Adverse Drug Reactions

26

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Key Points summary

In situations that involve patients with acute adverse drug reaction, certain general principles should be observed:

- If possible identify the physiopathologic mechanism involved in the reaction;
- Identify as rapidly as possible the drug inducing the reaction and always opt for its withdrawal; in some circumstances the choice is difficult as there is no alternative drug and its use is essential for the maintenance of life;
- A careful and intensive observation is recommended for the occurrence of warning signs regarding the appearance of a potentially severe adverse drug reaction, especially in relation to mucous, oral, ocular, and genital involvement and progression of any present cutaneous eruption;
- It is imperative that the drug responsible may be withdrawn on a permanent basis together with chemically related compounds, and this advice is also valid for first-degree relatives who can present the same type of reaction.

Introduction

Adverse reactions to drugs are complications that are of relevance to medicinal therapy [1]. It is estimated that 5–15% of patients treated with some medication develop adverse reactions [1].

The incidence of adverse reactions to drugs among hospitalized patients is roughly 30%, 2–3% of which constitute cutaneous reactions [1, 2]. Such reactions are seldom severe but may lead to high mortality rates [3].

In this chapter, three groups of cutaneous adverse drug reactions (ADRs) are discussed: (i) severe ADRs; (ii) moderate or mild cutaneous ADRs, and (iii) ADRs caused by chemotherapy drugs.

Severe Adverse Drug Reactions

Severe cutaneous adverse reactions to drugs (SCARDs) generally require hospitalization, sometimes in the intensive therapy or burn care unit for observation of vital signs and visceral

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function. The aim of this study is to describe these reactions in order to facilitate recognition and treatment. This group of drug reactions includes anaphylaxis, Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and, depending on the systemic involvement, erythroderma. In this chapter we approach the characteristics and treatment of some adverse reactions to drugs, including anaphylaxis, erythroderma, SJS, and TEN.

The prevalence of SCARDs is estimated at 1 in 1,000 hospitalized patients. SJS and TEN are particularly severe [4]. In general, fatal cutaneous drug-induced reactions occur in 0.1% of clinical patients and 0.01% of surgery patients [1].

SCARDs may be defined as usually requiring hospitalization, at times in intensive therapy or burn care units for close observation of vital signs and visceral function. This group of drug reactions includes anaphylaxis, SJS, TEN, drug hypersensitivity, and, depending on the systemic involvement, erythroderma, acute generalized exanthematous pustulosis (AGEP), cutaneous necrosis induced by anticoagulants, drug-induced vasculitis, and reactions such as serum disease [4].

Quick differentiation between a SCARD and a less severe eruption may be difficult, although essential. Withdrawal of the suspected drug is the surest way of intervening to reduce mortality [4].

Most cutaneous reactions to drugs are usually observed as a morbilliform or maculopapulous exanthema [2, 5, 6]. Unfortunately, erythema morbilliform (Fig. 26.1) most often characterizes the appearance at onset in the severest of cases, including TEN, serum disease, and drug hypersensitivity syndrome [4].

Djien et al. [3], studying 133 patients with reactions to drugs clinically presenting with erythematous cutaneous eruptions (morbilliform and scarlatiniform exanthema, maculopapulous, and small isolated papules), concluded that three types of severe clinical markers exist with respect to this kind of reaction: fever, lymphadenopathy, and extensive cutaneous affection. The authors excluded specific forms from the study, such as

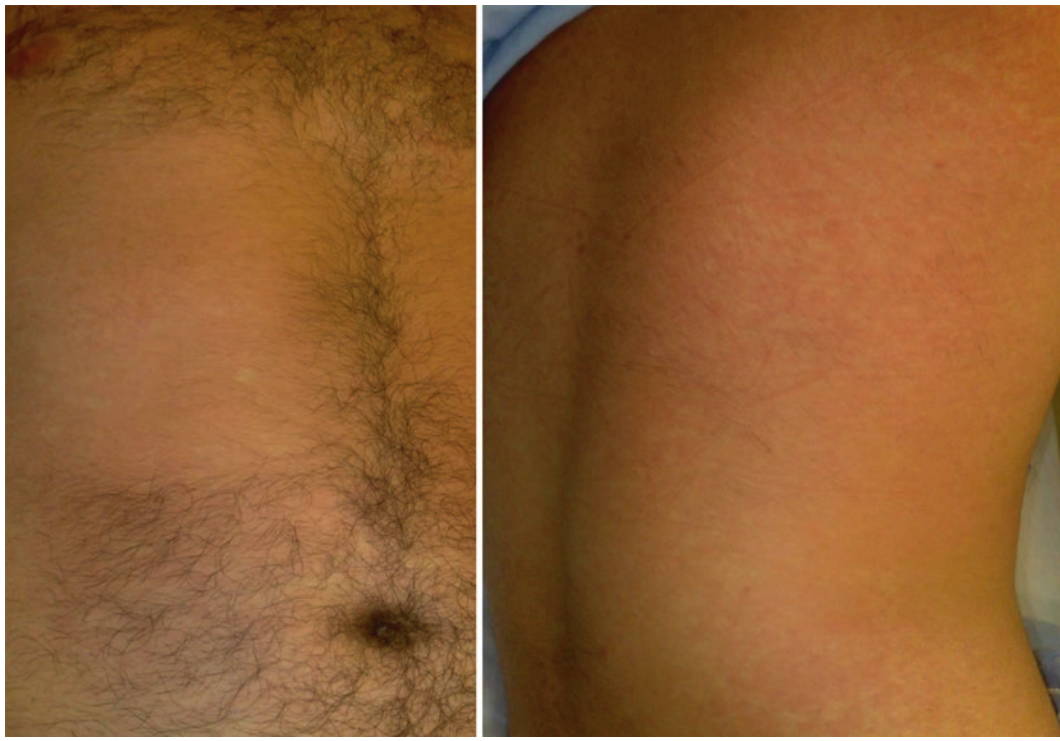

Fig. 26.1 Exanthema morbilliform

Chart 26.1 Symptoms or signs suggesting a progressive severe adverse drug reaction

Clinical findings	Mucocutaneous	Extensive erythema
		Skin pain
		Facial edema or centrofacial involvement
		Cutaneous necrosis
		Palpable purpura
		Bullous lesions or epidermal detachment
		Tongue edema or uvula edema
		Urticaria
		Positive Nikolsky sign
		Erosions on mucous membranes
	General symptoms or signs	High fever (>40 °C)
		Adrenomegaly
		Arthralgia or arthritis
		Tachypnea and or wheezing
		Hypotension
Laboratory abnormalities		Eosinophilia >1,000 mm^3
		Lymphocytosis with atypia
		Abnormalities of liver enzymes or function

SJS, TEN, fixed drug eruption (FDE), AGEP, phototoxicity, and vasculitis. This suggests that in cases of drug-induced reactions with extensive cutaneous affection, with or without lymphadenopathy, a laboratory investigation is required with a complete hemogram and hepatic function test.

In 1994, Roujeau and Stern [4] put forth clinical and laboratory criteria leading to the suspicion that a reaction to drugs could develop into more severe behavior (Chart 26.1).

We next discuss the following reactions: anaphylaxis and anaphylactoid reactions, erythroderma, and the clinical spectrum of SJS and TEN (Lyell's disease).

Anaphylaxis and Anaphylactoid Reactions

Anaphylaxis is a quick systemic reaction usually presenting a risk to life and resulting in immediate hypersensibility mediated by immunoglobulin E (IgE). Anaphylactoid reactions mimic anaphylaxis, although they are not related to immunologic mechanisms [4, 7]. These reactions lead to a powerful activation of mastocytes, with a massive release of mediators [7, 8].

Drugs are not the more important cause of anaphylaxis, as they are responsible for merely 13–20% of cases [8] .Drugs that do cause anaphylactic reactions include β-lactam antibiotics (responsible for 75% of fatal anaphylactic reactions in the United States), cephalosporin, sulfonamides, hemoderivatives, enzymes (trypsin, chymopapain, and streptokinase), insulin (very rare nowadays, owing to use of recombinant human insulin), vaccines (due to preservatives, proteic components, and gelatin; some reports of patients show sensitivity to eggs and allergic reactions to vaccines), allergenic extracts, protamine, and progesterone [7, 8].

Anaphylactoid reactions may occur with acetylsalicylic acid, nonhormonal anti-inflammatory drugs, iodide contrasts, angiotensin-converting enzyme (ACE) inhibitors, and fluorescein [7].

During general anesthesia, anaphylactic and anaphylactoid reactions may occur. These are difficult to differentiate because of the large amount of medications used, such as anesthetics, muscular relaxants, analgesics, nonhormonal anti-inflammatories, and antibiotics [7].

Their clinical emergence tends to occur suddenly, within 30-min to 1-h intervals after contact with the precipitating factor, although delayed reactions are rarer. They show an appearance of pruritus, urticaria (Fig. 26.2), rhi-

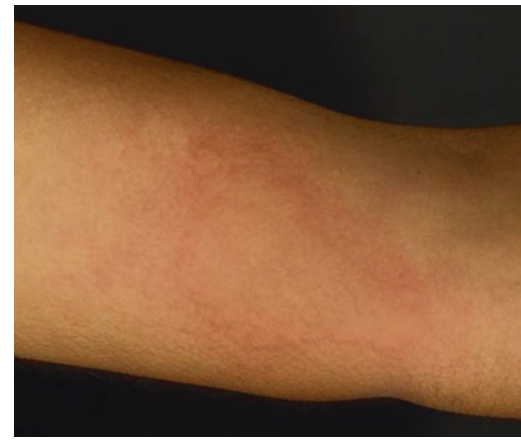

Fig. 26.2 Acute urticaria

noconjunctival symptoms, angioedema symptoms (especially laryngitis), hypotension, and lung sounds [7]. The following ailments may be observed: abdominal pain, diarrhea, vomiting, uterine contraction, and cardiac arrhythmia. After a few hours symptoms may reappear during a late phase, although this is by no means automatic [4, 7].

Patients with anaphylaxis must be identified as fast as possible, and treatment must be initiated immediately [8]. This reduces the risk of fatal reactions [8]. The following are signs of anaphylaxis that pose a risk to life: presence of stridor, edema of the glottis, intense dyspnea, lung sounds, hypotension, cardiac arrhythmia, shock, convulsions, and loss of consciousness [7, 8]. In patients using β-blockers, anaphylaxis is often severe and may be resistant to conventional treatment [8].

Various conditions must be considered in the differential diagnosis when suspecting anaphylaxis [8]: cardiac arrhythmias, acute myocardial infarction, food aspiration, convulsive disease, reaction to insulin, pulmonary embolism, syndrome etiology (e.g., the presence of carcinoid tumors or reaction to alcohol and chlorpropamide), hysterical behavior, vasovagal reactions, and fictitious allergic reactions. Vasovagal reactions are most often confused with anaphylaxis [8]. In general they are consequences of procedures such as injections, which present as a clinical condition consisting of facial paleness, nausea, profuse sweating, and syncope, with symptoms improving without treatment 20 to 30 min later [8]. Absence of pruritus in the presence of a slow pulse and normal blood pressure distinguish vasovagal reactions from anaphylaxis [8].

The treatment of anaphylaxis consists of short- and long-term measures [8]. The immediate goal is to maintain the permeability of the airways and blood pressure, in addition to administering oxygen in more severe cases [8]. Epinephrine must be administered as soon as possible, with a standard dose of 0.01 mg/kg of a 1:1,000 solution, up to a maximum of 0.3–0.5 ml, subcutaneously every 10–20 min until the patient is stabilized.

Erythroderma

This is a condition characterized by a state of generalized erythema and scaling (exfoliative dermatitis) of the skin. It has the morphologic appearance of various cutaneous diseases such as psoriasis, atopic dermatitis, T-cell cutaneous lymphoma, and reactions to drugs [9].

The dissemination of a maculopapular condition caused by medication may lead to the emergence of an erythrodermic syndrome. Various types of drug-induced cutaneous reactions (including contact dermatitis, photosensitivity, and maculopapulous reactions) would be responsible for roughly 7.3% of erythroderma cases [10].The secondary drug-induced erythroderma conditions, as opposed to erythrodermas resulting from other etiologies, most often set in quickly and also tend to regress quickly after withdrawal of the medication being used [10].

Pruritus arises 1–4 weeks after starting drug use, in association with diffuse erythema covering roughly 90% of the body surface, followed by lymphadenopathy and scaling. When acute, large amounts of epidermis are exfoliated; when chronic, it produces small elements [9] (Fig. 26.3). Pruritus and a sensation of diffuse burning occur [9].

Exfoliative dermatitis leads to systemic complications such as hydroelectrolytic and thermoregulatory disturbances, high cardiac insufficiency, tachycardia, capillary leak syndrome, and infection [11–13]. The effect of

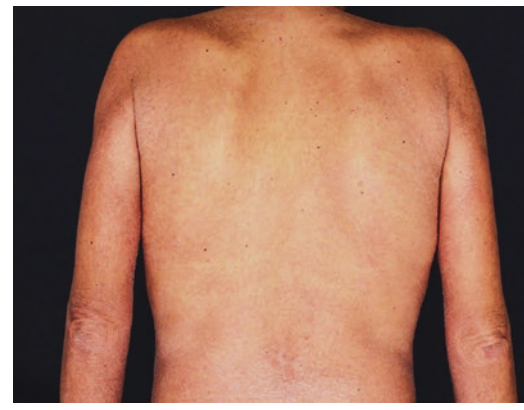

Fig. 26.3 Exfoliative dermatitis (erythroderma)

exfoliative dermatitis on the organism depends on the intensity and duration of the process [13].

Common laboratory findings in the erythrodermic state include light anemia, leukocytosis with eosinophil, high IgE, an increase of the hemosedimentation process, a drop in serum albumin, and a rise in uric acid [9, 13]. Increased IgE and eosinophil is a nonspecific finding and is found only in secondary drug-induced erythrodermas, although it might also be due to atopic dermatitis [9, 13].

Multiple cutaneous biopsies performed simultaneously on distinct points of the skin might increase the accuracy of the diagnosis of the base disease [9]. In drug reactions vacuolar alterations may be observed on the epidermis, as well as necrotic keratinocytes [9].

The initial treatment of drug reaction in an erythrodermic patient is identical to that for erythrodermas of other causes [9, 13]. Suspending the drug is the quickest way to improve the patient's condition. One ought to consider the nutritional state and hydroelectrolytic replacement, as well as administering local measures such as antiseptic baths, humid compresses on the crusts, application of soft emollients, and low-strength corticosteroids [9].

Classic oral antihistamines may be prescribed to alleviate the pruritus and anxiety. They provide the patient with a warm and humid environment so as to prevent hypothermia and improve cutaneous hydration [9, 13].

Symptoms and signs of cardiac and respiratory insufficiency may require emergency assistance and hospitalization [9]. The most aggressive and debilitating erythrodermic states may require care similar to that offered to SJS or TEN patients.

The differential diagnosis must be performed with other types of secondary erythrodermas to cutaneous diseases, such as psoriasis, contact dermatitis, seborrheic dermatitis, lichen planus, bullous pemphigoid, and pemphigus foliaceus, as well as systemic diseases such as leukemias, T-cell cutaneous lymphoma, and Hodgkin's lymphoma, in addition to erythrodermic states secondary to internal cancer [9, 13].

Clinical Spectrum of Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis (Lyell's Syndrome)

What currently exists is a combination of concepts according to which spectrum of erythema multiforme (EM), including EM minor and EM major (EMM), is separated from another spectrum of reactions, which includes SJS and TEN (Lyell's syndrome), referred to here as the SJS/TEN spectrum [14–17].

However, according to Assier et al. [18], it seems possible to separate EMM patients from true SJS patients based on clinical symptoms and disease origin. These authors define the EMM pattern as consisting of characteristic mucous erosions and cutaneous lesions (typical targets, with or without blisters), symmetrically distributed and commonly acral. SJS would be represented by mucous erosions and disseminated cutaneous purpuric macules that are frequently confluent, with a positive Nikolsky sign and epidermal scaling limited to less than 10% of the body surface [14, 18]. EM would include recurrent, postinfectious cases (especially related to herpes simplex and mycoplasma), or eventually related to exposure to medication, with a low mortality rate and without lethality. On the other hand, SJS would comprise a severe ADR with high mortality rates and a reserved prognosis for many cases [4, 14, 19].

In 1993, Bastuji-Garin et al. [19] put forward a clinical classification of the spectrum that included ME bullosa up to TEN. To better understand this classification [19], we note the characteristics of the dermatologic lesions of which the group consists, defined as follows:

- Epidermal detachment: refers to epidermal loss, which at times occurs in flaps (Fig. 26.4).
- Typical targets: lesions less than 3 cm in diameter, in disc shape, with well-defined borders, and exhibiting at least three distinct zones, namely two concentric halos around a central disc (Fig. 26.5).
- Atypical flat targets: lesions that are not raised, but are round or disc shaped, with two zones and/or borders that are not well defined.

- Atypical raised targets: round or disc-shaped lesions, palpable or raised, but without the two zones and/or well-defined borders.
- Macules/spots: erythematous or purpuric stains, irregularly shaped or confluent, with or without blisters (Fig. 26.6).

Insofar as the area of epidermal necrolysis makes up one of the two main factors of prognosis, a consensus was reached on classifying the spectrum [14, 19]: (i) SJS in cases with mucous erosions and disseminated purpuric macules and scaling of the epidermis below 10%; (ii) SJS/TEN superposition or transition in cases with epidermal scaling between 10%

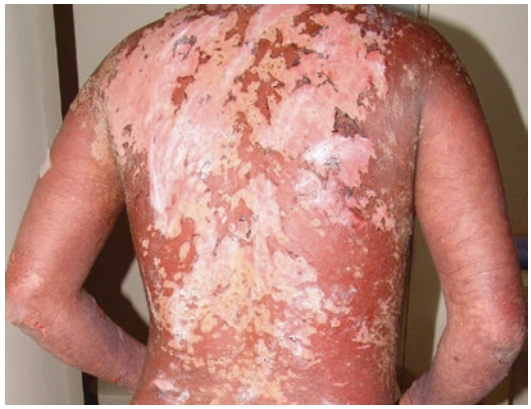

Fig. 26.4 Epidermal detachment in TEN

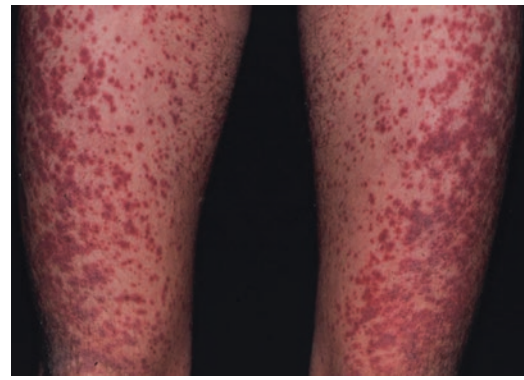

Fig. 26.6 Purpuric macules found in TEN and SJS

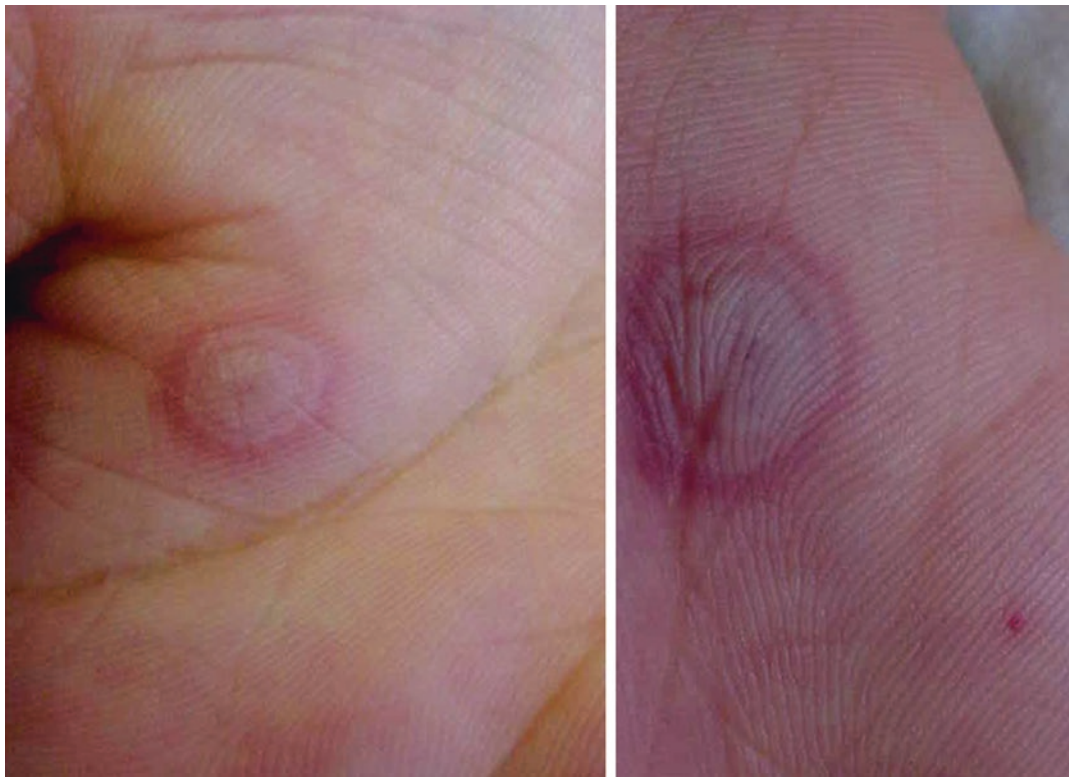

Fig. 26.5 Typical targets in the erythema multiform spectrum

and 30% of the body surface; and (iii) TEN in cases with disseminated purpuric macules and epidermal scaling above 30%; or (iv) in rare cases with disseminated necrolysis (over 10% scaling) without any of the lesions described above.

Stevens–Johnson Syndrome

SJS is an entity characterized by the presence of lesions similar to those of EM, but with purpuric macula and widely distributed blisters or even lesions in atypical targets dispersed over the dorsal aspect of the hands, palms, soles of the feet, extensor region of the extremities, neck, face, ears, and perineum; the face (Fig. 26.6) and trunk (Fig. 26.7) are prominently involved [4]. Incidence of SJS is estimated at roughly one in three cases per million residents yearly [20–22].

SJS may be preceded by a discrete maculopapulous eruption similar to exanthema morbilliform [19]. Blister formations are possible, though usually not determined by an epidermal detachment of over 10% of the body surface [4, 14, 19]. Mucous involvement occurs in roughly 90% of cases, generally on two distinct mucous surfaces; this may precede or follow cutaneous involvement [4, 14, 19]. Onset begins with enanthema and edema, which give rise to erosions and pseudomembranous formations on the eyes, mouth, genitals, pharynx, and upper airways [19]. Some 10–30% of cases occur with fever and lesions in the gastrointestinal and respiratory tracts [4]. Its prognosis seems to not be affected by the type and dose of the drug responsible, nor by human immunodeficiency virus (HIV) infection [4].

The therapeutic options for SJS are limited and controversial [4, 23, 24]. Corticosteroids are frequently used [25], although some cases have not shown a satisfactory response [24]. In agreement with most authors, the use of systemic corticosteroids on the initial SJS and TEN forms do not currently demonstrate any proven benefits. The advanced forms of this spectrum of relations have clearly deleterious effects on the patient [26]. The treatment and prognosis of SJS are tackled in combination with that of TEN.

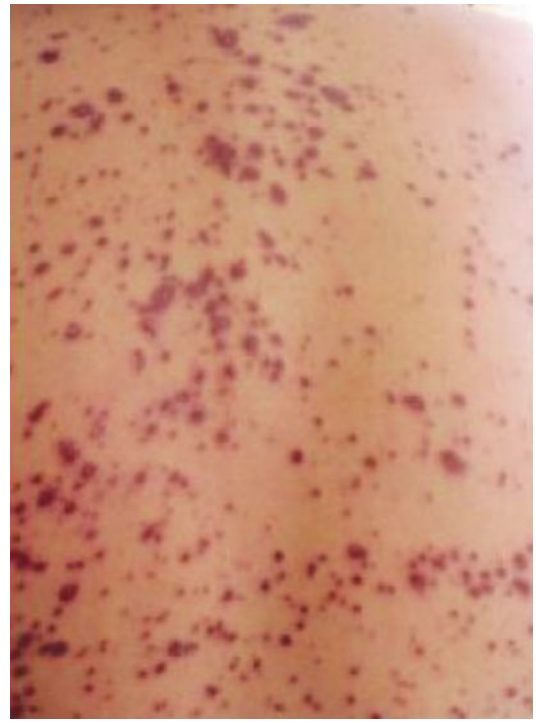

Fig. 26.7 Purpuric macules in SJS

Toxic Epidermal Necrolysis or Lyell's Syndrome

TEN is an entity characterized by extensive scaling of the epidermis in the wake of necrosis (epidermal necrosis) [4, 14, 15]. The term "toxic epidermal necrosis" was introduced by Lyell in 1956 [14]. Fortunately, it consists of a very rare adverse reaction to drugs. In Europe, its incidence is estimated to be at 1.1 [4] cases per million residents yearly [26].

In AIDS patients, however, the risk of this reaction does rise, estimated at one case in every 1,000 patients yearly [14]. In general, there is a slight predominance among women (1.5–2 cases in females for every male case). Indeed, the disease's occurrence in AIDS patients ends up balancing out the incidence rate between the sexes [14].

