

Letter to the Editor

Fixed drug urticaria: A report of two patients



Dear Editor

Fixed drug eruptions (FDE) represent a skin syndrome expressed clinically as a round, erythematous and edematous plaque, involving occasionally mucous membranes, that often recur in the same location, developing hyperpigmentation.¹ This type of cutaneous hypersensitivity reaction is mediated by cytotoxic CD4⁺, CD8⁺, and CD56⁺ T cells (type IVc reaction), and its progression is believed to be limited by regulatory T cells.^{1–3} Nevertheless, other clinical variants have been described, including dermatographic⁴ or papular eruptions.⁵ Either local anesthetics (LA)⁶ or non-steroidal anti-inflammatory drugs (NSAIDs)⁷ represent two major families of drugs causing FDE.

We present two patients who suffered from atypical FDE types. *Patient 1*: A 30-year-old woman with a personal history of rhinoconjunctivitis due to pollen sensitivity, and diagnosed with congenital multiple nevus syndrome. She denied having any allergic symptoms to latex exposure. This patient developed, in two different occasions after nevus exeresis (on the back and the neck, respectively), one itching and erythematous urticarial wheal on the outer face of her right arm. In both cases, the lesion appeared 20 min after the administration of ScandibsaTM (mepivacaine 2% [20 mg/ml], Inibsa, Barcelona, Spain) and spontaneously disappeared 15 min later without leaving neither desquamation nor hyperpigmentation. One month later, an allergological workup was undergone after granting her informed consent. *Patient 2*: A 50-year-old woman without a personal or familial history of atopy. Eight years ago, she had suffered more than 10 episodes of an itching and erythematous isolated urticarial wheal always located over the upper abdomen (epigastrium). It appeared after taking metamizole or acetaminophen for different pains or upper respiratory infections. All the episodes started 15–20 min after the drug intake and disappeared within 30 min spontaneously with no residual skin lesions. After the last episode, she has tolerated ibuprofen, dextketoprofen, and other NSAIDs. Two months later, an allergy study was undergone after receiving her informed consent.

We performed an allergological study for both cases. *Patient 1*: Skin prick testing (SPT) and intradermal tests (with immediate and late readings at 48 and 72 h) with commercial MepivacainaTM 1% (Braun, Barcelona, Spain) (10 ml of aqueous solution of mepivacaine 1% [10 mg/ml], sulphites-, and parabens-free) were carried out. The SPT was made with an undiluted solution of the commercial drug. For intradermal tests, 0.02 ml from two different concentrations were injected sequentially: 0.02 mg (1:10 dilution in

saline solution) and 0.2 mg (1:1 dilution). SPT with latex and epinephrine were also performed.

All cutaneous tests were negative. Subsequently, a graded-dose subcutaneous challenge test (0.1–0.5–1 ml out of a 10 mg/ml concentration) was carried out. Twenty minutes after accumulating 0.6 ml of MepivacainaTM 1% (Braun, Barcelona, Spain) on the left shoulder, itching, erythema and one hive appeared on the outer face of her right arm, in the same place and with the same characteristics as the patient had experienced on the previous two occasions. This lesion spontaneously disappeared in 30 min. Two months after finishing this study, the patient needed a new exeresis of four nevus located on her face and neck using LidocainaTM 1% (Braun, Barcelona, Spain) (10 ml of an aqueous solution of lidocaine 1% [10 mg/ml], sulphites-, and parabens-free). Twenty minutes after the intervention, the same cutaneous lesion appeared again on the outer face of her right arm (Fig. 1A).

The biopsy confirmed an urticarial lesion (Fig. 1B, C). An increase in the lymphocyte number was discarded. Stains for mast cells with Giemsa and immunohistochemistry for CD117 did not show any increase in the number of mast cells, hence discarding a mast cell accumulate, namely mastocytoma, or a flare-up phenomenon. In fact, no injection of LA was administered previously on the site where the urticaria took place, discarding a hypothetical flare-up reaction.

