

Cutaneous Manifestation of Drug Allergy and Hypersensitivity



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KEYWORDS

- Drug allergy • Drug hypersensitivity • Cutaneous manifestations
- Cutaneous adverse drug reactions (CADR) • Photoallergy

KEY POINTS

- Cutaneous eruptions are the most common manifestation of both allergic and nonallergic drug hypersensitivity.
- Different medications may cause identical skin symptoms, and hypersensitivity to a single drug may manifest with various patterns of symptoms.
- Immediate drug reactions, developing within 1 hour of the drug intake, manifest with urticaria, angioedema, and/or anaphylaxis.
- Delayed type of drug hypersensitivity may manifest with virtually all other cutaneous drug eruptions.
- Analysis of morphology of drug-induced lesions as well as timing of reaction is critical for the final diagnosis

INTRODUCTION

Adverse drug reactions (ADRs) are responsible for about 6% of all hospital admissions and around 9% of hospitalization costs. Only a fraction of these reactions (less than 10%) can be defined as type B, that is, drug hypersensitivity reactions (DHRs), which are usually not predictable and occur in susceptible individuals.¹ However, DHRs may result in potentially fatal outcomes; thus, proper diagnosis and prompt, careful

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management is required. The pathomechanism of DHR may be either immunologic (allergy, allergic hypersensitivity) or nonimmunologic (nonallergic hypersensitivity). Although DHRs may manifest with various symptoms (organ specific or systemic), the skin is most commonly affected. Drug-induced skin symptoms are usually mild and self-limiting but may herald the development of a severe systemic and potentially lethal reaction. Drug reactions adopt many faces and should be taken into account in the differential diagnosis of numerous skin rashes. Careful clinical evaluation of visible skin lesions could greatly help in establishing a proper diagnosis.²⁻⁴

Allergic and Nonallergic Drug Hypersensitivity

DHRs have been defined as objectively reproducible signs or symptoms initiated by a drug at a dose usually tolerated by normal subjects and represent type B ADRs (Fig. 1).⁵ DHRs with clearly defined immunologic (most often immunoglobulin E [IgE] mediated or T-cell mediated) mechanisms are referred to as drug allergy, whereas nonallergic drug hypersensitivity includes reactions with other, nonimmunologic pathogenic mechanisms (eg, aspirin hypersensitivity related to cyclooxygenase inhibition).^{6,7} Similar drug-induced cutaneous symptoms may be evoked by both allergic and nonallergic mechanism, and a single drug can trigger reactions involving either an immunologic (allergic) or nonimmunologic mechanism. Furthermore, allergic DHRs may represent a type I, II, III, or IV drug-specific immune responses according to the Gell and Coombs classification. Distinguishing between these types of hypersensitivity reactions is important in deciding to propose alternative drugs. In drug allergy it may be possible to replace a culprit drug with a drug belonging to the same class but having a different chemical structure (eg, penicillin may be replaced by another antibiotic), whereas in the case of nonallergic hypersensitivity, the whole class of drugs should be avoided (eg, all nonsteroidal antiinflammatory drugs [NSAIDs], which are cyclooxygenase-1 [COX-1] inhibitors, will cross-react in the case of aspirin hypersensitivity).

Hypersensitivity reactions to drugs may manifest with organ-specific or systemic symptoms, ranging in severity from mild skin symptoms (eg, rash) to life-threatening reactions involving multiple organs and systems. Timing of reactions ranges from immediate symptoms, occurring within minutes (eg, penicillin allergy), to symptoms developing within several days after drug intake. Reactions occurring within the first 24 hours are called immediate or acute, whereas delayed reactions, by definition, usually appear more than 24 hours after drug intake.

