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Case Series

NSAIDS induced cutaneous adverse drug reaction – a case series

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Abstract
Cutaneous adverse drugs reactions (CADRs) are quite usual among ADRs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the common and predictable causes of cutaneous adverse reactions (CADR's). NSAIDs can cause multiple cutaneous complications like urticaria, angioedema, acneiform eruption, stevens johnson syndrome (SJS), toxic epidermal necrolysis (TEN), vasculitis, fixed drug eruption (FDE) etc. NSAIDs are very frequently prescribed drugs and even one of the frequent over the counter sold medications, making it more critical to have a more particular knowledge about the wide spectrum of cutaneous complications it can cause. The present case series focuses on the conglomeration of the few cases of cutaneous complications experienced by the patients on NSAID therapy.

Keywords: NSAIDs, severe cutaneous adverse reactions (SCARs), cutaneous adverse drug reactions (CADRs), stevens johnson syndrome (SJS), fixed drug eruptions (FDEs), fixed dose combination (FDC), over the counter (OTC)

Introduction

Adverse reactions to medications are common and often manifest as a cutaneous eruption. Cutaneous adverse drug reactions may manifest as urticaria, hypersensitivity syndrome, photosensitivity, SJS, TEN or FDE (fixed drug eruption).

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FDE is an immunological response to a drug, characterized by the development of oval or annular erythematous patches following systemic exposure to a drug which resolve with hyperpigmentation. FDE are responsible for 10% of all adverse drug reactions and occur in all ages, more commonly seen in young adults [1]. FDE manifests as recurrent eruptions characterized by erythematous to violaceous macules that subsequently progress to a plaque. FDE are one of the commonest adverse drug reactions encountered by clinicians in their day to day practice. Though not fatal, FDE can cause cosmetic embarrassment especially as the tend to recur on the previously affected sites leaving behind residual hyperpigmentation. The lesions usually vary in size and can involve any part of the skin [1]. The pathogenetic mechanism underlying FDE is

still enigmatic. The patho-mechanism involves an antibody-dependent, cell-mediated cytotoxic response. The most commonly accepted hypothesis is the persistence of memory T cells in the affected skin. Diclofenac is a most commonly used NSAIDs, a phenylacetic acid derivative. It has got analgesic, antipyretic and anti-inflammatory activities [2]. Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening, immune-mediated reactions to drugs characterized by epidermal necrosis, extensive detachment of the epidermis, erosions of mucous membranes and severe constitutional symptoms [3,4].

Adverse drug reactions due to NSAIDs are numerous, but cutaneous adverse reactions also warrant special attention. The lack of proper diagnostic tests, makes the diagnosis yet more difficult. The clinician has to depend on physical examination rather than definite laboratory investigation for confirmation.

Case 1

A hypertensive, non diabetic woman, of 47 yrs presented with dark, violaceous, erythematous, slightly edematous plaque over her left hand [Fig 1a, b]. The reaction was seen after consumption of a fixed dose combination (aceclofenac 100 mg with paracetamol 325 mg) drug for two days. It was an OTC drug which the patient had taken for her knee pain. She had similar lesions in the same site before. However, she denies of history of allergy in her family. There were no associated symptoms like fever, body ache or any other mucosal involvement. Other laboratory parameters were normal. The case was diagnosed as bullous fixed drug eruption probably due to intake of aceclofenac. The medication was withdrawn and she was advised to take oral antihistamine levocetrizine 5 mg OD. The skin lesions subsided and disappeared without complications.

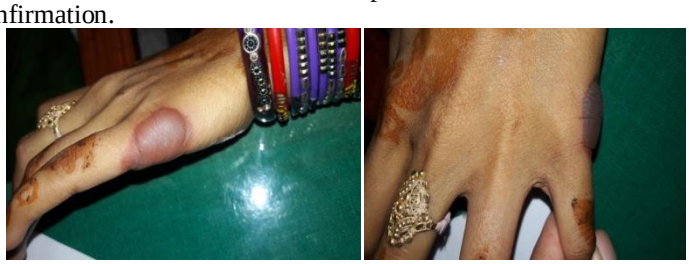


Figure 1 a, b: Bullous fixed drug eruption (dark, violaceous, erythematous, slightly edematous plaque) over her left hand

Case 2

A 42 years old, non-hypertensive non diabetic male presented with of violaceous round to oval painless mildly pruritic erythematous plaques on abdomen. The cutaneous complication ensued 2 days after consumption of diclofenac 50 mg tablets indicated for osteoarthritis pain. The lesions were mildly pruritic and confined to abdominal area only. There was no other area involved. The patient has similar experience of cutaneous reaction before. There was no positive familial history of known drug allergy. Other laboratory findings were within normal limits. The medication was withdrawn and he was put on oral antihistamine cetrizine 10 mg OD. The lesions resolved within 10 days after stoppage of the suspected medication. The provisional diagnosis was made as pigmenting type fixed drug eruption, probably due to intake of diclofenac [Fig. 2a,b]**.**

