



8. Ahlström M, G. Menné T, Topp A, M. et al. An investigation of causes of nickel allergy. *Ministry of Environment and Food of Denmark, Environmental Protection Agency, Environmental Project No. 1869*, 2016.
9. Serup-Hansen N, Gudum A, Sørensen M, M. Valuation of Chemical Related Health Impacts *Ministry of Environment and Food of Denmark, Environmental Protection Agency, Environmental Project No 929*, 2004.
10. Rui F, Bovenzi M, Prodi A, et al. Nickel, chromium and cobalt sensitization in a patch test population in North-Eastern Italy (1996-2010). *Contact Dermatitis*. 2012;68(1):23-31.
11. Lidén C, Johnsson S. Nickel on the Swedish market before the nickel directive. *Contact Dermatitis*. 2001;44(1):7-12.
12. Ahlström MG, Menné T, Thyssen JP, Johansen JD. Nickel allergy in a Danish population 25 years after the first nickel regulation. *Contact Dermatitis*. 2017;76(6):325-332.
13. Thyssen JP, Johansen JD, Menné T. Nickel allergy in Danish women before and after nickel regulation. *N Engl J Med*. 2009;360(21):2259-2260.
14. Thyssen JP. Nickel and cobalt allergy before and after nickel regulation – evaluation of a public health intervention. *Contact Dermatitis*. 2011;65(suppl 1):1-68.
15. Schuttelaar MLA, Ofenloch RF, Bruze M, et al. Prevalence of contact allergy to metals in the European general population with a focus on nickel and piercings: the EDEN fragrance study. *Contact Dermatitis*. 2018;79(1):1-9.
16. Menné T, Solgaard P. Temperature-dependent nickel release from nickel alloys. *Contact Dermatitis*. 1979;5(2):82-84.
17. Thyssen JP, Uter W, McFadden J, et al. The EU nickel directive revisited-future steps towards better protection against nickel allergy. *Contact Dermatitis*. 2011;64(3):121-125.
18. Shum KW, Meyer JD, Chen Y, Cherry N, Gawkrödger DJ. Occupational contact dermatitis to nickel: experience of the British dermatologists (EPIDERM) and occupational physicians (OPRA) surveillance schemes. *Occup Environ Med*. 2003;60(12):954-957.
19. Wennervaldt M, Ahlström MG, Menné T, Thyssen JP, Johansen JD. Diagnostic workup of occupational allergic nickel dermatitis in a nurse with multiple nickel exposures. *Contact Dermatitis*. 2019;81(4):311-313.
20. Bonin S, Larese FF, Trevisan G, et al. Gene expression changes in peripheral blood mononuclear cells in occupational exposure to nickel. *Exp Dermatol*. 2011;20(2):147-148.
21. Tammaro A, Romano I, De Marco G, et al. Effects of TIO NICKEL in patients with ACD and SNAS: experience on 700 patients in Italy. *J Eur Acad Dermatol Venereol*. 2017;31(4):e189-e191.

SUPPORTING INFORMATION

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

How to cite this article: Basso P, Mauro M, Miani A, Belloni Fortina A, Corradin MT, Larese Filon F. Sensitization to nickel in the Triveneto region: Temporal trend after European Union regulations. *Contact Dermatitis*. 2020;82:247-250. <https://doi.org/10.1111/cod.13450>

Systemic allergic dermatitis presenting as acute generalized exanthematous pustulosis due to betamethasone sodium phosphate

Daniele Gambini¹ | Paolo Sena¹ | Francesca Raponi¹ | Leonardo Bianchi² | Katharina Hansel² | Marta Tramontana² | Luca Stingeni²

¹UOC of Dermatology, ASST Papa Giovanni XXIII Bergamo, Bergamo, Italy

²Dermatology Section, Department of Medicine, University of Perugia, Perugia, Italy

Correspondence

Luca Stingeni, Section of Dermatology, Department of Medicine, University of Perugia, 06129 Perugia, Italy.

Email: luca.stingeni@unipg.it

KEYWORDS: acute generalized exanthematous pustulosis, betamethasone disodium phosphate, case report, corticosteroids, dexamethasone-21-phosphate disodium, patch test, severe cutaneous adverse drug reaction

Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse drug reaction characterized by generalized erythematous eruption with small, non-follicular, sterile pustules associated with fever and neutrophilia. The reaction is caused by drugs, mainly

beta-lactam and macrolide antibiotics, in at least 90% of cases.¹ We report a case of AGEP following systemic administration of betamethasone sodium phosphate in a patient contact sensitized to dexamethasone-21-phosphate disodium contained in eye drops.

