



Acute Generalised Exanthematous Pustulosis Due to Etodolac

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ABSTRACT

Acute generalized exanthematous pustulosis (AGEP) is a sudden-onset, severe and rare adverse skin reaction characterized by non-follicular sterile pustules tending to intertriginous localization. Lesions develop on erythematous and edematous skin. It is often triggered by drugs. This article presents a case diagnosed with AGEP due to etodolac. To the best of our knowledge, this is the second case of AGEP due to etodolac in the literature.

A 47-year-old female patient presented with diffuse erythema on the extremities, a purple purpuric rash on the extensor face of both legs, and millimetric pustules on an erythematous base on the inner surface of the left arm. She stated that the reaction developed after taking 3 medications, including etodolac tablets, and gargling the throat with povidone-iodine.

The patient was diagnosed with AGEP and her EuroSCAR AGEP Validation Score was calculated as 9 suggesting a definitive diagnosis of AGEP. All of the suspected drugs were discontinued. Methylprednisolone 16 mg/day, a local corticosteroid, and an oral antihistamine were started. Her symptoms resolved and laboratory abnormalities returned to normal within 2 weeks. Patch tests were performed 3 months after the reaction with the suspected drugs. The patch testing showed that only 10% etodolac at 48-, 72- and 96-hour readings were positive (++) . The patient was diagnosed with AGEP due to etodolac.

AGEP is often secondary reaction to drugs. The most frequent causative drugs are diltiazem, aminopenicillins, pristinamycin, terbinafine, sulphonamides, quinolones, and hydroxychloroquine. AGEP secondary to NSAIDs is very rare. Only one previous case of AGEP due to etodolac was reported in 2011.

Keywords: AGEP, etodolac, drug hypersensitivity

INTRODUCTION

Acute generalised exanthematous pustulosis (AGEP) is a sudden onset, severe, and rare adverse skin reaction characterized by non-follicular sterile pustules with a tendency of intertriginous localisation on erythematous and edematous skin (1). AGEP is accompanied by leukocytosis and fever greater than 38.8°C (1). Although mucosal involvement is rare, the most common mucosal involvement is seen in the oral cavity (2). Histological examination can reveal subcorneal and/or intraepidermal pustules and sometimes edema in the papillary dermis. It can also

reveal perivascular neutrophil and sometimes eosinophil infiltrates (2). AGEP is often triggered by drugs (quinolones, beta lactams, calcium channel blockers, etc.). Its incidence is 1-5 per million and its mortality is below 5% (1,2). AGEP can be diagnosed through clinical and histological findings. In 2001, the EuroSCAR group developed a score for confirming the diagnosis of AGEP (3).

Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) that is often used for orthopaedic reasons. It acts by inhibiting cyclooxygenase-1 and 2 (COX-1, COX-2). This article presents a case diagnosed with AGEP due to

etodolac. To the best of our knowledge, there is only one previously reported case of AGEP due to etodolac (4), and this is the second case of AGEP due to etodolac in the literature.

CASE REPORT

A 47-year-old female patient presented with a purple purpuric rash on the extensor face of both legs and millimetric pustules on an erythematous base on all of the extremities and folds, together with the trunk (Figure 1). There was no mucosal involvement and the remaining physical examination was normal except for the skin lesions. She reported that she had been ingesting a herbal food supplement (Silybum marianum, choline, turmeric), an etodolac tablet (400 mg), and a multi-vitamin tablet (calcium, vitamins A, C, B3, E, B5, B1, B2, B6, B12, D, K2, magnesium, ginseng, iron, coenzyme Q, zinc, manganese,

copper, folic acid, selenium, molybdenum, biotin, chromium) for the previous four days. Additionally, she said that she had rinsed her throat with povidone iodine 48 hours before the onset of her complaints. An itchy rash together with swelling in the arms, legs, and trunk started 24-36 hours after the last drug doses. She had accompanying fever and sweating. The medications the patient had used in the last 4 weeks were questioned, and there was no history of other suspicious drug use. On laboratory examination the white blood cell count was 17500 cells/mm³ (95% neutrophil predominance), CRP 119.4 mg/L, and total bilirubin 3.12 mg/dL. The patient's elevated bilirubin was not accompanied by liver dysfunction. At the follow-up the next day, the bilirubin level was 1.24 mg/dL. It returned to normal a week later and did not recur during follow-up. All other laboratory examinations were unremarkable.

