

## Etoricoxib-induced Acute Generalized Exanthematous Pustulosis

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Accepted August 28, 2007.

Sir,

Acute generalized exanthematous pustulosis (AGEP) is a rapid-onset skin syndrome consisting of generalized non-follicular small pustules on erythematous skin and systemic symptoms. In most cases AGEP is induced by drugs (1). Etoricoxib, a non-steroidal anti-inflammatory drug (NSAID) cyclo-oxygenase-2 (COX-2) inhibitor, is nowadays widely used due to its lower rate of gastrointestinal irritation. We report here the first documented case of etoricoxib-induced AGEP. The diagnosis was confirmed by typical clinical symptoms, histopathological findings and positive patch tests.

### CASE REPORT

A 55-year-old man was on no permanent medication, but had a 10-year history of rosacea, which had been treated periodically with tetracycline. His alcohol consumption was relatively high, and oesophagitis and haemorrhagic gastritis was diagnosed in 2005. For the past few years he had occasionally used ibuprofen and etoricoxib for gout symptoms.

In May 2006 the patient had been taking tetracycline for 3 weeks. On June 11<sup>th</sup> he took etoricoxib 60 mg twice, and 3 days later he was admitted to hospital because of fever and a pustular skin eruption, as described in AGEP (1). The patient was febrile (40.2°C) and his face appeared swollen. A spotty rash was seen on his skin, and small pustular lesions covered large areas of face, body and proximal extremities (Fig. 1). Petechial purpuric lesions were seen on his legs (Fig. 2). Laboratory results showed an elevation of C-reactive protein value (252 mg/l, normal <2.5 mg/l) and white blood cell count ( $21.9 \times 10^9/l$ , normal 3.7–10) without eosinophilia. Glutamyl transferase (GT) was elevated (223 U/l, normal 15–115 U/l), as was alanine aminotransferase (ALAT) (123 U/l, normal 10–70 U/l). Creatinine was slightly increased (106  $\mu\text{mol/l}$ , normal 60–100  $\mu\text{mol/l}$ ) and plasma sodium low (122 mmol/l, normal 137–144 mmol/l). Because of suspected septicaemia, combined cephtriaxone and clindamycin intravenous medication was started and the patient was transferred to the intensive care unit after becoming hypotensive and disorientated. Blood, skin, urine and cerebrospinal fluid cultures for bacteria were negative, as were the specific diagnostic tests for herpes virus, hepatitis, HIV, Epstein-Barr virus, cytomegalo, Sindbis, Puumala and enteroviruses. Chest X-ray and computed tomography of the brain were



Fig. 1. Spotty rash and small pustular lesions on body and extremities.

normal. After 2 days, methylprednisolone 240 mg/day was started. The dermatologist suspected AGEP and therefore corticosteroid and antibiotic treatments were tapered. The skin changes started to diminish and heavy diuresis started on the sixth day. In the next few days ALAT was normalized, whereas GT increased to 1041 U/l then slowly tapering during the following 6 weeks. Creatinine and plasma sodium were normalized during the first week. Slight pleural effusion detected 4 days after admission was normalized one week later.

Skin biopsy from one leg revealed spongiosis in the epidermis and dermis. A subcorneal exudate and a few leucocytes were seen near a hair follicle. Red cells and slight infiltration of neutrophils and eosinophils around the dermal vasculature suggested slight vasculitis. Immunofluorescence examination of the skin biopsy was negative. The histopathological findings supported a clinical diagnosis of AGEP, although distinct spongiform pustules were not seen.

The patient left the hospital 3 weeks after the admission and skin tests were carried out 3 months later. Skin prick test with the commercial product of etoricoxib



Fig. 2. Petechial purpuric lesions on legs.

