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Clinical and Experimental Dermatology 1996; 21: 293–295.

Toxic pustuloderma associated with clemastine therapy

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Accepted for publication 21 *June* 1996

Summary

Toxic pustuloderma is an acute pustular eruption of the skin occurring a few days after the initiation of treatment with the responsible drug. A case of toxic pustuloderma following treatment with the antihistamine clemastine is now reported.

Generalized pustulation is the clinical expression of various diseases, while acute and transient pustular erythema may occur following exposure to drugs. MacMillan *et al.* first described this condition in 1973[1] and Staughton *et al.*[2] designated it as 'toxic pustuloderma'. The acute pustulation and erythema of the disorder may be complicated by the features of vasculitis and the condition is a distinct entity, the acute and transient course being strikingly different from the more chronic dynamics of generalized pustular psoriasis and Sneddon–Wilkinson disease.[3,4] Toxic pustuloderma has been reported most commonly following treatment with doxycycline, amoxycillin and carbamazepine.[5,6]

Clemastine is an antihistamine which may occasionally induce cutaneous adverse effects, predominantly as an acute exanthem. Generalized clinical features such as severe fatigue, attacks of severe sweating and diarrhoea have also been described.[7,8] In this communication a patient demonstrating toxic pustuloderma following treatment with clemastine is described.

Case report

A 41-year-old man presented with a 10-year history of eczema affecting the hands and antecubital fossae. Previous and family history did not suggest the presence of atopic dermatitis or psoriasis. Epicutaneous patch tests were negative, the serum IgE was 13 U/ml and there was no eosinophilia. The patient had just taken a 6-day course of the antihistamine clemastine at a dose of 1 mg/day for his eczema; he then stopped the clemastine after consulting his family doctor because of deterioriation of his condition. He had not been on any other medication for at least 3 months previously. Two days after discontinuing the treatment, he was seen by a dermatologist with a pustular, non-confluent eruption, along with malaise, nausea, diarrhoea and pyrexia. Two days later again, he

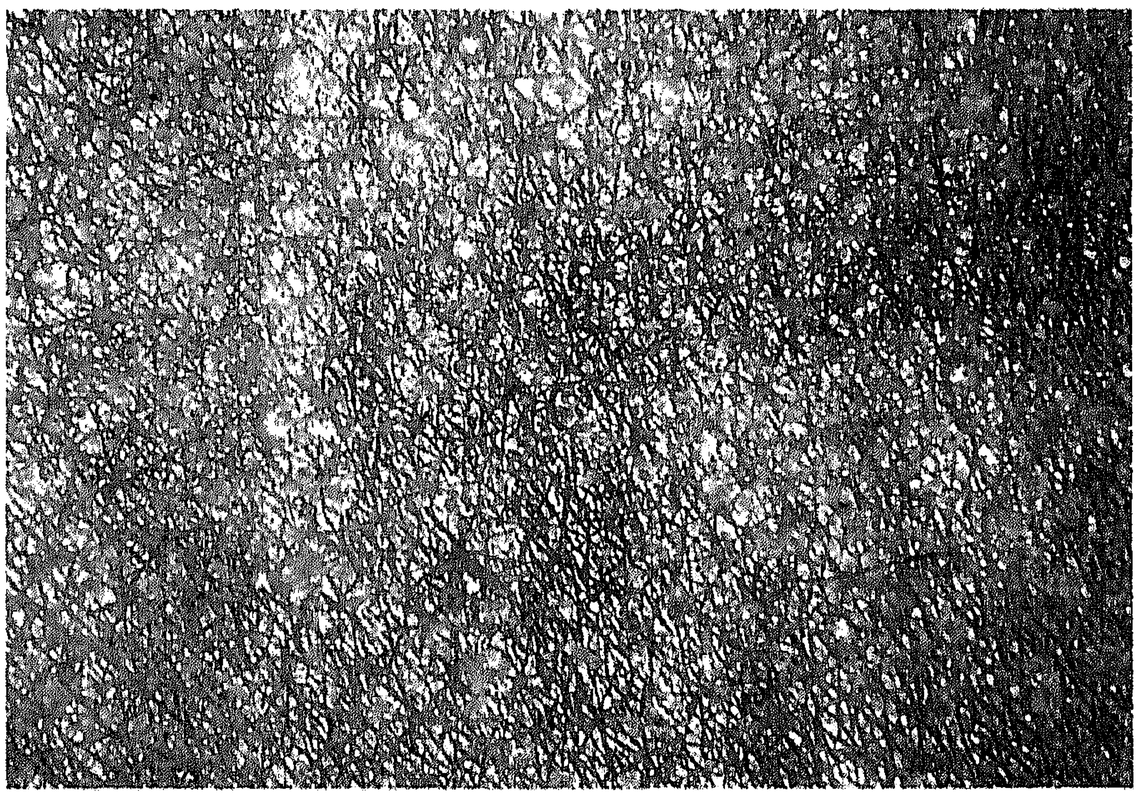

Figure 1. Several pin-head pustules arising within an area of widespread erythema.

