

Clinical Communications

Severe contact dermatitis due to ethylenediamine dihydrochloride in nystatin cream

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Clinical Implications

- Ethylenediamine was removed from many antifungal/steroid combination creams in the 1980s because of reports of contact dermatitis. Our case illustrates that generic formulations of nystatin cream may still contain this potent sensitizing agent and lead to contact dermatitis.

TO THE EDITOR:

Ethylenediamine dihydrochloride is a preservative, emulsifier, and stabilizer found in a variety of medications, laundry detergents, and industrial compounds.^{1,2} Initial reports of contact dermatitis due to ethylenediamine emerged in the 1950s in pharmacists who developed generalized eczematous eruptions after preparing aminophylline suppositories, which contain this substance.^{3,4} In the 1960s, cases of contact dermatitis due to sensitization to the ethylenediamine component in Mycolog cream, an antifungal/steroid combination cream, began to surface.^{2,5} Ethylenediamine enabled the stabilization of gramicidin and neomycin in the presence of nystatin in this formulation.⁶ These reports led to a reformulation of this combination cream devoid of ethylenediamine known as Mycolog-II in 1985.^{1,6,7} Although ethylenediamine was subsequently removed from many antifungal/steroid combination creams, certain generic formulations of nystatin-containing creams available in the late 1980s were still noted to contain this sensitizing agent for unclear reasons.^{6,8,9} The last 2 case reports of contact dermatitis due to generic ethylenediamine-containing nystatin cream and nystatin/triamcinolone combination cream were published in 1988.^{8,9} We present the first known case of contact dermatitis due to ethylenediamine dihydrochloride in a generic nystatin cream in almost 30 years.

A 39-year-old man with no significant medical history presented to the emergency department (ED) with a 4-week history of a pruritic erythematous papular eruption on the upper torso, axillae, and medial thighs. History was unrevealing except for his recent use of a communal washing machine for his laundry. He worked as a server in a sushi restaurant without any known exposure to potential sensitizing agents. Generic nystatin cream was prescribed because of concern for fungal infection. The patient liberally applied this cream for 5 days. On day 5, he returned to the ED with progression of his eruption to confluent erythema with superficial vesiculation and crusting involving more than 75% of his body surface area sparing the palms, soles, face, and oral mucosa (Figure 1). He was also noted to be febrile with a temperature of 101.6 °F associated with tachycardia (heart rate of 120 beats per minute). Laboratory analysis was notable for

an elevated white blood cell count (15.2 k/uL) with a neutrophilic predominance of 79%. The absolute eosinophil count was 0.2 k/uL on admission, peaked at 1.0 k/uL on hospital day 4, and declined to 0 k/uL with the initiation of oral steroids. C-reactive protein was elevated at 2.4 mg/dL. Basic metabolic panel and liver function tests were unremarkable. Diagnostic testing for HIV, hepatitis A, B, and C, parvovirus B19, anti-streptolysin O antibody, cytomegalovirus, syphilis, and nuclear antibody screen were negative. Epstein-Barr virus IgG antibody was positive. Blood cultures did not grow any bacteria. Skin biopsy revealed spongiotic dermatitis with many eosinophils suggesting eczematous dermatitis, particularly acute allergic contact dermatitis. He remained hospitalized for 6 days with an erythrodermic eczematous eruption complicated by impetiginization, which was considered a possible cause of his fever. He was treated with vancomycin, prednisone, topical hydrocortisone and triamcinolone ointments, and diphenhydramine and discharged on a 7-day course of doxycycline, 6-week prednisone taper, and triamcinolone ointment with marked improvement in his eruption. The patient also discontinued his use of the communal washing machines at the laundromat he previously used. He subsequently presented as an outpatient for further evaluation in the allergy and immunology clinic. Patch testing was performed 3 months after his hospitalization with our site's baseline and supplemental series using Finn chambers on Scanpor tape in compliance with the International Contact Dermatitis Research Group's guidelines. Patch tests were positive to ethylenediamine dihydrochloride 1% (2+), imidazolidinyl urea 2% (1+), diazolidinyl urea (1+), and p-phenylenediamine free base 1% (±) at 48 hours (Figure 2) and formaldehyde (in water) 1% (1+) and tixocortol pivalate 1% (1+) at day 6. The patient's generic nystatin cream was confirmed to contain ethylenediamine.

The etiology of the patient's initial eruption before his exposure to ethylenediamine-containing nystatin cream is unclear. The patient may have had repeated exposure to residual laundry detergents and fabric softeners, which may contain ethylenediamine, imidazolidinyl, diazolidinyl, and formaldehyde, given his recent use of communal washing machines. Ethylenediamine is used as a bleach activator in many laundry detergents. Imidazolidinyl and diazolidinyl, which are formaldehyde releasers, and formaldehyde are preservatives with potent antimicrobial properties found in many detergents.¹ Exposure to these potential detergent constituents may have contributed to the patient's initial contact dermatitis. However, the initial eruption severely worsened after additional exposure to an ethylenediamine-containing nystatin cream with involvement of the vault of the axillae and submammary folds, which are not typically involved in garment-related contact dermatitis. Involvement of these anatomic locations in addition to a positive patch test to ethylenediamine suggests that the patient was sensitized to nystatin cream. The patient did not have any known exposure to substances containing p-phenylenediamine (such as hair dye) to which he had only an equivocal patch-test reaction.

Although ethylenediamine has been removed from many antifungal/steroid combination creams and antifungal ointments, certain generic formulations may still contain this potent sensitizing agent and cause contact dermatitis. This case illustrates the



FIGURE 1. Erythematous papular eruption with confluent erythema, superficial vesiculation, and crusting involving more than 75% of the patient's body surface area including (A, B) upper torso, (C) axillae, and (D) medial thighs.

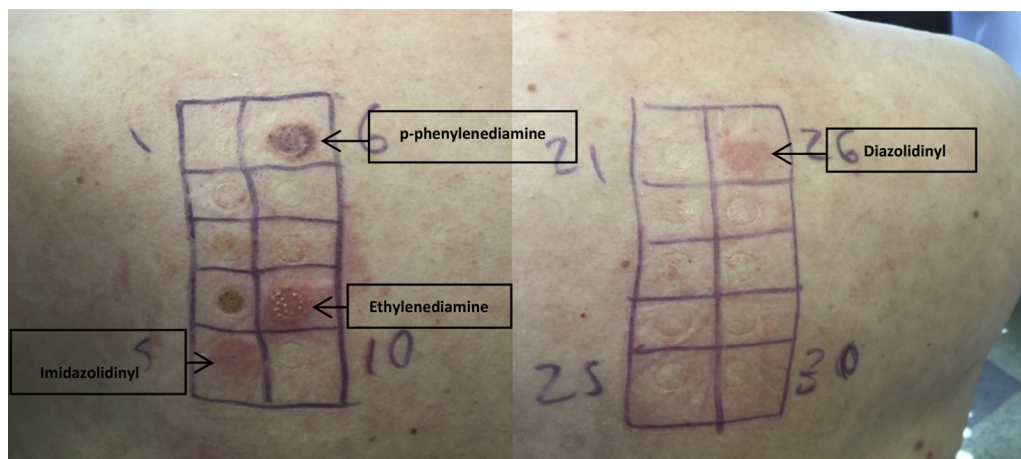


FIGURE 2. Patch test results at 48 hours.

importance of investigating the inactive ingredients found in topical medications, especially generic formulations, to search for the presence of hidden allergens in elusive cases of contact

dermatitis. Furthermore, because the utility of ethylenediamine in nystatin cream remains unclear, pharmaceutical companies should consider re-evaluating its use.

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