Flare-Up Phenomenon Triggered by Patch Testing of Topical Ointments Containing Nitrofurazone and Polyethylene Glycol

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Dear Editor,

Nitrofurazone-containing ointments are commonly prescribed as topical agents treatment of skin-related diseases by non-dermatology specialties, particularly surgical departments. However, the active ingredient nitrofurazone and the vehicle polyethylene glycol (PEG) are significant contact sensitizers that can result in allergic contact dermatitis.[1] Herein, we report a patient who had an allergic contact dermatitis due to nitrofurazone-containing ointment and a flare-up reaction after patch testing.

A 51-year-old male presented with erythema, edema, and yellow crusts on the left cheek as well as erythematous patches with multiple tiny pustules on the left neck to the back (Figure 1a, b). About 10 days before presentation, he had a soft tissue infection on his cheek and was administered oral amoxicillin-clavulanic acid and topical nitrofurazone-containing ointment. Nitrofurazone was the active ingredient in the topical ointment used by the patient, and the vehicles were PEG 300, PEG 1000, and PEG 4000. The patient did not have fever or lymphadenopathy. Laboratory tests were within normal limits, including the total blood count with differentials, erythrocyte sedimentation rate, and C-reactive protein level. Microbial cultures did not contain pathogenic microorganisms. Histopathological examination of the inflamed neck area revealed predominantly perivascular and interstitial infiltration of lymphocytes and eosinophils in the upper and mid dermis. The patient was diagnosed with allergic contact dermatitis caused by nitrofurazone-containing ointment. All lesions were cleared with systemic prednisolone at a dose of 0.8 mg/kg/day along with topical 0.05% clobetasol propionate cream within 6 days.

One month after ceasing treatment, the patient underwent patch testing using the TRUE test and a topical commercial ointment containing nitrofurazone and PEG, which are considered the causative agents of allergic contact dermatitis. Patch tests were evaluated according to the morphological criteria recommended by the International Contact Dermatitis Research Group.[2] The TRUE test was negative at 48th and 72th hours. However, the nitrofurazone-containing ointment (commercial product, applied directly) produced a weak positive reaction, 25% ointment (mixed with white petrolatum) produced a questionable reaction, and petrolatum (control area) produced no reaction (Figure 2). Additionally, itchy, irregularly bordered, erythematous, mildly edematous patches emerged on the neck, nape, and shoulders where

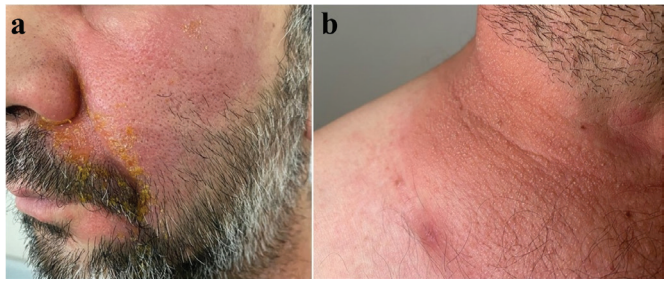

Figure 1. (a) Images showing erythema, edema, and yellow crust on the left cheek. (b) Erythematous patch with multiple tiny pustules on the left side of the neck

Submission: 05-Jul-2024 **Web Publication:** 12-Sep-2024
Acceptance: 29-Aug-2024

Access this article online

Quick Response Code:

Website: www.turkjdermatol.com

DOI: 10.4274/tjd.galenos.2024.88597

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How to cite this article: Yılmaz İpek B, Akoğlu G, Kalkan F, Demirel F. Flare-Up Phenomenon Triggered by Patch Testing of Topical Ointments Containing Nitrofurazone and Polyethylene Glycol. Turk J Dermatol. 2024;18(2):63-65.

previous allergic contact dermatitis had been observed (Figure 3a, b). The reaction was considered a flare-up phenomenon triggered by the skin patch test carried out with nitrofurazone-containing ointment. Within a few days, the response subsided with treatment with topical corticosteroids and systemic antihistamine.

A strong sensitizer, nitrofurazone, also known as nitrofural (5-nitro-2-furaldehyde semicarbazone), frequently causes severe allergic contact dermatitis in patients suffering from burns, stasis eczema, or other chronic dermatitis. Topical nitrofurazone sensitivity rates ranged from 3.3% to 36.2%.[1,3,4] Özkaya and Kılıç[1] reported reactions to PEG in 42% of 836 patients who underwent patch testing, and in 80% of these patients, nitrofurazone sensitivity was also detected. The strong correlation between nitrofurazone sensitivity and PEG sensitivity points out that PEG enhances the penetration of nitrofurazone, especially in regions of disrupted skin barrier.

