

# Acute generalised exanthematous pustulosis and toxic epidermal necrolysis induced by carbamazepine

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## ABSTRACT

Acute generalised exanthematous pustulosis and Stevens-Johnson syndrome (toxic epidermal necrolysis spectrum of severe cutaneous drug reactions) are believed to have distinct underlying pathophysiologies. Our patient, a 28-year-old Chinese woman, represents the first known reported case of clinically-consistent and histologically-proven acute generalised exanthematous pustulosis and toxic epidermal necrolysis overlap induced by carbamazepine in the English literature.

**Keywords:** acute generalised exanthematous pustulosis, carbamazepine, Stevens-Johnson syndrome/toxic epidermal necrolysis overlap

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## INTRODUCTION

Acute generalised exanthematous pustulosis (AGEP) is a cutaneous reaction pattern, where there is an acute febrile illness and a rapidly progressive generalised pustular skin eruption after exposure to drugs, and less commonly, viral infections and heavy metals such as mercury. Toxic epidermal necrolysis (TEN) is a life-threatening condition, where there is extensive detachment of the skin characterised by full-thickness necrosis of the epidermis. Causes include drugs, e.g. antibiotics, antiepileptics, allopurinol and non-steroidal anti-inflammatory drugs (NSAIDs); infections and autoimmune diseases. Both severe cutaneous adverse reactions are clinically and morphologically distinct, with different underlying pathophysiologies. This case illustrates an unusual overlap of these two entities in a single eruption episode.

## CASE REPORT

A 28-year-old Chinese woman presented in December 2005 with a rapidly progressive generalised eruption with fever. She had history of childhood epilepsy and was on antiepileptic medication previously until the age of nine years. She was unable to provide the name of the medication. She had a past history of drug exanthem to erythromycin and doxycycline. She had no personal or family history of skin problems, such as psoriasis. She was started on carbamazepine on November 24, 2005 for recurrence of seizures. She developed a macular rash, fever and mouth ulcers on December 7, 2005 (14



**Fig. 1** Photograph shows confluent erythema of the trunk.



**Fig. 2** Photograph shows bullae formation over the chest.

days after initiation of carbamazepine). The rash started on the face and progressed rapidly to her trunk and limbs over the next four days. The facial rash subsequently evolved into pustules, which also erupted over her neck and chest within 24 hours. The clinical impression was Stevens-Johnson syndrome (SJS)/TEN overlap induced by carbamazepine. Carbamazepine was stopped immedi-

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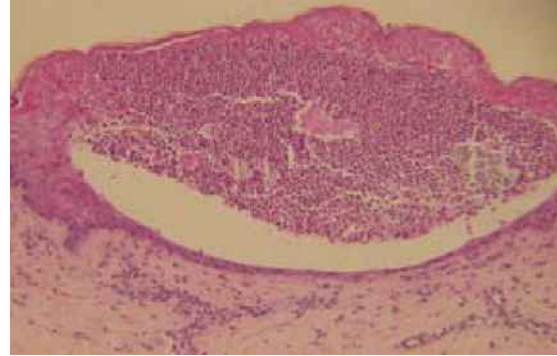
**Fig. 3** Photograph shows non-follicular pustules over the neck and face. Some pustules on the face has coalesced, forming purulent bullae.



**Fig. 4** Photograph shows non-follicular pustules over the chest.



**Fig. 5** Photomicrograph of the skin specimen from a chest pustule shows a subcorneal pustule (consistent with AGEP) with a full thickness necrosis of the epidermis (consistent with TEN) (Haematoxylin & eosin,  $\times 20$ ).



**Fig. 6** Photomicrograph of skin specimen from a chest pustule shows a subcorneal pustule. There is minimal spongiform change at the edge of the pustule and mild superficial perivascular lymphocytic infiltrate. (Haematoxylin & eosin,  $\times 100$ ).

ately and she was started on sodium valproate. She was given intravenous hydrocortisone for four days and intravenous immunoglobulins (IVIg) at 0.35 g/kg/day for two days, before she was transferred to our institution for further management on December 11, 2005.

Clinical examination of the skin (on day five of illness) revealed a generalised erythematous macular rash, confluent over the trunk and back (Fig. 1). Nikolsky's sign was positive. Targetoid lesions were noted over the thighs and upper limbs, including palms and soles, some of which had central clear bullae (Fig. 2). The total extent of the erythematous rash was 55% body surface area (BSA) and bullae accounted for 1% BSA. Of note, there were confluent lakes of pustules over the face (Fig. 3). Non-follicular pustules were also noted over the neck and the chest (Fig. 4). There were multiple erosions over the mouth and vulva, and her conjunctiva was inflamed. She was febrile. There was no hepatosplenomegaly or lymphadenopathy.

