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Case report

Clarithromycin-Induced Fixed Drug Eruption in a Paediatric Patient

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ABSTRACT

Fixed drug eruption (FDE) is a delayed cutaneous adverse drug reaction characterized by recurrent lesions at the same anatomical site upon re-exposure to the causative agent. We report the case of an 8-year-old girl with a history of recurrent skin eruptions initially diagnosed as urticaria multiforme in the context of suspected beta-lactam hypersensitivity. Previous allergological work-up, including specific IgE testing and skin prick tests, was negative.

At the age of 8 years, the patient developed recurrent, well-demarcated erythematous-violaceous lesions with post-inflammatory hyperpigmentation following exposure to clarithromycin, with reproducible recurrence at identical sites upon re-administration. The lesions were non-pruritic, persistent, and resolved with residual hyperpigmentation, leading to a clinical diagnosis of fixed drug eruption. Subsequent drug provocation tests excluded beta-lactam allergy, allowing reintroduction of these antibiotics.

This case highlights the diagnostic challenge of FDE in paediatric patients and underscores the importance of careful clinical history in identifying the culprit drug. Macrolides, although rarely reported, should be considered as potential triggers of FDE. Accurate diagnosis is essential to avoid unnecessary drug restrictions. This case underscores the importance of detailed clinical history and targeted allergological evaluation in guiding safe and effective management.

KEYWORDS: fixed drug eruption, drug, clarithromycin, beta-lactam allergy , drug provocation testing

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CASE PRESENTATION AND HISTORY

An 8-year-old Caucasian child presented to our clinic with a history of recurrent skin eruptions, each episode lasting a few days. Her past medical history was significant for adenoidectomy, recurrent tonsillitis, and asthmatic bronchitis treated with montelukast. Family history was positive for atopy and maternal Hashimoto's thyroiditis.

Between 2022 and 2023, when the patient was aged 5 years, she experienced multiple episodes of diffuse skin eruptions following treatment with beta-lactams (amoxicillin/clavulanic acid and cefpodoxime) for streptococcal tonsillitis. These episodes were initially diagnosed as urticaria multiforme (UM) by a pediatric dermatologist and managed with antihistamines, resolving within 10 days. However, the urticaria recurred two weeks later despite apparent clinical recovery, and again several months later following another course of cefpodoxime. Consequently, a beta-lactam allergy was suspected and avoidance of all penicillins and cephalosporins was recommended. Initial allergological investigations showed total IgE 113 UI/ml, while specific IgE for beta-lactams, food, and inhalants were negative. Skin prick tests for inhalants were

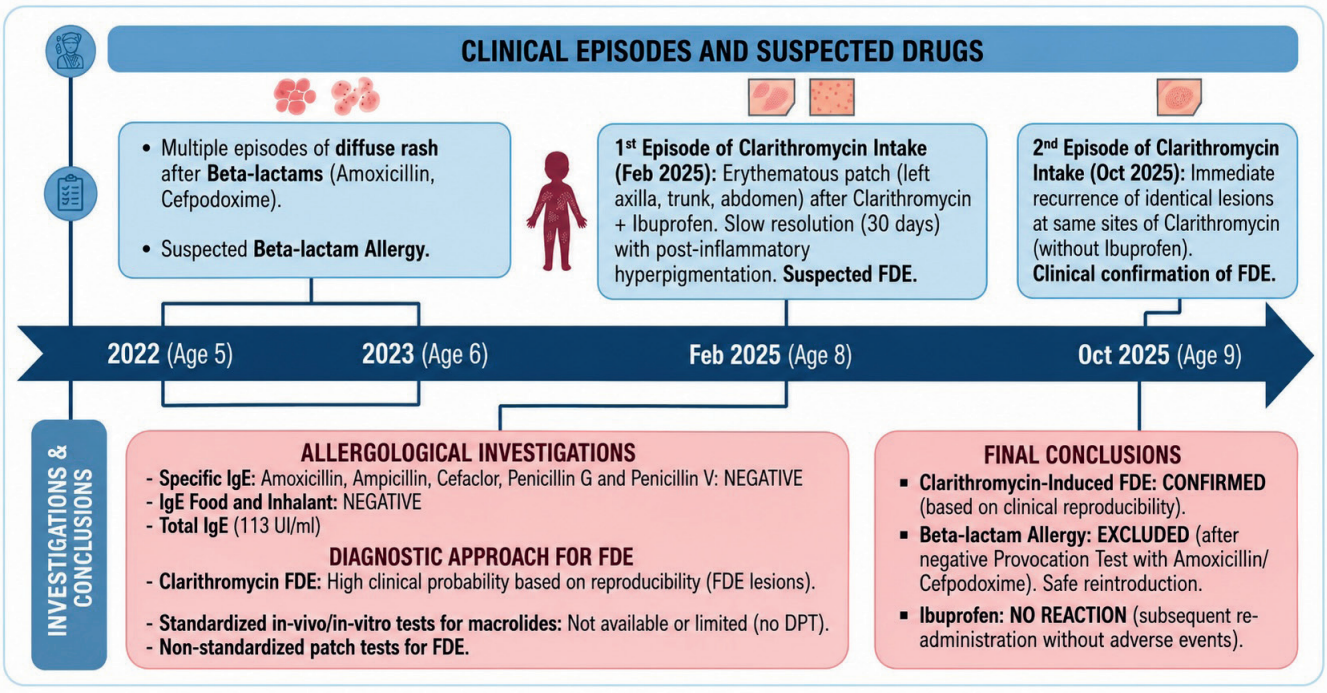


FIGURE 1. Clinical timeline of suspected drug reactions and diagnostic workup.

