



Drug-induced cutaneous pathology

P K Ramdial and D K Naidoo

J Clin Pathol 2009 62: 493-504 originally published online January 20, 2009
doi: 10.1136/jcp.2008.058289

Updated information and services can be found at:

<http://jcp.bmj.com/content/62/6/493.full.html>

These include:

References

This article cites 148 articles, 15 of which can be accessed free at:

<http://jcp.bmj.com/content/62/6/493.full.html#ref-list-1>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To order reprints of this article go to:

<http://jcp.bmj.com/cgi/reprintform>

To subscribe to *Journal of Clinical Pathology* go to:

<http://jcp.bmj.com/subscriptions>

Drug-induced cutaneous pathology

P K Ramdial,¹ D K Naidoo²

¹ Department of Anatomical Pathology, Nelson R Mandela School of Medicine, University of KwaZulu Natal and National Health Laboratory Service, Durban, KwaZulu Natal, South Africa; ² The Dermatology and Skin Care Institute, Durban, KwaZulu Natal, South Africa

Correspondence to:

Pratistadevi K Ramdial, Department of Anatomical Pathology, Level 3, Laboratory Building, Inkosi Albert Luthuli Central Hospital, 800 Bellair Road, Mayville, 4058, KwaZulu Natal, South Africa; ramdial@ukzn.ac.za

Accepted 7 January 2009
Published Online First
20 January 2009

ABSTRACT

Drug-induced cutaneous rashes, whether confined to the skin or part of a systemic disease, are characterised by a spectrum of inflammatory disease patterns that include perivascular dermatitis, nodular and diffuse dermatitis, vesiculobullous lesions, pustular eruptions, sclerodermoid reactions, vasculitis, folliculitis/perifolliculitis and panniculitis. While a single drug can elicit a range of reaction patterns, no reaction pattern is specific for a particular drug. Although the temporal link between initiation of drug therapy and the onset of the drug rash is critical to the diagnosis, drug reactions may also occur during the course of chronic drug ingestion. Clues to the drug-induced nature of the cutaneous eruption include the presence of overlapping histological reaction patterns and incongruent clinical and histopathological features. While eosinophils are an important tell-tale sign of a drug-induced reaction, they may also be conspicuous in skin rashes devoid of a drug association. Furthermore, eosinophils may be sparse or absent in some drug exanthems. Heightened awareness of the mimicry of a wide spectrum of cutaneous pathology by an ever-increasing range of therapeutic agents is pivotal to the diagnosis of drug-induced skin pathology.

The incidence of cutaneous adverse drug-induced reactions (CADRs) ranges from 2% to 5% of hospitalised patients suffering fatal disease.¹ Occurring more frequently in women, the incidence of CADRs increases with advancing age, the number of drugs being used, and concomitant HIV infection and other immunosuppressive states.^{2–3} The aetiology of CADRs may be immunological, encompassing all of the Gell and Coombs immune mechanisms, or non-immunological.^{4–5} CADRs may be confined to the skin or may be part of a systemic reaction. In this review, the histopathological reaction patterns of some common CADRs are described in association with their clinical presentation (box 1).

PREDOMINANTLY PERIVASCULAR DERMATITIS

Superficial perivascular dermatitis

Pigmented purpuric dermatoses

Pigmented purpuric dermatoses (PPDs) comprise asymptomatic to mildly pruritic pigmented lesions, with distinct clinical and histological findings.⁶ Although the aetiopathogenesis is unknown, steroids, antihistaminics, griseofulvin, ciclosporin, systemic steroids, psoralens, carbromal, carbutamide, meprobamate, glipizide, acetaminophen, zomepirac sodium, interferon α , diuretics, chlorthalidopoxide and aminoglutethimide are implicated in a minority of cases.^{3–7–9} A cell-mediated immune reaction has been proposed as the pathomechanism.^{7–10} Drugs that precipitate PPD act as haptens, leading to the formation of antibody-antigen

complexes that deposit in the endothelium causing vascular disruption.^{11–12} PPDs are characterised by solitary or multiple macules, papules, plaques or annular purpuric lesions, which are initially red-brown and subsequently golden yellow in colour.^{9–12} These lesions are typified by punctate petechiae or “cayenne pepper spots”. The histopathological features are indistinguishable from idiopathic PPD, being characterised by a moderately dense, superficial, perivascular lymphocytic infiltrate with extravasated erythrocytes and variable haemosiderin deposition. Additional features include spongiosis, granulomatous and lichenoid reactions.

Mixed infiltrate

Urticarial drug reaction

Acute and chronic drug-induced immunological and non-immunological urticarial reactions are responsible for approximately 5% of all CADRs.⁴ The main drugs causing immunological reactions are penicillins, cephalosporins, sulfonamides, tetracyclines, tumour necrosis factor (TNF) inhibitors, antihistamines, ketoconazole, aminoglycosides, phenytoin, carbamazepine, captopril and non-steroidal anti-inflammatory drugs (NSAIDs), oral antihyperglycaemics and radiographic contrast agents.^{4–13–16} Viral infections or connective tissue diseases may induce or augment urticarial drug reactions.⁴ Clinically, urticarial CADRs manifest as pruritic, oedematous erythematous wheals (fig 1).^{5–15} Histologically, urticarial drug reactions are characterised by dermal oedema and a superficial and deep perivascular and interstitial dermatitis. The mixed inflammatory infiltrate comprises lymphocytes, histiocytes, mast cells, eosinophils and neutrophils (fig 1). The presence of neutrophils and deep vascular plexus involvement may be a clue to the drug-induced nature of the urticaria.³ While vessel involvement is usually subtle, vasculitis may occur.⁴

Spongiotic drug reaction

Pityriasis-rosea-like drug reaction

The clinical characteristics that distinguish idiopathic pityriasis of Gibert (pityriasis rosea) from the drug-induced form include the absence of a “herald” patch, variable fir-tree distribution, fever, eosinophilia, larger violet-red lesions with greater scaling, severe pruritus and rash persistence beyond 6–8 weeks.^{2–17} The offending drugs include gold salts, metronidazole, meprobamate, bismuth, ACE inhibitors, NSAIDs, barbiturates, clonidine, isotretinoin, terbinafine, imatinib mesylate, arsenicals, D-penicillamine, levamisole, omeprazole and acyclovir.^{2–17–18–21} The pathomechanisms differ among drugs but encompass induction of increased plasma and tissue levels of kinins, inhibition of cyclooxygenases by NSAIDs, tyrosine kinase inhibition

Box 1 Algorithmic histopathological approach to cutaneous adverse drug-induced reactions³⁻⁵**Predominantly perivascular dermatitis**

Superficial perivascular dermatitis

▶ Pigmented purpuric dermatoses

Mixed infiltrate

▶ Urticarial drug reaction

Spongiotic drug reaction

▶ Pityriasis-rosea-like drug reaction

▶ Photosensitive drug reaction

Psoriasiform drug reaction

Interface drug reaction

▶ Vacuolar interface drug reaction

– Erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis

– Chemotherapy-induced interface dermatitis

– Fixed drug eruption

– Exanthematous (morbilliform) drug reaction

– Lupus-erythematosus-like drug reaction

▶ Lichenoid interface drug reaction

Predominantly nodular and diffuse dermatitis

Pseudolymphomatous drug reaction

Interstitial granulomatous drug reaction

Drug-induced Sweet syndrome

Predominantly vesiculobullous drug reactions

Linear immunoglobulin A bullous-dermatosis-like drug eruption

Drug-induced pemphigus

Drug-induced bullous pemphigoid

Drug-induced pseudoporphyria cutanea tarda

Predominantly pustular drug reactions

Acute generalised exanthematous pustulosis

Halogenoderma

Predominantly vasculitic drug reactions**Predominantly follicular/perifollicular drug reactions**

Acneiform drug eruptions

Drug-induced eosinophilic pustular folliculitis

Predominantly sclerodermoid drug reaction**Predominantly drug-induced panniculitis**

of metabolic pathways by imatinib mesylate, and a dose-related non-immunological response.^{17 20 22} The histological features, similar to those of idiopathic pityriasis rosea, include papillary dermal oedema, erythrocyte extravasation, a superficial perivascular infiltrate of lymphocytes and histiocytes, mild epidermal hyperplasia, basal vacuolar change, focal spongiosis and parakeratotic mounds containing scattered necrotic keratinocytes (fig 2A).²⁰ Eosinophils may be a clue to the drug-induced basis of the eruption.^{3 4 20}

Photosensitive drug reaction

Phototoxicity refers to an immediate or delayed inflammatory reaction reflecting direct cellular damage produced by the photochemical reaction between a chemical photosensitiser and the appropriate radiation on the skin.^{4 23 24} A photoallergic reaction is a delayed hypersensitivity reaction and is independent of dose or duration of exposure.^{4 23} Photoallergic and phototoxic reactions occur mainly on sun-exposed skin.³ The clinical appearances encompass pruritic, eczematous, bullous or

lichenoid lesions. Antibiotics (sulfonamides, nalidixic acid, tetracyclines, penicillins), NSAIDs, antidepressants, anticonvulsants, antihistamines, antifungals, lipid lowering agents, β blockers, methyldopa, amiodarone, antihyperglycaemic agents, contraceptives and retinoids are the offending agents.^{3 4 23 24} The histopathological features of photoallergic reactions are similar to those of allergic contact dermatitis, demonstrating papillary dermal oedema, a superficial and deep perivascular lymphohistiocytic infiltrate, and variable numbers of eosinophils (fig 3A). Early lesions demonstrate epidermal spongiosis, and late lesions, epidermal hyperplasia and parakeratosis.^{4 5} Acute phototoxic reactions are characterised by perivascular neutrophils, lymphocytes and histiocytes around the superficial and deep vascular plexuses, and variable transepidermal keratinocyte apoptosis. Chronic phototoxic reactions demonstrate variable epidermal disorganisation, dyskeratosis, hyperkeratosis, hypergranulosis, acanthosis, atrophy, melanocyte hyperplasia and increased melanin pigment.^{5 23} The dermal alterations include telangiectasia, elastotic degeneration and the appearance of stellate myofibroblasts.^{4 5 23 24}

Psoriasiform drug reaction

Drugs may exacerbate pre-existing psoriasis, induce new lesions on clinically normal skin in patients with psoriasis, and precipitate psoriasis in individuals with or without a family history of psoriasis.^{4 25} The clinical spectrum includes limited or generalised erythematous plaques with thick, large, silvery scales (fig 4), erythroderma or pustular lesions.^{26 27} Drugs with a short latency period of <4 weeks include NSAIDs and terbinafine, those with an intermediate 4–12 week latency period include antimalarial agents and ACE inhibitors, and those with a long (>12 weeks) latency period include lithium and β blockers.⁴ A paradoxical adverse psoriasiform cutaneous reaction has been documented with interferon α and the anti-TNF agents infliximab and etanercept.²⁸ All interferons may exacerbate psoriasis, but only interferon α induces de novo psoriasis.²⁶ Histologically, there is psoriasiform epidermal hyperplasia, neutrophils within parakeratosis, diminution of the stratum granulosum, variable interface dermatitis, focal dyskeratosis and superficial perivascular lymphocytes, histiocytes and eosinophils (fig 4).^{4 27 28} A helpful feature distinguishing drug-induced from idiopathic psoriasis is the absence of the psoriasiform diathesis that comprises tortuous papillary dermal capillaries and related suprapapillary epidermal thinning.⁴

Interface drug reaction**Vacuolar interface drug reaction*****Erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis***