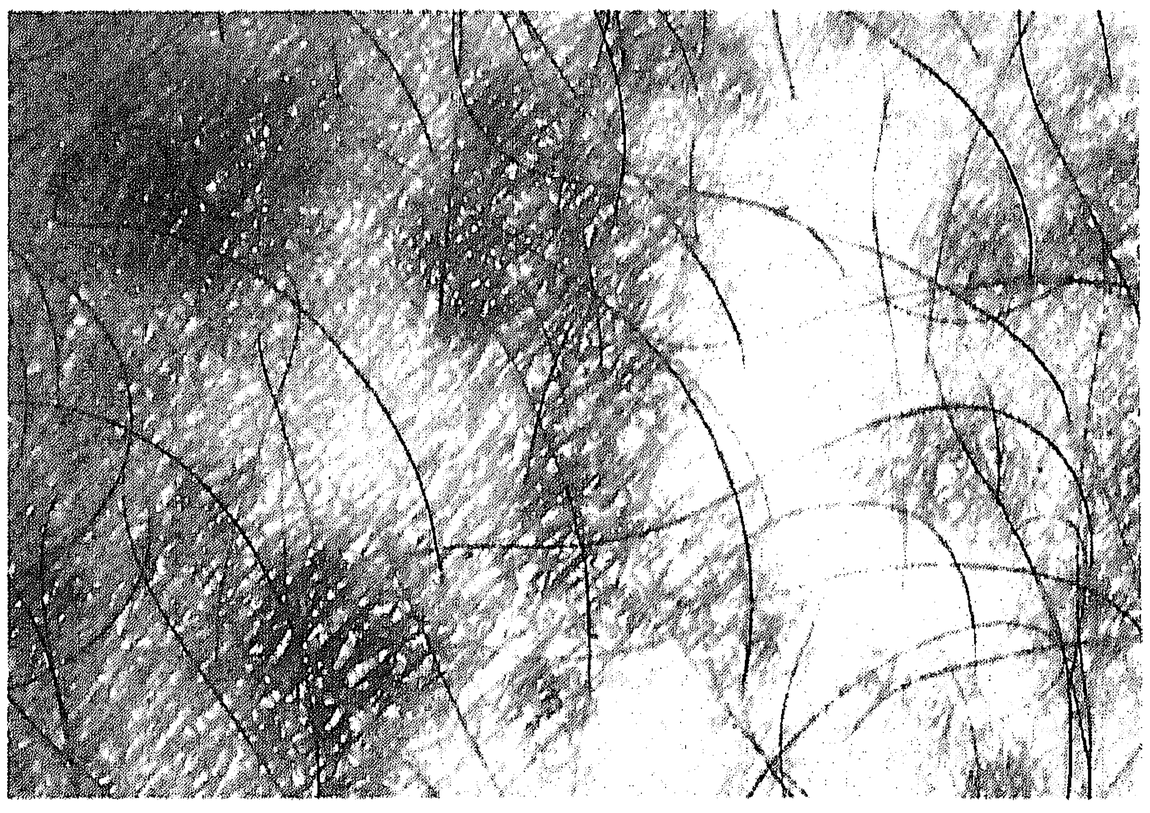

Figure 2. Spongiform pustule with a mixed infiltrate of neutrophils and eosinophils (H&E, ×200).

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Table 1. Dermatoses characterized by pustulation

Sneddon–Wilkinson subcorneal pustular dermatosis
Acute pustular psoriasis (von Zumbusch type)
Pustulosis palmaris et plantaris (Andrews type)
Acute generalized pustular bacteride
Subcorneal pustules of erythema multiforme
Subcorneal pustules of Sweet's syndrome
Impetigo herpetiformis

was admitted in very ill condition to our in-patient department with a fever of 39·5°C.

