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Clinics in Dermatology

Drug eruptions: Great imitators

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Abstract Drug eruptions are among the great masqueraders that sometimes cause diagnostic challenges in clinical practice. Pharmacologic agents may induce skin changes, sharing the same pathophysiologic mechanisms of specific dermatoses, or inducing drug eruptions with different pathologic mechanisms that have similar clinical presentations. The former conditions are usually called drug-induced skin diseases, whereas the latter conditions are termed "dermatosis–like drug eruptions." Both types are great imitators in dermatologic practice and can be easily misdiagnosed as other diseases or lead to unrecognized causative agents.

Introduction

The skin is among the parts of the body most commonly affected by adverse drug reactions.[1] Eruptions occur in approximately 0.1% to 1% of all patients being treated with pharmaceuticals.[2,3] Drug eruptions, defined as skin eruptions induced by drugs, are relatively common, affecting 2% to 3% of hospitalized patients.[1] The incidence may increase with age.[4] Drug eruptions are usually not characteristic for any specific drug or group of drugs, but experience has shown that certain clinical pictures commonly follow the use of certain drugs. Such untoward conditions may mimic other important skin diseases, thus causing substantial diagnostic challenges in clinical practice.

In 1887, Prince A. Morrow (1846-1913) wrote his famous book *Drug Eruptions: A Clinical Study of Irritant Effects of Drugs Upon the Skin.*[5] At that time, the abnormal phases of drug action were comparatively an unexplored field. Although it has long been known that eruptive disturbances of various kinds may result from the use of certain drugs, the number of drugs in common use capable of causing cutaneous disorders, the clinical appearances which they present, and the conditions that influence their development are not sufficiently familiar to the profession.[5]

Action mechanism

Drug-induced adverse reactions are often classified as type A and type B reactions. The type A reaction (pharmacotoxicologic) is intended to refer to predictable side effects that occur as a result of a pharmacologic action of the given drug, whereas type B (hypersensitivity) reactions are regarded as not being predictable.[1] The common drug eruptions are usually caused by hypersensitivity reactions or referred to as drug allergy. Cutaneous side effects of anticoagulant such as warfarin necrosis are due to the pharmacologic effects of the drug. The term "idiosyncratic drug reactions" refers to those occur rarely and unpredictably among the population. Idiosyncratic drug reactions are usually considered to be type B reactions, but some of them might be related to genetic predisposition rather than an immunologic mechanism.

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Diagnosis

The diagnosis of drug eruption is mainly made from the medical history, cutaneous examination, skin pathology, blood tests, or immunologic tests. Specific immunologically based tests to evaluate delayed drug reactions may be performed 1 to 6 months after the complete resolution of the clinical manifestations to confirm the etiology. These tests include patch testing, intradermal or skin prick testing, and *in vitro* testing such as the lymphocyte transformation test. Recently, genetic testing has also been used as a screening test for certain types of drug eruptions in some ethnic populations.

Pharmacogenetic association of HLA and drug hypersensitivity includes immediate type reactions, fixed drug reaction, drug reaction with eosinophilia and systemic clinical manifestations (DRESS)/drug-induced hypersensitivity syndrome (DiHS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). These associations are usually drug and ethnic specific, indicating that specific HLA molecules may have higher binding affinities for specific drug antigens and present the drug antigens to specific TCRs, causing a series of T-cell activations and adverse immune responses.[6] A strong genetic association between HLA-B*15:02 and CBZ-induced SJS/TEN was found in Han Chinese first,[7] and has further been validated in various other Asian populations, including Thai, Indian, Malaysian, Vietnamese, Singaporean, and Hong Kongese cohorts.[6] The HLA-B*15:02 allele has also been identified as the common risk factor for SJS/TEN caused by other aromatic antiepileptic drugs, such as phenytoin, oxcarbazepine, and lamotrigine.[6] The association between HLA alleles and CBZ-induced SCAR is phenotype and ethnic specific. The HLA-A*31:01 allele is a specific predictor of CBZ-induced DRESS but not CBZ-induced SJS/TEN in Europeans and Han Chinese.[6] HLA-B*58:01 is the genetic risk marker for allopurinol-induced hypersensitivity in Asian and European populations. Other pharmacogenomic associations include HLA-B*57:01 and abacavir-induced hypersensitivity reactions, HLA-B*13:01 and dapsone-induced hypersensitivity syndrome in Chinese, HLA-B*59:01 and methazolamide-induced SJS/TEN in Koreans and Japanese, HLA-B*73:01 and oxicam-induced SJS/TEN in Europeans, nevirapine-induced hypersensitivity in patients with HLADRB1*01:01 in Western Australia, HLA-B*35:05 in Thailand, and HLA-Cw8 in Japan.[6]

Although eosinophilia is a common feature of allergy, it is not usually present in patients with drug eruption. The presence of eosinophilia may occur in DRESS, but it is less often found in other types of drug eruptions such as acute generalized exanthematous pustulosis (AGEP) or SJS.

Clinical types for drug eruptions

A list of skin eruptions that are commonly caused by drugs is provided in the Table 1.

Acne–like (acneiform) drug eruptions

Acne–like drug eruptions, or acneiform drug eruptions, are dermatoses that resemble acne vulgaris. Lesions may be papular, pustular, nodular, or cystic. Although the mainstay of acne vulgaris consists of comedones, acneiform drug eruptions typically manifest as red papules and/or pustules without comedones on the face, scalp, chest, back, abdomen, or thighs (Figure 1). Bromides, iodides, lithium, and epidermal growth factor receptor (EGFR) inhibitors are common culprits associated with acneiform drug eruption.[1,8] The incidence of an acneiform eruption in patients treated with EGFR inhibitors ranges from 66% to 89%. The onset time for this skin toxicity ranges from 3 to 14 days after the initiation of EGFR inhibitor treatment.[8] The mechanisms of acneiform eruption may result from excretion of halogen via sweat or sebaceous glands, and then it causes an inflammatory reaction in the skin. Direct receptor inhibition by EGFR inhibitors downregulates the level of the phosphorylated EGFR in the outer layer of hair follicles, resulting in growth arrest and apoptosis of keratinocytes and also inducing inflammatory cytokine/chemokine release. The eventual influx of neutrophils contributes to the inflammation manifesting as superficial perifolliculitis or suppurative folliculitis, which also reflects the histopathologic changes, including neutrophilic infiltration of hair follicles, epidermal dysmaturation, neutrophil aggregation, red blood cell extravasation, and endothelium plumping. Management strategies for acneiform drug eruptions may include topical corticosteroids and antibiotics, or oral antibiotic according to the severity.[8]

Alopecia–like drug eruptions

Hair loss may be associated with antineoplastic agents, colchicine, clofibrate, testosterone and other androgens, tricyclic antidepressants, beta-blockers, heparin, interferons, progesterone derivatives, coumarin derivatives, and retinoids. Recently antitumor necrosis factor agents, cancer-targeting therapies (such as EGFR inhibitors and RAF inhibitors), and immune checkpoint inhibitors have also been reported to cause alopecia–like changes.[8–10]

Drugs may cause hair loss via two mechanisms:

- by inducing an abrupt cessation of mitotic activity in rapidly dividing hair matrix cells (anagen effluvium)
- by inducing the follicles into premature rest (telogen effluvium).

