

Delayed Cutaneous Manifestations of Drug Hypersensitivity

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KEYWORDS

- Drug hypersensitivity • Cutaneous manifestation
- Maculopapular exanthem • Urticaria • Vasculitis
- Acute generalized exanthematous pustulosis
- Drug-induced hypersensitivity syndrome/
drug reaction with eosinophilia and systemic symptoms

Adverse drug reactions (ADRs) affect a considerable number of patients. Between 10% and 15% of treated patients report an unwanted drug reaction, 2% to 5% of them have to be hospitalized, and in 1% to 3% of them mortality may result.¹

ADRs often involve the skin.² Particularly, hypersensitivity reactions may present with cutaneous manifestations only. However, a careful look may often reveal (minor) organ involvement as well, indicating that drug hypersensitivity reactions are systemic immune reactions. On the other hand, in some reactions, the skin involvement may be of minor importance (anaphylaxis or the drug hypersensitivity syndrome [DHS]).³

The skin may present a variety of different reaction patterns. The correct identification and diagnosis of the skin lesions are paramount for the diagnosis of drug-induced hypersensitivity. For this reason, as for syphilis, the term “the great imitator” has been attributed to drug-induced hypersensitivity reactions, because they can imitate a variety of other diseases.⁴ Therefore, in many clinical situations cutaneous ADRs present a challenge in the differential diagnosis.

INITIAL STEPS OF DIAGNOSIS

The approach to the patient with a presumed drug hypersensitivity is described in another article by B. Schnyder in this issue. In brief, the initial clinical diagnosis requires a detailed description of the morphology, particularly the cutaneous efflorescences and signs. The often-used term “rash” is not specific and clear enough for this

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purpose. The clinical investigation comprises a complete examination of the skin and its appendages, including the mucous membranes of the mouth, eyes, and genitals. The type (**Box 1**) and distribution (**Box 2, Fig. 1**) of the lesions as well as their evolution (**Fig. 2**) should be noted, for example, predominant affection of the trunk, acral localizations, involvement of face and scalp, or sparing or involvement of light-protected areas. Pruritus of variable severity is typically present. The morphologic presentations of cutaneous hypersensitivity reactions are manifold and variable. Although the skin has only a limited repertoire of inflammatory reaction patterns, a wide spectrum including pruritus, erythema, erythroderma, urticaria, angioedema and macular, papular, vesicular, bullous, vasculitic, hemorrhagic, or necrotic lesions (see **Box 1**) may be observed.^{5,6} Some manifestations are rather specific for an ADR, such as fixed drug eruption, whereas others may present a challenge in the differential diagnosis toward other skin disorders, particularly infectious exanthems.⁷ A histopathologic examination may be helpful in distinguishing drug eruptions from other dermatoses.⁸ Based on the information gathered by clinical investigation and history, a pathogenetic

Box 1 Drug induced cutaneous symptoms/signs
Pruritus
Indirect signs (erosions from scratching)
Urticaria, angioedema
Exanthems
Macular
Papular
Vesicular
Pustular
Bullous
Hemorrhagic
Necrotic
Lichenoid
Psoriasiform
Pityriasiform
Exfoliative
Erythroderma
Mucous membranes
Erythema
Erosions
Aphthous lesions
Ulcerations
<i>Data from Bircher AJ. Approach to the patient with a drug hypersensitivity reaction—clinical perspectives. In: Pichler W, editor. Drug hypersensitivity. Basel (Switzerland): Karger; 2007. p. 354.</i>

hypothesis of the reaction can be formulated. This facilitates the later selection of allergological test tools, which may help in the identification of the eliciting drug. The suspected drugs should be immediately stopped, particularly if danger signs such as bullous or hemorrhagic widespread lesions or mucosal affections are present.³

Etiologic Diagnosis

The next step includes the identification of the potentially eliciting drug or drugs. Information on their dosages, way of administration, and the chronology of the reaction and the identification of cofactors such as underlying disorders (eg, viral infections, hepatopathy, or renal diseases) are required. A standardized approach with a drug questionnaire and consultation of pertinent textbooks is recommended.⁹

