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Drug-Induced Skin, Nail and Hair Disorders

Laurence Valeyrie-Allanore,[1,2] *Bruno Sassolas*[3,4] and *Jean-Claude Roujeau*[1,2]

1 University of Paris XII, Créteil, France
2 Department of Dermatology, Hôpital Henri Mondor, Créteil, France
3 University of Bretagne Occidentale, Brest, France
4 Department of Dermatology, C.H.U. Morvan, Brest, France

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Abstract

Drug eruptions are among the most common adverse drug reactions, affecting approximately 3% of hospitalised patients. Although the rate of severe cutaneous adverse reactions to medications is low, these reactions can affect anyone who takes medication, and can result in death or disability. Two general patterns can be distinguished, depending on the type of onset of these cutaneous adverse drug reactions: acute or chronic. Acute-onset events are usually rather specific cutaneous 'syndromes' that constitute emergencies and should therefore be promptly recognised and treated, while chronic-onset events often present as dermatological diseases. The challenge is therefore to recognise the drug aetiology in front of a 'classical' dermatosis such as acne, lichen or pemphigus. Therefore, clinicians should carefully evaluate the signs or symptoms of all adverse reactions thought to be drug related, and discontinue the offending agent when feasible.

Erythematous drug eruptions are the most frequent and less severe acute immune drug-induced rashes, and are sometimes difficult to differentiate from viral eruptions. On the other hand, acute urticaria and angioedema are sometimes life-threatening eruptions for which a drug aetiology must be investigated. Photosensitivity, vasculitis and skin necrosis belong to the acute onset reactions, which are not always drug-induced, in contrast to fixed drug eruptions. The early recognition of acute generalised exanthematous pustulosis, DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome, Stevens-Johnson syndrome and toxic epidermal necrolysis are of high importance because of the specific mechanisms involved and the different prognosis of each of these diseases. Chronic onset drug-induced disorders include pigmentary changes, drug-induced autoimmune bullous diseases, lupus, pseudo lymphoma and acneiform eruptions; these are discussed, along with specific data on drug-induced hair and nail disorders.

As the disorders are numerous, the mechanisms and the drugs involved in the development of these various reactions are multiple. The list of drugs discussed in relation to the different disorders are as accurate as possible at the time of preparation of this review, but will need updating as new drugs emerge onto the market. We emphasize the clinical recognition, pathophysiology and treatment of skin, hair and nail adverse drug reactions, and the role of each doctor involved in the management of these patients in the notification of the adverse drug reaction to health authorities, using the minimal requirement for notification proposed.

Drug-induced adverse reactions represent a major health problem,[1] with skin being one of the most common targets.[2,3] Cutaneous reactions to drugs affect approximately 3% of hospital inpatients. According to the WHO definition, serious cutaneous drug reactions occur in approximately 0.1% of these patients, and can lead to disabling sequelae. The incidence of fatalities due to systemic and cutaneous drug reactions among inpatients is estimated at between 0.1% and 0.3%.[1,4]

The diagnosis of drug allergy is sometimes difficult because of the various possible clinical presentations. Prompt recognition of severe reactions and early withdrawal of the causative agent are the most important factors that can contribute to decrease morbidity (tables I and II).

The mechanisms of many drug-related adverse cutaneous reactions have not yet been clearly defined. There is growing evidence that the most common drug eruptions and many severe ones arise as a

result of an underlying immunological mechanism. The Gell and Coombs classification has proven to be helpful in clinical practice but may be an oversimplification when applied to drug reactions in which there are various T-cell-mediated immune mechanisms leading to distinct diseases.

Some researchers emphasise the key role of reactive drug metabolites that may act as haptens and initiate various types of reactions.[5] Others emphasise the heterogeneity of T-cell function and consequently subdivide delayed hypersensitivity reactions into four subgroups based on the recruitment of monocytes (type IVa), eosinophils (type IVb) or neutrophils (type IVd); CD4+ and CD8+ T cells can also exert cytotoxic function (type IVc).[6] In our opinion, the various clinical presentations, skin pathology, visceral involvement and biological markers suggest that the effector mechanisms differ between the different subtypes of drug hypersensitivity.[7]

However, allergy alone cannot explain the many types of drug-induced cutaneous reactions, particularly when considering all the chronic adverse reactions involving skin, hair and nails.

1. Diagnostic Features of Acute Adverse Cutaneous Reactions

1.1 Erythematous Drug Eruptions

The most common adverse drug reactions affecting the skin are exanthema or maculopapular eruptions, often reported as 'drug rashes' or 'drug eruptions'. The major underlying mechanism is probably immunological and is usually considered as a type IV delayed cell-mediated hypersensitivity reaction. Drugs can be stimulatory towards T cells if they bind covalently to proteins, but also if the drug has structural features that allow it to bind non-covalently to the major histocompatibility complex. Studies of circulating T cells, T cells eluted from the skin or from skin immunohistochemical staining suggest a dominant role for CD4+ T cells with a cytotoxic activity. Moreover, viral infections such as HIV and Epstein-Barr virus can increase the occurrence of maculopapular rash.[8]

Table I. Markers of severity: danger signs in immediate hypersensitivity reactions

Sign	Action
Urticaria	Discontinue drug as early as possible, treat as required
Severe pruritus (particularly of the face, palms of hands and soles of feet)	Discontinue drug and treat as required
Angioedema (particularly the tongue and larynx)	Immediately discontinue drug and treat as required
Flush (+ conjunctivitis/rhinitis)	Immediately discontinue drug and treat as required
Dyspnoea, bronchospasm	Immediately discontinue drug and treat as required
Hypotension	Immediately discontinue drug and treat as required

Erythematous skin eruptions usually occur between 4 and 14 days after starting a new drug therapy, but occasionally occur 1 or 2 days after drug therapy has ceased ('eruption of the ninth day'). In the case of rechallenge, an eruption can occur sooner. The lesions often consist of symmetric erythematous macules or papules, developing on the trunk or the upper extremities, which progressively become confluent, covering large patches of skin. The eruption is typically polymorphous with morbilliform or sometimes urticarial and purpuric lesions, but mucous membranes are not usually involved. Pruritus or low-grade fever is often associated with the eruption, which usually diminishes after a few days.

The histology may exhibit a mononuclear cell infiltrate of variable intensity around vessels of the dermis associated with eosinophils and interface dermatitis, and characterised by apoptosis of a few basal keratinocytes. Most of the infiltrating lymphocytes are CD4+, but this pattern is not specific and does not help in distinguishing a drug eruption from an eruption of another cause. Furthermore, in most cases of mild drug eruptions, the histological changes are so subtle that they are indistinguishable from normal skin.

