

Histopathology of drug-induced exanthems: is there a role in diagnosis of drug allergy?

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Purpose of review

Cutaneous eruptions are among the most common adverse drug reactions and may often represent a challenging diagnostic problem. This review focuses on histopathological and immunohistochemical findings of drug-induced maculo-papular exanthems and discusses the value of skin biopsies and consequent histopathological examination in the diagnosis of these reactions.

Recent findings

Data from immunohistological studies indicate that CD4+ T cells expressing cytotoxic granule proteins such as perforin and granzyme B are critically involved in the pathogenesis and contribute to the generation of typical histopathological features of drug-induced maculo-papular exanthems, i.e. an interface dermatitis with vacuolar alteration and some apoptotic basal keratinocytes. In addition, an upregulation of both type 1 (i.e. IFN- γ , TNF- α) and type 2 (i.e. IL-5) cytokines has been reported. IL-5 together with other chemokines (i.e. eotaxin/CCL-11) provides an explanation for tissue eosinophilia, which may be suggestive of a drug eruption if present.

Summary

There are no absolute histological or immunohistological criteria for the diagnosis of drug-induced maculo-papular exanthems and even if the observed histological changes are compatible with a drug-induced eruption, biopsy may not definitely exclude alternative causes since there is considerable overlap with features seen in other entities. In mild cases with no severe signs or symptoms and a clear temporal relationship, clinical information and the morphologic pattern of skin lesions are often sufficient for diagnosis. However, in complex and severe cases or when the precise morphology is unclear, histopathological findings may provide some clues and assist in reaching a correct diagnosis.

Keywords

drug eruptions, histology, skin

Abbreviations

MHC major histocompatibility complex
MPE maculo-papular exanthem
TEN toxic epidermal necrolysis

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Introduction

Cutaneous drug eruptions are one of the most common adverse reactions to drug therapy, with an overall rate of 2–3% in hospitalized patients [1–3]. They may encompass a large variety of clinical patterns, such as urticaria, macular or maculo-papular, papulosquamous, lichenoid, bullous, pustular and eczematous skin eruptions, fixed drug eruptions, erythema exsudativum multiforme as well as more severe reactions such as Stevens–Johnson syndrome or toxic epidermal necrolysis (TEN) or Lyell syndrome. Cutaneous drug reactions can mimic different skin diseases such as exanthems induced by viral and bacterial agents, collagen vascular disease, autoimmune blistering disease and neoplasia and therefore represent a challenging diagnostic problem. Furthermore, attributing a cutaneous drug reaction to a particular drug may be difficult since many patients receive a variety of drugs simultaneously. In clinical practice appropriate diagnosis of an acute cutaneous drug reaction is based on the following [4–6]: a detailed clinical history suggesting that the onset of the eruption correlates temporally to drug ingestion; the morphology and distribution of the skin lesions as well as the presence of extra-cutaneous signs (e.g. malaise, fever, lymphadenopathy, arthralgia, diarrhoea, hypotension, tachycardia, dyspnea); an alternative disease which may mimic a cutaneous drug reaction is unlikely; analysis of the literature in order to reveal historical data regarding the frequency with which a specific morphologic pattern may be related to the putative drug; different laboratory tests such as complete blood count (atypical lymphocytosis, neutrophilia, eosinophilia), liver and renal function tests, anti-nuclear antibody, bacterial and viral serology, culture (skin, blood, tissue) and medical imaging may also aid in confirming or ruling out potential diagnoses. In this context, histopathological examination may in some instances also be useful in the management of a cutaneous eruption. In the following review we mainly focus on the histopathological findings in drug-induced maculo-papular exanthems

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(MPEs) and discuss the value of skin biopsies in their diagnosis.

