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CASE REPORT

Cross-Reactivity: a Case of Paracetamol-Induced Generalized Bullous Fixed Drug Eruption Followed by Dipyrone-Induced Fixed Drug Eruption

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Abstract: A fixed drug eruption (FDE) is a recurring adverse drug reaction that manifests as lesions on the same cutaneous or mucosal sites after exposure to the causative drug. It is characterized by erythematous or violaceous, round-to-oval patches with a dusky center. With each recurrence, the number and size of lesions can increase, raising the risk for generalized bullous fixed drug eruption (GBFDE). GBFDE, a rare and severe variant, presents with widespread bullae accompanied by characteristic FDE lesions. Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the primary causes of FDE. Although cross-reactivity between different groups of NSAIDs has been rarely reported in FDE cases, in this report we present a case of paracetamol-induced GBFDE followed by FDE triggered by cross-reactivity with dipyrone (metamizole).

Keywords: generalized bullous fixed drug eruption, recurrence, paracetamol, dipyrone, cross-reactivity

Introduction

Fixed drug eruptions (FDEs) are relatively common forms of cutaneous drug reactions. They have been associated with over 100 drug types, with oral medications representing the most common cause of FDE. FDE is defined as reaction recurrence at the same site after re-exposure to a specific drug, with residual pigmentation after healing. This pigmentation can serve as an indicator for site identification. Lesions can occur on any part of the body, with a higher incidence on the external genitalia, perianal region, and lips, accounting for approximately 80% of such lesions. FDEs are classified according to their clinical morphology, with the most common types characterized by local erythema and vesicles. Identification of the causative drug is necessary for effective FDE diagnosis to prevent recurrence resulting from re-exposure to the drug. Multiple recurrences may lead to aggravated symptoms and even generalized bullous fixed drug eruption (GBFDE). The identification and management of rare GBFDE represents a significant clinical challenge,[1] and many patients previously considered to have bullous diseases such as TEN were later found to have GBFDE.[2]

Case Presentation

A 45-year-old man with a history of cirrhosis experienced recurrent episodes of erythema and blistering on both feet over the past six years but did not seek medical care. One year ago, he was treated for acute bullae and erosions on his lips, armpits, extremities, genitals, and anus. At that time, he was initially diagnosed with bullous pemphigoid (BP) due to the absence of a reported medication history. The patient refused treatment and left the hospital soon afterwards.

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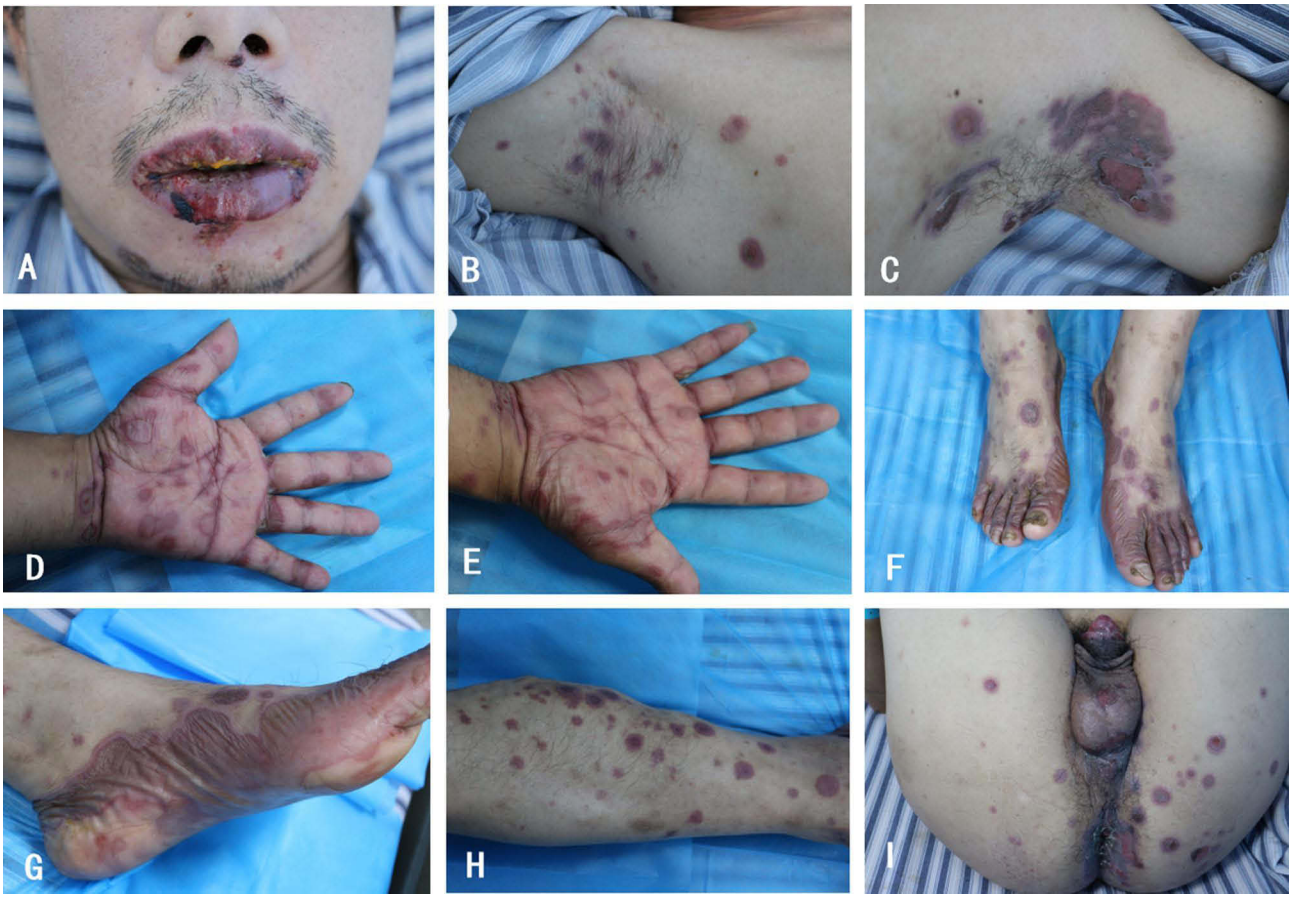