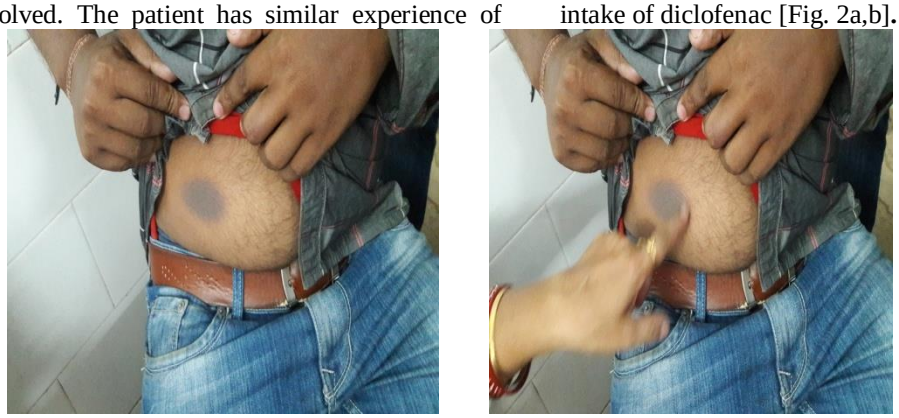


Figure 2a, b: Fixed drug eruptions

Case 3

A 33-year-old, non-diabetic, non-hypertensive male presented with a history of mildly pruritic rash for three days. To start with the rash was confined to orofacial area but soon involved distal aspect of forearm, and lateral aspect of neck. On examination, it was found to be well-defined erythematous plaques of varied sizes involving the orofacial area, distal aspect of right forearm, and lateral aspect of neck. The patient gives a history of intake of fixed dose combination (FDC) aceclofenac 100, paracetamol 325-FDC), twice daily) four days back. He had similar lesions at the same site before due to the intake of same medication of another brand. There was no significant family history of drug allergy. The suspected drug was withdrawn, and patient was advised oral antihistamines and topical steroids with complete recovery in 14 days. Provisional diagnosis was provisional pigmenting type fixed drug eruption probably due to intake of aceclofenac.

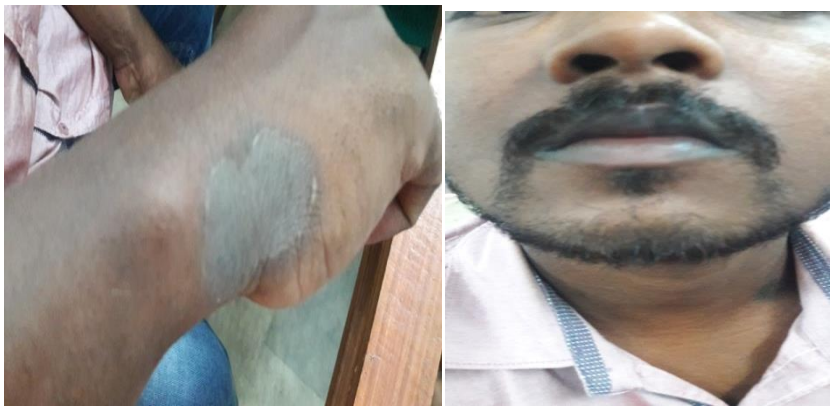


Figure 3 a, b: Fixed drug eruptions (pigmentory type)

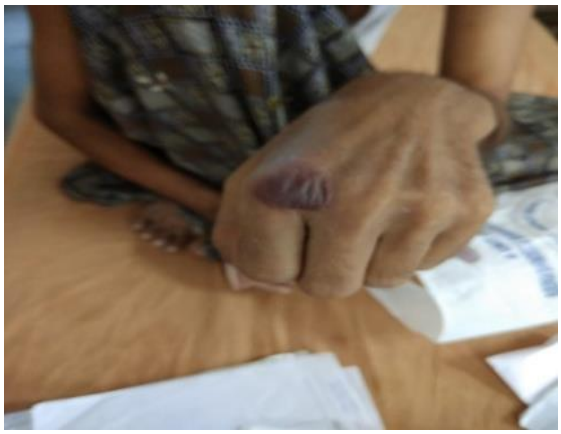
Case 4

A 24 yr old non-hypertensive non-diabetic female presented with hemorrhagic crusted lesions all throughout her body with oro-mucocutaneous ulcers desquamation of skin over lips, after consumption of aspirin 350 mg tabs as over the counter (OTC) for three days [Figure 4a, b]. To start with these lesions were erythematous, nontender, itchy associated with fever. The lesions first appear in face but soon involved other parts of the body as well. Two days after the rash patient had experienced formation of blisters in the same region, followed by hemorrhagic crusted lesions and desquamation of the skin. She continued to have fever and was taking oral Paracetamol. On examination it was found to have a body surface involvement of about 61%, hemorrhagic crusted lesions were prevalent all over face(involving inner mucosal areas), extensor surface of upper extremity. There was also conjunctival involvement for which ophthalmologists advise was taken. Her laboratory reports were normal. There was mild leucocytosis. She was managed conservatively with iv. fluids, antibiotics for a short course, cyclosporine 100 TDS. She was discharged after a hospital stay of 24 days with favorable conditions. A provisional diagnosis was made: a case of TEN probably due to intake of aspirin.