Chronology

The time period between the first dose and the occurrence of first symptoms does vary. First, a clear distinction between the situation of an immunologically naive person and a sensitized individual should be made. Sensitization to a drug or its metabolites takes at least 5 to 7 days of exposure but for several reasons it may take up to several

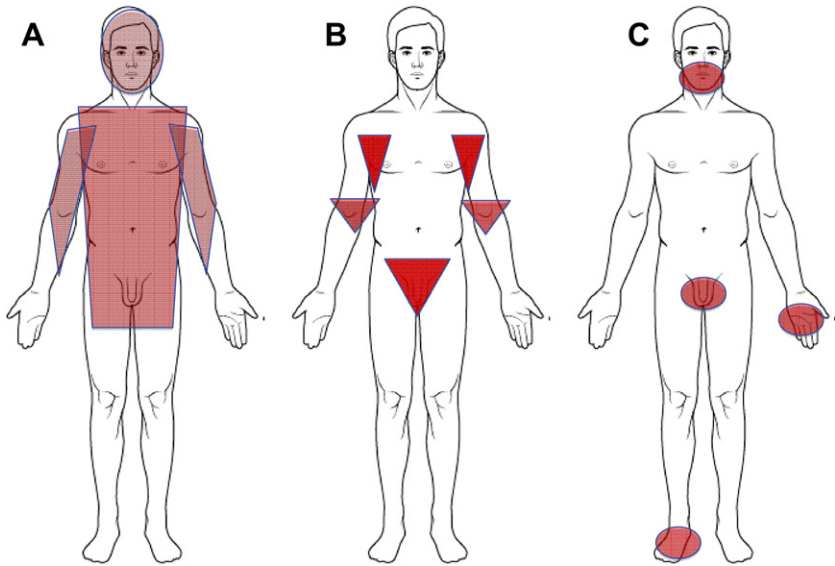


Fig. 1. Patterns of localization and distribution of common drug eruptions. (A) Maculopapular exanthem and urticaria: trunk and proximal extremities, rarely head. (B) Flexural exanthem (symmetrical drug-related intertriginous and flexural exanthem [SDRIFE]): perigenital and gluteal triangle, large folds (axillae, elbows). (C) Fixed drug eruption and angioedema: face and oral cavity, hands and feet, and male genitals. (Image reprinted with permission from Medscape.com, 2009.)

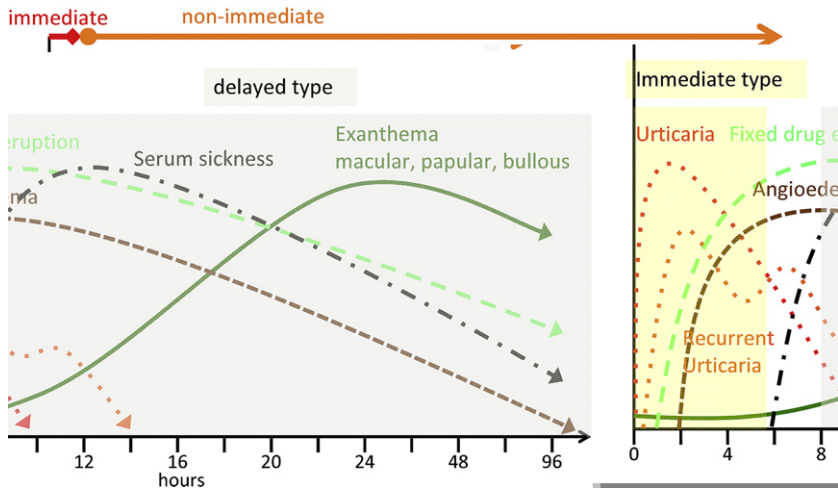


Fig. 2. Characteristic chronology of drug-induced eruptions. The separation at 1 hour into immediate or nonimmediate reactions does not sufficiently reflect the large overlap between the pathophysiologically determined immediate- and delayed-type clinical manifestations.