Controversy surrounds the inclusion of erythema multiforme (EM), Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) as variants within a continuous disease spectrum.²⁹ The clinical spectrum of EM, drug-induced in 20% of cases, is characterised by target or bull's eye lesions, macules, plaques, vesicles and bullae, mainly on the palms and soles but they may be widespread.^{1 4 29} The drugs implicated include carbamazepine, barbiturates, hydantoins, iohexol contrast media, penicillamine, phenobarbital, reverse transcriptase inhibitors, salicylates, penicillin, sulfonamides and tetracyclines.^{1 4 29} SJS is a more fulminant form of EM, with systemic involvement and severe mucosal erosions (fig 5A).^{1 4} TEN presents with an acute onset of generalised erythema followed by desquamation of >30% of the skin surface. Antituberculous

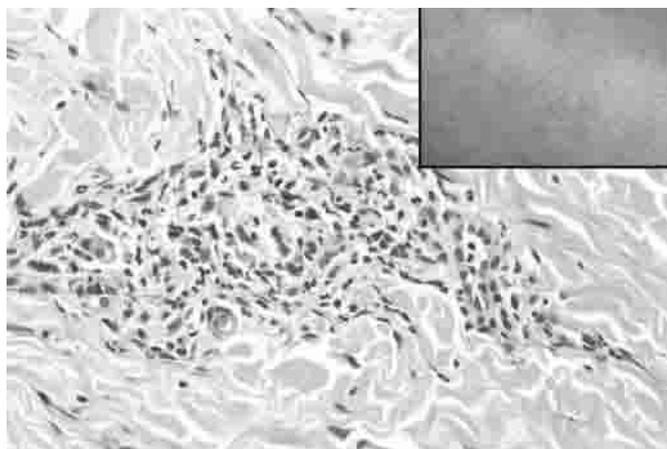


Figure 1 Captopril-induced urticaria with deep perivascular inflammation, including neutrophils. Inset: pruritic wheals.

drugs, trimethoprim–sulfamethoxazole, sulfonamides, tetracyclines, nitrofurantoin, hydantoin, allopurinol, NSAIDs, barbiturates, carbamazepine and phenylbutazone are the main offending drugs.^{1 4 29–31} The histopathology of early EM lesions is typified by a mild perivascular, mainly lymphohistiocytic, inflammatory infiltrate around the superficial vascular plexus, oedema and erythrocyte extravasation in the papillary dermis, basal and suprabasal keratinocyte necrosis, “streaked” dyskeratosis, and conspicuous vacuolar alteration and lymphocyte tagging at the dermo-epidermal junction (fig 5A). Late lesions demonstrate confluent epidermal necrosis, vacuolar alteration, subepidermal separation, intra-epidermal clefts, more intense inflammation and greater erythrocyte extravasation (fig 5B).^{1 4 5 29} Clues to the drug-induced aetiology include acrosyringeal concentration of keratinocyte necrosis and eosinophils within the dermal infiltrate.²⁹ In addition, TEN has distinctive dermal sweat duct alterations, including basal cell hyperplasia and vacuolopathy with variable lymphocytic infiltration, apoptosis, necrosis and loss.^{1 4 29} These abnormalities are predominantly in the distal duct and involve the proximal duct, in continuity, but to a lesser degree.³²

Chemotherapy-induced interface dermatitis

Common chemotherapy-induced reactions include keratinocyte apoptosis, alopecia and stomatitis.³³ Papular pruritic erythroderma (PPE) is a distinctive dose-dependent toxic reaction occurring in 60–64% of patients, associated mainly with cytarabine, docetaxel, 5-fluorouracil and doxorubicin.³⁴ Characterised by prodromal dysaesthesia and subsequent burning pain, swelling and symmetrical erythema mainly of the palms and soles, the pathogenesis includes increased thymidine phosphorylase levels in keratinocytes that result in accumulation of capecitabine metabolites.^{35 36} The excretion of cytotoxic drugs in eccrine units makes the palms and soles appropriate targets.³⁵ Whether PPE and hand–foot skin reaction (HFSR) are two distinct entities remains questionable.³ However, HFSR, induced by multikinase inhibitors sorafenib and sunitinib, tends to be more localised than PPE and has a greater tendency to blister formation and keratotic lesions.^{3 37 38} On histopathological examination there is interface dermatitis involving the epidermis, follicular and eccrine ducts and glandular epithelia with conspicuous maturation arrest, keratinocyte pleomorphism, striking dyskeratosis, variable acanthosis and basal layer hydropic degeneration (fig 6A–C).³³ Severity of

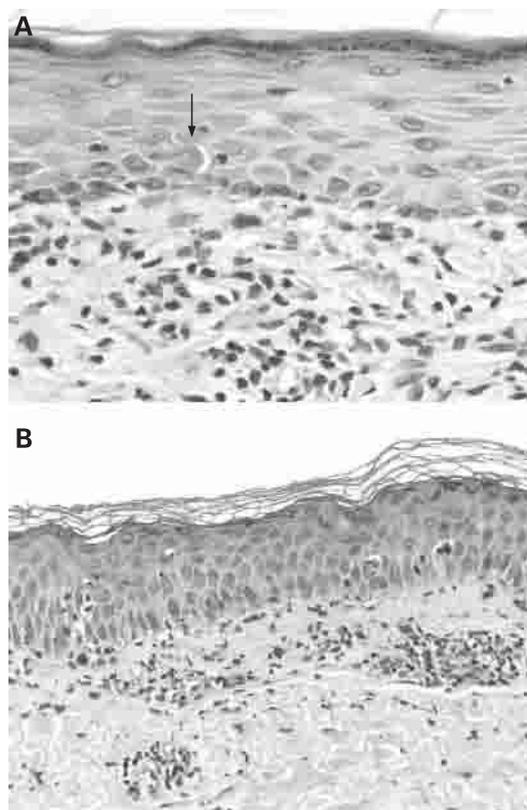


Figure 2 (A) Keratinocyte necrosis (arrow) and dermal perivascular inflammation. (B) Focal interface dermatitis and perivascular lymphocytes and eosinophils.

PPE is graded according to clinicopathological criteria (table 1).³⁴ Histologically, HFSR demonstrates intra-epidermal vesicle formation and intracytoplasmic eosinophilic bodies in necrotic keratinocytes.^{3 37 38}

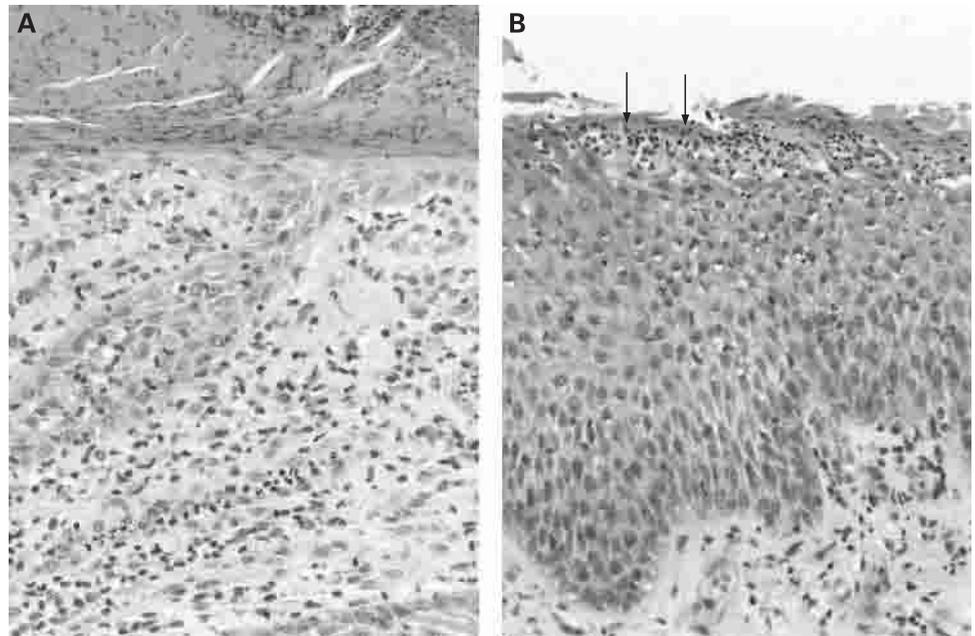
Fixed drug eruption

Fixed drug eruption (FDE) is characterised by the sudden onset of round and/or oval, oedematous, dusky-red macules and plaques on the skin and/or mucous membranes, accompanied by burning and/or itching and the re-appearance of the lesions over the previously affected area when the offending agent is re-used (fig 7).^{39 40} FDEs are caused by antibiotics (metronidazole, tetracyclines, penicillin, trimethoprim sulphamethoxazole, erythromycin, rifampicin, clarithromycin and fluoroquinolones), antifungals (griseofulvin, fluconazole, ketoconazole and terbinafine), analgesics (phenylbutazone, oxyphenbutazone, aspirin, ibuprofen, acetaminophen, naproxen, piroxicam, chlormezanone, celecoxib) and other agents (barbiturates, anticonvulsants, opium alkaloids, chlordiazepoxide, chloral hydrate, oxazepam and carbamazepine).^{3 4 39–45} Histologically, there is basal hydropic degeneration, pigmentary incontinence, upper epidermal keratinocyte necrosis, dermal oedema, vasodilatation and perivascular inflammatory cells (lymphocytes, neutrophils, histiocytes, mast cells) (fig 7).^{3 4 39 42 43}

Exanthematous (morbilliform) drug eruption

Exanthematous drug reactions, accounting for 40–90% of all reactions, are one of the most common CADRs.^{3 45} The eruption is characterised by erythematous macules and papules that first appear on the trunk, in areas of pressure and foci of trauma, with subsequent symmetrical peripheral spread.⁵ Antibiotics

Figure 3 (A) Phototoxic reaction with dermal oedema, eosinophils and neutrophils. (B) Acute generalised exanthematous pustulosis with superficial epidermal pustule formation (arrows).



