



Review Article

Adverse drug reactions and organ damage: The skin

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ABSTRACT

Cutaneous adverse drug reactions are frequent, affecting 2–3% of hospitalized patients and in one twentieth of them are potentially life-threatening. Almost any pharmacologic agent can induce skin reactions, and certain drug classes, such as non-steroidal anti-inflammatory drugs, antibiotics and antiepileptics, have drug eruption rates ranging from 1% to 5%. Cutaneous drug reactions recognize several different pathomechanisms: some skin manifestations are immune-mediated like allergic reactions while others are the result of non immunological causes such as cumulative toxicity, photosensitivity, interaction with other drugs or different metabolic pathways. Cutaneous adverse drug reactions can be classified into two groups: common non-severe and rare life-threatening adverse drug reactions. Non-severe reactions are often exanthematous or urticarial whereas life-threatening reactions typically present with skin detachment or necrosis of large areas of the body and mucous membrane involvement, as in the Stevens–Johnson syndrome or toxic epidermal necrolysis. Clinicians should carefully evaluate the signs and symptoms of all cutaneous adverse drug reactions thought to be due to drugs and immediately discontinue drugs that are not essential. Short cycles of systemic corticosteroids in combination with antihistamines may be necessary for widespread exanthematous rashes, while more aggressive corticosteroid regimens or intravenous immunoglobulins associated with supportive treatment should be used for patients with Stevens–Johnson syndrome or toxic epidermal necrolysis.

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1. Introduction

Cutaneous adverse drug reactions (ADRs) are frequent, affecting 2–3% of hospitalized patients and in one twentieth of them are potentially life-threatening [1]. Almost any pharmacologic agent can induce skin reactions, and certain drug classes, such as non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics and antiepileptics, have drug reaction rates approaching 1–5% [2]. Drug reactions may be caused by several different pathomechanisms. Some drug-induced skin manifestations are immune-mediated like allergic reactions, while others are the result of non immunological causes such as cumulative toxicity, photosensitivity, interaction with other drugs or different metabolic pathways [3].

From an epidemiological point of view, cutaneous ADRs can be classified into common non-severe and rare life-threatening cutaneous

ADRs [1]. Non-severe reactions are often exanthematous or urticarial, whereas life-threatening reactions typically present with skin detachment or necrosis of large areas of the body and mucous membrane involvement. In most cases drug eruptions, i.e. the breaking out of skin lesions, are reversible, resolving gradually after the causative drug is withdrawn, while others are persistent and potentially fatal [4]. Several risk factors for the development of more severe cutaneous ADRs have been identified, including female gender, older age, viral infections (notably HIV), iatrogenic immunosuppression, underlying immune-mediated diseases and cancer [5,6].

An increasing number of studies provide evidence on the relation between specific genetic markers and susceptibility to cutaneous ADRs. The evidence is particularly consistent for specific single nucleotide polymorphisms in the human leukocyte antigens (HLA) region [6]. The terms pharmacogenomics and pharmacogenetics connote the emerging field in which the importance of genetic factors in the metabolic or immunologic reaction to a medication is recognized [7].

In this review, we focus on the main cutaneous manifestations induced by a number of drugs widely used in internal medicine, ranging from common benign presentations, like exanthematous and urticaria eruptions, to rare but potentially fatal reactions, like the Stevens–Johnson syndrome/toxic epidermal necrolysis spectrum. Clinical

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features and pathophysiological aspects are discussed, in the attempt to provide a simple approach for diagnosis and management.

2. Exanthematous drug eruption

Exanthematous or maculo-papular eruptions, often designated as “drug rashes” or “drug eruptions”, are the most common ADRs affecting the skin. Prospective cohort studies have shown that these benign rashes account for more than 90% of all cutaneous ADRs [8,9]. They include an heterogeneous variety of skin reactions that literally burst forth on the skin; in fact, the term ‘exanthema’ just implies the appearance of any, mostly inflammatory, skin lesions without any further specification. The eruption usually occurs between 4 and 14 days after the beginning of a new medication, although it can develop sooner, especially in case of rechallenge. The rash usually resolves in a few days when the causative drug is stopped.

