

## ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS AS A SIDE EFFECT OF QUETIAPINE

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### INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP), a member of the “neutrophilic dermatoses” was first described by Baker and Ryan in 1968 as exanthematic pustular psoriasis (Baker & Ryan 1968). According to the European Study of Serious Cutaneous Adverse Reactions (EuroSCAR), the incidence ranges from 1 to 5 cases per million per year and the mortality rate approaches 1% to 2%, with the equal age and gender distribution. AGEP erupts suddenly within 1 or 2 days of drug exposure and generally resolves in approximately 2 weeks with sequelae of generalized desquamation. Sidoroff et al. (2001) identified two different temporal patterns of AGEP reaction from the beginning of administration to the onset of a reaction: a first group with a rapid onset (only a few hours to 2-3 days after drug intake, especially antibacterials) and a second group with an interval of 1 to 3 weeks (mean 11 days) for all other drugs.

Typical AGEP is a self-limiting disease characterised by an acute cutaneous eruption with non-follicular sterile pustules on an edematous erythema, accompanied by fever above 38°C. In most cases, the skin symptoms begin in the face or in the intertriginous areas, moving to the trunk and the lower limbs in a few hours. On a burning and/or pruritic erythematous background, hundreds of small (pinhead sized < 5 mm), whitish non-follicular sterile pustules arise, sometimes mimicking a positive Nikolsky's sign. The mean duration of the pustules is 9.7 days (4-10 days), followed by a characteristic postpustular pin-point desquamation for a few days. About 50% of patients exhibit other skin symptoms like marked edema of the face, purpura lesions (especially on the legs), Stevens-Johnson-syndrome-like “atypical targets”, vesicles and blisters have been described but are not typical. However, clinical diagnosis remains difficult if a monomorphic eruption located on hands and feet is presented. Mild mucous membrane involvement on a single site (mostly a few erosions on the mouth and tongue) may occur in about 20% of cases.

High fever usually begins abruptly on the same day (or within 2 to 3 days before or after the eruption) as the pustular eruption and lasts for about 1 week. Lymphadenopathy has been reported in some cases. Histologically, AGEP may demonstrate subcorneal pustules

with a background of dermal edema and spongiosis, leukocytoclastic vasculitis, perivascular eosinophils, and focal necrosis of keratinocytes with negative immunofluorescence. According to Speeckaert et al. (2010) AGEP is an uncommon clinical and histopathological reaction pattern, most often described in association with drugs (90% of the cases), acute viral infections (enterovirus (coxsackievirus A9 and B4, echovirus 11 and 30), cytomegalovirus, Epstein-Barr virus, hepatitis B virus, parvovirus B19), Escheria Coli, Chlamydia pneumoniae, Mycoplasma pneumoniae, Echinococcus granulosus, spider bites, heavy metals (mercury), dietary supplements, chemotherapy, radiation and PUVA.

Quetiapine is a dibenzothiazepine atypical antipsychotic. It has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D<sub>2</sub>) and serotonin type 2 (5-HT<sub>2</sub>) antagonisms. It is an antagonist at multiple neurotransmitter receptors in the brain: serotonin 5-HT<sub>1A</sub> and 5-HT<sub>2</sub>, dopamine D<sub>1</sub> and D<sub>2</sub>, histamine H<sub>1</sub>, and adrenergic alpha<sub>1</sub>- and alpha<sub>2</sub>-receptors.