(penicillins, cephalosporins, sulfonamides, amphotericin B and gentamicin), NSAIDs, barbiturates, benzodiazepines, carbamazepine, phenothiazines, phenytoin, lithium, allopurinol, captopril, thiazide diuretics, gold, oral antihyperglycaemic agents and quinidine have been implicated.^{3-5 46 47} Histologically, there is focal interface vacuolar dermatitis with scattered necrotic keratinocytes at the dermo-epidermal junction, dermal oedema

and a superficial perivascular lymphocytic infiltrate with admixed eosinophils (fig 2B).^{4 5}

Lupus-erythematosus-like drug reaction

Drugs may exacerbate pre-existing lupus erythematosus (LE), induce LE in predisposed individuals, or initiate a lupus-like syndrome independent of pre-existing or latent LE.⁴⁸ The diagnosis of drug-induced LE requires at least one manifestation of LE, the development of antinuclear antibodies in association with drug ingestion, and reversal of manifestations within 1 year of drug cessation (fig 8).³ The more frequently implicated drugs are carbamazepine, chlorpromazine, hydralazine, isoniazid, methyl dopa, minocycline, penicillamine, procainamide, quinidine, terbinafine, infliximab and etanercept.⁴⁵⁻⁵⁸ The exact pathogenesis of drug-induced LE is unknown, but reactive drug metabolites are implicated. The cutaneous histopathological and immunofluorescence findings of drug-induced systemic LE, subacute LE and discoid LE are indistinguishable from idiopathic LE (fig 8).^{4 51 54 56} Electron dense inclusions are identified in vascular endothelium in hyperpigmented chlorpromazine-induced lesions.⁴⁹

Lichenoid drug reaction

Unlike idiopathic lichen planus (LP), drug-induced LP is characterised by an extensive, symmetric eruption of flat-topped violaceous papules involving the trunk and extremities, instead of the flexural surfaces.^{3-5 59 60} Photodistribution of lesions and post-inflammatory hyperpigmentation may occur.⁴ The commonly implicated drugs include antibiotics, antihistamines, β blockers, ACE inhibitors, NSAIDs, oral antihyperglycaemics, antimalarials, anti-epileptic and lipid-lowering agents, antipsychotics, thiazide diuretics, gold, lithium, methyl dopa and quinidine.^{3 4 59-63} Histologically, drug-induced LP is characterised by the classic lichenoid interface inflammatory reaction, variable epidermal atrophy or acanthosis, basal vacuolopathy, and keratinocyte necrosis. Clues to the drug-induced aetiology include epidermal parakeratosis, absence of wedge-shaped hypergranulosis and epidermal hyperplasia, transepidermal necrotic keratinocytes, extension of the

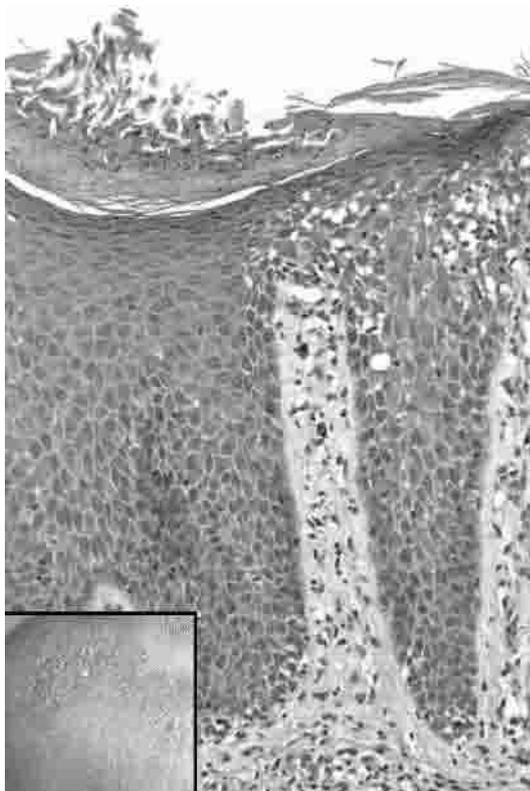
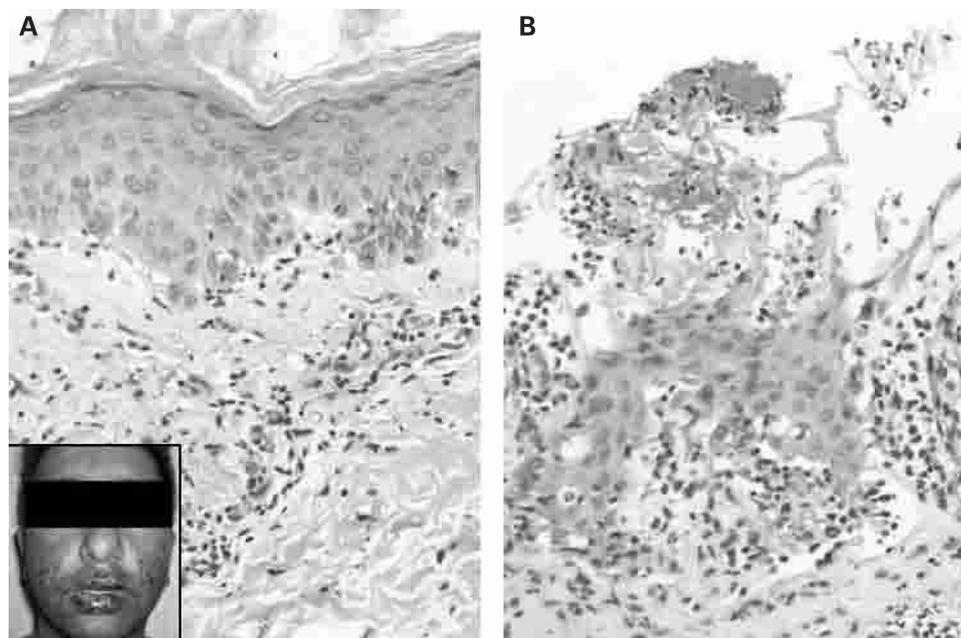


Figure 4 Psoriasiform reaction: intracorneal pustule formation, epidermal spongiosis and absent psoriasiform diathesis; inset: psoriasiform plaque.

Figure 5 (A) Early erythema multiforme with interface dermatitis and mild dermal inflammation; inset: Stevens Johnson syndrome with mucosal lesions. (B) Late erythema multiforme with confluent epidermal necrosis.



inflammatory infiltrate to the mid-dermal vascular plexus and the presence of eosinophils (fig 9A).^{3 4 59 60}

PREDOMINANTLY NODULAR AND DIFFUSE DERMATITIS

Pseudolymphomatous drug reaction

The clinical spectrum includes solitary or widespread papules, plaques or nodules (fig 10) occurring mainly on the face, chest and upper arms within weeks, months or years of initiation of therapy.^{5 64 65} The main offending agents are anticonvulsants, antipsychotics, antidepressants, antihistamines, antihypertensives and cytotoxic medication.⁶⁴⁻⁶⁶ Histologically, there is a predominant dense dermal infiltrate of lymphocytes and admixed plasma cells and eosinophils (fig 10). Epidermotropism and mucinous follicular degeneration are also

documented.^{64 66 67} There is immunohistochemical and molecular B and T cell pseudoclonalities.⁶⁴ Duplicate and triplicate polymerase chain reaction tests, close correlation of histopathological and immunohistochemical data, clinical resolution of the existing lesions, and absence of new lesions following drug withdrawal, are pivotal to the confirmation of a pseudolymphomatous drug reaction.^{64 66 68}

Interstitial granulomatous drug reaction

Interstitial granulomatous drug reaction (IGDR) presents as erythematous to violaceous non-pruritic plaques on the intertriginous areas, arms and groin.^{69 70} It is caused by chronic drug consumption, ranging from 4 weeks to 25 years (average, 5 years).⁷¹ The eruption resolves within 1 to 40 weeks (average,

Figure 6 Papular pruritic erythrodermia with interface dermatitis, keratinocyte necrosis, exocytosis (A), syringosquamous metaplasia and dyskeratosis (B), and eccrine duct necrosis (C).

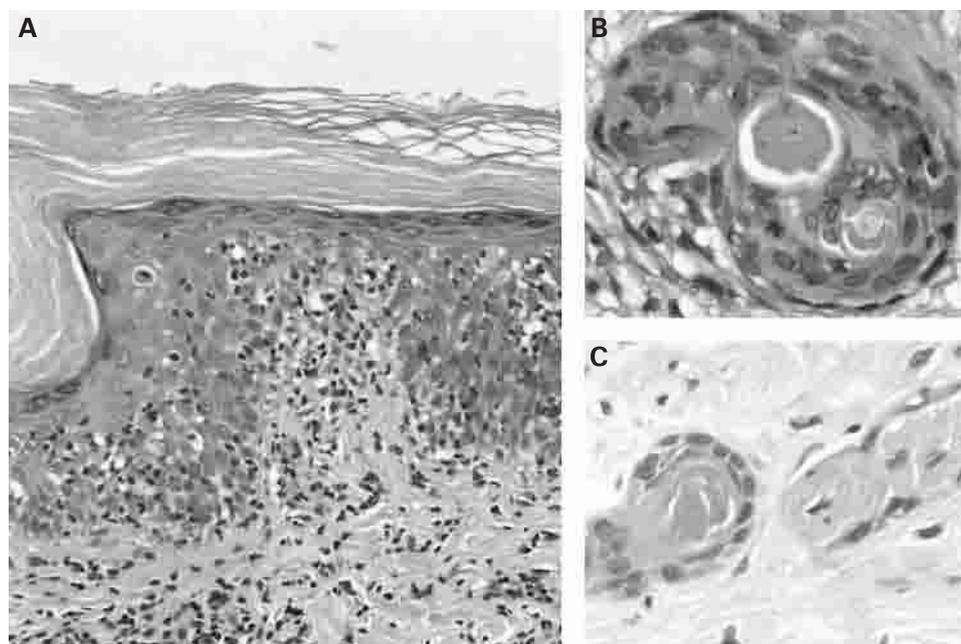


Table 1 World Health Organization clinicopathological grading criteria of papular pruritic erythroderma³⁴

Grade	Clinical lesion	Histological finding
1	Erythema	Dilated blood vessels in superficial dermal plexus
2	Erythema, oedema	Interface dermatitis, isolated necrotic keratinocytes in basal layer, dermal oedema
3	Erythema, oedema, fissuration	Interface dermatitis, blister, reticular desquamation, isolated necrotic keratinocytes higher in epidermis
4	Erythema, oedema, fissuration, blister	Transepidermal necrosis, eccrine syringosquamous metaplasia

8 weeks) after discontinuation of the offending drug.⁷¹ The drug groups implicated include calcium channel blockers, ACE inhibitors, β blockers, diuretics, NSAIDs, lipid-lowering drugs, anticonvulsants, antihistamines, antidepressants, herbal medications and four different anti-TNFs.^{71–78} The underlying pathogenesis may be related to an immune complex disorder and subsequent ischaemia and collagen alterations.^{69–71} The histological features include diffuse infiltration of the interstitium by lymphocytes, eosinophils, neutrophils and histiocytes, piecemeal collagen and elastic fibre fragmentation, vacuolar interface dermatitis and scant to absent mucin deposition (fig 9B).^{71 72 74 75} There is no collagen necrobiosis or vasculitis. Fifty per cent of cases demonstrate lymphocytic atypia.^{69–72}

An interstitial granulomatous reaction is also seen in interstitial granulomatous dermatitis (IGD) with arthritis and plaques and interstitial granuloma annulare (IGA).^{70 71} IGA lacks vacuolar basilar degeneration and complete collagen necrobiosis. Pandermal histiocytic infiltration is present in IGD.⁷⁰ Because of atypical or overlapping features between these disorders, it has been proposed that IGD may cover a wider pathological spectrum, ranging from IGA-like to IGD-like.⁷⁰

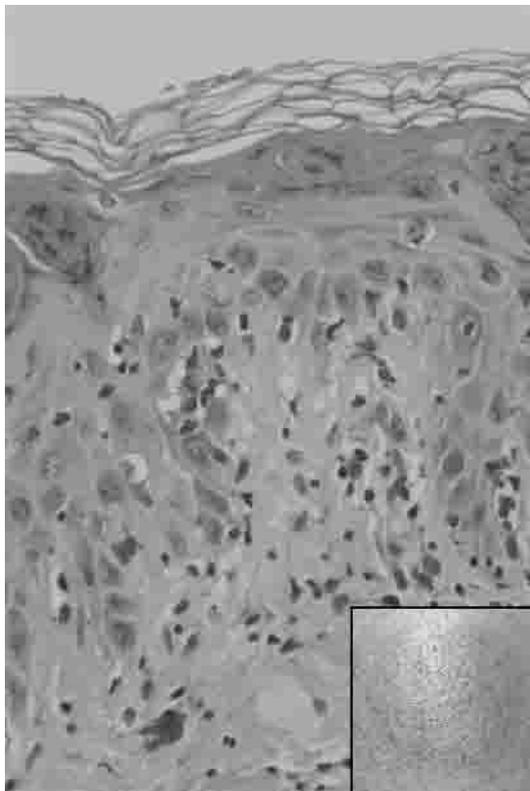


Figure 7 Fixed drug eruption: hyperpigmented macule (inset) with basal vacuolar change, keratinocyte necrosis, dermal oedema and perivascular inflammation.