CASE REPORT

An 80-year-old non-atopic woman, without a history of psoriasis, was referred to us because of a generalized papulopustular eruption on an erythematous base. Pustules were non-follicular, sterile, and coalescing (Figure 1A,B). The rash was associated with fever (38.5°C), malaise, itching, and moderate burning. The patient's history revealed an itching eczematous periocular dermatitis lasting 2 weeks, following the use of eye drops containing dexamethasone-21-phosphate disodium (Etacortilen, Sifi, Catania, Italy) for blepharitis. One day before consultation, because of worsening of the eyelid dermatitis, the patient was treated in the emergency room with an intramuscular injection of Bentelan 4.0 mg (Sigma Tau, Pomezia, Rome, Italy) containing betamethasone sodium phosphate 4 mg/2 mL. The patient was on no other medication.

Laboratory investigations showed leukocytosis ($12.3 \times 10^9/L$) with neutrophilia ($9.5 \times 10^9/L$) and an increase of C-reactive protein (8.3 mg/dL), an erythrocyte sedimentation rate of 35 mm/h, and elevated creatinine (1.5 mg/dL). Microbiological pustule cultures were negative. The histological examination showed subcorneal pustules with discrete perivascular and interstitial lymphocytic and neutrophilic inflammatory infiltrate in the dermis (Figure 1C). AGEP was diagnosed and the patient was treated with zinc-oxide-based cream and emollients. Pustules, erythema, and subsequent desquamation resolved within 3 weeks. Three months after complete resolution of the skin lesions the patient was patch-tested with the SIDAPA (Società Italiana di Dermatologia Allergologica Professionale e Ambientale) baseline series (FIRMA Diagent, Florence, Italy), Etacortilen eye drops "as is", and a topical corticosteroid series (Table 1). Patch tests were occluded for 2 days with the

Haye's Test Chambers (Haye's Service, Alphen aan den Rijn, The Netherlands) on Soffix tape (Artsana, Grandate, Italy) and readings were performed on day (D)2, D4, and D7.² Patch tests were positive for Etacortilen eye drops and its active ingredient dexamethasone-21-phosphate disodium (CAS no. 2392-39-4) (Figure 1D) (Table 1). Additional patch testing with systemic corticosteroids was not possible because of the patient's unexpected death by acute myocardial infarction.

DISCUSSION

Corticosteroids can induce delayed systemic hypersensitivity in subjects with or without previous contact allergy to topical corticosteroids.³ Here we describe systemic allergic dermatitis presenting as AGEP due to betamethasone sodium phosphate administered by intramuscular injection in a patient previously contact sensitized to dexamethasone-21-phosphate disodium contained in eye drops. Both corticosteroids belong to Group C of the Coopman classification of corticosteroids, based on the substitutions of the D ring and cross-reactivity patterns in patch tests,⁴ and to Cluster 3 corticosteroids according to the Baeck classification based on the function of the electrostatic and steric fields of corticosteroids.⁵ Betamethasone sodium phosphate and dexamethasone-21-phosphate disodium are stereoisomers, differing in the position of methyl group, placed in position 16 alpha in the former (pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, [11.beta.,16.alpha.]) and beta in the latter (pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, [11.beta.,16.beta.]). Based on these considerations and the short latency period between

