Histopathology of Drug Reactions

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Abstract

Cutaneous drug reactions can produce a variety of histopathologic inflammatory and even neoplastic patterns. Therefore, it is crucial to communicate to the dermatopathologist if a drug-related condition is suspected. When complicated histologic patterns are in view, the dermatopathologist should have a higher index of suspicion for a drug reaction as well. In this chapter, we will review common drug reactions patterns, and attempt to elucidate helpful histopathologic clues that point to the cutaneous condition being related to drug administration.

Keywords

Cutaneous drug reactions • Histology • Dermatopathology • Pathology • Eosinophils • Drug-induced pathology

Introduction

Cutaneous drug reactions can produce a variety of histopathologic inflammatory and even neoplastic patterns. Hence it is vitally important to know the clinical history and knowing if the clinician is suspecting a drug reaction. However, since the clinical morphologic appearance of many drug-induced diseases can so closely mimic the "true" non-drug-induced form, the pathologist should maintain a low threshold for suggesting the possibility of a drug-induced condition, as treatments may be significantly different. It is often stated that the skin may display only limited reaction patterns to different noxious stimuli, and with drug reactions this is also the case. However, certain clues can help point the observant pathologist or dermatopathologist to the correct diagnosis. We hope to summarize these most important clues in this chapter.

This chapter was also constructed with the idea that the reader has a basic understanding of the classic histologic findings of dermatologic conditions that can be mimicked when the skin reacts to a medication. If the reader desires a more detailed

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summary of the histologic features of these entities, it is recommended that the reader peruse a more in-depth dermatopathologic tome.

Pathologic Characteristics of Common Drug Reactions

Morbilliform (Maculopapular) Drug Eruptions (Exanthems)

This is the most common type of drug reaction. Morbilliform drug reactions have been associated with a number of inflammatory patterns. In one large study, a superficial perivascular and interstitial infiltrate containing eosinophils and sometimes neutrophils was described as the most common pattern. Vacuolar interface changes and/or spongiosis can also be present with or without Civatte bodies (individually dead or dying keratinocytes). Sometimes a nondescript sparse lymphocytic infiltrate is evident. Therefore, a definitive diagnosis may be difficult, and hence the importance of clinical information. A descriptive diagnosis, consistent with or compatible with a morbilliform drug eruption may be the only diagnosis a pathologist can render, even with accurate clinical history.

The histologic differential diagnosis depends on the predominant histologic pattern at hand and may include erythema multiforme, viral exanthem, connective tissue disorders such as lupus erythematosus, and dermatomyositis, early graft vs. host disease, urticaria, and early leukocytoclastic vasculitis, among others.

Urticarial Drug Reactions

This is the second most common pattern of drug reaction. Urticarial drug reactions are histologically indistinguishable from other urticarial reactions, such as idiopathic urticaria, and an arthropod bite reaction displaying a perivascular to interstitial infiltrate of lymphocytes, eosinophils, and occasionally neutrophils and sometimes dilated lymphatics in later lesions.

As noted above, the differential diagnosis histologically includes idiopathic urticaria, arthropod bite reaction, urticarial vasculitis, and on occasion tinea (dermatophytosis).

Fixed Drug Eruptions

Initially, there is an acute vacuolar interface reaction, with necrotic keratinocyte along the junctional zone (i.e. the stratum corneum is still "basket-weave") and there is no evidence of an altered cornified layer. This can progress to subepidermal vesiculation, and necrotic keratinocytes can also be found throughout the epidermis. In addition, there is a variable superficial and deep perivascular infiltrate composed in addition to lymphocytes, often of granulocytes, including neutrophils and eosinophils. There may be papillary dermal edema. This pattern is in contrast to erythema multiforme (EM), which can appear very similar except that in lesions of EM, the dermal inflammatory infiltrate is typically composed predominantly of lymphocytes (Fig. 3.1).

Established lesions that recur show similar features as in acute cases, but melanophages are also present in the superficial dermis.

The histologic differential diagnosis includes mainly erythema multiforme, urticarial bullous pemphigoid, and on occasion erythema dyschromicum perstans and variants.

Photosensitive (Photoallergic and Phototoxic) Drug Reactions

The photoallergic pattern may be difficult to distinguish from a prototypical spongiotic eczematous dermatitis. The perivascular infiltrate may on occasion extend to involve the deep vascular plexus. In severe acute cases, spongiotic vesiculation may occur. Long-standing lesions may show signs of chronicity, including stellate or multinucleate mesenchymal cells, telangiectasia, and lichenification. The histologic differential diagnosis includes other spongiotic dermatitides such as allergic contact dermatitis. The phototoxic reaction can be likened to a sunburn reaction, and the hallmark is epidermal necrosis of varying degree. On occasion, erythema multiforme and TEN/SJS might be considered.

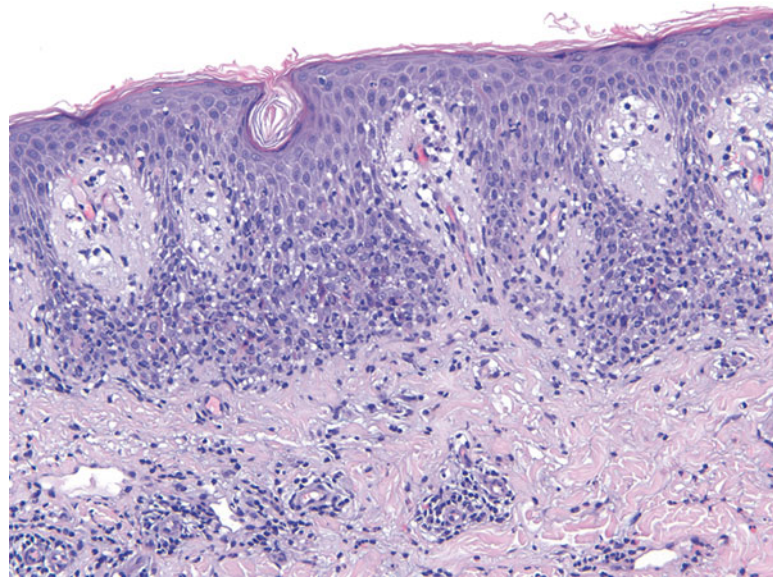


Fig. 3.1 Fixed drug eruption. There is an acute interface reaction, with an infiltrate containing granulocytes and melanophages (200×)

