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6

Severe Drug-Induced Skin Reactions: Clinical Pattern, Diagnostics and Therapy

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1. Introduction

Cutaneous drug eruptions are common, with a prevalence of approximately 2 % to 3 % in hospitalized patients.[Bigby, 2001, Bigby, et al., 1986] It has been estimated that 1 of every 1000 hospitalized patients has a serious cutaneous drug reaction.[Roujeau and Stern, 1994] In clinical practice, the diagnosis of a cutaneous drug eruption is based on a clinical history suggesting that the rash is temporally related to the consumption of a new drug, the gross morphology of the rash, and, often, the histopathologic examination of a skin biopsy. The diversity of cutaneous drug eruptions is broad.[Kaplan, 1984, Roujeau, 2005, Wintroub and Stern, 1985] The vast majority of drug reactions is represented by morbilliform (scarlatiniform or rubeoliform) exanthemas (40%).[Gerson, et al., 2008] Followed by urticaria and angioedema, they account for up to 95% of cutaneous reactions.[Crowson, et al., 2003, Kauppinen and Stubb, 1984, Stubb, et al., 1994] Although generalized and often developing fast with some systemic symptoms such as pruritus, burning or shiver, these drug reactions are not severe and usually stop rapidly without much intervention after cessation of the culprit drug.

Histopathologically, drug reactions may simulate each of the patterns of inflammatory diseases of the skin and subcutaneous fat. However, by far the most common pattern evoked by them is "interface dermatitis".[Ackerman, et al., 2005] That pattern usually is joined by an infiltrate that encircles only the venules of the superficial plexus, but, episodically, the infiltrate is present around venules of both vascular plexuses. Of the two types of interface dermatitis induced by drugs, namely, vacuolar and lichenoid, the vacuolar is the most common.

Severe drug-induced skin reactions include Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), moreover, generalized bullous fixed drug eruption (GBFDE), acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS). Furthermore, toxic erythemas after chemotherapy and drug-induced linear-IgA-dermatosis should be listed among them. Within the following chapter they will be elucidated from a clinical but in particular histopathologic point of view.

2. Stevens-Johnson syndrome and toxic epidermal necrolysis

2.1 Clinical presentation

SJS and TEN are viewed as a single disease entity of different severity.[Bastuji-Garin, et al., 1993] Both are characterized by a macular confluent erythema evolving into sometimes extensive blistering or epidermolysis that resembles a second degree burn (figures 1A and 2A). This is accompanied by mucosal erosions, especially affecting the mouth, the lips, the

(a)

(b)   (c)
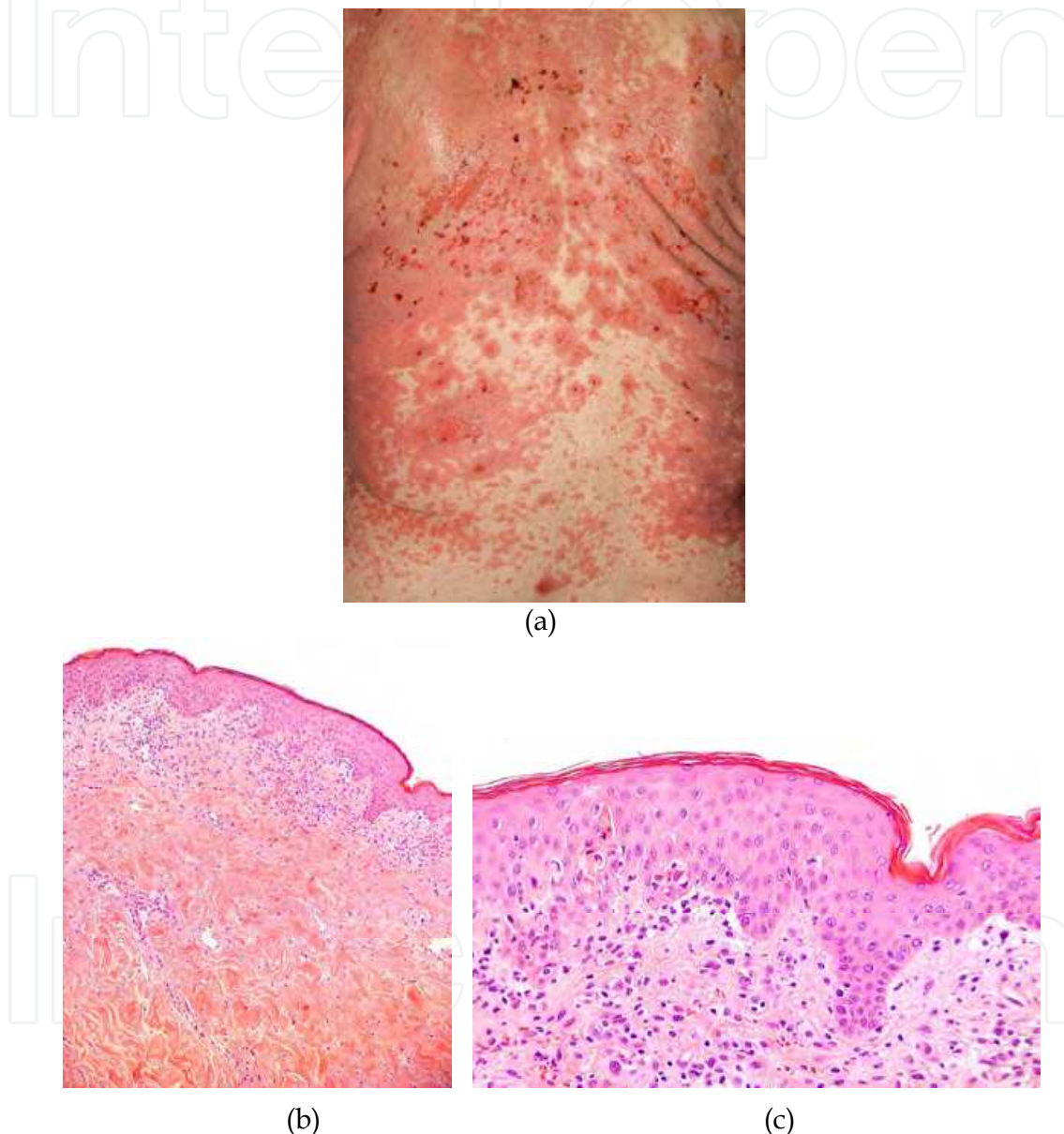
Fig. 1. A: SJS/TEN, early stage, with confluent erythematous macules, atypical targets and localized epidermolysis. The patient later developed more extensive epidermolysis.
B and C: Normal cornified layer. Dermal, superficial, sparse, perivascular and interstitial infiltrate of lymphocytes. Focal vacuolar alteration along the dermoepidermal junction in company with some lymphocytes. Focally scattered necrotic keratinocytes throughout the lower part of the epidermis. Extravasated erythrocytes. (B: hematoxylin-eosin, original magnification x100, C: hematoxylin-eosin, original magnification x400).

conjunctiva, and the genitals. The reactions are often accompanied by fever and malaise. SJS is characterized by a preference for the trunk or generalized dissemination of rather atypical target lesions and maculae. These are confluent and form blisters which may merge. Detachment of the skin affects less than 10 % of body surface area. The largest percentage of skin detachment, more than 30 %, occurs in TEN with maculae, whereas in the very rare form of TEN with widespread erythema the amount of blisters and erosions often affects little more than 10% of body surface area. A transitional form called SJS/TEN-overlap has been defined with blisters and erosions affecting 10 % to 30 % of body surface area.[Bastuji-Garin, et al., 1993].

Whereas SJS, SJS/TEN-overlap and TEN are considered as a single disease of different severity, erythema (exsudativum) multiforme majus (EM with mucosal involvement; E(E)MM) is different not only in terms of the clinical pattern, but also in terms of etiology. Especially shared histologic characteristics lead to the original thinking of a common disease spectrum. Typical or atypical raised targets are characteristic for EMM. They appear mainly on the limbs, but sometimes also on face and trunk, especially in children. Severe mucosal involvement is found in both, EMM and SJS/TEN, and does not allow a differentiation. Skin detachment in EMM is usually very limited, since only small blisters appear on the target lesions. While the minor and major form of EM are mainly triggered by infectious agents, such as acute or recurrent eruptions of herpes simplex, mycoplasma pneumonia, as well as other infections of the upper respiratory tract, flu, and flu-like infections, SJS/TEN are predominantly caused by drugs. [Auquier-Dunant, et al., 2002] Drugs with a high risk to induce SJS/TEN are allopurinol, antibacterial sulfonamides, non-steroidal anti-inflammatory drugs of the oxicam-type, various antiepileptic drugs, such as carbamazepine, lamotrigine, phenobarbital, phenytoin,, and the non-nucleoside reverse-transcriptase inhibitor nevirapine. [Mockenhaupt, et al., 2008]) SJS/TEN may end fatally in only a few days and mortality is more than 40% in TEN.[Mockenhaupt, 2008, Mockenhaupt and Norgauer, 2002] Despite the fact that a diagnosis of EMM and SJS/TEN in most cases can be made clinically and histopathologically with confidence, no judgment can be made, on morphologic grounds alone, about the cause of it. Moreover, there are currently no in vivo or in vitro tests that can identify the causative agent in SJS/TEN with certainty. Thus, causality assessment is mainly based on a thorough history of drug exposure and infection of the individual patient.

2.2 Histology

SJS and TEN share a particular histological pattern.[Ackerman, et al., 2005, Rzany, et al., 1996] In early erythematous macules, papules, or plaques a sparse to moderate perivascular and interstitial infiltrate of lymphocytes is present in the superficial dermis. Occasional eosinophilic granulocytes may be found. Vacuolar alteration is found along the dermoepidermal junction (DEJ) often in company with some lymphocytes. Necrotic keratinocytes are scattered throughout the lower part of the epidermis (figures 1B and 1C). Infundibular epidermis and acrosyringia of eccrine ducts may be involved. Slight ballooning of keratinocytes and spongiosis may be present. The cornified layer shows a normal basket-weave configuration. In fully developed stages of the disease, when epidermal detachment/epidermolysis appears, in addition to the above mentioned changes subepidermal vesiculation secondary to extensive vacuolar alteration and confluent necrosis of keratinocytes develops. Confluent necrosis can involve the upper part of infundibular epidermis and acrosyringia of eccrine ducts. Variable numbers of extravasated erythrocytes are present. As the process develops rapidly, usually neither melanophages nor

siderophages are found in the upper part of the dermis. The cornified layer remains unchanged (figures 2B, 2C, and 2D). In late hyperpigmented macules and patches a sparse superficial perivascular infiltrate of lymphocytes may still be present. Slight vacuolar alteration remains at the DEJ. Melanophages are scattered in variable numbers in the papillary dermis, optionally together with some siderophages. Re-epithelialization of the epidermis beneath a subepidermal blister can be mentioned. Cornified layer shows slight parakeratosis or sometimes scale-crust. In areas of epidermal necrosis and epidermolysis the dermis may be covered by a fibrinoid crust containing neutrophilic granulocytes. Some neutrophilic granulocytes may also be present in the adjacent dermis.