Exanthematous eruptions consist of erythematous macules or papules (Fig. 1), more rarely vesicles and pustules, usually with a symmetric distribution. The eruption begins usually on the trunk followed by centrifugal expansion to the proximal extremities. Skin lesions progressively become confluent and may progress symmetrically to cover large areas of the body. Pruritus and low-grade fever are often associated to the eruption. In some cases these exanthems may progress to erythroderma or more severe reactions.

Histological examination shows an interface dermatitis with vacuolar changes of keratinocytes at the basal cell layer and an upper dermal mononuclear cell infiltrate with some eosinophils [10]. Immunohistochemical analysis reveals an overexpression of several cytokines like interleukin (IL)-5 and IL-13, which are correlated with skin and blood eosinophilia and other effector molecules like perforin and granzyme B [11,12].

Uncomplicated drug-induced disseminated exanthemas can occur with almost any medicine, but the following drugs have higher risks (more than 3% of users): allopurinol, aminopenicillins, cephalosporins, antiepileptic agents, and antibacterial sulphonamides [8]. Viral infections may increase the incidence of morbilliform drug reactions, as seen in infectious mononucleosis under treatment with ampicillin. Although the pathomechanism of maculopapular drug rashes is still not completely understood, a type IV delayed cell-mediated immune mechanism involving drug-specific T lymphocytes is thought to be relevant [4].

Treatment is basically supportive. The first therapeutic measure is discontinuation of the causative agent, combined with the



Fig. 1. Exanthematous eruptions consisting of erythematous macules or papules involving the trunk.

administration of a short cycle of systemic corticosteroids (oral prednisone at initial dose of 0.5 mg/kg daily with progressively tapering dosages) and systemic H1 antihistamines (oral levocetirizine 5 mg daily, with possible up-dosing to 15 mg daily). If the suspected drug is of essential therapeutic importance for the patient, a structurally different, non-cross-reacting drug for future treatment should be suggested.

3. Urticaria and angioedema

Drug-induced urticaria is the second most common form of cutaneous drug reaction after exanthematous reactions [13]. Clinically, urticaria presents as itchy erythematous wheals, in variable number and size (Fig. 2). The single wheals can be localized anywhere on the body and last less than 24 h, leaving the skin with a normal appearance.

The histology shows dermal edema with a mixed dermal infiltrate consisting of lymphocytes, neutrophils and eosinophils. When edema involves subcutaneous tissues, it is known as angioedema. Urticaria and angioedema are associated in about 50% of cases. Clinically, angioedema consists of pale or pink swellings which affect the areas where the skin is lax rather than taut, especially the face (cheeks, eyelids, lips or ears) and genitalia, but also buccal mucosa, tongue, larynx and pharynx. It may last for several days. Urticaria and angioedema can be complicated by anaphylaxis, which can lead to respiratory collapse, shock and death [8,14]. Anaphylaxis has an incidence of 80–100 cases/million/year. Drug-related urticaria, angioedema or anaphylaxis begin within few minutes to a few hours after drug administration. They are generally a type I hypersensitivity reaction mediated by IgE antibodies. Other anaphylactoid mechanisms leading to direct and a non-specific liberation of histamine or other mediators of inflammation are also common for drug reactions [15,16].

Many drugs can induce urticaria. Antibiotics, especially penicillin, and general anaesthetics are classic causes of IgE mediated hypersensitivity reaction [17]. The two most frequent causes of drug-induced non-IgE-mediated urticaria and angioedema are non-steroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors [18]. NSAIDs induce urticaria through their pharmacologic activity of COX-1 enzyme inhibition. In susceptible subjects COX-1 inhibition results in generation of leukotriene C4 and activation of inflammatory cells [19]. Concerning ACE inhibitor-induced angioedema, ACE inhibitors exert their therapeutic effects by blocking angiotensin converting enzyme which is also the enzyme inhibiting the breakdown of bradykinin, a potent vasoactive peptide which increases vascular permeability, leading to angioedema [20]. Angioedema is described in 0.5% of patients treated with ACE inhibitors, and these patients may present a defect of other enzymes involved in bradykinin breakdown [21]. Specific testing, such as radioallergen sorbent test (RAST), enzyme-linked immunosorbent assay (ELISA) and skin prick tests may help to identify the cause. Treatment involves withdrawal of the causative agent. This can be combined with an oral antihistamine. Systemic corticosteroids and intramuscular injection of epinephrine are necessary if severe angioedema and anaphylaxis occur. A recent randomized clinical trial has demonstrated the efficacy and safety of the selective bradykinin B2 receptor antagonist icatibant in ACE inhibitor-induced angioedema [22].