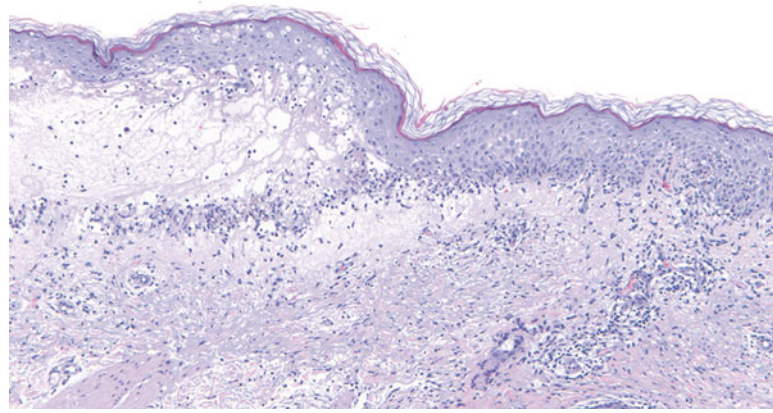


Fig. 3.2 Erythema multiforme. An acute interface reaction lies adjacent to a zone of subepidermal vesiculation (100×)

Erythema Multiforme (EM), Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

EM, SJS, and TEN are clinically different diseases, and classification depends in part upon the total body surface area involved by the disease. Lesions range from targetoid to vesicular, and in the case of TEN, larger expanses of epidermal necrosis. Although EM can be caused by drugs, infections are much more common, whereas, in contrast, drugs such as sulfonamides, antibiotics, anticonvulsants, and some NSAIDs are the major causes of SJS and TEN.

Histologically, EM, SJS, and TEN may have significantly overlapping features, and on occasion can be indistinguishable. All demonstrate a vacuolar interface reaction of varying intensity, also depending on the age of the lesion. The infiltrate is largely lymphocytic, and usually superficial, and eosinophils may also be present. Necrotic keratinocytes are also present in varying degree. In all forms of the disease, the process is acute, and thus the stratum corneum will retain its normal basket-weave pattern. Minor patterns also occasionally present include spongiosis and ballooning of keratinocytes . As vacuolar alteration progresses, a subepidermal vesicle or bulla may form (Fig. 3.2). In TEN, there is often full-thickness epidermal necrosis early in the course, and a sparse infiltrate (Fig. 3.3)

The differential diagnosis includes fixed drug eruption, acute graft vs. host disease, pityriasis

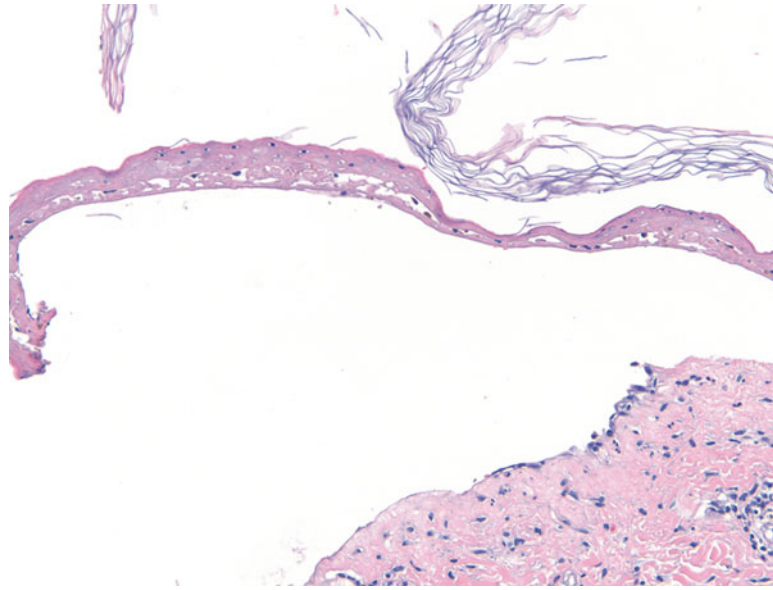


Fig. 3.3 Toxic epidermal necrolysis. There is full thickness epidermal necrosis, detachment of the epidermis, and a sparse dermal infiltrate (200×)

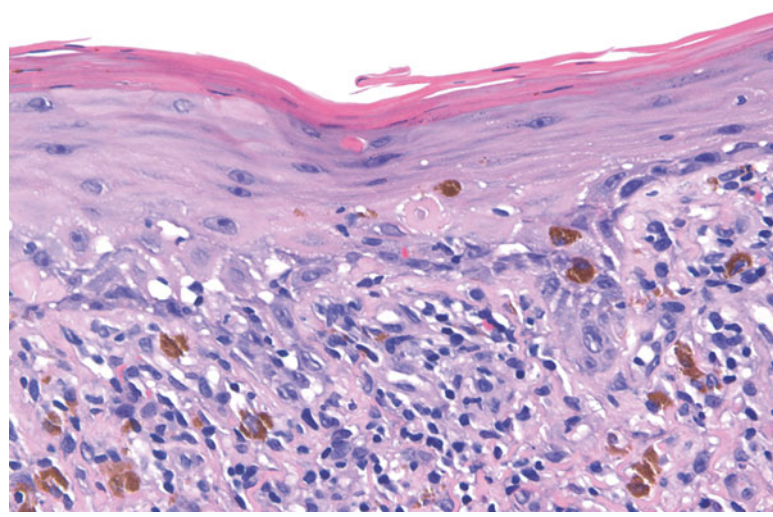


Fig. 3.4 Lichenoid drug eruption. In addition to a lichenoid infiltrate containing eosinophils, there are necrotic keratinocytes positioned superficially within the epidermis (400×)

lichenoides et varioliformis acuta (PLEVA), connective tissue disease and phototoxic dermatitis.

