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CASE REPORT

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Fixed Drug Eruption: An Underrecognized Cutaneous Adverse Drug Reaction in a 7-Year-Old Male – A Case Report

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ABSTRACT

Fixed drug eruptions (FDEs) are a distinctive delayed hypersensitivity reaction characterized by recurrent lesions at the same anatomical sites upon re-exposure to the culprit drug. Although paracetamol is widely used and generally considered safe at therapeutic doses, paracetamol-induced FDE is uncommon and often underrecognized. We report a case of a 7-year-old Filipino male with no history of atopy who developed recurrent episodes of pruritic, well-demarcated erythematous patches that consistently appeared within minutes after paracetamol intake and evolved into persistent hyperpigmented lesions at identical sites. Physical examination revealed multiple well-demarcated hyperpigmented patches without mucosal involvement. A supervised one-step oral paracetamol challenge at a low weight-based dose (10 mg/kg) reproduced pruritus and erythema over pre-existing lesions within 10 minutes, confirming the diagnosis of paracetamol-induced fixed drug eruption. This case emphasizes that paracetamol can cause FDE in children, highlighting the importance of recognizing lesion recurrence patterns, confirming diagnosis through a supervised challenge when appropriate, and ensuring avoidance of the offending drug with counseling on safe alternatives to prevent recurrence.

Keywords: fixed drug eruption, adverse drug reaction, paracetamol, drug hypersensitivity, case report

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INTRODUCTION

Cutaneous adverse drug reactions are drug reactions that affect the structure or function of the skin, its appendages, or mucous membranes. Common skin drug reactions typically present as pruritus, maculopapular eruptions, urticaria, angioedema, phototoxic and photoallergic reactions, fixed drug eruptions, vesiculobullous reactions, and exfoliative reactions.[1] In a Philippine study, the top 3 clinical presentations of cutaneous drug reactions were morbilliform rash, fixed drug eruption, and urticaria.[2] In pediatric patients, cutaneous adverse drug reactions account for around 35% of all suspected ADRs.[3] Among these, fixed drug eruptions (FDEs) account for about 5-22%.[4,5] These were once thought to be rare, but as awareness increased, they are now recognized to be much more common. It can affect anyone, but it is most common in the third and fourth decades of life.[6] The drugs that cause FDEs vary between countries and clinical settings due to prescribing patterns, but the most common are non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and antibiotics such as trimethoprim-sulfamethoxazole.[7,8]

Paracetamol is one of the most popular over-the-counter drugs that is commonly used as an antipyretic and an analgesic. Adverse reactions to paracetamol are not usually common at therapeutic doses. It can range from immediate type 1 or IgE-mediated hypersensitivity reactions presenting as angioedema, urticaria, and anaphylaxis to rare but serious delayed type IV or T cell-mediated reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and fixed drug eruptions.[9,10] These two mechanisms must be distinguished from cyclooxygenase hypersensitivity due to increased leukotriene production. They can be manifested as NSAID-exacerbated respiratory disease, NSAID-exacerbated cutaneous disease, or NSAID-induced urticaria or angioedema. Those with IgE-mediated paracetamol allergy can tolerate NSAIDs.[9] As paracetamol is widely available without prescription, usage data are difficult to obtain, and the true incidence of paracetamol hypersensitivity remains poorly characterized.[10] Paracetamol-induced FDE has been reported to account for less than 1.5% of all FDE cases in the literature.[11,12] In a study of hypersensitivity reactions among severe adverse events reported for paracetamol, the pediatric population accounted for 24.2% of the total number of adverse event reports.[10]

CASE

A 7-year-old boy, Filipino, from Mindoro was referred for recurrent generalized hyperpigmentation for 2 years. The lesion would become erythematous and raised whenever the patient had a febrile illness and took paracetamol (175 mg). Interestingly, the lesion would reappear at the same sites during each febrile illness and with paracetamol intake, but with an increase in size and a darker color, with new lesions. There was no mucosal involvement otherwise. A month before consult, the patient developed the same lesions 10–20 minutes after paracetamol (175 mg) was given. He was evaluated by several physicians and was prescribed cetirizine and topical antifungal.

Patient was diagnosed with atrial septal defect with partial anomalous pulmonary venous return, maintained on digoxin and captopril. Patient had no known prior food or drug allergies. He was able to take paracetamol previously without any adverse reaction.

