DERMATOLOGY PRACTICAL & CONCEPTUAL
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Histopathology of drug eruptions – general criteria, common patterns, and differential diagnosis

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Key words: drug eruptions, histopathology, skin

Citation: Weyers W, Metze D. Histopathology of drug eruptions – general criteria, common patterns, and differential diagnosis. Dermatol Pract Concept 2011;1(1):9. http://dx.doi.org/10.5826/dpc.0101a09.

Editor: Harald Kittler, M.D.

Received: April 11, 2011; **Accepted:** May 18, 2011; **Published:** October 31, 2011

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Funding: None.

Competing interests: The authors have no conflicts of interest to disclose.

Both authors have contributed significantly to this publication.

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ABSTRACT

Drug eruptions are among the most common inflammatory diseases of the skin and also among those biopsied most often. Yet, the value of histopathologic examination of drug eruptions has often been disputed. One reason is that the spectrum of histopathologic changes in drug eruptions is broad. Nevertheless, each histopathologic pattern assumed by drug eruptions has a limited number of differential diagnoses, and numerous criteria and clues are available to distinguish drug eruptions from other diseases associated with those patterns. By recognition of common patterns, consideration of differential diagnoses, and attention to distinct clues, a histopathologic diagnosis of drug eruption can usually be made with confidence.

Introduction

Drug eruptions are among the most common diseases of the skin. In most instances, they are diagnosed readily on the basis of clinical picture and clinical history, namely, a symmetrical, widespread maculopapular eruption following recent intake of a newly prescribed drug. In many cases, however, diagnosis is not so apparent because the patient does not give a reliable clinical history, because the patient takes several drugs since a long time, because the eruption is caused by food additives rather than a medication, or because the eruption mimicks other skin diseases. The latter may range from psoriasis to pityriasis rosea, from lichen planus to mycosis fungoides, from urticaria to the urticarial stage of autoimmune bullous diseases, from post-herpetic erythema multiforme to lupus erythematosus, and from porphyria to scleroderma. Because of their frequency and the wide spectrum of clinical presentations, drug eruptions are biopsied often and are among the most common inflammatory skin diseases encountered by histopathologists.

The spectrum of histopathologic presentations of drug eruptions, however, is not smaller than that of clinical ones.

In 1997, Ackerman emphasized that "drugs can elicit any of the nine basic patterns of inflammatory diseases in the skin, and none of those patterns is specific for a drug eruption. There is but one exception, to date, to the precept that drug eruptions cannot be diagnosed with specificity through the microscope, namely, fixed drug eruption" [1].

In more than a decade following that sobering assessment of the import of histopathological analysis for the diagnosis of drug eruptions, only little progress has been made. For some differential diagnoses, criteria have been set forth to facilitate distinction of drug eruptions from other inflammatory skin diseases, e.g., lichenoid drug eruption from lichen planus, psoriasiform drug eruption from psoriasis vulgaris, and granulomatous drug eruption from granuloma annulare. In a recent review of histopathologic patterns of cutaneous drug eruptions, one finding indicative of drug eruptions in general has been noted, namely, combination of different patterns in a single specimen. Another finding mentioned as "a diagnostic clue" to drug eruptions was presence of eosinophils, but the authors emphasized that "one must be cautious not to consider them the panacea of histologic diagnosis for a drug reaction as their presence does not make a drug reaction the correct diagnosis. Conversely, the absence of eosinophils does not rule out a drug eruption. In other words, they may or may not be present in these reactions" [2].

The vagueness of histopathologic descriptions of drug eruptions, and the caution exercised in interpretation of them, has created the impression that biopsy of drug eruptions has little value. Current textbooks of dermatology emphasize that, in reactions to drugs, "the histological changes are no more distinctive than are the clinical features," the only exceptions being "vegetating iododermas and bromodermas, certain lichenoid eruptions and fixed drug eruptions," in which "the histological changes … are not pathognomonic, but are sufficiently characteristic to be of importance in differential diagnosis" [3]. No such importance is attributed to histopathologic study of morbilliform drug eruptions, which have been estimated to account for 95% of all drug eruptions [4]. The latter are said to show only "non-specific lymphohistiocytic infiltrates in perivascular arrangement. For that reason, histopathologic examination can contribute only little to diagnosis and differential diagnosis" [5]. As a consequence, it has been stated unequivocally that "biopsy of morbilliform eruptions is not recommended" [6].

In our view, those conclusions are wrong and potentially harmful, as they may lead to incorrect diagnoses and mismanagement of patients. It is true that histopathologic diagnosis of drug eruptions may be difficult, may remain equivocal, and require clinico-pathologic correlation, but this is true for all diseases. Compared to other inflammatory diseases of the skin, histopathologic diagnosis of drug eruptions is impeded by the fact that drugs may not only cause eruptions mimicking other diseases, but may elicit those diseases, e.g., drug-induced psoriasis, pemphigus, lupus erythematosus, or linear IgA dermatosis. In those instances, naturally, biopsy specimens reveal changes of the authentic disease.

Some drug eruptions are thought to be caused by activation of a latent infection by viruses, such as human herpesvirus 6, cytomegalovirus, and Epstein Barr virus, which may explain why viral exanthemata and drug eruptions may be indistinguishable clinically and histopathologically [7-9]. Viral exanthemata are biopsied rarely, and the spectrum of histopathologic changes induced by them is not well known. This is another factor hampering distinction between viral exanthemata and drug eruptions. Viral diseases have been claimed to be associated commonly with a lymphocytic vasculitis, a finding that, in our experience, is rare in drug eruptions [10]. Some viral exanthemata can be recognized by distinctive changes, such as ballooning and multinucleated keratocytes in measles and keratocytes with steel-grey nuclei with margination of nucleoplasm in infections by herpesviruses [11–12]. Often, however, there are no such distinguishing features. Common patterns of viral exanthemata include a superficial perivascular infiltrate of lymphocytes without associated epidermal changes, a superficial vacuolar interface dermatitis, sometimes associated with eosinophils and neutrophils, a lichenoid dermatitis, and a mild spongiotic dermatitis. All those patterns may also be encountered in drug eruptions [10].

Despite those limitations, drug eruptions can usually be diagnosed with confidence on the basis of histopathologic changes alone. It is common practice in laboratories of dermatopathology to examine sections of biopsy specimens before obtaining any clinical information. If this is done, and the presumptive diagnosis of a drug eruption is rendered, it is our experience that the latter is usually corroborated by the clinical diagnosis of the referring physician. All histopathologic diagnoses must be submitted to critical review in the context of additional information, such as clinical findings, clinical history, and laboratory data. This does not distinguish drug eruptions from any other skin disease, and the reliability of histopathologic diagnosis of a drug eruption is not smaller than that of diseases for which biopsy is recommended without reservation, be it lichen planus, lupus erythematosus, or granuloma annulare.

In the following, we wish to discuss criteria that aid in recognition of drug eruptions in general, describe common patterns of drug eruptions, and discuss the differential diagnosis of those patterns. The statements made are based on personal experience of many years, on a review of the literature, and on systematic analysis of histopathologic findings in 60 cases of maculopapular drug eruption in which the eliciting drugs were known and the eruption cleared following cessation of them. In that study, cases diagnosed clinically

as drug-induced erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, as well as lichenoid and bullous drug eruptions were excluded. Results of that study are being published separately [13]. For this review, we re-examined biopsy specimens of 300 consecutive cases seen in our laboratory in which the diagnosis of a drug eruption of any kind was given both, histopathologically and clinically, but in which data concerning the eliciting drug and follow-up were available for only a minority of patients. The purpose of that endeavor was to assess the relative frequency of different histopathologic patterns of drug eruptions in the routine material of a laboratory of dermatopathology. Findings of that survey are summarized in Table 1.

General criteria

Several findings are typical of drug eruptions in general. Some of them may appear banal. Nevertheless, when encountered in association with a particular pattern, they may help to rule out other diseases associated with that pattern. These findings include:

1. Signs of acuteness

Drug eruptions, as their name indicates, are usually acute, eruptive diseases that appear suddenly and progress rapidly in both, extension and intensity. As a consequence, they are usually biopsied early in their course. Histopathologic evidence of an eruptive disease biopsied early in its course includes

- a normal basket-woven cornified layer despite spongiosis or hydrops of keratocytes in the basal or spinous zone (the reason being that the interval of time between onset of the eruption and biopsy of it is too small to permit alterations in the lower epidermis to affect to stratum corneum),
- edema of the papillary dermis,
- angiectases of capillaries and venules in the superficial dermis,
- many neutrophils in the lumina of dilated venules,
- extravasation of erythrocytes.