Hair loss due to anagen effluvium usually occurs within days to weeks of drug administration, whereas drug-induced hair loss from telogen effluvium usually occurs 2 to 4 months after starting treatment.[11] Anagen effluvium is seen most commonly with antineoplastic drugs. Telogen effluvium is associated with anticoagulants, retinoids, interferons, and antihyperlipidemic drugs.[11]

Alopecia, secondary to immune checkpoint inhibitors, has been reported in 1.0% to 2.0% of treated patients. It may present

Table 1 Clinical types of drug eruptions and the most common drugs that cause them

Clinical type	Clinical characteristics	Drug(s)
Acne-like or pustular lesions	Onset time: 3-14 days after the initiation of EGFR inhibitor treatment Clinical features: papular, pustular, nodular, or cystic lesions without comedones on the face, scalp, chest, back, abdomen, or thighs	Epidermal growth factor receptor (EGFR) inhibitors, bromides, iodides, lithium, testosterone, corticosteroids
Alopecia	Onset time: hair loss due to anagen effluvium usually occurs within days to weeks of drug administration, whereas drug-induced hair loss from telogen effluvium usually occurs 2-4 months after starting treatment	Antineoplastic agents, colchicine, clofibrate, testosterone and other androgens, tricyclic antidepressants, beta-blockers, heparin, interferons, progesterone derivatives, coumarin derivatives, retinoids, cancer-targeting therapies (such as EGFR inhibitors and RAF inhibitors), and immune checkpoint inhibitors
Angioedema	Angioedema consists of deep swelling of the dermis and subcutaneous tissues that may coexist with urticaria usually lasting for less than 24 hours	Antimicrobials, such as penicillins, cephalosporins, and sulfonamides; aspirin, NSAIDs, ACE inhibitors; morphine and codeine
Burn-like eruptions	SJS and TEN are characterized by epidermal necrosis and sloughing of the mucous membranes and skin	Anticonvulsants, sulfa-containing drugs, antibiotics, nonsteroidal anti-inflammatory drugs, and uric acid–lowering agents
Cellulitis-like drug eruptions	FDE is a distinctive reaction, characterized by acute development of erythematous and edematous plaques with a grayish center or frank bullae	NSAIDs (acetylsalicylic acid, ibuprofen, naproxen, mefenamic acid), antibacterial agents (trimethoprim-sulfamethoxazole, tetracyclines, penicillins, quinolones, dapsone), barbiturates, acetaminophen (paracetamol), and antimalarials
Eczematoid (eczema-like) drug eruptions	A drug eruption may also present as systemic contact dermatitis mimicking mercury exanthem or baboon syndrome Baboon syndrome (see also SDRIFE): Systemic contact dermatitis owing to ingestion, inhalation, or percutaneous absorption; symmetric diffuse acute light-red exanthema on the buttocks, anogenital area, major flexural areas of the extremities; peaks at day 2-5 of exposure to the involved allergens; resolves within 1 week; SDRIFE specifically refers to those cases induced by drugs Drug-induced phototoxic eruptions typically present as an exaggerated sunburn, often with blisters Photoallergy is characterized by widespread dermatitis in the sun-exposed areas, mainly the face, chest, and dorsum of the hands	Mercury (most often); also ampicillin, amoxicillin, ceftriaxone, penicillin, clindamycin, nickel, erythromycin, heparin, and food additives Nonsteroidal anti-inflammatory drugs (NSAIDs), quinolones, tetracyclines, amiodarone, phenothiazines, vemurafenib, voriconazole, doxycycline, and chlorpromazine are the most frequent causes of phototoxicity
Erythema nodosum–like eruption	Patients develop red, often tender, cutaneous plaques or nodules, particularly localized to the extremities	BRAF inhibitor, immune checkpoint inhibitors, and oral contraceptives
Erythroderma-like (exfoliative dermatitis–like) drug eruptions	Erythroderma is defined as chronic scaling erythema involving greater than 90% of the body surface area. Diffuse exfoliation is a characteristic feature of this disease. Drug reaction with eosinophilia and systemic clinical manifestation (DRESS); also called drug-induced hypersensitivity syndrome (DiHS): exanthematous or papulopustular febrile eruption with hepatitis (also possible lung, renal, thyroid involvement), lymphadenopathy, and eosinophilia	Aromatic antiepileptic agents (carbamazepine, phenytoin, lamotrigine, oxcarbazepine, and phenobarbital), allopurinol, and the sulfonamides

(continued on next page)

Table 1 (*continued*)

Clinical type	Clinical characteristics	Drug(s)
Hyperpigmentation	Pigmentation from chemotherapeutic agents may present as photo-distributed hyperpigmentation, serpentine supravenous hyperpigmentation, widespread reticulate hyperpigmentation, serpentine streaks on the back and buttocks, and acral pigmentation	5-Fluorouracil–based drugs, doxorubicin, melphalan, docetaxel, paclitaxel, cyclophosphamide, ifosfamide, thiotepa, and bleomycin
Ichthyosis	Characterized by dryness, roughness, and scaling changes As the condition progresses, fissures appear, and the skin becomes itchy and presents with a "crazy-paving" pattern similar to that seen in ichthyosis	EGFR inhibitors (gefitinib, erlotinib, afatinib, and osimertinib) and ponatinib
Lichen planus–like drug eruptions	Characterized by symmetrically distributed, violaceous, flat-topped, pruritic papules on the trunk and the extremities	Penicillamine, gold salts, β-blockers, thiazide diuretics, and antimalarials; TNF-α inhibitors and immune checkpoint inhibitors
Lupus erythematosus–like drug eruptions	The clinical manifestations of drug-induced SLE include fever, weight loss, pericarditis, and pleuro-pulmonary inflammation. In contrast, malar rash, discoid rash, and erythema multiforme–like lesions are rarely seen in drug-induced SLE.	Procainamide, hydralazine, minocycline, diltiazem, and penicillamine
Lymphoma–like drug eruptions	May be solitary or numerous, as well as localized or widespread with red papules, plaques, or nodules and even erythroderma-mimicking mycosis fungoides	Anticonvulsants, antidepressants, antihypertensives, beta blockers, calcium channel blockers, diuretics, and antibiotics
Measles–like drug eruptions	Usually consist of symmetrically distributed erythematous macules or papules that usually begin on the trunk and upper extremities and then become confluent	Antimicrobials, NSAIDs, and sulfonamides
Pellagra	Characterized by dermatitis, diarrhea, dementia, and eventually death due to niacin, or its precursor tryptophan, deficiency	Isoniazid, thallium poisoning
Pemphigoid	Drug-induced bullous pemphigoid is characterized by a younger age of onset than spontaneously occurring bullous pemphigoid. Lesions usually appear as tense bullae on normally appearing skin, or (more uncommonly) on an erythematous or even urticarial base.	Neuroleptics and antidiuretics (mainly aldosterone antagonists), loop diuretics, ACE inhibitors, anticoagulants, and diuretics; anti–TNF-α agents and dipeptidyl peptidase 4 inhibitors
Pemphigus	Pemphigus foliaceus–like lesions. Other features include prodromal pruritus clinical manifestations and absence of mucosal involvement.	Penicillamine and other thiol compounds, including captopril and piroxicam
Pityriasis rosea–like eruption	Presence of some oval-shaped erythematous patches with collarette scales	Allopurinol, nimesulide, acetyl salicylic acid, ACE inhibitors, and ACE inhibitors in combination with hydrochlorothiazide
Psoriasis–like drug eruptions	Drug-induced psoriasis: A drug can cause preexisting psoriatic skin lesions to aggravate. Upon discontinuation of the implicated drug, the psoriasis exacerbation can decrease. Drug-aggravated psoriasis: The induced psoriatic skin lesions can persist	Anti–TNF-α agents, lithium, immune checkpoint inhibitors
Pustular psoriasis–like drug eruptions	AGEP is characterized by the appearance of superficial pustules after drug ingestion or infection. Dozens of symmetrically distributed, nonfollicular small pustules arise on edematous erythema with burning and/or itching especially located on the folds.	Antibiotics, particularly penicillins and macrolides
Seborrheic dermatitis–like eruption	Some scaling erythematous patches on the face	Vemurafenib and other BRAF inhibitors
Vasculitis	Palpable purpura and/or petechiae with or without systemic clinical manifestations such as fever, urticaria, and arthralgia	Hydralazine, minocycline, propylthiouracil, and levamisole