The differential diagnosis of exanthematous drug reactions includes viral eruptions (e.g. Epstein-Barr virus, cytomegalovirus, human herpesvirus type 6, parvovirus B19), bacterial toxin eruptions,[9] acute graft-versus-host reaction, Kawasaki syndrome and

Table II. Markers of severity: danger signs in delayed onset reactions (listed in order of increasing severity)

From a macular exanthema to DRESS
Oedema of the central face (oedematous or infiltrated lesions)
Diffuse erythematous swelling
Involvement of extended body surface
Erythroderma
Infiltrated plaques
Associated signs: lymphadenopathy, arthralgia, high fever, eosinophilia, atypical lymphocytes, liver and kidney involvement
From a macular exanthema to TEN/SJS
Atypical targets
Mucosal erosions
Skin vesicles, bullae
Painful skin (early initial symptom)
Positive Nikolsky's sign
Epidermolysis
Associated fever
Haemorrhagic 'bloody' lesions
Palpable purpura
Haemorrhagic lesions
Necrotic lesions

DRESS = drug reaction with eosinophilia and systemic symptoms; **SJS** = Stevens-Johnson syndrome; **TEN** = toxic epidermal necrolysis.

Still's disease. Based on clinical experience, dermatologists usually consider that in children, viral infections are the cause of most skin eruptions, while in adults, drugs are more frequently responsible.

Treatment is basically supportive. The first therapeutic measure is discontinuation of the causative agent, combined with the administration of topical corticosteroid and systemic antipruritic agents. If the suspected drug is of essential therapeutic importance for the patient (e.g. antibacterial sulfonamides in AIDS patients), treating 'through the eruption' can be considered as an option in the absence of associated symptoms (see sections 1.7 and 1.9).[10] In most instances, the eruption diminishes spontaneously after the drug is withdrawn; however, a few patients may experience a progressive worsening. The progression of any drug rash should be carefully monitored in the first 48 hours to check its favourable course.

Most drugs have the potential to induce an erythematous eruption in approximately 1% of users. The following drugs are associated with higher risks (>3% of users): allopurinol, antiepileptic agents, antibacterial sulfonamides and antibacterials from the aminopenicillin and cephalosporin groups.[11]

1.2 Urticaria and Angioedema

Urticaria is a rather common, transient acute eruption of monomorphous erythematous and oedematous papules and plaques, usually associated with pruritus. The disease is characterised by the rapidity of its fluctuation. The involvement of dermal and subcutaneous tissues is known as angioedema. Urticaria and angioedema are often associated and can be complicated by a life-threatening anaphylactic reaction. Urticaria, angioedema and anaphylaxis result from either a type I hypersensitivity reaction mediated by IgE antibodies or from anaphylactoid mechanisms through direct and non-specific liberation of histamine or other mediators of inflammation.[12]

Clinically, itchy erythematous and/or oedematous papules and plaques develop in variable number and size, with wheals that wax and wane rapidly within a day. They may be localised anywhere on the body, including the palms of the hands, soles of the feet and scalp; the involvement of the head extremity is often associated with fever. They frequently last a few hours and disappear within 24 hours, without any scarring.[13] The exception is urticarial vasculitis, where lesions can last longer than 24 hours, with a small focus of bluish dermal haemorrhage remaining.

Angioedema consists of pale or pink swelling (as it is deeper in the skin structures), which affects the face (e.g. eyelids, lips, ears), but also the buccal mucosa, tongue, larynx and pharynx. A more severe reaction, such as anaphylaxis, can involve other systems and can lead to respiratory collapse, diarrhoea, shock and even death.

Urticaria is histologically non-specific, with a superficial dermal and deep sparse infiltrate of mononuclear cells accompanied by eosinophils and neutrophils, oedematous reticular dermis, vascular and lymphatic dilatation, and normal epidermis. This condition usually occurs within 36 hours of

drug administration, but may, in some cases, occur within a few minutes.

The main course of management involves withdrawal of the causative agent. This can sometimes be combined with use of histamine H_1 receptor blockers. Systemic corticosteroids and intramuscular injection of epinephrine (adrenaline) are necessary in an emergency if severe angioedema and anaphylaxis occur.

Many drugs can induce acute urticaria. Antibacterials, particularly penicillin, and myorelaxant used in general anaesthesia are classic causes of IgE-mediated hypersensitivity reaction. The radioallergosorbent test (RAST), enzyme-linked immunosorbent assay (ELISA) and skin prick tests can be useful in confirming the diagnosis, but the number of drugs for which there are commercially available assays is limited. Because they may induce an anaphylactic reaction in rare instances, skin prick tests must be performed only by experienced physicians, with strict surveillance of the patient. Drug-induced 'anaphylactoid' reactions, non-IgE-mediated urticaria and angioedema are mostly related to the use of NSAIDs, anticancer agents and ACE inhibitors. Angioedema occurs in 2–10/10 000 new users of ACE inhibitors. This rate is probably higher than the risk associated with penicillins (about 1/10 000 courses).[14]

1.3 Photosensitivity

Cutaneous photosensitivity diseases may be idiopathic, caused by endogenous photosensitisers (e.g. porphyrins) or associated with exogenous photosensitiser-like drugs. Photosensitising chemicals usually have a low molecular weight, are of planar, tricyclic or polycyclic configuration, often with heteroatoms in their structures that enable resonance stabilisation, and are able to absorb UV or visible radiation. The photosensitivity reactions are divided into two types – phototoxicity and photoallergy.[15]

1.3.1 Phototoxicity

Phototoxic disorders are not rare and are always predictable. They have a double dose-dependency to both the drug and light, as these disorders can occur in any person who receives sufficient quantities of a phototoxic drug, together with the required intensity of sunlight exposure. The reaction results directly from photochemistry involving the skin. Association of light with a photosensitising chemical in the skin creates unstable singlet or triplet states within the electrons as a result of energy transfer. This leads to the generation of reactive oxygen species responsible for damage to cellular lipids and proteins. Furthermore, as the drug changes to an excited state, free radicals are also generated with their specific cellular toxic effects.[15]

Clinical manifestations of phototoxicity usually present as exaggerated sunburn occurring only on sun-exposed areas of the skin. This is followed by hyperpigmentation, which is sometimes the only symptom of photosensitivity. Less common clinical forms are photo-onycholysis and pseudoporphyria (blisters on sun-exposed parts of the limbs).

Phototoxicity is characterised histologically by epidermal cell degeneration with necrotic keratinocytes, oedema, sparse dermal lymphocytic infiltrate and vasodilatation. Phototoxicity is easily documented *in vitro* or *in vivo*. The photopatch test will be positive in all individuals and is therefore not useful for assessment of the underlying cause. The minimal dose of UV in the UVB spectrum required to induce an erythema is decreased in patients during treatment with photosensitising drugs. Drugs that frequently induce phototoxicity include cyclines, quinolones, amiodarone, psoralens, methotrexate, voriconazole and furosemide (frusemide), with naproxen having the potential to induce pseudoporphyria.[15]

1.3.2 Photoallergy

Photoallergic reactions are considered to be a result of cell-mediated hypersensitivity. UV radiation is required to convert the drug into an immunologically active compound (photoantigen) that induces the immune response. The photoantigen is either absorbed by the patient or topically applied to the skin, where the reaction develops on photoexposed areas.

