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# Drug induced skin reactions

**Drug induced skin reactions**

Basel Seminars Skin Pathology,
Basel, June 9th-10th, 2017

The subject of “drug induced skin reactions” is very broad if one considers the definition given by the World Health Organization of an adverse drug reaction, namely,

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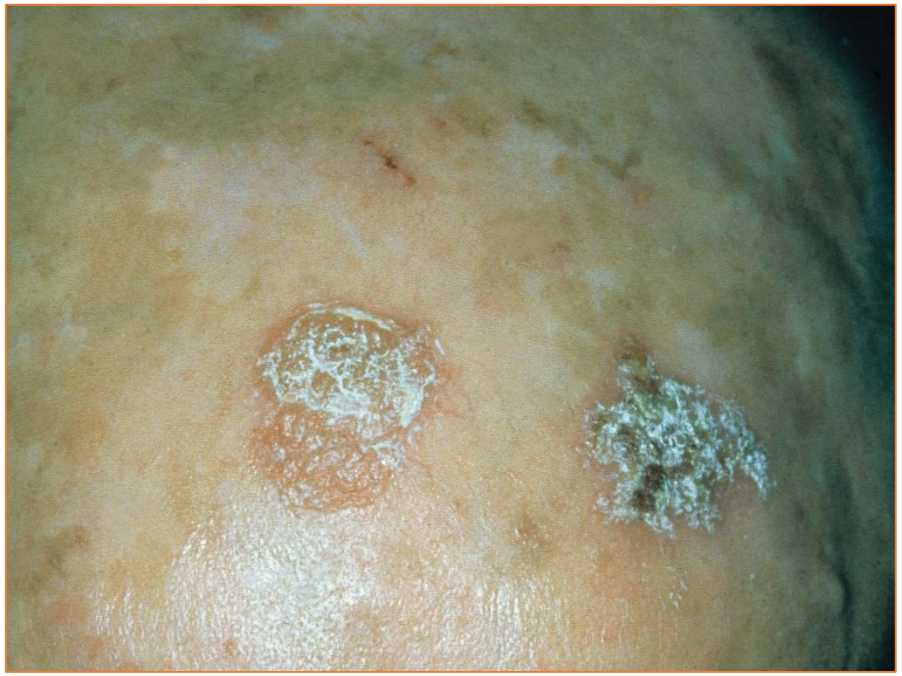
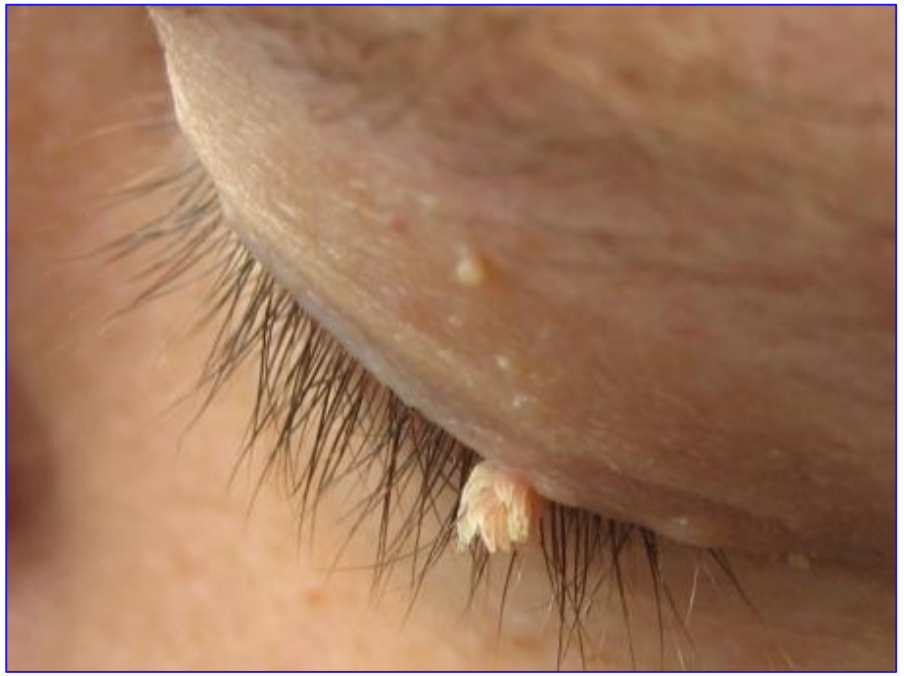
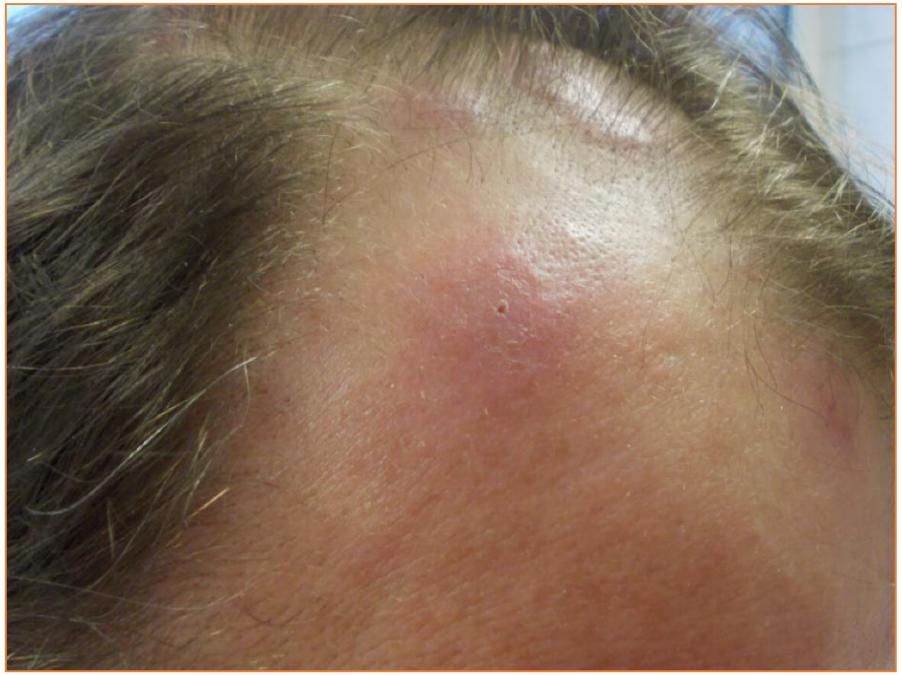
A response to a drug which is noxious and unintended, and which occurs at doses normally used in man. WHO, 1972

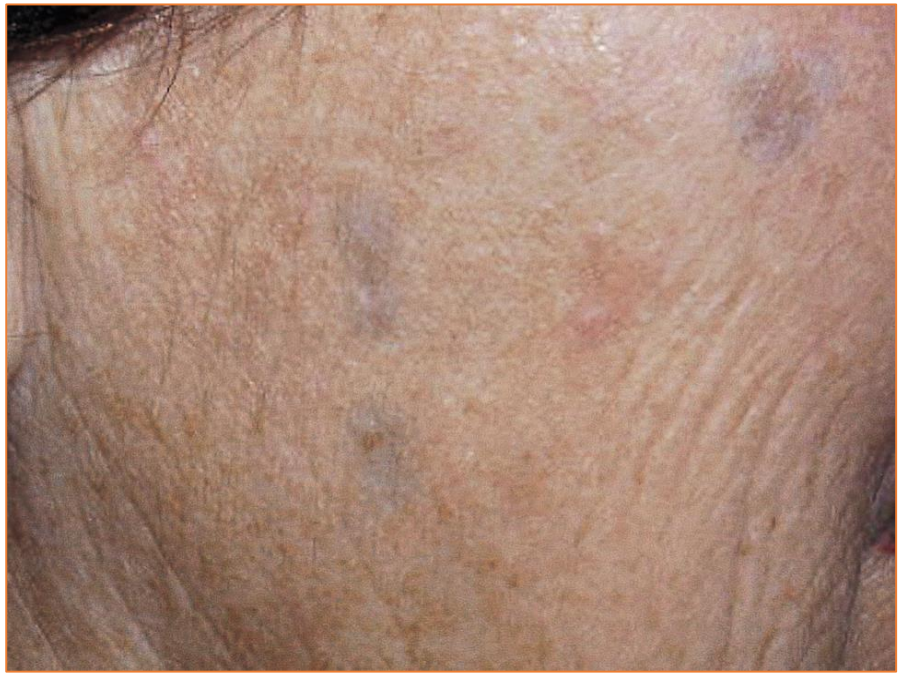
# Drug induced skin reactions

*“a response to a drug which is noxious and unintended, and which occurs at doses normally used in man.”*
Based on that definition, drug induced skin reactions



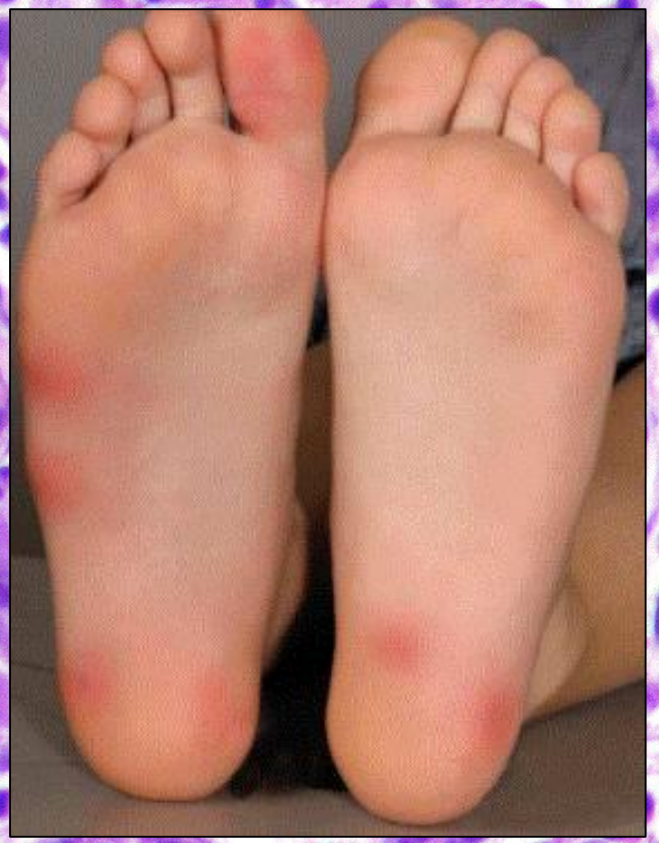




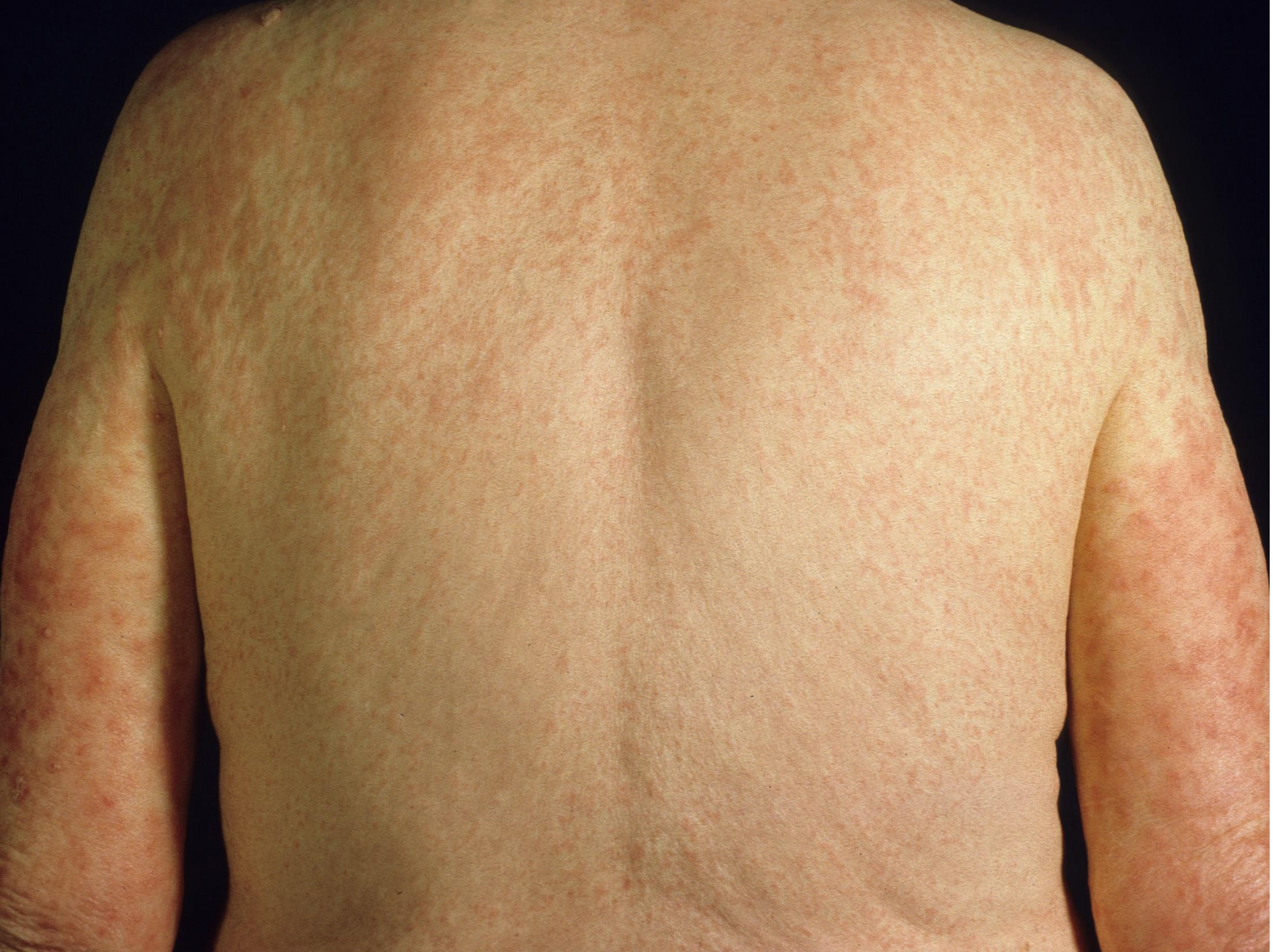


range from squamous cell carcinomas and viral warts induced by immunosuppressive or cytostatic agents to folliculitides induced by steroids or biologicals, and the effects of deposits in the skin, as in chrysiasis and argyria.

Many drug induced skin reactions are direct consequences of the pharmacological action of the drug that either occur in all patients treated with it, such as alopecia secondary to cytostatic therapy,

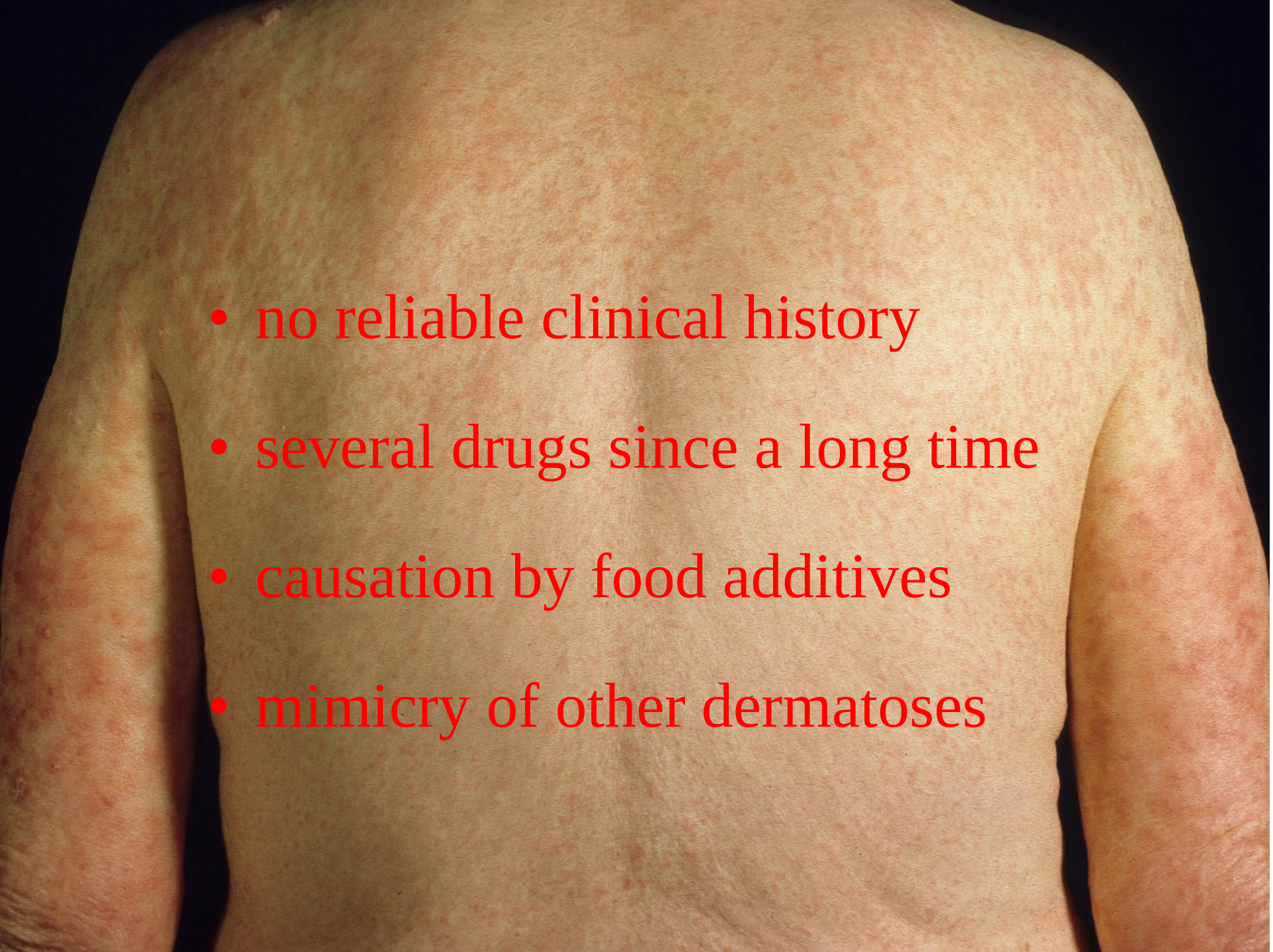


or in only few of them, such as eccrine neutrophilic hidradenitis that has been attributed to cytotoxic effects on cells of eccrine glands through which drugs are eliminated, followed by attraction of neutrophils.

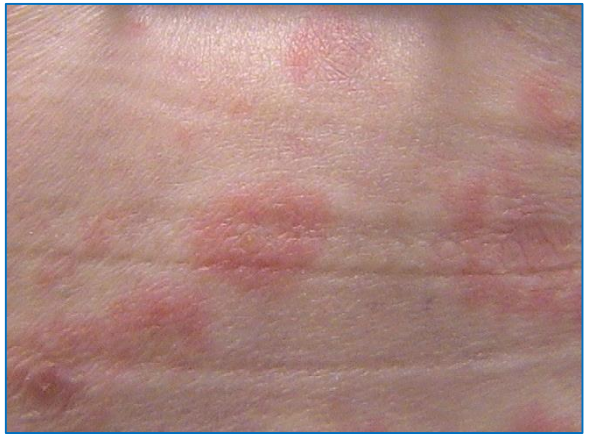
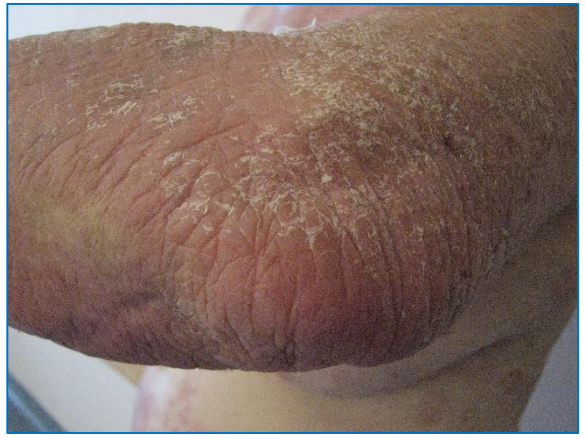
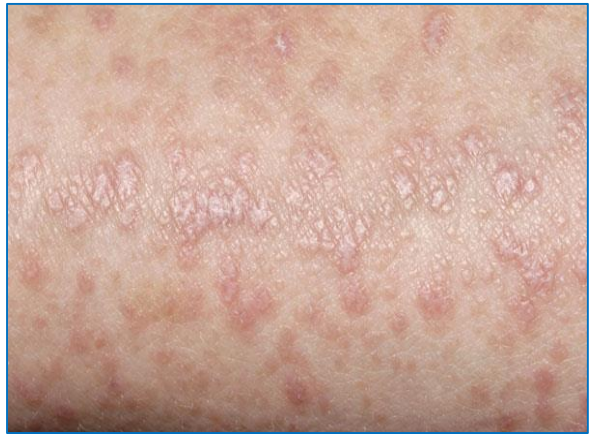
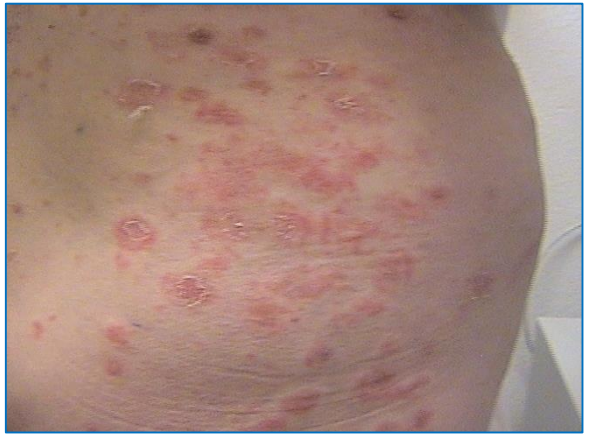
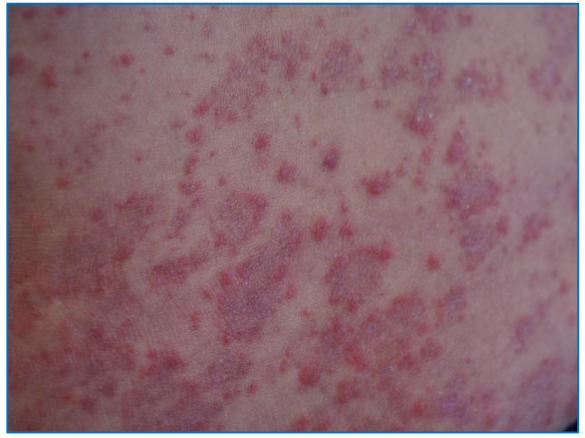
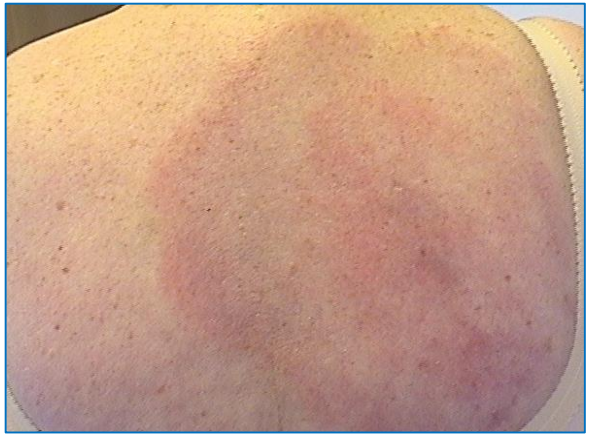
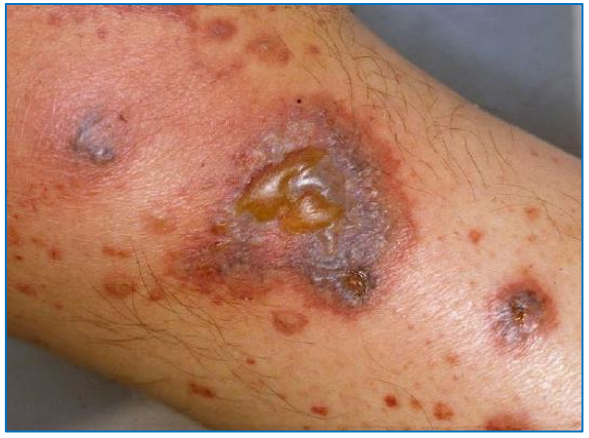
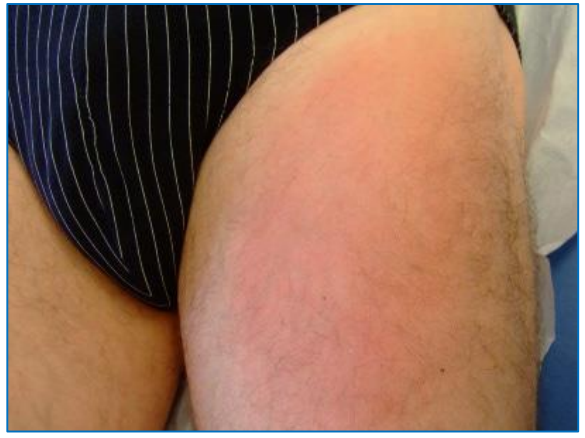
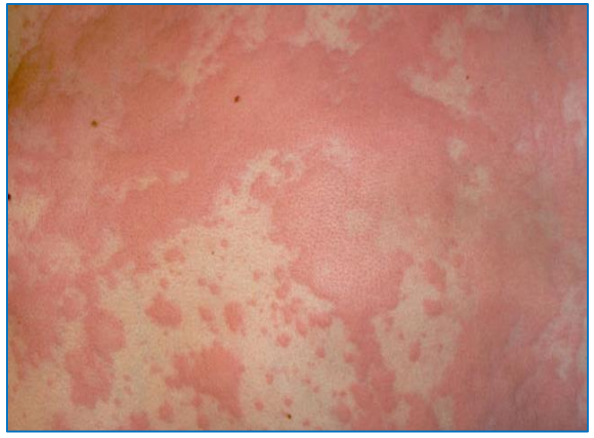


The majority of clinically relevant drug reactions, however, is caused by a cell-mediated immune reaction against the eliciting drug, and those will be in the focus of my presentation.

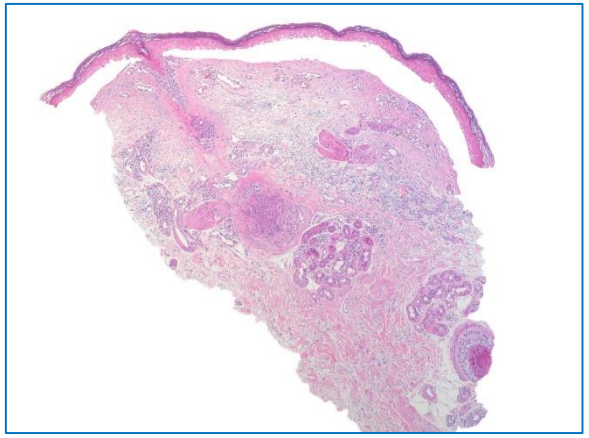
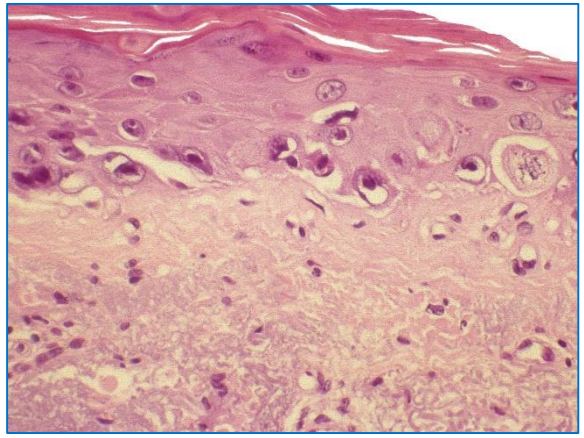
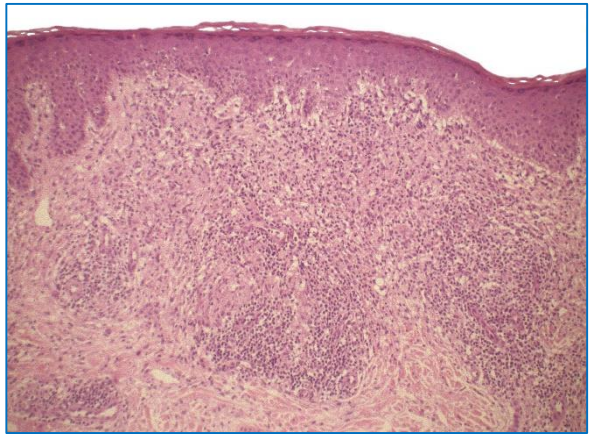
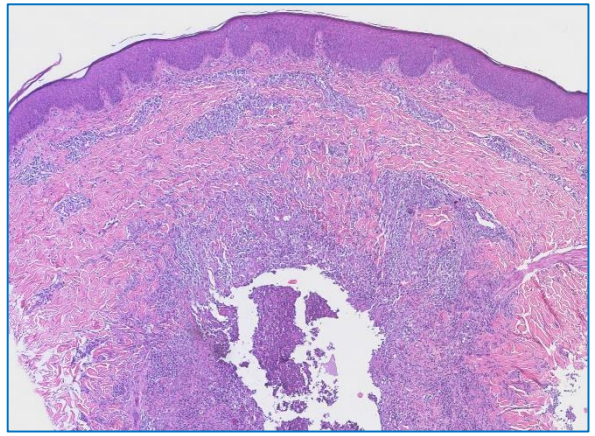
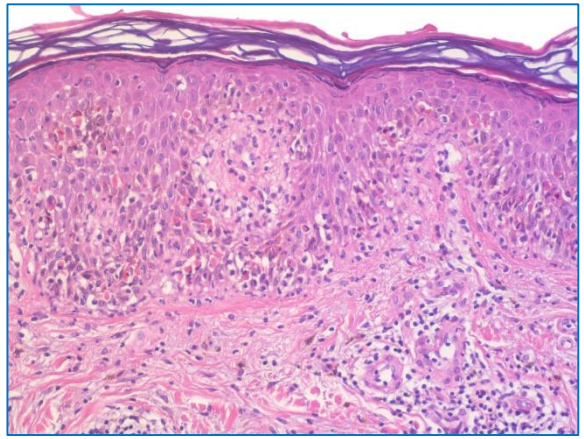
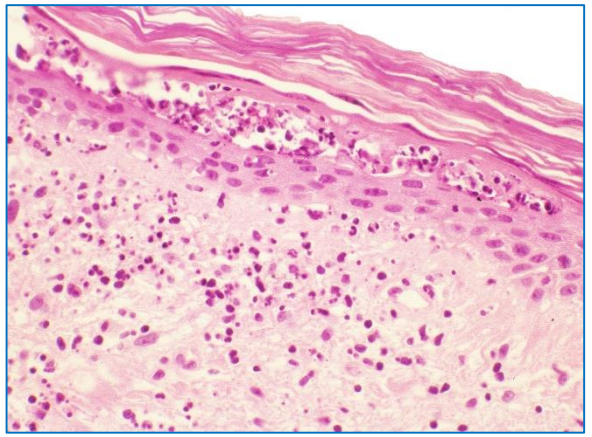
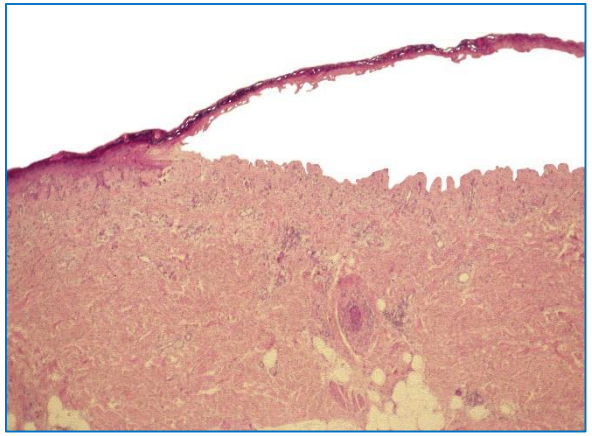
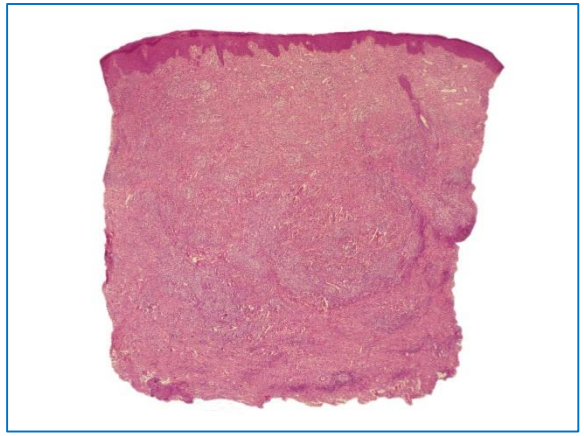
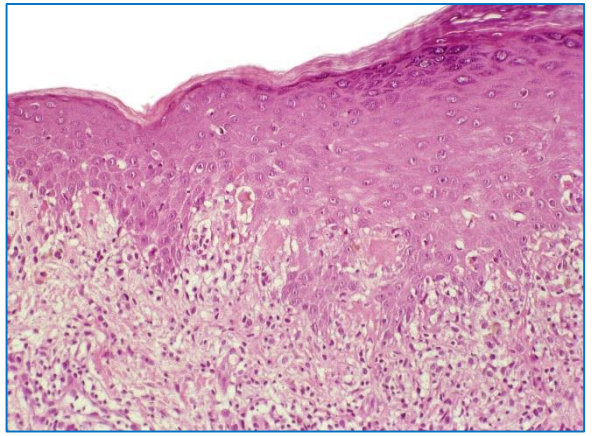
In general, such drugs eruptions represent no diagnostic challenge but can be recognized readily on the basis of clinical picture and clinical history, namely, a symmetrical, widespread maculopapular eruption following recent intake of a newly prescribed drug. In many cases, however, diagnosis is not so apparent



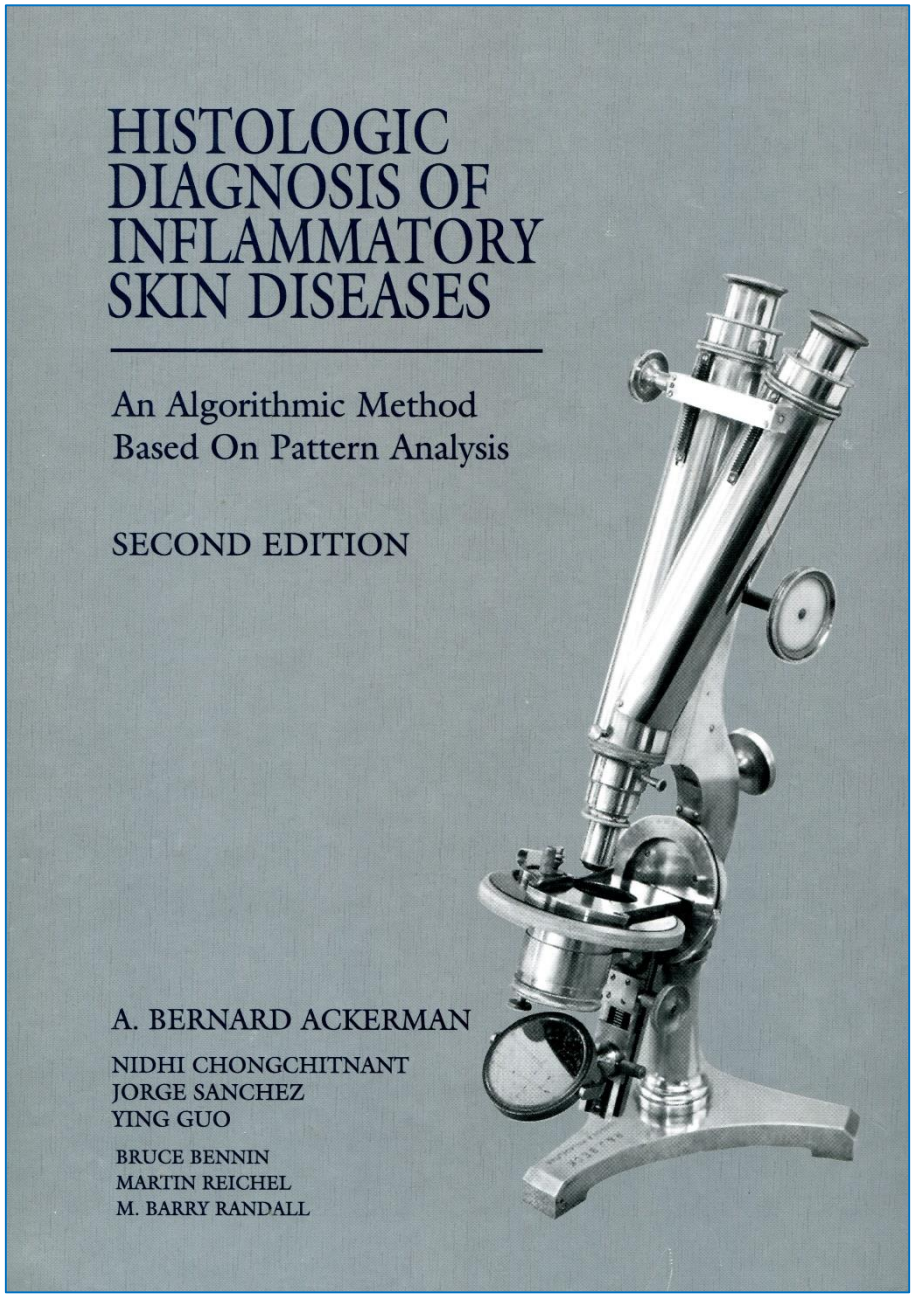

because the patient does not give a reliable clinical history, because the patient takes several drugs since a long time, because the eruption is caused by food additives rather than a medication, or because the eruption mimics other skin diseases.

The latter may range from psoriasis to lichen planus, from pityriasis rosea to borreliosis, and from autoimmune bullous diseases to urticaria. 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.

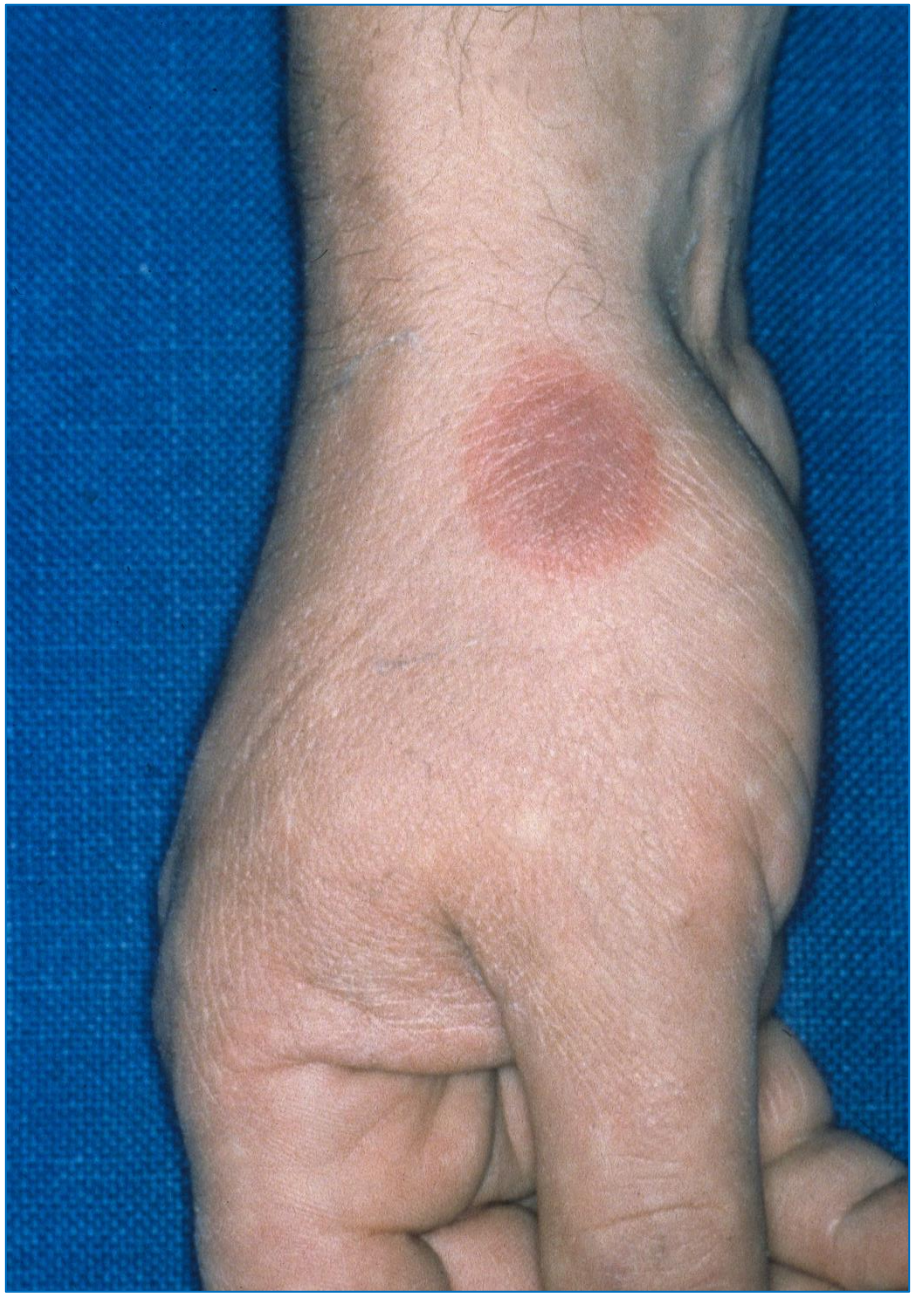










The spectrum of histopathologic presentations of drug eruptions, however, is not smaller than that of clinical ones.




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.

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."*



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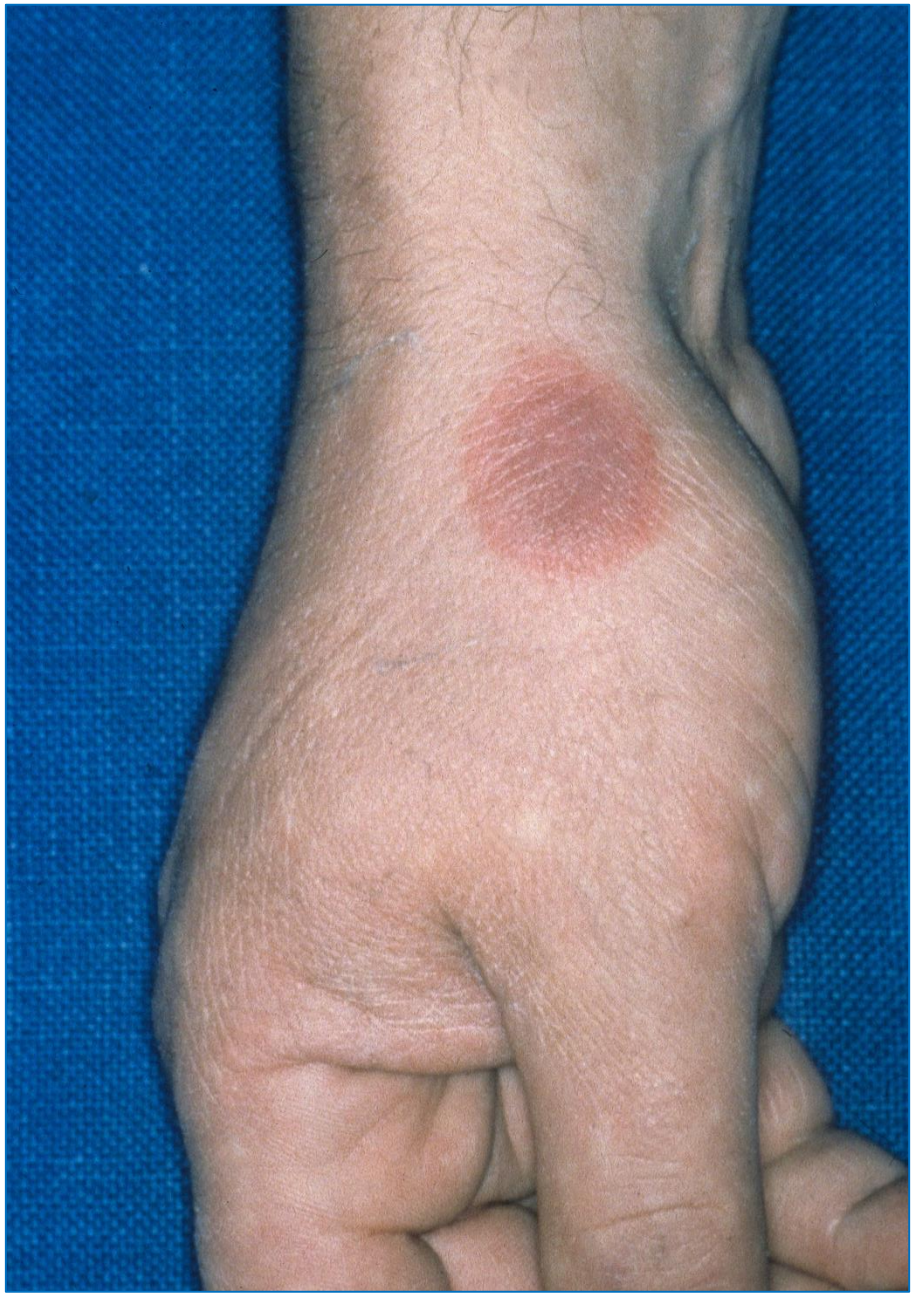
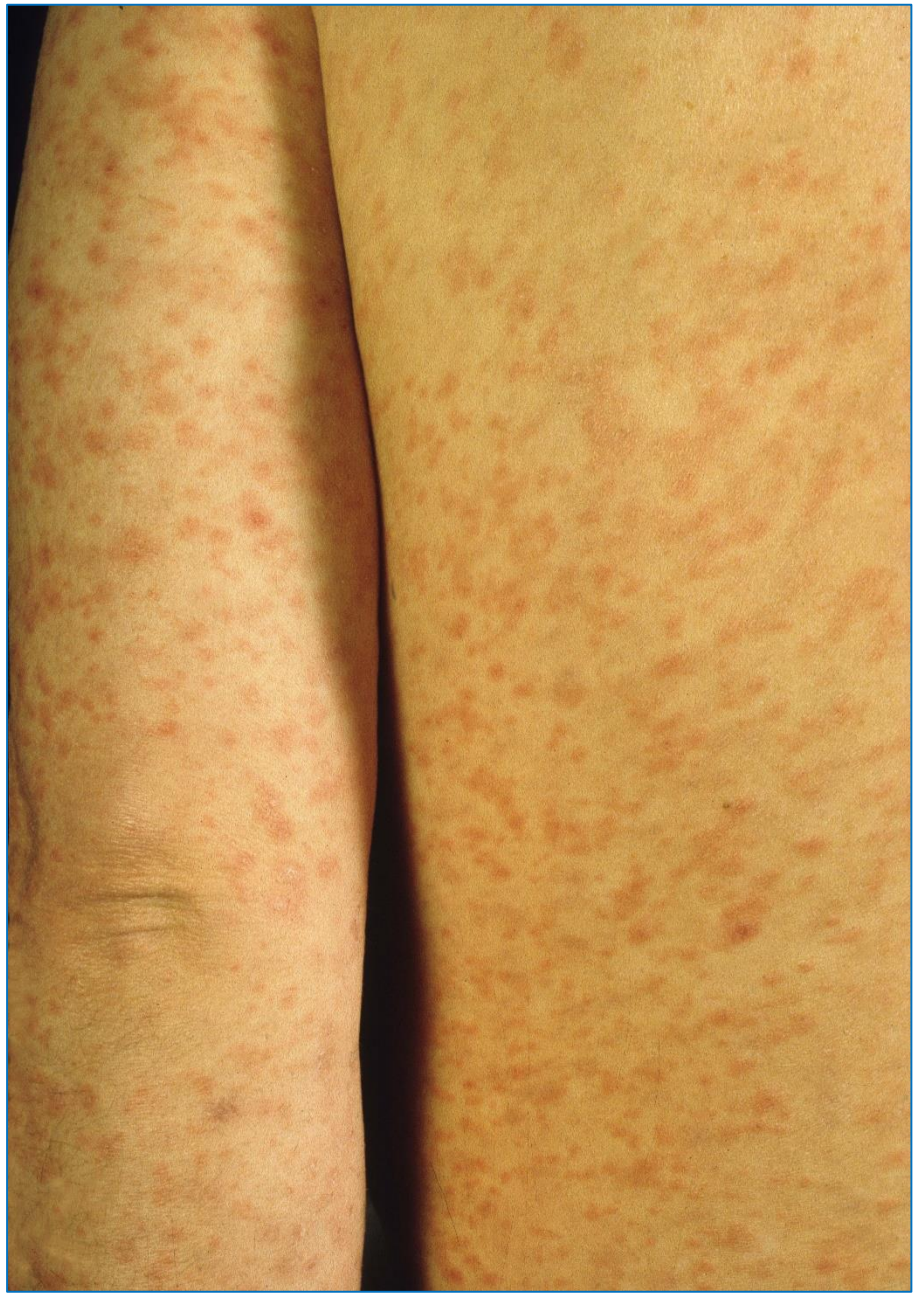
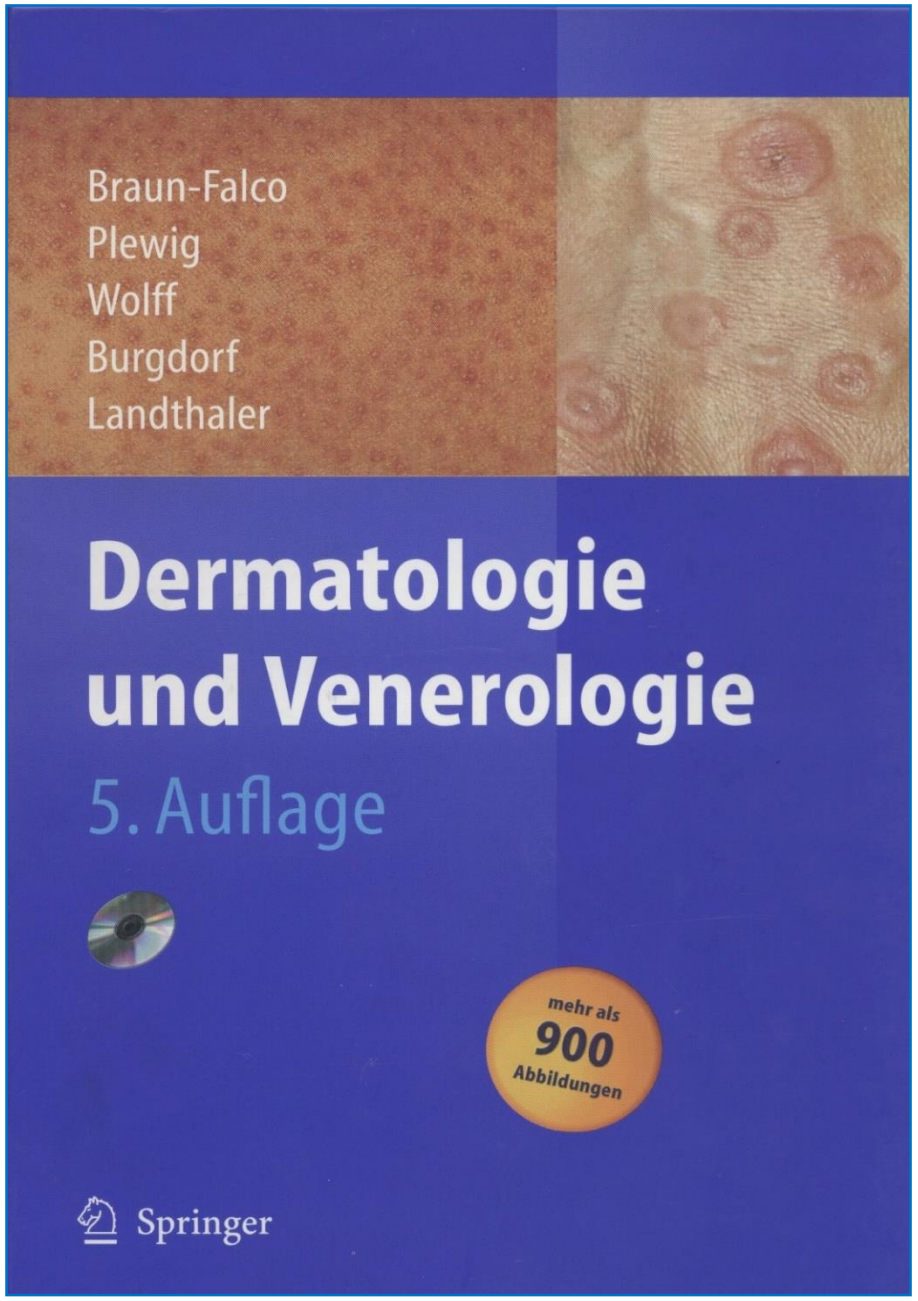
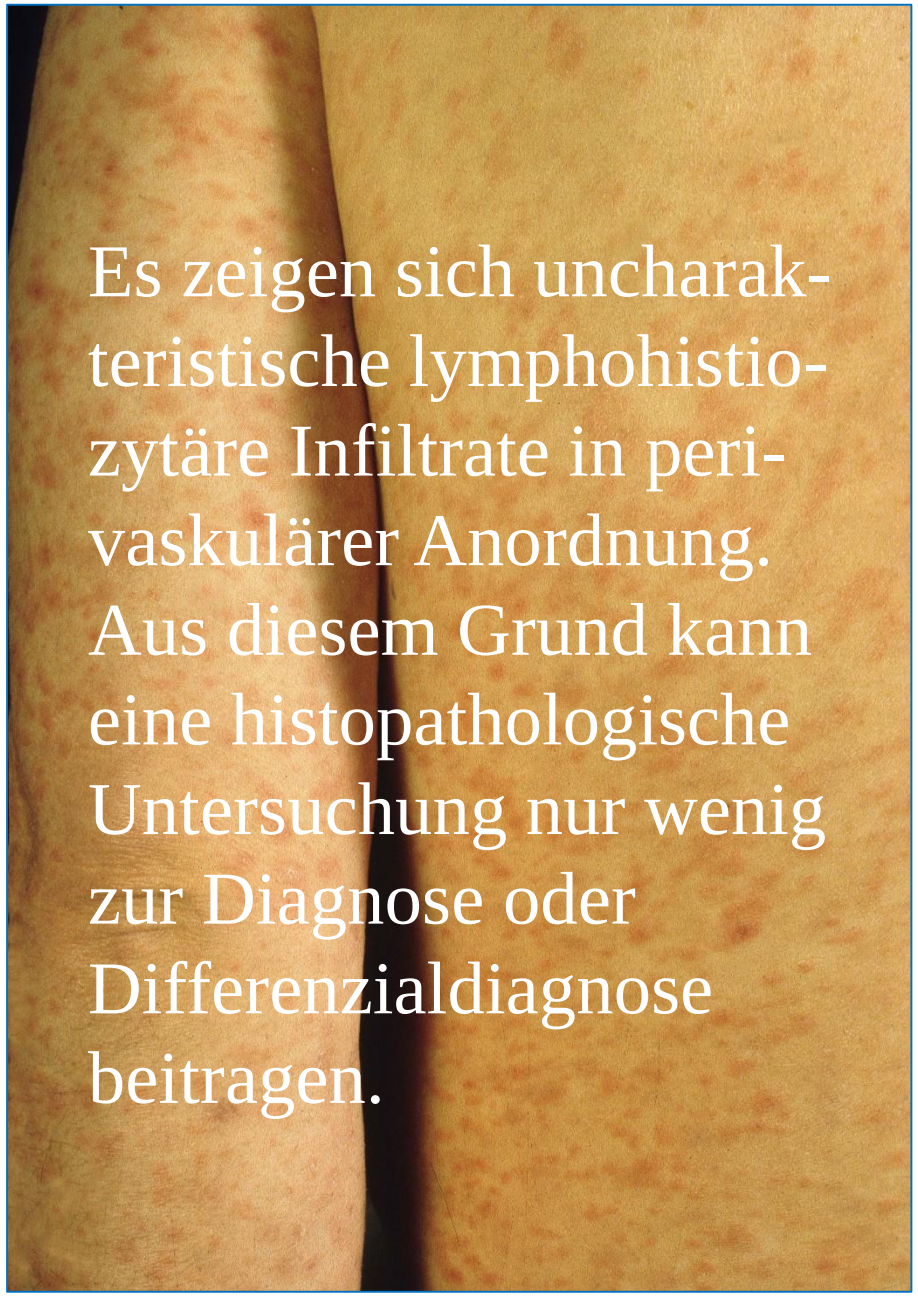
That sobering assessment describes the dilemma of histopathologists in the evaluation of drug eruptions. One must always think of them, but they are difficult to prove, an alleged exception being fixed drug eruption. Hence, biopsies in the latter are recommended, although lesions are usually already distinctive clinically.



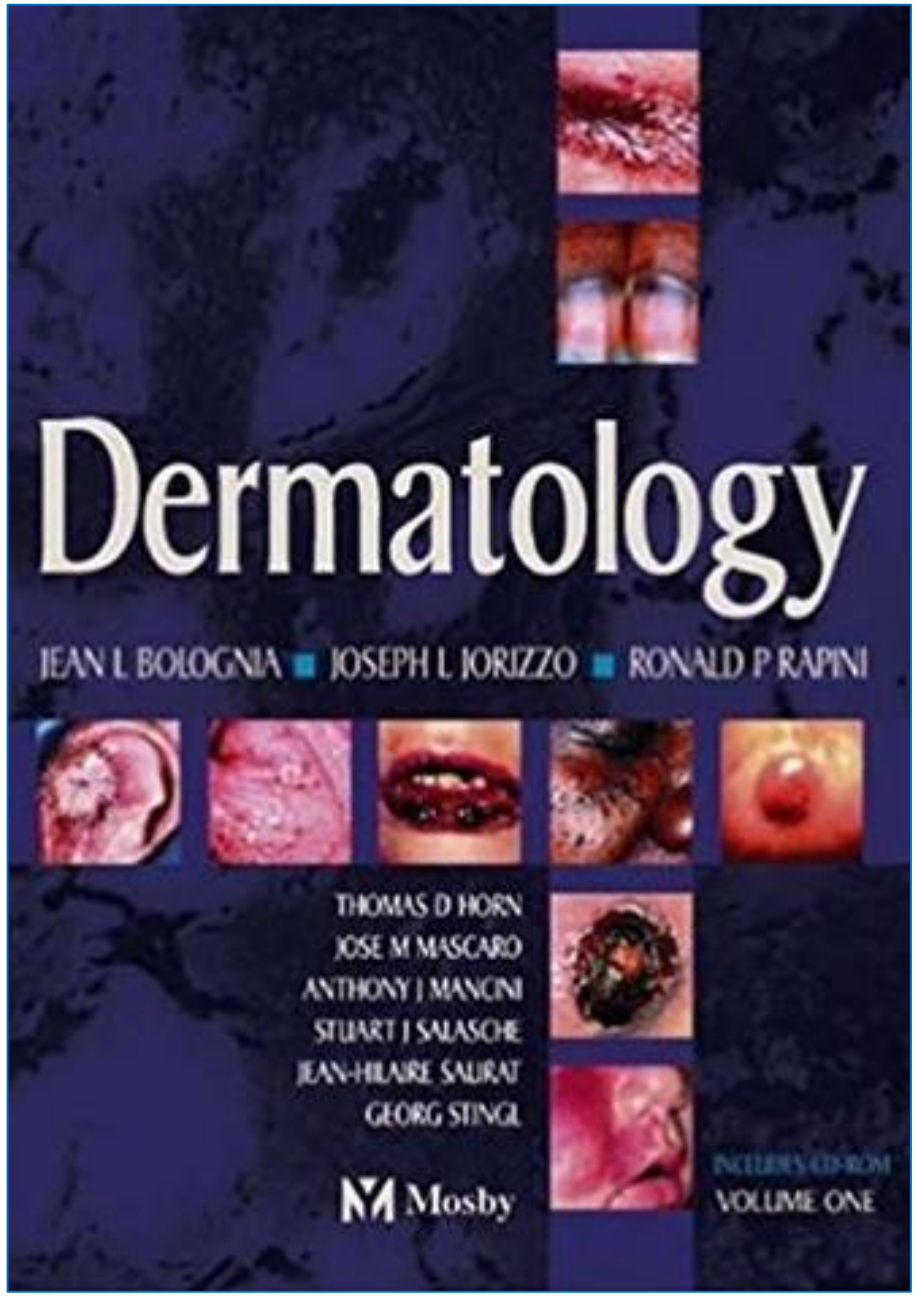


By contrast, many textbooks of dermatology discourage from taking biopsies in maculopapular eruptions because of the alleged non-specificity of histopathologic findings.




For example, the German textbook by Braun-Falco and co-workers claims, in the 5th edition, that there are only *“uncharacteristic lymphohistiocytic infiltrates in perivascular distribution”* and concludes that *“for that reason, histopathologic examination can contribute only little to diagnosis and differential diagnosis.”*





Likewise, the textbook by Bologna, Jorizzo, and Rapini states explicitly: *"A biopsy of morbilliform eruptions is not recommended as it would show non-specific changes consisting of a mild perivascular lymphocytic infiltrate and a few necrotic keratinocytes within the epidermis."*

In my view, those conclusions are wrong and potentially harmful, as they may lead to incorrect diagnoses and mismanagement of patients.

# Pattern Analysis of Drug-Induced Skin Diseases

*Hildamari Justiniano, MD, Alma C. Berlingeri-Ramos, MD, and Jorge L. Sánchez, MD*

**Abstract:** Drug eruptions are common adverse reactions to drug therapy and are a frequent reason for consultation in clinical practice. Even though any medication can potentially cause an adverse cutaneous reaction, some drugs are implicated more commonly than others. Histologically, drugs can elicit a variety of inflammatory disease patterns in the skin and panniculus, no pattern being specific for a particular drug. The most common pattern elicited by systemically administered medications is the perivascular pattern. Psoriasiform or granulomatous patterns are rarely caused by medications. The usual histologic patterns of drug eruptions are discussed in this review using the basic patterns of inflammatory diseases. Clinicopathologic correlation is established for relevant patterns. However, the changes of drug-induced skin disease must be made considering clinical presentation, histopathological analysis, and course of the disease.

**Key Words:** drug eruptions, histopathologic pattern

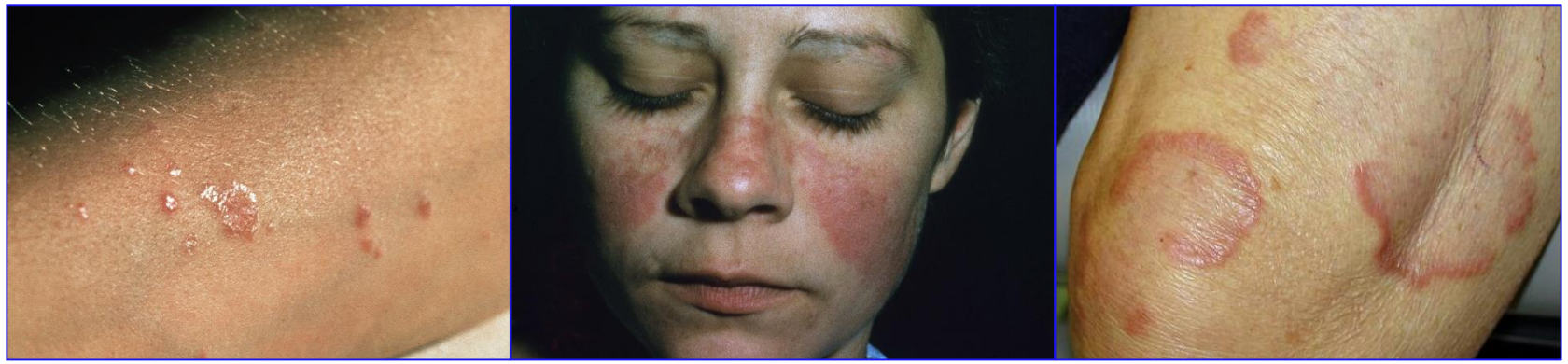
(*Am J Dermatopathol* 2008;30:352–369)

with the number of medications the patient uses. Patients with HIV and other immunosuppressive conditions have an increased incidence of drug reactions. In these cases, immune dysregulation is thought to play an important role.

Histologically, drugs can elicit a variety of inflammatory disease patterns in the skin and panniculus; no pattern is specific for a drug eruption. Any inflammatory pattern that does not exactly match the diagnosis for a given disease should promote the thought of a drug eruption. This is especially so in cases where 2 distinct patterns are present in the same tissue section. For example, a specimen with an interface pattern and marked spongiosis should raise the possibility of a drug-induced lesion. The most common histopathologic pattern elicited by systemic drugs is the perivascular pattern. Psoriasiform or granulomatous patterns are rarely caused by medications.

Usual histologic patterns of drug eruptions will be discussed in this review using the basic patterns of inflammatory skin diseases as established by Ackerman et al[2] (Table 1). Clinicopathologic correlation will be established for relevant patterns.

It is true that *"drugs can elicit a variety of inflammatory disease patterns in the skin and panniculus, no pattern being specific,"* let alone *"specific for a particular drug,"* but biopsies, nonetheless, can help to establish the diagnosis. It is also true, as emphasized in this article on "Pattern Analysis of Drug-Induced Skin Diseases," that *"clinicopathologic correlation … must be made considering clinical presentation, histopathological analysis, and course of the disease,"* but this is true for any inflammatory skin disease,



**Abstract:** Drug eruptions are common adverse reactions to drug therapy and are a frequent reason for consultation in clinical practice. Even though any medication can potentially cause an adverse cutaneous reaction, some drugs are implicated more commonly than others. Histologically, drugs can elicit a variety of inflammatory disease patterns in the skin and panniculus, no pattern being specific for a particular drug. The most common pattern elicited by systemically administered medications is the perivascular pattern. Psoriasiform or granulomatous patterns are rarely caused by medications. The usual histologic patterns of drug eruptions are discussed in this review using the basic patterns of inflammatory diseases. Clinicopathologic correlation is established for relevant patterns. However, the changes of drug-induced skin disease must be made considering clinical presentation, histopathological analysis, and course of the disease.

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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.

# Induction/Aggravation of Dermatoses Through Drugs

- psoriasis (β-blockers, lithium, chloroquine, interferon, NSAIDs, etc.)
- urticaria (acetylsalicylic acid and other NSAIDs, ACE inhibitors, etc.)
- pemphigus (penicillamine, ACE inhibitors, cephalosporins, etc.)
- linear IgA dermatosis (vancomycin, lithium, diclofenac, ACE inhibitors, etc.)
- lupus erythematosus (estrogens, hydralazine, procainamide, anticonvulsants, etc.) …

Compared to other diseases, 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, urticaria, pemphigus, linear IgA dermatosis, or lupus erythematosus. In those instances, naturally, biopsy specimens reveal changes of the authentic disease.

CLINICAL AND LABORATORY INVESTIGATIONS

DOI 10.1111/j.1365-2133.2006.07332.x

# Reactivation of human herpesvirus (HHV) family members other than HHV-6 in drug-induced hypersensitivity syndrome

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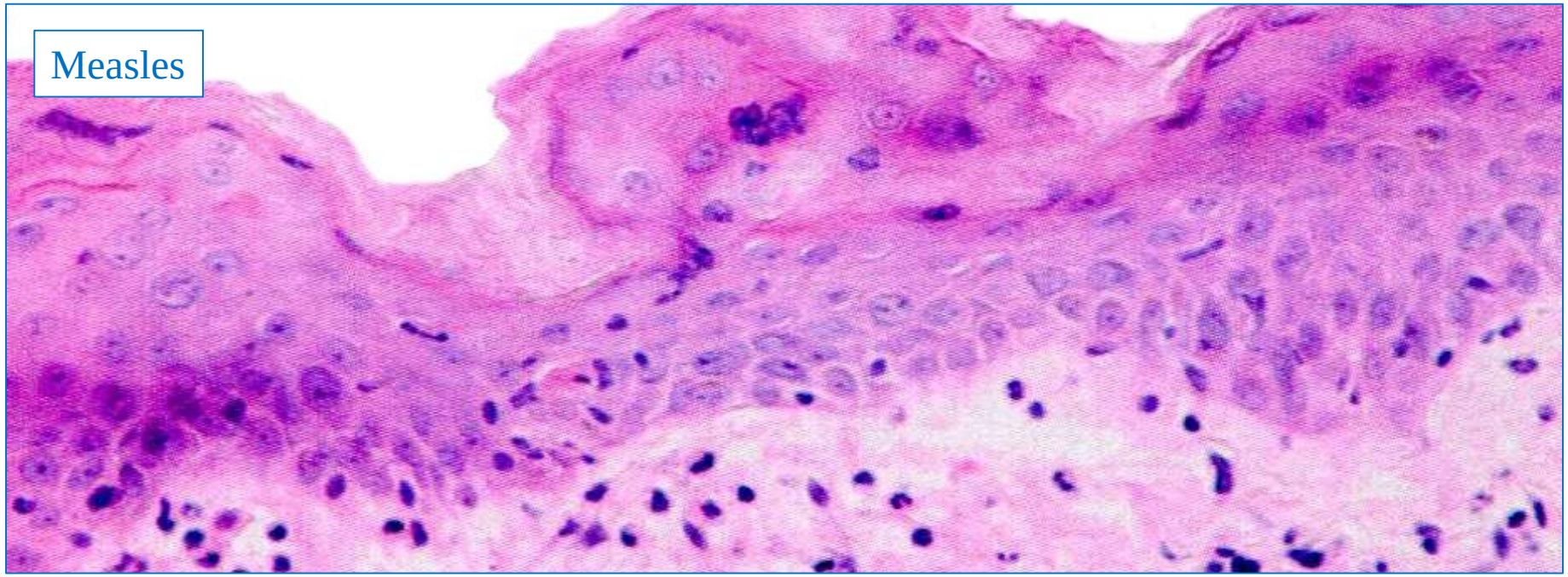
*Department of Dermatology, Ehime University School of Medicine, Toon City, Ehime 791-0295, Japan

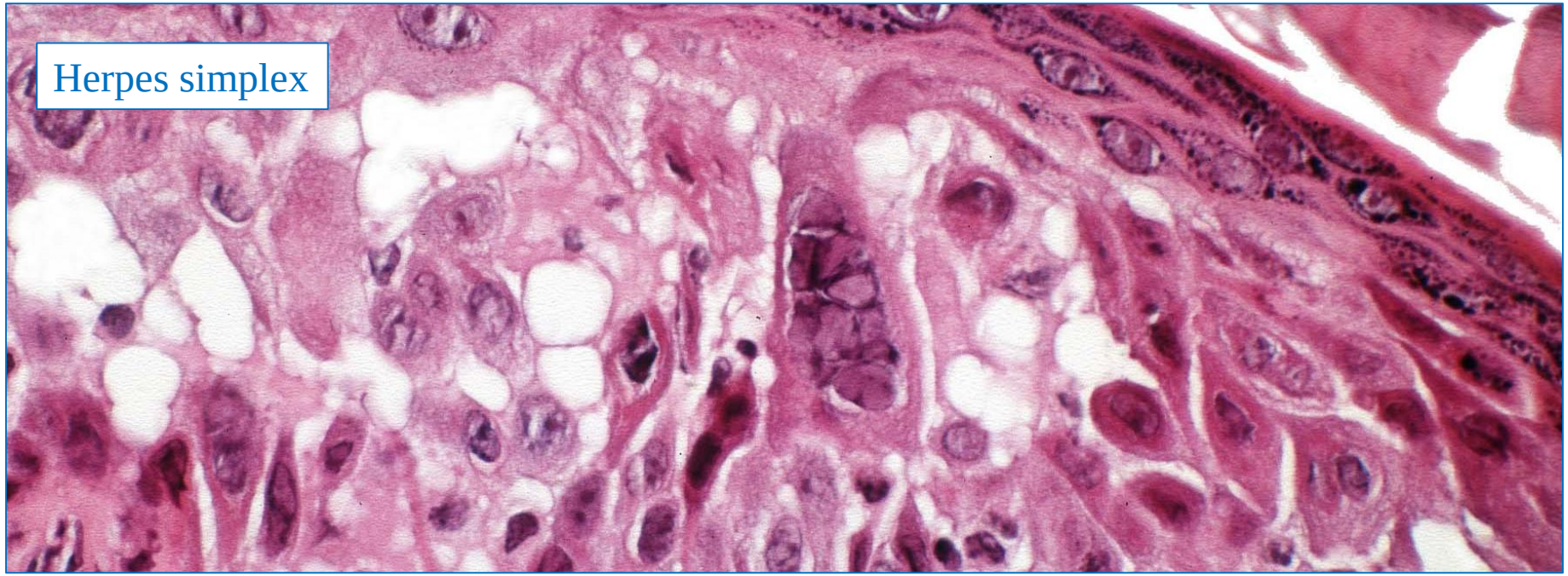
Some drug eruptions are thought to be caused by activation of a latent infection by viruses, such as human herpesvirus 6 or Epstein Barr virus, which may explain why viral exanthems and drug eruptions may be indistinguishable clinically and histopathologically.