Drug-induced Sweet syndrome

In contrast to the dominant head and neck involvement in classic Sweet syndrome, the upper extremities, followed by the lower extremities, face, trunk and neck are involved in drug-induced Sweet syndrome.⁷⁹ Neutrophilia and recurrent disease are uncommon associations of drug-induced Sweet syndrome.⁷⁹ The offending agents include antibiotics (trimethoprim–sulphamethoxazole, minocycline, nitrofurantoin), oral contraceptives, all-*trans*-retinoic acid, granulocyte colony stimulating factor (G-CSF), hydralazine, diclofenac, carbamazepine, diazepam and vaccines (influenza, BCG, pneumococcus).^{3 79–81} The pathogenesis remains clouded at present. G-CSF-induced Sweet syndrome is hypothesised to be a function of G-CSF-induced differentiation, chemotaxis and survival of neutrophils.⁷⁹ Histologically, there is a dense neutrophilic infiltrate without vasculitis.⁷⁹

PREDOMINANTLY VESICULOBULLOUS DRUG ERUPTIONS

Linear immunoglobulin A bullous-dermatosis-like drug eruption

Linear immunoglobulin (Ig)A bullous-dermatosis-like drug eruption (D-LABD) occurs in patients on multiple drugs (box 2).^{82 83} Antibiotics are the main inducers, with vancomycin bearing the strongest association.^{82 83} Typical vesiculobullous lesions and erythematous papules, erosions, urticaria, eczematous patches, TEN and EM may occur in D-LABD.⁸⁴ Mucosal involvement, described in 40% of patients with idiopathic linear IgA bullous dermatosis (I-LABD), may be lacking in D-LABD.^{85 86} Remission of disease occurs within 2–7 weeks of drug withdrawal whereas only 10–50% of patients with I-LABD have spontaneous remission.⁸⁵ Patients with D-LABD tend to be older than patients with I-LABD.⁴ Histologically, there is subepidermal blistering with intralesional neutrophils and eosinophils.^{82 87–89} Early lesions display a neutrophilic interface dermatitis with superficial perivascular mixed inflammatory cells, including eosinophils, and microabscesses in the dermal papillae.⁸⁷ Direct immunofluorescence investigations

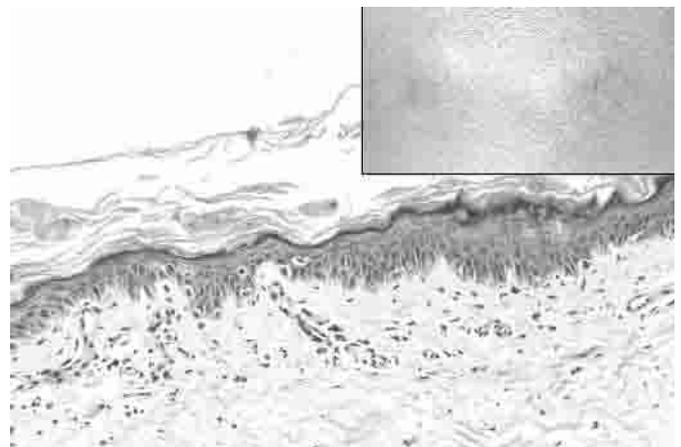


Figure 8 Lupus-erythematosus-like plaques (inset) with interface dermatitis, keratinocyte necrosis, dermal oedema and vasodilatation.

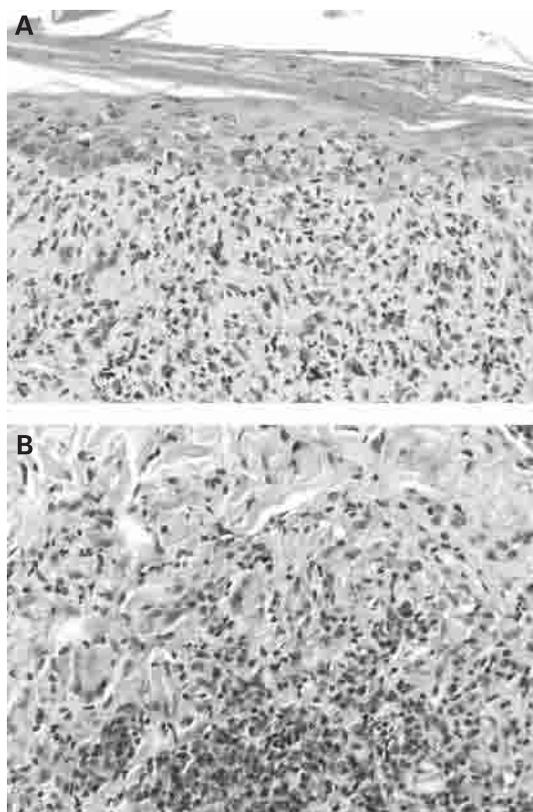


Figure 9 (A) Drug-induced lupus erythematosus with lichenoid inflammatory infiltrate with eosinophils. (B) Interstitial granulomatous drug reaction with interstitial lymphocytes, histiocytes, eosinophils.

demonstrate linear deposition of IgA or granular-linear deposition of IgA, IgG and C3 in the basement membrane zone.⁸⁷ Immunoelectron microscopy demonstrates similar features to I-LABD, with immune deposits being variably identified in the lamina lucida, sublamina densa and lamina densa. The suspicion of D-LABD should be higher in cases with only IgA and no IgG in the basement membrane zone.⁸⁷ Furthermore, some data suggest that fewer patients with D-LABD than with idiopathic LABD have circulating IgA basement membrane zone antibodies.⁸⁵ An additional confirmatory investigation is the absence of IgA in the basement membrane zone following drug withdrawal and disease remission.⁸⁸ In contrast, I-LABD displays persistence of IgA deposits.⁸⁸

Drug-induced pemphigus

As drug consumption increases, drug-induced pemphigus (DIP), a well-established variant of pemphigus, should be considered in every new patient with pemphigus and in every flare-up of the disease.⁹⁰ Drugs that may induce pemphigus can be divided into four main groups: (1) thiol drugs, including penicillamine, captopril, pyritinol, tiopronin and ampicillin; (2) drugs with an active amide group, such as penicillins; (3) non-thiol, non-amide drugs containing a phenol group, such as cefadroxil, rifampicin and levodopa; and (4) miscellaneous non-thiol, non-amide drugs.⁹⁰⁻⁹¹ DIP, unlike idiopathic pemphigus, presents with prodromic features of a morbilliform or urticarial eruption.⁹² The predominant clinical picture is that of pemphigus vulgaris, although the manifestations of pemphigus erythematosus or foliaceus may occur.⁴⁻⁹¹ The histopathological features are similar to idiopathic pemphigus. Pemphigus foliaceus morphology is characterised by upper spinous and/or granular layer

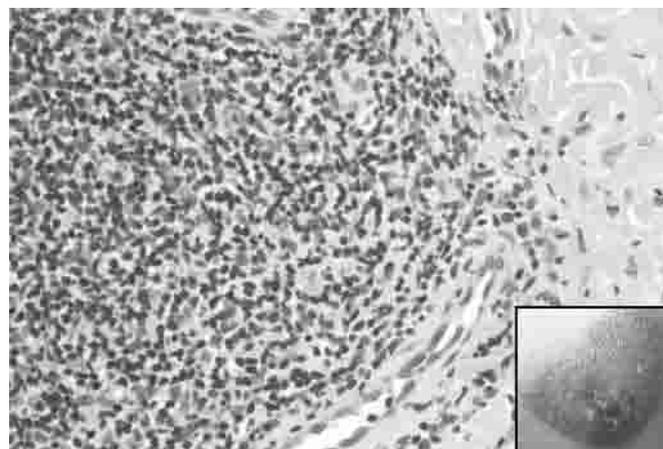


Figure 10 Nodular pseudolymphomatous lesion (inset) with dense lymphoplasmacytic infiltrate and eosinophils.

involvement, while pemphigus vulgaris clefts are located in a suprabasal location in the epidermis, folliculosebaceous and eccrine units (fig 11A).³⁻⁹¹⁻⁹³⁻⁹⁶ Immunofluorescence findings mimic idiopathic pemphigus (fig 11A), but circulating antibodies are demonstrated more often in patients with non-thiol-induced pemphigus.³

Drug-induced bullous pemphigoid

Drug-induced bullous pemphigoid (D-BP) shares clinicopathological features of idiopathic bullous pemphigoid (I-BP), but occurs in younger patients.⁹⁷ The drugs most commonly

Box 2 Drugs causing linear immunoglobulin A bullous-dermatitis-like drug eruption³

Antibiotics

- ▶ Vancomycin
- ▶ Trimethoprim–sulfamethoxazole
- ▶ Penicillin
- ▶ Cephalosporins
- ▶ Metronidazole
- ▶ Rifampicin

Cardiovascular agents

- ▶ Amiodarone
- ▶ Captopril
- ▶ Furosemide

Anti-inflammatories

- ▶ Diclofenac
- ▶ Piroxicam

Anti-epileptics

- ▶ Lithium
- ▶ Phenytoin

Others

- ▶ Glibenclamide
- ▶ Somatostatin
- ▶ Vigabratin
- ▶ Interferon δ
- ▶ Granulocyte colony stimulating factor
- ▶ Interleukin 2

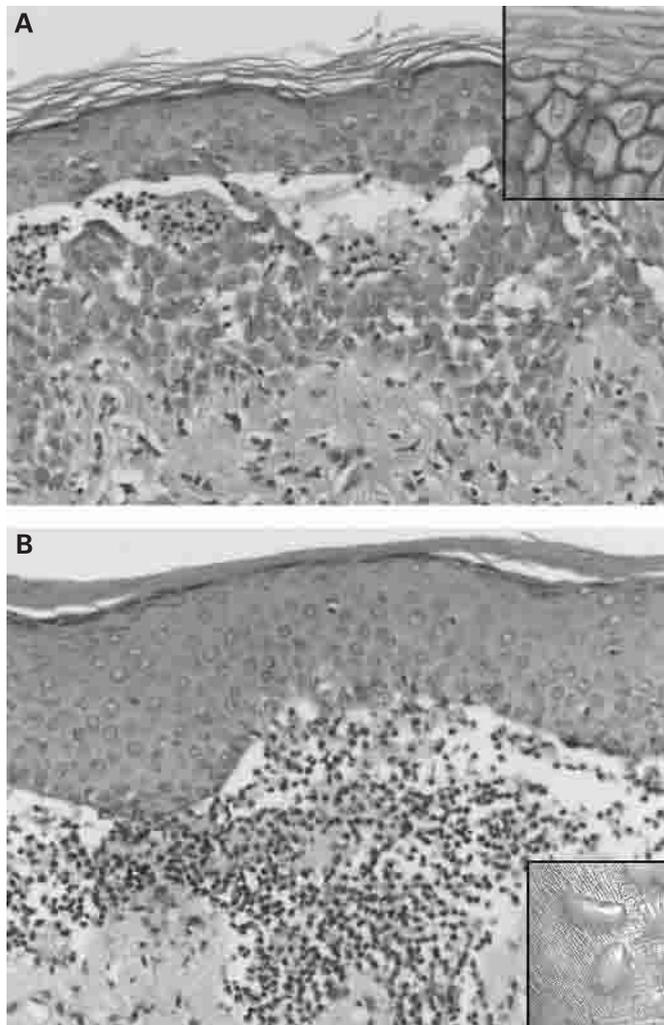


Figure 11 (A) Drug-induced pemphigus with suprabasal acantholysis and intercellular immunoglobulin G (inset). (B) Tense drug-induced bullous pemphigoid blisters (inset) with subepidermal eosinophil-rich infiltrate.