Photoallergic eruption is a more chronic disorder than phototoxicity, and is mainly eczematous and pruritic in nature. Lichen planus-like reaction has

also been reported. It is usually more marked in exposed sites, but may often progress outside these areas. In the chronic phase, erythema, scaling and lichenification predominate. Photoallergic reactions are usually transient and resolve after a variable length of time, when the causative agent has been removed. In rare cases, an extreme sensitivity to the sun may persist for months or years ('persistent light reactors'). Photopatch testing is valuable when photoallergy is suspected.

A multitude of different drugs can induce photoallergic reactions, including antibacterials (antibacterial and non-antibacterial sulfonamides, fluoroquinolones), NSAIDs (mainly propionic acid derivatives of aryl-carboxylic acid and piroxicam), phenothiazine, thiazide diuretics, antihyperlipidaemic agents (fibrates and statins), antimalarials, ACE inhibitors, calcium channel antagonists and some anticancer agents, as well as topical treatments, including antiseptics, sunscreen and cosmetic ingredients.[15]

In the case of phototoxic reactions, the management requires removal of the causative agent and/or avoidance of sun exposure. For drugs with a short elimination half-life, administration in the evening may be enough to decrease the risk of an adverse reaction below the clinical threshold. Drug withdrawal is recommended in cases of photoallergy because of the risk of a worsening reaction, even with low UV doses and/or low tissue concentration of the causative drug. The use of topical corticosteroids and systemic antipruritic agents may be useful.

1.4 Vasculitis

The definition of 'vasculitis' corresponds to inflammation and damage to the blood vessel wall. Possible causes are numerous, including infections and collagen vascular diseases; however, many cases remain idiopathic. The precise mechanism of drug-induced vasculitis is still unknown, but is believed to result from antibodies directed against drug-related haptens, direct drug toxicity against the vessel wall, autoantibodies reacting with endothelial cells or cell-mediated cytotoxic reactions against the vessels.[7]

Whatever the underlying cause of necrotising vasculitis, the eruption consists of palpable purpuric papules, which predominate on the lower extremities. Urticaria-like lesions, ulcers, nodules, haemorrhagic blisters, Raynaud's disease and digital necrosis also occur. The involvement of other organs, with fever, arthralgias, myalgias, headache, dyspnoea, neurological involvement and renal abnormalities, may sometimes be life threatening. The histology of skin lesions shows small blood vessels that exhibit leukocytoclastic or necrotising vasculitis, often with positive direct immunofluorescence, with IgM and C3 deposits on capillary walls. The presence of eosinophils increases the likelihood of an underlying drug cause.

Vasculitis occurs 7–21 days after drug administration, but in <3 days in the case of rechallenge. When detected, withdrawal of the drug usually leads to rapid resolution. Systemic corticosteroid treatment may benefit some patients when symptoms are severe or life threatening. Drug reactions account for a minority of cases of vasculitis (no more than 10% in large case series) and need to be differentiated from other possible causes of cutaneous vasculitis by specific investigations to rule out infection, autoimmune diseases (polyarteritis nodosa, Wegener's granulomatosis, cryoglobulinaemia) Schönlein-Henoch purpura and cancer.[16]

The main drugs implicated in vasculitis are allopurinol, NSAIDs, cimetidine, penicillin and other classes of antibacterials such as cephalosporins, fluoroquinolones or sulfonamide, hydantoin and propylthiouracil. However, in the case of antibacterials, it is often difficult to establish causality, as the infection being treated is itself a possible cause of vasculitis.

1.4.1 Serum Sickness-Like Eruption

Mostly reported in children, serum sickness-like eruption typically includes fever, arthralgias, rash (morbilliform, urticaria) and lymphadenopathy,[5,7] and occurs 1–3 weeks after initial drug exposure. Hypocomplementaemia, immune complexes, vasculitis and renal lesions are absent, in contrast to 'true' serum sickness reaction. This reaction occurs in approximately 1 in 2000 children who are ex-

posed to cefaclor. Minocycline, penicillins and propranolol can also be responsible for this type of eruption.

1.5 Anticoagulant-Induced Skin Necrosis

Anticoagulant-induced skin necrosis is a rare, sometimes life-threatening effect of warfarin, a long half-life coumarinic anticoagulant, which typically begins 3–5 days after initiation of therapy. Clinically, red, painful plaques evolve to necrosis, haemorrhagic blisters and ulcers, as a consequence of occlusive thrombi in the skin and subcutaneous vessels.[7] One in 10 000 patients exposed to warfarin will develop skin necrosis at onset of treatment. Hereditary deficiency of protein C is a risk factor because of a transient hypercoagulable state at the start of warfarin treatment. At an early stage, therapy includes discontinuation of warfarin, and administration of vitamin K, heparin (as an anticoagulant) and monoclonal antibody-purified protein C concentrate.

Heparin can also induce thrombosis and necrosis in the skin and other organs. If this occurs, the discontinuation of the drug and treatment with warfarin or an antiplatelet drug is useful.[17]

1.6 Acute Generalised Exanthematous Pustulosis

Acute generalised exanthematous pustulosis (AGEP) is an acute pustular eruption that must be differentiated from pustular psoriasis.[18] Its incidence is estimated to be 1–5 cases/million/year.[19] In a small number of cases, the aetiology of AGEP appears to be a viral infection (e.g. enterovirus, parvovirus B19) or hypersensitivity reaction to mercury. More than 90% of cases are drug-induced. Antibacterials, such as aminopenicillins and pristinamycin, as well as diltiazem and antimalarials, are the main drugs implicated in AGEP.

AGEP is characterised by a fever of >38°C, which generally begins the same day as the rash. Numerous, small and mostly non-follicular pustules arise on a widespread oedematous erythema. These pustules are mainly localised to the main folds (neck, axillae, groins), trunk and upper extremities. This eruption is often associated with a burning or itching sensation, or both. Oedema of the face and hands, purpura, vesicles, blisters, erythema multiforme-like lesions and mucous membrane involvement are possible features. The time between drug administration and the skin eruption is relatively short, i.e. <2 days. The eruption lasts for 1–2 weeks and is followed by a superficial desquamation.