(a)   (b)

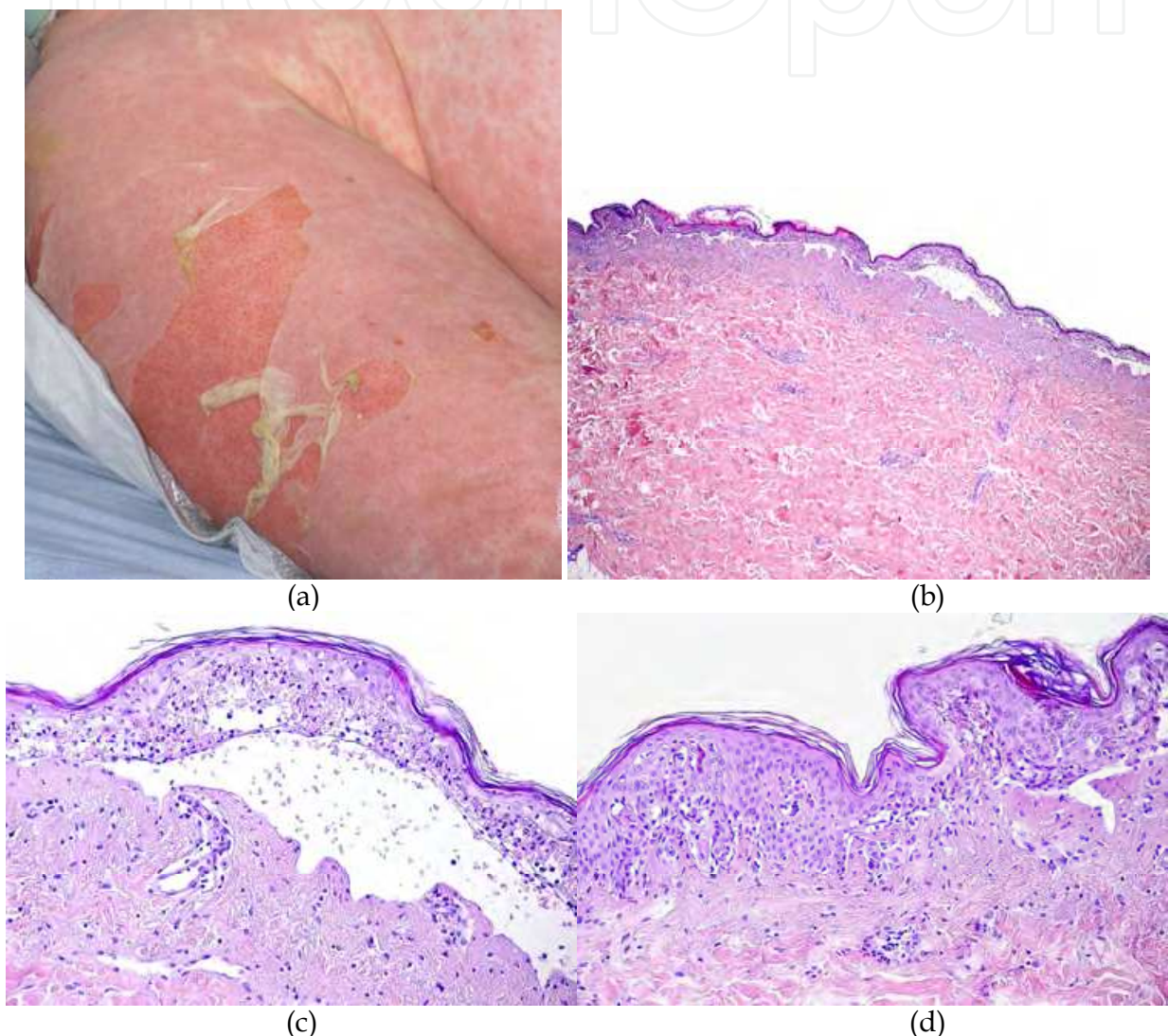(c)   (d)

Fig. 2. A: Toxic epidermal necrolysis, advanced stage, with confluent erythematous macules, atypical targets evolving into large erythema and widespread epidermolysis.
B and C: Subepidermal vesiculation secondary to extensive vacuolar alteration and confluent necrosis of keratinocytes. A dermal, superficial, very sparse, perivascular and interstitial infiltrate of lymphocytes. Unchanged cornified layer. (B: hematoxylin-eosin, original magnification x40, C: hematoxylin-eosin, original magnification x400)
D: Changes from the erythematous edge of a blister. Features correspond to early changes mentioned in figure 1B and C (hematoxylin-eosin, original magnification x400).
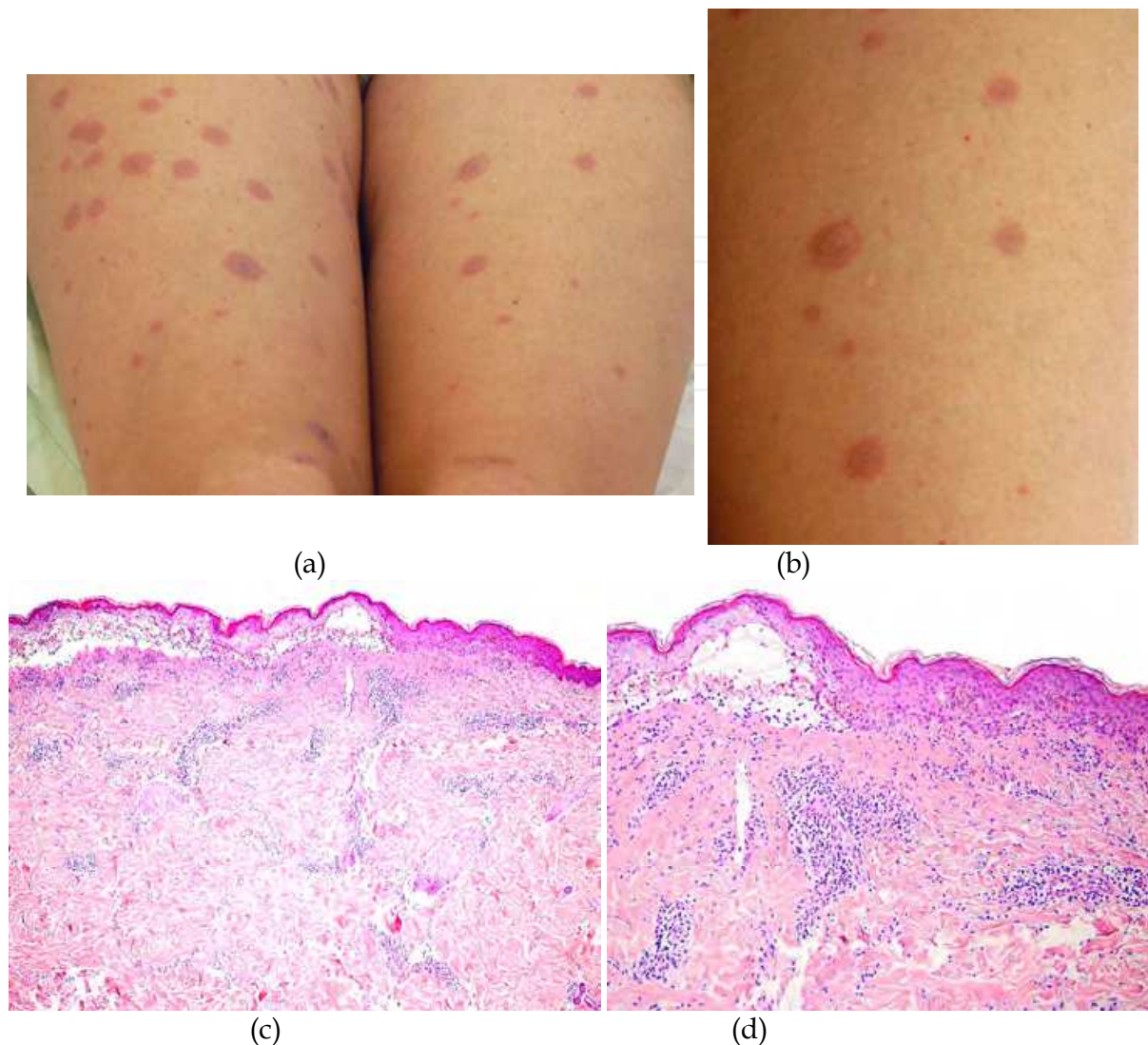
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Fig. 3. A and B: Erythema multiforme with target lesions on the extremities.
C and D: Subepidermal vesiculation secondary to extensive vacuolar alteration and confluent necrosis of keratinocytes. Dermal, superficial, moderate, perivascular and interstitial infiltrate of lymphocytes. Unchanged cornified layer. Changes are indistinguishable from those of Stevens-Johnson syndrome or toxic epidermal necrolysis. (C: hematoxylin-eosin, original magnification x40, D: hematoxylin-eosin, original magnification x200).

Immunohistochemically, there is a predominance of CD4+ cells in the dermis and CD8+ cells in the epidermis similar to graft-versus-host disease (GVHD). Cytotoxic T cells can initiate apoptosis, exacerbated by the release of perforins, cytokines such as tumor necrosis factor-alpha (TNF-α) and FAS-ligand.[Abe, et al., 2003, Chang, et al., 2004, Nassif, et al., 2004a, Nassif, et al., 2002] Recent findings demonstrate that secretory granulysin is a key molecule responsible for the disseminated keratinocyte death in SJS/TEN and highlight a mechanism for cytotoxic T lymphocyte- and natural killer cell-mediated cytotoxicity that does not require direct cellular contact.[Chung, et al., 2008] Granulysin concentrations in the blister fluids were two to four orders of magnitude higher than perforin, granzyme B or soluble FAS-ligand concentrations, therewith being the most highly expressed cytotoxic molecule.[Chung, et al., 2008] It is also thought that proteins such as FAS-antigen (CD95)

and p55-TNF-α-receptors promote keratinocyte apoptosis.[Abe, et al., 2003, Chang, et al., 2004, Viard, et al., 1998] In blister fluid obtained from patients with sulfonamide-induced TEN, it has been shown that the lymphocytes were only cytotoxic in the presence of cotrimoxazole or sulfamethoxazole, but not toward hydroxylamine metabolites of sulfamethoxazole. This is the first sign that lesional T lymphocytes exhibit a direct cytotoxic response towards autologous cells without prior re-stimulation.[Nassif, et al., 2004b] In addition, ligands such as TRAIL (tumor necrosis factor related apoptosis inducing ligand) and TWEAK (TNF-like weak inducer of apoptosis) are secreted by CD1a+ and CD14+ cells capable of inducing keratinocyte death in an MHC class I-independent manner, also seem to be present in the blister fluids of patients with TEN.[de Araujo, et al., 2011]

2.3 Differential diagnoses histopathologically

Erythema (exsudativum) multiforme majus (E(E)MM) and SJS/TEN share a similar histology.[Ackerman, et al., 2005, Rzany, et al., 1996] Individual cases may show minor differences, but these concern mostly quantitative aspects. The dermal infiltrate in EM, SJS/TEN is a superficial and mostly perivascular. However, it decreases with the severity of the disease, being intermediate or even dense in the majority of cases of EM and rather sparse in TEN.[Rzany, et al., 1996] Erythrocyte extravasation is found more often in EM.[Rzany, et al., 1996] Nevertheless, histopathologic differentiation is impossible (figures 3A, 3B, 3C, and 3D).

