

Pseudoephedrine May Cause “Pigmenting” Fixed Drug Eruption

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Fixed drug eruption (FDE) is a distinctive drug eruption characterized by recurrent well-defined lesions in the same location each time the responsible drug is taken. Two different clinical forms have been described: the common classic pigmenting form and the rare nonpigmenting form. Nonpigmenting FDE is mainly characterized by symmetrical large erythematous plaques and the dermal histopathologic reaction pattern. Pseudoephedrine is known as the major inducer of nonpigmenting FDE. Pigmenting FDE from pseudoephedrine has not been reported previously. Here, the first case of pseudoephedrine-induced pigmenting FDE is reported, showing the characteristic features of classic pigmenting FDE such as asymmetry, normal-sized lesions, and the epidermodermal histopathologic reaction pattern. Moreover, a positive occlusive patch-test reaction to pseudoephedrine could be demonstrated on postlesional FDE skin for the first time.

FIXED DRUG ERUPTION (FDE) is a distinctive drug eruption characterized by recurrent well-defined lesions in the same location each time the responsible drug is taken. Two different clinical forms have been described: the common classic pigmenting form and the rare nonpigmenting form.¹ Pseudoephedrine is known as the major inducer of nonpigmenting FDE.^{2–8} Pigmenting FDE induced by pseudoephedrine has not been reported previously. Here, the first case of classic pigmenting FDE induced by pseudoephedrine is reported with positive topical and systemic provocation test results.

Case Report

A 42-year-old nonatopic Turkish man presented with three discrete circular-to-oval hyperpigmented patches 3 to 5 cm in diameter on the abdomen, the flexural aspect of the left femoral area, and the glans penis. The patient reported recurrent site-specific attacks of itching and burning followed by marked redness and edema when he used cold remedies during the previous 4 years. The suspected drugs had pseudoephedrine in common.

After informed consent was obtained, oral provocation with 5 mL of Sudafed syrup (GlaxoSmithKline, İlaçları Sanayi ve Ticaret A. Ş., Istanbul, Turkey), containing

30 mg of pseudoephedrine hydrochloride as the only active ingredient, led to itching and burning at postlesional skin sites within 15 to 20 minutes, followed by complete reactivation with marked violaceous erythema and edema within 2 to 3 hours. The lesions cleared within 1 week with the administration of a topical corticosteroid, leaving an enlarged area of hyperpigmentation.

Three months later, occlusive patch testing was performed with pseudoephedrine hydrochloride (provided by Abdi İbrahim İlaç Sanayi ve Ticaret A. Ş., Istanbul, Turkey) 1%, 5%, and 10% aqueous on the hyperpigmented patch on the abdomen and 1%, 5%, and 10% in petrolatum (pet) on the hyperpigmented patch on the femoral area and on unaffected back skin. IQ Chambers (Chemotechnique Diagnostics, Vellinge, Sweden) were used. White petrolatum (Brial Allergen, Greven, Germany) was also tested as a negative control. Test strips were removed after 48 hours. Whereas patch-test results were negative on the abdominal and unaffected back sites, nearly complete reactivation with marked violaceous erythema and edema was observed on the femoral test area on day 2. Itching and burning had started in this area within 24 hours. The reaction was diffuse, but it was more prominent on the patch-test sites with the higher test concentrations of pseudoephedrine, sparing the white petrolatum patch-test area (Fig 1). Histopathology of the reactivated test area showed dyskeratosis, basal vacuolar degeneration, dense melanophages in the papillary dermis, and mononuclear perivascular inflammatory infiltration. The reaction gradually faded after 72 hours, leaving hyperpigmentation. One