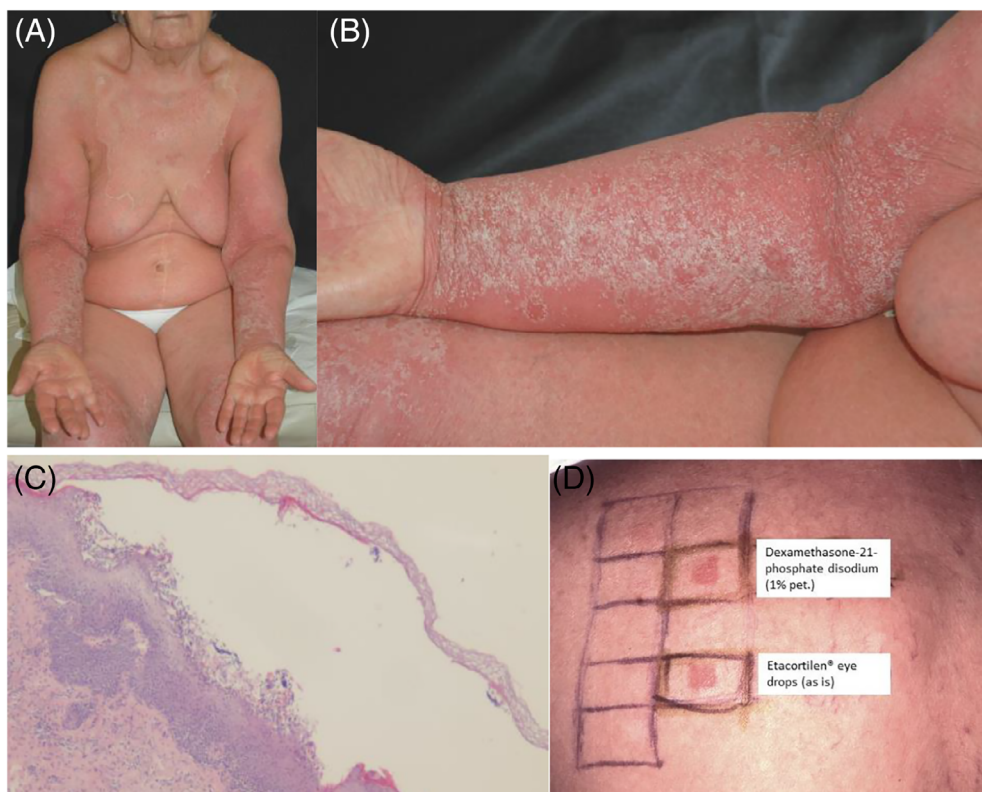


FIGURE 1 (A), Generalized erythematous and papulopustular eruption. (B), follicular, sterile, and coalescing pustules. (C), Subcorneal pustule with perivascular lymphocytic and neutrophilic inflammation (ematoxylin and eosin, 25X). (D), Positive patch test to dexamethasone-21-phosphate disodium and to Etacortilen eye drops "as is"

TABLE 1 Patch test results

			Day 2	Day 4	Day 7
SIDAPA baseline series			–	–	–
Etacortilen eye drops ("as is")			++	++	++
Topical corticosteroid series	Group	Cluster			
Tixocortol-21-pivalate (0.1%)*	A	1	–	–	–
Budesonide (0.01%)*	B	1	–	–	–
Triamcinolone acetonide (1%)*	B	2	–	–	–
Dexamethasone-21-phosphate disodium (1%)*	C	3	++	++	++
Betamethasone-17-valerate (1%)*	D	3	–	–	–
Aclo methasone-17,21-dipropionate (1%)*	D	3	–	–	–
Clobetasol-17-propionate (1%)*	D	3	–	–	–
Hydrocortisone-17-butyrate (1%)**	D	1	–	–	–

*In pet.; **in eth.; SIDAPA; Società Italiana di Dermatologia Allergologica Professionale e Ambientale.

administration of betamethasone sodium phosphate and AGEF onset, this systemic corticosteroid was considered cross-reacting with the topical dexamethasone-21-phosphate disodium.

To our knowledge, this is the first report of AGEF caused by betamethasone sodium phosphate. To date, 6 cases of AGEF due to systemic corticosteroids have been described⁶⁻¹⁰ (Table S1): in 4 patients due to corticosteroids belonging to Group A and Cluster 1, in one patient to Group C and Cluster 3, and in one patient to deflazacort, which is not included in any group or cluster because of its 16 α -17 α -2 methyloxazolinic ring.¹¹ Among these patients, only one experienced previous contact sensitization to prednisolone acetate cream; as in our case, this data is suggestive of systemic allergic dermatitis to prednisolone presenting as AGEF. In all reported patients, as well as in our patient, patch tests performed with the culprit corticosteroid or with corticosteroids belonging to the same group and cluster were positive. This emphasizes the value and safety of patch tests for identifying culprit drugs or cross-reacting drugs in AGEF,¹² a severe cutaneous adverse drug reaction rarely caused by corticosteroids.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ORCID

Katharina Hansel  <https://orcid.org/0000-0002-6674-4278>

Luca Stingeni  <https://orcid.org/0000-0001-7919-8141>

REFERENCES

1. Szatkowski J, Schwartz RA. Acute generalized exanthematous pustulosis (AGEP): a review and update. *J Am Acad Dermatol*. 2015;73(5):843-848.
2. Stingeni L, Bianchi L, Hansel K, et al. Italian guidelines in patch testing - adapted from the European Society of Contact Dermatitis (ESCD). *G Ital Dermatol Venereol*. 2019;154(3):227-253.
3. Barbaud A, Waton J. Systemic allergy to corticosteroids: clinical features and cross reactivity. *Curr Pharm Des*. 2016;22(45):6825-6831.