implicated are antirheumatic (D-penicillamine, phenacetin, mefenamic acid, sulfasalazine, gold, indomethacin), cardiovascular (furosemide, ACE inhibitors, clonidine, practalol, nadolol), antibiotics (penicillin, ampicillin) and miscellaneous (anti-influenza vaccine, antipsychotic, oral hypoglycaemic) agents.^{3 4 97–102} The clinical features of D-BP include tense blisters on an erythematous urticarial base, scarring, mucocutaneous plaques, bullous EM-like eruption and pemphigus-like morphology (fig 11B).^{97–101} Histologically, there are subepidermal blisters containing eosinophils with perivascular dermal eosinophils and lymphocytes (fig 11B). In penicillin-induced D-BP, there may be thrombi in dermal vessels, neutrophils, and intraepidermal vesicles containing necrotic keratinocytes.⁹⁸ Cephalax-induced D-BP may induce a predominant neutrophilic reaction.¹⁰¹ The hallmark features of D-BP may closely mimic those of epidermolysis bullosa acquisita, but, in contrast to the location of immune deposits in the sublamina densa in the latter, D-BP is characterised by immune deposits in the haemidesmosomes and upper lamina lucida, similar to that in I-BP.¹⁰¹ The location of the immune deposits does not differentiate I-BP from D-BP; however, in salt-split skin, immunoreactants that are usually found on the epidermal side may be identified on the dermal side.¹⁰¹

Drug-induced pseudoporphyria cutanea tarda

Pseudoporphyria cutanea tarda is a cutaneous disorder characterised by skin fragility in a photodistribution that may give rise to blistering, erosions and scarring, in the absence of abnormalities of haem biosynthesis and porphyrin excretion.¹⁰³ Affecting both sexes equally, PP has been reported in all age and race groups.¹⁰⁴ Clinical clues distinguishing PP from porphyria cutanea tarda (PCT) is the rare association of classic PCT features of hypertrichosis, hyperpigmentation and sclerodermoid changes.¹⁰⁵ While the more common offending drugs are NSAIDs, especially propionic acid derivatives, other drug associations of PP include antibiotics, voriconazole, diuretics, oral contraceptive drugs, amiodarone, cytotoxics and vitamin A derivatives.^{105–114} The pathogenesis includes drug-induced mimicry of endogenous photo-activated porphyrins, targeting specific structures in the skin, and protease-mediated damage of vascular endothelium following exposure to sunlight by the photo-active drug.^{104 110} Histologically PP and PCT share subepidermal cleft formation with festooning, erythrocytes, lymphocytes and neutrophils within the cleft and the accumulation of periodic acid–Schiff positive eosinophilic, hyalinised material in the venules and capillaries.^{104 106 110 112} Ultrastructurally, basement membrane splitting occurs in the lamina lucida in PP.¹¹² Clues to PP include eosinophils in the papillary dermis, thickening of blood vessel walls and the absence of solar elastosis.¹⁰⁶

PREDOMINANTLY PUSTULAR DRUG REACTIONS

Acute generalised exanthematous pustulosis

Acute generalised exanthematous pustulosis (AGEP), a rare clinical reaction pattern that is induced in >90% of the cases by systemic drugs, is triggered most frequently by anti-infectious agents, including antibiotics (β -lactam antibacterials, macrolides, cephalosporins, quinolone and tetracyclines) and anti-fungal agents (terbinafine, nystatin, itraconazole, fluconazole, griseofulvin and amphotericin).^{115–122} Simulating and once considered to be a variant of pustular psoriasis, AGEP is characterised by patchy erythema, oedema, pruritus, fever and leucocytosis usually within 1–2 weeks of initiating the medication.^{1 119 122} However, reactions can occur within hours of drug consumption.¹²¹ The pruritic, pinpoint, non-follicular, sterile eruption involves mainly the face and intertriginous areas.¹¹⁶ The pathomechanisms include a role for T cells, with drug-specific T cells expressing the potent neutrophil-attracting chemokine interleukin 8.¹¹⁵ While CD8 T cells promote local tissue destruction, CD4 T cells recruit neutrophils to the site.¹¹⁷ The histopathological features include spongiform subcorneal and/or intra-epidermal pustules, papillary dermis oedema, perivascular neutrophils and eosinophils and leucocytoclastic vasculitis (fig 3B).^{117 121 122} Drug withdrawal results in clearing of the pustules within 4–10 days, followed by a characteristic post-pustular pinpoint desquamation.¹²¹ While many diseases produce pustules, only pustular psoriasis, Sneddon Wilkinson disease, pustular necrotising angitis and staphylococcal scalded skin syndrome demonstrate the non-follicular pustules of AGEP.¹¹⁷ AGEP, unlike the other pustular diseases, has a rapid onset, wide distribution and rapid clearance of pustules, desquamation and resolution of the eruption following drug withdrawal.¹¹⁷ The eosinophilic infiltrate and the absence of psoriasiform epidermal alterations distinguish AGEP from pustular psoriasis.¹²²

Halogenoderma

Halogenoderma, encompassing iododerma, bromoderma and fluoroderma, is related to the ingestion of iodides, bromides and fluorides, respectively.⁵ The usual source of iodides is the potassium salt contained in expectorants and tonics, and amiodarone and iodine in radiocontrast media and seaweed.^{4 5} Iododermas are more common in patients with auto-immunity, renal failure or monoclonal gammopathy.¹²³ While acneiform eruptions are the most common presentation of these halide-induced lesions, ulcerating and crusted vegetative plaques and nodules may also occur.⁴ The usual sites of iododerma are the face, neck, back or upper extremity, sites most populous with sebaceous glands.¹²⁴ Histologically, there is pseudoepitheliomatous hyperplasia, intra-epithelial and dermal microabscesses, diffuse dermal neutrophilia, variable numbers of eosinophils and desquamated epithelial cells.^{4 5} The main clinical and histological features mimic deep fungal or atypical mycobacterial infection and blastomycosis-like pyoderma. While stains for micro-organisms are critical to the diagnosis of the first two entities, sporotrichosis may pose diagnostic difficulties as the disease is notorious for a dearth of organisms. Blastomyces-like pyoderma is confirmed by Gram staining. Heightened recognition of the halogenodermas as a cause for the clinicopathological picture is the gold standard of diagnosis. Complete resolution of the lesions on withdrawal of the halides is a slow and gradual process because of the slow elimination of these offending agents.⁵

PREDOMINANTLY VASCULITIC DRUG REACTIONS

Approximately 20–30% of cutaneous vasculitides arise as a consequence of drug ingestion within 7–10 days of administration of the offending drug.^{3 4} Manifesting as pruritic, palpable purpura and a purpuric maculopapular eruption, certain drugs are associated with a common histopathological appearance (box 3).^{4 65 125–127} Concomitant systemic disease may be present.^{4 126} Although eosinophils are not identified in all cases of drug-induced vasculitis, and they may be present in secondary vasculitis of connective tissue diseases and hypocomplementaemia, they may also serve as a valuable clue to the drug-related aetiology of vasculitis, especially in the absence of luminal thrombosis.⁴ Heightened awareness of drugs as a cause of vasculitis is critical to the diagnosis.

PREDOMINANTLY FOLLICULAR/PERIFOLLICULAR DRUG REACTIONS

Acneiform drug eruptions

Shared clinical features of acneiform eruptions and acne vulgaris include erythematous papules and pustules, mainly on the face, scalp, chest and upper back.¹²⁸ In contrast to acne vulgaris, acneiform eruptions are monomorphic, pruritic and lack white and blackhead comedones.¹²⁸ The drugs responsible for acneiform eruptions include antibiotics (tetracyclines, isoniazid), halogens (iodides, bromides), vitamins (B₁, B₆, B₁₂, D₂), immunosuppressive agents (azathioprine, cyclosporin, sirolimus), anti-epileptics (lithium, haloperidol, phenytoin), epidermal growth factor receptor inhibitors (EGF-RIs) and others (corticosteroids, androgens, oral contraceptives).^{128–132} EGF-RIs encompass two classes of drugs: the small molecule EGF-RIs gefitinib and erlotinib that selectively inhibit the tyrosine kinase activity of the intracellular domain, and monoclonal antibodies cetuximab and trastuzumab that bind to the extracellular domain of epidermal growth factor receptor (EGF-R).¹³⁰ Expressed abundantly in a range of malignant solid tumours,

EGF-R is also expressed in resident cells of the epidermis, sebaceous glands, eccrine units and hair follicles. The acneiform eruption is a cutaneous side-effect, probably due to an imbalance in the p27 associated differentiation and maturation of these cells, resulting in hyperkeratosis, abnormal desquamation, follicular plugging with variable bacterial overgrowth and development of acneiform lesions.^{128 130 131} It is an expected outcome and an important clinical tool for determining tumour response and survival.^{128 130 131} Alternatively, monoclonal antibody inhibitors may induce an inflammatory reaction by the activation of neutrophils and complement through the binding of its Fc domain.¹³⁰ Histologically, there is follicular dilatation with focal erosion of the infundibular epithelium, neutrophil aggregation, and a perifollicular lymphoneutrophilic infiltrate, including foreign body giant cells.^{128 129}

Drug-induced eosinophilic pustular folliculitis

Drug-induced eosinophilic pustular folliculitis (EPF) is characterised clinically by the repeated occurrence of crops of pruritic follicular papulopustules with a tendency to form annular configurations, mainly on the scalp, face, trunk and extensor surfaces of the arms.^{133–135} The implicated drugs include anti-cancer agents (cyclophosphamide, methotrexate, 5-fluorouracil), minocycline, carbamazepine, indeloxazine hydrochloride, allopurinol and prolonged corticosteroid treatment.^{133–138} The pathogenesis of EPF is unknown. A role for interleukin 5, cyclooxygenase-generated metabolites, intercellular adhesion molecule 1, and eosinophil chemotactic factor has been proposed.^{133–135} Histologically, drug-induced EPF is similar to classic EPF. There is follicular epithelial spongiosis with eosinophil microabscess formation, variable lymphocytic trafficking and a perifollicular, perivascular lympho-eosinophilic infiltrate.^{133 138} Heightened awareness of drug-induced EPF is critical as drug withdrawal is the mainstay of treatment, unlike classic EPF, in which protracted complex treatment modalities are required to control the disease.¹³⁶

PREDOMINANTLY SCLERODERMOID DRUG REACTION

Drug-induced sclerodermoid reactions, typified by cutaneous fibrosis, have been associated with bleomycin, L-tryptophan, docetaxel, bromocriptine, pentazocine, isoniazid, valproic acid, carbidopa, nitrofurantoin and fosinopril.^{139–145} The sclerodermoid reaction is heterogeneous.^{141 144} It may be characterised by shiny, hyperpigmented, indurated plaques (fig 12), mainly on the upper and lower extremities.^{139 144} Softening of the skin occurs after the medication is removed.¹⁴⁴ Increased production of procollagen 1 and glycosaminoglycans by fibroblasts, microvascular injury secondary to vasoconstrictive effects, and enhanced cytokine production are putative pathomechanisms.^{141 144} Histologically, early lesions demonstrate an interstitial mononuclear inflammatory cell infiltrate.^{141 144 145} Late lesions exhibit pandermal sclerosis with conspicuous thickening of collagen bundles, atrophy of the adnexal structures, loss of fat cushions around the eccrine secretory coils, and dermal elastic preservation.^{3 5 141 145}

