

Severe acute generalized exanthematous pustulosis (AGEP) induced by miconazole oral gel with overlapping features of drug reaction with eosinophilia and systemic symptoms (DRESS)

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Introduction

Acute generalized exanthematous pustulosis (AGEP) is a severe and potentially life-threatening cutaneous reaction characterized by the rapid development of sterile pustules especially on intertriginous regions. AGEP is mostly caused by drugs (e.g., beta-lactams, macrolides, chloroquine), and more rarely by viruses.¹ The most commonly implicated viruses are Epstein-Barr virus (EBV), enterovirus (Coxsackie, echovirus) and cytomegalovirus (CMV).²

We describe the case of a 50-year-old woman presenting severe miconazole oral gel (MOG)-induced AGEP with overlapping features of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.

Case report

A 50-year-old otherwise healthy woman was treated by MOG for oral candidiasis (Daktarin oral gel 2%, 10 mL daily). She reported an erythematous abdominal rash 48 hours after the initiation of miconazole, rapidly involving almost the whole body. She complained of fever (38.3°C), cough, and lower limb edema. Physical examination showed diffuse eruption involving about 90% of her body surface area, with numerous nonfollicular pustules mostly localized in intertriginous regions (**Figure 1A and 1B**). Laboratory tests revealed leukocytosis $21\,000\text{ mm}^{-3}$ ($N < 10\,000\text{ mm}^{-3}$) with $19\,200\text{ PNN mm}^{-3}$ ($N < 7500\text{ mm}^{-3}$) and eosinophilia up to 610 mm^{-3} ($N < 500\text{ mm}^{-3}$), hepatic cytolysis (aspartate aminotransferase: 183 U/L, alanine aminotransferase: 208 U/L; N: 10–35 U/L), troponin at 155 ng/L ($N < 14\text{ ng/L}$) and NT-proBNP at 4 782 ng/L ($N < 300\text{ ng/L}$). Laboratory tests also indicated past EBV infection (positive EBNA and ECA IgG, negative EBNA IgM) with EBV viral load in blood at 1 254 copies/mL ($N < 250\text{ copies/mL}$). Serologic tests for human immunodeficiency virus, hepatitis B virus, hepatitis C virus and CMV were all negative.

Cutaneous biopsy was performed on an axillary pustule and revealed a subcorneal non-follicular pustule containing neutrophils, exocytosis of neutrophils with papillary edema and lymphocytic infiltrate consistent with a diagnosis of AGEP (**Figure 2A and 2B**). On immunohistochemistry, the lymphocytic infiltrate was positive for CD8 and TIA1 (**Figure 2C and 2D**) while the *in situ* hybridization study of EBV RNA was negative. To explore cough and cardiac biomarker abnormalities, a transthoracic echocardiograph was performed and showed a small pericardial effusion with discrete alteration of systolic ejection fraction measured at 52%.

MOG was stopped and the rash completely healed spontaneously within 3 weeks. Cardiac and biological assessments after complete healing of cutaneous lesions were normal. Patch test was performed, 3 months after complete healing of the eruption, with IQ Ultra patch test chambers (Chemotechnique Diagnostics, Vellinge, Sweden) occluded for 3 days with TegadermTM film (3M Health Care, Neuss, Germany) and reading was performed on day (D) 3. We tested MOG 30% pet. in petrolatum with a positive reaction (+) on D3 (**Figure 1C**). To exclude irritant contact dermatitis caused by miconazole, a skin biopsy was done on the patch test area revealing spongiotic dermatitis consistent with allergic contact dermatitis, thus confirming the imputability of MOG. According to anamnestic, clinical and histologic data a diagnosis of AGEP/DRESS overlap induced by MOG was made.

Discussion

To the best of our knowledge, we report the first case of AGEP/DRESS overlap induced by MOG. According to EuroSCAR criteria, the patient scored +9, indicating a definite diagnosis of AGEP (**Table 1 in Supplement**).³ Due to the extent of the skin lesion, organ involvement and slow resolution of the skin rash (> 15 days), overlapping features of AGEP and DRESS were suspected. The RegiSCAR score was 3, which classified the present case as a possible

case of DRESS (**Table 2 in Supplement**).⁴ An immunohistochemical study of 50 biopsies of DRESS showed that a high proportion of granzyme B+ lymphocytes was found in most cases of DRESS. In our case, immunohistochemical staining was negative for granzyme B but positive for TIA1, which is also expressed by activated cytotoxic T lymphocytes.⁵ Reactivated EBV is typically associated with DRESS syndrome and is a well-documented cause of myopericarditis or hepatitis.