EXTRAORDINARY CASE REPORT

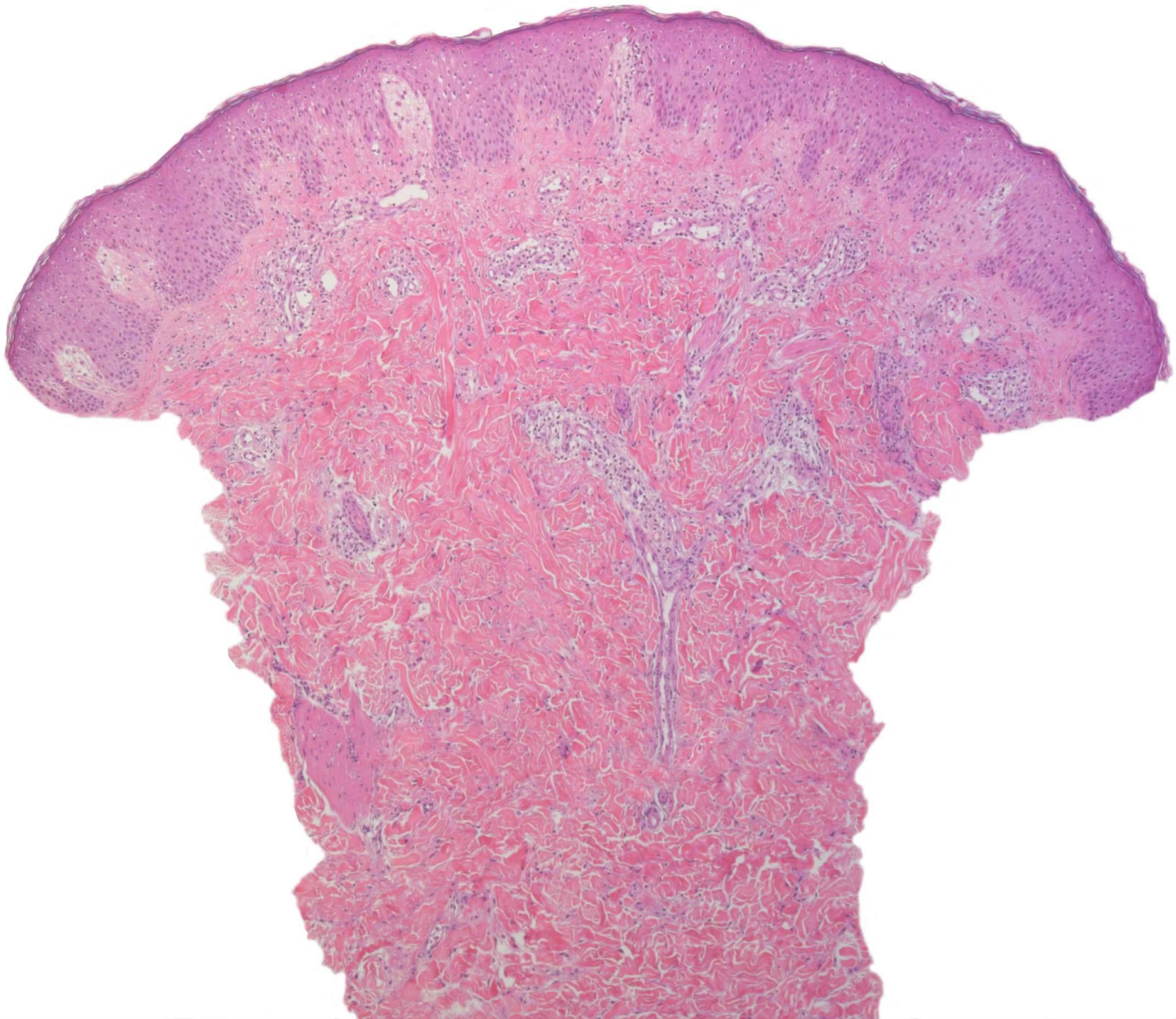
# Adverse Antibiotic-Induced Eruptions Associated With Epstein Barr Virus Infection and Showing Kikuchi-Fujimoto Disease-Like Histology

*J. Andrew Carlson, MD, FRCPC,* Amy Perlmutter, MD,* Ellis Tobin, MD,† Derek Richardson, MD,‡ and Angela Rohwedder, PhD§*

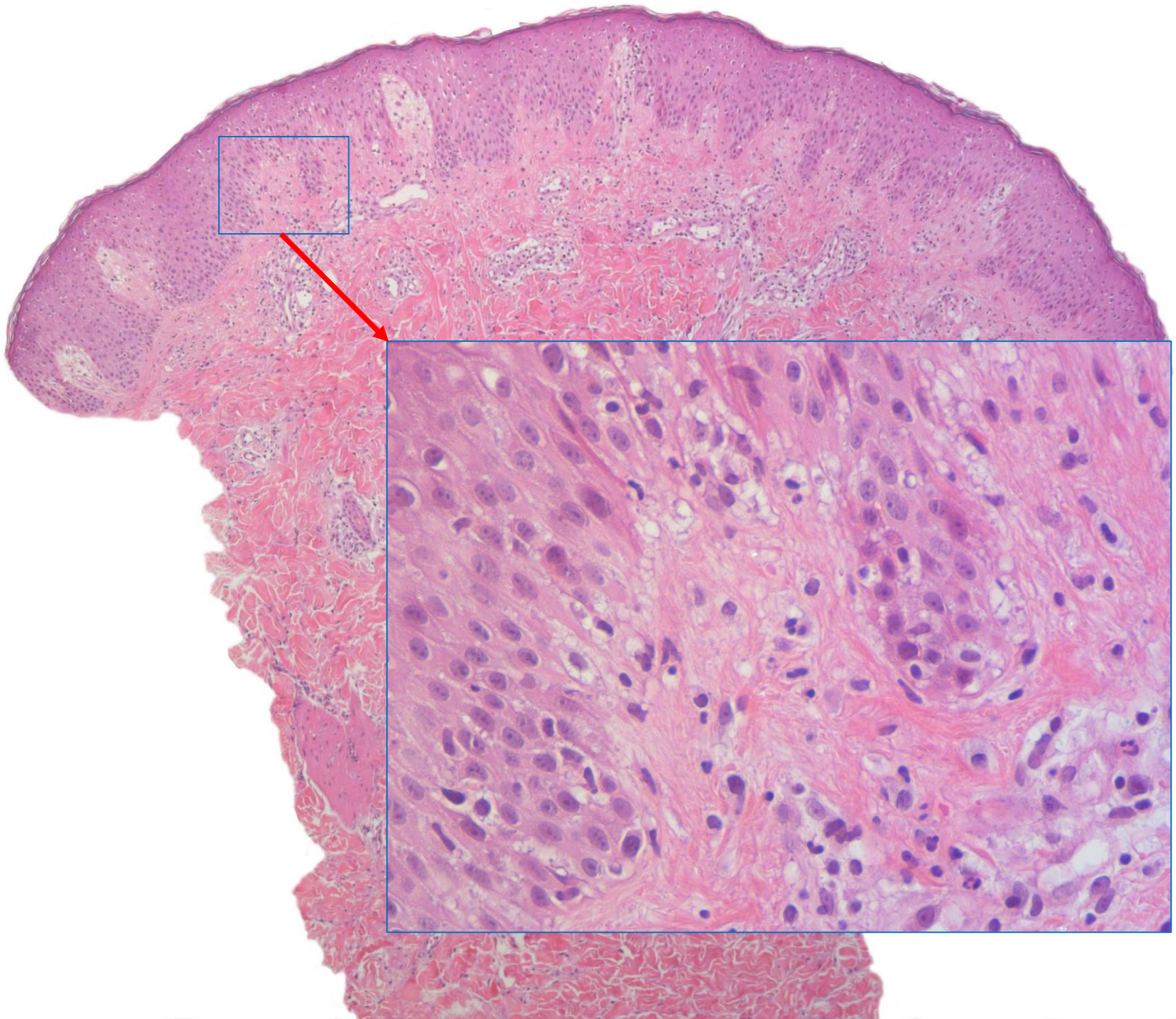


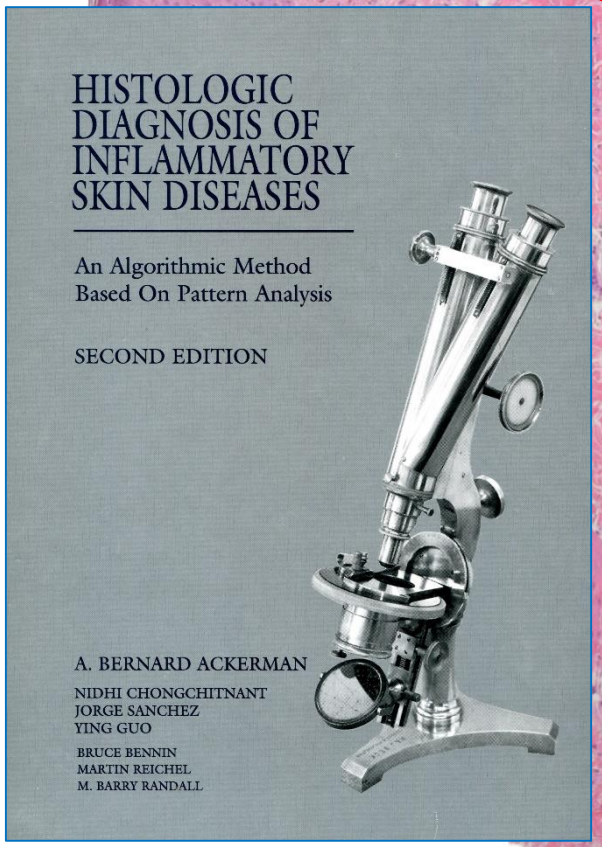

Some viral exanthems can be recognized by distinctive changes, such as ballooning and occasional multinucleated keratocytes in measles or keratocytes with steel-grey nuclei and margination of nucleoplasm in infections by herpesvirus. Often, however, there are no such distinguishing features.



In general, viral exanthems show a superficial perivascular infiltrate of lymphocytes only.

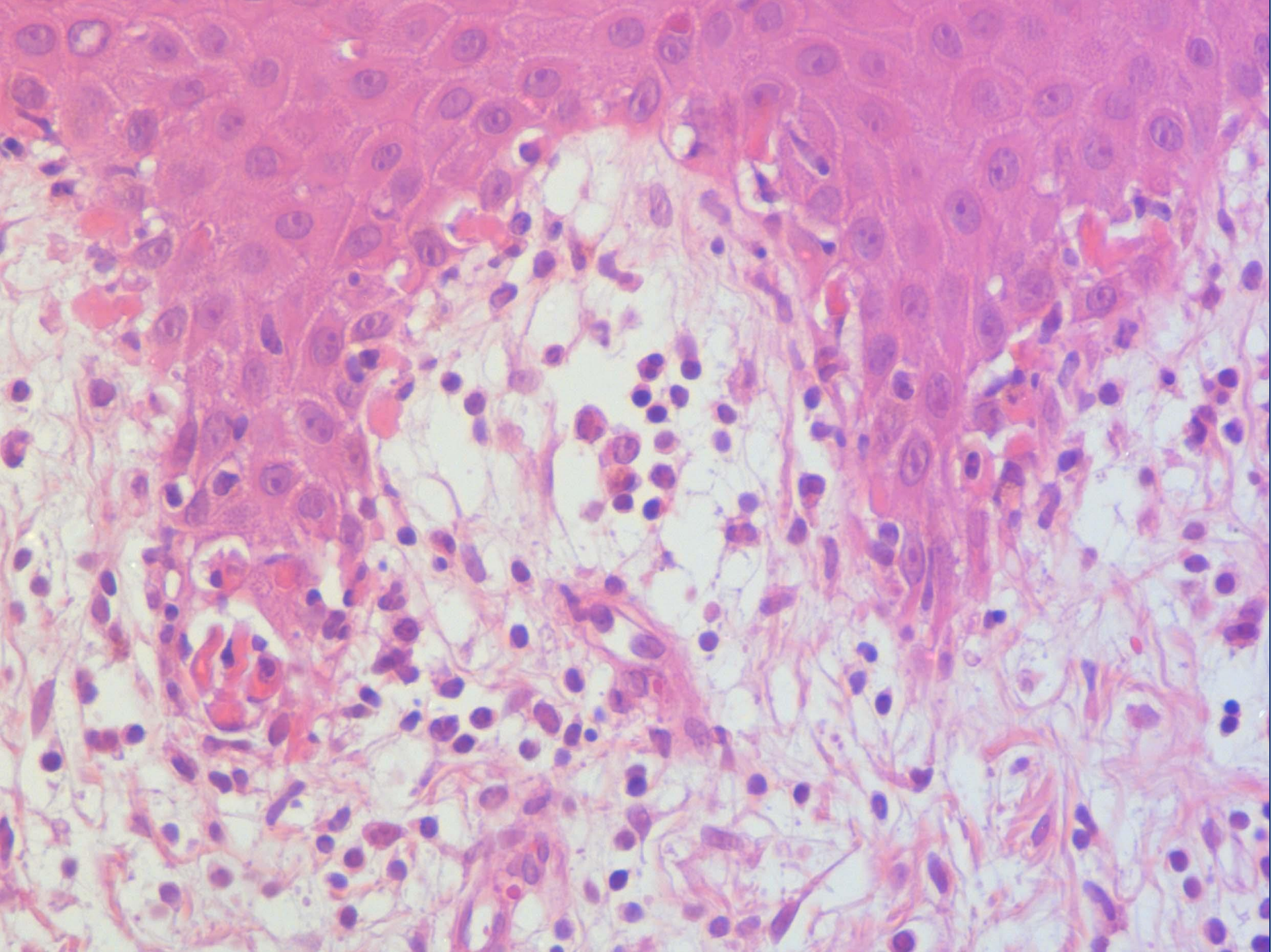


There may also be some neutrophils or eosinophils within the infiltrate as well as slight spongiosis or interface changes, features also seen in drug eruptions.

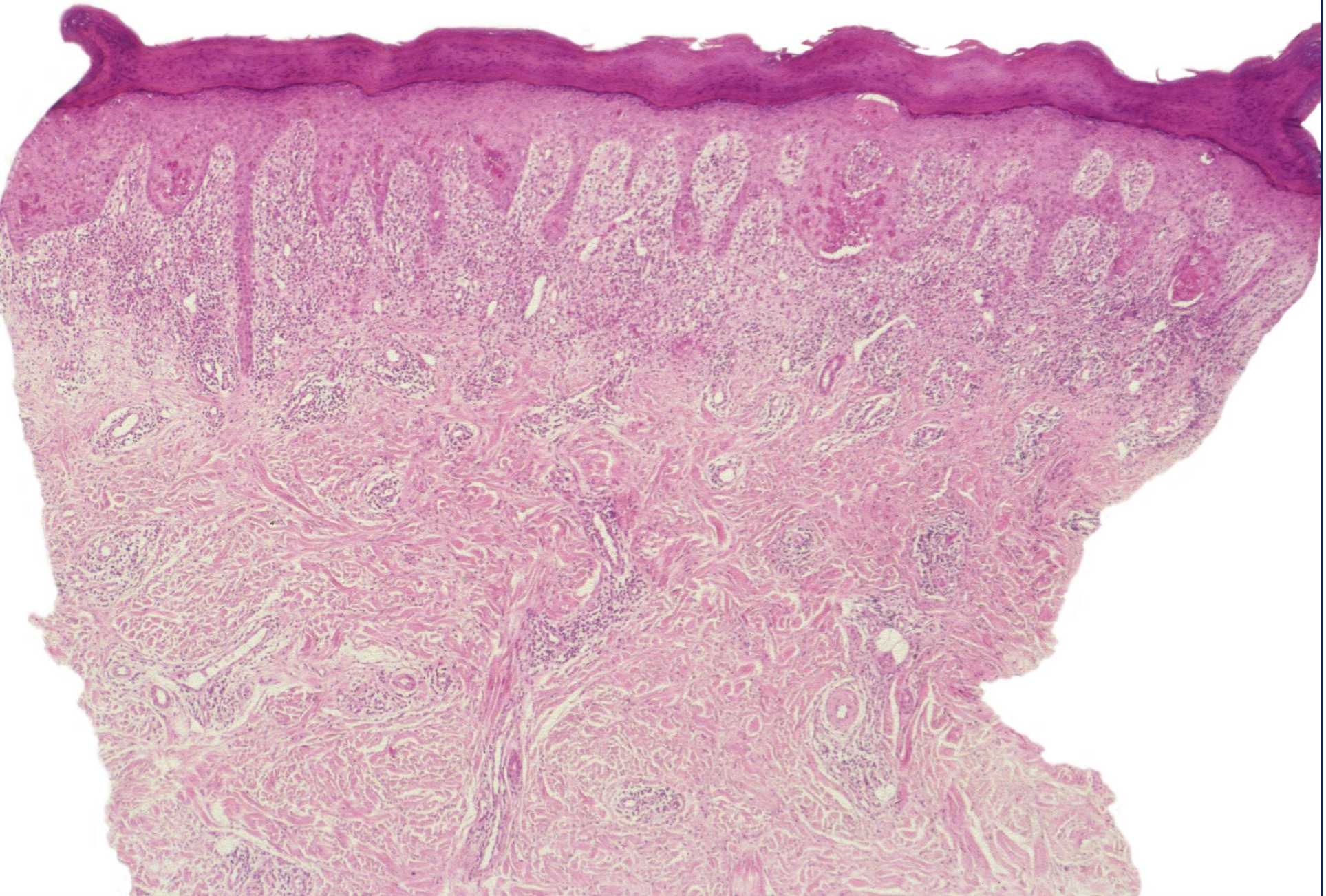



In most instances, viral exanthems do not show changes at the dermoepidermal junction or within the epidermis.

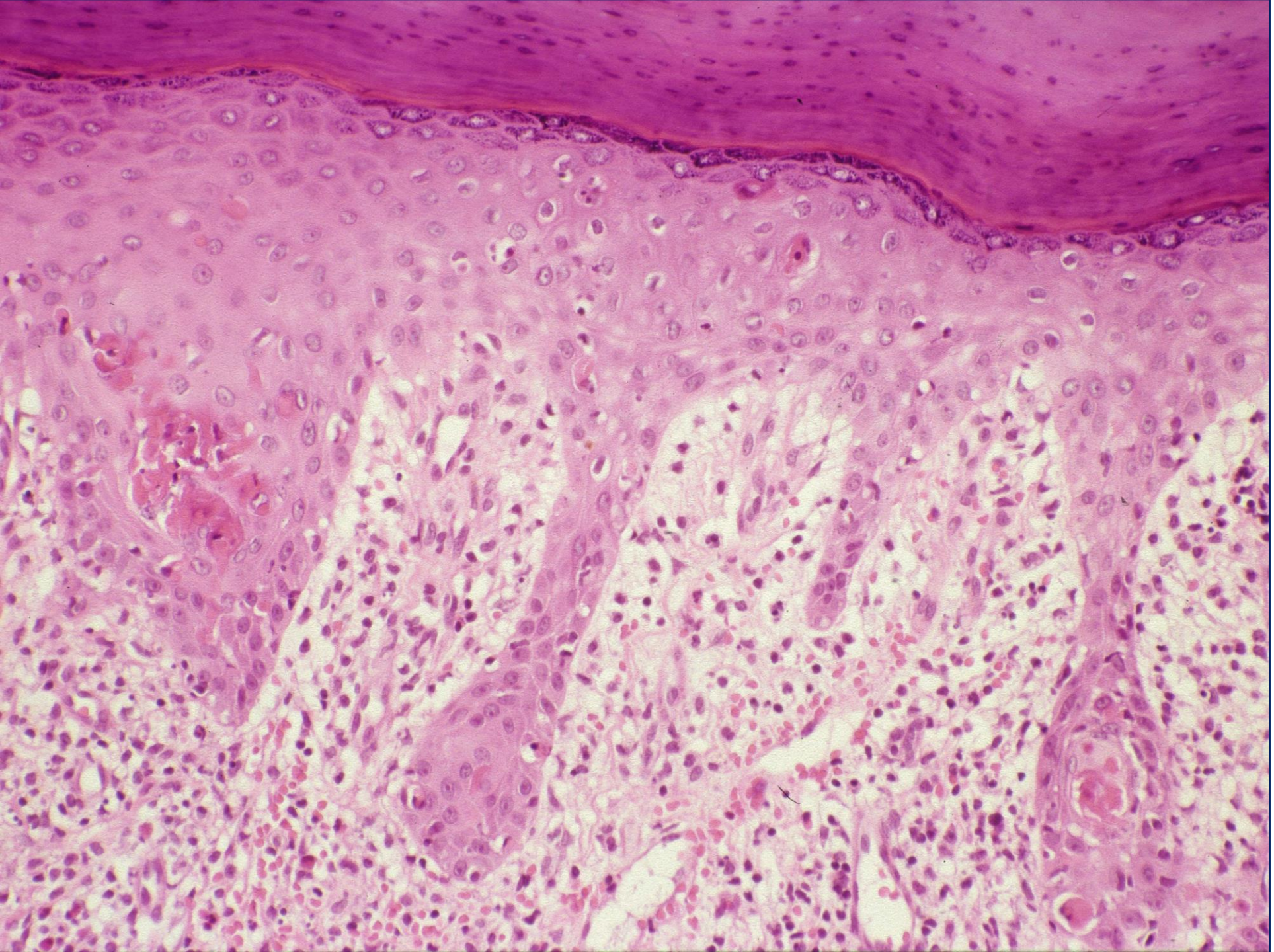
Nonetheless, as pointed out by Ackerman in his textbook on "Histologic Diagnosis of Inflammatory Skin Diseases," *"in most instances, viral exanthems do not show changes at the dermoepidermal junction or within the epidermis,"* and if they do, they are not marked.



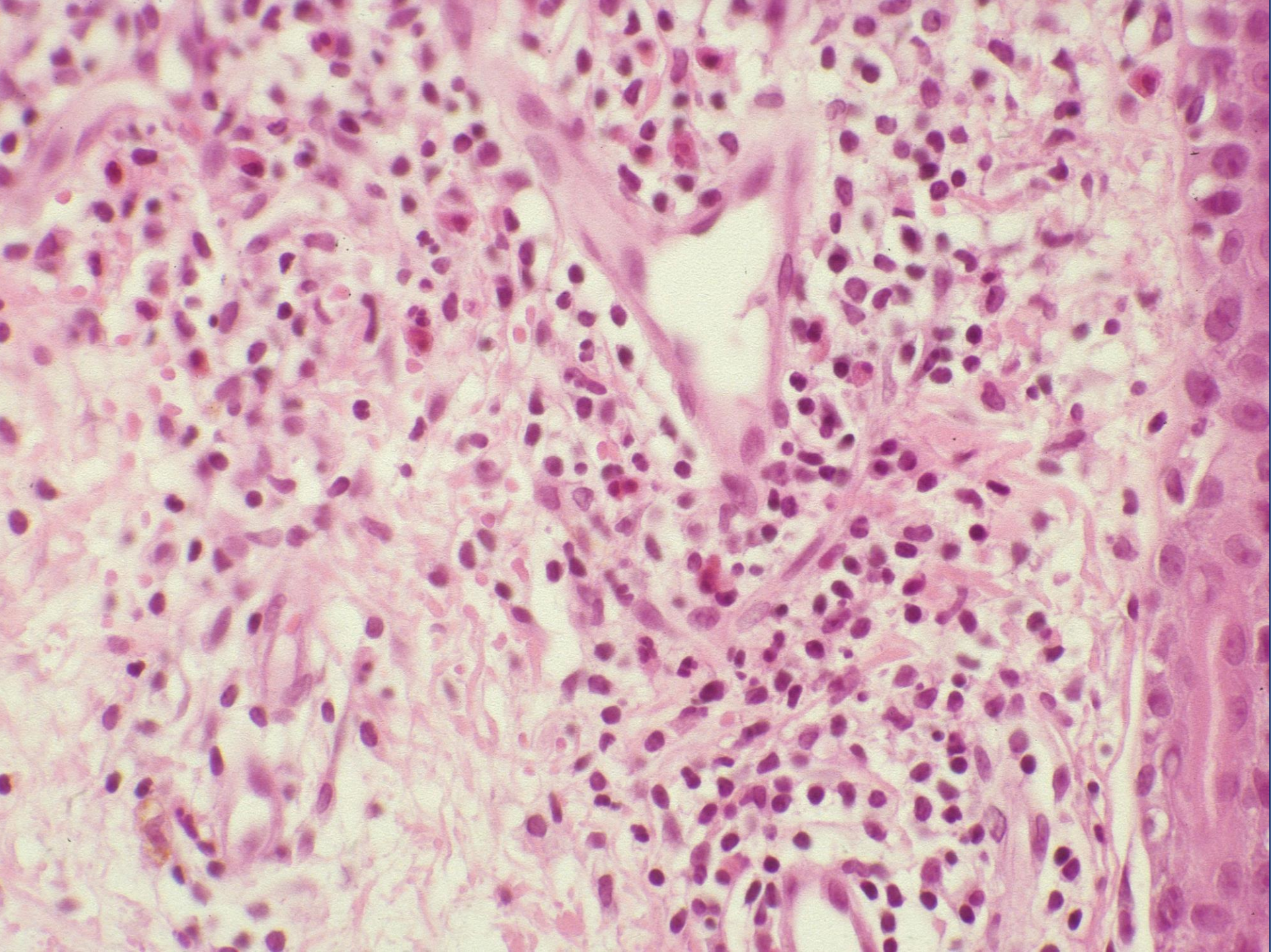
This distinguishes viral exanthems from drug eruptions in which epidermal changes are often pronounced.



This is the case especially in fixed drug eruption. This lesion from the palm shows typical changes, namely, a superficial and deep perivascular and interstitial infiltrate



with myriad necrotic keratocytes in all reaches of the epidermis. There is also extravasation of erythrocytes.

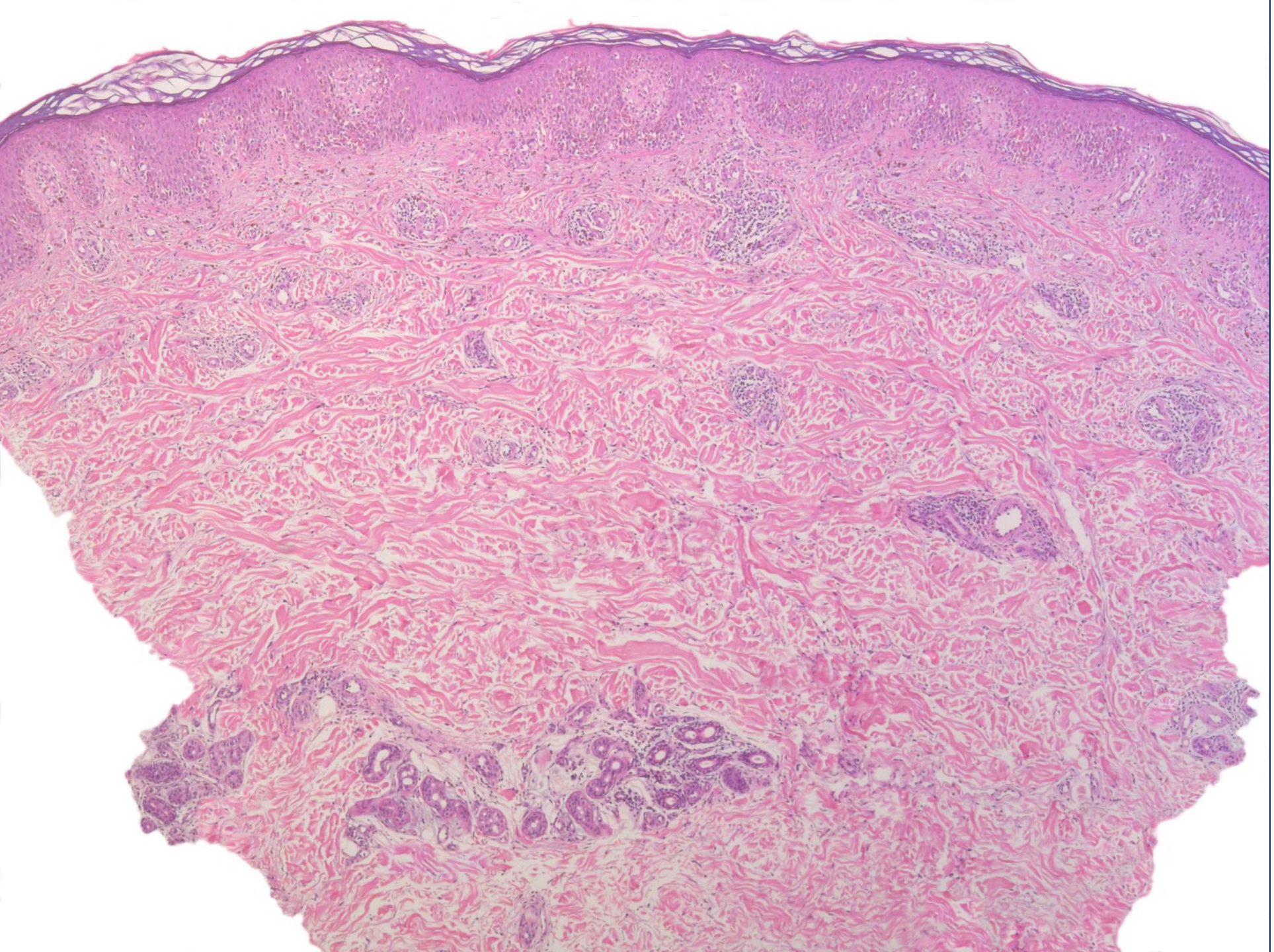


The infiltrate is composed of lymphocytes, neutrophils, and eosinophils, and there are some melanophages in the papillary dermis.

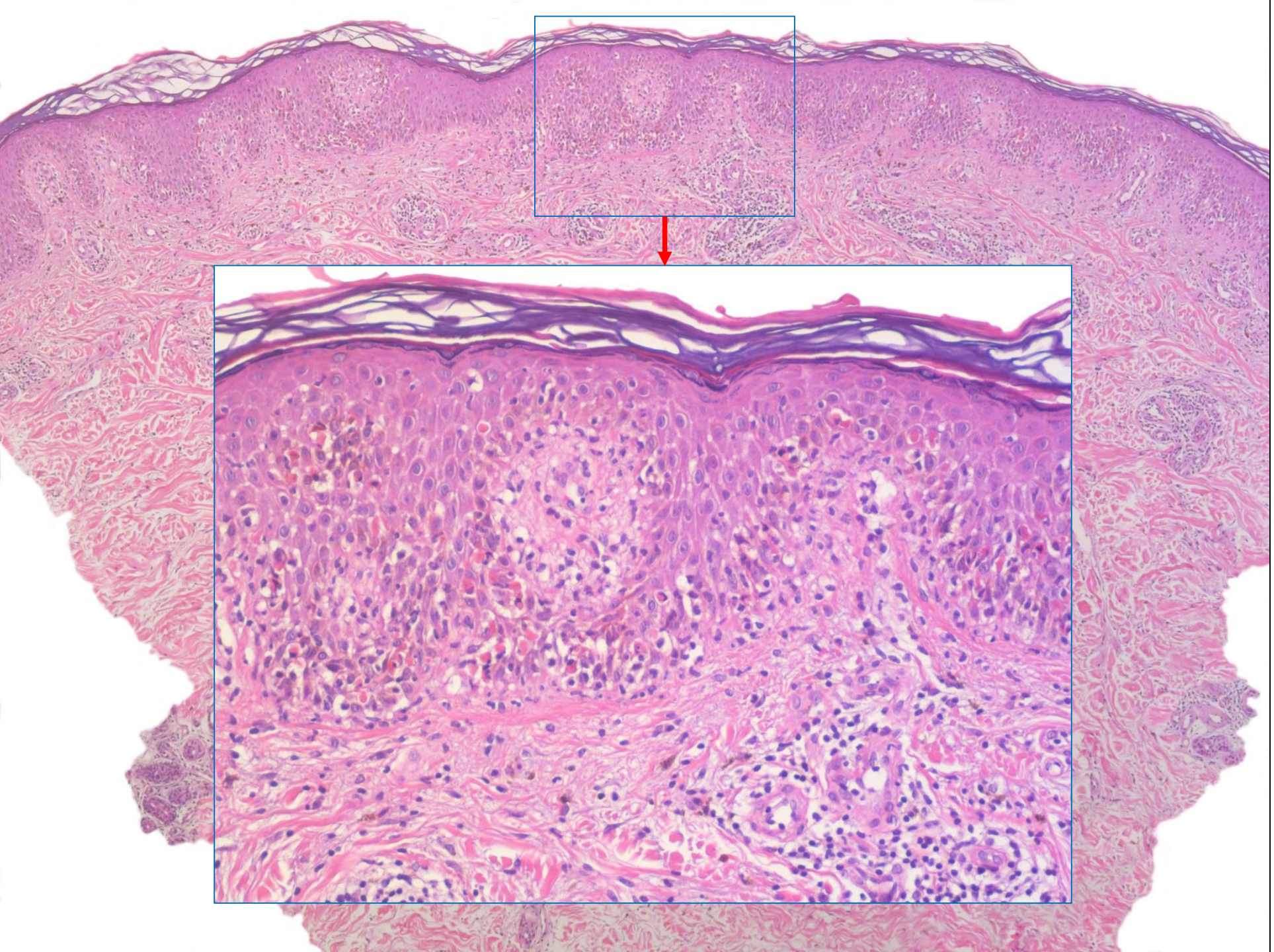
# Fixed drug eruption

- usually superficial and deep infiltrate
- lymphocytes in association with eosinophils and neutrophils
- edema of the papillary dermis
- melanophages in the papillary dermis
- vacuolar alterations at the dermoepidermal junction
- necrotic keratocytes in all layers of the epidermis
- spongiosis and hydrops of keratocytes
- normal cornified layer

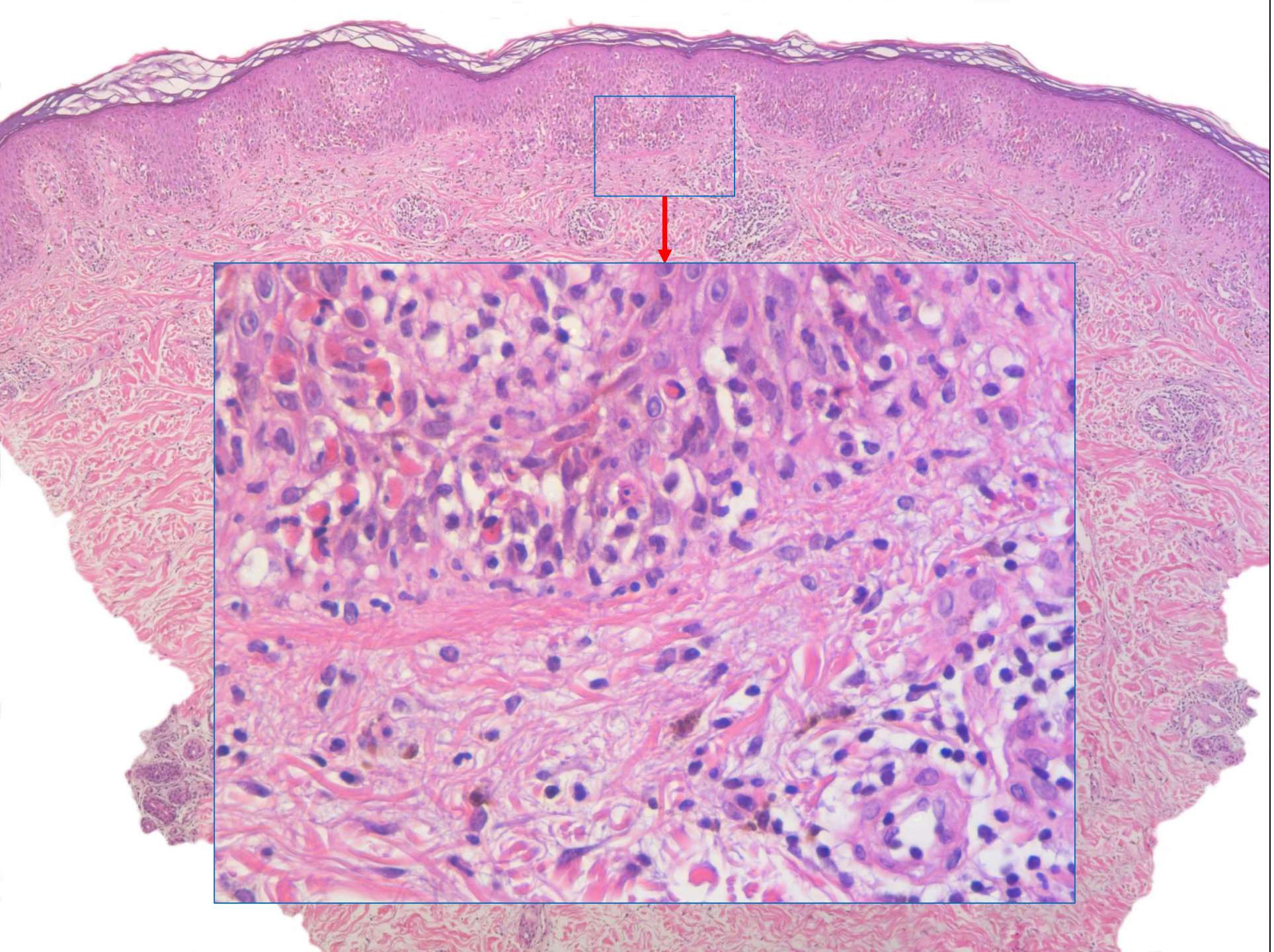
These are the criteria: a superficial and deep infiltrate, lymphocytes in association with eosinophils and neutrophils, edema of the papillary dermis, melanophages in the papillary dermis, vacuolar alterations at the dermoepidermal junction, necrotic keratocytes in all layers of the epidermis, spongiosis and hydrops of keratocytes, and, usually, a normal cornified layer.



Another example from non-glabrous skin: the cornified layer is still basket-woven. In the context of pronounced epidermal changes, this signifies an early stage in the evolution of the lesion which is usually the case in drug eruptions. The infiltrate is superficial and deep,

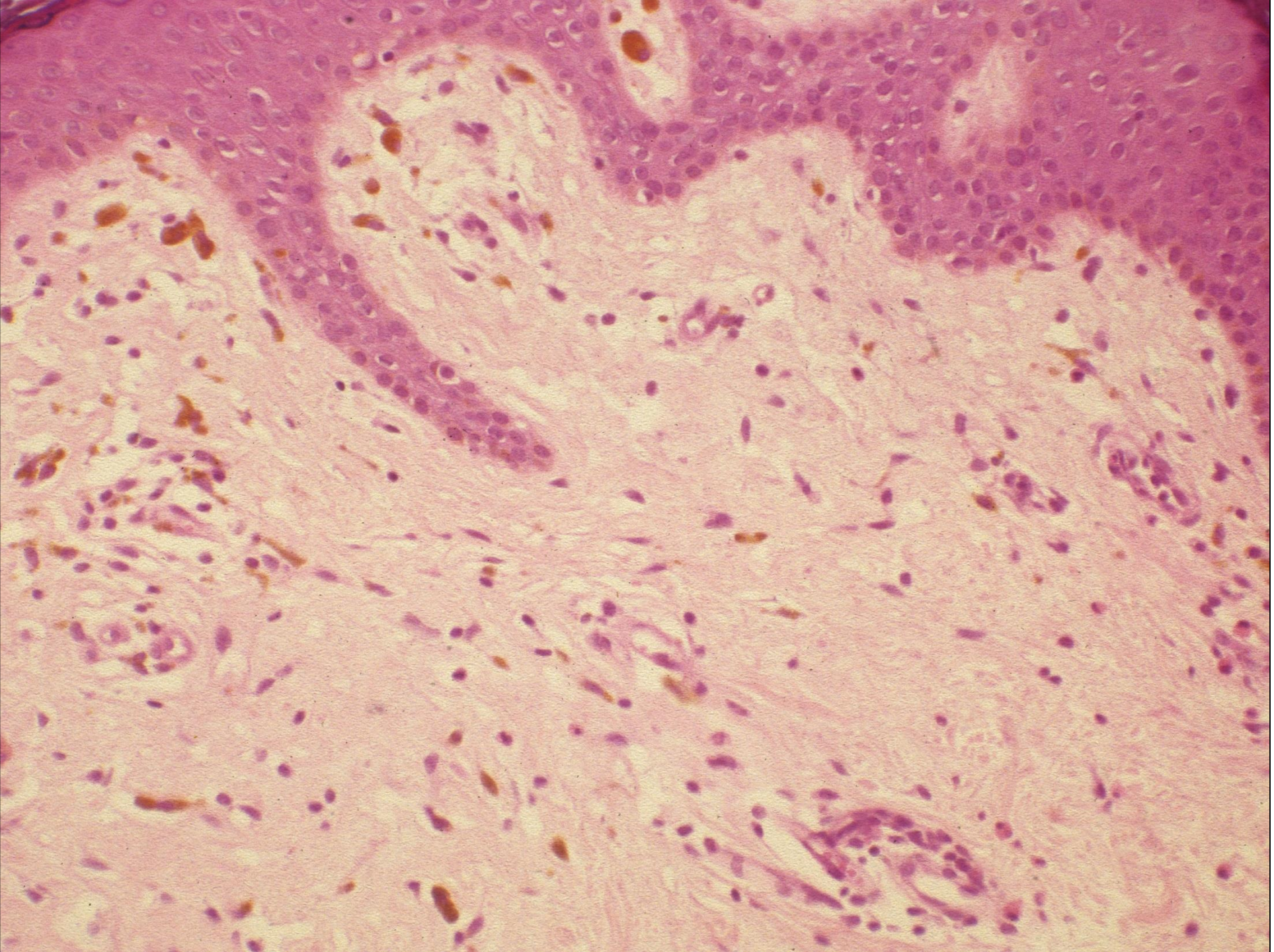


and there are many necrotic keratocytes in all reaches of the epidermis. The term “fixed drug eruption” reflects the repetitive occurrence of well-demarcated lesions at the same spot every time the eliciting drug is taken.



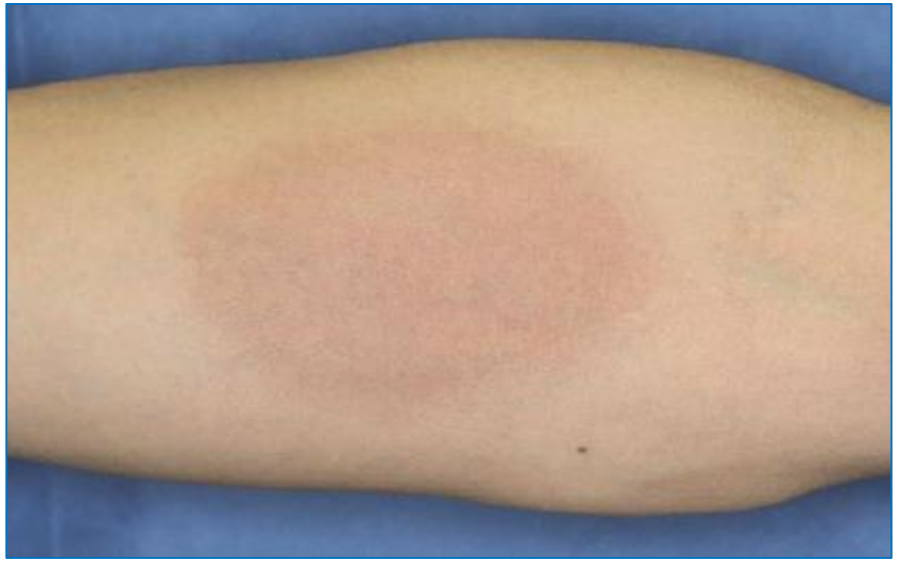
Eventually, the interface dermatitis leads to accumulation of melanophages in the papillary dermis. If there are many, this signifies previous episodes and is a clue to the diagnosis fixed drug eruption.

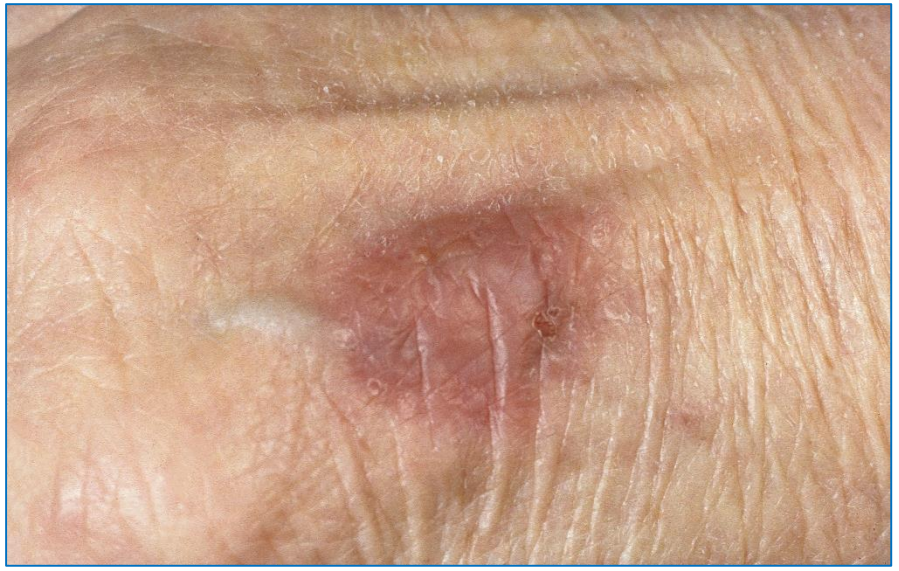
The presentation, however, varies depending on previous episodes, stage of evolution, and other factors. In this case, the infiltrate was composed entirely of lymphocytes, without admixture of neutrophils or eosinophils which are often very sparse, though they may occasionally predominate.

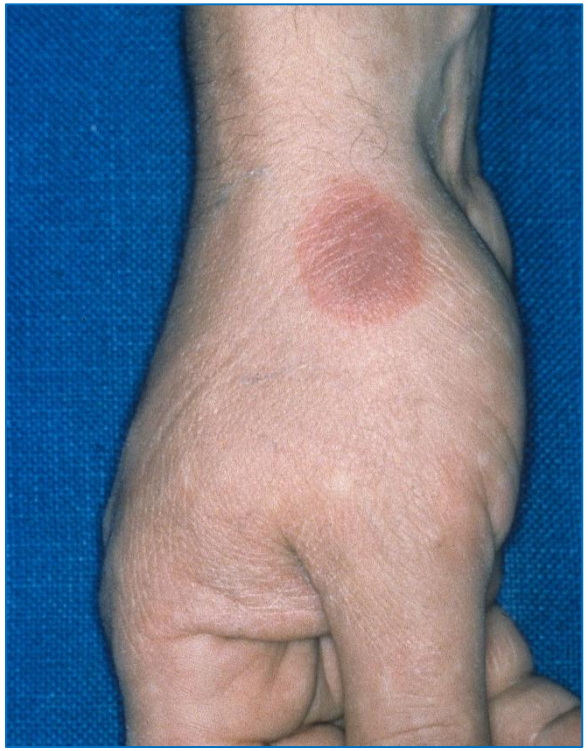


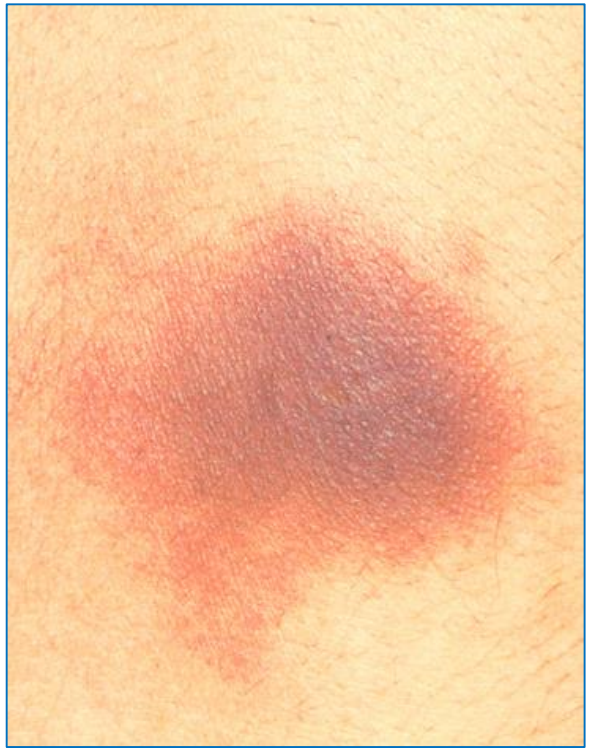
Other examples of fixed drug eruption show eosinophils and neutrophils in the infiltrate and numerous melanophages as evidence of previous episodes, but few, if any, epidermal changes.

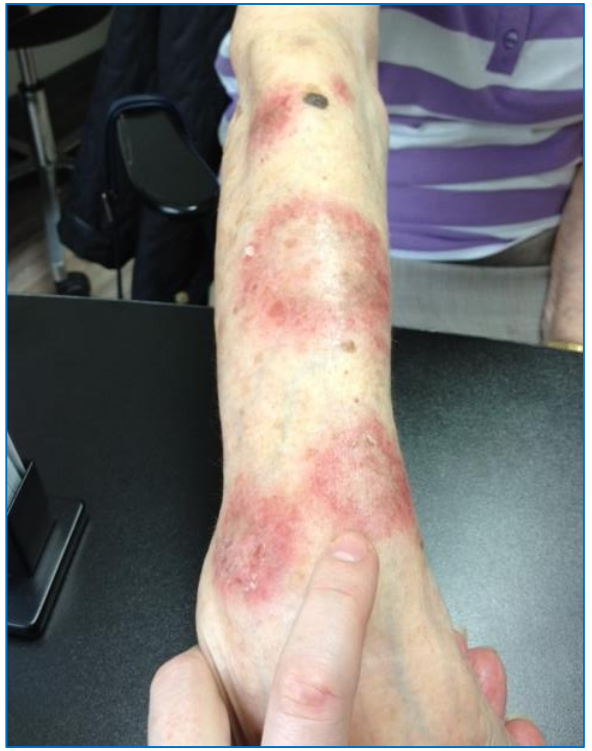
In brief, fixed drug eruption does not always present itself with the stereotypic features listed in textbooks. There is a spectrum of histopathologic changes,



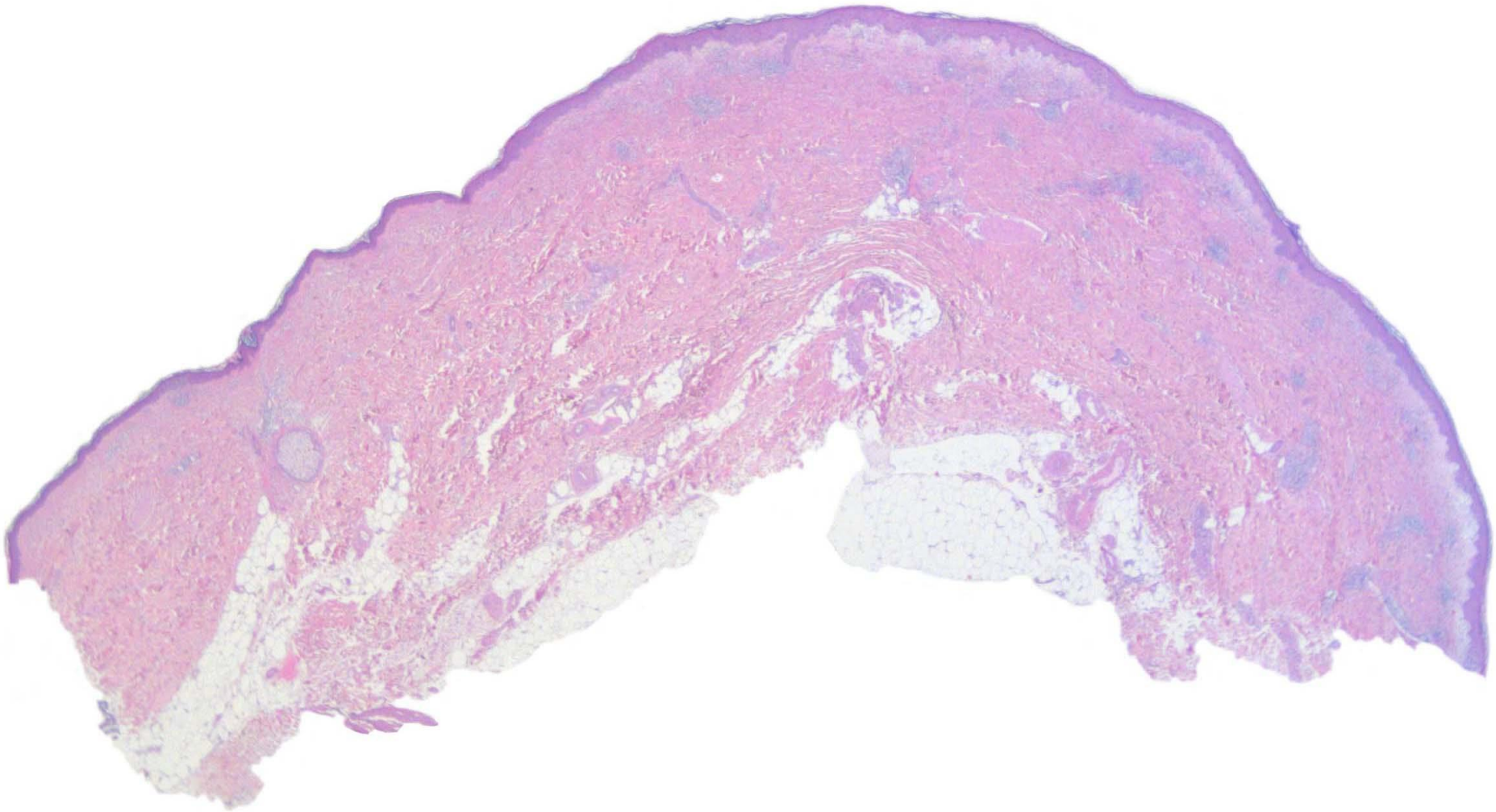




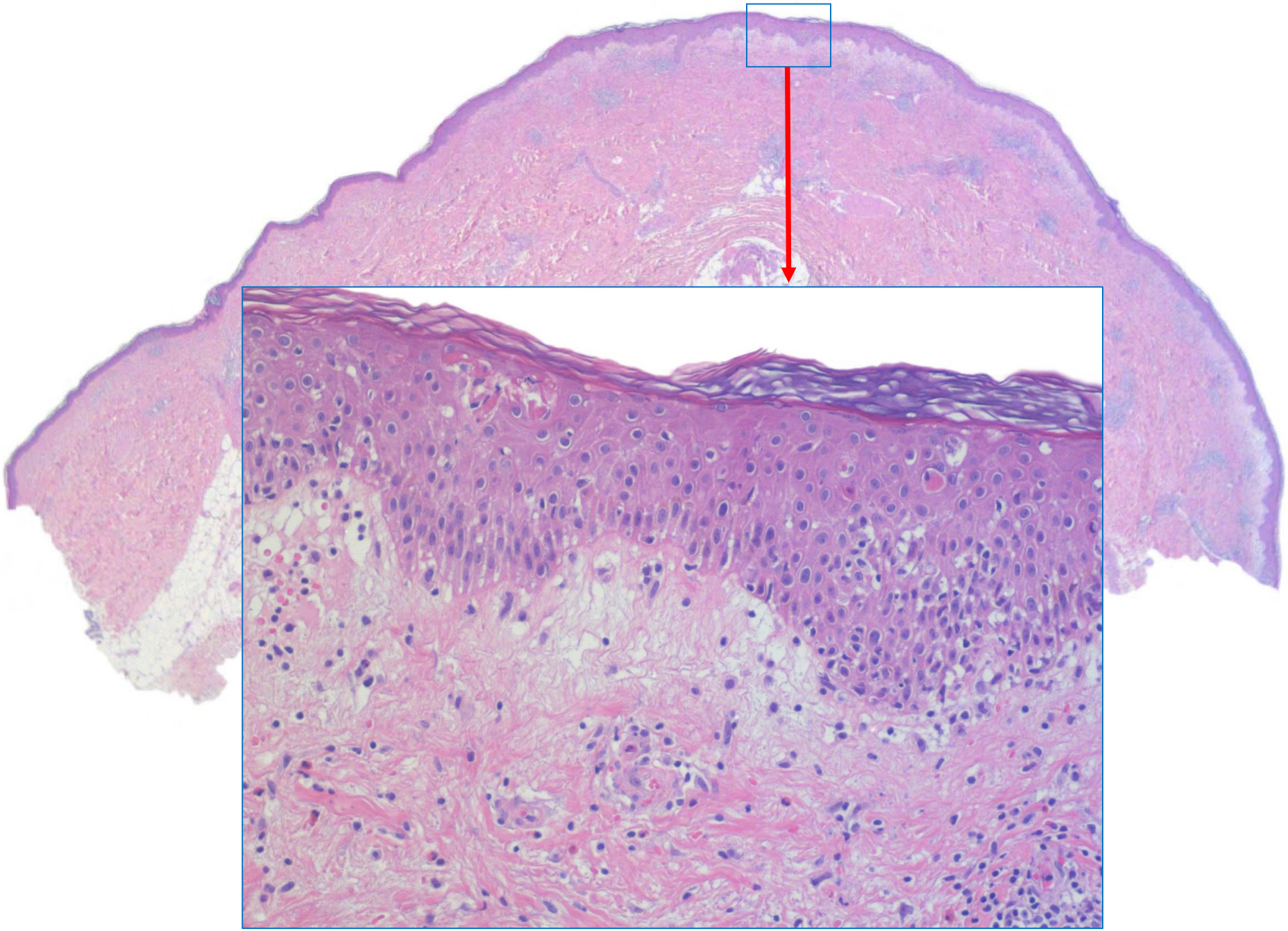




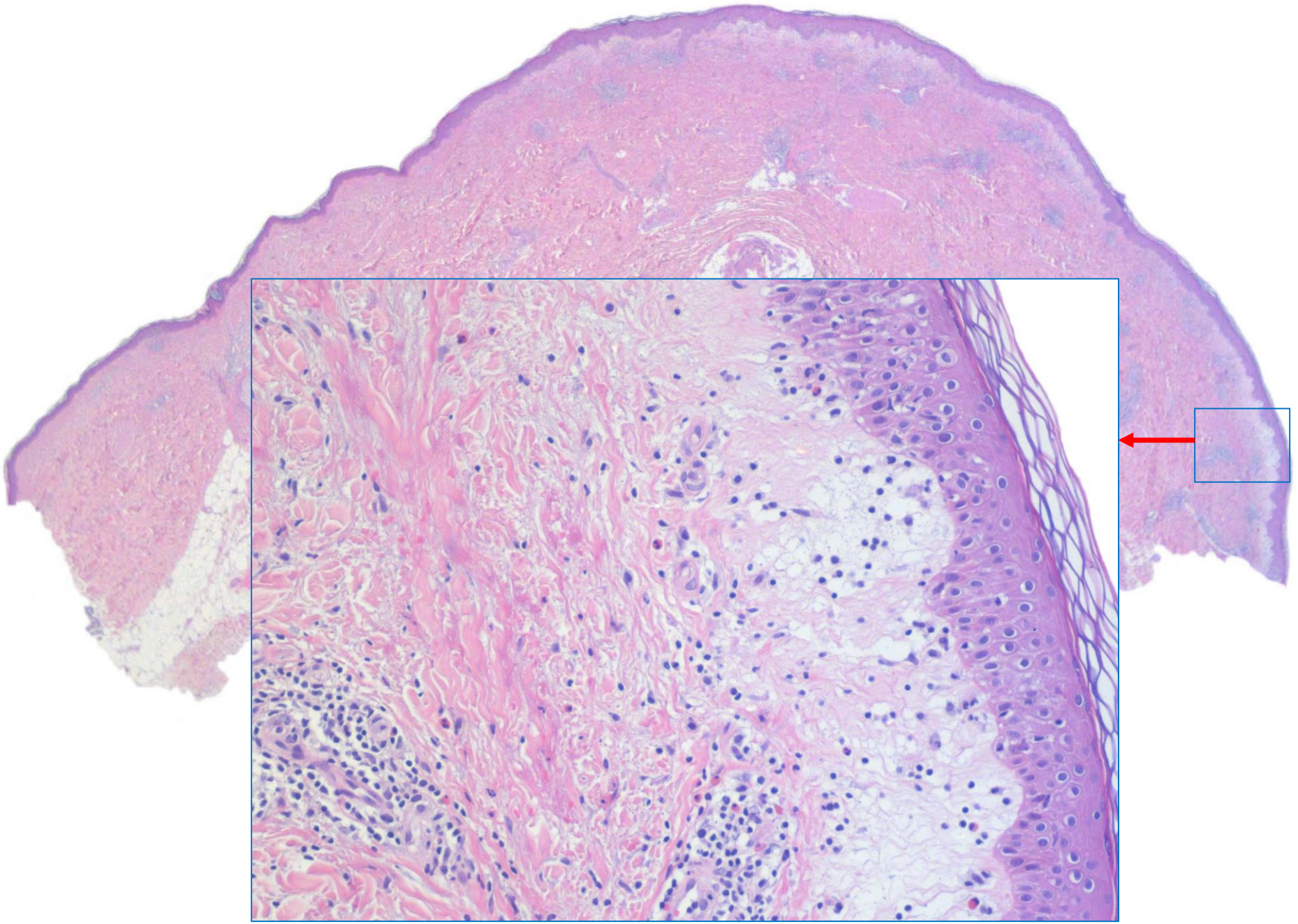
and the same is true clinically. Lesions may be seen early or late, they may be sharply or poorly circumscribed, relatively uniform in appearance or with an accentuated center, annular or targetoid, macular or bullous, solitary or multiple. Naturally, those differences are also reflected by the histopathologic picture,



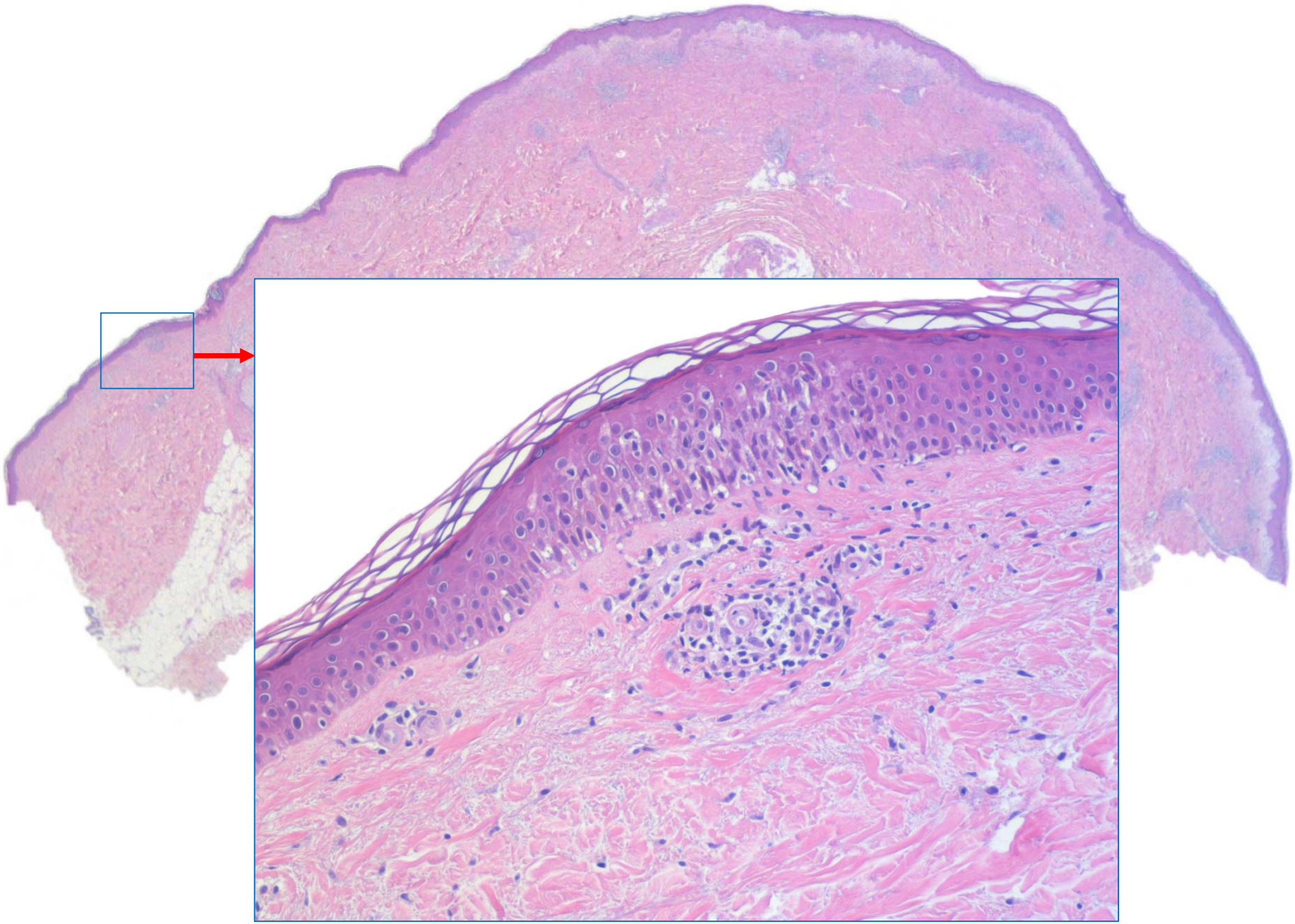
and in large biopsies, such as this one, one may see several patterns at the same time.



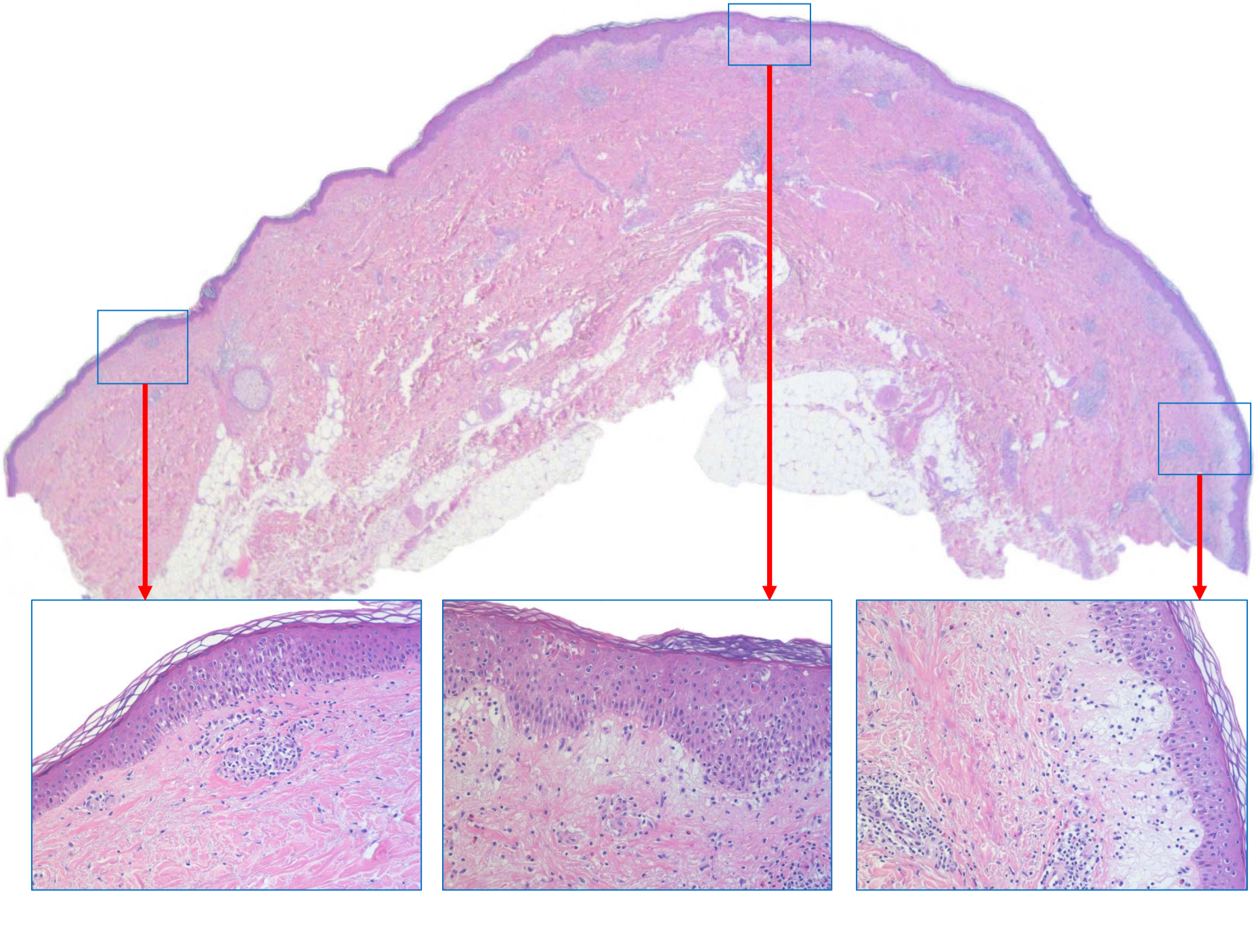
In the center, there are typical changes of fixed drug eruption, namely, a superficial and deep infiltrate, vacuolar changes at the junction and myriad necrotic keratocytes in all reaches of the epidermis beneath a basket-woven cornified layer, edema in the papillary dermis with extravasated erythrocytes as well as neutrophils and eosinophils in the infiltrate.



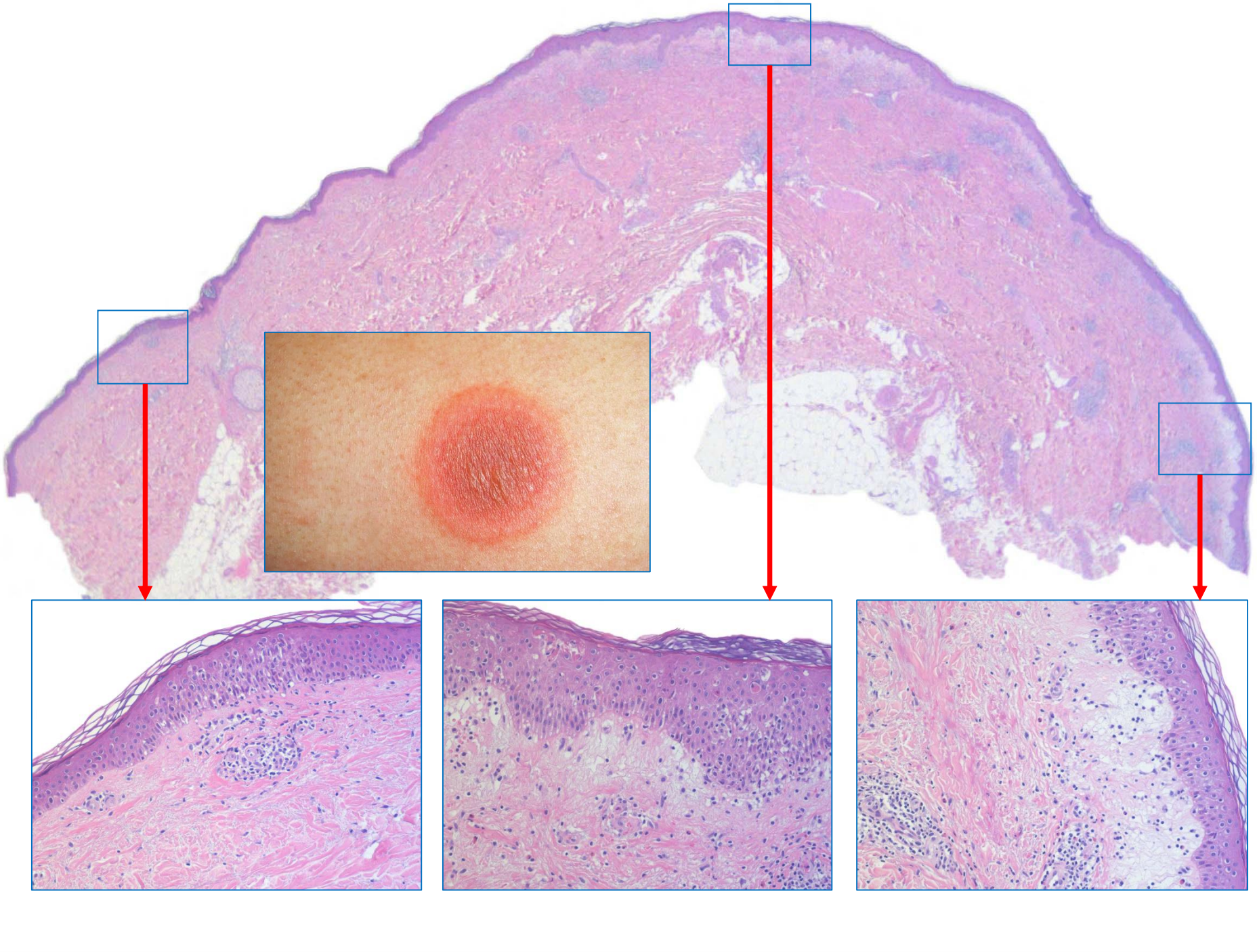
A few millimetres to the right, however, there are no epidermal changes. All that is left is edema of the papillary dermis and a relatively sparse perivascular and interstitial infiltrate with eosinophils and neutrophils – changes that are still suggestive of a drug eruption.



