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Two cases of pustular toxic epidermal necrolysis

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Summary

Toxic epidermal necrolysis (TEN) is a life-threatening, immune-mediated reaction, characterized by severe cutaneous and mucosal blisters and erosions. It often presents with flu-like symptoms, followed by a maculopapular, urticarial, purpuric or erythema multiforme-like eruption, which then evolves into blisters and sheet-like erosions. Presentation with pustules, however, is not well described in the English literature, and may lead to delayed diagnosis. We present two unusual cases of TEN that initially presented with pustular lesions.

Toxic epidermal necrolysis (TEN) is a life threatening immune-mediated reaction, characterized by extensive cutaneous and mucosal blisters and erosions. We present two unusual cases of TEN that presented initially with pustules.

Report

Patient 1 was a 19-year-old woman, who was prescribed penicillin V for an upper respiratory tract infection. Twenty-four hours later, she developed widespread erythema and severe soreness of her vulva, lips and eyes, associated with vomiting, shivering and malaise. She had no relevant medical history, and her only medication was the combined oral contraceptive pill. On admission she was febrile and tachycardic, with a widespread macular–papular erythema covering her face, trunk, upper arms and thighs. She also had small pustules on her trunk and limbs, with larger pustules on her face and neck (Fig. 1a). There were blisters and erosions on the lips with marked oral sloughing, and the conjunctivae were injected. The presence of pustules suggested a diagnosis of acute generalized exanthematous pustulosis (AGEP); however, the mucosal involvement was more suggestive of Stevens–Johnson syndrome (SJS). On histological examination of a biopsy, a lichenoid reaction pattern was seen at the dermo-epidermal junction, comprising a mild infiltrate of lymphocytes and a predominance of neutrophils. Epidermal spongiosis and subepidermal vesicles were noted, with an intact epidermal roof and no necrosis (Fig. 1b). The histologist commented that the neutrophilic predominance was unusual but the biopsy was keeping with erythema multiforme (EM). By day 2, the patient had developed numerous blisters on her face, trunk and limbs, affecting 20% of the body surface area (BSA), consistent with a progression towards TEN. Nikolsky sign was positive. A repeat biopsy was taken, and extensive full-thickness epidermal keratinocyte necrosis was seen, typical of TEN (Fig. 1d). Intravenous immunoglobulin (IVIg) 1 g/kg/day was given for 5 days, and the patient was transferred to the regional specialist intensive care unit. Subsequently, sheet-like erosions covered > 80% BSA (Fig. 1c), associated with severe vulval, oral and ocular mucosal erosions. The skin lesions re-epithelialized without any scarring or adhesions, and on day 23 the patient was discharged.

Patient 2 was a 50-year-old man with known metastatic deposits of rhabdomyosarcoma within his lungs. He was admitted with dyspnoea, fever and a 7-day history of a pruritic, erythematous eruption in his

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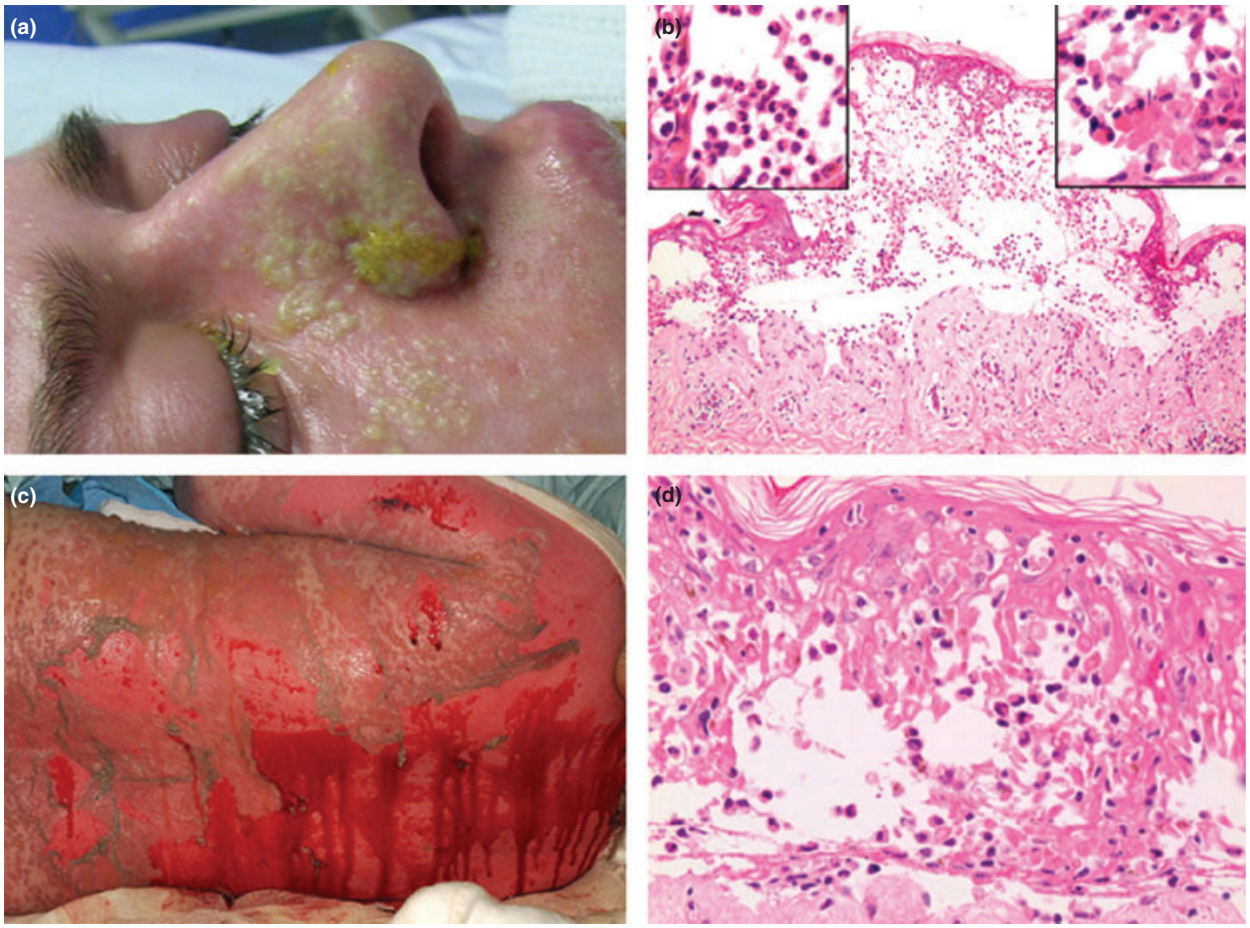

