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Not all pustules are infective in nature: acute generalised exanthematous pustulosis causing pustular eruptions in an elderly woman

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ABSTRACT

Acute generalised exanthematous pustulosis (AGEP) is an adverse drug reaction that can occur in any age group. It is commonly mistaken as pustular psoriasis or cutaneous infection, resulting in unnecessary commencement of medications such as methotrexate and antibiotics that can cause harm to the patient or interact and adversely affect the efficacy of other medications. Early diagnosis of AGEP avoids unnecessary investigations and treatment, which not only can harm the patient but also escalate health care, as the condition is self-limiting. This case report illustrates AGEP secondary to Cefaclor occurring in a 72-year-old Chinese woman. Although the literature has documented the occurrence of AGEP with Cefaclor, the unique feature of this case is the occurrence of AGEP following repeated uneventful courses of Cefaclor. This case highlights that AGEP must never be forgotten in the work-up for pustular eruptions in an elderly patient.

Keywords: acute generalised exanthematous pustulosis, cefaclor, drug allergy, pustular eruptions

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INTRODUCTION

This report illustrates a case of Cefaclor-induced acute generalised exanthematous pustulosis (AGEP). Although the literature had documented Cefaclor-induced AGEP[1], this case features AGEP following repeated uneventful courses of Cefaclor. This highlights the point that AGEP must be considered in the work-up for pustular eruptions.

CASE REPORT

A 72-year-old Chinese woman was admitted on the 15 January 2002 for a four-day history of pustular eruptions. She had a past history of diabetes mellitus, ischaemic heart disease and hypertension. She had no history of drug allergy, past or family history of psoriasis or any other dermatosis. There was no recent change to the medications for her

Fig. 1a Photograph of the patient's right shin shows an erythematous plaque studded with pustules.

Fig. 1b Photograph of the patient's left upper limb shows erythematous papules and plaques studded with pustules, some of which have dried up.

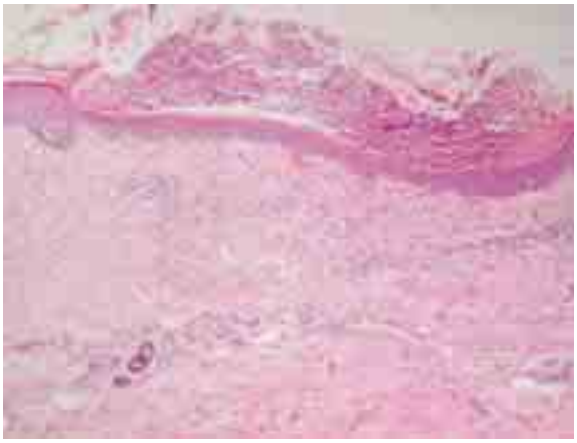

Fig. 2 Photomicrograph of a skin specimen taken from the patient's left shin shows a large sub-corneal pustule. The underlying epidermis was flat with loss of rete ridge pattern. The adjacent epidermis showed spongiotic changes. A superficial peri-vascular infiltrate of neutrophils, lymphocytes and some eosinophils is seen. No vasculitis was seen. [Haematoxylin & eosin, X40]

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chronic ailments. She was commenced on oral Cefaclor on 8 January 2002, to treat her chronic left heel ulcer. Four days later, she developed an outbreak of pustules.

Clinically, she was afebrile and was not toxic in appearance. Her vital signs were stable. She had erythematous patches and plaques studded with pustules on her upper and lower limbs, buttocks and lower back (Figs. 1a & 1b). Investigations revealed leucocytosis of 17 000/μL with a neutrophil count of 81% and an eosinophil count of 2.2%. The liver function test, urea and creatinine were normal. Culture of the pus and left heel ulcer grew Methicillin-resistant *Staphylococcus aureus* (MRSA) and coliforms that were regarded as wound contaminants. Blood cultures were negative for aerobic and anaerobic organisms. Biopsy was taken from her left shin and the histology was consistent with AGEP (Fig. 2).

Past history revealed she had multiple courses of antibiotics in the six months prior to this hospitalisation. She had received antibiotics such as Cefaclor (from 28 August to 17 September 2001, 18 September to 8 October 2001, and 4 to 8 December 2001), Erythromycin Ethylsuccinate (EES) (from 9 to 22 October 2001, and 23 October to 12 November 2001) and Bactrim (13 to 19 November 2001) from her family doctor to treat her chronic left heel ulcer. No wound cultures were performed prior to the commencement of her treatment. She also had a two-week course of intravenous Meropenem during her hospitalisation on 9 December 2001 for treatment of haemorrhagic cystitis. Her urine culture then revealed multi-drug resistant *E.coli* and *Enterobacter cloacae*. She subsequently recovered uneventfully.

