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 toxic epidermal necrolysis has been reported [1]. We report a case of EM induced by tramadol confirmed with an allergy work-up.

An otherwise healthy 47-year-old nonatopic woman was taking acetaminophen 325 mg/tramadol 37.5 mg (Pazital) every 8 hours and etoricoxib 60 mg every 24 hours for low back pain. After 4 weeks of treatment, she experienced an eruption with symmetrical distribution of target lesions on the palms, soles, arms, and torso and then on the oral mucosa 3 days later. She was evaluated in the dermatology department and treated with oral antihistamines, prednisone, lidocaine, topic fusidic-acid/hydrocortisone-acetate (Fucidine), and 0.05%/0.1% betamethasone-dipropionate/gentamicin-sulfate (Diprogenta). The lesions resolved within 2 months without sequelae or hyperpigmentation.

A biopsy specimen was taken from the right palm, and a polymerase chain reaction assay was performed to detect human herpesvirus 6, 7, and 8. The result of the serology study was negative, and infection, stress, and other possible targets of EM were not suspected. Histopathology confirmed a diagnosis of drug-induced EM (Figure). The patient was referred to the allergy department.

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

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.

With the test results and related history, we suspected acetaminophen as the most probable culprit drug and performed various dose-graded drug provocation tests (DPTs). The result for etoricoxib was negative. Unexpectedly, with tramadol, the patient experienced typical cutaneous lesions on the palms slightly over 1 hour after intake of 40 mg of tramadol (Supplementary Figure). The result of the DPT with acetaminophen was negative.

After the positive DPT result with tramadol, we performed a new LTT with Pazital as previously reported [2]. We obtained an SI of 2.08 and 2.04 for Pazital, 4.56 (10 µg/mL) and 5.67 (25 µg/mL) for tramadol, and <2 for acetaminophen, thus confirming tramadol as the culprit agent.

There are no reported cases of EM due to tramadol. In the present case, the patch test and LTT results were not sufficient to confirm the diagnosis and we had completed the study with DPT. We finally obtained a positive LTT result after the positive DPT result.

EM is a well-characterized skin syndrome consisting of a polymorphous eruption of macules, papules, and characteristic target lesions that are symmetrically distributed with a propensity for the distal extremities and minimal mucosal

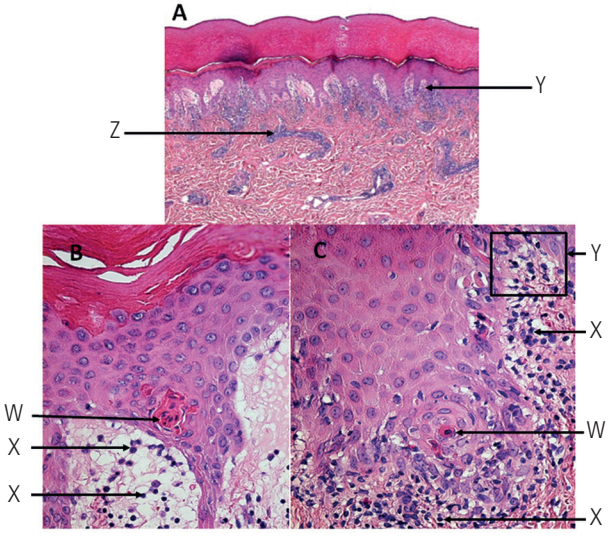

Figure. Histopathology image of an erythema multiforme skin lesion (original magnification, x4 [A] and x20 [B, C]). Necrotic keratinocytes throughout the epidermis (W). In the superficial dermis, note the inflammatory infiltrate characterized by lichenoid infiltrate rich in lymphocytes (X), with interface 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.

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_H2-type immune response, where T_H2 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, $\delta\gamma$ 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).

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