Drug-induced cutaneous pathology

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Drug-induced cutaneous pathology

P K Ramdial, D K Naidoo

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. 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. The aetiology of CADRs may be immunological, encompassing all of the Gell and Coombs immune mechanisms, or non-immunological. 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.

Although the aetiopathogenesis is unknown, steroids, antithrombinics, griseofulvin, ciclosporin, systemic steroids, psoralsens, carbamol, carbamidase, meprobamate, glipizide, acetaminophen, zomepirac sodium, interferon α, diuretics, chloridiazepoxide and aminogluthethimide are implicated in a minority of cases. A cell-mediated immune reaction has been proposed as the pathogenesis.

Drugs that precipitate PPD act as haptons, leading to the formation of antibody–antigen complexes that deposit in the endothelium causing vascular disruption. 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.

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. The main drugs causing immunological reactions are penicillins, cephalosporins, sulfonamides, tetraacyclines, tumour necrosis factor (TNF) inhibitors, antihistamines, ketoconazole, aminoglycosides, phenytoin, carbamazepine, captopril and non-steroidal anti-inflammatory drugs (NSAIDs), oral antihyperglycaemics and radiographic contrast agents. Viral infections or connective tissue diseases may induce or augment urticarial drug reactions. Clinically, urticarial CADRs manifest as pruritic, oedematous erythematous wheals (fig 1). 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. While vessel involvement is usually subtle, vasculitis may occur.

Spongiosic drug reaction

Pityriasis-rosea-like drug reaction

The clinical characteristics that distinguish idiopathic pityriasis of Gilbert (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. The offending drugs include gold salts, metronidazole, meprobamate, bismuth, ACE inhibitors, NSAIDs, barbiturates, clonidine, isoretinoin, terfinamine, imatinib mesylate, arsenicals, D-penicillamine, levamisole, omeprazole and acyclovir. 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 reactions

<table>
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<td>Predominantly sclerodermoderm drug reaction</td>
<td>Predominantly drug-induced panniculitis</td>
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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. A photoallergic reaction is a delayed hypersensitivity reaction and is independent of dose or duration of exposure. Photoallergic and phototoxic reactions occur mainly on sun-exposed skin. 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. 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 5A). Early lesions demonstrate epidermal spongiosis, and late lesions, epidermal hyperplasia and parakeratosis. 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. The dermal alterations include telangectasia, elastotic degeneration and the appearance of stellate myofibroblasts.

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. The clinical spectrum includes limited or generalised erythematous plaques with thick, large, silvery scales (fig 4), erythroderma or pustular lesions. 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. A paradoxical adverse psoriasiform cutaneous reaction has been documented with interferon α and the anti-TNF agents infliximab and etanercept. All interferons may exacerbate psoriasis, but only interferon α induces de novo psoriasis. 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). 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.

Interface drug reaction

Vascular 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. 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. The drugs implicated include carbamazepine, barbiturates, hydantoin, iohexol contrast media, penicillamine, phenobarbital, reverse transcriptase inhibitors, salicylates, penicillin, sulfonamides and tetracyclines. SJ is a more fulminant form of EM, with systemic involvement and severe mucosal erosions (fig 5A). TEN presents with an acute onset of generalised erythema followed by desquamation of >50% of the skin surface. Antituberculous...
drugs, trimethoprim–sulfamethoxazole, sulfonamides, tetracyclines, nitrofurantoin, hydantoins, allopurinol, NSAIDs, barbiturates, carbamazepine and phenylbutazone are the main offending drugs.\textsuperscript{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).\textsuperscript{14,52} Clues to the drug-induced aetiology include acrosyringeal concentration of keratinocyte necrosis and eosinophils within the dermal infiltrate.\textsuperscript{29} In addition, TEN has distinctive dermal sweat duct alterations, including basal cell hyperplasia and vacuolopathy with variable lymphocytic infiltration, apoptosis, necrosis and loss.\textsuperscript{14,29} These abnormalities are predominantly in the distal duct and involve the proximal duct, in continuity, but to a lesser degree.\textsuperscript{32}

**Chemotherapy-induced interface dermatitis**

Common chemotherapy-induced reactions include keratinocyte apoptosis, alopecia and stomatitis.\textsuperscript{33} Papular puritic erythrodysesthesia (PPE) is a distinctive dose-dependent toxic reaction occurring in 60–64% of patients, associated mainly with cytarabine, docetaxel, 5-fluorouracil and doxorubicin.\textsuperscript{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.\textsuperscript{35–36} The excretion of cytotoxic drugs in eccrine units makes the palms and soles appropriate targets.\textsuperscript{35} Whether PPE and hand–foot skin reaction (HFSR) are two distinct entities remains questionable.\textsuperscript{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.\textsuperscript{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).\textsuperscript{39} Severity of PPE is graded according to clinicopathological criteria (table 1).\textsuperscript{34} Histologically, HFSR demonstrates intra-epidermal vesicle formation and intracytoplasmic eosinophilic bodies in necrotic keratinocytes.\textsuperscript{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 reappearance of the lesions over the previously affected area when the offending agent is re-used (fig 7).\textsuperscript{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, acetylsalicylic acid, naproxen, piroxicam, chlormezanone, celecoxib) and other agents (barbiturates, anticonvulsants, opium alkaloids, chlordiazepoxide, chloral hydrate, oxazepam and carbamazepine).\textsuperscript{3,4,39–45} Histologically, there is basal hydropic degeneration, pigmented incontinence, upper epidermal keratinocyte necrosis, dermal oedema, vasodilatation and perivascular inflammatory cells (lymphocytes, neutrophils, histiocytes, mast cells) (fig 7).\textsuperscript{3,4,39,42,45}