The most important differential diagnoses for SJS/TEN are 'generalized bullous fixed drug eruption' (GBFDE) and 'staphylococcal scalded skin syndrome' (SSSS). The clinical presentation of GBFDE differs from SJS/TEN, as described below, and the Nikolsky sign is negative on healthy skin in GBFDE. Also in GBFDE and SSSS there may be limited involvement of mucous membranes. Histopathologically, differentiation may be hindered based on the fact that features of GBFDE show great overlap with those of EM, or SJS/TEN. To what extent histopathologic characteristics of localized fixed drug eruption can be transferred for GBFDE and therewith being helpful in differentiation from SJS/TEN has not yet been clarified. The dermal inflammatory infiltrate in localized fixed drug eruption is usually a superficial and deep, perivascular, lymphocytic infiltrate with some eosinophilic and neutrophilic granulocytes, the latter being dispersed also interstitially. However, it seems that those features are not necessarily present in GBFDE (data based on experience of the authors). Unlike the macular confluent exanthema seen in SJS/TEN, in SSSS there is widespread erythema sometimes evolving into erythroderma (figure 4A). The Nikolsky sign is often positive, but skin detachment is very superficial. SSSS is far less common than SJS/TEN and has a variable age distribution with peak incidences in early childhood and in adulthood.[Mockenhaupt, et al., 2005] The disease was previously known as pemphigus acutus neonatorum Ritter von Rittershain. Histology in SSSS shows acantholytic blistering within the stratum granulosum. There is either no or only a sparse superficial lymphocytic infiltrate (figures 4B and 4C). In order to determine the level of epidermal separation as quickly as possible and differentiate between TEN and SSSS, the Tzanck smear may be used, which employs exfoliative cytology of the blister fluid, which is spread on a slide and stained with Giemsa. In SSSS, wide epithelial cells with a small nucleus/cytoplasm ratio are seen; in TEN, cuboidal cells with a large cell nucleus/cytoplasm ratio are found. Rapid histopathologic diagnosis of a cryostat section is certainly more reliable for rapid differentiation between SSSS and TEN. In SSSS, the removed roof of the blister demonstrates subcorneal separation, while in TEN the separation is deeper, in the stratum spinosum.
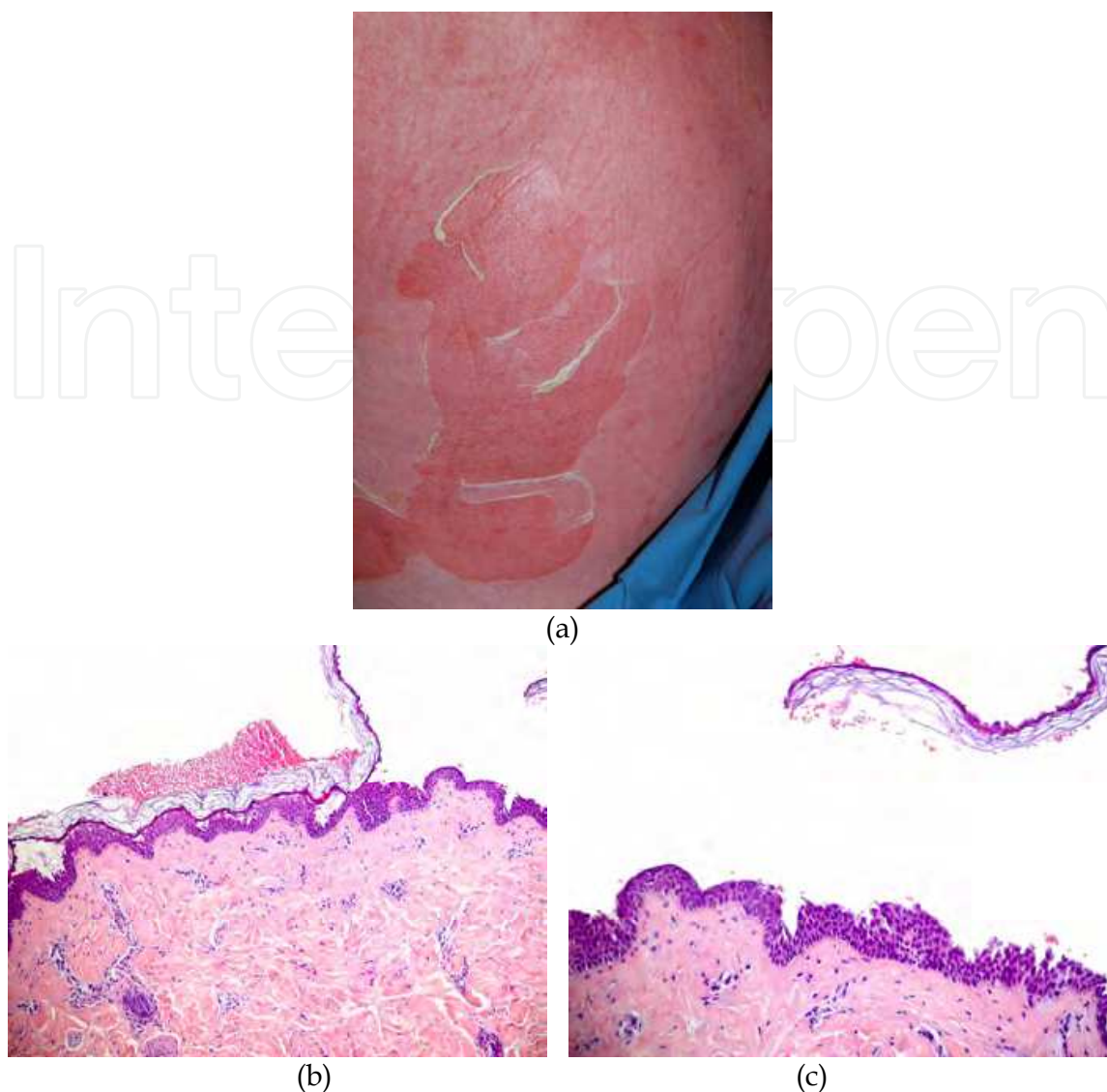
(a)

(b)   (c)

Fig. 4. A: Staphylococcal scalded skin syndrome with generalized erythema and widespread superficial epidermolysis.
B and C: Acantholytic blistering within the stratum granulosum. Very sparse superficial lymphocytic infiltrate (B: hematoxylin-eosin, original magnification x100, C: hematoxylin-eosin, original magnification x200).

Further, drug-induced exanthemas which sometimes demonstrate a multiform, target-like appearance without mucosal erosions, and which are histopathologically distinct must be considered as differential diagnoses. In particular, cyclooxygenase-2 inhibitors are able to induce widespread erythematous target-like skin reactions with certain additional symptoms, especially dyspnea and facial edema, and often also more widespread dermal edema (figure 5A).[Ziemer, et al., 2007] The exanthema is not accompanied by mucous membrane involvement and usually shows no or only very localized blisters (< 5% of the body surface). Histopathologically, biopsy specimens show a normal epidermis. Necrotic keratinocytes are not found. In the superficial dermis, there is a sparse perivascular and interstitial lymphocytic infiltrate, sometimes accompanied by a few eosinophilic granulocytes (figure 5B). A few lymphocytes may be found in the epidermis; which may in some cases focally be detached from the underlying skin as a result of severe edema in the papillary dermis.[Ziemer, et al., 2007]

(a)
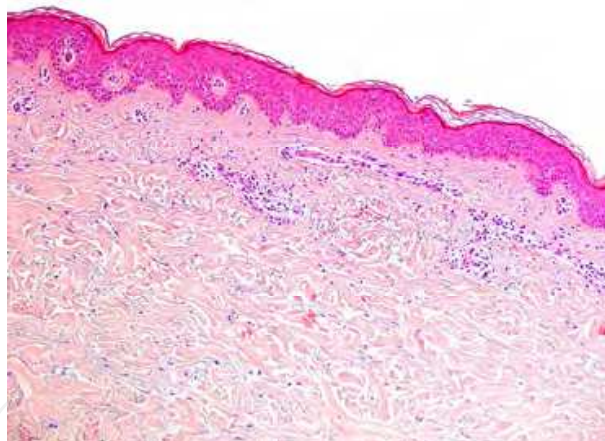
(b)

Fig. 5. A: Target-like or multiforme-like drug eruption. Extensive, confluent, erythematous-violaceous, target-like macules cover the entire body. (Reprinted with permission from JAMA & Archives) Cutaneous adverse reactions to valdecoxib distinct from Stevens-Johnson syndrome and toxic epidermal necrolysis. Arch Dermatol. 2007;143(6):711-6. Copyright© (2007), American Medical Association. All rights reserved.
B: Normal epidermis. Note a sparse perivascular and interstitial lymphocytic infiltrate in the superficial dermis and a few lymphocytes in the epidermis (hematoxylin-eosin, original magnification x40). (Reprinted with permission from JAMA & Archives) Cutaneous adverse reactions to valdecoxib distinct from Stevens-Johnson syndrome and toxic epidermal necrolysis. Arch Dermatol. 2007;143(6):711-6. Copyright© (2007), American Medical Association. All rights reserved.

Another, essentially distinct, severe and potentially fatal condition is 'drug reaction with eosinophilia and systemic symptoms' (DRESS). Although clinically well characterized, histology has not been studied systematically for this disease entity and reported findings are not consistent. If necrotic keratinocytes and basal cell vacuolar degeneration predominate together with a superficial lymphocytic infiltrate, histologic differentiation from SJS/TEN may be problematic. However, if present, necrotic keratinocytes in DRESS are scattered solitary within the epidermis, never provoking blister formation or epidermolysis (see subchapter 5).

In some instances differentiation from autoimmune bullous skin disorders may be necessary. Although histopathologically usually distinctive, in such cases immunofluorescence should be performed. This may be helpful in differentiating bullous drug eruptions from autoimmune-blistering diseases, such as bullous pemphigoid or pemphigus. In particular this can be of importance in diagnosing drug-induced linear-IgA-dermatosis, showing IgA-depositions along the basal membrane zone (see subchapter 7).

In a few further particular situations the diagnosis of SJS/TEN may be complicated to a maximum. This is the case in differentiation of SJS/TEN from advanced acute graft-versus-host disease of the skin and in differentiation of SJS/TEN from some manifestations of acute lupus erythematosus. In lupus erythematosus, vacuolar alteration of the DEJ and damage to keratinocytes are helpful in establishing diagnosis. Depending on the stage of evolution, necrotic keratinocytes can be seen either scattered throughout the lower part or in the entire epidermis in lupus erythematosus and SJS/TEN, leading to histopathologic misinterpretation. Because of the paucity of the rather superficial perivascular lymphocytic infiltrates and less epidermal atrophy, hyperkeratosis, basal membrane zone thickening and pigmentary incontinence, especially subacute-cutaneous lupus erythematosus and acute cutaneous lupus erythematosus may show considerable histopathologic overlap with SJS/TEN. However, the sum of changes and the notice of subtle histopathologic findings often allow differentiation [unpublished data from the German Registry of Severe Skin Reactions (Dokumentationszentrum schwerer Hautreaktionen, dZh), [Rzany, et al., 1996]). The same difficulty concerns clear histopathologic distinction of SJS/TEN from acute GVHD, where a morbiliform rash may rapidly progress to severe erythema and blisters (figure 6A). Histologically, in severe acute GVHD scattered necrotic keratinocytes predominate in the deeper epidermis. There may or may not be an accompanying lymphocytic infiltrate. Apart from a few investigations – none of them performed with an essentially necessary clinical correlation - considerable histopathologic studies do not exist.[Paquet, et al., 2001] The importance of a lymphocytic infiltrate is disputed and may not be compulsary for the diagnosis of GVHD.[Snover, 1990] Nevertheless, in GVHD a few eosinophilic granulocytes may be found within the infiltrate, a feature rarely observed in SJS/TEN. Moreover, adnexal involvement in SJS/TEN seems to be restricted to infundibular epidermis and epithelia of acrosyringia, whereas in GVHD lower parts of the hair follicle and epithelia of sebaceous glands may be involved (figures 6B and 6C).[Elliott, et al., 1987]

3. Generalized bullous fixed drug eruption

3.1 Clinical presentation
Generalized bullous fixed drug eruption (GBFDE) may be differentiated clinically from SJS/TEN.[Kauppinen, 1972] Classically, in GBFDE there are disseminated brownish

violaceous patches on which flaccid blisters arise. However, some cases present with bright erythematous patches, lacking the brownish discoloration (figures 7A and 7B).