She was diagnosed to have AGEP secondary to Cefaclor. Cefaclor was stopped and she was treated with topical 0.05% Bethametasone valerate ointment, aqueous cream and Potassium permanganate bath. The eruption subsided gradually over the next 15 days.

DISCUSSION

AGEP is the English translation of the French terminology, *exanthématiques aiguës généralisées*, first introduced by Beylot et al in 1980[2]. Most cases reported in the literature have been attributed to drugs, especially the beta-lactam[2,3] and macrolides[3,4] antibiotics. Differential diagnoses to be considered include pustular psoriasis, infective processes like impetigo, Sneddon Wilkinson syndrome and drug reaction with eosinophilia and systemic symptoms (DRESS).

Table I. The set of criteria established to facilitate the diagnosis of AGEP.

1. Numerous, small (<5mm), non-follicular pustules arising on a widespread edematous erythema.
2. Pathology reveals intra-epidermal/ sub-corneal pustules associated with one or more of the following
   - Dermal oedema
   - Vasculitis
   - Perivascular eosinophils
   - Focal necrosis of keratinocytes
3. Fever >38°C
4. Blood neutrophil count >7x10^9/L
5. Acute progression with spontaneous recovery within 15 days

In our case, pustular psoriasis was excluded by the absence of past history of psoriasis and the negative histological findings. Infective processes were unlikely as she was clinically afebrile and non-toxic. Although the culture of the pustule grew MRSA and coliforms, it was attributed to contamination of the wound swab (the wound culture from the long standing leg ulcer grew the same organisms). Sneddon Wilkinson syndrome was also excluded in view of the rapid resolution of the condition. Furthermore, unlike this patient's presentation, the blisters in Sneddon Wilkinson are usually larger and are often arranged in a circinate or serpiginous pattern. DRESS was excluded due to the absence of systemic involvement and eosinophilia.

In 1991, Roujeau et al proposed a set of criteria to facilitate AGEP diagnosis[3] (Table I). For this patient, she met the criteria except for fever. In view that Cefaclor was the only new medication started a few days prior to AGEP onset, it was attributed to be the trigger. AGEP is currently thought to be the consequence of a delayed hypersensitive (type IVd) reaction involving both CD4 and CD8 T cells with a preferential recruitment and activation of neurtophils[5,6]. These T cells express perforin and granzyme B which facilitate cell-mediated cytotoxic reactions that cause keratinocytes necrosis[7,8]. These T cells also express a milieu of cytokines such as interleukin (IL) 5 and 8[6,9]. IL-5 regulates the growth, differentiation and activation of eosinophils. A unique feature about AGEP is the high levels of IL-8 at the lesion site. This is in contrast to other drug reactions where there is moderate or no IL-8 production at the lesion site. IL-8 plays an important role in the recruitment of neutrophils[5].

At present, the drug sensitisation pathogenesis is not well appreciated. The innate immune system is credited to control the activation of adaptative immune responses[10]. An interesting aspect of this

case was that the patient had multiples episodes of exposure to the same drug, Cefaclor, without an allergic reaction. However, she could still develop AGEP secondary to Cefaclor. There are reports of higher frequency of drug allergies in individuals with autoimmune diseases or generalised infections. This could be the result of a "domino" effect; the massive stimulation of the innate and adaptative immune system by the autoimmune disease or infection triggers the initiation of an immune response to drugs[11-13].

This lady had haemorrhagic cystitis complicated by multi-drug resistant *E.coli* and enterococcal urinary tract infection and a chronic left foot ulcer that could have been a source as well as a portal of entry for infections. The repeated triggering of her innate and adaptative immunity may have initiated an immune response to Cefaclor, with AGEP consequently developing. The other possibility is that repeated exposure to Cefaclor could have resulted in her sensitisation to this drug. In conclusion, early diagnosis of AGEP avoids unnecessary investigations and treatment, which not only can harm the patient but also escalate health care, as the condition is self-limiting. This case highlights the need to consider adverse drug reaction, even if the drug had been administered safely before. A patch test can be used to search and confirm the causative agent[14].

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