**Exanthematous (morbilliform) drug eruption**

Exanthematous drug reactions, accounting for 40–90% of all reactions, are one of the most common CADRs.\textsuperscript{3,4} 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.\textsuperscript{3} Antibiotics

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

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

**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. 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). The more frequently implicated drugs are carbamazepine, chlorpromazine, hydralazine, isoniazid, methyldopa, minocycline, procainamide, quinidine, terbinafine, infliximab and etanercept. 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). Electron dense inclusions are identified in vascular endothelium in hyperpigmented chlorpromazine-induced lesions.

**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. Photodistribution of lesions and post-inflammatory hyperpigmentation may occur. 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, methyldopa and quinidine. 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

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

Figure 4  Psoriasiform reaction: intracorneal pustule formation, epidermal spongiosis and absent psoriasiform diathesis; inset: psoriasiform plaque.
inflammatory infiltrate to the mid-dermal vascular plexus and the presence of eosinophils (fig 9A). 345 96 0

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. 56 46 5 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 mucinotic follicular degeneration are also documented. 64 66 67 There is immunohistochemical and molecular B and T cell pseudoclones. 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,
8 weeks) after discontinuation of the offending drug. 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. The underlying pathogenesis may be related to an immune complex disorder and subsequent ischaemia and collagen alterations. 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). There is no collagen necrobiosis or vasculitis. Fifty per cent of cases demonstrate lymphocytic atypia.

An interstitial granulomatous reaction is also seen in interstitial granulomatous dermatitis (IGD) with arthritis and plaques and interstitial granuloma annulare (IGA). IGA lacks vacuolar basalar degeneration and complete collagen necrobiosis. Pandermal histiocytic infiltration is present in IGD. 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.

### 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. Neutrophilia and recurrent disease are uncommon associations of drug-induced Sweet syndrome. 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). G-CSF-induced Sweet syndrome is hypothesised to be a function of G-CSF-induced differentiation, chemotaxis and survival of neutrophils.

### 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. Antibiotics are the main inducers, with vancomycin bearing the strongest association. Typical vesiculobullous lesions and erythematous papules, erosions, urticaria, eczematous patches, TEN and EM may occur in D-LABD. Mucosal involvement, described in 40% of patients with idiopathic linear IgA bullous dermatosis (I-LABD), may be lacking in D-LABD. Remission of disease occurs within 2–7 weeks of drug withdrawal whereas only 10–50% of patients with I-LABD have spontaneous remission. Patients with D-LABD tend to be older than patients with I-LABD. Histologically, there is a dense neutrophilic infiltrate without vasculitis.

#### Table 1: World Health Organization clinicopathological grading criteria of papular pruritic erythrodysaesthesia

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical lesion</th>
<th>Histological finding</th>
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<tr>
<td>1</td>
<td>Erythema</td>
<td>Dilated blood vessels in superficial dermal plexus</td>
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<tr>
<td>2</td>
<td>Erythema, oedema</td>
<td>Interface dermatitis, isolated necrotic keratinocytes in basal layer, dermal oedema</td>
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<tr>
<td>3</td>
<td>Erythema, oedema, fissuration</td>
<td>Interface dermatitis, blister, reticular desquamation, isolated necrotic keratinocytes higher in epidermis</td>
</tr>
<tr>
<td>4</td>
<td>Erythema, oedema, fissuration, blister</td>
<td>Transepidermal necrosis, eccrine syringosquamous metaplasia</td>
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**Figure 7** Fixed drug eruption: hyperpigmented macule (inset) with basal vacuolar change, keratinocyte necrosis, dermal oedema and perivascular inflammation.

**Figure 8** Lupus-erythematosus-like plaques (inset) with interface dermatitis, keratinocyte necrosis, dermal oedema and vasodilatation.
demonstrate linear deposition of IgA or granular-linear deposition of IgA, IgG and C3 in the basement membrane zone. 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. Furthermore, some data suggest that fewer patients with D-LABD than with idiopathic LABD have circulating IgA basement membrane zone antibodies. An additional confirmatory investigation is the absence of IgA in the basement membrane zone following drug withdrawal and disease remission.