The histopathology shows spongiform pustules located under the stratum corneum, in the superficial layer of the epidermis. Papillary dermal oedema and perivascular polymorphous infiltrate are usually present and leukocytoclastic vasculitis and focal necrotic keratinocytes have also been reported. Psoriatic changes such as acanthosis and papillomatosis are usually absent. Hyperleukocytosis with elevated neutrophil count, transient renal failure and hypocalcaemia are frequently seen. *In vitro* analysis of drug-specific T-cell clones from patients with AGEP show an elevated expression of the neutrophil-attracting chemokines.[6,20]

Proposed diagnostic criteria for AGEP include: (i) an acute pustular eruption; (ii) fever of >38°C; (iii) neutrophilia with or without mild eosinophilia; (iv) subcorneal or intraepidermal pustules on skin biopsy; and (v) spontaneous resolution in <15 days.[19,21] AGEP must be differentiated from acute pustular psoriasis. As the pustules in both diseases are often clinically indistinguishable, the histopathology and medical history can be helpful. Other acute pustulosis dermatoses are easier to rule out, i.e. subcorneal pustular dermatosis, pustular vasculitis. Withdrawal of the causative drug is the main form of management, in association with topical corticosteroids and, occasionally, a systemic antipruritic agent.

1.7 DRESS-Hypersensitivity

'Hypersensitivity syndrome' refers to a specific severe skin reaction. The acronym of DRESS (drug reaction with eosinophilia and systemic symptoms) has been proposed as being more specific than 'hypersensitivity syndrome', which would be appropriate for most types of drug reactions described in the literature. The incidence of DRESS is estimated at

between 1 in 1000 and 1 in 10 000 exposures to antiepileptic drugs.[22]

In its complete form, this syndrome is typically characterised by a severe eruption, lymphadenopathy, fever, hepatitis, arthralgias, pulmonary infiltrates, interstitial nephritis and haematological abnormalities.[7,23,24] Multivisceral involvement differentiates hypersensitivity syndrome from common exanthematous eruption, from both a clinical and prognostic point of view.

The pathogenesis of the disorder has not yet been clarified. A genetically determined inability to detoxify the arene oxide metabolic products of anticonvulsant agents has been observed in patients with hypersensitivity syndrome, but this reaction also occurs in patients without such abnormalities.[24,25] Immune mechanisms are also implicated. Interleukin-5, which is released by activated T cells, leads to the generation of eosinophilia, a key feature of this syndrome.[26] Reactivation of herpes virus infections has been reported, including human herpes virus type 6, cytomegalovirus and Epstein-Barr virus.[27] The massive immune stimulation in the form of a generalised drug hypersensitivity reaction may cause reactivation of these lymphotropic viruses. On the other hand, the virus reactivation could be an additional stimulus for the immune system, leading to a chronic course of the disease.[22]

These hypersensitivity reactions/DRESS are more frequent among persons of African ancestry.[28] They usually begin 2–6 weeks after the first drug administration, later than most other acute skin reactions. Fever and skin rash are the most common symptoms. Cutaneous manifestations begin as a morbilliform rash, which later becomes infiltrated with an oedematous follicular accentuation. Erythroderma, vesicles, tight blisters induced by dermal oedema and follicular as well as non-follicular pustules can also occur. The face, upper trunk and extremities are initially involved, with oedema of the face frequently being present and suggestive of the diagnosis. Lymphadenopathy is frequent, due to benign lymphoid hyperplasia, and hepatitis and interstitial nephritis are also common. Involvement of the heart, lung, thyroid and brain is less frequent. Severe hepatitis may be life threatening and is responsible for the majority of deaths associated with this syndrome. Rash and visceral involvement may persist for several weeks after drug withdrawal.

Predominant eosinophilia is common and corresponds to the most characteristic biological feature of this reaction; it is often associated with atypical lymphocytosis. Raised levels of aminotransferases, alkaline phosphatase and/or bilirubin are present in approximately 50% of patients. An altered prothrombin time indicates a severe liver involvement. Histopathology of the skin is somewhat non-specific and exhibits a rather dense lymphocytic infiltrate in the superficial dermis and/or perivascular area, associated with dermal oedema. The differential diagnosis includes other cutaneous drug reactions, acute viral infection, idiopathic hypereosinophilic syndrome, lymphoma and pseudolymphoma.

Several antiepileptic agents (phenobarbital [phenobarbitone], carbamazepine, phenytoin, lamotrigine) sulfonamides, minocycline, allopurinol, gold salts and dapsone are the most frequent causes of DRESS. Early withdrawal of the causative agent is mandatory but not always sufficient to obtain a full recovery. Topical high-potency corticosteroids can be helpful in treating skin manifestations. Systemic corticosteroids are recommended when there is heart and lung involvement. A relapse of rash and hepatitis may occur when the dosage is tapered.

1.8 Fixed Drug Eruption

The fixed drug eruption is a rare but exclusively drug-induced cutaneous disease. Lesions usually develop <2 days after drug intake. Clinically, they are characterised by a solitary or a few, round, sharply demarcated erythematous and oedematous plaques, sometimes with a central blister, that recur at exactly the same sites when rechallenged with the causative drug. The eruption can occur anywhere on the body and may involve mucous membranes, principally the lips and external genitalia. The lesions fade within a few days to leave a post-inflammatory brown pigmentation. After several relapses the eruption may involve large areas of the body. This generalised bullous fixed drug eruption may be dif-

ficult to distinguish from toxic epidermal necrolysis (TEN). The absence of, or low numbers of, mucous membranes involved, and the absence of widespread erythematous macules, are features that differentiate these two diseases.

Histopathology reveals a superficial and deep dermal and perivascular infiltrate of lymphocytes, eosinophils and, sometimes, neutrophils, associated with necrotic keratinocytes. When present, dermal macrophages pigmented with melanin (melanophages) are considered as an important clue to the diagnosis, and useful in differentiating TEN from generalised bullous fixed drug eruption. The drugs most frequently associated with fixed drug eruption are phenazone derivates, barbiturates, tetracycline, sulfonamides and carbamazepine.[29]

1.9 Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson syndrome (SJS) and TEN are rare, but are the most severe drug-induced skin reactions. The incidence of TEN is estimated to be 0.4–1.2 cases/million person-years and the incidence of SJS 1–6 cases/million person-years.[7,30,31] The risk of developing SJS or TEN is increased in HIV-infected patients.[32] Drugs are responsible for at least 70% of cases.