On examination, the patient appeared alert and well-looking. His height and weight were on the 5th percentile for age. Multiple round hyperpigmented patches were noted on the left ulnar region (2.5 x 3 cm), left shoulder (2.5 x 3 cm), left back (10 x 5 cm), right upper chest (4 x 4.5 cm), left abdomen (6 x 7 cm), and left hip (5 x 4 cm). He had no lesions on the lips and genitalia. Other systems were unremarkable except for a systolic murmur on auscultation. A supervised one-step oral paracetamol challenge using the lowest recommended dose for weight, 10 milligrams per kilogram, was performed, resulting in generalized pruritus and erythema of pre-existing hyperpigmented lesions within 10 minutes (Figure 1). This gradually resolved after diphenhydramine was administered, as prescribed, for 5 days. Based on this, he was diagnosed with a fixed drug eruption secondary to paracetamol. He was advised to avoid paracetamol use in the future. Since he had a previous history of intake of ibuprofen with no untoward reactions, this was recommended as an alternative antipyretic and pain reliever.

DISCUSSION

Fixed drug eruptions (FDEs) are a specific type of mucocutaneous drug reaction in which lesions typically recur in the same location upon re-exposure to the same offending drug. Typically, FDEs are characterized by sharply demarcated, round-to-oval, solitary, erythematous (bright red or dusky red) macules that may evolve into an edematous patch. These lesions may be pruritic and may be painful when eroded. After an acute phase lasting for days to weeks, residual grayish or slate-colored hyperpigmentation develops.[6–8]

Upon administration of the offending agent, acute lesions appear within 30 minutes to 8 hours but may also appear up to 14 days later. When the drug is discontinued, lesions generally resolve spontaneously within 7–10 days, leaving residual post-inflammatory hyperpigmentation. Upon re-exposure to the offending drug, lesions recur in the same location within 24 hours.[6] In some cases, it may become



Figure 1. Fixed drug eruption before and after paracetamol challenge. Hyperpigmented patches prior to the paracetamol oral challenge **(A)** dorsal view and **(B)** anterior view. Pruritus and erythema over the same lesions after the challenge **(C)** dorsal view and **(D)** anterior view.

more widespread with bullous lesions and systemic manifestations like fever and arthralgia.[13] FDEs can affect any part of the body with a predilection for the genitalia, hands, and lips. The likelihood of this distribution may be influenced by the patient's gender or related to the causative drug, with women more commonly presenting with lesions on the hands and feet. In contrast, men present with lesions on the genitalia.[6,8]

FDEs are triggered exclusively by exogenous agents, most commonly drugs, and have not been reported to arise spontaneously or following infection.[6,13] Its pathogenesis remains unclear, but roles of drug pharmacokinetics, viral infection, and genetic factors have been studied. FDE is a delayed type IV-C immune reaction in which significant numbers of CD8+ T cells with an effector-memory phenotype align along the epidermal side of the dermo-epidermal junction and are critical in initiating destructive immune responses. Once activated through the CD3–T-cell receptor complex, these cells exert cytotoxic activity against target cells, including keratinocytes.[13] Tissue damage results when these cells are activated to directly kill surrounding keratinocytes and release large amounts of cytokines such as tumor necrosis factor alpha and interferon gamma, which perpetuate the inflammatory reaction.[6,8,14] Upon discontinuation of the offending drug, apoptosis of inflammatory cells and regeneration of the damaged basal cell layer will occur. Local macrophages

phagocytose leaked melanin but remain in the epidermis, contributing to the prolonged hyperpigmentation observed. CD8+ T cells give rise to memory cells, which lead to a more rapid response upon the next exposure. A genetic predisposition to FDE is strongly linked to specific human leukocyte antigen (HLA) genes, such as HLA-B22 and HLA-Cw1.[15] However, specific genetic markers for paracetamol-specific FDE patients have not been clearly identified.[15]

Paracetamol, although generally regarded as a safe antipyretic and analgesic, has been increasingly recognized as a potential cause of hypersensitivity reactions. Pharmacologically, paracetamol functions as a weak inhibitor of cyclooxygenase-1 (COX-1) and may induce reactions analogous to NSAIDs.[10] Many suspected paracetamol reactions are attributed to this pharmacological effect: when COX-1 activity is reduced, arachidonic acid is no longer efficiently converted to prostaglandins and thromboxane. Instead, it is shunted toward the 5-lipoxygenase pathway, generating cysteinyl leukotrienes. Excess leukotrienes can produce urticaria, angioedema, and bronchospasm, which accounts for the clinical overlap between paracetamol and NSAID hypersensitivity.[9]