Lichenoid Drug Reactions

Histologically, the pattern can be indistinguishable from lichen planus, with irregular epidermal hyperplasia, hypergranulosis, and hyperkeratosis, and both may contain eosinophils. However, focal parakeratosis is more often observed in lichenoid drug eruption. Another clue is the presence of dyskeratotic keratinocytes (cytoid bodies) in the granular and cornified layer. The inflammatory infiltrate may be deeper and may also contain plasma cells (Fig. 3.4).

The differential diagnosis also includes lichen planus-like keratosis (benign lichenoid keratosis), lichenoid photodermatitis, and on occasion, lupus erythematosus.

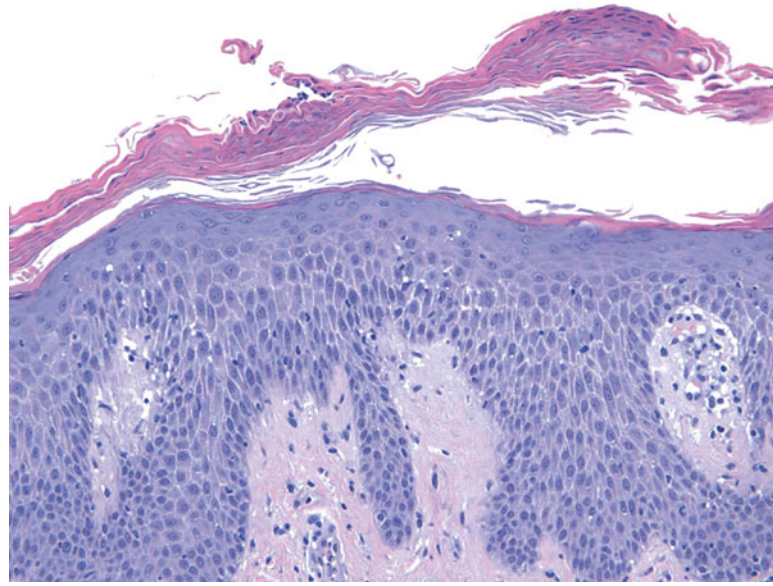


Fig. 3.5 Psoriasiform dermatitis due to TNF-alpha inhibitor. There is psoriasiform epidermal hyperplasia, parakeratosis, and occasional neutrophils as well as slight spongiosis, a pattern closely mimicking psoriasis, in a patient being treated for inflammatory bowel disease (200×)

Spongiotic Drug Reactions

Drug eruptions are usually included in the differential diagnosis of spongiotic (eczematous) dermatitis. There are no particularly distinguishing features, although eosinophils are usually present in drug eruptions. If other patterns are also present, forming a more complex pattern,—for example, cytotoxic/interface changes—this may point to a drug eruption.

The histologic differential diagnosis includes other spongiotic dermatoses such as atopic dermatitis, allergic contact dermatitis, id reaction, nummular dermatitis, seborrheic dermatitis, and dermatophytosis.

Pityriasis Rosea (PR)-Like Drug Eruptions

Often the histology is indistinguishable from typical PR reactions unrelated to drugs. Clinically, a herald patch is not evident. Histologic clues include eosinophils, subepidermal edema, and sometimes apoptotic keratinocytes, but clinical suspicion must be high.

The histologic differential diagnosis includes conventional pityriasis rosea, erythema annulare centrifugum, pigmented purpuric dermatosis, dermatophytosis, guttate psoriasis, and pityriasis lichenoides chronica.

Psoriasiform Drug Eruption

This, too, may appear similar histologically to classic psoriasis, but diagnostic features such as suprapapillary plate thinning and tortuous papillary dermal capillaries may be absent. Reactions to tumor necrosis factor (TNF) inhibitors, used in treatment of psoriasis and other autoimmune diseases, including inflammatory bowel disease, may present with a variety of reaction patterns, but most commonly a spongiotic to psoriasiform dermatitis. Separating this from psoriasis when used in treatment of that disorder can prove challenging (Fig. 3.5).

The histologic differential diagnosis includes conventional psoriasis, dermatophytosis, lichen simplex chronicus, pityriasis rubra pilaris, and chronic (eczematous) dermatitis, among others.

Drug-Induced Bullous Pemphigoid

This is also indistinguishable histologically from non-drug-induced bullous pemphigoid. Clinically it

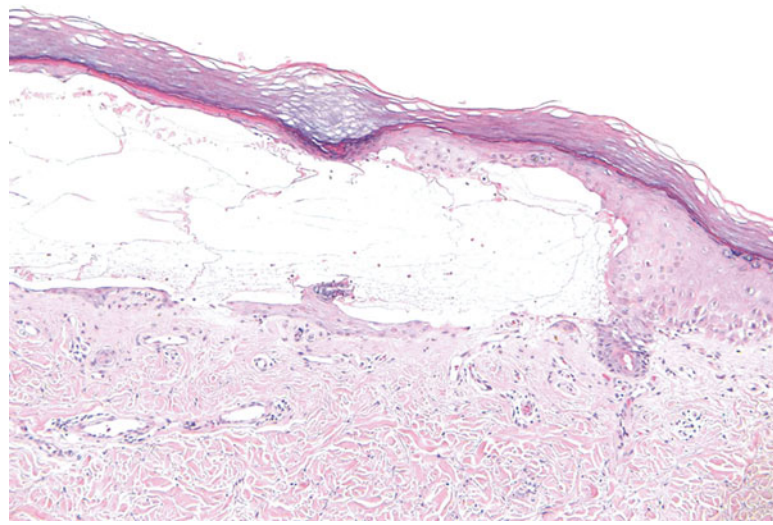


Fig. 3.6 Pseudoporphyria due to voriconazole. A pauci-inflammatory subepidermal bulla is evident, with some re-epithelialization (100×)

tends to occur in younger patients, and in salt-split skin immunoreactants may be found on the floor of the blister rather than the roof (as in idiopathic bullous pemphigoid). Direct immunofluorescence (DIF) findings are similar to non-drug-induced cases.

Differential diagnosis also includes epidermolysis bullosa acquisita (EBA), cicatricial pemphigoid, and, rarely, porphyria cutanea tarda and pseudoporphyria.