Miconazole is a synthetic imidazole antifungal which is an effective treatment for oral candidiasis. The most common adverse effect of topical imidazole antifungals is allergic contact dermatitis and cross-reactivity occurs between miconazole, econazole and isoconazole.⁶ Drug patch tests are essential and safe to confirm the culprit drug in cases of DRESS and AGEF.⁷

Our case illustrates a severe condition of AGEF/DRESS overlap and highlights the need to strictly verify all medications even local treatments such as oral gel.

References

- 1- Sidoroff A., Dunant A., Viboud C. Risk factors for acute generalized exanthematous pustulosis (AGEP)—results of a multinational case-control study (EuroSCAR). *Br J Dermatol.* 2007;157:989–996.
- 2- Ropars N, Darrieux L, Tisseau L, Safa G. Acute generalized exanthematous pustulosis associated with primary Epstein-Barr virus infection. *JAAD Case Rep.* 2014;1(1):9-11.
- 3- Sidoroff A, Halevy S, Bavinck JN et al. Acute generalized exanthematous pustulosis (AGEP) – a clinical reaction pattern. *J Cutan Pathol.* 2001; 28:113–19
- 4- Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. Variability in the clinical pattern of cutaneous side-effect of drugs with systemic symptoms: Does DRESS syndrome really exist? *Br J Dermatol.* 2007;156:609–11.

- 5- Ortonne N, Valeyrie-Allanore L, Bastuji-Garin S, et al. Histopathology of drug rash with eosinophilia and systemic symptoms syndrome: a morphological and phenotypical study. *Br J Dermatol*. 2015;173(1):50-58.
- 6- Dooms-Goossens A, Matura M, Drieghe J, Degreef H. Contact allergy to imidazoles used as antimycotic agents. *Contact Dermatitis*. 1995;33(2):73-77.
- 7- 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.

Figure 1. (A) Diffuse erythematous and pustular eruption involving about 90% of body surface area. (B) Non-follicular and coalescing pustules. (D) Positive patch test to miconazole 30% pet. in petrolatum.