Table 1 (*continued*)

Clinical type	Clinical characteristics	Drug(s)
Vitiligo–like drug eruptions	Drug-induced vitiligo has similar features to vitiligo, but it is often characterized by rapid onset and extension. Small confetti-like white macules are common in new body sites.	Imatinib, hydroquinone, and phenol derivatives

ACE, angiotensin-converting enzyme; AGEP, acute generalized exanthematous pustulosis; NSAID, nonsteroidal anti-inflammatory drugs; PUVA, psoralens and ultraviolet light; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema.

as alopecia areata or alopecia universalis during treatment with immune checkpoint inhibitor therapies for cancer.[12]

Angioedema/urticaria

Angioedema and/or urticaria may be presentations of an IgE-mediated (type I hypersensitivity) drug reaction. Antimicrobials, such as penicillins, cephalosporins, and sulfonamides, are common causes of angioedema/urticarialike drug allergy. There is very limited information in the published literature about whether patients with one of these reactions to penicillin will experience the same reaction to cephalosporin. Therefore most clinicians also avoid related antibiotics in the future; however, if there is a strong indication for cephalosporin, a drug allergy expert should be consulted, if available, to review the details of the case and assess the risk of restarting the same or similar medication.[13] The risk of cross-reactivity between penicillins and cephalosporins is low, and the risk with carbapenems is even lower. Previous studies suggest that 99% of patients reporting a penicillin allergy (without prior penicillin skin testing) tolerate cephalosporin, partly because most of these patients do not have an immediate allergy to penicillin.[13]

Drugs may also cause urticaria due to mast cell degranulation by a non–IgE-mediated mechanism. The most frequently implicated drugs in this respect are the opiate analgesics, such as morphine and codeine.[11]

Urticaria is characterized by intensely pruritic, circumscribed, raised, and erythematous wheals. Angioedema consists of deep swelling of the dermis and subcutaneous tissues that may coexist with urticaria. Angioedema (in the absence of urticaria) occurs in 2 to 10 out of 10,000 new users of angiotensin-converting enzyme (ACE) inhibitors and usually affects the mouth or tongue.[11]

Burn–like drug eruptions

Several types of drug eruptions may be confused with burn injury, especially scalded skin or sunburn.

SJS and TEN are characterized by epidermal necrosis and sloughing of the mucous membranes and skin.[1,11] The sudden onset of large areas of skin detachment may occasionally present like burns, leading to diagnostic challenges (Figure 2). SJS and TEN are thought be a spectrum of the same disease. They are classified based on the amount of body surface area involved; lesions affect less than 10% of the body surface in SJS and more than 30% of the body surface in TEN.

SJS and TEN are usually caused by a limited number of drugs, including anticonvulsants, sulfa-containing drugs, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and uric acid–lowering agents.[14] Patients with SJS/TEN usually develop mucosal erosions or ulcers with variable extents of skin detachment after taking causative agents for 1 to 3 weeks.[1] The mucosal lesions may include the oral cavity, lips, conjunctivae, and genital areas. Skin lesions are usually widespread with a predilection on the trunk and consist of atypical flat target lesions, which may become confluent or result in the formation of blisters.[14] Systemic clinical manifestations may develop, including fever, general malaise, flu-like clinical manifestations, and possible internal organ

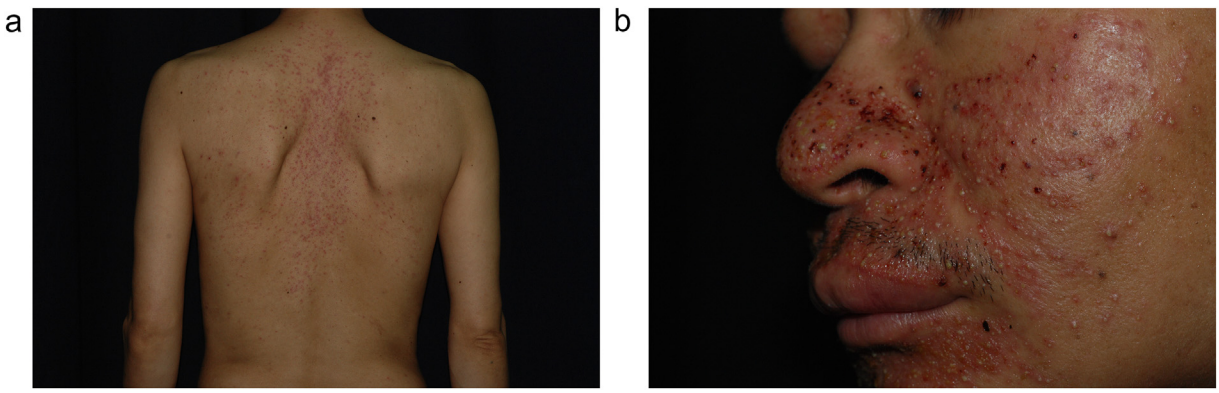

Fig. 1 **(a)** Acneiform drug eruptions manifest as red papules and/or pustules without comedones on the back. **(b)** Severe acneiform eruption on the face.

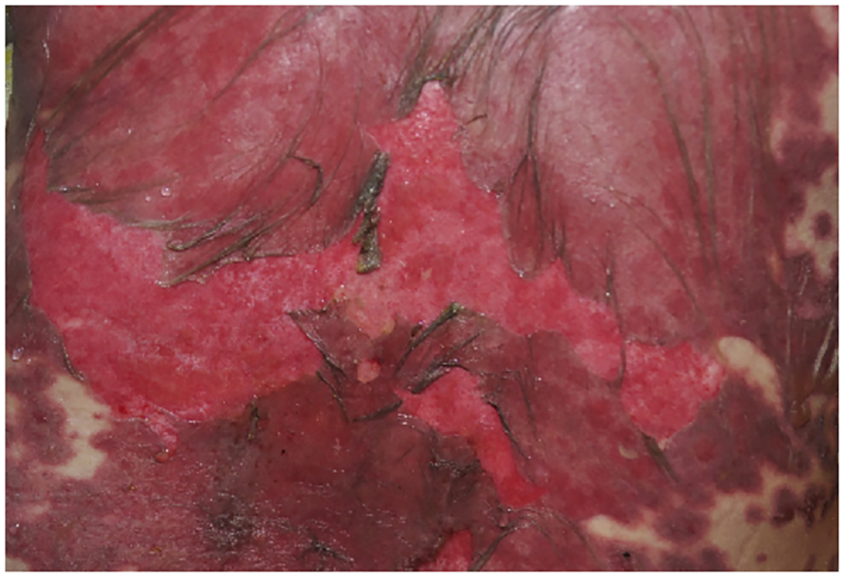

Fig. 2 Large areas of skin detachment in toxic epidermal necrolysis may present like burns.

involvement.[14] Histopathological examination is important to confirm the diagnosis of SJS/TEN. It is characterized by numerous apoptotic keratinocytes or forming confluent epidermal necrosis, basal layer vacuolarization, and scarce superficial dermal and perivascular lymphohistiocytic infiltrations. Granulysin exhibits potent toxic effects on keratinocytes and is thought to be the most important mediator in SJS/TEN. Granulysin is produced by intraepidermal natural killer (NK) cells and cytotoxic CD8+ T cells in the early phase of SJS/TEN.[14] There is still a lack of well-designed, randomized controlled trial to assess treatment efficacy in SJS/TEN due to rarity of the disease. Corticosteroid is by far the most commonly used treatment in SJS/TEN other than supportive care. Other potential treatments for SJS/TEN include intravenous immunoglobulin, cyclosporine, antitumor necrosis factor-α agent, and plasmapheresis.[14]

Cellulitis–like drug eruptions

Fixed drug eruption (FDE) is a distinctive reaction characterized by acute development of erythematous and edematous plaques with a grayish center or frank bullae. The mouth (lips and tongue), genitalia, face, and acral areas are the commonly involved sites. Because FDE usually occurs in acral regions with the sudden onset of erythematous edematous plaques, some cases of FDE might be misdiagnosed as cellulitis.[15,16] The drugs commonly involved in FDE include NSAIDs (acetylsalicylic acid, ibuprofen, naproxen, mefenamic acid), antibacterial agents (trimethoprim-sulfamethoxazole, tetracyclines, penicillins, quinolones, dapsone), barbiturates, acetaminophen (paracetamol), and antimalarials.[1]

The diagnosis of FDE in its typical presentation is usually straightforward, based on lesion morphology and history of recurrence in the same sites after the administration of the same drug or a chemically related drug. Patch testing can be performed to confirm the diagnosis by applying the suspected drug to an old FDE lesion to elicit a local reaction.