Cutaneous eruptions are the most common manifestations of drug hypersensitivity and may include exanthematous eruptions, urticaria, angioedema, contact dermatitis,

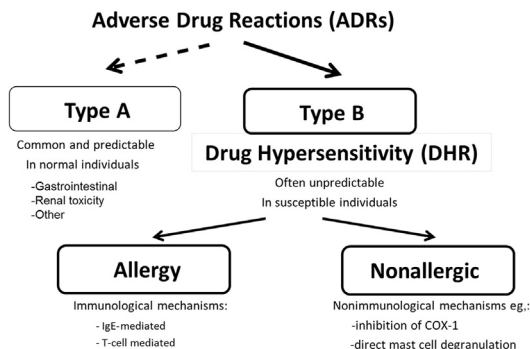


Fig. 1. Classification of ADRs and DHRs.

fixed drug eruptions (FDEs), erythema multiforme, acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), exfoliative dermatitis, toxic epidermal necrolysis (TEN), photosensitivity, purpura, and erythema nodosum. Different medications may cause identical skin symptoms, whereas, on the other hand, hypersensitivity to a single drug may manifest with various patterns of symptoms depending on the mechanism of the reaction. Immediate drug reactions, which develop usually within 1 hour of the intake of the culprit drug, manifest with urticaria, angioedema, and/or anaphylaxis. Delayed-type reactions may manifest with virtually all other cutaneous drug eruptions.⁸ In addition to analysis of the timing of the reaction, morphology of drug-induced lesions is important for the final diagnosis. Thus, here the authors present a morphologic approach to the diagnosis of cutaneous drug eruptions. Drugs most commonly eliciting specific cutaneous lesions are summarized in [Table 1](#).

Urticaria, Angioedema, and Anaphylaxis

Skin eruption

Urticaria is characterized by reddish itchy wheals. An individual wheal lasts up to 24 hours, but new wheals may continuously develop over a longer period of time. *Angioedema* presents as swelling of deep dermal and subcutaneous tissue, and drug-induced angioedema is usually unilateral and accompanied by a pain or burning sensation rather than pruritus. Generally it persists for 1 to 2 hours, but deep swelling can last even for 5 days. In an individual patient, urticaria and angioedema can develop at any location, either jointly or separately. Angiotensin-converting enzyme inhibitor (ACEI)-related angioedema is never accompanied by urticaria, and symptoms usually occur within 1 hour after drug exposure. ACEI-induced angioedema may first occur years after the beginning of treatment with an ACEI and recurs irregularly during such treatment.⁹ Urticarial rash is accompanied by fever and arthralgia and, if developing after 1 to 3 weeks of the culprit drug initiation, may represent *serum sickness-like reactions*.

Anaphylaxis is a severe multisystem reaction with rapid onset and life-threatening consequences. Clinically anaphylaxis is characterized by the development of skin lesions, such as erythema, urticaria, or angioedema, followed by hypotension and/or bronchospasm. UK guidelines underline poor clinical documentation of drug allergy and subsequent patient education/information on the subject.¹⁰

Cutaneous histopathology

In urticaria, stratum papillare, the uppermost layer of dermis, is involved with pronounced vasodilation and moderate edema. Sparse perivascular infiltrates with neutrophils, eosinophils, monocytes, and T-lymphocytes may also be present. In angioedema, the pathologic processes are localized in the deeper layers of the dermis, stratum reticulare, and in subcutaneous or submucosal tissue, as these processes can affect both skin and mucosae. Edema dominates the picture with no or moderate vasodilation; eosinophils may be seen in allergic angioedema, but otherwise there is little or no cellular infiltrate.

Underlying mechanisms

Urticarial lesions are induced by mediators released from activated mast cells. Non-immunologic mechanisms related to COX-1 inhibition are predominant in the development of skin symptoms induced by NSAIDs.^{11–13} Type I hypersensitivity reaction (involving IgE) is less frequently involved in drug-induced urticaria but seems to be frequent in anaphylactic reactions.¹⁴ Type III hypersensitivity is responsible for serum

Table 1
Cutaneous manifestations of drug allergy and hypersensitivity in relation to the most commonly eliciting drugs

