

A case of acute generalised pustulosis due to amoxicillin/clavulanic acid

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To the Editor,

Penicillins are very useful antibiotics with a long history. They are still widely used. Unfortunately, they are a common cause of adverse skin reactions. In daily practice, two types of skin reactions are seen.

Type I (acute, IgE-mediated) reactions mostly cause a general itching, erythema and urticaria. Anaphylaxis (dyspnoea, gastrointestinal symptoms, hypotension and even shock) can occur. Laboratory testing will reveal specific IgE for penicillins.¹ In contrast, type IV reactions (delayed type, T-cell mediated) primarily cause skin reactions due to high levels of T cells in the skin. This kind of allergy can be tested via patch testing.¹

We will present a case of an uncommon type IV hypersensitivity reaction after administration of amoxicillin.

CASE REPORT

A 41-year-old Caucasian male presented himself with an acute erythematous itching rash over his entire body. The day before presentation, he started on amoxicillin with clavulanic acid for treatment of a urinary tract infection. After the second antibiotic tablet, the rash arose suddenly starting in the groin. Physical examination showed a diffuse erythematous rash on arms, legs, trunk and anogenital region, with generalised pinpoint (1-2 mm) pustules. In addition localised purpura on the ankles and blisters were seen (*figure 1*). The patient had a low-grade fever (38.4 °C) and general malaise. Laboratory tests showed a leukocytosis of $20.6 \times 10^9/\text{ml}$ with a marked neutrophilia of $19.6 \times 10^9/\text{l}$, and an elevated C-reactive protein of 190 mg/l. There were no signs of renal failure or elevation of liver enzymes. Urinary and blood cultures were negative. Specific IgEs to penicillins (penicilloyl G, penicilloyl V and amoxicilloyl) were not detectable in the serum. Unfortunately, no patch tests were performed. Based on the clinical presentation and blood neutrophilia, our working diagnosis was an acute generalised

exanthemous pustulosis (AGEP). The differential diagnosis, taking into account the fever and night sweats, included a (viral) infection, a systemic autoimmune disease with vasculitis and a B-cell malignancy with paraneoplastic phenomena. He was admitted to hospital and treated with 60 mg oral prednisone once daily, 2 mg clemastine thrice daily and 0.5 mg/g fluticasone topically twice daily. The antibiotics were stopped. Skin biopsies of the upper leg and upper arm were taken. In the papillary dermis a mixed perivascular infiltrate of histiocytes, lymphocytes, neutrophils and eosinophils was seen, with oedema. The epidermis showed locally dense infiltrates of neutrophils, confirming the diagnosis of AGEP (*figure 2*). Initially, the itching and rash worsened, but two days after admission the rash and itching faded and the patient was discharged in good health.

DISCUSSION

AGEP is characterised by an acute erythematous eruption together with sterile pustules. As with our patient, this

Figure 1. Close-up of inguinal region, showing generalized erythematous rash superimposed with sterile pustules

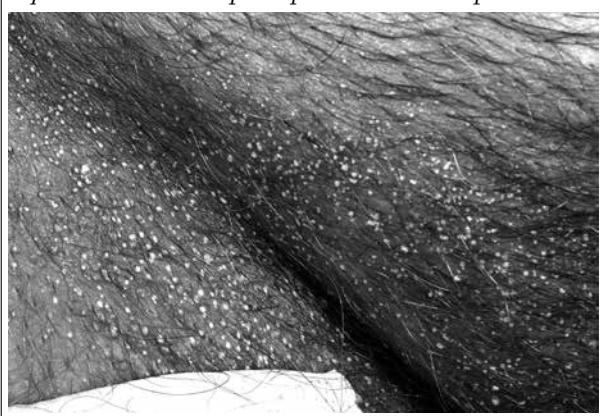
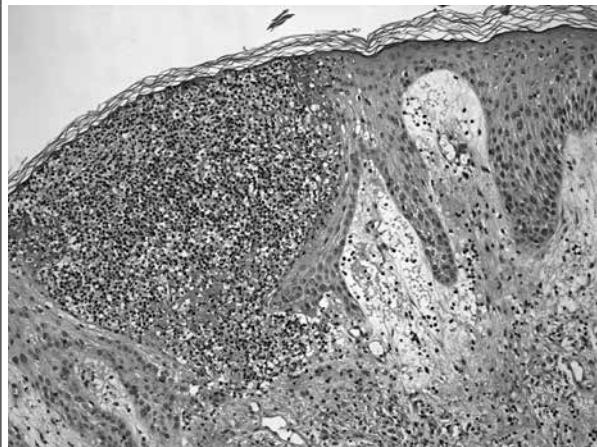


Figure 2. Skin biopsy of upper arm: in papillary dermis edema and perivascular mixed infiltrate of histiocytes/lymphocytes and neutrophils plus some eosinophils. Epidermis shows locally dense infiltrates of neutrophils



usually starts in the intertriginous areas.² Additionally, there can be blisters, vesicles and purpura, especially on the legs. A low-grade fever and marked neutrophilia are other hallmarks of the disease.³ It is primarily considered an adverse drug reaction, but can also be caused by viral infections. The incidence is 1-5 cases per million per year. Treatment consists of discontinuing the culprit drug, after which recovery takes 4-14 days.^{2,4} Although clinical evidence for the use of systemic immunosuppressive therapy is lacking, in common practice this is often given. A midway advice might be to administer topical steroids.⁵

Diagnosis is based on the clinical presentation, supported by patch testing (sensitivity 50%) and histology. Histology shows subcorneal pustules, sometimes with necrosis of the keratinocytes, oedema in the papillary dermis and a perivascular infiltrate of neutrophils and possibly eosinophils.^{3,4} Although the eruption resembles that of pustular psoriasis, psoriasiform changes such as papillomatosis and acanthosis do not appear.²

The drugs mostly associated with AGEP are antibiotics. The EuroSCAR study revealed that 18% of cases were due to aminopenicillins.^{3,6} An important difference between AGEP caused by antibiotics and AGEP due to other 'highly suspected' medications such as diltiazem and

hydrochloroquine is the time to onset of the eruption: in the case of antibiotics this is one day or less, with other drugs a median of 11 days. This may suggest different pathogenetic mechanisms.⁶

Studies explain that AGEP is a T-cell mediated immune reaction. Patients show proliferation of drug-specific polyclonal T cells.⁷ Skin biopsies and T-cell stimulation tests of AGEP patients show a high production of IL-8, higher than in patients with other drug reactions.^{8,9} IL-8 is known for attracting neutrophils and prolonging their survival. This leads to neutrophilic infiltration in the skin and the eruption of sterile pustules.¹⁰ Due to the involvement of both T cells and neutrophils, a classification as a type IVd hypersensitivity reaction has been suggested.¹

In summary, we present a patient who developed an adverse reaction to a very commonly used antibiotic. Although it is a very rare complication, it is important to keep in mind that such acute adverse reactions can also occur when the patient previously had never been exposed to the culprit drug.

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