PREDOMINANTLY DRUG-INDUCED PANNICULITIS

Drug-induced panniculitis may be a consequence of the direct injection of certain drugs (apomorphine, glatiramer, phosphatidylcholine), withdrawal of corticosteroids or a systemic drug-induced effect (thiazides, sulfonamides, corticosteroids, oral contraceptives, sulindac, chemotherapeutic agents).^{3 5 146–150} Erythema nodosum, a predominant granulomatous septal

Review

Box 3 Histopathological profile of drug-induced vasculitis^{4 65 125–127}**Leucocytoclastic**

- ▶ Allopurinol
- ▶ Erythromycin
- ▶ Penicillin
- ▶ Sulfonamides
- ▶ Thiazide diuretics
- ▶ Phenylbutazone
- ▶ Hydantoin

Polyarteritis nodosa like

- ▶ Acetylsalicylic acid
- ▶ Allopurinol
- ▶ Phenytoin
- ▶ Potassium
- ▶ Quinidine
- ▶ Sulfamethoxazole
- ▶ Sulfasalazine
- ▶ Sulfonamides
- ▶ Thiouracil

Henoch-Schönlein like

- ▶ Acetylsalicylic acid
- ▶ Gold
- ▶ Penicillins
- ▶ Quinidine
- ▶ Thiouracil

Pustular

- ▶ Carbamazepine
- ▶ Diltiazem
- ▶ Furosemide
- ▶ Mercury
- ▶ Naproxen
- ▶ Penicillins

Take-home messages

- ▶ Drugs not only elicit a range of cutaneous inflammatory reaction patterns, but also induce overlapping reaction patterns.
- ▶ Skin biopsy is an invaluable diagnostic modality because the clinical features of the drug-induced exanthem are often indistinguishable from their idiopathic counterparts.
- ▶ The mismatch between the clinical and histomorphological attributes may be a clue to the drug-induced nature of the rash.
- ▶ Eosinophils are a helpful clue to the possible drug-induced nature of the rash but they may be absent in bona fide drug rashes and conspicuous in skin reactions unrelated to drug use.
- ▶ Heightened awareness of the spectrum of clinical and histopathological manifestations of specific therapeutic agents is critical to the diagnosis.

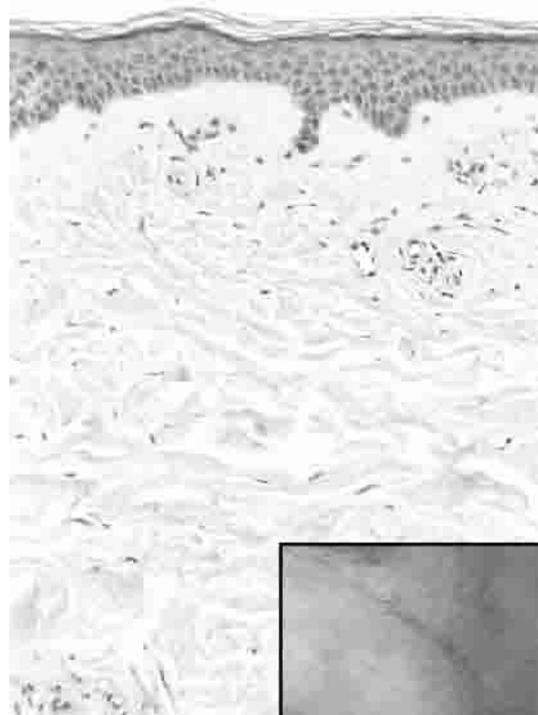


Figure 12 Sclerodermoid indurated plaque (inset) demonstrating dermal expansion and pandermal sclerosis.

panniculitis, is induced by sulfonamides, halogens, oral contraceptives, penicillin, salicylates, 5-lipoxygenase inhibitors and azathioprine.^{149 150} Chemotherapy-induced panniculitis may be septal but is more often lobular.^{148–150}

CONCLUSION

The expanding pharmacotherapeutic armamentarium mandates heightened awareness of CADRs that may mimic common cutaneous diseases.² Histologically, drugs may evoke a range of inflammatory disease patterns in the skin and subcutis, but no specific pattern is elicited.³ When an inflammatory pattern does not match the diagnosis for a given disease, when there are overlapping patterns, or when two distinct patterns are present in the biopsy, a CADR should be considered.^{3–5} Heightened awareness of drugs as the underlying cause of cutaneous pathology, even in patients on chronic therapeutic schedules, is pivotal to the diagnosis and management of afflicted patients.

Acknowledgements: Mrs M Moodley for administrative assistance and Mr S J Bagratee for help with the images.

Competing interests: None.

Patient consent: Obtained.

REFERENCES

1. **Martin T**, Hui LI. Severe cutaneous adverse drug reactions: a review on epidemiology, etiology, clinical manifestation and pathogenesis. *Chin Med J* 2008;**121**:756–61.
2. **Atzori L**, Pinna AL, Ferrelli C, *et al*. Pityriasis rosea-like adverse reaction: Review of the literature and experience of an Italian drug-surveillance center. *Dermatol Online J* 2008;**12**:1–6.
3. **Justiniano H**, Berlinger-Ramos AC, Sanchez JL. Pattern analysis of drug-induced skin diseases. *Am J Dermatopathol* 2008;**30**:352–69.
4. **Crowson AN**, Brown TJ, Magro CM. Progress in the understanding of the pathology and pathogenesis of cutaneous drug eruptions. *Am J Clin Dermatol* 2003;**4**:407–28.

