Case Report

Generalized Bullous Fixed Drug Reaction: A Close Similarity to Stevens–Johnson Syndrome

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Abstract

Generalized bullous fixed drug eruption is bullous type of fixed drug eruption characterized by sharply defined bullae at the same site following administration of offending drug. GBFDE has aggressive course unlike conventional FDE and requires aggressive treatment. Mucosa is usually spared and constitutional symptoms are mild. We came across two cases of GBFDE in which culprit drugs were B-Lactam antibiotics.

Keywords: Beta-lactams, generalized bullous fixed drug eruption, Stevens–Johnson syndrome

Introduction

Generalized bullous fixed drug eruption (GBFDE) is generalized bullous type of fixed drug eruption (FDE) characteristically recurring at the same site following the administration of the same offending drug and is characterized by multiple, sharply defined, deep-red macules and blisters of various sizes, bilaterally often in symmetric distribution.[1] It occurs abruptly within a few hours to days following exposure to offending drug or sometimes the drug of similar group. Many times in clinical practice, the clinical picture of GBFDE is similar to more sinister Stevens–Johnson syndrome or toxic epidermal necrolysis (SJS/TEN). Although prognosis and course of the disease are stated to be different in GBFDE and SJS/TEN, there appears to be clinical and histologic overlap between these two entities. We came across two such cases of GBFDE with close similarity to SJS/TEN.

Case Reports

Case 1

A 75-year-old male patient was admitted to our hospital with complaints of peeling of skin over the upper back, chest, lower abdomen, both arms, and legs since 5 days without the involvement of oral and genital mucosa. He had fever and sore throat 15 days back, for which he was prescribed tablet ofloxacin-ornidazole combination twice daily by a private practitioner, followed by tablet amoxicillin-clavulanic acid 625 mg BD 5 days back. He did not have similar complaints in the past and had no history of known drug allergies. On examination, patients’ general condition was fair and vitals were stable and he was afebrile. Systemic examination revealed no abnormality. On cutaneous examination, peeling of sheets of skin was seen over the trunk, both arms, and legs with confluent necrotic blisters present over the back, buttocks [Figure 1], and pseudo-Nikolsky’s sign was positive. Skin was tender on palpation. Oral and genital mucosa was normal. Further laboratory analysis showed deranged kidney function tests with serum creatinine - 4.2 mg/dl and serum blood urea - 143 mg/dl. Patient was started on hemodialysis treatment. Following hemodialysis, his blood urea decreased to 91 mg/dl along with serum creatinine to 3 mg/dl. Other investigations were normal. ELISA-HIV was non-reactive. Skin biopsy was not done as patient was not willing for skin biopsy. Based on clinical examination, patient was diagnosed as a case of GBFDE. Patient was treated with intravenous (i.v.) dexamethasone 8 mg i.v. 8 hourly for 7 days along with linezolid 600 mg i.v. 12 hourly and oral antihistamines. Supportive care was given in the form of liquid paraffin dressing, fluid management, and nutritive support.

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During the course of disease, patient developed high-grade fever and was started on injection ceftriaxone 500 mg 24 hourly, following a single dose of injection ceftriaxone. He developed blister over erythematous base on right foot [Figure 2] and the antibiotic was stopped. As patient had received amoxicillin-clavulanic acid combination before the development of FDE, recurrence of bullous FDE after a single ceftriaxone injection was thought to be cross-reactive drug reaction as ceftriaxone belonged to a similar class of drug. During the course of the disease, his kidney failure progressed further, and patient developed sudden cardiac arrest and succumbed to death. Pulmonary embolism was considered as the cause of the death in this patient. Naranjo adverse drug reaction probability scale[2] indicated a possible relationship with a score of 4 for ofloxacin-ornidazole and probable relationship with a score of 6 for amoxicillin-clavulanic acid and the development of GBFDE.

Case 2
A 55-year-old male patient was admitted to our hospital with complaints of fluid-filled lesion along with peeling of skin over arms and thighs, abdomen, back, and chest since three days without any mucosal involvement. He had fever and sore throat, for which he was prescribed tablet amoxicillin-clavulanic acid 625 mg BD 5 days back. He did not have similar complaints in the past. Patient was a known diabetic and hypertensive since 2 years. His general condition was normal; however, patient was febrile. Systemic examination was normal. On cutaneous examination, there was peeling of sheets of skin over the back, abdomen, both upper and lower limbs, and buttocks [Figure 3] along with blisters over erythematous base at few places. Pseudo-Nikolsky’s sign was positive. Skin was tender on palpation. Oral and genital mucosa was normal. Based on clinical examination, patient was diagnosed as a case of GBFDE which was confirmed on skin biopsy. Laboratory investigations were normal, and ELISA-HIV was non-reactive. Skin biopsy from the blister showed confluent necrosis of the epidermis [Figure 4]. Patient was treated with oral cyclosporine 100 mg OD for 7 days and tablet levocetirizine 5 mg OD along with supportive care. Patient recovered completely without any sequel [Figure 5]. Naranjo adverse drug reaction probability scale[2] indicated a probable relationship with a score of 5 for amoxicillin-clavulanic acid and the development of GBFDE.