### CASE REPORT

We present a case of 53 years old female VR admitted in Department of Dermatology and Venerology, Clinical Hospital Center in Split, Croatia, for diagnostic procedures and treatment of generalised skin erythematous and pruritic maculopustulas. VR is a person with mild mental retardation (F70) and for almost 15 years has been in psychiatric treatment for an implanted psychosis (F29). She had been treated with clozapine till seven days before admitted in hospital. Clozapine was substituted with quetiapine tbl a 100 mg. per os once daily. After 7 days of treatment with quetiapine erythematous maculas with partial confluence and exfoliated areas occurred throughout the body. Erythematous area was in general covered by numerous pustulas (2-3 mm). These efflorescences were mostly expressed on her chest and axillar regions, also on spine, thighs and adductor side of both upper arms. She had no history of severe somatic disorder, she was nonsmoker and didn't use alcohol. Regarding the allergic reactions she was positive on pollen, dust and mites. The patient had no personal or family history of psoriasis. No fever, arthralgias or myalgias, chills,

nausea, vomiting, were recorded. There was no hepatosplenomegaly or lymphadenopathy.

At the time of admission her vital signs were as follows: pulse rate of 68 beats/min, respiration rate of 16 breaths/min, systolic and diastolic blood pressure of 150/53 mmHg. Her total white blood cell count was  $10.4 \times 10^9/\text{uL}$ , thrombocytes  $279 \times 10^9/\text{L}$ , neutrophils 0.75, lymphocytes 0.18, monocytes 0.5, basophils 0.1, eosinophils 0.6. No atypical lymphocytosis or eosinophilia was noted. Sedimentation rate was 37 mm/h and CRP 84.6 mg/L. The remaining blood cell count and other relevant biological parameters (aspartate aminotransferase, alanine aminotransferase, bilirubin, creatinine, plasma proteins) were normal. A sample of superficial pus from a pustule on the trunk showed a significant number of leukocytes as well as a significant number of *Staphylococcus aureus* and *Pseudomonas* spp. Skin biopsy and direct immunofluorescence (DIF) were performed. Histopathological findings showed spongiform subcorneal intraepidermic pustules, polymorphous perivascular infiltrates, exocytosis of lymphocytes and polynuclear granulocytes. Papillary dermal edema was found. Perilesional DIF did not show IgA, C3, C4, i IgM intracellular, nor basal membrane deposits. All of these observations were consistent with a diagnosis of acute generalized exanthematous pustulosis (AGEP).

The patient was treated with Letizen, Ciprinol and Ninur. Local corticosteroids (Elocom) were also applied and there was complete regression of pustules in following weeks. The psychiatric treatment with quetiapine was discontinued. A psychiatrist was consulted and he introduced clozapine tbl a 25 mg orally three times a day.

## DISCUSSION

Our patient's medical history indicated an exposure to quetiapine within 1 week prior to her skin eruption. This time frame was parallel to the reports of average period for AGEP to occur. No fever, arthralgias or myalgias, chills, nausea, vomiting, were recorded, as in the case of AGEP induced with olanzapine (Christen et al. 2006). The diagnosis was corroborated by histopathology. According to Roujeau et al. (1991) the main histopathological findings in AGEP are spongiform superficial pustule, papillary edema, polymorphous perivascular infiltrate with eosinophils and leucocytoclastic vasculitis with fibrinoid deposits; most of the mentioned symptoms were present in our patient.

In clinical practice, patch testing has been reported to be a safe and irrefutable method in determining the culprit drug of AGEP. Patch testing with the offending drug has been shown to be more frequently positive in

AGEP than other cutaneous reactions, including SJS/TEN. Although patch testing may not be required in patients with a classic presentation (primary diagnosis is always based on a detailed history and a thorough clinical examination), it can help to narrow the differential diagnosis in ambiguous cases. We decided against patch testing in our patient because of the risk of generalised pustulation.

## CONCLUSION

Our patient represents the first known reported case of clinically-consistent and histologically-proven acute generalised exanthematous pustulosis overlap induced by quetiapine in the literature. Early diagnosis of AGEP and differentiation from other diseases (e.g., generalized pustular psoriasis) is important to avoid unnecessary investigations and/or the administration of expensive and sometimes risky antibiotics, including retinoids and immunosuppressive therapy. However, without the appropriate management the mortality for AGEP can be up to 5 percent.

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**Conflict of interest :** None to declare.

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