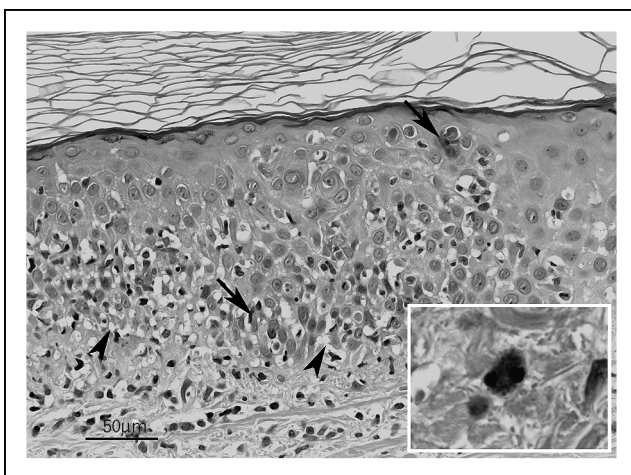
Maculo-papular drug exanthems

Erythematous or maculo-papular drug eruptions are by far the most frequent form of cutaneous drug reactions, accounting for up to 95% of all drug-induced cutaneous eruptions [7]. Clinically, the lesions often first appear on the trunk or in areas of pressure or trauma and subsequently spread to the extremities in a symmetrical fashion. Lesions are often morbilliform, rubelliform or scarlatiniform and may particularly mimic viral or bacterial exanthems. Pruritus and fever may be present. The rash usually lasts for 1–2 weeks and clears with cessation of the drug. In some cases, however, these exanthems may progress to erythroderma. Furthermore, maculo-papular lesions may also be seen in the early phases of other drug reactions like Stevens–Johnson syndrome, TEN or a drug rash with eosinophilia and systemic symptoms.

Histological findings in maculo-papular exanthems

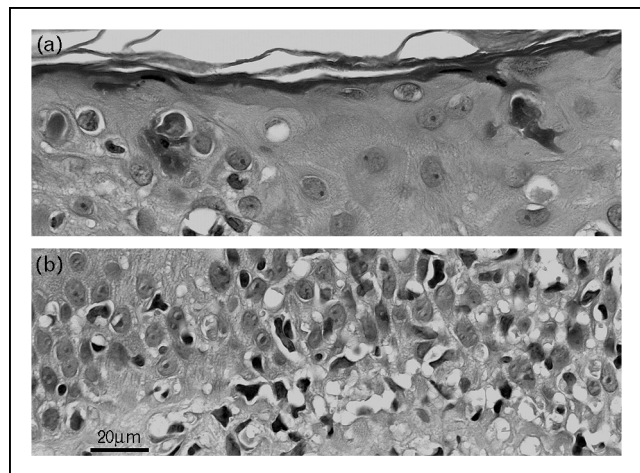
At a first glance, the histopathological changes in maculo-papular drug reactions appear non-specific, but they are often in fact quite characteristic. Typically, a mild interface dermatitis with a vacuolar alteration (a synonym being hydropic degeneration) of keratinocytes at the basal cell layer is seen (Figs. 1 and 2). In addition, small foci of spongiosis in the lower epidermis may be present occasionally along with scattered individual dyskeratotic keratinocytes and some infiltrating lymphocytes (Figs. 1 and 2). These findings correlate with observations made by electron microscopy, by which the primary

Figure 1. Maculopapular drug eruption



The eruption is characterized by orthokeratosis, focal basal spongiosis, mild exocytosis of lymphocytes, Civatte bodies – dyskeratotic or apoptotic keratinocytes (arrow) – in all epidermal layers, hydropic degeneration of basal keratinocytes (arrowhead) and a superficial perivascular infiltrate of lymphocytes with few eosinophils (inset). H&E staining.

Figure 2. Details of keratinocyte damage



(a) Dyskeratotic keratinocytes. (b) Basal hydropic degeneration. H&E staining.

changes of MPEs have been reported to be intercellular and intracellular edema as well as disruption of epidermal basal cells with some pyknotic nuclei [8]. It should be noted, however, that epidermal changes may be minimal or even absent in some reactions like mild scarlatiniform eruptions.

The papillary dermis is usually mildly edematous and vascular dilatation may be present. The inflammatory cell infiltrate, which consists of lymphocytes (some with large nuclei suggesting activation), macrophages, mast cells and occasional eosinophils (Fig. 1), is usually mild and predominately localized around the superficial vascular plexus [9,10].

Pathophysiology of maculo-papular drug exanthems

In recent years considerable advances have been achieved in understanding the pathophysiology of drug-induced MPEs [11••]. Immunohistochemical studies have shown that the cell infiltrate in drug-induced MPE is mainly composed of CD3+ T cells (40–70%) with a predominance of CD4+ cells [10]. Most of these cells are activated and express human leukocyte antigen-DR (major histocompatibility complex (MHC) class II molecules). Interestingly, an increase of circulating cutaneous lymphocyte-associated antigen (CLA)-positive T cells is found in these reactions compared to healthy controls [12]. In addition, a recent report has also demonstrated an increased percentage of CD3+CLA+ T cells and activated CD3+CD69+ T cells in peripheral blood lymphocytes in non-immediate cutaneous reactions versus viral induced cutaneous reactions in children [13]. Among the resident cells, endothelial cells and the majority of the basal keratinocytes are also activated and express MHC class II molecules and various adhesion molecules