By contrast, signs of chronicity militate against a drug eruption, namely,

- marked epithelial hyperplasia,
- marked hyperkeratosis,
- coarse collagen bundles in elongated dermal papillae,
- fibrosis of the papillary and superficial reticular dermis,
- numerous melanophages or siderophages in the superficial dermis.

Table 1: Histopathologic findings in 300 cases with the clinical and histopathologic diagnosis of drug eruption

	Pattern										
	Lymphocytic dermal without epidermal Changes (n=12)	*Superficial and deep dermal with eosinophils and neutrophils (n=12)*	*Severe vacuolar interface dermatitis (n=38)*	*Mild vacuolar interface dermatitis (n=83)*	*Lichenoid dermatitis (n=36)*	*Lichenoid psoriasiform dermatitis (n=18)*	*Spongiotic dermatitis (n=62)*	*Pustular dermatitis (n=19)*	*Subepidermal bullous dermatitis (n=6)*	*Granulomatous dermatitis (n=12)*	*Leukocytoklastic vasculitis (n=2)*
Superficial	10	0	28	55	26	11	54	18	4	0	0
Superficial and deep	2	12	10	28	10	7	8	1	2	12	2
Perivascular	11	0	5	12	0	0	6	0	0	0	0
Interstitial	1	12	33	71	36	18	56	19	6	12	2
Vacuolar											
+	0	0	0	83	28	17	41	11	3	6	1
++	0	0	38	0	8	1	0	2	3	0	0
Spongiosis											
+	0	0	38	44	16	18	56	12	2	3	0
++	0	0	0	0	0	0	6	7	0	0	0
Necrotic keratinocytes											
+	0	0	4	62	22	11	10	7	5	0	0
++	0	0	34	0	13	4	0	1	1	0	0
Eosinophils											
+	0	8	20	51	17	13	45	13	6	10	0
++	0	4	12	18	2	4	13	6	0	0	2
Neutrophils											
+	0	10	18	40	4	6	33	0	4	2	0
++	0	2	8	0	0	1	3	19	0	0	2
Neutrophils in vessels	1	10	19	29	9	7	26	16	3	6	2

Of course, drug eruptions may also be chronic and may be biopsied after many months. Signs of chronicity, therefore, do not rule out a drug eruption. For example, anticonvulsant drugs such as phenytoin and carbamazepin may elicit chronic drug eruptions that, because of a lichenoid infiltrate of lymphocytes with largish nuclei, epidermotropism, epidermal hyperplasia, and fibrosis of the papillary dermis, may mimick mycosis fungoides [14–17]. Fixed drug eruptions that have recurred several times at the same site are also associated with signs of chronicity, namely, marked fibrosis of the papillary dermis and many melanophages. Nevertheless, most drug eruptions show signs of acuteness rather than chronicity, and those signs are among the most important clues to histopathologic diagnosis of a drug eruption (Figure 1 a, b).

2. Vacuolar interface dermatitis

The most common histopathologic pattern of drug eruptions is a vacuolar interface dermatitis. The extent of interface changes varies greatly, from extensive vacuolar alteration at the dermo-epidermal junction and many necrotic keratocytes at all levels of the epidermis, as in most cases of fixed drug eruption and toxic epidermal necrolysis, to focal and very subtle changes. The latter may not be apparent immediately. When a drug eruption is suspected, it is worthwhile to screen all sections of the biopsy specimen for evidence of a subtle vacuolar interface dermatitis.

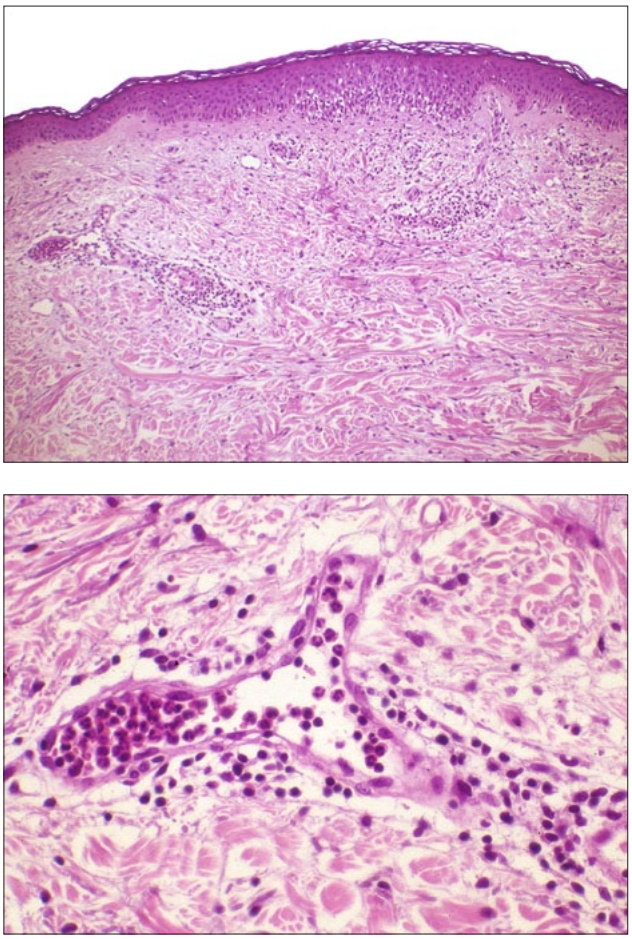

Figure 1. a) Spongiotic drug eruption with mild spongiosis in the lower half of the epidermis and a basket-woven cornified layer. b) umina of dilated venules in the upper dermis are filled with clusters of neutrophils.

3. Presence of neutrophils and eosinophils

Drug eruptions, like many other inflammatory diseases, are often associated with an infiltrate of eosinophils and/or neutrophils. In a recent study of morbilliform drug eruptions, eosinophils were found in 50% and neutrophils in 36% of cases [18]. In our study of maculopapular drug eruptions in which the eliciting agents were known, the numbers were higher, namely, 60% for eosinophils and 50% for neutrophils. In brief, eosinophils and/or neutrophils are present in the majority of drug eruptions. Eosinophils are more common, but because they are seen in such a wide variety of diseases, they are less distinctive for drug eruptions. An infiltrate of neutrophils is rarer but of greater diagnostic import. The combination of both, eosinophils and neutrophils, is seen in only a limited number of diseases, including urticaria, autoimmune bullous diseases, Sweet's syndrome, reactions to arthropod assaults, some folliculitides, and, most commonly, drug eruptions.

Most of those differential diagnoses are characterized by findings not usually seen in drug eruptions, such as a very dense infiltrate of neutrophils in Sweet's syndrome, a wedge-shaped infiltrate in responses to arthropod assaults, or a florid suppurative folliculitis. Drug eruptions also have additional features that often allow a specific diagnosis to be made. A sparse perivascular and interstitial infiltrate of neutrophils and eosinophils in concert with subtle vacuolar changes at the dermo-epidermal junction is virtually diagnostic of a drug eruption.

4. Several histopathologic patterns in a biopsy specimen

Drug eruptions may present themselves with different histopathologic patterns. Each of those patterns may be caused by a variety of inflammatory skin diseases. A combination of two or more patterns in a single biopsy specimen, however, favors a drug eruption.

As mentioned above, the most common pattern of drug eruptions is an interface dermatitis which is usually also seen when patterns are combined. Regardless of the pattern of inflammation, ranging from superficial perivascular to superficial and deep perivascular and interstitial, from spongiotic to granulomatous, and from subcorneal pustular to subepidermal bullous, presence of tiny foci of vacuolar changes at the junction, sometimes associated with but a few necrotic keratocytes, should raise suspicion of a drug eruption (Figure 2 a, b).