Drug-Induced Pseudoporphyria

NSAIDs are the most common culprit. Voriconazole toxicity has more recently been associated with this pattern. This is often indistinguishable from non-drug-induced cases, but papillary dermal eosinophils may be a clue. The absence of solar elastosis may be a clue to distinguish from PCT (Fig. 3.6).

The histologic differential diagnosis also includes pauci-inflammatory bullous pemphigoid, bullous amyloidosis, and EBA.

Acute Generalized Exanthematous Pustulosis (AGEP)

This subcorneal pustular dermatitis is a close mimic of pustular psoriasis. Clinical features, including the time course of the eruption and its resolution upon withdrawal of a putative drug culprit, may be essential. Histologically, subcorneal pustules are often present in a background of spongiosis. Scattered apoptotic keratinocytes, if present, can be a helpful clue. Papillary dermal edema is also more common than in pustular psoriasis. The dermis shows a mixed infiltrate, often with eosinophils and neutrophils, but a similar infiltrate can be present in pustular psoriasis. Eosinophils are less common in conventional plaque psoriasis. As with most skin specimens that contain neutrophilic pustules, a PAS-D stain could be considered to rule out a fungal infection (Fig. 3.7).

The histologic differential diagnosis (in addition to pustular psoriasis and bullous dermatophytosis) includes subcorneal pustular dermatosis (also known as Sneddon-Wilkinson disease), candidiasis, pemphigus foliaceus, IgA pemphigus, and bullous impetigo.

Interstitial Granulomatous Drug Reactions

These have been described for several drugs, including TNF inhibitors such as adalimumab (Humira), calcium channel blockers, ACE Inhibitors, beta-blockers, lipid-lowering agents, and others. There is often an interstitial infiltrate of histiocytes and lymphocytes, typically with

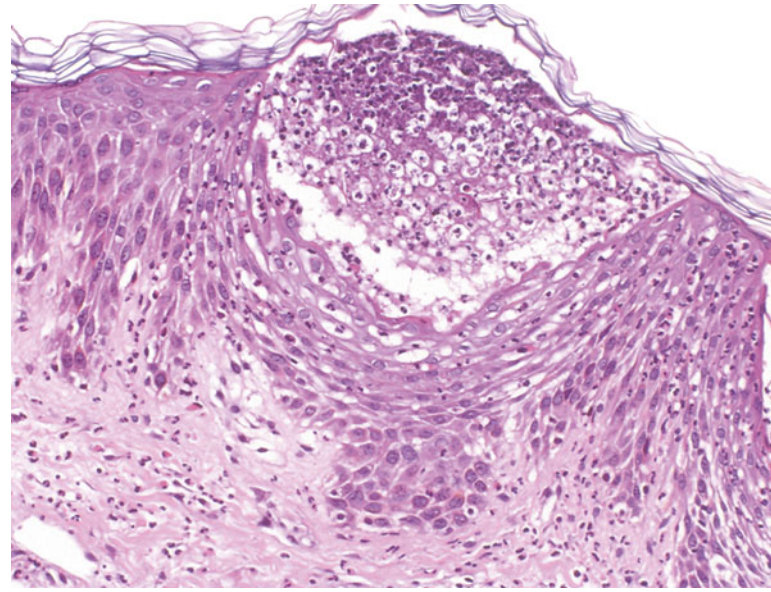


Fig. 3.7 Acute generalized exanthematous pustulosis. There is a subcorneal neutrophilic pustule with slight spongiosis, with a subjacent infiltrate containing eosinophils (200×)

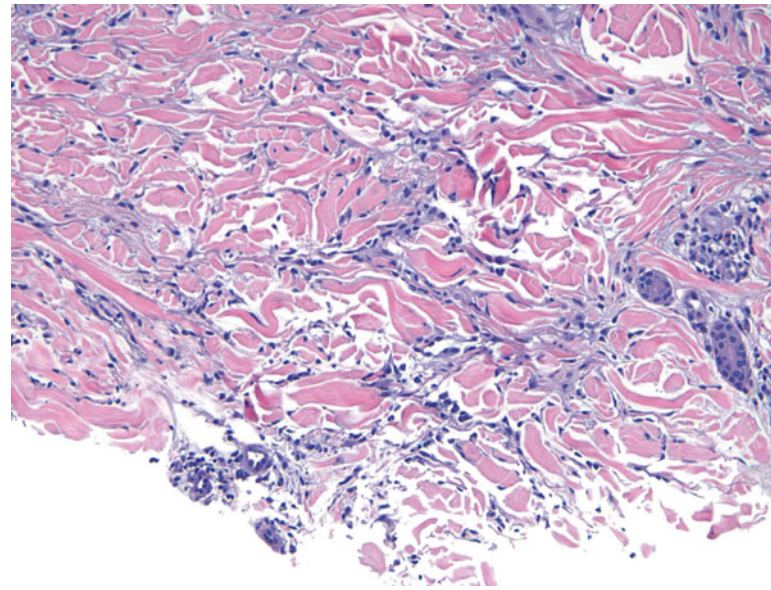


Fig. 3.8 Interstitial granulomatous dermatitis due to a TNF-alpha inhibitor. The interstitial and slightly palisaded infiltrate of histiocytes is a close mimic of granuloma annulare (200×)

variable alteration of collagen and elastic fibers, and occasionally interspersed neutrophils and eosinophils. A vacuolar interface reaction may be observed concurrently (Fig. 3.8).

The main histologic differential diagnosis is interstitial granuloma annulare, but interstitial granulomatous dermatitis with arthritis, interstitial mycosis fungoides, and early eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome) can be considered as well.

Pseudolymphomatous Drug Reactions

These have historically been divided into two different categories of drug reactions that histologically mimic lymphoma. The first is a hypersensitivity syndrome with an acute onset, severe skin disease, hematologic abnormalities (including hyperpeosinophilia and atypical lymphocytes), other organ involvement, especially

hepatic, and lymphadenopathy (now known by the name of drug rash with eosinophilia and systemic symptoms or DRESS) . The pseudolymphomatous variant is but one of many patterns associated with DRESS, to be discussed in more detail below. A second type has a more insidious onset without other associated symptoms and can be difficult to distinguish from lymphoma. This section will discuss the latter type.