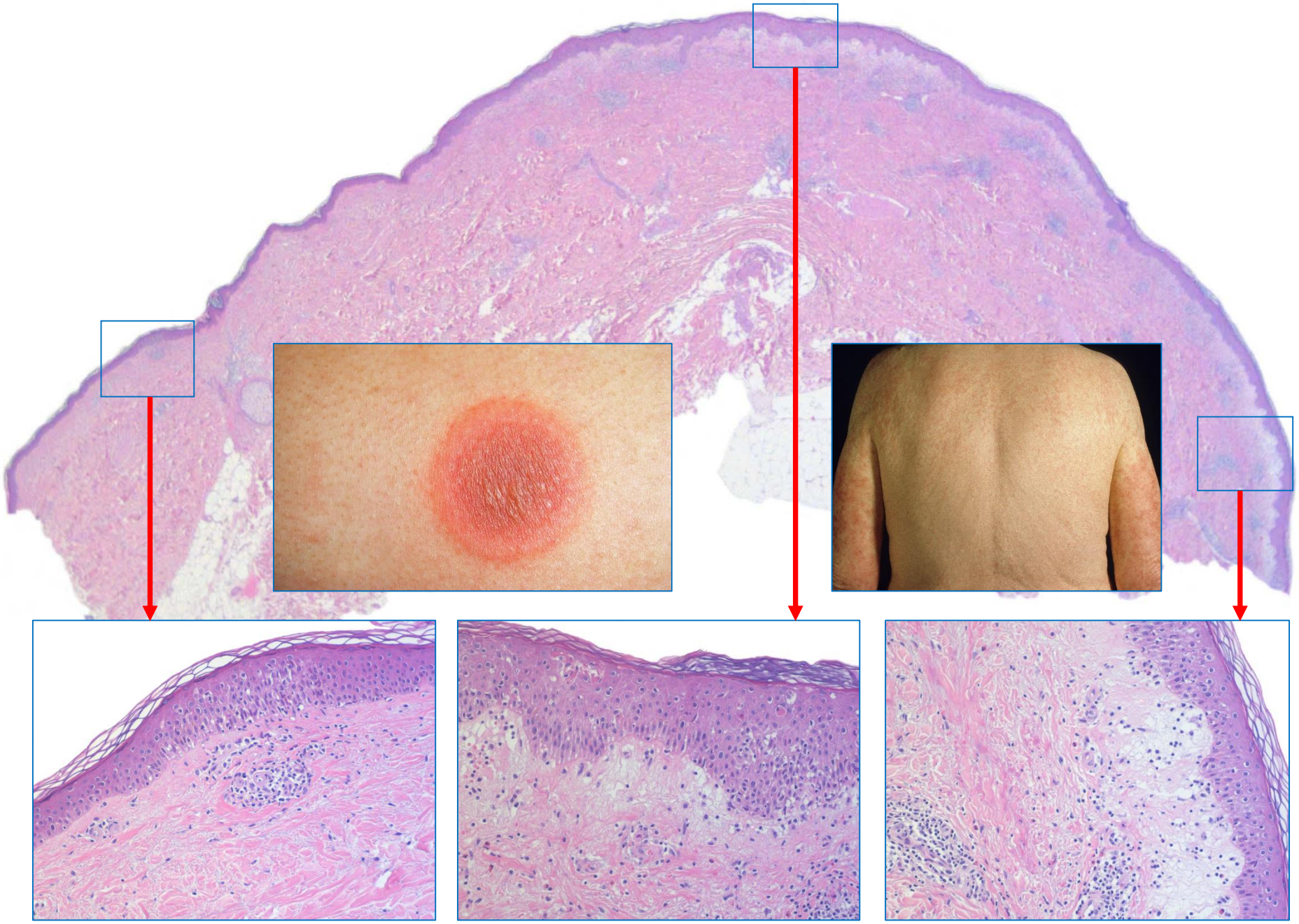
If we go to the left, the changes are far more subtle: nothing but a superficial perivascular infiltrate of lymphocytes with slight spongiosis and some lymphocytes within the epidermis. Because of those lymphocytes in the epidermis in concert with scant spongiosis, the changes are somewhat reminiscent of a very early stage of mycosis fungoides. However, there are no wiry bundles of collagen in the papillary dermis which militates against an early patch of mycosis fungoides and should alert to the possibility of a drug eruption.



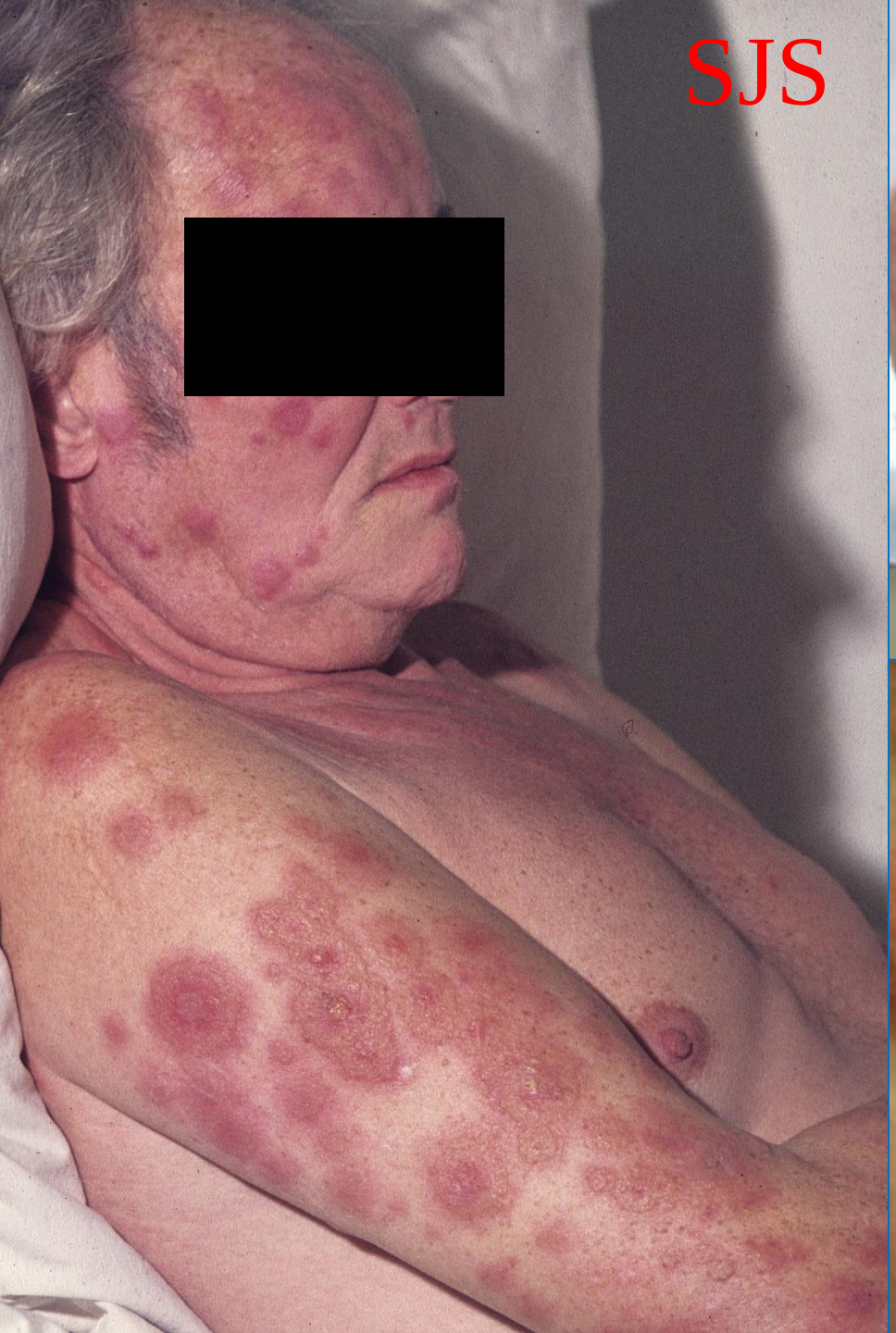
Depending on the site of biopsy, histopathologic diagnosis of fixed drug eruption may not be possible. However, even subtle findings often allow a tentative diagnosis of a drug eruption to be made,



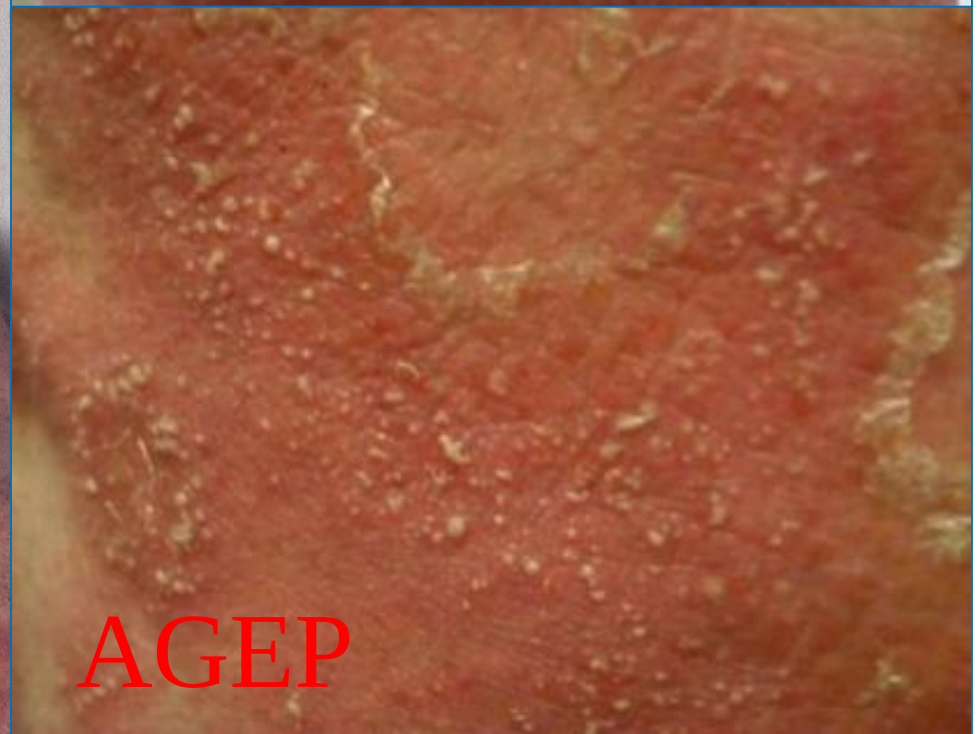
and in the context of an individual lesion, fixed drug eruption is the only choice. The opposite is also true, namely, in the presence of all histopathologic hallmarks of fixed drug eruption, one may not deal with a localized



but with a widespread morbilliform eruption which may show just the same features. In other words, fixed drug eruption does not deserve the special place accorded to it in some textbooks of dermatopathology; its histopathologic presentation differs from that of morbilliform eruptions only by findings usually being more pronounced.








The same is true for other severe reactions that are chiefly defined clinically, such as Stevens-Johnson syndrome, DRESS syndrome, and acute generalized exanthematous pustulosis. The histopathologic findings encountered in them are not unique but an exaggeration of findings seen in more conventional presentations of cell-mediated drug eruptions.

# Histopathologic Features of Exanthematous Drug Eruptions of the Macular and Papular Type

*Majdy Naim,* Wolfgang Weyers,† and Dieter Metze‡*

**Abstract:** Although exanthematous drug eruptions of the macular and papular type are common and often cause diagnostic problems, histopathologic features are not precisely defined in the literature. We present the first prospective histopathologic study of maculopapular drug eruption in 48 patients in whom the diagnosis had been made on the basis of clinical examination, history of a known offending drug, and follow-up. Because more than 1 biopsy was taken in 11 patients, 60 biopsy specimens could be examined. The most consistent epidermal features were mild spongiosis mainly of the lower layers (97% of biopsies), some hyperplasia (72%), a few lymphocytes (82%), and neutrophils (32%). The dermoepidermal junction revealed discrete vacuolization (97%), scattered lymp
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**Key Words:** drug eruption, maculopapular, histopathology, interface dermatitis, neutrophils

(*Am J Dermatopathol* 2011;33:695–704)

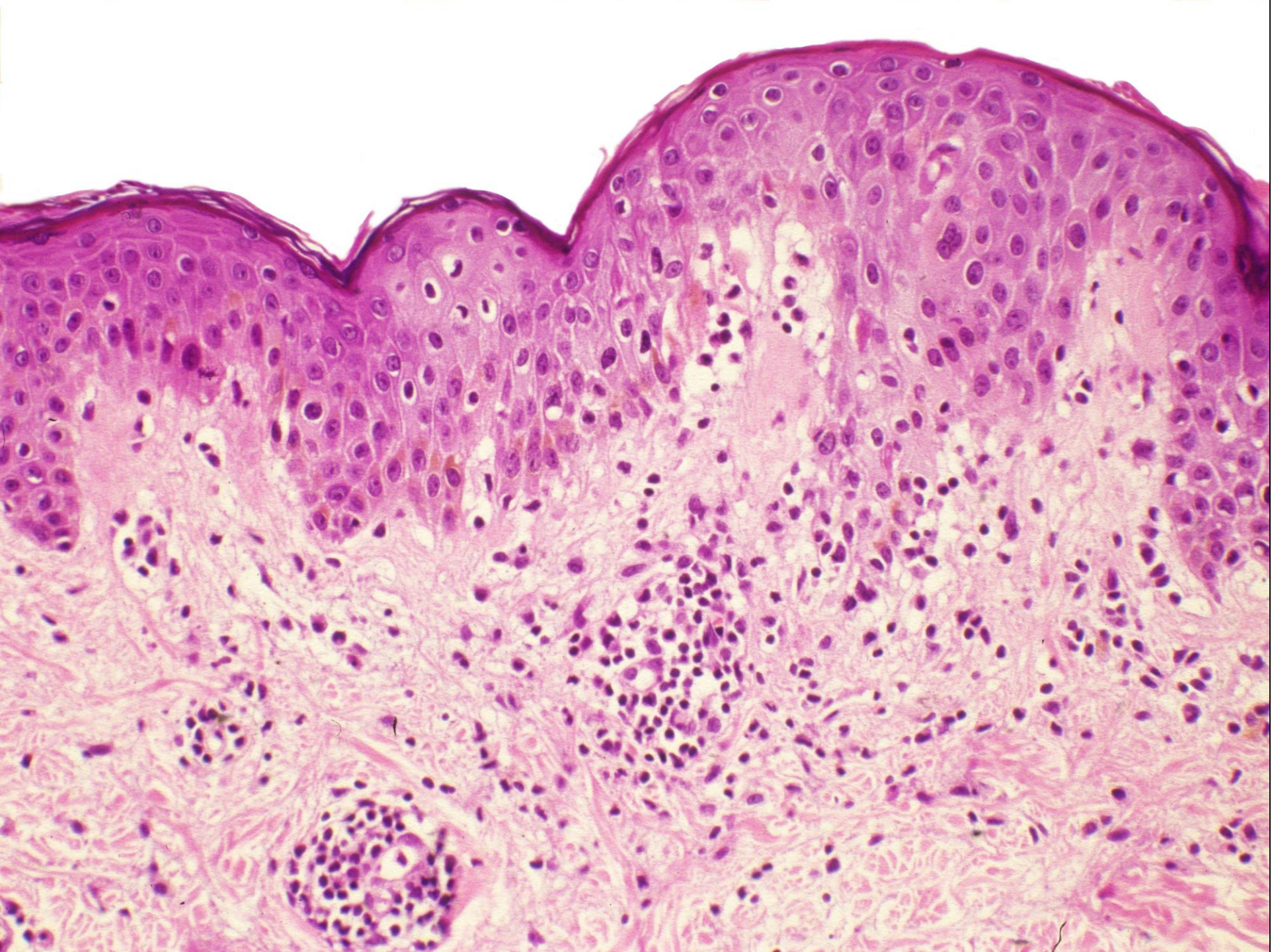
morbilliform drug eruptions to account for approximately 95% of all skin reactions to drugs.[6] Offending drugs are chiefly antibiotics, and, less frequently, nonsteroidal anti-inflammatory drugs, anticonvulsants and anxiolytics, antihypertensives, diuretics, allopurinol, and oral hypoglycemic agents, but virtually any drug can be responsible.[3] The risk increases with the intake of several drugs that interfere in their metabolism, comedication with immunomodulatory agents (allopurinol and others), viral infections (Epstein–Barr virus, cytomegalovirus, and human immunodeficiency virus), lupus erythematodes, Sjögren syndrome, Still syndrome, and chronic lymphatic leukemia.[7–10]

**TABLE 2.** Dermoepidermal Junction

| | Number (total = 60) | % |
|---|---|---|
| Vacuoles | 58 | 97 |
| Focal | 26 | 43 |
| Continuous | 32 | 53 |
| Lymphocytes | 45 | 75 |
| Necrotic keratinocytes | 19 | 32 |

The prevalence of drug reactions, in general, and exanthematous drug eruptions, in particular, is increasing.[3] Because they may cause problems in differential diagnosis, more and more skin biopsies are being submitted for histopathologic examination. Despite the importance of the subject, the histopathology of exanthematous drug eruptions

What are those findings? One is signs of interface dermatitis. We recently performed a *"prospective histopathologic study of maculopapular drug eruption in 48 patients in whom the diagnosis had been made on the basis of clinical examination, history of a known offending drug, and follow-up."* When evaluating biopsy specimens from those patients, we found some signs of interface dermatitis, such as vacuoles at the dermo-epidermal junction, lymphocytes at the junction, or necrotic keratocytes in the majority of them. Sometimes those changes were conspicuous,



sometimes only subtle.

Another common finding in drug eruptions is an infiltrate with participation of eosinophils and neutrophils. Especially eosinophils have traditionally been emphasized as a hallmark of drug eruptions.

# Pattern Analysis of Drug-Induced Skin Diseases

*Hildamari Justiniano, MD, Alma C. Berlingeri-Ramos, MD, and Jorge L. Sánchez, MD*

**Abstract:** Drug eruptions are common adverse reactions to drug therapy and are a frequent reason for consultation in clinical practice. Even though any medication can potential cutaneous reaction, some drugs are implicated others. Histologically, drugs can elicit a va disease patterns in the skin and panniculus, no for a particular drug. The most common pa temically administered medications is the Psoriasiform or granulomatous patterns are r cations. The usual histologic patterns of drug e in this review using the basic patterns of i Clinicopathologic correlation is established However, the changes of drug-induced skin disease must be made considering clinical presentation, histopathological analysis, and course of the disease.

**Key Words:** drug eruptions, histopathologic pattern

(*Am J Dermatopathol* 2008;30:352–369)

with the number of medications the patient uses. Patients with HIV and other immunosuppressive conditions have an increased incidence of drug reactions. In these cases, immune

Eosinophils present a diagnostic clue as these may be present in many drug-induced reaction. However, one must be cautious not to consider them the panacea of histologic diagnosis for a drug eruption 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.

systemic drugs is the perivascular pattern. Psoriasiform or granulomatous patterns are rarely caused by medications.

Usual histologic patterns of drug eruptions will be discussed in this review using the basic patterns of inflammatory skin diseases as established by Ackerman et al[2] (Table 1). Clinicopathologic correlation will be established for relevant patterns.

In their recent review of different *"patterns of drug-induced skin diseases,"* Sánchez and colleagues were more reserved: *"Eosinophils present a diagnostic clue as these may be present in many drug-induced reaction. However, one must be cautious not to consider them the panacea of histologic diagnosis for a drug eruption 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."*

J Cutan Pathol 2012: 39: 413–418
doi: 10.1111/j.1600-0560.2012.01891.x
John Wiley & Sons. Printed in Singapore



Journal of
Cutaneous Pathology

# Assessment of the 'no eosinophils' rule: are eosinophils truly absent in pityriasis lichenoides, connective tissue disease, and graft-vs.-host disease?

Eosinophils are often present in the inflammatory infiltrate of an interface dermatitis, but the diagnostic specificity of eosinophils in interface dermatitis has not been formally evaluated. We retrospectively identified 97 examples of interface dermatitis with clinically confirmed diagnoses, including lupus erythematosus (LE), lichen planus, pityriasis lichenoides (PL), graft-vs.-host disease (GVHD), dermatomyositis (DM) and drug reaction. Diagnoses were clinically confirmed by at least two dermatologists. Slides were reviewed in a blinded fashion by at least two dermatopathologists. The average eosinophil count per 10 ×200 (×20 objective) fields was lowest for PL (0.2), DM (0.3), GVHD (0.4), and LE (0.5) [defined as Group 1] and was higher for lichen planus, drug reactions, erythema multiforme (major and minor) and viral exanthems [defined as Group 2]. Distinction between Group 1 and Group 2 was maximized using an eosinophil count cutoff of 1.1. In conclusion, eosinophils are usually rare to absent in PL, DM, most forms of LE and GVHD. While final interpretation requires a composite assessment of all features, our results suggest that the presence of even a single eosinophil within nine or ten ×20 fields argues against a diagnosis of PL, DM or LE.

**Victoria R. Sharon[1], Thomas H. Konia[1,2], Keira L. Barr[1,2] and Maxwell A. Fung[1,2]**

[1]Department of Dermatology, University of California Davis, Sacramento, CA, USA and [2]Department of Pathology and Laboratory Medicine, University of California Davis, Sacramento, CA, USA

If this is the case, why are they still a *"diagnostic clue"*? Because they are usually absent in important differential diagnoses, such as pityriasis lichenoides, dermatomyositis, graft-versus-host disease, and lupus erythematosus. This does not imply that eosinophils rule out those diagnoses, but if they are found in number, it strongly militates against them.

# Histopathologic Features of Exanthematous Drug Eruptions of the Macular and Papular Type

*Majdy Naim,* Wolfgang Weyers,† and Dieter Metze‡*

**Abstract:** Although exanthematous drug eruptions of the macular and papular type are common and often cause diagnostic problems, histopathologic features are not precisely defined in the literature. We present the first prospective histopathologic study of maculopapular drug eruption in 48 patients in whom the diagnosis had been made on the basis of clinical examination, history of a known offending drug, and follow-up. Because more than 1 biopsy was taken in 11 patients, 60 biopsy specimens could be examined. The most consistent epidermal features were mild spongiosis mainly of the lower layers (97% of biopsies), some hyperplasia (72%), a few lymphocytes (82%), and neutrophils (32%). The dermoepidermal junction revealed discrete vacuolization (97%), scattered lymphocytes (75%), and rare necrotic keratinocytes (32%). All cases showed a dermal perivascular inflammatory infiltrate that was superficial only in 72% of biopsies and superficial and deep in 28% of biopsies. An interstitial infiltrate in the papillary dermis could be found in 93%, more often patchy than lichenoid. In general, the perivascular infiltrate was mild and composed of lymphocytes (100%), eosinophils (60%), and neutrophils (50%). In the papillary dermis, neutrophils often outnumbered the eosinophils. Another feature were the clusters of neutrophils (38%) and eosinophils (20%) in the lumina of dilated, otherwise normal, blood vessels. Rashes induced by anticonvulsants and anxiolytics were characterized by predominance of neutrophils and largish lymphocytes. Edema of the papillary dermis was encountered frequently (85%), whereas wiry collagen bundles were an exceptional finding. In conclusion, our study defined a constellation of histopathologic findings highly suggestive of the diagnosis of exanthematous drug eruption of the macular and papular type.

**Key Words:** drug eruption, maculopapular, histopathology, interface dermatitis, neutrophils

(*Am J Dermatopathol* 2011;33:695–704)

**TABLE 3.** Dermal Inflammatory Infiltrate

| | Number (total = 60) | % |
|---|---|---|
| Perivascular infiltrate | 60 | 100 |
| Superficial | 43 | 72 |
| Superficial and deep | 17 | 28 |
| Lymphocytes | 60 | 100 |
| Scattered large lymphocytes | 23 | 38 |
| Eosinophils | 36 | 60 |
| Neutrophils | 30 | 50 |
| Macrophages | 47 | 78 |
| Mast cells | 5 | 8 |
| Plasma cells | 4 | 7 |
| Erythrocytes | 17 | 28 |
| Interstitial infiltrate in the papillary dermis | 56 | 93 |
| Patchy | 42 | 70 |
| Lichenoid | 14 | 23 |
| Lymphocytes | 53 | 88 |
| Eosinophils | 33 | 55 |
| Neutrophils | 46 | 77 |
| Macrophages | 39 | 65 |
| Melanophages | 2 | 3 |
| Mast cells | 0 | 0 |
| Plasma cells | 0 | 0 |
| Erythrocytes | 17 | 28 |
| Interstitial infiltrate in the reticular dermis | 29 | 48 |
| Upper dermis | 24 | 40 |
| Upper and lower dermis | 5 | 8 |
| Lymphocytes | 29 | 48 |
| Eosinophils | 46 | 77 |
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In our study of exanthematous drug-eruptions in which the offending drug was known, eosinophils were not always present but were found in only 60% of cases. In other words, they are not a highly sensitive criterion for drug eruptions. Their diagnostic value, however, is limited not only by the relatively high number of drug eruptions without eosinophils, but also by the wide variety of diseases sporting eosinophils in the infiltrate.

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The range of diseases with neutrophils in the infiltrate in much smaller and, therefore, neutrophils which were found in 50% of drug eruptions have higher distinguishing value.

# Histopathologic Features of Exanthematous Drug Eruptions of the Macular and Papular Type

*Majdy Naim,* Wolfgang Weyers,† and Dieter Metze‡*

- urticaria
- autoimmune bullous diseases
- Sweet's syndrome
- reactions to arthropod assaults
- folliculitides

vacuolization (97%), scattered lymphocytes (75%), and rare necrotic keratinocytes (32%). All cases showed a dermal perivascular inflammatory infiltrate that was superficial only in 72% of biopsies and superficial and deep in 28% of biopsies. An interstitial infiltrate in the papillary dermis could be found in 93%, more often patchy than lichenoid. In general, the perivascular infiltrate was mild and composed of lymphocytes (100%), eosinophils (60%), and neutrophils (50%). In the papillary dermis, neutrophils often outnumbered the eosinophils. Another feature were the clusters of neutrophils (38%) and eosinophils (20%) in the lumina of dilated, otherwise normal, blood vessels. Rashes induced by anticonvulsants and anxiolytics were characterized by predominance of neutrophils and largish lymphocytes. Edema of the papillary dermis was encountered frequently (85%), whereas wiry collagen bundles were an exceptional finding. In conclusion, our study defined a constellation of histopathologic findings highly suggestive of the diagnosis of exanthematous drug eruption of the macular and papular type.

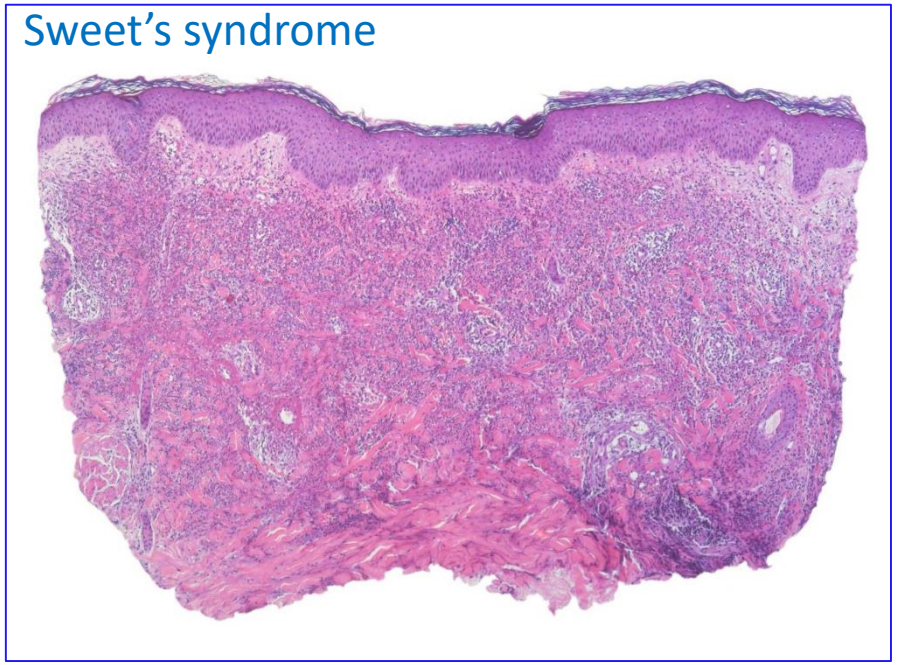
**Key Words:** drug eruption, maculopapular, histopathology, interface dermatitis, neutrophils

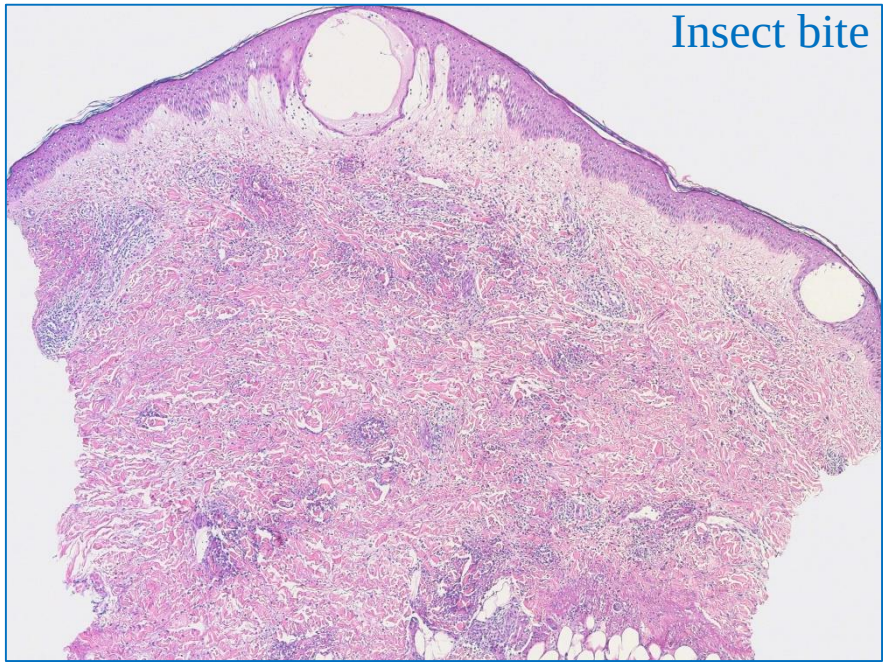
(*Am J Dermatopathol* 2011;33:695–704)

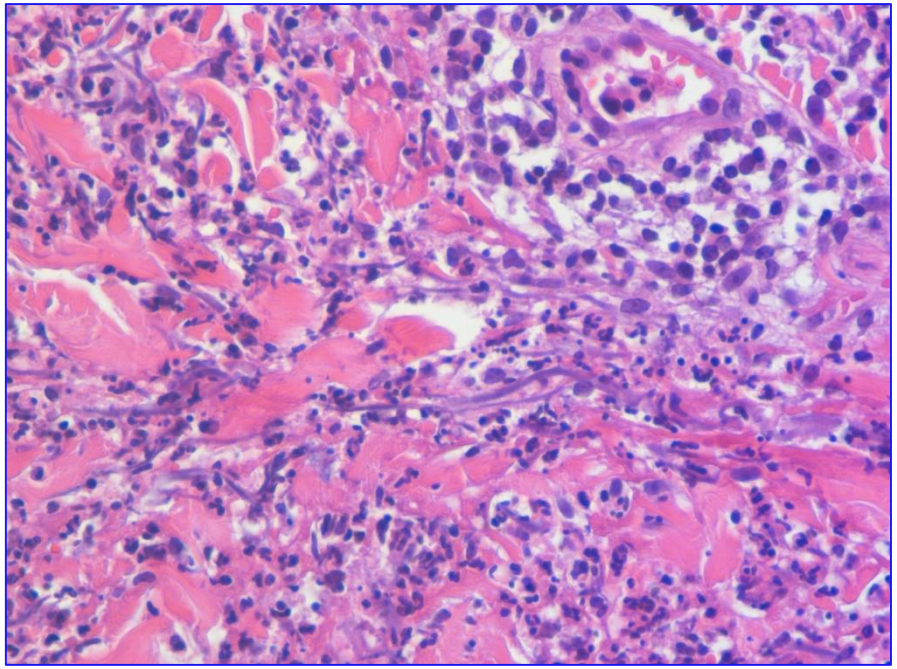
**TABLE 3.** Dermal Inflammatory Infiltrate

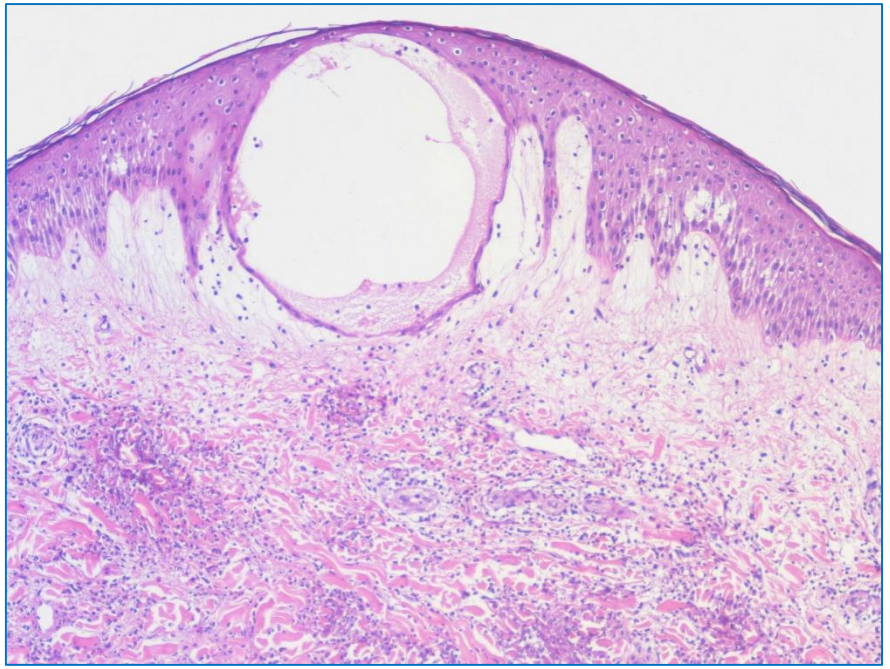
| | Number (total = 60) | % |
|---|---|---|
| Perivascular infiltrate | 60 | 100 |
| Superficial | 43 | 72 |
| Superficial and deep | 17 | 28 |
| Lymphocytes | 60 | 100 |
| Scattered large lymphocytes | 23 | 38 |
| Eosinophils | 36 | 60 |
| Neutrophils | 30 | 50 |
| Macrophages | 47 | 78 |
| Mast cells | 5 | 8 |
| Plasma cells | 4 | 7 |
| Erythrocytes | 17 | 28 |
| Interstitial infiltrate in the papillary dermis | 56 | 93 |
| Patchy | 42 | 70 |
| Lichenoid | 14 | 23 |
| Lymphocytes | 53 | 88 |
| Eosinophils | 33 | 55 |
| Neutrophils | 46 | 77 |
| Macrophages | 39 | 65 |
| Melanophages | 2 | 3 |
| Mast cells | 0 | 0 |
| Plasma cells | 0 | 0 |
| Erythrocytes | 17 | 28 |
| Interstitial infiltrate in the reticular dermis | 29 | 48 |
| Upper dermis | 24 | 40 |
| Upper and lower dermis | 5 | 8 |
| Lymphocytes | 29 | 48 |
| Eosinophils | 46 | 77 |
| Neutrophils | 38 | 63 |
| Macrophages | 8 | 13 |
| Mast cells | 5 | 8 |
| Plasma cells | 0 | 0 |
| Erythrocytes | 5 | 8 |

This is especially true for the combination of eosinophils and neutrophils which is seen in only a limited number of diseases, such as urticaria, autoimmune bullous diseases, Sweet's syndrome, reactions to arthropod assaults, and some folliculitides. Most of those differential diagnoses are characterized by findings not usually seen in drug eruptions,

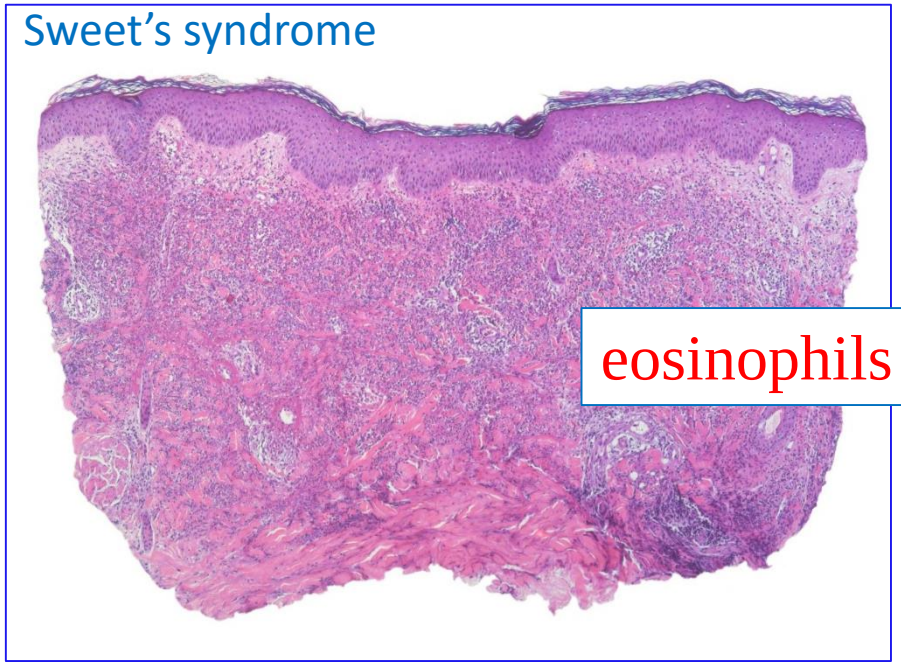


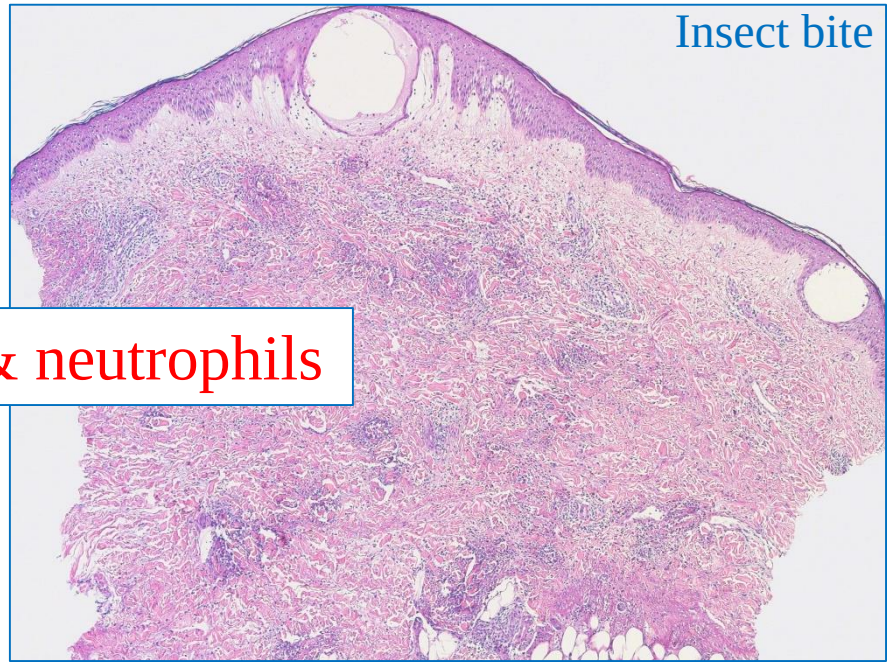



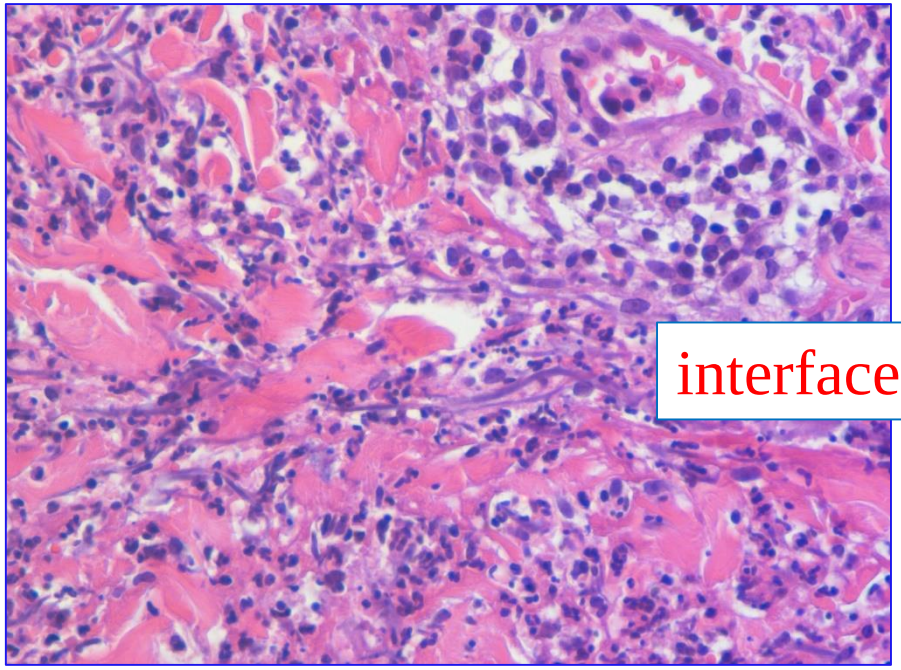


such as a very dense infiltrate of neutrophils with abundant neutrophilic nuclear dust in Sweet's syndrome or a wedge-shaped infiltrate beneath a very large spongiotic blister in a reaction to an insect bite.

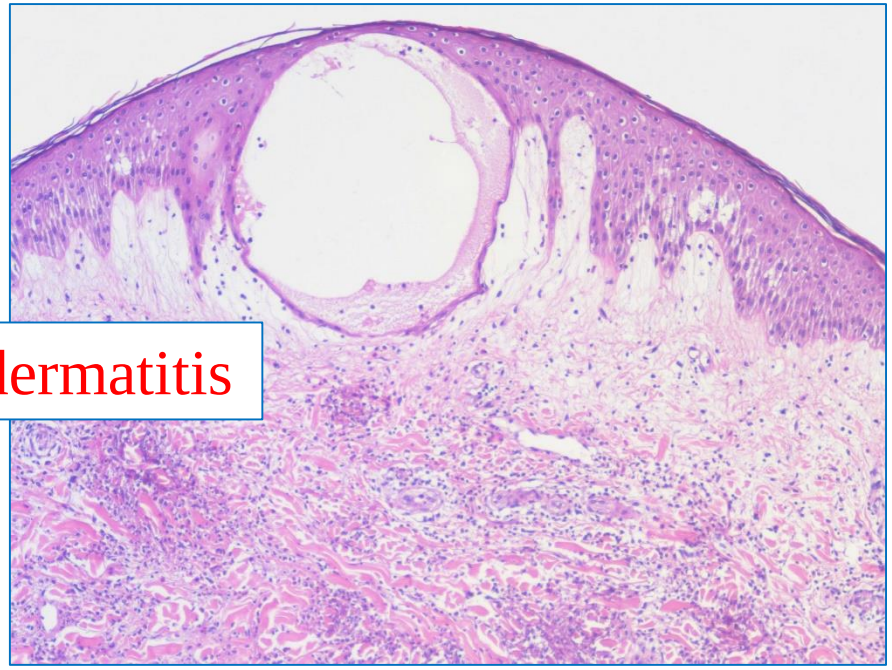


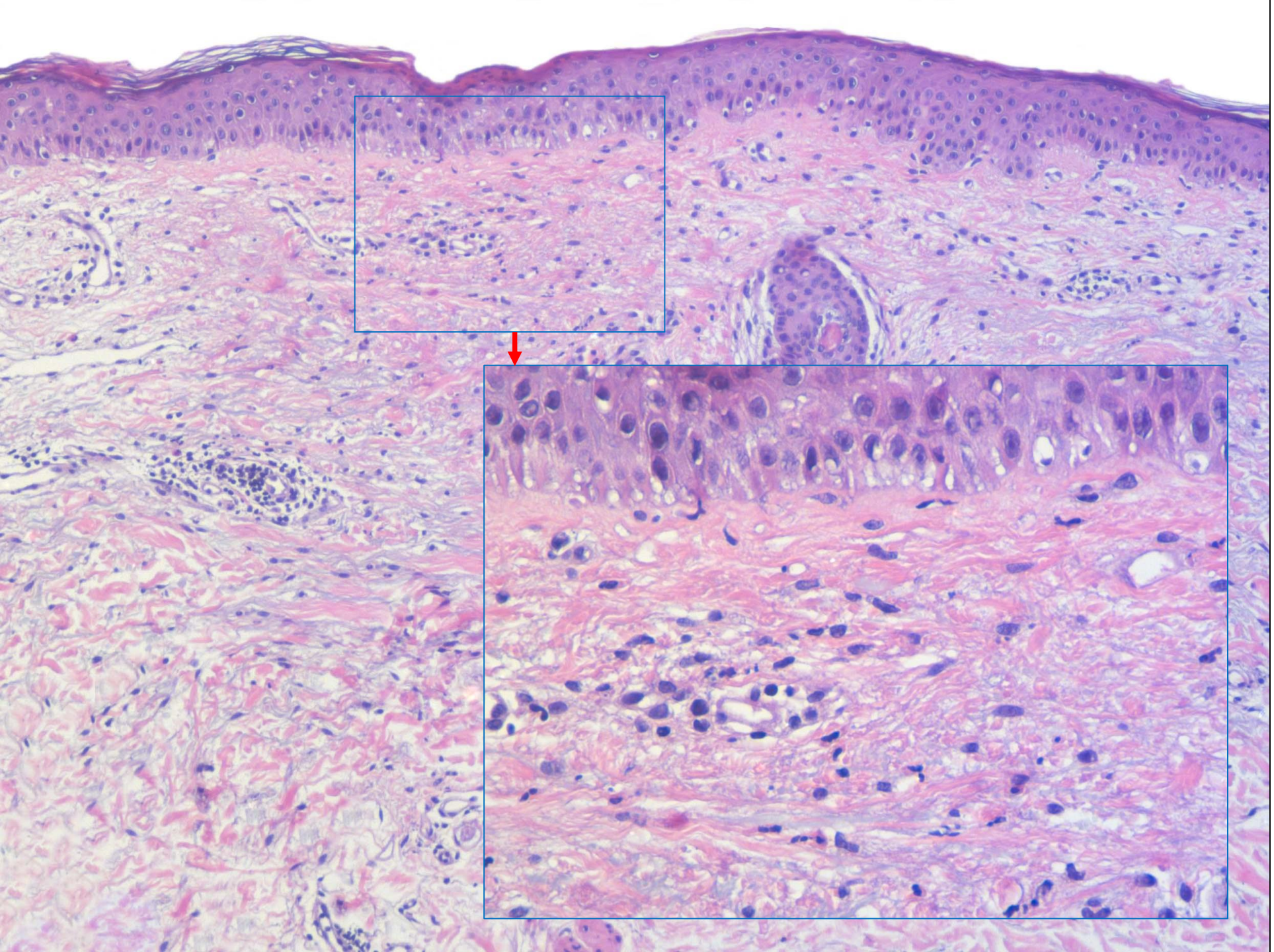

eosinophils & neutrophils



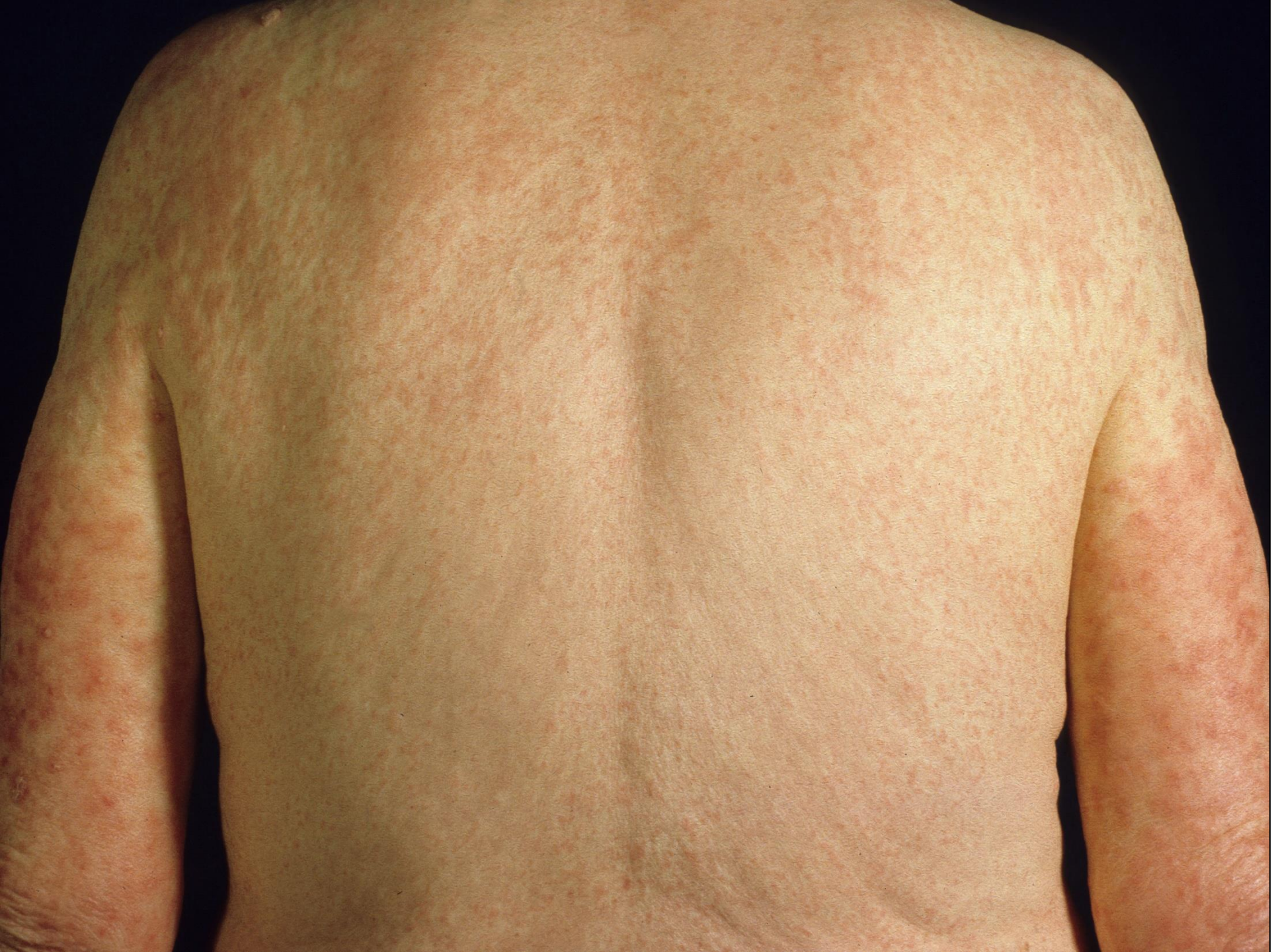
interface dermatitis



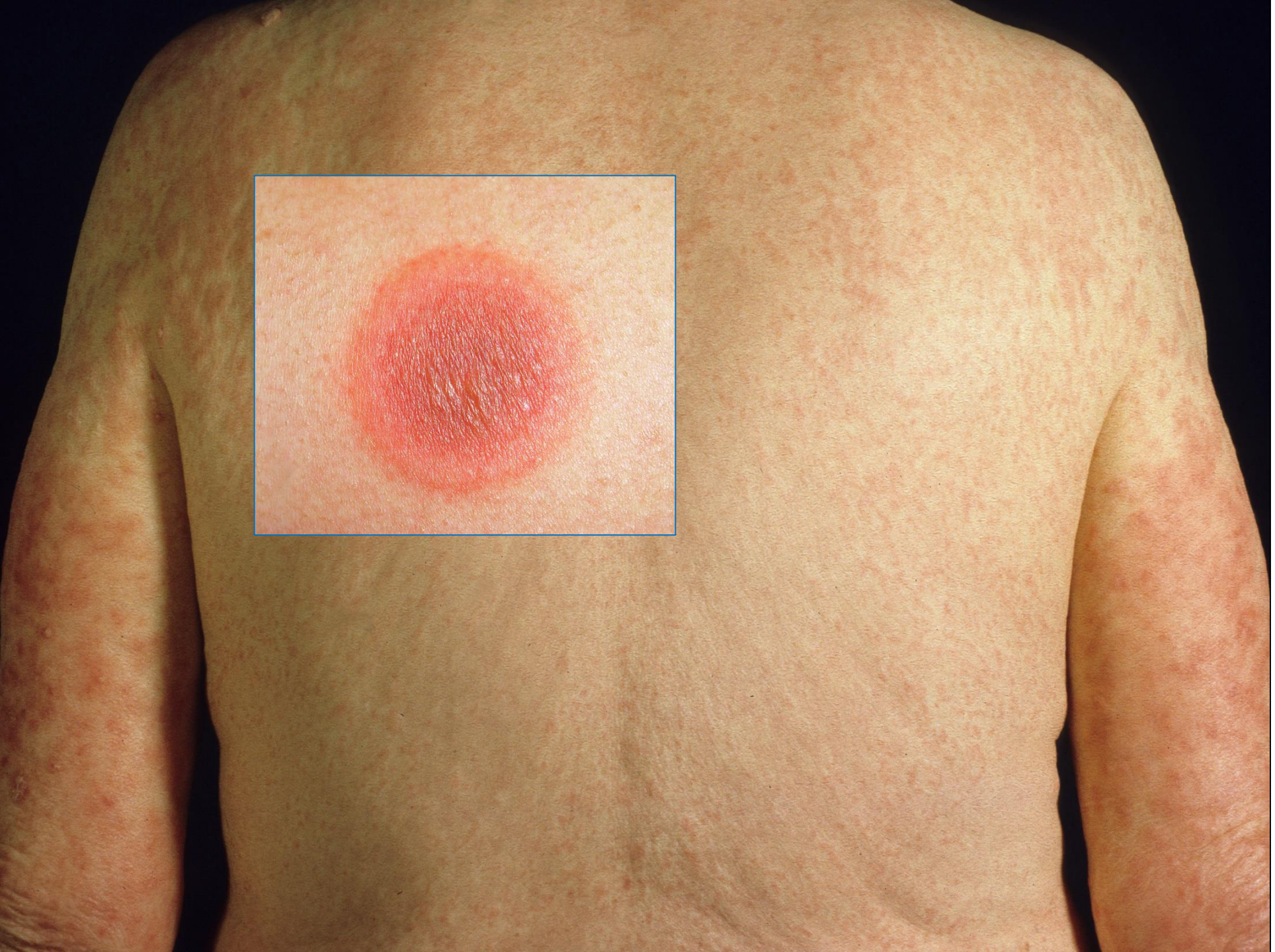
Taken together, those two criteria – an infiltrate with eosinophils and neutrophils and signs of interface dermatitis – are highly suggestive of a drug eruption because most diseases associated with eosinophils and neutrophils do not show signs of interface dermatitis, and most interface dermatitides are associated with an infiltrate composed almost entirely of lymphocytes. Although some eosinophils may occur in diseases such as lupus erythematosus, graft-versus-host disease, or post-herpetic erythema multiforme, they are hardly ever numerous and not associated with neutrophils.



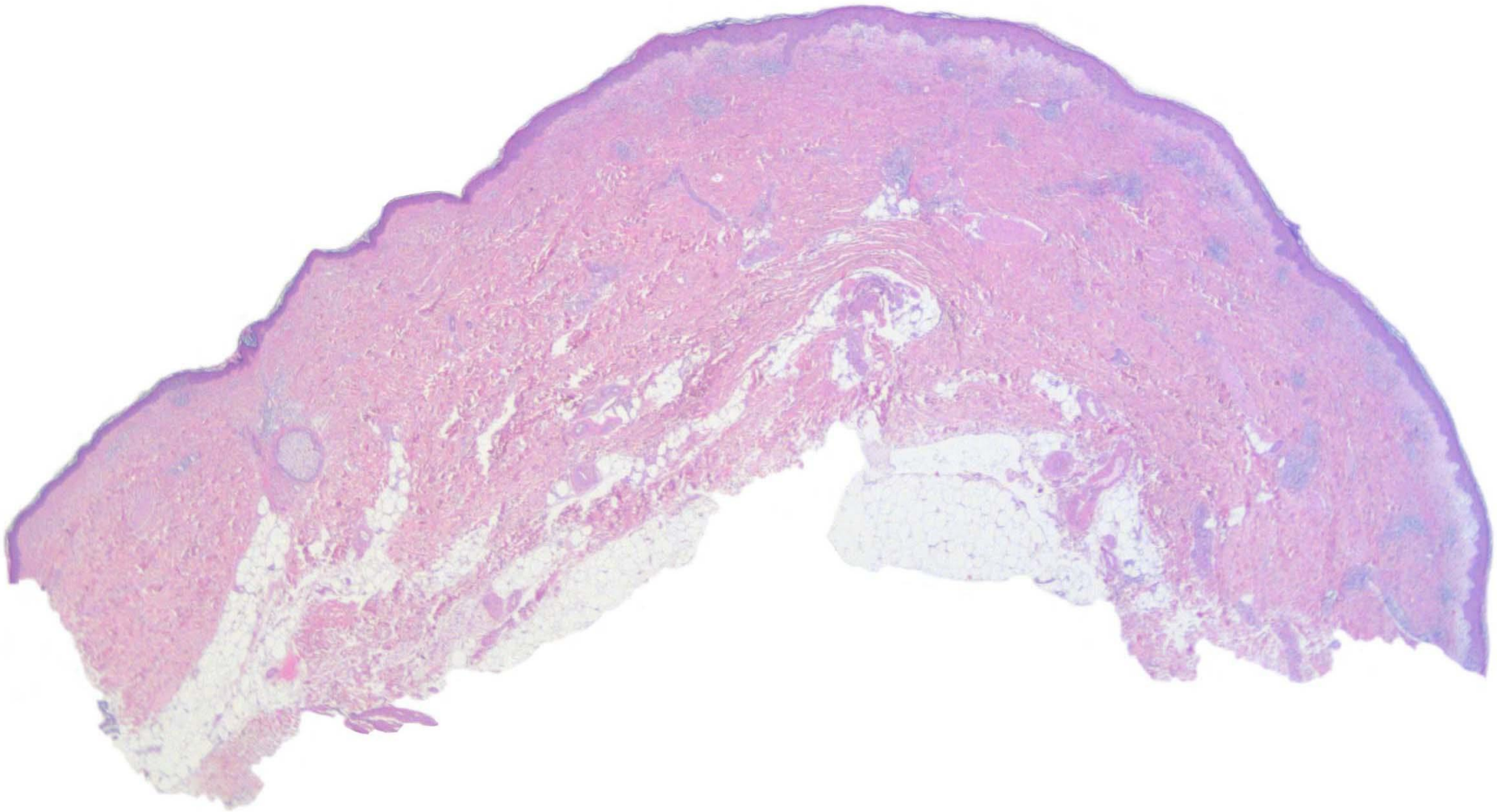
A sparse perivascular and interstitial infiltrate of neutrophils and eosinophils in concert with subtle vacuolar changes at the dermo-epidermal junction is nearly diagnostic of a drug eruption.



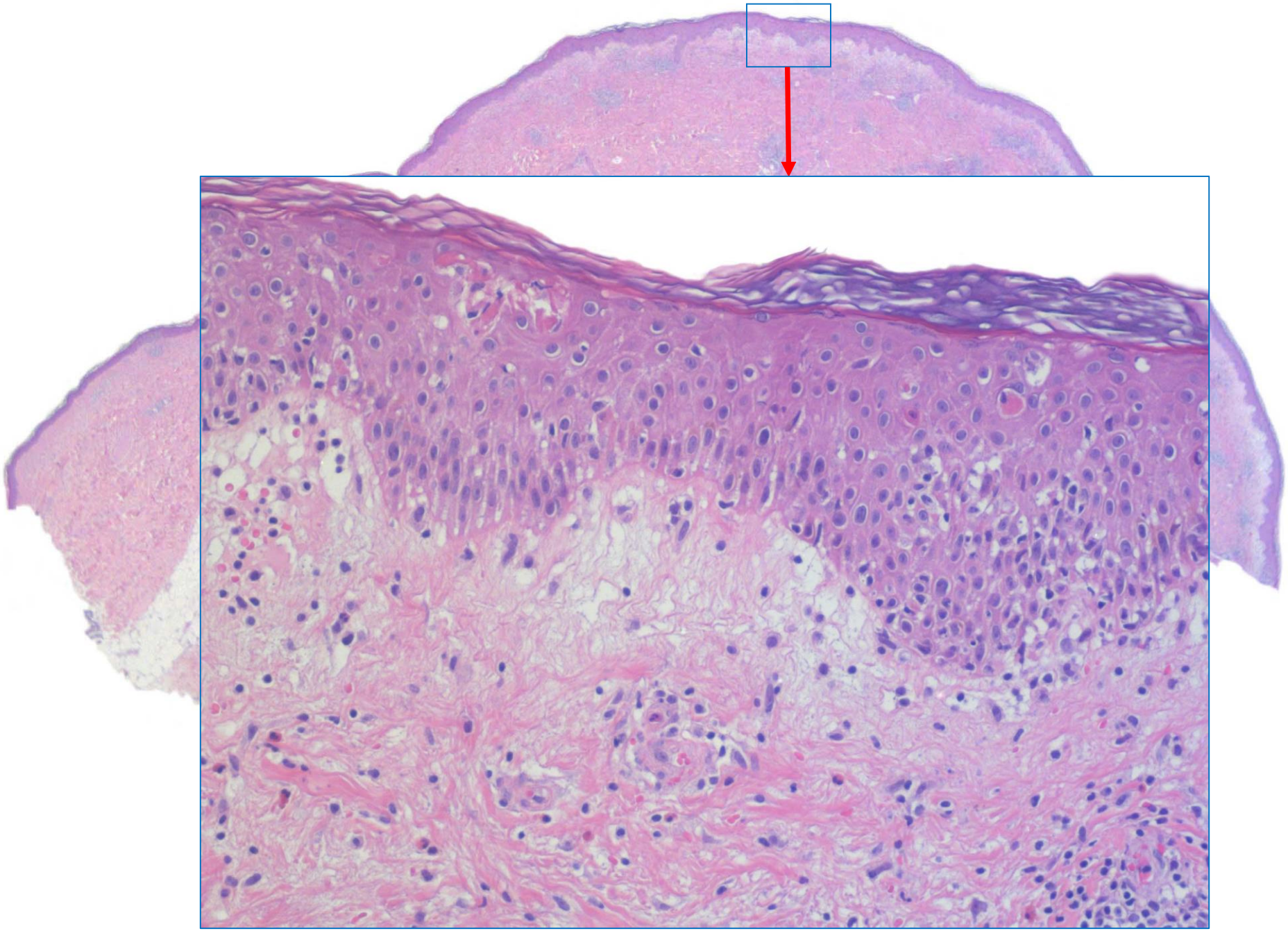
What other findings are suggestive of drug eruptions in general? Among them are signs of acuteness. As the name denotes, drug eruptions are eruptive. In general, they appear suddenly and progress rapidly in both, extension and intensity. As a consequence, they are usually biopsied early in their course.



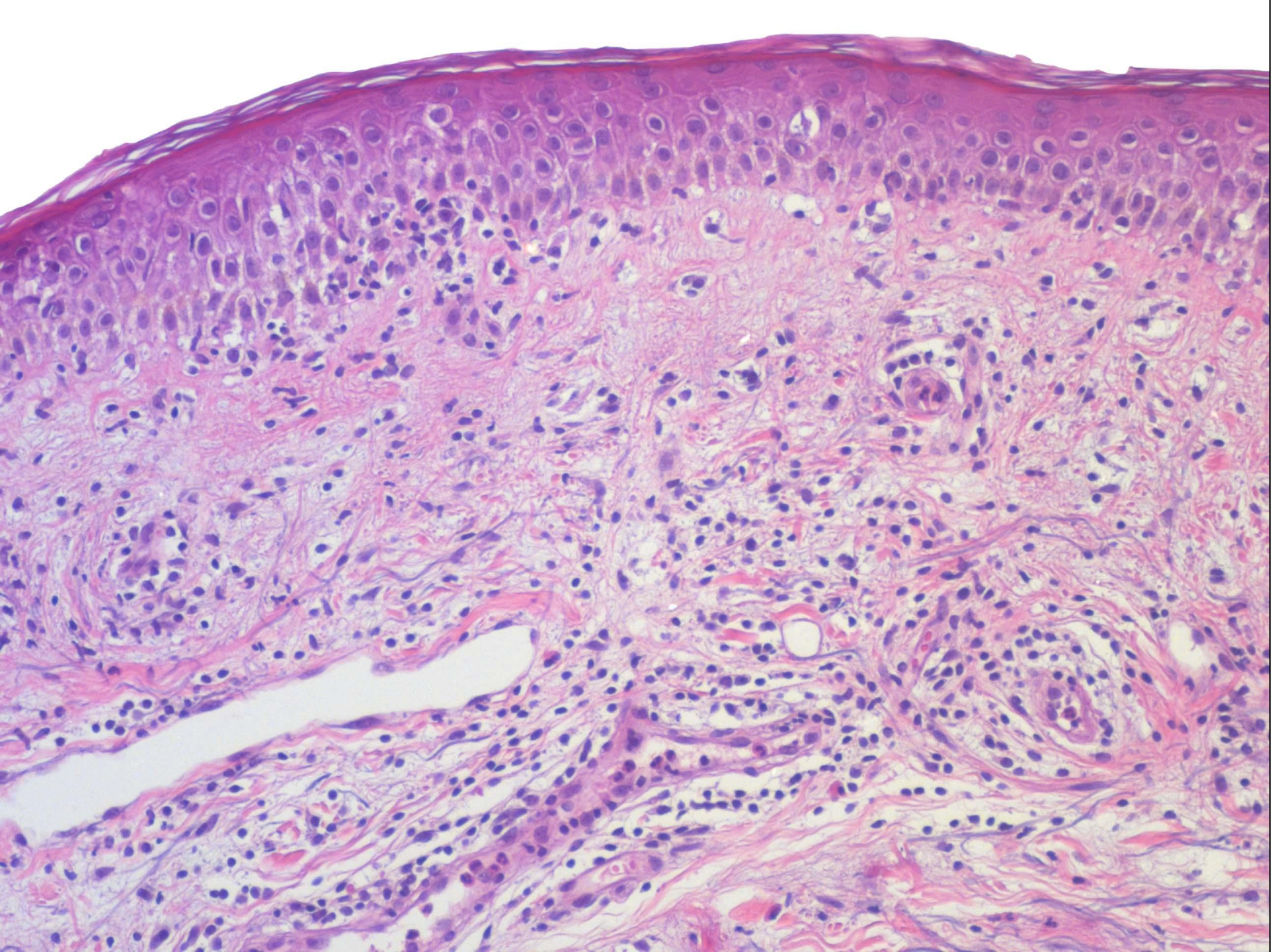
Signs of acuteness are among the criteria used for the diagnosis of fixed drug eruption,



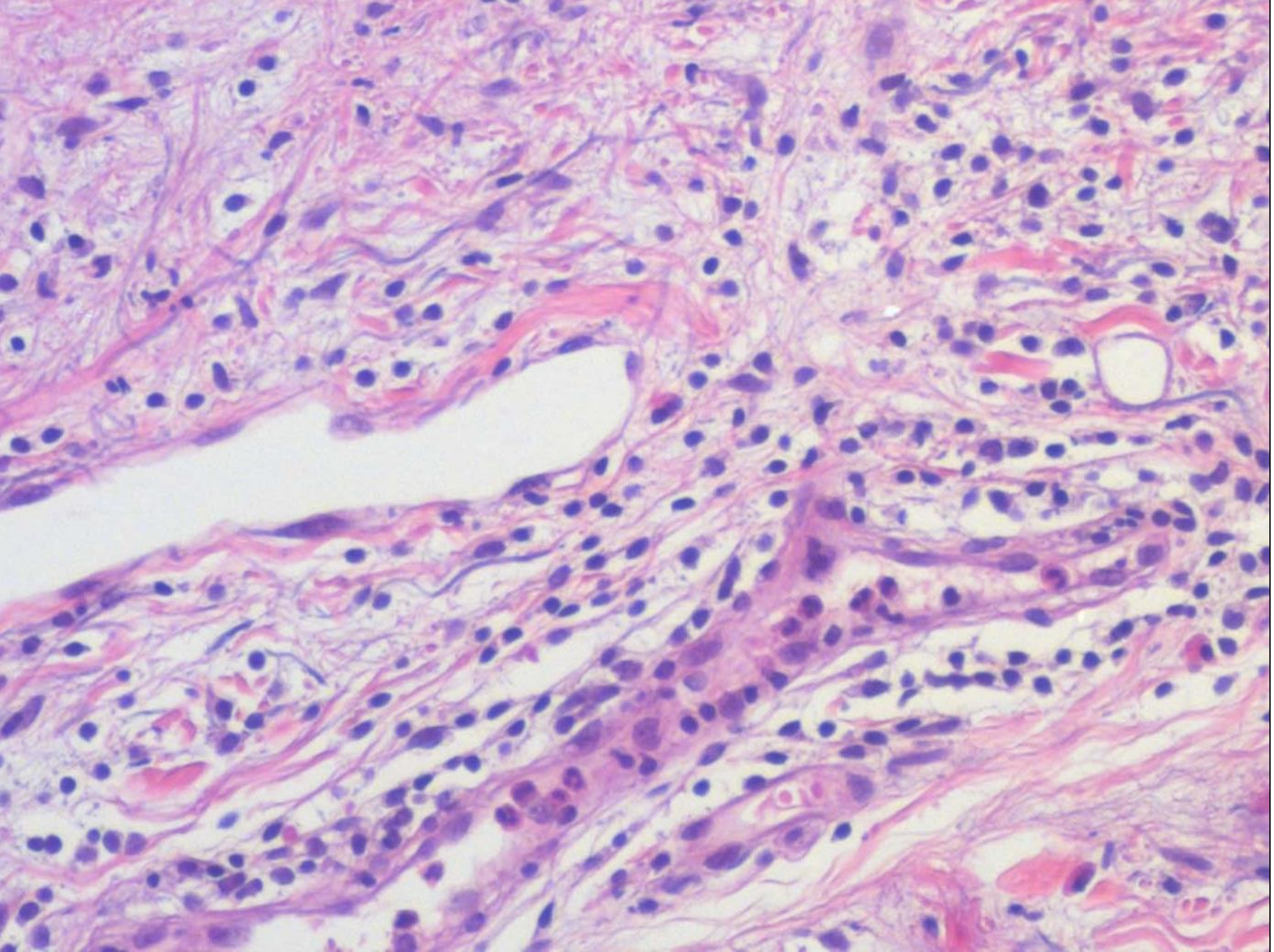
as already shown in the large biopsy of it. Among them are



edema of the papillary dermis, extravasation of erythrocytes, and 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).



Other signs of acuteness are widely dilated capillaries and venules in the superficial dermis



and many neutrophils in the lumina of dilated venules.  Of course, neutrophils are commonly seen in the lumina of blood vessels, and if there a few, it does not mean a thing, but if there are myriads, it is a sign of acuteness that may be used as a diagnostic clue.

# Signs of acuteness

- normal cornified layer despite spongiosis or hydrops
- edema of the papillary dermis
- extravasation of erythrocytes
- angiectases in the superficial dermis
- many neutrophils in the lumina of ectatic venules

In sum, signs of acuteness are common in drug eruptions and include a normal cornified layer despite spongiosis or hydrops in the epidermis, edema of the papillary dermis, extravasation of erythrocytes, angiectases in the superficial dermis, and many neutrophils in the lumina of ectatic venules.

# Signs of chronicity

- marked epidermal hyperplasia
- marked hyperkeratosis
- coarse collagen bundles in elongated dermal papillae
- fibrosis of the papillary and superficial reticular dermis
- many melanophages and/or siderophages

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.

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.

# Carbamazepine-induced eruption histologically mimicking mycosis fungoides

**S. Welykyj, R. Gradini, J. Nakao, M. Massa**

Department of Dermatology and Pathology, Loyola University Medical Center, Maywood, Illinois, U.S.A.

Carbamazepine is an important drug used in the management of seizures, trigeminal neuralgia, and chronic pain syndromes. It has been associated with a variety of adverse skin reactions including urticaria, lichenoid eruptions, erythroderma, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A 39-year-old white male had been sta mazepine for intractable pain which resulted from crush injury. Approximately 3 months after the st the patient had developed a generalized skin erup an entire day of sun exposure. Skin biopsies revea lymphoid infiltrate in the dermis with collections lymphocytes within spongiotic vesicles in the epid ive of mycosis fungoides. The patient was treated prednisone. Subsequent biopsies failed to reveal a phocytes. Previous reports have described spongio with foci of atypical lymphocytes in contact derma patients treated with phenytoin. To the best of ou this is the first reported case of a carbamazepine-i tion simulating mycosis fungoides histologically.