Figure 1 Erythematous to violaceous patches with flaccid blisters, bullae, and erosions on the lips(**A**), armpits (**B** and **C**), extremities (**D**–**H**), genitals and anus(**I**), with intervening areas of normal skin.

Six months before, the patient had developed recurrent erythematous plaques, bullae, and erosions at the same anatomical sites within hours after oral intake of paracetamol (acetaminophen) capsules for nasal congestion. Dermatological examination revealed multiple sharply demarcated erythematous to violaceous patches with flaccid blisters, bullae, and erosions on his lips, armpits, extremities, genitals, and anus (Figure 1). Aside from itching, the patient reported no systemic symptoms, including fever. Blood tests revealed an elevated C-reactive protein level (39 mg/L), with no significant abnormalities in other hematological, liver, or kidney function tests. An inquiry about the patient's medical history elicited the information that for many years, he would often take irregular oral doses of paracetamol due to respiratory tract diseases. This often led to the development of a rash shortly after taking the paracetamol. According to the Naranjo Adverse Drug Reaction Probability Scale, a score of 10 indicates a definite causal relationship between rash development and a drug. The clinical presentation led to a diagnosis of GBFDE, confirmed by a skin biopsy. Histopathology showed epidermal-dermal separation, liquefaction degeneration of the basal epidermal layer, scattered dyskeratotic cells, dermal papillary edema, subepidermal fissures, perivascular lymphocytic and eosinophilic infiltration, and melanophages (Figure 2). The patient was treated with intravenous methylprednisolone and appropriate wound care. Two weeks after discharge, his lesions resolved, leaving residual hyperpigmentation.

Recently, the patient presented again with erythema and blisters on his hands and lips. This time, he reported taking dipyrone (metamizole) instead of paracetamol one day before the onset of symptoms. According to the Naranjo Scale, a score of 6 indicated a probable causal relationship between the rash and dipyrone. He refused hospitalization and was prescribed intramuscular diprosone and oral olopatadine hydrochloride in an outpatient setting.

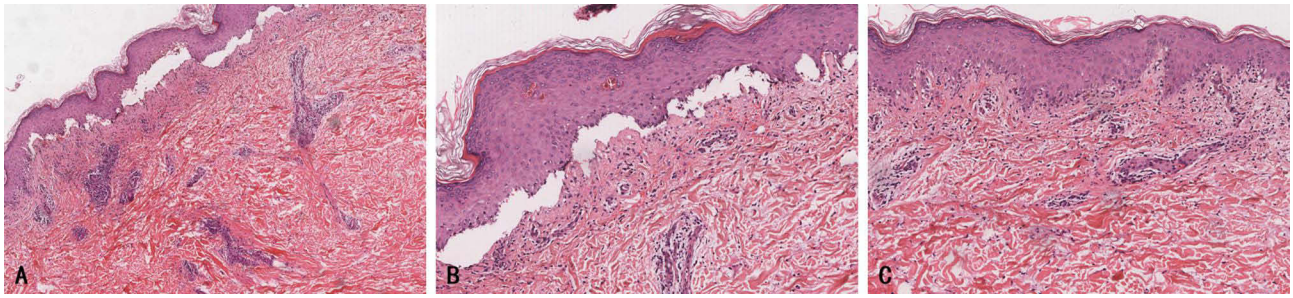

Figure 2 Histopathology showing: epidermal-dermal separation, liquefaction degeneration of the basal epidermal layer, scattered dyskeratotic cells, dermal papillary edema, subepidermal fissures, perivascular lymphocytic and eosinophilic infiltrates, and melanophages (haematoxylin–eosin stain; original magnification (**A**) × 40, (**B**) × 100, (**C**) × 100).