Her total white blood cell count was  $4 \times 10^9/\mu\text{L}$  (normal  $4\text{--}10 \times 10^9/\mu\text{L}$ ). No atypical lymphocytosis or

eosinophilia was noted. She had mild transaminitis, alkaline phosphatase (ALP) 181 (normal 32–103) U/L, alanine aminotransferase (ALT) 176 (normal 7–36) U/L, aspartate aminotransferase (AST) 140 (normal 15–33) U/L. Swabs of the facial pustules grew *Corynebacterium acne*, which was likely to be a bystander commensal on the skin with no pathogenic role. Skin biopsies were performed on day four of hydrocortisone and day two of IVIg over a chest pustule and a left arm bulla. The chest specimen showed a subcorneal pustule with an overlying confluent necrosis of the epidermis (Fig. 5). Mild spongiosis was present with sparse perivascular lymphocytic infiltrate (Fig. 6). Her left arm biopsy also showed confluent necrosis of the epidermis with a subepidermal bulla.

The patient was continued on a higher dose of IVIg at 0.5 g/kg/day for next four days. Hydrocortisone was withdrawn. Progression of erythema was arrested by day seven of illness, with maximal extent of 60% BSA. Her facial pustules healed with minimal scarring. Fever settled on day eight, and skin re-epithelisation started on day nine of illness. Sodium valproate was discontinued

**Table I. Summary of case reports of subcorneal pustulosis in TEN/EM , or AGEP with TEN features**

Paper	Causes	Clinical features	Morphology	Histology
Int J Dermatol 2001 <sup>(11)</sup>	Cefuroxime and panadol	No fever; mucosal intact TW: $26 \times 10^9$	Erythema and denudation. Nikolsky's +ve generalised pustules, no target lesion	<b>Pustules × 2:</b> subcorneal and intraepidermal spongioform pustules, papillary oedema, perivascular mononuclear infiltrates. No keratinocyte necrosis
Burns 2005 <sup>(12)</sup>	Valdecoxib	Fever, TW: $23 \times 10^9$	Pustules on generalised erythema (80%) Nikolsky's -ve, target lesions	Spongiform pustules
Eur J Dermatol 2002 <sup>(13)</sup>	Unknown	Fever, conjunctivitis, mouth, genital erosions, TW: $12 \times 10^9$	Solitary/coalescing pustules, targetoid lesions	<b>Pustule:</b> subcorneal and intraepithelial pustules, spongiosis <b>Target:</b> vacuolar interface dermatitis with necrotic keratinocyte and lymphocytic infiltrates oedema of papillary dermis
Br J Dermatol 1973 <sup>(14)</sup>	URTI	Fever, conjunctivitis, mouth, genital erosions, TW : $7 \times 10^9$ CXR : pneumonia,	Target lesions over the upper & lower limbs with bullae containing pus and clear supernatant	<b>Pustule:</b> subcorneal pustule, no intercellular oedema, necrosis of basal cell <b>Target:</b> no biopsy
Arch Dermatol 1988 <sup>(15)</sup>	Carbamazepine	Fever, mouth ulcers	Erythematous maculopapular rash with target lesions, followed by pustular eruption	<b>Pustule:</b> no biopsy <b>Target:</b> confluent epidermal necrosis and degeneration of basal layer, lymphohistiocytic infiltrate

URTI: urinary tract infection; TW: total white; CXR: chest radiograph

on day seven of illness due to persistent transaminitis. She remained seizure-free and was discharged on day 13 of illness.

## DISCUSSION

Our patient presented with both pustulosis and generalised confluent erythema with erosions and mucosal ulceration, which is consistent with AGEP and the SJS/TEN spectrum of disease. This poses a diagnostic challenge, because SJS/TEN spectrum and AGEP represent clinically and pathologically distinct entities. Use of corticosteroids in TEN is associated with increased adverse outcomes,<sup>(1)</sup> but does not seem to confer similar risk in AGEP. TEN carries a high mortality of up to 20%–30%,<sup>(2)</sup> and patients benefit from intensive care or management in the burns unit.<sup>(1,2)</sup> AGEP, however, follows a relatively self-limiting clinical course, with a relatively low incidence of multi-organ dysfunction. Hence, early and accurate diagnosis impact on the management and the outcome of the patient.

In our patient, the clinical course was relatively short, with pustules developing over 24 hours and maximal involvement of skin within seven days. This is more in keeping with AGEP than TEN. Her pustules were only limited over the face and chest, but AGEP patients typically have more extensive involvement, with more than 100 pustules in 70% of patients.<sup>(3)</sup> However, it must be noted that her disease course may have been modified by IVIg and corticosteroids. Presence of targetoid lesions is more consistent with SJS/TEN, although 20% of histologically-proven AGEP patients have erythema multiforme-like lesions.<sup>(4)</sup> Involvement of two mucosal surfaces, the mouth and vagina, is more suggestive of TEN. Mucosal involvement in AGEP is,

however, reported in only about 20% of cases, and it usually involves only a single mucosa.<sup>(4)</sup> Our patient had a low white cell count, which is more commonly found in TEN. More than 90% of AGEP patients have hyperleucocytosis with elevated neutrophil counts ( $> 7 \times 10^9/L$ ).<sup>(5)</sup>

Epicutaneous rechallenge has been used to ascertain the culpability of the drug in drug eruptions. Patch testing with the offending drug has been shown to be more frequently positive in AGEP than other cutaneous reactions, including SJS/TEN.<sup>(5)</sup> We decided against patch testing in our patient because of the risk of generalised pustulation.<sup>(6)</sup> Furthermore, its sensitivity is at most fair, only 50% for AGEP in a case series.<sup>(5)</sup> Although the use of patch testing in confirming a ciprofloxacin-induced AGEP, which clinically mimicked a bullous drug eruption, has been described,<sup>(7)</sup> the role of patch testing in differentiating one cutaneous drug reaction from another has not been validated.