The precise sequence of molecular and cellular events that leads to the development of TEN is only partially understood. The immunopathological pattern of early lesions suggests a cell-mediated cytotoxic reaction against epidermal cells. Drug-specific cytotoxic T cells expressing the skin homing receptor cutaneous lymphocyte-associated antigen are observed in the development of cutaneous lesions. Cytokines such as interferon (IFN)-γ, tumour necrosis factor (TNF)-α and Fas-ligand could participate in the massive and widespread apoptosis of epidermal cells.[33-36]

Genetic susceptibility could also play an important role in SJS and TEN. A strong association was reported in Han Chinese between the human leukocyte antigen HLA-B*1502 allele and SJS induced by carbamazepine, and between the HLA B*5801 allele and SJS induced by allopurinol.[37,38]

Clinically, SJS/TEN begins within 4 weeks (usually 7–21 days) of initial drug exposure, sometimes a few days after the drug has been withdrawn. It occurs more rapidly with rechallenge. Usually, fever and signs or symptoms affecting cutaneous and mucous membranes precede the appearance of skin blisters or mucous erosions by 1 or 2 days. The eruption is initially symmetrically distributed on the face, upper trunk and proximal extremities; however, the rash can rapidly extend to the rest of the body. The initial skin lesions are characterised by irregularly shaped, erythematous, dusky-red, purpuric macules, which progressively coalesce. Confluence of necrotic lesions leads to extensive and diffuse erythema. Nikolsky's sign is positive, flaccid blisters develop and necrotic epidermis detachment on pressure points reveals large areas of exposed, red, sometimes oozing dermis. According to the percentage of skin detachment, patients are classified into one of three groups: SJS when affecting <10% of body surface area (BSA); SJS/TEN overlap when affecting between 10% and 30% of BSA; TEN when >30% of BSA is affected.[39] Mucous membrane involvement is noted in around 85% of patients with erythema and painful erosions of the buccal, ocular, nasal and genital mucosa.[40] The epithelium of the respiratory tract or gastrointestinal tract can also be involved. Skin pathology shows a full-thickness necrosis of the epidermis with very mild lymphocytic infiltrate in the upper dermis and negative immunofluorescence.

Systemic manifestations include slight elevation of hepatic enzymes (overt hepatitis in 10% of cases), intestinal and pulmonary manifestations (with sloughing of epithelia similar to the epidermal detachment). Leukopenia is frequent and eosinophilia unusual.

Death occurs in 10% of patients with SJS and in >30% of patients with TEN, mainly due to sepsis or pulmonary involvement.[41,42]

In association with other investigators, we proposed the consideration of SJS and TEN as severity variants of the same drug-induced disease, and to separate SJS from erythema multiforme majus (EMM), which is mostly related to infections, par-

ticularly herpes virus.[40,43,44] In our experience, EMM is rarely drug-induced. Most of the cases reported or published as drug-induced EMM are either cases that would fit SJS diagnostic criteria or cases of erythematous drug eruptions with polymorphous widespread target-like lesions. TEN must also be differentiated from exfoliative dermatitis, staphylococcal skin-scaled syndrome, linear IgA bullous disease and acute generalised exanthematous pustulosis.

To date, treatment of SJS and TEN is mainly symptomatic, consisting of nursing care, maintenance of fluid and electrolyte balance and nutritional support. Early withdrawal of all potentially responsible drugs is essential. Short courses of corticosteroids early in the disease have been advocated, but their effectiveness has never been demonstrated in controlled trials. Thalidomide has been shown to be detrimental in TEN[35] and, in our experience, high-dose intravenous immunoglobulins were disappointing.[45]

Recent drug exposure is responsible for at least 70% of cases of both SJS and TEN.[5] Antibacterial sulfonamides, antiepileptic drugs, oxicam and pyrazolone NSAIDs, allopurinol, and nevirapine are the drugs associated with higher risks of developing SJS/TEN. An international case-control study of SJS and TEN found relative risks between 50 and 172 for new users (treatment duration of <2 months) of the above-mentioned drugs.[46]

2. Diagnostic Features of Chronic Adverse Cutaneous Reactions

Chronic adverse cutaneous reactions often manifest as induction or exacerbation of any cutaneous disease. Atypical clinical presentation or unusual evolution of a common skin disease despite correct specific therapy should raise the suspicion of a possible drug reaction but is often difficult to confirm. From that point of view, questioning about both regular and occasional drug intake should be mandatory for each patient consulting a dermatologist.

2.1 Pigmentary Changes

Drug-induced skin pigmentation may result from a variety of mechanisms, including enhanced melanin production, deposition of drugs or their metabolites (sometimes in combination with melanin or iron) and post-inflammatory changes secondary to subliminal phototoxicity. This condition may be more pronounced on sun-exposed areas or may involve only mucous membrane.

The drugs most commonly implicated in cutaneous hyperpigmentation include minocycline, antimalarials, amiodarone, oral contraceptives, imipramine, chemotherapeutic agents and clofazimine.[47,48] Hypopigmentation can occur with the long-term use of several topical medications, including tretinoin (retinoic acid) and corticosteroids; depigmentation is associated primarily with the application of monobenzyl ether of hydroquinone or exposure to catechols, phenols or quinones.

2.2 Drug-Induced Pemphigus

Pemphigus is a chronic autoimmune blistering disease provoked by autoantibodies reacting with normal proteins that provide attachment between epidermal cells. It presents clinically with flaccid intraepidermal blisters that become rapidly covered with crusts, and/or erosions of the skin and mucous membranes. Nikolsky's sign, linked to the loss of intraepidermal cohesion, is present.[49]

Histology shows the detachment of epidermal cells (acantholysis), responsible for intraepidermal blisters. Direct immunofluorescence performed on a perilesional skin biopsy specimen reveals immunoglobulin deposits around keratinocytes in the epidermis. This pattern, specific of pemphigus, may be absent in drug-induced cases.[50] In serum, the presence of autoantibodies reacting against the epidermis can be detected by indirect immunofluorescence, western-blotting or ELISA.

Two decades ago, up to 10% of cases of pemphigus in Western countries were drug-induced, with the disorder beginning weeks or months after initial drug exposure. The drugs involved were mainly D-penicillamine and, more rarely, other drugs containing a thiol radical, such as piroxicam, captopril or

other ACE inhibitors. With decreasing use of D-penicillamine, the incidence of drug-induced pemphigus has been reduced.

2.3 Drug-Induced Bullous Pemphigoid

Bullous pemphigoid classically corresponds to an autoimmune blistering disease characterised by subepidermal blister formation with linear continuous deposits of IgG along the epidermal membrane zone. However, in a few cases, systemic drugs such as diuretics (e.g. spironolactone, an aldosterone antagonist) and antipsychotics can lead to bullous pemphigoid.[51]

2.4 Drug-Induced Lupus

There are several theories regarding the pathogenesis of drug-induced lupus.[52] It is important to distinguish between drug-induced systemic lupus erythematosus (LE) and drug-induced subacute cutaneous LE. Clinical manifestations of drug-induced systemic LE are mainly systemic, including fever, weight loss, pericarditis and pleuro-pulmonary inflammation, whereas cutaneous involvement, such as butterfly malar rash, photoeruptions and discoid or erythema multiforme-like lesions, is rare. There is no gender predilection. Vasculitis and renal or neurological involvement are rarely associated. The symptoms usually develop >1 year after the medication is begun.

Many of the drugs that induce systemic lupus are used less nowadays (e.g. procainamide, hydralazine, chlorpromazine, isoniazid, methyldopa, propylthiouracil, D-penicillamine, minocycline). More recent biological treatments (e.g. IFN, anti-TNF) can also induce autoimmune diseases, including lupus.

