Childhood Acute Generalized Exanthematous Pustulosis Induced by Oral Ketoconazole

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SUMMARY Acute generalized exanthematous pustulosis is a rare disorder characterized by an acute onset of generalized, nonfollicular, pustular eruption associated with fever. It is usually drug-induced and is uncommon in children. We report a 12-year-old girl with acute generalized exanthematous pustulosis induced by oral ketoconazole. To our knowledge, in spite of its relatively frequent use, acute generalized exanthematous pustulosis due to ketoconazole has not been previously reported.

KEY WORDS: acute generalized exanthematous pustulosis, ketoconazole, antifungal agents, drug eruption, adverse drug reactions

INTRODUCTION
The term acute generalized exanthematous pustulosis (AGEP) was first introduced by Beylot et al. in 1980 (1) to describe a pustular eruption characterized by an acute onset after an infection and/or drug ingestion in subjects with no history of psoriasis, evolution towards spontaneous healing after a single attack, and existence of a marked dermal vasculitis in addition to nonfollicular subcorneal sterile pustules (2,3). We report the occurrence of AGEP as the result of ketoconazole use. To our knowledge, this is the first reported case of ketoconazole-induced AGEP.

CASE REPORT
A 12-year-old girl with a one-year medical history of dermatomyositis was evaluated for the sudden onset of high fever and a widespread erythematous rash of 5-days duration. Soon multiple, small pustules covered her trunk and extremities. The child had been on methylprednisolone therapy for one year from the onset of dermatomyositis with initial dose of 40 mg daily. Methylprednisolone had been gradually tapered and a maintenance dose of 4 mg daily had been established for 15 days prior to the current presentation and was continued during and after AGEP episode. One day before the onset of fever and rash, only ketoconazole 200 mg/day was prescribed as prophylactic therapy for oral candidiasis.

On physical examination, fever was detected (38.8 °C). Numerous erythematous and edematous patches with superficial, nonfollicular pustules were evident over the trunk and extremities (Fig. 1). Mucous membranes and her nails were...
Results of laboratory evaluation revealed white blood cell count of $21 \times 10^9/L$ (NR 4.5-9×10^9/L), with neutrophil count 12.2×10^9/L (NR 2-6×10^9/L) and erythrocyte sedimentation rate (ESR) of 28 mm/h. Liver function tests, urea, creatinine, electrolytes, and serum calcium level were within the normal limits. Viral serology, C-reactive protein, antistreptolysin O titers and bacteriologic studies of pustules were negative.

Histological examination of the skin revealed a large subcorneal pustule and moderate acanthosis. The papillary dermis was edematous with a mixed perivascular inflammatory cell infiltrate of lymphocytes, neutrophils, and a few eosinophils. In some areas, leukocytoclastic vasculitis was observed. The endothelial cells appeared swollen; the blood vessels had decreased lumens (Fig. 2).

The treatment with ketoconazole was stopped. However, methylprednisolone 4 mg daily was continued as to maintain dermatomyositis during and after AGEP episode. Symptomatic treatment with topical 0.1% hydrocortisone-17-butyrate cream and levocetirizine 5 mg daily was initiated.

**DISCUSSION**

Acute generalized exanthematous pustulosis is a rare, rapidly evolving dermatosis characterized by numerous small, sterile nonfollicular pustules arising on a widespread edematous erythema, accompanied by high fever (temperature >38 °C), and neutrophilia of >7×10^9/L. More than 50% of patients have other cutaneous signs, including purpura, vesiculobullae, target-like lesions, and mucous membrane involvement (2). In extensive cases, a positive Nikolsky sign has been observed (2,3). Characteristic laboratory findings include an elevated total blood cell count, which is usually predominantly neutrophilic (7×10^9/L). Eosinophilia may also be present. Hypocalcemia is less frequent, mainly related to hypoalbuminemia and renal failure (2). The main histopathologic findings in AGEP are spongiform superficial pustules. Papillary dermal edema, polymorphous perivascular infiltrates with eosinophils, leukocytoclastic vasculitis, and necrotic keratinocytes are variably present (2). Pustular eruption of necrotizing vasculitis, Sneddon-Wilkinson disease, staphylococcal scalded skin syndrome, and toxic epidermal necrolysis can be distinguished more easily on the clinicopathologic basis. The pathogenetic basis of AGEP remains to be clarified, although T cells seem to play a crucial role (3).

