Non-Pigmented Fixed Drug Eruption Caused by Ibuprofen

A 71 year old female presented to the outpatient dermatology department with complaints of erythematous skin lesions associated with burning sensation and itching over body for past 7 days. She revealed that she took ibuprofen for fever 5 days ago. She recalled having two previous episodes of similar lesions at same sites; first episode 5 years back following intake of quinolones, and second episode 3 years back after intake of ibuprofen. There was no history of edema, breathing difficulty, dizziness or any food allergy. She is a diabetic and hypertensive for last 10 years on regular medications with no change in recent past. Cutaneous examination revealed well defined, discrete, erythematous plaques over abdomen, back, buttocks, lower and upper limbs [Figure 1a and b]. At follow up visit 15 days after onset, the lesions eventually healed with no pigmentation [Figure 2a and b]. The causality assessment as per the World Health Organization-Uppsala Monitoring Centre scale, Naranjo ADR probability scale and Hartwig scale were possible, probable (score of 7) and moderate respectively. Patient did not consent for skin biopsy even after repeated counselling. Due to fear of recurrence of the reaction, patient did not consent for oral provocation test also. She was handed a list of possible drugs causing fixed drug reaction and was advised to strictly avoid these drugs in future or to take it under observation and monitoring if necessary.

Cutaneous adverse drug reactions (CADRs) are seen in about 1-2% cases.[1] Fixed drug eruption (FDE) is responsible for about 10% of all CADRs. The term FDE was first introduced by Brocq in 1894.[2] It is a delayed type of hypersensitivity reaction in which lesions recur at the same skin site due to repeated intake of an offending drug. They occur 30 minutes to 8 hours after drug administration. FDE has multiple variants, including generalized, linear, bullous, urticarial, pigmenting, nonpigmenting, wandering, eczematous, psoriasiform, erythema dyschromicum perstans like, vulvitis and oral.[3] Normally, when the acute phase resolves, it usually leaves behind residual pigmentation that becomes more prominent after each recurrence. However, in non-pigmented fixed drug eruption (NPFDE), no such pigmentary change occurs. The site of the drug hypersensitivity response in NPFDE is hypothesized to be dermal. Pseudoephedrine has been reported to be the most common drug causing NPFDE.

The patho-mechanism of FDE is not well understood. It has been postulated that it is a delayed Type IVc hypersensitivity reaction mediated by CD8+ T cells. ICAM 1 expression has been found in lesional skin, suggesting that it provides a localized initiating stimulus for the activation of disease associated epidermal T cells. These CD 8 T cells that are present in the basal layer of resting lesions on activation causes tissue injury by rapidly producing large amount of IFN- gamma. A genetic susceptibility to develop a FDE with an increased incidence of human leukocyte antigen-B22 has also been documented.[1]

Abramowitz and Noun first proposed the concept of NPFDE in 1937.[4] Fifty years later, Shelly and Shelly

described a distinctive type of NPFDE that consisted of symmetric, tender, large, erythematous plaque.[5] There have been many cases reported of nonpigmented fixed drug eruptions, common drugs being responsible were pseudoephedrine, tetrahydrozoline, piroxicam, thiopental, radioopaque contrast media (iothalamate), diflunisal, ephedrine and pseudoephedrine.[6] Recently, reports of non-pigmenting fixed drug eruption to eprazinone, sorafenib, tadalafil, esomeprazole and fluoroquinolones have also been described,[7] but there are no case reported with NSAIDS. The characteristics of nonpigmented fixed drug eruptions include large, symmetric scarlet-colored erythematous areas appearing on the axilla, buttock, and inguinal regions. Histologically, marked basal cell hydropic degeneration with pigmentary incontinence, scattered keratinocyte necrosis with eosinophilic cytoplasm and pyknotic nucleus (civatte bodies) are seen in the epidermis. Infiltration of lymphocytes, histiocytes, and neutrophil polymorphs is evident in the upper dermis. IN NPFDE, usually there is no pigment incontinence and consequently no pigmentary evidence of an eruption at the site is present after the initial lesion subsides. Also, in contrast to classic fixed drug eruptions, infiltration of lymphocytes into the epidermis is minimal in NPFDE and no necrosis of the epidermis is detected. In our case, we could not take skin biopsy as patient was not willing for the same.