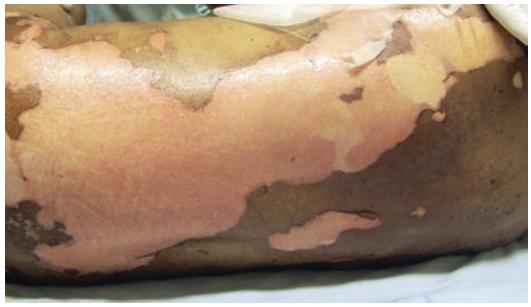

Fig. 26.8 Toxic epidermal necrolysis (TEN)

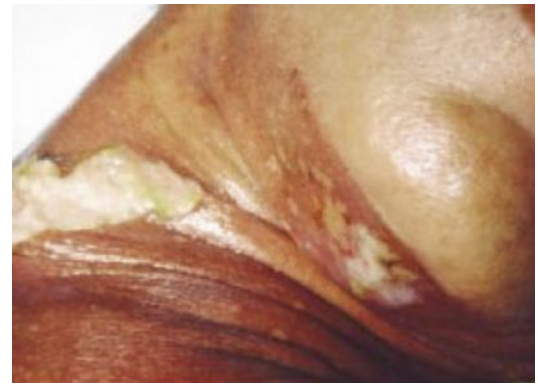

Fig. 26.9 TEN resulting from cephalexin

The initial characteristics of TEN are nonspecific influenza-like symptoms, such as fever, sore throat, coughing, and burning eyes. These are considered prodromic manifestations preceding a cutaneous and mucous affection by 1–3 days [4]. An erythematous eruption emerges symmetrically on the face (Fig. 26.8) and the upper part of the trunk, extending to the craniocaudal region and provoking symptoms of burning or painful skin [4, 14].

The individual cutaneous lesions are, for the most part, characterized by erythematous macules with poorly defined contours and a purple center. They progressively spread over the anterior thorax and back [4, 14]. Less commonly, the initial eruption may consist of an extended scarlatiniform exanthema. In roughly 2–5 days or, at times, within a few hours, or more seldom in about a week, complete extension of the cutaneous condition occurs [14]. At first, some cases may present lesions persisting in sun-exposed areas of the skin [14]. The apex of the process consists of characteristic denuding of the necrotic epidermis, standing out as veritable red strips or flaps on the areas affected by the base erythema (Fig. 26.9) [4, 14].

The epidermis is raised by the serum content of flaccid blisters, which are progressively confluent and provoke rupture of the blisters and detachment of the skin. This causes an aspect of severe burns on the patient's skin, with the skin denuded, bleeding, and with an erythematous-purple color, as well as continued elimination of serosity, which contributes to hydroelectrolytic unbalance and accentuated protein loss [4, 14]. The Nikolsky sign is positive over widespread areas of the skin [4, 14].

The areas of the skin subjected to pressure, such as the lower shoulders, back, and buttocks, are the first to release epidermal flaps [4, 14]. Cutaneous extensor affection might determine a state of acute cutaneous failure [15, 27]. The cutaneous surface can virtually be 100% affected, although scalp affection is exceptional [14].

The mucous membranes are affected in 85–95% of patients, commonly preceding skin involvement by a day or two [14]. In the order of frequency, the disease afflicts the oropharynx, eyes, genitalia, and anus [14]. Extensive and painful erosions lead to labial crusts, salivation, feeding obstruction, photophobia, and painful urination and evacuation [14].

Severe eye sequelae, with the formation of synechiae between the eyelids and conjunctiva by pseudomembranous conjunctival erosions, and blindness may occur [4, 14]. Ceratitis and corneal erosions have been reported, as well as a secondary sicca-like syndrome [14].

High fever or hypothermia may occur because of a thermoregulatory imbalance until complete healing, even in the absence of concomitant infections [14]. The abrupt drop in temperature is more indicative of sepsis than of fever itself [14]. Psychomotor agitation and

mental confusion are not uncommon, and usually indicative of hemodynamic complications and sepsis [14]. Many internal organs are affected by the same pathologic process that involves the skin and determines a spectrum of systemic manifestations [4, 14].

Systemic involvement occurs, causing erosion in the esophagus and gastrointestinal tract, which may progress to esophageal constrictions, transaminase increases in 50% of cases (hepatitis in 10%), pseudomembranous colitis, and pancreatitis [23]. In the respiratory tract tracheobronchial erosions and secondary pulmonary interstitial edema, with the correction of hypovolemia, can be found [15]. Anemia can be constantly observed, as well as lymphopenia in up to 90% of patients [15]. Thrombocytopenia is found in 15% of patients; neutropenia occurs in 30% of cases, and when present indicates a worse prognosis [15, 23].

The medications most commonly causing TEN are sulfas, phenobarbital, carbamazepine, dipyrone, piroxicam, phenylbutazone, aminopenicillin, allopurinol, and nevirapine. However, it is necessary to consider that new drugs are continually being reported as triggering TEN [4, 14, 15, 23].

Considerations on the Physiopathology of SJS and TEN

The exact mechanism by which SJS and TEN develop is not well defined.

Some authors have suggested the participation of the altered metabolism of drugs with the predominance of a slow acetylator genotype in SJS and TEN patients, and a deficiency in the mechanisms involved in detoxification of reactive intermediary metabolites [28–30].

In addition to the metabolic mechanisms, there is evidence to suggest that, especially in TEN, the epidermal necrosis is mediated immunologically [4, 14, 30]. It is known today that SJS and TEN are disturbances mediated by T cells, similarly to acute graft-versus-host disease (GVHD), with cytotoxic T cells being responsible for the epidermal necrosis through an apoptosis in keratinocytes [14, 30].

Posadas et al. [31] have shown the association of high tumor necrosis factor α (TNF-α) levels with the severity of the reaction. This cytokine has been related to an induction in the adhesion and activation of T cells and monocytes. It also participates in apoptosis, irrespective of the action of perforins [31]. It has been demonstrated also that apart from TNF-α, the perforins granzyme B (GRB) and Fas ligand (FasL) are found to be high in the initial stages of a drug reaction, particularly in SJS and TEN. This reinforces the hypothesis of the participation of cytotoxic mechanisms [31]. Nowadays, cytotoxic reaction caused by granulosin liberation from T cells is the major mediator involved in cell apoptosis, and the spectrum of SJS/TEN is grouped in Type IVc of immune reactions, as classified by Pichler.

Correia et al. [32] have observed a similar seric cytokine profile between TEN and acute GVHD. These authors showed a significantly high serum level of interleukin (IL)-6 and IL-10 in TEN and acute GVHD patients as opposed to normal blood donors [32]. IL-6 is a multifunctional proinflammatory cytokine produced by various cells, including keratinocytes. It consists of a main circulating endogenous pyrogen [32]. This explains the presence of fever that is unrelated to the infection in the first days of TEN and GVHD [32]. In turn, IL-10 is an endogenous antipyrogen agent. It is produced by keratinocytes with the purpose of blocking inflammatory cytokines such as IL-1, IL-6, and TNF-α, in addition to being a powerful suppressant of macrophage, T-cell, and natural killer cell functions [32].

By contrast, as IL-10 recruits $CD8^+$ lymphocytes from the peripheral blood, its increase in blister fluid explains the high number of these cells in patients' epidermis [32] .The elevation of IL-10 creates a natural mechanism against excessive tissue inflammatory reaction [32].

Chosidow et al. [33] have suggested that the cellular cytotoxic targets are viral antigens with a potential to alter immune responses resulting from exposure to medications.

Considerations on Treating SJS and TEN

Treatment for SJS and TEN patients is similar to that for patients who have suffered extensive burns, with a number of rare exceptions [23]. All patients have to submit to cutaneous biopsy to confirm the diagnosis [23]. The patient must be observed in an intensive therapy unit, in an isolated and heated environment so as to avoid any cutaneous trauma [4, 14, 23]. The treatment must proceed by suspending any drug that is not essential to the patient's life and begin replacement of intravenous fluid, mainly when an oral mucous lesion obstructs liquids from being ingested [4, 14, 23]. Isolation and feeding must be carried out through the nasogastric probe because the patient shows calorie and protein loss [4, 14, 23].

Corticosteroids should only be administered within 48 h of the condition's onset. It has not proved to be beneficial after this period because of its delaying epithelialization and increasing protein catabolism, in addition to increasing the risk of infection [23, 26].

Antibiotic therapy has to be administered to cases whereby a sudden drop in temperature occurs and with a concomitant drop in the general status or increase of cultivated bacteria on the skin with a predominance of a single strain [23, 26]. It must be emphasized that during the first days, the most common infections are by *Staphylococcus aureus* and later by Gram-negatives (*Pseudomonas aeruginosa*) or *Candida albicans* [23].

Noncontrolled reports and studies on the treatment of TEN exist, reporting the use of intravenous immunoglobulin, cyclosporine, cyclophosphamide, plasmapheresis, and anticytokine monoclonal antibodies, among others, in an attempt to curb the process of epidermal necrosis. The value of these studies has been questioned, however, particularly owing to the fact that in most patients who are hospitalized the phenomenon of necrosis virtually comes to a halt [15].

Prins et al. [34] published a multicenter, retrospective study on intravenous immunoglobulin use in treating TEN patients, which obtained excellent results. A 48-patient cohort, average age 43 years (±24) and consisting of 24 women and 24 men, with a 10–95% variation of epidermal detachment of the total body surface area, was treated. Mucous membrane was affected in 91.7% of these patients. The patients received intravenous infusion of gammaglobulins begun on average 7 days after onset of TEN (with a variation of 2–30 days). It was administered over a period of 1–5 days, in doses varying from 0.65 to 5.8 g/kg (mean total dose of 2.7 g/kg). An objective positive response to treatment occurred with a break in the progression of TEN, observed in 43 (90%) of the 48 patients. In all there were six deaths. The authors concluded that early use of intravenous gammaglobulin is safe, with a recommended dose of 1 g/kg daily for 3 days in a row. In contrast to the studies of Prins et al. [34], a French group (Bachot, Revuz, and Roujeau) led a noncomparative prospective study of 34 patients diagnosed with SJS (nine patients), SJS/TEN overlapping (five patients), and TEN (20 patients). They concluded that intravenous gammaglobulin in a 2-g/kg daily dose, administered for 2 days in a row, did not reduce patient mortality [35].

Until such discrepancies in the results have been cleared up, intravenous gammaglobulin use in treating TEN will remain controversial [36]. However, as the volume of data encourages its application and effective alternative therapies remain lacking, it seems difficult to not suggest a high dose of intravenous gammaglobulin, especially as a way of intervening early in quickly progressing TEN cases.

Considerations on the Prognosis

Whereas mortality rate is low for EMM (<1%) and SJS (roughly 5%), it is above 40% for TEN patients with macules [37]. The mortality rate

Chart 26.2 SCORTEN grade for TEN prognosis on hospital admission

Prognostic factors	Parameters	Estimated mortality related to point score
Age	≥40 years old	1 (3.2%) 2 (12.2%) 3 (35.5%) 4 (58.3%) ≥5 (90.0%)
Heart frequency	≥120 bpm	
Cancer presence	Yes (1 point); No (0 points)	
Percent of epidermal detachment over total body area	>10%	
Serum urea (BUN)	>28 mg/dl or >10 mmol/l	
Serum bicarbonate	<20 mEq/l	
Serum glucose	>14 mmol/l (or >252 mg/dl	

rises with age range and increased surface area of the epidermal scaling [37].

We reiterate the classification methodology adopted by multicenter studies, prospectively named SCARD (Severe Cutaneous Adverse Reactions). The results of the latter were recently published based on the analysis of 552 patients and 1,720 controls [38]. This classification system (named SCORTEN) is summarized in Chart 26.2.

Despite the large range and amount of drugs that may pose a great risk of contracting SJS and TEN, an annual risk rate of five cases per year among medication users has not been exceeded [39, 40].

Drug Hypersensitivity Syndrome: DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) [41–43]

DRESS syndrome is an acronym derived from the term "Drug Rash with Eosinophilia and Systemic Symptoms" coined by Bocquet et al. Also known as drug-induced hypersensitivity syndrome (DIHS), it was first recognized in 1950 by Chaiken in a patient using an anticonvulsant. There are many synonyms used, most of them referring to the origin of the drugs involved in the drug reaction, such as dapsone syndrome, allopurinol hypersensitivity syndrome or the anticonvulsant hypersensitivity syndrome. Although a dermatosis is usual in DRESS, the extent of skin involvement is variable and therefore the "R" in DRESS was subsequently changed from "rash" to "reaction."

Clinically, in its complete form, this syndrome includes an extensive mucocutaneous rash, fever, lymphadenopathy, hepatitis, and hematologic abnormalities with eosinophilia and atypical lymphocytes, and may involve other organs with eosinophilic infiltration, producing damage in several systems, especially in kidney, heart, lungs, and pancreas. This multivisceral involvement differentiates DRESS from other common skin reactions to drugs. Another unique feature of this syndrome is its late onset in relation to the period of introduction of the causative drug, i.e., at around 3 weeks to 3 months, and its possible persistence or worsening despite the withdrawal of the offending drug.

Incidence

The incidence of this syndrome is estimated to vary from one case among 1,000–10,000 drug exposures. Adults are more affected than children, and although the precise incidence of drug reaction has not yet been determined, it is much more common than SJS, which has an incidence of 1.2–6 cases per million person-years, and most cases are sporadic, with no gender predilection. Recognition of this syndrome is of paramount importance, since the mortality rate is about 10–20% and a specific therapy may be necessary.

Etiopathogenesis

The exact mechanism of DRESS/DIHS remains to be determined but, in cases related to anticonvulsant drugs, three components are considered: (i) deficiency or abnormality of the epoxide hydroxylase enzyme that detoxifies the metabolites of aromatic amine anticonvulsants (metabolic pathway); (ii) associated sequential reactivation of herpesvirus family; and (iii) ethnic predisposition with certain human leukocyte antigen (HLA) alleles (immune response).

Drugs Involved and Metabolism

This type of reaction is most commonly seen using seven different drug groups: (i) anticonvulsants, such as the aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital, primidone), mexiletine, lamotrigine, valproate, ethosuximide, and zonisamide; (ii) antidepressants (desipramine, amitriptyline, fluoxetine); (iii) sulfonamides and sulfones (dapsone, sulfasalazine, trimethoprim-sulfamethoxazole, salazosulfopyridine); (iv) anti-inflammatory drugs (piroxicam, naproxen, diclofenac, sundilac, phenylbutazone, ibuprofen); (v) anti-infectives (abacavir, cidofovir, terbinafine, nevirapine, minocycline, linezolid, doxycycline, telaprevir, nitrofurantoin, zalcitabine, spiramycin, metronidazole, piperacillin-tazobactam, ceftriaxone); (vi) angiotensin-converting enzyme inhibitors (captopril, enalapril); and (vii) β-blockers (atenolol, celiprolol). Cases have been reported with allopurinol, gold salts, thalidomide, calcium channel blockers (diltiazem), ranitidine, sorbinil, azathioprine, dobutamine, methimazole, propylthiouracil, and efamizulab.

The cases more consistent with DRESS/DIHS were caused by aromatic anticonvulsants, dapsone, salazosulfopyridine, allopurinol, and minocycline. Other drugs causing less typical cases are reported in the literature, but less frequently. Aromatic anticonvulsants have an estimated occurrence of DRESS/DIHS of one case for every 5,000 people exposed to the drug, and the reaction is especially common among black patients. The aromatic anticonvulsant drugs that have been associated most frequently with DRSS/DIHS are phenytoin, phenobarbital, and carbamazepine. However, newer anticonvulsant medications also containing aromatic structure (felbamate, oxcarbazepine, zonisamide, and lamotrigine) can also be involved, and the cross-reactivity between the various aromatic anticonvulsant drugs is well documented, varying between 40% and 80%. Nonaromatic anticonvulsant drugs (topiramate, levetiracetam, tiagabine, ethosuximide, valproic acid, and gabapentin) appear to be safe.

Cacoub et al. recently reviewed the literature of published cases of DRESS and found 44 drug-related out of 172 case reports published in the literature in PubMed/MEDLINE from January 1997 to May 2009. In about one-third of cases, the aromatic anticonvulsant drugs were more related to the onset of ADR (Chart 26.3).

Chart 26.3 Drugs reported as possible cause of DRESS/DHIS

Drugs related to DRESS
Abacavir
Allopurinol
Amoxicillin plus clavulanic acid
Amitriptyline
Atorvastatin
Aspirin
Captopril
Carbamazepine
Cefadroxil
Celecoxib
Chlorambucil
Clomipramine
Clopidogrel
Codeine phosphate
Cotrimoxazole/cefixime
Cyanamide
Dapsone
Diaphenylsulfone
Efalizumab
Esomeprazole
Hydroxychloroquine
Ibuprofen
Imatinib
Lamotrigine
Mexiletine
Minocycline
Nevirapine
Olanzapine
Oxacarbamazepine
Phenobarbital
Phenylbutazone
Phenytoin
Quinine and thiamine
Salazosulfapyridine
Sodium meglumine ioxitalamate
Sodium valproate/ethosuximide
Spironolactone
Streptomycin
Strontium ranelate
Sulfasalazine
Sulfamethoxazole
Tribenoside
Vancomycin
Zonisamide

Some patients experience a prodrome of flu-like symptoms about 4 weeks before the clinical reaction. There are reports of DRESS/DIHS even in patients using anticonvulsants for about 40 years.

The pathogenic mechanism of idiosyncratic reactions to drugs, such as DRESS/DIHS, has not been fully elucidated. Sullivan and Shear proposed a multifactorial model for the pathogenesis of DRESS/DIHS. Its occurrence would be determined by the combination of exposure to a drug capable of causing adverse reaction given in sufficient dosage and period of use to a susceptible patient.

A certain group of drugs associated with DRESS/DIHS, including the aromatic anticonvulsants, is metabolized to reactive oxygen intermediates that appear to be inefficiently detoxified in patients with acquired or pharmacogenetic variations in the metabolism of these drugs.

Aromatic anticonvulsants such as carbamazepine, phenytoin, and phenobarbital are metabolized by the hepatic cytochrome P450 enzymes and undergo oxidation by aromatic hydroxylation, with subsequent formation of arene oxides. Arene oxides are toxic reactive intermediates that are normally enzymatically converted to nontoxic metabolites by epoxide hydroxylase or glutathione transferase. In addition, spontaneous conversion to nontoxic phenol derivatives can occur. In cases of defective or deficient epoxide hydroxylase, arene oxides can accumulate and cause direct cellular toxicity or immune response (Fig. 26.10).

Drug interactions can be important in this syndrome. Concomitant use of lamotrigine and valproic acid increases the occurrence of the syndrome. It is thought that the mechanism for this drug interaction is the competition between valproic acid and lamotrigine for hepatic metabolism by glucuronidation, which doubles the half-life of lamotrigine and predictably would increase the possibility of adverse effects.

Positive patch tests and testing of blast transformation of lymphocytes indicate the presence of an immune reaction in which T cells participate in specific core function. Clones of drug-specific T cells have been isolated from patients sensitive to carbamazepine and lamotrigine.

Sequential Reactivation of Herpesvirus in DRESS/DIHS

Several clinical similarities that could be observed between DRESS/DIHS and infectious mononucleosis (IM) have led researchers to implicate a possible range of viruses as triggers for this syndrome. In addition, unique features of this syndrome are its late onset in relation to the period of introduction of the causative medication and frequent clinical and laboratory deterioration, as well as episodes of exacerbation despite the withdrawal of the offending drug, so that these characteristics are not necessarily typical of a reaction of specific drug etiology.

Although there are conflicting views on the pathogenesis of DRESS/DIHS in different parts of the world, recent studies have suggested a close relationship between human herpesvirus 6 (HHV-6) and the development of DRESS/DIHS.

Sporadic reports have shown that not only HHV-6, but also other herpesviruses such as HHV-7, Epstein–Barr virus (EBV), and cytomegalovirus (CMV), can be reactivated during the course of the DRESS/DIHS.

Results obtained with analysis by polymerase chain reaction showed that various herpesviruses are sequentially reactivated during the course of DRESS/DIHS in most patients. The cascade of viral reactivation is initiated by EBV or HHV-6 and extends over a period to HHV-7 and eventually to CMV [1]. In some patients, the clinical manifestations of this syndrome persist despite discontinuation of the drug involved, coinciding with the reactivation of herpesvirus, as shown in Fig. 26.11.

The reactivation of HHV-6 is evidenced by increases in the titers of IgG anti-HHV-6 DNA levels, and HHV-6 is commonly found in the second or third week after the onset of rash, despite the high variability of clinical manifestations among patients with this drug reaction. Since the reactivation of HHV-6 can be detected only in patients with DRESS/DIHS, but not other ADRs, in Japan this diagnostic test has become sensitive and specific for the diagnosis of all patients with DRESS/DIHS [7]. The detection of HHV-6 reactivation seems to be the gold-standard diagnostic test for DRESS/DIHS in Japan, with other Asian countries and Europe helping to confirm the identification of this condition.

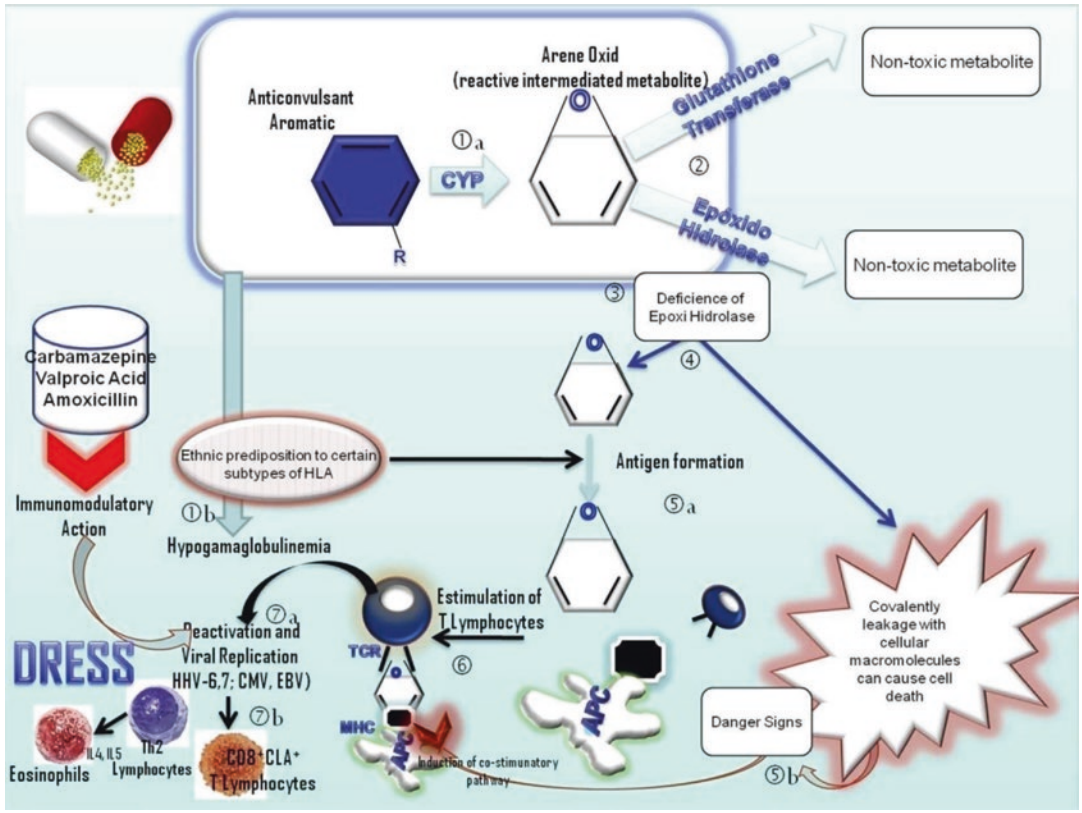

Fig. 26.10 Sequence of events of drug-virus-immune system interaction in patients with DRESS/DIHS triggered by aromatic anticonvulsants. Aromatic anticonvulsants are metabolized by the oxidation system of cytochrome P450 in arene oxide radicals (intermediate reactive metabolite). (*1a*) These arene oxides are detoxified by glutathione transferase and epoxide hydrolase in nontoxic metabolites. (*2*) In genetically predisposed individuals or by additional factors, an impaired detoxification and accumulation of these metabolites occur (*3*), which can cause cellular damage generating danger signs that can stimulate resting T cells, inducing costimulatory pathways (*4*). In addition, ethnic predisposition to certain HLA types may contribute to the formation of neoantigens from the combination of these intermediary reactive metabolites with tissue macromolecules and formation of haptens (*5a*), which can be presented via the human histocompatibility complex class I (HLA-DR) or class II (HLA-A, -B or -C), to CD4 or CD8 T cells (*6*). It was demonstrated that carbamazepine, valproic acid, and amoxicillin are able to exert immunomodulatory actions by inhibiting histone decarboxylase on B lymphocytes, producing a hypogammaglobulinemia that precedes the clinical onset of DRESS/DIHS. The clonal expansion of T cells requires sequential reactivation of latent herpesvirus, and at the same time $CD8^+$ CLA^+ T cells are produced, which are directed toward skin, $CD8^+$ $CCR4^+$ T cells addressed to the lungs (*7b*), and $CD4^+$ IL-4, IL-5 producer and IL-17 CD4 $Th17^+$ producer that cause tissue and peripheral eosinophilia

However, it is still unknown how detection of the viral genome in peripheral blood reflects the true status of viral reactivation in progress in many different organs and systems. Specifically, it is possible that in different compartments and organs such as spleen and lymph nodes, different herpesviruses can reactivate in sequential order completely independent of what occurs in the blood, which would explain why blood samples negative for the viral genome are obtained during the clinical activity of DRESS/DIHS.

What remains unclear is the role of herpesvirus in early DRESS/DIHS. There are two possibilities:

(i) DRESS/DIHS began as an "allergic" immune reaction to a particular drug, which seems to possess an innate ability to stimulate T cells.

