

Acute Generalized Exanthematous Pustulosis Induced by Topical Morphine and Confirmed by Patch Testing

To the Editor:

Acute generalized exanthematous pustulosis (AGEP) is a rare adverse cutaneous reaction to several triggers, where oral medications constitute the majority of the identified triggers.^{1,2} Acute generalized exanthematous pustulosis is clinically characterized by the acute appearance of generalized edematous erythema, speckled with small pinheaded nonfollicular sterile pustules that can become confluent, usually with accompanying fever ($\geq 38.5^{\circ}\text{C}$) and peripheral blood leukocytosis, with marked neutrophilia.^{3,4}

We report here a case of AGEP after topical application of a combination of lidocaine with 10% morphine, confirmed by patch testing. A 72-year-old woman presented to her general practitioner with back pain and was prescribed lidocaine with 10% morphine formulation to be applied topically. Within 10 days after initiation of topical application, she developed severe generalized pustular erythema with a fever of 39°C (Fig. 1A). Histological examination of a lesional biopsy showed epidermal spongiosis, subcorneal/superficial epidermal pustules, and inflammation around adnexal structures (Figs. 1B, C). The clinical and histological findings were consistent with AGEP. The symptoms resolved after discontinuation of the topical application and initiation of a short course of oral prednisone.

We elected to patch test the patient to the following: the North American Contact Dermatitis Group standard screening

series to allergens (SmartPractice, Phoenix, AZ) using Finn chambers (SmartPractice), textile series (Chemotechnique Diagnostics, Vellinge, Sweden) using IQ Ultimate chambers (Chemotechnique Diagnostics; distributed by Dormer Laboratories, Inc, Toronto, Ontario, Canada), and medicament series (Chemotechnique Diagnostics). Scanpor tape (Actavis Norway AS, Norgesplaster, Norway) was applied over all patch-test panels.

Patch-testing protocols, reaction quantification, and final readings were determined according to standard North American Contact Dermatitis Group protocol.⁵ We had the Ottawa Hospital inpatient pharmacy mix up all of the drugs that she brought diluted at 30% petrolatum. This included cephalexin, Robax Platinum, cetirizine, dimenhydrinate (Gravol), fexofenadine (Allegra), dextansoprazole (Dexilant), ranitidine, pregabalin, amitriptyline, amoxicillin, tramadol, ibuprofen (Advil), and paracetamol (Tylenol). In addition, some of her own topical medicaments were applied using IQ Ultimate chambers (Chemotechnique Diagnostics; distributed by Dormer Laboratories, Inc), including lidocaine with 10% morphine cream (local pharmacy-made, compounded using pluronic lecithin organogel base). Readings were done at 48 hours, and the final reading was done at 72 hours.

The patient had a 3+ strong spreading reaction to the lidocaine with 10% morphine cream (Fig. 1D). She also developed a recall reaction characteristic of AGEP on her face. The patient also underwent a provocative use test using the base pluronic lecithin organogel and showed a negative reaction.

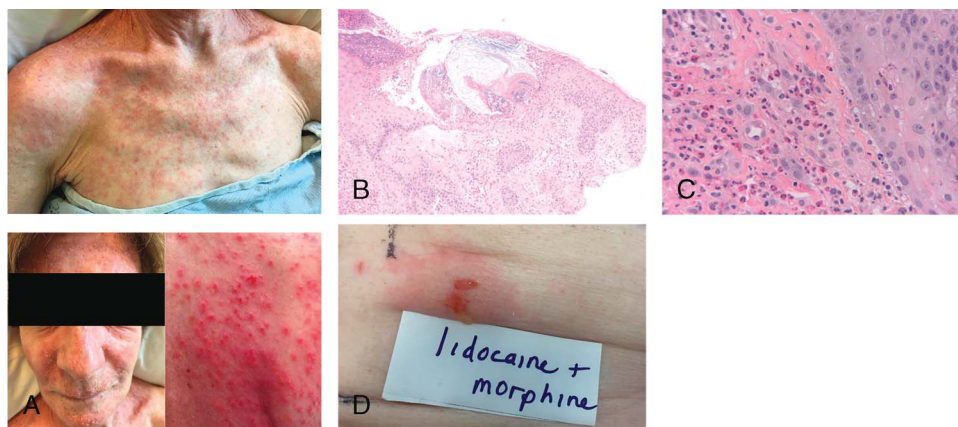


Figure 1. A, Clinical photographs showing generalized edematous erythema, speckled with many small pinheaded nonfollicular pustules. B, Histology findings demonstrating spongiosis and subcorneal/superficial epidermal pustules in the epidermis and (C) higher-magnification images showing superficial mixed inflammation with numerous eosinophils and admixed neutrophils. D, Patch testing showing robust positive reaction to lidocaine and 10% morphine, as seen by the eruption of coalescing vesicles.

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The patient also reacted to other allergens. She had a 3+ reaction to nickel sulfate hexahydrate (2.5% petroleum), 2+ reaction to methylchloroisothiazolinone/methylisothiazolinone (0.02%

aqueous = 200 ppm), 1+ reaction to fragrance mix 1 (8% in petroleum), 1+ reaction to hydroperoxides of linalool 1% in petroleum, 2+ reaction to methylisothiazolinone (0.2% aqueous = 2000 ppm), and 1+ reaction to benzisothiazolinone (0.1% in petroleum). Notably, the patient was tested twice to lidocaine-HCL, 15% in petroleum and had no reactions, confirming morphine was indeed the culprit drug.

This report is one of very few to implicate topical medications causally with AGEF. To our knowledge, this is the first reported case of AGEF associated with topical application of morphine and confirmed by patch testing. The identification of this culprit for AGEF is important for clinicians to be aware of.

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Flushing at Sites of Topical Tacrolimus Application Induced by Drinking Alcohol

To the Editor:

We encountered a 29-year-old woman with episodic flushing associated with a burning sensation limited to sites of application of 0.1% tacrolimus ointment for periorbital and perioral dermatitis. The flushing followed a consistent pattern that started 15 to 30 minutes after drinking red wine and resolved within an hour after such consumption. She underwent renal transplant 6 years ago and has been stable on cyclosporine. She reported no prior reactions after drinking alcohol.

Transient ethanol-induced flushing at topical tacrolimus application sites is documented in the literature at a prevalence ranging from 3.4% to 6.9%.^{1,2} The mechanism is unclear, with the leading hypothesis suggesting that inhibited aldehyde-dehydrogenase activity by topical calcineurin inhibitors produces accumulation of acetaldehyde in skin after ingesting ethanol.³ Another explanation is tacrolimus-triggered neuropeptide release with downstream capsaicin-mediated vasodilation potentiated by ethanol.³ A double-blind controlled evaluation of 2 patients with the condition, which showed improvement with oral acetylsalicylic acid and exacerbation with oral histamine blockers, led the authors to theorize that prostaglandins rather than histamine are responsible for acetaldehyde-related vasodilation.⁴

Given that the vast majority of reported cases were asymptomatic except for the flushing, we consider the burning sensation in our case to be an outlier.³ In the only other reported case of associated burning, refrigeration of the tacrolimus ointment before application relieved that sensation.⁵ Pimecrolimus has also been reported to cause ethanol-induced application site flushing, but much less commonly.⁴

Of note, our patient was on a systemic calcineurin inhibitor (cyclosporine) when she developed the flushing. Our review of the literature did not disclose any cases of ethanol-induced flushing associated with systemic calcineurin inhibitors. Given the ubiquity of topical calcineurin inhibitors for treating several skin conditions, patients should be counseled about this ephemeral but bothersome adverse effect.

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