Pseudolymphomatous drug eruptions can mimic either B-cell or T-cell lymphoma and also lymphoid hyperplasia. The B-cell patterns are more common. There is typically a dense, nodular, top-heavy (meaning lymphocyte nodularity is most dense towards the superficial dermis or dense throughout) lymphocytic infiltrate. Much rarer are pseudolymphomatous drug reactions that mimic a T-cell lymphoma, often mycosis fungoides, with a band-like infiltrate containing occasional atypical lymphocytes. A mix of plasma cells, histiocytes, and eosinophils in addition to small lymphocytes can be a clue to the diagnosis of a pseudolymphoma. Epidermotropism and adnexotropism are rare and more common in lymphoma. Immunohistochemical stains and genotypic analysis may be necessary to exclude lymphoma, and a full discussion of such studies is beyond the scope of this chapter.

The differential diagnosis also includes a pseudolymphomatous reaction to an arthropod bite, as well as pseudolymphomatous folliculitis and pseudolymphomatous lupus erythematosus.

Erythroderma

On occasion, a drug eruption can be manifest as erythroderma. A biopsy in this setting can be disappointing with respect to elucidating the cause, as many conditions which can eventuate in erythroderma, including psoriasis, may have similar histologic features in this setting, and may include eosinophils within the infiltrate, unlike typical plaque-type psoriasis, for example. The Sézary variant of cutaneous T-cell lymphoma may also lack diagnostic features in this setting, but atypical lymphocytes can be helpful. The gold standard for this diagnosis rests on peripheral blood studies, however, including flow cytometry.

The histologic differential diagnosis also includes pityriasis rubra pilaris, subacute spongiotic (eczematous) dermatitis, scabetic dermatitis, and DRESS.

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) or Drug-Induced Delayed Multiorgan Hypersensitivity (DIDMOHS)

DRESS may display a variety of histologic patterns from urticarial to interface, to spongiotic to psoriasiform, and pseudolymphomatous (Fig. 3.9). The clinical criteria, including evidence of organ damage, are essential to arriving at the diagnosis. This is a severe form of adverse drug reaction with a mortality rate of 10 %, and a prolonged resolution phase upon long-term treatment with corticosteroids. Despite the name, eosinophils may be present or absent histologically. Dyskeratotic keratinocytes can be a helpful clue, as in other drug eruptions, and some may be present high with the epidermis. The papillary dermis may be edematous, and vascular dilatation can also be seen. DRESS can sometimes mimic a cutaneous lymphoma histologically, with slightly atypical lymphocytes present, and sometimes a band-like infiltrate as in mycosis fungoides.

Linear IgA (LIGA) Bullous Dermatosis-Like Drug Eruption

This is indistinguishable from non-drug induced LIGA, except that there is loss of linear IgA along the dermal-epidermal junction on direct immunofluorescence (DIF) upon removal of the responsible drug. The typical histology of LIGA includes a subepidermal vesicle with numerous neutrophils, and often eosinophils, and a superficial perivascular lymphocytic infiltrate. Positive DIF with linear IgA along the dermal-epidermal junction is necessary for the diagnosis.

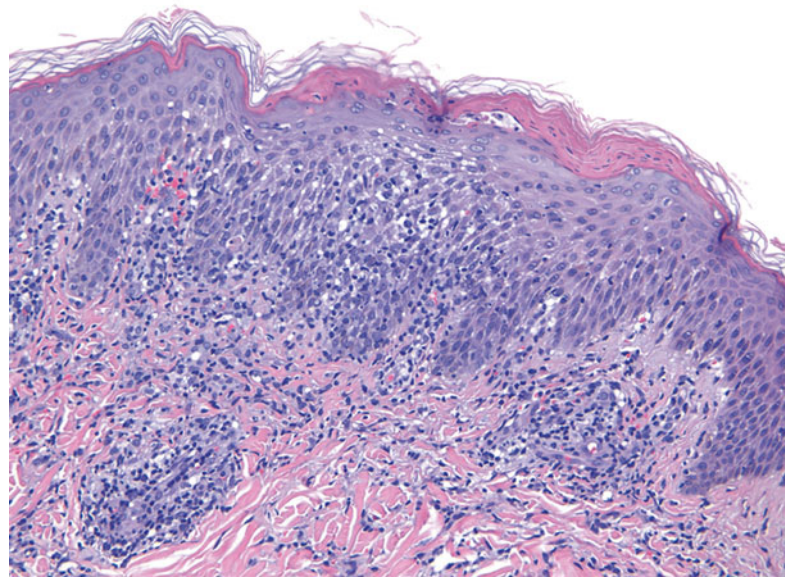


Fig. 3.9 Drug reaction with eosinophilia and systemic symptoms (DRESS). A psoriasiform spongiotic reaction with dyskeratosis is evident. The infiltrate also contained eosinophils (200×)

The differential diagnosis includes dermatitis herpetiformis, bullous pemphigoid and variants, and bullous lupus erythematosus.

Warfarin-Induced Skin Necrosis

Warfarin-induced skin necrosis is a very rare complication of warfarin (Coumadin) therapy (affecting approximately 1 in 10,000 patients on warfarin), and usually occurring early in the therapeutic period. Microscopically, the lesions appear as a thrombotic vasculopathy, with fibrin thrombi within small vessels throughout the dermis, without a significant surrounding inflammatory infiltrate. Extravasated red blood cells are common and, eventually, the thrombotic vessels lead to cutaneous necrosis of varying degree. The findings in heparin- and enoxaparin-induced coagulopathy are similar (Fig. 3.10).

The main differential diagnosis includes other thrombotic vasculopathies such as purpura fulminans, antiphospholipid antibody syndrome, cryoglobulinemia, clotting factor abnormalities, cryofibrinogenemia, cocaine-induced retiform purpura (recently described), homocystinemia, and thrombotic vasculopathies due to infection. Other ancillary laboratory studies may be needed such as culture, and hypercoagulability testing (inherited and acquired).