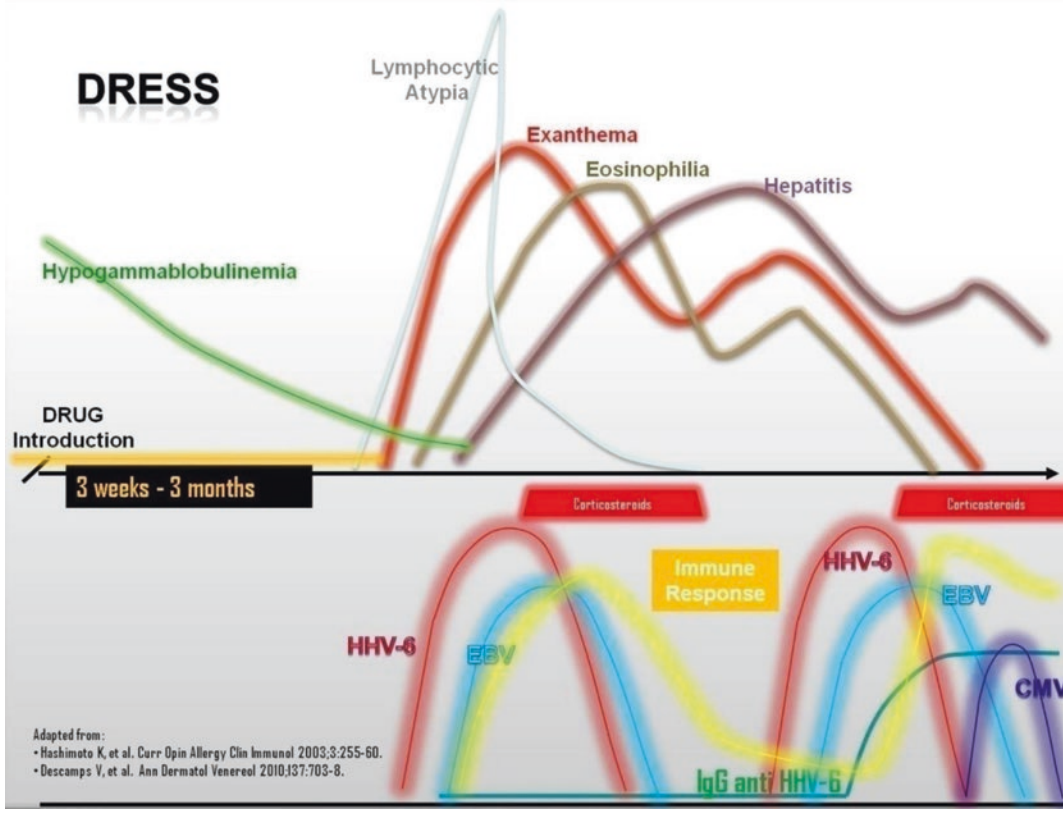

Fig. 26.11 DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)/DHIS: successive events since drug exposure, symptom onset, and viral replication

In the context of T-cell activation is a massive activation of herpesvirus housed in these cells, since the stimulation of T cells by the drug may reactivate the viral genome into the cell. Thus, the drug in turn can activate a specific cellular and humoral immune response to herpesvirus. This could explain why different herpesviruses are activated and because in another intense immune process, so-called GVHD, a similar reactivation can be observed.

(ii) The viral reactivation can occur but is initially clinically unapparent. However, T cells stimulated by virus present significant cross-reactivity with certain drugs, and exposure to these drugs leads to an expansion of T cells specific to the drug (and viruses), which persists even after drug withdrawal due to persistence of viral antigens. The simultaneous appearance of multiple concurrent viral reactivation could be explained by the ability of HHV-6 and HHV-7 counterparts to reactivate virus. Thus, if the symptoms of DRESS/DIHS are mediated by both the various gene products and herpesvirus immune responses to viral replication, the frequent deterioration or the several exacerbations that occur despite withdrawal of the offending drug could derive, at least in part, from the sequential activation of this herpesvirus.

The viral reactivation may provide a "danger signal" (danger sign) that stimulates massive clonal expansion of both $CD8^+$ and $CD4^+$ non-specific T cells and causes the complete development of the syndrome. Shiohara et al. proposed the possibility that the clinical symptoms during the course of evolutionary DRESS/DIHS do not seem to be only mediated by oligoclonal expansion of drug-specific T cells, but also by antiviral T cells that cross-react with drugs.

Therefore, necessary for the occurrence of DRESS/DIHS are: (i) drugs; (ii) the virus; and (iii) their interrelationship with the immune system. A genetic predisposition has been linked to DRESS/DIHS.

How is HHV-6 acquired? HHV-6 infects almost all humans around 2 years of age. Most infections arise through the exchange of infected saliva during the first year of life, although perinatal transmission can occur. It was demonstrated that the DNA of HHV-6 can be integrated into the host DNA, and once part of the human DNA, congenital transmission can occur [7]. This was also demonstrated in the course of the DRESS/DIHS.

The temporal relationship between onset of drug use and the onset of DRESS/DIHS (3 weeks to 3 months) suggests that viruses have no primary function in the syndrome, favoring primary pathogenesis related to drug allergy.

Immune Aspects Involved in DRESS/DIHS

Patients with DRESS/DIHS have decreased total serum IgG, IgA, IgM, and B-lymphocyte count at onset, while there is an expansion of memory T cells that cross-react with both drug and virus. It is noteworthy that the lymphocyte transformation test is negative in the first week of illness and remains negative in 90% of patients 2 weeks after the onset of symptoms, becoming positive only 5–7 weeks after the initial drug reaction. This could be due to the expansion of regulatory T cells (which suppress the proliferation of memory T cells) in the early stages of the disease and its subsequent reduction by apoptosis.

Several cytokines are increased during DRESS/DIHS. In particular, levels of TNF-α and IL-6, which are typically proinflammatory cytokines, are elevated in this syndrome before the reactivation of HHV-6. Interestingly, IL-6 becomes undetectable during viral replication and increases again after the infection in most patients.

DRESS/DIHS is an entity distinct from other serious ADRs because of the dynamic changes in the immune response observed during the course of the disease. The phenotype of circulating $CD4^+$ T cells is changed to $CD8^+$ phenotype at the time of viral reactivation. Regulatory T cells are initially increased in number in the circulation and skin, but decrease in parallel the function of the different organs or systems.

The reactivation of HHV-6 is considered a condition requiring immunosuppression, demonstrated on several immune abnormalities in the early syndrome: marked decrease of serum immunoglobulins, the number of circulating B cells, and regulatory T-cell dysfunction.

Moreover, the participation of skin inflammation may be involved in the induction of immunosuppressive conditions. Sugita et al. demonstrated a reduction in the number of plasmacytoid dendritic cells (pDC) in peripheral blood of patients, but an increase in the expression of these cells in skin affected by the rash. The pDC human leukocyte subtypes are capable of producing large amounts of interferon-α (IFN-α), which induces the maturation of B cells in order to produce IgG and plays a critical role in antiviral defense. The pDC from circulation may accumulate in the skin and thus reduce the number of pDC in the circulation. Therefore, antiviral responses may be reduced, facilitating viral reactivation in peripheral blood and tissues other than the skin.

Although the terms DRESS and DIHS are often and mistakenly used interchangeably, there is currently a tendency to believe that the DIHS represents the most severe cases of DRESS, with reactivation of HHV-6 detected in a large majority of patients and only in a limited number of patients with DRESS [6].

Associations of HLA Alleles with DRESS/DIHS and Maculopapular Eruption Induced by Aromatic Anticonvulsants or Other Drugs (Pharmacogenomics)

The most popular hypothesis to explain the immunoallergic reactions to drugs is the theory of hapten/pro-hapten: according to this hypothesis, the drug (or metabolite) is processed by antigen-presenting cells (APCs) and expressed in the cell membrane in the context of HLA-A, -B, or -C type I (MHCI) or HLA-D type II (MHCII). The complex HLA drug (hapten) is presented to

native T cells (naive) via their T-cell receptor (TCR), which initiates different types of immune responses, depending on the HLA expressed on the APC and the cytokine environment.

The story of "HLA–drug" correlation truly began in the twenty-first century with abacavir. In 2002, two independent groups observed the abacavir hypersensitivity syndrome and that this was restricted to the allele HLA-B*5701, which conferred an elevated odds ratio (>100). GlaxoSmithKline (London, UK) led the largest international randomized pharmacogenetic clinical trial to date, which demonstrated the correlation between abacavir hypersensitivity reactions and patients with this allele, and proved that the exclusion of abacavir introduction to the patients with this allele resulted in the disappearance of the syndrome, which was first seen in 5% of patients overall who received the drug during the first weeks of antiretroviral treatment. This allele test is now routinely used before the introduction of abacavir in several countries.

The HLA alleles have a high negative predictive value but low positive predictive value in relation to ADRs, indicating that these biogenetic markers are necessary but not sufficient to trigger the allergic immune reactions. According to the theory of HLA–drug (hapten), the complex hapten only triggers an immune-allergic reaction in the presence of a specific HLA allele.

Thus, prospective HLA screening should prevent some patients from having serious idiosyncratic reactions such as DRESS/DIHS, SJS, and TEN if they have a specific risk allele by not receiving the drug related to it. HLA pharmacogenomics is a recent field of study that has been rapidly developed and implemented into clinical practice and has improved drug prescription, which is likely to become more and more important in coming years.

Besides causing SJS and TEN, carbamazepine also induces other types of ADRs, including maculopapular exanthema (MPE) and DRESS/DIHS. The association between HLA-B*1502 and carbamazepine-induced MPE was not detected in populations of ethnic Han Chinese and Hong Kong or Thai populations. Studies involving 18 Han Chinese residents in Taiwan and 56 Caucasians showed no association between cases of DRESS/DIHS caused by carbamazepine and HLA-B*1502. These data indicate that the association between HLA-B*1502 and cutaneous ADRs induced by carbamazepine are specific to SJS/TEN.

Kano et al. showed that in four of their 13 Japanese patients (30.8%) with DRESS/DIHS in whom reactivation of HHV-6 was proved, the syndrome was triggered by aromatic anticonvulsants (carbamazepine in ten, phenobarbital in two, and phenytoin in one) had HLA-B*1301. The frequency of this allele was much higher than in the Japanese population (1.3%). Although this difference was not statistically significant after correction for multiple comparisons, the authors proposed that the presence of certain alleles of HLA-B on the reactivation of the virus contributed, at least in part, to the association of HLA-B allele with DRESS/DIHS.

Kashiwagi et al. demonstrated a significant association between adverse skin reactions to carbamazepine and HLA-A*3101 among 22 Japanese patients, including erythema multiforme, erythroderma, DRESS/DIHS, SSJ, and other drug reactions. Eleven of these patients (50%), including two patients with SJS and others, were carriers of HLA-A*3101 and allele frequency was much higher in these patients (25%) than in the Japanese population (7.1%) ($p = 4 \times 10^{-4}$, odds ratio (OR) = 4.33).

In a case-control study in a Han-Chinese population a strong association between the presence of HLA-B*5801 and SJS/TEN, or DRESS/DIHS triggered by allopurinol among 51 patients (100%) was found, compared with 20 out of 135 (15%) allopurinol-tolerant patients and 19 out of 93 controls (20%) (p (Pc value $4.7 \times 10(-24)$, OR = 580).

Japanese patients with different clinical types of cutaneous ADRs caused by allopurinol, including SJS, TEN, and DRESS/DIHS, had the same HLA-B*5801 allele.

Pirmohamed et al. found an increased frequency of HLA-DR3 and HLA-DQ2 in a group of patients with carbamazepine-induced DRESS/DIHS (respectively $p = 0.01$, OR = 3.3; $p = 0.04$, OR = 2.7). It was demonstrated that activation of $CD4^+$ T cells with IL-2 is essential for the spread

of HHV-6 in vitro. Genotyping of patients revealed that they had positive HLA-DR3 (DRB1*0301) and HLA-DQ2 (DQB1*0201).

Thus, in recent years increased attention has been given to genetic factors as a cause of variation in both the interpersonal effectiveness and adverse effects of medicines. Idiosyncratic reactions are often mediated through immune, usually severe, and unpredictable course. The main region of human DNA with genetic variations that predispose to drug hypersensitivity reactions is the region HLA. This region harbors the gene locus of most diseases and contains many genes associated with immune functions.

Although strong associations have been demonstrated between certain HLA alleles and some types of adverse skin reaction to drugs, there is no definitive evidence or published data concerning the functions involved in these alleles. The activation of T cells restricted to HLA is necessary for the induction of immune reactions and, moreover, there is the possibility that some HLA proteins have high binding affinity combined with other drugs or a metabolite of the drug through covalent and noncovalent mechanisms. On the other hand, a protective effect of HLA has also been suggested. Alfirevic et al. reported a potential protective effect of HLA-B*0702 against severe adverse skin reactions induced by carbamazepine in Caucasian patients.

The implications of pharmacogenomics are varied; one example is the recommendation of the US Food and Drug Administration (FDA), which currently recommends genetic testing for users of more than ten drugs currently marketed in that country.

Histopathology

Histopathology of the skin shows a diffuse, dense superficial and/or perivascular lymphocytic infiltrate. Eosinophils in the dermis or swelling may or may not be present (Fig. 26.12a). On some occasions there is a band-like infiltrate with atypical lymphocytes simulating epidermotropism such as mycosis fungoides.

Fernando et al. described a patient with DRESS/DIHS triggered by carbamazepine whose rash biopsy presented an unusual form of superficial perivascular inflammatory infiltrate, in which tiny granulomas along with a moderate number of lymphocytes were found. The authors speculated that granuloma formation may be due to a sustained exposure to the drug, even after the onset of DRESS/DIHS. The expansion of $CD4^+$ T cells producing IFN and other cytokines results in recruitment of macrophages which, as a result of maintained exposure to the drug and persistence of cytokine release, promote differentiation into epithelioid cells, which then secrete TNF to promote fusion of these cells into multinucleated giant cells.

Thus, biopsies of organs involved in DRESS/DIHS, such as skin and liver, on a significant number of patients may demonstrate the true frequency of granulomatous infiltration in the disease and assist in understanding the pathogenesis of the reaction.

Symptoms and Signs

The syndrome usually develops within 2 months after drug introduction, more often in 3 weeks to 3 months of the introduction of the drug, or earlier if constituting readministration. Fever, often high (38°–40 °C), which is the most common symptom (seen in 90–100% of cases), and rash (87% of cases) are the first signs, especially when related to antiepileptic drugs. The cutaneous eruption consists of a morbilliform rash, which is indistinguishable from the rash of other less severe reactions (Fig. 26.12b, c).

The face, upper trunk, and upper extremities are initially affected, with subsequent progression to the lower extremities occurring in about 90% of cases, which later spreads to the legs and the development of erythrodermic rash.

The maculopapular eruption later becomes infiltrated with edematous follicular accentuation. Swelling of the face, with marked periorbital involvement, is a warning for the diagnosis, occurring in about 25% of patients, and can be so intense that the patient becomes disfigured.

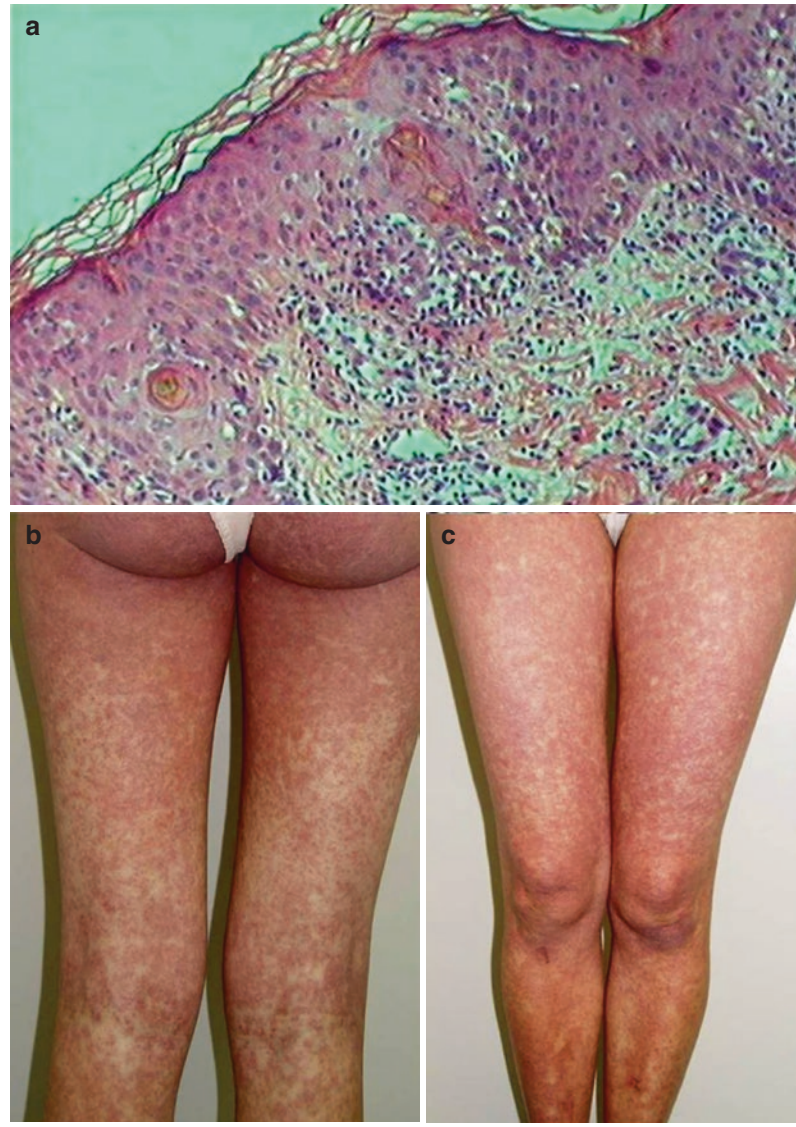

Fig. 26.12 Clinical and histopathologic findings in a patient with DRESS caused by dapsone during leprosy treatment. (**a**) Epidermis showing spongiosis, apoptotic keratinocytes, exocytosis of lymphocytes, and inflammatory infiltrate in the superficial dermis (hematoxylin–eosin, ×200 OM); (**b**, **c**) Exanthema in DRESS in Caucasian woman

Vesicles may arise, and fine bubbles caused by edema of the dermis can be present. No necrosis of the epidermis such as TEN occurs, except in rare cases of overlapping DRESS/DIHS and TEN. Small sterile perifollicular pustules and nonfollicular pustules may appear, which are different from acute generalized exanthematous pustulosis and do not predominate on the main ridges of the skin. Often atypical targets may arise. Over time the rash becomes purplish, with sharp definition on lower limbs and the resolution of scaling Another form of presentation is a picture of exfoliative dermatitis, which may be associated with mucosal involvement, such as cheilitis, erosions, pharyngitis, and enanthematous enlarged tonsils.

Bilateral edema and infiltration of the salivary glands with xerostomia has been frequently reported.

Lymphadenopathy is common (70–75% of cases), limited to the lymph nodes or generalized, and painful, gradually resolving with the withdrawal of the drug. The lymph nodes may reveal two distinct types of involvement: a benign pattern of lymphoid hyperplasia with maintenance of normal lymph node architecture, and another

standard pseudolymphomatous aspect, with obliteration of normal architecture by a polymorphous infiltrate composed of atypical cells, plasma cells, histiocytes, and eosinophils, with areas of necrosis, edema, and mitotic figures but no Reed–Sternberg cells or capsular invasion. This histopathologic pattern can simulate a malignant lymphoma.

Various hematologic abnormalities are observed, which consist of marked leukocytosis, eosinophilia (30% of cases), and atypical lymphocytes similar to mononucleosis. These findings guide the diagnosis toward DRESS, but can sometimes be difficult to distinguish from viral infections such as infection by EBV or hematologic diseases. Lymphopenia, leukopenia, or leukocytosis usually precedes it, although they often are not detected because they occur several days before establishment of the clinical syndrome. Leukocytosis may be high, up to 50,000 leukocytes/mm^3, and eosinophilia reaches values higher than 20,000/mm^3. The eosinophilia may determine the involvement of internal organs with pulmonary infiltrates. In general, eosinophilia may be observed about 1–2 weeks after the onset of the syndrome, or may even occur after the increase in liver enzymes has normalized.

Hemophagocytic syndrome (HPS) can rarely be observed in the course of DRESS/DIHS. HPS is associated with and triggered by various conditions, including viral infections, particularly EBV, malignant tumors, or autoimmune diseases. When involved with the course of DRESS/DIHS, HPS usually occurs 2 weeks after the onset of drug eruption. There is a decrease in white blood cells and platelets that are detected simultaneously with elevation of lactate dehydrogenase (LDH). Bone marrow aspirate reveals hemophagocytosis in an increased number of macrophages.

Multiorgan involvement may include a wide variety of organs and systems with myocarditis/myositis, pericarditis, interstitial nephritis (11% of cases), necrotizing granulomatous vasculitis in kidney, brain involvement (encephalitis or meningitis), colitis, and thyroiditis. This potentially fatal visceral involvement form may be symptomatic or not, and begins 1–2 weeks after the onset of rash. We observed a patient who developed acute pancreatitis that evolved into a lethal course.

There are reports of shock and respiratory distress syndrome with hypotension, pyrexia, hepatitis, and renal failure related to a hydantoin reaction.

Arthritis or arthralgia may occur in the context of this syndrome, including myositis.

Liver involvement is the most common visceral manifestation (50–60% of patients) after lymphadenopathy. Hepatomegaly may constitute a finding on physical examination. Hepatitis with isolated elevation of liver transaminases is common (51% of cases), usually anicteric, but liver failure is a leading contributory factor to mortality. Liver biopsy shows central lobular necrosis and dense inflammatory infiltrate of lymphocytes and eosinophils or granulomas. The reaction is accompanied by cholestasis and hepatocyte necrosis. In more severe cases, widespread or focal hepatic necrosis may be present. The presence of an active coinfection with hepatitis viruses B and/or C often determines deterioration in liver function and prolonged liver dysfunction.

There are few cases reported in the literature of DRESS/DIHS with severe acute hepatitis (defined by the presence of alanine aminotransferase (ALT) to more than 10× upper limit of normal and/or acute liver failure, such as coagulopathy and encephalopathy), mostly observed in women between the second and fourth decade of life, especially in relation to the use of sulfasalazine. About 15% result in death or liver transplantation, and the course of the disease is apparently unchanged by the use of immunosuppressants. The rapid recognition of the syndrome and prompt withdrawal of the drug can limit the liver damage, although this may be possibly even worse for several weeks and take months to resolve.

Renal involvement occurs in about 11% of cases, being particularly evident in cases arising from the use of allopurinol, whereby there was an increase in serum creatinine and urea and decreased creatinine clearance. In urine tests, increased content of eosinophils can be observed.

Although pulmonary involvement is rarely reported in DRESS/DIHS, interstitial pneumonia

with eosinophilia is often observed among patients whose syndrome was triggered by minocycline. Possibly the cases with lower intensity of pulmonary manifestations are less reported, leading to a bias in the published literature. Pulmonary complications include acute interstitial pneumonitis, lymphocytic interstitial pneumonia, and adult respiratory distress syndrome (ARDS).

Myocarditis may develop at the beginning of the syndrome or up to 40 days after establishment. Symptoms include heart failure, chest pain, sudden tachycardia, dyspnea, and hypotension in early DRESS/DIHS, but some patients are asymptomatic. The echocardiogram shows a reduction in ejection fraction, chest X-ray demonstrates cardiomegaly, and the electrocardiogram shows nonspecific changes in the ST-T segment. There is an increase in enzymes such as CPK and CK-MB, but no apparent changes in levels of troponin-1.

Neurologic complications include meningitis and encephalitis. Meningoencephalitis occurs about 2–4 weeks after initiation of drug reaction, and may lead to coma, seizures, headaches, disorders of speech, and paresis and paralysis of the cranial nerve.

Gastrointestinal bleeding may be an abrupt complication caused by ulcers derived from CMV. Endoscopic examination reveals arterial bleeding from punched-out gastric ulcerations.

Kennebeck compiled the frequency of clinical manifestations and laboratory data of the anticonvulsant hypersensitivity syndrome: fever (90–100%), cutaneous eruption (87–90%), lymphadenopathy (70%), hepatitis (50–60%), hematologic abnormalities (23–50%), periorbital and orofacial edema (25%), myalgia and arthritis (20%), nephritis (11%), pharyngitis (10%), and pulmonary manifestation (9%).

The visceral involvement in acute DRESS/DIHS until resolution of clinical disease is, therefore, extensive and varied, some of these events being closely related to HHV reactivation: enterocolitis and intestinal bleeding, hemophagocytic syndrome (HPS), hepatitis, limbic encephalitis, myocarditis, nephritis, mumps, pneumonia, pleurisy, and the syndrome of inappropriate antidiuretic hormone (SIADH).

The exclusion of other serious infections, particularly bacteremia, neoplastic diseases (lymphoma, leukemia, hypereosinophilic syndrome, paraneoplastic syndrome), and autoimmune or connective tissue conditions (adult-onset Still's disease, lupus erythematosus, vasculitis) is necessary for an accurate diagnosis of DRESS/DIHS.

Complications are rare and include limbic encephalitis, thyroid disease, renal failure, splenic rupture, eosinophilic colitis, eosinophilic esophagitis, enterocolitis, and fatal CMV.

The mortality rate can reach 20%, especially in cases related to advanced age, renal impairment, jaundice, and hepatitis with reactivation of CMV. By contrast, cases where there is a reactivation of EBV seem to have a less severe course, but are more likely to later (usually after several years) develop autoimmune diseases such as diabetes mellitus type 1 and autoimmune hypothyroidism.