4. Erythroderma

Erythroderma refers to a generalized sustained erythema of the skin (Fig. 3), involving more than 90% of the body surface accompanied by a variable degree of scaling. It is a rare but severe syndrome that may be accompanied by systemic symptoms, such as fever, lymphadenopathy and anorexia. Possible complications include hypothermia, fluid and electrolyte loss, and infection, which may engage the vital prognosis. Pruritus is found in almost all patients [23]; erythroderma of long duration may cause hair loss and nail dystrophy.

Erythroderma is usually the consequence of several conditions other than drug consumption, mainly skin disorders, such as psoriasis and



Fig. 2. Urticarial lesions involving the lower extremities. The wheals appear pale (left panel) or erythematous (right panel).

eczema, and more rarely some malignancies, including internal malignancies and cutaneous T cell lymphoma [24,25]. In drug-induced cases, the onset of erythroderma is typically sudden and the resolution faster than for the other causes [26]. Histopathology usually reveals a non-specific picture characterized by hyperkeratosis, parakeratosis, acanthosis and a chronic perivascular inflammatory infiltrate often rich in eosinophils.

The main drugs implicated are sulfonamides, chloroquine, penicillin, phenytoin, carbamazepine, allopurinol and isoniazid.

Currently, the mechanism of erythroderma is unclear. Adhesion molecules and their ligands play a significant role in endothelial-leukocyte interactions, which impact the binding, transmigration and infiltration of lymphocytes and mononuclear cells during inflammation, injury or immunological stimulation [27]



Fig. 3. Erythroderma characterized by generalized erythema involving almost all the body surface.

The initial management of erythroderma is the same regardless of aetiology. This should include replacement of nutritional, fluid and electrolyte losses, and local skin-care measures, such as bland emollients and low-potency corticosteroids [28]. The most severe cases should be treated with a systemic corticosteroid regimen, notably intravenous methylprednisolone 0.5–1.0 mg/kg daily at progressively tapering dosages; systemic antibiotics guided by antibiogram should be added to control bacterial superinfections.

5. Stevens–Johnson syndrome and toxic epidermal necrolysis

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), also known as Lyell syndrome, are the most serious and life-threatening cutaneous ADRs. The incidence of TEN is evaluated to 0.4–1.2 cases per million person-years and of SJS from 1 to 2 cases per million person-years [8,29]. SJS and TEN are now considered as severity variants of the same drug-induced disease, characterized by widespread keratinocyte death resulting in extensive epidermal loss with mucous membrane erosions and frequent impaired general condition [30].

The main features of SJS/TEN are acute onset and rapid progression of painful lesions of the skin and mucous membranes that develop to blisters and erosions arising on purple macules. In SJS, confluence of blisters on limited areas leads to detachment below 10% of the body surface area. TEN is characterized by the same lesions than SJS but with an



Fig. 4. Toxic epidermal necrolysis. Purpuric macules and large skin detachment.

involvement of more than 30% of the body surface area (Fig. 4). Cases with detachment between 10 and 30% are labelled as overlap SJS-TEN [8,31]. A positive Nikolsky's sign, which implies epidermal dislodge by tangential pressure due to the loss of epidermal coherence, is an important clinical clue. Hemorrhagic erosions of mucous membranes are present in about 95% of cases of SJS/TEN.