Chemotherapy-Related Drug Reactions

In a skin biopsy from a patient who is being treated with systemic chemotherapy and/or radiation, with radiation recall, striking keratinocyte atypia, including mitotic figures in some cases, and dysmaturation can often be seen, and should not be mistaken for malignant or premalignant change. This can be observed as part of an eruption, but also in normal-appearing skin. There may be a loss of normal polarity of kertatinocytes in the basilar and spinous layers, and scattered atypical keratinocytes with large nuclei but also abundant cytoplasm. Some specific agents such as etoposide, are associated with starburst mitotic figures (Fig. 3.11). As always, clinicopathologic correlation is also very important to make sure the patient has received a medication that could explain the keratinocyte atypia and point to a chemotherapeutic culprit and/or recent radiation therapy.

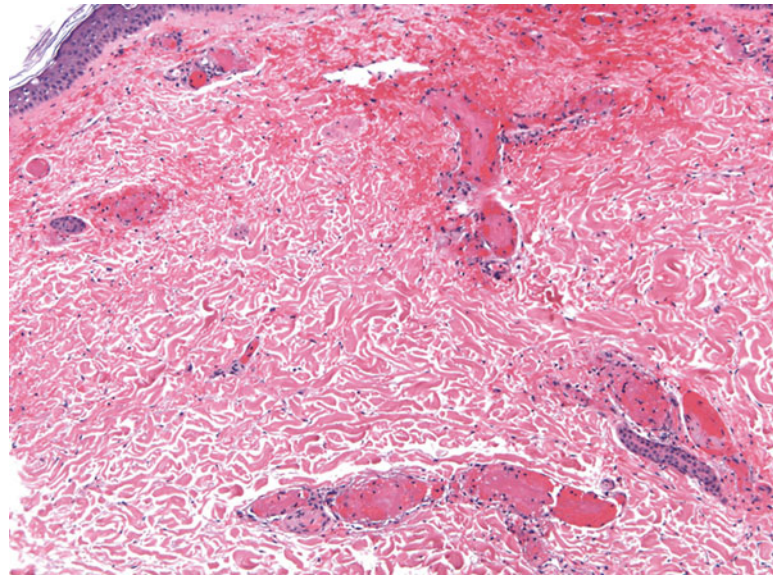


Fig. 3.10 Coumadin necrosis. Multiple fibrin thrombi are evident, without a significant associated inflammatory infiltrate (100×)

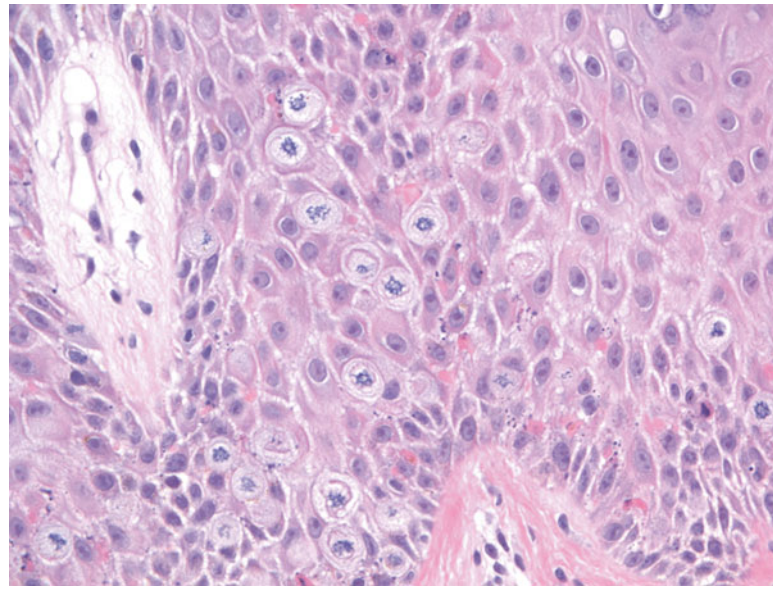


Fig. 3.11 Chemotherapy reaction due to etoposide. There is keratinocyte dysmaturation, consisting of enlarged keratinocytes within the lower epidermis (loss of normal polarity), and many mitotic figures with a starburst pattern of chromatin are evident (200×)

There are also a few specific diseases related to chemotherapy that need to be mentioned, and are discussed below.

Hand–Foot Skin Reaction (a.k.a Palmar-Plantar Eerythrodysesthesia)

The multi-targeted tyrosine kinase inhibitors sorafenib and sunitinib are the two most common culprits, but other chemotherapeutic agents have been implicated, especially cytosine and arabinoside. Histologically, it presents with intraepidermal, subcorneal, or even subepidermal vesicle formation with extensive and linear keratinocyte necrosis with intracytoplasmic eosinophilic bodies. This is followed by acanthosis and hyperkeratosis/parakeratosis. Dermal telangiectasias and a sparse lymphocytic infiltrate without eosinophils may be noted. The diagnosis is usually made clinically, and thus histologic descriptions are scant.

Bleomycin, Cisplatin, Busulfan and Other Chemotherapeutic Agents

These agents can cause skin hyperpigmentation following prolonged use (see also section below on other drugs that can cause hyperpigmentation). Bleomycin classically causes "flagellate streaks" or reticulate pigmentation that histologically shows a marked increase of melanin pigment within basal keratinocytes and melanophages in the papillary dermis, with a normal number of melanocytes. A lymphocytic vasculitis has been described in one case.

The histologic differential diagnosis includes postinflammatory hyperpigmentation, erythema dyschromica perstans, and resolving lichen planus.

Neutrophilic Eccrine Hidradenitis

This classically shows a dense neutrophilic infiltrate surrounding and typically localized to eccrine glands. This progresses to prominent vacuolar change of the basement membrane and finally to necrosis of the eccrine glands. Numerous chemotherapeutic agents have been implicated, but infectious etiologies and malignancies unrelated to chemotherapy have also been associated with this pattern.

The histologic differential diagnosis includes Sweet syndrome, cryopyrin-associated periodic syndrome (CAPS), cellulitis, and palmoplantar eccrine hidradenitis.