Several authors have reported the occurrence of autoimmune diseases and/or the production of autoantibodies after the resolution of DRESS/DIHS, in a period ranging from several months or years after the resolution of the syndrome, and some are similar to those seen after bone marrow transplant. The related conditions include diabetes mellitus type 1, lupus erythematosus, Hashimoto's thyroiditis, enteropathy, sclerodermiform lesions, GVHD, and bullous pemphigoid.

Diagnostic Criteria

The diagnosis is difficult since there are incomplete or less characteristic clinical features, for example, hepatitis without rash, or merely pulmonary infiltrate with eosinophilia. Bocquet, Bagot, and Roujeau were the first authors who proposed criteria for DRESS diagnosis. According to these authors the diagnosis is established if there are at least three criteria present:

1. Drug rash
2. Hematologic abnormalities
   (a) Eosinophilia >1,500/mm^3
   (b) Presence of atypical lymphocytes

3. Systemic involvement (adenopathy (>2 cm in diameter) or hepatitis (transaminase elevation at least twice the normal values) or interstitial nephritis, pneumonitis, or carditis.

There is still no international consensus on the best criteria for the definition of DRESS/DIHS diagnosis. Bocquet et al. and Southeimer and Houpt have proposed different definitions and nosology for DRESS/DIHS in order to clarify clinical and pathologic characteristics of this syndrome.

The Japanese study group for severe cutaneous adverse reactions to drugs (SCAR-J) has adopted other criteria, as presented on Chart 26.4.

However, the universal adoption of these criteria may be impaired, because one of the criteria is viral replication during the course of infection, and some tests, such as measurement of IgG titer anti-HHV-6, are not yet routinely available in all hospitals or laboratories.

In our view, the criteria adopted by the European group RegiSCAR, published by Kardaun et al. in 2007, is the best to meet the needs in the diagnosis of DRESS/DIHS. Here the use of a system score for the diagnosis of DRESS/DIHS was suggested, based on the presence of symptoms and clinical and laboratory signs, as displayed in Table 26.1.

Chart 26.4 Diagnostic criteria for DRESS/DIHS proposed by Japanese group

1. Maculopapular rash developing >3 weeks after starting therapy with a limited number of drugs
2. Persistent clinical findings after drug withdrawal
3. Fever (>38 °C)
4. Hepatic abnormalities (glutamic pyruvic transaminase >100 U/l)[a]
5. Leukocyte abnormalities (at least one present)
(a) Leukocytosis (>11,000/mm^3)
(b) Atypical lymphocytosis (>5%)
(c) Eosinophilia (>1,500/mm^3)
6. HHV-6 reactivation[b]

The diagnosis is confirmed by the presence of the seven criteria (typical DIHS) or of the first five criteria (atypical DIHS)

[a]This can be replaced by other organ involvement such as renal involvement

[b]Reactivation is detected from the second to third week after symptom onset, through IgG anti-HHV-6 titer elevation

Complementary Tests During Follow-Up of Patients with DRESS/DIHS

Given the suspicion of the syndrome relevant examinations should be performed, keeping in mind that this syndrome has evolutionary behavior. The initial tests are oriented to verify the data and research into hematological visceral involvement, as proposed by Descamps et al. At admission: complete blood count, ALT, aspartate aminotransferase (AST), total bilirubin, γ-glutamyl transferase, alkaline phosphatase, sodium, potassium, creatinine and creatinine clearance, 24-h urine protein and urinary eosinophil count, CPK, LDH, ferritin, triglycerides, calcium and parathyroid hormone, blood glucose, prothrombin time and activated partial thromboplastin time, lipase, protein electrophoresis, C-reactive protein, quantitative PCR for HHV-6, -7, EBV, and CMV, blood culture, and antinuclear factor.

Follow-up (two times per week): complete blood count, ALT, AST, creatinine, LDH, and other laboratory tests according to changes found on admission tests. Evolutive follow-up: quantitative PCR for HHV-6, -7, EBV, and CMV, complete blood count, ALT, AST, alkaline phosphatase, creatinine, LDH, ferritin, and triglycerides.

Treatment

The early recognition of ADRs and withdrawal of the offending drug is the most important and essential steps toward clinical improvement. Empiric treatment with antibiotics or anti-inflammatory drugs should not be administered during the acute disease, since they may confuse or worsen the clinical picture of patients because of an unexplained cross-reactivity between drugs.

Prognosis is generally worse in the elderly while the recovery is usually faster and usually complete in children.

For many years, the treatment of DRESS has been based on the use of systemic corticoste-

Table 26.1 Scoring system for classifying DIHS/DRESS cases as definite, probable, possible, or no case (Adopted by RegiSCAR (Register of Severe Cutaneous Adverse Reactions) [44])

Score	−1	0	1	2	Max	Min
Fever ≥38.5 °C	No/U	Yes			−1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia:		No/ U			0	2
Eosinophils			0.7–1.499 × 210^9 l^{-1}	≥1.5 × 10^9 l^{-1}		
Eosinophils, IF leukocytes <4.0 × 10^9 l^{-1}			10–19.9%	≥20%		
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					−2	2
Skin rash extent (% body surface area)		No/U	>50%			
Skin rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	No/U				
Organ involvement*:					0	2
Liver		No/U	Yes			
Kidney		No/U	Yes			
Muscle/heart		No/U	Yes			
Pancreas		No/U	Yes			
Other organ		No/U	Yes			
Resolution ≥15 days	No/U	Yes			−1	0
Evaluation of other potential causes:						
Antinuclear antibody (FAN)						
Blood culture						
Serology HAV/HBV/HCV						
Chlamydia/mycoplasma						
*If none positive and ≥3 of above negative			Yes		0	1
Total score					−4	9

U unknown/unclassifiable, *HAV* hepatitis A virus, *HBV* hepatitis B virus, *HCV* hepatitis C virus
After exclusion of other explanations: *1* one organ, *2* two or more organs. Final score <2, no case; final score 2–3, possible case; final score 4–5, probable case; final score >5, definite case
*Organ involvement

roids (dose equal to or greater than 1–1.5 mg/kg/day of prednisone or equivalent) with marked improvement of symptoms and laboratory parameters only several days after the start of treatment. Systemic corticosteroids should have their dose reduced, after clinical and laboratory control of the disease, slowly over 6–8 weeks to prevent recurrence of the symptoms of disease. Abrupt deterioration of various symptoms is observed when the withdrawal is accidental or by rapid reduction of the dose of corticosteroids. Shiohara et al. recommend that all patients should be hospitalized even when the initial presentation is mild.

If symptoms worsen despite the use of oral corticosteroids, other options used in case series are the use of pulsed methylprednisolone (30 mg/kg intravenously for 3 days), intravenous immunoglobulin (IVIG), and plasmapheresis, or a combination of these therapies. It should be remembered that the immunosuppressive therapies may increase the risk of infectious complications and sepsis. Mild cases can recover simply by drug withdrawal and supportive treatment after a few weeks, even without the use of corticosteroids. However, even in mild cases, the monitoring of liver function tests should be conducted and appropriate tests ordered to rule out the involvement of other organs such as lungs, thyroid, and heart.

Special attention should be given to possible reactivation of CMV, especially in patients with severe DRESS/DIHS. Physicians should also pay attention to a proper balance between the needs of corticosteroids for relief of symptoms and

clinical signs and their possible negative influence on viral load.

High doses of IVIG have two immunologic effects: (i) it compensates for the decrease in concentration of immunoglobulins in patient's blood and the defects in immune protection against HHV-6; and (ii) high doses of IVIG have an anti-inflammatory effect that can regulate immune responses, as seen in the treatment of autoimmune diseases.

The French Society of Dermatology published the results of a consensus of experts on the therapeutic management of DRESS/DIHS regarding drug reactions:

- Absence of signs of gravity: corticosteroids (potent or very potent), emollients, H1-antihistamines
- Presence of signs of severity (transaminases >5 times normal renal organic, pneumonia, hemophagocytosis, cardiac, etc.): corticosteroids equivalent to 1 mg/kg per day of prednisone, multidisciplinary evaluation
- Life-threatening signs (hemophagocytosis with bone marrow failure, encephalitis, severe hepatitis, renal failure, respiratory failure): steroids generally associated with IVIG at a dose of 2 g/kg over 5 days. The IVIG should not be proposed without associated steroids. These treatments to be conducted through multidisciplinary evaluation
- Presence of signs of gravity with confirmation of a major viral reactivation: Combining steroids and antiviral (ganciclovir) and/or IVIG

Kano et al. reported the occurrence of herpes zoster in 3 of 28 patients with DRESS/DIHS within 6 months after the onset of DRESS/DIHS; all three patients had been given systemic corticosteroids and the ADR was triggered by anticonvulsants. The authors suggested that the administration of systemic corticosteroid for the treatment of DRESS/DIHS may have contributed to the increased risk of herpes zoster. Indeed, herpes zoster was not detected in patients with DIHS/DRESS who were treated with only supportive care. Presumably, the altered underlying immunologic pathomechanism of DIHS/DRESS caused by the systemic corticosteroid might have played an important role in the onset of herpes zoster. It has been shown that DIHS/DRESS is a manifestation of newly observed immune reconstitution syndrome (IRS), and herpes zoster is observed as the most common manifestation of IRS after highly active antiretroviral therapy for AIDS. Relevant clues related to DRESS syndrome include:

- DRESS/DIHS is an ADR caused by an apparent group of drugs, and one-third of cases are related to anticonvulsants, in addition to sulfonamides and allopurinol, which can cause 10–20% mortality.
- The syndrome is characterized by a latency period ranging between 3 weeks and 3 months after the introduction of the offending drug, and its course is marked by apparent sequential reactivation of HHV and subsequent development of autoimmune diseases, providing an opportunity to establish a connection between viral infections and the emergence of autoimmune diseases.
- In early DRESS/DIHS hypogammaglobulinemia and reduced peripheral B cells are found, and $CD4^+$ $CD25^+$ $FoxP3^+$ (regulatory T cells) levels are high at the beginning of the syndrome, regardless of whether or not patients are treated with corticosteroids. This clonal expansion of regulatory T cells appears to prevent activation of antiviral T cells in an appropriate manner and sequential reactivation of virus is presented in the syndrome. These regulatory T cells have the phenotype $CCR4^+$ and CLA^+, which address the skin. In the last stage of the syndrome's activity, phenotype of cytotoxic T cells becomes prominent and $CD4^+$ lymphocytes are intensely diminished. These cells are depleted over time, suffering apoptosis and becoming reduced after the resolution of the syndrome, which could be a predisposing factor for the development of autoimmunity.

Acute Generalized Exanthematous Pustulosis [45]

AGEP is a clinical entity that appears in the intertriginous areas or on the face as a diffuse erythema (scarlatiniform) with acute presentation. Patients

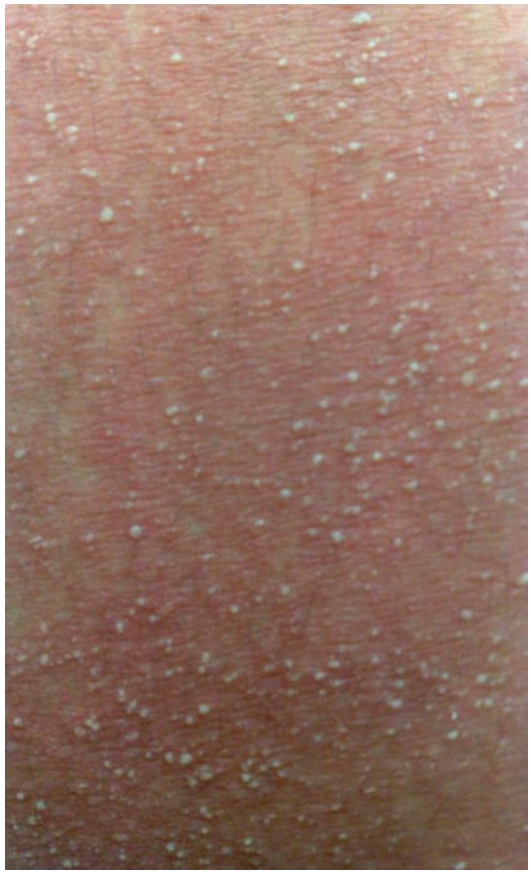

Fig. 26.13 AGEP. Several pinhead sterile pustules over erythematous skin

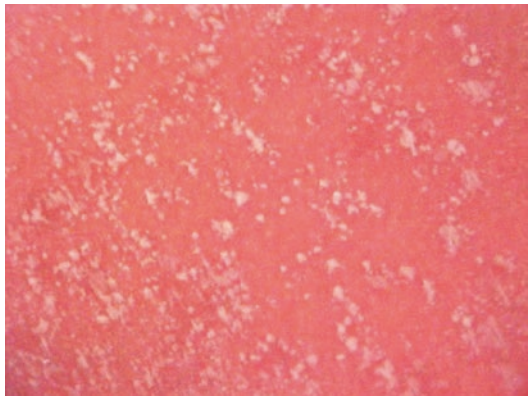

Fig. 26.14 AGEP. Detail of confluent pinhead pustules

report pruritus or local burning sensation. After this appearance, the erythema is replaced by hundreds of nonfollicular sterile small pustules (<5 mm in diameter) (Figs. 26.13 and 26.14). These pustules may sometimes converge and mimic Nikolsky's sign, leading to misdiagnosis as TEN. Intense edema of the face may occur, with purpuric lesions mainly on the legs and the onset of lesions similar to EM of the legs.

There may be mucous involvement in about 20% of the patients, although it is usually mild and self-limited, occurring in just one location. The cutaneous symptoms are almost always accompanied by fever of >38 °C. Frequently there is leukocytosis in the blood count, and eosinophilia may also occur in one-third of the patients.

Usually this eruption regresses within 4–10 days after withdrawal of the drug and in typical cases leaves a lamellar or punctiform desquamation. Disease prognosis worsens when there is hyperthermia or infection of the lesions, and when it affects elderly individuals, who should be hospitalized.

The drugs described as a cause of AGEP are most frequently β-lactams (penicillin, cephalosporins), macrolides (azithromycin, erythromycin), cyclines (doxycycline), sulfonamides (trimethoprim, sulfasalazine), chloramphenicol, isoniazid, streptomycin, vancomycin, quinolones (ciprofloxacin, norfloxacin), itraconazole, terbinafine, allopurinol, carbamazepine, phenytoin, diltiazem, nifedipine, chromium picolinate, diclofenac, enalapril, disulfiram, furosemide, hydroxychloroquine, paracetamol, mercury, thalidomide, protease inhibitors, and bamifylline.

Sidoroff and et al. proposed some characteristics that might aid in the differentiation between pustular psoriasis and AGEP. In the latter, a history of psoriasis is rare, the lesions are most frequent in the cutaneous folds, the duration of the fever and the pustules is short, and there is usually a history of recent exposure to the drug; arthritis is rare.

Histopathology may show subcorneal and/or intraepidermal spongiform pustules, edema of the papillary dermis, vasculitis, exocytosis of eosinophils, and focal necrosis of keratinocytes (Fig. 26.15). On the other hand, in pustular psoriasis a history of psoriasis is common, the involvement is generalized, the duration of the fever and the pustules is longer, history of drug exposure is less frequent, arthritis occurs in about 30% of the patients, and histopathologic

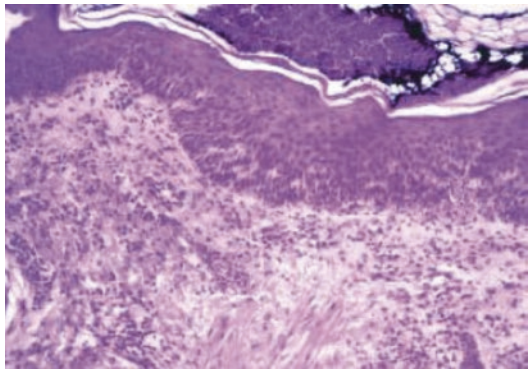

Fig. 26.15 AGEP histopathology. Subcorneal pustule without psoriasiform epidermal hyperplasia

examination shows subcorneal and/or intraepidermal pustules, papillomatosis, and acanthosis of the epidermis.

Skin tests for late-phase reactions may be useful tools for identifying the etiologic agent of AGEP when the systemic readministration is potentially dangerous. Approximately 50% of the cases of AGEP present positive contact tests for the suspect drug, usually reproducing the lesion in both a clinical and histologic form.

Recently, Britschgi and colleagues demonstrated high expression of IL-8 in these patients. It is known that IL-8 is a chemokine with potent activity in the recruitment of neutrophils, which is produced by the keratinocytes and mononuclear cells of the cutaneous inflammatory infiltration. These authors concluded that AGEP might be the expression of a reaction whereby a cell bound to the drug triggers a drug-specific $CD4^+$ and $CD8^+$ immune response, which results in high expression of IL-8 (Type VId in the Pichler classification).

Drug-Induced Serum Sickness [45]

In 1905, Von Piquet and Shick described serum sickness in children treated with horse serum containing diphtheria antitoxin. More recently serum sickness has been observed in patients treated with horse antithymocyte globulin or vaccines of rabbit antihuman diploid cells. This constitutes a type III hypersensitivity reaction, mediated by immunocomplexes deposited on the walls of the vessels, activation of the complement, and recruitment of granulocytes.

It presents particular cutaneous manifestations: typically there is erythema in the lateral portion of the fingers and toes that precedes a more disseminated eruption (occurring in 90% of cases), which frequently is morbilliform (two-thirds of the patients) and sometimes urticariform. The presence of urticaria, leukocytoclastic vasculitis, and multiform erythema is rarely observed. In half of the cases there is visceral involvement [1]. The following clinical findings are common: fever, cutaneous eruption, constitutional symptoms, arthritis, and arthralgia.

The disease begins about 8–14 days after the initial exposure to the foreign protein. The drugs related with this type of manifestation are the heterologous sera and vaccines. Serum sickness-like reactions can also be caused by penicillin, cephalosporin, minocycline, propranolol, streptokinase, and nonhormonal anti-inflammatories. There are no data on the prevalence of this disease in Brazil, although reports of cases of this disease are not infrequent in the medical literature.

Fractions C3 and C4 of the complement are strongly decreased in serum sickness while they are usually normal in serum sickness-like reactions.

Treatment of the disease constitutes withdrawal of the drug allied to the use of systemic corticosteroids, in addition to antihistamines for symptomatic relief of pruritus when present. Careful observation of the clinical course of the patient's systemic involvement is imperative.

Drug-Induced Vasculitis [45, 46]

Several medications can induce a cutaneous vasculitis-type response, the histopathologic definition of which is the presence of inflammation and necrosis in the wall of the cutaneous blood vessels. Clinically it presents as tangible purpura or maculopapular purpuric eruption. This disease can also occur in the form of hemorrhagic blisters, urticaria, ulceration, nodules, Raynaud's disease, and digital necrosis. The same vasculitis

process can involve internal organs, such as the kidneys, liver, gastrointestinal tract, or the central nervous system, and any area of the tegument, including the mucous membranes and the palmar and plantar regions.

The disease develops about 7–21 days after initiating the drug; however there can be a longer time interval, and any medication instituted within the 2 months prior to the presentation should be considered suspect. Given the absence of confirmatory tests for this entity, one should value anamnesis and the correlation with drug exposure, which in general occurs 1–3 weeks before onset of the cutaneous picture. However, the exposure can have occurred in periods as disparate as 2 days to 9 years. Withdrawal of the drug leads to a rapid resolution of the picture, and systemic corticosteroids can benefit some patients. The process is usually solved without sequels.

The clinical, epidemic, and pathologic characteristics of drug-induced vasculitis have been little reported in the medical literature, since there is no consensus in the definition of this disease, with various revisions using different criteria for inclusion of cases. Vasculitis attributed to exposure to medicines is rare, but seemingly account for about 10–20% of dermal vasculitis cases. It is difficult to quantify the frequency with which drug-induced vasculitis is strictly cutaneous.

Clinical experience suggests that most of the cases are confined to the skin and have a self-limited course, although it can be associated with varied degrees of systemic symptoms including arthralgia, indisposition, and fever. Visceral involvement is well described and pathologically heterogeneous. Glomerulonephritis and interstitial renal disease, varied degrees of hepatocellular damage, and formation of granulomas in the liver have been described, besides involvement of the heart, lungs, and central nervous system. Furthermore, there are rare cases of drug-induced vasculitis with renal and hepatic involvement in the absence of cutaneous disease.

The drugs most frequently referred to in the literature, in the form of case reports or series studies, as causative of vasculitis are propylthiouracil, hydralazine, granulocyte colony-stimulating factor (G-CSF), cefaclor, minocycline, allopurinol, D-penicillamine, phenytoin, isotretinoin, and methotrexate.

As many of the cases of drug-induced vasculitis are not reported in the literature, other drugs are also possible important causative agents of this reaction type. Other drugs have been reported less often as causal agents of vasculitis: several antibiotics, etretinate, didanosine, zidovudine, acebutolol, atenolol, sotalol, propranolol, chlorothiazide, furosemide, diltiazem, nifedipine, methyldopa, captopril, enalapril, lisinopril, losartan, procainamide, quinidine, antithyroid medications, painkillers and antipyretics, levamisole, tamoxifen, arabinoside C, interferon, interleukin-2, sulfasalazine, etanercept, gold, carbamazepine, antidepressants, zafirlukast, chromalin, cimetidine, ranitidine, L-tryptophan, radiocontrast, streptokinase, heparin, coumarin, chlorpromazine, metformin, pimagedine, and diphenhydramine.

Drugs that induce vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) include hydralazine, propylthiouracil, minocycline, and anti-TNFα biological agents.

About 20% of the patients who use propylthiouracil develop ANCA, a fact that is related to a higher risk of glomerulonephritis. A particularly relevant form among the drug-induced vasculites is propylthiouracil hypersensitivity vasculitis. There are cases with other antithyroid compounds, such as methimazole, thiamazole/methylthiouracil, and carbimazole, which, similarly to propylthiouracil, contain a thioamide group and cause allergic cross-reactions. Although uncommon, nowadays a larger number of case reports of this entity are observed, suggesting that cases were previously not reported or were included among other nosologic entities, since propylthiouracil is a drug classically dedicated to the treatment of hyperthyroidism.

The clinical symptoms and signs begin after initiating propylthiouracil. Although the duration of drug use is extremely variable, from 1 week to 13 years, it appears under a classic tetrad of symptoms that include fever, sore throat, arthralgia and cutaneous eruption; there can also be myalgia, fatigue, weight loss, conjunctivitis, rhinitis, and hemoptysis.

The disease course is that of a systemic vasculitis. There can be a lupus-like syndrome, Wegener-like granulomatosis, or nodular-like polyarthritis with multiple involvement of organs, such as kidneys, joints, lungs, and others associated with cutaneous lesions. The cutaneous lesions usually consist of plaques or acral purpuric nodules arranged in a livedoid pattern, with a preference for the extremities (Fig. 26.16), face, breasts, and characteristically the lobes and helices of the ears, mimicking the leprosy type reaction of Lucio's phenomenon. Hemorrhagic blisters appear on these lesions that progress to central necrosis of the skin, which can be so extensive that it simulates the clinical presentation of purpura fulminans observed in septic infectious states with disseminated intravascular coagulation.

Laboratory tests reveal anemia, leukopenia, and platelet depletion in the blood count; increased erythrocyte sedimentation rate, urea, creatinine, transaminases, and bilirubin; hypoalbuminemia; alterations in the coagulation time, prothrombin time, and partial activated thromboplastin time; and immunological abnormalities such as positive ANCA, rheumatoid factor, and hypergammaglobulinemia can be found. Positivity can also be present in anti-SSA, anti-double-stranded DNA, anticardiolipin, anti-smooth muscle antibodies, antimitochondrial, parietal, and antiadrenergic antibodies, besides hypocomplementemia, cryoglobulinemia, and elevation of C-reactive protein.

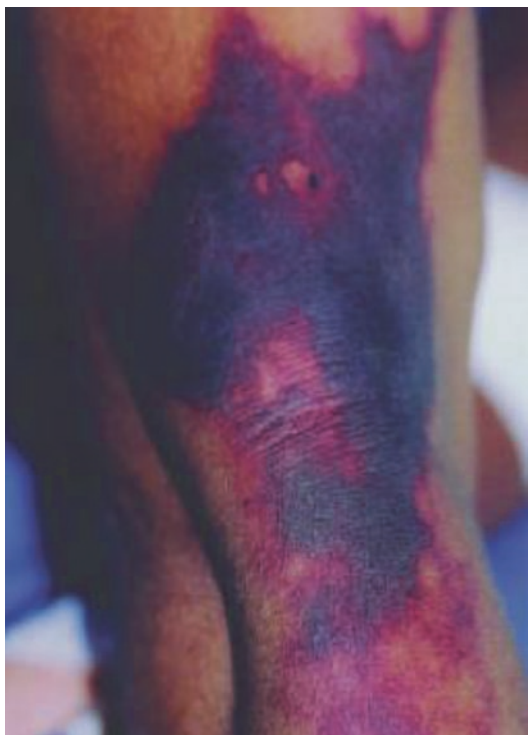

Fig. 26.16 Retiform purpura in drug-induced ANCA-positive vasculitis caused by propylthiouracil

Histopathologic study demonstrates a leukocytoclastic vasculitis of the superficial and profound vessels of the dermis. The finding of immunocomplexes deposited in the vascular wall is uncommon, such that some authors have named them pauci-immune ANCA-positive vasculitis. Most of the patients recover completely following withdrawal of propylthiouracil, although some develop impairment of the kidneys or other internal organs, or skin, requiring high doses of prednisone for several months.