Patients with SJS or TEN have high fever and severe malaise. Systemic manifestations include mild elevation of hepatic enzymes, intestinal and pulmonary manifestations with sloughing of epithelia. Death occurs in 10% of patients with SJS and to more than 40% of patients with TEN, mainly due to sepsis or pulmonary involvement [32]. The severity and prognosis of SJS/TEN are assessed based on the SCORTEN (SCORE of Toxic Epidermal Necrosis) scale within 24 h of admission of the patient [33]. This score includes seven independent equivalent factors; the probability of dying increases as the score increases. The factors are: (1) age (≥ 40 years), (2) heart rate ($\geq 120/\text{min}$), (3) underlying malignant disease, (4) $\geq 10\%$ detachment of the body surface area on the first day, (5) serum urea ($\geq 10 \text{ mmol/l}$), (6) serum bicarbonate ($< 20 \text{ mmol/l}$), and (7) serum glucose ($\geq 14 \text{ mmol/l}$).

The majority of survivors suffer from sequelae that impair often seriously their quality of life. Mucosal adhesions are the most frequent complication. In particular, symblepharon with entropion and trichiasis is a dramatic complication for patients [32,34]. The skin usually heals with scarring and hyper- or hypo-pigmentation persisting for months to years. The histopathology shows extensive detachment of the epidermis resulting from apoptosis of keratinocytes on the full or nearly full thickness of the epidermis; the dermis usually exhibits a scarce superficial lymphohistiocytic infiltrate [35].

Medications are responsible for at least 70% of cases of both SJS and TEN. Antibacterial sulfonamides, anticonvulsants, oxicam-NSAIDs, allopurinol and nevirapine are drugs associated with the higher risks [36]. SJS/TEN can develop during the first treatment cycle, is dose-independent, and occurs four days to four weeks after initiation of the involved drug [37]. In the remaining one third of cases, an infection may act as trigger while a few cases may be idiopathic. Risk factors include concomitant HIV infection, radiotherapy, lymphomas, leukaemias and systemic lupus erythematosus [38].

Recent progresses were done on the mechanisms of SJS/TEN, which are regarded as T cell-mediated reactions. The drugs or their toxic metabolites act as haptens providing antigenic stimulus. SJS-TEN spectrum is a paradigm of delayed hypersensitivity reaction [39]; in particular, immunohistochemical studies have shown drug specific CD4+ cells in the dermis and CD8+ cells in the epidermis [40]. Widespread apoptosis results from the massive release of a number of cytokines and soluble factors, such as perforin, granzyme B, and granulysin [39]. Notably, granulysin released by cytotoxic T lymphocytes and natural killer cells induces apoptosis by causing damage to mitochondria, resulting in activation of caspases involved in the programmed cell death pathway [41,42]. Keratinocyte apoptosis is also triggered via receptor–ligand interaction between the cell surface receptor Fas (death receptor) and its physiologic ligand FasL [39,43]. Genetic factors have been shown to play a role in the development of SJS/TEN by facilitating drug activation of cytotoxic T cells and natural killer cells [44]. Recent data indicates that some alleles of HLA, which are specific for a certain active substance, are the genetic determinants of drug hypersensitivity reactions; notably, HLA-B*15:02 is strongly associated with carbamazepine induced SJS/TEN [39,45,46].

To date, no specific treatment has been proven to be effective [47]. Because immunological pathomechanisms are involved, therapeutic interventions include corticosteroids, other immunosuppressants and agents expected to block soluble death mediators or their receptors. None of the proposed treatments was evaluated in a randomized controlled trial due to the extreme disease rarity [48]. The best available evidence has been provided by the Euro-SCAR cohort analysis [49]. The results showed a strong, but not significant, reduction of mortality with the use of corticosteroids and no benefit from using intravenous

immunoglobulins; however, intravenous immunoglobulins are widely used due their safety in patients prone to a number of septic complications [48,49]. The burn unit and intensive care unit are the ideal setup for management of these patients, and supportive treatment is crucial. Antiseptic solutions or gels should be used for topical treatment, and drug-free nonadherent mesh gauze can be applied to areas affected by blisters. If necessary, the ambient temperature should be raised, intravenous fluids given and adequate analgesia started [32,36]. Local antiseptic therapy is recommended for mucosal erosions too. In the case of severe ocular involvement, a daily ophthalmological consult is advisable. Besides antibiotic and/or antiinflammatory eye drops, symblepharon prophylaxis is often required in order to avoid late complications [36].