Cutaneous Manifestation	Most Commonly Eliciting Drugs
Urticaria	NSAIDs, antibiotics, narcotic analgesics
Angioedema	NSAIDs, ACE inhibitors, angiotensin antagonists
Anaphylactic reactions	NSAIDs, antimicrobials, neuromuscular blockers
Erythematous eruptions	Antibiotics, sulfonamides, antiepileptic drugs, non-nucleoside reverse transcriptase inhibitors
Acneiform eruptions	ACTH, androgens, bromides, glucocorticoids, isoniazid, iodides, lithium, phenytoin, selective serotonin reuptake inhibitors, vitamins B1, B6, B12, cyclosporine, sirolimus, isoniazid, EGF inhibitors, bevacizumab, TNF-alpha inhibitors
AGEP	Aminopenicillins, macrolides, carbamazepine, quinolones, diltiazem, antimalarials, mercury
Pseudoporphyria	NSAIDs, antibiotics
Drug-induced LABD	Vancomycin, paracetamol, amiodarone, ceftriaxone, furosemide, metronidazole, phenytoin
Drug-induced pemphigus	Penicillamine and other thiol drugs
Drug-induced pemphigoid	Psoralens, furosemide, ibuprofen, ACE inhibitors, spironolactone, ampicillin, penicillin, levofloxacin, penicillamine, metronidazole, chloroquine
Lichenoid eruptions	Beta-blockers, penicillamine, ACE inhibitors
Cutaneous pseudolymphoma reaction	Anticonvulsants
Drug-induced vasculitis	Allopurinol, penicillins, sulfonamides, phenytoin, thiazides
Drug-induced lupus	Hydralazine, isoniazid, penicillamine, minocycline
Allergic contact dermatitis to drugs	Topical: antibiotics (neomycin, gentamycin, bacitracin), glucocorticosteroids, antiseptics (chlorhexidine, quinolones, benzalkonium chloride)
Photoallergic dermatitis to drugs	NSAIDs
Phototoxic reactions	Psoralens, thiazides, chlorpropamide, nalidixic acid, phenothiazines, tetracyclines, hormonal contraceptives
FDE	Ibuprofen, sulfonamides, tetracyclines, quinolone
SJS/TEN	Allopurinol, antiretrovirals, aromatic amine anticonvulsants, NSAIDs, sulfa-antimicrobials
DRESS	Allopurinol, anticonvulsants, antiretrovirals, NSAIDs, minocycline, sulfasalazine, dapsone, fludione, proton pump inhibitors, strontium ranelate

Abbreviations: ACE, angiotensin-converting enzyme; ACTH, adrenocorticotrophic hormone; EGF, epidermal growth factor; LABD, linear IgA bullous disease; TNF, tumor necrosis factor.

sickness-like reactions presenting as urticarial rash.¹⁵ ACEI-related angioedema is due to kinin-dependent mechanisms.⁹

Erythematous Eruptions

Skin eruptions

Erythematous eruptions (other names: maculopapular or morbilliform eruptions) are the most common clinical presentation of drug eruptions representing about 95% of

all drug-induced skin symptoms. They present as erythematous lesions without blisters or pustules (**Fig. 2**). The trunk is the most common location of the first skin lesions, which spread peripherally in a symmetric way. Almost all patients have pruritus. The first lesions usually develop within a week of the therapy introduction and resolve within 1 to 2 weeks. Typically, during the resolution phase, the eruptions fade in color from deep red into brownish hues with subsequent desquamation of variable intensity.¹⁶

Cutaneous histopathology

Demonstrates moderate perivascular infiltrate composed mainly of lymphocytes and eosinophils. Some vacuolization of the dermal-epidermal junction may be present.

Underlying mechanisms

It is usually a type IVc or IVb delayed-type reaction whereby T cells directly recognize the drug and activate other inflammatory cells. In some cases, viral infection is a necessary cofactor.

Pustular Eruptions

Skin eruptions

Acneiform eruptions present as scattered pustules that emerge independently of hair follicles and sebaceous glands and may, thus, localize beyond the seborrheic areas, for example, on arms, trunk, lower back, and genitals, typically with absence of comedones and cysts.¹⁷

Cutaneous histopathology

Inflammatory monomorphic infiltrates with intraepidermal spongiosis and pustule formation occur independent of sebaceous glands.

Underlying mechanisms

The underlying mechanisms remain mostly unknown. Delayed type IVd hypersensitivity may be responsible in some cases.

