Erythema Multiforme Induced by Tramadol: An Allergy Assessment

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Erythema multiforme (EM) is a severe inflammatory skin disorder caused mainly by infections and rarely by drug hypersensitivity. Sulfamides, penicillins, and antiinflammatory drugs are the most common causes of drug-induced EM. A weak association between tramadol and Stevens-Johnson syndrome and drugs are the most common causes of drug-induced EM. A weak hypersensitivity. Sulfamides, penicillins, and antiinflammatory skin disorder caused mainly by infections and rarely by drug.

The LTT showed a mild positive result for Pazital, with a stimulation index (SI) of 2.25 and negative results (<2) for etoricoxib, acetaminophen, and tramadol. In addition, the patient reported having taken Pazital some weeks before the reaction and that this had led to micropapules on her palms that resolved spontaneously in 5 days after intake. One month after the reaction resolved, the patient took acetaminophen with ibuprofen and experienced palmar pruritus with no lesions. She interrupted drug intake and experienced no further symptoms. She subsequently tolerated ibuprofen.

Figure. Histopathology image of an erythema multiforme skin lesion (original magnification, x4 [A] and x20 [B, C]). Necrotic keratinocytes throughout the epidermis (W). In the superficial dermis, note the inflammatory infiltrate characterized by lichenoid infiltrate rich in lymphocytes (X), with interface damage, lymphocytic exocytosis (Y), and blood extravasation (Z). A perivascular inflammatory infiltrate can be seen in the dermis, with no fibrinoid necrosis in the walls of the blood vessels.

Key words: Erythema multiforme. Drug hypersensitivity. Tramadol. Pazital.

involvement. The severity of EM varies, and the condition has been classified as EM minus (less severe) and EM majus (more severe) [3]. Our case fits the description of EM minus. We found few publications reporting drug-induced EM confirmed with biopsy and a positive DPT result, as reported here [4].

In their review of 37 cases of drug-induced EM from 2010 to 2016, Roujeau et al [5] reported that the diagnosis was considered definite/probable in 6 cases (16%), possible in 7 cases (19%), and ‘no case’ in 24 cases (65%). Therefore, 65% did not fulfill the published clinical criteria for EM, and none of the 6 cases of probable EM were supported by evidence of drug causality [5].

The novelty of the present case lies in the rapid onset of target lesions on the palms after taking tramadol in the DPT. Given the rapid onset in the positive provocation test with tramadol, we might consider the reaction to be a fixed drug eruption (FDE) resembling EM. Nonetheless, we think that the reaction was EM. The morphology of targetoid lesions (Figure) is typical of EM. FDE can present with targetoid lesions that mimic EM (erythema multiforme–like FDE), although in FDE, these lesions have only 2 concentric zones of color with a darker, dusky hue in the center. This description differs from that of the present case, and the palms are not usually affected in FDE. Many atypical histologic reaction patterns have been described in FDE. In the present case, a lymphocytic infiltrate was involved in the dermoepidermal junction, with no melanin incontinence (frequently found in repeated lesions of FDE) or residual lesions, as is usually the case in FDE [6].

Type IVb nonimmediate drug reactions correspond to a T\(_{\text{H}}\)-type immune response, where T\(_{\text{H}}\)2 T-cells secrete IL-4 and IL-13, thus potentially accounting for the rapid onset of the 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 transform into effector memory T cells; when these are located on the skin (palms in the case we report) as tissue-resident memory CD8\(^+\) T cells, they can produce a faster response than the previous one in the next contact with the drug (skin-homing T cells) [2,7].

The LTT yielded positive results, probably owing to the proliferation of activated lymphocytes in the reaction as memory CD8\(^+\) T cells, \(\delta_T\) cells, NK cells, and NKT cells [7,9]. The reproducibility of the LTT has been proven elsewhere [10], with a coefficient of variation <9% for phytohemagglutinin stimulation, thus illustrating the good quality of the technique. Therefore, our LTT result was interpreted as correct and can explain the timing of the nonimmediate reaction.

We describe EM induced by tramadol assessed using an allergy study and with negative skin test results. The diagnosis was based on clinical data and confirmed by histopathology and LTT, after a positive DPT result. The rapid onset of target lesions on the palms after the DPT highlights the intriguing immunological nature of this entity.

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**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**Previous Presentation**

The data from this study were presented in part in poster form at the 43rd Spanish National Congress of Dermatology and Venereology (May 2015, Seville, Spain) and in poster form at the Meeting of the European Academy of Allergy and Clinical Immunology (June 2015, Barcelona, Spain).

**References**


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