cross-reactivity. This type of sensitization has been shown not only for the β -lactam ring in penicillins and cephalosporins and quinolones¹⁰ but also for sulfonamides and aromatic antiepileptic drugs. Once an individual is sensitized, the time period between the exposure to the eliciting dose and the first occurrence of symptoms, the so-called reaction interval, varies depending on the pathomechanism and type of eruption (see **Fig. 2**).^{4,11} In IgE-mediated reactions, the typical eliciting or reaction period varies between a few minutes and some hours (see the article by Lumsuwan and Demoly elsewhere in this issue for further exploration of this topic). In the so-called pseudoallergic reactions, mainly to nonsteroidal antiinflammatory drugs (NSAIDs) and radio contrast media, the reaction period is also short, although no IgE-mediated mechanism has been definitely proved for NSAIDs, with the exception of reactions from pyrazolones¹² and possibly metabolites from diclofenac.¹³ In T cell-mediated (many exanthems) reactions the time delay ranges typically between a few hours and 2 days. Typically, there is also a certain inherent dynamism in the reaction, for example, an exanthema may set out with an erythematous flush or macules within hours, which then turn into papules that peak at 48 to 72 hours, that is, not only the distribution and extent of the eruption but also the single lesions may vary over time. In immediate reactions (eg, urticaria), this aspect is less pronounced; however, also in IgE-mediated reactions, the delay after drug intake (eg, by the oral route) may last up to several hours.¹⁴ Many factors, eg, the route of administration (intravenous > intramuscular > subcutaneous > topical > oral), drug metabolism, and other cofactors (food intake, drug interactions) play a modifying role. For this reason, the somewhat rigid separation between immediate and nonimmediate reactions at 1 hour based on the chronology only^{15,16} may be problematic, because there is a considerable overlap of a period of approximately 2 to 6 hours between the reaction period of urticarial and exanthematous eruptions (see **Fig. 2, Table 1**). The terms immediate and delayed are also commonly used to depict the pathophysiology (ie, type I [IgE mediated] and type IV [T cell mediated]). This is most important with regard to the selection of appropriate diagnostic tests.

DELAYED OCCURRING CUTANEOUS MANIFESTATIONS OF DRUG HYPERSENSITIVITY

The clinical characteristics of the more common and some more severe drug-related manifestations with a delayed occurrence are reviewed.⁷ Also, urticaria and angioedema are briefly mentioned because they may develop with a delay of several hours after exposure to the eliciting drug. Some drug-induced syndromes have been defined to delineate them from other diseases (**Table 2**). However, there is no general agreement on the terminology. More detailed information on the severe bullous reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) is presented in other articles of this issue.

General Symptoms

Generally, patients with allergic reactions do not often suffer substantially from the ongoing immune process: many patients may feel surprisingly good considering that a generalized immune reaction takes place. They mainly suffer from pruritus. If, however, nonspecific symptoms, such as general malaise, fatigue, headache, elevated body temperature, and gastrointestinal ailments (vomitus, diarrhea) are present, then they should be considered as an ominous sign of a more severe reaction (in particular acute generalized exanthematous pustulosis [AGEP], SJS/TEN, and DHS/drug reaction with eosinophilia and systemic symptoms [DRESS]).