6. Acute generalized exanthematous pustulosis

In 1980 the term 'acute generalized exanthematous pustulosis' (AGEP) was introduced to describe acute pustular reactions resembling pustular psoriasis, but usually occurring as a drug reaction in patients with no history of psoriasis [50]. AGEP, considered among the SCARs, is rare, with an incidence of 1–5 patients per million per year [51]. The Euro-SCAR study revealed a mean age of 56 (SD ± 21) years and a female preponderance, confirmed by other case series [52,53]. AGEP has been reported in children too [54].

The clinical manifestations are characterized by fever, itching or burning and widespread oedematous erythema followed by the rapid appearance of numerous very small ($< 5 \text{ mm}$) non-follicular sterile pustules, located in the main folds, trunk and extremities (Fig. 5A) [51]. Confluence of pustules may result in subcorneal detachment [56]. Edema of the face, purpura, vesicles and erythema multiforme-like lesions are occasionally present. A mild, nonerosive mucous membrane involvement occurs in 20% of patients and is in general restricted to one site, mostly oral. Internal organ involvement is uncommon and usually is confined to a slight reduction in creatinine clearance, mild elevation of aminotransferases and hypocalcemia. Peripheral leukocytosis and neutrophilia are present in 90% patients. The time between the

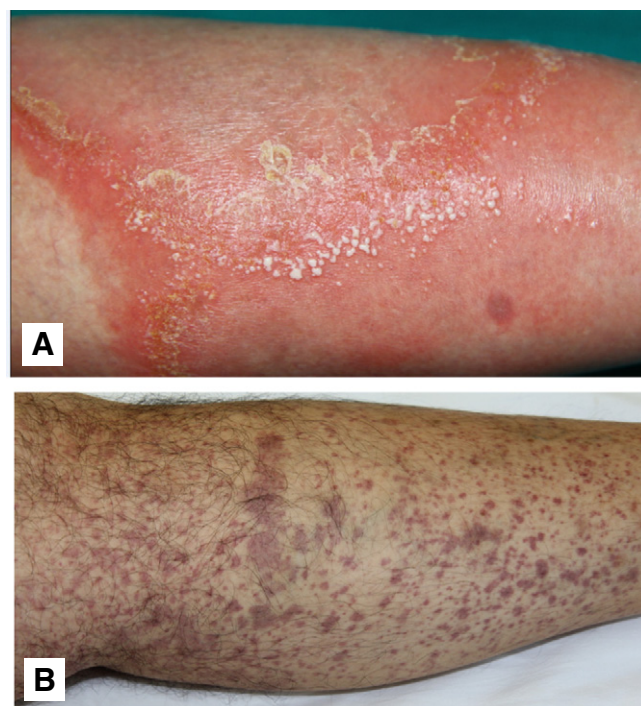


Fig. 5. Panel A: acute generalized exanthematous pustulosis characterized by small pustules surrounded by erythema and scaling. Panel B: cutaneous small vessel vasculitis presenting with palpable purpura.

beginning of drug administration and the skin eruption is relatively short, varying for different drugs. For antibiotics, including sulphonamides, the median latent period is 1 day while it is longer for other drugs [52]. The clinical course is characterized by spontaneous resolution of skin and systemic manifestations over a period of up to 15 days once the offending agent is withdrawn [51]. The eruption is followed by a superficial desquamation. Proposed diagnosis criteria include: 1) an acute pustular eruption; 2) fever above 38 °C; 3) neutrophilia with or without mild eosinophilia; 4) subcorneal or intraepidermal pustules on skin biopsy; and 5) spontaneous resolution in less than 15 days [51]. AGEF has a favourable prognosis; the reported mortality rate is up to 5% and poor outcomes usually result from secondary infection, which occurs particularly in the elderly with significant comorbidities [55].