(a)

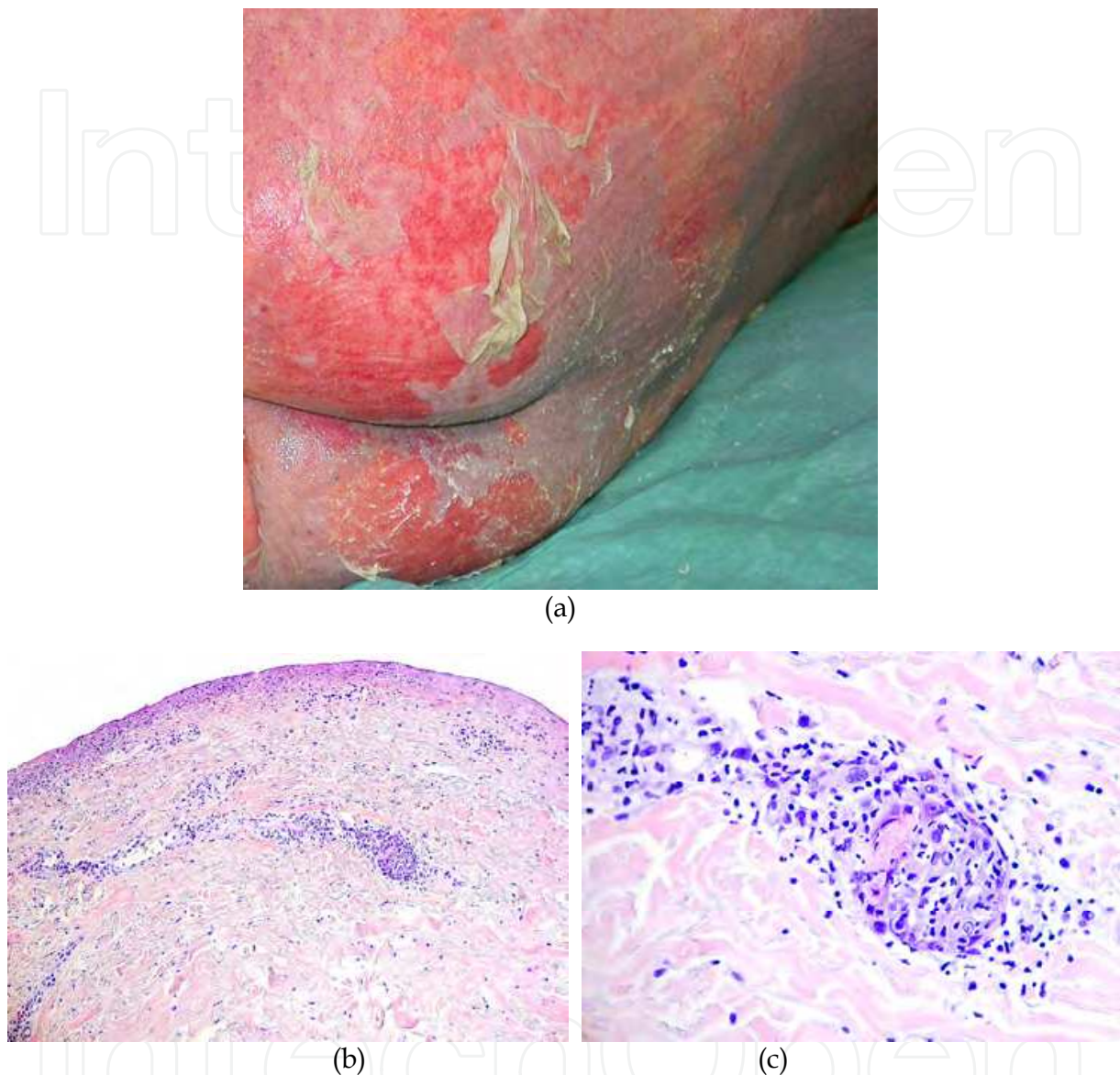(b)   (c)

Fig. 6. A: Severe acute cutaneous graft-versus-host disease with confluent erythematous macules evolving into large erythema and widespread epidermolysis.
B: Completely lost epidermis due to subepidermal blister formation. Superficial, dermal, perivascular and periadnexal infiltrate of lymphocytes and occasionally eosinophilic granulocytes. (hematoxylin-eosin, original magnification x40)
C: Scattered necrotic keratinocytes and vacuolar alteration throughout the lower part of eccrine duct in company with lymphocytes. (hematoxylin-eosin, original magnification x400).

Blistering usually affects only a small percentage of body surface area and between the large blisters there are sizable areas of intact skin. Erosive mucosal involvement was reported as being rare and rather mild. However, recent data show that in 77% of patients

with GBFDE mucous membranes were affected with a predominance of genitalia in both men (58%) and women (48%).[Mockenhaupt, et al., 2010] Patients usually do not feel sick, however, a fever may occur. Most patients report a history of a similar, often local reaction (fixed drug eruption).[Mockenhaupt, et al., 2010, Mockenhaupt and Norgauer, 2002] Nearly always GBFDE develops after re-exposure of the drug, possibly worsening with repeated use. This clearly distinguishes GBFDE from SJS/TEN, which generally appear during the first cycle of medication use, that is, without prior sensitization. Nevertheless, repeated GBFDE events can lead to increasingly widespread detachment of the skin and thus to serious disease. The overall mortality in such cases within six weeks after the onset of the reaction was reported to be 21%; all but one patient with lethal outcome were more than 70 years old.[Mockenhaupt, et al., 2010] Cotrimoxazole has been identified as the most common cause of GBFDE.[Mahboob and Haroon, 1998] In the recent case series most frequently associated drugs were co-trimoxazole (50%), followed by analgesics such as paracetamol (20%) and metamizole (18%).[Mockenhaupt, et al., 2010] The average duration between beginning of drug use and onset of the disease ranged from one day to about five days.[Mockenhaupt, et al., 2010]

3.2 Histology

As mentioned above it is still unclear to what extent histopathologic characteristics of localized fixed drug eruption are identical with those of GBFDE. Early lesions of localized fixed drug eruption show a sparse superficial and usually deep perivascular and interstitial mixed-cell infiltrate of lymphocytes with neutrophilic and eosinophilic granulocytes scattered interstitially. The papillary dermis may reveal some edema. Lymphocytes in company with neutrophilic and/or eosinophilic granulocytes sprinkled along the DEJ in conjunction with vacuolar alteration. The epidermis shows slight spongiosis and ballooning. Individual necrotic keratinocytes are found in the basal and spinous layers. The cornified layer is normal. In fully developed lesions vacuolar alteration at the DEJ is more extensive and may eventuate in subepidermal clefts and subepidermal vesicles. Spongiosis is more marked with intraepidermal vesicles. Necrotic keratinocytes are more numerous and the entire epidermis sometimes becomes necrotic (figures 7C and 7D). In late stages a sparse superficial perivascular infiltrate of lymphocytes with numerous melanophages remains in the papillary and sometimes upper reticular dermis. Melanophages at the base of a thickened papillary dermis in the context of a mixed infiltrate of inflammatory cells that includes neutrophils and eosinophils and of an epidermis that houses necrotic keratinocytes are a clue to fixed drug eruption recurrent at a particular site. [Ackerman, et al., 2005]

3.3 Differential diagnoses histopathologically

SJS/TEN displays changes at the DEJ and in the epidermis identical to those of fixed drug eruption, but the perivascular infiltrate usually is superficial only and is made up almost exclusively of lymphocytes. Eosinophils usually are few, if they are present at all, and neutrophils are absent unless confluent necrosis of the epidermis is prominent and attracts them chemotactically. Fixed drug eruption, in contrast to SJS/TEN, usually affects the venules of the deep as well as the superficial plexus, and the infiltrate of inflammatory cells is mixed, consisting of lymphocytes, eosinophils, and neutrophils perivascular, in the interstitium, along the DEJ, and in the epidermis.[Ackerman, et al., 2005]
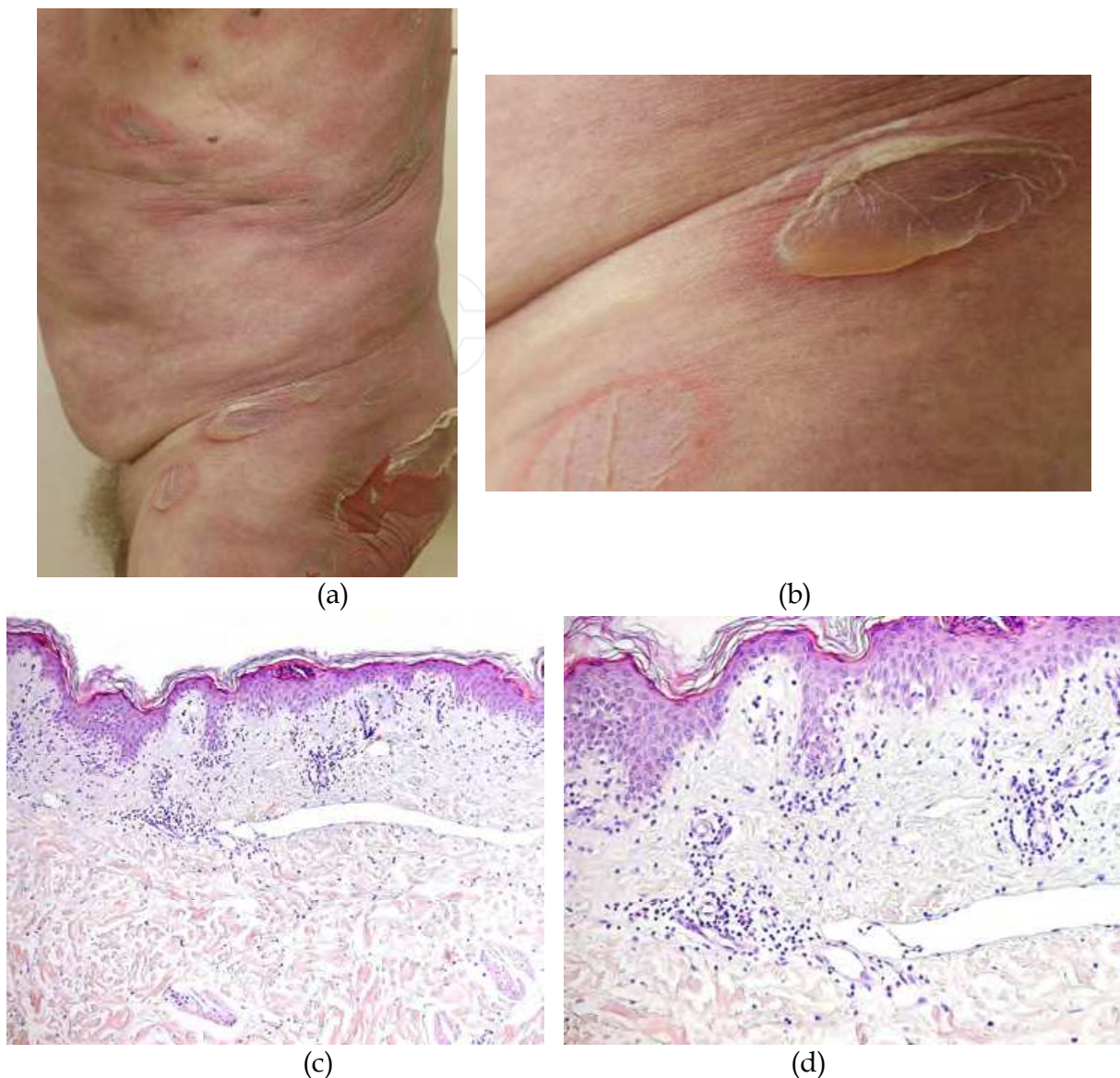
(a)