The other differential diagnosis for our patient is anticonvulsant hypersensitivity syndrome (AHS) induced by carbamazepine. Its manifestations include pustulation, confluent erythema, and even extensive denudation in severe cases. However, lymphadenopathy, eosinophilia and atypical lymphocytosis, which are features of AHS, were absent in our patient. The interval between carbamazepine exposure and skin eruption was only two weeks. This is shorter than the classic 4–6 weeks described in AHS. In addition, prolonged treatment with steroids is usually required for AHS even after the culprit drug is withdrawn. Our patient, however, required only four days of hydrocortisone.

Our patient therefore presents with a unique clinical overlap, which fulfils both the case definition of probable AGEP (score of 6, according to the criteria in AGEP validation score of EuroSCAR study group)<sup>(4)</sup> and that of SJS/TEN overlap by the EuroSCAR study group.<sup>(2)</sup> Her biopsy showed subcorneal pustules with mild spongiosis, a feature of AGEP, as well as confluent epidermal necrosis with subepidermal bullae, consistent with TEN. Our patient represents the first reported case of clinically-consistent and histologically-proven AGEP/TEN overlap in the English literature.

The pathogenesis of AGEP and SJS/TEN spectrum of reaction pattern is believed to be distinct. Positive patch test lesions in AGEP patients have provided *in vivo* models for elucidating the pathogenesis.<sup>(8)</sup> Biopsies of patch test lesions at 48 hours, which reflect early events of the reaction, show epidermal vesicles containing mainly CD4+ T-cells, with few polymorphonuclear cells.<sup>(9)</sup> This is contrasted with biopsies of diseased skin in the fully-evolved stages, which show intra-epidermal pustules, with relative paucity in T-cells. Immunophenotyping reveals more perforin, granzyme B and Fas ligand (FasL) staining T-cells in the early stages than in the later stages.<sup>(8)</sup> Drug-specific T-cell clones from AGEP patients produce significantly more interleukin-8 (IL-8), a potent neutrophil chemotactic cytokine, compared with that from non-AGEP patients.<sup>(9)</sup> It is therefore postulated that the initial vesiculation is mediated by keratinolytic cytokines, including perforins, granzymes and FasL produced by drug specific CD4+ T-cells infiltrating the epidermis.<sup>(8,10)</sup> They also express IL-8, which causes the subsequent infiltration of neutrophils and pustule formation.<sup>(9)</sup> In SJS/TEN, there is also an initial drug specific T-cells cytotoxicity by perforins and granzymes. This is followed by massive activation of death receptor pathways including mainly Fas/FasL and tumour necrosis factor  $\alpha$  (TNF $\alpha$ ), resulting in widespread keratinocyte apoptosis.<sup>(1)</sup> Therefore, in both AGEP and SJS/TEN, initial keratinolysis may be mediated by T-cell production of perforins and granzymes. However, the trigger for the subsequent switch to uncontrolled auto-amplification of apoptosis in TEN, or the preferential IL-8 production in AGEP remains unknown.

Similar clinical overlap syndromes of SJS/TEN and pustulation have been described in the literature (Table I), but they have no supporting histological evidence of both AGEP and TEN. Some patients had clinical features of TEN with sheet-like denudation and positive Nikolsky's signs;<sup>(11,12)</sup> however, their biopsy findings were consistent with AGEP. This was attributed to coalescent pustulation, resulting in denudation. On the other hand, other patients had subcorneal pustulation in association with erythema multiforme,<sup>(13,14)</sup> but not full-thickness epidermal necrosis, as in TEN. Commens and Fischer described a patient with carbamazepine-induced TEN with pustulation clinically, but the biopsy showed TEN without features of AGEP.<sup>(15)</sup> These case reports may very well share the

same disease process as our patient, though they are not histologically-proven due to sampling errors during biopsies. These past case reports and our patient may actually represent a different manifestation of cutaneous drug eruption – AGEP/TEN overlap. This may be mediated by a unique drug-specific subset of T-cells in a susceptible host, which is capable of activating the Fas/FasL and TNF $\alpha$  pathways, as well as producing IL-8 at the same time in a single drug exposure.

The AGEP and SJS/TEN spectrums of severe drug reactions are believed to have distinct underlying pathogeneses. Our patient represents the first known reported case of clinically-consistent and histologically-proven AGEP/TEN overlap in the English literature. Past similar case reports and our patient may actually represent a new manifestation of cutaneous adverse drug reaction – TEN/AGEP overlap. More studies will be required to further characterise the clinical course and the underlying pathogenesis of this overlap manifestation.

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