The histopathology of AGEF is distinctive but not diagnostic, and is characterized by subcorneal or intraepidermal abscesses containing neutrophils and occasional eosinophils [57]. The dermal infiltrate consists of neutrophils with scattered lymphocytes and eosinophils.

AGEF is caused by drugs in at least 90% of cases, with 80% of cases caused by antibiotics [58]. According to the Euro-SCAR study, the agents conferring the highest risk are aminopenicillins, hydroxychloroquine, antibacterial sulphonamides, terbinafine and diltiazem [51]. The role of infectious agents in AGEF has been suggested in various case reports [54] but it was not confirmed by the Euro-SCAR study [52]. Reports of AGEF associated with spider envenomation, mercury exposure and radiocontrast exposure can be found in the literature. AGEF seems to develop also without preceding medication or disease [59].

The pathogenesis of AGEF involves the activation, expansion and subsequent migration of drug-specific CD4 and CD8 cells to the skin. The initial influx of cytotoxic T-cells results in apoptosis of keratinocytes and the formation of subcorneal vesicles [60]. Neutrophils are a central component in the pathophysiology of AGEF. In particular, the adaptive immune system regulates neutrophil recruitment and activation by the T helper 17 (Th17) response [61]. CD4 + T helper cells and CD8 + cytotoxic T cells produce the Th17 cytokines IL-17, IL-22, GCSF and TNF- α , all of which are involved in the recruitment of neutrophils [39]. Moreover, the infiltrating CD4 cells and keratinocytes release chemokines, such as CXCL-8 and IL-8, which result in the recruitment of neutrophils as well as granulocyte macrophage-colony stimulating factor (GM-CSF), which prevents apoptosis of neutrophils [62]. These events result in the conversion of vesicles into pustules. CD4 cells also release IFN- γ and IL-5, which contribute to the eosinophilia observed in some patients [63].

AGEF is a self-limiting disease, the most important measure being the discontinuation of the causative agent. This usually leads to rapid resolution of the cutaneous reaction. Use of systemic or topical corticosteroids is often recommended, however, there is so far no evidence of their advantage over purely symptomatic therapy (antipyretic, antipruritic) [64].

7. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

The Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a rare, potentially life-threatening adverse drug reaction with cutaneous manifestations, fever, hematologic abnormalities (eosinophilia or atypical lymphocytes) and internal organ involvement [65]. The other noteworthy features are a delayed onset (usually 2–6 weeks after the initiation of drug therapy) and the possible persistence or aggravation of symptoms despite discontinuation of the culprit drug [66,67]. In recent years, 2 separate scoring systems based on diagnostic criteria have been developed [68,69]. The estimated incidence of this syndrome ranges from 1 in 10,000 to 1 in 1000 drug exposures [70]; it can occur at any age, with a slight female predominance [66].

DRESS often begins with prodromal symptoms of pruritus, burning pain, flu-like symptoms, lymphadenopathy, dysphagia and high fever ranging from 38 °C to 40 °C. Pyrexia generally precedes cutaneous

eruptions and may last for several weeks. Although skin manifestations can be polymorphous, a morbilliform rash is the most common and is characterized by a diffuse, pruritic and macular exanthema [65,71]. Usually it first involves the face, upper trunk and upper extremities, and later spreads to the lower extremities, becoming infiltrative with associated edema [72]. Facial edema, mostly pronounced in the periorbital region, constitutes a warning signal. Vesicles, bullae, atypical targetoid plaques, purpura, urticaria and sterile small pustules may be evident [73]. The rash may also involve nearly the entire surface of the skin, producing an exfoliative dermatitis or erythroderma. Mucosal involvement, mainly of the lips and oral cavity, is frequent, but rather mild and less haemorrhagic when compared with the findings in SJS/TEN [65]. The rash frequently evolves after its acute presentation, taking on a more violaceous appearance with diffuse scaling. These clinical features may remain for weeks or months after discontinuing the culprit drug [71]. Multiple organ systems can be affected in the DRESS syndrome. The most common systemic findings, besides hypereosinophilia, involve the lymphatic, hematologic, and hepatic systems, followed by renal, pulmonary, and cardiac manifestations [67].