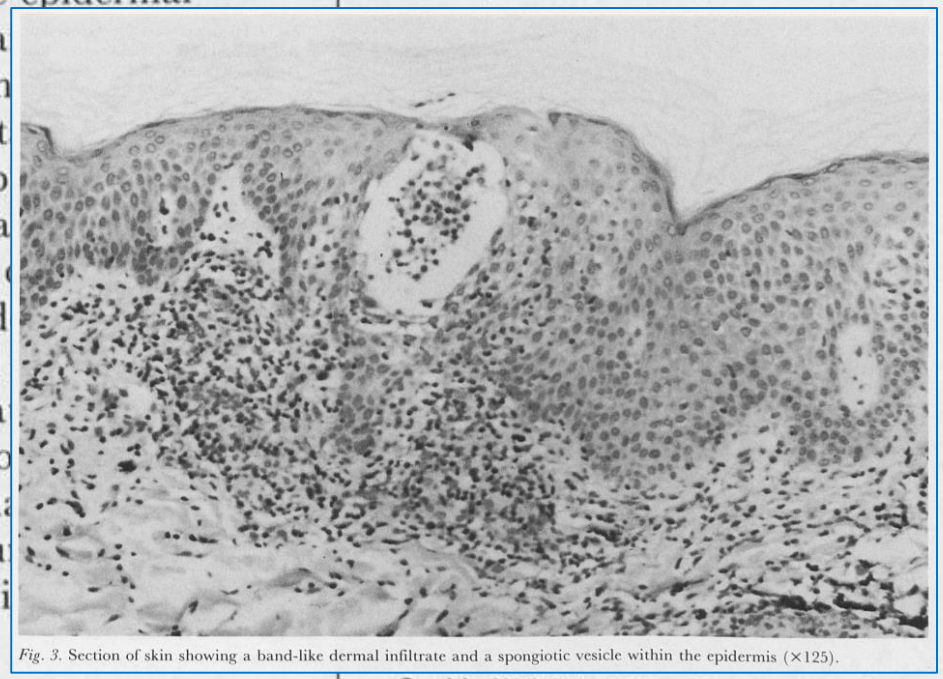


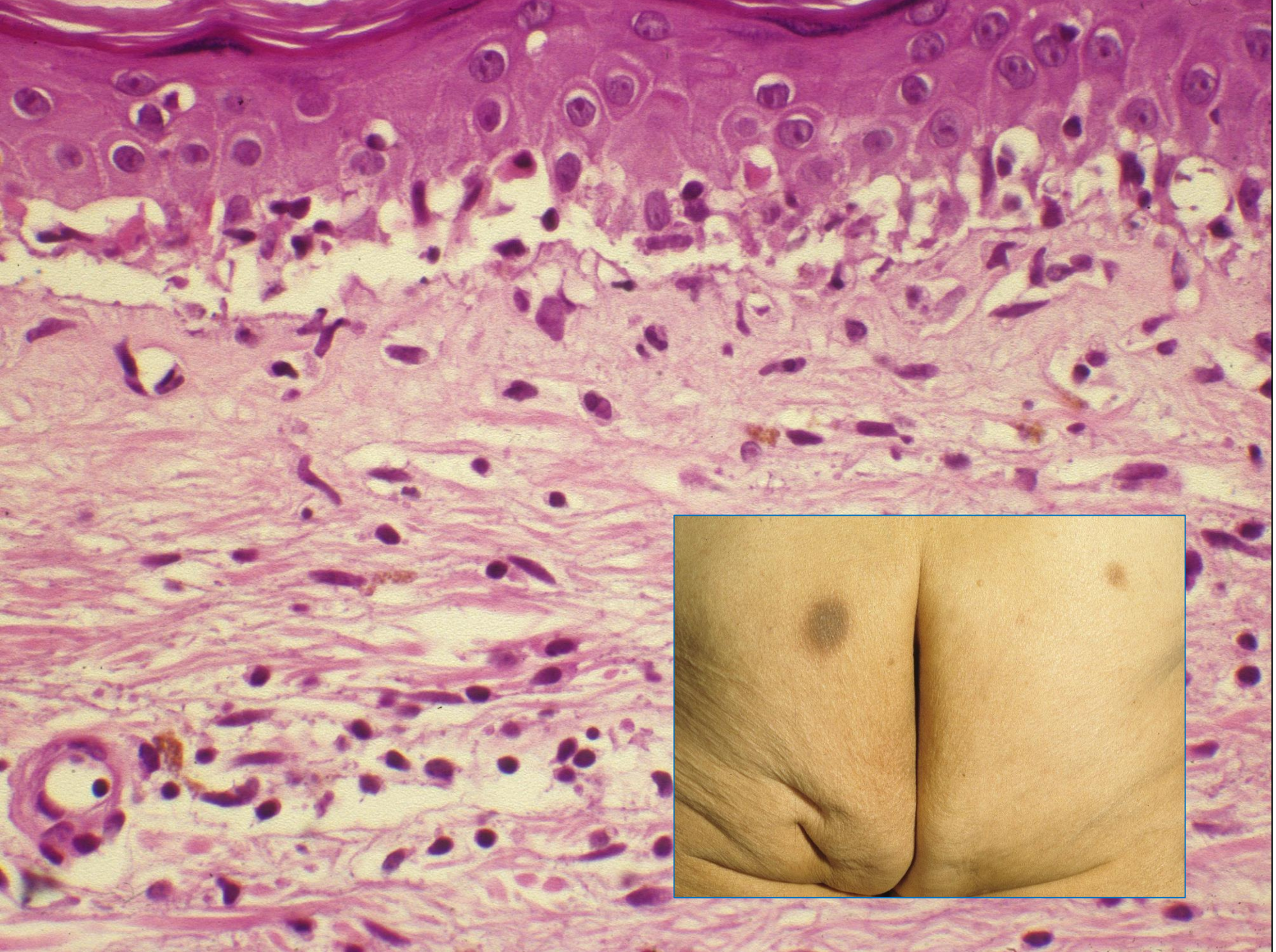
*Fig. 3.* Section of skin showing a band-like dermal infiltrate and a spongiotic vesicle within the epidermis (×125).

Welykyj S, Gradini R, Nakao J, Massa M. Carbamazepine-induced eruption histologically mimicking mycosis fungoides. J Cutan Pathol 1990: 17: 111–116.

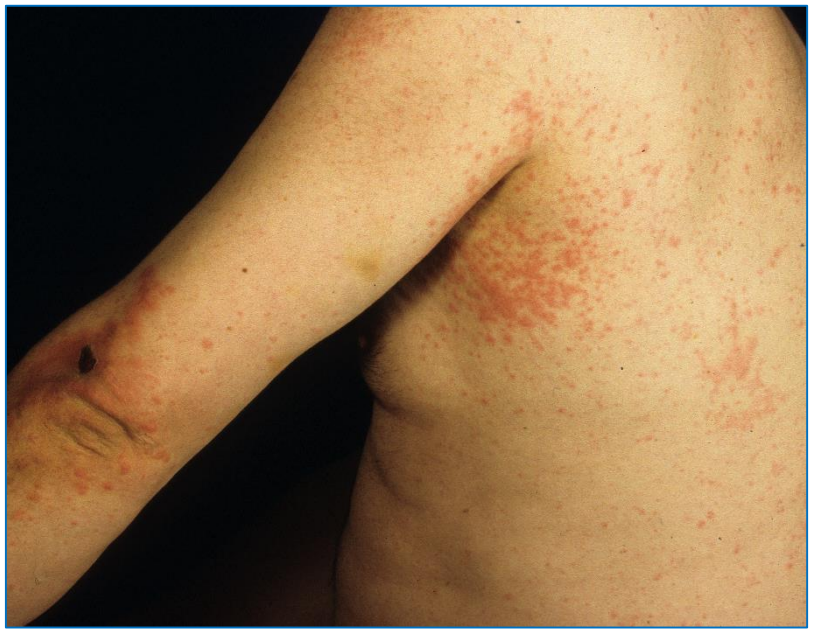
Sophia Welykyj, M.D., Department of Dermatology, Loyola University Medical Center, Maywood, Illinois, U.S.A.

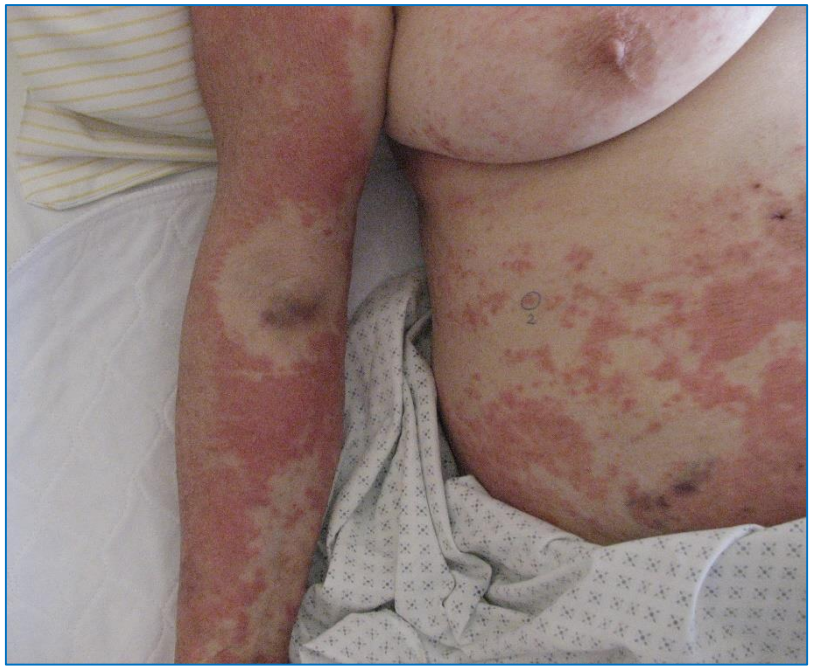
Accepted September 9, 1989

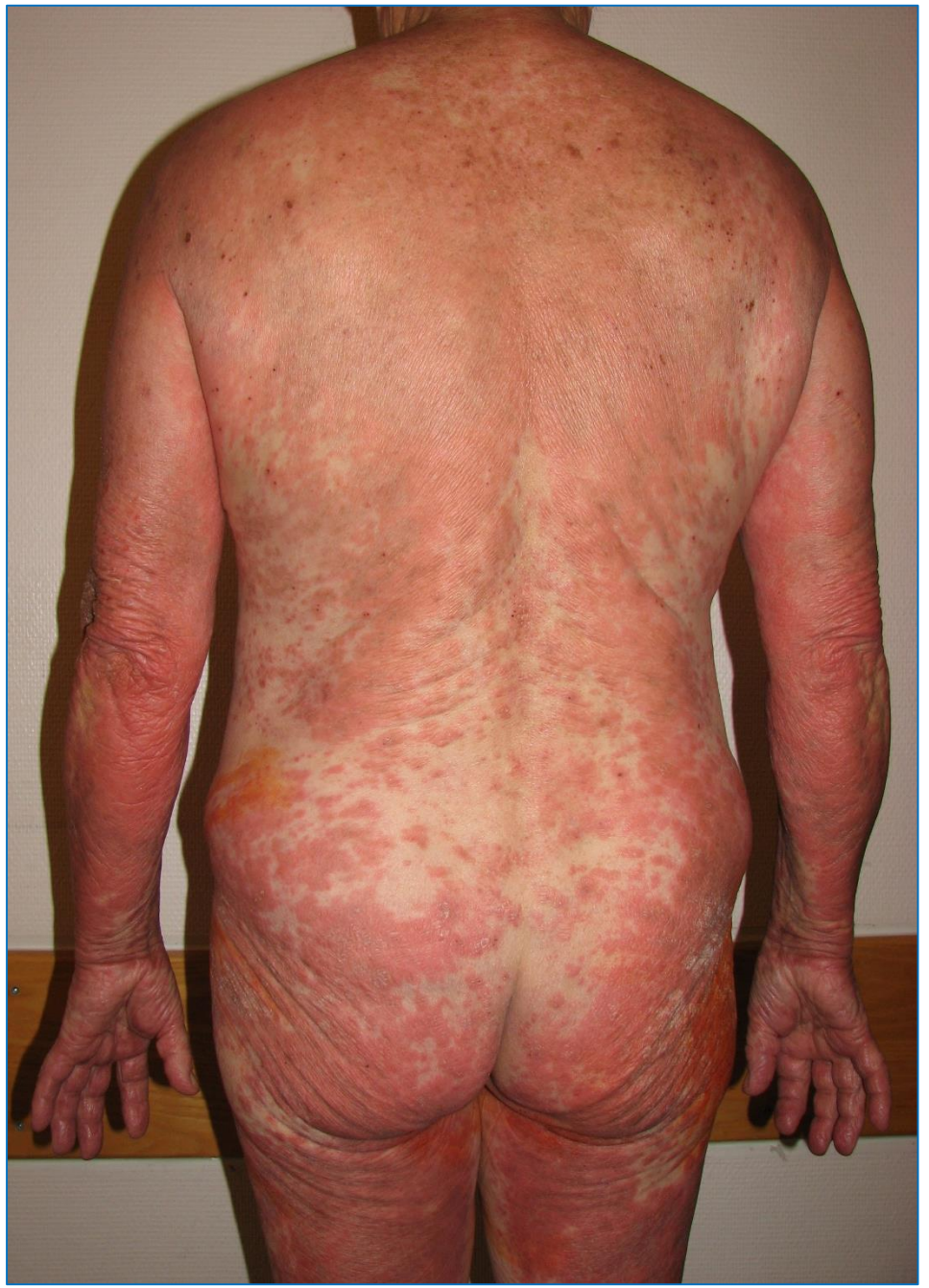
For example, anticonvulsant drugs such as phenytoin and carbamazepin may elicit chronic drug eruptions that, because of a lichenoid infiltrate of lymphocytes with largish nuclei, epidermotropism, epidermal hyperplasia, and fibrosis of the papillary dermis, may mimick mycosis fungoides.



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.





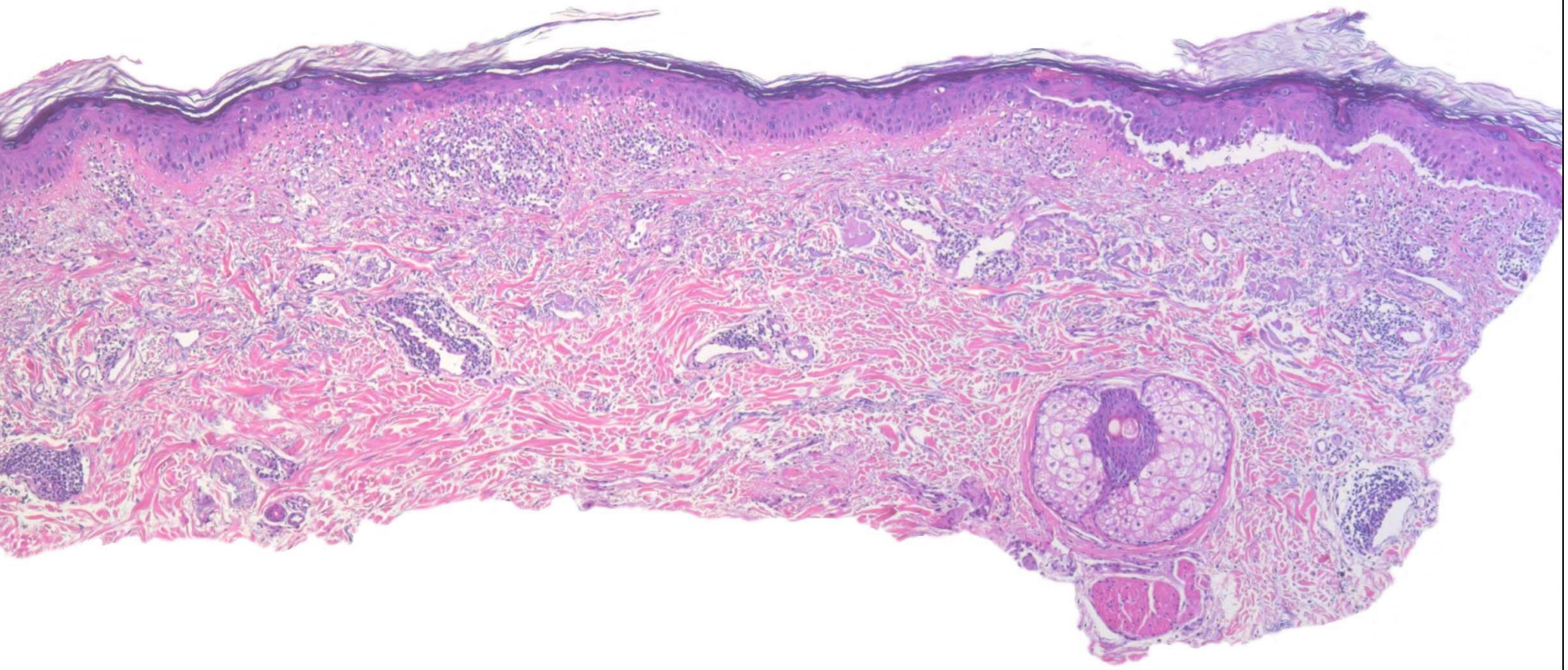


There are various other clues, some general, some more specific. Among the general considerations are the age of patients and the anatomic site. Drug-induced skin reactions are usually widespread eruptions affecting chiefly trunk and extremities. Palms and soles are involved only rarely, and if they are, there are usually also lesions at other sites better suited for performing a biopsy.

# Biopsy sites militating against a drug eruption

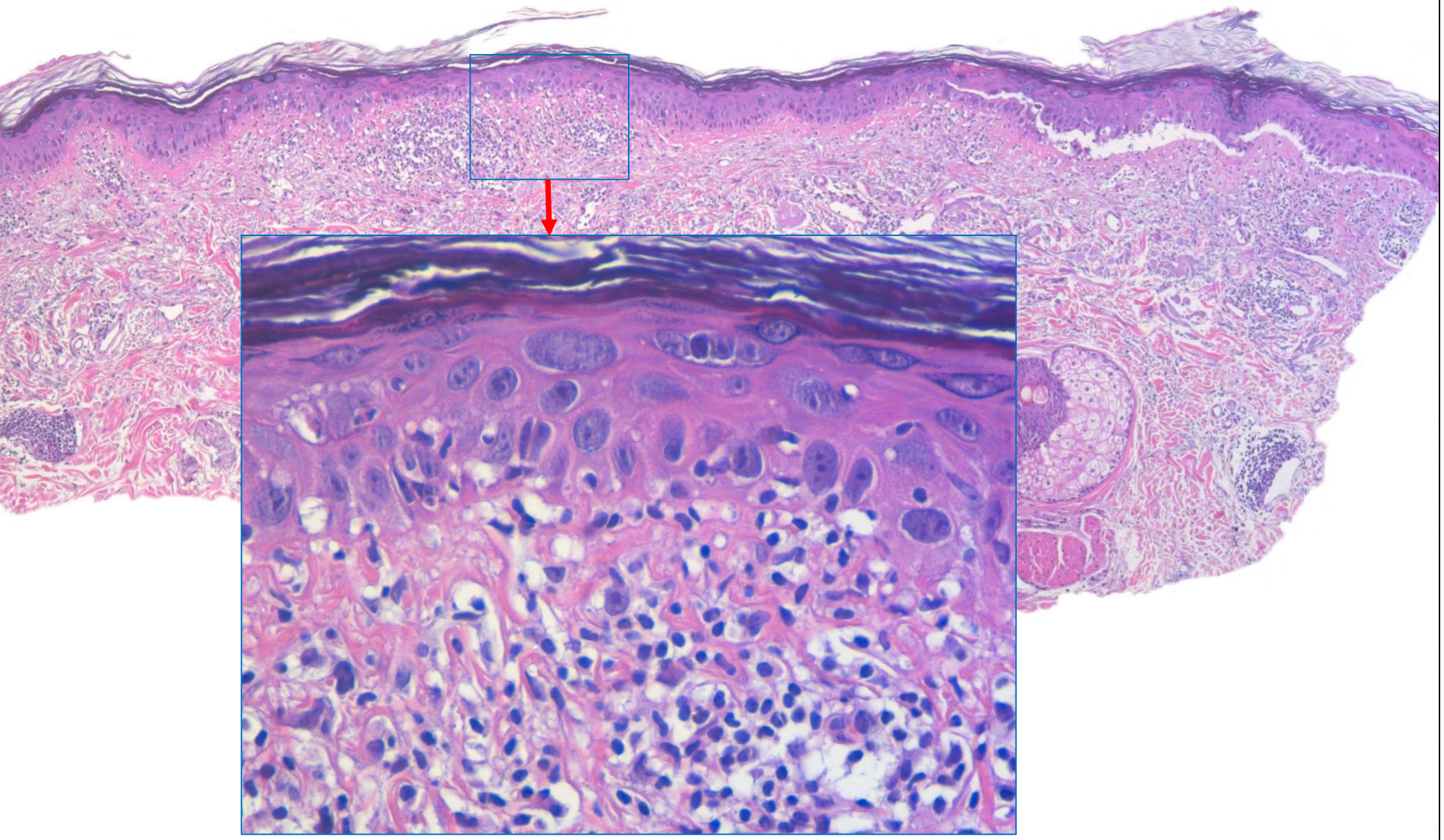
- palms and soles (thick epidermis with compact cornified layer; no hair follicles)
  exception: fixed drug eruption
- genitalia (thin or absent cornified layer, highly vascularized) exception: fixed drug eruption
- scalp (many terminal hair follicles reaching down into the subcutis)
- face (large sebaceous glands, solar elastosis)
- ears (vellus follicles)

As a consequence, drug eruptions, with the exception of fixed drug eruption, are biopsied rarely on palms, soles or genitalia. The same is true for scalp, face, and ears. Hence, when one sees a biopsy specimens with anatomic features typical of those sites, a drug eruption is unlikely.



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

Drug eruptions may be associated with atypia of keratocytes.



The affected cells are swollen, have large nuclei, sometimes with prominent nucleoli or irregularly dispersed chromatin. In contrast to epithelial neoplasms, atypical keratocytes are not crowded together closely.

Cameo

# Toxic epidermal necrolysis following combination of methotrexate and trimethoprim–sulfamethoxazole

Chih-hsun Yang, MD, Lih-Jen Yang, MD, Tang-Her Jaing, MD, and Heng-Leong Chan, MD

From the Department of Dermatology, and Department of Pediatrics, Division of Hematology and Oncology, Chang Gung Memorial Hospital, Taipei, Taiwan

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A 15-year-old boy with T-cell acute lymphoblastic leukemia (ALL) (FAB L1), diagnosed in 1995, received combination chemotherapy consisting of 6 weeks of induction (vincristine, epirubicin, L-asparaginase, prednisolone) and 2 weeks of consolidation (cytosine arabinosides, etoposide). After achieving remission, for further maintenance of remission, he was

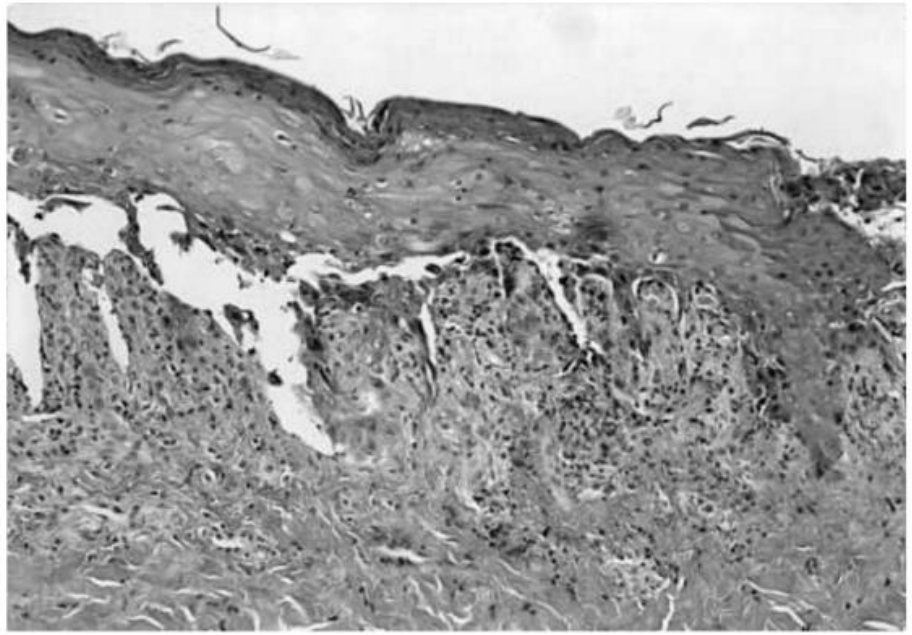

**Figure 2** Biopsy specimen showing lichenoid tissue reaction, including parakeratosis, detached acanthotic epidermis with scattered necrotic keratinocytes, dyskeratotic cells, nuclear atypia, and many neutrophils in the papillary dermis

*International Journal of Dermatology* 2000, **39**, 616–623


day) and the addition of 25 meq/L sodium bicarbonate to the intravenous fluid to alkalinize the

They have been described especially in reactions to chemotherapeutic drugs, such as methotrexate

Cameo

# Toxic epidermal necrolysis following combination of methotrexate and trimethoprim–sulfamethoxazole

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CUTANEOUS MANIFESTATIONS OF LONG-TERM HYDROXYUREA THERAPY

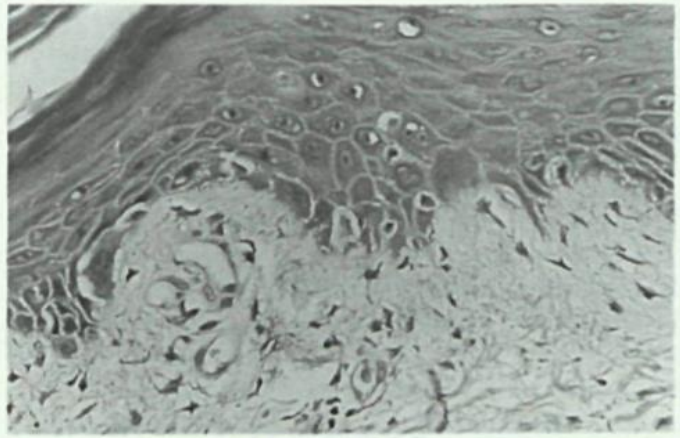
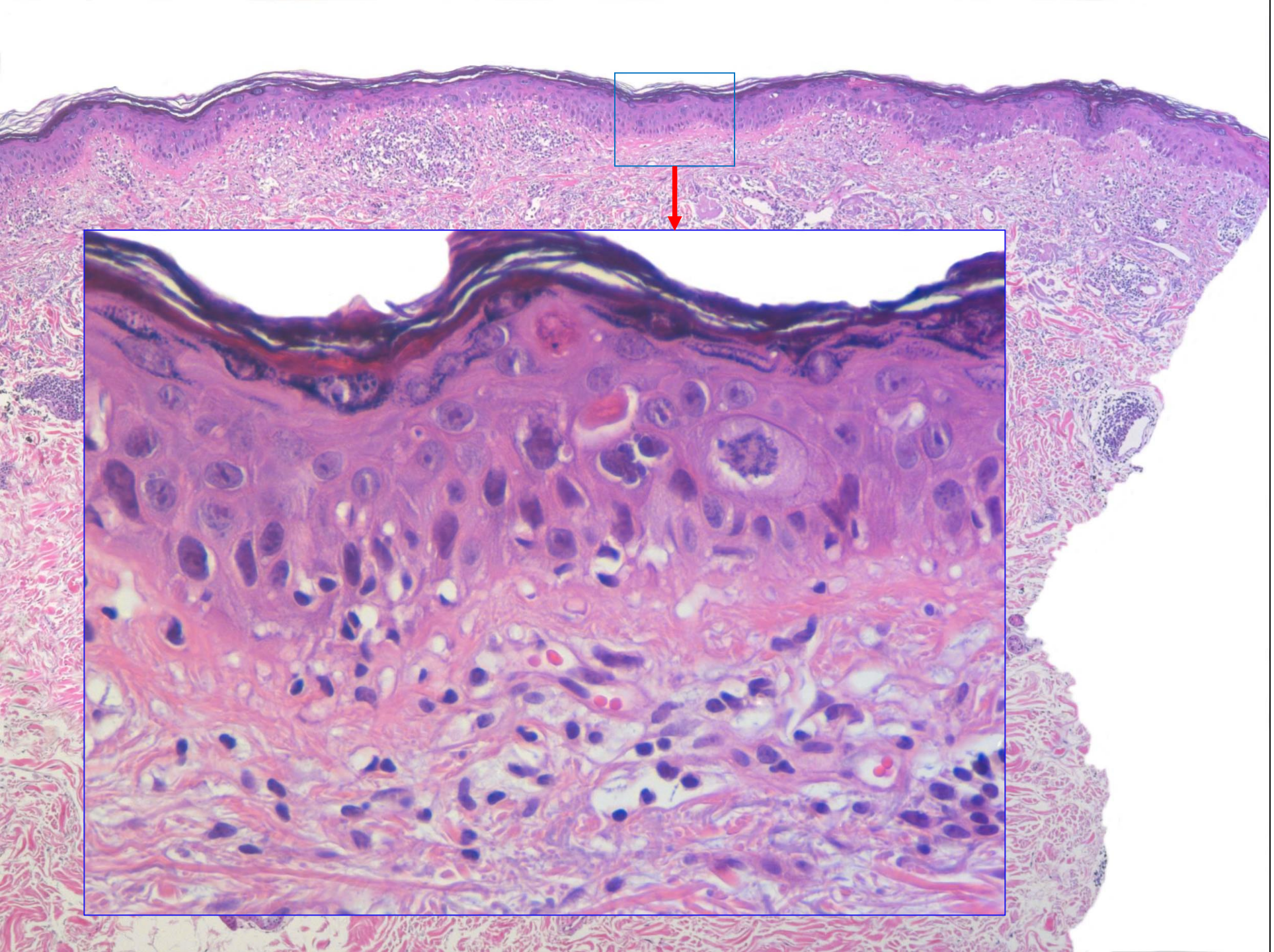


FIGURE 4—A biopsy from an erythematous scaly patch on the dorsal hand showing basal layer degeneration, necrotic keratinocytes and cytological atypia most marked in the basal layer. In other areas colloid body formation was prominent. In spite of epidermal atypia there is no solar elastosis in the dermis and the inflammatory infiltrate is scanty. (H&E x 40)

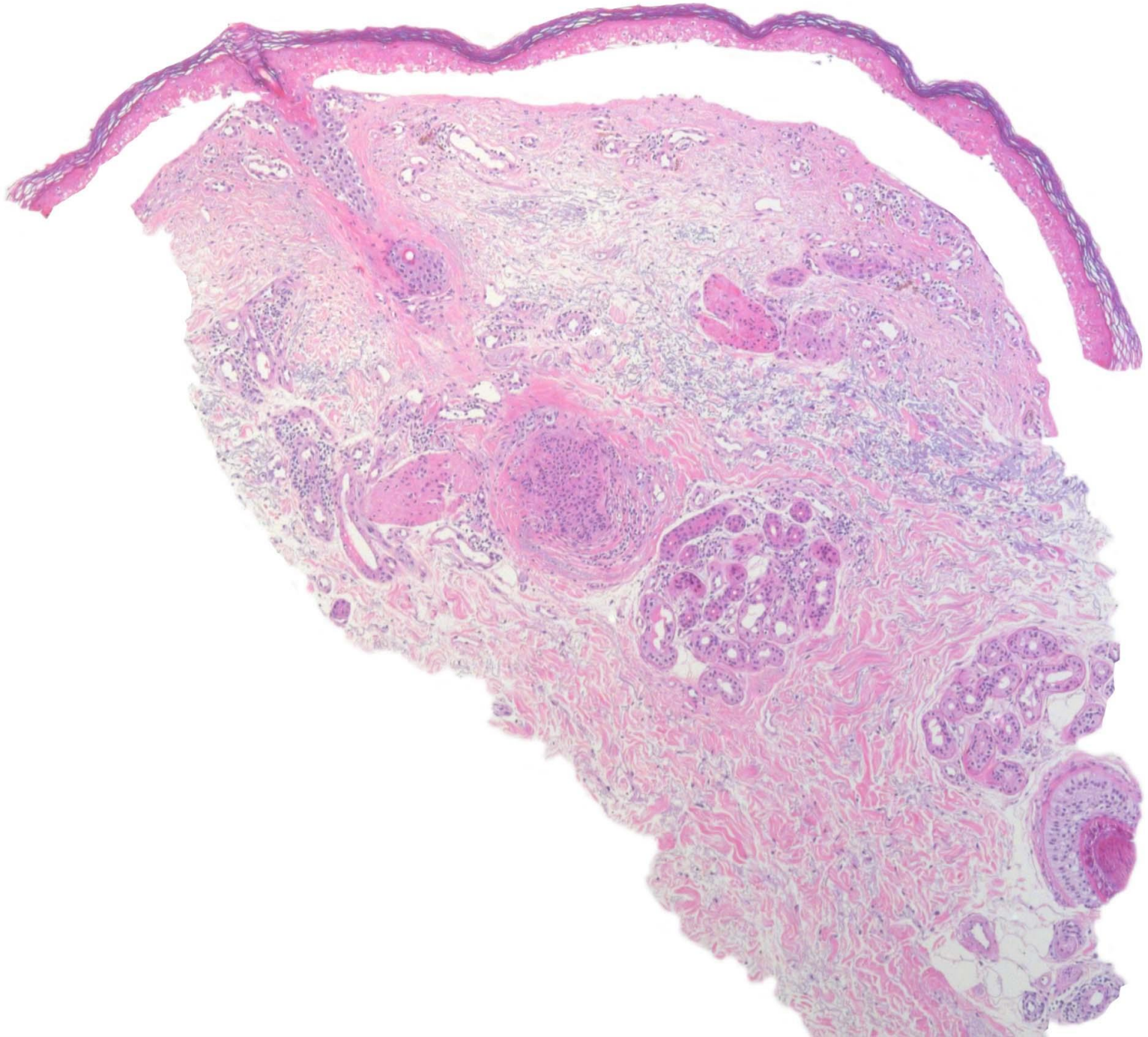
dryness and scaling consistent with ichthyosis,[6] erythema and scaling of the palms and soles;[1,6] advanced cutaneous atrophy of hands and forearm;[1] a dermatomyositis like eruption on the dorsal hands with prominent nail fold telangiectasia,[3,6] and buccal mucosal ulceration.[3] Accelerated development of premalignant and malignant skin tumours has also been documented with hydroxyurea[6] and it would seem relevant in this man as he had a relatively small degree of lifetime sun exposure having always lived in England with little participation in outdoor activities. However on examination he had a weathered appearance and changes that one would usually attribute to severe actinic damage. He also had marked telangiectatic facial erythema that has been recorded previously with hydroxyurea[1] and was more dramatic than could be explained by acne roscea, with telangiectasia in areas not

day) and the addition of 25 meq/L sodium bicarbonate to the intravenous fluid to alkalinize the

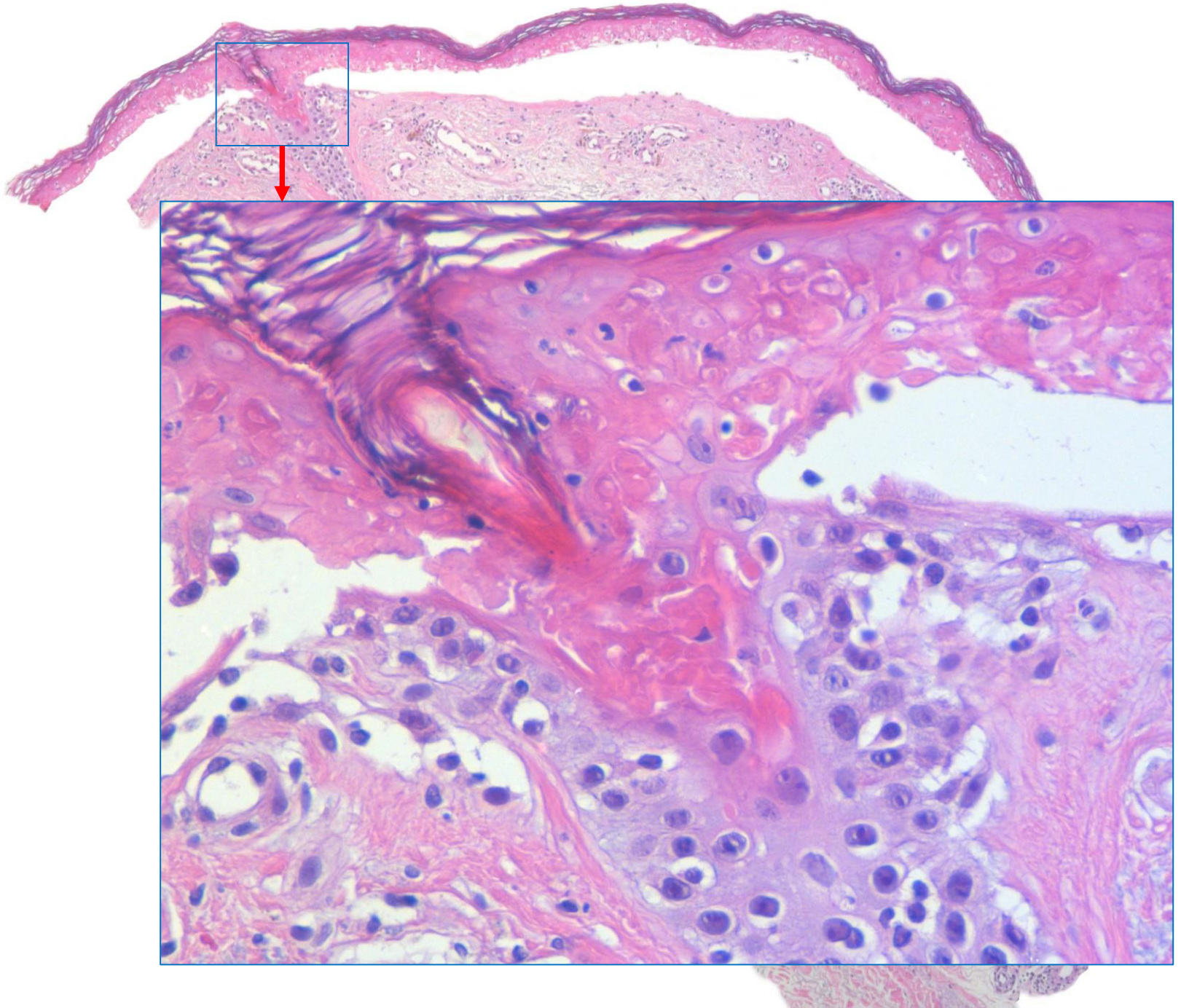
or hydroxyurea. However, they may be seen in response to a wide variety of drugs.



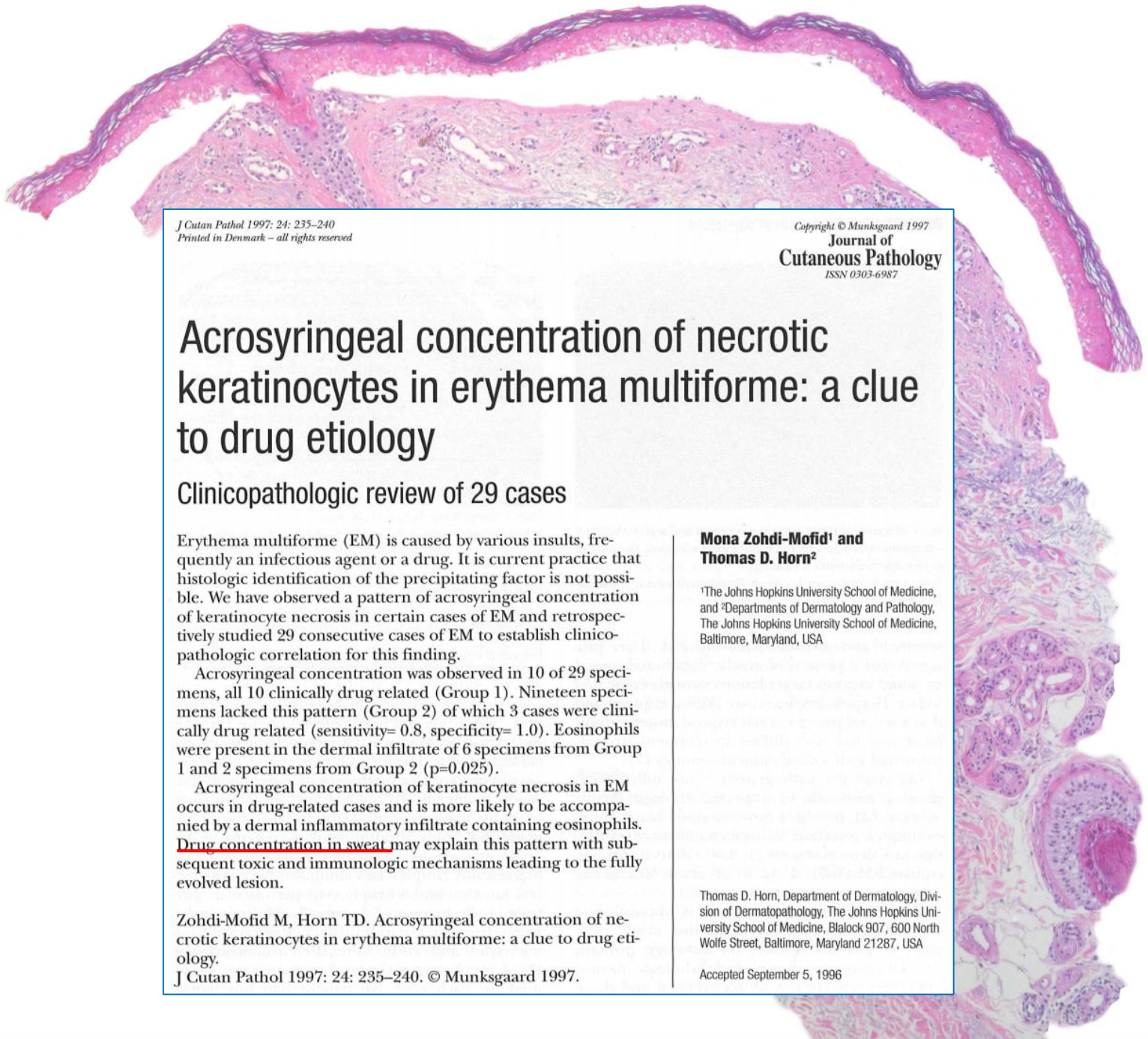
In this instance, it was a beta-blocker. The phenomenon seems to be related to interface changes, since it is also encountered episodically in other interface dermatitides, such as lichen sclerosus and lupus erythematosus. In brief, atypical keratocytes are neither a sensitive nor a specific finding. 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. In addition to atypical keratocytes, drug eruption episodically show slightly atypical lymphocytes as a sign of activation of them.



Another clue to drug eruptions is accentuation of pathologic findings around eccrine structures, In this case with confluent necrosis of the epidermis,



necrosis of individual cells extends down the eccrine duct.



J Cutan Pathol 1997: 24: 235–240
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Journal of
Cutaneous Pathology
ISSN 0303-6987

# Acrosyringeal concentration of necrotic keratinocytes in erythema multiforme: a clue to drug etiology

## Clinicopathologic review of 29 cases

Erythema multiforme (EM) is caused by various insults, frequently an infectious agent or a drug. It is current practice that histologic identification of the precipitating factor is not possible. We have observed a pattern of acrosyringeal concentration of keratinocyte necrosis in certain cases of EM and retrospectively studied 29 consecutive cases of EM to establish clinicopathologic correlation for this finding.

Acrosyringeal concentration was observed in 10 of 29 specimens, all 10 clinically drug related (Group 1). Nineteen specimens lacked this pattern (Group 2) of which 3 cases were clinically drug related (sensitivity= 0.8, specificity= 1.0). Eosinophils were present in the dermal infiltrate of 6 specimens from Group 1 and 2 specimens from Group 2 (p=0.025).

Acrosyringeal concentration of keratinocyte necrosis in EM occurs in drug-related cases and is more likely to be accompanied by a dermal inflammatory infiltrate containing eosinophils. Drug concentration in sweat may explain this pattern with subsequent toxic and immunologic mechanisms leading to the fully evolved lesion.

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Accepted September 5, 1996

Zohdi-Mofid M, Horn TD. Acrosyringeal concentration of necrotic keratinocytes in erythema multiforme: a clue to drug etiology.
J Cutan Pathol 1997: 24: 235–240. © Munksgaard 1997.

In erythema multiforme, *“acrosyringeal concentration of necrotic keratinocytes”* has been emphasized as a *“clue to drug etiology”* and has been attributed to drug concentration in sweat.

J Cutan Pathol 2011: 38: 905–910
doi: 10.1111/j.1600-0560.2011.01776.x
John Wiley & Sons. Printed in Singapore



Journal of
Cutaneous Patholo

# Eccrine hidradenitis sine neutrophils: a toxic response to chemotherapy

We present a case of hidradenitis occurring in a patient after chemotherapy for acute myeloid leukemia (AML) in the setting of profound neutropenia. Neutrophilic eccrine hidradenitis (NEH) presents as tender erythematous papules and plaques and is often associated with chemotherapy for AML. NEH is postulated to be due to toxic injury to the sweat glands followed by neutrophilic inflammation. Alternatively, some hypothesize that NEH represents a primary neutrophilic process. Our patient's clinical presentation was similar to previously reported cases of NEH; however, degenerative changes of the sweat ducts were noted on microscopy without neutrophilic inflammation. She had fewer than 0.01 thousand neutrophils per microliter for 4 days preceding the biopsy. At the same time, a separate area of superficial skin infection developed because of *Staphylococcus epidermidis* and also lacked neutrophilic inflammation. The similar clinical course and shared histopathologic features between our case and NEH argue that neutrophils are a secondary response to a toxic effect rather than the primary effector in NEH. Neutrophil-poor variants of hidradenitis, both infectious and due to drug toxicity, should be considered diagnostically in neutropenic patients.

*Keywords:* chemotherapy, hidradenitis, neutropenia, neutrophilic eccrine hidradenitis, toxic erythema

Yeh I, George E, Fleckman P. Eccrine hidradenitis sine neutrophils: a toxic response to chemotherapy.
J Cutan Pathol 2011; 38: 905–910. © 2011 John Wiley & Sons A/S.

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Accepted for publication July 7, 2011

## Neutrophilic eccrine hidradenitis to acetaminophen

*Editor*

Neutrophilic eccrine hidradenitis (NEH) is a rare transient complication that occurs in leukaemic patients receiving chemotherapy.[1] We report a new case of NEH to acetaminophen in a patient with untreated chronic lymphocytic leukaemia (CLL).

A 68-year-old woman was admitted to hospital for non-controlled diabetes. Her past medical history consisted of untreated CLL, type 2 diabetes, hypertension, atrial fibrillation and hyperlipidaemia. She was treated since several years with glibenclamide 5 mg three tabs/day, amlodipine

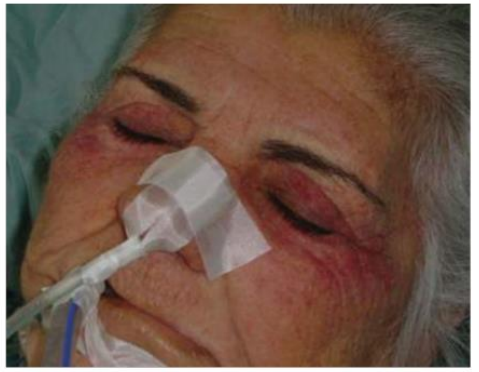


fig. 1 On day 7: Patient intubated with periorbital violaceous patches.



JEADV 2006, 20, 1328–1399 © 2006 European Academy of Dermatology and Venereology

An official Publication of the Indian Pharmacological Society
Indian Journal of Pharmacology



Indian J Pharmacol. 2013 Jan-Feb; 45(1): 91–92.
doi: 10.4103/0253-7613.106445
PMCID: PMC3608306

## Neutrophilic eccrine hidradenitis: A new culprit-carbamazepine

Prakash Bhanu, K. V. Santosh,[1] Sruthi Gondi, K. G. Manjunath, S. C. Rajendaran, and Niranjana Raj

Author information ▶ Article notes ▶ Copyright and License information ▶

## Neutrophilic eccrine hidradenitis in a patient with Crohn's disease and azathioprine hypersensitivity syndrome

*Editor*

Neutrophilic eccrine hidradenitis (NEH) is an uncommon entity which may lie on the spectrum of neutrophilic dermatosis (ND).[1] Around 10% of patients with Crohn's disease (CD) may present with ND,[2] although NEH has not been described in this context.

## *Neutrophilic Eccrine Hidradenitis*

### *Evidence Implicating Bleomycin as a Causative Agent*

LLAN, MD, ANNE H. KETTLER, MD, MOISE L. LEVY, MD, AND JAIME A. TSCHEN, MD

**r-old girl receiving multiple agent chemotherapy for osteosarcoma was found to have neutrophilic idradenitis (NEH). This dermatosis is marked histopathologically by necrosis of the eccrine s with a neutrophilic infiltrate. Clinically, the presentation is variable and the differential diagnosis ive. Our patient's clinical picture was unique in that she had hyperpigmented plaques instead of nodules or erythematous plaques as described previously. Currently, NEH is felt to be a com- of chemotherapy. The most likely causative agent in our patient was bleomycin. Physicians e aware of this entity and its variable clinical presentation.**

***Cancer* 62:2532–2536, 1988.**

The same reasoning has been used to explain eccrine neutrophilic hidradenitis which is a well-known side effect especially, but not exclusively, of cytotoxic drugs.

# Pattern Analysis of Drug-Induced Skin Diseases

*Hildamari Justiniano, MD, Alma C. Berlingeri-Ramos, MD, and Jorge L. Sánchez, MD*

**Abstract:** Drug eruptions are common adverse reactions to drug therapy and are a frequent reason for consultation in clinical practice. Even though any medication can potentially cause an adverse cutaneous reaction, some drugs are implicated more commonly than others. Histologically, drugs can elicit a variety of inflammatory disease patterns in the skin and panniculus, no pattern being specific for a particular drug. The most common pattern elicited by systemically administered medications is the perivascular pattern. Psoriasiform or granulomatous patterns are rarely caused by medications. The usual histologic patterns of drug eruptions are discussed in this review using the basic patterns of inflammatory diseases. Clinicopathologic correlation is established for relevant patterns. However, the changes of drug-induced skin disease must be made considering clinical presentation, histopathological analysis, and course of the disease.

**Key Words:** drug eruptions, histopathologic pattern

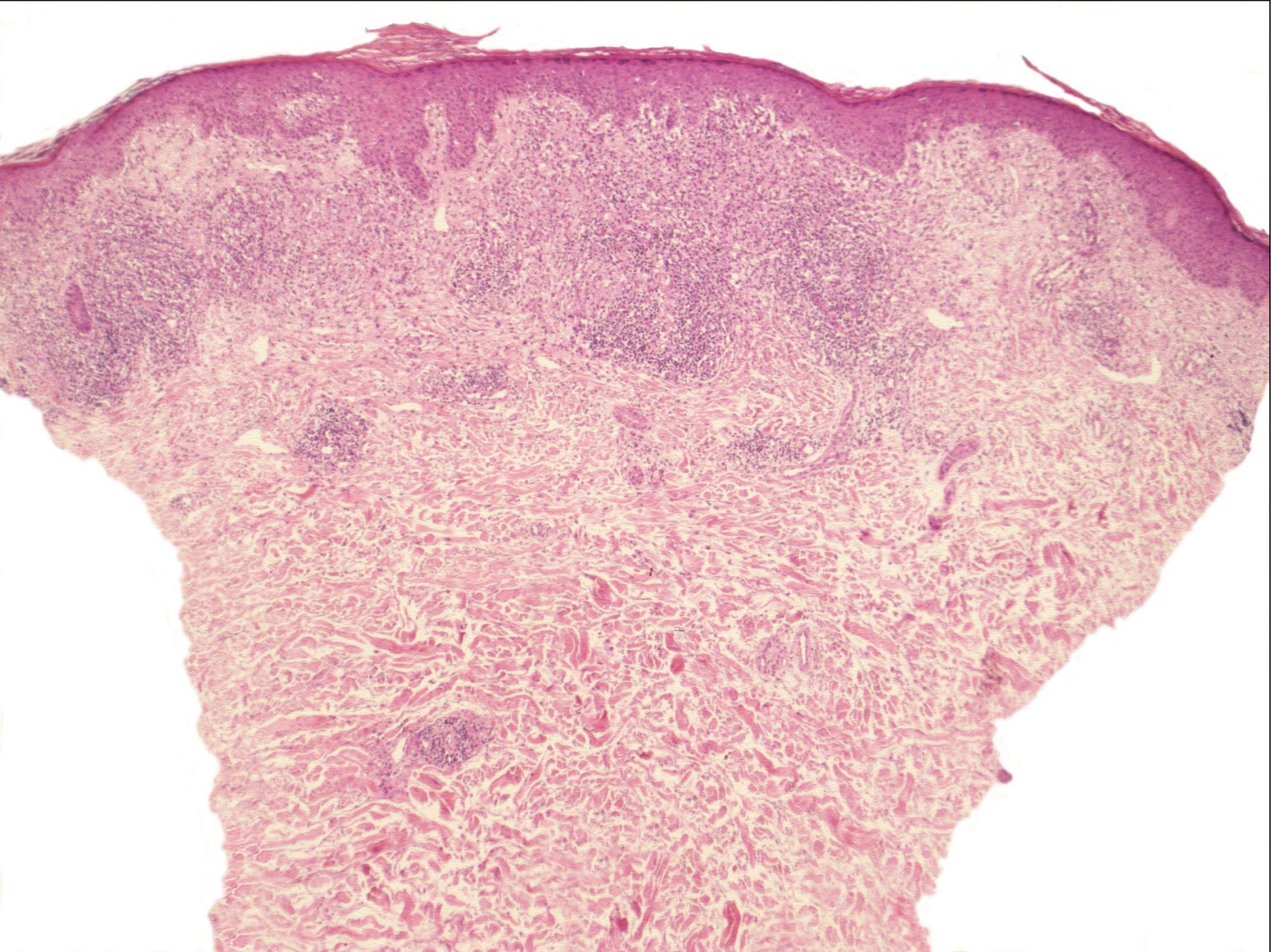
(*Am J Dermatopathol* 2008;30:352–369)

with the number of medications the patient uses. Patients with HIV and other immunosuppressive conditions have an increased incidence of drug reactions. In these cases, immune dysregulation is thought to play an important role.

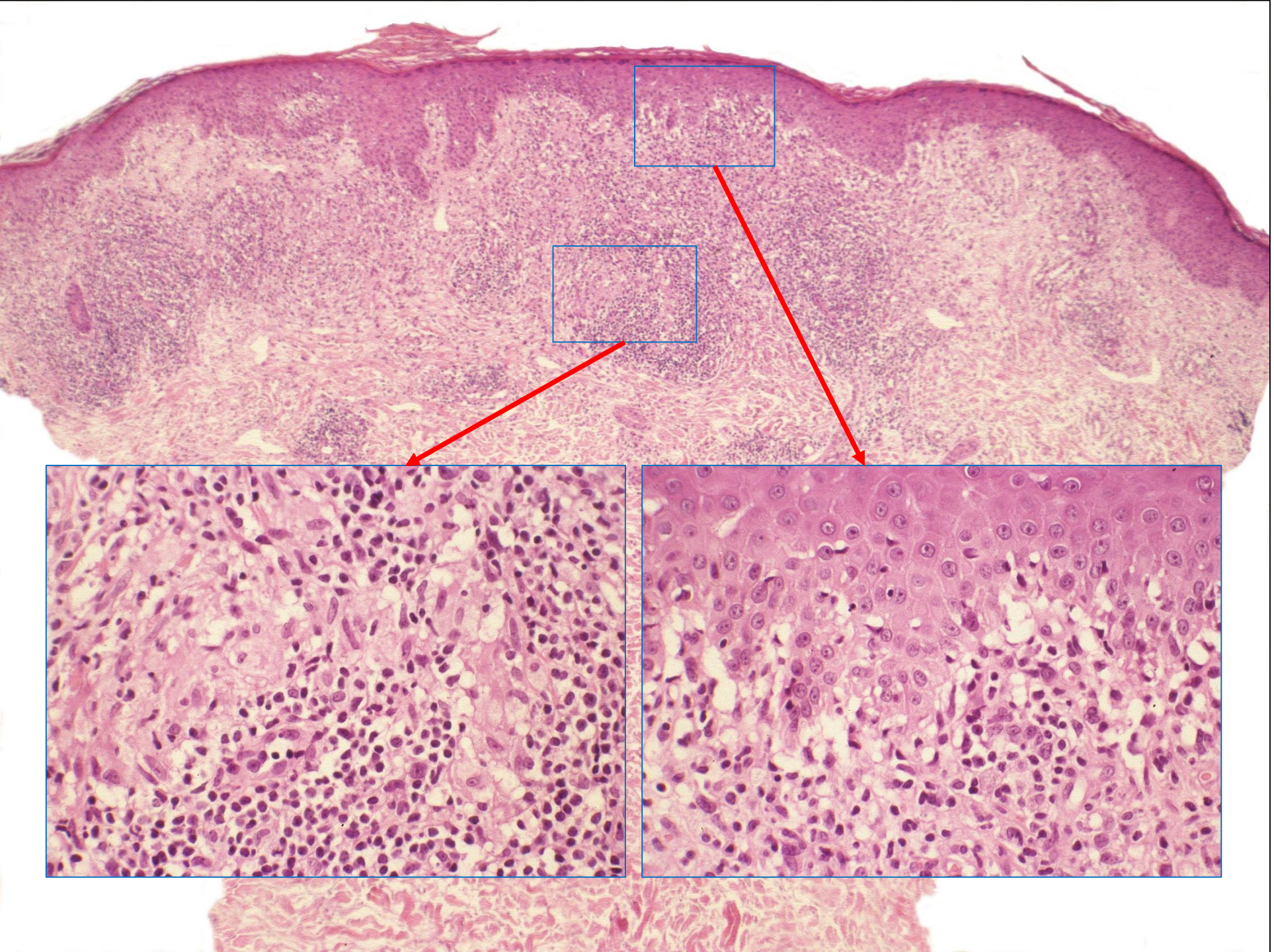
Histologically, drugs can elicit a variety of inflammatory disease patterns in the skin and panniculus; no pattern is specific for a drug eruption. Any inflammatory pattern that does not exactly match the diagnosis for a given disease should promote the thought of a drug eruption. This is especially so in cases where 2 distinct patterns are present in the same tissue section. For example, a specimen with an interface pattern and marked spongiosis should raise the possibility of a drug-induced lesion. The most common histopathologic pattern elicited by systemic drugs is the perivascular pattern. Psoriasiform or granulomatous patterns are rarely caused by medications.

Usual histologic patterns of drug eruptions will be discussed in this review using the basic patterns of inflammatory skin diseases as established by Ackerman et al[2] (Table 1). Clinicopathologic correlation will be established for relevant patterns.

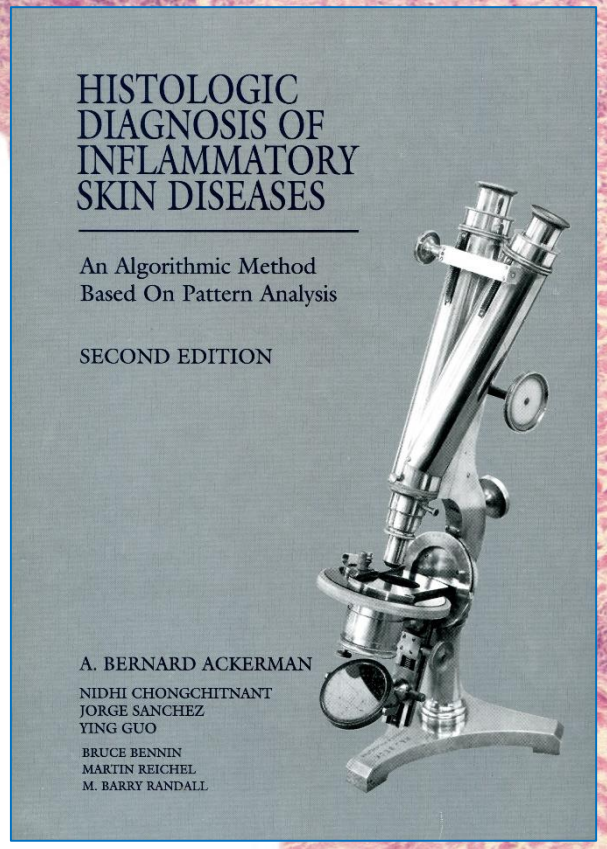
Yet another clue to a drug eruption emphasized by Sánchez and co-workers is presence of *"2 distinct patterns … in the same tissue section."*



This is an example: a psoriasiform dermatitis

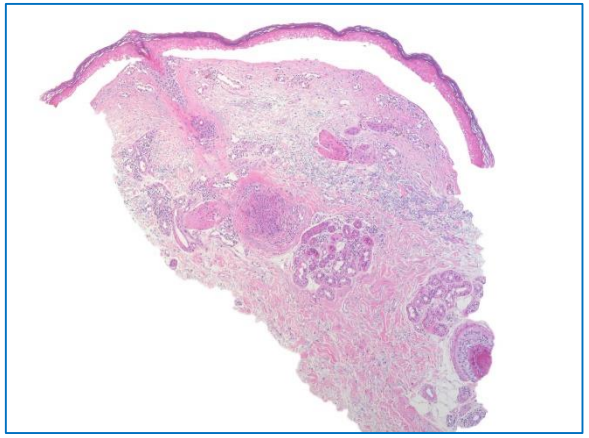
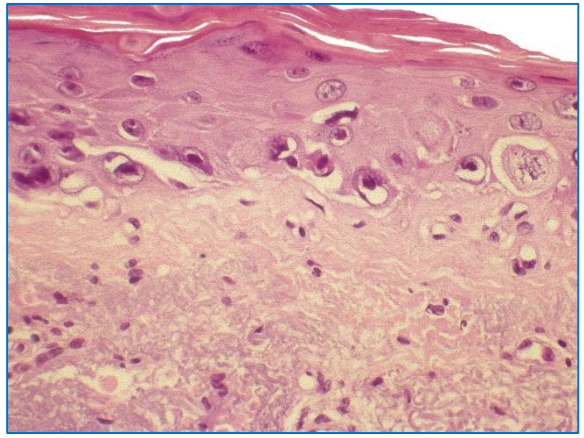
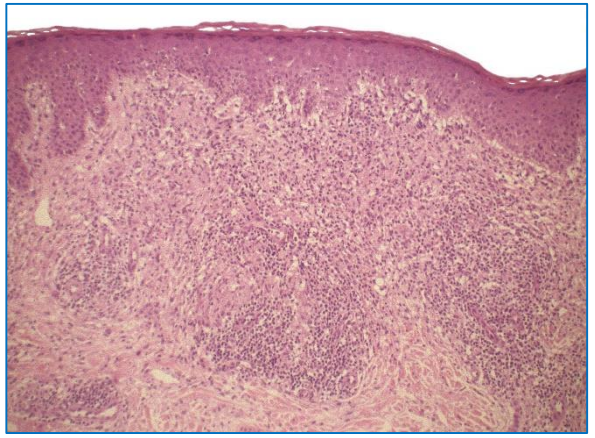
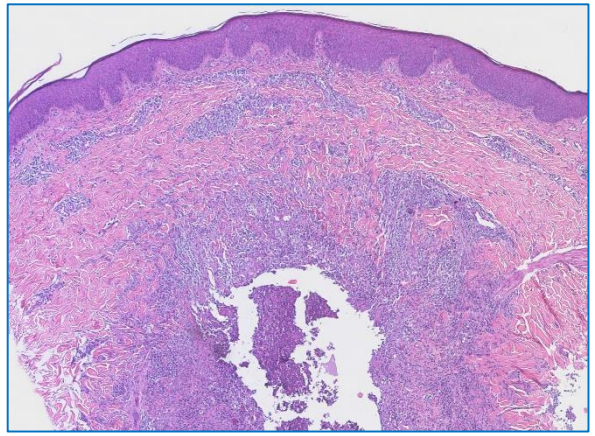
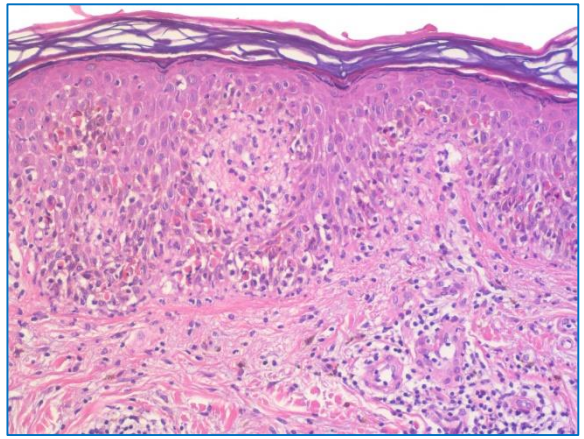
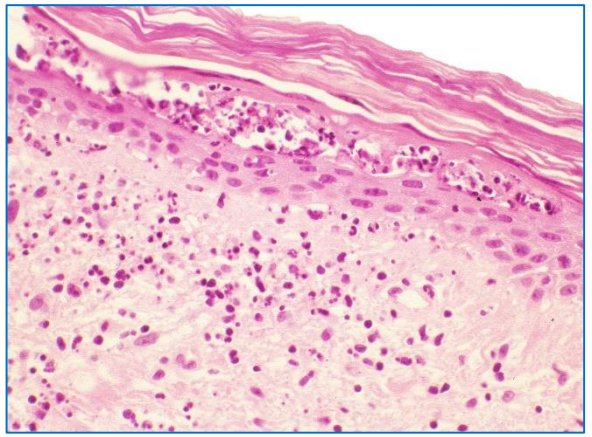
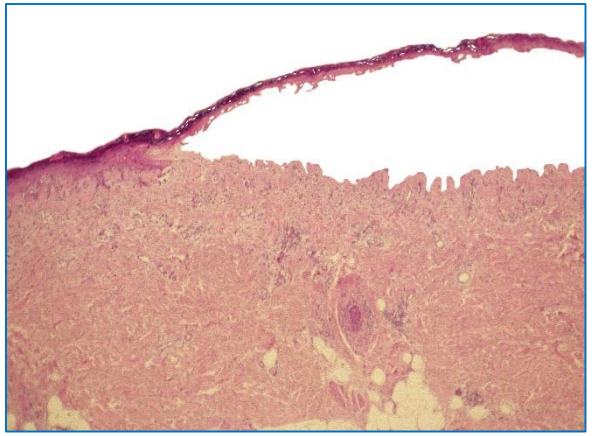
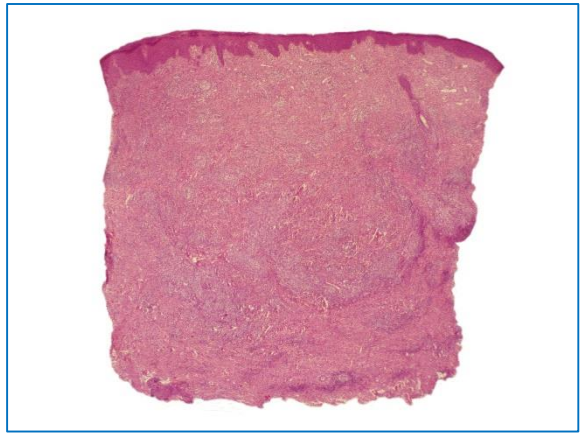
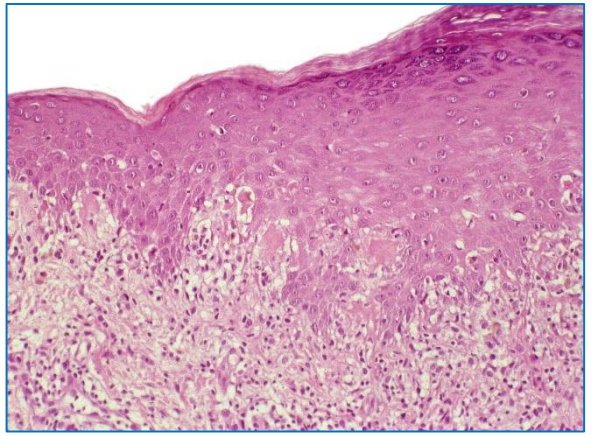


associated with granulomas and vacuolar interface changes. This combination of patterns does not correspond to any well-defined disease,




Any inflammatory process that does not conform to any well-defined disease should prompt suspicion of a drug eruption.

and already Ackerman pointed out, in the second edition of his classic textbook, "Histologic Diagnosis of Inflammatory Skin Diseases," in 1997 that *"any inflammatory process that does not conform to any well-defined disease should prompt suspicion of a drug eruption."*

In sum, even though the histopathologic presentation of drug eruptions is variable and may correspond to *"any of the nine basic patterns of inflammatory diseases in the skin,"* as defined by Ackerman, there are numerous clues that usually allow a diagnosis to be made with confidence, even in the absence of additional clinical information, namely,

| | | |
|---|---|---|
| vacuolar changes at the dermo-epidermal junction | atypical keratocytes and/or lymphocytes | eosinophils and neutrophils in the infiltrate |
| combination of different patterns | accentuation of findings around eccrine structures | changes not conforming to any well-defined disease |
| biopsy from “easy” sites | signs of acuteness | signs of advanced age of patients |

vacuolar changes at the dermoepidermal junction, eosinophils and neutrophils in the infiltrate, signs of acuteness, atypical keratocytes and/or lymphocytes, accentuation of findings around eccrine structures, a combination of different patterns, changes not conforming to any well-defined disease as well as a biopsy from “easy” sites, such as trunk or extremities, rather than palms, soles, face, or scalp, and signs of an advanced age of patients. Consideration of those clues allows differential diagnosis of common patterns of inflammatory skin disease to be performed in rational fashion.

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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



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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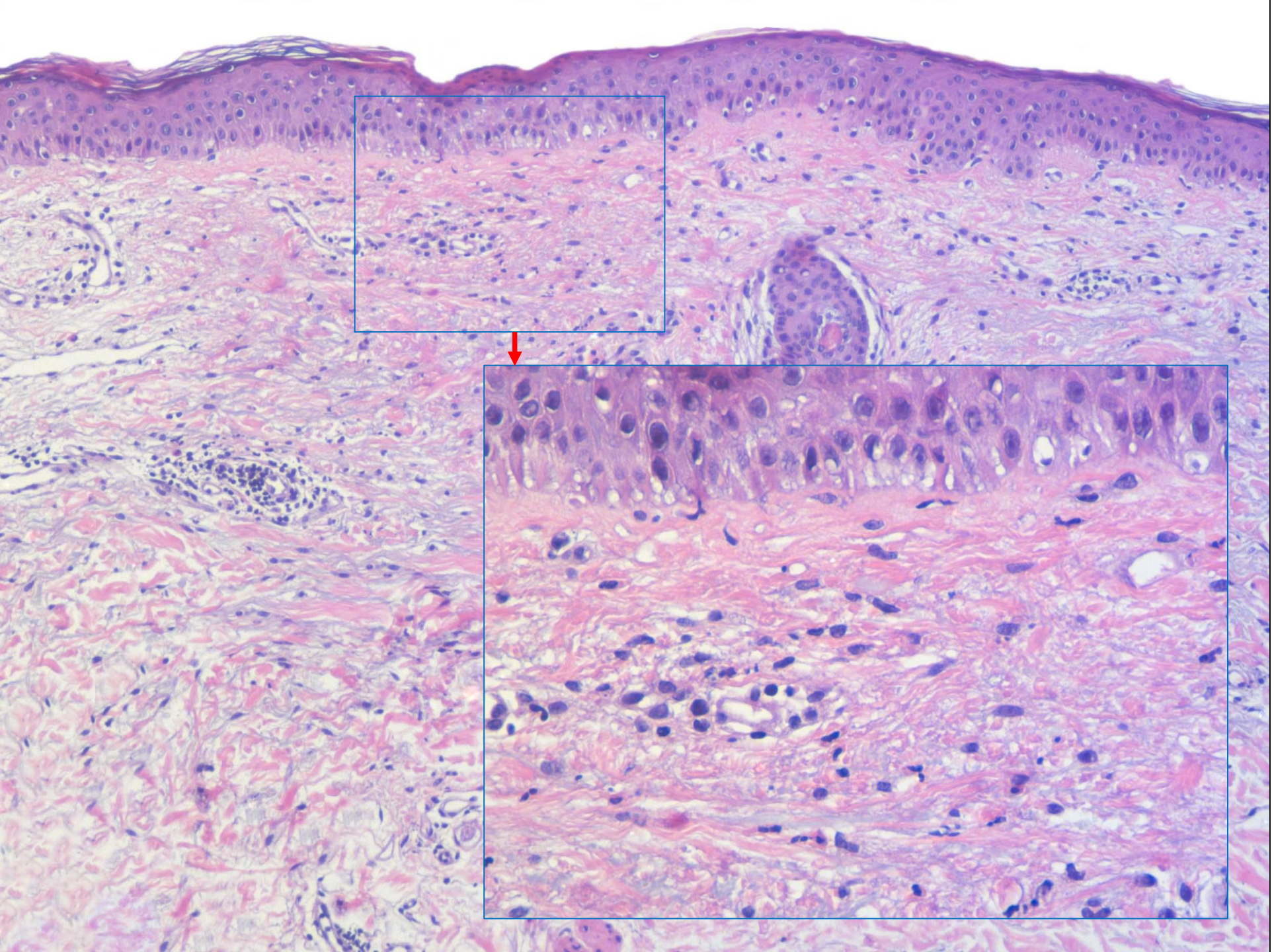
A few years ago, we have studied retrospectively 300 cases submitted as drug eruption to our laboratory, and diagnosed as such histopathologically, in order to get a sense for the relative frequency of different histopathologic patterns and for problems in differential diagnosis.