If FDE forms blisters, it may mimic a burn characterized by well-demarcated, dusky-red, or heavily pigmented patches involving the skin and mucosa. In recurrent episodes, patients tend to develop lesions at the same sites.[17] Bullous FDE is a particular form of FDE characterized by blister formation and erosions on the erythematous lesions of FDE, which may look like scald burns (Figure 3).

Eczematoid (eczema–like) drug eruptions

Gold eruptions are highly variable and may mimic many other skin conditions. They are characterized as nonspecific dermatitis, contact dermatitis, or dyshidrotic dermatitis. Some patients may even have associated stomatitis.[11]

A drug eruption may also present as systemic contact dermatitis mimicking mercury exanthem or baboon syndrome. The term "baboon syndrome" is used for a specific skin eruption resembling the red gluteal area of baboons occurring after systemic exposure to contact allergens.[1,11] Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), or intertriginous drug eruption, specifically refers to drug-related baboon syndrome with the distinctive clinical pattern. SDRIFE occurs a few hours to a few days after the administration of the offending drug. The dermatitis presents as a sharply demarcated V-shaped erythema in the gluteal/perianal or inguinal/perigenital areas, often with involvement of at least one other flexural or intertriginous fold, in the absence of systemic findings.[1]

Drug-induced phototoxic eruptions are caused by the absorption of ultraviolet light by the causative drug, which releases energy and damages cells directly.[11] Such eruptions

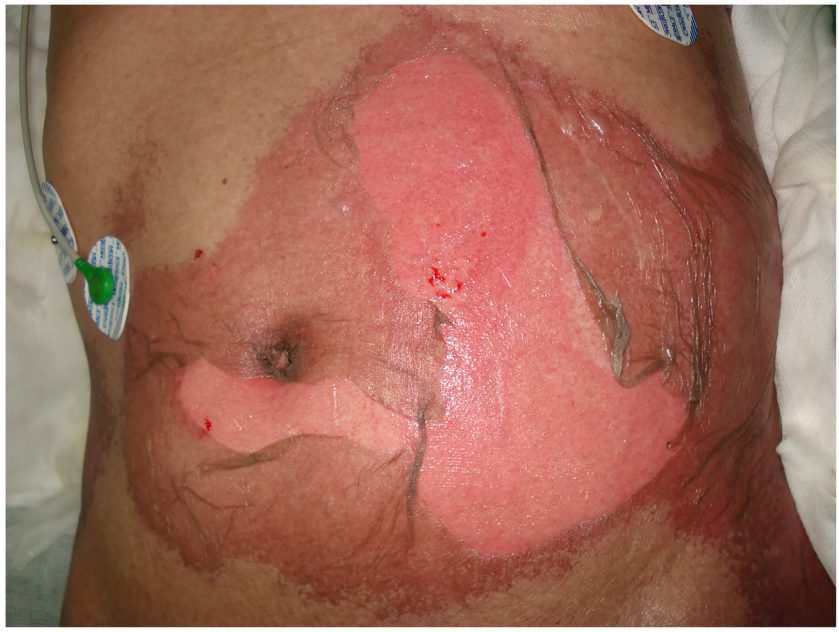

Fig. 3 Bullous fixed drug eruption may look like scald burns.

typically present as an exaggerated sunburn, often with blisters (Figure 4). In contrast, photo-allergic reactions are lymphocyte-mediated reactions caused by exposure to ultraviolet A light (UVA). It is postulated that the absorbed radiation converts the drug into an immunologically active compound that is then presented to lymphocytes by Langerhans cells, causing spongiotic dermatitis (eczema). NSAIDs, quinolones, tetracyclines, amiodarone, and the phenothiazines are the most frequent causes of phototoxicity. UVA is the wavelength most commonly implicated, although ultraviolet B light (UVB) and visible light can elicit reactions with some drugs such as doxycycline.[11] Molecularly targeted agents such as vemurafenib may also cause phototoxic reactions.[18] In a recent systematic review of 240 eligible studies with a total of 2,466 subjects, there were 1,134 cases of suspected phototoxicity associated with 129 drugs. Most of those associations were supported by either very-low-quality or low-quality evidence (89.1% of the studies), whereas the medications implicated by stronger evidence were vemurafenib, NSAIDs, and certain antimicrobials—

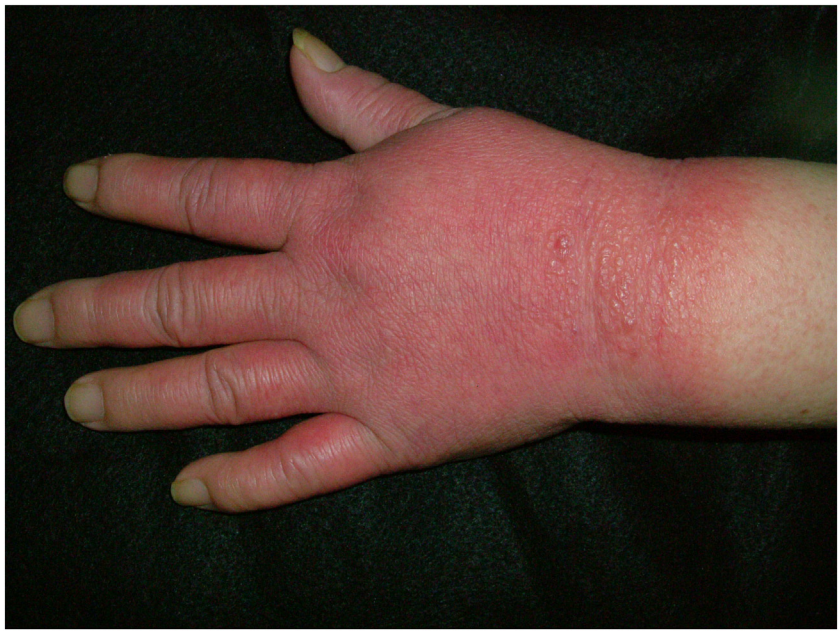

Fig. 4 Drug-induced phototoxic eruptions present as an exaggerated sunburn.

specifically, fluoroquinolones and tetracyclines. The most frequently implicated drugs are vemurafenib, voriconazole, doxycycline, hydrochlorothiazide, amiodarone, and chlorpromazine.[18]