Acute Generalized Exanthematous Pustulosis

Skin eruptions

An erythematous rash with pustulosis (nonfollicular, sterile pustules <5 mm in diameter) accompanied by fever and neutrophilia develops typically within 48 hours to 3 weeks after drug ingestion. The typical localization is intertriginous areas and the face.^{18,19} In most cases AGEP is a self-limited disease. The following features are

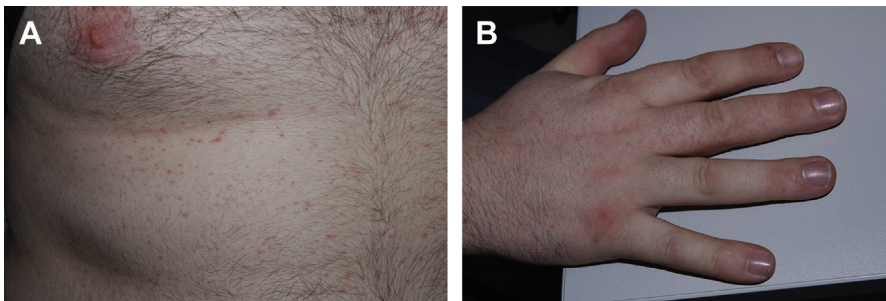


Fig. 2. Erythematous maculopapular eruption that emerged on the trunk (A) and on the back of the hand (B) after 7 days of clindamycin therapy. (Courtesy of Radoslaw Spiewak, MD, PhD, Krakow, Poland.)

taken into account in establishing AGEP diagnosis: pustules, erythema, distribution/pattern, pustular desquamation, course, mucosal involvement, acute onset, resolution, fever ($>38^{\circ}\text{C}$), neutrophils greater than $7000/\text{mm}^3$, and histology. The European Study of Severe Cutaneous Adverse Reactions (EuroSCAR) developed a grading system for AGEP diagnosis assigning it as possible (1–4 points), probable (5–7 points), or definite (8–12 points).²⁰

Cutaneous histopathology

It typically demonstrates intraepidermal pustules with edema of the papillary dermis and perivascular infiltrates of neutrophils and eosinophils.

Underlying mechanisms

Delayed type IVd hypersensitivity related to CD4+ T cells expressing interleukin 8 initiate neutrophilic infiltration and subsequently pustule formation.²¹

Bullous Eruptions

Several types of bullous eruptions may be related to drug hypersensitivity.

Pseudoporphyria

Skin eruption Skin fragility results in formation of blisters that heal with scarring on sun exposed areas. Skin lesions can develop in the first day of the offending drug ingestion as well as after 1 year of therapy. No abnormalities in porphyrin metabolism have been found.²²

Cutaneous histopathology It usually reveals split at the dermo-epidermal junction, absent or slight inflammation, and no damage to the epidermis.

Underlying Mechanisms The involved processes remain unknown, phototoxic mechanisms hypothesized.

Drug-Induced Linear Immunoglobulin A Bullous Diseases

Skin eruptions

Skin eruptions are quite heterogeneous and resemble erythema multiforme, bullous pemphigoid, and/or dermatitis herpetiformis. Mucosal and conjunctival lesions are less common than in the idiopathic form of linear IgA bullous diseases.

Cutaneous histopathology

Immunopathology reveals IgA deposits in the basement membrane zone.

Underlying mechanisms

Acantholysis is induced by immunologic mechanisms involving antibody production.

Drug-Induced Pemphigus

Skin eruption

Flaccid bullae and/or crusted erosions predominate. Lesions could develop up to 1 year after drug therapy.

Cutaneous histopathology

There are intraepidermal blisters with intercellular deposition of IgG within suprabasal epidermis.

Underlying mechanisms

Acantholysis is induced either by immunologic mechanisms involving antibody production or directly by drug, in the absence of antibody formation.

Drug-Induced Bullous Pemphigoid

Skin eruptions

Considerable variety is present, including a few bullous lesions; numerous, large, tense bullae on erythematous and urticarial base; and scarring plaques or nodules with bullae, with moderate involvement of the oral mucosa.

