

Acute generalized exanthematous pustulosis due to codeine confirmed by patch testing, without cross-reactivity to other opioids

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Clinical Implications

We describe a rare case of acute generalized exanthematous pustulosis due to codeine confirmed on patch testing, with the notable absence of cross-reactivity to other natural and synthetic opioids. We propose this suggests probable drug-specific type IV (T-cell-mediated) hypersensitivity to codeine.

Acute generalized exanthematous pustulosis (AGEP) is a rare and severe cutaneous adverse reaction (SCAR), with drugs being the main elicitors.¹ Examples of common drug culprits include β -lactam antibiotics, proton pump inhibitors, antifungals, iodinated contrast media, benzodiazepines, and nonsteroidal anti-inflammatory drugs. Other nondrug-induced causes include infection, mercury, and spider bites.¹ AGEP should be carefully differentiated from generalized pustular psoriasis (GPP) both clinically and histopathologically.² In drug-induced AGEP, there are 2 recognized patterns with respect to the onset of the eruption after drug intake, with a median treatment duration of 1 day for antibiotics and >10 days for other drugs.³

The diagnosis of AGEP is typically achieved by the presence of characteristic clinical features that include fever, acute onset, pinhead-sized sterile pustules on an erythematous base with cephalocaudal spread, and flexural accentuation. The EuroSCAR study group has developed a standardized AGEP validation score (for clinical and research purposes), which is based on various clinical, laboratory, and histopathological parameters. Once scored, the cases are classified as definite, probable, possible, or no AGEP.^{1,4} Various *in vivo* and *in vitro* test modalities can be used to elucidate the causative drug agent (ie, patch test, intradermal test, lymphocyte transformation tests, and oral challenge).¹

Here we present a rare case of codeine-induced AGEP confirmed on patch testing, without cross-reactivity to other opiates.

A 25-year-old patient was referred to our allergy department for a suspected adverse drug reaction. She had no history of atopy or other medical history. She received codeine phosphate and diazepam for severe back pain, and within 24 hours she noticed a prickly hot erythematous rash on her face and neck associated

with full facial edema. The rash gradually spread diffusely in a cephalocaudal manner over the next day to involve her entire body surface with flexural accentuation, and she developed small pinhead-sized pustules notably on the face, neck, and back. There were no oral-mucosal lesions or recorded fever. She was also taking ibuprofen at the time, which had been commenced 1 week before the reaction. The patient attended the emergency department and was treated with antihistamine (loratadine) and fluocinolone cream. Blood tests and a skin biopsy were not performed. She was instructed by her emergency physicians to stop codeine (on the presumption that codeine was the cause of the eruption); however, she was continued on the ibuprofen and diazepam given her ongoing need for pain relief. The rash resolved on discontinuation of codeine over 8 days with desquamation, dryness, and crusting of the skin.

AGEP was suspected based on the clinical presentation. The AGEP EuroSCAR validation score was calculated to be 7 (pustules [+2], erythema [+2], distribution/pattern [+2], post-pustular desquamation [+1], mucosal involvement [0], acute onset [0], resolution ≤ 15 days [0], fever $\geq 38^{\circ}\text{C}$ [0], polynuclear-neutrophils $\geq 7000/\mu\text{L}$ [0], and histology [0]), which was classified as “probable AGEP.” We also used the Naranjo algorithm⁵ to assess the likelihood of it being a drug reaction, with codeine scoring 6 (probable) and ibuprofen and diazepam both scoring 4 (possible). Informed consent was obtained from the patient for publication.

At our allergy clinic, 4 months later, patch tests were performed on the upper back using IQ Ultra chambers (Chemotechnique Diagnostics, Vellinge, Sweden) with codeine phosphate (30% in petrolatum [pet]), ibuprofen (30% pet), and diazepam (30% pet). Drug dilutions for patch testing were prepared from commercialized tablets and incorporated at 30% in white petrolatum, in accordance with European Society of Contact Dermatitis guidelines.⁶ The patch tests were read on day 2 (D2) and day 4 (D4) in accordance with the International Contact Dermatitis Research Group criteria.⁷ All patch testing was conducted at skin sites previously affected by the reaction. Patch tests to diazepam and ibuprofen were unequivocally negative at D4. However, there was a weak positive reaction (+) to codeine observed at D4, and to confirm this, the patch test was repeated at a second site on the right forearm, which again was positive (Figure 1). To exclude false positivity (irritancy), we also conducted healthy control subject patch testing to codeine in 10 volunteers that were all entirely negative.