Discussion

This case represents a classic presentation of GBFDE in a patient with a history of irregular medication use of paracetamol and recurrent fixed-area rashes. There were no systemic symptoms other than the observed skin manifestations. With repeated episodes, the lesions worsened, culminating in generalized bullous lesions involving multiple body areas. Both clinical and pathological findings confirmed the diagnosis of GBFDE, with paracetamol identified as the initial causative drug. This aligns with existing literature, which highlights the association of paracetamol with bullous lesions.[3] Subsequently, the patient experienced another FDE episode triggered by dipyrone, indicating cross-reactivity between these two drugs. Both episodes developed rapidly within 24 hours of drug administration. This thus represents a rare case of cross-reactivity between different NSAID groups. The limitations of this case lie in the fact that, due to the extensive nature and severity of the lesions, as well as the patient's refusal, oral provocation tests and patch testing for the two drugs (particularly the tests for dipyrone) were not performed.

FDE is generally a mild drug eruption that recurs at the same sites upon re-exposure to the causative drug, with lesion size and number increasing over time. FDE results from activation of CD8+T cells within the skin by drug antigens, leading to the release of cytokines that recruit immune cells and attack keratinocytes and melanocytes.[4] The presence of resident memory CD8 + T cells during the regeneration of basal layer keratinocytes is associated with FDE recurrence at the same site.[5,6] CD8 + T cells play a key role in inflammation by recognizing drug antigens associated with specific MHC Class I molecules found on keratinocytes. Several HLA-A or HLA-B genes corresponding to MHC Class I molecules have been linked to FDE.[7]

In rare cases, widespread erythematous plaques with blisters and bullae may develop, leading to GBFDE.[8,9] GBFDE is a rarer and more severe disease that typically affects at least three of six anatomical sites (head and neck, anterior trunk, back, upper and lower extremities, and genitalia).[2] It must be differentiated from Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), both of which also present with widespread epidermolysis. Unlike SJS/TEN, GBFDE occurs rapidly (often within 24 hours of drug administration),[3,10] involves smaller areas of the body surface while leaving intact skin between lesions, and lacks significant systemic symptoms, with patients generally presenting with better overall health than that of SJS/TEN patients. Mucosal erosion is rare, and GBFDE lesions tend to resolve with residual hyperpigmentation, without permanent scarring.[11] Previous reactions are reported in many GBFDE cases but not in SJS/TEN cases.[1] GBFDE continues to frequently be misdiagnosed as SJS, and the differences in the prognoses of these two conditions remain poorly defined, although GBFDE is generally believed to be linked to better patient outcomes. Clinicians should remain vigilant as GBFDE is often misdiagnosed due to incomplete medication histories. Pathological examination, patch testing, and oral provocation tests may aid in differentiation. While Oral provocation has long been the gold standard for diagnosis, it is now generally contraindicated due to the risk of widespread FDE or GBFDE. Patch testing is methodologically easier and safer. Biopsy is appropriate for patients with unclear diagnosis or with systemic symptoms such as fever, discomfort, or joint pain, as well as for specific subtypes. In FDE, histopathology typically shows more pronounced inflammation and melanophage accumulation.[12]

Although cross-reactivity among chemically related NSAIDs has been documented, reports of immune cross-reactivity between unrelated NSAIDs are scarce.[13,14] Misdiagnosis of such cases can delay treatment and exacerbate symptoms. Once FDE is identified, both the causative drug and potentially cross-reactive drugs should be avoided, given that these episodes become more severe with each subsequent exposure. When feasible, patch or oral provocation tests should be conducted on previously affected skin areas before prescribing medications. Given the widespread use of NSAIDs, awareness of their cross-reactivity potential is crucial. Previous studies have proposed that cross-reactivity may be associated with the activation of pre-existing memory T cells by non-specific components of unrelated drugs, thereby triggering associated immune responses.[15] Alternatively, this phenomenon may be linked to the immunocompromised area.[16] Further research is needed to elucidate the mechanisms underlying cross-reactivity.

Conclusion

This case underscores the importance of accurate drug histories, early recognition of FDE/GBFDE, and heightened vigilance among healthcare professionals and patients. To manage these conditions, patients are advised to timeously disclose all potentially relevant events occurring before and during symptom onset to facilitate diagnostic evaluation. Physicians are obligated to not only instruct patients to strictly avoid causative agents, but also exercise caution in terms of potential cross-reactive agents. In addition, pharmacists should proactively counsel patients on the potential risk of possible side effects when dispensing medications.

Ethics Statement

The case received approval from the Ethics Committee of Shanghai Dermatology Hospital. Written informed consent was obtained from the patient before treatment and again for the publication of this case report including any potentially identifiable images or data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Yuanyuan Wang and Huan Xue are co-first authors for this study. The authors declare no conflicts of interest in this work.

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