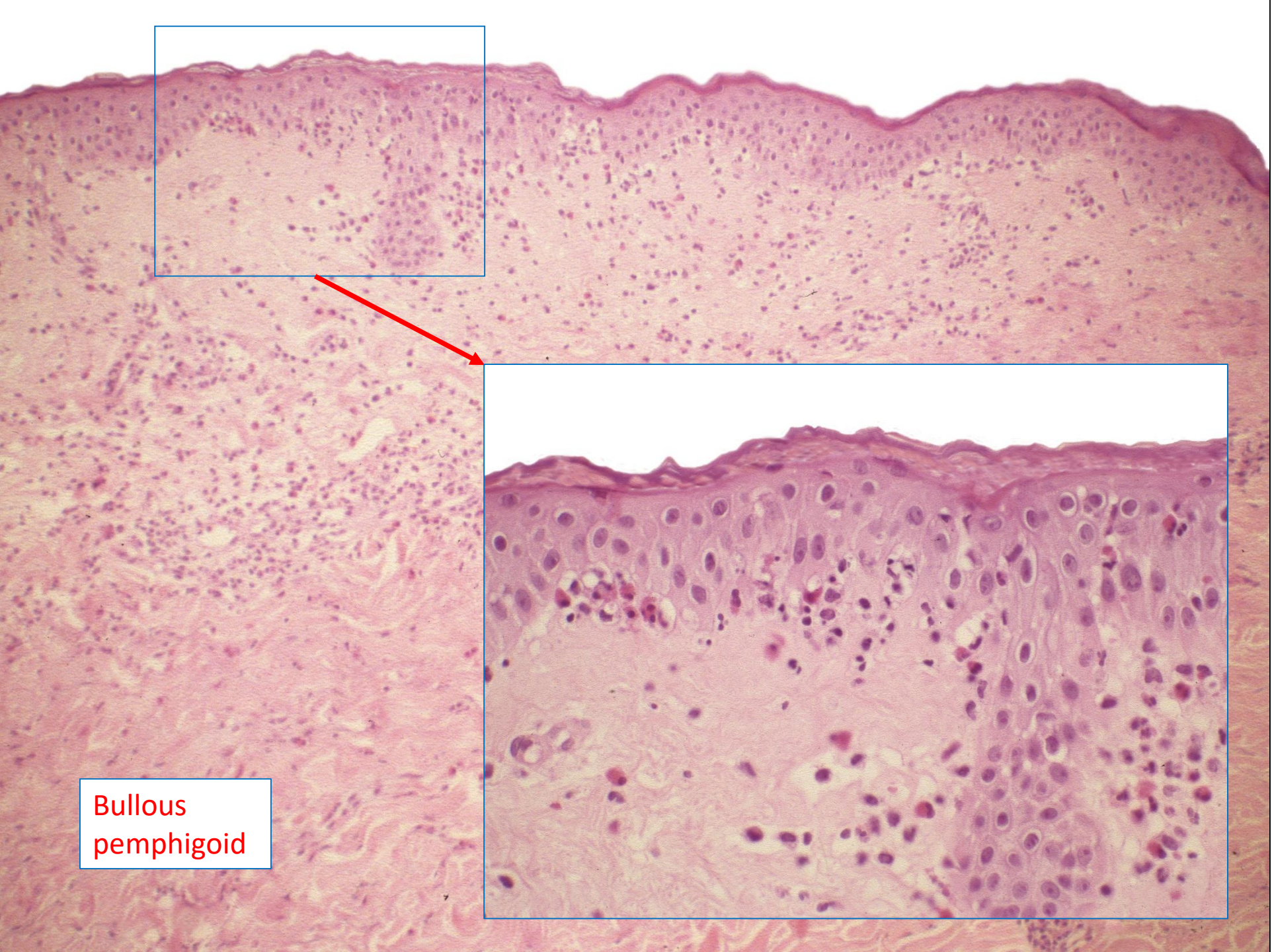
Table 1: Histopathologic findings in 300 cases with the clinical and histopathologic diagnosis of drug eruption

| | Pattern | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Lympho-cytic dermal without epidermal Changes (n=12)* | *Superficial and deep dermal with eosino-phils and neutrophils (n=12)* | *Severe vacuolar interface dermatitis (n=38)* | *Mild vacuolar interface dermatitis (n=83)* | *Lichenoid dermatitis (n=36)* | *Lichenoid pso-riasiform dermatitis (n=18)* | *Spongiotic dermatitis (n=62)* | *Pustular dermatitis (n=19)* | *Subepi-dermal bullous dermatitis (n=6)* | *Granulo-matous dermatitis (n=12)* | *Leukocy-toklastic 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 |

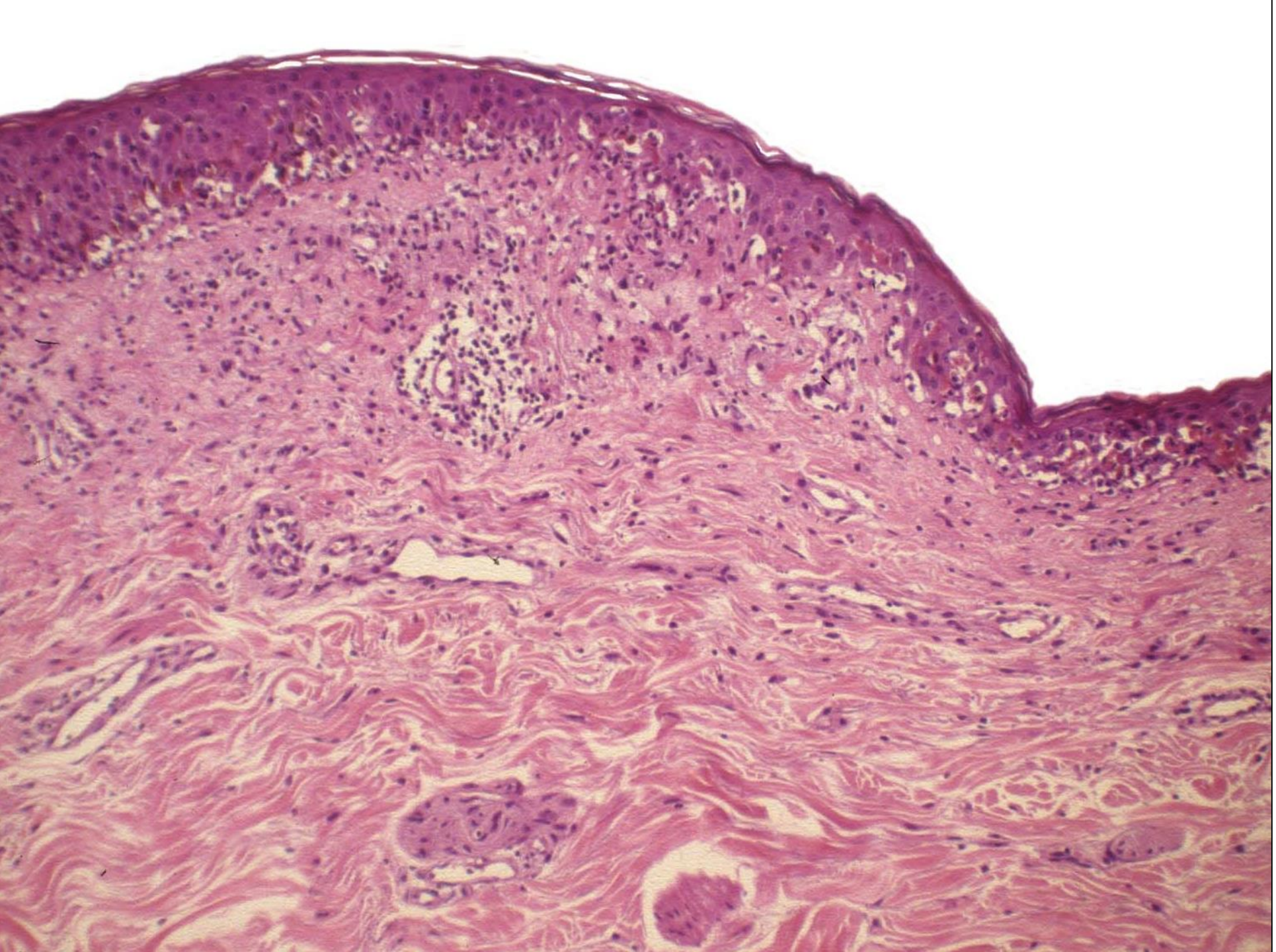
The most common pattern by far, accounting for 83 of 300 cases, was a mild vacuolar interface dermatitis.



As already noted, that pattern, in association with a sparse infiltrate of eosinophils and neutrophils, is strongly suggestive of a drug eruption.

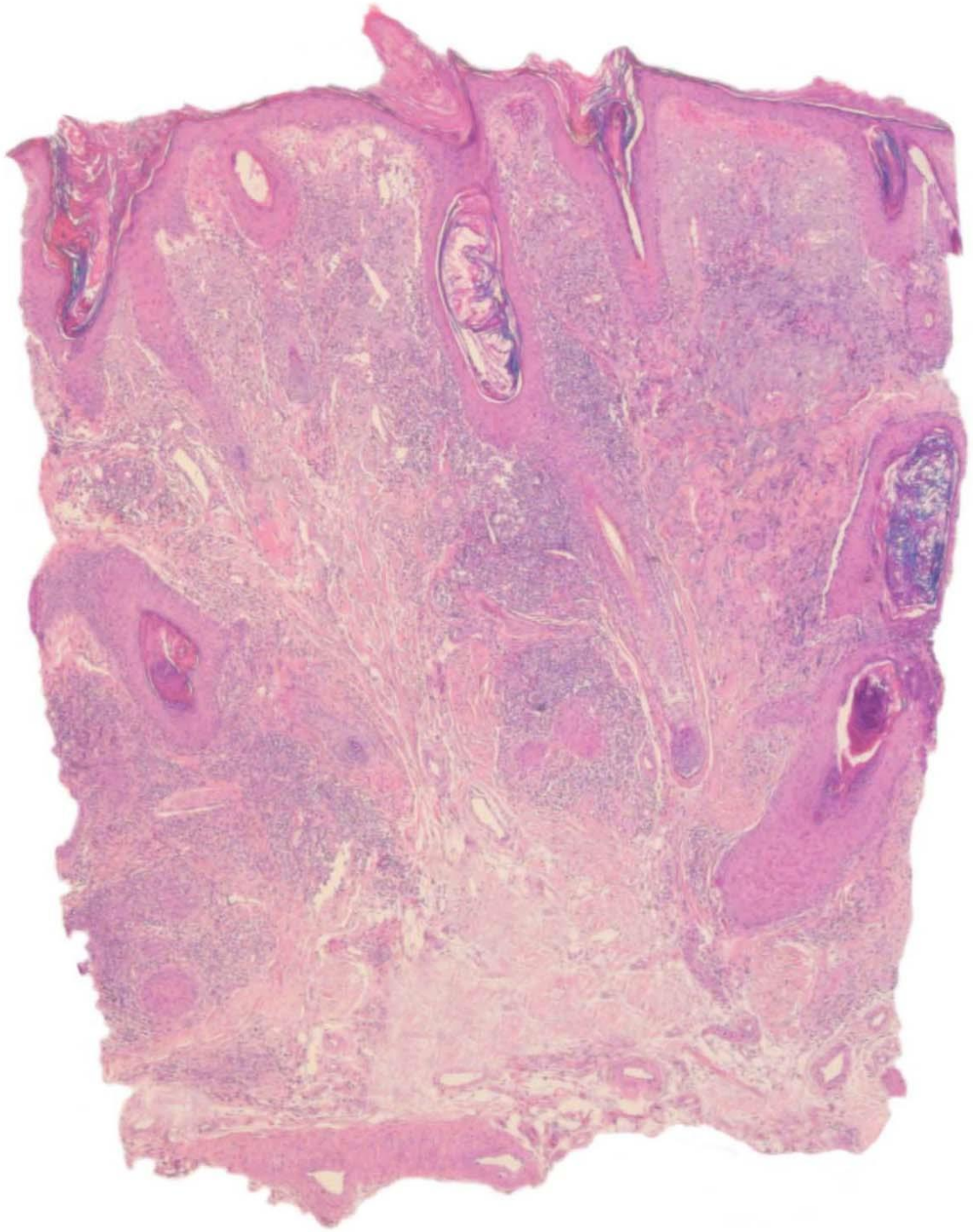



One differential diagnosis is bullous pemphigoid that shows the same type of infiltrate and that may be associated with slight interface changes. A finding in favour of bullous pemphigoid and militating against a drug eruption is presence of eosinophils at the dermo-epidermal junction.



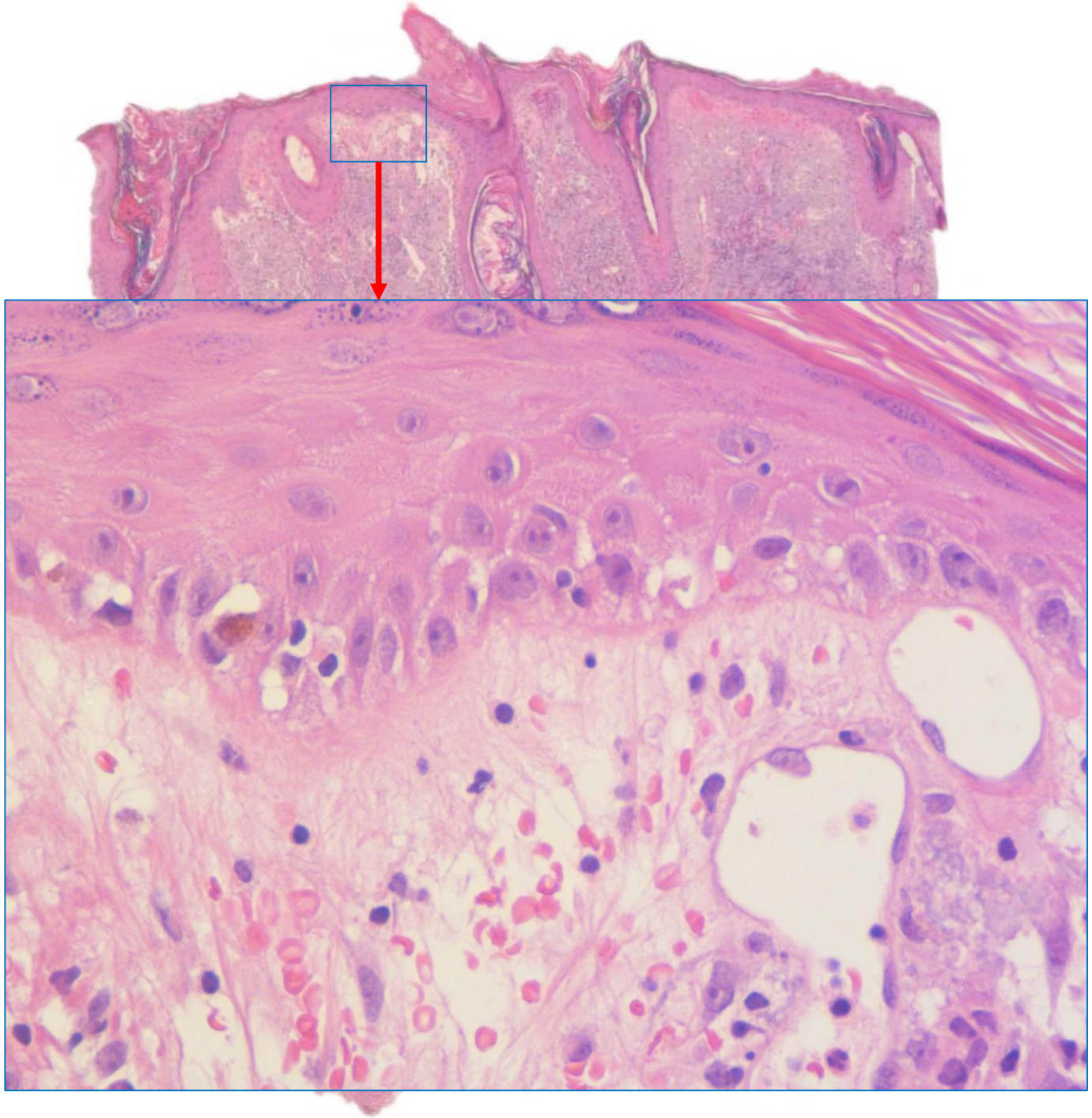
Vice versa, more pronounced interface changes with presence of necrotic keratocytes virtually rule out bullous pemphigoid.

If a drug eruption shows a vacuolar interface dermatitis but an infiltrate composed of lymphocytes only, the differential diagnosis is more difficult.



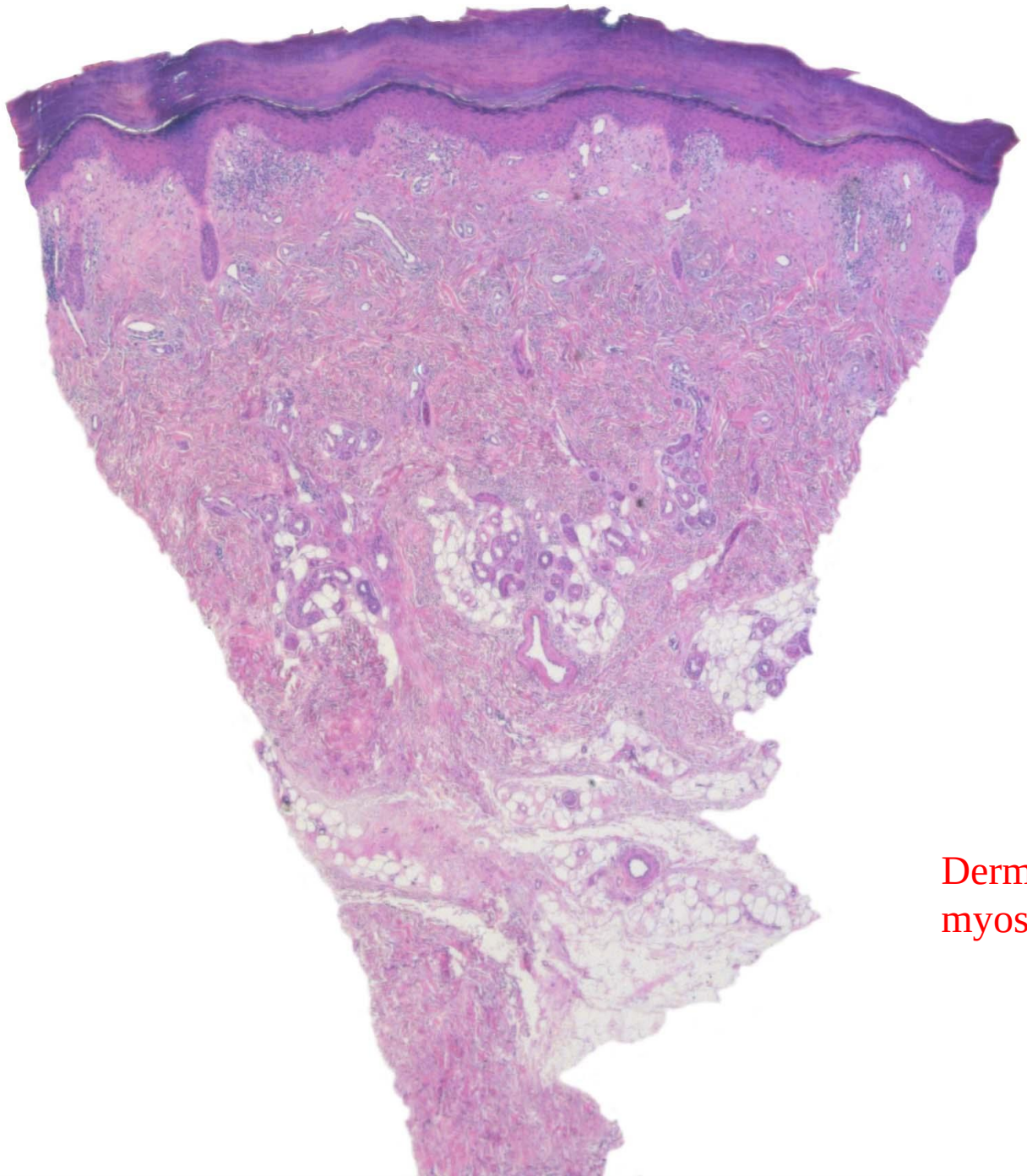
Lupus erythematosus

One possibility is lupus erythematosus. Of course, distinction is easy if LE shows a dense, bottom-heavy perifollicular infiltrate, follicular hyperkeratosis, mucin in the reticular dermis, folliculotropism of the infiltrate, and a thickened basement membrane, none of which are features of a drug eruption. However, those changes may not be present and, especially in shave biopsies, distinction may be difficult. One clue, in the absence of any additional information, is the wrong anatomic site. This specimen comes from the face which is practically never biopsied in drug eruptions.



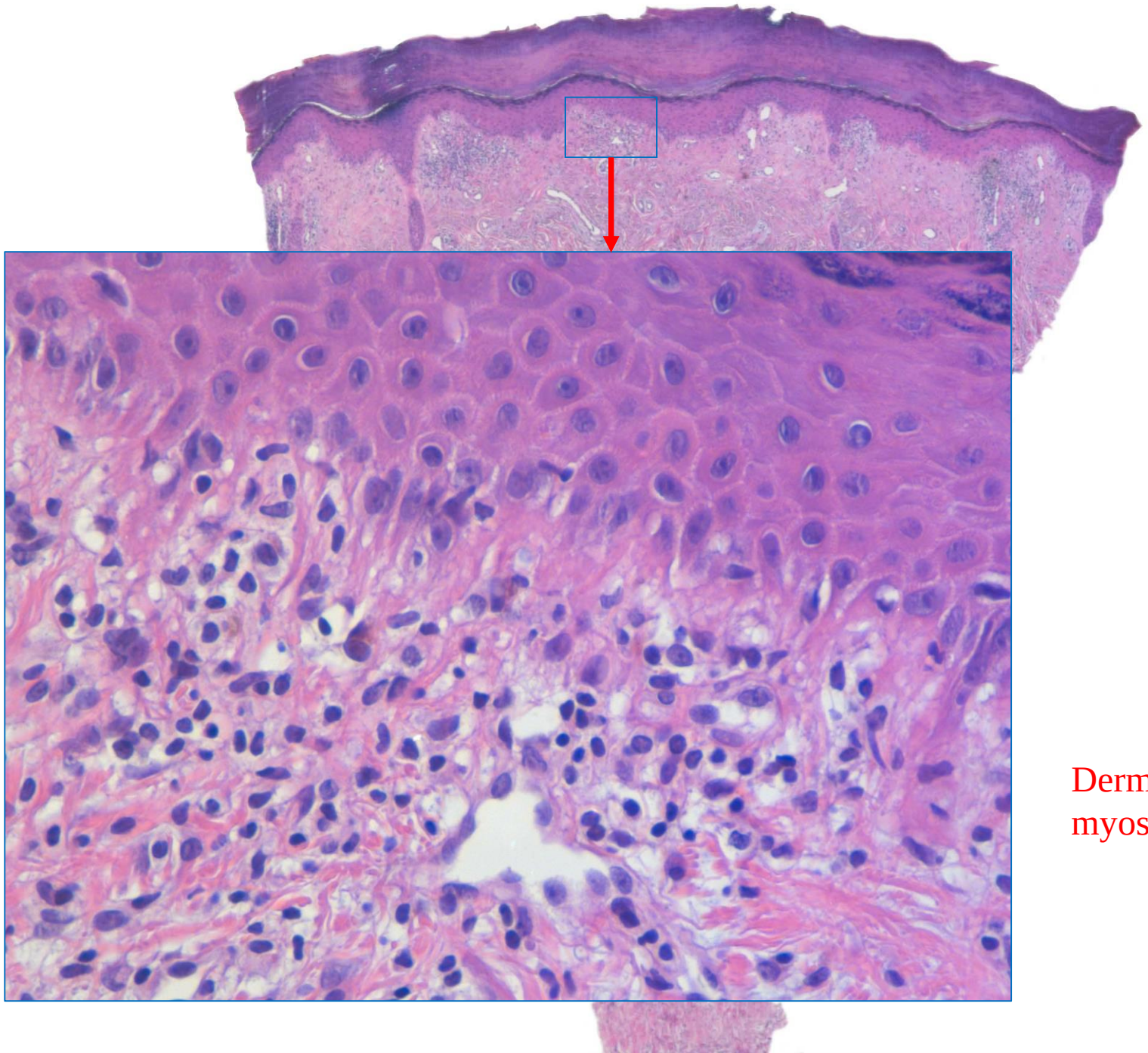
Lupus erythematosus

Another finding usually seen even in subtle manifestations of LE is smudging of the dermo-epidermal junction that makes it difficult to perceive where the epidermis ends and the dermis begins.



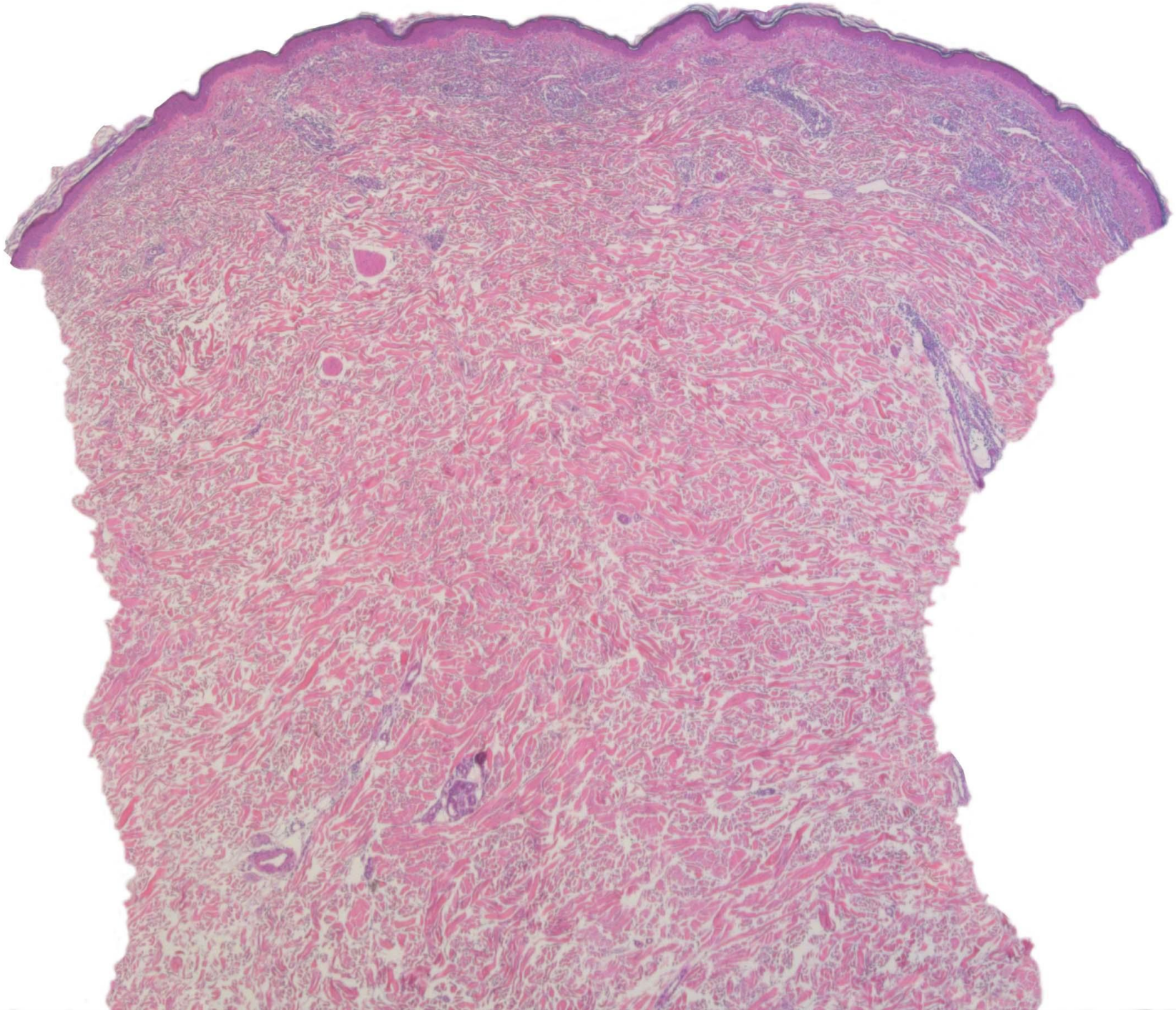
Dermato-
myositis

The same applies to dermatomyositis. Once again, this is the wrong anatomic site, a specimen from the hand. Moreover, the infiltrate is too focal for a drug eruption in which it is usually more evenly distributed.

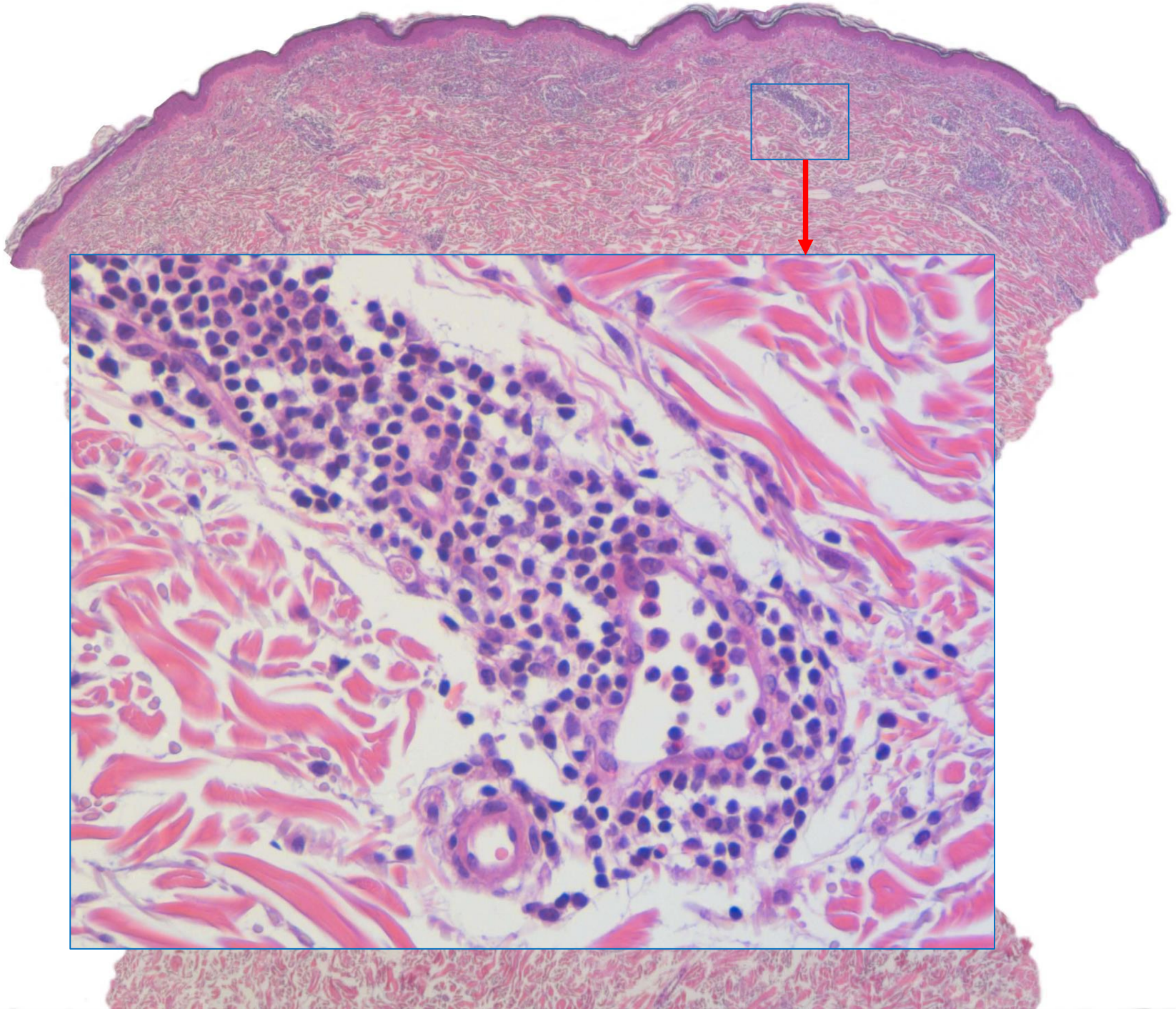


Dermato-
myositis

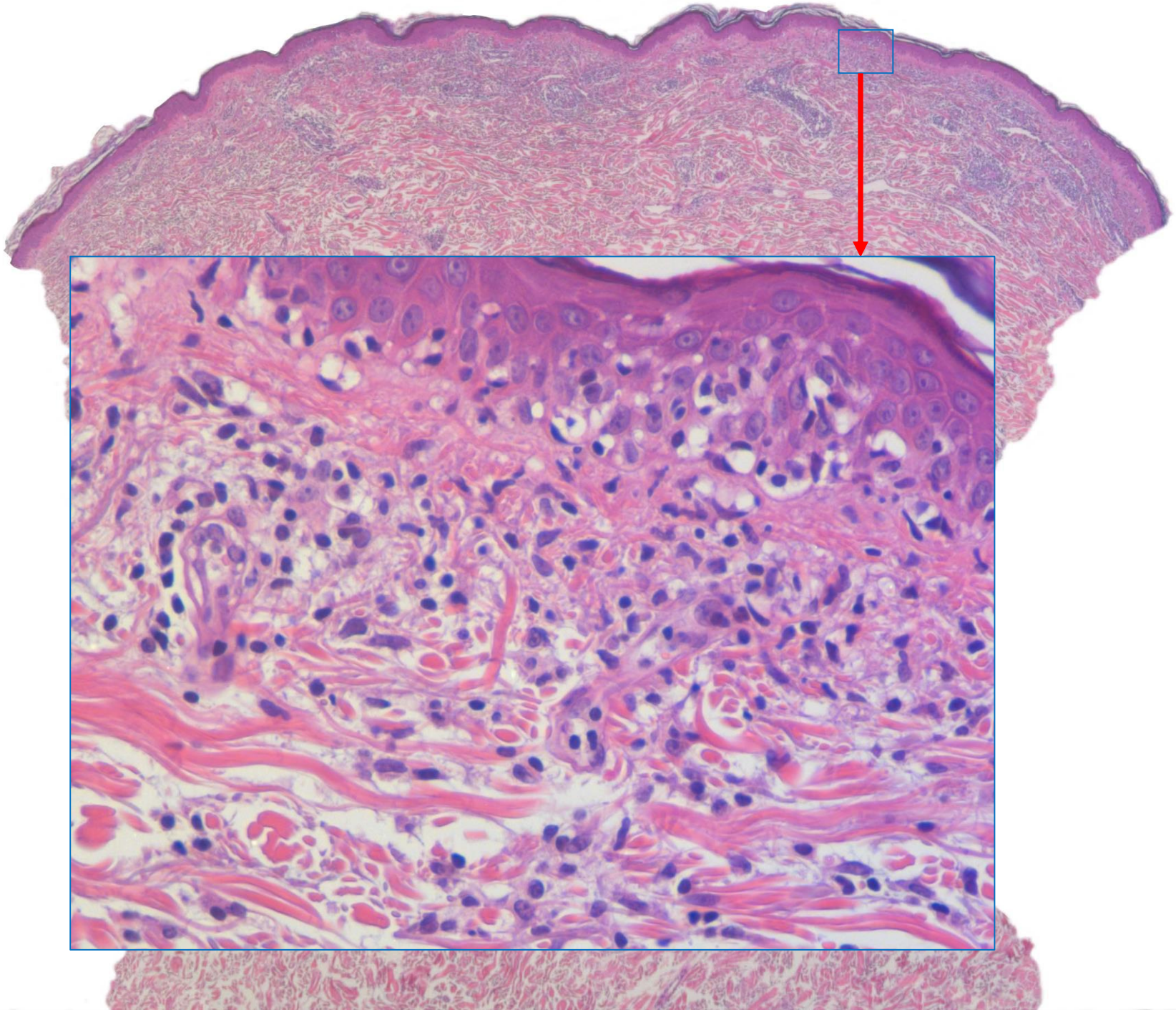
Last, there is again smudging of the dermo-epidermal junction. That finding militates against a drug eruption, but it often only focal and one must look for it.



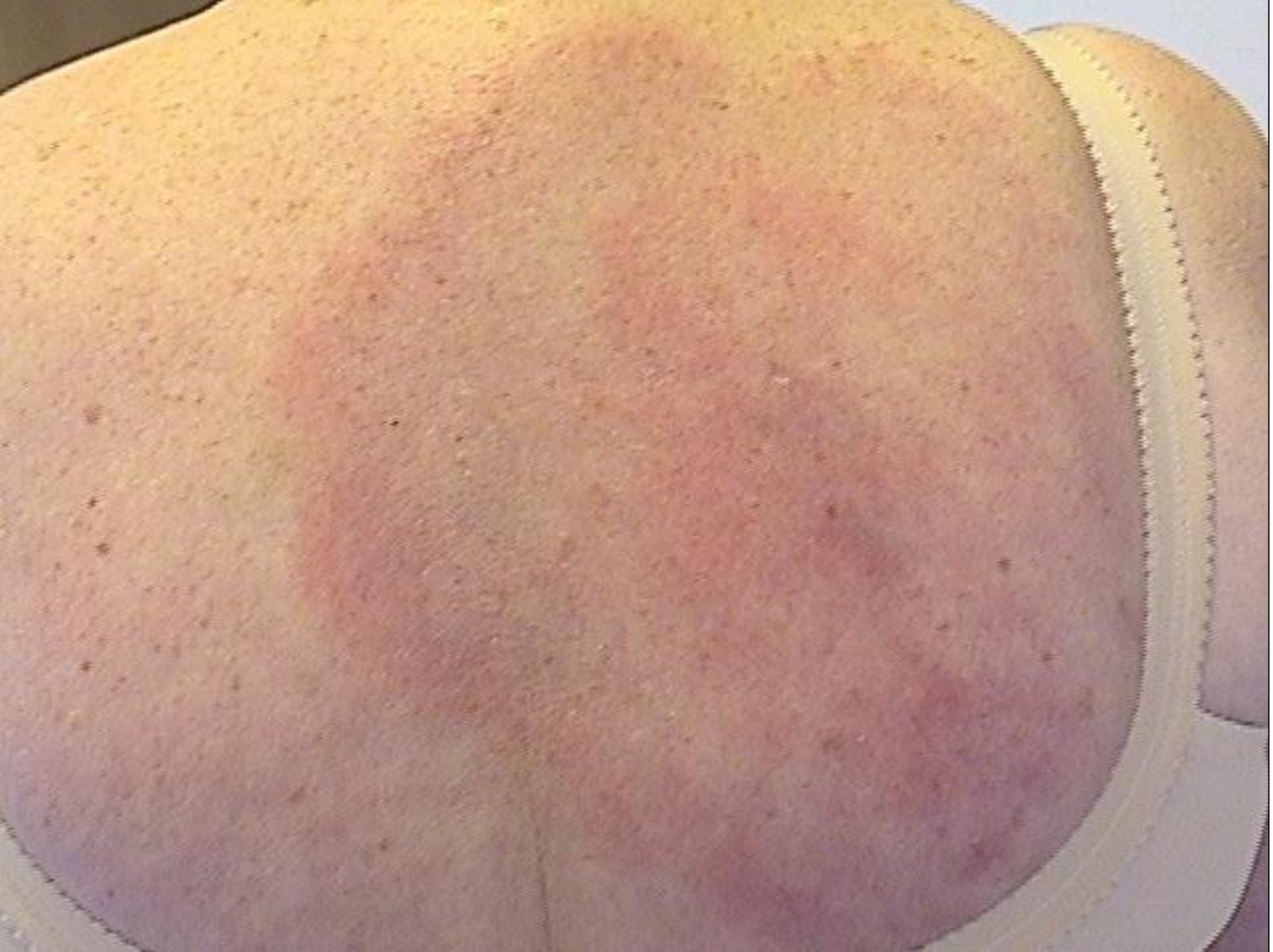
Especially in the absence of eosinophils and neutrophils, one must take care not to overcall drug eruptions which happened to me in this case: there is a superficial and mid dermal perivascular infiltrate of lymphocytes



associated with ectatic venules in the upper dermis, some of which house numerous neutrophils in their lumen,



And subtle vacuolar interface changes. That combination of findings prompted me to suggest a drug eruption until I received a clinical picture.



It was a large solitary, annular lesion on the back, a case of erythema migrans, and the diagnosis was confirmed by PCR studies revealing DNA of borrelia in the tissue.

J Cutan Pathol 2016: 43: 32–40
doi: 10.1111/cup.12620
John Wiley & Sons. Printed in Singapore



Journal of
Cutaneous Pathology

# The many masks of cutaneous Lyme disease

Early cutaneous Lyme disease, erythema migrans, may show different histopathologic patterns. The intent of this case series is to raise awareness of these findings to prevent misdiagnosis and keep this entity in the differential. Erythema migrans develops after a tick bite and subsequent infection with the spirochete, *Borrelia burgdorferi*. It most commonly manifests as a solitary, annular lesion with a bull's-eye appearance. Classic histopathologic findings include superficial and deep perivascular and interstitial lymphocytic infiltrates mixed with plasma cells and eosinophils. We identified and reviewed eight cases of early erythema migrans. Each patient had confirmed *B. burgdorferi* IgM seropositivity and IgG seronegativity. Histopathologic evaluation of these biopsies reveals a diversity of patterns. Seven of eight cases show sparse to mild perivascular and interstitial mixed infiltrate of variable amount of lymphocytes, eosinophils, neutrophils and plasma cells, with only one case showing a dense inflammatory infiltrate. Epidermal changes such as spongiosis and interface change are seen in some cases. Additionally, perineural lymphocytic infiltrate is seen in one case, periadnexal infiltrate in four cases and pigment incontinence in one case. Based on variable histopathologic findings, it is important to consider erythema migrans in the differential diagnosis for prompt diagnosis and treatment.

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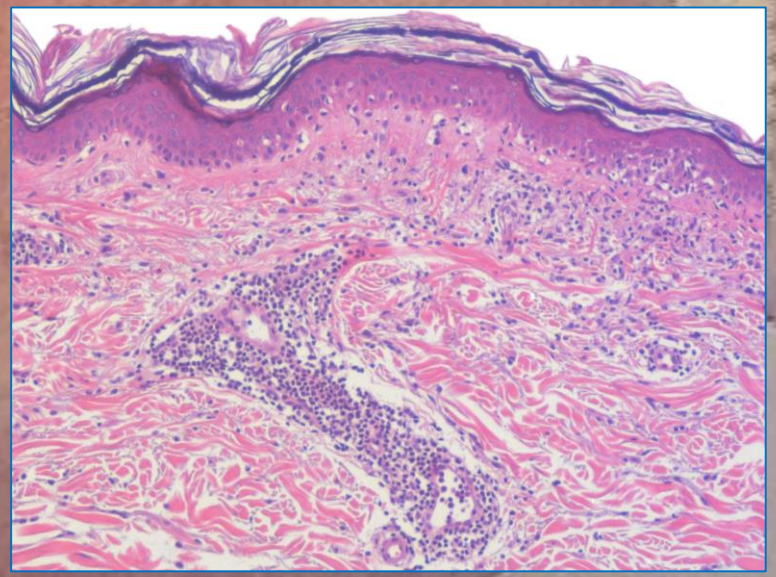


One has to beware of “the many masks of cutaneous Lyme disease,” one of which is a subtle vacuolar interface dermatitis.

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

| | Pattern | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Lympho-cytic dermal without epidermal Changes (n=12)* | *Superficial and deep dermal with eosino-phils and neutrophils (n=12)* | *Severe vacuolar interface dermatitis (n=38)* | *Mild vacuolar interface dermatitis (n=83)* | *Lichenoid dermatitis (n=36)* | *Lichenoid pso-riasiform dermatitis (n=18)* | *Spongiotic dermatitis (n=62)* | *Pustular dermatitis (n=19)* | *Subepi-dermal bullous dermatitis (n=6)* | *Granulo-matous dermatitis (n=12)* | *Leukocy-toklastic vasculitis (n=2)* |
| Superficial | 10 | 0 | 28 | 55 | | | | | | | |
| Superficial and deep | 2 | 12 | 10 | 28 | | | | | | | |
| Perivascular | 11 | 0 | 5 | 12 | | | | | | | |
| Interstitial | 1 | 12 | 33 | 71 | | | | | | | |
| Vacuolar | | | | | | | | | | | |
| + | 0 | 0 | 0 | 83 | | | | | | | |
| ++ | 0 | 0 | 38 | 0 | | | | | | | |
| Spongiosis | | | | | | | | | | | |
| + | 0 | 0 | 38 | 44 | | | | | | | |
| ++ | 0 | 0 | 0 | 0 | | | | | | | |
| Necrotic keratinocytes | | | | | | | | | | | |
| + | 0 | 0 | 4 | 62 | | | | | | | |
| ++ | 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 |

- erythema multiforme (post-herpetic)
- lupus erythematosus
- dermatomyositis
- graft-versus-host disease
- phototoxic dermatitis
- viral exanthems
- bullous pemphigoid
- secondary syphilis
- borreliosis
- vitiligo

…

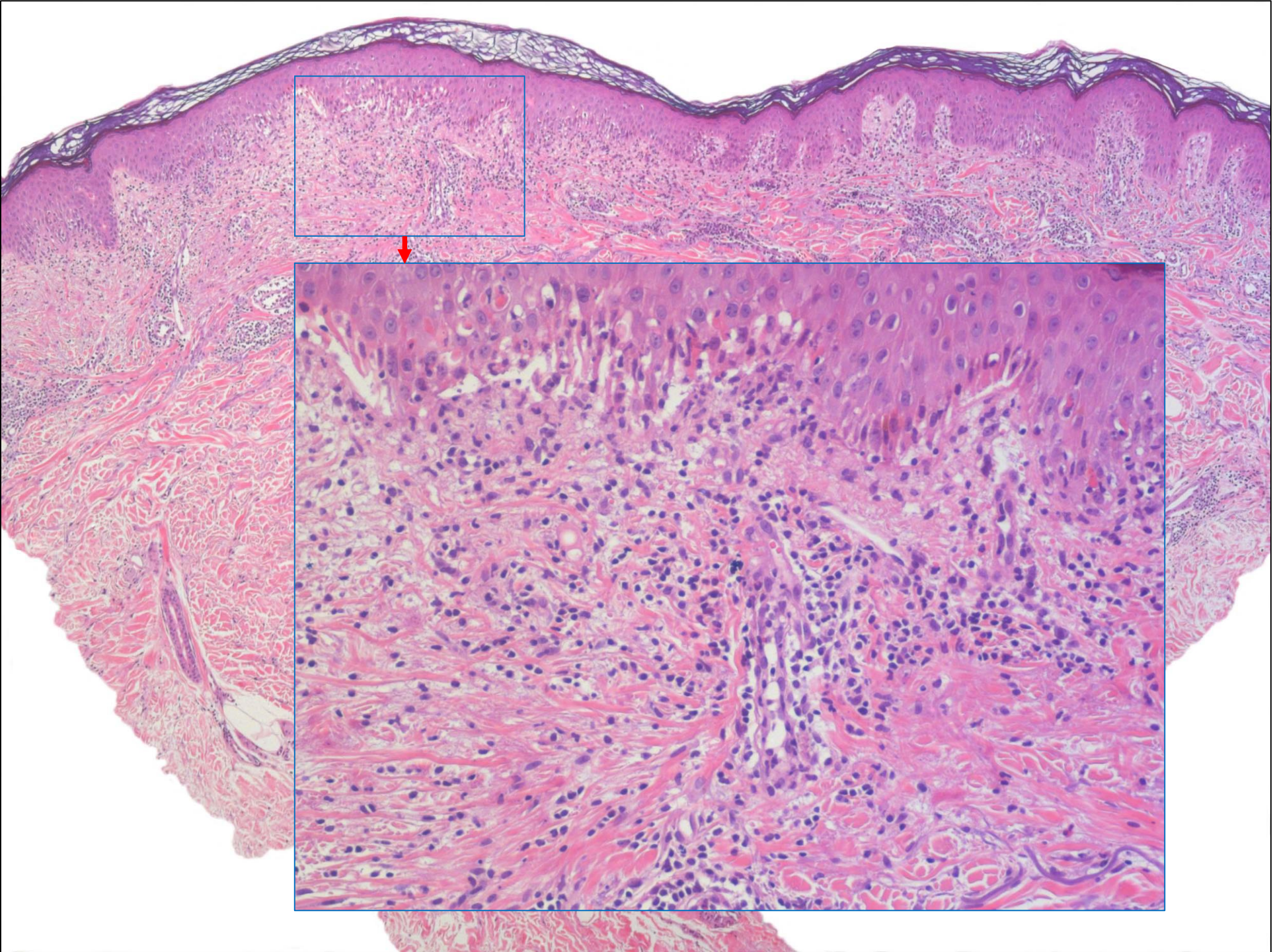
In sum, many diseases may show a mild vacuolar interface dermatitis and need to be considered in the differential diagnosis of drug eruptions. Especially in the absence of eosinophils and neutrophils, clinico-pathologic correlation is essential, and one may have to discuss the entire list of differential diagnoses with the referring physician.

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

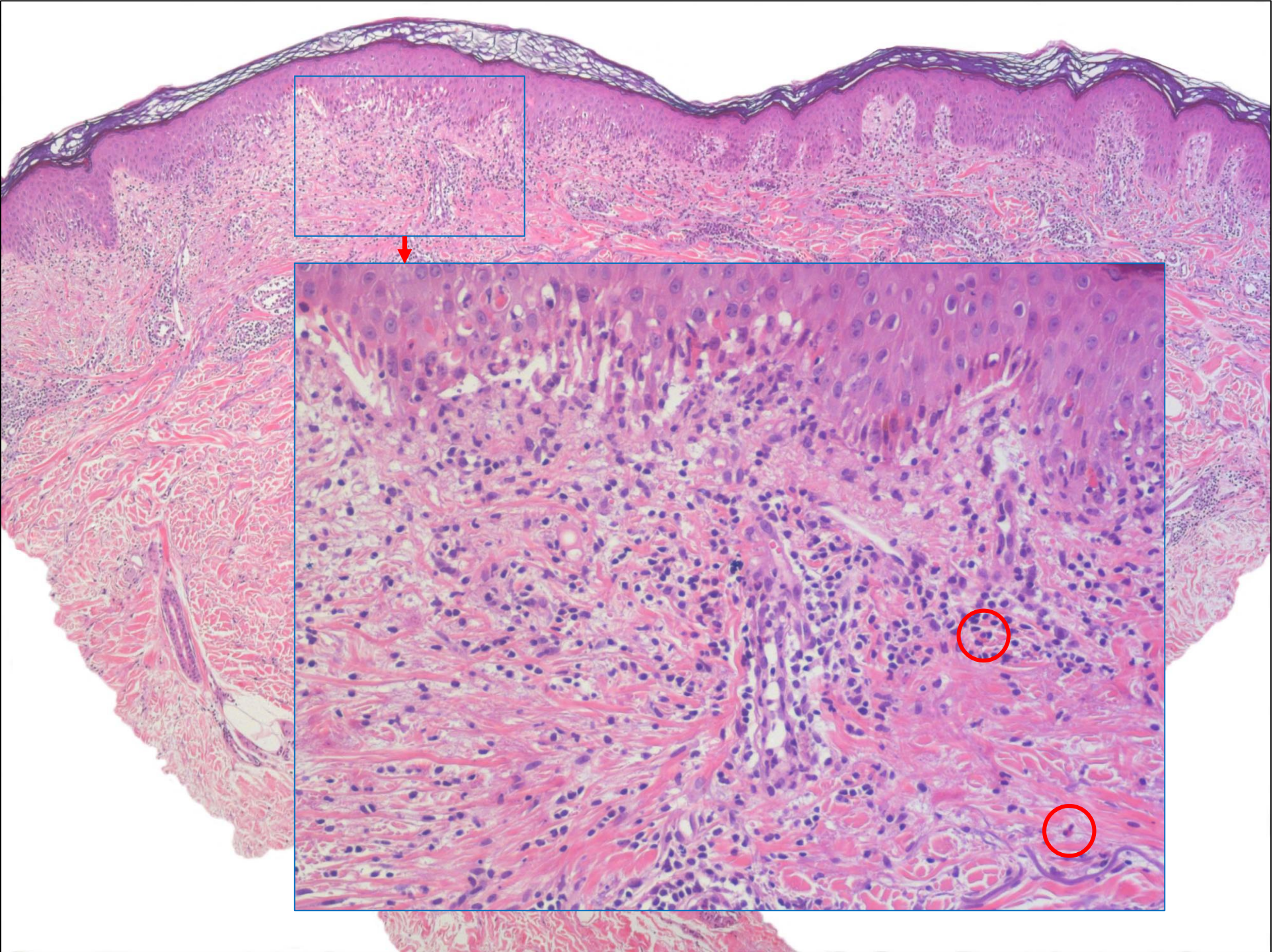
| | Pattern | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Lympho-cytic dermal without epidermal Changes (n=12)* | *Superficial and deep dermal with eosino-phils and neutrophils (n=12)* | *Severe vacuolar interface dermatitis (n=38)* | *Mild vacuolar interface dermatitis (n=83)* | *Lichenoid dermatitis (n=36)* | *Lichenoid pso-riasiform dermatitis (n=18)* | *Spongiotic dermatitis (n=62)* | *Pustular dermatitis (n=19)* | *Subepi-dermal bullous dermatitis (n=6)* | *Granulo-matous dermatitis (n=12)* | *Leukocy-toklastic vasculitis (n=2)* |
| Superficial | 10 | 0 | 28 | 55 | | | | | | | |
| Superficial and deep | 2 | 12 | 10 | 28 | | | | | | | |
| Perivascular | 11 | 0 | 5 | 12 | | | | | | | |
| Interstitial | 1 | 12 | 33 | 71 | | | | | | | |
| Vacuolar | | | | | | | | | | | |
| + | 0 | 0 | 0 | 83 | | | | | | | |
| ++ | 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 |

- erythema multiforme (post-herpetic)
- lupus erythematosus
- dermatomyositis
- graft-versus-host disease
- phototoxic dermatitis

That list shortens considerably if interface changes are more severe and associated with numerous necrotic keratocytes.



The most important differential diagnosis is erythema multiforme due to herpes virus infections or other non-drug related causes. The epidermal changes are indistinguishable from drug-induced cases, often with many necrotic keratocytes in all reaches of the epidermis, but the infiltrate usually consists of lymphocytes only.



A few eosinophils are not decisive, but eosinophils in number are strongly suggestive of a drug eruption. In this case, there are several eosinophils

J Cutan Pathol 1997: 24: 235–240
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Journal of Cutaneous Pathology
ISSN 0303-6987

## Acrosyringeal concentration of necrotic keratinocytes in erythema multiforme: a clue to drug etiology

### Clinicopathologic review of 29 cases

Erythema multiforme (EM) is caused by various insults, frequently an infectious agent or a drug. It is current practice that histologic identification of the precipitating factor is not possible. We have observed a pattern of acrosyringeal concentration of keratinocyte necrosis in certain cases of EM and retrospec-

**Mona Zohdi-Mofid[1] and Thomas D. Horn[2]**

[1]The Johns Hopkins University School of Medicine, and [2]Departments of Dermatology and Pathology, The Johns Hopkins University School of Medicine

and another *"clue to drug etiology"* emphasized by Horn and co-workers, namely *"acrosyringeal concentration of necrotic keratinocytes."* In our study of 300 cases, we found such accentuation in only nine of 40 cases with severe vacuolar interface changes but, when present, that finding may be a helpful clue.

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

| | Pattern | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Lympho-cytic dermal without epidermal Changes (n=12)* | *Superficial and deep dermal with eosino-phils and neutrophils (n=12)* | *Severe vacuolar interface dermatitis (n=38)* | *Mild vacuolar interface dermatitis (n=83)* | *Lichenoid dermatitis (n=36)* | *Lichenoid pso-riasiform dermatitis (n=18)* | *Spongiotic dermatitis (n=62)* | *Pustular dermatitis (n=19)* | *Subepi-dermal bullous dermatitis (n=6)* | *Granulo-matous dermatitis (n=12)* | *Leukocy-toklastic vasculitis (n=2)* |
| Superficial | 10 | 0 | 28 | 55 | 26 | | | | | | |
| Superficial and deep | 2 | 12 | 10 | 28 | 10 | | | | | | |
| Perivascular | 11 | 0 | 5 | 12 | 0 | | | | | | |
| Interstitial | 1 | 12 | 33 | 71 | 36 | | | | | | |
| Vacuolar | | | | | | | | | | | |
| + | 0 | 0 | 0 | 83 | 28 | | | | | | |
| ++ | 0 | 0 | 38 | 0 | 8 | | | | | | |
| Spongiosis | | | | | | | | | | | |
| + | 0 | 0 | 38 | 44 | 16 | | | | | | |
| ++ | 0 | 0 | 0 | 0 | 0 | | | | | | |
| Necrotic keratinocytes | | | | | | | | | | | |
| + | 0 | 0 | 4 | 62 | 22 | | | | | | |
| ++ | 0 | 0 | 34 | 0 | 13 | | | | | | |
| 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 |

- lichen planus
- lichen-planus like keratosis
- pityriasis lichenoides
- lupus erythematosus
- lichenoid photodermatitis
- lichenoid purpura
- lichen sclerosus
- lichen nitidus
- lichenoid sarcoidosis
- secondary syphilis
- mycosis fungoides …

Less common than the vacuolar type of interface dermatitis is the lichenoid one. The differential diagnosis includes a wide spectrum of diseases, the most important of which is lichen planus.

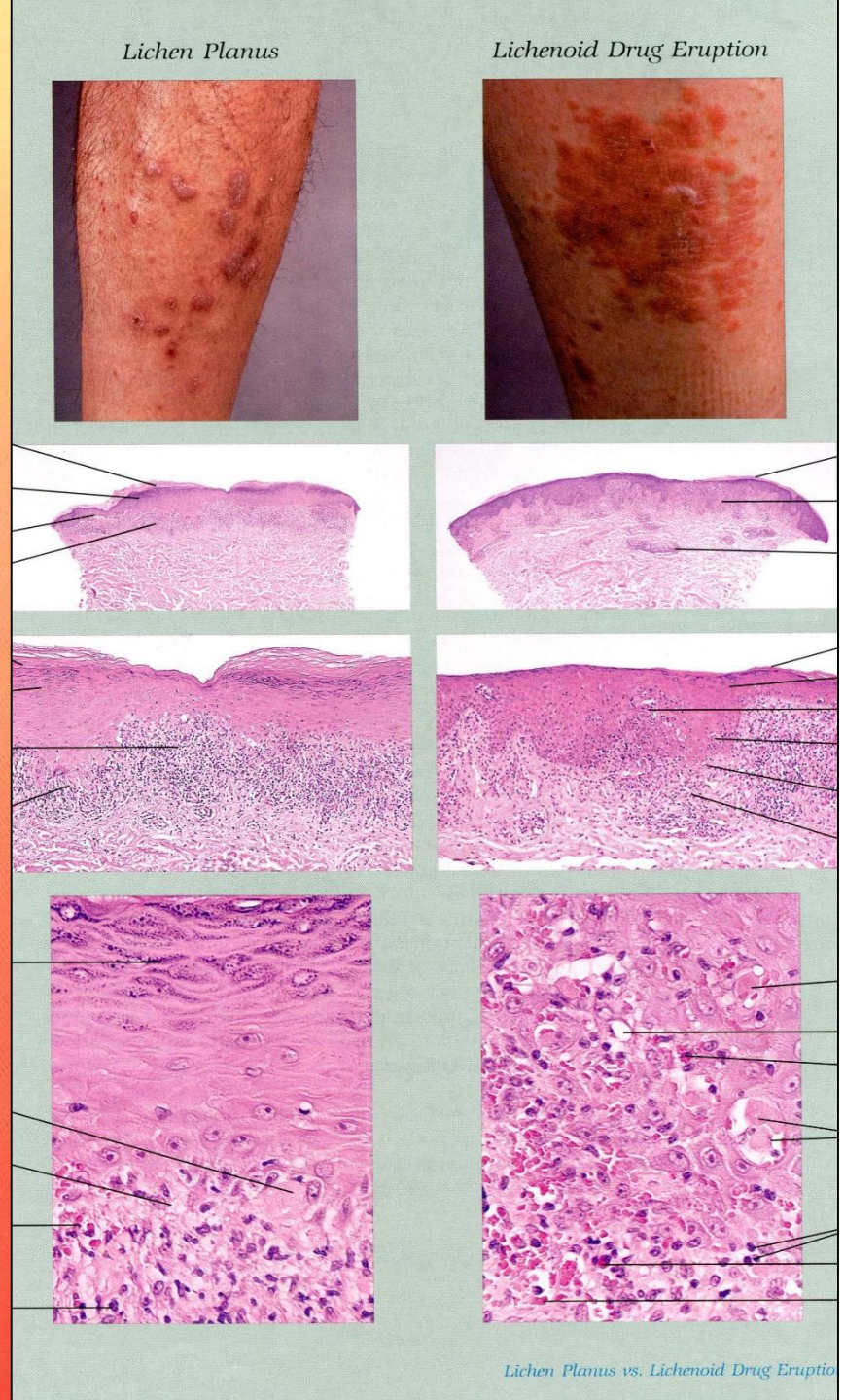
Differential Diagnosis in Dermatopathology III

Differential Diagnosis in Dermatopathology III

Differential Diagnosis in Dermatopathology III

# Differential Diagnosis in Dermatopathology III

A. Bernard Ackerman
PEDRO L. BRIGGS
FRANCISCO BRAVO

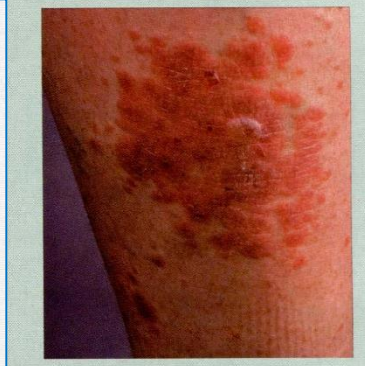


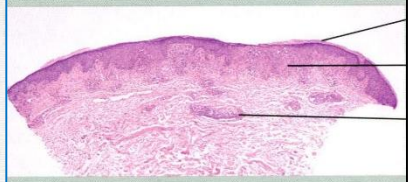

Because of its importance, this diagnostic challenge has already been dealt with by Bernard Ackerman in one of his classic books on “Differential Diagnosis in Dermatopathology.”

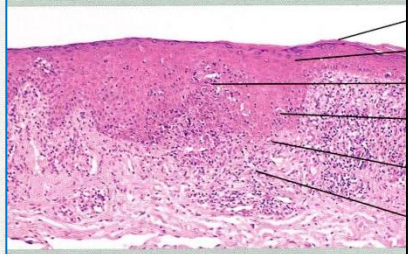
# 5. Lichen Planus *vs.* Lichenoid Drug Eruption

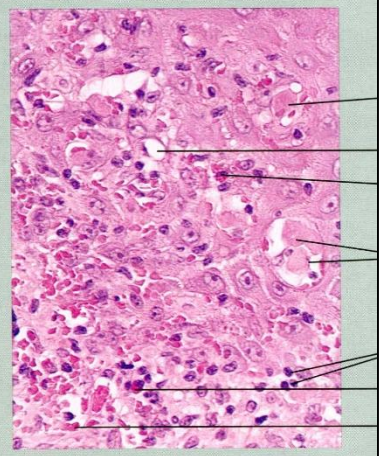
| *Lichen Planus* | *Lichenoid Drug Eruption* |
|---|---|
| 1. Epidermis not thinned focally | 1. Epidermis often thinned focally |
| 2. No parakeratosis | 2. Parakeratosis often |
| 3. Wedge-shaped hypergranulosis | 3. No wedge-shaped hypergranulosis usually |
| 4. Granular zone intact across an entire section | 4. Granular zone decreased focally |
| 5. No necrotic keratinocytes in the granular zone usually | 5. Necrotic keratinocytes in the granular zone sometimes |
| 6. Focal keratinocytic hyperplasia in a repeatable pattern | 6. Keratinocytic hyperplasia, but not in a repeatable pattern |
| 7. Rete ridges usually jagged and bases obscured by inflammatory cells | 7. Rete ridges sometimes rounded at their bases and not obscured by inflammatory cells |
| 8. Lichen simplex chronicus may be prominent; collagen bundles are aligned in vertical streaks | 8. No lichen simplex chronicus usually |
| 9. Infiltrate superficial as a rule | 9. Infiltrate sometimes superficial and deep |
| 10. No eosinophils as a rule; few, if any | 10. Some eosinophils present often; many sometimes |
| 11. No plasma cells | 11. Few plasma cells episodically |
| 12. No granulomatous foci | 12. Granulomatous foci sometimes |
| 13. Few if any extravasated erythrocytes | 13. Numerous extravasated erythrocytes often |

*Lichen Planus* *Lichenoid Drug Eruption*



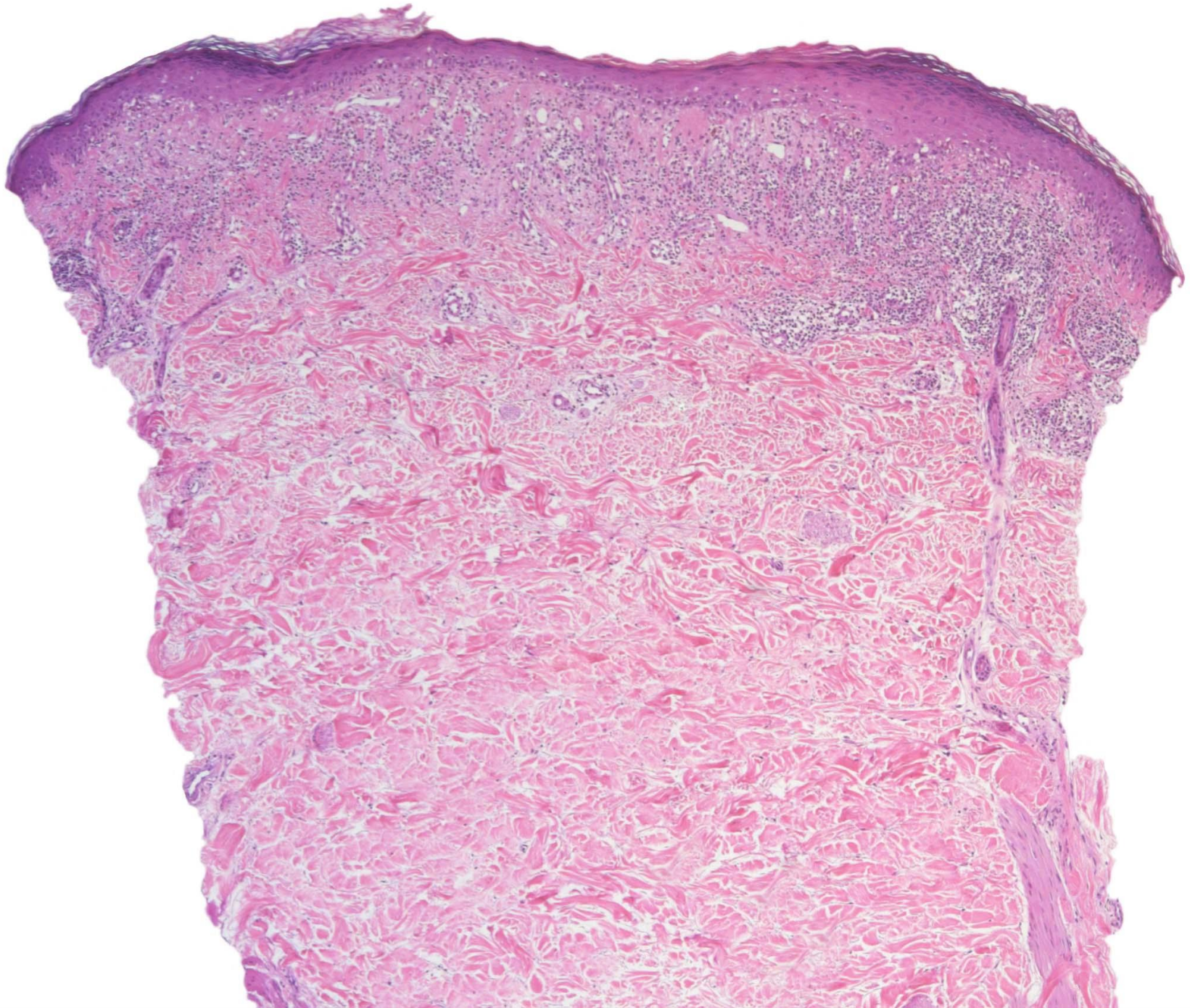




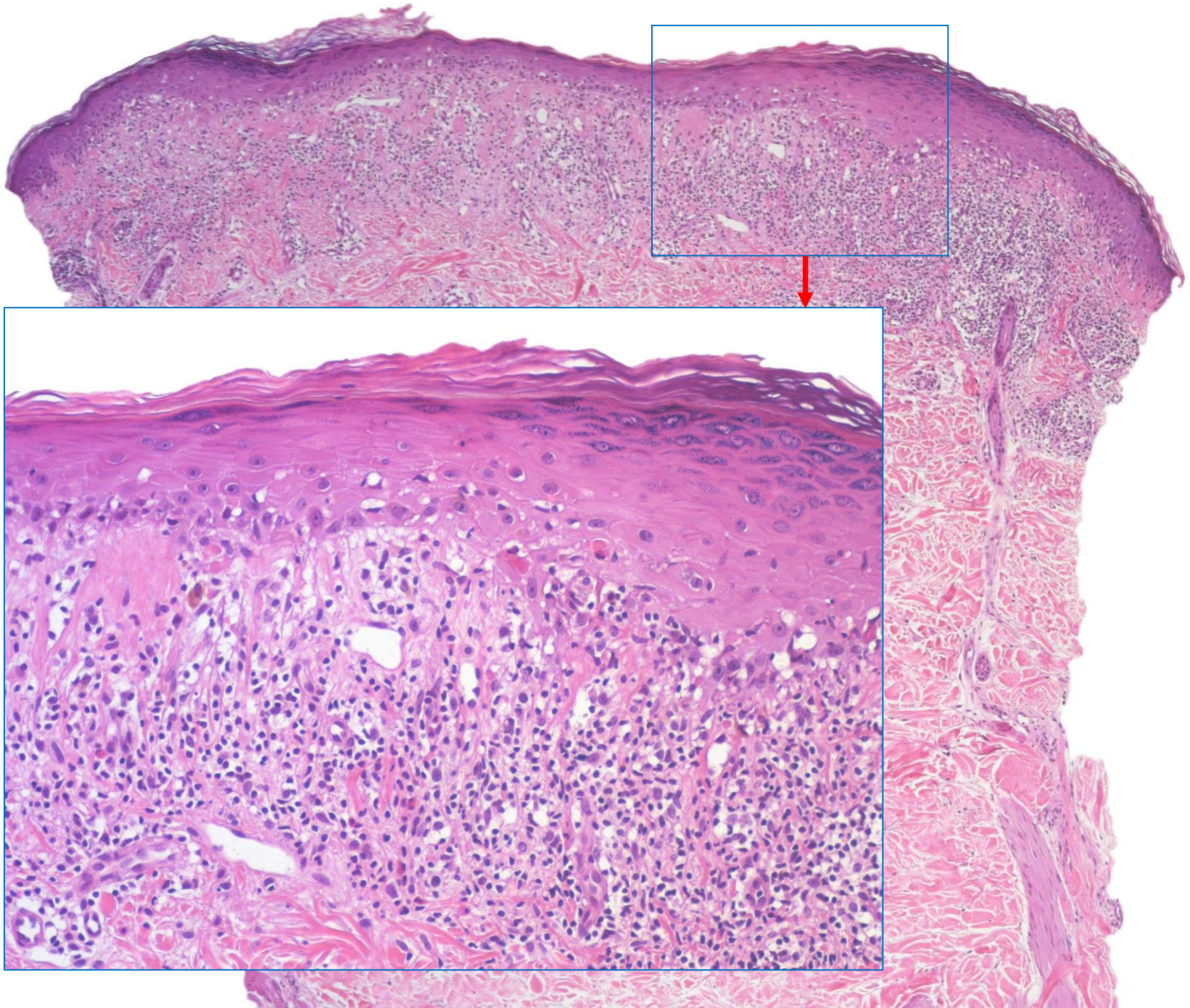


*Lichen Planus vs. Lichenoid Drug Eruptio*

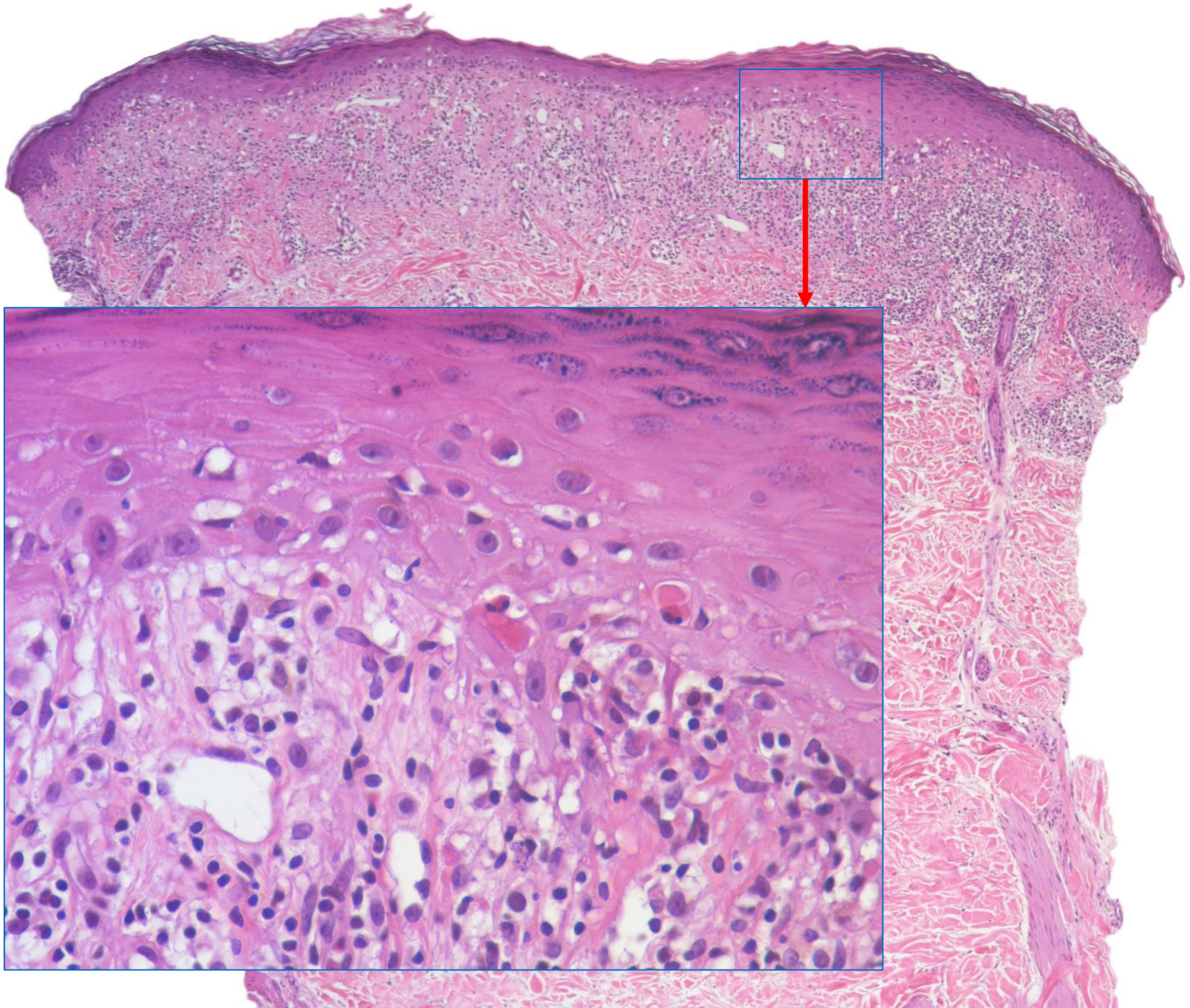
Among the clues to a drug eruption given were some parakeratosis, a focally decreased granular zone, a superficial and deep, rather than only superficial, infiltrate, some eosinophils, and extravasated erythrocytes.