Figure 4a, b: A case of TEN, presented with hemorrhagic crusted lesions all throughout her body with oro-mucocutaneous ulcers desquamation of skin over lips

Case 5

A 48 year old male presented with 2 day history of multiple fluids filled mildly pruritic purplish blisters over the right hand shoulder. The lesions had appeared after consumption of oral etoricoxib 30 mg BD which was prescribed to him by the orthopedic physician. O/E multiple purplish- bullae was found over the fingers of right hand and over shoulder. Patient had past history of some drug allergy due to some unknown medications. He was afebrile and his vitals were within the normal range. He was treated with oral corticosteroids with an advice to strictly avoid the drug in future. The lesions resolved within 14 days after stoppage of the suspected medication. He was provisionally diagnosed as a case of bullous FDE probably due to intake of etoricoxib [Fig. 5a, b].



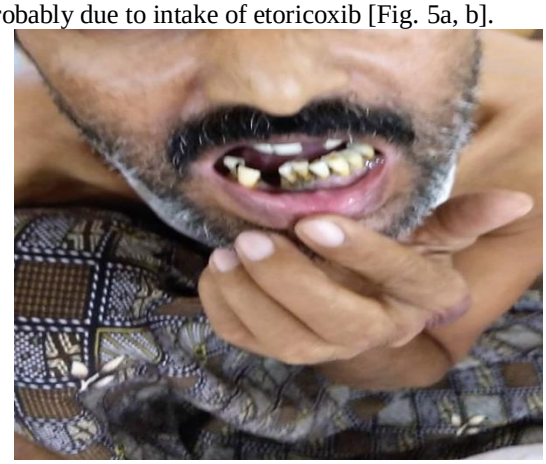


Figure 5a, b: Bullous FDE

Discussion

Cutaneous presentation is possibly the most common manifestation of adverse reactions to a drug [5].

It may manifest as urticaria, angioedema, fixed drug eruption or maculopapular rash. Of these, 2% are severe, and a few even poor outcomes [6]. Severe cutaneous adverse reactions (SCARs) include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis. SCARs can be life-threatening, with mortality rates ranging from 23% to 45% for patients with TEN and 10% for those with DRESS [7, 8]. NSAIDs are known to be the most frequently prescribed medications worldwide, and are also thought to be leading agents of drug adverse reactions [9, 10]. NSAIDs may invoke immunological reactions, mediated by IgE, which arise due to activation of T cells [11, 12]. A wide spectrum of cross-reactions among NSAIDs is widely known, which may be an immediate hypersensitive response, manifesting as asthma, urticaria, angioedema and even anaphylaxis. However, there is lack of evidence concerning the cross reactivity of different NSAIDs. The pathophysiology of SCARS is not completely understood yet. It has been found that major type of hypersensitivity reactions due to NSAIDs happen to be cross tolerant, which is related to an imbalance in the arachidonic acid pathway that leads to COX-1 inhibition.

In the above case series majority of cases were diagnosed as fixed drug eruptions, and there was only one case of TEN. Clinical diagnosis was made by the treating physician. Causality assessment was done by Naranjo scoring scale and all were “probable” category. The severity of all were assessed by Hartwig Seigel Scale and found to be moderate in majority of cases and severe for one case. All the events were reported under Pharmacovigilance Programme of India [PvPI].Management includes delineating the causative drug through a detailed medication history, along with other allergic laboratory investigations Drug sensitization is advised in few cases where benefit outweighs risk, but seldom practiced. Management includes prompt withdrawal of the offending agent, followed by use of topical steroids, or disease specific. SCARs may necessitate the use of immunomodulatory agents such a cyclosporine, and even systemic steroids.

Conclusion

NSAIDs being widely prescribed and known to be a frequent OTC drug are not devoid of complications. Cutaneous adverse reactions, commonly experienced as adverse effect of NSAIDs consumption, should be managed with prompt withdrawal of the putative drug.

Avoidance of the similar drug through proper patient counseling may avoid such complications in future. The diagnosis of drug allergy has by far been clinical with little or no scope for confirmation through laboratory tests. Admittedly, the detailed understanding of drug allergy cases has been in general constrained with a relative lack of access to standardized laboratory diagnostic tests.

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