Cutaneous histopathology

There are mainly lymphocytic perivascular infiltrates with few eosinophils and neutrophils, intraepidermal vesicles, thrombi in dermal blood vessels, and lack of tissue-bound and circulating antibasal membrane zone IgG.

Underlying mechanisms

Acantholysis is induced either by immunologic mechanisms involving antibody production or directly by drug in the absence of antibody formation.

Lichenoid Eruptions

Skin eruption

There are lichenoid papules with a reddish hue, both clinically and on histopathology consistent with the idiopathic form of lichen planus. The first skin lesions typically develop on the trunk (Fig. 3). The mucous membranes and nails are spared. The regression of the lesions proceeds without scarring. The period from drug introduction to skin lesion development ranges between 2 months and 3 years.

Cutaneous histopathology

Cutaneous histopathology of lichenoid drug eruption demonstrates focal parakeratosis, cytoid bodies in the cornified and granular layers, focal interruption in the granular layer, and inflammatory infiltrate with eosinophils and plasma cells, also situated in the deep dermis.

Underlying mechanisms

Type IV hypersensitivity reaction is implied in the formation of lichenoid lesions.



Fig. 3. Lichenoid reaction to hydrochlorothiazide. The first episode in this patient developed after 2 months of taking a combination drug including enalapril and hydrochlorothiazide. The lesions resolved within 3 weeks after stopping the medication; however, they returned in less than a week after another doctor unaware of the patient's past history prescribed her with another combination drug of hydrochlorothiazide with valsartan. (Courtesy of Radoslaw Spiewak, MD, PhD, Krakow, Poland.)

Cutaneous Pseudolymphoma Reaction

Skin eruptions

Skin lesions are solitary in most cases but could be fairly widespread and present as erythematous nodules, plaques, or papules. Most patients manifest fever, eosinophilia, lymphadenopathy, and hepatosplenomegaly. Skin lesions develop after at least 1 week but may even occur after up to 5 years of drug exposure.

Cutaneous histopathology

It requires specific staining for differential diagnosis with malignant lymphoma. Polymorphic infiltrates containing T or B lymphocytes are observed in the dermis and the subcutaneous tissue.

Underlying mechanisms

There is a delayed type IV reaction and disturbances in enzymatic detoxification of culprit drugs.

Drug-Induced Vasculitis

Skin eruption

Palpable purpura typically located on the lower limbs is a hallmark of cutaneous vasculitis (Fig. 4). Small vessel vasculitis could clinically manifest as urticarial wheals. Persistence of a single lesion in the same location for more than 24 hours is a characteristic feature of urticarial vasculitis. Hemorrhagic bullae, ulcers, nodules, and distal necrosis can develop. The vasculitic process can involve internal organs, including



Fig. 4. This patient had episodes of recurring vasculitis over a period of 17 years. Careful diagnosis revealed that relapses were provoked by nitrofurantoin, which she took occasionally for recurring urinary tract infections. (Courtesy of Radoslaw Spiewak, MD, PhD, Krakow, Poland.)

the liver, gut, kidney, and central nervous system, leading to serious consequences, including life-threatening ones. Drug-induced vasculitis is frequently a diagnosis of exclusion.^{23,24}

Cutaneous histopathology

Dilatation and damage of blood vessels with lymphocytic infiltrate and mast cell degranulation are observed in the edematous dermis.

Underlying Mechanisms

Type III mechanisms mediate the process.

Drug-Induced Lupus

Skin eruption

Skin eruptions are consistent with typical lupus erythematosus lesions, that is, erythematous lesions with edema. Annular or papulosquamous eruptions resembling subacute cutaneous lupus erythematosus are also encountered. Skin lesions are frequently accompanied by systemic symptoms, such as fever, weight loss, musculoskeletal complaints, pleuropulmonary involvement, and less frequently renal, neurologic, and vascular abnormalities.

Cutaneous histopathology

Epidermal atrophy, hyperkeratosis, basal layer degeneration, dermal edema, inflammatory infiltrate, is seen with occasional vasculitis, immunoglobulins, and complement at the dermo-epidermal junction.

