Dermatology

Editorials

Dermatologische Zeitschrift Dermatologica–Dermatology: A Centenary 1893–1993 1
Holubar, K. (Vienna)

In vivo Confocal Microscopy: A New Paradigm in Dermatology 4
Piérard, G.E. (Liège)

Comment

Clinical Investigation of Skin Microcirculation 6
Bongard, O.; Bounameaux, H. (Geneva)

Clinical and Laboratory Investigations

Cutaneous Malignant Melanomas with Other Coexisting Neoplasms: A True Association? 12
Schallreuter, K.U.; Levenig, Ch.; Berger, J. (Hamburg)

Comparison of the Pathology of Fascia in Eosinophilic Myalgia Syndrome Patients and Idiopathic Eosinophilic Fasciitis 18
Umbert, I.; Winkelmann, R.K.; Wegener, L. (Scottsdale, Ariz.)

Severity Scoring of Atopic Dermatitis: The SCORAD Index. Consensus Report of the European Task Force on Atopic Dermatitis 23
European Task Force on Atopic Dermatits (Bordeaux)

Evolving Pattern of Drug-Induced Toxic Epidermal Necrolysis 32
Correia, O.; Chosidow, O.; Saiag, Ph.; Bastuji-Garin, S.; Revuz, J.; Roujeau, J.-C. (Créteil)

Effects of All-Trans-Retinoic Acid on Melanocyte Adhesion and Motility 38
Situ, R.; Inman, D.R.; Fligiel, S.E.G.; Varani, J. (Ann Arbor, Mich./Allen Park, Mich.)

Soluble CD14 Monocyte Antigen in Suction Blister Fluid and Serum of Patients with Psoriasis 45
Schopf, R.E.; Dobmeyer, J.; Dobmeyer, Th.; Morsches, B. (Mainz)

In vivo Vision of the Human Skin with the Tandem Scanning Microscope 50
Corcuff, P.; Lévêque, J.-L. (Aulnay-sous-Bois)

Pharmacology and Treatment

Azelaic Acid Has Antimycotic Properties in vitro 55
Brasch, J.; Christophers, E. (Kiel)

Onychomycosis: Successful Treatment with Once-Weekly Fluconazole 59
Nahass, G.T.; Sisto, M. (Miami, Fla.)

Therapeutic Efficacy of Oral Low-Dose Cyclosporin A in Severe Psoriatic Arthritis 62
Wagner, S.A.; Peter, R.U.; Adam, O.; Ruzicka, T. (Munich)

Case Reports

Epidermolysis bullosa simplex Dowling-Meara: Troublesome Blistering and Pruritus in an Adult Patient 68
McGrath, J.A.; Burrows, N.P.; Jones, R.R.; Eady, R.A.J. (London)

Primary Infection by Human Parvovirus B19 72
Veraldi, S.; Rizzitelli, G.; Lunghi, G.; Cardone, R. (Milano)

Acute Generalized Exanthematous Pustulosis due to Doxycycline 75
Trüeb, R.M.; Burg, G. (Zürich)

Letters to Dermatology

Topical Podophyllotoxin in Psoriasis vulgaris 79
Wantke, F.; Fleischl, G.; Götz, M.; Jarisch, R. (Vienna)

Positive Response to 5HT-2 Antagonists in a Family Affected by Epidermolysis bullosa Dowling-Meara Type 80
Tadini, G.; Ermacora, E.; Cambiaghi, S.; Brusasco, A.; Cavalli, R. (Milan)

ISSN 1018–8665
DERAEG
186(1) 1–80 (1993)

S. Karger
Medical and Scientific
Publishers

KARGER

Case Report

Dermatology 1993;186:75–78

R.M. Trüeb
G. Burg

Department of Dermatology,
University Hospital, Zurich, Switzerland

Acute Generalized Exanthematous Pustulosis due to Doxycycline

Key Words
Pustular drug rash
Lymphocyte transformation test
Rechallenge
Allergy to doxycycline

Abstract
Sterile epidermal neutrophilic pustulation can be observed in a variety of diseases. Though drug hypersensitivity is an uncommon cause, it is yet a known entity to be considered in the differential diagnosis of generalized pustulosis. In a 40-year-old woman, who developed a generalized pustular eruption after starting on doxycycline therapy of bronchitis, the rash was concluded to be drug induced after exclusion of other pustular dermatoses. Sensitization to doxycycline was demonstrated by in vitro lymphocyte testing and correlated with clinical drug hypersensitivity after recurrence of the pustular eruption on nonintentional rechallenge with doxycycline.