also negative (Fig. 1).In February 2025, following the administration of clarithromycin and ibuprofen, the child developed a skin eruption characterized by an oval erythematous patch with a purpuric hue in the left axilla, associated with smaller similar lesions on the lower abdomen and chest (Figs. 2, 3). Unlike the previous "urticarial" episodes, these lesions were non-pruritic and resolved slowly over 30 days, leaving residual post-inflammatory hyperpigmentation (Fig. 1).

Eight months later, following the administration of a single dose of clarithromycin, without ibuprofen, the patient experienced an immediate reactivation of the lesions occurred at the exact same anatomical sites. Dermatological examination revealed hyperpigmented oval patches with slight scaling on the trunk and a hyperkeratotic plaque in the left axilla. Two weeks later, the lesions were still present although the patient remained otherwise in good clinical condition (Fig. 1).

The characteristic residual hyperpigmentation led to the clinical diagnosis of fixed drug eruption (FDE). Therefore, the avoidance of the involved drug (clarithromycin) was recommended, along with further allergological investigations and treatment with topical steroids and emollients.

DISCUSSION

Pathogenesis and Clinical Features

FDE is an acute cutaneous drug reaction. It is characterized by solitary or multiple well-demarcated, dusky-red to violaceous patches or plaques that recur at the exact same anatomical site upon re-exposure to the offending drug. Lesions typically resolve leaving residual hyperpigmentation that last for months or years. They are generally asymptomatic, although pruritus and burning are sometimes reported [1,2]. The literature suggests that the primary anatomical distribution of FDE varies by sex: in males, genital involvement is more commonly reported, whereas females, more frequently present with lesions affecting the upper extremities. Lesions on the trunk, periorbital, and perigenital involvement have also been described [3,4].

The pathogenesis of FDE is mediated by skin-resident memory CD8+ T cells located at the basal layer of the epidermis. Upon re-exposure to the causative drug, these cells become rapidly activated and release pro-inflammatory cytokines, such as interferon-gamma and TNF-alpha, leading to localized epidermal necrosis [3]. The self-limiting nature of the lesions is thought to be regulated by CD4+ T cells producing IL-10. After resolution of the acute phase, resident memory T cells remain quiescent at the site, accounting for the "fixed" recurrence pattern of the disease [2,5].

Differential Diagnosis and Potential Triggers

In pediatric patients, FDE is frequently misidentified or underdiagnosed due to its variable clinical presentation and its ability to mimic more common pediatric dermatoses-

Solitary Lesions

A single FDE lesion can simulate arthropod bites, arachnidism, or



FIGURE 2. Well-demarcated erythematous-violaceous patches on the chest and left axilla during the acute phase after clarithromycin intake.



FIGURE 3. Residual hyperpigmented patches on the trunk and axilla, consistent with post-inflammatory changes of fixed drug eruption.

localized allergic contact dermatitis. Contact dermatitis can be clinically differentiated by its intense pruritus and classic eczematous morphology (vesiculation and oozing) rather than a dusky-red, well-circumscribed patch. When localized to the genitalia, FDE enters the differential diagnosis with balanitis or herpes simplex virus (HSV) infection [2].

Multiple Lesions and Severe Cutaneous Adverse Reactions (SCARs)

Given the presentation of acute, multiple cutaneous lesions in a child, several major differential diagnoses must be rigorously evaluated:

- **Erythema Multiforme (EM):** Distinguished from FDE by its typical three-zoned "target" or iris lesions, a predominantly symmetrical acral distribution, and frequent mucosal involvement.
- **Urticaria Multiforme (UM):** Characterized by transient, migratory annular wheals that typically last less than 24 hours. Unlike FDE, UM does not exhibit a fixed recurrence at identical anatomical sites, does not culminate in post-inflammatory hyperpigmentation, and is predominantly driven by a post-infectious rather than a pharmacological etiology [6].
- **Severe Cutaneous Adverse Reactions (SCARs):** The bullous or generalized variants of FDE must be differentiated from life-threatening conditions such as Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome. SJS/TEN evolves rapidly with severe systemic impairment, a positive Nikolsky sign, and extensive detachment involving at least two mucous membranes. Similarly, DRESS syndrome diverges fundamentally from FDE due to the presence of high-grade fever, diffuse lymphadenopathy, hematological abnormalities (such as eosinophilia or atypical lymphocytosis), and multi-organ involvement, particularly hepatic or renal dysfunction [1].
- **Leukocytoclastic Vasculitis:** Although it can mimic the acute inflammatory phases of FDE, it typically manifests as palpable purpura, characteristically predilects the lower extremities, and may be associated with systemic or visceral manifestations [1].
- **Infectious Exanthems and immune-mediated Reactive Eruptions:** Viral exanthems are often challenging to differentiate from drug-induced eruptions; however, they are characterized by prodromal features and manifest as rapid-onset, symmetric, erythematous macules and papules that typically follow a distinct craniocaudal progression.