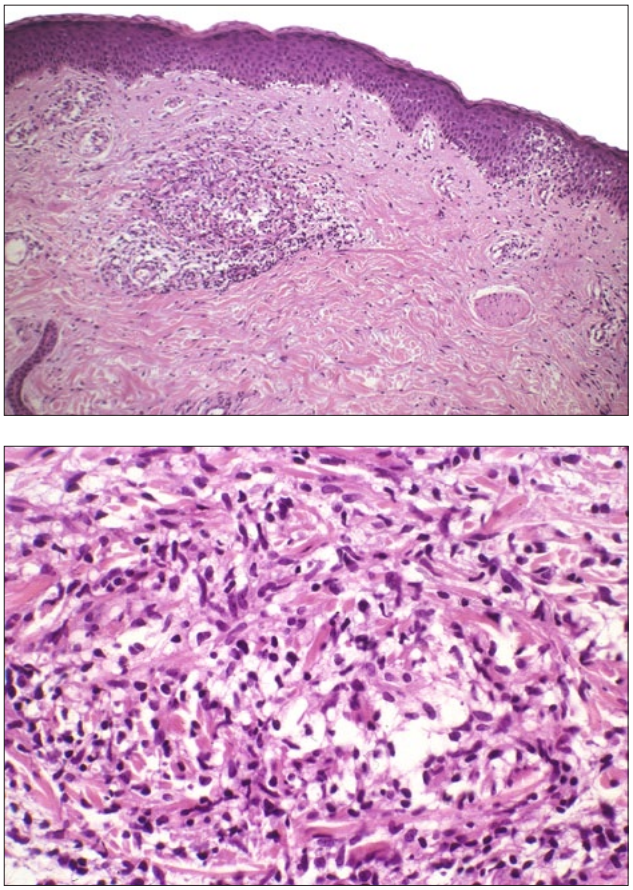

Figure 2. a) Combination of patterns in a granulomatous drug eruption: vacuolar changes at the dermo-epidermal junction are associated with focal spongiosis and a small granuloma in the upper dermis. b) Small granuloma interspersed with many lymphocytes in the upper dermis.

5. Several discrete foci of inflammation in a biopsy specimen

Most maculopapular drug eruptions are generalized eruptions in which the degree of inflammation varies. Individual lesions tend to be circumscribed poorly and blend into one another. Accordingly, there may be two or more discrete foci of inflammation in a punch biopsy specimen, separated from one another by areas in which the inflammation is less pronounced. This may help to distinguish drug eruptions from diseases with distinct papules, such as lichen planus and pityriasis lichenoides.

6. Constellation of findings not corresponding to any well-defined disease

Drug eruptions may mimic many other skin diseases. Sometimes, histopathologic findings of a drug eruption are indistinguishable from those of another disease, but in most instances, the histopathologic presentation of the latter is modified, e.g., by parakeratosis and a diminished granular zone in what seems to be lichen planus, by numerous eosinophils in what seems to be pustular psoriasis, or by deep extension of the infiltrate in what seems to be bullous pemphigoid. A constellation of findings that does not correspond to any well-defined disease should raise suspicion of a drug eruption [2].

7. Other clues to diagnosis of a drug eruption

Drug eruptions usually affect trunk and extremities. Palms and soles are involved only rarely, and if they are, there are usually also lesions at other sites that are selected for biopsy. As a consequence, drug eruptions, with the exception of fixed drug eruption, are biopsied rarely on palms and soles. The same is true for the face and scalp. Hence, when one sees a biopsy specimen from face, scalp, or palmar and plantar surfaces, a drug eruption is unlikely.

Drug eruptions are most common in elderly patients. Consideration of the age of patients, including histopathologic indicators of it, such as pronounced solar elastosis, may facilitate especially distinction between drug eruptions and viral exanthemata.

Drug eruptions may be associated with atypia of keratocytes. The affected cells are swollen, have large nuclei, and either large, prominent nucleoli or irregularly dispersed chromatin. Nuclei may also be hyperchromatic. In contrast to epithelial neoplasms, atypical keratocytes are usually confined to discrete foci and are not crowded together closely. They have been described especially in reactions to chemotherapeutic drugs [19–20]. However, they may be seen in response to a wide variety of drugs and seem to be related to interface changes, since they are also encountered episodically in other interface dermatitides, such as lichen sclerosus and lupus erythematosus. In brief, atypical keratocytes are neither a sensitive nor a specific finding. Nevertheless, because they are more common in drug eruptions than in other inflammatory skin diseases, they may serve as a clue to histopathologic diagnosis of a drug eruption (Figure 3 a, b).

Common patterns and differential diagnoses

Lymphocytic dermatitis without epidermal changes

This is the least distinctive pattern of a drug eruption. It is not very common, accounting for only 12 of 300 (4%) consecutive cases examined. Often subtle vacuolar changes at the junction or slight spongiosis in the lower half of the spinous zone can be detected in sections of what, at first blush, seems to be a perivascular lymphocytic dermatitis without epidermal changes. In other cases, scrutiny reveals eosinophils and/or neutrophils in addition to lymphocytes.

When neither subtle vacuolar changes at the junction, spongiosis, nor eosinophils and neutrophils are present, the differential diagnosis includes a wide variety of diseases. A

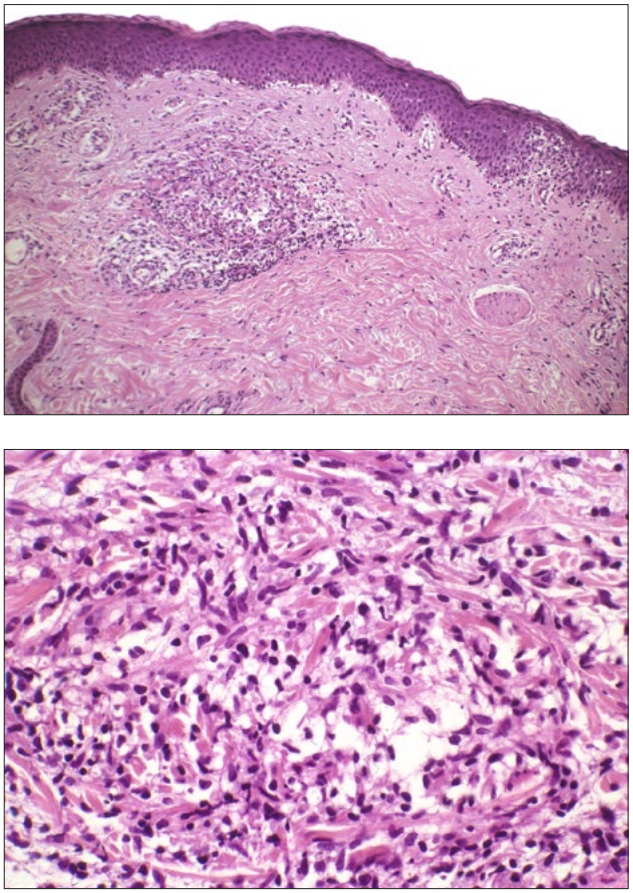

Figure 3. a) Superficial vacuolar interface dermatitis with atypical keratocytes caused by an angiotensin-converting enzyme antagonist. b) Nuclei of keratocytes are large; some are hyperchromatic, others have prominent nucleoli.

sparse superficial perivascular infiltrate of lymphocytes is physiologic and may be seen in clinically normal skin as well as in the earliest stage of diseases that, at a later stage, are associated with distinctive histopathologic findings. Hence, if the infiltrate is very sparse, a specific diagnosis, and even a meaningful differential diagnosis, cannot be rendered.

A relatively dense perivascular infiltrate of lymphocytes without associated epidermal changes, however, is not physiologic and excludes diseases that, given the degree of inflammation, should also sport additional findings. In that instance, the differential diagnosis includes Schamberg's disease, secondary syphilis, erythema chronicum migrans, polymorphous light eruption, pernio, lupus erythematosus tumidus (including Jessner's lymphocytic infiltration and reticular erythematous mucinosis), viral exanthemata, and drug eruptions.

Drug eruptions with a wholly lymphocytic infiltrate usually affect only the superficial dermis. In the 300 consecutive cases diagnosed clinically as a drug eruption, we encountered only two with a superficial and deep wholly lymphocytic infiltrate. By contrast, the infiltrates in infections by borrelia, polymorphous light eruption, pernio, and tumid lupus erythematosus usually affect the entire dermis. Other findings may also be helpful to rule out differential diagnoses, such as mucin in the interstitial dermis in tumid lupus erythematosus, some plasma cells in secondary syphilis, and erythrocytes in dermal papillae and epidermis in Schamberg's disease. Drug eruptions are also associated commonly with extravasation of erythrocytes and may be indistinguishable from Schamberg's disease [2]. In hemorrhagic drug eruptions, however, erythrocytes are mostly seen around venules of the superficial plexus rather than in discrete collections in dermal papillae. When consisting of lymphocytes only, the infiltrate in drug eruptions tends to be restricted to perivascular areas with only little involvement of the interstitium. This helps to distinguish drug eruptions from infections by borrelia which are usually associated with many lymphocytes in the interstitial dermis.