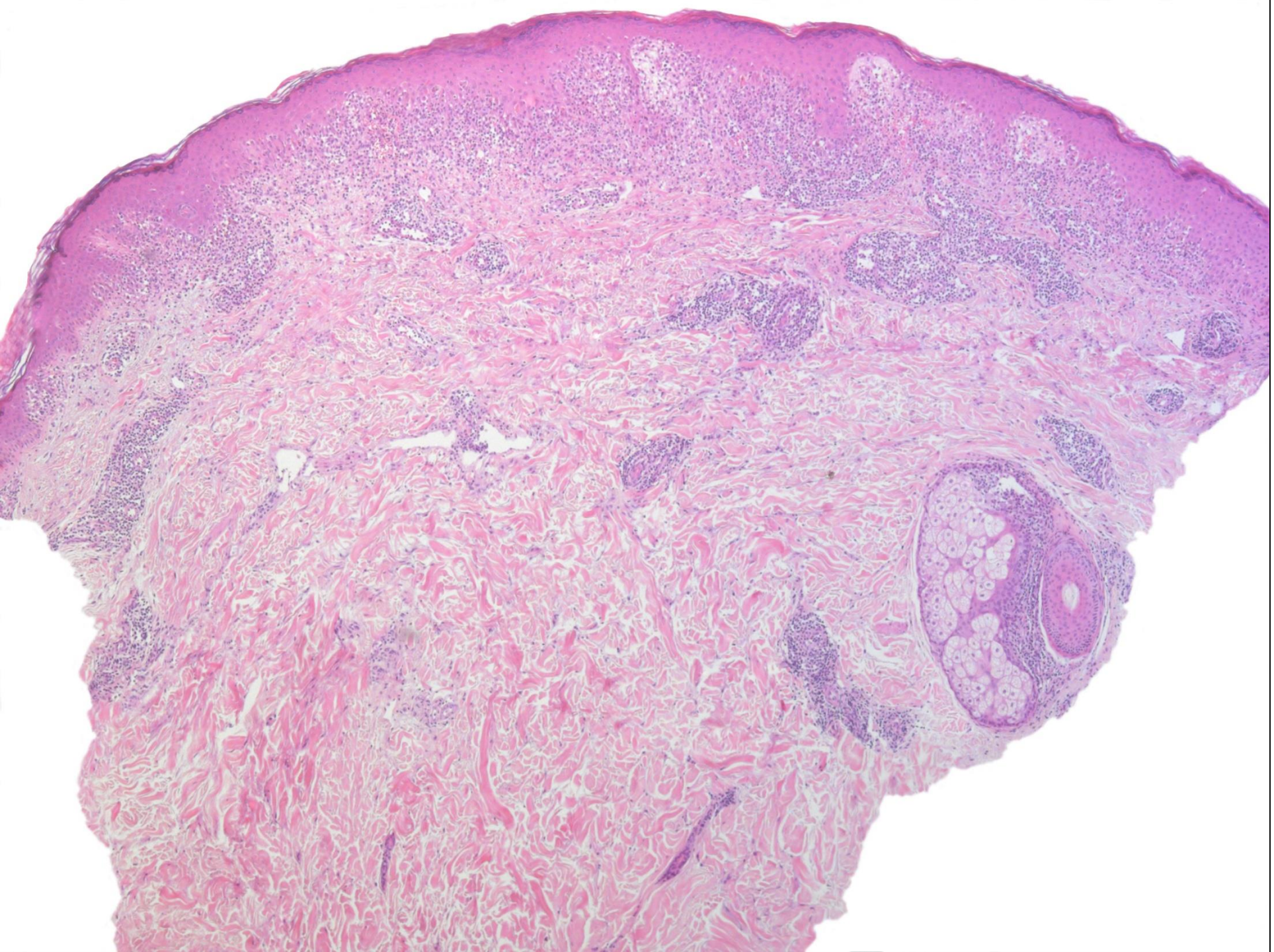
Let’s look at some examples: A superficial lichenoid dermatitis with epidermal hyperplasia, wegde-shaped zones of hypergranulosis, and compact orthokeratosis, just as in lichen planus,



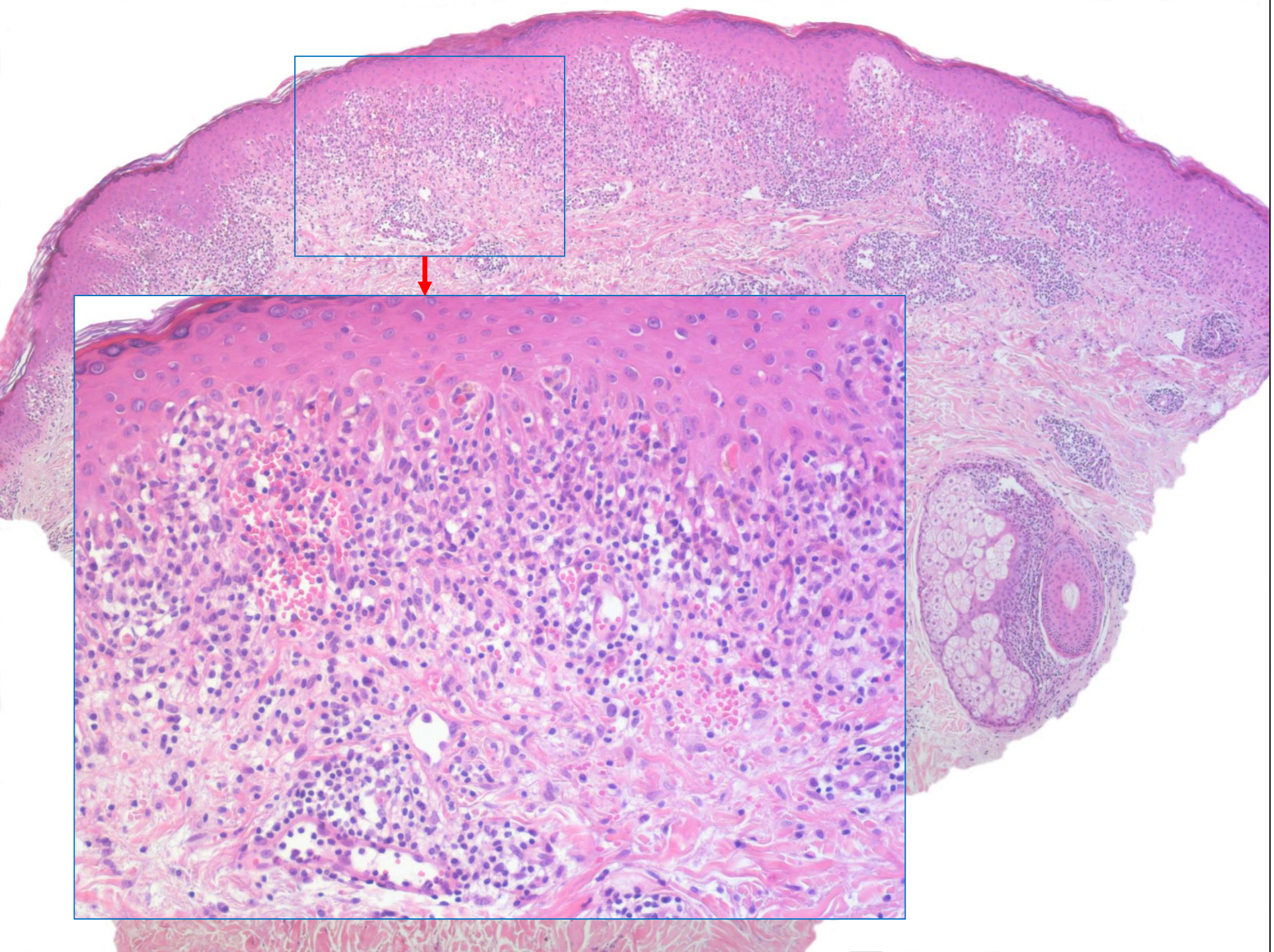
but a preserved basket-woven cornified layer in foci, focal decrease of the granular zone, some parakeratosis, and eosinophils in the infiltrate,



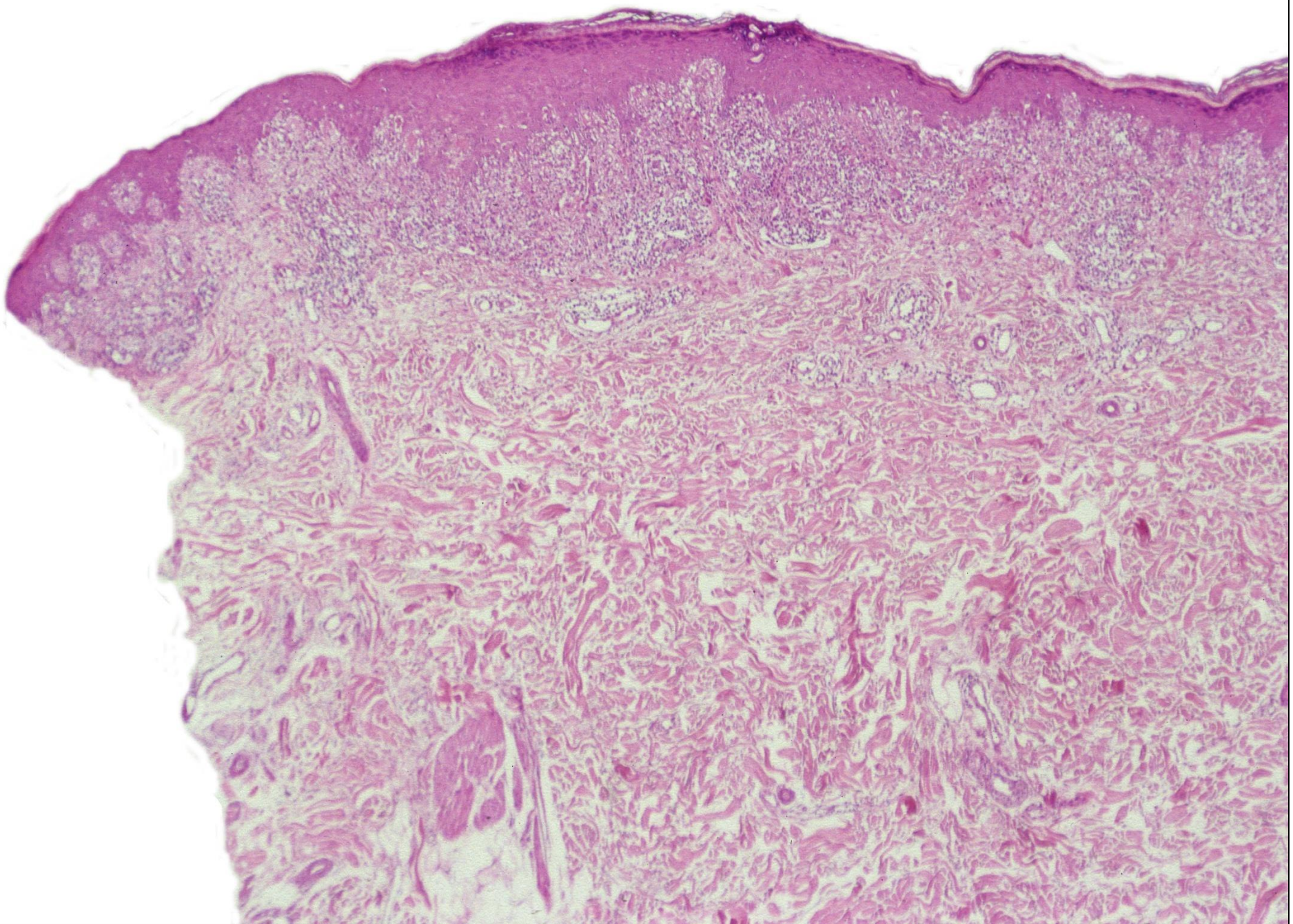
including some within the epidermis. This cannot be lichen planus.



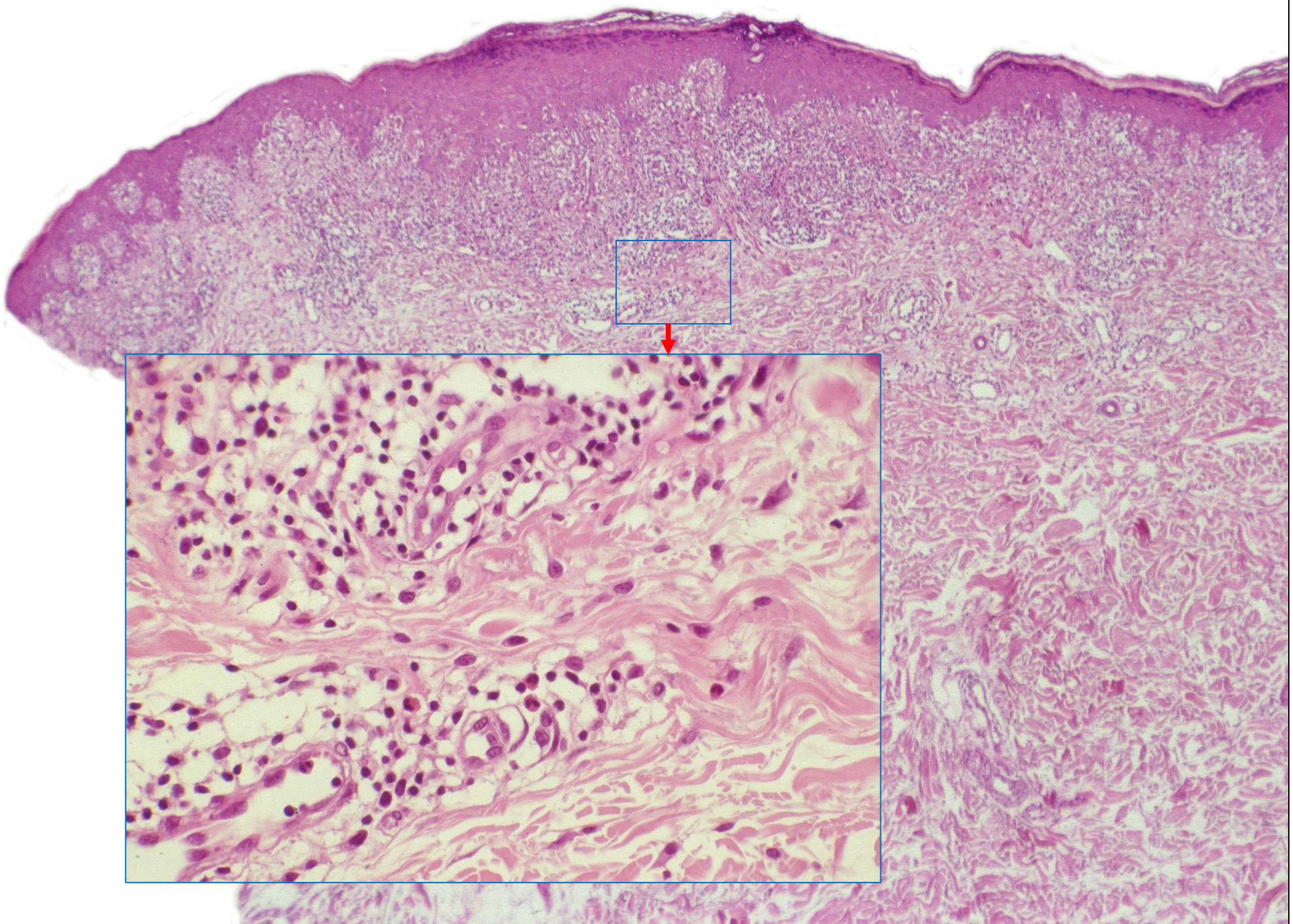
Once again epithelial hyperplasia with a “saw-tooth pattern of rete ridges” and wedge-shaped zones of hypergranulosis, but the infiltrate is superficial and deep,



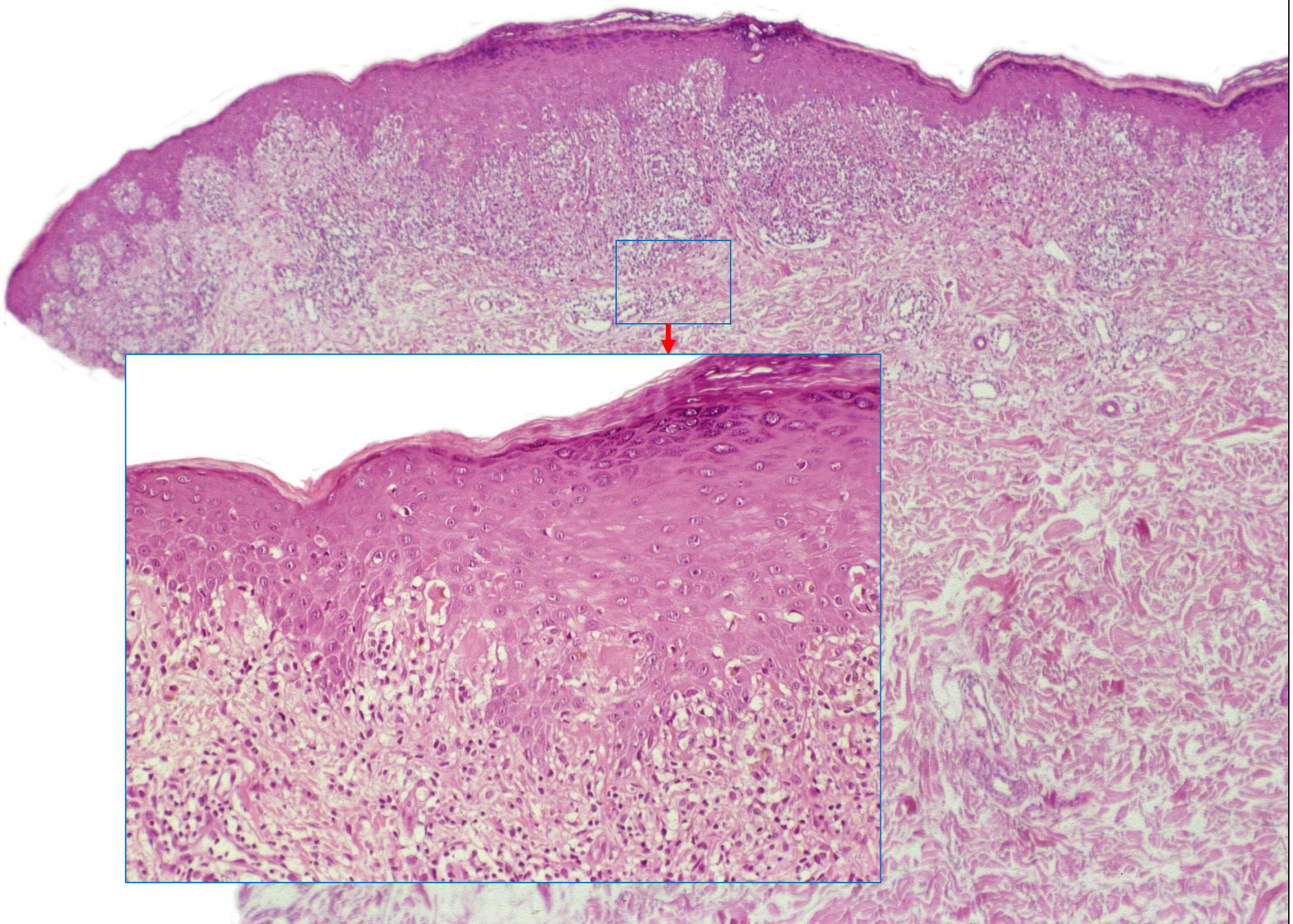
and there are abundant extravasated erythrocytes.



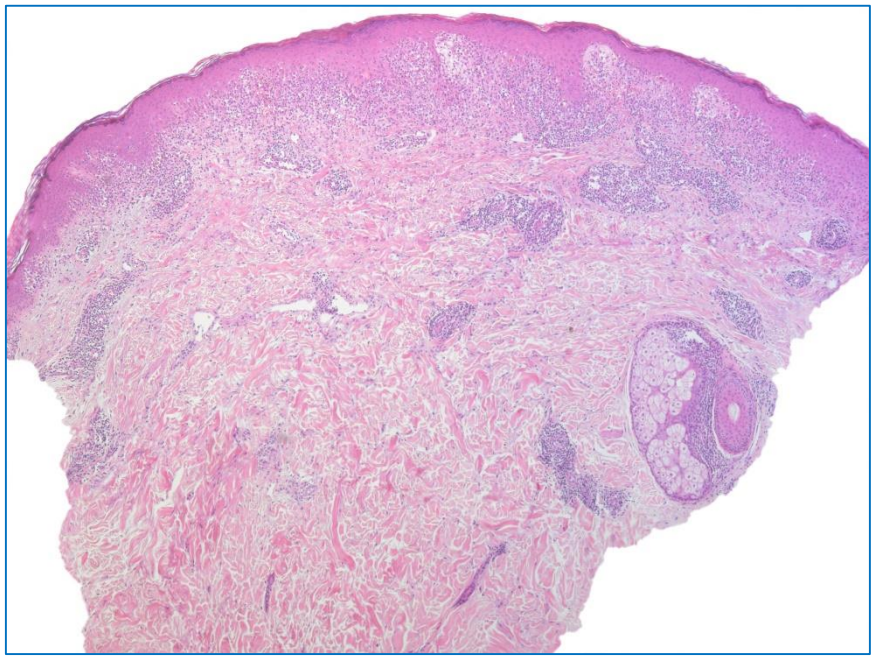
An epidermal pattern just as in lichen planus,

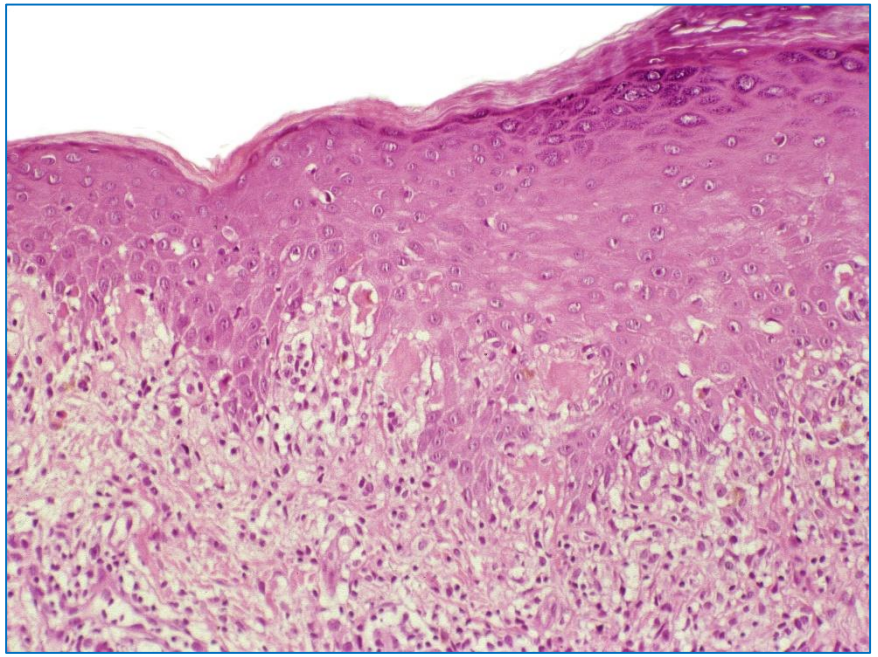


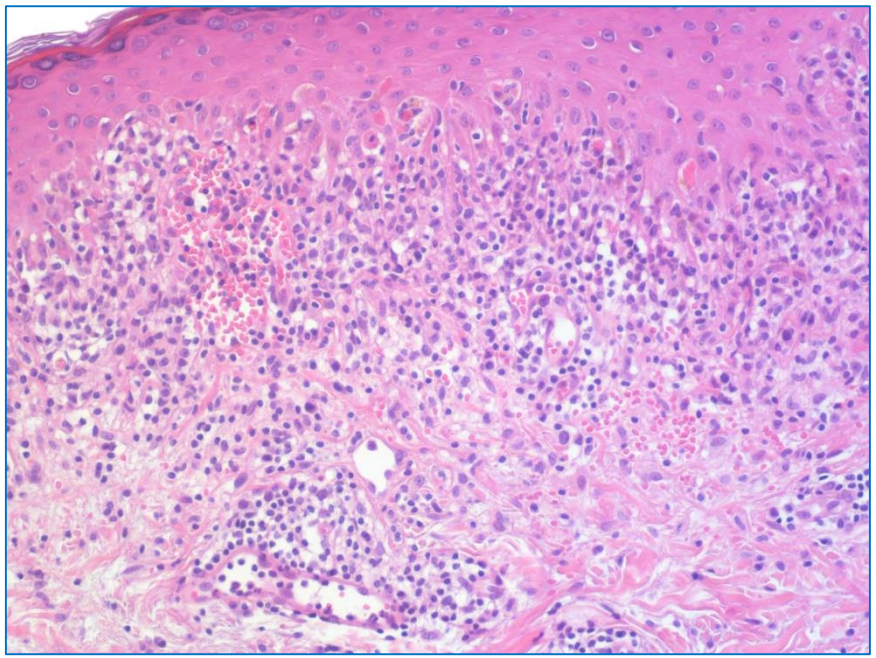
but once again eosinophils in the infiltrate,

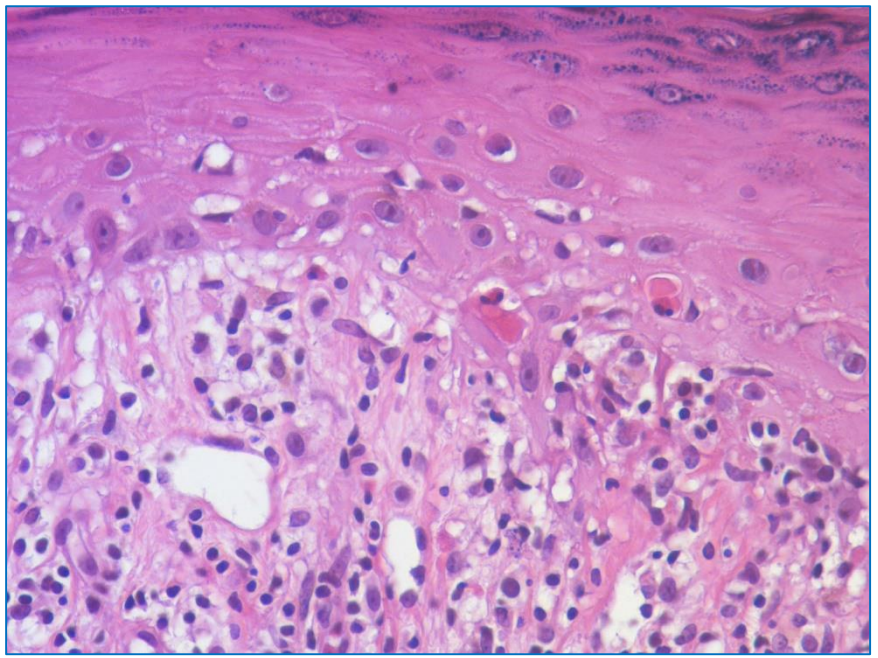


focal thinning of the granular zone, some parakeratosis, and, a criterion not mentioned in Ackerman's book, a surfeit of necrotic keratocytes.

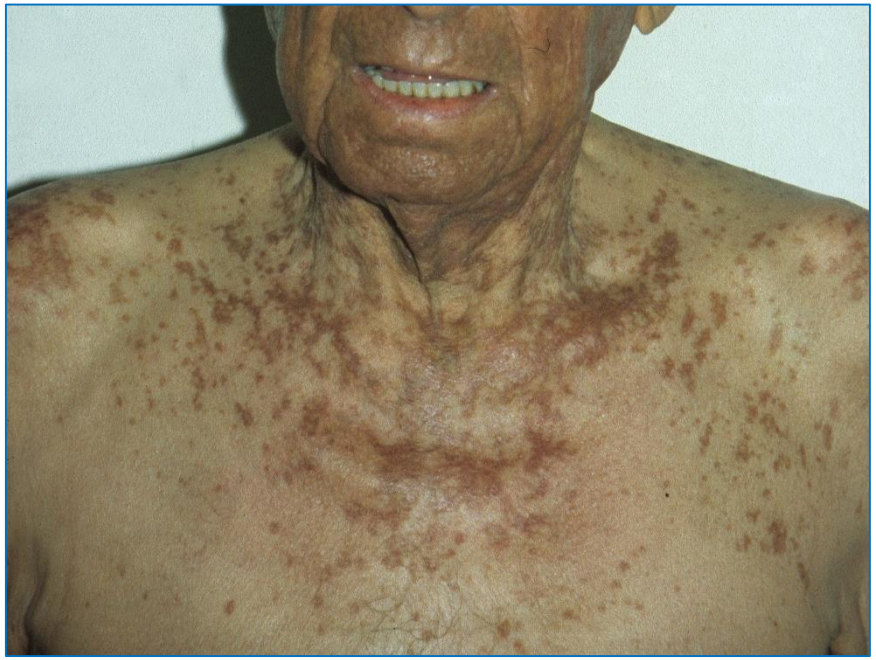


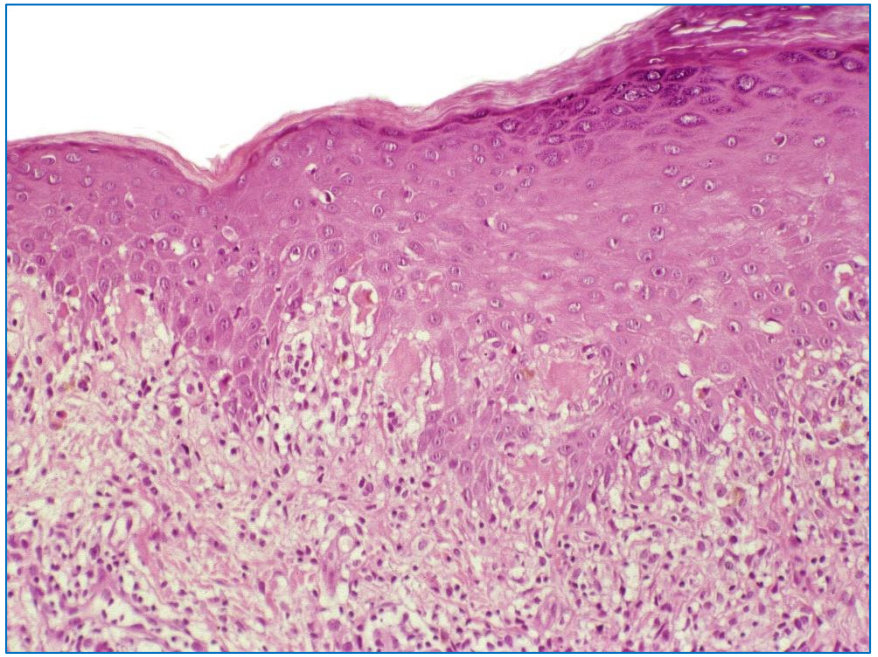


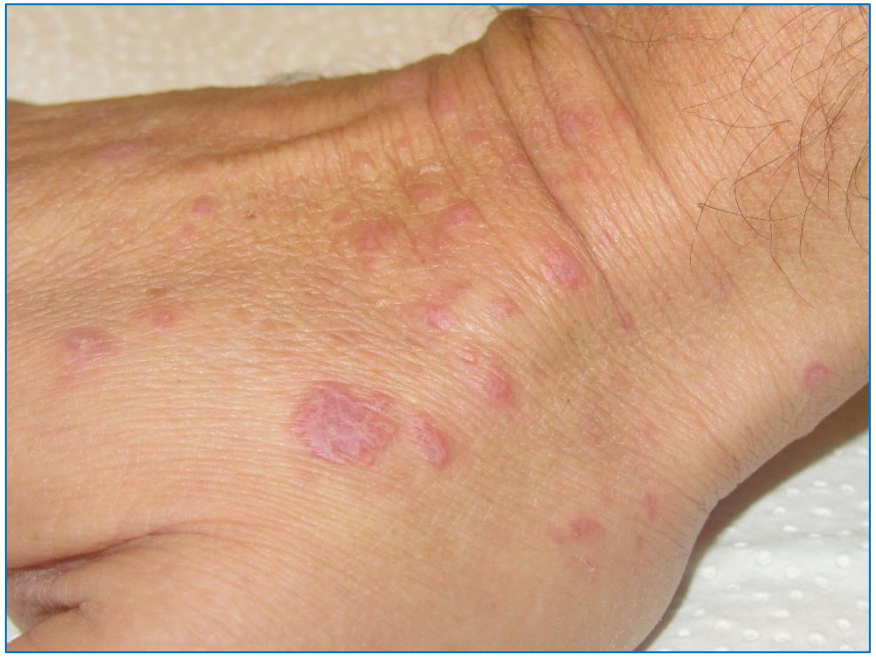


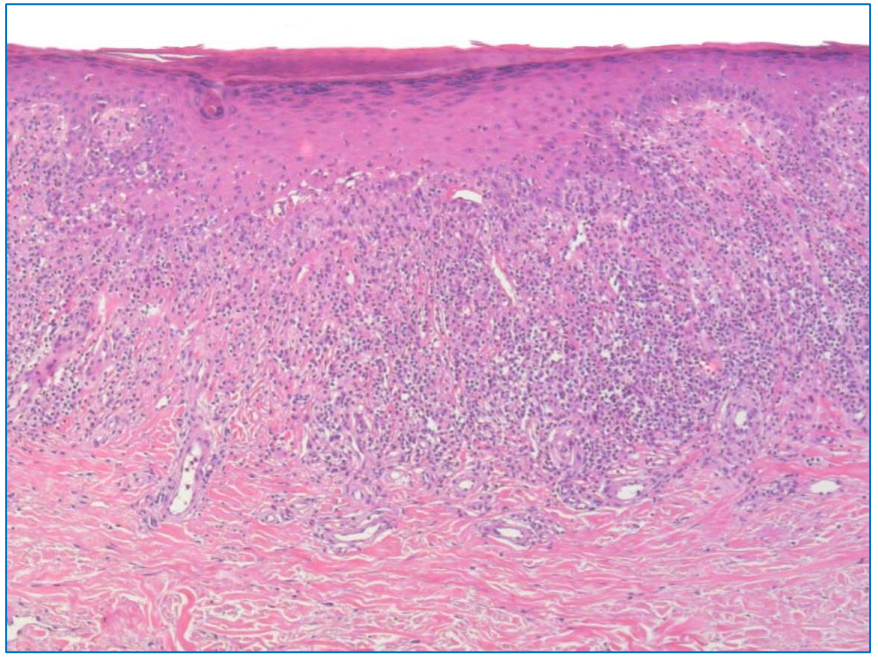


All those changes may be seen episodically in lichen planus, and they may not be present in lichenoid drug eruption, but, together, they usually allow a correct diagnosis to be made. However, because lichenoid drug eruption may be indistinguishable from classical examples of lichen planus,

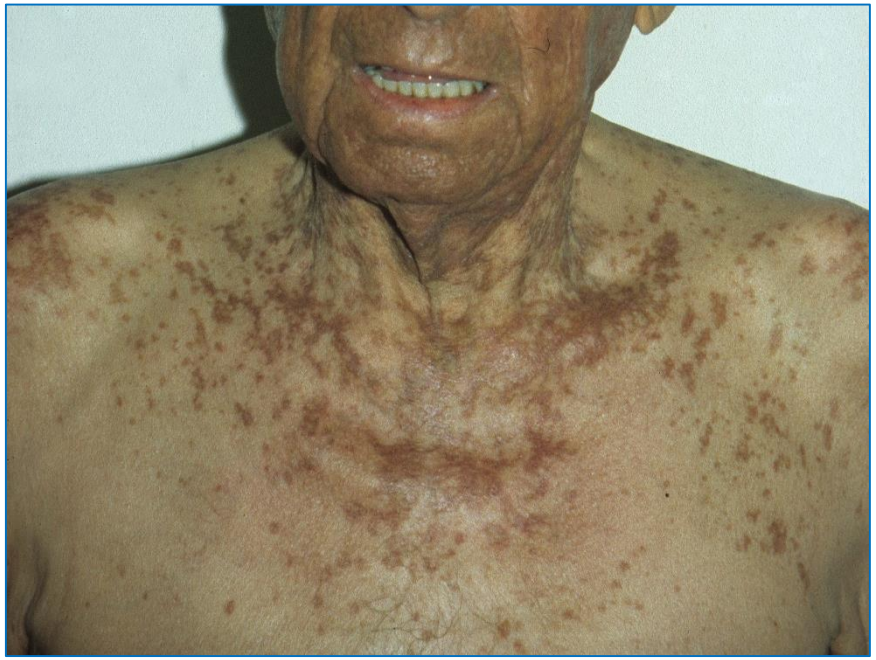


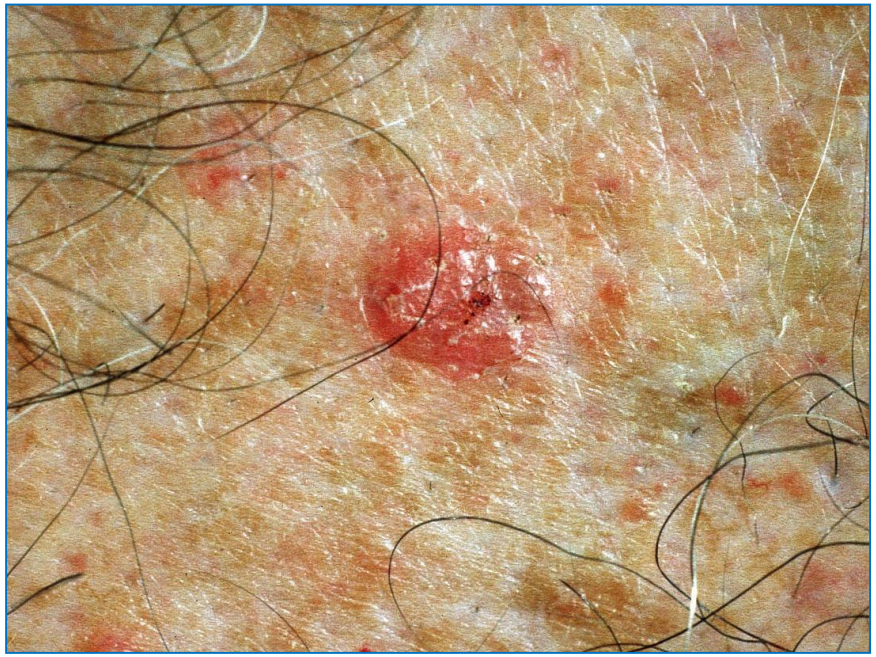


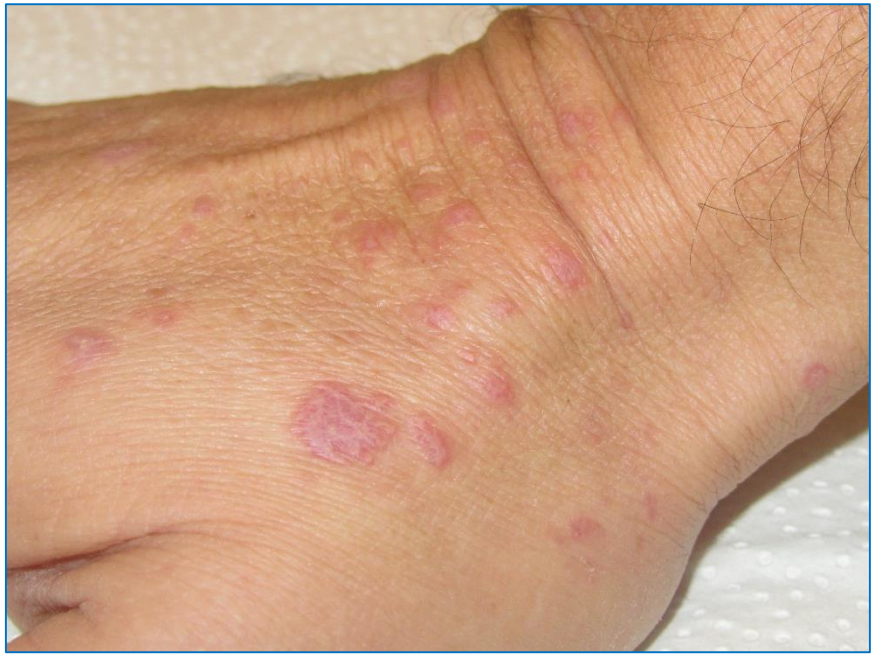


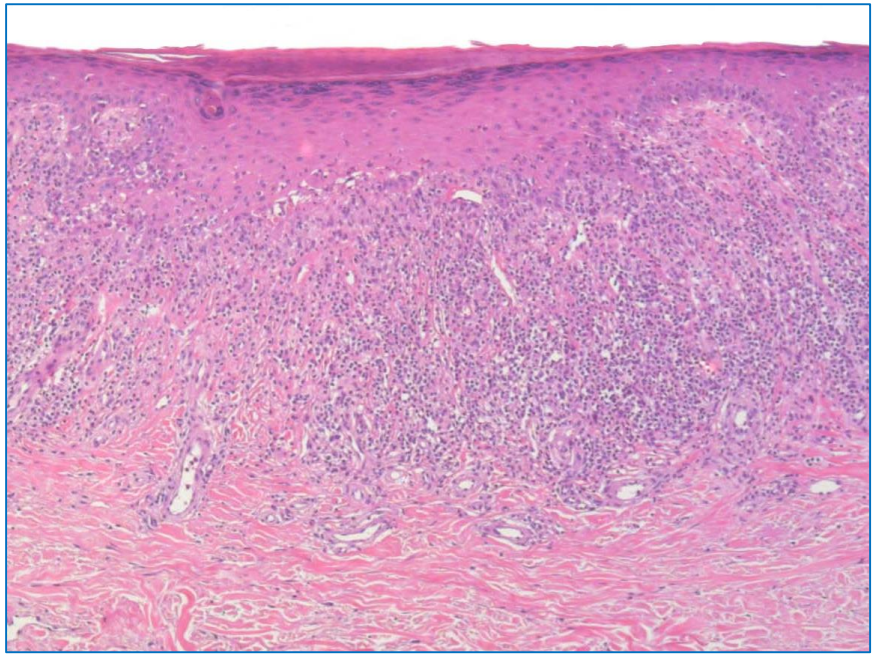


clinico-pathologic correlation is essential, such as advanced age of the patient, involvement of anatomic sites not corresponding to the areas of predilection of lichen planus, and, of course, a history of medications.





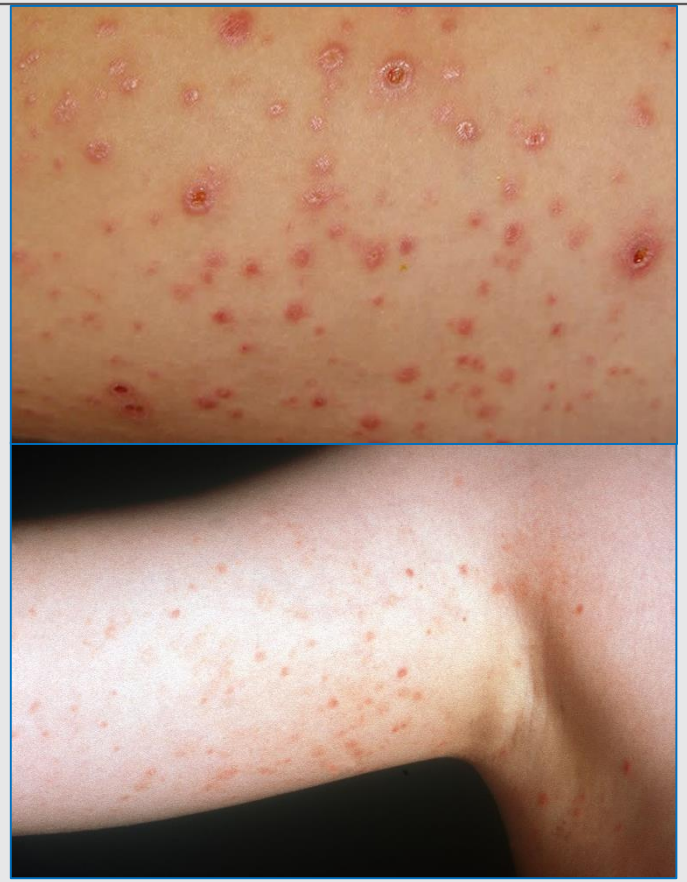




Clinico-pathologic correlation also helps to rule out other differential diagnoses, especially lichen planus-like keratosis that may be indistinguishable from a lichenoid drug eruption but usually presents itself as a small solitary lesion.

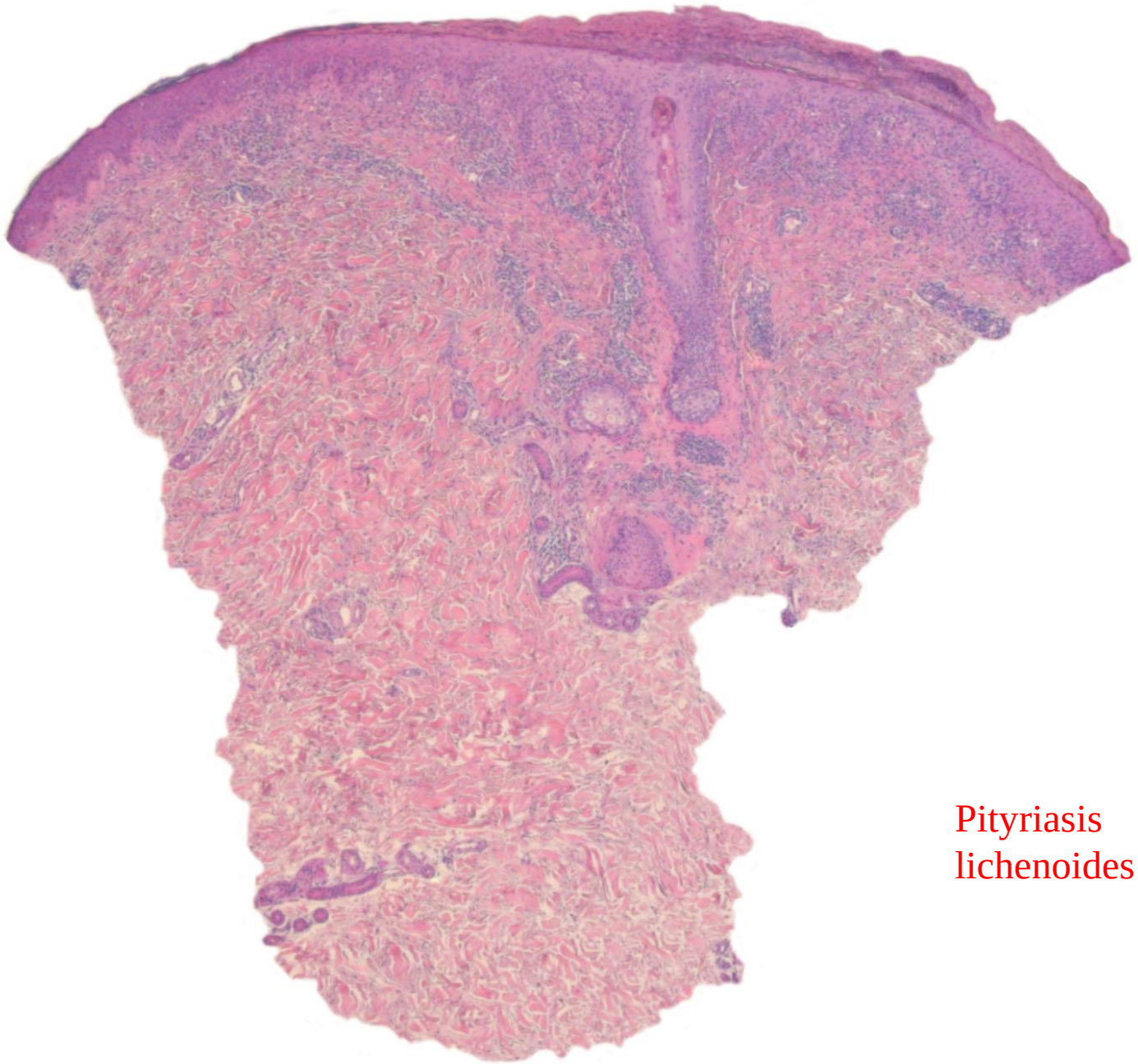
Table 1: Histopathologic findings in 300 cases with the clinical and histopathologic diagnosis of drug eruption

| | Pattern | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Lympho-cytic dermal without epidermal Changes (n=12)* | *Superficial and deep dermal with eosino-phils and neutrophils (n=12)* | *Severe vacuolar interface dermatitis (n=38)* | *Mild vacuolar interface dermatitis (n=83)* | *Lichenoid dermatitis (n=36)* | *Lichenoid pso-riasiform dermatitis (n=18)* | *Spongiotic dermatitis (n=62)* | *Pustular dermatitis (n=19)* | *Subepi-dermal bullous dermatitis (n=6)* | *Granulo-matous dermatitis (n=12)* | *Leukocy-toklastic vasculitis (n=2)* |
| Superficial | | | | | 26 | | | | | | |
| Superficial and deep | | | | | 10 | | | | | | |
| Perivascular | | | | | 0 | | | | | | |
| Interstitial | | | | | 36 | | | | | | |
| Vacuolar | | | | | | | | | | | |
| + | | | | | 28 | | | | | | |
| ++ | | | | | 8 | | | | | | |
| Spongiosis | | | | | | | | | | | |
| + | | | | | 16 | | | | | | |
| ++ | | | | | 0 | | | | | | |
| Necrotic keratinocytes | | | | | | | | | | | |
| + | | | | | 22 | | | | | | |
| ++ | | | | | 13 | | | | | | |
| Eosinophils | | | | | | | | | | | |
| + | | | | | 17 | 13 | 45 | 13 | 6 | 10 | 0 |
| ++ | | | | | 2 | 4 | 13 | 6 | 0 | 0 | 2 |
| Neutrophils | | | | | | | | | | | |
| + | | | | | 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 |



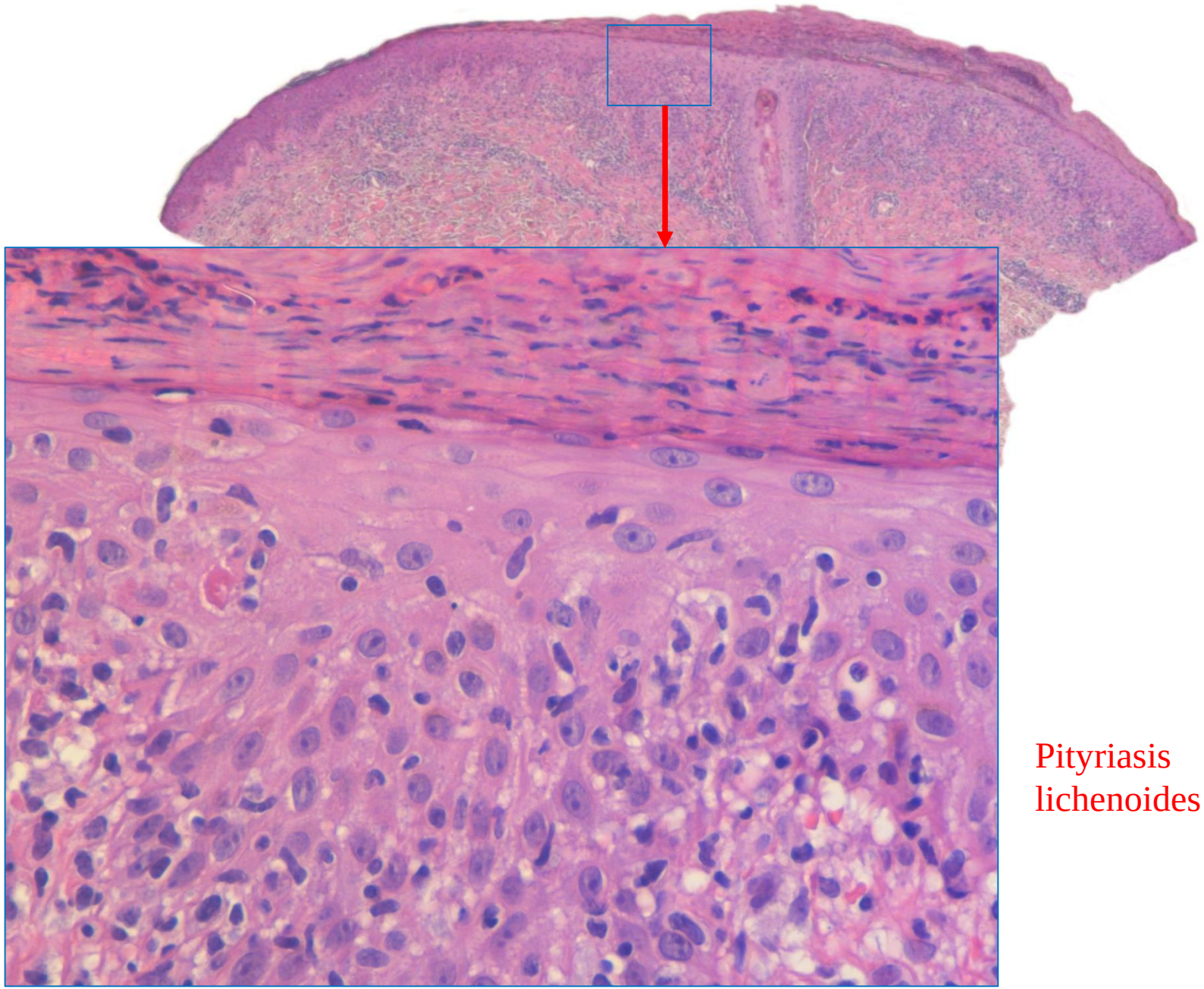
- lichen planus
- lichen-planus like keratosis
- pityriasis lichenoides
- lupus erythematosus
- lichenoid photodermatitis
- lichenoid purpura
- lichen sclerosus
- lichen nitidus
- lichenoid sarcoidosis
- secondary syphilis
- mycosis fungoides …

Of course, differential diagnosis is most important for diseases that can easily be confused with drug eruptions clinically. One of them is pityriasis lichenoides which is characterized by disseminated papules. The latter are often umbilicated, and patients are usually young or middle-aged, but clinical distinction from a drug eruption may be difficult.



Pityriasis lichenoides

Histopathologically, pityriasis lichenoides usually shows a wegde-shaped infiltrate which is not a feature of drug eruptions. The infiltrate is usually composed of lymphocytes only.

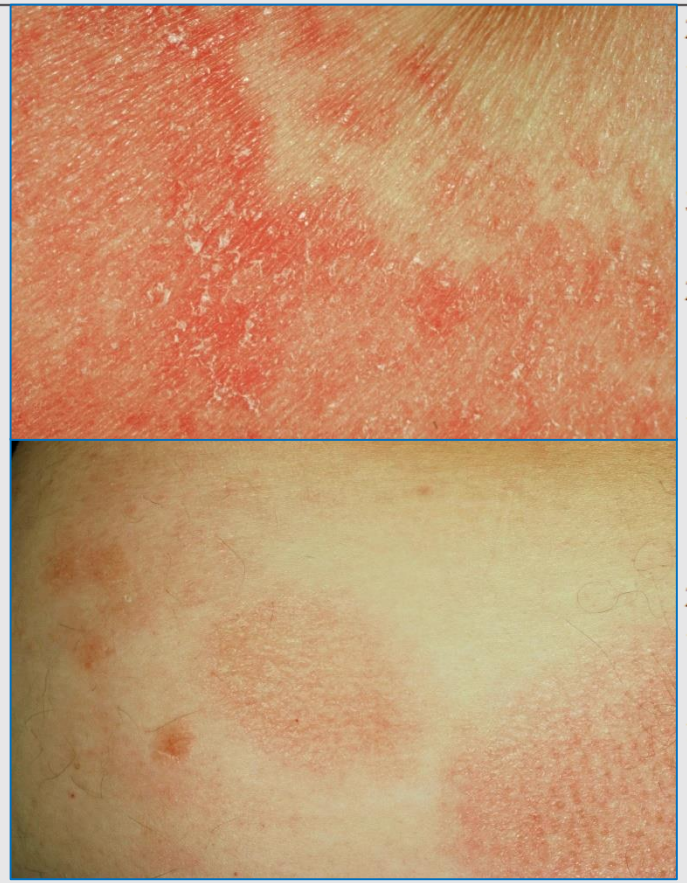


Pityriasis lichenoides

As in drug eruptions, there may be many extravasated erythrocytes and necrotic keratocytes in all reaches of the epidermis, but lesions are often covered by elongated mounts of parakeratosis housing neutrophils, which is not the case in drug eruptions.

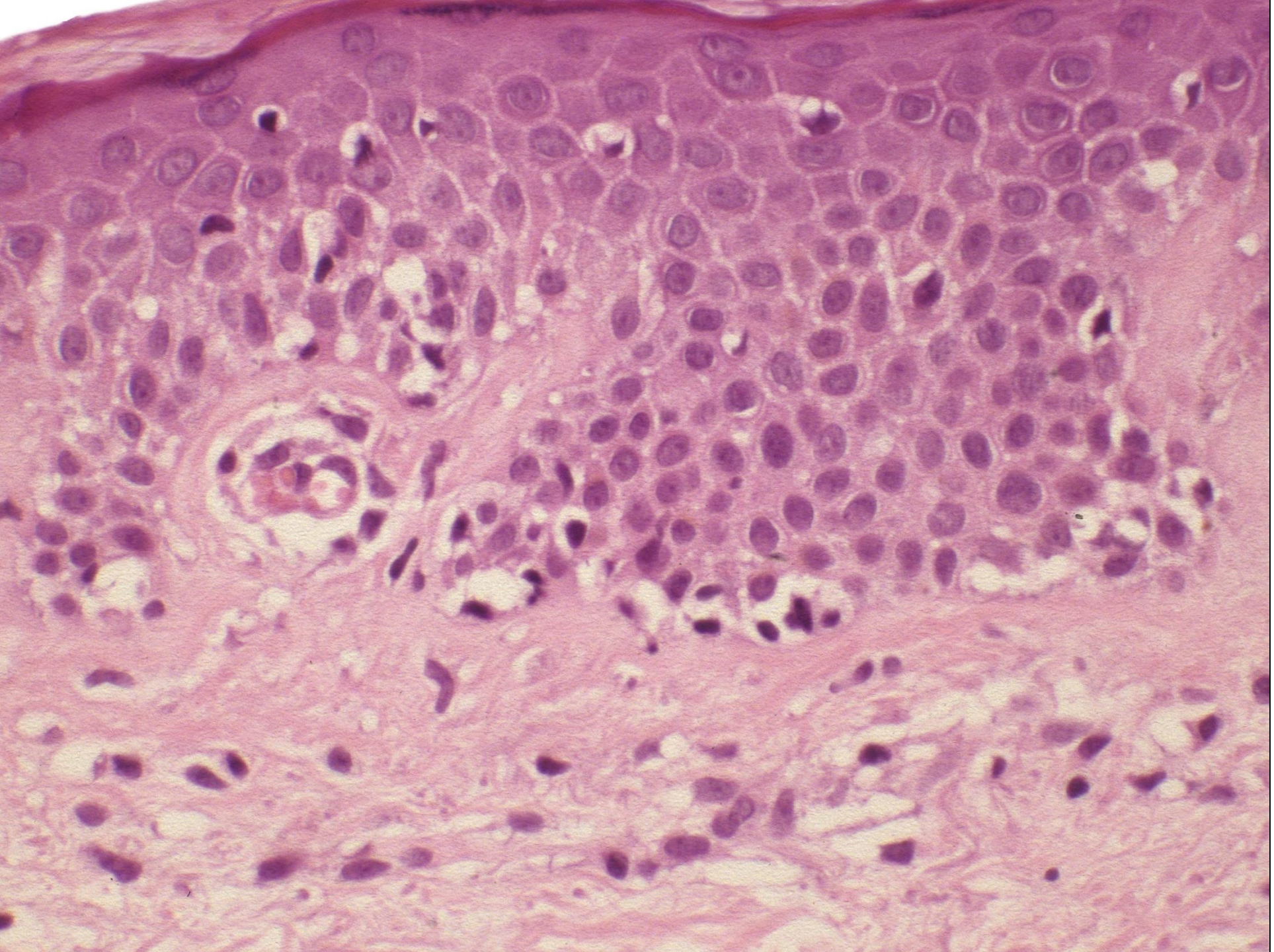
Table 1: Histopathologic findings in 300 cases with the clinical and histopathologic diagnosis of drug eruption

| | Pattern | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Lympho-cytic dermal without epidermal Changes (n=12)* | *Superficial and deep dermal with eosino-phils and neutrophils (n=12)* | *Severe vacuolar interface dermatitis (n=38)* | *Mild vacuolar interface dermatitis (n=83)* | *Lichenoid dermatitis (n=36)* | *Lichenoid pso-riasiform dermatitis (n=18)* | *Spongiotic dermatitis (n=62)* | *Pustular dermatitis (n=19)* | *Subepi-dermal bullous dermatitis (n=6)* | *Granulo-matous dermatitis (n=12)* | *Leukocy-toklastic vasculitis (n=2)* |
| Superficial | | | | | 26 | | | | | | |
| Superficial and deep | | | | | 10 | | | | | | |
| Perivascular | | | | | 0 | | | | | | |
| Interstitial | | | | | 36 | | | | | | |
| Vacuolar | | | | | | | | | | | |
| + | | | | | 28 | | | | | | |
| ++ | | | | | 8 | | | | | | |
| Spongiosis | | | | | | | | | | | |
| + | | | | | 16 | | | | | | |
| ++ | | | | | 0 | | | | | | |
| Necrotic keratinocytes | | | | | | | | | | | |
| + | | | | | 22 | | | | | | |
| ++ | | | | | 13 | | | | | | |
| Eosinophils | | | | | | | | | | | |
| + | | | | | 17 | 13 | 45 | 13 | 6 | 10 | 0 |
| ++ | | | | | 2 | 4 | 13 | 6 | 0 | 0 | 2 |
| Neutrophils | | | | | | | | | | | |
| + | | | | | 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 |

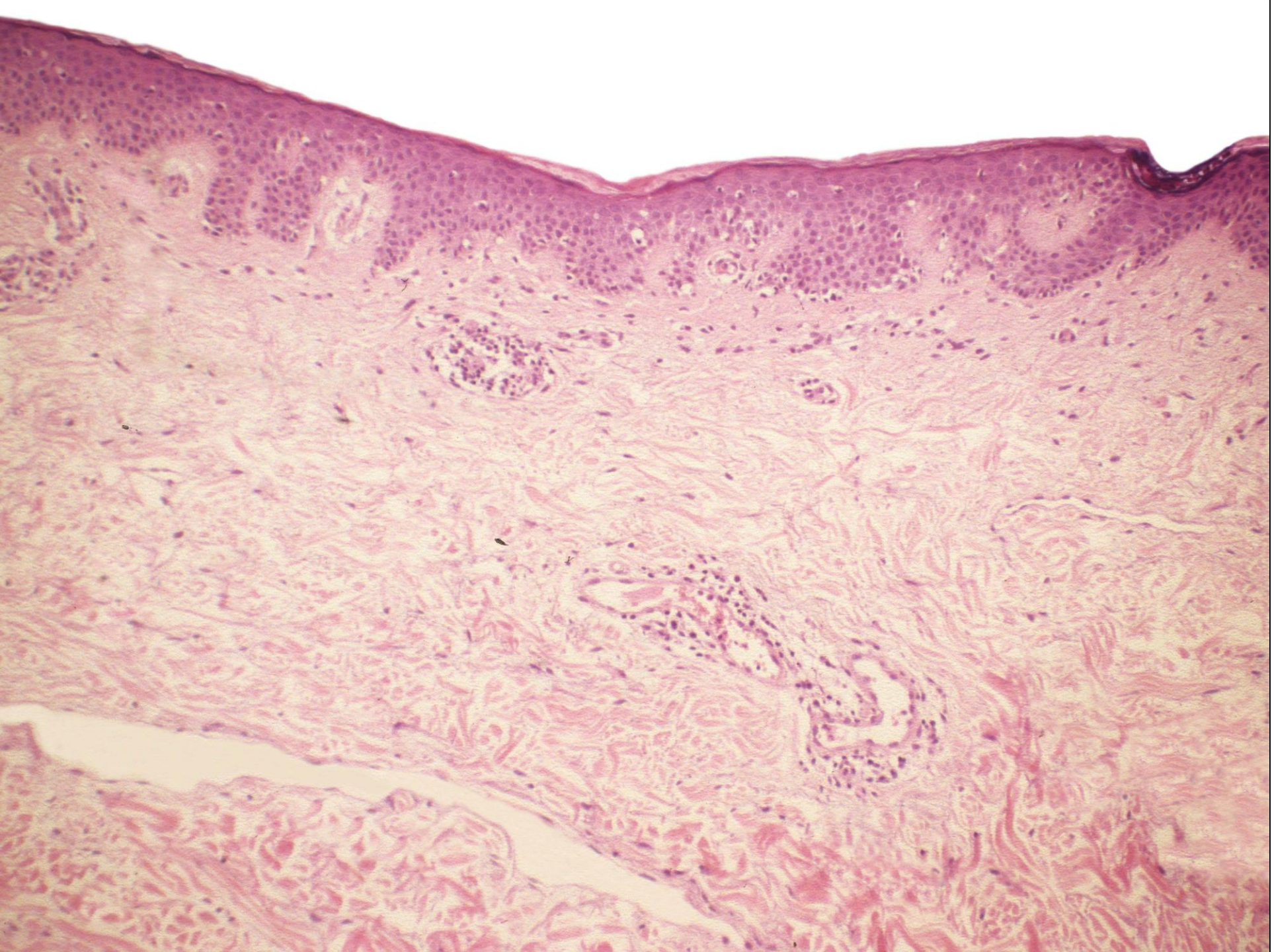


- lichen planus
- lichen-planus like keratosis
- pityriasis lichenoides
- lupus erythematosus
- lichenoid photodermatitis
- lichenoid purpura
- lichen sclerosus
- lichen nitidus
- lichenoid sarcoidosis
- secondary syphilis
- mycosis fungoides …

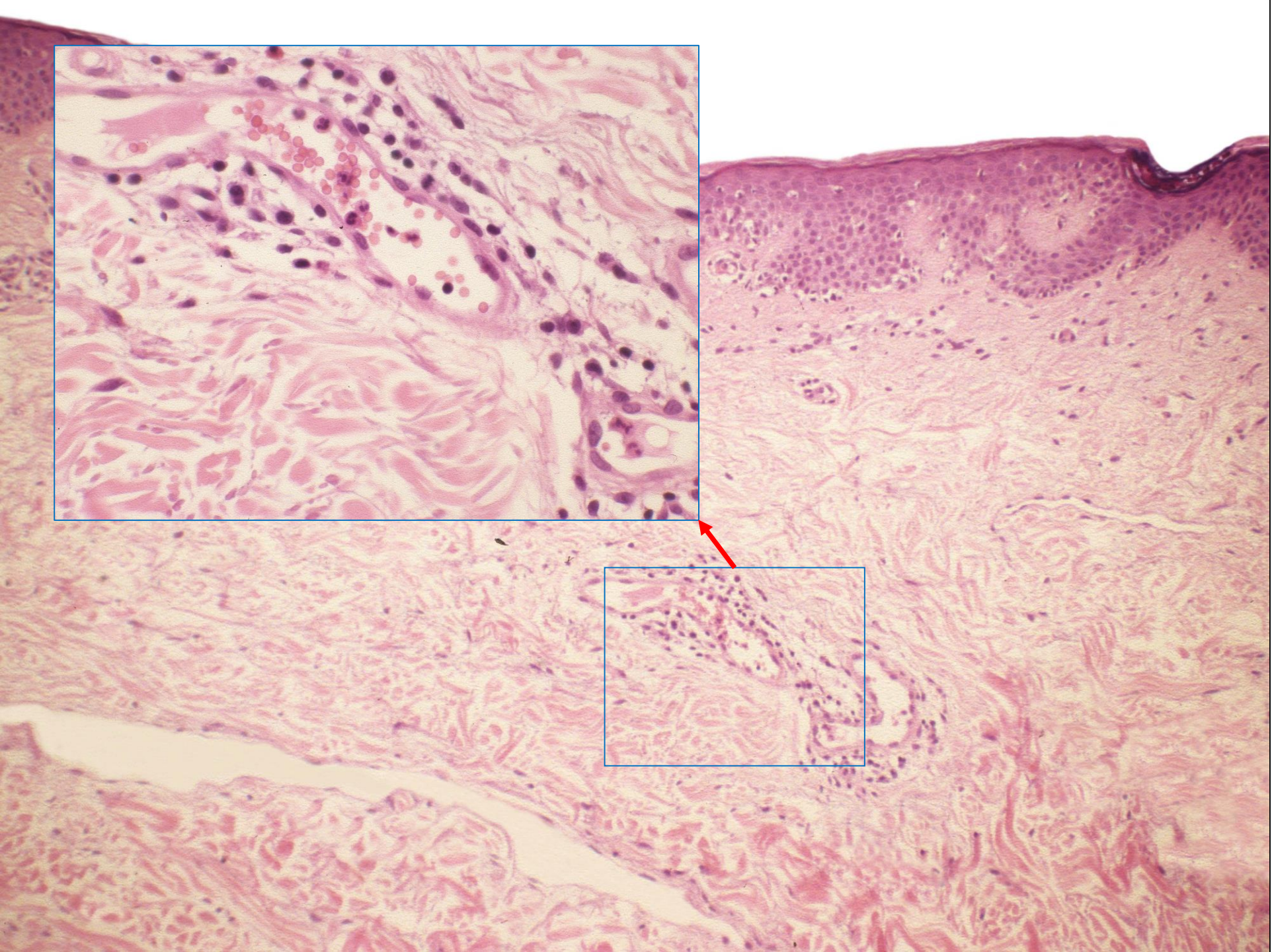
Another differential diagnosis that may be exceedingly difficult clinically is the patch stage of mycosis fungoides.



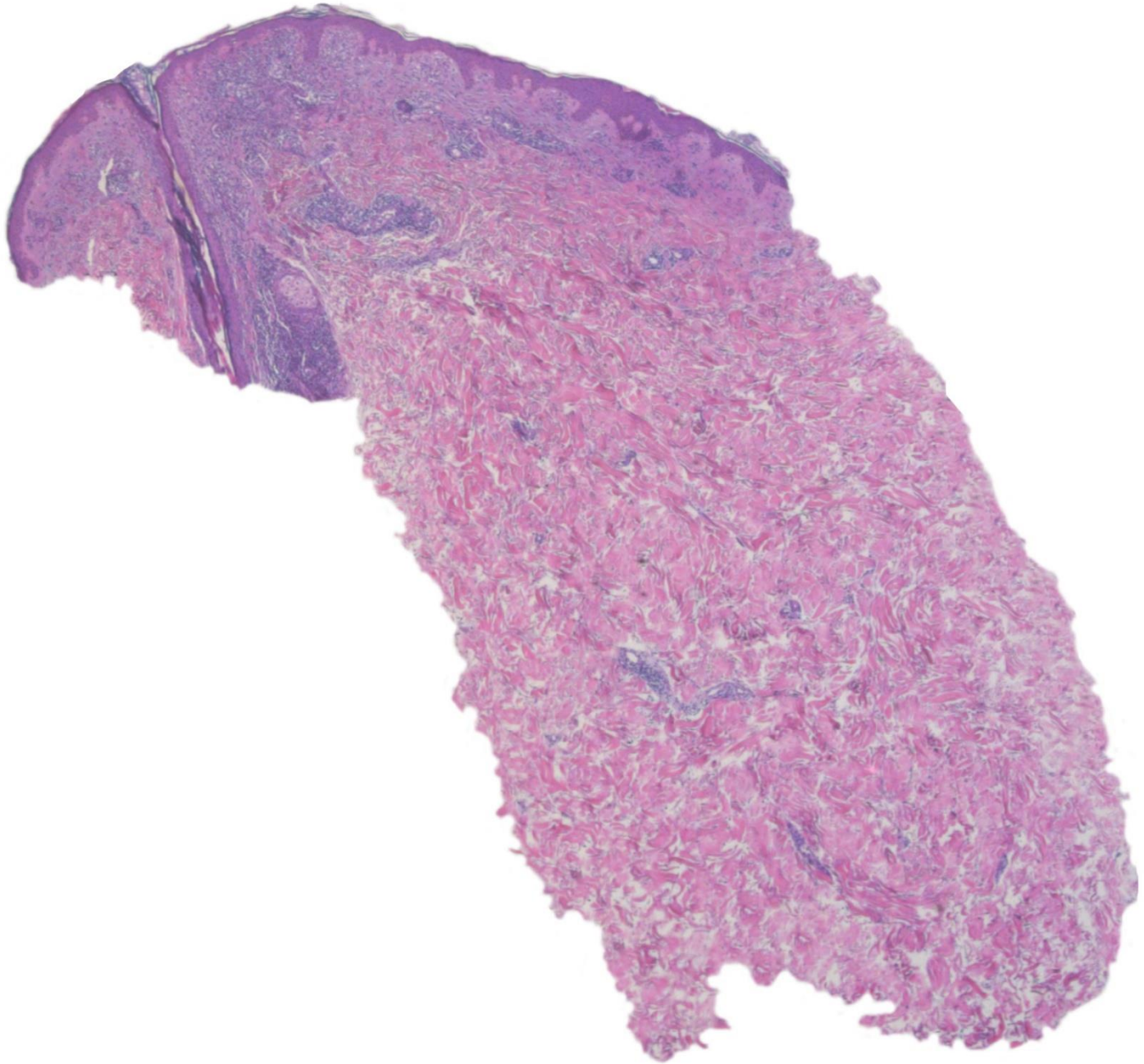
Distinction may also be difficult histopathologically because drug eruptions may mimick mycosis fungoides. Lymphocytes may be largish, they may infiltrate the epidermis in the context of only scant spongiosis, and they may be aligned along the dermo-epidermal junction.