Figure 1 Patient 1. (a) Erythema studded with pustules on the face. (b) Intra-epidermal vesiculation and subepidermal blister with light perivascular lymphocytic infiltrate. Insets highlight abundant neutrophils (left) with occasional apoptotic keratinocytes (right). Haematoxylin and eosin, original magnification × 100 (insets × 400). (c) Sheet-like erosions on the back exposing a bleeding dermis. (d) Fresh frozen section confirming extensive cell necrosis of individual keratinocytes, typical of toxic epidermal necrolysis (haematoxylin and eosin, original magnification × 400).

groins, which had spread to his axillae, abdomen and neck on the day of admission. He had been started on levofloxacin and augmentin 9 days previously for a presumed chest infection. Within the erythematous area, numerous pustules developed (Fig. 2a), suggesting a diagnosis of AGEP. Histological examination of a biopsy taken from an area of pustulation found intra-epidermal and subcorneal pustules with accompanying pustular spongiosis consistent with AGEP (Fig. 2b). The antibiotics were altered, and supportive measures for the skin were started. At review on day 2, the clinical picture was found to have altered considerably, with blisters appearing around the neck, abdomen and back (Fig. 2c). Nikolsky sign was positive, and clinically the condition now appeared to be TEN. The patient was started on IVIg 1 g/kg/day for 5 days. On transfer to the regional intensive care unit, 95% of the patient's BSA was erythematous, with 33% blistering. No mucosal involvement occurred. Examination of a subsequent biopsy confirmed the diagnosis of TEN with full thickness epidermal necrosis (Fig. 2d). Despite a stormy disease course, the patient gradually improved and went home 28 days later.

TEN is characterized by skin and mucosal blisters and erosions covering > 30% of the body surface. Blisters are often preceded by an erythematous, urticated, purpuric or EM-like rash.[1] Presentation with pustules, however, is not well described, and may lead to a delay in diagnosing TEN if physicians are not aware that pustules can occur. There is only one previous case in the English literature where pustules are described in a patient with TEN;[2] however, they occurred in conjunction with, rather than preceding the erosions. In a French review, two cases of TEN were presented, with