Pathology of DRESS, albeit non specific, may help diagnosis. The most common findings are a relatively dense, perivascular lymphocytic infiltrate in the papillary dermis, with the presence of extravasated erythrocytes and dermal edema. Eosinophils may be present [8,73,74]. The culprit drugs most commonly associated with DRESS are allopurinol, anticonvulsants (mainly phenobarbital, carbamazepine, phenytoin, lamotrigine and sodium valproate), minocycline, sulfasalazine, abacavir, fluindione and proton pump inhibitors [66,75,76].

The pathogenesis of DRESS syndrome is not fully understood. Failure of drug detoxification pathways, leading to an accumulation of harmful metabolites which trigger autoimmune responses against skin or liver cells, has been hypothesized to play a major role in the development of DRESS, especially in hypersensitivity to anticonvulsants [77]. Accordingly, individuals carrying specific mutations in genes that encode drug detoxification enzymes have been shown to have a higher risk of DRESS [65].

An immunologic mechanism is widely believed to underlie a major component of DRESS syndrome, with a delayed cell-mediated immune model being suggested [39,65,78,79]. Eosinophil activation and an inflammatory cascade may be induced by IL-5 release from drug-specific CD4 + and CD8 + T cells [12,80]. Another pathophysiological mechanism involves viral reactivation. Indeed, the observation of human herpesvirus (HHV) reactivation, especially HHV6, occurring during the acute phase of DRESS has led to suggestions of a mechanistic link [81]. The mechanism underlying the direct drug–virus interaction remains controversial [82,83]. It is increasingly apparent that there is a genetic predisposition to DRESS. In particular, individuals with specific human leukocyte antigen (HLA) haplotypes are predisposed to develop DRESS syndrome when exposed to an inciting drug [84].

No prospective randomized trials are available on the management of DRESS syndrome. Early discontinuation of the causal drug and an evaluation of disease severity are the first intervention [85]. Patients with severe DRESS syndrome should be given systemic glucocorticoid therapy (oral prednisone 1 mg/kg/day) until complete disease control is achieved. The dose is then tapered, often over several months [67,76]. Life-threatening forms, particularly associated with viral reactivation, require intravenous immunoglobulins. Supportive care with accurate fluid and electrolyte balance is a must. Whether or not there may be a role for anti-viral agents to potentially limit the course of symptoms and reduce systemic organ damage in DRESS has not been corroborated by clinical studies [86].

8. Vasculitis

Vasculitis is defined as a pathological process characterized by inflammation and damage of the blood vessel wall. It may be triggered by various antigenic agents, such as infection or drug, or may be related

to an underlying disease, such as connective tissue, inflammatory bowel, myelodysplastic or other malignancies [87]. Nevertheless, many vasculitides occur with no demonstrable triggering agents. Skin may be the single involved organ or may be part of vasculitis affecting also internal organs. Cutaneous small vessel vasculitis (CSVV), also known with the histologic term of leukocytoclastic vasculitis which affects mainly the post-capillary skin venules, is the most common form of vasculitis limited to the skin [88].

Concerning drug-induced CSVV, the interval between the first exposure and the appearance of vasculitis signs can be extremely variable, usually ranging from few days to weeks [89]. The major cutaneous manifestation of CSVV is palpable purpura, ranging in size from a pinpoint to several centimetres (Fig. 5B); this purpura can remain the sole feature or may progress to a wide array of manifestations including papules, nodules or plaques as well as pustules or vesiculo-bullae, the latter usually evolving into ulcerative–necrotic lesions which heal with post-inflammatory hyperpigmentation [87,90]. Other cutaneous findings include livedo reticularis, which describes a mottled red or bluish discoloration of the skin with a net-like pattern and urticarial lesions. Lesions typically occur in areas prone to stasis, particularly the lower legs; sometimes they may extend to involve the ankles, the lower portion of the trunk and upper extremities [90,91]. Burning, pain and more rarely pruritus may be experienced. The skin lesions of CSVV typically arise as a simultaneous “crop” and usually resolve within some weeks upon drug withdrawal; however, sometimes immunosuppressive treatment is required. The cutaneous picture may be accompanied by systemic symptoms including fever, arthralgia, myalgia and anorexia. Renal or other organ system involvement is possible but uncommon.