Table 1 Clinical manifestations, chronology and morphology		
Clinical Diagnosis	Chronology of Elicitation	Morphology and Localization
Urticaria, Angioedema	Immediate Typically minutes to 1–2 h, angioedema up to 6 h Rapid change and resolution (Urticaria <24 h) Angioedema 24–72 h	Urticarial wheals, pale swelling surrounded by erythematous border Pruritus No cutaneous sequelae Trunk, face, generalized, mucosae
Anaphylaxis	Immediate Typically few minutes to 1–2 h Rapid change and resolution (<24 h) NB: biphasic anaphylaxis	Flush (face, trunk, folds) Urticaria (disseminated) Angioedema Palmoplantar or inguinal pruritus No cutaneous sequelae
Maculopapular Exanthem	Delayed Typically 6–24 h Peak at 48–72 h Resolution 5–7 d	Macules, papules confluence, desquamation Trunk, proximal extremities, dissemination
Fixed Drug Eruption	Delayed Typically 0.5–8 h Resolution 3–5 d	Erythematous or lilac macule or plaque, central bulla, erosion, permanent hyperpigmentation, burning, pruritus Fixed (identical) Acral localization, mucosa
Pustular Exanthem (AGEP)	Delayed Typically 6–12 h up to 24–48 h Resolution 5–7 d	Confluent erythema, pinpoint nonfollicular pustules, pruritus, massive desquamation Folds, trunk, dissemination generalized
Vesiculobullous exanthems	Delayed Typically 24–48 h Resolution 14–21 d	Macules, bullae, epidermolysis, mucositis Initially painful skin Trunk, face, dissemination generalized

Abbreviation: AGEP, acute generalized exanthematous pustulosis; NB, nota bene.

Data from Bach S, Bircher AJ. Drug hypersensitivity reactions: from clinical manifestations to an allergologic diagnosis. *Eur Ann Allergy Clin Immunol* 2005;37(6):213–8.

Drug Fever

Fever may be the only manifestation of a drug hypersensitivity reaction; its frequency is estimated at a few percent in all ADRs. Many patients suffer from additional symptoms, such as headaches and myalgias. Physical factors, pyrogens, and immune complexes contributing to the pathogenesis are discussed. Drugs that may elicit an isolated drug fever are antibiotics, cytostatics, sulfonamides, antidepressants, and many others.¹⁷ On the other hand, fever may precede or accompany particularly the more severe drug-induced exanthems, such as DHS or AGEP. In the latter, fever and neutrophilia are the diagnostic criteria.

Pruritus

Itch is a very common symptom of many skin diseases and, in particular, allergic reactions. It may be mediated by histamines in immediate-type symptoms and by proinflammatory cytokines in delayed-type reactions. Pruritus is present in many

Table 2
Major features of some delayed drug-induced syndromes

Drug-Induced Syndromes	Morphology	Localization	Internal Organ Involvement	Systemic Signs	Pertinent Laboratory Findings
SDRIFE (Baboon Syndrome)	Erythema Papules (pustules) Rarely bullae	Flexural/ intertriginous, rarely dissemination	Not affected	Usually none	None
DHS/DRESS	Maculopapular exanthem Erythroderma	Generalized centrofacial edema	Required Lymphadenopathy Hepatitis Pneumonitis Nephritis	Fever Malaise Fatigue	Eosinophilia, atypical lymphocytes Pathologic liver, renal function tests
AGEP	Erythroderma Pustules (small, numerous)	Disseminated generalized, rarely flexural	Possible but rare	High fever (temperature >38°C)	Neutrophilia
SJS/TEN	Macular Bullous lesions Epidermal necrolysis Stomatitis, conjunctivitis	Disseminated generalized	Common Pneumonitis Mucosal lesions (gastrointestinal tract)	Fever Malaise Fatigue	Lymphopenia

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DHS, drug hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; SDRIFE, symmetrical drug-related intertriginous and flexural exanthem; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Data from Scherer K, Bircher A. Unerwünschte arzneimittelreaktionen an der haut: zwischen trivial und fatal. Internist 2009;50(2):171–8 [in German].

cutaneous drug reactions and may even be the only manifestation of drug hypersensitivity. Drugs associated with isolated pruritus include analgetics and NSAIDs, antibiotics, cardiovascular drugs, opiates, hydroxyethyl starch, radio contrast media, and vitamin A derivatives. The pathomechanism is often not elucidated.