The dermatologic findings in patients with drug-induced vasculitis associated with ANCA include plaques and purpuric acral nodules, which appear more commonly on the extremities, face, breasts, and ears. In addition, the patients report the same signs and symptoms as found in other small-vessel vasculites associated with ANCA (Wegener's granulomatosis, Churg–Strauss syndrome), including glomerulonephritis, pulmonary hemorrhage, and digital gangrene.

Besides withdrawal of the offending drug, it is generally necessary to use corticosteroids in high doses or in pulse therapy, plasmapheresis, and immunosuppressants for several months. The mortality rate is approximately 10%.

Anticoagulant-Induced Skin Necrosis [45]

This is a rare and severe adverse effect from treatment with warfarin (anti-vitamin K agents), occurring with cutaneous necrosis secondary to occlusive thrombosis in the vessels of the skin and subcutaneous cellular tissue. It usually presents 3–5 days after use of the drug, as painful

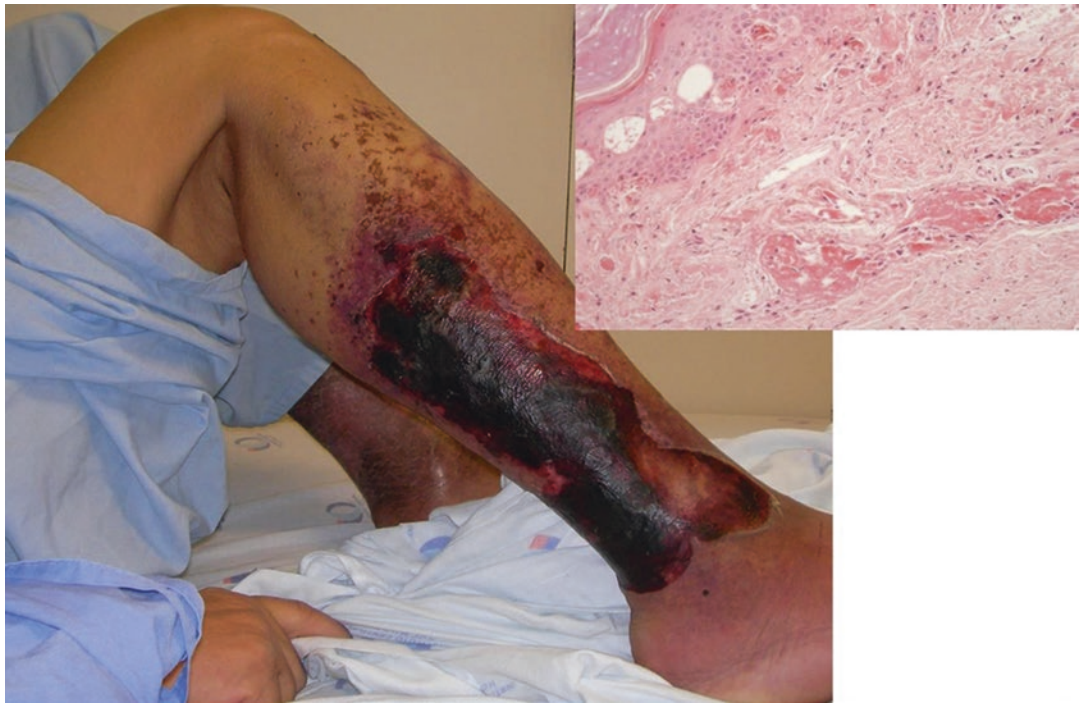

Fig. 26.17 Anticoagulant-induced skin necrosis caused by warfarin. Note thrombosis of femoral vessels in histopathologic examination

erythematous plaques that course to necrosis (Fig. 26.17), with hemorrhagic blisters or necrotic scars in the areas rich in subcutaneous tissue, such as buttocks, breasts, and hip. The risk of this disease increases in patients who are female, obese, and users of high doses of the medication [1]. The necrotic tissue requires debridement and grafts. This type of reaction has also been described with the use of heparin.

Moderate or Mild Cutaneous Adverse Drug Reactions (CADRs) or Uncomplicated CADRs

This kind of ADR is represented by several conditions related to drug exposure, which do not represent life-threatening conditions to the patients except discomfort. There is no severe temporary or permanent remaining lesions or long-term internal organ sequelae and, in most of cases, no mortality or severe impact on patients' health. In contrast to severe ADRs, in the clinical setting of uncomplicated CADRs admission to the intensive care or burn unit is usually not necessary for the majority of patients.

For this reason, the physician must be able to identify the signs and symptoms that indicate severe CADR [47]. In particular, dermatologists must pay attention to identifying these reactions, since the skin is among the most common organs or systems of clinical manifestation of ADRs and concurs with at least 15% of ADRs [47].

The most common forms of CADRs are urticarial and exanthematous eruptions, which together constitute 90–95% of all CARDs [47]. These two types carry few to no long-term consequences [47]. The severe ADRs (SADRs), described earlier in this chapter, probably represent around 2% of all ADRs [47]. SADRs often are associated with high levels of morbidity and mortality, and therefore a prompt recognition of the reaction, withdrawal of all possible offending agents, and appropriate triage, hospital admittance, workup, and specific treatment are critical [47].

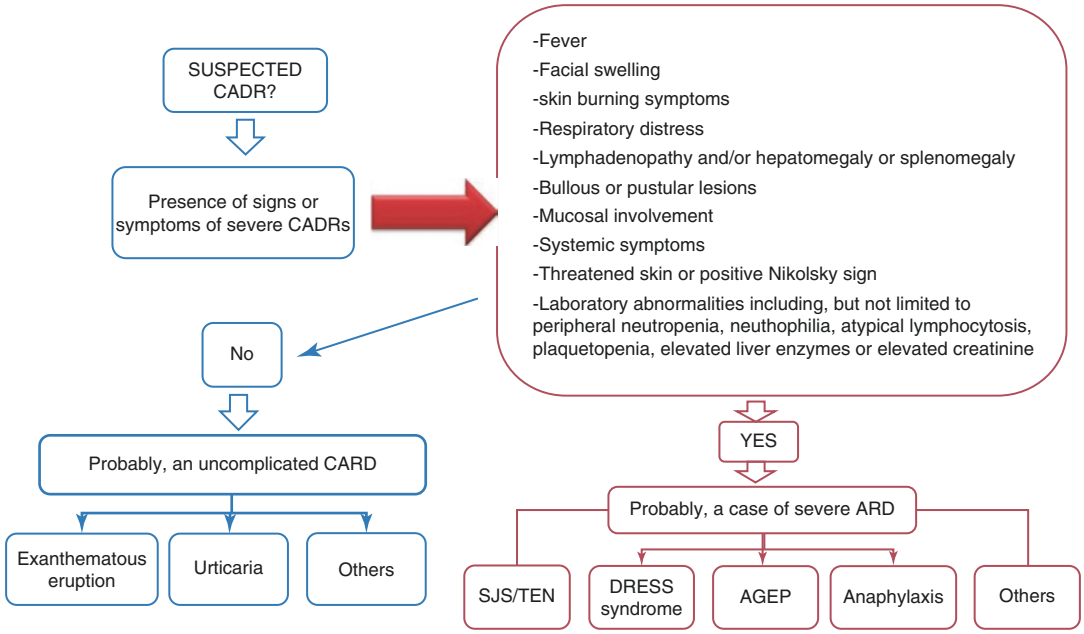

Fig. 26.18 Algorithm for evaluation of patients with ADR based on signs and symptoms indicating a severe or an uncomplicated ADR

Regarding studies of severe versus uncomplicated ADRs, Swanson and Colven [47] proposed a staged patient evaluation as shown in Fig. 26.17. Signs and symptoms severe ADR are listed in Fig. 26.18, and in this clinical scenario the physician should have a low threshold to admit the patient to hospital, perform a complete workup including evaluation of other medical specialties, withdraw suspected medications, and initiate adequate therapy when indicated [47].

Another relevant aspect in recognizing the type of ADR is the time from medication introduction to the onset of a cutaneous reaction, since this is related to the subtype of ADR, as proposed in Fig. 26.19 [47]. Often patients have been exposed to several medications in the same period, and creating a "drug list" that details the dates of all medications taken is helpful in narrowing down the most probable culprits [47].

Physicians should pay attention to prodromal symptoms (skin pain, fever, malaise, throat pain or discomfort, arthralgia, etc.) that can to precede the cutaneous eruption, and associated internal symptoms (abdominal pain, ocular discomfort, dysuria, respiratory distress, etc.), and proceed to complete physical examination including full skin examination of groin, genitalia, eyes, oropharynx, thorax auscultation, abdomen, and lymph node palpation [47].

The physician needs remember that several risk factors for the development of more severe cutaneous ADRs have been identified, including female gender, older age, viral infections (herpesvirus family or HIV), genetic susceptibility (specific single-nucleotide polymorphisms in the HLA region), iatrogenic immunosuppression, underlying immune-mediated diseases, and cancer [48].

Exanthematous Drug Eruptions [48, 49]

Exanthematous or maculopapular drug eruptions, sometimes inappropriately designated "drug rashes" or "drug eruptions" by some generalists, are the most common ADRs in the skin. The eruption usually occurs between 4 and 14 days after the initiation of a new medication or chemical substance, although it can develop sooner,

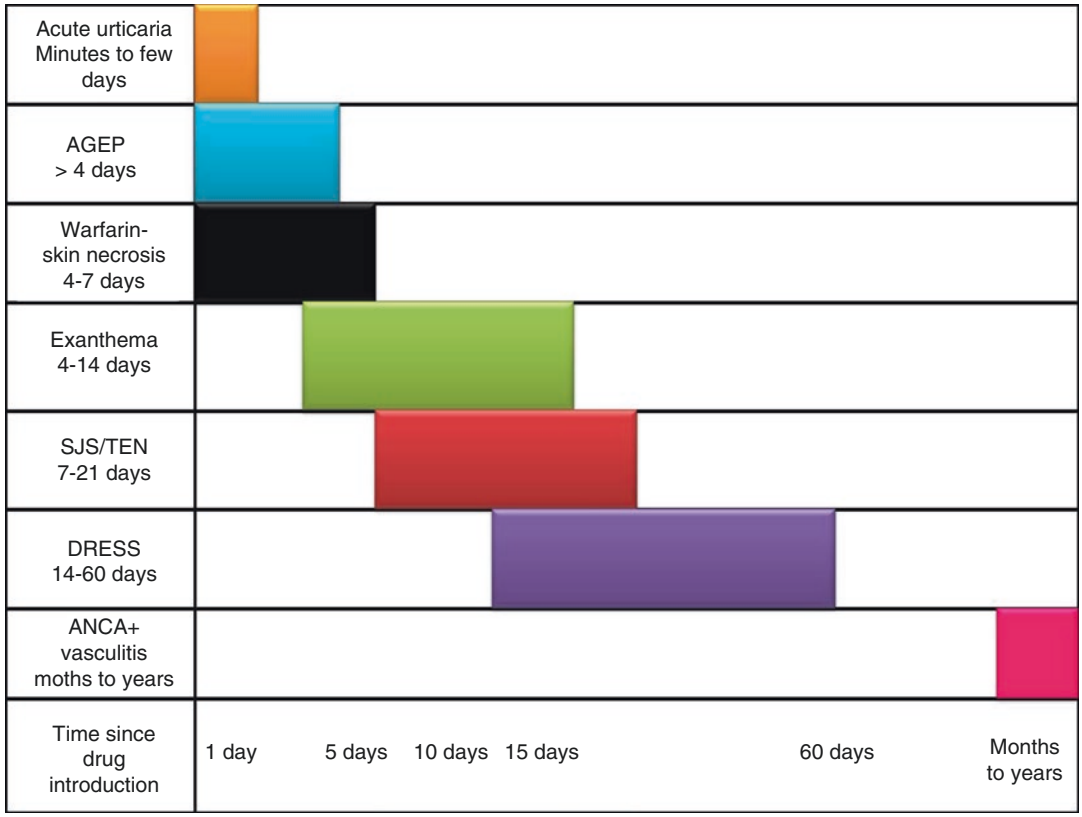

Fig. 26.19 Approximate timing of drug eruptions after the onset of drug introduction

especially in case of a new exposition to the same or parent drug. Uncomplicated exanthematous drug reactions usually resolve in a few days when the causative drug is stopped.

Exanthematous eruptions generally are composed of erythematous macules and/or papules and more rarely by vesicles or pustules, usually with a pattern of symmetric distribution on skin. The eruption often begins on the trunk followed by centrifugal dissemination to the proximal limbs. Skin lesions progressively become confluent and may cover large areas of the body (Fig. 26.20). Pruritus and/or low-grade fever are often associated with the exanthema. In some patients the exanthema may progress to erythroderma or more severe reactions such as SJS/TEN or DRESS syndrome after some days or weeks.

Under histopathology examination this type of ADR demonstrates interface dermatitis with vacuolar changes in keratinocytes at the basal layer of the epidermis, and upper dermal mononuclear cells infiltrate with some eosinophils. The pathogenesis involves the overexpression of several cytokines of Th2 pattern, such as IL-5 and IL-13, causing epidermal damage by

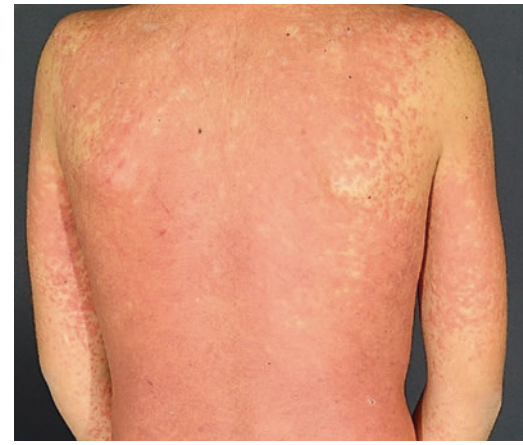

Fig. 26.20 Morbilliform drug-induced exanthema

molecules of perforin, granzyme B, and peripheral blood eosinophilia (a type IVb delayed cell-mediated immune mechanism, as proposed by Werner Pichler).

Uncomplicated exanthematous drug eruptions can occur with almost any medication, but the following drugs have higher risks (more than 3% of patients): allopurinol, aminopenicillins, cephalosporins, antiepileptic drugs, and antibacterial sulfonamides. Viral infections may increase the incidence of morbilliform drug eruptions, as seen in the setting of mononucleosis infection under treatment with ampicillin, or in severe exanthema with internal damage as in DRESS syndrome related to the HHV family (EBV, cytomegalovirus, HHV-6 and -7).

Morbilliform reaction is the most common presentation of exanthematous drug eruption. Morbilliform is defined as a rash resembling measles and is clinically depicted by erythematous macules and/or papules, often coalescing into larger plaques. Many studies have shown that cutaneous biopsy alone cannot distinguish with certainly that a reaction is due to a drug. There are some clues that suggest the diagnosis: (i) Epidermis (mild spongiosis is the most consistent feature, with occasional hyperplasia of the epidermis. Few lymphocytes are commonly present in the epidermis. In 97% of biopsies, vacuolization was found in the dermoepidermal junction); (ii) Dermis (perivascular infiltrate is virtually always present, composed of lymphocytes and in 60% of cases scattered eosinophils); (iii) papillary dermal edema; (iv) dilated lymph and blood vessels.

The primary differential diagnosis for morbilliform eruptions includes viral exanthemas (e.g., EBV, HHV-6, and CMV), bacterial toxin resection (streptococcal or staphylococcal), Kawasaki syndrome, and others such as secondary syphilis, scarlet fever, acute HIV, or acute GVHD.

The treatment is supportive. The first measure is the withdrawal the causative agent. Topical corticosteroids and systemic antihistamines can be administered in the first step. If necessary, this can be combined with a short cycle of systemic corticosteroids (oral prednisone, 0.5 mg/kg/day, with progressively tapering dosages over several days). Antihistamines are indicated as adjuvant therapy in cases of itching.

Acute Urticaria and Angioedema [48–50]

Drug-induced urticaria is the second most common form of cutaneous drug reaction after exanthematous reactions.

Urticarial eruption can be broken down into simple acute urticarial eruptions, those involving angioedema or anaphylaxis, and serum sickness-like reactions as previously described in this chapter. Simple urticarial reactions caused by drugs consist of erythematous and edematous lesions, which have central clearing with a red border. The lesions can be located anywhere on the body and wax and wane over hours to days. Pruritus is an associated symptom. This type of drug reaction takes place minutes to days after exposure to the offending drug.

Common drugs responsible for urticarial reactions include antibiotics, such as penicillins, cephalosporins, sulfonamides, and tetracyclines, generally due to IgE-mediated hypersensitivity reaction. Another common class of drugs related to urticarial eruptions is nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs cause most frequently non-IgE-mediated urticaria and angioedema because of their pharmacologic activity of cyclooxygenase-1 enzyme inhibition, particularly of prostaglandin E2, and results in the generation of leukotriene C4 and activation of inflammatory cells.

Urticaria and angioedema are associated in about 50% of cases. Regarding ACE inhibitors, angioedema is described in 0.5% of patients treated with this class of drugs, and often without urticarial lesions. Rarely, angiotensin II receptor blockers result in the same complication.

Oral or injectable antihistamines and systemic corticosteroids are sometimes needed for severe acute urticaria and intramuscular epinephrine for angioedema. In cases of isolated angioedema caused by ACE inhibitors, epinephrine will not control the symptoms and it is necessary to use the selective bradykinin B2 receptor antagonist icatibant in this clinical setting.

Fixed Drug Eruptions [49, 51]

This entity is defined as recurrent lesions that, upon repeated uptake of the causative drug, always appear at the same skin or mucosal sites. FDEs present as well as circumscribed, single or multiple, often pruritic or burning erythematous, dusky patches (Fig. 26.21), ranging from several millimeters to over 10 cm in diameter. Vesicles or even blisters can develop. As the lesions resolve, they leave residual hyperpigmentation. The hallmark of FDEs is geographic memory. If a reaction recurs, it tends to recur in the same location as previously (although a new location can also be involved).

Lips, hands, genitalia (especially male genitalia), and occasionally oral mucosa are favored sites of FDE occurrence, although the lesions can be found anywhere on the skin and mucous membranes. After intake of the offending drug, FDE appears within minutes up to several hours (about 30 min to 8 h). The cutaneous lesions can be accompanied by general symptoms such as fever, nausea, dysuria, abdominal cramps, and diarrhea, though rarely. On occasion the disease presents in an atypical form with blunt-margined, nonpigmented, giant (>20 cm in diameter), urticarial, purpuric, targetoid, linear, reticular, and butterfly-like lesions.

The histopathologic hallmark is brisk interface dermatitis with varying amounts of epidermal necrosis as well as melanophages and eosinophils in the upper dermis. FDEs reveal a reaction pattern with lichenoid or erythema multiforme-like changes. Atypical histopathologic reaction patterns such as leukocytoclastic vasculitis, neutrophilic reaction, and a predominantly dermal reaction without pigment incontinence in what is termed nonpigmented FDE have been reported.

The pathogenesis of FDE is based on the new subclassification of delayed type IV immune reactions (Werner Pichler), a type IVc reaction. In this kind of immune response cytotoxic T cells play a predominant function, whereby autoaggressive $\alpha\beta^{+}CD8^{+}$memory T cells persist intraepidermally in previous FDE sites and play a central role in new flare-ups during drug recall. Under drug exposition, keratinocytes are stimulated to participate in immune response through TNF-α and a rapid expression of ICAM-1 molecule, and then stimulate $CD8^{+}$ T cells to produce IFN-γ and

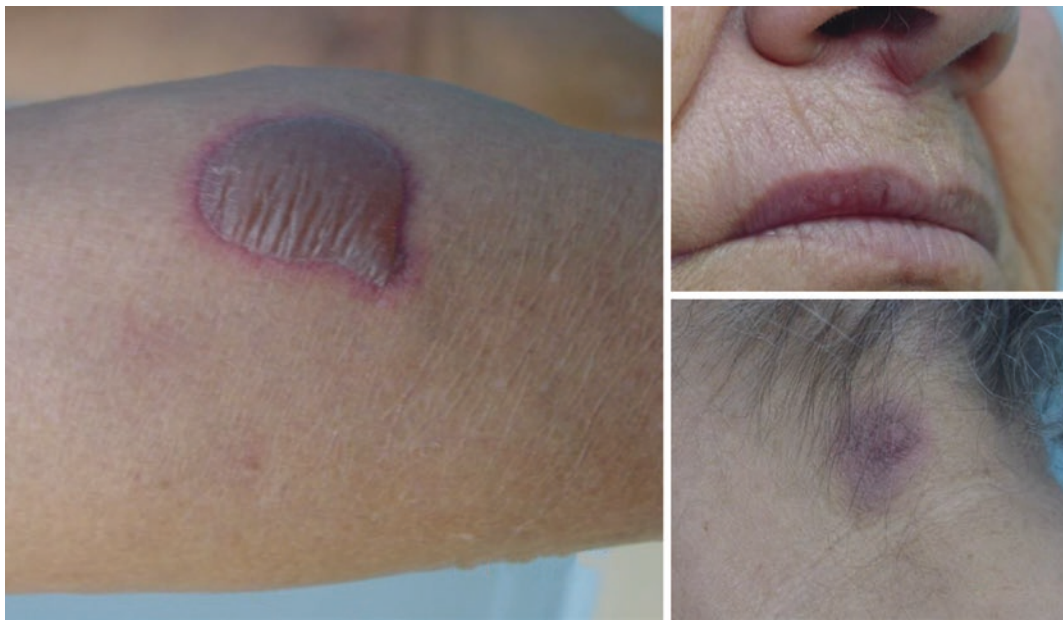

Fig. 26.21 Multiple lesions of fixed drug eruption in a patient taking a nonsteroidal anti-inflammatory drug

express FAS-FAS ligand in the epidermal basal layer to induce apoptosis of keratinocytes. On the other hand, transient intraepidermal migration of $CD4^+$ T cells is capable of releasing a downregulation profile of IL-10, inducing suppression of the flare-up reaction in FDE.

Many drugs have been found to cause FDE, with common offenders including sulfonamides, NSAIDs (e.g., ibuprofen), allopurinol, barbiturates, hydroxyzine, laxatives, tetracycline, phenolphthalein, and feprazone. Usually there is only one causative drug (monosensitivity), although sometimes several drugs can induce FDEs in the same patient (multisensitivity). The most common multisensitivity is the cross-reaction between chemically related drugs such as tetracyclines. Less frequently, multisensitivity can occur because of polysensitivity, whereby two or more chemically unrelated drugs either induce the identical FDE lesion or each drug determine flare-ups in separate lesions.

Treatment is mainly symptomatic with discontinuation of offending agent, topical corticosteroids, and antihistamines.

Acneiform Eruptions [49, 52]

This kind of ADR produces lesions resembling acne vulgaris, but unlike acne vulgaris, drug-induced acneiform eruptions typically are not associated with the presence of comedones (blackheads and whiteheads). Acneiform drug eruptions appear as erythematous papules or erythematous pustules on the face and trunk (Fig. 26.22) and proximal extremities, but sometimes can be present on the forearms and legs, an unusual site in acne vulgaris. The most relevant hallmark is the monomorphous pattern of this eruption and the resolution without scarring. Drug-induced acneiform eruptions represent only 1% of drug eruptions.

Several medications are related to flare-ups of drug-induced acneiform eruptions, the most strongly associated being lithium, androgens, oral contraceptives, corticosteroids, vitamin B complex, and nowadays epidermal growth receptor (EGFR) inhibitors for chemotherapy. Iodine, bromide, isoniazid, actinomycin D, and phenytoin have also been associated. In the last decade, the use of supplementary complexes by bodybuilders, such as milk and whey protein-based products, have been reported as being involved in acneiform eruptions. This is an effect caused by elevations of postprandial insulin and basal insulin-like growth factor I plasma levels.

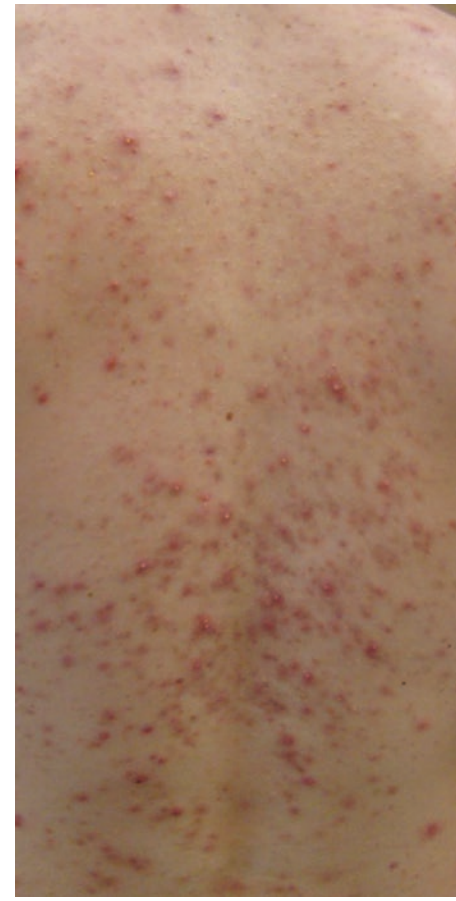

Fig. 26.22 Acneiform eruption resulting from the combination of intramuscular injectable vitamin B complex and betamethasone for orthopedic pain

Treatment involves discontinuing the use of the offending drug, except in the case of EGFR inhibitors, when discontinuation may not be possible. Benzoyl peroxide, topical retinoids, and topical or oral antibiotics, such as doxycycline, can be used to treat the reaction, similar to the treatment of acne vulgaris.