Underlying mechanisms

Hapten/prohapten theory, direct cytotoxicity, lymphocytes activation, disturbances in immunologic tolerance.

Allergic Contact Dermatitis to Drugs

Allergic contact dermatitis (ACD; synonym: allergic contact eczema) is an inflammatory skin disease that develops in a person hypersensitive to a low-molecular-weight chemical (hapten), following reexposure to this hapten. There are 4 major clinical variants: localized ACD restricted to the area of contact with the culprit drug, localized ACD with satellites due to redistribution via lymphatic vessels of the absorbed hapten, generalized hematogenous ACD due to blood-borne redistribution of hapten absorbed through the skin, and finally the systemic reactivation of ACD (SRACD) after extracutaneous exposure to hapten (injection, ingestion, inhalation).²⁵ The last form frequently manifests flexural or fold involvement. Drug-related SRACD is frequently referred to as symmetric drug-related intertriginous and flexural exanthema or baboon syndrome.^{26,27} The diagnosis of ACD is confirmed by patch tests that should be carried out in line with expert guidelines.²⁸

Skin eruptions

There are eczematous skin lesions with exudation in the acute phase and hyperkeratosis and lichenification in the chronic phase (Figs. 5 and 6).

Cutaneous histopathology

Epidermal edema, dermal vessels dilatation, epidermal, dermal, and perivascular inflammatory infiltrate, keratinocyte apoptosis leading to spongiosis with formation of vesicles.



Fig. 5. ACD of eyelids in a patient with contact allergy to antibiotics gentamicin, neomycin, and preservative benzalkonium, all of which were present in ophthalmic drugs that she has used for more than 20 year for recurring sties. (Courtesy of Radoslaw Spiewak, MD, PhD, Krakow, Poland.)



Fig. 6. ACD to a glucocorticosteroid (budesonide) on the right leg secondary to prolonged treatment of venous insufficiency and stasis dermatitis. (Courtesy of Radoslaw Spiewak, MD, PhD, Krakow, Poland.)

Underlying mechanisms

Delayed-type hypersensitivity, overlapping subtypes IVa, and IVc (cytotoxic lymphocytes).

Photoallergic Dermatitis to Drugs

Photoallergic dermatitis is a variant of ACD in which additional energy in the form of photons is required to initiate a photochemical reaction between hapten and carrier protein, which subsequently induces the same delayed-type hypersensitivity mechanisms as in ACD.²⁹ Photopatch tests are required to confirm photoallergy to a suspected drug and the ultimate diagnosis of photoallergic dermatitis.³⁰

Skin eruptions

The morphology and clinical course of the disease is identical with ACD, except that irradiation (typically UVA from sunlight) is necessary for the development of the disease; thus, areas exposed to both the drug and light are involved (**Fig. 7**), regardless of the route of drug exposure (topical or systemic).^{31–33}

Underlying Mechanism

There is a delayed type IV reaction.

Phototoxic Reactions**Skin eruption**

There are cutaneous lesions of variable morphology (erythema, eczema, lichenoid, petechiae, bullae, hyperpigmentation) localized on sun-exposed areas. There are usually sharp borders between areas exposed to light and those covered by clothing, jewelry, watches, and so forth.³⁴

Cutaneous histopathology

It is variable depending on the morphology of skin lesions.

Underlying mechanisms

There is damage to lipid membranes, proteins, and DNA by free oxygen or nitrogen radicals produced in photochemical reactions facilitated by the presence of a phototoxic drug in the skin.³⁵



Fig. 7. Photoallergic dermatitis to terbinafine taken orally. Regardless of systemic exposure to the drug, areas covered by clothing were spared; dermatitis is also visibly milder in areas less exposed to direct sunlight, that is, under the hair, behind the ears, under the chin, in the orbital fossae. (Courtesy of Radoslaw Spiewak, MD, PhD, Krakow, Poland.)

Severe cutaneous adverse reactions, although often involving bullous eruptions, are presented in a separate section later.