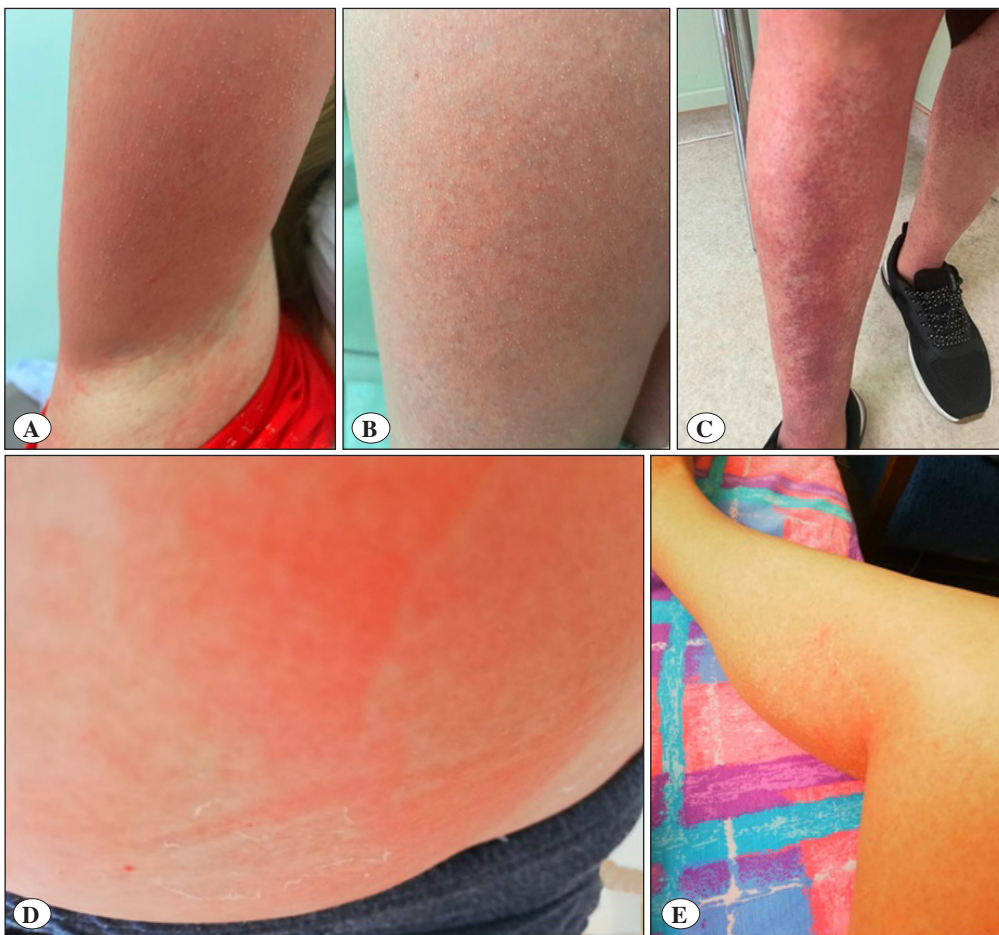


Figure 1. A) Diffuse erythema on the inner surface of the left arm, B) Millimetric pustules on an erythematous base on the inner surface of the left arm, C) Purple purpuric rash on the extensor face of both legs, D) Diffuse erythema on the abdominal area, E) Diffuse erythema on the inner surface of the left knee.

She was diagnosed with AGEP and all of the suspected drugs were discontinued, and methylprednisolone 16 mg/day, a local corticosteroid, and an oral antihistamine were started. Facial edema developed during the second day of treatment. Subsequently her symptoms resolved gradually and the laboratory abnormalities returned to normal within 2 weeks.

Patch tests were performed 3 months after the reaction with the herbal food supplement (silymarin, choline, turmeric) in saline at 10% concentration, etodolac 400 mg in 10% petrolatum, the multi-vitamin tablet in 10% petrolatum, and povidone iodine in saline at 10% concentration. Patch test readings were performed at 48, 72, 96 hours and 7 days. The patch testing showed that only 10% etodolac at the 48-, 72- and 96-hour readings were positive (++) (Figure 2). The patient was diagnosed with AGEP due to etodolac and her EuroSCAR AGEP Validation Score (3) was calculated as 9 suggesting a definitive diagnosis of AGEP (Table I).



Figure 2. The patch test image at 96 hours.

Table I: The EuroSCAR AGEP Validation Score.

Morphology	
Pustule	
Typical	+2
Compatible	+1
Insufficient	0
Erythema	
Typical	+2
Compatible	+1
Insufficient	0
Distribution/pattern	
Typical	+2
Compatible	+1
Insufficient	0
Postpustular desquamation	
Yes	+1
No/insufficient	0
Course	
Mucosal involvement	
Yes	-2
No	0
Acute onset	
Yes	0
No	-2
Resolution (15 ≤ days)	
Yes	0
No	-4
Fever ≥38 °C	
Yes	+1
No	0
Polymorphonuclear neutrophils >7000/mm ³	
Yes	+1
No	0
Histology	
Other diseases	-10
Not representative/no histological examination	0
Exocytosis of polymorphonuclear neutrophils	+1
Subcorneal and/or intraepidermal nonspongiform or NOS pustule(s) with papillary edema or subcorneal and/or intraepidermal spongiform or NOS pustule(s) without papillary edema (NOS: not otherwise specified)	+2
Spongiform subcorneal and/or intraepidermal pustule(s) with papillary edema	+3
Interpretation: 0: no AGEP, 1–4: possible, 5–7: probable, 8–12: definite.	