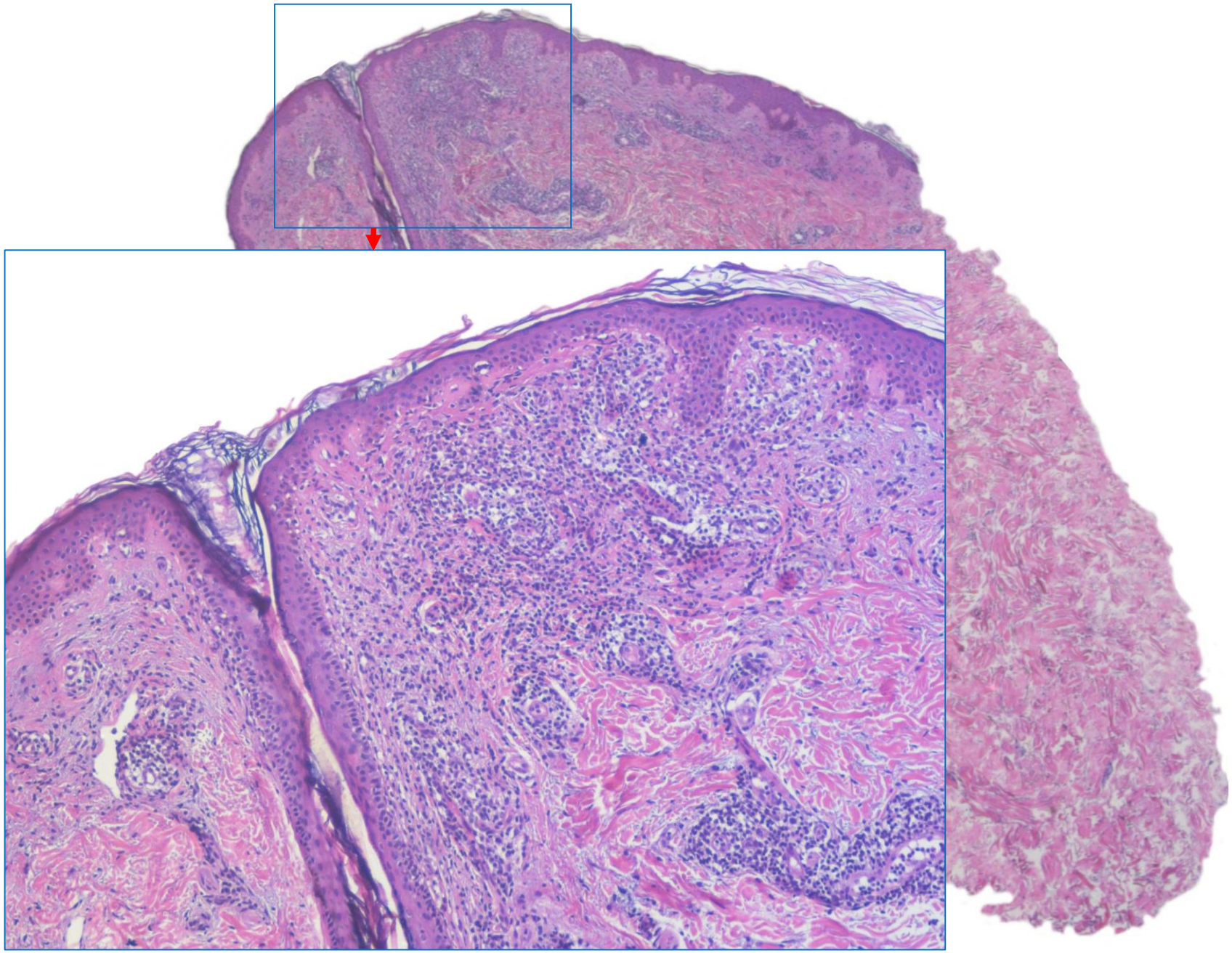
Moreover, there may be subtle fibrosis of the papillary dermis. In this case, a feature militating against mycosis fungoides and favouring a drug eruption is widely dilated venules in the upper dermis,



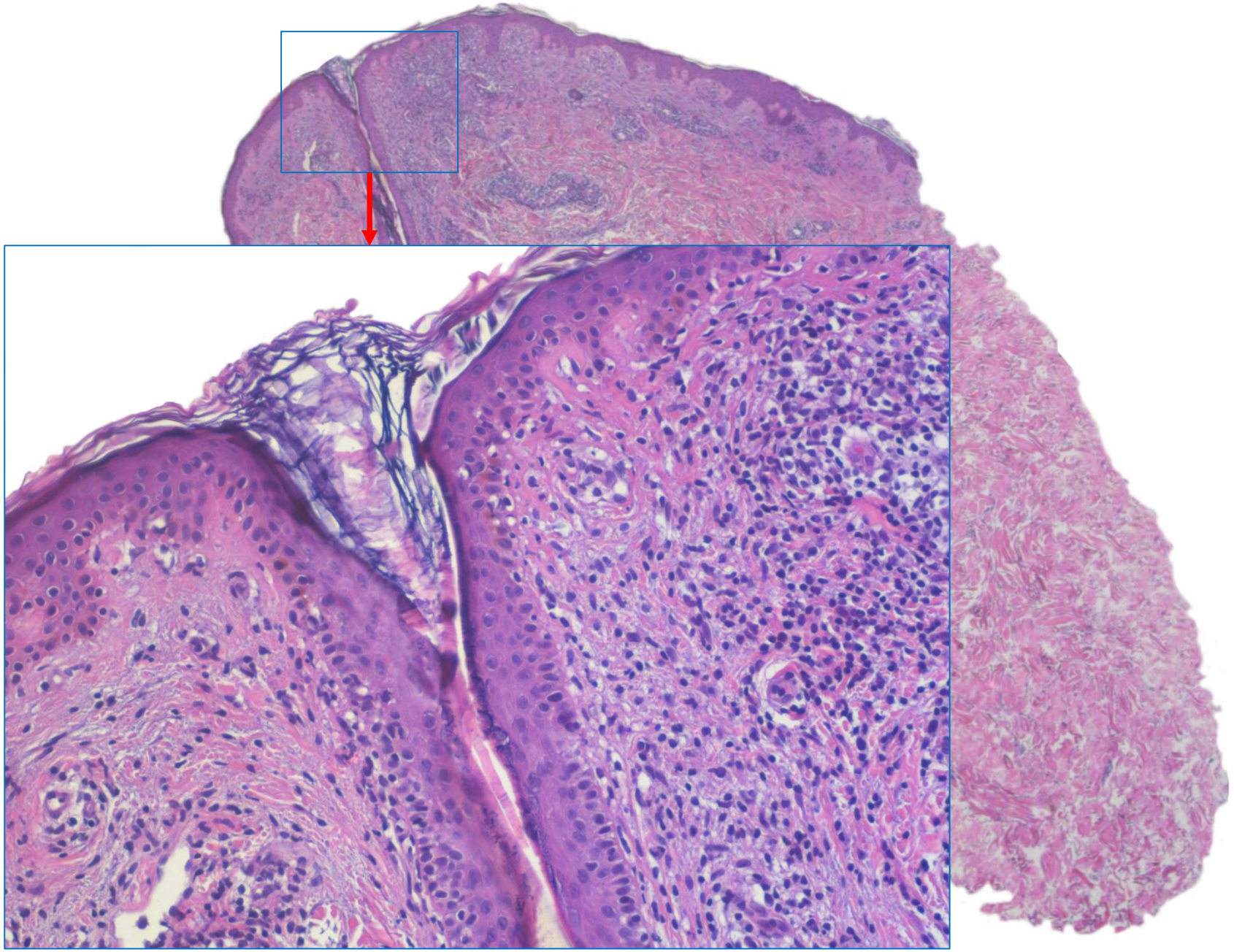
some of which house numerous neutrophils.



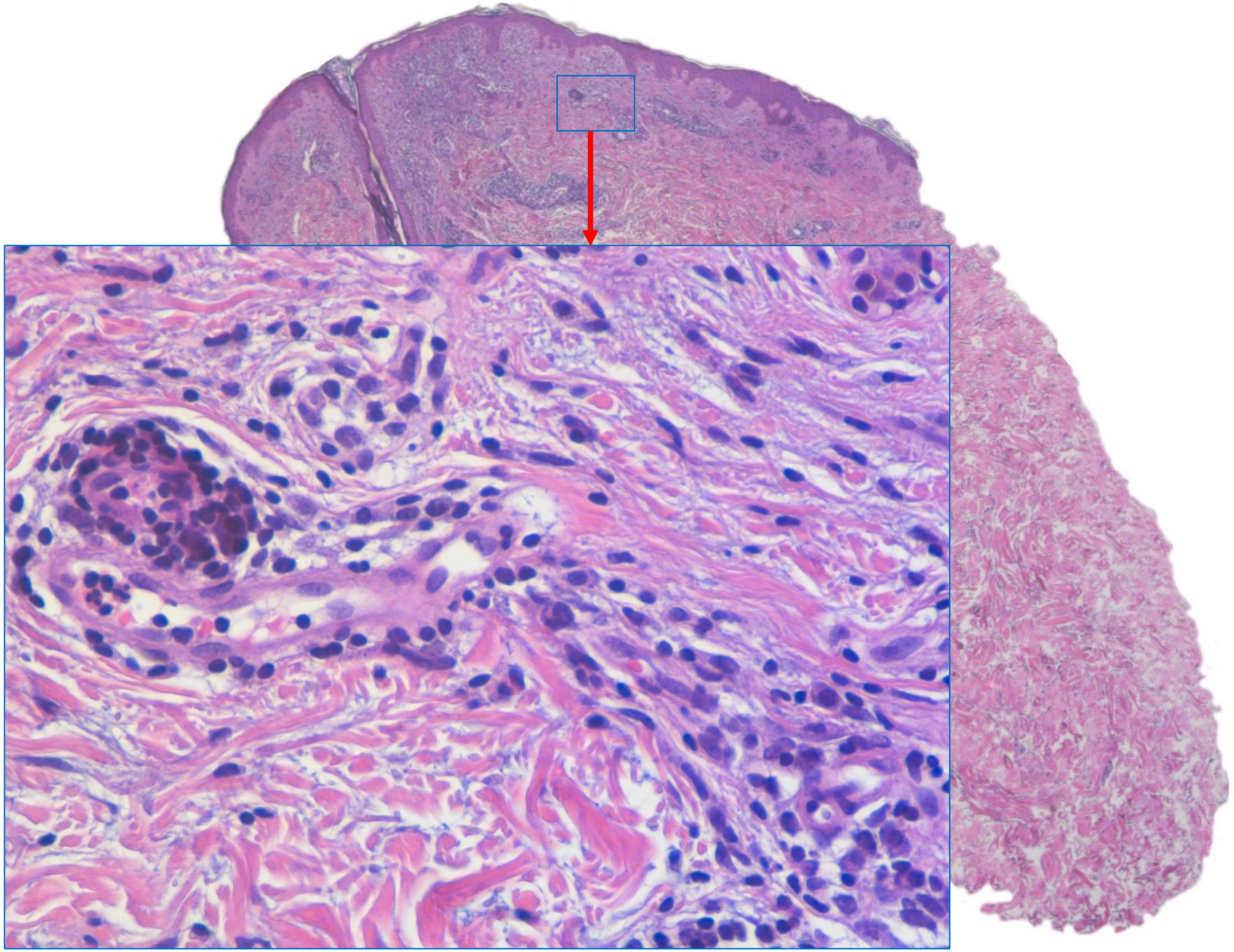
Another example of a superficial lichenoid dermatitis



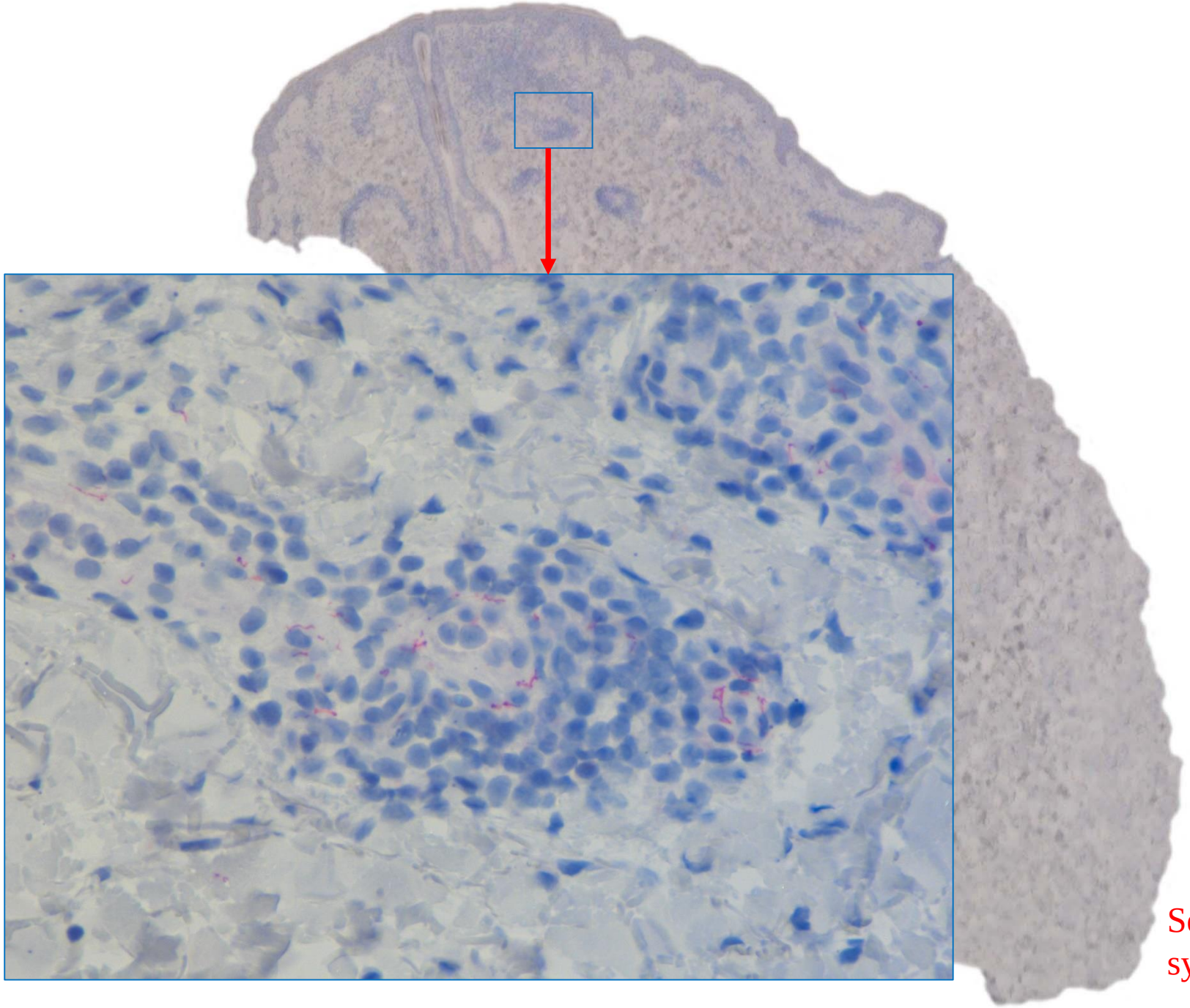
In which there are subtle interface changes. There is also slight fibrosis of the papillary dermis that is suggestive of the patch stage of mycosis fungoides.



A chronic drug eruption must also be considered but, again, there are no neutrophils and eosinophils. This does not exclude a drug eruption, but in consideration of the density of the infiltrate, it should caution against that diagnosis.

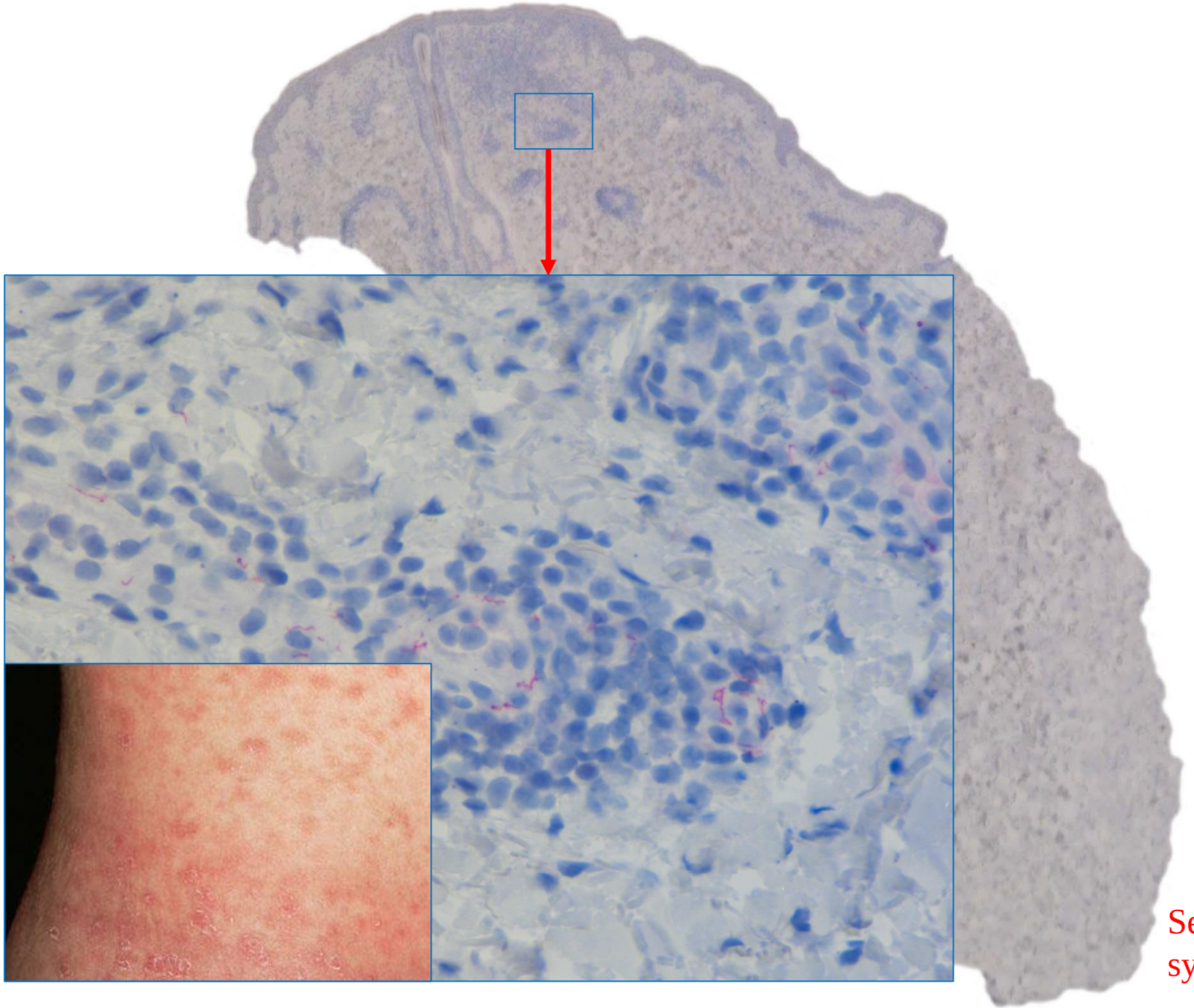


The of drug eruptions, infiltrate also contained some plasma cells,



Secondary syphilis

And immunohistochemistry with antibodies against Treponema pallidum revealed spirochetes around vessels. It is important to consider the possibility of syphilis in a subtle lichenoid interface dermatitis, especially if there are no eosinophils and neutrophils in the infiltrate,



Secondary syphilis

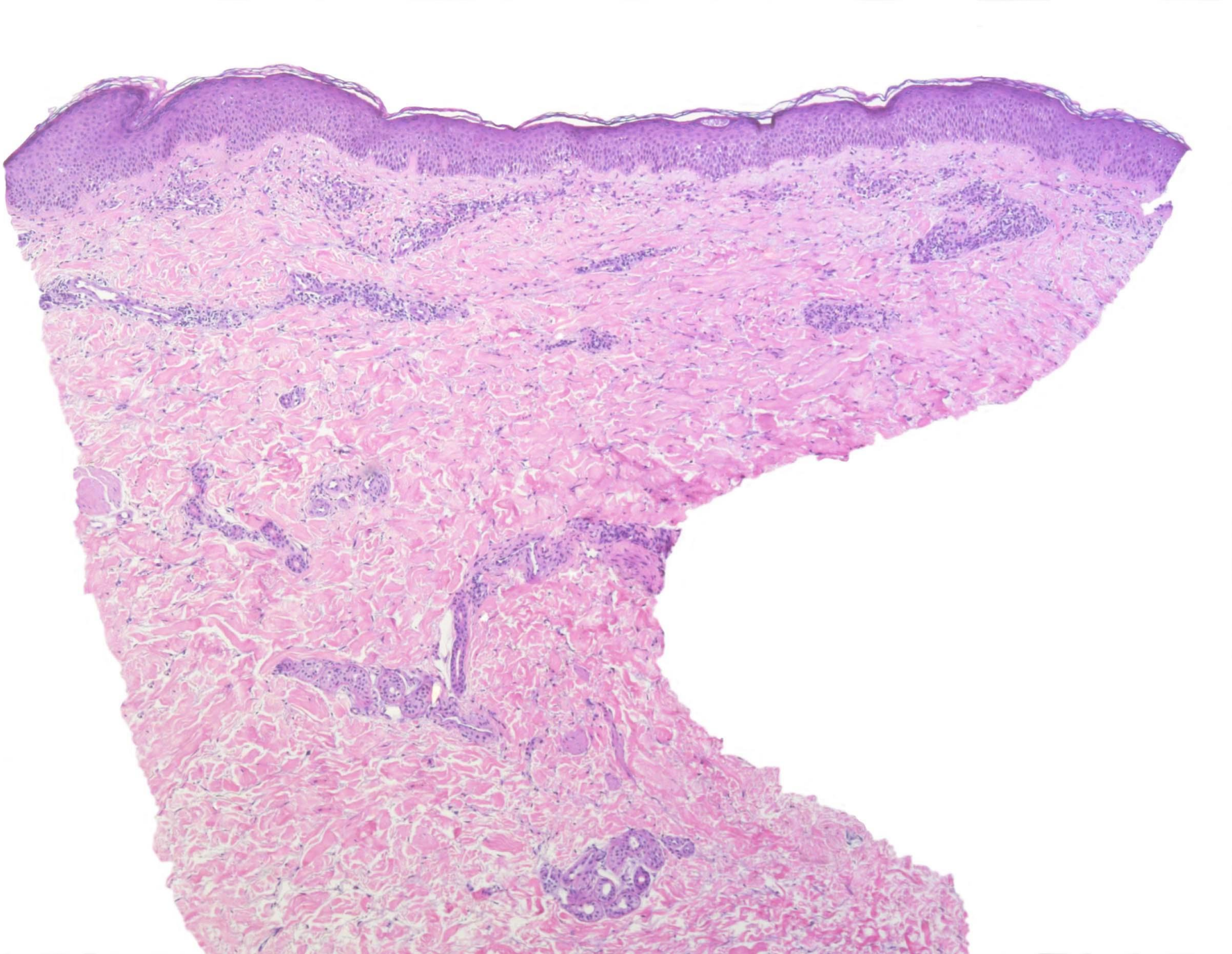
even more so because secondary syphilis is characterized by sudden onset of a maculo-papular eruption that may also be confused with a drug eruption clinically.

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

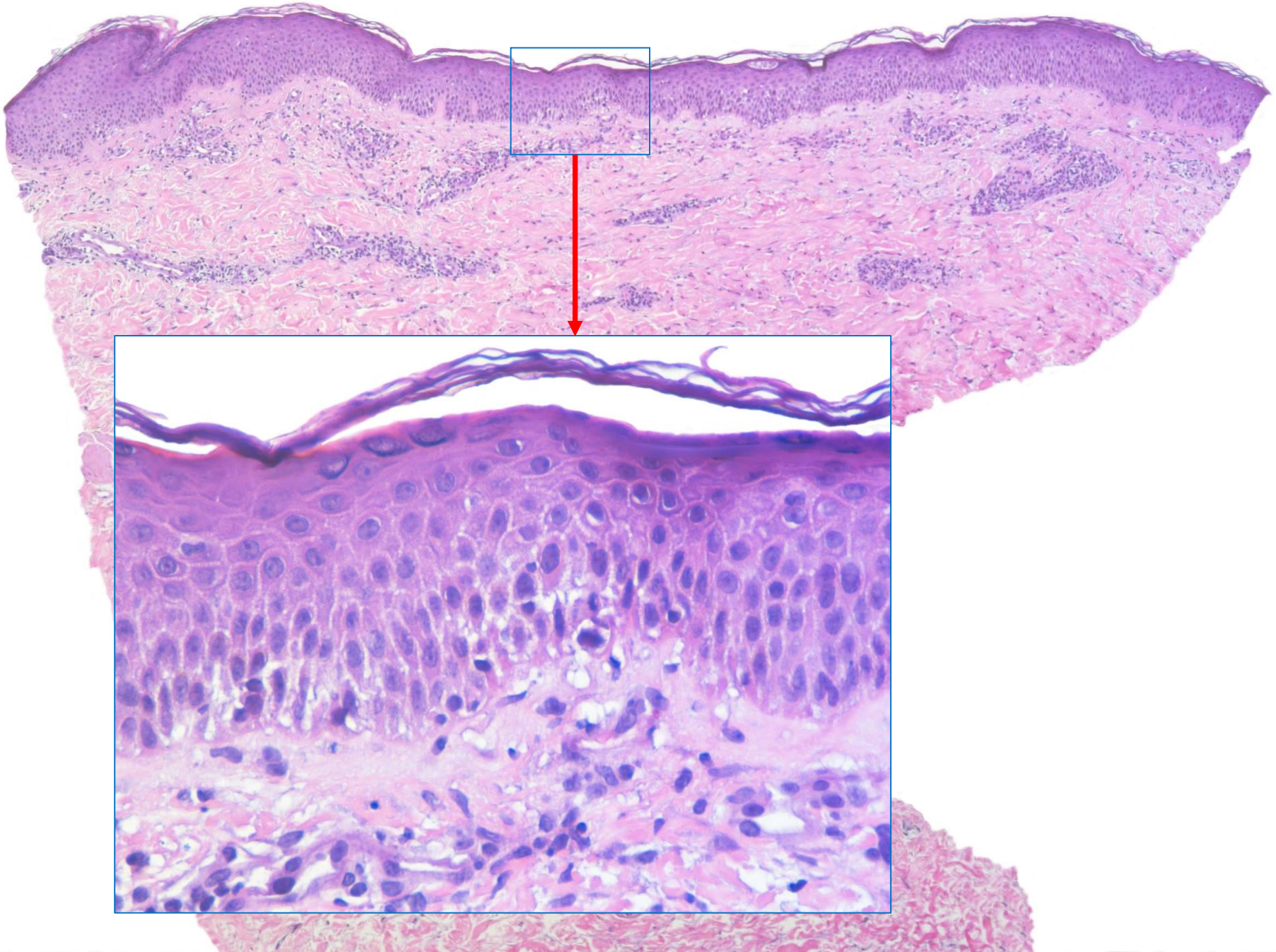
| | Pattern | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Lympho-cytic dermal without epidermal Changes (n=12)* | *Superficial and deep dermal with eosino-phils and neutrophils (n=12)* | *Severe vacuolar interface dermatitis (n=38)* | *Mild vacuolar interface dermatitis (n=83)* | *Lichenoid dermatitis (n=36)* | *Lichenoid pso-riasiform dermatitis (n=18)* | *Spongiotic dermatitis (n=62)* | *Pustular dermatitis (n=19)* | *Subepi-dermal bullous dermatitis (n=6)* | *Granulo-matous dermatitis (n=12)* | *Leukocy-toklastic vasculitis (n=2)* |
| Superficial | | | | | 26 | 11 | 54 | 18 | 4 | 0 | 0 |
| Superficial and deep | | | | | 10 | 7 | 8 | 1 | 2 | 12 | 2 |
| Perivascular | | | | | 0 | 0 | 6 | 0 | 0 | 0 | 0 |
| Interstitial | | | | | 36 | 18 | 56 | 19 | 6 | 12 | 2 |
| Vacuolar | | | | | | | | | | | |
| + | | | | | 28 | 17 | 41 | 11 | 3 | 6 | 1 |
| ++ | | | | | 8 | 1 | 0 | 2 | 3 | 0 | 0 |
| Spongiosis | | | | | | | | | | | |
| + | | | | | 16 | 18 | 56 | 12 | 2 | 3 | 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 |

- contact/nummular dermatitis
- pityriasis rosea
- erythema anulare centrifugum
- response to arthropod assault
- miliaria . . .

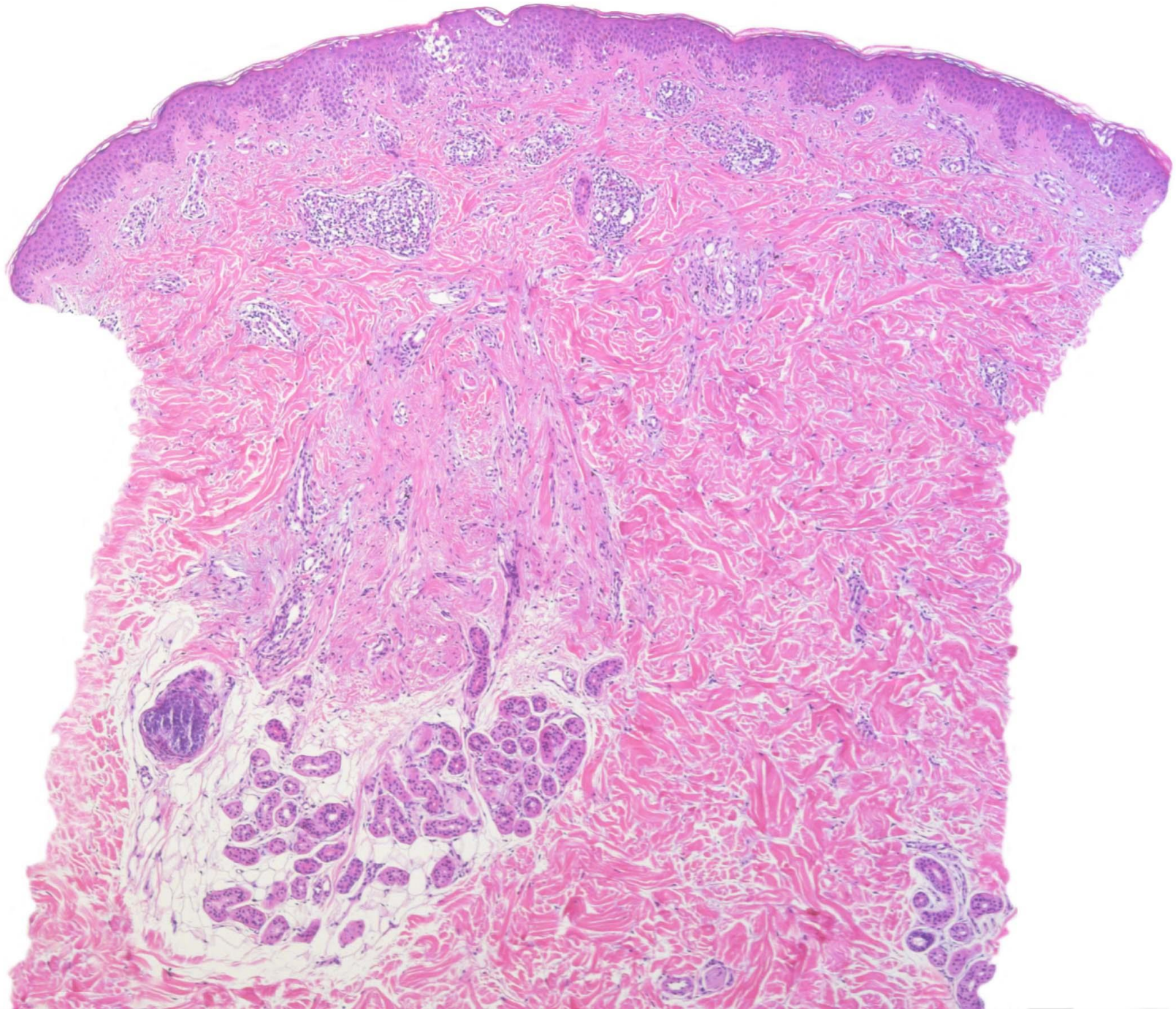
A very common pattern of drug eruptions is the spongiotic one that was the predominant pattern in nearly one fourth of the cases of our study.



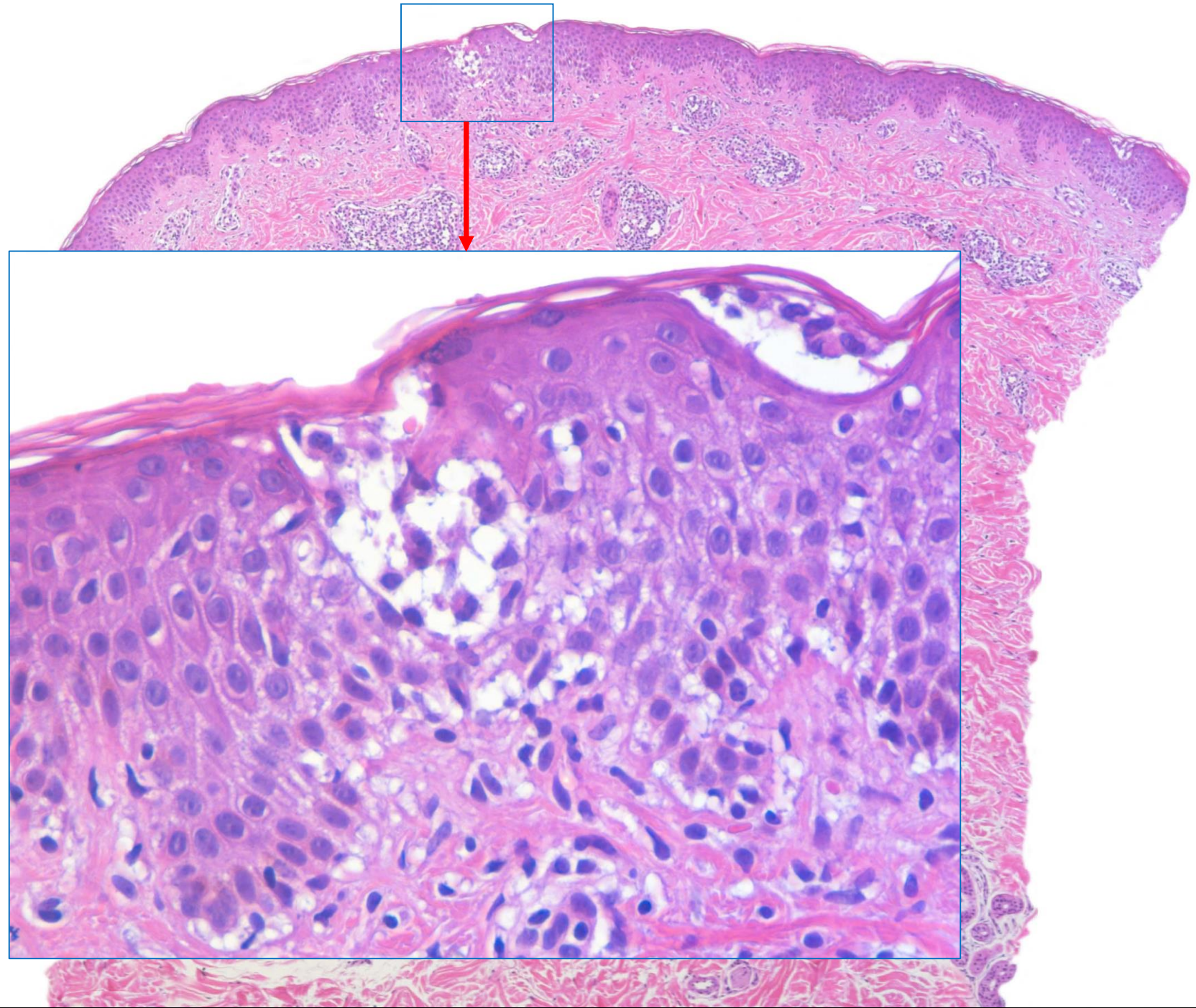
Spongiosis is hardly ever marked across a broad front, and there are usually no scale crusts, as in contact or nummular dermatitis. Other features distinguishing from dug eruptions from most differential diagnosis are extension of the infiltrate into the deep dermis, a finding encountered in nearly one third of our cases of spongiotic drug eruption,



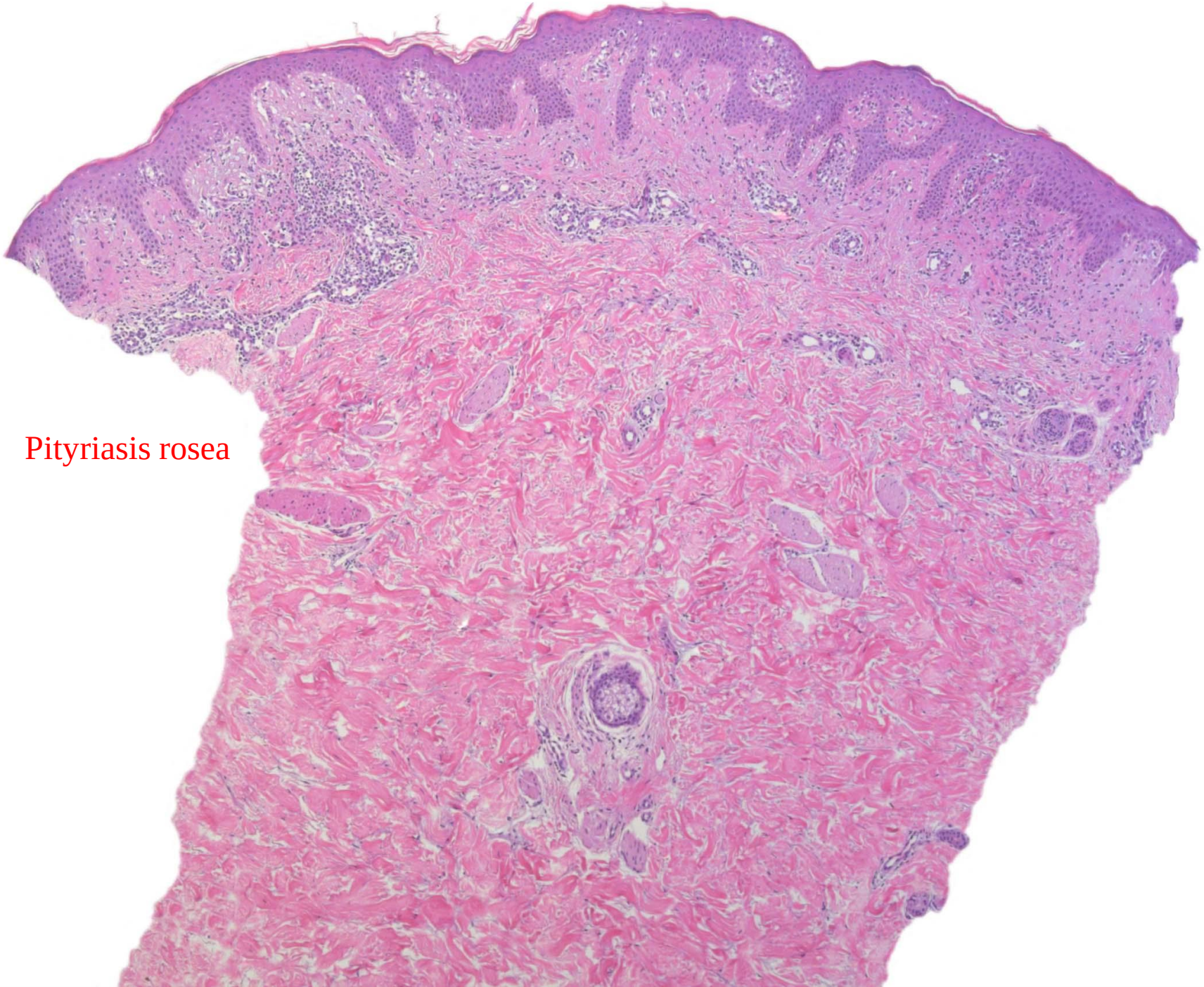
and a preserved, basket-woven cornified layer, a consequence of biopsies being taken at an early stage. In most instances, spongiosis is mild and confined to the lower half of the epidermis. That finding, in the context of a deep reaching infiltrate and a basket-woven cornified layer, is quite distinctive.



Another pattern of spongiotic drug eruption consists of tiny spongiotic vesicles separated from one another by more or less normal epidermis. That pattern of isolated spongiotic vesicles resembles pityriasis rosea and superficial erythema annulare centrifugum,

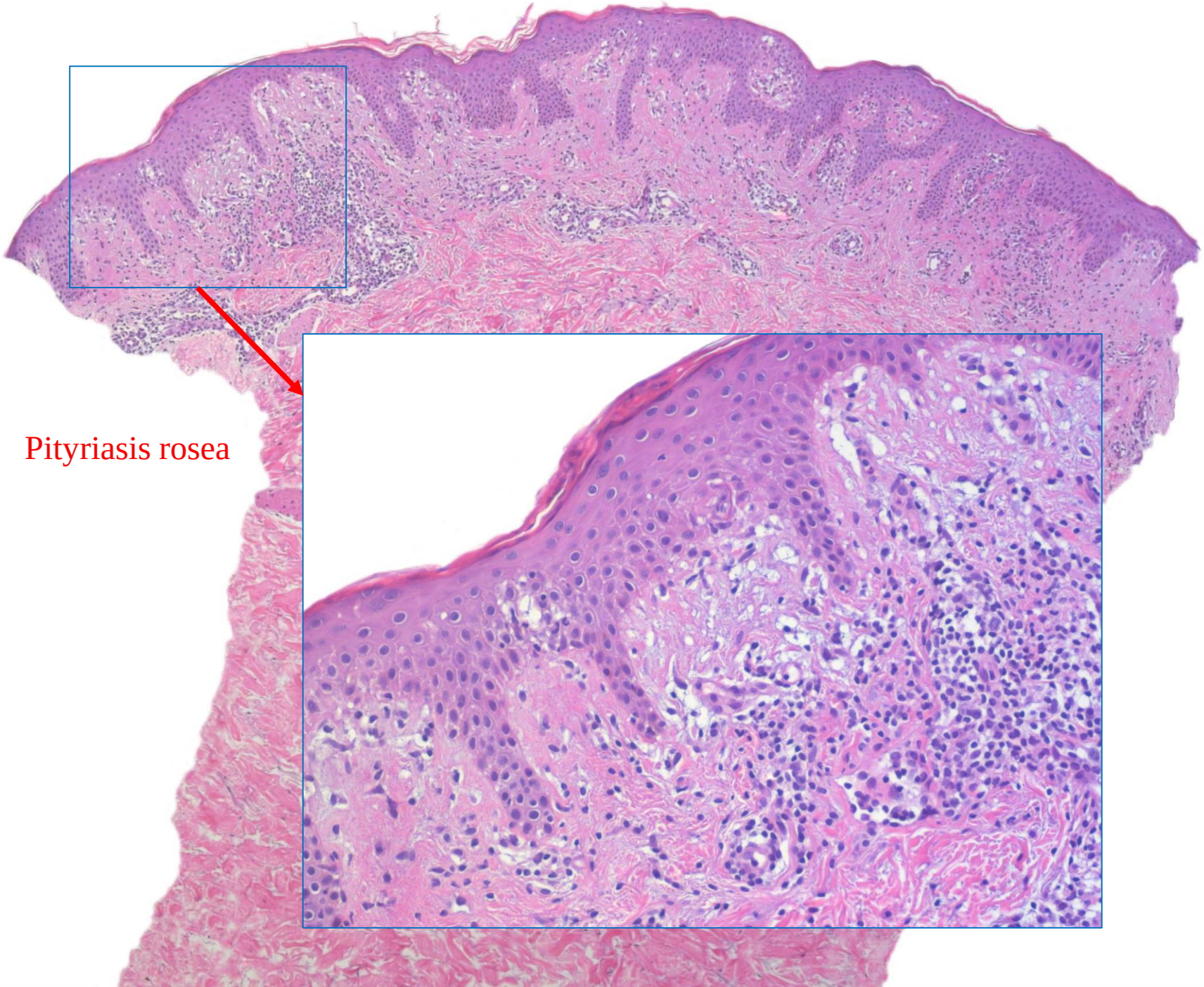


distinction of which is complicated further by the mutual finding of some eosinophils and extravasated erythrocytes in all three conditions.

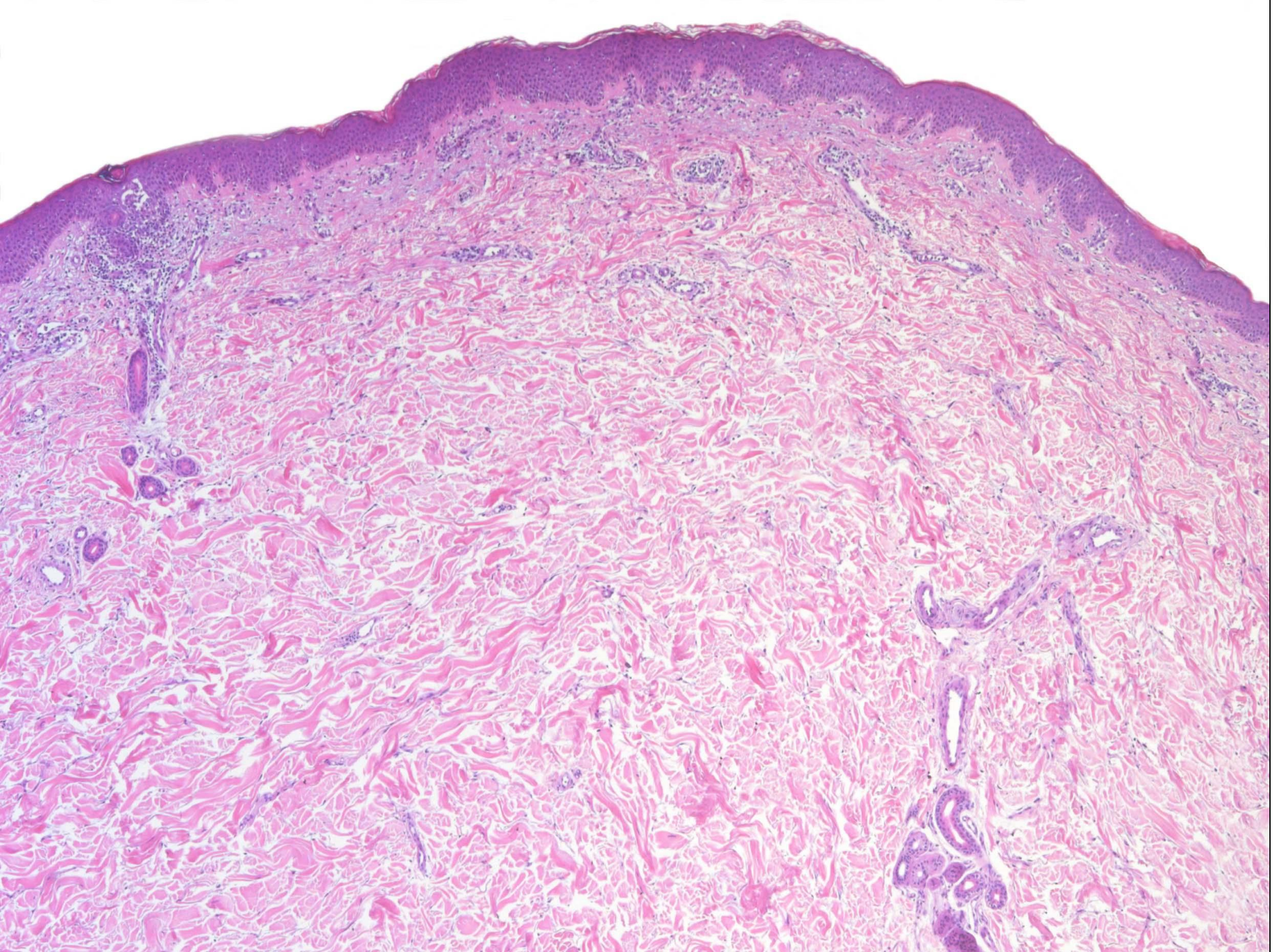


Pityriasis rosea

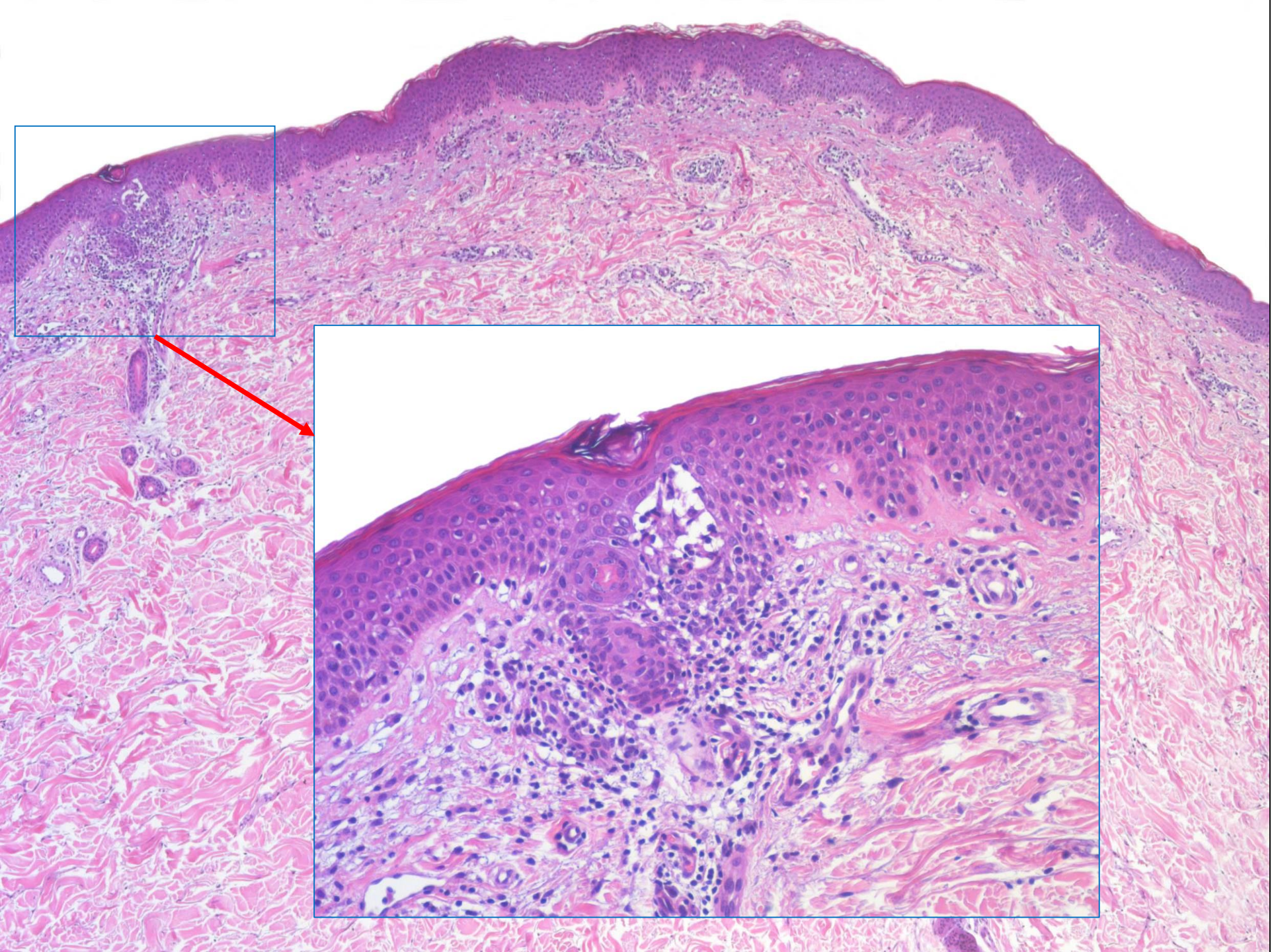
However, the infiltrate in pityriasis rosea is usually superficial, rather than superficial and deep, and there may be focal scale-crusts which are exceptional in drug eruptions.



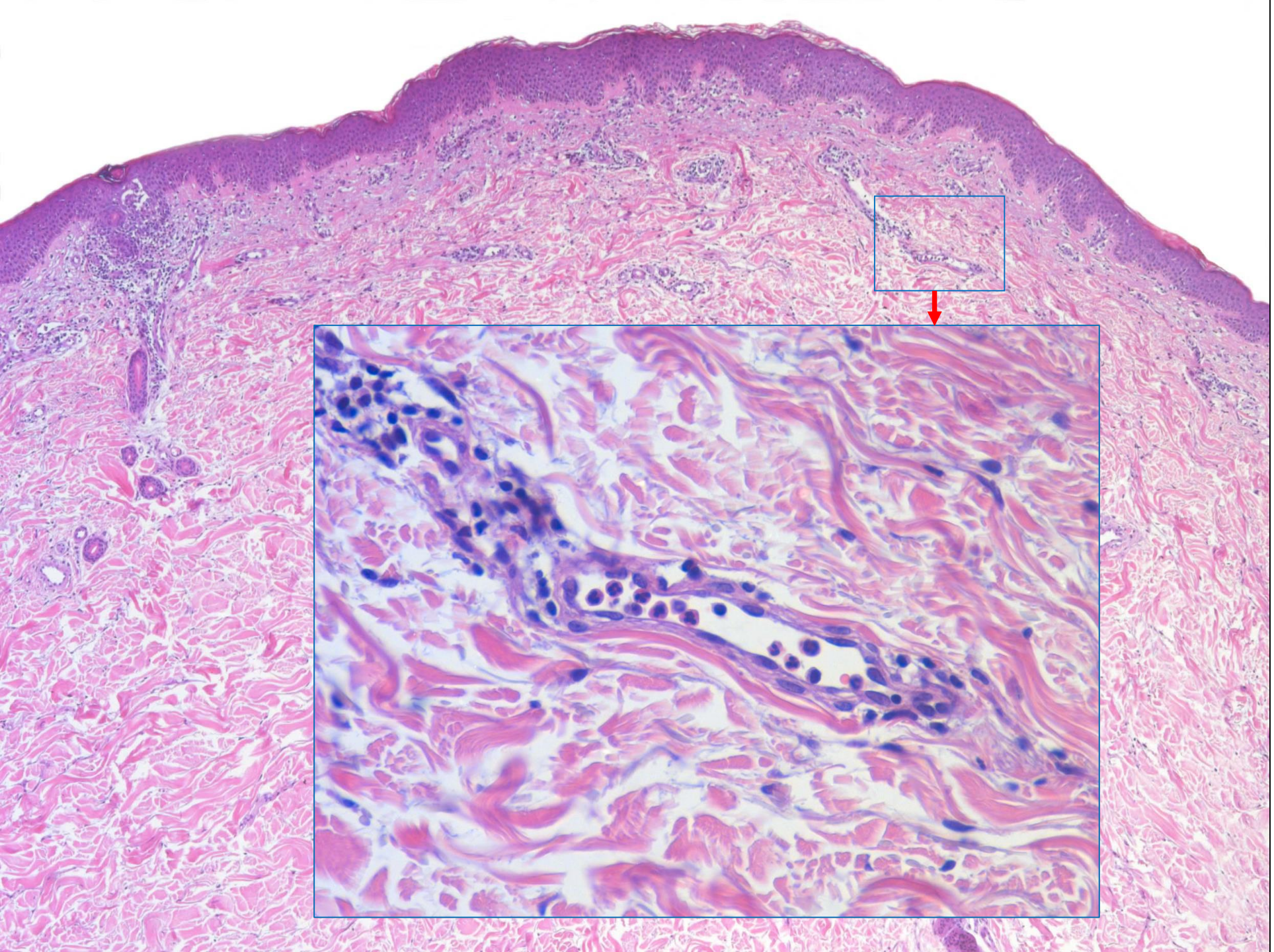

Moreover, there is often slight psoriasiform hyperplasia with rete ridges more delicate than in psoriasis, yet another finding militating against a drug eruption.



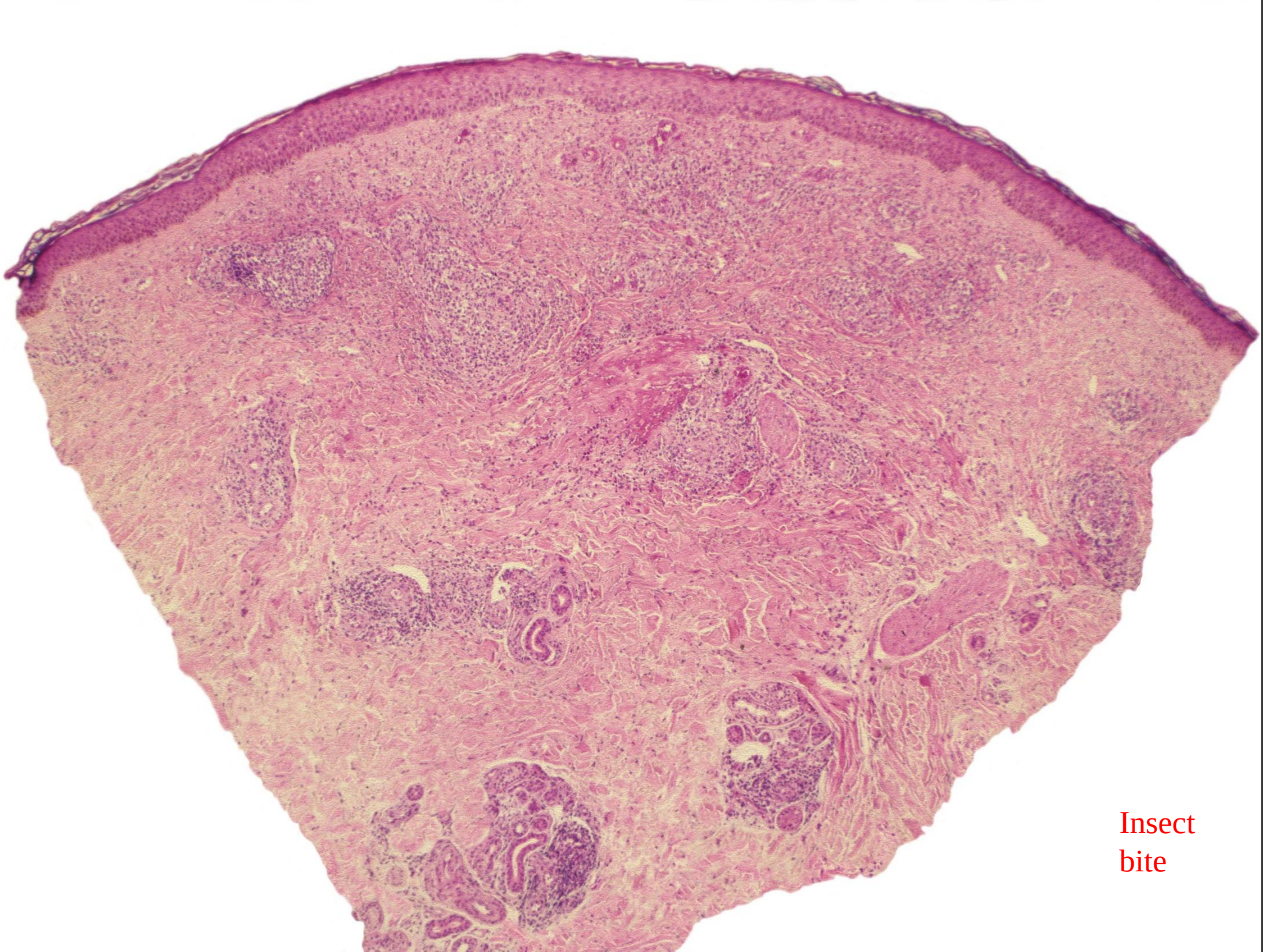
Vice versa, spongiotic drug eruptions may show accentuation of spongiosis around acrosyringia,



just as necrotic keratocytes may be concentrated there in lichenoid drug eruptions. The picture may thus resemble miliaria, but other findings are in favor of a drug eruption,

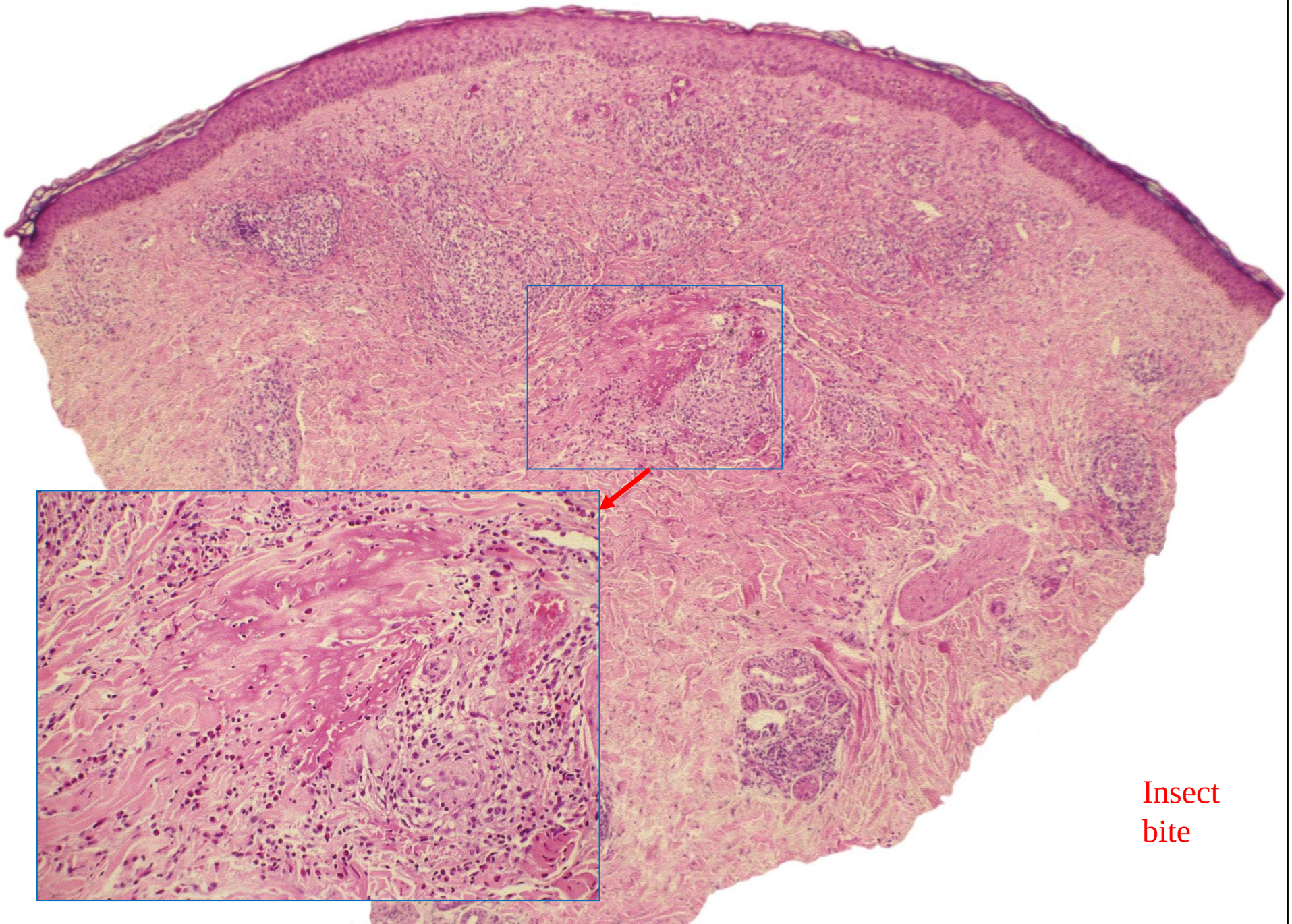


namely, dilated venules in the upper dermis with numerous neutrophils in their lumina.



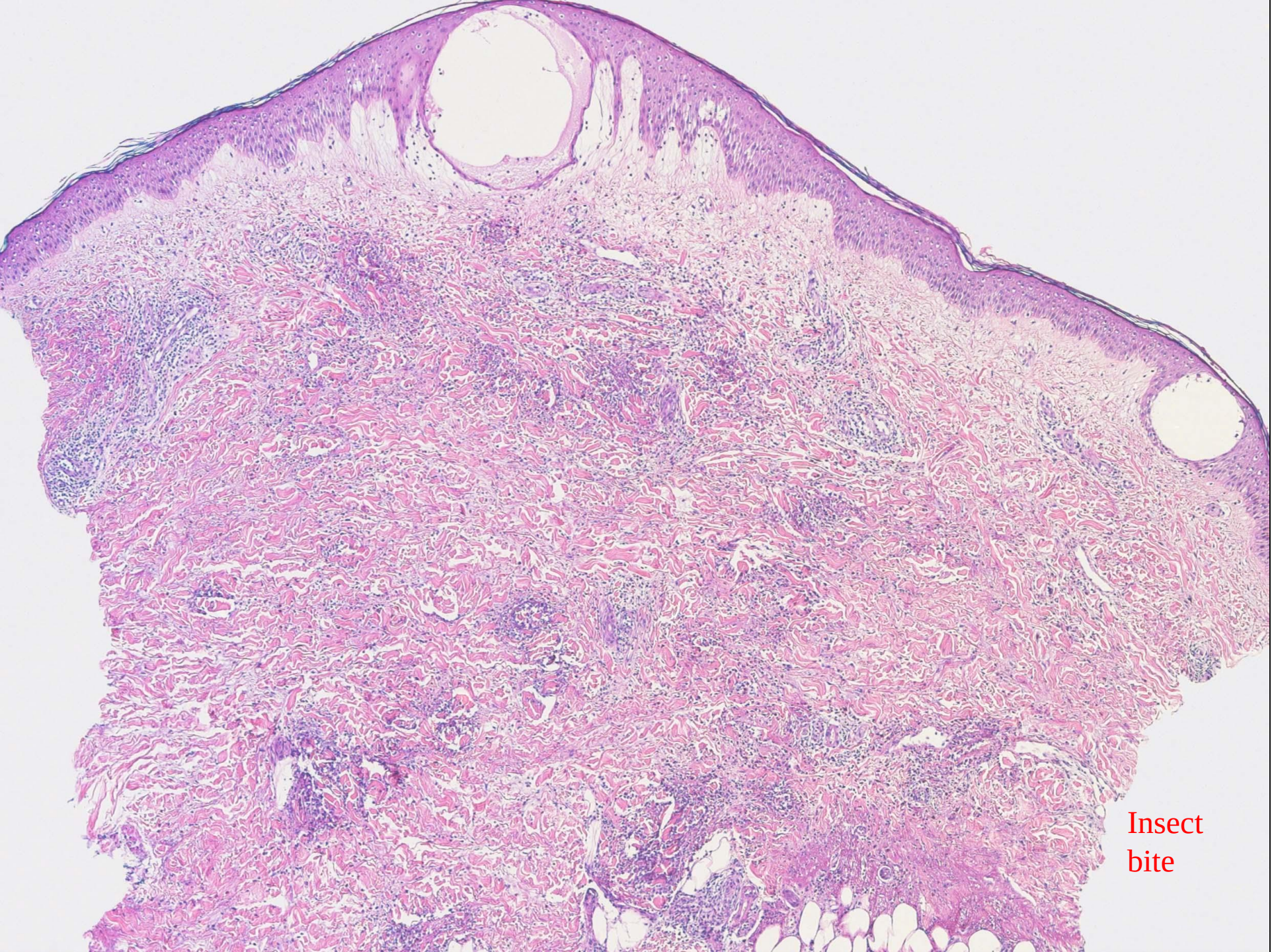
Insect bite

The infiltrate is usually sparse in spongiotic drug eruptions, but it may vary in density, and so may the number of eosinophils contributing to it. If there are myriads of them, the fore-mentioned differential diagnoses are unlikely and others must be considered, such as reactions to an insect bite. The latter may be distinguished by the typical wedge-shaped configuration of the infiltrate not seen in drug eruptions.

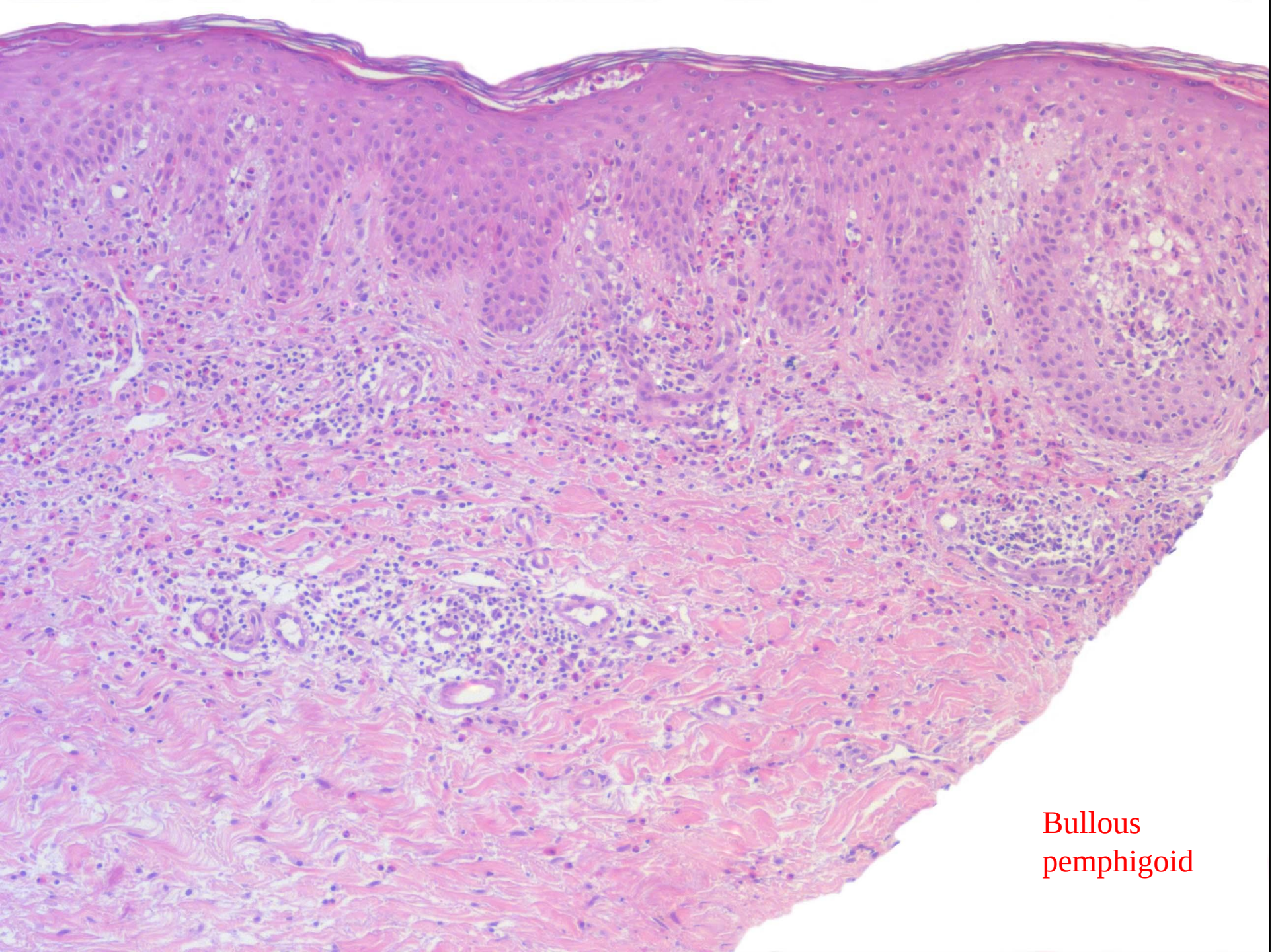


Insect bite

Moreover, the collagen in the reticular dermis is often smudged, and there may be deposits of fibrin.

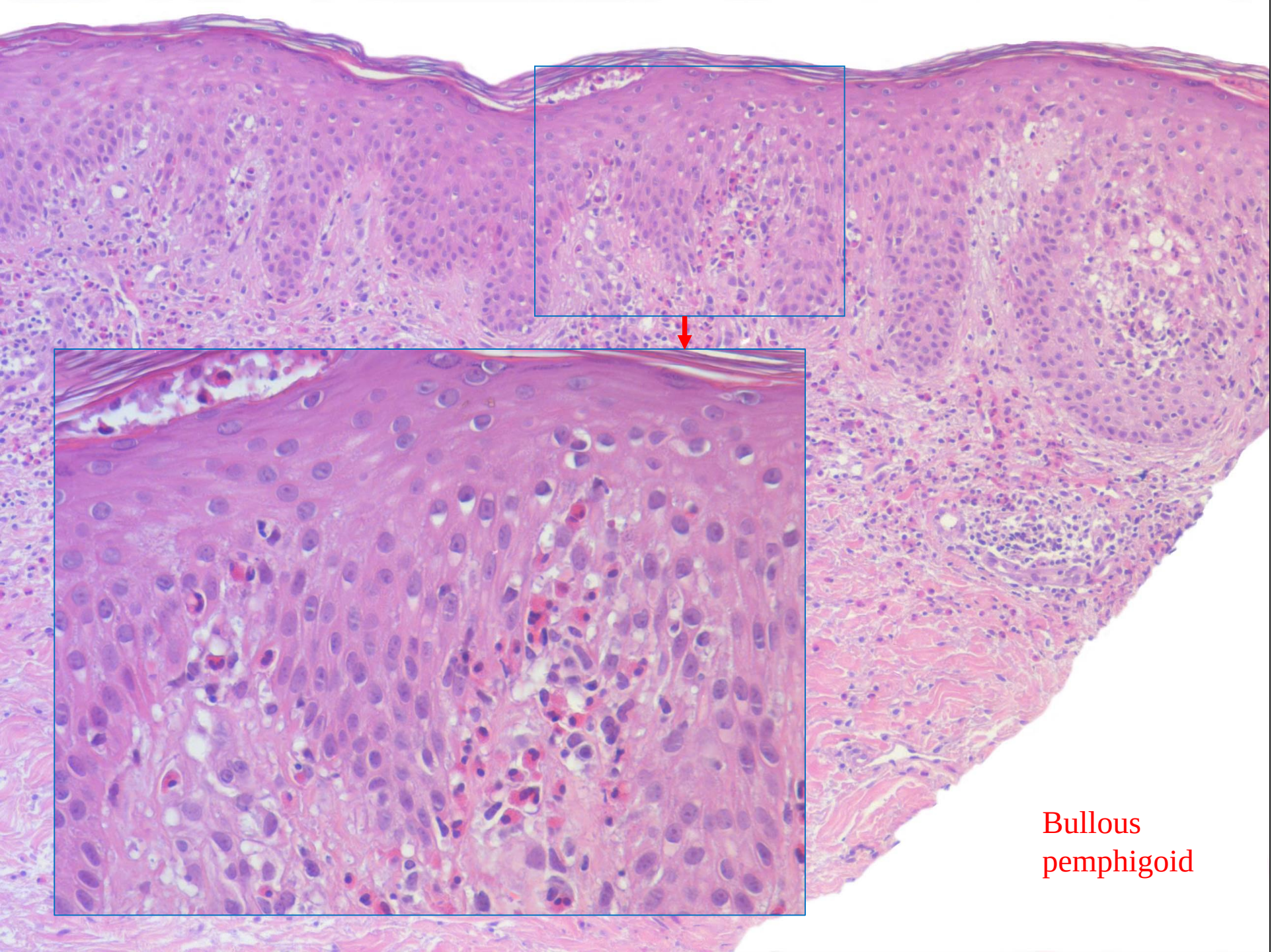



If there are spongiotic vesicles in reactions to insect bites, the largest one is usually located immediately above the deepest extension of the infiltrate.