4. Coopman S, Degreef H, Doooms-Gossens A. Identification of cross-reaction patterns in allergic contact dermatitis from topical corticosteroids. *Br J Dermatol*. 1989;121(1):27-34.
5. Baeck M, Chemelle JA, Goossens A, Nicolas JF, Terreux R. Corticosteroid cross-reactivity: clinical and molecular modeling tools. *Allergy*. 2011;66(10):1367-1374.
6. Demitsu T, Kosuge A, Yamada T, Usui K, Katayama H, Yaoita H. Acute generalized exanthematous pustulosis induced by dexamethasone injection. *Dermatology*. 1996;193(1):56-58.
7. Mussot-Chia C, Flechet ML, Napolitano M, Herson S, Frances C, Chosidow O. Pustulose exanthématique aiguë généralisée à la méthylprednisolone. *Ann Dermatol Venerol*. 2001;128(3):241-243.
8. Buettiker U, Keller M, Pichler WJ, Braathen LR, Yawalkar N. Oral prednisolone induced acute generalized exanthematous pustulosis due to corticosteroids of group A confirmed by epicutaneous testing and lymphocyte transformation tests. *Dermatology*. 2006;213(1):40-43.
9. Ziemssen T, Bauer A, Bär M. Potential side effect of high-dose corticosteroid relapse treatment: acute generalized exanthematous pustulosis (AGEP). *Mult Scler*. 2009;15(2):275-277.
10. Pacheco D, Travassos AR, Antunes J, Silva R, Lopes A, Marques MS. Allergic hypersensitivity to Deflazacort. *Allergol Immunopathol (Madr)*. 2013;41(5):352-354.
11. Bianchi L, Hansel K, Antonelli E, Bellini V, Rigano L, Stingeni L. Deflazacort hypersensitivity: a difficult-to-manage case of systemic allergic dermatitis and literature review. *Contact Dermatitis*. 2016;75(1):54-56.
12. Barbaud A, Collet E, Milpied B, et al. A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions. *Br J Dermatol*. 2013;168(3):555-562.

SUPPORTING INFORMATION

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

How to cite this article: Gambini D, Sena P, Raponi F, et al. Systemic allergic dermatitis presenting as acute generalized exanthematous pustulosis due to betamethasone sodium phosphate. *Contact Dermatitis*. 2020;82:250-252. <https://doi.org/10.1111/cod.13451>

Online supplemental TABLE 2 Reported cases of acute generalized exanthematous pustolosis to systemic corticosteroids

Author (year)	Triggering systemic corticosteroids			Previous contact dermatitis to topical corticosteroids		Patch test results	
	Active ingredient (route administration)	of	Group/ Cluster	Y/N - Active ingredient	Group/ Cluster	Positive reactions	Group/ Cluster
Demitsu et al (1996) ⁶	Dexamethasone sodium phosphate (sc)		C/3	N	---	Dexamethasone sodium phosphate	C/3
Mussot- Chia et al (2001) ⁷	Methylprednisolone (iv)		A/1	N	---	Hydrocortisone Prednisolone Tixocortol-21-pivalate	A/1 A/1 A/1
Buettiker et al (2006) ⁸							
case 1	Prednisolone Prednisolone tetrahydrophthalate (o)	(o)	A/1 A/1	Y Prednisolone acetate	- A/1	Prednisone	A/1
case 2	Prednisolone (o)		A/1	N	---	Budesonide Hydrocortisone Prednisolone Prednisone Tixocortol-21-pivalate	B/1 A/1 A/1 A/1 A/1
Ziemssen et al	Prednisolone Prednisone (o)	(iv)	A/1 A/1	N	---	Methylprednisolone Prednicarbate	A/1 D/1

(2009)⁹

Pacheco	Deflazacort (o)	NI	N	---	Deflazacort	NI
et al					Hydrocortisone	A/1
					Tixocortol-21-pivalate	A/1

(2013)¹⁰

sc: subcutaneous; iv: intravenous; o: oral

NI: not included in any Coopman's group and Baeck's cluster¹¹