



Acute generalized exanthematous pustulosis (AGEP)-like contact dermatitis resulting from topical therapy in a polysensitized patient

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Acute generalized exanthematous pustular eruption (AGEP) is an acute reaction consisting of a widespread erythematous rash with non-follicular sterile pustules that is generally induced by drugs and rarely by topical agents. Fever and peripheral blood leukocytosis are usually present.^{1,2} AGEP-like contact dermatitis is a singular variant of non-eczematous allergic contact reaction mimicking AGEP that has uncommonly been reported to be caused by topical agents such as corticosteroids or methylchloroisothiazolinone.^{3–5}

CASE REPORT

A 67-year-old epileptic man developed a pruritic symmetrical non-follicular pustular eruption initially involving the dorsa of his hands and rapidly spreading to his forearms, arms, face, and trunk (Figure 1). Fever was absent. Some days before, the patient had suffered from seizures in the kitchen and accidentally burned his hands. The wounds had been treated with oral ciprofloxacin and topically with silver sulfadiazine creams (Flammazine [RecipharmParets, Barcelona, Spain] and Silvederma [Aldo Unión, Barcelona, Spain]), a nitrofurazone ointment

(Furacin; SEID, Barcelona, Spain), and an impregnated gauze dressing (Linitul; Alfasigma España, Tarragona, Spain).

The results of a full laboratory analysis were normal. A skin biopsy was performed, and histopathological examination showed subcorneal pustules, some necrotic keratinocytes, and perivascular inflammatory infiltrates with neutrophils and eosinophils in the absence of vasculitis. Lesions cleared after therapies were discontinued and oral and topical corticosteroids were prescribed. Six months later, the patient remained symptom-free.

Patch tests with the baseline series of the Spanish Contact Dermatitis Research Group (GEIDAC), and leg ulcer and fragrance series, as well as the patient's own products (first step) were prepared on Curatest chambers (Lohmann & Rauscher, Neuwied, Germany), applied on the patient's back, and fixed with Omnifix E (Hartmann, Heidenheim, Germany). Exposure times and scoring of readings were according to the ESCD guidelines.⁶ The baseline series (TRUE Test) was supplied by AllergEaze, SmartPractice (Calgary, Canada), and supplementary allergens by Chemotechnique Diagnostics (Vellinge, Sweden). The leg ulcer series was supplied by AllergEaze. The fragrance series supplied by Chemotechnique Diagnostics.



FIGURE 1 Symmetrical erythematous rash with numerous non-follicular pin-size pustules involving the face, lateral aspects of the neck, the V of the neck/décolleté, arms, forearms, antecubital folds, and hands (particularly the dorsal aspect of the left hand, where the burn occurred). Other large body folds, such as axillae and groins, were spared

TABLE 1 Patch test results

Tested series and products	Readings on D2/D4
First step: Baseline GEIDAC series Leg ulcer series Fragrance series The patient's own products (Linitul, Furacin, Flammazine, Silvederma cream ^a) "as is" Ciprofloxacin (10% and 20% pet. in-house-diluted)	Myroxylon pereirae (800 µg/cm ²) (++/++) (CR) Fragrance mix I (6% pet.) (ss): (+/++) (UR) Fragrance mix II (14% pet.) (ss): (+/?) (UR) Benzalkonium chloride (0.1% pet.) (++/++) (UR) Sorbitan sesquioleate (20% pet.) (++/++) (UR) Propylene glycol (5% pet.) (+/++) (CR) Geraniol (2% pet.) (+/+) (UR) Evernia prunastri (2% pet.) (ss) (+/+) (UR) Rose absolute (2% pet.) (+/–) (UR) Linitul "as is" (+++/++) (CR) Furacin "as is" (++/++) (CR) Flammazine "as is" (++/++) (CR) Silvederma cream "as is" (++/++) (CR)
Second step (individual ingredients): Furacin cream: nitrofurazone (1% pet.), PEG 4000 (4% and 10% pet.), PEG 300 (4% and 50% pet.), PEG 1500 (4% and 40% pet.)	Nitrofurazone (1% pet.) (+++/++) (CR) PEG 300 (4% pet.) (?/++) (CR) PEG 300 (50% pet.) (+++/++) (CR)
Flammazine cream: propylene glycol (5% aq.), polysorbate 80 (5% aq. and 10% pet.), polysorbate 60 (5% aq. and 10% pet.), cetyl alcohol (5% pet.), liquid paraffin "as is," glyceryl monoestearate "as is," silver sulfadiazine (5% pet.)	Propylene glycol (5% aq.) (+/++) (CR) Polysorbate 80 (5% aq.) (+/+) (CR) Silver sulfadiazine (5% pet.) (+/–) (CR)
Linitul: liquid pet. "as is," balsam of Peru (NT), castor oil "as is," pet. "as is," paraffin "as is," beeswax "as is"	Castor oil "as is" (++/++) (CR)