The flare-up phenomenon refers to a drug-induced acute inflammatory skin reaction that emerges in areas of the skin where dermatitis has previously taken.[5,6] Twelve hours after exposure to contact allergens, skin-resident CD8-positive tissue resident memory cells trigger a sudden and strong neutrophil infiltration in the epidermis, resulting in a flare-up reaction.[6] Although nitrofurazone-containing topical are widely used, no flare-up phenomena have been reported in the literature after patch testing with nitrofurazone or PEG. The diagnosis of allergic contact dermatitis due to nitrofurazone-containing ointments is quite simple by taking a detailed medical history from a patient living in countries where these agents are prescribed frequently. Therefore, patch testing is not typically required. Commercially available tests lack nitrofurazone and PEG, so physicians should prepare test samples using these agents in the test area. In summary, if the frequency of patch testing is low, the flare-up phenomenon will be less frequent. Detailed dermatological examination of the whole body may be needed to notice a flare-up phenomenon to observe subtle yet newly developed phenomena that are not yet symptomatic. Mild reactions can be easily underdiagnosed and unreported.

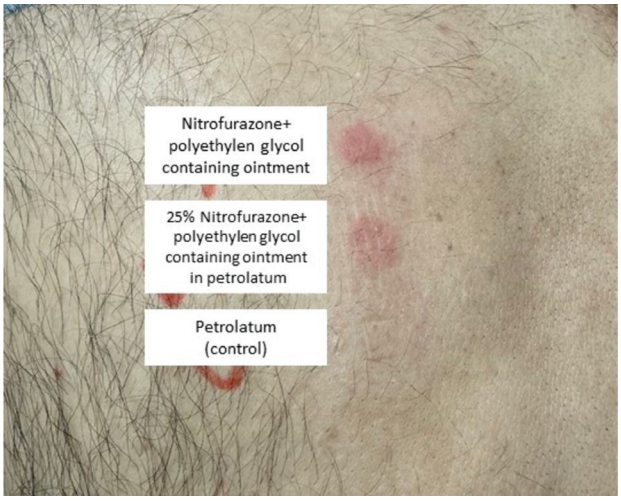

Figure 2. Patch test results at 48th hour: weak positive reaction with nitrofuzarone and polyethylene glycol ointment, questionable reaction with 25% ointment in petrolatum, and negative reaction with petrolatum

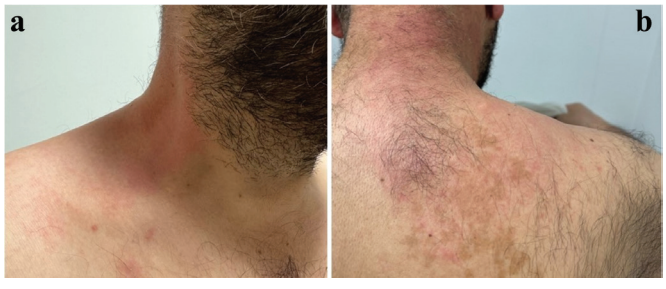

Figure 3. (a) Flare-up phenomenon on the left side of the neck at the 48th hour of the skin patch test. (b) Flare-up phenomenon on the nape and back during the 48th hour of the skin patch test

The limitation of our case report was the lack of pure test samples, including only nitrofurazone and PEG products, due to unavailability. Testing had to be performed using the commercial ointment that the patient had used. Consequently, we could not determine whether nitrofurazone or PEG is responsible for dermatitis. Therefore, the patient was advised not to use medications and cosmetics, including either agents along with PEG-containing foods.

In conclusion, nitrofurazone and PEG may induce allergic contact dermatitis, and patch testing including these agents may cause flare-up phenomenon in skin areas where dermatitis has previously existed.

Ethics

Informed Consent: Informed consent to publish their photographs and related clinical information was obtained from the patient. The patient signed a consent form allowing the use of their images and details for scientific and educational purposes and ensuring anonymity.

Authorship Contributions

Surgical and Medical Practices: G.A., B.Y.İ., Concept: G.A., F.D., F.K., Design: G.A., Data Collection or Processing: B.Y.İ., F.K., Analysis or Interpretation: G.A., B.Y.İ., F.D., F.K., Literature Search: G.A., B.Y.İ., F.D., F.K., Writing: G.A., B.Y.İ.

Conflict of Interest: The authors declared that they have no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

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