Superficial and deep perivascular and interstitial dermatitis with eosinophils and neutrophils

This pattern, in the absence of significant epidermal changes, was found in 12 of 300 consecutive cases of drug eruptions (4%). If the infiltrate is sparse, the most important differential diagnosis is urticaria. In such cases, the epidermis and papillary dermis should be screened for subtle alterations that may be visible only in step sections, such as slight focal spongiosis or interface changes, slight subepidermal fibrosis or some melanophages. Any of those findings militates against urticaria. The same is true for perivascular accentuation of the infiltrate. Other clues to an urticarial drug eruption are pronounced edema of the papillary dermis and more neutrophils than normally seen in urticaria [2]. However, even in cases in which none of those clues to a drug eruption are encountered, causation of urticaria by a drug cannot be ruled out.

If the infiltrate is denser, the most important differential diagnosis is a response to an arthropod assault. Features in favor of the latter include focal accentuation of the infiltrate or confinement of it to one area of the biopsy specimen, wedge-shaped configuration of the infiltrate, marked edema of the reticular dermis with smudging of collagen fibers, and a single focus of spongiosis, especially if located above the deepest extension of the infiltrate. By contrast, features favoring a drug eruption include a relatively homogeneous distribution of the infiltrate and several foci of subtle epidermal changes.

Vacuolar interface dermatitis

Vacuolar interface dermatitis is the most common pattern of drug eruptions. In a recent study of morbilliform drug eruptions, interface changes were described in 53% of cases [18]. In our study of maculopapular drug eruptions, subtle vacuolar changes at the dermo-epidermal junction were noticed in 58 of 60 cases (97%), and of the 300 consecutive cases,

141 (47%) were classified as vacuolar interface dermatitis, although subtle vacuolar changes at the junction were also present in cases in which another pattern predominated.

The degree of interface changes is highly variable, ranging from slight vacuolar alteration at the junction with few, if any, necrotic keratocytes to severe vacuolar changes with myriad necrotic keratocytes at the junction and in the upper reaches of the epidermis and, sometimes, confluent epidermal necrosis. Cases with severe interface changes correspond, at least in part, to drug-induced erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. The diseases entering into differential diagnosis of that pattern are different from those that must be considered in drug eruptions with only mild interface changes. For that reason, we made a distinction between severe and mild vacuolar interface dermatitides.

a) Severe vacuolar interface dermatitis

This pattern was encountered in 38 of 300 cases (13%), 13 of which were diagnosed clinically as fixed drug eruption. The latter did not differ substantially from other cases of this group. In 26 cases, numerous eosinophils and neutrophils were present in the infiltrate, and in 10 cases, at least some eosinophils and/or neutrophils could be detected. Only four cases were associated with a wholly lymphocytic infiltrate. Areas of confluent epidermal necrosis were observed in nine cases, including four cases of fixed drug eruption. In 10 cases (including five of fixed drug eruption), the infiltrate extended into the lower half of the dermis.

The differential diagnosis of these cases includes post-herpetic erythema multiforme. The epidermal changes are indistinguishable. In general, the infiltrate in post-herpetic erythema multiforme is more perivascular and restricted to the superficial dermis, but involvement of the interstitium and the lower dermis may occur. In the vast majority of cases of post-herpetic erythema multiforme, the infiltrate is wholly lymphocytic. In the literature, eosinophils have been reported in erythema multiforme but, with rare exceptions [21], no clear distinction was made between post-herpetic and drug-induced cases [22–23]. When those cases were distinguished, eosinophils were found to be more common in drug-induced erythema multiforme [24–25]. This corresponds to our own experience. For the purpose of this study, we re-examined biopsy specimens of five patients with recurrent post-herpetic erythema multiforme and four patients with erythema multiforme who were younger than 20 years. In three cases of post-herpetic erythema multiforme, few neutrophils were spotted in the papillary dermis, and in one case, a single eosinophil was found. This differs markedly from the high frequency and often high number of eosinophils and neutrophils in drug eruptions with severe vacuolar interface changes (Figure 4 a, b).

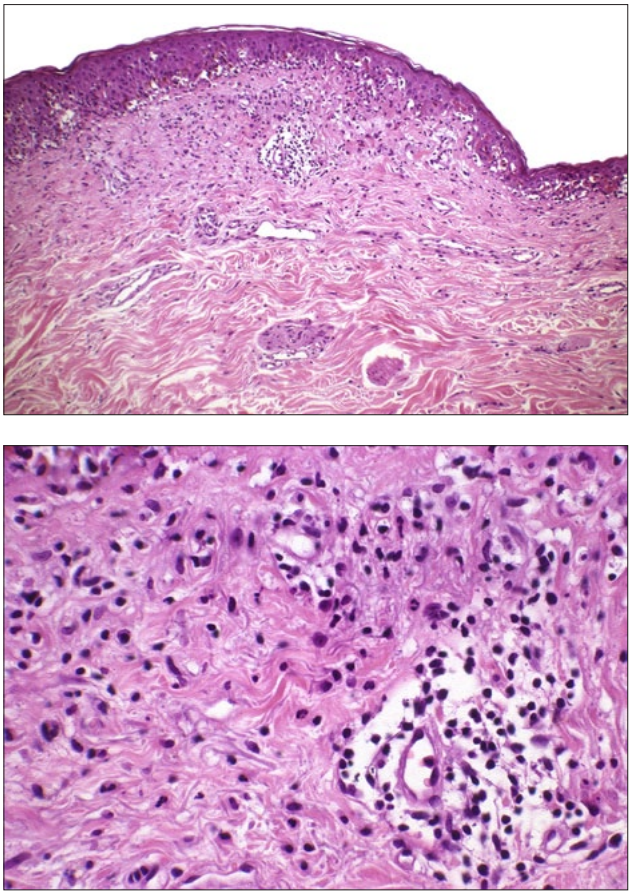

Figure 4. a) Superficial vacuolar interface dermatitis with a relatively sparse perivascular and interstitial infiltrate, dilated venules in the upper dermis, many necrotic keratocytes, and a basket-woven cornified layer. b) The infiltrate consists of lymphocytes, eosinophils, and neutrophils. The constellation of findings is typical of a drug eruption.

Another clue to drug etiology that has been reported in erythema multiforme is acrosyringeal concentration of necrotic keratocytes, a phenomenon that may be related to concentration of drugs in sweat and to direct toxic effects on eccrine ductal epithelium [25]. We found an accumulation of necrotic keratocytes around acrosyringia in nine of the 40 drug eruptions with severe vacuolar interface changes, whereas it was not encountered in post-herpetic erythema multiforme. Hence, although present in only a minority of cases, concentration of necrotic keratocytes around acrosyringia may help to distinguish drug eruptions from post-herpetic erythema multiforme.

Other diseases entering into the differential diagnosis of drug eruptions with severe vacuolar interface changes are acute cases of pityriasis lichenoides and lupus erythematosus. In the latter conditions, the infiltrate is usually superficial and deep, whereas it is only superficial in the majority of DEs with severe interface changes. In pityriasis lichenoides, the infiltrate is often wedge-shaped, a pattern not observed in drug eruptions, and usually consists of lymphocytes only, whereas most drug eruptions are associated with neutrophils

and/or eosinophils. Other findings encountered commonly in pityriasis lichenoides, but not in drug eruptions, are mounts of parakeratosis and/or scale-crusts housing neutrophils.

Lupus erythematosus is typified by a superficial and deep perivascular vacuolar interface dermatitis composed of lymphocytes only. Drug eruptions may also show a wholly lymphocytic infiltrate, but in those cases, the infiltrate is usually confined to the superficial dermis, which is rare in lupus erythematosus. Cases of lupus erythematosus confined to the superficial dermis usually show a perivascular arrangement of the infiltrate. By contrast, it has been emphasized that presence of interface changes in drug eruptions is "strongly associated with an interstitial infiltrate" [18]. This corresponds to our own experience.

In acute cases of lupus erythematosus, the infiltrate tends to be perivascular and interstitial and is associated with neutrophils and, sometimes, eosinophils. These cases may be very similar to drug eruptions. However, eosinophils, if present at all, are rare and outnumbered vastly by neutrophils. The infiltrate, while often extending to the interstitium, tends to show a stronger perivascular accentuation than in most drug eruptions. Moreover, some cases of acute lupus erythematosus show smudging of the dermo-epidermal interface and increased amounts of mucin in the reticular dermis. Together, those criteria usually allow acute lupus erythematosus to be distinguished from drug eruptions.