(b)

(c)

(d)

Fig. 7. A and B: Disseminated violaceous patches with flacid blisters on trunk and extremities.
C and D: Superficial, perivascular and interstitial, mixed-cell infiltrate of lymphocytes with neutrophilic and eosinophilic granulocytes scattered interstitially also in deeper parts of the dermis. Lymphocytes in company with some neutrophilic granulocytes sprinkled along the DEJ in conjunction with vacuolar alteration. Epidermis shows slight spongiosis. Individual necrotic keratinocytes are found in the basal and spinous layers. (C: hematoxylin-eosin, original magnification x100, D: hematoxylin-eosin, original magnification x200).

4. Acute generalized exanthematous pustulosis

4.1 Clinical presentation

In AGEP there is very acute widespread erythema with hundreds of small, flaccid, confluent, non-follicular pustules, especially along the skin folds and on the flexor surfaces (figure 8A). The reaction rarely involves mucous membranes, and when it does, symptoms are mild. Patients have acute fever and neutrophilia on blood tests.[Roujeau,

et al., 1991, Sidoroff, et al., 2001] AGEP shows spontaneous resolution in less then 15 days with characteristic desquamation. The main causes for AGEP are aminopenicillins, quinolones, macrolides, diltiazem, and antimalarial drugs such as (hydroxy-)chloroquine. Pristinamycine, which is approved for use in selected countries, is associated with a high relative risk of AGEP.[Mockenhaupt, et al., 2008, Sidoroff, et al., 2007] The latency period between initiation of the drug and onset of the cutaneous reaction is only a few days.

4.2 Histology

Histology typically shows non-follicular, spongiform, subcorneal and/or intraepidermal pustules, sometimes with marked edema of the papillary dermis. The epidermis is otherwise normal with an orthokeratotic stratum corneum, housing in foci neutrophilic granulocytes. The adjacent dermis shows superficial, perivascular and interstitial lymphocytic infiltrates with neutrophilic (figure 8B) and in most instances eosinophilic granulocytes.[Burrows and Russell Jones, 1993, Halevy, et al., 2010, Kardaun, et al., 2010a, Sidoroff, et al., 2001] Apart from neutrophils a few eosinophilic granulocytes may be found within the epidermis. [Sidoroff, 2001] Vasculitis and/or a small number of necrotic keratinocytes[Kardaun, et al., 2010a, Sidoroff, et al., 2001] have been reported in a few cases, however, such features are not typical for the disease. Moreover, presence of vasculitis could not be confirmed in a recent histopathologic study.[Kardaun, et al., 2010a] In summary, comparing AGEP and generalized pustular psoriasis, the presence of eosinophils, necrotic keratinocytes, a mixed perivascular and interstitial mid-dermal infiltrate and absence of tortuous or dilated blood vessels are in favor of AGEP.[Kardaun, et al., 2010a] Immunohistology shows neutrophilic leukocytes in subcorneal pustules that are surrounded by activated CD4+ and CD8+ T cells. The keratinocytes, as well as T-cells that have migrated to the epidermis, express interleukin-8 (IL-8), which attracts neutrophils. Presumably drug-specific T-cells migrate first, induce blistering, and then recruit neutrophilic leukocytes.[Britschgi, et al., 2001, Pichler, et al., 2002]

4.3 Differential diagnoses histopathologically

The main clinical differential diagnosis of an acute developing generalized pustular rash is acute generalized (exanthematous) pustular psoriasis. The morphology of the pustules is indistinguishable in both diseases. For the differentiation of AGEP from pustular psoriasis, criteria for histopathologic distinction have been proposed, i.e. papillary edema, vasculitis, exocytosis of eosinophils and single-cell necrosis of keratinocytes in AGEP and acanthosis and papillomatosis in pustular psoriasis.[Sidoroff, et al., 2001] However, acanthosis and papillomatosis are never suspected findings in acute generalized pustular psoriasis. Moreover, vasculitis and single-cell necrosis of keratinocytes, have only eventually been observed in AGEP. The fact that in patients with AGEP the allele HLA-DR-B1*07 has been detected, which is also present in psoriasis patients, might explain the interaction between T-cells and neutrophilic leukocytes in both diseases.[Britschgi, et al., 2001, Pichler, et al., 2002] Discrimination is impossible on the basis of histological criteria, but rather depending on the clinical course, since AGEP ameliorates rapidly following discontinuation of the trigger in contrast to pustular psoriasis that frequently exhibits a prolonged course and is characterized by a difficult therapeutic management.[Sidoroff, et al., 2001, Ziemer and Böer, 2006].

(a)
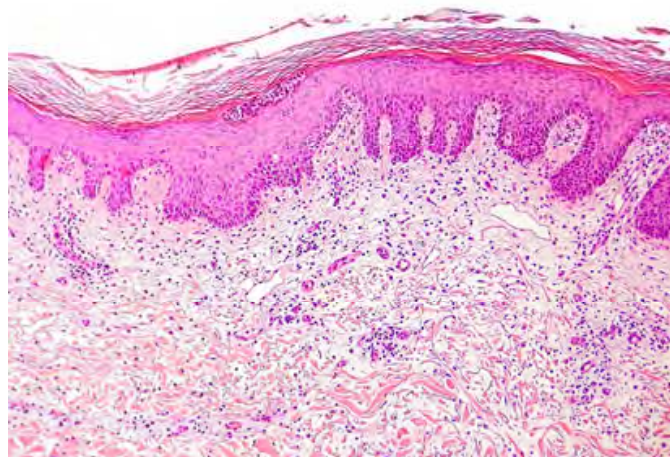
(b)

Fig. 8. A: Acute generalized exanthematous pustulosis. Widespread erythema with hundreds of small, flaccid, confluent, non-follicular pustules, especially along the groins and on the flexor surfaces of the legs.
B: Subcorneal pustules. The epidermis is slightly acanthotic with an orthokeratotic stratum corneum. The adjacent dermis shows superficial, perivascular and interstitial lymphocytic infiltrates with some neutrophilic granulocytes. Features are practically indistinguishable from acute eruptive lesions in pustular psoriasis (hematoxylin-eosin, original magnification x200).

Histopathologically, subcorneal and intraepidermal pustules are moreover the pathognomic feature in IgA-pemphigus.[Harman, et al., 1999] IgA-pemphigus is a rare intraepidermal autoimmune disease characterized by tissue-bound and circulating IgA autoantibodies that target the desmosomal proteins of the epidermis, mainly desmocollin 1 and desmogleins. The main clinical characteristics are erythematous skin lesions with vesiculopustules, erosions, crusts and desquamation favoring the trunk, groins, axillas, and proximal

extremities (figures 9A and 9B). The average age of onset is approximately 50 years. Histological hallmarks of IgA-pemphigus are subcorneal or intraepidermal pustules, and neutrophilic infiltration. Scant epidermal acantholysis may be found, however, acantholysis is not as characteristic as it is in classic pemphigus (figures 9C and 9D). Finally, histologic discrimination of AGEP from IgA-pemphigus is only possible by immunofluorescence. Direct immunofluorescence reveals IgA deposits in the intercellular space throughout the epidermis, more intense in superficial layers and less intense in lower layers. Nevertheless, in some cases IgA autoantibodies do not react with desmogleins or desmocollins.[Niimi, et al., 2000]
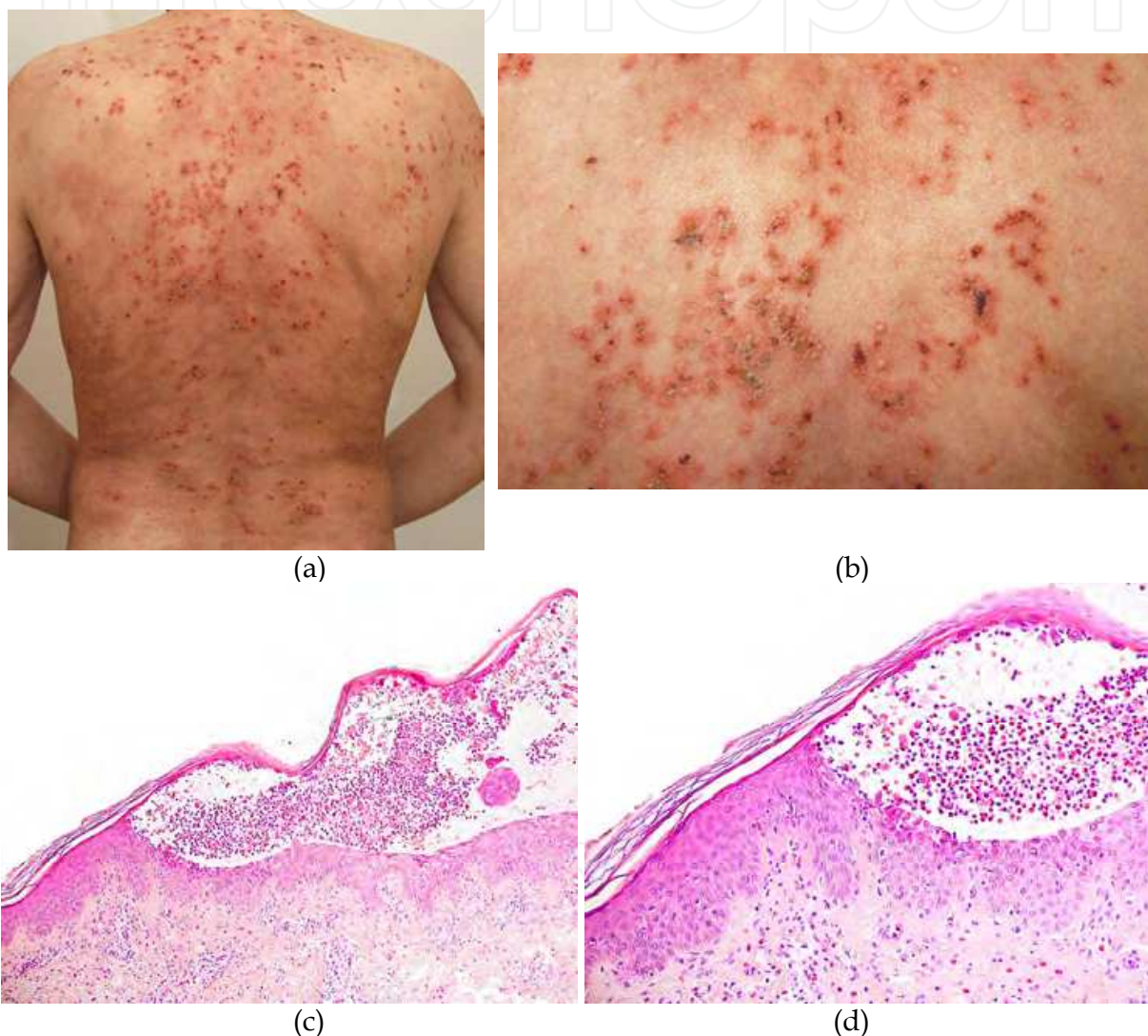