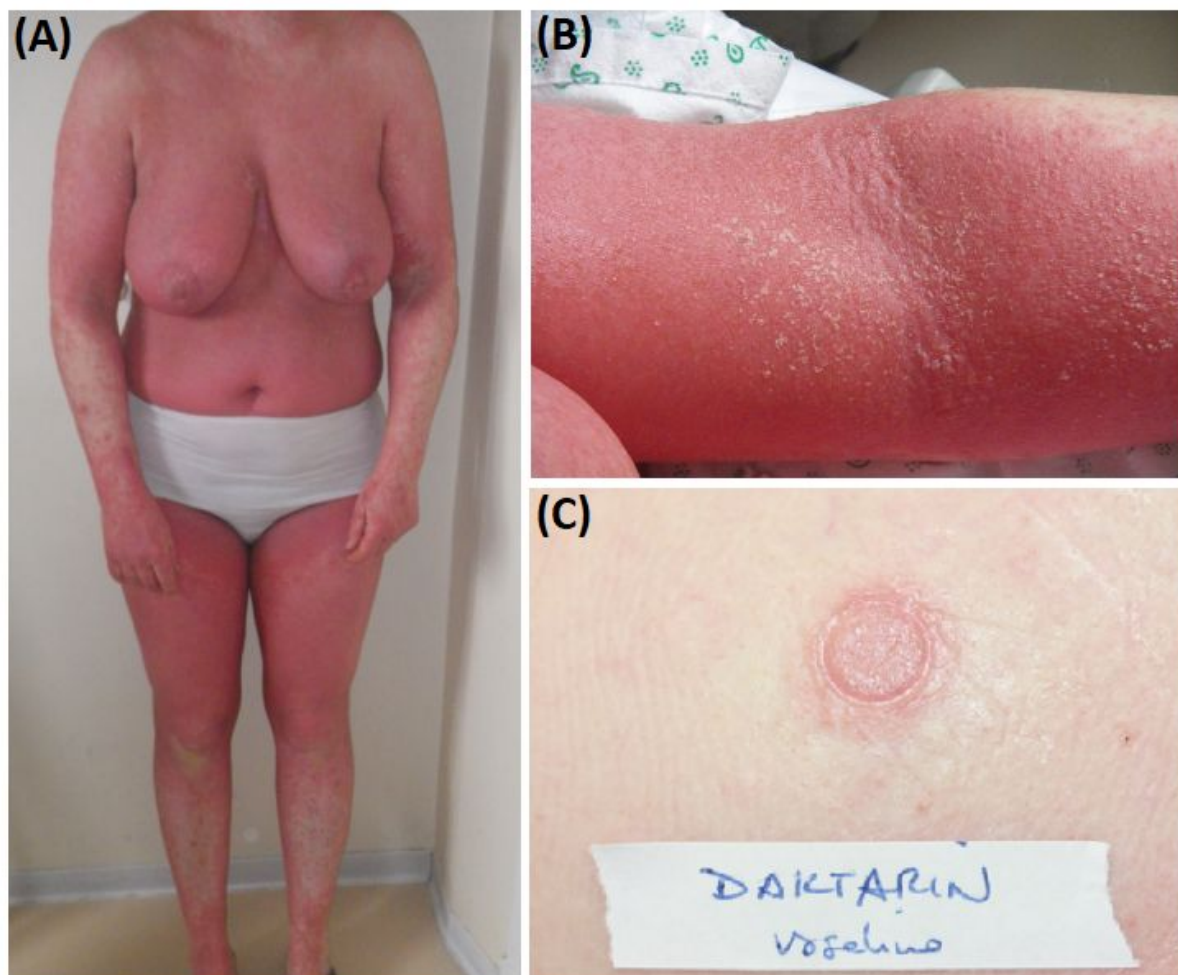


Figure 2. (A) Skin biopsy showed a non-follicular pustule (*solid arrow*) with papillary edema (*dotted arrow*) (hemotoxylin-eosin-saffron stain, original magnification x10). (B) Higher magnification with exocytosis of neutrophils (*arrowheads*) (H&E, x20). Immunohistochemistry staining showing CD8 (C) and TIA1 (D) positive lymphocytes (x10).