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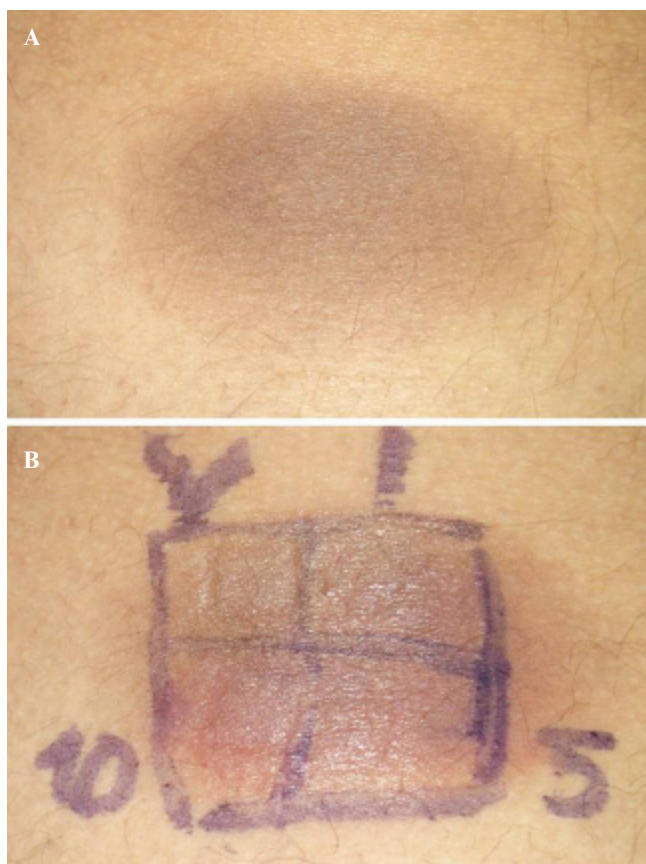


Figure 1. A, Postlesional hyperpigmented site of a fixed drug eruption on the flexural aspect of the left femoral area. B, Nearly complete reactivation with marked violaceous erythema and edema in the femoral test area at day 2 of occlusive patch testing with pseudoephedrine 1%, 5%, and 10% in petrolatum (respectively marked as 1, 5, and 10). Note that the reaction is more prominent on the patch-test sites with higher test concentrations of pseudoephedrine, sparing the patch-test area with white petrolatum (marked as V).

month later, a new site-specific attack occurred after the patient took another brand of oral pseudoephedrine-containing cold remedy that he mistakenly believed to be free of pseudoephedrine. The Naranjo adverse drug reaction probability score was 11, suggesting a definite causal relationship between pseudoephedrine and the eruption according to the following criteria⁹ (individual scores in parentheses): previous conclusive reports of this eruption (+1), appearance of the eruption after administration of the suspected drug (+2), improvement of the eruption after discontinuation of the drug (+1), re-appearance of the eruption following re-administration of the drug (+2), absence of causes other than the drug (+2), dose-dependent severity of the eruption (+1), history of similar reaction to the same drug or similar drugs (+1), and confirmation by topical and oral provocation tests (+1). Probability categories according to total score were

defined as definite (≥ 9), probable (5–8), possible (1–4), and doubtful (≤ 0).⁹

Discussion

Site-specific attacks following intake of pseudoephedrine-containing medication, positive topical and oral provocation test results, and histopathology confirmed the diagnosis of pseudoephedrine-induced pigmenting FDE in the presented case.

Nonpigmenting FDE was first described in 1937¹⁰ and was later suggested as a distinctive reaction pattern,¹ pseudoephedrine being the major causative agent.^{2–8} Classic pigmenting FDE is mainly characterized by solitary or asymmetrical lesions, whereas nonpigmenting FDE was claimed to occur in the form of symmetrical erythematous plaques.¹ Most reports on pseudoephedrine-induced nonpigmenting FDE were consistent with this pattern, but solitary lesions have also been reported.^{7,8} The erythematous plaques are usually large, with common involvement of flexural intertriginous areas and the buttocks.^{1,3,6} Histopathology is characterized by a dermal reaction pattern.^{1,3}

Oral provocation is the “gold standard” for verifying the causative drug in FDE. Pseudoephedrine-induced FDE has been verified by topical provocation on postlesional skin only once previously.⁴ Interestingly, open tests with pseudoephedrine hydrochloride 10% and 50% pet produced an erythematous reaction without induration, whereas the result of a 48-hour occlusive patch test with pseudoephedrine hydrochloride 10% pet remained negative.⁴ Erythema (with or without induration) that starts within 24 hours in an open test at a healed FDE site and lasts at least 6 hours was defined as a positive test reaction.¹¹ The International Contact Dermatitis Research Group criteria are not suitable for the evaluation of patch-test reactions in the case of FDE because FDE is not an eczematous reaction. As an important point, positive patch-test reactions showed both erythema and edema in our case; furthermore, they were achieved with pseudoephedrine in white petrolatum only and not with aqueous test preparations.

Conclusion

This was the first reported case of pseudoephedrine-induced pigmenting FDE that had the characteristic features of classic pigmenting FDE such as asymmetry, normal-sized lesions, and the epidermodermal histopathologic reaction pattern. Moreover, a positive occlusive patch-test reaction to pseudoephedrine could be demonstrated on postlesional FDE skin for the first time.

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