Fixed Drug Eruption

Skin eruptions

They are characterized by solitary (or less frequently multiple) oval reddish plaques that resolve with residual grayish hyperpigmentation (**Fig. 8**). Blisters may develop within the lesions. Lesions develop at the same location each time the culprit drug is taken and are most frequently found within the genital and perianal region; however, they can occur anywhere on the skin. The lesions can develop 30 minutes to 16 hours after culprit drug ingestion. When the culprit drug is reintroduced, not only the lesion reappears in the same locations but also totally new lesions frequently develop. In the acute phase, patients can complain of a burning or stinging sensation. Sometimes fever, malaise, and abdominal symptoms even develop.

Cutaneous histopathology

Cutaneous histopathology shows erythema multiforme features with quite pronounced interface dermatitis together with signs of epithelial degeneration with



Fig. 8. Fixed drug reaction to paracetamol (acetaminophen) in an 8-year-old boy. He experienced 5 recurrences over the last 5 years because of easy access and widespread presence of paracetamol in various combination drugs for children. (Courtesy of Radoslaw Spiewak, MD, PhD, Krakow, Poland.)

dyskeratosis and lymphocyte infiltrates at the dermoepidermal junction. Within FDE lesions, chronic changes, including acanthosis, hypergranulosis, hyperkeratosis eosinophils, and neutrophils, could also be visible.

Underlying mechanisms

T helper and suppressor lymphocytes are increased in the lesional skin. They are thought to contribute to recurrence of the lesions in the same locations after the culprit drug ingestion.

Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

SJS and TEN are the most severe type of DHR with an estimated mortality rate of 1% to 10% and 20% to 35%, for TEN and SJS, respectively. A severity-of-illness score for TEN is the most frequently used scoring system to predict the course of SJS/TEN.³⁶

In about 50% of patients with SJS/TEN, the disease begins with nonspecific prodrome symptoms, such as fever, malaise, headaches, cough, rhinitis, sore throat, chest pain, arthralgias, myalgias, diarrhea, and vomiting. Those symptoms could precede skin lesion development by 1 to 14 days.

Skin eruption and organ involvement

SJS/TEN is characterized by acute-onset blistering skin lesions. SJS is diagnosed when epidermal detachment is observed on less than 10% of total body surface area (BSA). TEN requires more than 30% of the BSA epidermal detachment, whereas SJS/TEN overlap is defined as epidermal detachment of 10% to 30% BSA.

SJS/TEN presents with the following skin lesions: macular, often morbilliform rash (first on the face, neck, and central trunk areas and then spreading to the rest of the body); erosions of the mucous membranes; target lesions (with dusky center); and epidermal necrosis. Skin lesions heal with transient hypopigmentation and/or hyperpigmentation. Scarring of mucosal membranes is quite frequent, and there are late complications in about 30% of patients with TEN. The most serious consequences of scarring are observed in the eyes.

The most severely affected parts are the mucous membranes of the mouth (mainly buccal mucosa, palate, and vermilion border) and the eyes (mainly bulbar conjunctiva and anogenital region). Mucous membrane lesions occur either in parallel with or preceding the rash. All 3 sites are involved in about 40% of cases.

Patients report sore and burning sensations of the buccal mucosa, conjunctivae, and lips. Edema and erythema of the skin and mucous membranes follow with blister formation. They subsequently rupture leaving extensive, hemorrhagic erosions covered by white-grayish pseudomembranes composed of fibrin and necrotic epithelium. Numerous hemorrhagic crusts cover the lips. Oral lesions are very painful and lead to eating and breathing inconvenience and excessive saliva production.

Conjunctival involvement demonstrates mainly as inflammation, vesiculation, erosions, and lacrimation. Photophobia, pseudomembranous purulent conjunctivitis, anterior uveitis, corneal ulceration, and panophthalmitis are less frequently observed.

Genital mucous membrane involvement mainly manifests as sore hemorrhagic bullous-erosive or purulent lesions of fossa navicularis, glans penis, vulva, and vagina. Those abnormalities could lead to phimosis in males and/or urinary retention in both sexes.