Yet another differential diagnosis is acute graft-versus-host disease. The latter typically presents itself as a superficial vacuolar interface dermatitis with a relatively sparse, wholly lymphocytic infiltrate and numerous necrotic keratocytes. Sometimes, however, the infiltrate may be relatively dense and associated with eosinophils. Irrespective of whether or not eosinophils are present, a drug eruption can never be excluded. Because eosinophils have been reported to occur in only 5 to 15% of cases of acute graft-versus-host disease [26–28], their presence has led repeatedly to misdiagnosis as a drug eruption, thereby delaying treatment of graft-versus-host disease [29]. As a consequence, it has been recommended not to perform skin biopsies in settings with high probability of acute graft-versus-host disease, such as following allogenic stem cell transplantation [30]. However, in addition to eosinophils that are of limited diagnostic value, other findings may serve to distinguish a drug eruption from acute graft-versus-host disease, including deep extension of the infiltrate and presence of neutrophils. Extension of the infiltrate into the deep dermis is observed in only a minority of drug eruptions, but neutrophils are commonly found and were numerous in more than half of our drug eruptions associated with severe interface changes, sometimes exceeding eosinophils in number. By contrast, in one study of acute graft-versus-host disease, not a single neutrophil was observed in 98 biopsy specimens [26].

b) Mild vacuolar interface dermatitis

A mild vacuolar interface dermatitis with only subtle vacuolar changes at the dermo-epidermal junction and few, if any, necrotic keratocytes is the most common pattern of drug eruptions. In our study of 300 consecutive drug eruptions, it was observed in 83 cases (28%). As mentioned previously, the constellation of mild vacuolar interface changes and a sparse superficial perivascular and interstitial infiltrate of lymphocytes, eosinophils, and neutrophils is virtually diagnostic of a drug eruption (Figure 5 a, b).

The differential diagnosis of drug eruptions with mild vacuolar interface changes includes diseases normally associated with a more pronounced interface dermatitis, such as lupus erythematosus and acute graft-versus-host disease, but also diseases that are never associated with severe interface changes, including viral exanthemata and some autoimmune bullous diseases, especially the urticarial stage of bullous pemphigoid. Because the latter may also be associated with a superficial perivascular and interstitial infiltrate of eosinophils and neutrophils, distinction of it from a drug eruption may be particularly challenging. A clue to diagnosis of bullous pemphigoid is presence, and sometimes cluster-

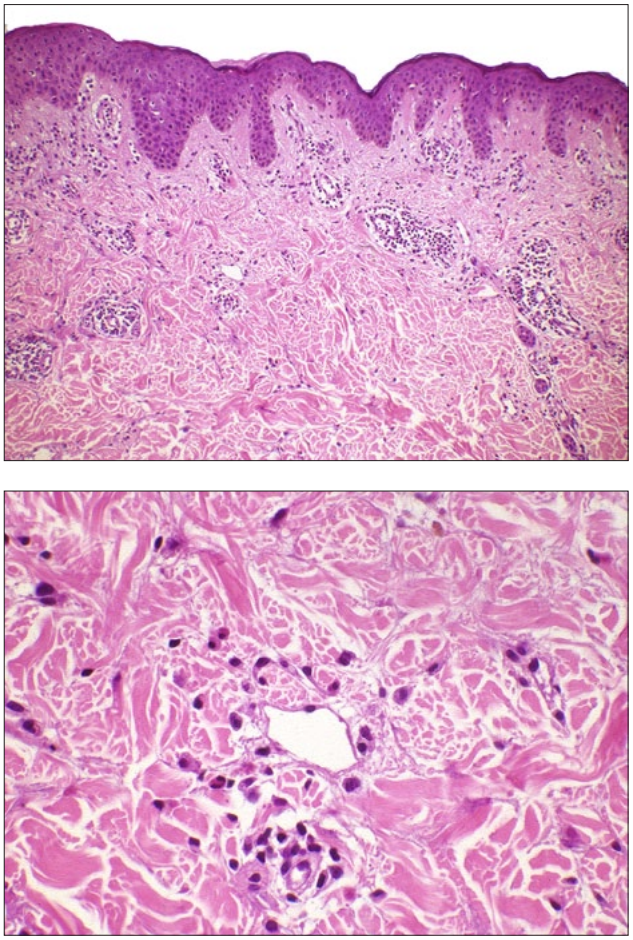

Figure 5. a) Superficial perivascular and interstitial dermatitis with focal, very subtle vacuolar changes at the junction. b) The infiltrate consists of lymphocytes, eosinophils, and neutrophils. The constellation of findings is typical of a drug eruption.

ing, of eosinophils at the dermo-epidermal junction to which they are attracted following binding of autoantibodies to hemidesmosomes. Accumulation of eosinophils at the junction is not a feature of drug eruptions. Likewise, eosinophils in the epidermis are commonly seen in the urticarial stage of bullous pemphigoid but are rare in drug eruptions. In our study of maculopapular drug eruptions, neutrophils in the epidermis were found in 19 of 60 cases (17%), but eosinophils in only two cases (3%). Features favoring a drug eruption are necrotic keratocytes that are exceedingly rare in bullous pemphigoid, predominance of neutrophils that are sparse or absent in bullous pemphigoid, perivascular accentuation of the infiltrate, and subepidermal fibrosis. The latter may be observed in drug eruptions but does not occur in the urticarial stage of bullous pemphigoid whose lesions are either evanescent or, if persisting at the local site, eventuate into a subepidermal blister.

Lichenoid dermatitis

This pattern was found in 36 of 300 consecutive cases of drug eruptions (12%). It was nearly always associated with lichen-planus-like epidermal changes, namely, irregular acanthosis, an at least focal saw-tooth pattern of rete ridges, wedge-shaped zones of hypergranulosis, and compact orthokeratosis. In general, the lichenoid pattern seems to correspond to a later stage of drug eruption. Neutrophils in the epidermis, dermis, or lumina of venules are exceptional. Eosinophils were found in only about half of our cases and, with few exceptions, were not abundant. By contrast, most cases showed some fibrosis of the papillary dermis and numerous melanophages, indicating a lesion of longer standing.

The most important differential diagnosis is lichen planus. Some lichenoid drug eruptions are indistinguishable histopathologically from lichen planus. In those cases, a specific diagnosis can only be made on the basis of clinical history and subtle clinical differences, such as larger, domed and slightly scaly papules and preferential involvement of trunk and extensor surfaces of extremities in lichenoid drug eruptions, rather than small, flat-topped, monomorphous papules on the flexor aspects of forearms, skins, ankles, genitalia, and oral mucous membranes in lichen planus [31]. Often, however, there are histopathologic differences that allow lichenoid drug eruptions to be distinguished from authentic lichen planus, including focal thinning of the epidermis, a diminished granular zone, foci of parakeratosis, abundance of necrotic keratocytes that may form clusters and may be seen in all layers of the epidermis, extravasation of erythrocytes, deep extension of the infiltrate, and presence of eosinophils in the infiltrate [31–34]. Because lichen planus usually affects middle-aged patients, whereas drug eruptions are more common in the elderly, high age and signs thereof, especially abundant solar elastosis, favor a drug eruption. Yet another distinguishing feature noted in 16 of our 36 cases of lichenoid drug eruption is slight spongiosis. In 10 cases, clusters of neutrophils were present in dilated venules of the papillary dermis (Figure 6 a, b). None of those findings excludes lichen planus, but a combination of several of them is a strong indicator of a lichenoid drug eruption. At least two of the aforementioned distinguishing feaures were observed in 31 of 36 lichenoid drug eruptions (86%). Another clue to diagnosis of a lichenoid drug eruption noted in the literature, but not observed in any of our cases, is presence of multinucleated histiocytic giant cells at the dermo-epidermal junction or within epidermal or adnexal epithelium [36–36].

Lichenoid psoriasiform dermatitis

A lichenoid psoriasiform dermatitis was observed in 18 of 300 consecutive drug eruptions (6%). In addition to a patchy lichenoid infiltrate of lymphocytes and uneven psoriasiform epidermal hyperplasia, those cases were associated with very scant spongiosis, some lymphocytes in the epidermis, and subtle fibrosis with coarse collagen fibers in the papillary dermis.