Lichenoid Eruptions [49, 53]

Drug-induced lichenoid eruptions are uncommon ADRs that appear similar or even identical to lichen planus, with shiny violaceous polygonal papules and plaques (Fig. 26.23). Drug-induced lichenoid eruptions can present virtually anywhere on the body surface, but certain clues in the distribution can help suggest drug eruption over lichen planus. Drug-induced lichenoid eruptions tend to be absent from the flexor surface of the wrists, genitals, and mucous membranes, whereas these locations are often involved in common lichen planus. Lichen planus drug eruptions also often favor sun-exposed areas of the body.

Several drugs have been reported to be related to drug-induced lichenoid eruptions: gold salts, antimalarials, methyldopa, NSAIDs, penicillamines, lithium, sulfonylureas, phenylenediamine derivatives, thiazide diuretics, β-blockers, omeprazole, and pantoprazole. The time from initiation of the drug to onset of lichenoid drug eruption varies greatly depending on the causative medication. Reactions caused by naproxen, for example, tend to occur approximately 10 days after administration. By contrast, certain drugs such as lithium, methyldopa, and acebutolol can develop lichenoid eruptions several years later. HIV infection can contribute to lichenoid drug eruptions on photoexposed areas of the body.

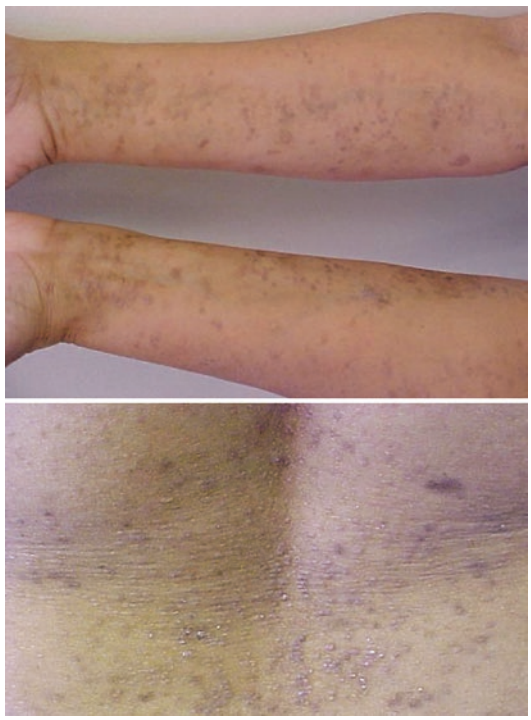

Fig. 26.23 Lichenoid drug eruption

Treatment typically is symptomatic, with topical corticosteroids a mainstay. Once discontinuation of the medication has been accomplished, the eruption resolves spontaneously after a period of a few weeks or months.

Photosensitivity Reactions [54–56]

Acute photosensitivity ranges from common polymorphous light eruptions to phototoxicity, or rare photoallergies. Photosensitivity refers to reactions that occur when a photosensitizing agent (chromophore substance) in or on the skin reacts with ultraviolet (UV) radiation, often in doses smaller than those associated with sunburn. Up to 8% of cutaneous drug reactions are photosensitivity eruptions. Typically, a photosensitivity reaction occurs within hours to days of exposure to sunlight and may last for up to 1 week or more.

More frequent reactions are named "phototoxic reactions," in which skin signs resemble moderate to severe sunburn, with erythema, blistering, weeping, and desquamation. Photoallergic reactions resemble eczematous lesions, often in subacute or chronic presentation. Phototoxic and photoallergic reactions occur in sun-exposed areas of the skin; however, widespread eruptions can occur, which may suggest a systemic photosensitizing agent (photoallergy).

These reactions are dose related and are most commonly seen in patients who have been exposed to high doses of both the drug and UV radiation. One's susceptibility to this type of syndrome is variable and likely based on drug absorption and metabolism, as well as the amount of melanin in the skin.

Piroxicam, fluoroquinolone antibiotics, tricyclic antidepressants, and NSAIDs are classes

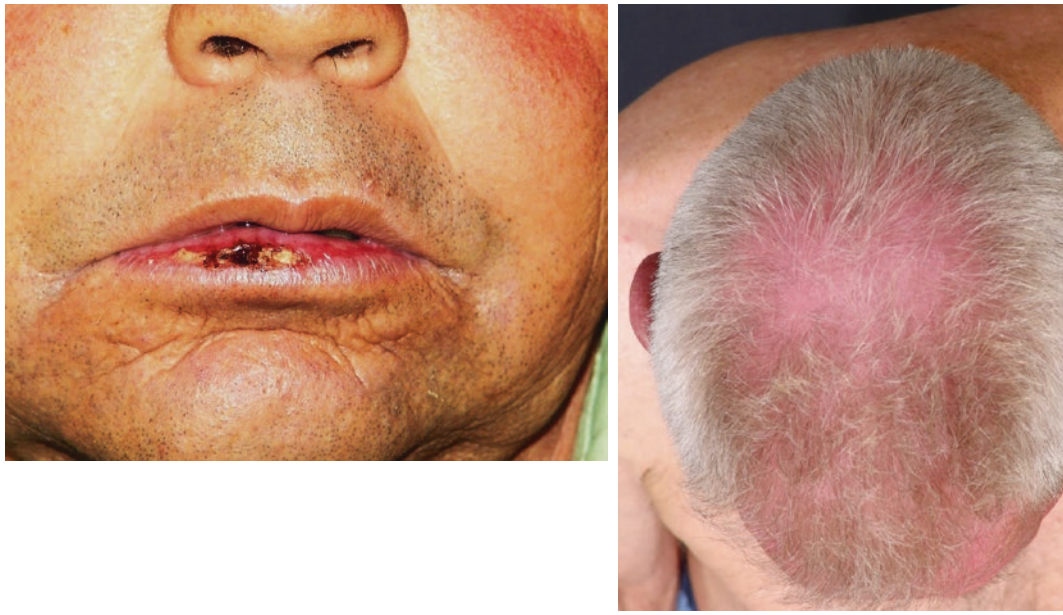

Fig. 26.24 Photosensitivity due to voriconazole causing severe cheilitis

of drugs that have been reported to be frequent photosensitizers, with fluoroquinolones being the most potent. Other antibiotics, such as TMP-SMX and tetracyclines, have also been implicated. Recently voriconazole, a third generation of azole antifungal agents, has been reported as a photosensitivity agent, especially in phototoxic reactions (Fig. 26.24), in 8% of outpatients treated, besides increasing the potential of nonmelanoma skin cancer (particularly squamous cell carcinomas) arising from potential photocarcinogenesis related to voriconazole.

Phototoxic reactions are the most common dermatologic adverse effect of amiodarone therapy, affecting 25–75% of patients on long-term treatment. Photoallergy is considerably less likely to occur, but the risk also increases with prolongation of the therapy. Skin changes usually occur after at least 4 months of therapy and with the minimal cumulative dose, which is 40 g.

Management of photosensitivity reactions includes limiting exposure to sunlight, using potent sunscreen, and wearing protective clothing. Oral and topical corticosteroids agents may be employed in the treatment.

Drug-Induced Coma Blisters [57, 58]

Coma blisters are uncommon skin eruptions seen in patients with impaired consciousness. The original case was described in a patient who was heavily sedated because of barbiturate intoxication. Subsequently anticonvulsants have been reported, including certain benzodiazepines such as clobazam (Fig. 26.25), and valproic acid and amitriptyline overdose. There were a few reports of coma blisters and peripheral neuropathy caused by amitriptyline overdose. These blisters are most often seen in pressure areas, particularly over bony prominences in contact with hospital beds.

The hallmark histologic feature that defines coma blisters is eccrine gland necrosis in the skin. Differential diagnosis with bullous pemphigoid is obtained with a negative direct immunofluorescence biopsy of the skin. Until recently, coma blisters were thought to be a self-limiting process that did not require withdrawal of the offending agent. However, in some patients the eruption resolves only upon withdrawal of the drugs.

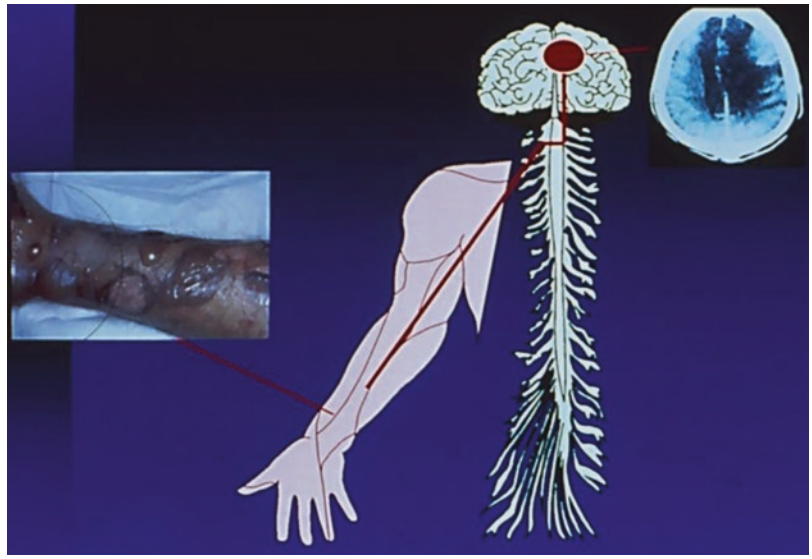

Fig. 26.25 Coma blisters in forearm of a patient with stroke under medication with barbiturates

Drug-Induced Erythema Nodosum [59]

Erythema nodosum is a skin reaction manifested by tender or painful erythematous subcutaneous nodules, located usually on the extensor aspects of the lower extremities. Histologically it is a septal panniculitis without vasculitis. Several conditions can be induce and act as an antigenic stimuli, including drugs, benign and malignant systemic diseases, leprosy, and bacterial (e.g., tuberculosis) and fungal infections. Frequently the cause is unknown.

Drugs that may cause erythema nodosum are antimicrobial agents (amoxicillin, penicillin, sulfonamides), bromide, iodine, gold salts, analgesics and antipyretics (including paracetamol), carbimazole, isotretinoin, azathioprine, vemurafenib, GM-CSF, oral contraceptives (estrogens/progesterones), and estrogens. Erythema nodosum disappears within a couple of weeks after withdrawal of the causative drug.

Drug-Induced or Exacerbating Psoriasis [57, 60]

Drug-induced psoriasis is well documented. Such eruptions may occur in patients with pre-existing psoriasis (exacerbation phenomenon) or those without a personal or family history. Lesions typically improve with drug withdrawal, although persistent disease is possible. More frequent drugs involved are β-blockers, lithium, antimalarials, NSAIDs, anti-TNFα agents (Fig. 26.26), and bupropion.

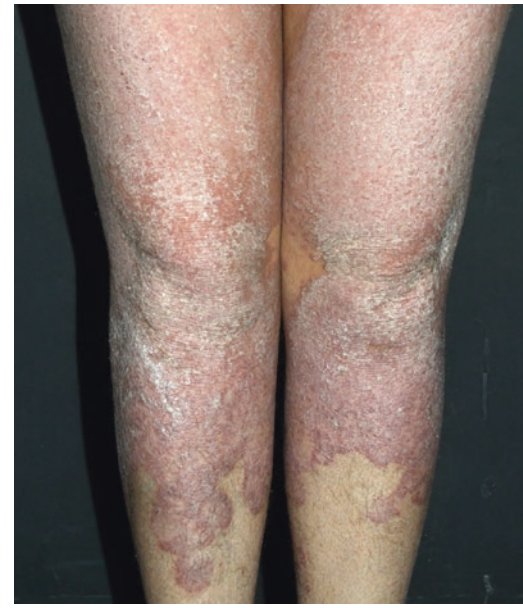

Fig. 26.26 Psoriasis exacerbation after using anti-TNF-α agents

Exacerbation of psoriasis caused by the following medications has also been observed: adrenergic antagonists, IFN, gemfibrozil, iodine, digoxin, and clonidine.

Symmetric Drug-Related Intertriginous and Flexural Exanthema [61]

In individuals previously sensitized to an allergen through contact, systemic exposure results in the development of a condition classically termed systemic contact dermatitis. One of the most common manifestations of this condition is so-called baboon syndrome (BS).

A subsequent study by Hausermann et al. [62] examined a series of 100 cases of BS and found that about half of the patients exhibited no evidence of prior skin sensitization. For that group the authors proposed the term "symmetric drug-related intertriginous and flexural exanthema" (SDRIFE) to describe a peculiar form of drug rash with symptoms similar to those of true BS.

BS is historically often equated with a mercury-induced exanthem in patients with previous contact sensitization. SDRIFE specifically refers to the typical clinical pattern of this drug eruption, and the following diagnostic criteria are proposed [62]: (1) exposure to a systemically administered drug either at the first or repeated dose (excluding contact allergens); (2) sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area; (3) involvement of at least one other intertriginous/flexural localization (Fig. 26.27); (4) symmetry of affected areas; and (5) absence of systemic symptoms and signs.

Several drugs are reported to induce SDRIFE [63]: (i) β-lactam antibiotics (amoxicillin, ampicillin, amoxicillin/clavulanic acid, pivampicillin, penicillin V, ceftriaxone, cefuroxime, cephalexin) and non-β-lactam antibiotics (including clindamycin, roxithromycin); (ii) corticosteroids: deflazacort; (iii) radiocontrast barium; (iv) other drugs: sulfate iomeprol, iopromide, monoclonal antibodies (cetuximab, glembatumumab), vedotin (CR011, vcMMAE), psychopharmaceuticals (risperidone loflazepate ethyl), allopurinol, cimetidine hydroxyurea, heparin (intravenous), IVIG, mitomycin C, naproxen, oxycodone, pseudoephedrine, salsalate, terbinafine, and valacyclovir.

Nicolau Syndrome or Embolia Cutis Medicamentosa (ECM) [64, 65]

In 1924, Freudenthal described full-thickness dermal necrosis associated with intramuscular injection of oily bismuth suspension, which was

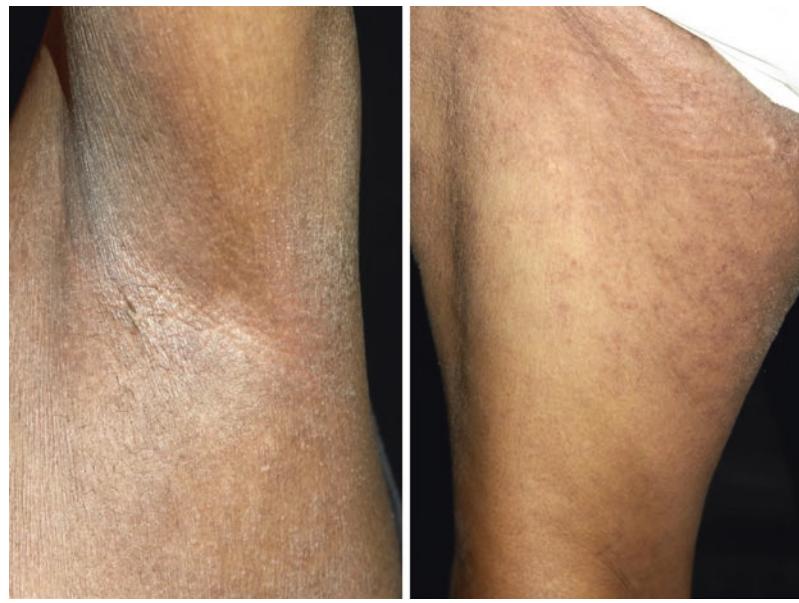

Fig. 26.27 Symmetric drug-related intertriginous and flexural exanthema (axillae and groin)

used to treat syphilis at that time. He described the histologic appearance of these suspended particles deep within the cutaneous arteries, distant from the injection site. This condition was also described by Nicolau the following year, and the syndrome more often bears his name despite Freudenthal's precedence in the literature.

Nicolau syndrome is an iatrogenic syndrome caused by intramuscular injection leading to variable degrees of tissue necrosis, with variable severity, including the skin and deeper tissues. Intense pain in the immediate postinjection period and purplish discoloration of the overlying skin, with or without a reticulate pattern (livedo racemosa-like pattern), is highly characteristic of this syndrome. Intramuscular, subcutaneous, intravenous, and intra-articular injections have been reported to produce this syndrome. The skin necrosis resolves with severe and disfiguring scarring. It is therefore important that dermatologists and cutaneous surgeons are aware of this agonizing and deforming iatrogenic complication of injections.

Discoloration of the skin may result in necrosis and ulceration, which might involve the subcutaneous tissue and the muscular layer. Paralysis of the lower extremities has been reported and attributed to embolization of the medication, mainly resulting from the force of injection from the gluteal vessels into the internal iliac arteries, and ischemia of sciatic nerve. Application of cold devices or compress tends to aggravate the tissue injury and necrosis.

Several drugs are related to ECM: (i) intramuscular injections (vitamin K, NSAIDs, hydroxyzine, vaccination, bismuth, benzathine penicillin, penicillin G); (ii) intravenous injections (polidocanol 1%); (iii) subacromial injection (triamcinolone acetate); (iv) subcutaneous injection: pegylated IFN-α, glatiramer acetate; and (v) intra-articular: glucocorticoid.

Aspirating just before injecting has been suggested as a method of preventing Nicolau syndrome, as it is thought to help prevent embolism caused by intra-arterial deposition of medication. However, it is doubtful as to whether Nicolau syndrome can be prevented by this method, as the spasm of the vessel or vasocompressive effect in Nicolau syndrome is usually difficult to recognize.

The essential difference between those cases of ECM and the pathophysiology seen with vascular obstruction by dermal fillers (hyaluronic acid, polymethylmethacrylate microspheres) is that the former often involves inflammatory pathways being activated by the injected material, whereas the latter typically involves a more purely mechanical vascular obstruction (although some dermal fillers may promote blood clotting, hyaluronic acid-based dermal fillers by design are minimally reactive in tissues). The phenomena are similar in that the inciting event is accidental intravascular injection, followed by some degree of intravascular transport, finally resulting in distal vascular obstruction, ischemia, and so forth, such that the ultimate clinical presentation is the same.

Diagnosis is mainly clinical; cutaneous biopsy reveals necrotic changes caused by ischemia. Ultrasonography study of the skin and magnetic resonance imaging help in delineating the extent of damage. Prompt treatment has been reported to avert necrosis of the skin. In the immediate post-event period, treatment is based on various approaches to improve blood supply such as pentoxyphylline, hyperbaric oxygen, intravenous alprostadil, and thrombolysis with heparin. Intralesional corticosteroid has also been used to reduce inflammation. Surgical debridement of the necrotic scar is of utmost importance as it reduces infection and enhances wound healing.

Drug-Induced Linear IgA Bullous Dermatosis (LABD) [49, 66]

LABD often presents a singularity in its presentation. It has been reported that almost two-thirds of LABD cases may be drug induced, although this is rare in children, in whom LABD behaves as an idiopathic autoimmune blistering disease.

The clinical picture consists of an acute development of vesicles and bullous lesions often on sites of noninflamed skin. Typically, new lesions develop around previous lesions forming rosette-like plaques, widely distributed on the face, trunk, and extremities, especially around the perioral and genital areas. Mucosal involvement in drug-induced LABD is less common than in

the autoimmune form. The most commonly used medication associated with this kind of ADR is vancomycin; however, other drugs include amiodarone, atorvastatin, captopril, ceftriaxone, diclofenac, furosemide, lithium, metronidazole, penicillin, phenytoin, piroxicam, rifampin, and trimethoprim-sulfamethoxazole.

Treatment of drug-induced LABD includes discontinuation of the causative agent and treatment with topical or systemic steroids, dapsone, and/or nonsteroidal systemic immunosuppressive agents.

Drug-Induced Bullous Pemphigoid [49]

This entity is very similar to the autoimmune form. Multiple tense bullous lesions appear on the skin and pruritus is a common symptom. Often the medications associated with drug-induced bullous pemphigoid include furosemide, ACE inhibitors (especially captopril and enalapril), penicillin, ampicillin, chloroquine, psoralen-UVA treatment, and sulfasalazine.

Treatment is aimed at discontinuation of the offending drug as well as topical or systemic corticosteroids and steroid-sparing immunosuppressive drugs as indicated.

Drug-Induced Pemphigus [49]

Similar other drug-induced reactions related to counterpart autoimmune conditions, drug-induced pemphigus most closely resembles pemphigus foliaceus, with flaccid vesicles or bullae that rupture, creating crusted or desquamated erosions, with mucous membranes often spared.

The histologic hallmark of this drug-induced eruption is the acantholysis of epidermal cells, but this phenomenon is not a pathognomonic sign of this type of ADR. Both autoimmune (idiopathic) and drug-induced pemphigus have a positive Nikolsky sign, as observed in the SJS/TEN spectrum, although SJS/TEN does not demonstrate acantholysis in the skin biopsy.

Drugs containing thiol molecules (penicillamine, thiopurine, pyritinol, gold sodium thiomalate, captopril) are responsible for 80% of the cases, and other drugs implicated include levodopa, penicillin, phenobarbital, piroxicam, propranolol, and rifampicin. Drug-induced pemphigus can occur any time within the first year of initiation of one of the offending drugs. Treatment generally consists of withdrawal of the drug and use of systemic corticosteroids.

Adverse Mucocutaneous Reactions to Chemotherapeutic Drugs [44, 67–70]

The skin, mucous membranes, annexes (sebaceous and sudoriferous glands), and the phaneros (hair and nails) are tissues with rapid cellular proliferation and are thus susceptible to adverse reactions (toxic or hypersensitive) resulting from systemic chemotherapeutic treatment.

Antineoplastic agents are defined as substances that inhibit or prevent the proliferation of neoplasms. Because of their high metabolic rate, the skin, mucous membranes, and annexes are the most important target organs of the toxicity associated with chemotherapy. Reactions can present with disseminated exanthematous eruptions, nonspecifically, or as distinct cutaneous lesions. Some drugs can trigger localized reactions caused by extravasation to tissues adjacent to the areas of application.

Exanthematous reactions, such as nonspecific erythema multiforme, are more common, and many of them are attributed to hypersensitivity mechanisms. Certain local toxicity, such as alopecia, mucositis, nail alterations, or hand-foot syndrome, is more specific and less common, frequently associated with particular drugs or groups of drugs.

The identification of the reaction pattern associated with the trigger drug and of the possible dose-limiting toxicity is of extreme importance to the physician, as is the differential diagnosis with infectious processes and specific manifestations of the neoplasm.

Alterations of the Phaneros and Cutaneous Annexes [44, 67–70]

Alopecia [44, 67–70]

Alopecia is the most common adverse skin manifestation of chemotherapeutic treatment. There are two types of drug-induced alopecia: the anagen effluvium and the telogen effluvium. In the anagen effluvium hair loss occurs because of the sudden interruption of the mitotic activity of the hair matrix, 1–2 weeks after the start of chemotherapy, leading to lack of hair production or its thinning (Pohl–Pinkus constrictions). The weakening of the hair shaft in this context predisposes the hair to breakage and shedding during the act of combing. They involve the hair, eyebrows, beard, axillary hair, and pubic hair. It is dose-dependent and reversible. New hairs often grow back with a different color and texture. In the telogen effluvium, hairs move prematurely to a resting phase with subsequent loss of normal hair.

The antineoplastic agents that most frequently cause the anagen effluvium lead to diffuse hair loss, of sudden onset, from 7 to 10 days after the start of chemotherapy. Hair loss becomes more pronounced about 1–2 months after the start of treatment. Even though hair loss is intense, about 10% of the pilous follicles are usually in a resting phase at the time of the administration of the drug, and this determines incomplete hair loss. With repeated treatment cycles, alopecia totalis may occur. This type of effluvium is generally reversible when treatment is suspended, and occasionally permanent with the use of cyclophosphamide and busulfan. Hair grows around 1 cm per month, possibly showing new texture and color. The chemotherapeutic drugs more often associated with alopecia when used in isolation are: (i) complete alopecia (cyclophosphamide at high dose, doxorubicin, docetaxel, dactinomycin, irinotecan, topotecan, bleomycin, paclitaxel); (ii) incomplete alopecia (etoposide, ifosfamide, mitomycin C, 5-fluorouracil, melphalan, mitoxantrone, gemcitabine, vinca alkaloids).

Most reactions can be reversed by dose reduction or by increasing the interval between doses. Some toxic effects can be successfully treated or prevented. Medication administered before the chemotherapeutic treatment can prevent hypersensitivity reactions. The use of oral antiseptic solutions is useful in the control of mucositis.

Some dermatologic reactions to new antineoplastic agents, such as EGFR inhibitors, have been associated with anticancer efficacy.

Other adverse effects may be mistaken for reactions to chemotherapeutic drugs and include infections resulting from immunosuppression, paraneoplastic syndromes, GVHD, nutritional deficiencies, development of skin malignancies, and metastatic primitive tumor.

There are several classifications of reactions to antineoplastic drugs. The lack of a systematized multidisciplinary approach does not provide all the microscopic data and physiopathogenic mechanisms that delineate the lesions. Therefore, the classification adopted didactically groups with the eruptions based on the target cells and mechanism of action of the drugs.

Preventive measures to limit hair loss have had limited success. Hypothermia of the hair scalp or tourniquets applied in this region may reduce the perfusion of the drug in the pilous follicles and delay the start of or minimize hair loss. This procedure is contraindicated for patients with hematologic neoplasms such as leukemias, lymphomas, and other potentially metastatic tumors of the hair scalp. Topical minoxidil is not effective in the prevention of drug-induced alopecia, but may shorten its duration.

Trichomegaly and Hair Curling [44, 67–70]

Hair alterations with acceleration of growth and shaft changes are observed with the use EGFR inhibitors (Fig. 26.28).

