

Erythema multiforme induced by tramadol: an allergy assessment

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Erythema multiforme (EM) is a severe inflammatory skin disorder mainly due to infections, infrequent to drug hypersensitivity. Sulfamides, penicillins and anti-inflammatories have been the most described drugs. Tramadol has showed weaker association inducing Stevens–Johnson syndrome and toxic epidermal necrolysis [1]. We report a case of EM induced by tramadol with an allergy work-up.

A 47-year-old non-atopic woman, without medical history of interest. She took PazitalTM (acetaminophen 325mg/tramadol 37.5mg) every 8hours and etoricoxib 60mg every 24 hours, for low back pain. After 4 weeks of treatment, she had an eruption with symmetrical distribution of target lesions in palms, soles, arms and torso, adding oral mucosa lesions 3 days later. She was evaluated in the Dermatology Department, treated with oral antihistamines, prednisone, lidocaine, topic FucidineTM (fusidic-acid/hydrocortisone-acetate) and DiprogentaTM 0,05%/0,1% (betamethasone-dipropionate/gentamicin-sulfate). The lesions were resolved within 2 months without sequelae or hyperpigmentation.

A biopsy from the right hand palm and a PCR for Human Herpesvirus 6, 7 and 8 were performed. The serology study displayed a negative outcome and there wasn't any suspicious of a possible infection, stress or other possible targets of EM. The

histopathology confirmed the diagnosis (Figure). She was diagnosed with possible drug induced EM and referred to our Allergy Department.

We performed epicutaneous tests with acetaminophen 5% and 10%, tramadol 5% and etoricoxib 10%, (petrolatum as vehicle). Two non-atopic patients were controls. We obtained negative results at 48 and 96 hours lectures. A lymphocyte transformation test (LTT) was performed.

LTT showed a mild positive result for Pazital™, stimulation index (SI) of 2.25, being negative (<2) for etoricoxib, acetaminophen and tramadol. In addition, the patient added new information: some weeks before the described reaction, she had taken Pazital™, presenting micropapules in palms, which spontaneously resolved in 5 days after drug intake. Also, a month after the recovery of reaction the patient took acetaminophen with ibuprofen and noticed palm pruritus with no lesions and she interrupted drug intake, with no other symptoms. Afterwards the patient tolerated ibuprofen.

With the test results and related history, we suspected from acetaminophen as the most probable culprit drug, so we performed different dose-graded drug provocation tests (DPT). Etoricoxib showed a negative result. Unexpectedly, with tramadol the patient showed typical cutaneous lesions on the hand palms just over one hour after the intake of 40mg of tramadol (Supplementary figure). DPT with acetaminophen was negative.

After positive DPT with tramadol, we underwent a new LTT with Pazital™, tramadol and acetaminophen, as previously referred [2]. We obtained a SI of 2.08 and

2.04 for Pazital™, SI 4.56 (10µg/ml) and 5.67 (25µg/ml) for tramadol and under 2 for acetaminophen, confirming tramadol as the culprit agent.

There are no reported cases of EM due to tramadol. In our case, the epicutaneous tests and the LTT were not enough to diagnose and we had completed the study with DPT. We finally obtained a positive LTT after the positive DPT.

EM is a well-characterized skin syndrome, it consists of a polymorphous eruption of macules, papules, and characteristic "target" lesions that are symmetrically distributed with a propensity for the distal extremities, with minimal mucosal involvement. EM may have different severity, it has been classified into EM minus (less severe) and EM majus (more severe) [3]. Our case fits in EM minus. We can find scarce publications with a diagnosis of EM induced by drugs confirmed with biopsy and positive DPT, as in our patient [4].

In Roujeau's review of 37 reported cases of drugs-induced-EM, from 2010 to 2016, the diagnosis was considered as definite/probable EM in 6 cases (16%), possible in 7 cases (19%) and 'no case' in 24 (65%). Therefore 65% did not fulfill the published clinical criteria for EM and none of the six probably EM provided evidence of drug causality [5].

The novelty of our case relays on the rapid onset of targets lesions on palms after taking tramadol in DPT.

Due to the rapid onset of the positive provocation test with tramadol we might think it could be a fixed drug eruption (FDE) resembling EM. Nonetheless, we think it is an erythema multiforme. The morphology of target-like lesions (Figure) are typical of EM. FDE may present with targetoid lesions that mimic EM (erythema multiforme-like

FDE) but in FDE these lesions have only two concentric zones of color with a darker, dusky hue, in the center, different from the patient's lesions, also the localization in the palms is not usually in FDE. Many atypical histologic reaction patterns have been described in FDE; in our patient a lymphocytic infiltrate is involved in the dermo-epidermal junction, without melanin incontinence (frequently found in repeated lesions of FDE) and with no residual lesions left, as we usually find in FDE [6].

Type IVb nonimmediate drug reactions corresponds to Th2-type immune response, where Th2 T-cells secrete IL-4, IL-13 which could justify the rapid onset of skin lesions [7,8]. The activated T-cells migrate to the tissue and kill tissue cells, such as keratinocytes in a perforin/granzyme-B and/or FasL-dependent manner [9]. Part of the activated T-cells will transform into effector memory T-cells; when they are located in the skin (in our case, in the patient's palms), as tissue-resident-memory CD8⁺T-cells, they can produce a faster response than the previous in the next contact with the drug (skin-homing T-cells) [2,7].

LTT had positive result probably due to the proliferation of different activated lymphocytes we could find in the reaction, as memory CD8⁺T-cells, $\delta\gamma$ T-cells, NK and NKT cells [7,9]. The reproducibility of LTT technique was proven [10] reporting a coefficient of variation less than 9% for PHA stimulations showing a good quality of the technique. Therefore, our LTT result was interpreted as correct and can explain the timing of nonimmediate reaction.

We describe an EM induced by tramadol with an allergy study performed, with negative skin tests. Diagnosis was made clinically and confirmed by histopathology and LTT, after positive DPT. We highlight the rapid onset of target lesions on palms after

provocation test, that leads us to think of the intriguing immunological nature of this entity.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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