In contrast to drug-induced phototoxic eruption, photoallergy is characterized by widespread dermatitis in the sun-exposed areas, mainly the face, chest, and dorsum of the hands. It is a lymphocyte-mediated reaction, caused by exposure to UVA. The absorbed radiation converts the drug into an immunologically active compound that is then presented to lymphocytes by Langerhans cells. Systemic photoallergens, such as the phenothiazines, chlorpromazine, sulfa products, and NSAIDs, can produce photoallergic reactions, although most of their photosensitive reactions are phototoxic.[11] A distinction between the photoallergic and phototoxic reactions may be difficult, but some principles have been established. Phototoxic drug reactions, besides happening much more often, will supposedly occur in all individuals exposed to high enough doses of the drug and the radiation at the appropriate wavelengths. The phototoxic reaction is the result of direct tissue and cellular injury by a photoproduct. Usually, it is dose dependent and does not require prior sensitization. It occurs minutes to hours after sunlight exposure and manifests clinically as exaggerated sunburn with associated burning and itching sensations localized on sun-exposed areas.[19]

Erythema nodosum–like drug eruptions

Several case series of BRAF inhibitor–treated patients who developed red, often tender, cutaneous plaques or nodules, particularly localized to the extremities, reminiscent of erythema nodosum (EN), have been published.[20,21] More recently, EN-like panniculitis has also been reported to be associated with treatment with immune checkpoint inhibitors.[22]

Erythroderma–like (exfoliative dermatitis–like) drug eruptions

Erythroderma is defined as chronic scaling erythema involving greater than 90% of the body surface area. Diffuse exfoliation is a characteristic feature of this disease.

Drugs are responsible for approximately 20% of erythrodermas. The aromatic antiepileptic agents (carbamazepine, phenytoin, lamotrigine, oxcarbazepine, and phenobarbital),

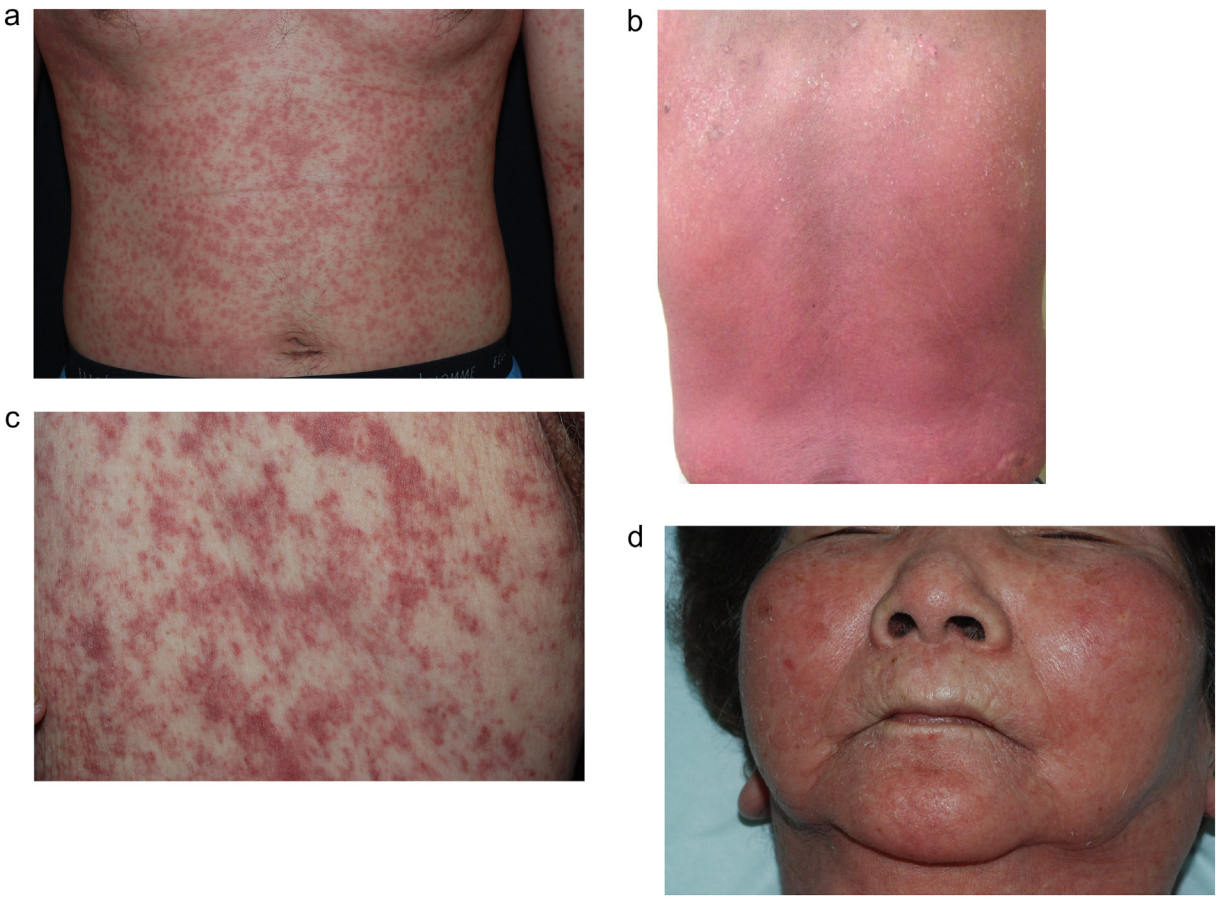

Fig. 5 Drug reaction with eosinophilia and systemic clinical manifestations (DRESS) may present as **(a)** maculopapular, **(b)** exfoliative, or **(c)** purpuric lesions. **(d)** Facial edema is the hallmark feature of the disease.

allopurinol, and the sulfonamides are the most frequent causes of erythroderma–like eruption.[11] In some patients, exfoliative dermatitis may be a manifestation of drug reaction with eosinophilia and systemic clinical manifestations (DRESS) or DiHS. DRESS is a severe adverse drug reaction characterized by fever, generalized skin eruption, lymphadenopathies, eosinophilia, and visceral organ involvement.[1,11,23,24] The most peculiar feature of DRESS is its long latent period, which ranges from 3 to 8 weeks after the commencement of the drugs.[23,24] The latency period of DRESS syndrome is longer than those of SJS and TEN.

The lesions of DRESS or DiHS are usually infiltrative papules and plaques with markedly purpuric change. These cutaneous lesions are frequently of polymorphic presentations, which can be reported as maculopapular, urticarial, exfoliative, lichenoid, pustular, bullous, target–like, or eczema–like lesions. Facial edema is the hallmark feature of the disease (Figure 5). Later, desquamation presents in the stage of resolution.[23] Both hematological abnormalities and impairments of solid organs may be observed in patients with DRESS syndrome. Eosinophilia is present in 66% to 95% of patients.[23] Atypical lymphocytosis in the blood can be identified in 27% to 67% of patients. In addition, lymphadenopathy can be found in 54% of patients by physical examinations or image studies.[23] Multiple internal organs may be damaged over the course of DRESS syndrome. Liver injury is the most common type of organ damage and has been found in 75% to 94% of patients. Renal involvement is also prevalent in patients with DRESS syndrome, occurring in around 12% to 40% of patients. Allopurinol-induced SJS/TEN or DRESS is more likely to develop in patients with underlying renal impairment due to the prolonged clearance of an allopurinol metabolite, oxypurinol, observed in these patients.[23]

Hyperpigmentation

Hyperpigmentation is a common skin toxicity related to anticancer chemotherapy. Unless it has a specific pattern of distribution, drug-induced hyperpigmentation may be confused with other pigmentary disorders such as lentiginosis, postinflammatory hyperpigmentation, Laugier-Hunziker syndrome, or *Peutz-Jeghers syndrome*. Pigmentation from chemotherapeutic agents may present as photo-distributed hyperpigmentation, serpentine supravenous hyperpigmentation, widespread reticulate hyperpigmentation, serpentine streaks on the back and buttocks, and acral pigmentation (Figure 6). Common chemotherapeutic agents that cause hyperpigmentation include 5-fluorouracil–based drugs, doxorubicin, melphalan, docetaxel, and paclitaxel. The alkylating agents such as cyclophosphamide, ifosfamide, and thiotepa may also produce hyperpigmentation, whereas bleomycin can cause flagellate dermatitis and pigmentation.[1]