The typical histopathological pattern of CSVV is the so-called leukocytoclastic vasculitis, characterized by fibrinoid necrosis of vessel walls and upper dermal perivascular infiltrates mainly composed of neutrophils with karyorrhexis of nuclei [91,92]. The presence of numerous eosinophils in the inflammatory infiltrate increases the likelihood of an underlying drug cause [93]. Direct immunofluorescence shows IgM and/or complement C3 deposits on capillary walls in over 80% of cases.

Antibiotics, diuretics, NSAIDs, anticonvulsants, antipsychotics, TNF- α inhibitors, rituximab, and IFN- β are the main drugs implicated in CSVV [87].

The major pathogenetic mechanism in CSVV is an immune complex reaction, namely Gell and Coombs type 3 reaction [90,94–96]. Interacting with the complement system, the drug-induced immune complex deposition stimulates the production of proinflammatory cytokines, chemokines and vasoactive amines, which in turn induce the expression of adhesion molecules on endothelial cells. This leads to the recruitment of neutrophils. Degranulation and destruction of these cells with release of collagenases and elastases and generation of reactive oxygen species, ultimately result in inflammation and fibrinoid necrosis of vessel walls. CD4 + T helper lymphocytes act in the CSVV pathophysiology secreting cytokines (notably IL-1, IFN- γ and TNF- α) and recruiting CD8 + cytotoxic T cells, B cells and natural killer cells [1,4].

Identifying the offending drug is the most important aspect of treatment as its discontinuation is usually followed by a rapid improvement of vasculitis. In these patients with mild disease, topical corticosteroids in combination with oral antihistamines can be used to produce a decrease in symptoms like burning or itching [87,90]. In cases with painful ulcerative–necrotic skin lesions, treatment with systemic corticosteroids is necessary (oral prednisone at the initial dose of 0.5–1 mg/kg daily with progressively tapering dosages).

9. Conclusions

Cutaneous ADRs are usually not severe but a small fraction of them may be life-threatening or lead to disabling sequelae. The most frequent ADRs present with a morbilliform exanthematous rash or less commonly as urticaria and angioedema, while the prototype of the severe forms

is represented by the SJS/TEN spectrum, with large skin detachments and extensive mucosal erosions. A number of pharmacological agents can induce skin reactions, but certain drug classes, such as NSAIDs, antibiotics and antiepileptics are frequently involved. Clinicians should carefully evaluate the signs and symptoms of all ADRs thought to be due to drugs and immediately discontinue all drugs that are not essential. Short cycles of systemic corticosteroids in combination with antihistamines may be necessary for widespread exanthematous rashes, while more aggressive corticosteroid regimens or intravenous immunoglobulins associated with supportive treatment should be used for SJS/TEN patients.

10. Learning points

- Cutaneous adverse drug reactions (ADRs) are frequent (2–3% of hospitalized patients) and in one twentieth of them are potentially fatal.
- Many drugs can induce skin reactions but non-steroidal anti-inflammatory drugs, antibiotics and antiepileptics are most frequently involved.
- Drug-induced skin manifestations may be immune-mediated or be the result of non immunological causes such as cumulative toxicity, photosensitivity or interaction with different metabolic pathways.
- The most frequent ADRs present with exanthematous rashes or less commonly manifest as urticaria/angioedema, while the prototype of rare severe forms is the SJS/TEN spectrum with large skin detachments and mucosal erosions.
- Therapy of ADRs is based on the withdrawal of the alleged drug but corticosteroid regimens and supportive treatment may be necessary for widespread rashes and life-threatening forms.

Conflict of interest

The authors state that they have no conflicts of interest.

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