* Please note that the numbers written in bold are representative of the patient's score from each section.

DISCUSSION

AGEP is often secondary reaction to drugs. However, it can rarely be observed secondary to viral, bacterial, or parasitic infections, herbal products, or mercury exposure (3,5). The most frequent causative drugs are diltiazem, aminopenicillins, pristinamycin, terbinafine, sulphonamides, quinolones, and hydroxychloroquine (2). The lesion development time after drug intake is approximately 48 hours (2). This period can vary from 24 hours to 3 weeks (2,6). AGEP secondary to NSAIDs is very rare. Only one previous case of AGEP due to etodolac was reported in 2011 (4) and the current case is the second reported case of AGEP due to etodolac in the literature. In a study evaluating 97 cases with a definite diagnosis of AGEP, 3 cases were reported secondary to oxicams (2).

After exposure to the responsible agent, antigen-presenting cells present the antigen via MHC molecules and cause activation of specific CD4-CD8 T cells. These T cells proliferate and migrate to the dermis and epidermis (7). AGEP is a T cell-mediated, sterile neutrophilic inflammatory response (Type IVd reaction). The role of differentiation of CD4 and CD8 T cells into drug-specific clusters in the development of AGEP has been demonstrated by patch tests and in vitro tests. It is thought that drug-specific cytotoxic T cells and cytotoxic proteins such as granzyme B and perforin can penetrate subcorneal vesicles by inducing keratinocyte apoptosis (8). In vitro tests have shown that drug-specific T cells overproduce CXCL8/IL-8, which is potent in neutrophil chemotaxis in patients with AGEP (8). CXCL8/IL-8 is thought to play a central role in the development of pustules in AGEP (8).

The skin manifestations of AGEP are characterized by tens to hundreds of small, sterile, nonfollicular pustules on a pruritic, erythematous background. It likes to settle on the trunk and folds. Usually there is no mucosal involvement, but rarely a small focus may be involved on the lip or buccal mucosa (7). In addition to diffuse erythema and small non-follicular sterile pustules mostly beginning in intertriginous areas, other skin symptoms like purpuric lesions especially on the legs and edema of the face may be observed as seen in the current case in patients with AGEP.

Fever ($\geq 38^{\circ}\text{C}$) and leukocytosis with the dominance of neutrophils ($>7.5 \times 10^9/\text{L}$) are features of AGEP. Hepatic, renal and pulmonary dysfunction is the most

common findings of systemic involvement (7). However, organ involvement in patients with AGEP has been rarely reported in large case series. Hepatic involvement progresses with high liver function tests, and a cholestatic pattern with high GGT and ALP. Fatty or enlarged liver can be observed on abdominal ultrasonography (7). In a review including 340 AGEP patients diagnosed in 10 health centers across the US between 2000 and 2020, liver involvement was seen at 8.4%, and no information was given about the elevation of bilirubin levels (9). In a study evaluating 58 AGEP cases who received inpatient treatment in a dermatology center in the UK between 2000 and 2010, systemic involvement (liver, kidney, bone marrow and lung) was observed in 17% of the cases (10). In a study in which 63 AGEP cases diagnosed in 9 dermatology clinics in France were examined, mild liver transaminase elevations were observed in 7 cases, and two of them were previously diagnosed with viral hepatitis (11). Elevated bilirubin levels have been reported very rarely. In AGEP which developed in a patient who was started on sorafenib treatment with the diagnosis of hepatocellular carcinoma, serum bilirubin elevation was also observed (12). It was also reported that an increase in total bilirubin value was observed in an AGEP case secondary to *Staphylococcus pettenkopheri* infection (13). In our case, bilirubin elevation was also observed and returned to normal after treatment. High neutrophil and CRP levels may be associated with multi-organ involvement (7). With the discontinuation of the responsible drug, the skin lesions heal by peeling in a few days. Mortality is less than 5% and it develops due to multiorgan failure or disseminated intravascular coagulation (7).

The AGEP diagnosis is made based on clinical and histological criteria. The clinical findings of the patient in the present case report were consistent with AGEP, and the score was calculated as 9 (8-12: definitely AGEP) according to the EuroSCAR AGEP Validation Score (3). Since the clinical findings of the present case were sufficient for the diagnosis, histopathological examination was not performed.

Patch tests and late readings of intradermal tests may be useful as a diagnostic test in delayed drug reactions (14). The present case showed positivity with etodolac in patch tests. In a study investigating the value of the patch tests in severe drug-induced skin reactions, 14 AGEP cases were evaluated and patch test positivity was found in 7/14 (50%) on the third day (15).

In conclusion, etodolac, like other NSAIDs, may be the cause of AGEP. In addition to diffuse erythema and small non-follicular sterile pustules, mostly beginning in intertriginous areas, other skin symptoms like purpuric lesions especially on the legs and edema of the face may be observed in patients with AGEP.

Conflict of Interest

We have no conflict of interest.

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Author Contributions

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