Ichthyosis–like drug eruptions

Xerosis, being dry skin, is characterized by dryness, roughness, and scaling changes. The scales may be associated with inflammatory erythema or pigmentation. As the condition progresses, fissures appear, and the skin becomes itchy and presents with a "crazy-paving" pattern similar to that seen in ichthyosis (Figure 7).[8] Ichthyosis–like, or ichthyosiform, eruptions have been reported in association with many drugs, such as EGFR inhibitors (gefitinib, erlotinib, afatinib, and osimertinib) and ponatinib.[8,25,26] Recently, a case series of 52 patients receiving osimertinib found that xerosis was the most frequent dermatologic adverse effects, with 54% of the patients reporting some grade of this condition.[25]

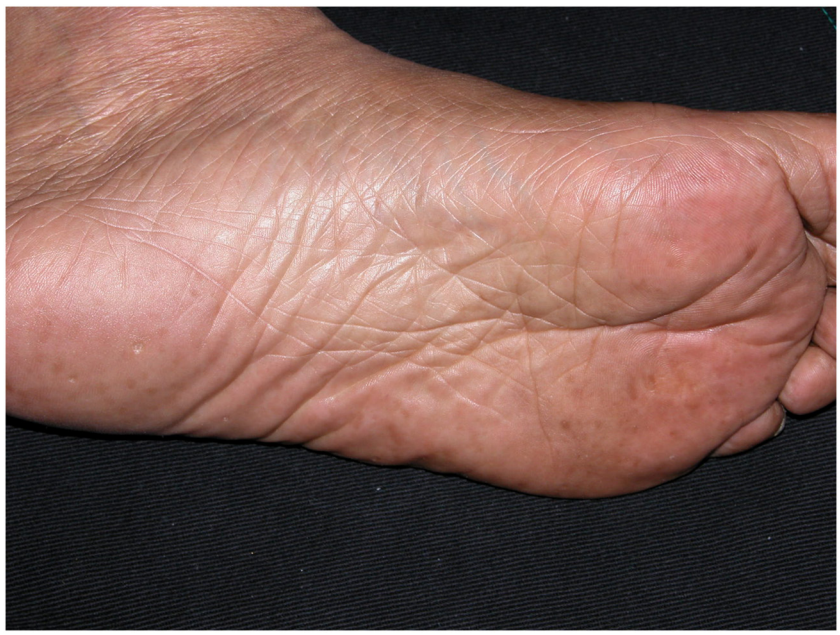

Fig. 6 Acral pigmentation in a patient receiving pemetrexed treatment.

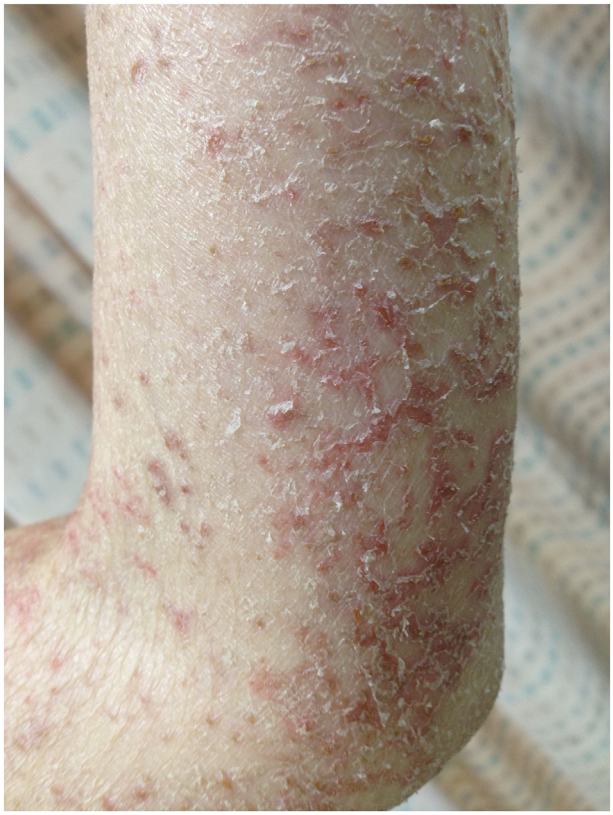

Fig. 7 Ichthyosis-like eruptions in a patient under the treatment with epidermal growth factor receptor inhibitor.

Lichen planus–like drug eruptions

Lichen planus–like, or lichenoid drug eruptions, are characterized by symmetrically distributed, violaceous, flat-topped, pruritic papules on the trunk and the extremities. It shares the same features with lichen planus and usually develops insidiously. The time interval between the initiation of the offending drug and the appearance of the cutaneous lesions varies from months to years.[1]

The differential diagnosis between lichenoid drug eruptions and lichen planus is difficult; however, the lesions of lichenoid drug eruptions are less monomorphic, and may have eczematous or psoriasiform morphology with marked desquamation and without obvious Wickham striae.[27] Skin pathology may be used for differential diagnosis. Histopathological features that favor a diagnosis of lichenoid drug eruption include focal parakeratosis, cytoid bodies in the cornified and granular layers, presence of eosinophils in the filtration, exocytosis of lymphocytes in the upper epidermis, and perivascular infiltration in the deep dermis.[27]

Many drugs are known to induce lichenoid drug eruptions (Figure 8). Penicillamine, gold salts, β-blockers, thiazide diuretics, and antimalarials are important common etiologic agents for lichenoid drug eruptions.[1] Recently, TNF-α inhibitors and immune checkpoint inhibitors have also been identified as important culprits for this particular type of drug eruption.[7,28,29]

Lupus erythematosus–like drug eruptions

Drug-induced lupus includes drug-induced systemic lupus erythematosus (SLE) and drug-induced subacute cutaneous lupus erythematosus (SCLE).[1]

The clinical manifestations of drug-induced SLE include fever, weight loss, pericarditis, and pleuro-pulmonary inflammation. In contrast, malar rash, discoid rash, and erythema multiforme–like lesions are rarely seen in drug-

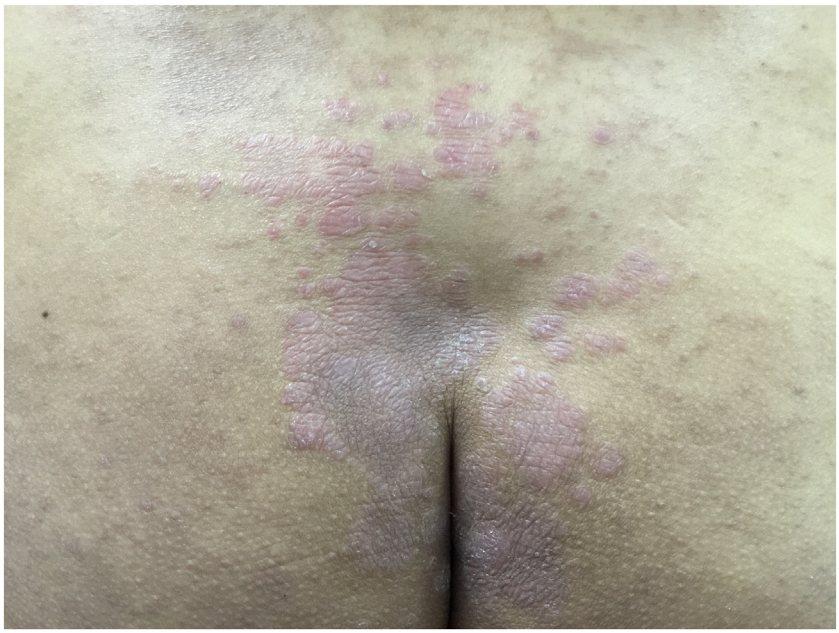

Fig. 8 Lichenoid drug eruptions related to immune checkpoint inhibitors.

induced SLE.[1] Drugs commonly associated with drug-induced SLE are procainamide, hydralazine, minocycline, diltiazem, and penicillamine. Recently some biologic agents, such as infliximab and etanercept, have also been reported to induce SLE.