To assess cross-reactivity with other opiates, further patch testing was performed to dihydrocodeine (30% pet), morphine sulfate (30% pet), fentanyl (30% pet), tramadol (30% pet), and oxycodone (30% pet), as well as delayed-reading intradermal testing to aqueous morphine sulfate (diluted to 0.1 mg/mL), which were also all negative at D2 and D4 readings. Subsequently, she underwent oral drug challenges to diazepam (2.5 mg), ibuprofen (400 mg), tramadol (50 mg), and morphine sulfate (10 mg), which were all negative.

She was diagnosed with AGEP due to codeine phosphate after the extensive allergy testing, with the additional notable absence

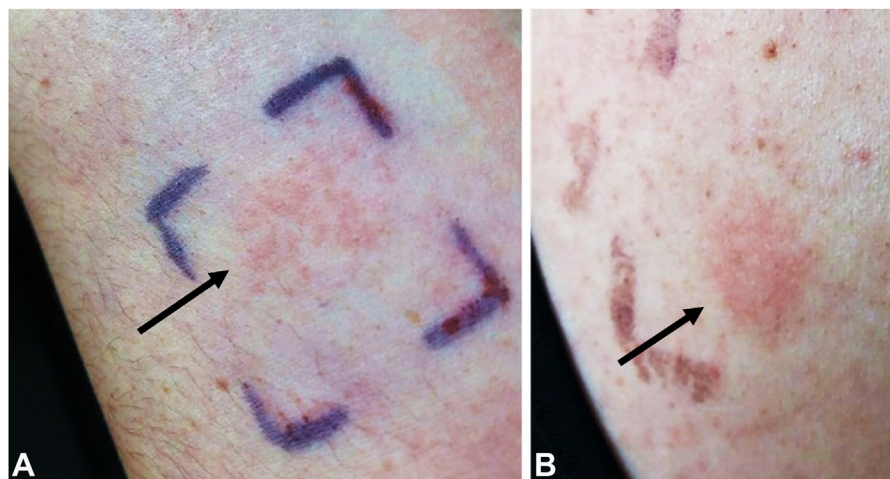


FIGURE 1. Positive patch test readings (+) at day 4 to codeine phosphate (30% pet), on the (A) right arm and (B) upper back.

of cross-reactivity to other opiates. She was advised to avoid codeine entirely but deemed safe to receive the other opiates and agents that tested negative.

The precise pathogenesis of AGEF is unknown; however, a T-cell-mediated delayed (type IVd) hypersensitivity reaction with a sterile neutrophilic response is the most commonly accepted mechanism (especially with regard to drug-induced cases). Evidence of sensitization from positive *in vivo* (patch/intradermal) and *in vitro* T-cell assays (lymphocyte proliferation) has supported this theory.¹

In SCAR cases (including AGEF), patch testing is often regarded as the first *in vivo* diagnostic test to be undertaken,¹ and a recent prospective study on drug patch testing has highlighted its efficacy (phenotype/drug dependent) and safety.⁸ A recent detailed literature review on patch testing in AGEF noted amoxicillin as the lead agent producing positive patch test reactions, followed by pristinamycin, diltiazem, amoxicillin-clavulanic acid, clindamycin, and iomeprol.¹

Codeine-induced AGEF is very rare with only 1 prior published case in the literature in a patient with psoriasis (without *IL36RN* mutation).⁹ *IL36RN* gene encodes the anti-inflammatory IL-36 receptor antagonist, which has been found to underlie AGEF and several different pustular skin eruptions as well as GGP.⁹ Another case of AGEF caused by dihydrocodeine in a patient with psoriasis (with *IL36RN* mutation) has also been described.² In both cases, diagnosis was confirmed on the oral provocation test, and furthermore, no assessment of cross-reactivity to other opiates was conducted.^{2,9} Notably, our patient had no history of psoriasis.

Here we report a rare case of AGEF induced by codeine confirmed by patch testing, with the additional finding of the absence of cross-reactivity to other natural and synthetic opioid agents (as demonstrated by negative skin and provocation tests). We propose this suggests probable drug-specific type IV (T-cell-mediated) hypersensitivity to codeine only. Codeine can induce other type IV drug eruptions such as maculopapular exanthemas (most commonly), and prior case studies have confirmed this on patch testing; however, in contrast to our report, these studies revealed evidence on patch testing of cross-reactivity to morphine (natural opiate), combined with the

absence of cross-reactivity to the synthetic opioids (ie, tramadol, fentanyl).^{10,11}

To conclude, our rare case of codeine-induced AGEF highlights the importance of a structured and comprehensive testing approach in evaluating these complex type IV drug hypersensitivity (SCAR) cases using patch testing first, followed by intradermal testing and oral provocation tests if deemed safe and appropriate. A thorough evaluation of cross-reactivity should also not be overlooked, as this may provide the patient with therapeutic alternatives in the future.

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