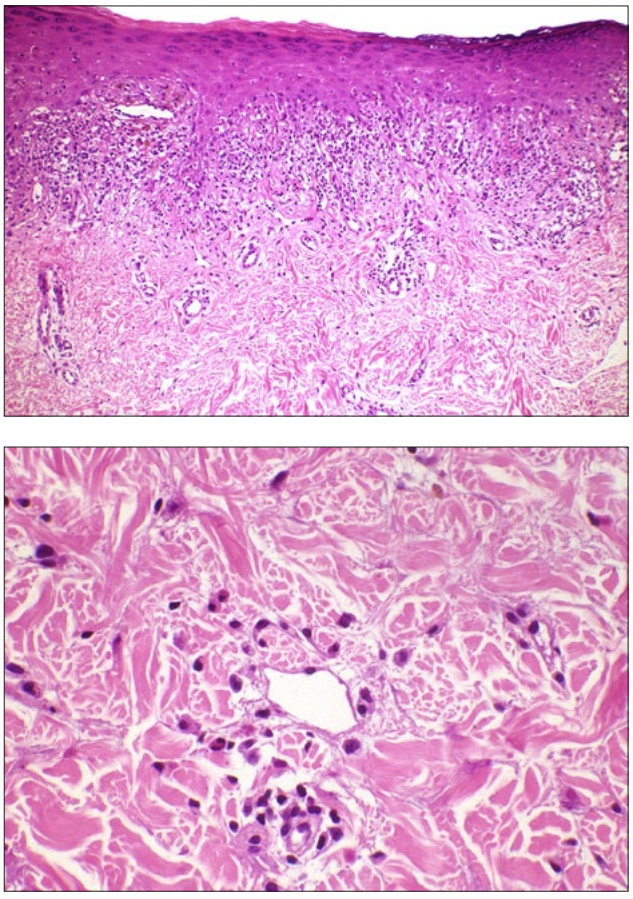

Figure 6. a) Lichenoid drug eruption that resembles lichen planus because of irregular epithelial hyperplasia, focal hypergranulosis, orthokeratosis, and a "saw-tooth" pattern of rete ridges. b) Some eosinophils within the infiltrate and numerous neutrophils in the lumina of dilated venules militate against lichen planus and favour a drug eruption.

All those features are also seen in the patch stage of mycosis fungoides. Moreover, subtle vacuolar changes at the dermo-epidermal junction, lymphocytes with largish nuclei, and eosinophils may be seen in both diseases. In the literature, drug eruptions mimicking mycosis fungoides have been reported especially following intake of carbamazepin and phenytoin [14-17], but other compounds have also been implicated [37-41]. Because drug eruptions may also simulate mycosis fungoides clinically, differentiation of those diseases is all the more challenging. It has been claimed that drug-induced pseudolymphomas "cannot be differentiated from true lymphomas through clinical, pathological or molecular findings," the only way of differentiation being "resolution of the lesions after the medication involved is suspended" [17].

Although this is true for individual cases, there are several histopathologic clues that help to distinguish mycosis fungoides from mycosis fungoides-like drug eruptions. In the patch stage of mycosis fungoides, one may see lymphocytes aligned in the basal layer, dense infiltrates of lymphocytes in dermal papillae, lymphocytes in the epidermis that are larger than those in the dermis, and intra-epidermal collections of largish lymphocytes, findings hardly ever encountered in drug eruptions. Drug eruptions that present themselves as a lichenoid psoriasiform dermatitis with fibrosis in the papillary dermis are chronic lesions, following prolonged intake of the eliciting drug. Nevertheless, they tend to retain signs of acute inflammation not normally seen in mycosis fungoides, including a wholly basket-woven cornified layer, edema of the papillary dermis, sometimes presence of neutrophils in the infiltrate, markedly dilated venules in the papillary dermis, and, not uncommonly, many neutrophils in the lumina of dilated venules (Figure 7 a, b). Early patches of mycosis fungoides usually do not show a striking predominance of CD4-positive lymphocytes, but if such predominance is found, it militates against a drug eruption in which CD4- and CD8-positive lymphocytes are present in roughly equal numbers [41].

Another differential diagnosis of lichenoid psoriasiform drug eruptions is secondary syphilis. In both diseases the infiltrate may be composed of lymphocytes, histiocytes, eosinophils, neutrophils, and plasma cells. However, in syphilis, epithelioid histiocytes and plasma cells are common and may outnumber lymphocytes, whereas eosinophils are exceptional. The opposite is true for drug eruptions. Another finding commonly seen in secondary syphilis, but not in drug eruptions, is pallor of keratocytes in the upper part of the epidermis.

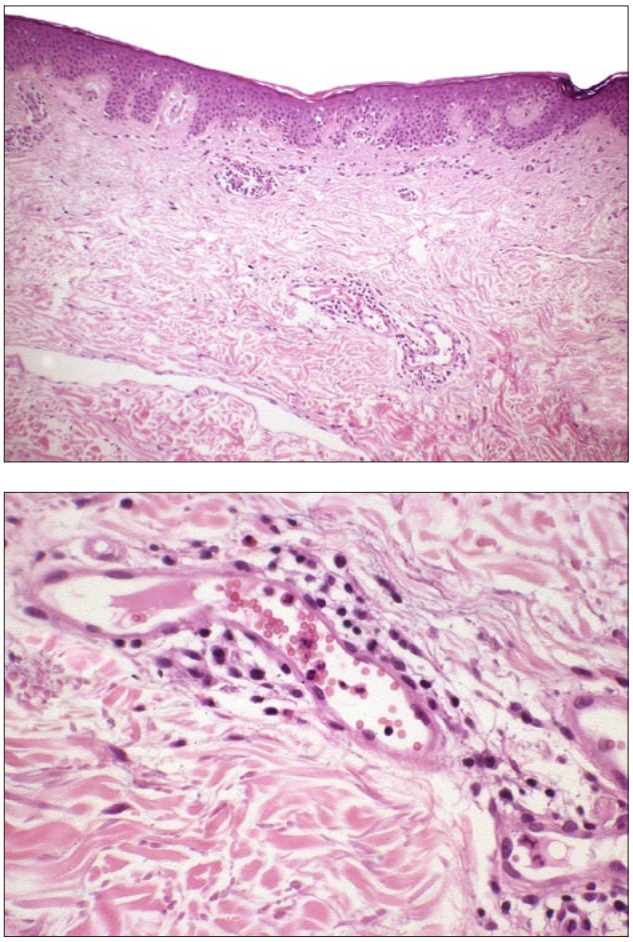

Figure 7. a) Lichenoid psoriasiform drug eruption mimicking the patch stage of mycosis fungoides because of a patchy lichenoid infiltrate, focal presence of lymphocytes in the epidermis in concert with scant spongiosis, focal alignment of lymphocytes in the basal layer of the epidermis, and wiry bundles of collagen in the papillary dermis. b) Features militating against mycosis fungoides are scattered eosinophils, widely dilated venules in the upper dermis, and, especially, numerous neutrophils in the lumina of venules.

Spongiotic dermatitis

Drug eruptions commonly present themselves as a spongiotic dermatitis. We found a spongiotic dermatitis in 62 of 300 consecutive drug eruptions (21%), and some spongiosis was also present in many other cases in which it was not the predominant pattern. In our study of maculopapular drug eruptions in which the eliciting agents were known, 58 of 60 cases (97%) were associated with at least subtle spongiosis [11]. Most commonly, spongiosis is mild and confined to the lower half of the epidermis. Spongiotic vesicles were seen in less than half of the cases classified as spongiotic dermatitis. Those vesicles were usually small and confined to one or two foci, a pattern observed in 20 of 62 cases (32%). Marked spongiosis across a broad front with large confluent vesicles was seen in only 6 cases (10%), all of which were associated with at least some eosinophils and neutrophils in the epidermis.

Spongiotic drug eruptions must be distinguished from other spongiotic dermatitides, especially pityriasis rosea, erythema annulare centrifugum, and contact and nummular dermatitis. Unlike drug eruptions, those diseases are rarely

associated with neutrophils, and although eosinophils are common, they tend to be less abundant than in spongiotic drug eruptions, the latter sometimes showing clusters of eosinophils in the upper dermis. Another common finding in drug eruptions that is rare, or less pronounced, in other spongiotic dermatitides, is many neutrophils in dilated venules.