The differentiation of drug-induced lupus from idiopathic SLE may sometimes be difficult due to the frequent occurrence of arthralgia or arthritis, fever, and serositis with a positive anti–nuclear antibodies (ANA) in both disorders; however, anti–double-strand DNA antibodies are not found in most forms of drug-induced lupus. In contrast, antihistone antibodies are strongly associated with some forms of drug-induced lupus, especially those induced by procainamide, hydralazine, chlorpromazine, and quinidine.[30]

Drug-induced SCLE may present as psoriasiform and annular lesions on the upper portion of the trunk and extensor surfaces of the arms, which are similar to those seen in real SCLE.[1] Drugs that induce SCLE include thiazide diuretics, calcium channel antagonists, terbinafine, and griseofulvin.

Lymphoma–like drug eruptions

Lymphoma–like drug eruptions include DRESS and drug-induced pseudolymphoma.[31] The cutaneous lesions of lymphoma–like drug eruptions may be solitary or numerous, as well as localized or widespread with red papules, plaques, or nodules and even erythroderma-mimicking mycosis fungoides. Two types of pseudolymphomas are also found based on histopathological features: T cell pseudolymphoma and B cell pseudolymphoma. T cell pseudolymphomas more often have a band–like pattern that simulates mycosis fungoides. In contrast, a nodular pattern is more often observed in B-cell pseudolymphoma.[31] Some histopathological pictures such as a plentiful histiocytic component in T-cell proliferation or a mixed cellular infiltrate in B-cell proliferation are diagnostic clues for pseudolymphoma.[31]

Drug-induced pseudolymphoma is differentiated from DRESS, there being no visceral involvement with normal blood cell count and serum chemistries.[31] Anticonvulsants, antidepressants, antihypertensives, beta blockers, calcium channel blockers, diuretics, and antibiotics have all been linked with lymphoma–like drug eruption.[11]

Measles–like drug eruptions

The most common adverse drug reactions affecting the skin, being responsible for approximately 90% of all drug reactions, are drug-induced exanthem or maculopapular eruptions. These eruptions are also referred to as exanthematous or morbilliform (measles–like) eruptions (Figure 9).[1,11,32] Such eruptions usually occur between 4 and 14 days after a patient begins taking a new medication; however, they can develop sooner, especially in case of rechallenge.[1] These eruptions usually consist of symmetrically distributed erythematous macules or papules that usually begin on the trunk and upper extremities and then become confluent. The most commonly prescribed medications, such as antimicrobials, NSAIDs, and sulfonamides, are common causes of this type of drug eruption.

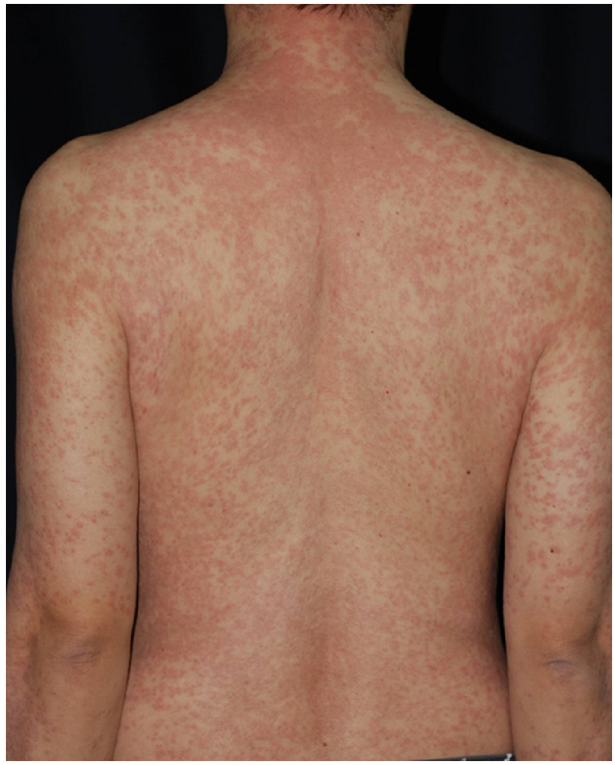

Fig. 9 Maculopapular eruptions are also referred to as exanthematous or morbilliform (measles-like) eruptions.

Pellagra

Pellagra is characterized by dermatitis, diarrhea, dementia, and eventually death due to niacin, or its precursor tryptophan, deficiency. Pellagra is a well known complication of isoniazid therapy.[33] Thallium poisoning may also result in cutaneous lesions such as acneiform eruptions, pellagra–like lesions, crusted eczematous lesions, and dry scaling of the distal parts of the extremities.[34]

Pemphigoid

Drug-induced bullous pemphigoid is characterized by a younger age of onset than spontaneously occurring bullous pemphigoid. Lesions usually appear as tense bullae on normally appearing skin, or (more uncommonly) on an erythematous or even urticarial base.[35] Some other proposed features favoring a diagnosis of drug-induced bullous pemphigoid include recent new drug exposure, positive Nikolsky sign, mucosal involvement, presence of intraepidermal blister and necrotic keratinocytes in histopathology, rapid response to oral corticosteroids, improvement after discontinuing the inciting drug, and nonrelapsing clinical course.[35]

There are two types of drug-induced bullous pemphigoid. It can (1) present as acute, self-limited blisters that resolve after drug withdrawal or (2) manifest like chronic pemphigoid lesions precipitated by drug administration that eventually assume all the characteristics of pemphigoid.[11,35] Its clinical manifestations include tense vesicles and bullae on an inflammatory base distributed on the arms, legs, and trunk of older patients.[11]

Several studies have revealed associations of bullous pemphigoid with certain drugs, including neuroleptics and antidiuretics (mainly aldosterone antagonists),[36] loop diuretics,[37] ACE inhibitors, anticoagulants, and diuretics.[38] Neuroleptics, antidiabetics, and antiarrythmics are also considered important culprits.[38] In recent years, anti–TNF-α agents[39–43] and dipeptidyl peptidase 4 inhibitors[44–47] have been associated with drug-induced pemphigoid. Different studies all revealed that, among the dipeptidyl peptidase 4 inhibitors, vildagliptin entails the highest risk of developing pemphigoid.[44–47]

Pemphigus

Pemphigus is an autoimmune bullous disease that may be drug induced or drug triggered. The latter term refers to the unmasking of a latent disease by a particular drug.[11] Clinically, drug-induced pemphigus most often presents as pemphigus foliaceus–like lesions. Other features include prodromal pruritus clinical manifestations and absence of mucosal involvement. The drugs most often implicated are penicillamine and other thiol compounds, including captopril or drugs such as piroxicam that are metabolized into thiols. Patients with drug-induced pemphigus have a higher rate of spontaneous recovery when discontinuing the drug, whereas in drug-triggered pemphigus the patients usually do not have spontaneous recovery after stopping the drug.