Drug-induced subacute cutaneous LE presents with psoriasiform and annular lesions, usually of the upper trunk and extensor surfaces of the arms, which are clinically and histologically indistinguishable from those seen in the idiopathic form of the disease. Drugs that induce this disorder include thiazide diuretics, calcium channel antagonists, terbinafine, NSAIDs and griseofulvin. Resolution of the eruption may or may not occur after discontinuation of the drug.

2.5 Pseudolymphoma

Drug-induced pseudolymphoma is an insidious disease that simulates lymphoma clinically and histologically. It develops some months or years after the drug responsible is first administered.

Cutaneous lesions may be solitary or numerous, localised or widespread, with red papules, plaques or nodules. Lymphadenopathy can often occur in association with this disease, but can also be isolated.[23] Histologically, dense lymphocytic infiltrates mimic T-cell or B-cell lymphomas. The distinct feature is based on polyclonality of the infiltrating lymphocytes.

Complete recovery occurs a few weeks after withdrawal of the drug responsible for inducing this disease. The majority of drug-induced pseudolymphomas have been reported with hydantoin, butabarbital, carbamazepine, ACE inhibitors, amiloride and D-penicillamine.

2.6 Acneiform Eruption

Acneiform eruptions represent approximately 1% of drug-induced skin eruptions.[53] Clinically, papules and/or pustules are seen primarily on the face and upper trunk, the same sites favoured by acne; comedones are usually absent. The interval between drug exposure and acneiform eruption depends on the causative agent. The major drugs implicated in acneiform eruptions include corticosteroids, androgens, hydantoins, lithium, halogen-containing derivatives and oral contraceptives (more often those that contain progestins with androgen-like effects). Epidermal growth factor receptor antagonists used in oncology are also responsible for acneiform eruptions. Folliculitis occurs in 43–85% of patients who take these drugs; this applies to all epidermal growth factor receptor antagonists.[54]

3. Drug-Induced Hair Disorders

3.1 Drug-Induced Hair Loss

A considerable number of medications have been reported to induce hair loss.[55,56] These agents may affect follicles through two main modalities, at two

different phases of the hair follicle cycle, leading to anagen or telogen effluvium. In the case of anagen effluvium, hair loss occurs within days to weeks of drug administration, whereas in telogen effluvium, the delay is approximately 2–4 months. Clinically, this condition is usually described as diffuse non-scaring alopecia. Drug-induced alopecia is usually reversible after discontinuation of the causative agent.

The extent and severity of alopecia depend on the drug as well as on the individual's predisposition. Diagnosis of drug-induced alopecia remains difficult. The only way to confirm this is to observe whether or not any improvement occurs after discontinuation of the suspected drug. Drugs that have been reported to induce hair loss include antineoplastic agents (e.g. alkylating agents, bleomycin, vinca alkaloids, platinum compounds), antiepileptic drugs (carbamazepine, sodium valproate), antihypertensive drugs (β-blockers), antidepressants, antithyroid drugs, IFNs, oral contraceptives and lipid-modifying agents.

3.2 Hirsutism

Hirsutism is an excessive growth of coarse hair with masculine characteristics observed in females. Hair growth tends to be localised on the lateral aspects of the face and back and is the result of an androgenic stimulation of hormone-sensitive hair follicles. Anabolic steroids, oral contraceptives of the non-steroid progesterone group, testosterone, and corticotropin can induce hirsutism.[56]

3.3 Hypertrichosis

Iatrogenic hypertrichosis is mainly localised on the forehead and temporal areas of the face. It is usually reversible and differs from drug-induced hirsutism. The main drugs responsible for hypertrichosis include streptomycin, anti-inflammatories, glucocorticosteroids, vasodilators (diazoxide, minoxidil), diuretics (acetazolamide), antiepileptic drugs (phenytoin), immunosuppressive agents, psoralens and zidovudine.[56]

3.4 Change in Hair Colour

Drug-induced changes in hair colour are not a common adverse effect of medications. The main drugs associated with hair discolouration include chloroquine, IFN-α and chemotherapeutic agents. Recently, abnormalities of hair pigmentation have been reported with tyrosine kinase inhibitors. Hair pigmentation is dependent on modulation of tyrosine kinases related to the c-kit (stem cell factor) pathway. Blocking KIT and platelet derived growth factor receptors with imatinib induces hair repigmentation, whereas sunitinib is responsible for hair depigmentation.[57,58]

3.5 Change in Hair Structure

Hair modifications have recently been observed in patients administered EGFR antagonists. It has been reported that after 2–3 months of treatment scalp hair can become more brittle, fine and curly. Trichomegaly of eyelashes has also been described with EGFR antagonists. The only other acquired disorder known to be associated with eyelash trichomegaly is HIV infection.[54,59]

4. Drug-Induced Nail Disorders

A large number of drugs can be responsible for the development of nail changes, usually involving several or all nails and needing several months to recover after withdrawal of the causative agent. The pathogenesis is most often toxic in nature. Drug-induced nail changes include Beau's line (transversal depression of the nail plate, indicating a history of transient nail bed trauma not severe enough to result in detachment of the nail plate), onycholysis, onychomadesis, pigmentation, paronychia and ischaemic changes.[60]

4.1 Onycholysis

Onycholysis corresponds to detachment of the nail plate from the nail bed, beginning on the distal part of the nail. This disorder develops because of the presence of air in the subungual space. Onycholysis can sometimes lead to nail loss, and can be associated with many conditions, including secon-

dary to drug treatments such as tetracyclines, fluoroquinolones, psoralens, NSAIDs, captopril, retinoids, phenothiazines and sodium valproate. The role of associated sunlight exposure is noteworthy in the case of some of these drugs.

Many chemotherapeutic agents are also responsible for onycholysis. Most of these agents are related to anthracyclines or taxanes such as paclitaxel and docetaxel.[61] In these cases, the risk of onycholysis in patients receiving cytotoxic drugs can be increased by sunlight exposure. Additional risk factors for onycholysis are the use of docetaxel or mitoxantrone, the combined use of an anthracycline and a taxane, and prolonged weekly paclitaxel administration. The real incidence of onycholysis associated with chemotherapeutic agents cannot be determined, but it does occur in a significant minority of patients.