In order to evaluate a possible cross-reactivity among different LA, and to offer a safe alternative to the patient, one week later, we carried out a SPT and intradermal tests with commercial BupivacainaTM 0.25% (Braun, Barcelona, Spain) (10 ml of an aqueous solution of bupivacaine 0.25% [2.5 mg/ml], sulphites-, and parabens-free). The SPT performed with an undiluted solution of the commercial drug was negative. For intradermal tests we used 1:10 and 1:1 dilutions in saline solution, with negative results. We carried out a double-blind, placebo-controlled challenge test with bupivacaine at therapeutic doses subcutaneously, reaching 1.6 ml accumulated, and the patient experienced no reaction. Of note, all the SPT and intradermal tests were performed on the volar face of her left forearm, and all the challenge tests, on the outer face of her left shoulder.

Patient 2: Due to the fact that the patient reactions did not have clinical significance, we performed an open challenge test with acetaminophen and metamizole in different days. In both cases, a unique urticarial wheal located on epigastrium appeared in 15 min (Fig. 2A), being spontaneously resolved in 30 min in the acetaminophen case, and taking a biopsy in the metamizole case. The biopsy confirmed a neutrophilic-type urticarial pattern (Fig. 2B, C). Staining for mast cells did not show any increase in the number of these cells. An increase in the lymphocyte number was also discarded. Due to the evanescent nature of the lesions,

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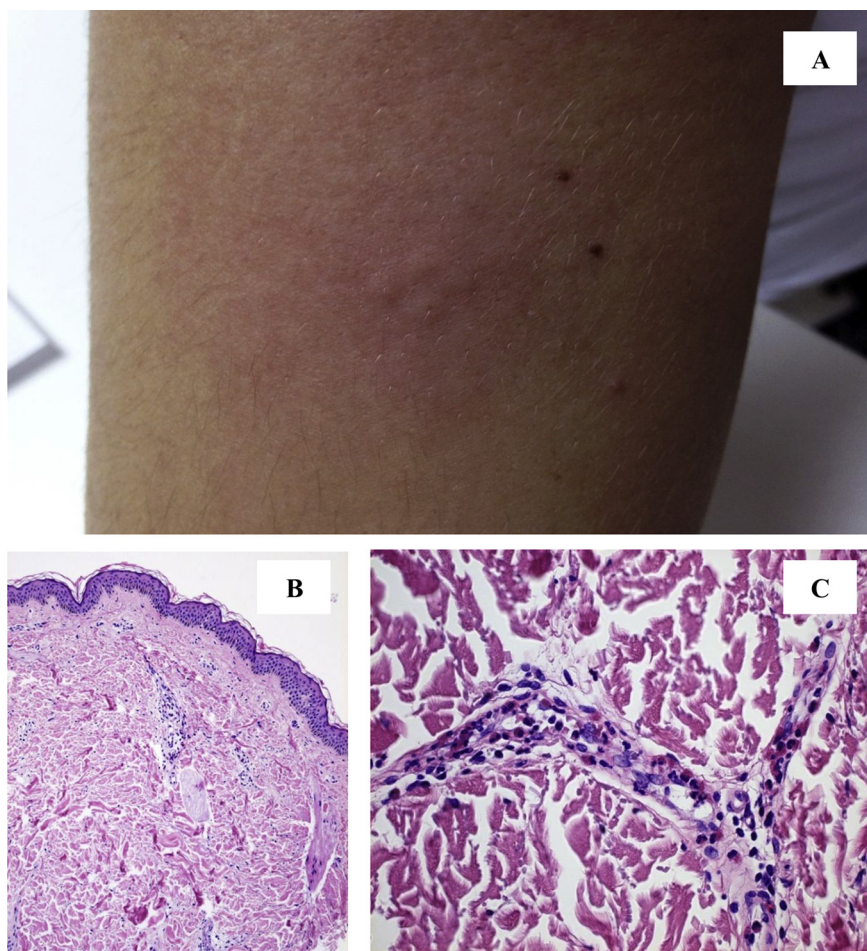


Fig. 1. (A) Hive located on the outer face of the right arm after challenging with lidocaine. (B) Mild dermal edema, lymphatic and small blood vessel dilation, and perivascular lymphocyte infiltrate (hematoxylin and eosin stain, original magnification $\times 10$). (C) Large numbers of perivascular and small vessel wall eosinophils (hematoxylin and eosin stain, original magnification $\times 40$).