Pustular eruption is an uncommon manifestation of drug sensitivity [1]. A variety of dermatoses presenting with sterile epidermal neutrophilic pustulation must be considered in its differential diagnosis. Toxic pustuloderma [2, 3] has been delineated as a clinical entity characterized by a single self-limiting pustular eruption and some degree of a vasculitic reaction pattern [4, 5]. It is most frequently precipitated by drugs, in particular antimicrobials [6, 7]. The pathogenesis of toxic pustuloderma has remained subject to speculation. A severe form of toxic erythema has been proposed [3], also a reaction pattern favored by a psoriatic background has been suggested, though clinically and histologically different from pustular psoriasis [7]. We report a case in which drug allergy to doxycycline could be demonstrated by lymphocyte transformation testing.

Case Report

A 40-year-old woman suffering from allergic bronchial asthma was treated with doxycycline prior to the development of a pruritic erythematous rash, beginning in the flexural areas of the groin and elbows to subsequently spread over the trunk and limbs with a pustular eruption. Other medication at the time included acetylsalicylic acid, acetaminophen, N-acetylcystein, theophylline and salbutamol. She had neither a personal nor a familial history of any other skin disease. On admission to the hospital in June 1990 she exhibited a widespread patchy erythematopapular rash superimposed with several superficial pinhead-sized nonfollicular pustules (fig. 1).

The white cell count at the time was 11,200/mm^3 with 84% neutrophils, the erythrocyte sedimentation rate was 28 mm/h. Blood chemistry was within normal limits. Cultures repeatedly taken from pustular lesions showed negative findings for bacterial or fungal organisms.

Skin biopsy revealed subcorneal pustules with neutrophils and a perivascular infiltrate in the superficial dermis composed of polymor-

Received:

Dr. R.M. Trüeb

phonuclear cells and lymphocytes (fig. 2). Direct immunofluorescence testing did not demonstrate any immunoglobulin or complement deposits in the skin or vessel walls.

Patch-scratch testing was performed failing to reveal any hypersensitivity reaction to the implicated medicaments. A lymphocyte transformation test performed with doxycycline and acetylsalicylic acid in the Institute of Clinical Immunology of the University of Berne (director: Prof. Dr. A.L. de Weck) by Prof. Dr. W.J. Pichler demonstrated sensitization to doxycycline by a stimulation index of 13, whereas a stimulation index of up to 2 can be regarded as nonsignificant in regard to drug-specific hypersensitivity [pers. commun. of Prof. Dr. W.J. Pichler].

All previous medication was stopped and prednisone administered at a dose of 40 mg daily. Within few days the rash cleared with subsequent desquamation of the affected skin. In March 1991 the patient presented again with recurrence of the generalized pustular eruption after accidental ingestion of doxycycline. Other medication included theophylline, salbutamol and levomepromazine. After withdrawal of doxycycline and a short course of oral prednisone the pustular exanthema resolved within a week. There has been no recurrence since then.

Discussion

There is a variety of dermatoses presenting with generalized sterile epidermal neutrophilic pustulation. It is not an uncommon event. Any infectious cause of the pustules must first be excluded. Pustular eruption is a rather unusual manifestation of drug sensitivity [1], yet a known entity [7] to be considered. Its diagnosis is based on the temporal relationship incriminating the presumed causative agent, an often strikingly short intervall between administration of the drug and the skin reaction [7], and on the exclusion of other pustular dermatoses (table 1). Among drug-induced pustular dermatoses the acneiform eruptions (e.g. halogen acne) must be differentiated from nonfollicular pustuloderma.

In 1984, Staughton et al. [2] delineated toxic pustuloderma as a new entity comprising a self-limiting syndrome presenting with an erythematous and pustular eruption associated with fever, peripheral blood leukocytosis and subcorneal pustules. The eruption is more frequently precipitated by drugs [1–3, 6–19], although other causative agents [3, 7, 12, 17] have been incriminated (table 2).