Over the face, neck, trunk and upper extremities there was a sharply demarcated erythema with numerous non-follicular, partly confluent, pinhead-sized pustules (Fig. 1). On the lower extremities the same picture was complicated by petechiae. Ill-defined erythema with crusts and pustulation was observed on the palms and volar and interdigital aspects of the fingers. The nails and mucous membranes were normal. No enlargement of tonsils or pharyngeal lymph nodes was observed. Laboratory examination revealed a leucocytosis of 14×10^9/l with 98% neutrophils and an erythrocyte sedimentation rate of 3 mm/h. Blood cultures were negative; however, culture of a pustule revealed a mild growth of group G *Streptococci* and *Staphylococcus aureus*, considered unlikely nevertheless to have a causal role in his generalized skin eruption.

Histopathological examination of a 4-mm punch biopsy from the skin of the thigh revealed a partly spongiotic epidermis with some intraepidermal pustules containing both eosinophils and neutrophils (Fig. 2); no acanthosis or enlargement of the rete ridges was observed. The papillary dermis was oedematous and a mixed inflammatory infiltrate of mainly lymphocytes, histiocytes and eosinophils around dermal blood vessels was seen, with some perivascular neutrophils and diapedesis of red blood cells. Prednisone was then prescribed at a dosage of 40 mg/day for 4 days; the eruption subsided within 1 week without scarring. Six months after the cutaneous reaction to clemastine, no relapse had occurred. After 4 months, epicutaneous and intracutaneous testing was carried out. The epicutaneous test was negative, but intracutaneous testing with 0·2 ml

Table 2. Drugs which may induce toxic pustuloderma

Drug classes	Drug	Reference
Analgesics	Acetaminophen, Naproxen	9, 15
	Phenylbutazone	16
Antibiotics	Amoxycillin, Ampicillin	9–18, 19
	Cephalexin, Cefazolin	21, 22
	Cephradine, Ceftazidime	23, 28
	Cefuroxime, Chloramphenicol	28, 1
	Clindamycin, Cotrimoxazole	28, 24
	Doxycycline, Erythromycin	6–9, 9
	Gentamicin, Imipinem	28, 25
	Norfloxacin, Pristinamycin	29, 9
	Penicillin, Josamycin	9–28, 27
	Metronidazole, Isoniazid	28, 26
	Rovamycin, Spiramycin	32, 9
	Roxithromycin, Vancomycin	9, 9–28
	Trimethoprim	26
	Pipemidic acid	9
Antiepileptics	Carbamazepine	9, 30–31
	Phenytoin	33
Antidiabetic	Carbutamide	9
Anthelminthic	Piperazine	1
Antihypertensives	Nifedipine, Diltiazem	9, 34
Diuretic	Frusemide	1
Antimalarials	Hydroxychloroquine, Pyrimethamine	32–35, 1
Carbonic anhydrase inhibitor	Acetazolamide	20
Expectorant	Eprazinone	36
Glucocorticoid	Prednisolone	17
Sympathicomimetic	Buphenine	37
Tranquillizer	Clobazam	9
Others	Bufexamac, Disulfiram	9, 37
	Nadoxolol, 8-Methoxypsoralen	9, 38

Adapted from Süss and Korting.[5]

of clemastine (1 mg/ml) in the right ventral forearm with a control of 0·2 ml saline in the left forearm produced a weal and flare reaction with a weal diameter of 28·0 mm at 10 min persisting for more than 24 h; no pustules developed. Seven healthy control subjects were tested similarly, weal size being less in them at 10·5 to 16·0 mm (mean 13·6 mm); however, the specificity of the positive provocation test in our patient is clearly not absolutely certain.

Discussion

Various dermatoses are characterized by pustulation (Table 1). Within the spectrum of such dermatoses, toxic pustuloderma has unique characteristics: (i) the time relationship between administration of the drug and the appearance of the eruption;[8] (ii) the acute onset of the disorder with malaise and fever; (iii) the presence of spongiform superficial pustules, papillary oedema and a polymorphous perivascular infiltrate with numerous eosinophils, also present in the epidermis; (iv) signs of vasculitis;[10,11] (v) the absence of comedones;[12] and (vi) negative bacterial and viral cultures.[13]

Recently a variety of drugs have been reported to cause generalized pustular drug rashes (Table 2), and the variability of the drug classes which may cause the condition suggests that a common pathway is likely to be responsible for this reaction pattern. The patient described in this report developed the disorder following clemastine therapy. Although we have not been able to prove a definite causal association, we feel that it is likely that the drug precipitated the condition. The pathogenesis might be either a drug-specific immune response, or else a non-immunological process.[14]

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