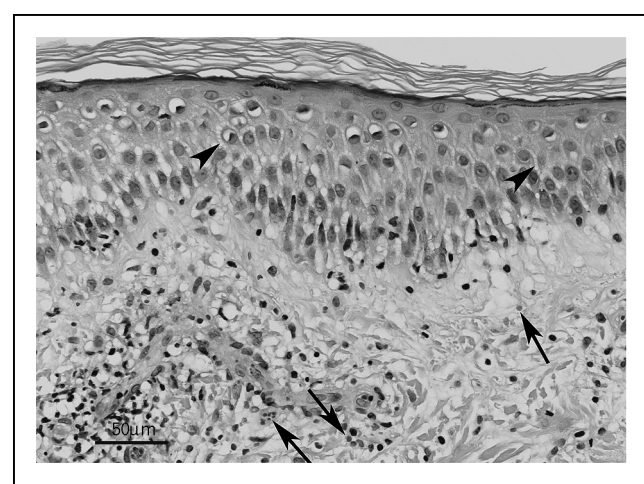
[10,14,15]. Interestingly, increased numbers of CD4+ and CD8+ T cells containing the cytotoxic granule proteins perforin and granzyme B are found at the dermo-epidermal junction zone or in the epidermis, along with signs of keratinocyte cell damage [10]. Recently, Posadas *et al.* also demonstrated an increased expression of perforin and granzyme B, but not of Fas ligand in maculopapular exanthems [16]. These cytotoxic granule proteins trigger cell death by forming pores in the target cell membrane and inducing degradation of their DNA. Together with in-vitro data on cytotoxic, drug-specific T cell clones [17,18] it is conceivable that drugs bind to MHC class I or II-peptide complexes on keratinocytes, which may lead to drug-induced cytotoxicity mediated through CD8+ as well as CD4+ T cells. Interestingly, Hari *et al.* [19] reported an almost exclusive CD4+ T cell infiltration in MPE, suggesting that activated CD4+ T cells alone may be sufficient to cause the pathology of such exanthems [19]. Furthermore, it is also of interest that activation of CD8+ T cells has particularly been reported in association with bullous drug reactions [20,21]. Taken together these data suggest that cytotoxic CD4+ T cells contribute to keratinocyte damage in MPEs, whereas the predominant activation of cytotoxic CD8+ T cells leads to more severe tissue destruction such as in bullous exanthems.

Further studies have revealed that various cytokines and chemokines are also upregulated in drug-induced MPEs. Interestingly, a heterogeneous cytokine profile including both type 1 (i.e. IFN- γ , TNF- α) and type 2 (i.e. IL-5) cytokines has thereby been reported [10,16,22–24]. The increased IFN- γ production provides an explanation for the upregulation of MHC class II on keratinocytes, which subsequently enables drug presentation to CD4+ T cells [17]. IL-5 together with eotaxin (CCL-11) are of particular importance, since they are both known to be key factors in regulating the growth, differentiation and activation of eosinophils, which may be increased in these reactions and contribute to the generation of tissue damage by the release of various toxic granule proteins [25]. Although the presence of eosinophils in the infiltrate is suggestive of drug eruption, it is important to note that they may also be absent. Furthermore, a recent report has pointed to the involvement of CCL27 (CTACK)–CCR10 interactions in the recruitment of CD4+ and CD8+ T cells in MPEs and particularly in severe exanthems like Stevens–Johnson syndrome and TEN [26].

Clues to histological differential diagnosis of maculo-papular exanthems

The main differential diagnoses of erythematous or maculo-papular drug eruptions are viral and bacterial (e.g. secondary syphilis) infections, connective tissue diseases like acute lupus erythematosus and acute graft-versus-host disease. In order to differentiate these

Figure 3. Viral exanthem

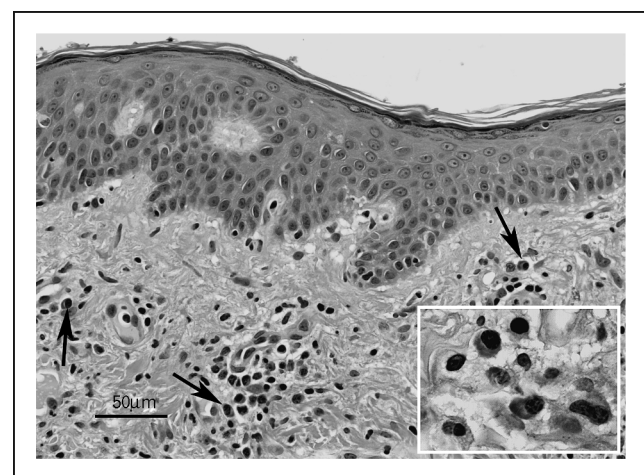


In addition to basal hydropic degeneration of keratinocytes and occasional Civatte bodies a viral exanthem may often show some spongiosis (arrowhead) and dermal hemorrhage (arrow). H&E staining.

