cells secrete IFN-gamma and release cytotoxic granules (granulysin/granzyme B) to induce keratinocyte apoptosis. This is a Type 1 immune response, which typically suppresses Th2/eosinophilic pathways. The presence of massive eosinophilia usually heralds a different condition: Drug reaction with eosinophilia and systemic symptoms (DRESS). However, we rigorously excluded DRESS based on the absence of fever, lymphadenopathy, and internal organ involvement

(RegiSCAR criteria). Furthermore, the exhaustive exclusion of helminthic infection via negative stool studies and serology implies that the eosinophilia was, indisputably, drug-driven.

To explain this paradox, we propose an uncoupling hypothesis unique to Generalized FDE. In localized FDE, the inflammatory burden is too small to alter systemic blood counts. However, in Generalized FDE, the sheer surface area of epidermal injury is massive. We hypothesize that this widespread keratinocyte damage releases a flood of alarmins (epithelial-derived cytokines), specifically IL-33 and Thymic Stromal Lymphopoietin (TSLP). These alarmins are potent activators of Group 2 innate lymphoid cells (ILC2s), which in turn secrete massive amounts of IL-5. This systemic IL-5 surge stimulates the bone marrow to overproduce and release eosinophils into the peripheral circulation, resulting in the leukocytosis observed in our patient.[18]

However, the second half of the equation—the recruitment of these eosinophils into the skin—fails. Eosinophil recruitment requires specific chemokines, primarily Eotaxin-1 (CCL11) and Eotaxin-3 (CCL26). The inflammatory milieu of FDE is dominated by CXCL9 and CXCL10 (chemokines that recruit Th1 cells and CD8+ T cells), not Eotaxins. Therefore, while the bone marrow is stimulated to produce eosinophils (Type IVb feature) due to the systemic alarmin signal, the skin lesion lacks the specific address code (chemokines) to invite them in, leaving the local pathology to remain strictly cytotoxic (Type IVc). Thus, the eosinophils circulate in the blood but do not infiltrate the lesion. This finding suggests that GFDE represents a transitional phenotype—a cytotoxic reaction with systemic Th2 spillover—bridging the gap between localized FDE and systemic hypersensitivity syndromes.

The diagnostic delay of four months observed in this case underscores the chameleon nature of GFDE in tropical dermatology. In regions like Indonesia, where Hansen's disease (leprosy) remains endemic, any patient presenting with widespread, non-pruritic, hyperpigmented or violaceous plaques is often instinctively categorized as a leprosy suspect.[19] The clinical overlap is significant: lepromatous leprosy can present with diffuse infiltration and plaques that mimic the generalized plaques of FDE. While the absence of anesthesia and a negative slit-skin smear were definitive in excluding leprosy, this case highlights that the most reliable discriminator is not spatial, but temporal. The acute latency of recurrence is the red flag. Leprosy and other mimics like erythema dyschromicum perstans (EDP) are characterized by an insidious, slow progression over months or years. In stark contrast, FDE is characterized by an on-off phenomenon. The recurrence of lesions within six hours of drug ingestion is pathognomonic. This hyper-acute to acute timeframe serves as the most powerful diagnostic tool in the anamnesis, capable of cutting through the differential diagnosis of chronic pigmentary disorders. Clinicians in endemic areas must be trained to prioritize this temporal pattern assessment to prevent the misdiagnosis of drug eruptions as infectious diseases, which spares patients from the stigma and unnecessary antibiotic burden of leprosy treatment.

The scientific integrity of this report requires the acknowledgment of certain limitations. The primary constraint was the inability to perform patch testing to identify the specific culprit molecule within the analgesic cocktail. While the Naranjo scale validates the probability of the reaction, only patch testing or oral provocation with the isolated ingredients (pure Phenylbutazone vs. Dexamethasone) could definitively identify the chemical hapten.[20] Additionally, our uncoupling hypothesis regarding the eosinophil paradox relies on theoretical frameworks of cytokine biology. We did not perform serum cytokine arrays (to measure IL-5 or TSLP) or immunohistochemical staining for Eotaxins in the biopsy specimen. Future research into generalized FDE should aim to quantify these specific mediators to definitively prove why circulating eosinophils fail to enter the FDE lesion.

4. Conclusion

This case report contributes significant nuances to the existing literature on severe cutaneous adverse drug reactions. Primarily, it validates steel-blue peppering visualized via polarized dermoscopy as a reliable, non-invasive surrogate for deep pigment incontinence. The establishment of a structural correlation between the blue spectrum on dermoscopy and the depth of dermal melanin provides clinicians with a robust diagnostic framework, allowing for the rapid differentiation of generalized fixed drug eruption from chronic mimics such as lichen planus pigmentosus without the immediate need for invasive biopsy.

Furthermore, the identification of a massive peripheral eosinophilia in the absence of parasites or tissue infiltration suggests a unique, uncoupled immunological profile in generalized cases. This immunological paradox challenges the strict binary classification of drug eruptions. It suggests that determining the severity of a drug reaction requires looking beyond the skin; in extensive FDE, the systemic immune system may mount a Th2-type alarm response (eosinophilia) even while the local skin pathology remains strictly cytotoxic (Th1). Clinicians, particularly those managing geriatric populations with polypharmacy, should be aware that high blood eosinophils do not rule out FDE, nor do they strictly mandate a diagnosis of DRESS. When faced with recurrent, widespread pigmentary plaques, the combination of an acute timeline, steel-blue dermoscopic findings, and a high Naranjo score should prompt a diagnosis of GFDE, ensuring the immediate cessation of the offending agent and preventing further iatrogenic morbidity.

5. References

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