Pityriasis rosea–like drug eruptions

Pityriasis rosea–like eruptions may be associated with several drugs, including allopurinol, nimesulide, acetyl salicylic acid, ACE inhibitors, and ACE inhibitors in combination with hydrochlorothiazide.[48]

Psoriasis–like drug eruptions

There are several ways in which a drug can affect psoriasis. First, a drug can cause preexisting psoriatic skin lesions to aggravate. Upon discontinuation of the implicated drug, the psoriasis exacerbation can decrease (ie, drug-induced psoriasis). Alternatively, the induced psoriatic skin lesions can persist (ie, drug-aggravated psoriasis). Second, a drug can cause onset of new psoriasis lesions at clinically uninvolved skin in a patient with a personal history of psoriasis. Third, medication use can provoke psoriasis de novo in a patient without a personal or family history of psoriasis.[49]

Anti–TNF-α agents are used to treat a variety of autoimmune and inflammatory conditions, including psoriasis. Paradoxically, numerous reports have documented the new onset or exacerbation of psoriasis or psoriasiform skin lesions in patients treated with these agents for conditions other than psoriasis, particularly in adults with inflammatory bowel disease.[4,50] Lithium may also induce psoriasiform lesions.

Psoriasis–like or psoriasiform eruptions have also been reported as one of the most common reactions to immune checkpoint inhibitors (Figure 10).[51]

There are no clear clinical criteria to distinguish the morphology of drug-induced psoriasis or psoriasiform eruptions to that of typical psoriasis. Clinically, skin lesions in drug-induced psoriasis are almost similar to those of classic psoriasis, but they usually lack certain characteristics of psoriasis such as well demarcated borders or lack the coarse scaling typical of psoriasis.[49]

Pustular psoriasis–like drug eruptions

Acute generalized exanthematous pustulosis (AGEP) is characterized by the appearance of superficial pustules after drug ingestion or infection. The cutaneous eruption begins on the face or intertriginous areas and disseminates within a few hours. Dozens of symmetrically distributed, non–follicular small pustules arise on edematous erythema with burning

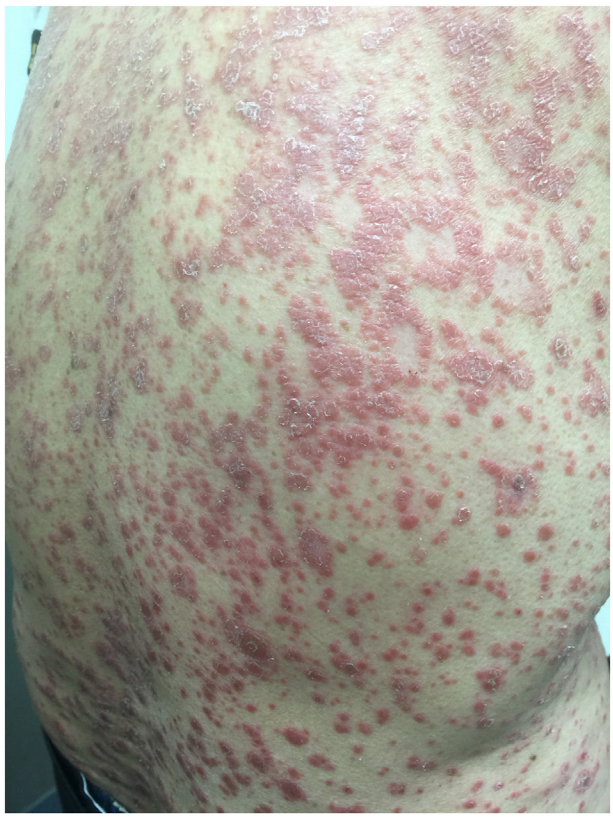

Fig. 10 Psoriasiform eruptions related to immune checkpoint inhibitors.

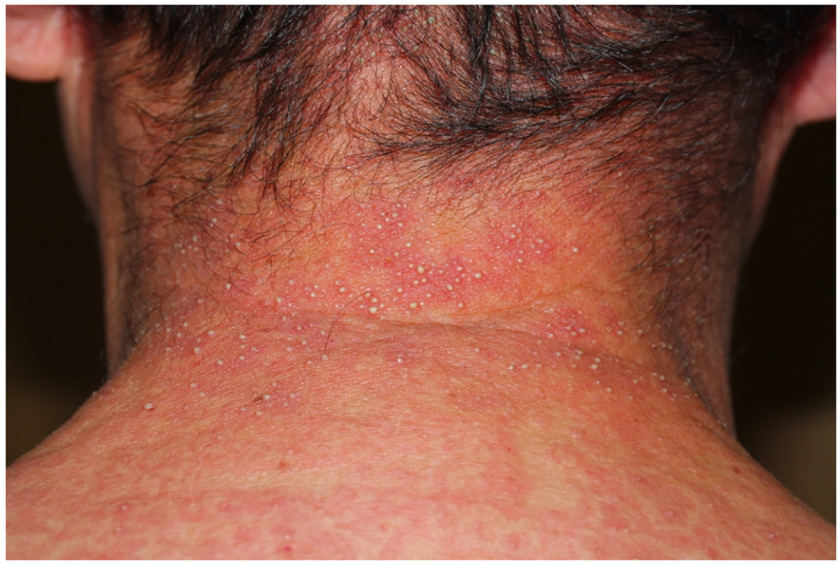

Fig. 11 Acute generalized exanthematous pustulosis looks like generalized pustular psoriasis.

and/or itching especially located on the folds. The above features make AGEP looks like generalized pustular psoriasis (Figure 11); however, the following criteria suggest a diagnosis of generalized acute pustular psoriasis: a history of psoriasis, longer duration of fever and pustular eruption, absence of drug exposure, and histologic finding of subcorneal pustules with acanthosis and papillomatosis. Antibiotics, particularly penicillins and macrolides, are the most important culprits.[1,11]

Seborrheic dermatitis–like drug eruptions

Patients receiving vemurafenib and other BRAF inhibitors may develop seborrheic dermatitis–like reactions of the face.[52–54]

Vasculitis

Drugs may induce cutaneous small vessel vasculitis (hypersensitivity vasculitis), or cutaneous leukocytoclastic vasculitis, which is indistinguishable from vasculitis due to other causes. It usually presents with palpable purpura and/or petechiae with or without systemic clinical manifestations such as fever, urticaria, and arthralgia. Common culprits of this type of drug reactions include hydralazine, minocycline, propylthiouracil, and levamisole.[11]

The clinical manifestations of drug-induced vasculitis usually begin 7 to 10 days after exposure to the offending drug; however, the latent period may be as short as 2 to 7 days with a secondary exposure or longer than 2 weeks with a long-acting drug such as penicillin G benzathine.[11] Discontinuation of the offending drug should lead to resolution of the signs and clinical manifestations within days to a few weeks.

Vitiligo–like drug eruptions

Drug-induced vitiligo has similar features to vitiligo, but it is often characterized by rapid onset and extension. Small confetti-like white macules are common in new body sites. Drug-induced vitiligo has flat patches of depigmented skin with irregular but defined borders. The most likely affected sites include the face, elbows and knees, dorsal hands, and the genitals.

Imatinib may induce depigmentation of the skin mimicking vitiligo. It may have a localized, patchy, or diffuse distribution. This is consistent with the documented role of c-kit in the physiology of melanocytes, including the regulation of melanogenesis and the proliferation, migration, and survival of melanocytes.[1] Other common causes of drug-induced depigmentation include hydroquinone and the use of phenol derivatives.

Conclusions

Drug eruptions may mimic many different skin diseases and cause substantial diagnostic challenges in clinical practice. In rare cases, cutaneous reactions might be severe as they can result in serious skin damage or involve multiple organs.[55] A detailed medical history, cutaneous examination of the morphology, and distribution of skin lesions are always needed to make a correct diagnosis; therefore, familiarity with the various clinical presentations of drug eruptions are important to every clinicians. In some cases, skin biopsies and blood tests may provide further clues. Specific immunologically based tests, including patch testing, intradermal or skin prick testing, and genetic testing, may also be used for certain types of drug eruptions.

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