Three histological patterns to drug-induced pustular eruptions have recently been described: (a) one indistinguishable from the changes in Sweet's syndrome, (b) leukocytoclastic vasculitis and (c) the subcorneal polymorphonuclear microabscesses and upper dermal perivascular infiltrate composed of lymphocytes and neutrophils of toxic pustuloderma. It has been suggested to possibly consider these changes as a continuous spectrum in which neutro-

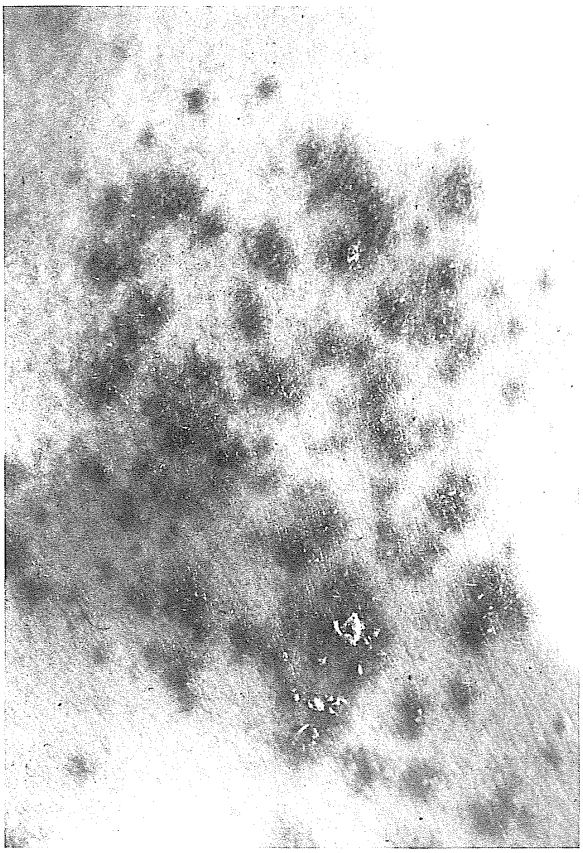

Fig. 1. Generalized exanthematous pustulosis: superficial pinhead-sized nonfollicular pustules superimposed on a background of patchy erythema.

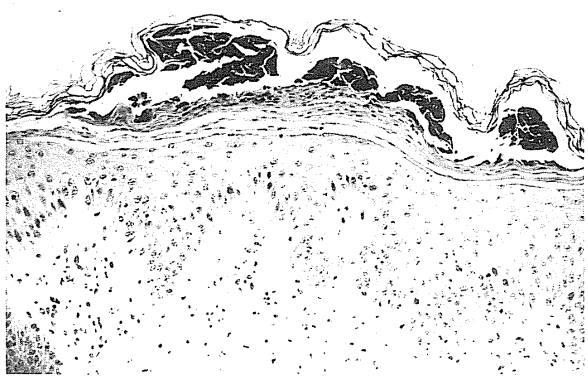

Fig. 2. Histologic features of acute generalized exanthematous pustulosis: subcorneal pustule with polymorphonuclear leukocytes. Hematoxylin-eosin. ×200.

Table 1. Differential diagnosis of acute generalized exanthematous pustulosis

Subcorneal pustular dermatosis
Generalized pustular psoriasis
Impetigo herpetiformis
Pustulosis acuta generalisata
Pustular necrotizing angitis
Pustular erythema multiforme
Intraepidermal immunoglobulin A pustulosis

Table 2. Causative agents in acute generalized exanthematous pustulosis

Cause	Reference
Drugs	
Acetaminophen	7
Acetazolamide	16
Amoxicillin	6, 7
Ampicillin	7
Bufexamac	7
Carbamazepine	2, 7
Carbutamide	7
Cefaclor	16
Cefazoline	13
Cefradine	10
Cefuroxime	3
Cephalexin	12
Chloramphenicol	1
Clobazam	7
Cyclines	7, 11
Diltiazem	14
Erythromycin	7
Furosemide	1
Hydroxychloroquine	15
Nifedipine	7
Penicillin	7
Phenytoin	8
Pipemidic acid	7
Piperazine	1
Pristinamycin	7
Pyrimethamine	1
Quinidine	7
Roxithromycin	7
Spiramycin	7
Streptomycin	9
Sulbutiamine	7
Vancomycin	7
Other causes	
Viral infection	7, 17
Mercury	7
Food poisoning	3

phils collect around the dermal blood vessels, form subepidermal pustules and are then eliminated transepidermically [5].