Furthermore, *Mycoplasma pneumoniae*-associated rash and mucositis (MIRM) represents a crucial differential diagnosis. MIRM characteristically presents with severe, painful mucosal involvement affecting at least two mucosal sites accompanied by polymorphic skin targets or macules, and is typically preceded by prominent respiratory symptoms such as cough and fever [7].

In our patient, the complete absence of mucosal lesions, prodromal respiratory symptoms, or systemic impairment strongly argued against MIRM, SJS/TEN, DRESS syndrome, and leukocytoclastic vasculitis. Classic viral exanthems were confidently ruled out by the lack of a diffuse craniocaudal progression, the absence of associated systemic symptoms (fever, lymphadenopathy), and the highly localized, invariant anatomical distribution of the lesions.

DIAGNOSTIC CHALLENGES IN PEDIATRIC PATIENTS

The diagnosis of FDE is primarily clinical.

Drug hypersensitivity reactions are categorized into immediate (occurring within 1-6 hours, typically IgE-mediated) and delayed-type reactions (occurring hours to days later, typically T-cell-mediated). While immediate phenotypes such as classic urticaria, angioedema, or anaphylaxis – justify the diagnostic use of serum specific IgE (sIgE) assays and skin prick testing, these modalities hold absolutely no diagnostic utility in delayed-type, cell-mediated reactions (Type IV) such as FDE [8].

Because the pathogenesis of FDE is strictly orchestrated by localized, skin-resident memory CD8+ T cells rather than circulating antibodies, serum sIgE levels will invariably yield negative results [9].

In vivo testing for FDE carries unique challenges. Patch testing performed on previously affected skin site has a reported sensitivity ranging 30-70% [10]. False-negative results may occur when responsible agent poorly penetrates the skin or when the reaction is caused by a drug metabolite [9,11]. Nevertheless, patch testing represents a safe alternative to oral provocation tests, especially in the paediatric patients and in cases involving multiple agents [12,13]. However, drug provocation testing (DPT), remains the diagnostic gold standard. In the pediatric setting, the procedure must be justified by balancing the risks and benefits [3,14].

Histopathological examination is generally reserved for atypical clinical presentation. The characteristic biopsy pattern includes hydropic degeneration of the basal layer, pigmentary incontinence, scattered necrotic keratinocytes (dyskeratotic cells) and a dermal inflammatory infiltrate of lymphocytes, eosinophils, PMNs, and neutrophils [2].

RESOLUTION OF THE CASE...

In our patient, despite the suggestive clinical history, allergological investigations were necessary to avoid unnecessary drug restriction of beta-lactam antibiotics.

From an allergological perspective, DPT with amoxicillin and cefpodoxime were performed; both yielded negative results, thereby allowing reintroduction of beta-lactams antibiotics. Ibuprofen was not investigated, as the patient had already re-administered the drug without adverse reactions.

Regarding the suspected FDE, diagnosis was mainly based on clinical history and the characteristic recurrence of lesions at the same site following re-exposure to the offending drug. In this case, clarithromycin had been administered by the mother on two separate t occasions, both followed by the appearance of identical lesions in the same anatomical location — strongly supporting the diagnosis of FDE.

A DPT with macrolides in our case was not performed, considering the high diagnostic probability supported by the clinical reproducibility of the clinical manifestations and the explicit preference of the patient's family. However, Sillcox et al., suggest that direct DPT is a safe, effective strategy for pediatric patients with skin-limited symptoms [14]. Currently, there are no standardized and validated in vivo or in vitro allergological tests available for macrolides [9]. Furthermore, most cases described in the literature have reported negative patch tests despite positive DPT, a circumstance that further limits diagnostic options [15].

CONCLUSIONS

This case highlights that macrolide-induced FDE, although rare in the pediatric population, should be considered when recurrent lesions appear at the same anatomical site following drug exposure. Furthermore, the allergological workup also successfully ruled out beta-lactam allergy, thereby preventing unjustified drug avoidance and preserving important therapeutic options for the future treatments.

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Ethical consideration

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Conflicts of interest statement

With regards to the present work, the Authors have no conflict of interest to declare.

Authors' contributions

FT and AG: conceived the manuscript, wrote the first draft, and finalized it. All authors revised the manuscript and approved the final version.

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