Drugs that Can Cause Hyperpigmentation

Minocycline-Induced Hyperpigmentation

This is characterized by brown/black pigmented granules freely within the dermis and often deposited along elastic fibers, within macrophages, along vessels, and surrounding eccrine units within myoepithelial cells. Hemosiderin and/or melanin can be detected. Three distinct types of pigmentation occur and stain differently histologically depending on the type. Type I (Fig. 3.12a) minocycline typically affects the face and is Perls' stain positive. Type II (Fig. 3.12b) typically occurs on normal skin of pretibial areas and forearms and is Perls' and Fontana Masson stain positive. Type III (Fig. 3.12c) gives a muddy-brown pigmentation to all sun exposed skin and is only positive for Fontana Masson stain. Type III minocycline is slightly different histologically in that it shows increased melanin staining in the basal layer of keratinocytes and dermal melanophages. The pigment deposition is not as widespread as in types I and II.

The main histologic differential diagnosis is with other drug deposition such as argyria, ochronosis, and amiodarone, and sometimes blue nevus/dermal melanocytosis variants.

Amiodarone

In rare patients being treated with amiodarone for cardiac dysrythmias, blue-gray skin pigmentation can occur on sun-exposed areas in patients on long-term high-dose therapy. Histologically it shows yellow-brown granules that are deposited within macrophages that are often found around blood vessels and along the junction of the papillary and reticular dermis. The granules stain positively with Fontana-Masson, PAS, Ziehl-Nielson, and Sudan black. Although the pigment was originally thought to be due to lipofuscin deposition, more recent research suggests that amiodarone skin hyperpigmentation appears to be due to direct drug deposition.

The histologic differential diagnosis includes argyria, minocycline hyperpigmentation, melasma, and post inflammatory hyperpigmentation.

Argyria (Silver Deposition)

At one point, argyria was much more common due to use of medications containing silver salts. Currently, occupational exposure, and especially colloidal silver preparations used in the alternative health industry and available on the Internet, have resulted in a resurgence. The histology consists of numerous small brown-black granules that are typically deposited around sweat glands, pilosebaceous units, and within elastic fibers in the superficial dermis (Fig. 3.13).

Chrysiasis (Gold Deposition)

In some patients receiving gold injections for rheumatoid arthritis and pemphigus treatment, blue-gray pigmentation can occur. Histologically round to oval black granules deposited within macrophages that often surround blood vessels are seen. The deposition is typically found in the papillary and mid dermis.

Hydroquinone

Hydroquinone is typically used to lighten the skin, but it can at times cause hyperpigmentation if formulations are used for too long. It is also used in some antimalarial drug formulations. These cases are typically seen in patients in malaria-endemic areas. Prolonged use has also been associated with exogenous ochronosis.

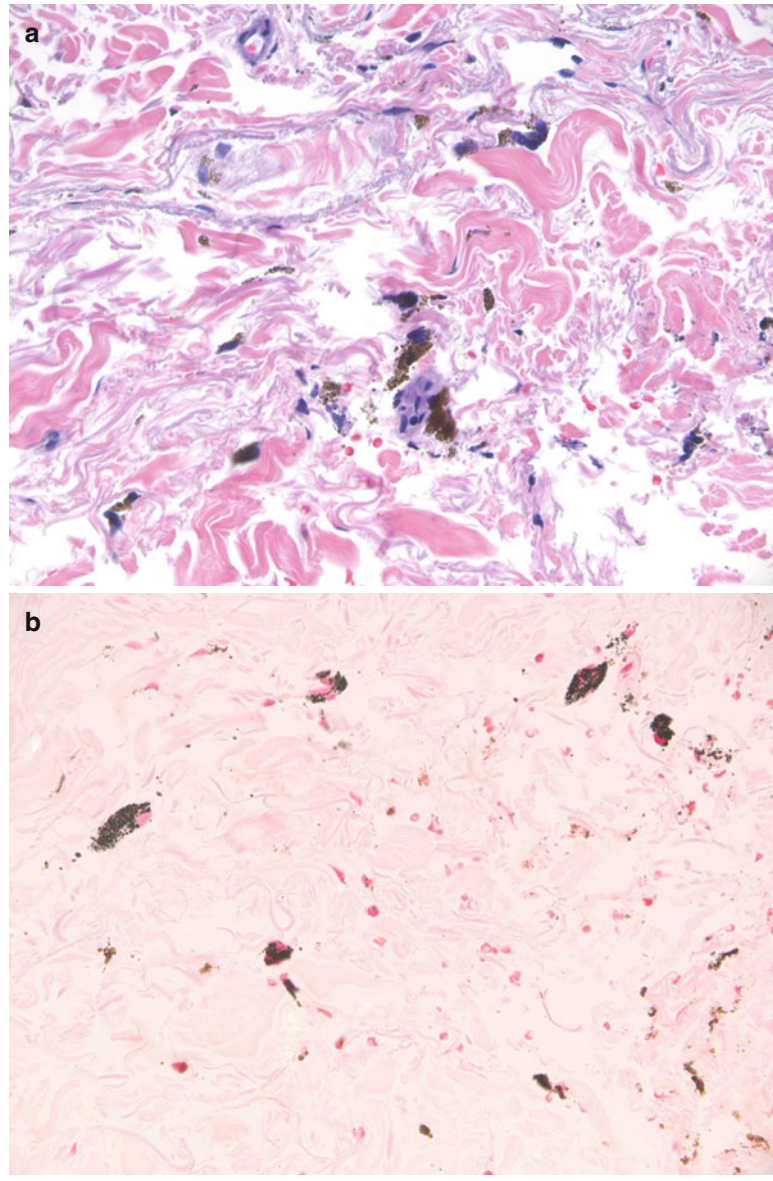


Fig. 3.12 (**a**) Minocycline pigmentation type II. Pigmented macrophages are present within the reticular dermis. They stain with both (**b**) Fontana-Masson and (**c**) Perls' stains (400×)

Fig. 3.12 (continued)