Discussion
FDE is the most common cutaneous drug reaction seen in India, characterized by pruritic, well-circumscribed erythematous patches at the same site on re-exposure to an offending drug.[3] The lesions are well-defined, round to oval erythematous and edematous plaque that may be surmounted by a bulla which heals with hyperpigmentation on discontinuation of drug. FDE usually occurs within 30 min to 8 h after drug intake.[1] Initial lesion is seen on lips or genitalia, followed by multiple round to oval well-marginated erythematous edematous plaques or blisters over the skin and mucocutaneous junction. The pathomechanism of FDE is not well understood. Intercellular adhesion molecule-1 expression has been found in lesional skin, suggesting it to be localized initiating stimulus for activation of disease-associated epidermal T-cells.[1] It is due to T-cell-mediated cytotoxicity and apoptosis of keratinocytes, i.e., enhanced or uncontrolled activation of intraepidermal T-cells contribute to severe tissue injury by rapidly producing a large amount of interferon-γ.[1] The site specificity in FDE is considered to be due to IL-20 (interleukin 20).[4] Drugs commonly causing FDE are amoxicillin, Ciprofloxacin and
other quinolones, tetracyclines, ampicillin, kanamycin, tetracycline, phenytoin, nonsteroidal anti-inflammatory drugs, dapsone, barbiturates, metronidazole, etc. In our case, beta-lactam antibiotics were the culprit drugs.

GBFDE is generalized bullous type of FDE which characteristically recurs at the same site following the administration of the same offending drug and characterized by multiple, sharply defined, deep-red macules and blisters of various sizes, occurring bilaterally often symmetric in distribution. It occurs abruptly and continues to increase in size and number even after cessation of offending drug for several days. Classical FDE is usually localized with or without mucosal involvement and therefore is less likely to cause complications such as fluid loss, electrolyte imbalance, infection, etc. On the contrary, GBFDE being generalized or extensive involves larger areas of the skin causing skin loss such as SJS/TEN and thus can be associated with systemic complications such as SJS/TEN. Generalized bullous FDE is also defined as the presence of typical FDE lesions with blisters involving at least 10% of body surface area or at least three of six different anatomic sites. Mucosa is usually spared, and constitutional symptoms are mild. It is clinically confused with the more sinister SJS/TEN. A diagnostic hallmark is the reappearance of the lesions over the previously affected sites when the offending drug is reused as with localized FDE cases. Histopathology of GBFDE is similar to FDE showing superficial and deep perivascular mixed cell infiltrate of lymphocytes, neutrophils, and eosinophils with focal necrosis of epidermis and numerous melanophages in the dermis, suggestive of melanin incontinence. In our case, full thickness epidermal necrosis was seen which is mostly seen in SJS/TEN. Based on histologic findings, it is not always possible to differentiate between FDE, TEN, and erythema multiforme. Lin et al. reported two cases of GBFDE with close resemblance to SJS/TEN and concluded that lack of mucosal involvement and histologic findings of vacuolar interface dermatitis, numerous necrotic keratinocytes, and eosinophilic infiltrates were clues for diagnosis of FDE in both cases of GBFDE. It has also been stated that GBFDE is immunopathologically distinct disease than SJS/TEN. Lesions of GBFDE have increased dermal CD4(+) cells including Foxp3(+) regulatory T cells, fewer intraepidermal CD56(+) cells, and fewer intraepidermal granulysin(+) cells. GBFDE has aggressive course unlike conventional FDE and should be treated aggressively. In this case–control analysis study of 58 patients of GBFDE, 13 died with a mortality rate of 22%. As GBFDE has extensive involvement, fluid loss and other complications due to extensive skin loss are expected to result in more mortality rates. It could not be proven from this study that GBFDE has a better prognosis as compared to SJS/TEN and has been mentioned that active attention should be given. For the similar reason, we initiated cyclosporine therapy in the second patient to minimize complications. The main goal of treatment is to identify the offending drug and mostly symptomatic management including antihistamines and systemic immunosuppressive therapy.

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**Conflicts of interest**

There are no conflicts of interest.

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