Ungual, Subungual, and Periungual Alterations [44, 67–70]

Nail alterations can present with a reduction of the nail growth speed, fragility, lines of discoloration (Mees' lines), transversal depressions (Beau's lines), hyperpigmentation, onycholysis with subungual aseptic abscesses, photo-onycholysis, paronychia, and pyogenic granulomas of the periungual folds. Nearly all antineoplastic agents

Fig. 26.28 Blepharitis and trichomegaly caused by cetuximab (image under dermoscopy, ×10)

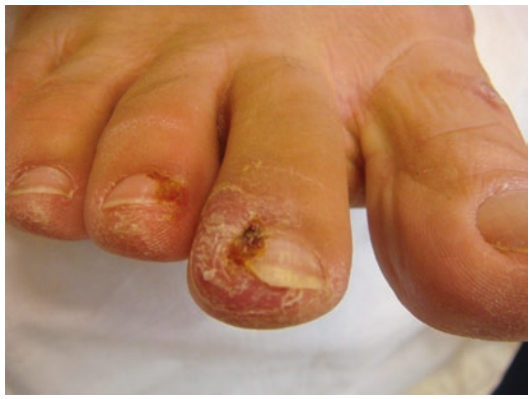

Fig. 26.29 Ingrown nail and pyogenic granuloma in a patient using erlotinib

can lead to reduction of growth speed, nail fragility, Mees' lines, and Beau's lines.

Hyperpigmentation can occur after the use of cyclophosphamide, hydroxyurea, fluoropyrimidines such as 5-fluorouracil, and especially anthracyclines such as doxorubicin and daunorubicin. Painful onychomycosis and subungual abscesses are due to the use of taxanes (docetaxel/paclitaxel) and anthracyclines (doxorubicin).

Ingrown nails, paronychia, and pyogenic granuloma are associated with the use of tyrosine kinase inhibitors of EGFR (Fig. 26.29), such as erlotinib and gefitinib. The fenestration or avulsion of the lamina should be considered when abscesses that involve more than 50% of the nail bed are present. In these more severe cases, the temporary suspension of treatment, longer intervals between cycles, and dose reduction should be considered.

Neutrophilic Eccrine Hidradenitis [44, 67–70]

This rare, nonspecific disease often occurs when chemotherapeutic drugs are used in combination, making it difficult to know which drugs are responsible for causing the disease.

Cytarabine is the most commonly cited drug; however, others are also implicated, such as bleomycin, chlorambucil, cyclophosphamide, cytarabine, doxorubicin, lomustine, mitoxantrone, busulfan, carmustine, cisplatin, cyclophosphamide, etoposide, 5-fluorouracil, methotrexate, and thiotepa. Some authors consider neutrophilic eccrine hidradenitis (NEH) as a paraneoplastic phenomenon, since it has been found in an early case of acute myeloid leukemia not yet treated. It has been associated with HIV infection, *Nocardia*, *Serratia*, *Enterobacter*, *Staphylococcus*, and with patients receiving GM-CSF. The mechanism is unknown, but may be due to the excretion of the chemotherapeutic drug by the eccrine glands and its direct toxic effect on the eccrine epithelium.

The clinical condition may be preceded by fever and unspecific clinical signs. Skin eruptions are distributed in the head, neck, trunk, and extremities, with lesions that vary from erythema, papules, nodules, and pustules to papular plaques. Lesions may be purpuric or hyperchromic, single or multiple. They appear between 2 days and 3 weeks from the start of treatment, regressing spontaneously without scarring or sequelae 1–4 weeks after the suspension of the drug.

The differential diagnosis is vast and includes sepsis, septic embolism in a post-chemotherapeutic neutropenic patient, vasculitis, leukemia cutis, hypersensitivity reaction, urticaria, polymorphous erythema, and neutrophilic dermatoses such as Sweet's syndrome, bullous pyoderma gangrenosum, and atypical pyoderma gangrenosum.

Owing to the unspecific clinical presentation of the disease and the great number of differential diagnoses, some authors suggest that NEH be included in the diagnostic hypotheses of any

eruption that may occur in patients undergoing chemotherapy, and its final diagnosis is established by histopathology. Therefore, histopathology is essential for conclusive diagnosis. It is constituted by a dense neutrophilic infiltrate, inside and around the eccrine glands, with necrosis of the eccrine epithelium cells. Involvement of the apocrine glands has been reported. Occasionally, squamous syringometaplasia, hemorrhage and edema of the dermis, spongiosis and/or vacuolization of the basal layer of the epidermis, necrosis of keratinocytes, and mucin deposits inside and around the eccrine glands may occur.

In patients with severe neutropenia, the neutrophilic infiltrate may be absent; however, necrosis of the eccrine epithelium is typical. NEH is a self-limiting adverse reaction. Frequently the process resolves within a month, without treatment. In other chemotherapy cycles, 60% of the patients may relapse. The efficacy of the prophylactic or therapeutic use of systemic corticosteroids, dapsone, or nonhormonal anti-inflammatories is still questionable.

Eccrine Squamous Syringometaplasia [44, 67–70]

Eccrine squamous syringometaplasia is an unusual adverse reaction to chemotherapeutic drugs. It can also be found in association with chronic ulcerations, skin tumors, exposure to toxic agents, and several inflammatory processes. Therefore, it is not a histopathologic reaction exclusive to the use of chemotherapeutic drugs. The mechanism of neutrophilic eccrine hidradenitis is unknown, but it can be the result of the excretion of the drug by the eccrine glands and its direct toxic effect on the eccrine epithelium. It is postulated that eccrine squamous syringometaplasia represents the final noninflammatory spectrum of adverse reactions to chemotherapeutic drugs in the eccrine glands.

Similarly to NEH, eccrine squamous syringometaplasia also has an unspecific clinical presentation, constituted by erythematous maculae, papules, and papular plaques or vesicles, localized or disseminated. Lesions develop between 2 and 39 days after the start of chemotherapy and improve spontaneously after 4 weeks.

The diagnosis is histopathologic, characterized by the presence of squamous metaplasia of the eccrine glands in the papillary dermis. Minimal and focal necrosis of the eccrine gland epithelium, fibroblastic proliferation, and edema of the periductal stroma may occur. Contrary to NEH, the neutrophilic infiltrate is minimal or absent. Squamous eccrine syringometaplasia has been described as an accidental histologic finding in other conditions not associated with chemotherapy.

Eccrine squamous syringometaplasia does not appear to be associated with a specific chemotherapy agent or malignancy. Numerous drugs have been related such as cytarabine, mitoxantrone, daunorubicin, cisplatin, 5-fluorouracil, doxorubicin, cyclophosphamide, etoposide, methotrexate, busulfan, melphalan, and carmustine.

Eccrine squamous syringometaplasia has been observed in association with palmoplantar erythrodysesthesia syndrome, in radiation-induced memory reactions, and in patients who underwent bone marrow transplantation and received high doses of chemotherapeutic drugs. The condition often spontaneously resolves.

Acral Erythema or Palmoplantar Erythrodysesthesia Syndrome [44, 67–70]

First described in 1974, this syndrome is also known as Burgdorf's syndrome, palmoplantar erythema, hand-foot syndrome, and toxic erythema of the palms and soles. It occurs more frequently in patients treated with cytarabine and, fluoropyrimidines, especially capecitabine, which is the oral 5-fluorouracil prodrug.

After alopecia and mucositis, it is the most common adverse reaction to chemotherapy. Other agents less frequently associated with palmoplantar erythrodysesthesia syndrome are cisplatin, cyclophosphamide, cytarabine, doxorubicin, daunorubicin, doxifluridine, etoposide, floxuridine, hydroxyurea, mercaptopurine, methotrexate, mitotane, paclitaxel, docetaxel, and vinorelbine.

It is estimated that this adverse reaction occurs in 6–64% of the patients treated with different chemotherapeutic regimens.

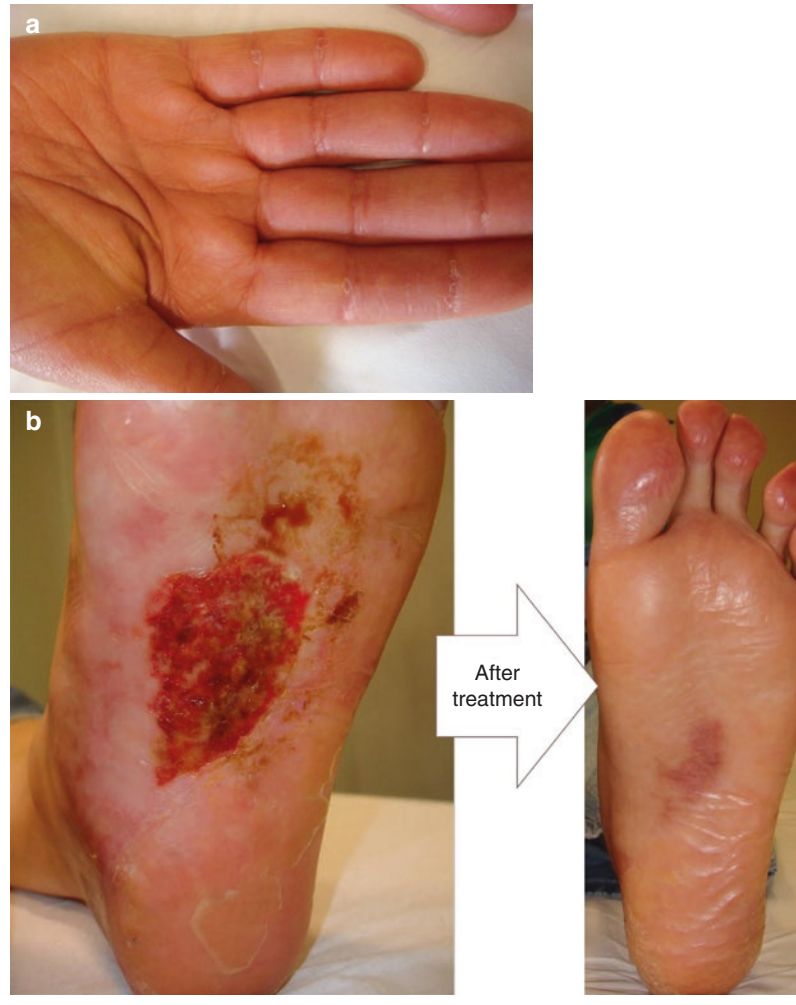

Fig. 26.30 (**a**) Palmoplantar erythrodysesthesia syndrome. (**b**) Palmoplantar erythrodysesthesia syndrome with plantar ulceration and the treatment result with topical dimethyl sulfoxide and an adopted large interval on doxorubicin treatment

Most patients show a prodrome of dysesthesia, with a tingling (pins and needles) sensation on the palms and soles. Within a few days the reaction evolves to a feeling of pain and burning with a well-demarcated edema and erythema. The erythema is symmetric and sometimes more pronounced on the soft parts of the distal phalanges. Hands are often more affected than feet (Fig. 26.30a). Some patients show light scaling with or without erythema. A bullous variant has been described (Fig. 26.30b), representing a more severe form of the reaction, specifically associated with cytarabine and methotrexate. Lesions are aggravated if the treatment is not suspended, and the associated pain and edema may limit the movement of fingers. When the drug is suspended, the reaction progressively improves within 2 weeks.

In some patients, when treatment is maintained despite the development of erythrodysesthesia syndrome, palmoplantar keratodermia may occur. The reaction occurs more frequently in patients who undergo oral or continuous infusional therapy with fluoropyrimidines (2–18%), as compared with those submitted to bolus therapy (0.4–3%).

It is thought that in the pathogenesis of the process the local accumulation of the drug leads to degeneration with necrosis of the sweat glands, because its microscopic aspects are similar to those of eccrine squamous syringometaplasia and neutrophilic eccrine hidradenitis.

In the differential diagnosis the following should be considered: polymorphous erythema, erythromelalgia, eccrine squamous syringometaplasia, and neutrophilic eccrine hidradenitis. The most relevant differential diagnosis is acute GVHD. The fundamental difference is that acute GVHD occurs in patients who have received a bone marrow transplant, in addition to extracutaneous involvement with gastrointestinal alterations (abdominal pain and diarrhea, elevation of hepatic enzymes). In cases of acute GVHD without extracutaneous manifestations, differentiation may be difficult.

Nevertheless, acute GVHD presents with diffuse erythema and can form papules, whereas palmoplantar erythrodysesthesia syndrome shows a well-demarcated erythema and edema. There are no relevant histopathologic differences between them, except for necrosis of the satellite cell in all layers of the epidermis (apoptotic keratinocytes adjacent to lymphocytes) in acute GVHD and sometimes presence of squamous syringometaplasia in palmoplantar erythrodysesthesia syndrome. The differentiation between these two disorders is essential because the use of cyclosporine is necessary to treat acute GVHD, but worsens the patient's pain if used in the treatment of palmoplantar erythrodysesthesia.

Apart from dose reduction, longer intervals between the cycles of chemotherapy and, as a last resort, the suspension of the drug, there is no specific treatment for palmoplantar erythrodysesthesia syndrome that has proved to be effective in a large series of cases. Some treatments have been suggested for small series of patients or case reports. General measures should be taken, such as reduction or suspension of the drug, longer intervals between chemotherapy cycles, dressings, elevation of the extremity, cold compresses, analgesic medication, and emollients.

As a specific treatment, pyridoxine can be used if 5-fluorouracil, liposomal doxorubicin, doxorubicin, docetaxel, and etoposide have been administered; hand cooling (docetaxel); oral corticosteroids (doxorubicin, 5-fluorouracil); strong topical corticosteroids (liposomal doxorubicin, cisplatin, and 5-fluorouracil); and topical dimethyl sulfoxide (DMSO) at 99% (liposomal doxorubicin). Symptoms can be relieved with lesion care to prevent infection and elevation of the limb to reduce the edema.

Cooling of hands and feet during treatment reduces the blood flow in these areas and may decrease the severity of the reaction. Strong topical corticosteroids have been used with mixed results when associated with emollients. Systemic corticosteroids are useful in some situations. Pyridoxine (vitamin B6) in doses of 200–300 mg/day can be useful to treat and prevent this reaction, except when cytarabine or vincristine is used. Topical DMSO at 99% four times a day for 14 days has cured some cases of palmoplantar erythrodysesthesia syndrome induced by pegylated liposomal doxorubicin.

Toxic Erythema Caused by Chemotherapeutic Drugs [44, 67–70]

Some authors prefer to associate toxic erythema caused by chemotherapy with clinical lesions that present with painful erythema, with or without edema, often affecting the hands and feet, intertriginous areas such as the axillary and inguinal regions, and less frequently the elbows, knees, and auricular pavilion. These eruptions may have a bullous component, are self-limited, and generally evolve with resolution and scaling associated with postinflammatory hyperpigmentation.

Many denominations used refer to histopathologic findings or those given by various authors on different occasions. Disorders such as eccrine squamous syringometaplasia, NEH, acral erythema, and palmoplantar erythrodysesthesia syndrome would be, according to these authors, grouped under toxic erythema caused by chemotherapeutic drugs.

The objective to group many disorders under the same denomination seeks to emphasize the superposition of clinical characteristics and promote an easy dialogue between medical specialties and with the patient.

The clinical characteristics of the toxic erythema associated with chemotherapy are: (1) maculae or erythematous and/or edematous plaques on the hands and feet, intertriginous areas, and less frequently on the elbows, knees,

and auricular pavilions, often appearing 2–3 days after the administration of the drug; (2) associated symptoms of pain (that may be debilitating), burning, paresthesia, pruritus, and/or hypersensitivity; (3) pale color, petechiae, and/or sterile blisters, followed by erosion in areas of intense erythema; (4) scaling and spontaneous resolution without specific treatment; and (5) chance of relapse if an equal or higher dose is administered.

Isolated papules may be found in the periphery of plaques. Papules and plaques may also be found in the head, cervical region, trunk, and extremities. Onset of lesions after 2–10 months can be observed.

The histologic characteristics observed are atypia (larger cells and nuclei and nuclear pleomorphism), apoptosis of keratinocytes, mitotic figures and bizarre mitotic configurations (astral mitosis), loss of polarity of the epidermal cells and apoptosis of keratinocytes, vacuolar degeneration of the basal layer of the epidermis, dermal edema, and eccrine squamous syringometaplasia. Moreover, necrosis of the upper epidermis, similar to the alterations observed in pellagra, may also occur. The inflammatory infiltrates are usually minimal despite their abundant clinical profile. From these observations, it has been suggested that erythema is secondary and results from damage to keratinocytes, leading to the release of cytokines and vasodilation.

Acneiform Eruption [44, 67–70]

Acneiform eruption is the adverse effect more often associated with the use of EGFR inhibitors. Onset occurs 1 week after the start of treatment with the EGFR inhibitor as a self-limiting eruption, dose-related, that affects the face, central region of the thorax, upper dorsum and, more rarely, limbs.

It presents with follicular erythematous papules, pustules with or without comedones, and scaling of the interfollicular skin (Fig. 26.31). Often an association with the following conditions is observed: acral asteatosis, paronychia with pyogenic granuloma, oral and nasal aphthous ulcerations, and hair alterations.

Palms and soles are often free of lesions. Excessive follicular hyperkeratosis leading to the obstruction of the ostium with formation of a follicular corneal plug, rupture of the glandular wall, and consequent inflammatory process are suggested as pathogenic mechanisms.

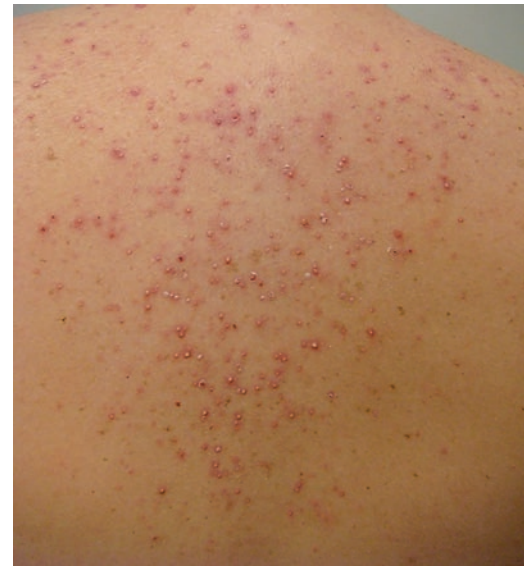

Fig. 26.31 Cetuximab-induced acneiform eruption on trunk

In the histopathologic examination a prominent corneal plug, with dilated infundibulum, with or without neutrophilic folliculitis, is observed. There is a positive correlation between the severity of the eruption and the tumoral response and survival. We emphasize the need for attention to the eruption to improve adherence to the chemotherapeutic treatment. The use of topical anti-acne agents and oral tetracyclines improve the condition. Topical emollients are indicated to treat xerosis.

Mucous Membrane Alterations [44, 67–70]

Stomatitis [44, 67–70]

Oral mucositis is the main dose-limiting reaction of most chemotherapeutic drugs. About 40% of the patients being treated show some type of oral complication. These complications are often associated with drugs that affect the synthesis of DNA. The main causative agents are antimetabolic drugs and antitumoral antibiotics.

The drugs more frequently associated with stomatitis are bleomycin, dactinomycin, methotrexate, topotecan, and 5-fluorouracil. Unusually, the stomatitis caused by 5-fluorouracil is related to its continuous infusional administration or to the use of its oral prodrug, capecitabine, and is less frequently observed when 5-fluorouracil is administrated in bolus. The main mechanism is the direct toxicity of the drug, but it can result secondarily from the indirect effects of the drug on the bone marrow. In patients with head and neck tumors, cisplatin used during radiotherapy acts as a strong radiosensitizer. In these cases there is more tumoral control but also greater severity of stomatitis caused by a boost in the direct effect of radiotherapy.

Since oral epithelium cells have a high mitotic index (renewal every 7–14 days), they become susceptible to the toxic effects of chemotherapeutic drugs. Moreover, there is atrophy of the oral mucosa, causing odynophagia, burning, xerostomia, and mucous membrane ulcerations. Ulcerations may be initially focal and then become diffuse and confluent, with occasional vesicles and blisters. These alterations are more common in the nonkeratinized mucosa and appear 4–7 days after use of the drug. Resolution of lesions may occur after treatment is suspended, often within 3–4 weeks.

Spontaneous or induced hemorrhage, especially gingival, may occur when the platelet count is below 10,000/mm^3. Patients at a higher risk of developing stomatitis are those with hematologic neoplasms, those who are under 20 years old (high mitotic activity of the epithelium), and patients with pre-existing oral disease and poor mouth hygiene.

Preventive measures include proper maintenance of oral hygiene by washing the mouth with water, saline solution, sodium bicarbonate, or hydrogen peroxide. The use of cold water to prevent mucositis induced by 5-fluorouracil and melphalan in high doses appears to be helpful. Other alternative clinical procedures, still not fully proven, consist in the use of chlorhexidine gluconate, β-carotene, and benzydamine chlorhydrate or sucralfate.

Treatment essentially consists of support with oral care, using agents such as magnesium or aluminum hydroxide and vitamin E. In addition, pain-relief drugs such as paracetamol and opioids (codeine and morphine) may be necessary when the use of topical anesthetics such as benzocaine and lidocaine are not effective. Additional complications occur because of secondary bacterial, viral, or fungal infections that may become systemic.

Palifermin, when used prophylactically, reduces the occurrence and duration of severe stomatitis in patients with hematologic tumors and submitted to bone marrow transplantation. Palifermin is a human recombinant factor of keratinocyte growth and protects various epithelial tissues. It acts not only on stomatitis but also on mucositis in general. A possible tumoral stimulating factor still limits its use in patients with epithelial tumors.

Scrotum Ulcer After Intraperitoneal Hyperthermic Chemotherapy with Mitomycin C [71–73]

Peritoneal carcinomatosis frequently signals the terminal stage in some cancers of gastrointestinal and gynecologic origins. Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy was introduced in the early 1990s and has become the mainstay of treatment in particular clinical settings for patients with peritoneal carcinomatoses, especially in pseudomyxoma peritonei, significantly improving overall survival rates.

There are four case reports of this recently described entity using a new procedure to treat peritoneal carcinomatosis after intraperitoneal hyperthermic chemotherapy with mitomycin C. One of them was described [71] in a male patient after 9 days of the procedure. The patient developed pain and scrotal necrosis on the anterior aspect of the scrotum (Fig. 26.32).

Two possible causes of the scrotal ulcers were proposed. (i) A patent processus vaginalis, allowing mitomycin C to become sequestered in the scrotum, inducing an inflammatory reaction, resulting in scrotal wall inflammation and subsequent ulceration (Fig. 26.33). This was proposed since previous studies have shown that intradermal

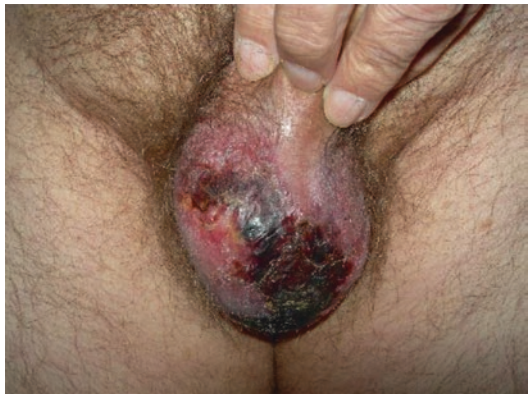

Fig. 26.32 Scrotal necrosis on anterior aspect of scrotum caused by intraperitoneal hyperthermic chemotherapy with mitomycin C

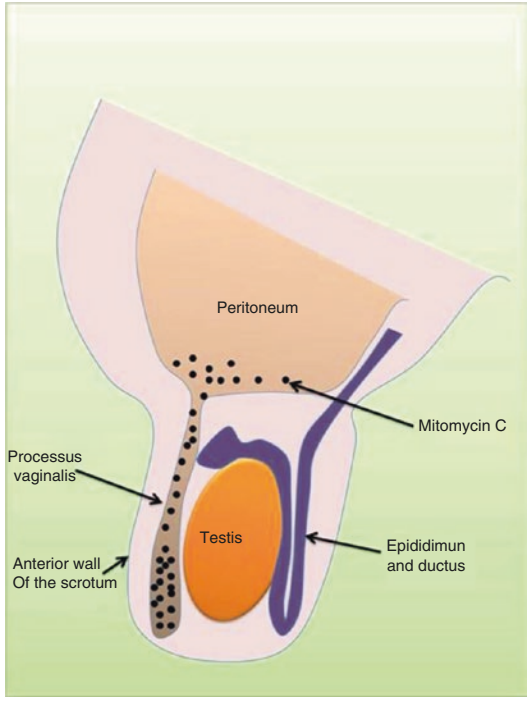

Fig. 26.33 Probable mechanism of mitomycin C deposition in a patent processus vaginalis into the scrotum

administration of mitomycin C inhibits wound healing and induces skin necrosis. (ii) Local spillage of mitomycin C onto the scrotal skin, with resulting inflammation and ulceration.

Previous studies with patients on continuous ambulatory peritoneal dialysis (CAPD) have shown that 10% of CAPD patients developed genital swelling [3]. A possible cause of the scrotal swelling is a patent processus vaginalis causing a communicating hydrocele, which can be found in 15–37% of adult men and may not be clinically evident until CAPD has begun.

Patients may develop this complication months after the surgery; hence, any complaint of scrotal pain or discomfort in these patients should warrant immediate investigation and attention, even if the complaints present much later.

Our group suggests that an image investigation, such as computed tomographic peritoneography, should be considered for male patients prior to intraperitoneal chemotherapy, since this complication is potentially serious for the patient.

Vascular Conditions Associated with Chemotherapy [74]

Vasomotor Changes [74]

Various vascular alterations have been described, probably as a result of a direct effect on arterial smooth muscle fibers or by acting on the autonomic nervous system.

Manifestations may include blood vessel spasms with livedo, Raynaud's phenomenon, and distal necroses, which may be triggered by bleomycin and cisplatin. Vasodilatation with erythema and flushing may result from the use of bleomycin, cisplatin, asparaginase, dacarbazine, taxanes, 5-fluorouracil, doxorubicin, cyclophosphamide, gefitinib, and carmustine.