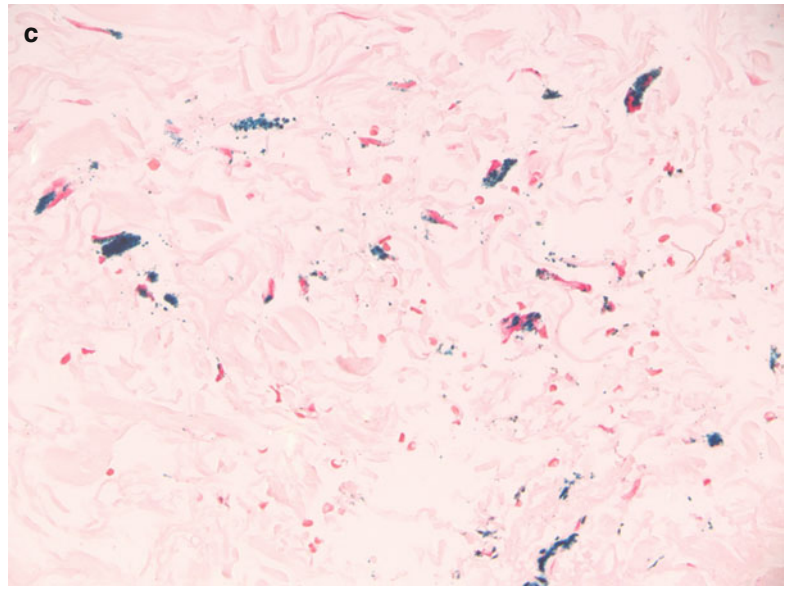
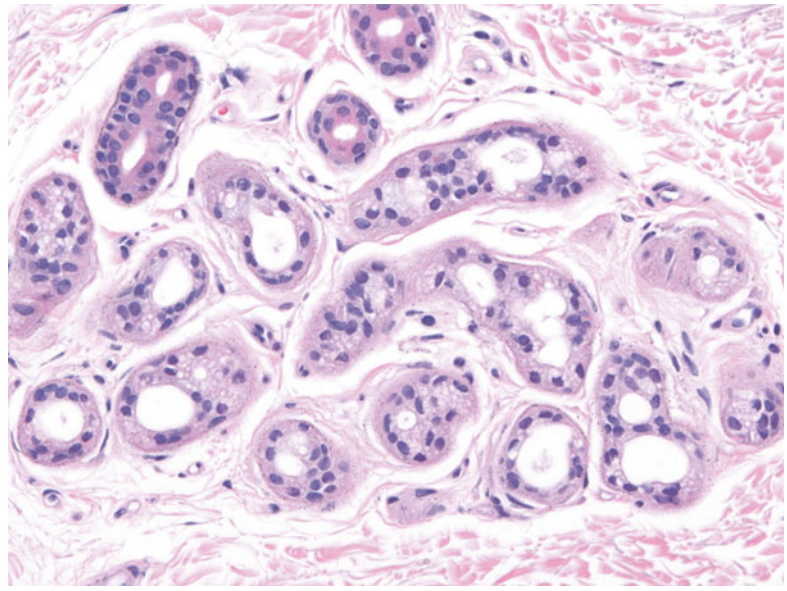


Fig. 3.13 Arygyria. Fine silver granules are evident in the basement membrane surrounding eccrine coils (400×)



Skin biopsy is typically not needed for diagnosis (because detailed clinical history is usually sufficient) but will typically show features of ochronosis, which is indistinguishable from alkaptonuric ochronosis. Banana-shaped brown to yellow ("ochre") pigmented fibers are evident within the superficial dermis (Fig. 3.14). These pigment deposits can displace the collagen and elastic fibers. At times histiocytes will also take up pigment, and pigment may also be found as extracellular granular deposits.

There are also a variety of other conditions that are beyond the scope of this chapter, and can also be extremely difficult to distinguish from non-drug-induced forms without proper clinical history or clinical suspicion. They are listed here:

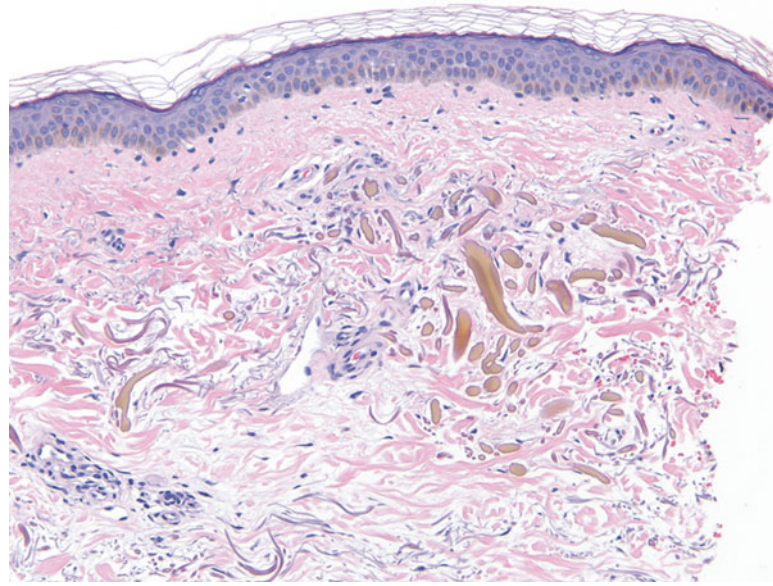


Fig. 3.14 Ochronosis. Golden banana-shaped fibers are evident in the superficial dermis (200×)

- Lupus-like drug reactions
- Leukocytoclastic vasculitis
- Drug-induced Sweet syndrome
- Sclerodermoid drug reactions
- Acneiform drug reactions
- Drug-induced eosinophilic pustular folliculitis
- Drug-induced pemphigus
- Pigmented purpuric dermatoses
- Exogenous ochronosis

For histologic features of these conditions, as well as histologic differential diagnoses, a general dermatopathology textbook is recommended.

Conclusions

As the number and class of medications increases, and the longer these are used in clinical practice, it should be expected that these iatrogenic dermatologic reactions are also observed in higher frequency. It will be important for both the dermatologist and pathologist to keep up with the literature of newly reported reactions to help decipher if a certain drug can be implicated in the histopathologic findings. However, as such reactions share or may duplicate features seen in other inflammatory and even neoplastic conditions, this can be a difficult undertaking. Communication between clinician and pathologist regarding the onset of the cutaneous eruption in relation to any possible new drugs will remain paramount. It is also important to keep in mind the possibility of a drug reaction whenever the histopathologic picture is complex and/or does not seem to fit a known entity.

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