5. **Weedon D.** Cutaneous drug reactions. In: Weedon D, ed. *Skin Pathology*. 2nd edn. Edinburgh: Churchill Livingstone, 2002:581–92.
6. **Diaz-Jara M**, Tornero P, Barrio MDE, et al. Pigmented purpuric dermatosis due to pseudoephedrine. *Contact Dermatitis* 2002;**46**:300–1.
7. **Abbeck D**, Gross GE, Kuwert C, et al. Acetaminophen-induced progressive pigmentary purpura (Schamberg's disease). *J Am Acad Dermatol* 1992;**27**:123–4.
8. **Adams BB**, Gadenne AS. Glipizide-induced pigmented purpuric dermatosis. *J Am Acad Dermatol* 1999;**41**:827–9.
9. **Yung A**, Goulden V. Pigmented purpuric dermatosis (capillaritis) induced by bezafibrate. *J Am Acad Dermatol* 2005;**53**:168–9.
10. **Crowson AN**, Magro CM, Zahorchak R. Atypical pigmentary purpura: a clinical, histopathologic, and genotypic study. *Hum Pathol* 1999;**30**:1004–12.
11. **Ratnam KV**, Su WPD, Peters MS. Purpura simplex (inflammatory purpura without vasculitis). *J Am Acad Dermatol* 1991;**25**:642–7.
12. **Tsao H**, Lerner LH. Pigmented purpuric eruption associated with injection medroxyprogesterone acetate. *J Am Acad Dermatol* 2000;**43**:308–10.
13. **Kozel MMA**, Mekkes JR, Bossuyt PMM, et al. The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. *Arch Dermatol* 1998;**134**:1575–80.
14. **Tutar E**, Ekici F, Nacar N, et al. Delayed maculopapular, urticarial rash due to infliximab in two children with systemic onset juvenile idiopathic arthritis. *Rheumatol* 2004;**43**:674–5.
15. **Kränke B**, Mayr-Kanhäuser S. Urticarial reaction to the antihistamine levocetirizine dihydrochloride. *Dermatol* 2005;**210**:246–7.
16. **Chang YS**, Kwon HS, Cho SH, et al. A case of urticaria induced by both hydroxyzine and cetirizine but not by levocetirizine. *Allergy* 2007;**62**:819–21.
17. **Atzori L**, Ferrelli C, Pinna AL, et al. Pityriasis rosea-like adverse reaction to lisinopril. *Eur Acad Dermatol Venereol* 2004;**18**:736–48.
18. **Kaplan B**, Grunwald MH, Halevy S. Pityriasis rosea-like eruption associated with BCG vaccination. *Isr J Med Sci* 1989;**25**:570–2.
19. **Buckley C**. Pityriasis rosea-like eruption in a patient receiving omeprazole. *Br J Dermatol* 1996;**135**:652–68.
20. **Brazzelli V**, Prestinari F, Roveda E, et al. Pityriasis rosea-like eruption during treatment with imatinib mesylate. *J Am Acad Dermatol* 2005;**53**:S240–3.
21. **Mavarak L**. Pityriasis rosea occurring during acyclovir therapy. *Ind J Dermatol Vener Leprol* 2007;**73**:200–1.
22. **Wilkinson SM**, Smith AG, Davis MJ, et al. Pityriasis rosea and discoid eczema: dose related reactions to treatment with gold. *Ann Rheum Dis* 1992;**51**:881–4.
23. **Gonzalez E**, Gonzalez S. Drug photosensitivity, idiopathic photodermatoses, and sunscreens. *J Am Acad Dermatol* 1996;**35**:871–85.
24. **Moore DE**. Drug-induced cutaneous photosensitivity. *Drug Safety* 2002;**25**:345–72.
25. **Gupta AK**, Sibbald RG, Knowles SR, et al. Terbinafine therapy may be associated with the development of psoriasis de novo or its exacerbation: four case reports and a review of drug-induced psoriasis. *J Am Acad Dermatol* 1997;**36**:858–62.
26. **Wolfe JT**, Singh A, Lessin SR, et al. De novo development of psoriatic plaques in patients receiving interferon alpha for treatment of erythrodermic cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1995;**32**:887–93.
27. **Tan B**, Foley P. Guttate psoriasis following ecstasy ingestion. *Austr J Dermatol* 2004;**45**:167–9.
28. **Sfikakis PP**, Iliopoulos A, Elezoglou A, et al. Psoriasis induced by anti-tumor necrosis factor therapy. *Arth Rheum* 2005;**52**:2513–8.
29. **Zohdi-Mofid M**, Horn TD. Acrosyringal concentration of necrotic keratinocytes in erythema multiforme: a clue to drug etiology. Clinicopathologic review of 29 cases. *J Cutan Pathol* 1997;**24**:235–40.
30. **Callaly EL**, FitzGerald O, Rogers S. Hydroxychloroquine-associated, photo-induced toxic epidermal necrolysis. *Clin Exp Dermatol* 2008;**33**:572–4.
31. **Wolf R**, Orion E, Davidovici B. Toxic epidermal necrolysis caused by tetrazepam. *Int J Dermatol* 2006;**45**:1260–1.
32. **Akosa AB**, Elhag AM. Toxic epidermal necrolysis: a study of the sweat glands. *J Cutan Pathol* 1995;**22**:359–64.
33. **McKee PH**, Calonje E, Granter SR. Cutaneous adverse reactions to drugs. In: McKee PH, Calonje E, Granter SR, eds. *Pathology of the skin with clinical correlations*. 3rd edn. Philadelphia: Elsevier, 2005:623–71.
34. **Nagore E**, Insa A, Sanmartin O. Antineoplastic therapy-induced palmar plantar erythrodysesthesia ("Hand-Foot") Syndrome. *Am J Clin Dermatol* 2000;**1**:225–34.
35. **Webster-Gandy JD**, How C, Harrold K. Palmar-plantar erythrodysesthesia (PPE). *Eur J Oncol Nurs* 2007;**11**:238–46.
36. **Janusch M**, Fischer M, Marsch WC, et al. The hand-foot syndrome – a frequent secondary manifestation in antineoplastic chemotherapy. *Eur J Dermatol* 2006;**16**:494–9.
37. **Suwattee P**, Chow S, Berg BC, et al. Sunitinib: a cause of bullous palmoplantar erythrodysesthesia, periungual erythema, and mucositis. *Arch Dermatol* 2008;**144**:123–5.
38. **Yang CH**, Lin WC, Chuang CK, et al. Hand-foot skin reaction in patients treated with sorafenib: a clinicopathologic study of cutaneous manifestations due to multitargeted kinase inhibitor therapy. *Br J Dermatol* 2008;**158**:592–6.
39. **Sehgal VN**, Srivastava G. Fixed drug eruption (FDE): changing scenario of incriminating drugs. *Int J Dermatol* 2006;**45**:897–908.
40. **Mahboob A**, Haroon TS. Drugs causing fixed eruptions: a study of 450 cases. *Int J Dermatol* 1998;**37**:833–8.
41. **Özkaya-Bayazit E**. Specific site involvement in fixed drug eruption. *J Am Acad Dermatol* 2003;**49**:1003–7.
42. **Zanolli MD**, McAlvany J, Krowchuk DP. Phenolphthalein-induced fixed drug eruption: a cutaneous complication of laxative use in a child. *Paediatrics* 1993;**91**:1199–201.
43. **Alanko K**, Kanerva L, Mohell-Talolahti M, et al. Non-pigmented fixed drug eruption from pseudoephedrine. *J Am Acad Dermatol* 1996;**35**:647–8.
44. **Young PC**, Montemarano AD, Lee N, et al. Hypersensitivity to paclitaxel manifested as a bullous fixed drug eruption. *J Am Acad Dermatol* 1996;**34**:313–4.
45. **Vilaplana J**, Romaguera C. Fixed drug eruption from sodium benzoate. *Contact Dermat* 2004;**49**:290–1.
46. **Fiszenson-Albala F**, Anzerie V, Mahe E, et al. A 6 month prospective survey of cutaneous drug reactions in a hospital setting. *Br J Dermatol* 2003;**149**:1018–22.
47. **Hernández-Salazar A**, Ponce-de-León Rosales S, Rangel-Frausto S, et al. Epidemiology of adverse cutaneous drug reactions. A prospective study in hospitalised patients. *Arch Med Res* 2006;**37**:899–902.
48. **Cetkovská P**, Pizinger K. Coexisting subacute and systemic lupus erythematosus after terbinafine administration: successful treatment with mycophenolate mofetil. *Int J Dermatol* 2006;**45**:320–2.
49. **Cameron HA**, Ramsay LE. The lupus syndrome induced by hydralazine: a common complication with low dose treatment. *Br Med J* 1984;**289**:410–2.
50. **Pavlidakey GP**, Hashimoto K, Heller GL, et al. Chlorpromazine-induced lupus like disease. Case report and review of the literature. *J Am Acad Dermatol* 1985;**13**:109–15.
51. **Reed BR**, Huff JC, Jones SK, et al. Subacute cutaneous lupus erythematosus associated with hydrochlorothiazide therapy. *Ann Int Med* 1985;**103**:49–51.
52. **Magro CM**, Crowson AN, Harnist TJ. The use of antibody to C5b-9 in the subclassification of lupus erythematosus. *Br J Dermatol* 1996;**134**:855–62.
53. **Goebel C**, Vogel C, Wulferink M, et al. Procainamide, a drug causing lupus, induces prostaglandin H synthase-2 and formation of T cell-sensitizing drug metabolites in mouse macrophages. *Chem Res Toxicol* 1999;**12**:488–500.
54. **Balestrero S**, Ciambellotti A, Parodi A, et al. Minocycline-induced lupus-like syndrome. *Int J Dermatol* 2001;**40**:472–84.
55. **Stratigos AJ**, Antoniou C, Stamatioudaki S, et al. Discoid lupus erythematosus-like eruption induced by infliximab. *Clin Exp Dermatol* 2004;**29**:150–3.
56. **Benucci M**, Gobbi FL, Fossi F, et al. Drug-induced lupus after treatment with infliximab in rheumatoid arthritis. *J Clin Rheumatol* 2005;**11**:47–9.
57. **Kang M-J**, Lee Y-H, Lee J. Etanercept-induced systemic lupus erythematosus in a patient with rheumatoid arthritis. *J Korean Med Sci* 2006;**21**:946–9.
58. **Spillane AP**, Xia Y, Sniezek PJ. Drug-induced lupus erythematosus in a patient treated with adalimumab. *J Am Acad Dermatol* 2007;**56**:S114–6.
59. **Van der Haute V**, Antoine JL, Lachapelle JM. Histopathological discriminant criteria between lichenoid drug eruption and idiopathic lichen planus: retrospective study on selected samples. *Dermatologica* 1989;**179**:10–3.
60. **Halevy S**, Shai A. Lichenoid drug eruptions. *J Am Acad Dermatol* 1993;**29**:249–55.
61. **Dalmaj J**, Peramiqnel L, Puig L, et al. Imatinib-associated lichenoid eruption: acitretin treatment allows maintained antineoplastic effect. *Br J Dermatol* 2006;**154**:1213–6.
62. **Hague JS**, Ilchysyn A. Lichenoid photosensitive eruption due to capecitabine chemotherapy for metastatic breast cancer. *Clin Exp Dermatol* 2006;**32**:102–3.
63. **Pérez-Pérez L**, Cabanillas M, Pereiro Ferreiros MM, et al. Photosensitive lichenoid eruption and inhaled tiotropium bromide. *Dermatol* 2007;**214**:97–8.
64. **Böer A**, Tirumalae R, Bresch M, et al. Pseudoclonality in cutaneous pseudolymphomas: a pitfall in interpretation of rearrangement studies. *Br J Dermatol* 2008;**159**:394–402.
65. **Crowson AN**, Magro CM. Recent advances in the pathology of cutaneous drug eruptions. *Dermatol Clin* 1999;**17**:537–60.
66. **Albrecht J**, Fine LA, Piette W. Drug-associated lymphoma and pseudolymphoma: recognition and management. *Dermatol Clin* 2007;**25**:233–44.
67. **D'Incan M**, Souteyrand P, Bignon YJ, et al. Hydatoin-induced cutaneous pseudolymphoma with clinical, pathologic, and immunologic aspects of Sézary syndrome. *Arch Dermatol* 1992;**128**:1371–4.
68. **Holm N**, Flaig MJ, Yazadi AS, et al. The value of molecular analysis by PCR in the diagnosis of cutaneous lymphocytic infiltrates. *J Cutan Pathol* 2002;**29**:447–52.
69. **Magro CM**, Crowson AN, Schapiro BL. The interstitial granulomatous drug reaction: a distinctive clinical and pathological entity. *J Cutan Pathol* 1998;**25**:72–8.
70. **Perrin C**, Lacour J-P, Castanet J, et al. Interstitial granulomatous drug reaction with a histological pattern of interstitial granulomatous dermatitis. *Am J Dermatopathol* 2001;**23**:295–8.
71. **Alvarez-Ruiz S**, Peñas PF, Fernández-Herrera J, et al. Maculopapular eruption with enlarged macrophages in eight patients receiving G-CSF or GM-CSF. *J Eur Acad Dermatol Venereol* 2004;**18**:310–3.
72. **Deng A**, Harvey V, Sina B, et al. Interstitial granulomatous dermatitis associated with the use of tumor necrosis factor α inhibitors. *Arch Dermatol* 2006;**142**:198–202.
73. **Fujita Y**, Shimizu T, Shimizu H. A case of interstitial granulomatous drug reaction due to senoside. *Br J Dermatol* 2004;**150**:1028–54.
74. **Lee H-W**, Yun W-J, Lee M-W, et al. Interstitial granulomatous drug reaction caused by Chinese herbal medication. *J Am Acad Dermatol* 2005;**52**:712–3.
75. **Lee M-W**, Choi J-H, Sung K-J, et al. Interstitial and granulomatous drug reaction presenting as erythema nodosum-like lesions. *Acta Derm Venereol* 2002;**82**:473–4.
76. **Lim AC**, Hart K, Murrell D. A granuloma annulare-like eruption associated with the use of amlodipine. *Austr J Dermatol* 2002;**43**:24–7.
77. **Scott GA**. Report of three cases of cutaneous reactions to granulocyte macrophage-colony-stimulating factor and a review of the literature. *Am J Dermatopathol* 1995;**17**:107–14.