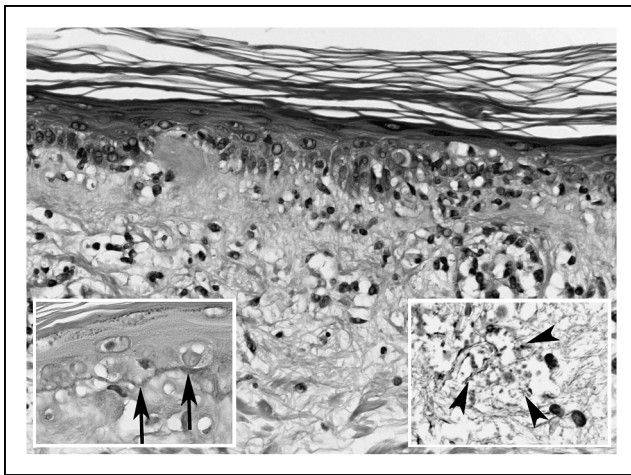
diseases from drug-induced reactions a detailed patient history as well as performance of various laboratory tests (e.g. viral and bacterial serology, anti-nuclear antibody and subsets) are of primary importance. However, in complex cases, such as patients with multiple comorbidities on different drugs, skin biopsies can be useful, since the presence of certain histological features, albeit subtle, may indeed favor a particular diagnosis.

One histopathological finding that supports a drug eruption over a viral exanthema is the presence of tissue eosinophilia (Figs. 1 and 3). Furthermore, dermal hemorrhage is usually not seen in drug-induced maculo-papular

Figure 4. Syphilitic infection



A syphilitic infection not only shows hydropic degeneration of basal keratinocytes and occasional dyskeratotic keratinocytes but also focal psoriasiform epidermal hyperplasia and a plasma cell-rich dermal inflammatory infiltrate (arrow and inset). H&E staining.

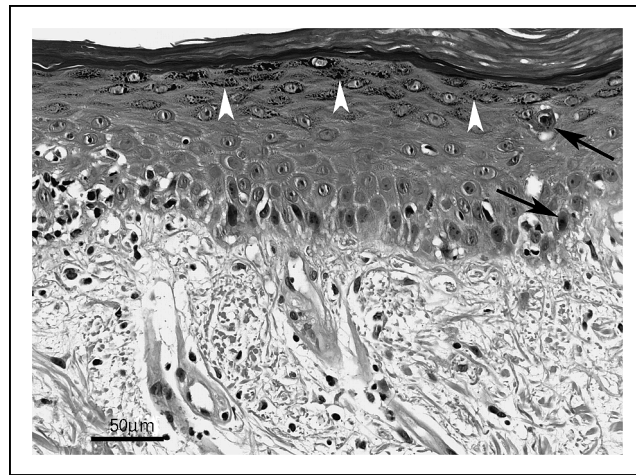
Figure 5. Lupus erythematosus

Lupus erythematosus showing epidermal atrophy, hydropic degeneration of basal keratinocytes and dyskeratosis mainly in the basal cell layer can be further differentiated from a maculopapular drug eruption by demonstration of thickening of the basement membrane (left inset, arrow, PAS-staining) and dermal mucinosis (right inset, arrowhead, colloidal iron stain). H&E staining.

reactions, but may be present in some viral exanthemas (Fig. 3) [27]. In contrast to drug-induced maculo-papular reactions, histopathologic findings of secondary syphilitic lesions demonstrate a plasma cell-rich mononuclear infiltrate (Fig. 4) [28]. A connective tissue disease would be favored if epidermal atrophy, focal parakeratosis (retention of nuclei in the stratum corneum) and dermal mucinosis accompany the interface dermatitis [28]. Furthermore, fibrinoid material may be deposited in the dermis around capillary blood vessels, on collagen and in the interstitium and account for thickening of the basement membrane zone (Fig. 5) [27]. In acute graft-versus-host disease epidermal atrophy, focal or confluent parakeratosis and hypergranulosis are present. In addition, necrotic keratinocytes may often be found in the infundibula (Fig. 6) [28,29]. Kohler *et al.* [30] reported, however, that using the classic criteria (apoptotic keratinocytes in epidermis and appendages, basal cell vacuolization, satellitosis) investigators found in a correlative study that no single or combined feature above could predict clinical graft-versus-host disease. Nevertheless, dermatopathologists are still asked for the most likely diagnosis because of the devastating consequences of not recognizing early graft-versus-host disease.