Abbreviations: CR, current relevance; GEIDAC, Spanish Contact Dermatitis Research Group; NT, non tested; PEG, polyethylene glycol; ss, hapten emulsified with sorbitan sesquioleate; UR, unknown relevance.

^a Individual ingredients of Silvederma were not tested. Silvederma components are: silver sulfadiazine, cetearyl alcohol, isopropyl myristate, white pet., polyoxyl 40 stearate, sorbitanoleate, propylene glycol, and methyl 4-hydroxybenzoate.

TABLE 2 Differential diagnoses of acute generalized exanthematous pustulosis (AGEP)-like contact dermatitis

	Distribution	Systemic symptoms (fever, leukocytosis)	Concomitant eczematous lesions	Drug intake history	Topical agent exposure history	Positive patch test reactions to culprit agents
AGEP	Widespread, symmetrical	Yes	No	Yes	No	+/–
AGEP induced by topical agents	Widespread, symmetrical	Yes	No	No	Yes	+/–
AGEP-like ACD	Widespread, less symmetrical	No	Possible	No	Yes	+
Pustular ACD	Circumscribed	No	Possible	No	Yes	+

Abbreviations: ACD, allergic contact dermatitis.

Multiple positive reactions were seen (Table 1). Further patch tests with the individual ingredients of the topical products provided by the manufacturers that had become positive were performed (second step), and numerous additional positive reactions were obtained (Figure 2). Patch, prick, intradermal and oral provocation tests with ciprofloxacin gave negative results (Table 1).

DISCUSSION

Differential diagnoses of AGEP-like contact dermatitis include: AGEP induced by systemic drugs, AGEP induced by topical agents, and the uncommon pustular variant of allergic contact dermatitis (the so-called "pustular contact dermatitis"). These entities are clinically very similar (Table 2). We reviewed the English-language literature on the three topics, and the results shown in Supporting Information Table S1 highlight the overlap among them.

In our patient, AGEP was initially suspected because of the history of drug intake and the widespread and fairly symmetrical distribution of the lesions. However, a final diagnosis of AGEP-like contact dermatitis was eventually reached, because of the lack of systemic symptoms and the confirmation of sensitization to several components of the topical burn therapeutic agents by the use of patch testing. Additionally, both immediate and delayed sensitizations from ciprofloxacin were ruled out. The disseminated distribution of the lesions could be attributable to systemic absorption of the culprit agents through burned skin.

The positive results of patch tests were very strong (Figure 2). We believe that the simultaneous use of multiple topical preparations on the damaged skin may have played a role in the polysensitization involving our patient, who became allergic to numerous non-related compounds. However, in addition to polysensitization, we believe that some of the multiple reactions are possibly attributable to cross-reactions or common ingredients such as sorbitan sesquioleate, which is contained in fragrance mix I, geraniol and oak moss.