Review

78. **Valks R**, Vargas E, Muñoz E, *et al*. Dermal infiltrate of enlarged macrophages in patients receiving chemotherapy. *J Cutan Pathol* 1998;**25**:259–64.
79. **Walker DC**, Cohen PR. Trimethoprim-sulfamethoxazole-associated acute febrile neutrophilic dermatosis: case report and review of drug-induced Sweet's syndrome. *J Am Acad Dermatol* 1996;**34**:918–23.
80. **Sáez M**, García-Bustinduy M, Noda A, *et al*. Drug-induced Sweet's syndrome. *J Eur Acad Dermatol Venereol* 2004;**18**:233.
81. **Tan AW**, Tan H-H, Lim PL. Bullous Sweet's syndrome following influenza vaccination in a HIV-infected patient. *Int J Dermatol* 2006;**45**:1254–5.
82. **Waldman MA**, Black DR, Callen JP. Vancomycin-induced linear IgA bullous disease presenting as toxic epidermal necrolysis. *Clin Exp Dermatol* 2004;**29**:633–6.
83. **Wiadrowski TP**, Reid CM. Drug-induced linear IgA bullous disease following antibiotics. *Austr J Dermatol* 2001;**42**:196–9.
84. **Armstrong AW**, Fazeli A, Yeh SW, *et al*. Vancomycin-induced linear IgA disease manifesting as bullous erythema multiforme. *J Cutan Pathol* 2004;**31**:393–7.
85. **Kuechle MK**, Stegmeier E, Maynard B, *et al*. Drug-induced linear IgA bullous dermatosis: report of six cases and review of the literature. *J Am Acad Dermatol* 1994;**30**:187–92.
86. **Nousari HC**, Kirnyai-Asadi A, Caeiro JP, *et al*. Clinical, demographic and immunohistologic features of vancomycin-induced linear IgA bullous disease of the skin: report of 2 cases and review of the literature. *Medicine (Baltimore)* 1999;**78**:1–8.
87. **Plunkett RW**, Chiarello SE, Beutner EH. Linear IgA bullous dermatosis in one of two piroxicam-induced eruptions: a distinct direct immunofluorescence trend revealed by the literature. *J Am Acad Dermatol* 2001;**45**:691–6.
88. **Primka EJ**, Liranzo MO, Bergfeld WF, *et al*. Amiodarone-induced linear IgA disease. *J Am Acad Dermatol* 1994;**31**:809–11.
89. **Yawalkar N**, Reimers A, Hari Y, *et al*. Drug-induced linear IgA bullous dermatosis associated with ceftriaxone and metronidazole-specific T cells. *Dermatology* 1999;**199**:25–30.
90. **Brenner S**, Bialy-Golan A, Ruocco V. Drug-induced pemphigus. *Clin Dermatol* 1998;**16**:393–7.
91. **Ghaffarpour G**, Jalali MHA, Yaghamai B, *et al*. Chloroquine/hydroxychloroquine-induced pemphigus. *Int J Dermatol* 2006;**45**:1261–3.
92. **Pisani M**, Ruocco V. Drug-induced pemphigus. *Clin Dermatol* 1986;**4**:118–32.
93. **Brenner S**, Bialy-Golan A, Anhalt GJ. Recognition of pemphigus antigens in drug-induced pemphigus vulgaris and pemphigus foliaceus. *J Am Acad Dermatol* 1997;**36**:919–23.
94. **Campagne G**, Roca M, Martinez A. Successful treatment of a high-grade intraepithelial neoplasia with imiquimod, with vulvar pemphigus as a side effect. *Eur J Obstet Gynaecol Reprod Biol* 2003;**109**:224–7.
95. **Landau M**, Brenner S. Histopathologic findings in drug-induced pemphigus. *Am J Dermatopathol* 1997;**19**:1–5.
96. **Wolf R**, Ruocco V. Gaining more insight into the pathomechanisms of thiol-induced acantholysis. *Med Hypotheses* 1997;**48**:107–10.
97. **Vassileva S**. Drug-induced pemphigoid: bullous and cicatricial. *Clin Dermatol* 1998;**16**:379–87.
98. **Alcalay J**, David M, Ingber A, *et al*. Bullous pemphigoid mimicking bullous erythema multiforme: an untoward side effect of penicillins. *J Am Acad Dermatol* 1988;**18**:345–9.
99. **Van Joost Th**, Crone RA, Overdijk AD. Ocular cicatricial pemphigoid associated with praxolol therapy. *Br J Dermatol* 1976;**94**:447–50.
100. **Van Joost Th**, Faber WR, Manuel HR. Drug-induced anogenital cicatricial pemphigoid. *Br J Dermatol* 1980;**102**:715–8.
101. **Czechowicz RT**, Reid CM, Warren LJ, *et al*. Bullous pemphigoid induced by cephalixin. *Austr J Dermatol* 2001;**42**:132–5.
102. **Mehravaran M**, Gyulai R, Husz S, *et al*. Drug-induced erythema multiforme-like bullous pemphigoid. *Acta Derm Venereol* 1999;**79**:233–54.
103. **Borroni G**, Brazzeli V, Baldini F, *et al*. Flutamide-induced pseudoporphyria. *Br J Dermatol* 1998;**138**:711–2.
104. **Tolland JP**, McKeown PP, Corbett JR. Voriconazole-induced pseudoporphyria. *Photodermatol Photoimmunol Photomed* 2007;**23**:29–31.
105. **Antony F**, Layton AM. Nabumetone-associated pseudoporphyria. *Br J Dermatol* 2000;**142**:1067–8.
106. **Breier F**, Feldmann R, Pelz M, *et al*. Pseudoporphyria cutanea tarda induced by furosemide in a patient undergoing peritoneal dialysis. *Dermatology* 1998;**197**:271–3.
107. **Epstein JH**, Tuffanelli DL, Seibert JS, *et al*. Porphyria-like cutaneous changes induced by tetracycline hydrochloride photosensitization. *Arch Dermatol* 1976;**112**:661–6.
108. **Judd L**. Pseudoporphyria due to Cola. *Int J Dermatol* 1991;**30**:674–5.
109. **Markus R**, Reddick ME, Rubenstein MC. Rofecoxib-induced pseudoporphyria. *J Am Acad Dermatol* 2004;**50**:647.
110. **McDonagh AJG**, Harrington CI. Pseudoporphyria complicating etretinate therapy. *Clin Exp Dermatol* 1989;**14**:437–8.
111. **Meggitt SJ**, Farr PM. Pseudoporphyria and propionic acid non-steroidal anti-inflammatory drugs. *Br J Dermatol* 1999;**141**:573–609.
112. **O'Donoghue NB**, Higgins EM. Naproxen-induced pseudoporphyria. *Clin Exp Dermatol* 2002;**27**:339–40.
113. **Phung TL**, Pipkin CA, Tahan SR, *et al*. β -Lactam antibiotic-induced pseudoporphyria. *J Am Acad Dermatol* 2004;**51**:S80–2.
114. **Poh-Fitzpatrick MB**. Porphyria, pseudoporphyria, pseudopseudoporphyria...? *Arch Dermatol* 1986;**122**:403–4.
115. **Beltraminelli HS**, Lerch M, Arnold A, *et al*. Acute generalized exanthematous pustulosis induced by the antifungal terbinafine: case report and review of the literature. *Br J Dermatol* 2005;**152**:780–3.
116. **Beylot C**, Doutre M-S, Beylot-Barry M. Acute generalized exanthematous pustulosis. *Semin Cutan Med Surg* 1996;**15**:244–9.
117. **Byerly FL**, Nelson KC, Granko RP, *et al*. Valdecoxib-associated acute generalized exanthematous pustulosis. *Burns* 2005;**31**:383–7.
118. **Häusermann P**, Scherer K, Weber M, *et al*. Ciprofloxacin-induced acute generalized exanthematous pustulosis mimicking bullous drug eruption confirmed by a positive patch test. *Dermatology* 2005;**211**:277–80.
119. **Heinemann C**, Wiesend CL, Hipler C, *et al*. Acute generalized exanthematous pustulosis (AGEP) after oral use of amphotericin B. *J Am Acad Dermatol* 2007;**57**:S61–3.
120. **Mengesha YM**, Bennett ML. Pustular skin disorders. *Am J Clin Dermatol* 2002;**3**:389–400.
121. **Sidoroff A**, Halevy S, Bavincck JNB, *et al*. Acute generalized exanthematous pustulosis (AGEP)-a clinical reaction pattern. *J Cutan Pathol* 2001;**28**:113–9.
122. **Yesudian PD**, Penny M, Azurdia RM, *et al*. Ibuprofen-induced acute generalized exanthematous pustulosis. *Int J Dermatol* 2004;**43**:208–10.
123. **Sovia C**, Allegue F, Espana A, *et al*. Vegetating iododerma with underlying systemic diseases: report of three cases. *J Am Acad Dermatol* 1990;**22**:418–22.
124. **Boudoulas O**, Siegle RJ, Grimwood RE. Iododerma occurring after orally administered iopanoic acid. *Arch Dermatol* 1987;**123**:387–8.
125. **Carlson JA**, Ng BT, Chen K-R. Cutaneous vasculitis update: Diagnostic criteria, classification, epidemiology, etiology, pathogenesis, evaluation and prognosis. *Am J Dermatopathol* 2005;**27**:504–28.
126. **García-Porrúa C**, Llorca J, González-Louzao C, *et al*. Hypersensitivity vasculitis in adults: a benign disease usually limited to skin. *Clin Exp Rheumatol* 2001;**19**:85–8.
127. **Kluger N**, Pagnoux C, Guillemin L, *et al*. Comparison of cutaneous manifestations in systemic polyarteritis nodosa and microscopic polyangiitis. *Br J Dermatol* 2008;**159**:615–20.
128. **Galimont-Collen AFS**, Vos LE, Lavrijsen APM, *et al*. Classification and management of skin, hair, nail and mucosal side-effects of epidermal growth factor receptor (EGFR) inhibitors. *Eur J Cancer* 2007;**43**:845–51.
129. **Kunzle N**, Venetz J-P, Pascual M, *et al*. Sirolimus-induced acneiform eruption. *Dermatol* 2005;**211**:366–9.
130. **DeWitt CA**, Siroy AE, Stone SP. Acneiform eruptions associated with epidermal growth factor receptor-targeted chemotherapy. *J Am Acad Dermatol* 2007;**56**:500–5.
131. **Journagan S**, Obadiah J. An acneiform eruption due to erlotinib: Prognostic implications and management. *J Am Acad Dermatol* 2006;**54**:358–60.
132. **Lee H-H**, Song I-H, Friedrich M, *et al*. Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor- α antagonists. *Br J Dermatol* 2007;**156**:486–91.
133. **Laing ME**, Laing TA, Mulligan NJ, *et al*. Eosinophilic pustular folliculitis induced by chemotherapy. *J Am Acad Dermatol* 2006;**54**:729–30.
134. **Maejima H**, Mukai H, Hikaru E. Eosinophilic pustular folliculitis induced by allopurinol and timepidium bromide. *Acta Derm Venereol* 2002;**82**:316–7.
135. **Mizoguchi S**, Setoyama M, Higashi Y, *et al*. Eosinophilic pustular folliculitis induced by carbamazepine. *J Am Acad Dermatol* 1998;**38**:641–3.
136. **Ellis E**, Scheinfeld N. Eosinophilic pustular folliculitis: a comprehensive review of treatment options. *Am J Clin Dermatol* 2004;**5**:189–97.
137. **Mizukawa Y**, Shiohara T. Eosinophilic pustular folliculitis induced after prolonged treatment with systemic corticosteroids in a patient with pustulosis palmoplantaris. *Acta Derm Venereol* 1998;**78**:221–2.
138. **Ooi CG**, Walker P, Sidhu SK, *et al*. Allopurinol induced generalized eosinophilic pustular folliculitis. *Austr J Dermatol* 2006;**47**:270–3.
139. **Cleveland MG**, Ajaikumar BS, Reganti R. Cutaneous fibrosis induced by docetaxel. A case report. *Cancer* 2000;**88**:1078–81.
140. **Ferzli GT**, El-Tal A, Kibbi A-G, *et al*. Localised morphea: a rare adverse effect of valproic acid. *Pediatr Neurol* 2003;**29**:253–5.
141. **Itoh M**, Yanaba K, Kobayashi T, *et al*. Taxane-induced scleroderma. *Br J Dermatol* 2007;**156**:363–7.
142. **King SL**, Lichter AC, Rowe DW, *et al*. Bleomycin stimulates pro- α 1(I) collagen promoter through transforming growth factor β response element by intracellular and extracellular signaling. *J Biol Chem* 1994;**269**:13156–61.
143. **Leshin B**, Piette WW, Caplan RM. Morphea after bromocriptine therapy. *Int J Dermatol* 1989;**28**:177–9.
144. **Kluger N**, Girard C, Bessis D, *et al*. Methysergide-induced scleroderma-like changes of the legs. *Br J Dermatol* 2005;**153**:224–5.
145. **Kupfer I**, Balguerie X, Courville P, *et al*. Scleroderma-like cutaneous lesions induced by paclitaxel: a case study. *J Am Acad Dermatol* 2003;**48**:279–81.
146. **Assouline S**, Laneuville P, Gambacorti-Passerini C. Panniculitis during dasatinib therapy for imatinib-resistant chronic myelogenous leukemia. *N Engl J Med* 2006;**354**:2623–4.
147. **Dellaripa PF**, Wechsler ME, Roth ME, *et al*. Recurrent panniculitis in a man with asthma receiving treatment with leukotriene-modifying agents. *Mayo Clin Proc* 2000;**75**:643–5.
148. **Jagdeo J**, Campbell R, Long T, *et al*. Sweet's syndrome-like neutrophilic lobular panniculitis associated with all-trans-retinoic acid chemotherapy in a patient with acute promyelocytic leukemia. *J Am Acad Dermatol* 2007;**56**:690–3.
149. **Ugurel S**, Lahaye T, Hildenbrand R, *et al*. Panniculitis in a patient with chronic myelogenous leukaemia treated with imatinib. *Br J Dermatol* 2003;**149**:678–9.
150. **Requena L**, Yus ES. Panniculitis. Part I. Mostly septal panniculitis. *J Am Acad Dermatol* 2001;**45**:163–83.