(a)

(b)

(c)

(d)

Fig. 9. A and B: Erythematous plaques with vesiculopustules (in parts with circinar arrangement), erosions, crusts and desquamation, on the trunk of a patient with IgA-pemphigus.
C and D: Subcorneal pustules and neutrophilic infiltration (subcorneal pustular dermatosis type of IgA-pemphigus). Superficial epidermal acantholysis. Dermal superficial mixed cell infiltrate with lymphocytes, eosinophilic and neutrophilic granulocytes, with lymphocytes and eosinophilic granulocytes being also in blister content (C: hematoxylin-eosin, original magnification x100, D: hematoxylin-eosin, original magnification x200).

Within the spectrum of intraepidermal neutrophilic dermatoses is subcorneal pustular dermatosis of Sneddon and Wilkinson.[Sneddon and Wilkinson, 1956] Sneddon and Wilkinson reported a chronic disease with flaccid and aseptic pustules developing predominantly on the trunk and in the groins, axillae and submammary areas. However, subcorneal pustulosis Sneddon-Wilkinson no longer seems to be considered an authentic clinical entity, since under this term unrelated diseases such as pustular psoriasis and IgA-pemphigus are subsumed.[Ziemer and Böer, 2006]

Finally, dermatophyte infections may present with intracorneal and intraepidermal pustules together with a superficial perivascular lymphocytic infiltrate containing neutrophilic granulocytes. Histochemical staining with periodic acid-Schiff (PAS) may be helpful in revealing fungi (figures 10A and 10B).
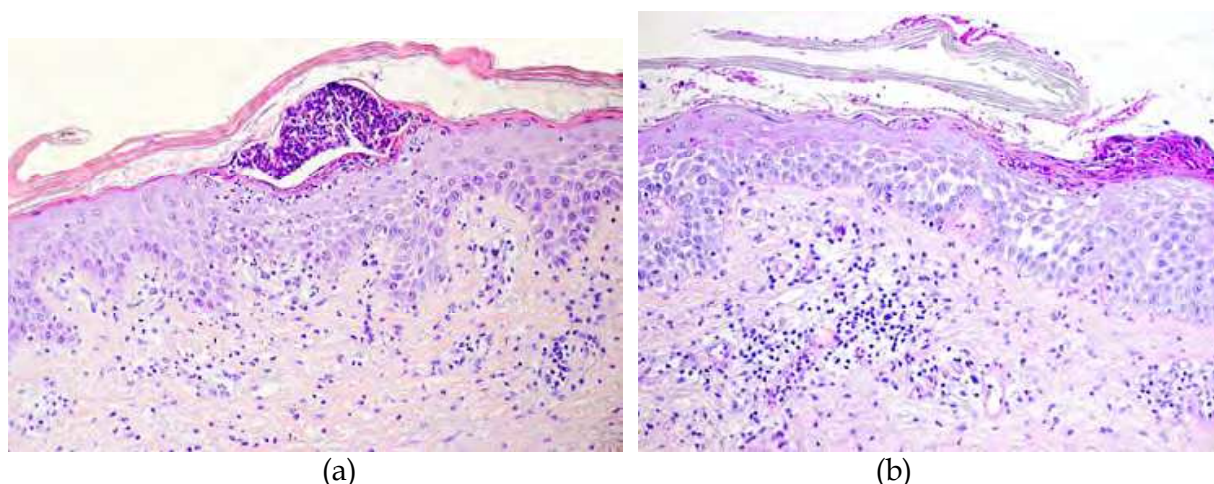

| (a) | (b) |

Fig. 10. A: Tinea corporis. Intra- and subcorneal as well as intraepidermal pustules together with spongiosis and a superficial perivascular lymphocytic infiltrate containing neutrophilic granulocytes. Numerous hyphae within the stratum corneum (hematoxylin-eosin, original magnification x200).

B: Numerous intracorneal hyphae (periodic acid-Schiff, original magnification x200).

5. Hypersensitivity syndrome / drug reaction with eosinophilia and systemic symptoms

5.1 Clinical presentation

In 1996, Bocquet et al. coined the term 'drug rash with eosinophilia and systemic symptoms' (DRESS) for a cutaneous adverse drug reactions associated with fever, exanthema and facial edema, lymphadenopathy, hematologic abnormalities and organ involvement.[Bocquet, et al., 1996] This clinical entity was reported under various names including 'anticonvulsant hypersensitivity syndrome' (HSS), 'drug-induced delayed multiorgan hypersensitivity syndrome' (DIDMOHS) and DIHS (drug-induced hypersensitivity syndrome). The clinical presentation of DRESS includes beside exanthema (figure 11A), hematologic abnormalities, enlargement of lymph nodes and organ involvement.[Bocquet, et al., 1996] The initial exanthema in DRESS may have a morbilliform, sometimes target-like appearance, but then often evolves into erythroderma. Patients have facial edema, which often is more pronounced in the

periorbital region. Sometimes the reaction is accompanied by cheilitis and redness of the pharynx and small erosions on the oral mucosa. Most commonly aromatic anti-convulsant drugs such as phenytoin, carbamazepine, and phenobarbital as well as allopurinol have been reported as triggering DRESS.[Kardaun, et al., 2010b] There are also numerous reports of DRESS after administration of minocycline, thalidomide, and sulfonamides. [Bocquet, et al., 1996] Furthermore, a variety of other drugs, such as lamotrigine as well as valproic acid and non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with this clinical entity.[Wolf, et al., 2005a, Wolf, et al., 2005b] It has also been suggested that virus reactivation may play an important role in the development of DRESS, and possibly also in a recurrent course or persistence of disease.[Kano, et al., 2006] Japanese research groups have consistently shown that human herpes virus 6 (HHV-6) reactivation can be detected in the vast majority of their patients who meet the criteria for DRESS.[Shiohara, et al., 2007, Shiohara, et al., 2006] These authors included HHV-6 reactivation as a diagnostic criterion and coined the term 'drug-induced hypersensitivity syndrome' (DHIS). They speculate that patients fulfilling the criteria of DIHS may represent those with a more severe form of DRESS.[Shiohara, et al., 2007, Shiohara, et al., 2006] However, it has still not been conclusively explained whether the reactivation of HHV-6 and other members of the human herpes virus family are part of the disease itself or whether they are better interpreted as a complication.

To date, various diagnostic criteria have been identified: maculopapular rash developing more than 3 weeks after starting a drug, prolonged clinical symptoms 2 weeks after discontinuation of the causative drug, fever (> 38°C), hematological abnormalities such as eosinophilia (> 1.5×10^9/l), leukocytosis (>$11x10^9$L) and/or the presence of atypical lymphocytes in peripheral blood (> 5%), systemic involvement with lymph node enlargement and involvement of at least one internal organ such as hepatitis (more than twofold increase in transaminase values), interstitial nephritis, interstitial pneumonia, and carditis.[Kardaun, et al., 2007, Shiohara, et al., 2007] Along with the previously mentioned changes seen in blood work, patients may also experience thrombocytopenia and a drop in hemoglobin levels. Pathological liver, kidney, and other laboratory values should be present for several days. Lymph node enlargement should be present at a minimum of two different sites. In organ manifestations, interstitial inflammation (kidney, lung) predominates. Furthermore, joint pain and myositis, including myocarditis may occur.

5.2 Histology

The skin changes seen in DRESS are highly variable, and so is histology, which has not been studied systematically for this disease entity. A variety of histopathologic features has been described in patients with DRESS. Histology in many cases shows solitary to many scattered necrotic keratinocytes with basal cell vacuolar degeneration and papillary edema. The accompanying lymphocytic infiltrate (drug-specific T-cells also play a role in DRESS) may be dense lichenoid with melanophages and some eosinophilc granulocytes, resembling the pattern of a lichenoid drug eruption, or very sparse making the findings compatible with early features of EM (figure 11B). Dermal edema may be present, but is not necessarily so. Sometimes a band-like infiltrate consisting of atypical lymphocytes with epidermotropism is noted that resembles mycosis fungoides.[Bocquet, et al., 1996] Furthermore, leukocytoclastic vasculitis and pseudolymphomatous histology were described in patients with DRESS.[Bocquet, et al., 1996, Chiou, et al., 2008]

(a)
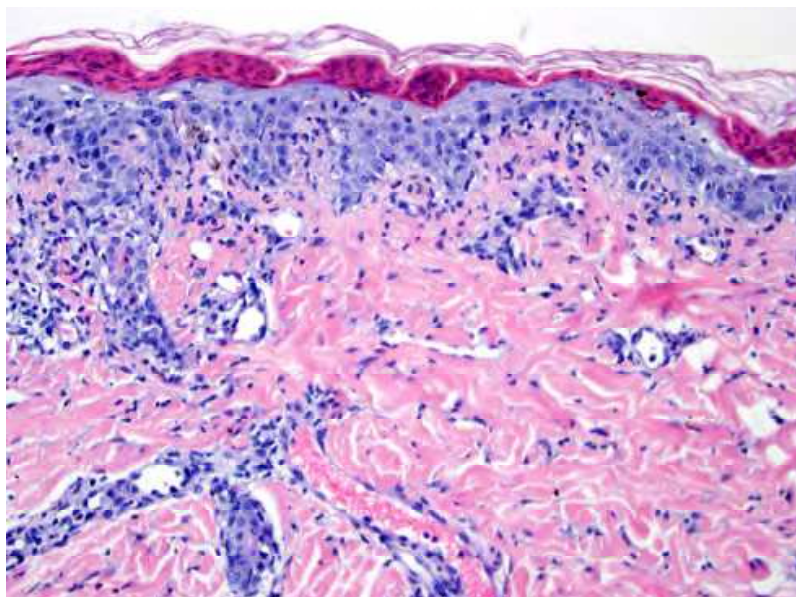
(b)

Fig. 11. A: Generalized erythematous confluent maculo-papules. Detail from the shoulder.
B: One of the possible histopathologic presentations of DRESS. A confluent zone of
parakeratosis below a basket-weave cornified layer. Dermal, superficial, sparse, perivascular
and interstitial infiltrate of lymphocytes. Focal vacuolar alteration along the
dermoepidermal junction in company with some lymphocytes. Scattered necrotic
keratinocytes throughout the entire epidermis. Necrotic keratinocytes also along an
acrosyringium. (hematoxylin-eosin, original magnification x200).