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. Drugs that may induce pemphigus can be divided into four main groups: (1) thiol drugs, including penicillamine, captopril, pyrithione, 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. DIP, unlike idiopathic pemphigus, presents with prodromic features of a morbilliform or urticarial eruption. The predominant clinical picture is that of pemphigus vulgaris, although the manifestations of pemphigus erythematosus or foliaceus may occur. The histopathological features are similar to idiopathic pemphigus. Pemphigus foliaceus morphology is characterised by upper spinous and/or granular layer involvement, while pemphigus vulgaris clefts are located in a suprabasal location in the epidermis, folliculosebaceous and eccrine units (fig 11A). Immunofluorescence findings mimic idiopathic pemphigus (fig 11A), but circulating antibodies are demonstrated more often in patients with non-thiol-induced pemphigus.

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

| Box 2 Drugs causing linear immunoglobulin A bullous-dermatosis-like drug eruption
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<td>- Penicillin</td>
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<td>- Rifampicin</td>
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<td>- Interferon-α</td>
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<td>- Granulocyte colony stimulating factor</td>
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<td>- Interleukin 2</td>
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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. Affecting both sexes equally, PP has been reported in all age and race groups. Clinical clues distinguishing PP from porphyria cutanea tarda (PCT) is the rare association of classic PCT features of hypertrichosis, hyperpigmentation and sclerodermoid changes. 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. 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. 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. Ultrastructurally, basement membrane splitting occurs in the lamina lucida in PP. Clues to PP include eosinophils in the papillary dermis, thickening of blood vessel walls and the absence of solar elastosis.

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 antifungal agents (terbinafine, nystatin, itraconazole, flucanazole, griseofulvin and amphotericin). 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. However, reactions can occur within hours of drug consumption. The pruritic, pinpoint, non-follicular, sterile eruption involves mainly the face and intertriginous areas. The pathomechanisms include a role for T cells, with drug-specific T cells expressing the potent neutrophil-attracting chemokine interleukin 8. While CD8 T cells promote local tissue destruction, CD4 T cells recruit neutrophils to the site. The histopathological features include spongiform subcorneal and/or intra-epidermal pustules, papillary dermal eosinophils and neutrophils, and intraepidermal vesicles containing necrotic keratinocytes. Cephalex-induced D-BP may induce a predominant neutrophilic reaction. 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. 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.

Halogenoderma

Halogenoderma, encompassing iododerma, bromoderma and fluoroderma, is related to the ingestion of iodides, bromides and fluorides, respectively. The usual source of iodides is the potassium salt contained in expectorants and tonics, and amiodarone and iodine in radiocontrast media and seaweed. Iododerma are more common in patients with auto-immunity, renal failure or monoclonal gammapathy. While acniform eruptions are the most common presentation of these halide-induced lesions, ulcerating and crusted vegetative plaques and nodules may also occur. The usual sites of iododerma are the face, neck, back or upper extremity, sites most populous with sebaceous glands. Histologically, there is pseudoepitheliomatous hyperplasia, intra-epithelial and dermal microabscesses, diffuse dermal neutrophilia, variable numbers of eosinophils and desquamated epithelial cells. 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. Blastomycoses-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.

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. Manifesting as pruritic, palpable purpura and a purpuric maculopapular eruption, certain drugs are associated with a common histopathological appearance (box, 5). Concomitant systemic disease may be present. 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. Heightened awareness of drugs as a cause of vasculitis is critical to the diagnosis.

PREDOMINANTLY FOLLICULAR/PERIFOLLICULAR DRUG REACTIONS

Acniform drug eruptions

Shared clinical features of acniform eruptions and acne vulgaris include erythematous papules and pustules, mainly on the face, scalp, chest and upper back. In contrast to acne vulgaris, acniform eruptions are monomorphic, pruritic and lack white and blackhead comedones. 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). 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). 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 acniform 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 acniform lesions. It is an expected outcome and an important clinical tool for determining tumour response and survival. Alternatively, monoclonal antibody inhibitors may induce an inflammatory reaction by the activation of neutrophils and complement through the binding of its Fc domain. Histologically, there is follicular dilatation with focal erosion of the infundibular epithelium, neutrophil aggregation, and a perifollicular lymphoepithelial infiltrate, including foreign body giant cells.

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. The implicated drugs include anti-cancer agents (cyclophosphamide, methotrexate, 5-fluorouracil), minocycline, carbamazepine, indeloxazene hydrochloride, allopurinol and prolonged corticosteroid treatment. 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. 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-epinosphilic infiltrate. 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.

PREDOMINANTLY SCLERODERMOID DRUG REACTION

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

PREDOMINANTLY DRUG-INDUCED PANNICULITIS

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

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**Box 3 Histopathological profile of drug-induced vasculitis**\(^{65, 125–127}\)

**Leucocytoclastic**
- Allopurinol
- Erythromycin
- Penicillin
- Sulfonamides
- Thioucaril

**Polyarteritis nodosa like**
- Acetylsalicylic acid
- Thiazide diuretics
- Phenylbutazone
- Hydantoin

**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

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