The most reliable way to verify the cause of a suspected drug eruption is oral provocation. It is however a tedious and time taking procedure and may be hazardous to the patient. In FDE, positive results of epicutaneous skin tests have been obtained with certain drugs at sites of previous lesions but not on normal unaffected skin. A negative skin test gives no reliable information but a positive result could exclude the need for oral challenge. Also certain causality assessment scales regarding drug reaction can also be used like the Naranjo ADR probability scale, WHO-Uppsala Monitoring Centre causality assessment system and Hartwig scale. Treatment includes stopping the offending drug along with administration of oral and topical steroids, emollients, and oral antihistamines if required.

Ibuprofen which is one of the commonly prescribed NSAIDS, is known to cause various CADRs including FDE. However, an extensive literature search did not reveal any case of non-pigmenting fixed drug eruption caused by this drug. With this report, we intend to highlight the possibility that Ibuprofen can trigger non-pigmenting fixed drug eruptions as well.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be

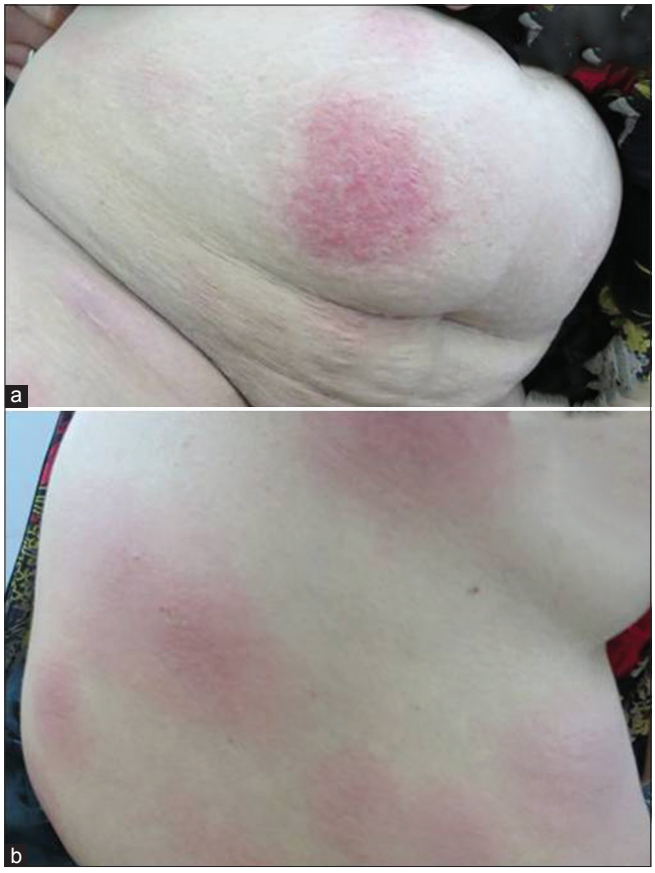

Figure 1: Well defined, discrete erythematous plaques over (a) front aspect of abdomen, (b) lateral aspect of lower abdomen