60 mg (Arcoxia<sup>®</sup>, distributed by MSD, Espoo, Finland) granulated and moistened with physiological saline was negative. The patch tests were performed with 3 different concentrations of granulated etoricoxib 60 mg (Arcoxia<sup>®</sup>) in petrolatum (petr.), with 30% celecoxib 100 mg (Celebra<sup>®</sup>, distributed by Pfizer, Helsinki, Finland) and with 30% parecoxib 40mg (Dynastat<sup>®</sup>, Pfizer). Etoricoxib 30% petr. caused ++ allergic reaction, 10% and 1% + reaction. Celecoxib 30% gave + reaction and parecoxib was negative. Patch tests in 5 control persons tested with etoricoxib 30% were all negative. Patch tests and photopatch tests with tetracycline gave negative results. The patient also started treatment with tetracycline for rosacea with no adverse reactions.

## DISCUSSION

AGEP represents a distinct entity with specific clinical characteristics. The systemic symptoms seen in AGEP

may lead to a wrong diagnosis of septic infections, leading to unnecessary treatment. AGEP usually resolves spontaneously within 15 days of onset. The development of AGEP is most often triggered by variable drugs capable of inducing different immunological reactions (1–3). The usefulness of patch testing in the diagnosis of AGEP has been reported earlier (4), and was apparent in our patient.

COX-2 inhibitors were developed to reduce the adverse effects of non-selective COX-1 inhibitors. Since then the side-effects on long-term cardiovascular events have limited the selection of COX-2 inhibitors. Etoricoxib has been regarded as well tolerated (5). Many patients with NSAID-induced asthma (6), urticaria or angioedema (7) seem to tolerate etoricoxib. Nimesulide (8), valdecoxib (9) and celecoxib (10)-induced AGEP has been described earlier. This is the first report of etoricoxib-induced AGEP.

## REFERENCES

1. Roujeau J-C, Bioulac-Sage M, Bourseau C, Guillaume JC, Bernard P, Lok C, et al. Acute generalized exanthematous pustulosis. *Arch Dermatol* 1991; 127: 1333–1338.
2. Padial MA, Alvarez-Ferreira J, Tapia B, Blanco R, Manas S, Blanca M, et al. Acute generalized exanthematous pustulosis associated with pseudoephedrine. *Br J Dermatol* 2004; 150: 139–142.
3. Beltraminelli HS, Lerch M, Arnold A, Bircher AJ and Hausermann P. Acute generalized exanthematous pustulosis induced by the antifungal terbinafine: a case report and review of the literature. *Br J Dermatol* 2005; 152: 780–783.
4. Wolkenstein P, Chosidow O, Flechet ML, Robbiola P, Paul M, Dume L, et al. Patch testing in severe adverse drug reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. *Contact Dermatitis* 1996; 35: 234–236.
5. Dallob A, Hawkey CJ, Greenberg H, Wight N, De Schepper P, Waldman S, et al. Characterization of etoricoxib, a novel, selective COX-2 inhibitor. *J Clin Pharmacol* 2003; 43: 573–585.
6. El Miedany Y, Youssef S, Ahmed I, El Gaafary KM. Safety of etoricoxib, a specific cyclooxygenase-2 inhibitor, in asthmatic patients with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2006; 97: 105–109.
7. Sanchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A. Safety of etoricoxib, a new cyclooxygenase-2 inhibitor, in patients with nonsteroidal anti-inflammatory drug-induced urticaria and angioedema. *Ann Allergy Asthma Immunol* 2005; 95: 154–158.
8. Teixeira M, Silva E, Selores M. Acute generalized exanthematous pustulosis induced by nimesulide. *Dermatol Online J* 2006; 12: 20.
9. Byerly FL, Nelson KC, Granko RP, Morrell DS, Cairns BA. Valdecoxib-associated acute generalized exanthematous pustulosis. *Burns* 2005; 31: 383–387.
10. Yang CC, Lee JY, Chen WC. Acute generalized exanthematous pustulosis caused by celecoxib. *J Formos Med Assoc* 2004; 103: 555–557.