Urticaria and Angioedema

Urticaria is a disseminated skin eruption characterized by rapidly emerging, migrating, and itching wheals. A wheal is a rather flat, pale red elevation caused by edema in the upper part of the dermis. Wheals mainly affect trunk and extremities. After clearing they leave the intact skin behind. The lesions typically appear within minutes and usually persist for less than 24 hours at one location. Angioedema is a tense nonpitting edema of the corium layers, affecting mainly the face, lips, oral mucosa, and male genitals. It is usually pale due to vasocompression and causes a tingling and pressure sensation.

Urticaria and angioedema can result not only from a type I (IgE mediated) reaction but also from a nonimmunologic reaction, the so-called pseudoallergic mechanism such as aspirin intolerance. These reactions appear rather rapidly after drug uptake. Eliciting drugs include antibiotics, NSAIDs, radio contrast media, general anesthetic drugs, and many others. According to Coombs and Gell classification, there are also other types of reactions, for example, type III (immune-complex mediated) reactions to antibiotics, which manifest with urticaria only after several hours or even days.¹⁸ This implies that the above-mentioned separation of immediate and nonimmediate reactions at 1 hour is problematic, because particularly urticaria may manifest after several hours or even days. The pathomechanism in such delayed reactions is not elucidated and may involve antibody- or T cell-mediated mechanisms. It is striking that in a study on 20 children with ADR to aminopenicillins with negative skin tests, in more than 50% urticarial manifestations developed after a 5-day oral provocation test. In most children, the symptoms developed 1 to 2 days after completion of the reexposure.¹⁸ This implies that a very schematic approach is problematic.

Maculopapular Exanthems

These are the most common delayed manifestations. They manifest initially with erythematous macules and infiltrated papules, affecting particularly the trunk and the proximal extremities. Classic maculopapular exanthems (eg, seen with amoxicillin) appear after 7 to 10 days, sometimes even after cessation of therapy (eg, after 10 days of aminopenicillin treatment, exanthema appears on day 12). In stronger reactions, exanthems are confluent, resulting in erythrodermia. Typically, a more or less pronounced desquamation occurs after clearing of the inflammatory lesions within 7 to 10 days. The differential diagnosis includes the classic infectious exanthems such as measles and rubella; therefore, these exanthems were also called morbilliform and rubeoliform, respectively. In more severe reactions, elevated eosinophil counts can be observed in approximately 50% of patients, which help to distinguish maculopapular exanthems from viral exanthems. Common elicitors include antibiotics (such as aminopenicillins¹⁵ and quinolones¹⁰), antiepileptic drugs,¹⁹ and radio contrast media,²⁰ among many others. According to Coombs and Gell, exanthems normally result from a type IV (T cell mediated) reaction, whereby in maculopapular exanthems cytotoxic CD4⁺ T cells seem to play the major role (see the article by Pichler W elsewhere in this issue for further exploration of this topic). During initial drug exposure, about 1 week's time is required for expansion of drug-reactive cells and development of symptoms, whereas a sensitized individual may develop symptoms 24 to 48 hours after a renewed drug exposure. First signs such as a discrete erythema may even appear after a few hours.

Fixed Drug Eruption

The clinical manifestation of a fixed drug eruption is virtually pathognomonic for a drug-induced reaction.²⁴ A livid erythematous and sometimes edematous plaque with often a later-developing bullous center may be observed (**Fig. 4**). Typically, a residual hyperpigmentation persists; rarely there are nonpigmented forms.²⁵ The reaction always occurs in the same localization upon reexposure to the eliciting drug. The fixed drug eruption is typically singular, but multilocular disseminated forms have been observed. They have to be distinguished from SJS or TEN. Isolated mucosal lesions may be present in the oral cavity or on the male genitals; in women, genital localization is extremely rare. Commonly eliciting agents include sulfonamides, tetracyclines, pyrazolones, NSAIDs, and carbamazepine. In sensitized individuals, the lesions typically occur with a mean time delay of 2 hours (0.5–8 hours). The pathophysiology involves local memory CD8⁺ T cells, which may be counteracted by regulatory T cells preventing extended or disseminated tissue damage.²⁴