The most common pattern of spongiosis in drug eruptions, namely, mild spongiosis without vesiculation across a broad front in the lower half of the epidermis, is relatively distinctive (Figure 8). Cases with tiny isolated spongiotic vesicles resemble pityriasis rosea and erythema annulare centrifugum (Figure 9). The latter diseases are often associated with focal scale-crusts, which are rare in spongiotic drug eruptions, and they hardly ever show extension of the infiltrate into the deep dermis, a finding encountered in nearly one third of our cases of spongiotic drug eruptions. In acute cases of contact and nummular dermatitis, there is more spongiosis in relationship to the density of the infiltrate. In drug eruptions associated with marked spongiosis and confluent spongiotic vesicles, the infiltrate is usually very dense,

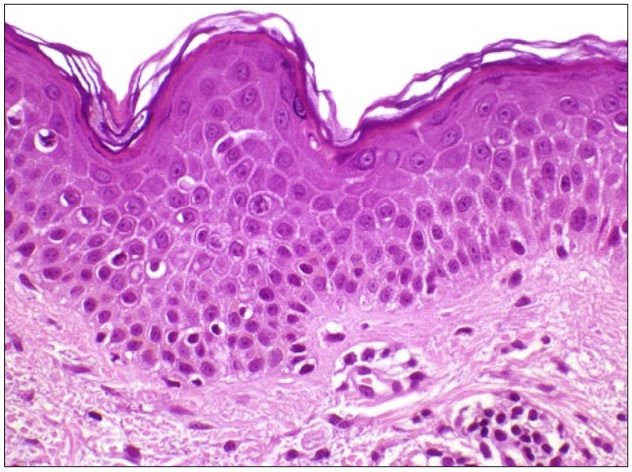

Figure 8. Maculopapular drug eruption with mild spongiosis in the lower half of the epidermis and a basket-woven cornified layer.

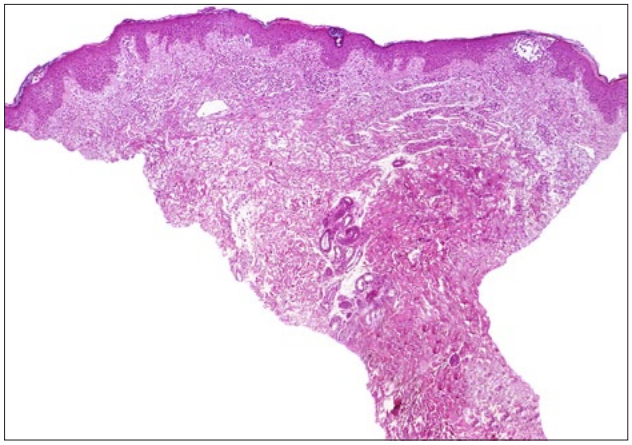

Figure 9. Spongiotic drug eruption with isolated spongiotic vesicles. The cornified layer is mostly basket-woven. Typical of a drug eruption are widely dilated vessels in the upper dermis.

and eosinophils in the epidermis are more common than in contact and nummular dermatitis. The latter diseases usually show broad zones of parakeratosis. By contrast, a spongiotic dermatitis in which the cornified layer is mostly basket-woven should raise suspicion of a drug eruption. Chronic lesions of contact and nummular dermatitis usually show epidermal hyperplasia, which is rare or minimal, in spongiotic drug eruptions.

Pustular dermatitis

Neutrophils in the epidermis are commonly observed in drug eruptions. In our study of maculopapular drug eruptions in which the eliciting agents were known, 19 of 60 cases (32%) were associated with at least some neutrophils in the epidermis. The latter were mostly seen in or immediately beneath the cornified layer. Large aggregations of neutrophils with formation of spongiform pustules, however, are relatively rare. We observed that pattern in 19 of 300 consecutive drug eruptions (6%). Three of those cases were diagnosed clinically as acute generalized exanthematous pustulosis. The latter cases were among those in which pustules were aggregated most closely but, otherwise, they were indistiguishable from other pustular drug eruptions. All cases were associated with eosinophils and edema of the papillary dermis, which sometimes was prominent. In eight of 19 cases, necrotic keratocytes were scattered in the epidermis. Two cases not diagnosed clinically as acute generalized exanthematous pustulosis were associated with subtle signs of leukocytoclastic vasculitis, namely, fibrin in the wall of at least one venule and some nuclear dust.

The differential diagnosis of pustular drug eruptions includes pustular psoriasis, deficiency disorders such as necrolytic migratory erythema and acrodermatitis enteropathica, and pemphigus, especially IgA pemphigus. In pemphigus, the infiltrate tends to be relatively evenly distributed. In the dermis, it is usually restricted to the upper half and does not show significant perivascular accentuation. In the epidermis, neutrophils may be dispersed evenly across a broad front in concert with scant spongiosis [42]. By contrast, the infiltrate in drug eruptions is often accentuated around blood vessels and may be deep as well as superficial. In the epidermis, neutrophils are not scattered broadly but usually aggregated in discrete foci. Evidently, signs of acantholysis favor pemphigus and militate against a drug eruption, although some acantholytic cells may also be found in pustules of drug eruptions. In cases of doubt, this differential diagnoses can be resolved easily by immunofluorescence studies.

Intra- or subcorneal abscesses in deficiency disorders are usually elongated rather than discrete, as in most cases of pustular drug eruptions. When drug eruptions are associated with elongated abscesses, the infiltrate is usually very dense

and associated with many eosinophils, whereas disorders of deficiency, as a rule, show a mild or moderately dense infiltrate and few or no eosinophils. In pustular drug eruptions, the cornified layer is mostly basket-woven, whereas disorders of deficiency usually show confluent parakeratosis. A clue to diagnosis of disorders of deficiency is pallor of the upper half of the epidermis. By contrast, in drug eruptions, the lower half of the epidermis may appear pale due to mild spongiosis there.

Prurigo pigmentosa is a rare disease of unknown etiology characterized by sudden onset of papules and papulovesicles in a reticular pattern on the back, neck, and chest that tends to resolve within days, leaving behind net-like hyperpigmentation. Histopathologically, early stages are characterized by a superficial infiltrate predominated by neutrophils that are scattered in the epidermis where they may form subcorneal pustules. Because lesions may also show prominent edema in the papillary dermis, subtle vacuolar changes at the junction, necrotic keratocytes, and some eosinophils in the infiltrate, a distinction from pustular drug eruptions may be impossible. However, eosinophils tend to be sparse in number, whereas there are often abundant eosinophils in drug eruptions. Moreover, unlike pustular drug eruptions, lesions of prurigo pigmentosa commonly exhibit nuclear dust [43].

The most important differential diagnosis of pustular drug eruptions is pustular psoriasis. Pustular psoriasis is more difficult to distinguish from drug eruptions than other types of psoriasis because of lack of epidermal hyperplasia and common presence of some eosinophils. In drug eruptions, however, eosinophils are more numerous and may be seen in clusters, a finding militating strongly against psoriasis. In a recent comparison of acute generalized exanthematous pustulosis and pustular psoriasis, criteria with the highest distinguishing value in favor of the former diagnosis were eosinophils, especially when present within pustules, necrotic keratocytes, focal leukocytoclasia, and deep extension of the infiltrate [44]. Moreover, spongiosis in pustular drug eruptions has been claimed to be "usually mild, in contrast to that seen in pustular psoriasis." [2]

Subepidermal bullous dermatitis

Autoimmune subepidermal bullous diseases may be induced by drugs, a phenomenon especially common in linear IgA dermatosis. Subepidermal blisters in drug eruptions, however, may also result from an interface dermatitis and, rarely, from massive edema in the papillary dermis. We observed subepidermal blisters in six of 300 consecutive drug eruptions (2%), all of which showed signs of interface dermatitis (Figure 10 a, b). In four of those cases, a clinical differential diagnosis of drug eruption versus bullous pemphigoid was given, and the latter diagnosis was excluded by failure to detect autoantibodies in ELISA and/or immunofluorescence studies.