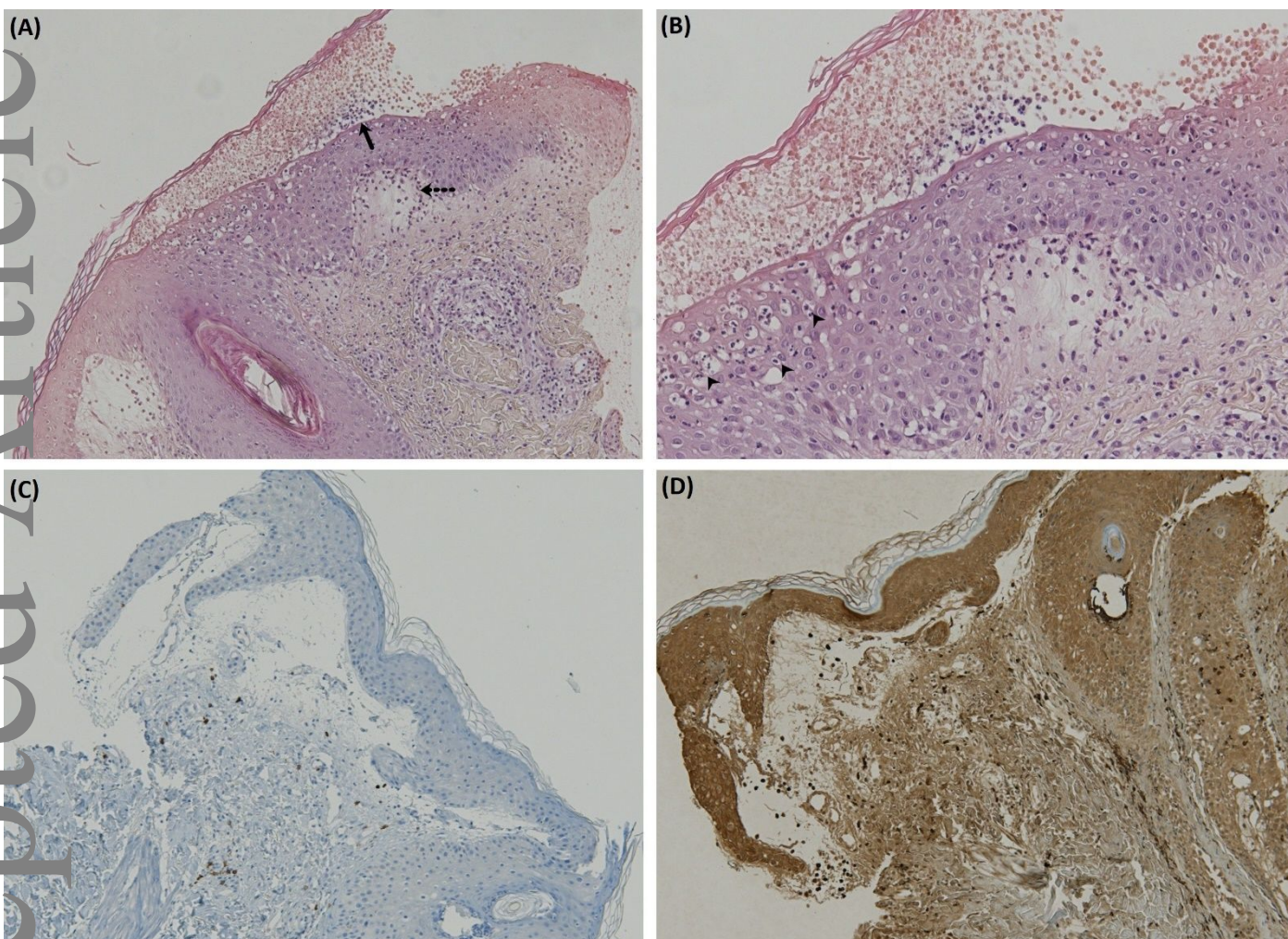


Table 1. The patient's AGEP score according to the EuroSCAR validation score.

Criteria	Description	Score
EuroSCAR score		
<i>Morphology</i>		
Pustules	Typical	+2
Erythema	Typical	+2
Distribution	Typical	+2
Postpustular desquamation	Yes	+1
<i>Course</i>		
Mucosal involvement	No	0
Acute start (< 10 days)	Yes	0
Resolution < 15 days	No	-4
Fever ($\geq 38^{\circ}\text{C}$)	Yes	+1
Polymorphonuclear ($\geq 7000/\text{mm}^3$)	Yes	+1
<i>Histopathology</i>		
Biopsy of skin	Intraepidermal pustules with papillary edema	+3
TOTAL SCORE		+8

Interpretation of EuroSCAR score: ≤ 0 : absence of AGEP; 1-4: possible AGEP; 5-7: probable AGEP; 8-12: AGEP as certain diagnosis.

Table 2. The patient's DRESS score according to the RegiSCAR validation score.

Criteria	Description	Score
RegiSCAR score		
<i>Fever $\geq 38.5^{\circ}\text{C}$</i>	No	-1
<i>Enlarged lymph nodes</i>	No	0
<i>Atypical lymphocytes</i>	No	0
<i>Eosinophils $\geq 700/\text{mm}^3$</i>	No	0
<i>Skin Rash</i>		
Extent $>50\%$	Yes	+1
Rash suggesting DRESS	Yes	+1
Biopsy suggesting DRESS	No	-1
<i>Organ involvement</i>	Yes (two organs)	+2
<i>Resolution in ≥ 15 days</i>	Yes	0
<i>Excluding other causes</i>	Yes	+1
TOTAL SCORE		+3

Interpretation of RegiSCAR score: <2 : no case; 2-3: possible case; 4-5: probable case; >5 : definite case.

Table 1. The patient's AGEP score according to the EuroSCAR validation score.

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EuroSCAR score		
<i>Morphology</i>		
Pustules	Typical	+2
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Mucosal involvement	No	0
Acute start (< 10 days)	Yes	0
Resolution < 15 days	No	-4
<i>Fever ($\geq 38^{\circ}\text{C}$)</i>	Yes	+1
<i>Polymorphonuclear ($\geq 7000/\text{mm}^3$)</i>	Yes	+1
<i>Histopathology</i>		
Biopsy of skin	Intraepidermal pustules with papillary edema	+3
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Table 2. The patient's DRESS score according to the RegiSCAR validation score.

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<i>Enlarged lymph nodes</i>	No	0
<i>Atypical lymphocytes</i>	No	0
<i>Eosinophils $\geq 700/\text{mm}^3$</i>	No	0
<i>Skin Rash</i>		
Extent $>50\%$	Yes	+1
Rash suggesting DRESS	Yes	+1
Biopsy suggesting DRESS	No	-1
<i>Organ involvement</i>	Yes (two organs)	+2
<i>Resolution in ≥ 15 days</i>	Yes	0
<i>Excluding other causes</i>	Yes	+1
TOTAL SCORE		+3

Interpretation of RegiSCAR score: <2 : no case; 2-3: possible case; 4-5: probable case; >5 : definite case.