The clinical identification of adverse drug reactions is largely based on subjective criteria [18]. Direct challenge provides the most definitive information on the relationship of a suspected drug to a given clinical syndrome but is usually not justified because of the potential morbidity involved. After implicating the causative agent, the clinician dealing with a drug reaction is faced with three issues: (1) immunologic versus nonimmunologic origin of the drug reaction, (2) detection of the responsible one of multiple drugs in case of an immunologic drug reaction, (3) risk of eliciting an allergic reaction to readministration of the drug [18]. To prove the immunologic origin of a given drug reaction, an immune response to the drug and a similar drug-initiated clinical reaction must be demonstrated. Because of the aforementioned difficulties associated with readministration of suspected drug allergens, in vitro tests have been devised to demonstrate a drug-specific immune response [20]. To detect drug-specific cellular immune response in drug hypersensitivity states, delayed tuberculin-type skin testing and the lymphocyte transformation test [21] have been used. The former is however of limited value with a possible risk of reexposing the sensitized patient to antigen, whereas with the latter in most instances it has not been possible to correlate the cell-mediated responses with clinical drug hypersensitivity. In our case the lymphocyte transformation test disclosed sensitization to doxycycline. Nonintentional rechallenge with doxycycline occurred. Recurrence of the rash on this occasion permitted the most clear-cut correlation of the in vitro demonstrated cell-mediated immune response with clinical hypersensitivity to doxycycline. We believe this has demonstrated a drug-specific cell-mediated immune response as causative in our case of an acute generalized exanthematous pustulosis.

References

1 Macmillan AL: Generalized pustular drug rash. Dermatologica 1973;146:285–291.
2 Staughton RCD, Rowland Payne CME, Harper JI, McMichen H: Toxic pustuloderma – A new entity? J R Soc Med 1984;77(suppl 4):6–8.
3 Rustin MHA, Robinson TWE, Dowd PH: Toxic pustuloderma: A self-limiting eruption. Br J Dermatol 1990;123:119–124.
4 Beylot C, Bioulac P, Doutre MS: Pustuloses exanthématiques aigües généralisées. Ann Dermatol Vénéréol 1980;107:37–48.
5 Burrows NP, Jones RR: Pustular drug eruptions: A histopathological spectrum. In press.
6 Armster H, Schwarz Th: Arzneimittelreaktion auf Amoxicillin unter dem Bild eines toxischen Pustuloderms. Hautarzt 1991;11:713–716.
7 Roujeau JC, Bioulac-Sage P, Bourseau C, Guillaume JC, Bernard P, Lok C, Plantin P, Claudy A, Delavierre C, Vaillard L, Wechsler J, Danan G, Bémichou C, Beylot C: Acute generalized exanthematous pustulosis. Analysis of 63 cases. Arch Dermatol 1991;127:1333–1338.
8 Stanley J, Fallon-Pellici V: Phenytoin hypersensitivity reaction. Arch Dermatol 1978;114:1350–1353.
9 Kushimoto H, Anoki T: Toxic erythema with generalized follicular pustules caused by streptomycin. Arch Dermatol 1981;117:444–445.
10 Kalb R, Grossman ME: Pustular eruption following administration of cephradine. Cutis 1986;38:58–60.
11 Delavierre C, Milpied B, Bureau B, Litoux P: Les pustuloses exanthématiques aiguës généralisées: À propos de 5 cas. Sémin Hôp Paris 1988;64:365–367.
12 Jackson H, Vion B, Levy PM: Generalized eruptive pustular drug rash due to cephalexin. Dermatologica 1988;177:292–294.
13 Fayol J, Bernard P, Bonnetblanc JM: Pustular eruption following administration of cefazolin: A second case report. J Am Acad Dermatol 1988;19:571.
14 Lambert DG, Dalac S, Beer F, Chavannet P, Portier H: Acute generalized exanthematous pustular dermatitis induced by diltiazem (letter). Br J Dermatol 1988;118:308–309.
15 Lotem M, Ingber A, Segal R, Sandbank M: Generalized pustular drug rash induced by hydroxychloroquine. Acta Derm Venereol 1990;70:250–251.
16 Ogoshi M, Yamada Y, Tani M: Acute generalized exanthematic pustulosis induced by cefaclor and acetazolamide. Dermatology 1992;184:142–144.
17 Rouchouse B, Bonnefoy M, Pallot B, Jacquelin L, Dimoux-Dime G, Claudy AL: Acute generalized exanthematous pustular dermatitis and viral infection. Dermatologica 1986;173:180–184.
18 Wintroub BU, Stern RS, Arndt KA: Cutaneous reactions to drugs; in Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg I, Austen KF (eds): Dermatology in General Medicine. New York, McGraw-Hill International Book Co, 1986, pp 1353–1366.
19 Kramer MS: An algorithm for the operational assessment of adverse drug reactions. JAMA 1979;242:623.
20 Parker CW: Drug allergy. New Engl J Med 1975;292:511, 732, 957.
21 Rocklin RE: Clinical application of in vitro lymphocyte tests; in Schwartz RS (ed): Progress in Clinical Immunology. New York, Grune & Stratton, 1974, vol II, p 21.