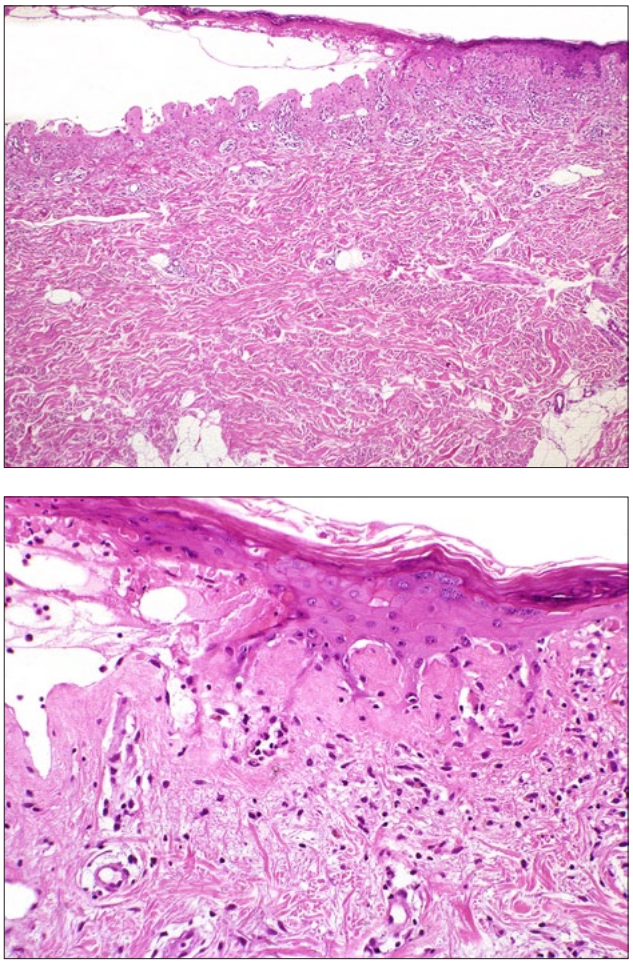

Figure 10. a) Bullous drug eruption with a large subepidermal blister caused by Simvastatin. b) The edge of the blister reveals signs of an interface dermatitis with vacuolar changes at the dermo-epidermal junction and numerous necrotic keratocytes. There are no eosinophils at the junction.

Histopathologic differentiation between bullous pemphigoid and bullous drug eruptions may be difficult because both diseases, in addition to subepidermal blisters, may show a perivascular and interstitial infiltrate with many eosinophils and some neutrophils in the superficial and mid dermis. Necrotic keratocytes may also be seen in both diseases. In bullous pemphigoid, however, the latter are restricted to the roof of the blister. Necrotic keratocytes at the edge of the blister, where the epidermis has not yet detached from the dermis, strongly favor a drug eruption. The same is true for other signs of interface dermatitis, including prominent vacuolar alteration at the junction and melanophages in the papillary dermis. Neutrophils are less common in bullous pemphigoid and, when present, usually sparse (Figure 8 a, b).

Granulomatous dermatitis

Drug eruptions may be associated with granulomatous inflammation. We observed granulomas in 12 of 300 consecutive drug eruptions (4%). Two patterns of granulomatous inflammation could be distinguished. In five cases, there were

one or few small, round to oval, sharply circumscribed granulomas in the upper dermis. In three of those cases, at least one granuloma was situated in close proximity to an eccrine duct, suggesting damage to the duct and leakage of sweat as a possible cause of granulomas. All five cases were associated with epidermal changes, either focal spongiosis (two cases), or foci of interface dermatitis (two cases), or both (one case). The associated epidermal changes distinguished those drug eruptions from the most important differential diagnosis, sarcoidosis (Figures 2 a, b). Another clue to diagnosis of a drug eruption observed in two cases were neutrophils in the lumina of venules, a finding hardly ever observed in sarcoidosis.

The second pattern of granulomatous dermatitis was scatter of histiocytes among collagen bundles in one or more poorly circumscribed areas in the superficial and/or deep dermis. There also was a perivascular lymphocytic infiltrate. Those changes resembled the interstitial type of granuloma annulare. Of seven cases with that pattern, two were indistinguishable from granuloma annulare. In both, a drug eruption could be diagnosed with confidence because of onset of lesions following administration of a new drug (captopril and allopurinol, respectively) and gradual resolution after cessation of it. In those two cases, numerous eosinophils were present, but the latter may also be seen in granuloma annulare. The five other cases could be distinguished from granuloma annulare because of associated epidermal changes, namely, interface changes in four and spongiosis in one of them. Subtle signs of an interface dermatitis have been described as a histopathologic clue to diagnosis of a granuloma annulare-like drug eruption [45]. In five of our seven cases of granuloma annulare-like drug eruption, eosinophils and neutrophils were sparse or absent. A clue to diagnosis of a drug eruption present in four of seven granuloma annulare-like lesions was presence of neutrophils in the lumina of venules.

Leukocytoclastic vasculitis

In our study of 300 consecutive drug eruptions, two cases showed signs of leukocytoclastic vasculitis. In both, a clinical diagnosis of drug eruption had been given because of onset of lesions shortly after administration of a new drug. In one of those cases, the same type of eruption had occurred once before following administration of the same drug (azithromycin). Both cases showed stereotypic features of leukocytoclastic vasculitis, namely, fibrin in the walls of venules, extravasation of erythrocytes, and an inflammatory infiltrate composed of lymphocytes, neutrophils, and eosinophils in concert with nuclear dust. In both cases, there were more eosinophils than normally seen in leukocytoclastic vasculitis, including focal clusters of eosinophils. This is in concurrence with a recent study in which a significantly higher number of eosinophils was found in drug-induced than in non-drug-induced cases of leukocytoclastic vasculitis. In that study, the course of drug-induced cases was found to be less severe, with lower incidence of extra-cutaneous involvement and faster resolution [46]. Although presence of many eosinophils does not exclude other causes of leukocytoclastic vasculitis, it may serve as a clue to causation by a drug.

Discussion

Adverse cutaneous reactions to drugs may occur in many different forms. So divergent are the patterns of drug eruptions that they cannot be considered variants of a single pathologic process. Evidently, the cytokines involved in eruptions presenting as a pustular, spongiotic, or severe interface dermatitis must be very different from one another. When several biopsies are taken from the same patient, they usually show the same predominant pattern, although associated findings, such as focal spongiosis in a vacuolar interface dermatitis, may be seen in only one of two biopsy specimens. Moreover, patients with recurrent drug eruptions usually show always the same type of response.

And yet, there is some overlap. Signs of interface dermatitis, for example, are extremely common in drug eruptions. They are mostly mild and most often seen in maculopapular drug eruptions, but even in the latter, they may be pronounced, reaching the degree expected in erythema multiforme and Stevens-Johnson syndrome. By contrast, the two latter conditions may be associated with only mild interface changes. Likewise, histopathologic changes typical of fixed drug eruption, i.e., a pronounced superficial and deep vacuolar interface dermatitis with many necrotic keratocytes and eosinophils and neutrophils in the infiltrate, may be seen in widespread maculopapular drug eruptions, whereas cases diagnosed clinically as fixed drug eruption may be nearly devoid of interface changes. In fact, two of our cases with the clinical diagnosis of fixed drug eruption and associated with many eosinophils and neutrophils showed focal spongiosis as the only epidermal alteration.

Maculopapular drug eruptions may be associated with sub- and intracorneal pustules indistinguishable from those of acute generalized exanthematous pustulosis, the latter possibly being an exaggerated form of the same process. Not uncommonly, pustular drug eruptions are associated with focal signs of an interface dermatitis. The same is true for spongiotic and granulomatous eruptions. In brief, although clinical entities, such as Stevens-Johnson syndrome, fixed drug eruption, and acute generalized exanthematous pustulosis are associated with distinctive histopathologic changes, and may be recognized by them, the spectrum of those changes is broader than often suggested in the literature, and it is not always possible to distinguish them from other types of drug eruptions.

Because of overlap of presentations, it was often difficult to attach individual cases to one of the categories of patterns. This, however, is not only unavoidable, but irrelevant for the purpose of distinguishing drug-induced cutaneous eruptions from those not induced by a drug. For that purpose, it is helpful to consider the differential diagnosis of a given pattern and findings that allow drug eruptions to be recognized in that particular context. The categories of patterns discussed above do not encompass the entire spectrum of drug eruptions. For example, there were no examples of nodular dermatitis and panniculitis among our cases. Nevertheless, the vast majority of drug eruptions can be assigned to one of the aforementioned categories, and if general criteria for recognition of drug eruptions are observed, and the particular differential diagnoses considered, histopathologic diagnosis of a drug eruption can usually be made with confidence. As in all other inflammatory diseases, the histopathologic diagnosis must be substantiated by clinicopathologic correlation.

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