4.2 Onychomadesis

Onychomadesis is caused by temporary arrest of nail matrix mitotic activity. The most common drugs reported to induce onychomadesis include carbamazepine, lithium and retinoids. Chemotherapeutic agents such as cyclophosphamide and vincristine are also commonly implicated in this disorder.[62,63]

4.3 Paronychia and Pseudopyogenic Granuloma

Paronychia and multiple pyogenic granulomas are well known adverse effects of treatment with systemic retinoids.[64] Multiple periungual pyogenic granulomas associated with paronychia have also been described in patients taking lamivudine and indinavir.[65] Symptoms may appear 2–12 months after the beginning of treatment and tend to persist, as it is not possible to discontinue use of these antiretroviral agents. Topical application of a strong antimicrobial agent and topical corticosteroids may significantly improve the lesions. Recently, anti-EGFR monoclonal antibodies (cetuximab and gefitinib) have been associated with the development of paronychia, with progressive and painful periungual abscesses of the fingers and toes.[66,67]

4.4 Nail Discolouration

4.4.1 Melanonychia

Several drugs are responsible for nail bed hyperpigmentation, which is most likely due to melanocyte stimulation. Among these drugs, chemotherapeutic agents such as anthracyclines, taxanes, doxorubicin, daunorubicin and fluorouracil are associated with nail hyperpigmentation.[48] Nail pigmentation can also progressively develop with zidovudine; however, it appears to be reversible and dose-dependent.[68]

4.4.2 Discolouration (Non-Melanin)

Several other drugs can induce discolouration of nails, including minocycline, antimalarials, gold and clofazimine.[69,70] The required conditions for resolution depend on the severity of pigmentation and can be dose-dependent.

5. Minimal Requirements for Notification or Publication of a Case of Drug Eruption

The clinical presentation of drug eruption is highly variable, ranging from the most common transient and benign erythema to the most severe life-threatening diseases as already described (table III). It is important for clinicians, with the help of a dermatologist when possible, to recognise and properly categorise these adverse skin reactions when reporting a case to a pharmacovigilance surveillance centre. The more severe the case is, the more precise the documentation should be.

A logical approach begins with a precise description of the lesions (supported by a series of daily clinical photographs), the type of primary lesions, their distribution and the extent of cutaneous involvement, the existence or absence of involvement of mucous membranes, and associated symptoms such as fever, lymph nodes and/or visceral enlargement. The reporting of timing-of-onset, progression and regression of all these events should be as precise as possible.

With the widespread use of digital cameras, it is easier to obtain and transmit good quality photographs that will help case confirmation by experts.

Table III. The different clinical presentations of cutaneous adverse drug reactions

Condition	Minimum criteria for diagnosis of the condition/case definition (where applicable)	Specific features supporting drug aetiology	Known non-drug causes	Established drug causes
Exanthematous eruptions	Widespread maculopapular rash	Polymorphism of skin lesions 4–14 days after drug introduction	Viral infection	Allopurinol; antiepileptic drugs; aminopenicillins; cephalosporins; sulfonamide; antibacterials
Urticaria	Erythematous and oedematous papules and plaques; pruritus	Rapid onset (≤36 hours) after drug introduction	Food; contact with vegetals; insect bites	Antibacterials; anaesthetics; NSAIDs; ACE inhibitors
Angioedema	Subcutaneous or mucosal swelling	Rapid onset (≤36 hours) after drug introduction	C1 inhibitor deficiency	Antibacterials; anaesthetics; NSAIDs; ACE inhibitors
Phototoxicity	Unusual sunburn or bullous lesions on dorsum of hands	Sun exposure	Phytophotodermatosis	Cyclins; quinolones; amiodarone; psoralens; voriconazole; methotrexate; naproxen; furosemide (frusemide)
Photoallergy	Acute eczema on sun-exposed areas of skin; lichenification is more characteristic in chronic lesions	Sun exposure (delayed)	Contact eczema; atopic eczema	NSAIDs (propionic acid derivatives, piroxicam); phenothiazine; thiazide diuretics; sulfonamide derivatives; fibrates and statins (lipid-modifying agents); ACE inhibitors and calcium channel antagonists; dacarbazine and other chemotherapy agents; sunscreen ingredients; topical antiseptics; cosmetic ingredients
Vasculitis	Purpuric or necrotic papules mainly on lower legs	7–21 days after initiation of drug introduction	Autoimmune disease; infection; Schönlein-Henoch purpura; cancer	Allopurinol; NSAIDs; cimetidine; antibacterials; hydantoin; propylthiouracil
Serum sickness-like eruption	Morbilliform or urticarial rash; lymphadenopathy	1–3 weeks after drug introduction; normal complement level; no immune complexes; no vasculitis	Serum of animal origin containing antitoxin	Cefaclor; minocycline; penicillin; propranolol
Anticoagulant-induced skin necrosis	Painful erythematous plaques; haemorrhagic blisters; necrosis	3–5 days after initiation of warfarin; protein C deficiency	Intravascular disseminated coagulation; systemic infections (streptococcal, pneumococcal, meningococcal)	Coumarin derivatives; anticoagulants; heparin
AGEP (acute generalised exanthematous pustulosis)	Skin erythematous; oedematous eruption (with numerous non-follicular pustules predominant on manifolds); fever; hyperleukocytosis; subcorneal or intra-epidermal pustules on skin pathology	Rapid onset, rapid recovery 1–2 days after drug introduction	Pustular psoriasis; viral infection (enterovirus, parvovirus B19); mercury exposure	Diltiazem; hydoxychloroquine; pristinamycin; aminopenicillins; terbinafine

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Table III. Contd

Condition	Minimum criteria for diagnosis of the condition/case definition (where applicable)	Specific features supporting drug aetiology	Known non-drug causes	Established drug causes
DRESS (drug reaction with eosinophilia and systemic symptoms	Severe erythematous and infiltrate eruption plus some or all of the following: fever, lymphadenopathy, haematological abnormalities, hepatitis, arthralgias, pulmonary infiltrates, interstitial nephritis	Predominant eosinophilia; facial oedema	Acute viral infection; idiopathic hypereosinophilic syndrome; lymphoma and pseudolymphoma	Phenobarbital (phenobarbitone); carbamazepine; phenytoin; sulfonamides; minocycline; allopurinol; gold salts; dapsone
Fixed drug eruption	Erythematous/violaceous or oedematous plaque with or without blister evolving to pigmented macules that recur at same sites at each rechallenge. After several relapses, may involve large areas of skin. When present on skin biopsy, melanophages are diagnostic	Only caused by drugs	Only caused by drugs	Phenazones; barbiturates; tetracycline; sulfonamides; carbamazepine; oxicam NSAIDs; paracetamol (acetaminophen); cysteine derivatives
SJS (Stevens-Johnson syndrome) and TEN (toxic epidermal necrolysis)	Skin and mucous blistering or erosive lesions with diffuse erythema and Nikolsky's sign; full thickness epidermal necrosis on skin biopsy; negative direct immunofluorescence	Onset 7–21 days after drug exposure	Mainly caused by drugs; differs from erythema multiforme, exfoliative dermatitis, staphylococcal scaled skin syndrome	Antibacterial sulfonamides; antiepileptics; NSAIDs (oxicam and pyrazolone); allopurinol; nevirapine
Pigmentary changes	Localised or widespread darkening of skin or mucosa; specific colouration due to accumulation of specific heavy metals; hypo-pigmentation	Possibly sun exposure; gold, silver, arsenic	Chronic inflammation; vitiligo	Minocycline; antimalarials; amiodarone; oral contraceptives; imipramine; chemotherapy agents; clofazimine; tretinoin (retinoic acid), corticosteroids, quinone derivatives
Pemphigus	Flaccid and/or crusted blisters; Nikolsky's sign; mucous membrane erosions; acantholysis with positive intra-epidermal direct immunofluorescence on skin biopsy	Direct immunofluorescence on skin biopsy	Autoimmune pemphigus; paraneoplastic pemphigus	Drugs containing a thiol radical: D-penicillamine; captopril and other ACE inhibitors; piroxicam
Lupus	Fever, general inflammatory symptoms (heart, lung, kidney) in systemic lupus erythematosus; annular or psoriasiform cutaneous lesions on trunk or arms in subacute lupus erythematosus	Long duration of drug exposure, i.e. 1 year	Non-drug-induced lupus	Procainamide; hydralazine; chlorpromazine; isoniazid; methyldopa; propylthiouracil; practolol, D-penicillamine; psoralens; minocycline; thiazide diuretics; calcium channel antagonists; terbinafine; NSAIDs; griseofulvin