5.3 Differential diagnoses histopathologically

As the histopathologic findings in DRESS are very heterogeneous, final diagnosis is mainly
based on clinical criteria and specific lab values as indicated by the diagnostic score
published by Kardaun and colleagues. [Kardaun, et al., 2007].

6. Toxic erythemas after chemotherapy

6.1 Clinical presentation

Usually toxic erythema after chemotherapy develops on the palms, soles, as well as fingers and toes beginning with dysesthesia followed by edema and erythema. Such condition is known as palmoplantar erythrodysesthesia (PPE). Fissuring and ulceration develop in severe cases, observed in about one third of treated patients, associated with extreme pain, impeded walking and grasping.[Fabian, et al., 1990, Lokich and Moore, 1984, Muggia, et al., 1997, Vogelzang and Ratain, 1985, Zuehlke, 1974] Apart from palms and soles, or rather hands and feet in general, lesions may develop on any other skin area. Severe involvement has been reported on buttocks[Lopez, et al., 1999] and os sacrum.[Muggia, et al., 1997, Uziely, et al., 1995] Further locations are mentioned occasionally. Such changes have been reported under different names, to wit, "chemotherapy-induced toxic erythema" or intertriginous epidermal dysmaturation".[English, et al., 2003, Skelton, et al., 2002] However, proceeding from the influence of mechanical stress in the pathogenesis of palmoplantar erythrodysesthesia and the increased accumulation of the drug in sweat glands, involvement of more extensive parts of the body is most likely. Flexural areas are predisposed due to lasting influence of friction and dense distribution of sweat glands (figures 12A and 12B). Such clinical manifestations are in the spectrum of chemotherapy-induced epidermal changes, showing identical clinical as well as histopathologic features.

6.2 Histology

Despite the numerous publications, histopathologic features have not systematically been described. Typical features include a vacuolar degeneration of the basal layer of the epidermis together with necrotic keratinocytes and mild spongiosis. Dermal changes may include slight papillary edema, dilated blood vessels and a sparse superficial perivascular lymphocytic infiltrate.[Nagore, et al., 2000] Other authors described the condition as marked by hyperkeratosis.[Comandone, et al., 1993, Gordon, et al., 1995] However, hyperkeratosis is not related to the drug reaction but simply explained by the volar location of the lesions. In cases of PPE developing on non-volar skin, this feature is not present. Histopathologic changes of PPE are indistinguishable from other chemotherapy-induced toxic erythemas such as generalized erythema [Hymes, et al., 1985b, Yokel, et al., 1987] or lesions reported as "intertriginous epidermal dysmaturation".[English, et al., 2003] Those conditions show similar epidermal changes with vacuolization and necrotic keratinocytes that are disposed solitary or in clusters near the junction and sometimes also within the middle and upper spinous layers. Often chemotherapeutics cause epidermal maturation disturbances with individual enlarged keratinocytes with abnormally large nuclei and prominent nucleoli (figure 12 C).

6.3 Differential diagnoses histopathologically

Similar changes, however without keratinocyte maturation disturbances, are also present in SJS/TEN or fixed drug eruption. Fixed drug eruptions comparatively show a superficial perivascular, and interstitial infiltrate that includes eosinophilic and neutrophilic granulocytes in most instances. SJS/TEN is best differentiated by clinical impression; however, diagnosis might be difficult in early stages. Principally, it is true that similar histologic features appear in acute graft-versus-host disease.[Beard, et al., 1993] However, graft-versus-host disease is distinguishable, in particular together with the patient's history of stem cell or bone marrow transplantation.

(a)   (b)
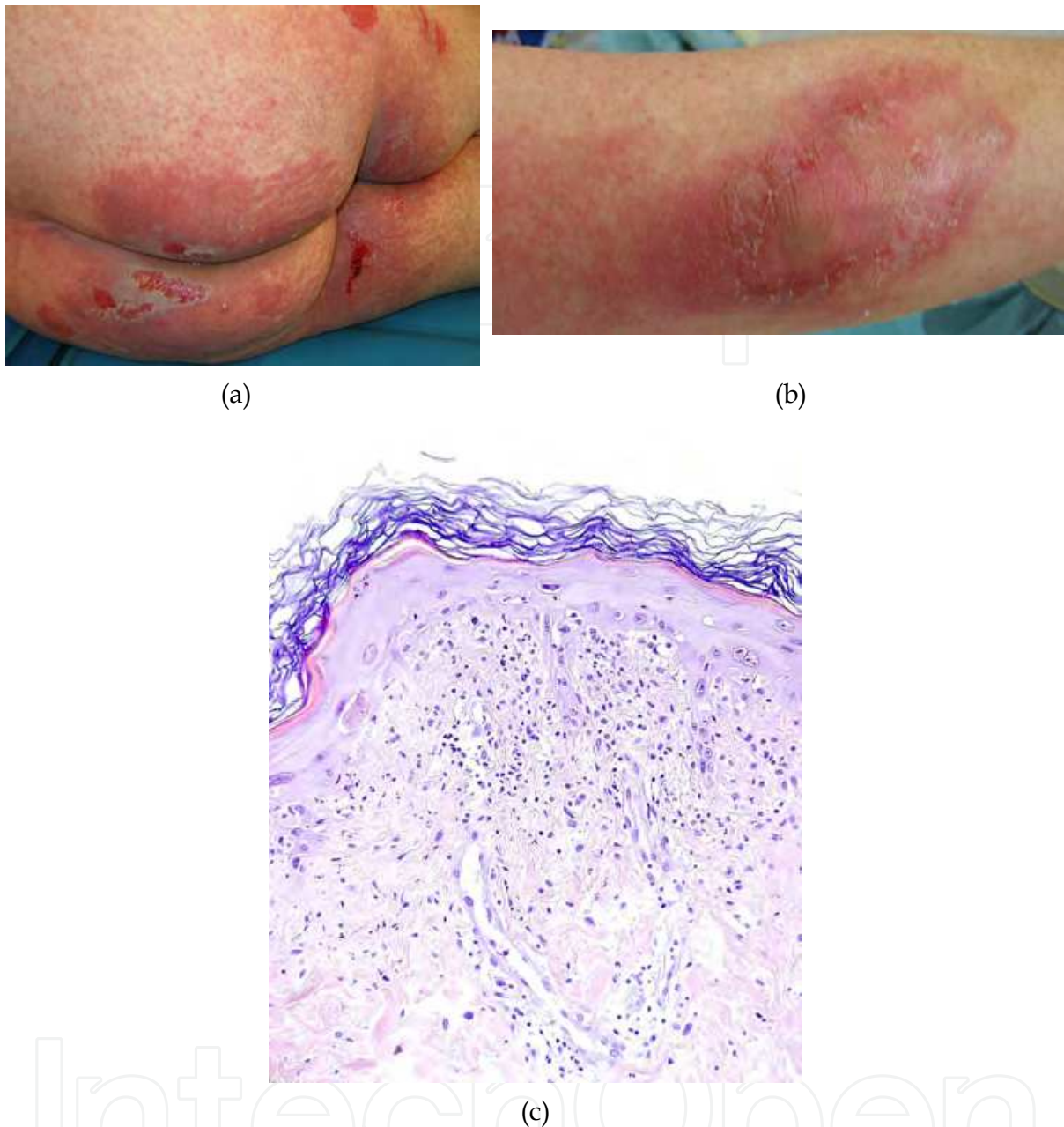

(c)

Fig. 12. A and B: Toxic erythema after chemotherapy with pegylated doxorubicine.
Confluent erythematous macules to large erythemas with epidermolysis. Severe
involvement of mechanically stressed areas such as the buttocks, sacrum and elbows.
C: Vacuolization and necrotic keratinocytes disposed solitary near the junction. Epidermal
maturation disturbances with individual enlarged keratinocytes with prominent nucleoli
(hematoxylin-eosin, original magnification x40).

7. Drug-induced linear-IgA dermatosis

7.1 Clinical presentation

Linear IgA dermatosis (LAD) is a rare autoimmune subepidermal blistering disorder.
Although in most instances idiopathic, LAD may be drug-related. Multiple drugs have been

reported to cause LAD, but vancomycin is reported most frequently.[Brinkmeier, et al., 2003] Classically, LAD shows tense blisters with a linear or annular arrangement on erythematous or normal appearing skin (figures 13A and 13B). Sites of predilection are the trunk, lower extremities, face, perineum and groins. Mucous membrane involvement, reported in idiopathic LAD with about 50%, is observed less often. However, the clinical presentations of both idiopathic and drug-related LAD are variable and may mimic other blistering disorders, such as bullous pemphigoid, dermatitis herpetiformis, and SJS/TEN. In drug-induced LAD, the onset of blisters usually occurs within 7–15 days after beginning of drug use with a mean onset of 8 days and resolution within 2–7 weeks upon drug withdrawal.[Nousari, et al., 1999] Circulating IgA-antibodies are found in less than 40% of cases.[Nousari, et al., 1999] Antigenic targets are heterogeneous.[Wojnarowska, et al., 1999] Patient's sera react against the basement membrane similar to the pattern observed with antibodies to the hemidesmosome components, the alpha6beta4 integrin and the bullous pemphigoid antigens BP230 and BP180, 255-kD and 285-kD proteins as well as collagen VII.[Wojnarowska, et al., 1999]

7.2 Histology

Histologically, LAD shows subepidermal blisters most often with an infiltrate primarily consisting of neutrophils (figures 13C and 13D). As much as clinically, LAD is variable histopathologically, resembling bullous pemphigoid, dermatitis herpetiformis, or epidermolysis bullosa aquisita. Even LAD under the clinical picture of SJS/TEN has been reported.[Schneck, et al., 1999] Direct immunofluorescence of perilesional skin shows linear deposition of IgA along the basement membrane zone, usually in a homogenous pattern (figure 13E). Examples of granular linear deposition at the BMZ have also been identified.[Kuechle, et al., 1994] In addition, C3 deposition at the BMZ is also found on occasion.[Kuechle, et al., 1994]

7.3 Differential diagnoses histopathologically

The diagnosis of LAD cannot be made exclusively based on histopathology. Clinical data as well a results form direct and indirect immunofluorescence have to be considered. Differentiation has to be made in particular from bullous pemphigoid, dermatitis herpetiformis, and epidermolysis bullosa aquisita.