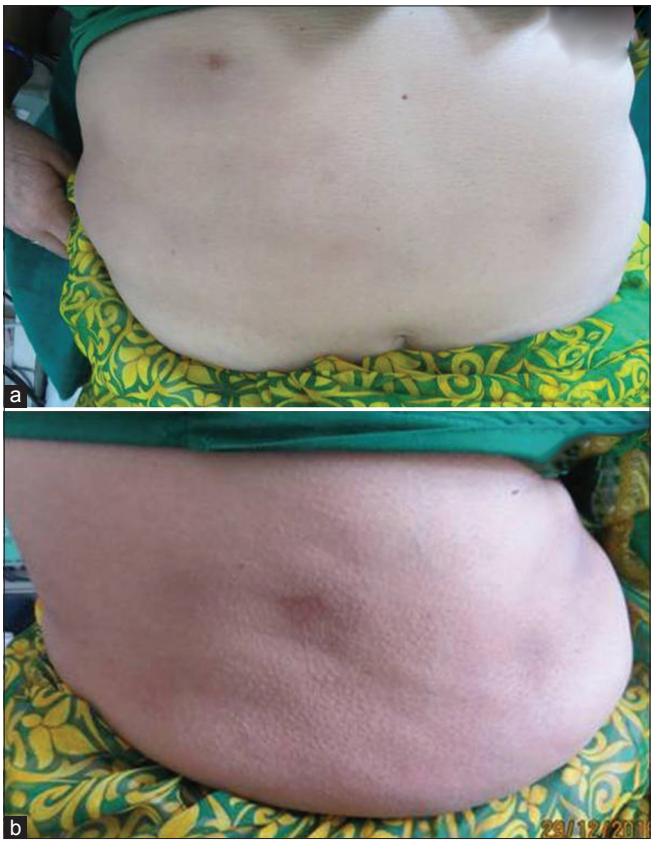

Figure 2: No pigmentation in follow up over (a) front aspect of abdomen, (b) lateral aspect of lower abdomen

reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Rochit R. Singhal, Niral K. Sheth, Pragya A. Nair

Department of Dermatology and Venereology, Pramukhswami Medical College, Karamsad, Gujarat, India

Address for correspondence:
Dr. Pragya A. Nair,
Department of Dermatology and Venereology,
Pramukhswami Medical College, Karamsad,
Gujarat - 388 325, India.
E-mail: drpragash2000@yahoo.com

References

1. Rönnau AC, Sachs B, von Schmiedeberg S, Hunzelmann N, Ruzicka T, Gleichmann E, *et al*. Cutaneous adverse reaction to ciprofloxacin: Demonstration of specific lymphocyte proliferation and cross-reactivity to ofloxacin *in vitro*. Acta Derm Venereol 1997;77:285-8.
2. Sehgal VN, Srivastava G. Fixed drug eruption (FDE): Changing scenario of incriminating drugs. Int J Dermatol 2006;45:897-908.
3. Nair PA. Ciprofloxacin induced bullous fixed drug reaction: Three case reports. J Fam Med Primary Care 2015;4:269-72.
4. Abramowitz EW, Noun MH. Fixed drug eruptions. Arch Dermatol Syphil. 1997;35:875-92.
5. Shelley WB, Shelly ED. Nonpigmenting fixed drug eruption as a distinctive reaction pattern. J Am Acad Dermatol. 1987;17:403-7.
6. Matsumoto K, Mikoshiba H, Saida T. Nonpigmenting solitary fixed drug eruption caused by a Chinese traditional herbal medicine, mabuang (Ephedra Hebra), mainly containing pseudoephedrine and ephedrine. J Am Acad Dermatol. 2003;48:628-30.
7. Gupta LK, Beniwal R, Khare AK, Mittal A, Mehta S, Balai M. Non-pigmenting fixed drug eruption due to fluoroquinolones. Indian J Dermatol Venereol Leprol 2017;83:108-12.

Access this article online	
Website: www.idoj.in	**Quick Response Code**
DOI: 10.4103/idoj.IDOJ_200_18	

How to cite this article: Singhal RR, Sheth NK, Nair PA. Non-pigmented fixed drug eruption caused by Ibuprofen. Indian Dermatol Online J 2019;10:341-3.

Received: July, 2018. **Accepted:** October, 2018.