Pathologic processes of the upper respiratory tract can involve the nasal cavity, gingival, tongue, pharynx, larynx, esophagus, and respiratory tree. In the course of SJS/TEN, otitis media as well as internal organ involvement may develop.

Respiratory and gastrointestinal tract symptoms are most commonly noted. However, development of the following abnormalities could be observed: cytopenias (mostly anemia and lymphocytopenia), gastritis, hepatitis, myocarditis, nephritis, and pneumonitis.

Cutaneous histopathology

It reveals massive necrosis of keratinocytes and epidermis shedding, with minimal or absent dermal inflammatory infiltrate.

Underlying mechanisms

There is a cytotoxic reaction aimed at destruction of keratinocytes expressing foreign (ie, drug-related) antigens. The drug may specifically activate CD8+ T cells, natural killer (NK) cells, and NKT cells to secrete granzyme, leading to upregulation of Fas-Ligand by keratinocytes and to activation of a death receptor-mediated apoptotic pathway. Alternatively, the drug may interact with major histocompatibility complex (MHC) I-expressing cells, causing drug-specific CD8+ cytotoxic T cells to accumulate within epidermal blisters, releasing perforin and granzyme B, which induce keratinocyte death without the need for cell contact. Recent pharmacogenomics studies documented a strong association with MHC.^{37–39}

Drug Reaction with Eosinophilia and Systemic Symptoms

DRESS, also known as drug-induced hypersensitivity syndrome (DIHS) or hypersensitivity syndrome (HSS), is a potentially life-threatening condition characterized by both skin and internal organ involvement. The mortality rate in DRESS/DIHS/HSS is estimated at 10% of the affected cases, mainly due to hepatic and renal involvement. In patients with DRESS, leukocytosis at presentation could be regarded as a prognostic marker for prolonged hospitalization.^{40,41}

Skin eruption and organ involvement

Clinical presentation of DRESS typically starts with such prodromal symptoms as skin itch and fever followed by cutaneous eruption of erythematous morbilliform rash and then lymphadenopathy development with pharyngitis, oral ulcers, and subsequently systemic symptoms.

Systemic abnormalities encountered in DRESS are as follows: hepatic, hematologic, gastrointestinal, renal, neurologic, cardiac, and endocrine. Liver seems to be the organ most frequently involved in DRESS. Until now, no formal diagnostic criteria for DRESS have been accepted; but in clinical practice both Japanese and RegiSCAR criteria are used.^{42,43} Maculopapular rash is usually developing 3 weeks after drug administration, and clinical symptoms persist for 2 or more weeks after drug withdrawal.

Cutaneous histopathology

Coexistence of 3 patterns (ie, eczematous, interface dermatitis, and vascular) seems to be most frequently encountered and suggestive of higher trend of hematological abnormalities and human herpes virus 6 reactivation.⁴⁴

Underlying mechanisms

DRESS has been associated with specific HLA antigens in some ethnic groups with certain culprit drugs. HLA-B*58:01 is associated with allopurinol-induced disease, whereas HLA-B*57:01 with abacavir-induced disease. HLA-B*51:01 was significantly associated with phenytoin-related DRESS.³⁸ DRESS seems to be more common in Asia than in other parts of the world.

SUMMARY

Cutaneous eruptions are the most common manifestation of both allergic and nonallergic drug hypersensitivity. Different medications may cause identical skin symptoms, and hypersensitivity to a single drug may manifest with various patterns of symptoms depending on the pathogenetic mechanism involved. Immediate drug reactions, developing within 1 hour of drug intake, manifest with urticaria and/or angioedema and may herald development of a severe anaphylactic reaction. A delayed type of drug hypersensitivity may manifest with various cutaneous symptoms, including exanthematous eruptions, FDEs, erythema multiforme, and purpura or erythema nodosum. The most severe reactions, SJS and TEN and some cases of DRESS, may be fatal. Analysis of morphology of drug-induced lesions as well as timing of reaction is critical for the final diagnosis. Further studies will lead to better understanding of the pathogenic mechanism (genetic, immunologic, and nonimmunologic) underlying the skin manifestation of drug hypersensitivity allowing for earlier identification of the culprit drug and more effective management and prevention.

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