Continued next page

Table III. Contd

Condition	Minimum criteria for diagnosis of the condition/case definition (where applicable)	Specific features supporting drug aetiology	Known non-drug causes	Established drug causes
Pseudolymphoma	Red skin papules plaques or nodules, adenopathy; polyclonal dense T- or B-lymphocytic infiltrate on skin biopsy	Long duration of drug exposure, i.e. from many months to years; polyclonality of cutaneous infiltrate	Non-Hodgkin's lymphoma	Hydantoin, butabarbital; carbamazepine; ACE inhibitors; amiloride; D-penicillamine
Acneiform eruption	Late-onset acne	Temporality	Juvenile acne; cosmetic-induced acne; premenstrual acne	Corticosteroids; androgens; hydantoins; lithium; halogen-containing derivatives; oral contraceptives; EGFR antagonists
Hair loss	Non-scarring reversible alopecia	Temporality	Alopecia areata	Chemotherapy; antiepileptic drugs; antihypertensive drugs; antidepressants; anti-thyroid drugs; interferons; oral contraceptives; lipid-modifying agents
Hirsutism	Excessive growth of coarse hair (in females)	Temporality	Endocrinopathy	Anabolic steroids; oral contraceptives (non-steroid progesterone group); testosterone; corticotropin
Hypertrichosis	Reversible forehead or temporal hair growth	Temporality	Porphyria	Streptomycin; glucocorticosteroids; diazoxid; minoxidil; acetazolamide; phenytoin; ciclosporin; psoralens; zidovudine
Hair colour change	Discolouration; repigmentation	Temporality	Ageing	Chloroquine, interferon-α; chemotherapy; tyrosine kinase inhibitors
Hair structure change	Acquired brittle, curly or fine hair	Temporality	HIV infection	EGFR antagonists
Onycholysis	Distal nail plate detachment from the nail bed	Temporality; possibly sun exposure	Psoriasis; trauma; epidermolysis bullosa	Tetracyclines; fluoroquinolones; psoralens; NSAIDs; captopril; retinoids; phenothiazine; sodium valproate; chemotherapy
Onychomadesis	Detachment of the proximal part of the nail plate	Temporality	Local trauma; epidermolysis bullosa	Carbamazepine; lithium; systemic retinoids; chemotherapy
Paronychia and pseudopyogenic granuloma	Inflammation of peri-ungueal skin on hands or toes	Temporality	Infection; trauma	Systemic retinoids; lamivudine, indinavir; EGFR antagonists
Melanonychia	Nail-bed hyperpigmentation	Temporality	Lentigines	Chemotherapy agents; zidovudine
Nail discolouration	Progressive discolouration of nail	Temporality	Renal or hepatic insufficiency	Minocycline; antimalarials; gold salts; clofazimine

EGFR = epidermal growth factor receptor.

Table IV. Checklist for notification of a cutaneous drug-induced adverse event

Patient details
Initials or other relevant identifier
Age/date of birth
Sex
Weight/height
History
Allergy
Drug or alcohol abuse
Family history
Previous reaction(s)
Tobacco use
Disease states, e.g. diabetes mellitus
Suspected medicinal product(s)
Trade name
Generic name (international nonproprietary name)
Batch number
Indication(s) for use
Dosage form and strength
Daily dose and regimen (specify units, e.g. mg, mL, mg/kg)
Route of administration
Start date
Stop date or duration of treatment
Concomitant drugs
Include, for example, over-the-counter (non-prescription) medicinal products and non-medicinal product therapies
Provide the same information as for the suspected product
Details of suspected adverse drug reaction(s)
Full description of reaction(s), including photographs, body site involvement and severity, as well as the criteria for regarding the report as serious
Start date of onset of reaction
Stop date or duration of reaction
Dechallenge and rechallenge information
Outcome
Information on recovery and any sequelae; tests or treatment required
Hospitalisation
In case of death, state cause (include autopsy or other postmortem findings when available) and date of death
Unknown
Details of person reporting the adverse drug reaction
Name/address/telephone number/profession (speciality)
Administrative and sponsor/company details (when needed)
Source of report: spontaneous, literature, other
Date report was received by manufacturer
Country in which reaction occurred
Type of report: initial vs follow-up
Name and address of manufacturer
Name, address, telephone number and fax number of contact person from manufacturer (this number is the same for both initial and follow-up reports)

Although a skin biopsy may be of little help in the investigation of the most common drug-induced rashes or urticaria, it is of tremendous value when investigating severe forms of skin adverse drug reactions.

Data regarding all the drugs taken by the patient, the dates of drug initiation or withdrawal and the doses administered need to be systematically collected. The chronology of drug administration is of paramount importance. The time between initiation of the drug treatment and the onset of the skin eruption is a key element in identifying the causative agent. Monitoring the course of the reaction after drug withdrawal can also be helpful.

Every physician reporting a severe case of an adverse drug reaction should understand that insufficiently documented reports may induce bias in the evaluation of the risk. Doubts regarding the nature of the reaction, failure to recognise duplicate reports of the same cases from several sources, and doubts regarding drug causality are some of the common problems that may impair decision-making by pharmaceutical companies or regulatory agencies. The minimal required data for notification are listed in table IV, and the specific format of suspected adverse reaction report forms prepared by the Council for International Organisations of Medical Sciences can be downloaded from http://www.cioms.ch/cioms.pdf.

6. Conclusion

Due to the increasing use of new drugs in a larger aging population, the recognition of drug-induced skin, nail and hair disorders is of high importance to better health care. In the case of severe cutaneous adverse drug reactions with high mortality or morbidity rates, the recently improved knowledge of the immune mechanisms involved should allow further studies to establish specific drug therapies that will improve survival rates and avoid potential sequellae.

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Correspondence: Dr *Jean-Claude Roujeau*, Service de Dermatologie, Hôpital Henri Mondor, 94010 Créteil, France.
E-mail: jean-claude.roujeau@hmn.aphp.fr