Flushing [74]

Flushing consists of a temporary erythema of the face, neck, upper chest, ears, or upper abdomen. The mechanism responsible for flushing is a transitory vasodilation mediated by the autonomic nervous system or by the direct effect of circulating substances that act on the musculature of the vessel walls.

The nerves of the autonomic nervous system also control the sweat glands so that flushing mediated by these nerves is known as "wet flushing," whereas when the substance acts directly on the vascular wall muscles it is known as "dry flushing." Derivatives of biological agents

such as L-asparaginase and bleomycin are notorious for causing flushing, which occurs soon after infusion. Irinotecan, a topoisomerase I inhibitor, causes dysautonomia, the symptoms of which include diarrhea, bradycardia, and flushing.

Hormonal agents such as antiestrogens (tamoxifen, anastrozole), LHRH analogs (leuprolide), and antiandrogens (flutamide and diethylstilbestrol) may result in flushing. Other agents that also deserve mention include 5-fluorouracil, carboplatin, cisplatin, cyclophosphamide, dacarbazine, doxorubicin, etoposide, and methotrexate.

Interactions with Radiation [74]

Interaction with UV Light [74]

Eruptions resulting from photosensitivity are caused by various agents, principally following exposure to UV radiation. Phototoxicity caused by dacarbazine, fluoropyrimidines (systemic 5-fluorouracil, topical 5-fluorouracil, tegafur, and capecitabine) and vinblastine has been well documented.

Phototoxicity caused by dactinomycin, doxorubicin, hydroxyurea, procarbazine, brequinar sodium, mitomycin, 6-thioguanine, and flutamide, as well as by the porphyrin compounds that are used in photodynamic therapy, is uncommon.

Reactivation of sunburn is a well-documented adverse effect following the use of methotrexate. It occurs when the drug is administered 1–3 days after exposure to UV radiation, when the erythema from the previous exposure has been in the process of disappearing. Leucovorin does not prevent this reaction.

Phototoxic reactions resemble intense sunburn in areas of the skin that are exposed to light, with erythema, edema, pain, or pruritus. Blisters may be present and desquamation may occur in severe cases. Residual hyperpigmentation may persist for months.

Hydroxyurea has been described as being associated with development of dermatomyositis-like eruption due to photosensitivity (Fig. 26.34) [74, 75].

Hydroxyurea is an anticancer agent that inhibits its DNA synthesis through its action on the enzyme ribonucleotide reductase [75]. It is used in chronic myeloproliferative diseases such as polycythemia vera, chronic myeloid leukemia, and essential thrombocytosis, although it has also been prescribed to patients with refractory psoriasis [75]. Patients on long-term therapy with hydroxyurea can develop various side effects, including a wide variety of mucocutaneous manifestations, which appear in 10–35% of patients [75]. The most common skin changes are facial erythema, hyperpigmentation, xerosis, alopecia, skin atrophy, melanonychia, and ulcers on the

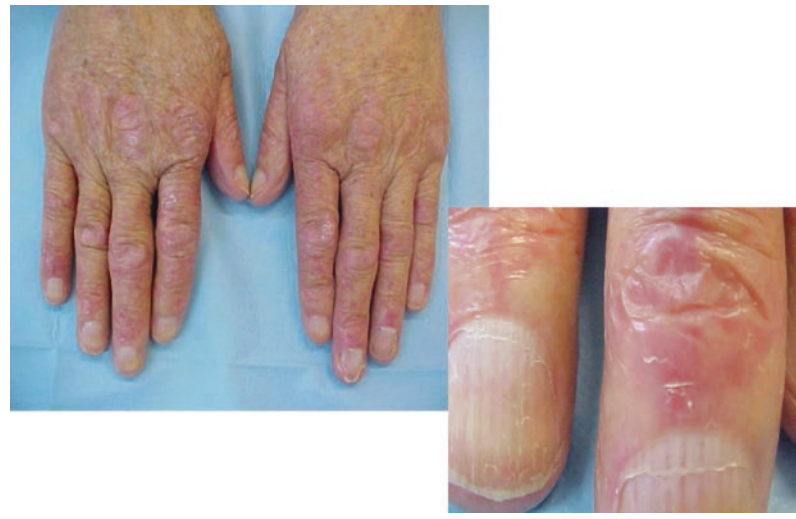

Fig. 26.34 Dermatomyositis-like eruption caused by hydroxyurea

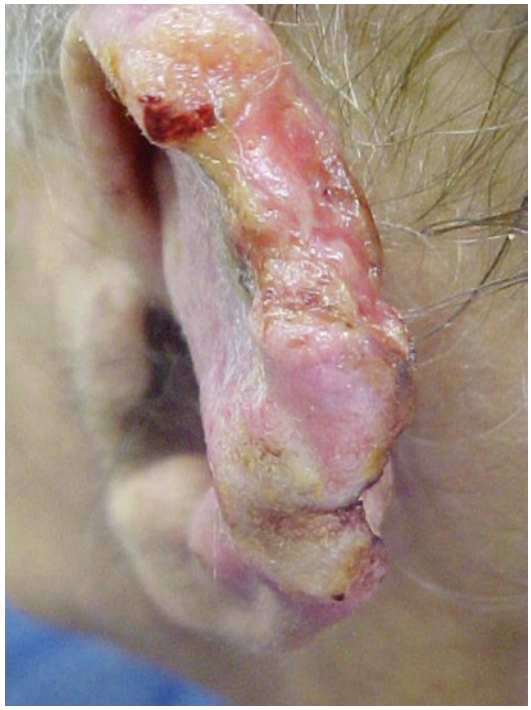

Fig. 26.35 An aggressive squamous cell carcinoma on the ear of a patient under treatment with hydroxyurea

lower limbs [75]. Other less frequent adverse effects are dermatomyositis-like rash and non-melanoma skin cancer (Fig. 26.35) [75].

Dermatomyositis-like rash resembles true dermatomyositis both clinically and histologically [75]. It presents as desquamating erythematous papules or plaques on the dorsum of the hands, typically associated with facial erythema and pronounced xerosis of the skin. Patients rarely report other accompanying symptoms and there are usually no significant alterations of laboratory tests [75]. Histologically, a lichenoid inflammatory infiltrate is found at the dermoepidermal interface, with vacuolization of the basal layer, dyskeratosis, and, rarely, mucin deposition (Fig. 26.36) [75].

Diagnosis is made according to the distribution of the lesions and by the temporal relationship between chemotherapy and light exposure. Treatment includes discontinuation of the agent and protection from the sun for at least 2 weeks. Physical sunscreens are recommended. Cold compresses, systemic antihistamines, and topical or oral corticosteroids are used as associated symptomatic treatment.

Radiation Recall [74]

This is a phenomenon whereby the chemotherapeutic agent induces an inflammatory reaction in an area previously exposed to radiation. These reactions are predominantly cutaneous; however, they may affect internal organs such as the lungs, heart, bladder mucosa, esophagus, oral or bowel mucosa, and supraglottic larynx.

It occurs more often with the use of doxorubicin, dactinomycin, and gemcitabine and is less common with bleomycin, etoposide, hydroxyurea, methotrexate, trimetrexate, vinblastine, 5-fluorouracil, lomustine, daunorubicin, melphalan, cyclophosphamide, cytarabine, docetaxel, edatrexate, idarubicin, paclitaxel, tamoxifen, and vinblastine.

The mechanism of radiation recall is unknown but it is probably related to DNA repair. Relapsing dermatitis or radiation recall may occur between 8 and 15 days following radiotherapy and generally appears hours to days after administration of the chemotherapeutic agent.

Clinically, the patient may or may not experience a painful erythema with or without vesiculation, edema, desquamation, and pruritus. The borders of the lesion are well defined and correspond to the exact site at which the radiation was applied. In severe cases, necrosis and ulceration may occur.

The severity appears to directly reflect the brevity between radiation and chemotherapy as well as the doses of both radiation and chemotherapy. The reaction improves spontaneously within hours or weeks following cessation of chemotherapy, treatment being symptomatic.

The use of systemic corticosteroids associated with the discontinuation of chemotherapy generally results in a marked improvement and may permit reintroduction of the treatment.

Exacerbation of Radiation [74]

This occurs when a chemotherapeutic agent increases the toxicity of radiotherapy. This phenomenon may occur in virtually all the organs of the body including the skin, mucosa, esophagus,

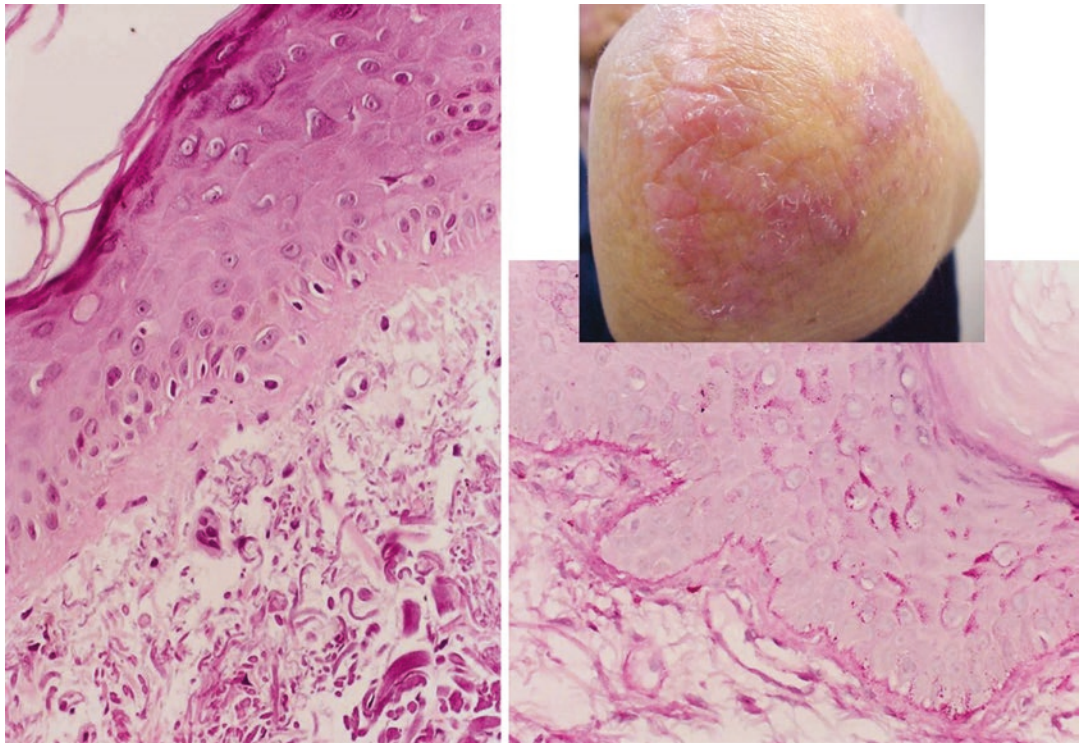

Fig. 26.36 Interface dermatitis on elbow of a patient under treatment with hydroxyurea

lungs, heart, digestive tract, kidneys, liver, brain, bladder, and eyes.

The agents most associated with exacerbation of radiation are bleomycin, gemcitabine, dactinomycin, doxorubicin, 5-fluorouracil, hydroxyurea, 6-mercaptopurine, oxaliplatin, and methotrexate.

Clinically, the reaction resembles residual dermatitis secondary to acute dermatitis from radiation, with erythema, edema, vesiculation, blisters, or erosions. The reaction generally appears at the site of radiation; however, the area affected may be more extensive. Severe mucositis may occur.

The reaction is associated with the dose, the type of drug used, and the sequence of time between radiation and the use of chemotherapy. Toxicity may be additive or supra-additive (synergic). In supra-additive toxicity, the reaction is greater than that of the sum of each one of the types of treatment alone.

Treatment is symptomatic: applying cold compresses, taking precautions at the site to prevent infection and avoiding trauma, heat, and UV light. Sequelae such as fibrosis, skin atrophy, and telangiectasia-related disorders may occur.

Hypersensitivity Reactions Caused by Chemotherapy Agents [74]

In theory, all chemotherapeutic agents may trigger hypersensitivity eruptions. With certain drugs derived from biological agents such as L-asparaginase, mitomycin C, and bleomycin in addition to paclitaxel, the incidence of hypersensitivity reactions is high. In the case of paclitaxel, this is due to the fact that it is dissolved in Cremophor EL castor oil.

According to the classification system defined by Gell and Coombs, the majority of hypersensitivity reactions are type I, i.e., IgE-mediated. They present as urticaria, pruritus, angioedema, and anaphylaxis. They generally occur within the first hour after use of the drug, but onset may be delayed until up to 24 h after using the medication.

Type III reactions occur because of formation of circulating immunocomplexes, and cause eruptions such as polymorphous erythema and vasculitis. Nonetheless, L-asparaginase and procarbazine cause urticarial reactions via type III reactions.

Allergic contact dermatitis, a type IV reaction, may occur, principally as a consequence of the topical use of nitrogen mustard (mechlorethamine).

Other severe reactions may occur, such as SJS and TEN, as well as exanthematous eruptions, all currently classified as type IV reactions according to the extended Gell and Coombs classification, i.e., SJS and TEN, respectively (type IVc, mediated by Fas, granzymes, and perforin) and exanthematous eruptions (type IVb, mediated by T cells with IL-5 production, with chemotaxis of eosinophils).

Local Reactions to Chemotherapy Agents [74]

Local Toxicity [74]

Antineoplastic drugs may be classified according to their potential aggressiveness toward blood vessels and adjacent tissues. They may be nonirritating, irritating, or vesicant, causing effects that range from mere local discomfort to tissue necrosis.

Nonirritating drugs (thioguanine, asparaginase, bleomycin, cyclophosphamide, chlorambucil, methotrexate, hydroxyurea) provoke an edema that is indicative of a site of extravasation; however, they do not cause necrosis or tissue irritation.

Irritating drugs (5-fluorouracil, carmustine, docetaxel, and etoposide) cause tissue damage that does not progress to necrosis. They trigger erythema, pain, inflammation at the puncture site and along the venous pathway, burning, and local edema, without blistering. The vesicant drugs (dactinomycin, doxorubicin, melphalan, vincristine, vinblastine, and dacarbazine) cause severe skin irritation with pain, erythema, edema, blistering, and necrosis with functional and aesthetic damage.

Drug Extravasation [74]

This is defined as the leakage of a chemotherapeutic drug from the vessel bed to the surrounding tissues, either as a result of vascular rupture or by direct infiltration.

The frequency of this event in adults is estimated at 0.1–6% and it is more common among children. Severe sequelae are rare. The severity of tissue damage is related to the type of chemotherapeutic agent used and the quantity and concentration of the drug administered.

Cytotoxic agents are classified as irritants or vesicants as a function of their potential for local toxicity. An irritant is defined as an agent that causes an inflammatory reaction, paresthesia, pain, or phlebitis at the puncture site or along the venous pathway.

Clinical signs include sclerosis and hyperchromia along the passage, as well as burning, increased temperature at the site, discomfort, erythema, and pain at the area of extravasation. Necrosis does not occur with this condition. The symptoms are generally short-lived and leave no sequelae. The drugs most associated with this complication are 5-fluorouracil, carboplatin, cisplatin, bleomycin, mitomycin, dactinomycin, idarubicin, daunorubicin, dacarbazine, ifosfamide, cyclophosphamide, mechlorethamine, carmustine, mitoxantrone, paclitaxel, docetaxel, streptozotocin, vinblastine, vinorelbine, and etoposide.

The vesicant agents (melphalan, bleomycin, mechlorethamine, carmustine, mitomycin, mitoxantrone, cisplatin, paclitaxel, dacarbazine, dactinomycin, daunorubicin, streptozotocin, doxorubicin, epirubicin, vinblastine, vincristine, etoposide, vindesine, and vinorelbine) have the potential to cause more severe and long-lasting tissue damage, including necrosis of the affected area.

The initial manifestations are often subclinical and may appear immediately following extravasation or after several days or weeks. The initial signs include local burning or paresthesia at the site of infusion, mild erythema, pruritus, and edema. A change in the infusion rate or the absence of venous return in the aspirate may

indicate the occurrence of extravasation. After 2–3 days, erythema increases and there is pain, a brownish discoloration, induration, dry desquamation, or the appearance of blisters. If the amount extravasated was small, the signs and symptoms may disappear in the following weeks. If a significant amount was extravasated, the following symptoms may appear in the coming weeks: necrosis, formation of eschar and painful, necrotic ulceration with raised, erythematous borders and a yellowish base. There is generally no granulation tissue with these ulcerations. They may resolve slowly or persist, increasing gradually in area. Involvement of the tendons, nerves, and vessels may occur if appropriate treatment is not given, leading to severe sequelae such as nerve compression syndrome, a reduction in joint mobility, contractures, neural deficits, and reflex sympathetic dystrophy. Cellulitis and the formation of abscesses are rare events.

The interval between detecting the condition and adopting the appropriate measures should be short as possible. The nursing team should be trained in this respect.

Preventive measures should be adopted such as avoiding puncturing emaciated limbs, lower limbs, limbs with multiple punctures, limbs with phlebitis or those that have been subjected to radiation, the ipsilateral limb to a mastectomy, in vena cava syndrome, and in veins that protect joints, nerves, and tendons. It is important to evaluate the venous conditions of the patient and, if necessary, to use an indwelling catheter.

The use of common needles for venous access should be avoided. Adequate fixation should be performed and blood reflux should be tested, with an infusion of 0.9% saline solution or 5% glucose-saline solution used for every 2 ml of the chemotherapeutic agent. After administration of all the drugs, 20 ml of saline or glucose-saline solution should be infused to reduce any possibly toxic residues.

Vesicant drugs should always be given first. In prolonged sessions of chemotherapy (those lasting over an hour) with vesicant drugs, central venous access should be used. Always listen to the patient's complaints. If extravasation occurs, stop the infusion immediately.

Remove the puncture device and elevate the affected limb. In the case of extravasation of drugs such as etoposide, paclitaxel, vinblastine, vincristine, and vinorelbine, apply local heat (leading to vasodilation and dilution of the drug) for 30 min and ice (venous constriction and greater degradation of the toxic metabolites in addition to alleviating pain and inflammation) every 30 min, six times a day in the first 48 h. For the other drugs, apply ice every 30 min, six times a day. When indicated, the specific antidote for the drug in question should be used.

The use of intralesional corticosteroid and sodium bicarbonate should be avoided. Ulcers that fail to heal may require debridement and grafting. In case of persistent edema and erythema and pain without ulceration that persists despite conservative therapy or in the presence of extensive areas of necrotic tissue or skin ulceration, surgery may be indicated.

Periorbital Edema [74]

Edema of the eyelids has been described with the use of gemcitabine.

Cutaneous Eruption of Lymphocyte Recovery [74]

Cutaneous eruption of lymphocyte recovery (ELR) is observed in leukemia patients who receive bone marrow ablation. In general, it appears between the 6th and 21st days after chemotherapy. This point corresponds to the beginning of the recovery of peripheral lymphocytes following the nadir of leukocyte count induced by chemotherapy.

Although the exact mechanism has yet to be clarified, it is believed that the eruption is caused by the return of immunocompetent lymphocytes to peripheral circulation with cutaneous cytotoxicity. T lymphocytes and Langerhans cells are found on histopathologic evaluation of these reaction sites.

Clinically, the condition consists of pruriginous, erythematous macules, papules, or papulous plaques that become confluent. Erythrodermia may occur. In addition, this

condition is associated with an elevation in body temperature that occurs together with the appearance of the eruption.

The temperature falls in the following 2–3 days and the skin eruption tends to diminish after several days, progressing with desquamation and mild residual hyperchromia. The drugs most associated with these reactions are cytarabine, daunorubicin, amsacrine, etoposide, cyclophosphamide, and vincristine.

Differential diagnosis should be made with sepsis, viral exanthems, GVDH, leukemia or lymphoma cutis, and drug hypersensitivity or toxicity. Histopathology is nonspecific. The most characteristic findings are superficial perivascular mononuclear cell infiltrate, mild epidermal alterations such as spongiosis, vacuolar alteration of the basal cell layer, and loss of keratinocyte maturation secondary to chemotherapy.

Dyskeratotic keratinocytes are rare and eosinophils are absent. On occasions when the patient was treated with GM-CSF associated with IL-3, atypical lymphocytes with large pleomorphic and hyperchromatic nuclei were found at histopathology.

Differentiation may be difficult between ELR and GVHD.

Skin Toxicity Associated with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors [74]

Anti-EGFRs currently consist of panitumumab, cetuximab, erlotinib, and gefitinib. Skin toxicity with anti-EGFRs is actually more of a pharmacologic effect than a hypersensitivity reaction, since this is a clinical marker of the efficacy of the inhibiting effect of these drugs on the tumor, with the severity of the eruption corresponding to tumor response.

The skin effects observed with the anti-EGFR are alterations in capillary growth and in the texture of the hair, paronychia with or without secondary infection, or the formation of pyogenic granuloma, generalized asteatosis, skin desquamation, and blepharitis.

The most characteristic and intense manifestation is a papulopustular, follicular, comedone, or non-comedo (acneiform eruption) that occurs on the head, neck, and the central portion of the chest and back, which later disseminates.

There may be pruritus, which differentiates this reaction from the acneiform eruptions caused by corticosteroids, antiepileptic drugs, and vitamins B6 and B12. Acneiform eruptions occur in more than 50% of patients with use of cetuximab, and this percentage may reach as high as 75–100%. The manifestations generally occur in the first weeks (2 days to 6 weeks) after the beginning of treatment (cetuximab and panitumumab).

The eruption is dose dependent; however, the duration of the condition does not correlate with the duration of treatment. The acneiform eruptions induced by monoclonal antibodies are more severe and extensive than those resulting from the use of tyrosine kinase inhibitors. Blepharitis caused by anti-EGFRs may range from mild to intense.

Histopathology of the papulopustular lesions shows no increase in sebaceous gland activity, comedones, or follicular rupture that would explain the inflammation, differentiating it from acne vulgaris. The follicles are rather wide and at times obstructed by an excess of keratinocytes. In the dermis, neutrophilic infiltrate may be found, particularly involving the follicular infundibulum. Intraepidermal acantholysis may be present in association with the eccrine gland ducts. In the lesions of patients using gefitinib, there is an expressive thinning of the stratum corneum layer with loss of the normal basket-weave pattern.

Paronychia occurs in around 10–15% of patients who are using cetuximab and gefitinib, appearing at 6–8 weeks of treatment or sometimes after 6 months. It affects various fingers and the first toes. Treatment consists of potent topical corticosteroids. In case of onychocryptosis, anti-EGFR may be temporarily interrupted and canthotomy performed. Asteatosis occurs in around 35% of patients, particularly with the use of gefitinib. There is a predilection for the areas previously or simultaneously affected by acneiform eruption.

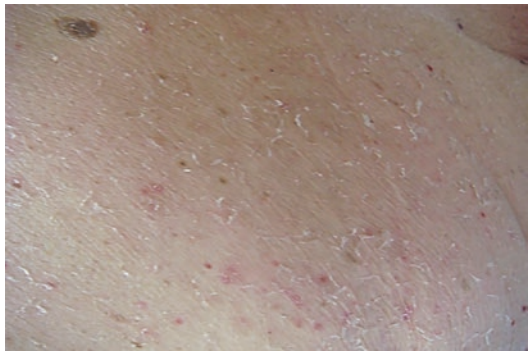

Fig. 26.37 Intense xerosis caused by erlotinib

Some patients have xerosis of the vaginal mucosa, with dysuria. Xerosis may progress to chronic asteatotic eczema (Fig. 26.37), with a greater susceptibility to *Staphylococcus aureus* infection or HHV-1.

Emollients and topical corticosteroids should be used for the eczema. Fissures can be treated with a solution of 50% propylene glycol under plastic occlusion or a hydrocolloid dressing.

Glossary

Adverse drug reactions (ADRs) Include all unintended pharmacologic effects of a drug except therapeutic failures, intentional overdosage, abuse of the drug, or errors in administration. They can be classified as predictable (type A – 80% of the ADRs) or unpredictable (type B).

Anaphylaxis An immediate systemic reaction that occurs when a previously sensitized individual is re-exposed to an allergen. It is caused by rapid IgE-mediated immune release of vasoactive mediators from tissue mast cells and blood basophils with a potential late component. This is a systemic severe ADR affecting skin, mucous membranes, gastrointestinal tract, respiratory tract, and cardiovascular system.

Drug allergy An immunologically mediated response to a pharmaceutical and/or formulation (excipient) agent in a previous sensitized patient.

Drug idiosyncrasy An abnormal and unexpected effect that is unrelated to the intended pharmacologic action of a drug and has an unknown mechanism. It is not mediated by a humoral or cellular immune response but is reproducible on readministration. It may be due to underlying abnormalities of metabolism, excretion, or bioavailability.

Drug intolerance An undesirable pharmacologic effect that may occur at low or conventional doses of the drug without underlying abnormalities of metabolism, excretion, or bioavailability of the drug. Humoral or cellular immune mechanisms are not thought to be involved, and a definitive mechanism for such exaggerated responses has not been established (e.g., acetylsalicylic acid-induced tinnitus at low doses).

Pseudoallergic (anaphylactoid) reactions Immediate systemic reactions that mimic anaphylaxis but are caused by non–IgE-mediated release of mediators from mast cells and basophils. Often caused by radiocontrast agents.

Severe ADRs Include all adverse effects which are unpredictable life-threatening ADRs and need prompt recognition to reduce integumentary and internal organ damage and, thus, morbidity and mortality.

Uncomplicated ADRs Include mild or moderate adverse drug effects on healthy patients, not involving life-threatening situations.

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