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Review Article

Adverse drug reactions and organ damage: The skin

Angelo V. Marzano [a], Alessandro Borghi [b], Massimo Cugno [c,*]

[a] Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Unità Operativa di Dermatologia, IRCCS Fondazione Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy
[b] Dipartimento di Scienze Mediche, Sezione di Dermatologia e Malattie Infettive, Università degli Studi di Ferrara, Ferrara, Italy
[c] Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Unità Operativa di Medicina Interna, IRCCS Fondazione Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy

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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.

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

* Corresponing author at: Medicina Interna, Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Ospedale Maggiore Policlinico, Fondazione IRCCS Ca' Granda, Via Pace, 9, 20122 Milano, Italy. Tel.: +39 0255035340; fax: +39 0250320742.
E-mail address: massimo.cugno@unimi.it (M. Cugno).

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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 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.

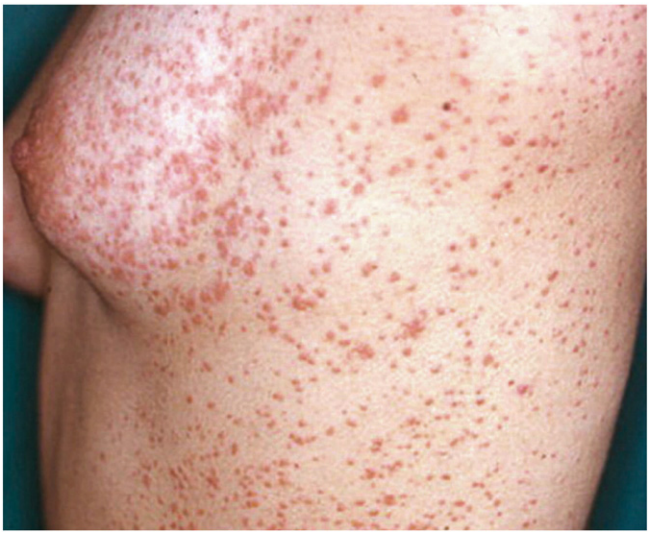

Fig. 1. Exanthematous eruptions consisting of erythematous macules or papules involving the trunk.

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