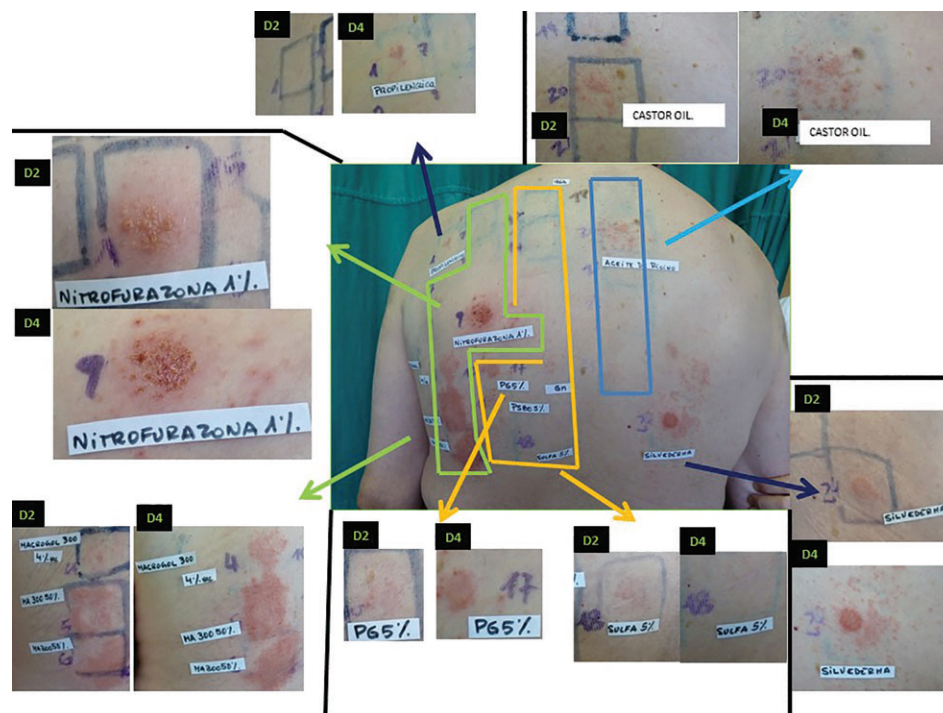


FIGURE 2 Patch tests (second step) with the individual ingredients of the positive topical products (Flammazine, Furacin, and Linitul) provided by the manufacturers, and Silverderma “as is.” *Myroxylon pereirae* (one of the ingredients of Linitul), which had been positive in the previous tests, was not included. Pustular reactions caused by Silverderma “as is,” castor oil, and nitrofurazone, and intense spreading reactions caused by polyethylene glycol, Silverderma and castor oil, are shown

Severe allergic contact dermatitis caused by nitrofurazone (CAS no. 59-87-0) is common.^{7,8} Interestingly, the first case of pustular contact dermatitis reported was described in relation to topical nitrofurazone.⁹ Topical nitrofurazone preparations usually contain polyethylene glycols (PEGs) (CAS no.107-21-1) as vehicles, and simultaneous sensitization to both nitrofurazone and PEGs in these products has often been reported.^{10–14}

Myroxylon pereirae (balsam of Peru; CAS no. 8007-00-9) is the main sensitizer in the gauze Linitul. Interestingly, our patient was also sensitized to castor oil (CAS no. 8001-79-4), which is a natural oil that is frequently used by the pharmaceutical and cosmetic industries.

Finally, we would like to emphasize the value of patch testing with topical preparations brought in by our patients, as well as with their individual ingredients when positive reactions are seen. If we assume that the sensitization is attributable to the active compounds and miss this step, sensitization caused by the vehicle components or polysensitization will probably be underdiagnosed.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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**ONLINE SUPPLEMENTAL TABLE 3. ENGLISH LITERATURE REVIEW ON ACUTE GENERALIZED
EXANTHEMATOUS PUSTULOSIS (AGEP)-LIKE CONTACT DERMATITIS, PUSTULAR ALLERGIC CONTACT
DERMATITIS AND AGEP INDUCED BY TOPICAL AGENTS.**

Disorder/case number		Author/ year	Sex/ age	Location	Patch tests relevant positive results	Other non-relevant positive results. Other symptoms or signs	Source of exposure
AGEP- like ACD	1	Broesby-Olsen/ 2005 (3)	M/ 62	Foot, thighs, arms, hands	Hydrocortisone-17- butyrate (0.1% pet.)	Nickel sulphate, potassium dichromate, budesonide (0.01% pet.)	Topical corticosteroid
	2	Toghi/ 2009 (4)	F/ 31	Back, lower limbs, neck, axilla, arms	Hydrocortisone 17- butyrate 21-propionate (0.1% pet.)		Pandel® ointment
	3	Córdoba/ 2011 (5)	F/ 37	Trunk, limbs	MCI		Bath gel
	4	González-Cantero/ 	M/67	Hands, forearm, arms, antecubita	Balsam of Peru, PEG, Linitul® ‘as is’ Furacin® ‘as is’,	FM I, FM II, benzalkonium chloride, sorbitansesquioleat	Linitul® Furacin® ointment Flammazine®