8. Principles and techniques of skin biopsies in drug eruptions [Ackerman, et al., 2005, Weyers and Diaz, 2002]

In patients with severe skin reactions, a skin biopsy should be taken whenever possible. The clinician is obliged to present rudimentary information to the dermatohistopathologist. In several instances histopathologic diagnosis is impossible without any clinical information. Such information is: age and gender of the patient, duration of the disease/biopsied lesion, distribution, configuration and arrangement of lesions, morphology of the individual lesion, localization and type of biopsy, suggested clinical diagnosis and differential diagnosis. The skin biopsy itself follows an essential sequence beginning with the selection of one or more lesions for biopsy, sampling of the tissue with optimal technique, correct fixation of the tissue and finally the accurate histopathologic diagnosis.
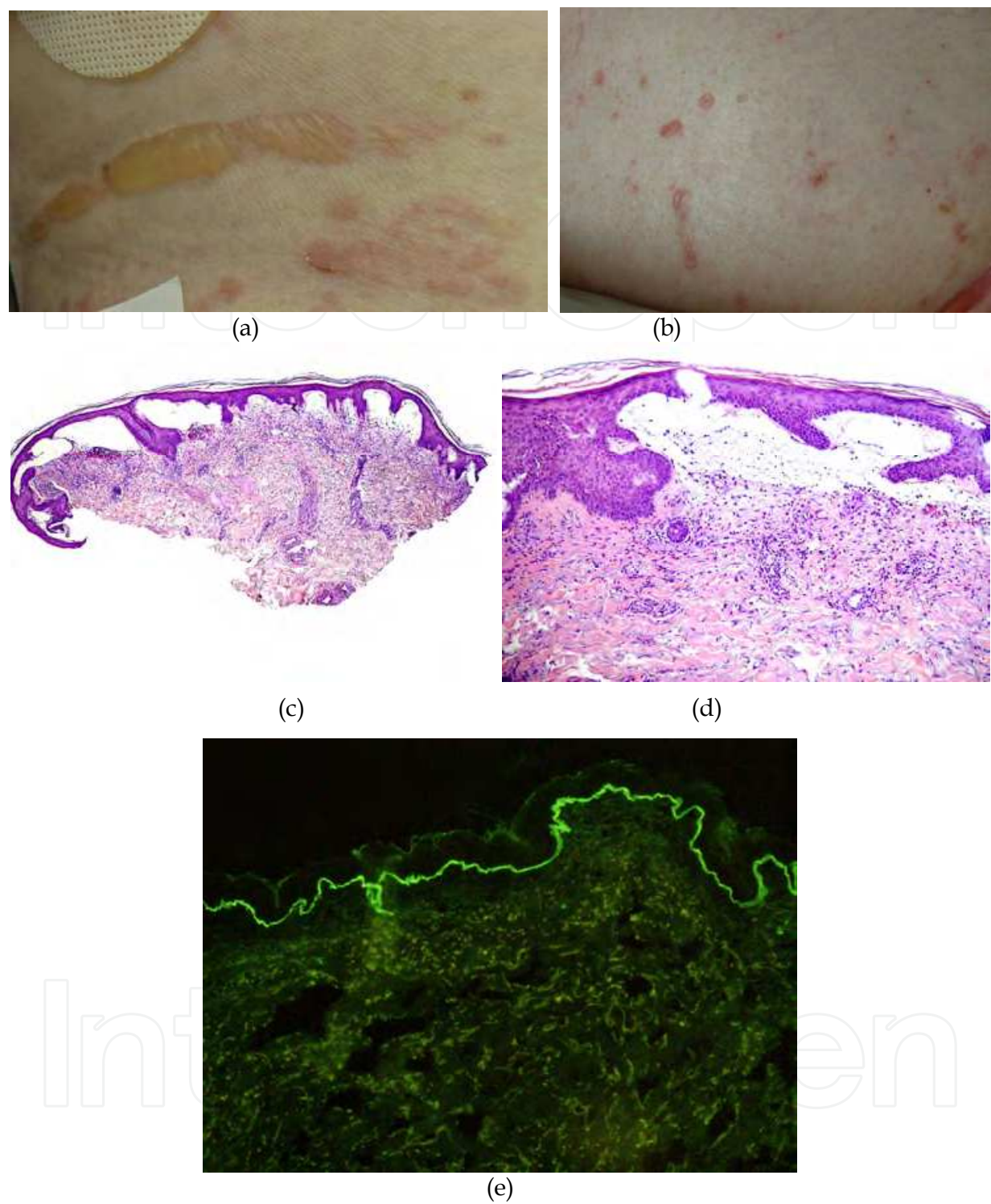
(a)

(b)

(c)

(d)

(e)

Fig. 13. A and B: Tense blisters with a linear or annular arrangement on erythematous but mostly normal appearing skin.
C and D: Subepidermal blisters with an infiltrate of neutrophilic and eosinophilic granulocytes (B: hematoxylin-eosin, original magnification x40, C: hematoxylin-eosin, original magnification x200).
E: Direct immunofluorescence of perilesional skin with linear homogenous deposition of IgA along the basement membrane zone (original magnification x200).

The very-first criterion for the selection of the biopsy-site is the appearance of the efflorescence. As a general rule, biopsies should not be performed from excoriated or scarred lesions, and postinflammatory pigmentary changes. Those, in most instances, do not provide enough information for evaluation of the nature of the underlying inflammatory process. Preferentially, a fresh primary lesion should be selected, without secondary changes. Such are: macules and papules (papules are preferred to macules), papulovesicles, vesicles or pustules. If similar lesions are present on the legs and elsewhere, the biopsy should not be taken from the legs below the knee. In the latter localization changes could be superimposed by stasis dermatitis, complicating the correct histopathologic diagnosis. The biopsy should be performed in the most inflamed area. In some situations it could be helpful to take several or sequential biopsies, in particular if primary lesions are present in different stages of evolution. In cases of vesicular or bullous lesions or even widespread epidermolysis the biopsy should be performed at the periphery of the blister/bulla including larger parts of the surrounding erythema. A biopsy from the blister itself or from the surrounding of older blisters has to be avoided. If the biopsy is taken from the blister itself, the roof of the blister usually gets lost and consequently is not available for histopathologic evaluation. However, even if present, the blister roof is mostly already totally necrotic. Moreover, direct immunofluorescence (where necessary for differential diagnosis) from the blister itself gives false negative results. Furthermore, older blisters are often contaminated with bacteria, show signs of re-epithelialization and again do not allow for direct immunofluorescence. In most instances a punch biopsy is adequate. The biopsy punch is penetrated up to the subcutaneous adipose tissue. The dermis easily separates from the subcutis and the tissue cylinder can be removed gently (to avoid squeezing artefacts) with anatomic forceps. The resulting defect is in most instances closed with a simple suture. A sufficient size (advised are at least 6mm) of the biopsy punch has to be chosen. It has to be kept in mind that subsequent formalin fixation and paraffin embedding reduce the tissue-volume up to one third. Alternatively an excision biopsy with a scalpel can be performed. In particular, biopsies from bullous skin diseases have, apart from tiny tense vesicles, to be performed with a scalpel since a punch biopsy leads to the loss of the epidermis. Shave biopsies *are inadequate*. A shave in general is not a proper technique for biopsy of inflammatory dermatoses. Moreover, histopathologic analysis of a biopsy taken from a blister only does not allow the various types of reaction to be distinguished. After removal of the specimen it should be added to a fixative solution. The common fixative for skin tissue is 4 % or 10 % buffered formalin (formaldehyde). The amount of formalin should excess the volume of the specimen by about 20times. Before further technical preparation, the specimen should be kept in formalin at least for several hours to obtain optimal fixation. No refrigeration is needed. Formalin is inappropriate as transport medium for direct immunofluorescence. Diverse electrolyte solutions have been suggested for immunofluorescence and vary in laboratories of different countries (e.g. Michel´s medium; isotonic sodium chloride solution; or a ready-to-use 'electrolyte solution 77 with glucose 5', Serumwerk Bernburg AG; Germany). In the vast majority of cases histopathologic diagnosis is based on a few hematoxylin & eosin sections. Slides should be systematically screened in all its layers. Further histochemical stainings (such as periodic-acid-Schiff (PAS), Masson Fontana, Giemsa) are usually not necessary, but can be helpful for differential diagnosis. Immunhistochemical stainings are not routinely performed. Immunhistochemical stainings, using polyclonal or monoclonal antibodies binding specifically to tissue antigens, may be of scientific interest concerning CD-antigens or antibodies against cytokines or cytokine receptors. If differential diagnosis includes autoimmune bullous skin disorders,

immunofluorescence should be performed and an additional biopsy specimen (or part of a biopsy) should be taken for direct immunofluorescence. Direct immunofluorescence uses single antibodies which are chemically linked to a fluorophore which can be detected via microscope. Routinely, IgG, IgM, IgA, complement factors (C3) and fibrin are used to detect intra- and subepidermal, basal membrane zone, or perivascular depositions. These may be helpful in differentiating bullous drug eruption from primarily autoimmune-blistering diseases, such as bullous pemphigoid or pemphigus. In particular, this can be of importance in diagnosing drug-induced linear-IgA-dermatosis. For sampling of tissue for direct immunofluorescence the following has to be considered: a biopsy for direct immunofluorescence is more suitable from direct perilesional skin. The biopsy of a blister itself has to be avoided.

Sine qua non, however, prior to any sophisticated technique, is a close contact to the clinician and whenever possible a clinical-histopathologic correlation. In case direct consultation of the patient is not possible, means of teledermatology can be used. Dermatology is ideally suited for telemedicine techniques, as has been shown in a number of recent studies investigating feasibility and reliability of teledermatology.[Massone, et al., 2008] It has generally demonstrated high levels of concordance in diagnoses compared with face-to-face consultations. Moreover, the implementation of virtual slide systems for teledermatopathology has allowed avoiding the limitations imposed by conventional microphotography.[Massone, et al., 2008]

9. Conclusion

Severe cutaneous adverse reactions - mainly related to drugs - include several distinct clinical entities. Within the past decades enormous endeavor has been made to clinically classify SJS, TEN and transitional forms and separate them clinically from EMM. In addition, new disease entities have been described, among them AGEP and DRESS, formerly referred to as hypersensitivity syndrome. GBFDE has been recognized as a severe form of the well known localized fixed drug eruption. In clinical terms, for all those entities substantiated classification criteria have been developed and established in clinical practice. However, despite all these efforts, some diagnostic gaps still exist from a histopathologic point of view. This is based on the fact that several entities of severe cutaneous adverse reactions have histopathologic features in common, impeding the exact separation among each other. In addition, superficially or insufficiently performed biopsies complicate the diagnosis. Generally accepted standards of biopsy and sample processing including (additional) stainings or techniques are still missing. Histopathologic assessment and report of findings is still arbitrary with many inter-observer variations. Since all named entities are quite rare, the quality of histopathologic assessment depends mainly on the experience of the histopathologist. Besides this, difficulties may occur in differentiation of severe cutaneous adverse reactions from unrelated inflammatory skin diseases.

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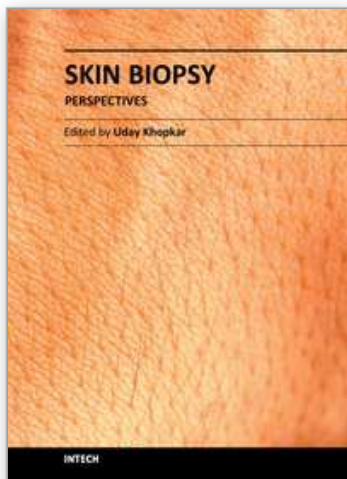
Skin Biopsy - Perspectives

Edited by Dr. Uday Khopkar

Skin Biopsy - Perspectives is a comprehensive compilation of articles that relate to the technique and applications of skin biopsy in diagnosing skin diseases. While there have been numerous treatises to date on the interpretation or description of skin biopsy findings in various skin diseases, books dedicated entirely to perfecting the technique of skin biopsy have been few and far between. This book is an attempt to bridge this gap. Though the emphasis of this book is on use of this technique in skin diseases in humans, a few articles on skin biopsy in animals have been included to acquaint the reader to the interrelationship of various scientific disciplines. All aspects of the procedure of skin biopsy have been adequately dealt with so as to improve biopsy outcomes for patients, which is the ultimate goal of this work.

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