Cross-sensitivity between paracetamol and NSAIDs has been reported, particularly among aspirin-sensitive asthmatic patients, with frequencies ranging from 0-29%.[10] This highlights the importance of careful drug history taking and cautious selection of alternative antipyretics in susceptible individuals. However, paracetamol can also induce true delayed hypersensitivity reactions independent of COX inhibition, such as FDEs, which are manifested by drug-specific T-cell responses.[9,16]

Several pediatric case reports in the literature describe paracetamol-induced FDEs with a similar temporal relationship to drug intake but varying clinical presentations compared to the present case. An 11-year-old male developed recurrent hyperpigmented perioral and eyelid lesions with mucosal involvement within 24 hours of paracetamol intake, initially misdiagnosed as herpes simplex infection, with lesions recurring at identical sites and leaving a residual hyperpigmentation.[14] Similarly, a 2-year-old female developed a bullous lesion over the third finger of the right hand extending to almost the dorsal surface of the finger following paracetamol administration.[17] Another reported case involved a 9-year-old female with an erythematous violaceous patch over the buttocks and back and a bullous lesion of the upper extremities.[18] In contrast to our patient, these cases demonstrated involvement of additional cutaneous or mucosal sites, most notably the lips and other exposed areas.

The precise diagnosis of FDEs can be made initially with careful history taking about intake of medications and a prior history of recurrent lesions in the same sites. Oral provocation testing under the supervision of an allergist is considered the gold standard for identifying the causative drug due to its high sensitivity and specificity. The main purpose of rechallenge is to induce a similar eruption in a milder form, and a dose less than a therapeutic dose would generally be sufficient.[19] However, a consensus on the appropriate dose of the suspected drug sufficient to induce a mild reaction or the timing of the test after resolution of the initial eruption has not been reached.[20]

Management of FDE involves identification and discontinuation of the offending drug. Many patients do not warrant any further treatment since it is usually self-limiting. Symptomatic treatment includes oral antihistamines to control pruritus.[6] The prognosis of paracetamol-induced FDE is generally excellent once the offending drug is discontinued. Although FDE lesions cannot be reversed acutely and post-inflammatory hyperpigmentation may persist for prolonged periods, most patients experience complete clinical resolution within days to weeks.[6] Residual pigmentation typically fades gradually over several months. Prevention remains the cornerstone of management, as recurrence at the same site or with increased severity is common upon re-exposure. Patients and their families should be counseled to strictly avoid the culprit drug and any chemically related medications and be provided with a written list of both generic and brand names to minimize inadvertent re-exposure.[14] In our case, early recognition and confirmation through oral challenge allowed prompt counseling and avoidance, contributing to a favorable outcome consistent with previous reported cases. Since the patient had taken ibuprofen with no untoward reactions, it was recommended as an alternative antipyretic and pain reliever.

CONCLUSION

This case highlights that paracetamol, a drug commonly used in children and generally regarded as safe, can cause FDEs. Recognition of the characteristic recurrence of lesions at the same sites with re-exposure is key to diagnosis. A supervised oral challenge is required when history is suggestive. Early identification and discontinuation of the offending drug, combined with patient education on avoidance and alternative medications, are essential to prevent recurrent episodes and improve outcomes.

Ethical Considerations

This case report was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent for participation and publication was obtained from the patient's legal guardian after a clear

explanation of the nature, purpose, risks, and benefits of the report. In addition, a verbal assent was obtained from the minor patient and documented using an assent script appropriate for children aged 7 to less than 12 years, in accordance with ethical guidelines for research involving minors.

The protocol was submitted for review and was approved by the University of Santo Tomas Hospital – Research and Ethics Committee to ensure compliance with institutional and national ethical standards. Patient confidentiality and privacy were strictly maintained throughout this case report, in accordance with the Data Privacy Act of 2012. All identifiable personal information was anonymized with no details that could directly or indirectly reveal the patient's identity. The patient's data and chart were secured and accessed only by the authors of this case report.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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