Pustular Exanthems

Isolated pustules may be observed in maculopapular exanthems; however, for disseminated forms the acronym AGEP has been proposed.²⁶ On a generalized erythema, multiple 1- to 3-mm measuring sterile pustules associated with pruritus or burning are observed. The initial lesions may start in the face or in the intertriginous areas after 12 to 24 hours and may disseminate within few days. Fever and leucocytosis are always present. A diagnostic algorithm for this not uncommon drug hypersensitivity reaction has been proposed.²⁷ The reaction is most often elicited by β -lactam antibiotics, particularly aminopenicillins and cephalosporins, and sometimes by exposure to mercury vapors. The reaction has also been observed to a large number of other drugs.^{26,27} (See the article by French and colleagues elsewhere in this issue for further exploration of this topic.) The differential diagnosis includes pustular psoriasis and bacterial infections.

Acute Febrile Neutrophilic Dermatitis (Sweet Syndrome)

Sweet syndrome comprises a symptom complex including fever; neutrophilia; and tender erythematous papules, nodules, and plaques.²⁸ Three forms of the syndrome are distinguished: classical (idiopathic), malignancy-associated, and drug-induced Sweet syndrome (DISS). For the diagnosis of DISS 5 criteria are required: (1) abrupt onset of painful erythematous plaques or nodules, (2) histopathologic evidence of



Fig. 4. Fixed drug eruption of the palm due to mefenamic acid.

a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis, (3) fever with a temperature greater than 38°C, (4) temporal relationship between drug ingestion and manifestation or temporally related recurrence after oral challenge, and (5) temporally related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids.²⁸ A large number of drugs have been implicated; however, the best documented evidence exists for granulocyte-macrophage colony-stimulating factor, all-trans retinoic acid, vaccines, and probably for minocycline.²⁹ Other frequently reported drugs are bortezomib, azathioprine, and sulfonamides.

Pityriasis Rosea-like Drug Eruptions

Pityriasis rosea is a common probably infectious skin disorder; an association with human herpesvirus types 6 and 7³⁰ and also with human herpesvirus 8³¹ has been proposed. Typically, it begins with a solitary, erythematous slightly elevated patch with fine scaling borders called the “herald patch.” It occurs usually on the trunk and more rarely on the limbs. After about 2 weeks, a generalized eruption acutely develops. These secondary oval patches are smaller and symmetrically oriented along the cleavage lines (Christmas tree distribution). Many drugs have been incriminated as possible triggers of pityriasis rosea-like eruptions: gold, captopril, tyrosine kinase inhibitors, and NSAIDs among many others. Also, vaccines such as diphtheria, smallpox, pneumococcus, hepatitis B, and BCG have been reported as triggering agents. In drug-induced pityriasis rosea, however, a morphologic atypicality is accompanied by histopathologic features with interface dermatitis and eosinophils. They may be followed by lichen planus-like changes, leaving marked hyperpigmentation, and clear after drug withdrawal.³⁰

Lichenoid Drug Reactions

Lichen planus or lichen planus-like reactions have been reported.³² In terms of location, morphology, and histology, lichen planus and drug-induced lichenoid eruptions may be identical. The skin lesions are small, shiny, polygonal papules with the characteristic Wickham striae. The oral mucosa may also be affected. Most often gold, antimalarials, methyldopa, β -blockers, and lithium salts have been incriminated.³²

Macular exanthems may proceed into very pruritic infiltrated lesions with the histologic presentation of a pseudolymphoma. They have a slower and more protracted time course, and therefore, the relation to the eliciting drug may be obscure. Cases from carbamazepine, phenytoin,³³ angiotensin-converting enzyme inhibitors, and quinidine have been reported.²²

Vesicular and Bullous Exanthems

The severe vesicular bullous exanthems are not an entity but include a range of disorders. Among these are the minor and major forms of erythema exsudativum multiforme, SJS, and TEN.^{6,34} They are differentiated from each other by the presence or absence of typical target lesions and particularly by the extent of the skin and mucosal manifestations and associated symptoms.³⁵ In erythema exsudativum multiforme major, SJS, and TEN or Lyell disease, the skin may be initially painful before bullous lesions evolve and affection of the mucosae is always present. This may involve the conjunctival, oral, genital, and perianal mucosa as well as mucosal surfaces of internal organs. Lethal outcome is present in approximately 30% of TEN cases (see the article by French and colleagues elsewhere in this issue for further exploration of this topic).