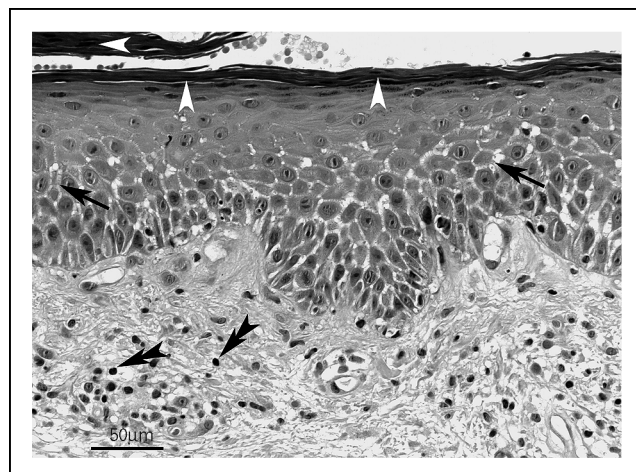
Suberythroderma and erythroderma

In some patients drug-induced maculo-papular lesions may progress to sub-erythroderma or erythroderma. Erythroderma can be caused by a variety of diseases, most commonly eczema, psoriasis, drug reactions and neoplasia (i.e. cutaneous T cell lymphoma). In common practice finding the cause is often challenging and seldom feasible on clinical basis alone. In particular, physicians

Figure 6. Graft-versus-host-reaction

In contrast to maculopapular drug eruptions graft-versus-host-reactions often show a typical hypergranulosis (arrowhead) and some parakeratosis frequently associated with the acrosyringium and the infundibulum. Dyskeratotic keratinocytes (arrow) may be seen in all epidermal layers. H&E staining.

who are not trained in dermatology often may not be able to differentiate erythematous or maculo-papular from eczematous skin lesions. In these cases histopathology may be helpful, since distinctive features pointing to a specific disease may be evident. In contrast to drug-induced reactions, acute eczema does not typically show an interface dermatitis but a stronger degree of spongiosis (intraepidermal intercellular edema) and exocytosis (presence of inflammatory cells within the epidermis, often in association with spongiosis) of lymphocytes

Figure 7. Eczema

All forms of eczema may have some hydropic degeneration of basal keratinocytes but they all have a predominant spongiosis (arrow). In addition the stratum corneum shows mounds of parakeratosis (arrowhead) and the dermal inflammatory infiltrate containing some eosinophils (double arrowhead) is confined to the upper dermis whereas in maculopapular drug eruptions an invasion of the mid-dermis is frequently observed. H&E staining.

and sometimes eosinophils (Fig. 7). On the other hand psoriasiform epidermal hyperplasia, hypogranulosis or agranulosis under foci of neutrophil-containing parakeratosis and dilated vessels in the dermis are clues that point to psoriasis. Epidermotropism (presence of usually large lymphocytes within the lower half of the epidermis without significant spongiosis) and Pautrier microabscess (aggregates of lymphocytes) point to cutaneous T cell lymphoma [27].

Conclusion

It is important to note that there are no absolute histological criteria for the diagnosis of drug-induced maculo-papular eruptions. Furthermore, skin biopsies do not allow for identification of the causative drug and even if the observed histological changes are compatible with a drug-induced eruption, biopsy may not definitely exclude alternative causes for the observed reaction pattern. In straightforward cases, such as one offending drug and a clear temporal relationship, clinical information and the morphologic pattern of skin lesions are often sufficient for diagnosis. Thus, particularly for mild maculo-papular eruptions with no severe signs or symptoms, no histopathological examination is required. Many drug reactions occur, however, in elderly patients with multiple comorbidities on multiple medications without a clear cut temporal relationship between intake of a certain drug and the exanthema. Furthermore, in many cases the physician may not be experienced enough to recognize the precise morphology of the lesions, for example, maculo-papular or eczematous or psoriasiform. Therefore, in complex cases histopathological findings may provide some clues and assist in reaching a correct diagnosis. In particular, in recurrent or persistent eruptions and eruptions with potentially serious signs, early and accurate diagnosis is mandatory before instituting any treatment or recommendations. Indeed, histological findings can sometimes distinguish between a drug-induced disease and other diseases; for example, a TEN can mimic a staphylococcal scalded skin syndrome, but a skin biopsy would differentiate between the two.

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