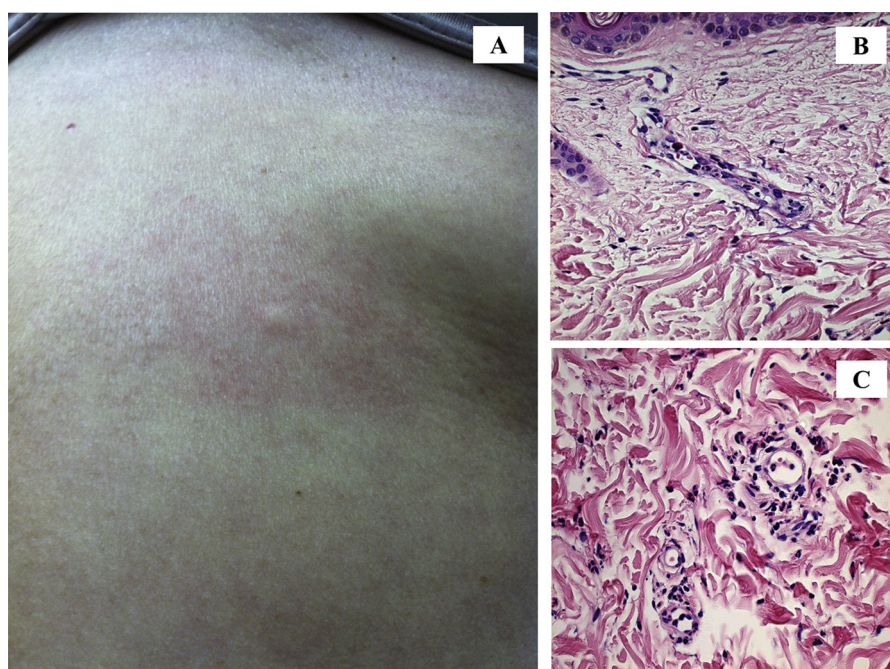


Fig. 2. (A) Hive located on epigastrium after an oral challenge test with metamizole. (B) Mild perivascular inflammatory infiltrate in the deeper and upper dermis, with neutrophils and occasional eosinophils (hematoxylin and eosin stain, original magnification $\times 20$). (C) Discreet dilation of small blood vessels with intravascular neutrophils and a mild dermal edema (hematoxylin and eosin stain, original magnification $\times 40$).

we suspected an urticarial lesion by an IgE-mediated mechanism which was confirmed by skin biopsies. In spite of this, we performed patching test with the implicated drugs in petrolatum 20% (mepivacaine, lidocaine, metamizole and acetaminophen) at the site of a previous lesion spontaneously resolved and on skin never injured, in order to discard a T-cell-mediated mechanism. The results were negative in both patients, supporting a type I hypersensitivity reaction and discarding a type IV mechanism.

To the best of our knowledge, these two cases represent the first reported patients diagnosed with fixed drug urticaria. Morais-Almeida et al.⁸ reported a patient that exhibited an extensive local urticaria after local lidocaine, where skin tests with lidocaine, bupivacaine, mepivacaine, and ropivacaine, were positive. Nevertheless, Prieto et al.⁹ reported a patient that reacted to mepivacaine, with a cross-reactivity with ropivacaine, but tolerating lidocaine and bupivacaine. The patient ≠ 1 presented an unusual immediate hypersensitivity reaction to mepivacaine and lidocaine, and a good tolerance to bupivacaine was demonstrated. And regarding to NSAIDs, the site of involvement of the FDE for either acetaminophen or metamizole was on the trunk in a series of 105 patients,¹⁰ as in the patient ≠ 2. This patient tolerates the rest of NSAIDs.

In conclusion, herein, we present two exclusive cases of a fixed drug reaction manifested as an urticaria, always located in the same area in both patients, after the injection of mepivacaine and lidocaine in different places, or after taking acetaminophen and metamizole. Further investigation must be carried out in order to enlighten the real immunologic mechanism involved in this kind of lesion.

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Conflict of interest

The authors have no conflict of interest to declare.

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