Serum Sickness–like Disease

Serum sickness classically manifests itself with fever, macular and urticarial exanthems, lymphadenopathy, arthralgia, and sometimes peripheral edemas. Classic serum sickness is an example of an immune complex–mediated type III reaction. The symptoms manifest typically after 6 to 8 hours.³⁴ Antibiotics such as penicillins,³⁶ co-trimoxazole, cefaclor, and rifampicin may induce a serum sickness–like disease without measurable immune complexes or complement activation among others. More recently, biologicals such as rituximab have elicited serum sickness–like syndromes based on the development of antirrituximab antibodies.³⁷

Vasculitis

Drugs may rarely elicit cutaneous or systemic vasculitis.³⁸ A typical manifestation is the cutaneous small-vessel vasculitis, so-called allergic or hypersensitivity vasculitis. Morphology includes purpura, papules, bullae, and necrotic lesions. Affection of internal organs such as the gastrointestinal tract, the kidneys, the liver, and the central nervous system has to be excluded.³⁹ Drug-induced vasculitis and drug-induced lupuslike disease are seen in long-term treatments and typically occur with a long delay. Approximately 100 drugs have been reported of inducing vasculitic syndromes. The clinical manifestations vary from isolated cutaneous or organ involvement to severe systemic inflammatory disease dominated by vasculitis. Pathophysiologically, antineutrophil cytoplasmic antibodies with specificity to more than 1 lysosomal antigen have been recently implicated. Combined with presence of antibodies to histones and beta2-glycoprotein 1 they constitute a useful serologic profile for drug-induced vasculitis or drug-induced lupuslike disease.³⁸

Erythema nodosum, histologically a septal panniculitis, is a cutaneous reaction pattern presenting with painful nodules on the legs and induced by heterogenous causes.⁴⁰ Histology represents a typical panniculitis. Apart from infections (tuberculosis, leprosy) and inflammatory disorders (sarcoidosis, inflammatory bowel disease), some drugs have also been implicated such as sulfonamides, analgesics, antipyretics, oral contraceptives, and some others have been reported.⁴¹

Other Organs

Particularly the liver and the circulating blood cells may be affected in drug-induced reactions, either as single manifestation or in complex syndromes (see **Table 2**). Also, lymphadenopathy, nephritis, and pneumonitis have been observed, and other organs such as the myocardium, the thyroid gland, and the gastrointestinal tract may be affected. Some of these organs may be involved in the context of drug-induced autoimmune disorders such as lupus⁴² and vasculitis.⁴³ In addition, a variety of drugs elicit exclusive reactions in liver, kidney, or lung, often without skin symptoms; such reactions are difficult to recognize, which often delays the diagnosis. A peripheral eosinophilia may help in the diagnosis and as a hint for a drug allergic process.

Diagnostic Approach

The specific cause-oriented allergy diagnosis should be usually performed the earliest—3 to 4 weeks after complete clearing of all clinical symptoms and signs. On the other hand, after a time interval of more than 6 to 12 months, some drug tests may already have become negative, resulting in false-negative results.

According to the clinical manifestations and the time pattern, a hypothesis of the putative pathogenesis should be generated to select appropriate test procedures.

A histologic analysis of the cutaneous lesions may help to further specify the manifestation and to differentiate it from other skin disorders.⁸

SUMMARY

Drugs and drug allergens may elicit a wide variety of clinical manifestations that are based on various pathogenetic mechanisms. However, there still remain many clinical reactions, in which the pathomechanism is not known, and therefore, no validated

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