The most frequent triggers of AGEP are medication, specifically β-lactam antibiotics, macrolides, vancomycin, doxycycline, diltiazem, nifedip-
ine, quinidine, anti-HIV protease inhibitors, non-
steroidal anti-inflammatory drugs, and corticoste-
roids (2-6). Other, less common causes of AGEP
are enterovirus, adenovirus, Epstein-Barr virus, cyto-
meagalovirus, hepatitis B virus, mycoplasma
pneumoniae, and hypersensitivity to mercury
(2,6). Oral corticosteroids have been implicated in
AGEP (6). In our case, the possibility that meth-
yprednisolone could be a mitigating or modifying
factor should be excluded as the patient had been
on systemic corticosteroid therapy for one year to
maintain dermatomyositis under control.

AGEP is remarkable for its rapid evolution with
spontaneous resolution of pustules in less than 15
days (2). It is also more common in women than men,
and unusual in children (6), although it was recently
described in 20 Chinese children, attributed mainly
to antibiotics, sulfonamides, antipyretic analgesics
and vaccines (7), and in a pregnant woman (8).

AGEP has been reported with the systemic
antimycotics fluconazole (9), terbinafine (10,11),
itraconazole (12,13) and nystatin (14). As far as
we are aware, there have been no reports of its
occurrence with the use of ketoconazole. Keto-
conazole itself is a highly safe agent, although it is
possible that, due to its widespread use, a hyper-
sensitivity reaction, especially AGEP, may appear.
Ketoconazole-induced allergic reactions are in-
frequent and usually consist of urticaria, rash and
pruritus. In a small number of cases, ketoconazole
triggered angioedema. Major allergic reactions, in-
cluding anaphylaxis, have been reported (15).

In our case, the diagnosis of AGEP induced
by ketoconazole was established based upon the
history of recent ingestion, clinical presentation,
clinical course, and laboratory and histologic find-
ings. We consider the occurrence of dermatomy-
sitis to be incidental, with AGEP as a drug reaction
to oral ketoconazole. Patch testing may be used to
diagnose drug-induced AGEP (16), but it has the
potential to trigger the original generalized eruption
(17,18). Therefore, patch test was not performed
in our case. Recently, an in vitro γ-interferon re-
lease test has been used to diagnose AGEP, but its
role remains investigational (5). Although the child
described herein responded well to 0.1% hydro-
cortisone-17-butyrate cream and levocetirizine, in
severe cases systemic steroids may be employed
and the use of cyclosporine considered (19).

References
1. Beylot C, Bioulac P, Doutre MS. Pustuloses ex-
anthematiques aignes generalises: a propos
de 4 cas. Ann Dermatol Venereol 1980;107:37-
48.
2. Roujeau JC, Bioulac P, Doutre MS. Acute
generalized exanthematous pustulosis: analysis
3. Sidoroff A, Dunant A, Viboud C, Halevy S, Bal-
vick JN, Naldi L, et al. Risk factors for acute
generalized exanthematous pustulosis (AGEP)
– results of a multinational case-control study
4. Yesudian PD, Penny M, Azudria RM, King M. Ib-
uprofen-induced acute generalized exanthema-
5. Halevy S, Cohen AD, Livini E. Acute generali-
zed exanthematous pustulosis associated with
polysensitivity to paracetamol and bromhex-
ine: the diagnostic role of in vitro interferon-γ
6. Meadows KP, Egan CA, Vanderhofhout S.
Acute generalized exanthematous pustulo-
sis (AGEP), uncommon condition in children.
Case report and review of literature. Pediatr
Dermatol 2000;17:399-402.
7. Zhang JL, Chen X, Li J, Xie HF. Clinical ana-
lysis of childhood acute generalized exanthe-
matus pustulosis. Zhongguo Dang Dai Er Ke
8. Reich A, Szepietowski JC, Baran E. Severe
acute generalized exanthematous pustulosis
9. Alsadhar A, Taher M, Krol A. Acute generali-
zed exanthematous pustulosis induced by oral
B, Kempf W. Drug reaction to terbinafine si-
mulating an acute generalized exanthematous
11. Rubegni P, Mandato F, Sbano P, Fimiani M.
Terbinafine-induced acute generalized exan-
thematous pustulosis. G Ital Dermatol Vene-
reol 2008;143:151-5.
exanthematous pustulosis induced by oral
13. Cançado GG, Fujiwara RT, Freitas PA, Cor-
rea-Oliveira R, Bethony JM. Acute generalized
exanthematous pustulosis induced by itraco-
14. Kuchler A, Hamm H, Weidenthaler–Barth B,
Kampgen E, Blocker EB. Acute generalized


Innoxa – put your skin in ‘milky’ condition; year 1929. (From the collection of Mr. Zlatko Puntijar)