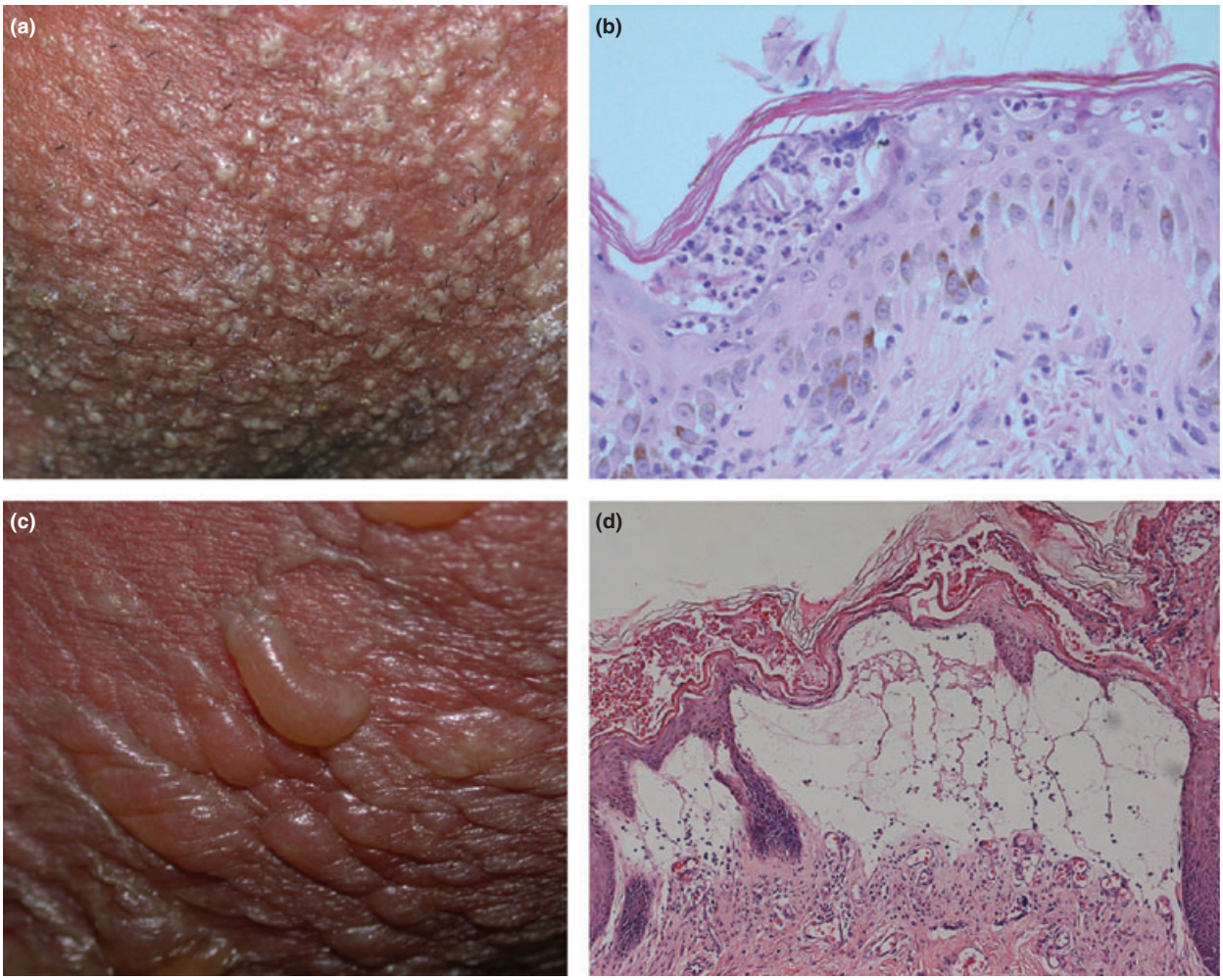

Figure 2 Patient 2. (a) Multiple pustules with an erythematous background on the neck. (b) Intraepidermal and subcorneal pustules (haematoxylin and eosin, original magnification × 400). (c) Blisters on the flank 24 h later. (d) Full-thickness epidermal necrosis (haematoxylin and eosin, original magnification × 100).

features suggestive of pustular psoriasis.[3] A report in a Dutch journal described a patient with clinical and histological features of both TEN and AGEP.[4] It is possible that pustules may have occurred in other patients with TEN but they may have gone unrecognized or unreported, particularly if they are an early phenomenon.

Recent work on the immunological mechanism of TEN and AGEP suggests that there is some similarity in their pathogenesis.[5] In TEN, keratinocyte death is probably caused by two main mechanisms. Firstly, CD8+ lymphocytes release perforin and granzyme B, which, after forming a pore in the keratinocyte membrane, promote apoptosis. Secondly, soluble Fas ligand, a member of the tumour necrosis factor family, is thought to mediate apoptosis via Fas receptors expressed on keratinocyte cell membranes. A study of five patients with AGEP found that keratinocytes were also destroyed by perforin/granzyme B and to a variable degree Fas ligand-mediated mechanisms were also involved.[6] Cellular destruction leads to formation of subcorneal vesicles, which later become pustules, after the release of interleukin-8 by CD4+ cells stimulates the influx of neutrophils.

Work to elucidate the mechanisms of pustular and bullous drug eruptions may help to explain why there is sometimes clinical and histological overlap in drug-mediated reactions, and should help to develop future therapeutic options. It may be that the clinical and histological pattern of a drug reaction is determined by the balance between various cytokine pathways. We feel it is important for clinicians to be aware of the

clinical and histopathological overlap between disparate adverse cutaneous reactions to anticipate the appropriate treatments for such rapidly progressive and potentially fatal eruptions.

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