		2018 (present case)		l fossae, face, neck, neckline	Flammazine® ‘as is’, nitrofurazone, PEG 300, polysorbate 80, silver sulfadiazine, castor oil, Silvederma® cream ‘as is’	e, geraniol, oak moss absolute, rose absolute	cream Silvederma® cream
Pustular ACD	1	Burk hart CG/ 1981 (9)	F/ 75	Arms (extensor surfaces, legs, trunk	Nitrofurazone (without pustules)	-	Nitrofurazone topical cream
	2	Cond e - Salaz ar L/ 1983 (15)	F/ 25	Neck, trunk.	Trichloroethylene 5% in olive oil (red scaly reaction; 20 negative controls).	-	Trichloroethyle ne
	3	Doo ms- Goos seNS /1985 (16)	M/23	Flexor forearms, wrist, thighs, trunk	Sodium hexafluorosilicate: positive use test (3 applications a day on the forearms)	-	Foam rubber materials (pillows, mattresses
	4	Sánc hez- Mont illa JM/ 1998 (17)	F/ 26	Scalp, forehead, eyelid	Minoxidil (with pustules)	-	Lacovin® (2% minoxidilhydro alcoholicsolutio n)
	5	Barra zza V/19 99(1	F/ 34	Left 2 nd finger	Not performed	-	Ready-to-use compress with merbromine

		8)					
	6	Chapman MS/ 2002 (19)	M/53	Palms, trunk, limbs	Neoprene motorcycle grip samples (with pustules, <i>flare up</i> phenomenon)	Cynnamic aldehyde, Balsam of Peru, fragrance	Neoprene motorcycle grip
	7	Chavarría-Mur E/ 2005 (20)	M/33	Flexural areas legs, arms, abdomen and eyelids	Budesonide, betamethasone 17 valerate, betamethasone dipropionate, betamethasone valerate		
	8	Verm a A / 2015 (21)	M/80	Foot, body face scalp	<i>Everniaprunastr</i> absolut e, cytral, tea tree oil, FM II, black Suede™ aftershave (with pustules); balsam of Peru (without pustules), D-limonene, FM I (without pustules)	Diphenyl guanidine, dibutyl thiourea, dodecyl mercaptan, carba mix, cetearyl alcohol, glycerin/white soft paraffin/ liquid paraffin in aqueous cream, black rubber mix, chloroxylonol, 2-bromo-2-nitropropane -1,3-diol, iodopropynylbutylc	Fragrance, facial moisturizer, soap substitute, intensive moisturizer

						arbamate, BHA, phenoxyethanol, Betadine, budesonide, PPD, glove (upper), boots (upper)	
	9	Hotta E / 2017 (22)	F/ 47	Back, thighs, chest, abdomen, axillae,	D. yellow 3 (without pustules)	D.blue 106, D. blue 124 and D. orange 1 (without pustules); dress sample; acetone and methanol extraction of the dress and PPD (without pustules)	Dark blue dress
AGEP induced by topical agents	1	Roujeau JC/ 1991 (1)		-	-	-	Topical bufexamac
	2	Barraza V/ 1998 (23)	M/27	Trunk, thighs, upper arms	Metallic mercury	Fever	Ophthalmologic cream with mercury
	3	Wei-Hsin J/ 2004 (24)	M/10	Neck, trunk, arms, thighs	Not done	Fever, leukocytosis	Topical lindane
	4	Belhadjali H/	F/ 3	Face, body	Bufexamac	Fever, leukocytosis	Parfederm [®] , (topical bufexamac

		2008 (25)					cream)

Abbreviations: ACD: allergic contact dermatitis; AGEP: acute generalized exanthematous pustulosis; BHA: butylatedhydroxyanisole; D: disperse; F: female; FM: fragrance mix; M: male; MCI: Methylchloroisothiazolinone; Mo: months; PEG: polyethyleneglycol; PPD: *p*-Phenylenediamine.

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