Bullous pemphigoid

If an infiltrate loaded with eosinophils is more diffuse and chiefly located in the upper dermis, one must think of autoimmune bullous diseases, especially bullous pemphigoid.



Bullous pemphigoid

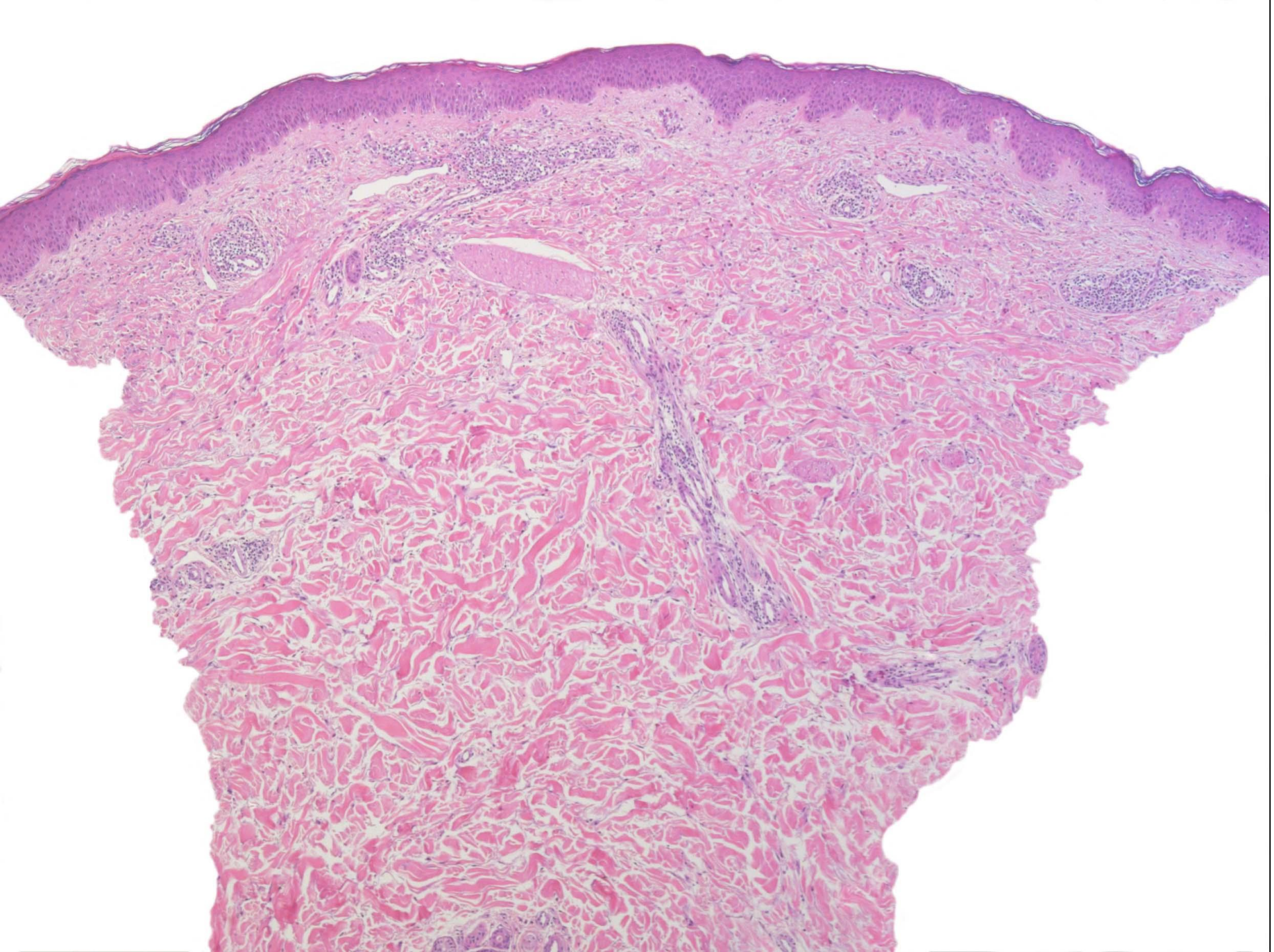
The latter can often be distinguished from spongiotic drug eruptions by clustering of eosinophils in the basement membrane zone.

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

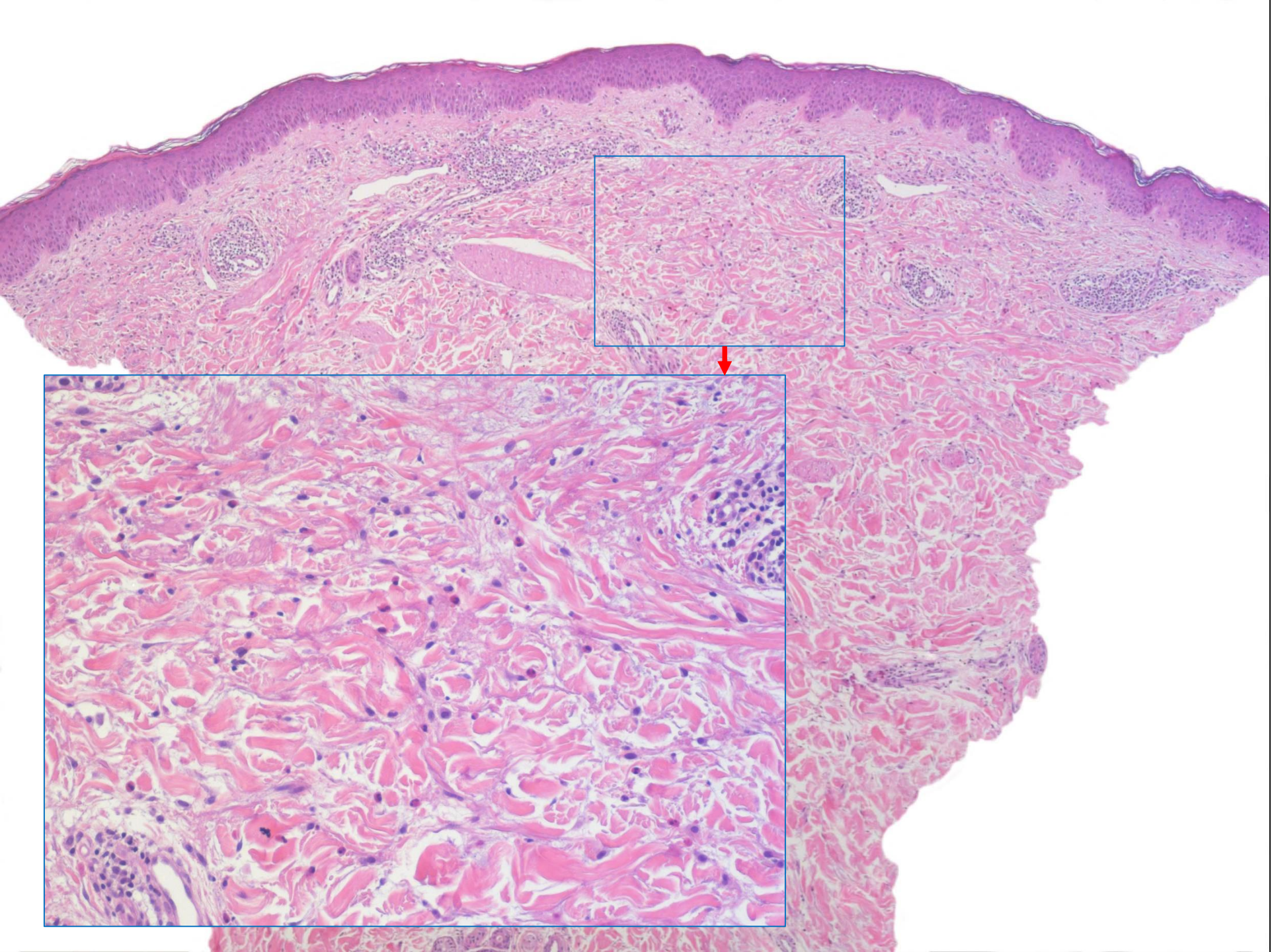
| | Pattern | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Lympho-cytic dermal without epidermal Changes (n=12)* | *Superficial and deep dermal with eosino-phils and neutrophils (n=12)* | *Severe vacuolar interface dermatitis (n=38)* | *Mild vacuolar interface dermatitis (n=83)* | *Lichenoid dermatitis (n=36)* | *Lichenoid pso-riasiform dermatitis (n=18)* | *Spongiotic dermatitis (n=62)* | *Pustular dermatitis (n=19)* | *Subepi-dermal bullous dermatitis (n=6)* | *Granulo-matous dermatitis (n=12)* | *Leukocy-toklastic vasculitis (n=2)* |
| Superficial | 10 | 0 | 28 | 55 | 26 | 11 | | | | | 0 |
| Superficial and deep | 2 | 12 | 10 | 28 | 10 | 7 | | | | | 2 |
| Perivascular | 11 | 0 | 5 | 12 | 0 | 0 | | | | | 0 |
| Interstitial | 1 | 12 | 33 | 71 | 36 | 18 | | | | | 2 |
| Vacuolar | | | | | | | | | | | |
| + | 0 | 0 | 0 | 83 | 28 | 17 | | | | | 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 |

- Sweet's syndrome
- bullous pemphigoid
- viral exanthems
- vicinity of folliculitis
- urticaria

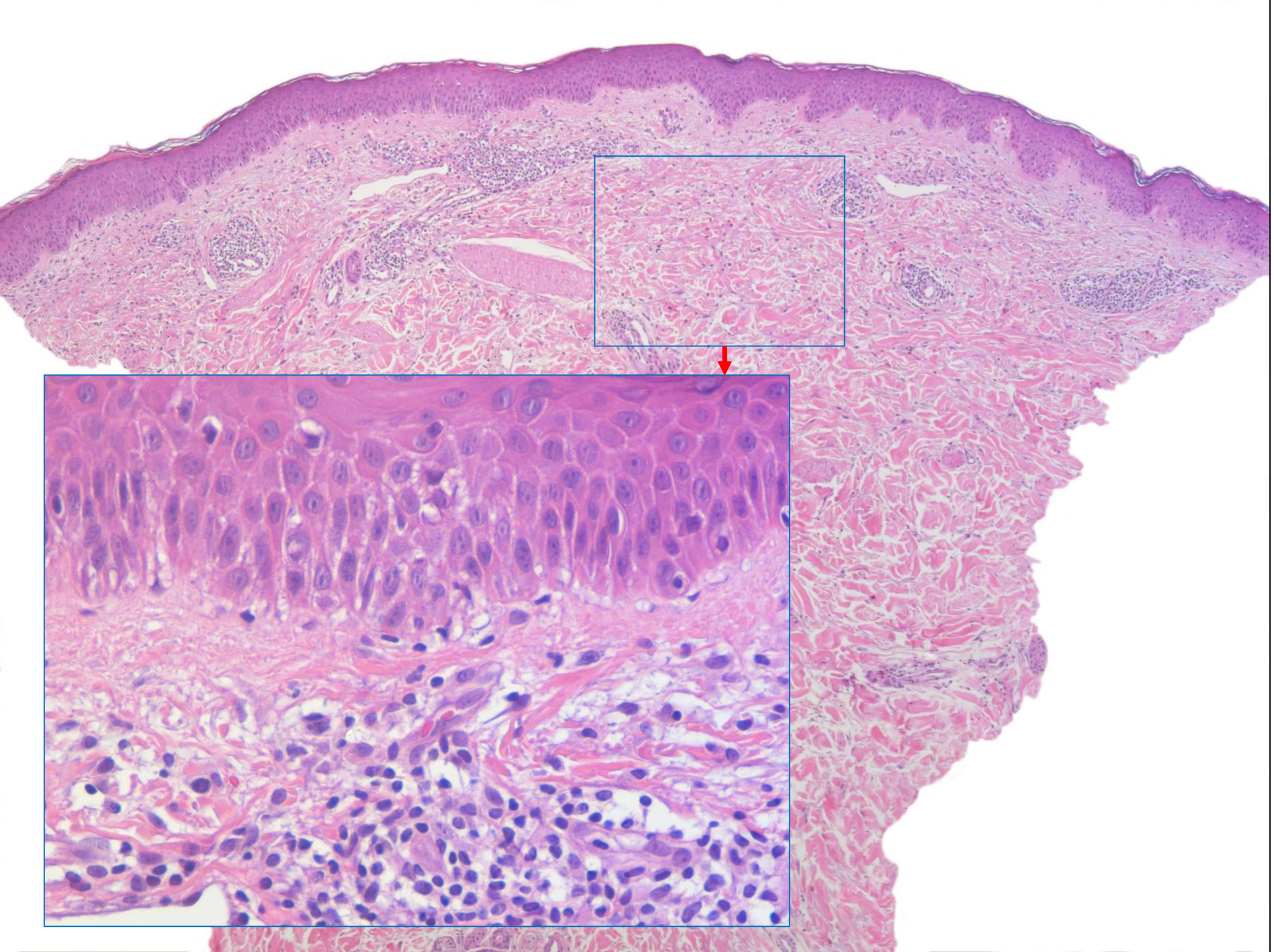
If the epidermis is unaffected, distinction of drug eruptions from bullous pemphigoid or other autoimmune blistering diseases may be impossible. The pattern of a superficial and deep dermatitis with eosinophils and neutrophils in the absence of significant epidermal changes, however, was seen in only 12 of 300 cases in our study. The differential diagnosis depends on the density of the infiltrate and may range from Sweet's syndrome on the one hand to urticaria on the other.



Especially chronic idiopathic urticaria may be difficult to distinguish from urticarial drug eruptions, both conditions being typified



by a sparse interstitial infiltrate of eosinophils and neutrophils. In this case, perivascular accentuation of the infiltrate militates against chronic urticaria and favors a drug eruption,



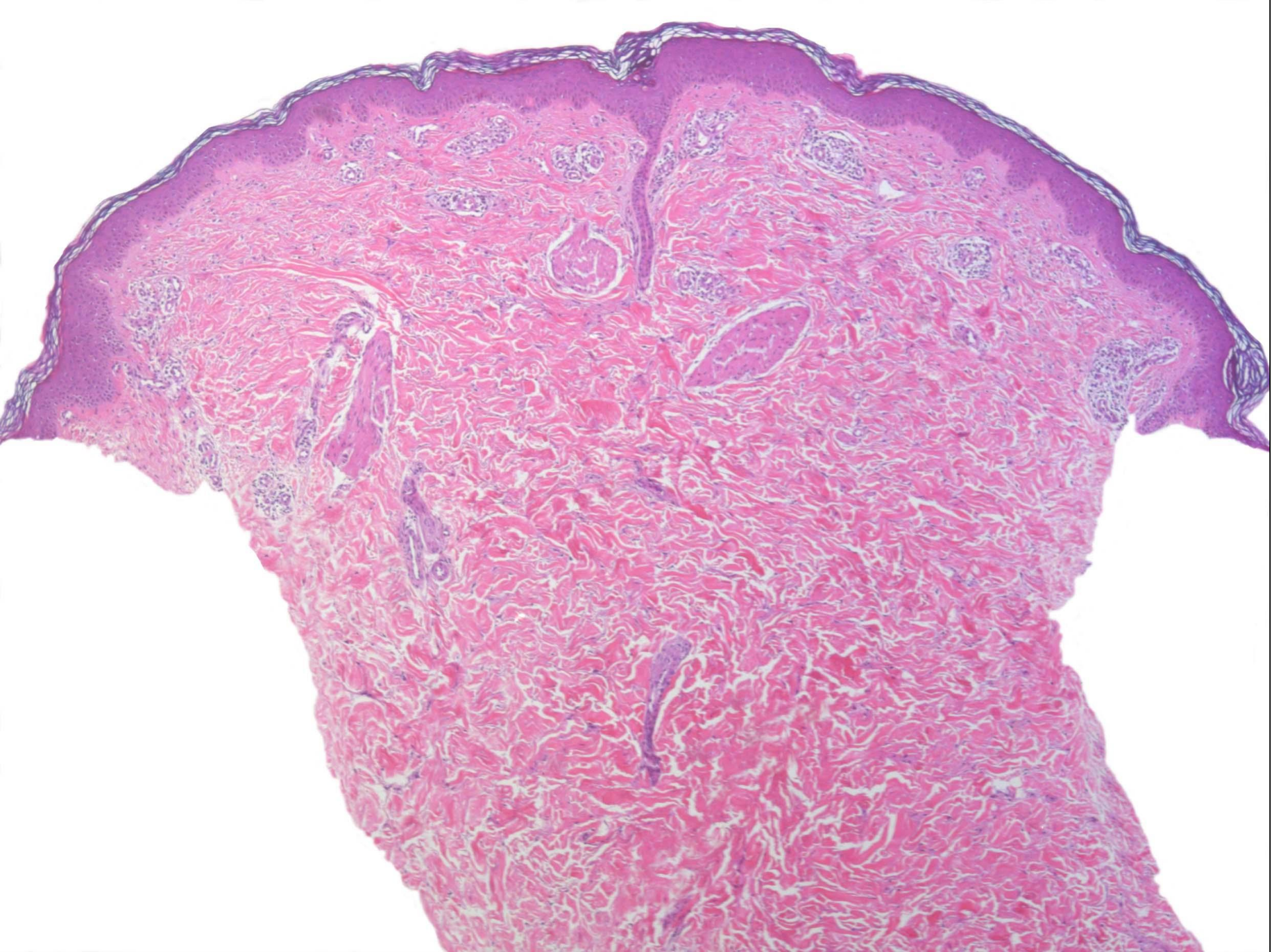
but it is worthwile to look carefully for minimal epidermal changes, such as slight focal spongiosis that is not a feature of urticaria.

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

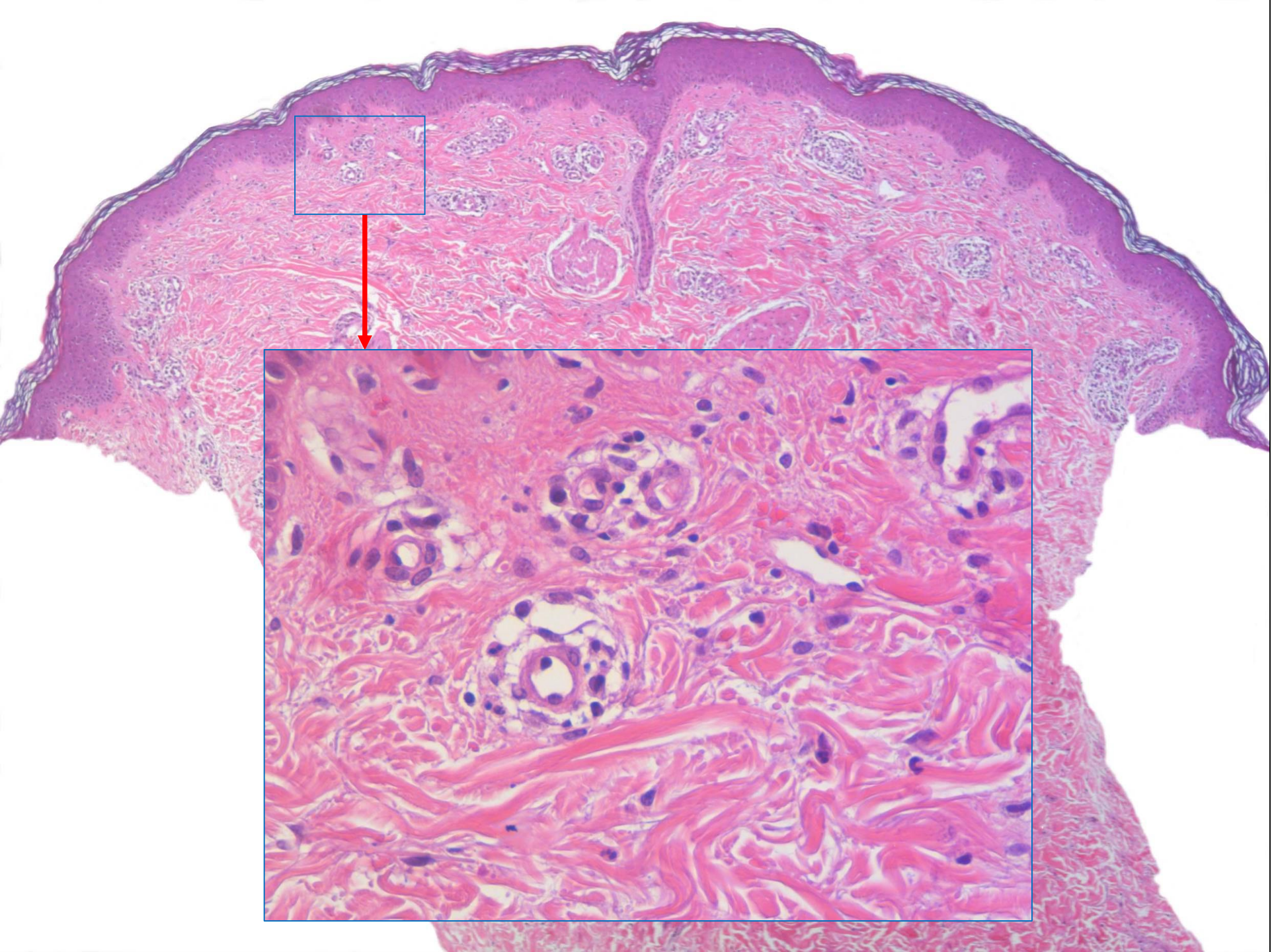
| | Pattern | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Lympho-cytic dermal without epidermal Changes (n=12)* | *Superficial and deep dermal with eosino-phils and neutrophils (n=12)* | *Severe vacuolar interface dermatitis (n=38)* | *Mild vacuolar interface dermatitis (n=83)* | *Lichenoid dermatitis (n=36)* | *Lichenoid pso-riasiform dermatitis (n=18)* | *Spongiotic dermatitis (n=62)* | *Pustular dermatitis (n=19)* | *Subepi-dermal bullous dermatitis (n=6)* | *Granulo-matous dermatitis (n=12)* | *Leukocy-toklastic vasculitis (n=2)* |
| Superficial | 10 | 0 | 28 | 55 | 26 | 11 | | | | | 0 |
| Superficial and deep | 2 | 12 | 10 | 28 | 10 | 7 | | | | | 2 |
| Perivascular | 11 | 0 | 5 | 12 | 0 | 0 | | | | | 0 |
| Interstitial | 1 | 12 | 33 | 71 | 36 | 18 | | | | | 2 |
| Vacuolar | | | | | | | | | | | |
| + | 0 | 0 | 0 | 83 | 28 | 17 | | | | | 1 |
| ++ | 0 | 0 | 38 | 0 | 8 | 1 | | | | | 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 |

- viral exanthem
- Schamberg's disease
- secondary syphilis
- early stages of diseases that eventually affect the epidermis

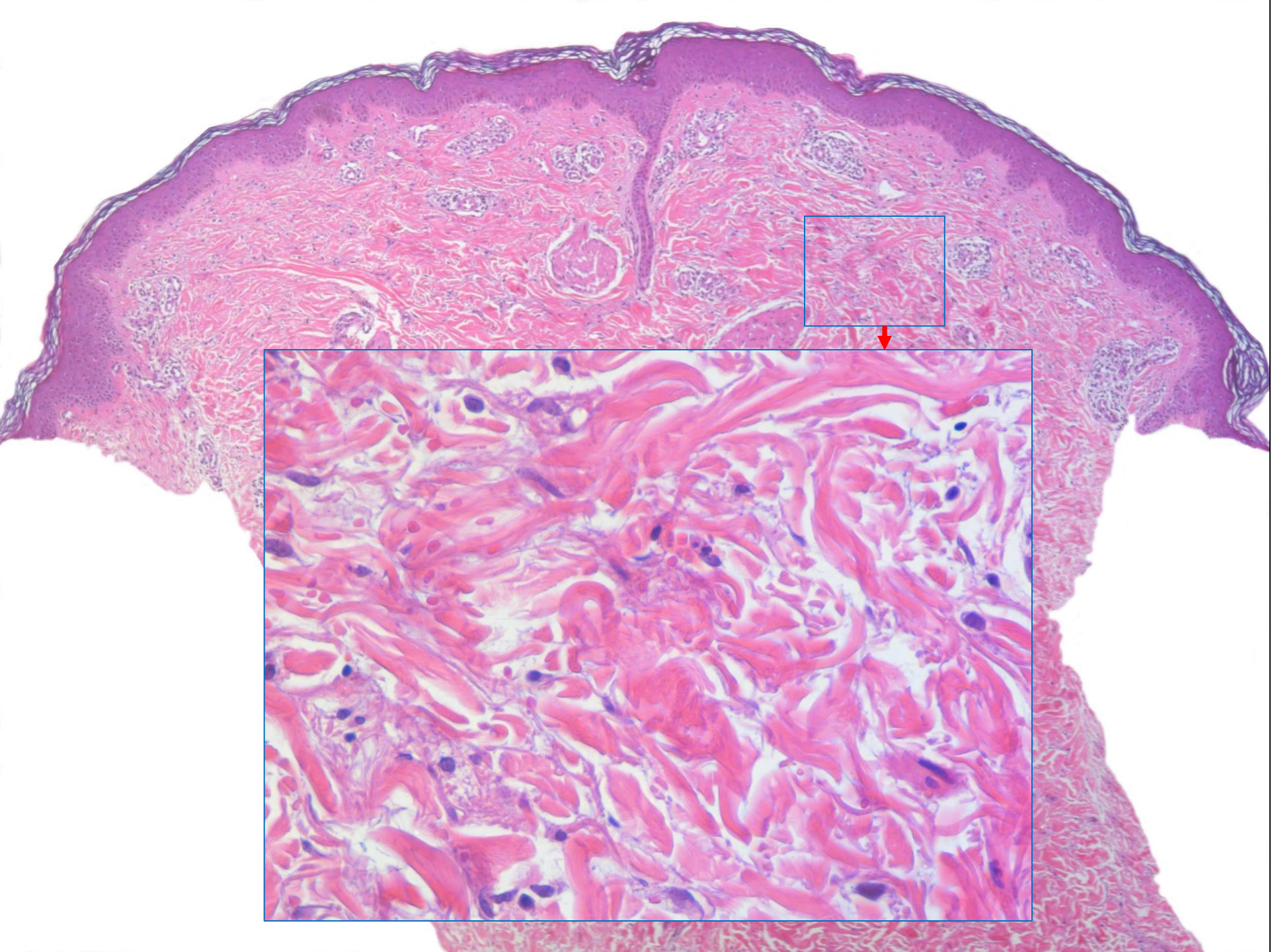
If there are no epidermal changes and no eosinophils and neutrophils in the infiltrate, diagnosis becomes even more difficult, the reason being that those findings may be seen not only in viral exanthems, Schamberg's disease, and secondary syphilis, but also in the early stages of a wide variety of other diseases that eventually affect the epidermis. In brief, the pattern is non-diagnostic because it leaves too many possibilities.



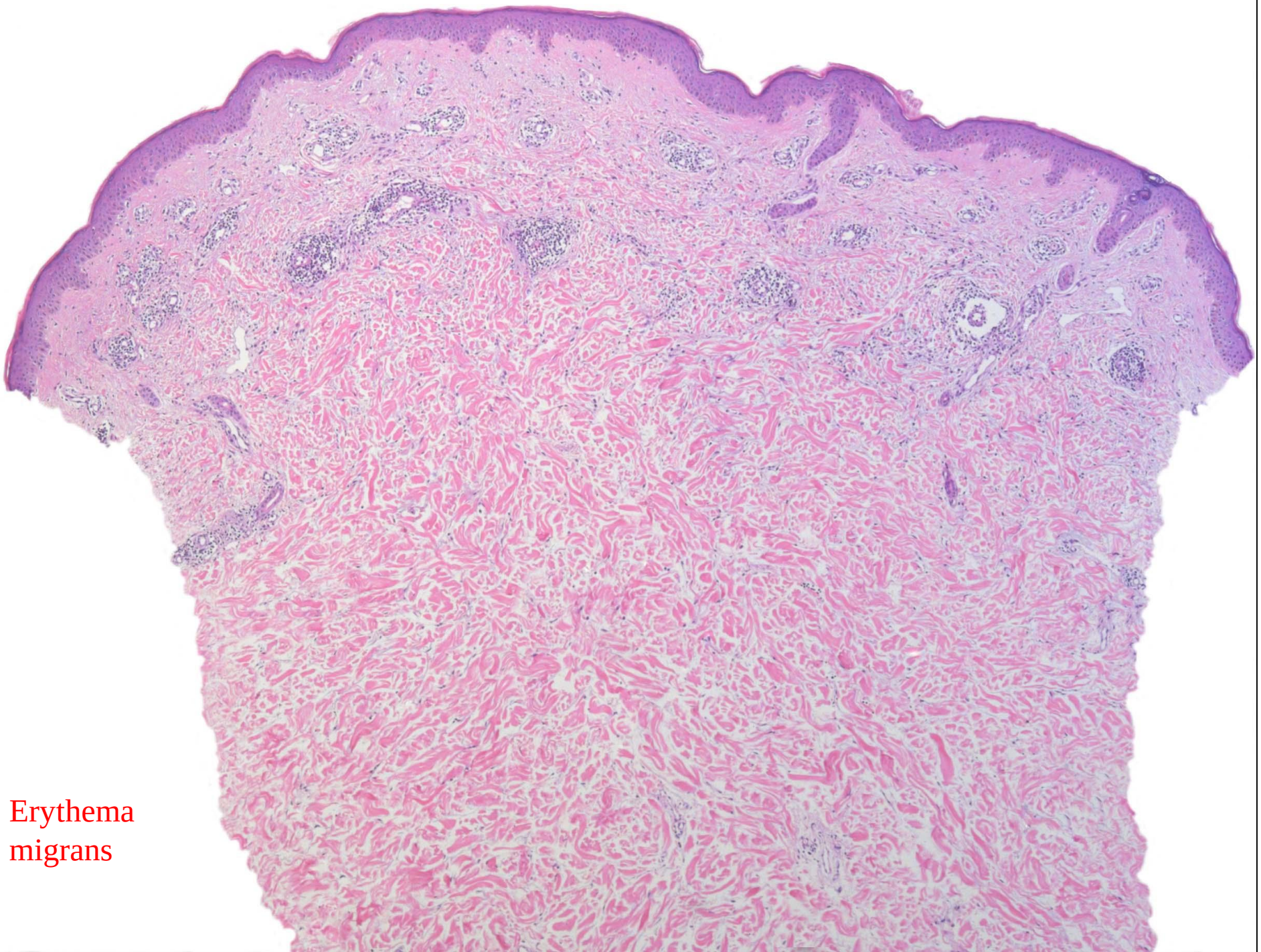
In a case with a sparse perivascular infiltrate such as this one, one might consider Schamberg's disease



because of extravasation of erythrocytes in the papillary dermis.

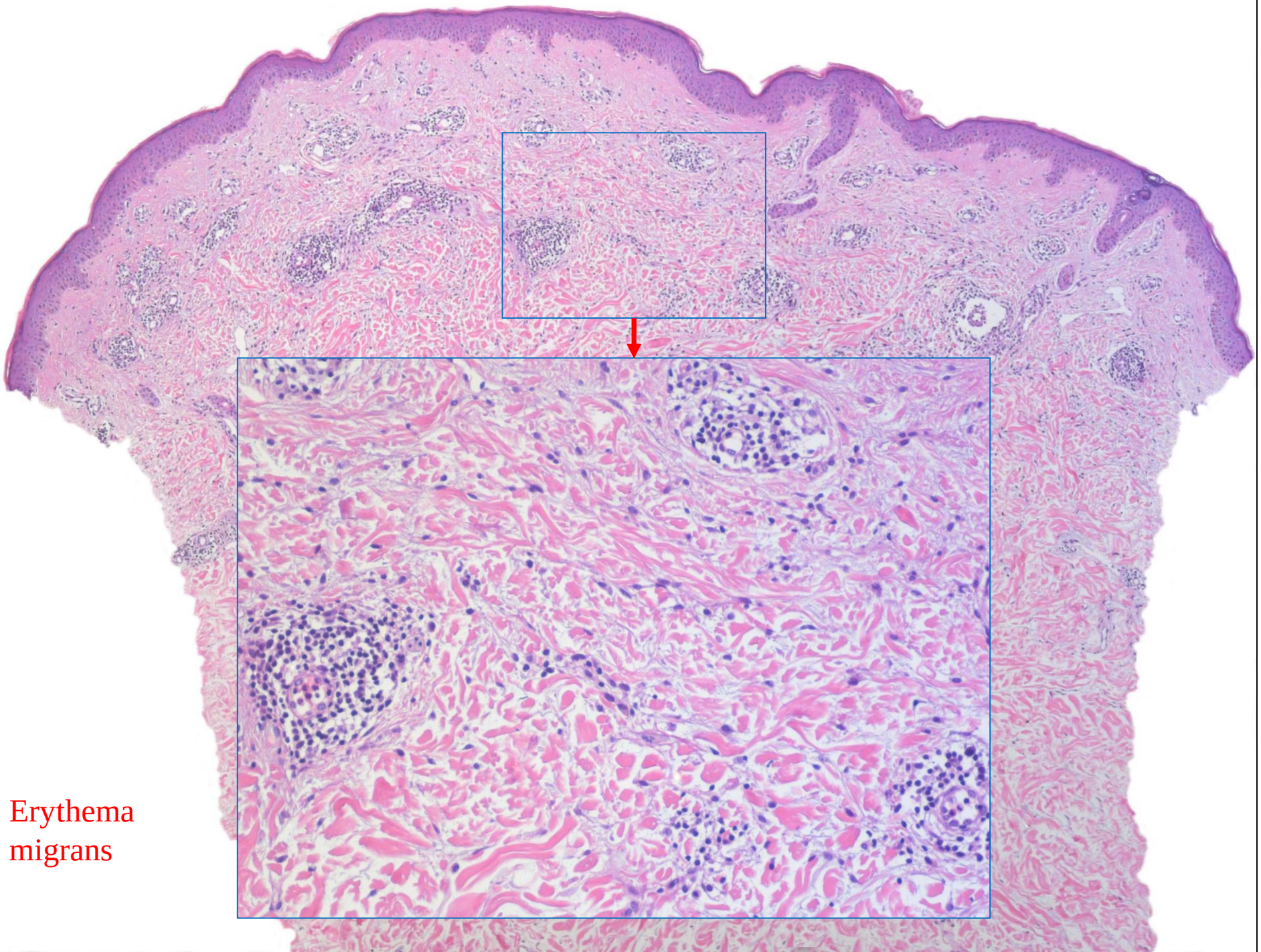


However, if extravasated erythrocytes are also spotted deeper down in the reticular dermis, this militates against Schamberg's disease and favors a drug eruption.



Erythema migrans

When consisting of lymphocytes only, the infiltrate in drug eruptions tends to be restricted to perivascular areas with only little involvement of the interstitium.



Erythema migrans

This helps to distinguish drug eruptions with a wholly lymphocytic infiltrate from infections by borrelia that are usually associated with many lymphocytes in the interstitial dermis.

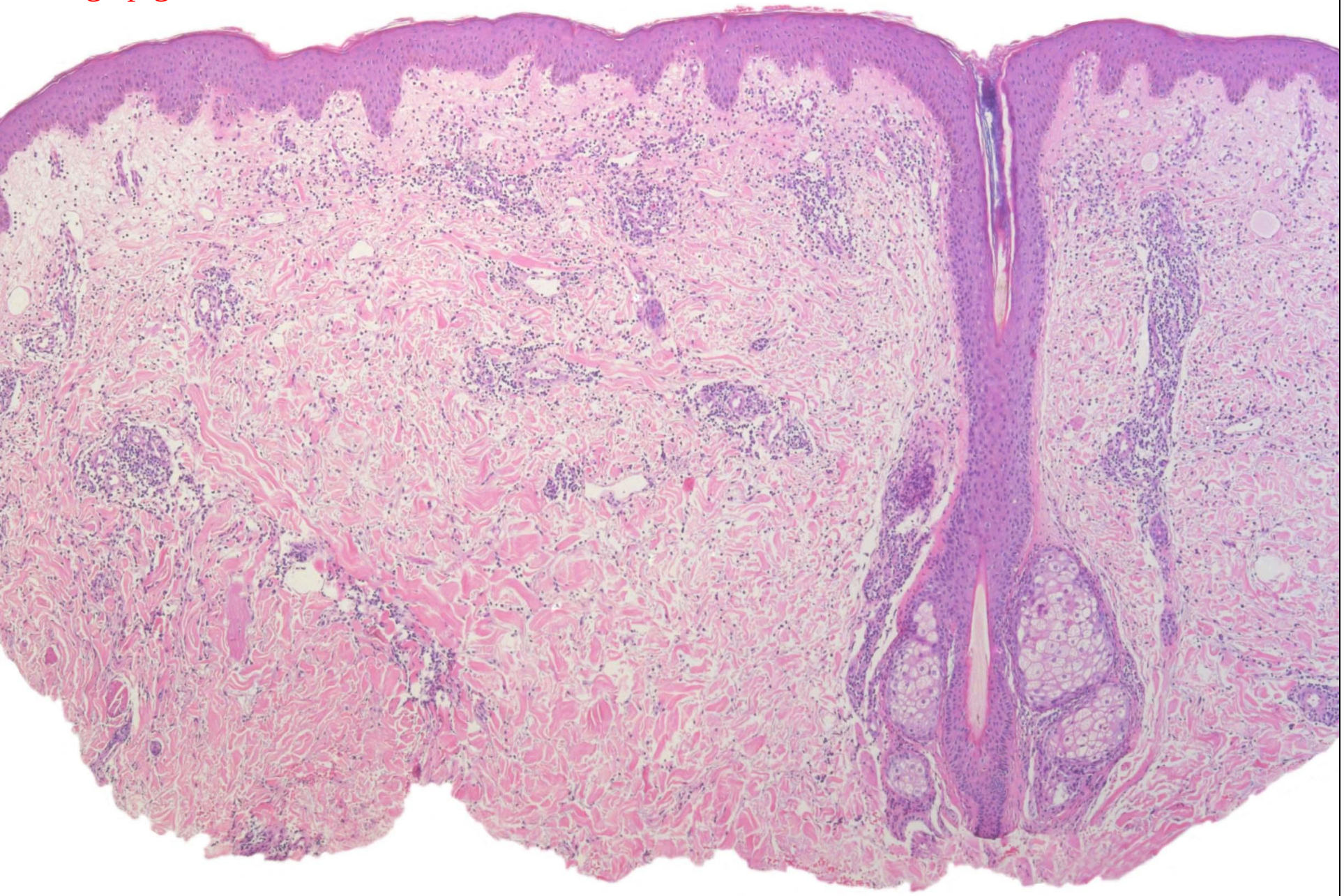
Table 1: Histopathologic findings in 300 cases with the clinical and histopathologic diagnosis of drug eruption

| | Pattern | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Lympho-cytic dermal without epidermal Changes (n=12)* | *Superficial and deep dermal with eosino-phils and neutrophils (n=12)* | *Severe vacuolar interface dermatitis (n=38)* | *Mild vacuolar interface dermatitis (n=83)* | *Lichenoid dermatitis (n=36)* | *Lichenoid pso-riasiform dermatitis (n=18)* | *Spongiotic dermatitis (n=62)* | *Pustular dermatitis (n=19)* | *Subepi-dermal bullous dermatitis (n=6)* | *Granulo-matous dermatitis (n=12)* | *Leukocy-toklastic vasculitis (n=2)* |
| Superficial | | | | | | | 54 | 18 | 4 | 0 | 0 |
| Superficial and deep | | | | | | | 8 | 1 | 2 | 12 | 2 |
| Perivascular | | | | | | | 6 | 0 | 0 | 0 | 0 |
| Interstitial | | | | | | | 56 | 19 | 6 | 12 | 2 |
| Vacuolar | | | | | | | | | | | |
| + | | | | | | | 41 | 11 | 3 | 6 | 1 |
| ++ | | | | | | | 0 | 2 | 3 | 0 | 0 |
| Spongiosis | | | | | | | | | | | |
| + | | | | | | | 56 | 12 | 2 | 3 | 0 |
| ++ | | | | | | | 6 | 7 | 0 | 0 | 0 |
| Necrotic keratinocytes | | | | | | | | | | | |
| + | | | | | | | 10 | 7 | 5 | 0 | 0 |
| ++ | | | | | | | 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 |

- pustular psoriasis
- deficiency diseases
  (e.g. necrolytic migratory erythema, acrodermatitis enteropathica)
- pemphigus
  (esp. IgA pemphigus)
- prurigo pigmentosa

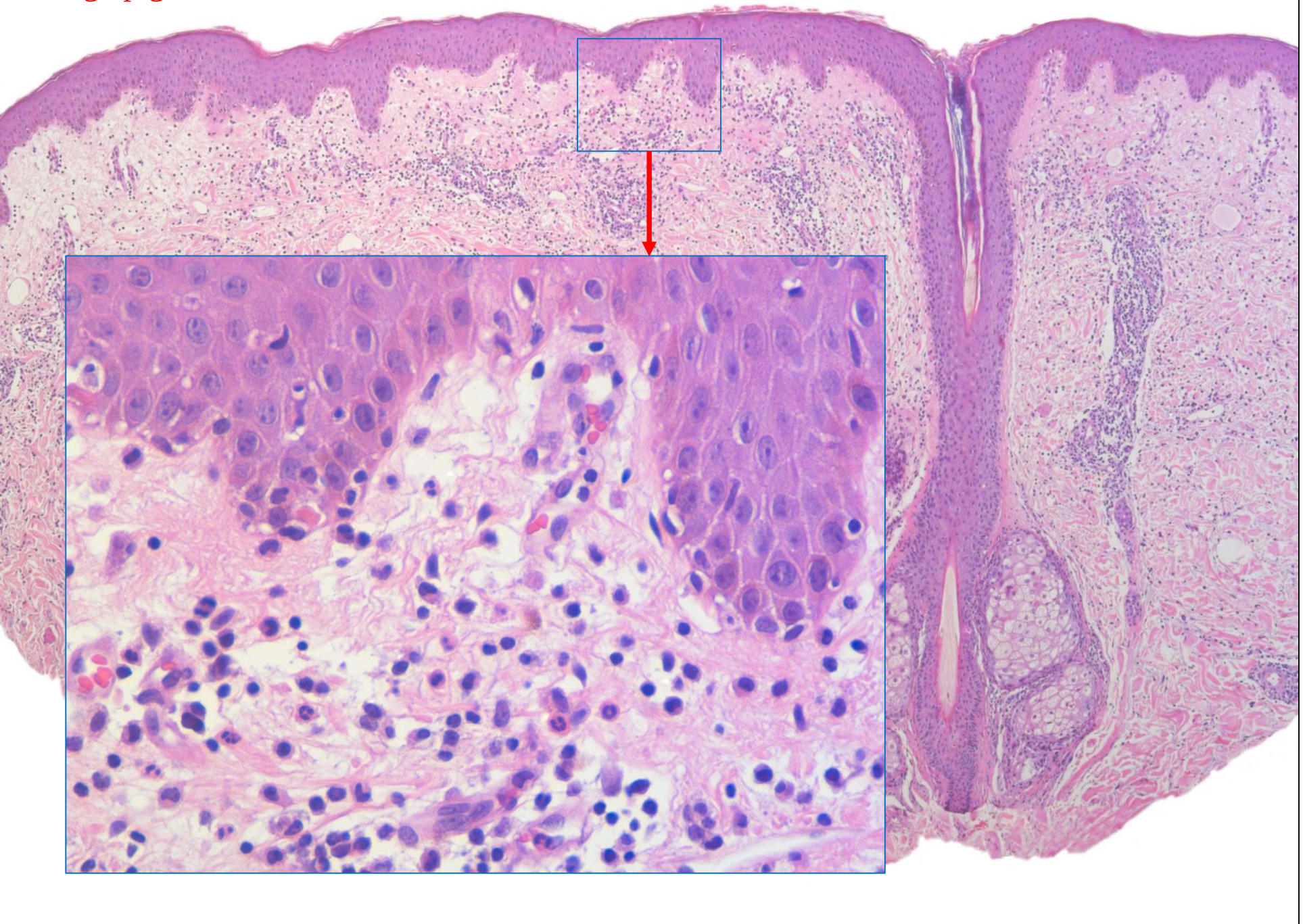
Considering the frequency of neutrophils in the infiltrate, it is not surprising that drug eruptions may present themselves as a pustular dermatitis. When fully developed, this variant has been referred to as acute generalized exanthematous pustulosis or “AGEP”. The histopathologic differential diagnosis includes pustular psoriasis, deficiency diseases such as necrolytic migratory erythema or acrodermatitis enteropathica, pemphigus, especially IgA pemphigus, and prurigo pigmentosa.

Prurigo pigmentosa



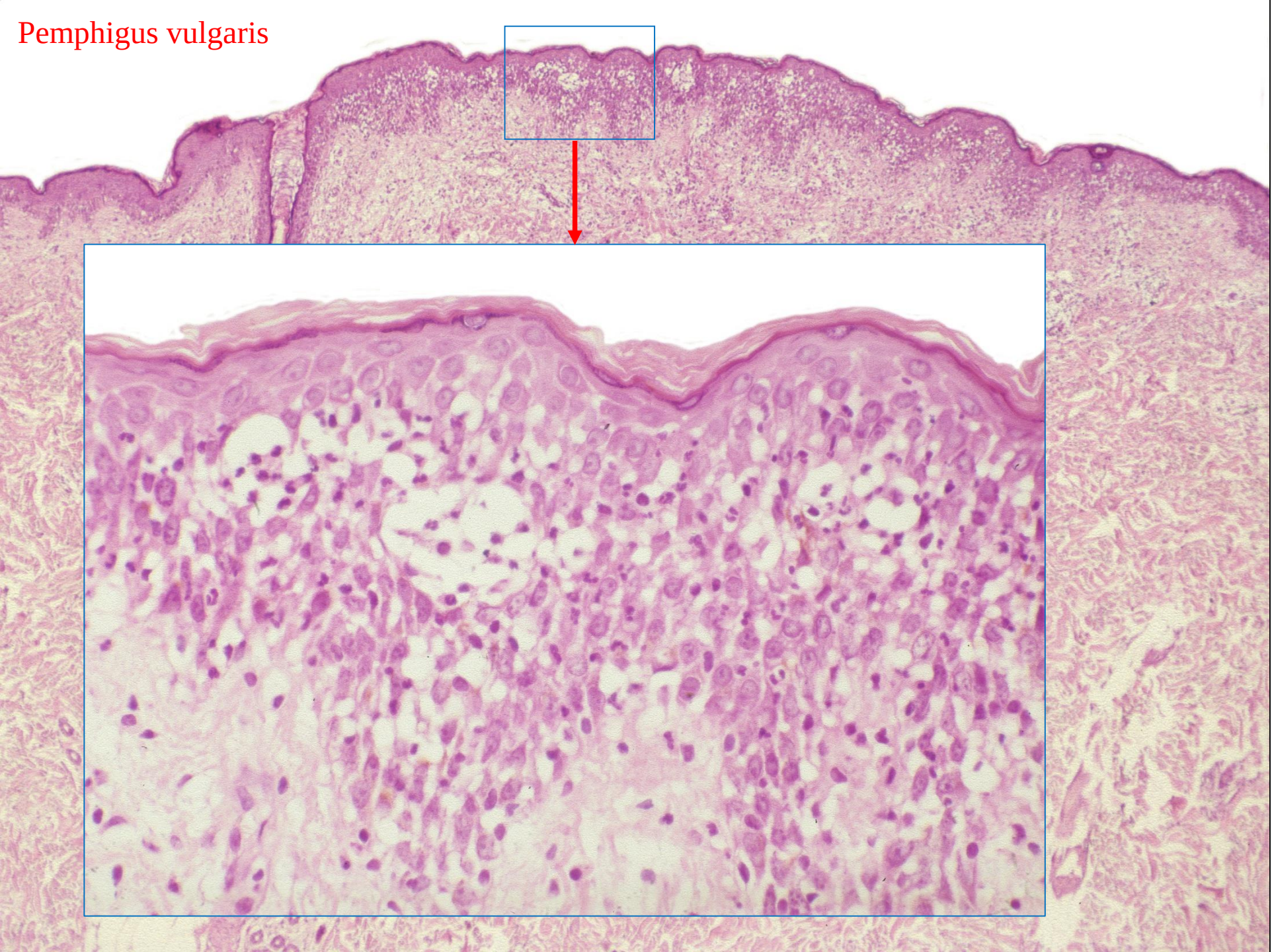
The latter disease may mimick drug eruptions closely because, in its early stages, it presents itself as a perivascular and interstitial dermatitis with edema of the papillary dermis,

# Prurigo pigmentosa

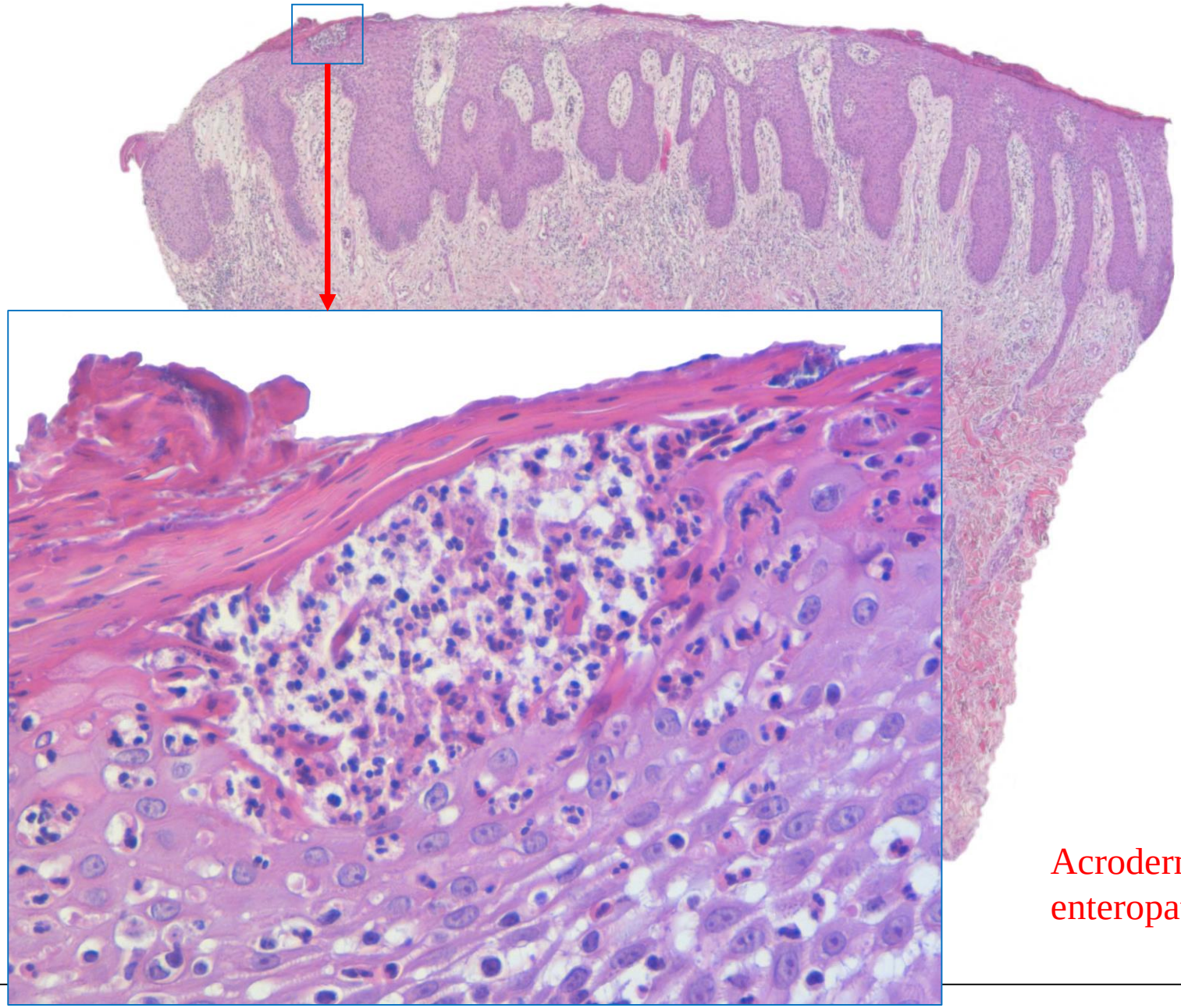


vacuolar interface changes, and a predominance of neutrophils in the infiltrate. The latter may also enter the epidermis and lead to tiny pustules. In contrast to drug eruptions, eosinophils are not usually seen in prurigo pigmentosa.

# Pemphigus vulgaris

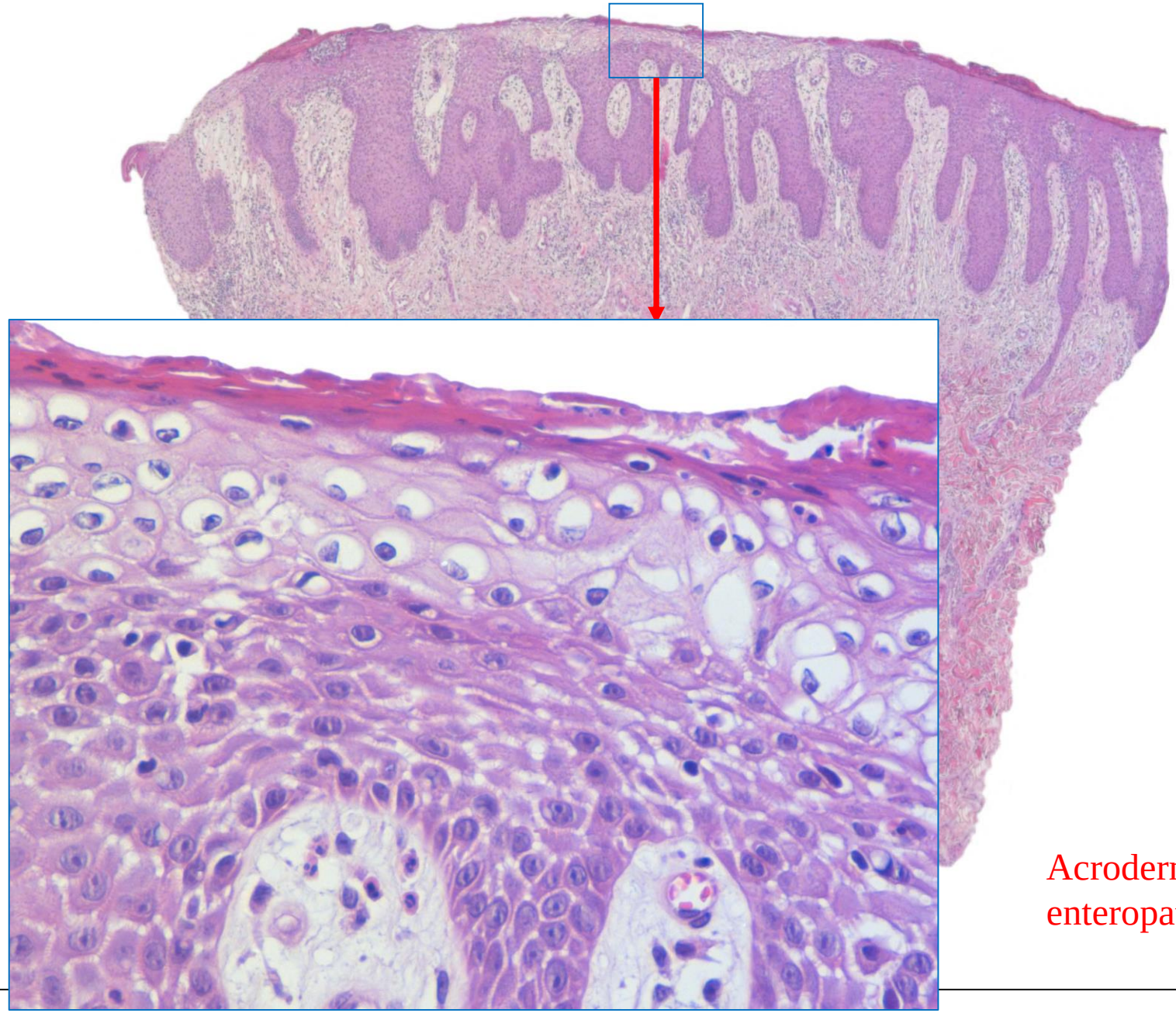


In pemphigus, there may be no signs of acantholysis but only spongiosis with myriad neutrophils in the epidermis. Characteristically, neutrophils are scattered evenly across a broad front, whereas they are usually confined to small foci in pustular drug eruptions.



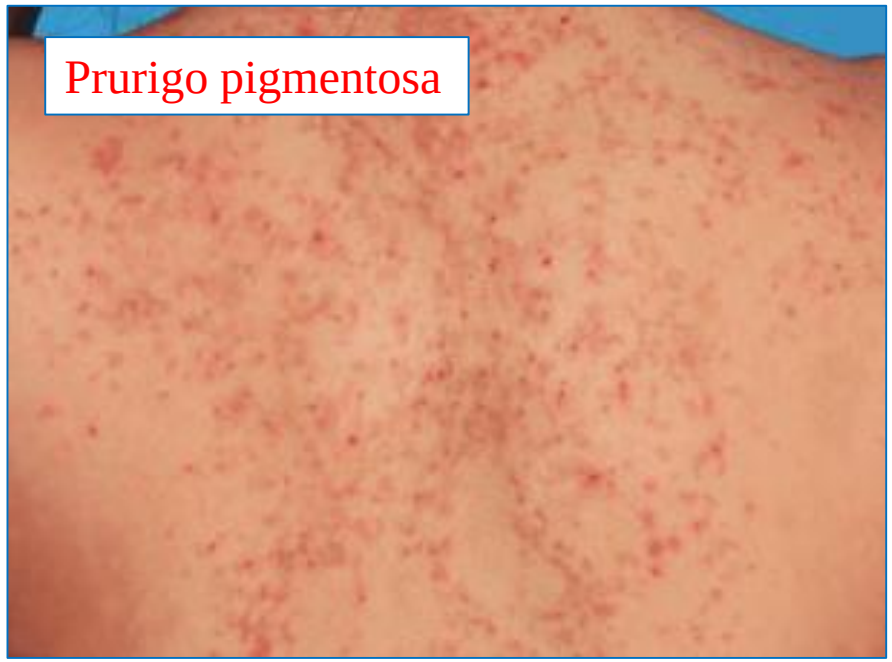
Acrodermatitis enteropathica

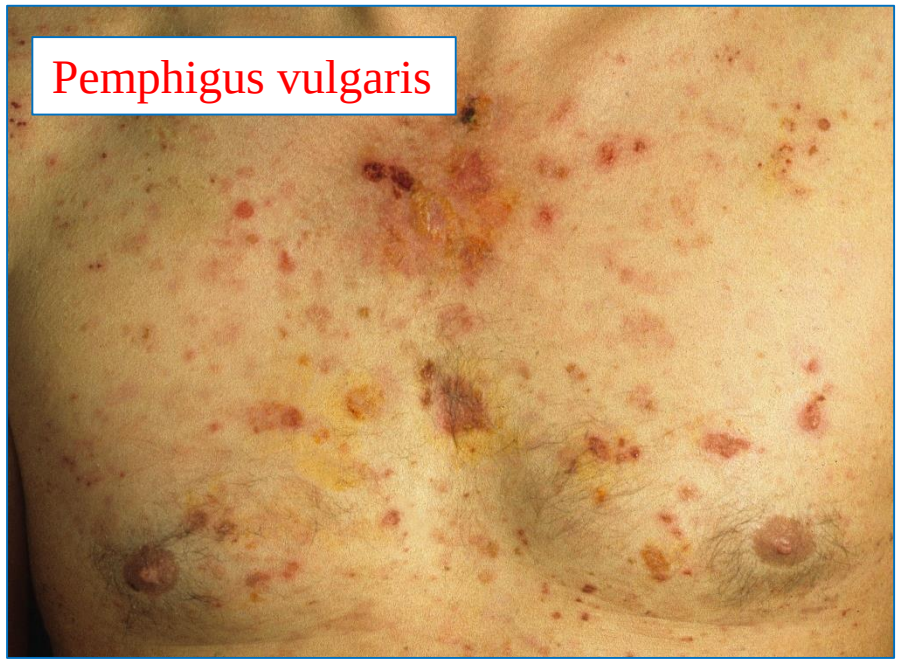
Deficiency diseases may show tiny subcorneal pustules, as in pustular drug eruptions,



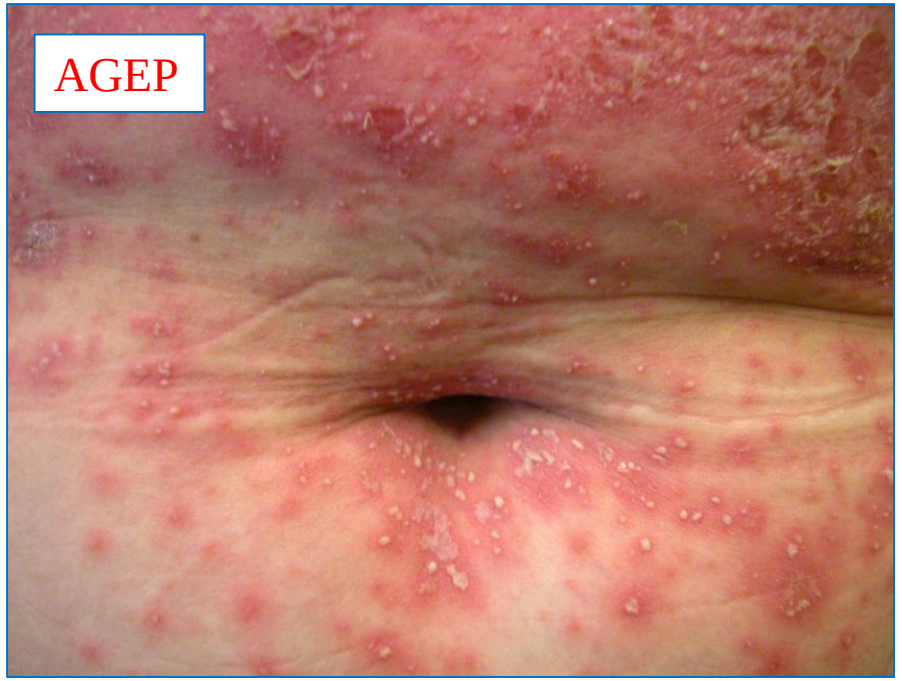
Acrodermatitis enteropathica

but they can usually be distinguished on other grounds, such as psoriasiform hyperplasia and pallor of the upper spinous zone.








In general, the forementioned diseases can be readily distinguished from pustular drug eruptions clinically. By contrast, pustular psoriasis may look just like AGEP clinically

# The histopathological spectrum of acute generalized exanthematous pustulosis (AGEP) and its differentiation from generalized pustular psoriasis

**Background:** Acute generalized exanthematous pustulosis (AGEP) represents a severe, acute, pustular skin reaction that is most often induced by drugs. AGEP can be difficult to differentiate from generalized pustular psoriasis (GPP) both clinically and histopathologically. We present a systematic description of the histopathological spectrum of AGEP and GPP with a focus on discriminating features.
**Materials and methods:** A retrospective, descriptive, comparative histopathological study was completed utilizing step sections of 43 biopsies of 29 cases with a validated diagnosis of probable or definite AGEP and 24 biopsies of 19 cases with an established diagnosis of GPP.
**Results:** In AGEP, biopsies from erythema and pustules showed minor differences, whereas histopathology of the acute stage of GPP showed major differences compared to the chronic stage. Comparing AGEP and GPP, the presence of eosinophils, necrotic keratinocytes, a mixed interstitial and mid-dermal perivascular infiltrate and absence of tortuous or dilated blood vessels were in favor of AGEP. Moreover, chronic GPP was characterized by prominent epidermal psoriatic changes. The frequency of a psoriatic background of AGEP patients in our study was higher than that of psoriasis in the general population. However, histopathology of a subgroup of AGEP patients with a personal history of psoriasis revealed no significant differences from the other AGEP patients.
**Conclusions:** The spectrum of histopathological features of both AGEP and GPP is presented. Despite considerable overlap, subtle consistent histopathological differences and the grade of severity of specific features can help in differentiation. We could neither substantiate earlier reports that follicular pustules exclude AGEP nor did we see vasculitis as a specific feature in AGEP. Our study also supports the concept that AGEP is a separate entity that is distinct from GPP.

**Sylvia H. Kardaun[1], Hilde Kuiper[2], Vaclav Fidler[3] and Marcel F. Jonkman[1]**

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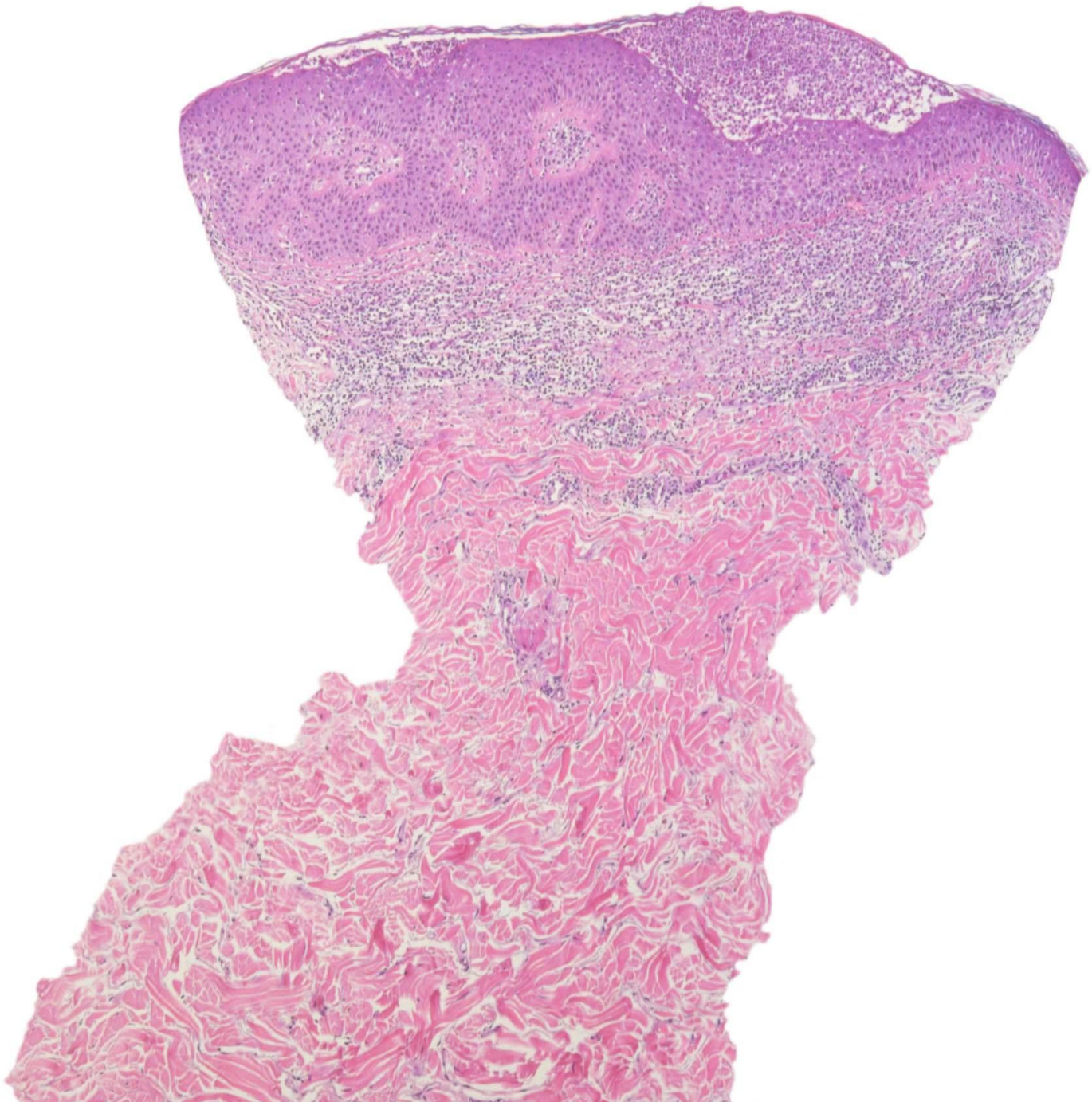
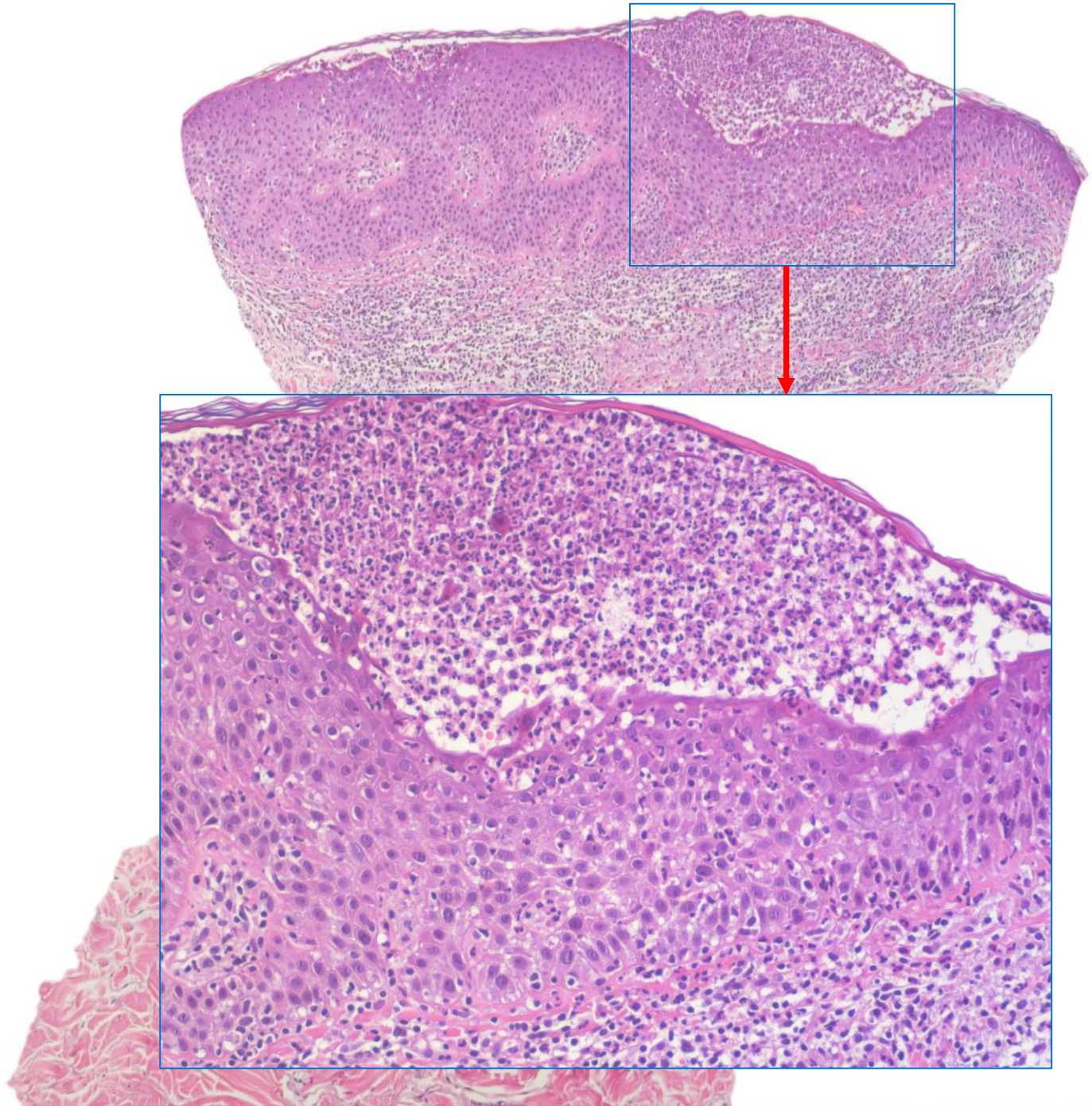
Sylvia H. Kardaun, MD, University Medical Center Groningen, Department of Dermatology, Hanzeplein 1, 9713 GZ Groningen, The Netherlands

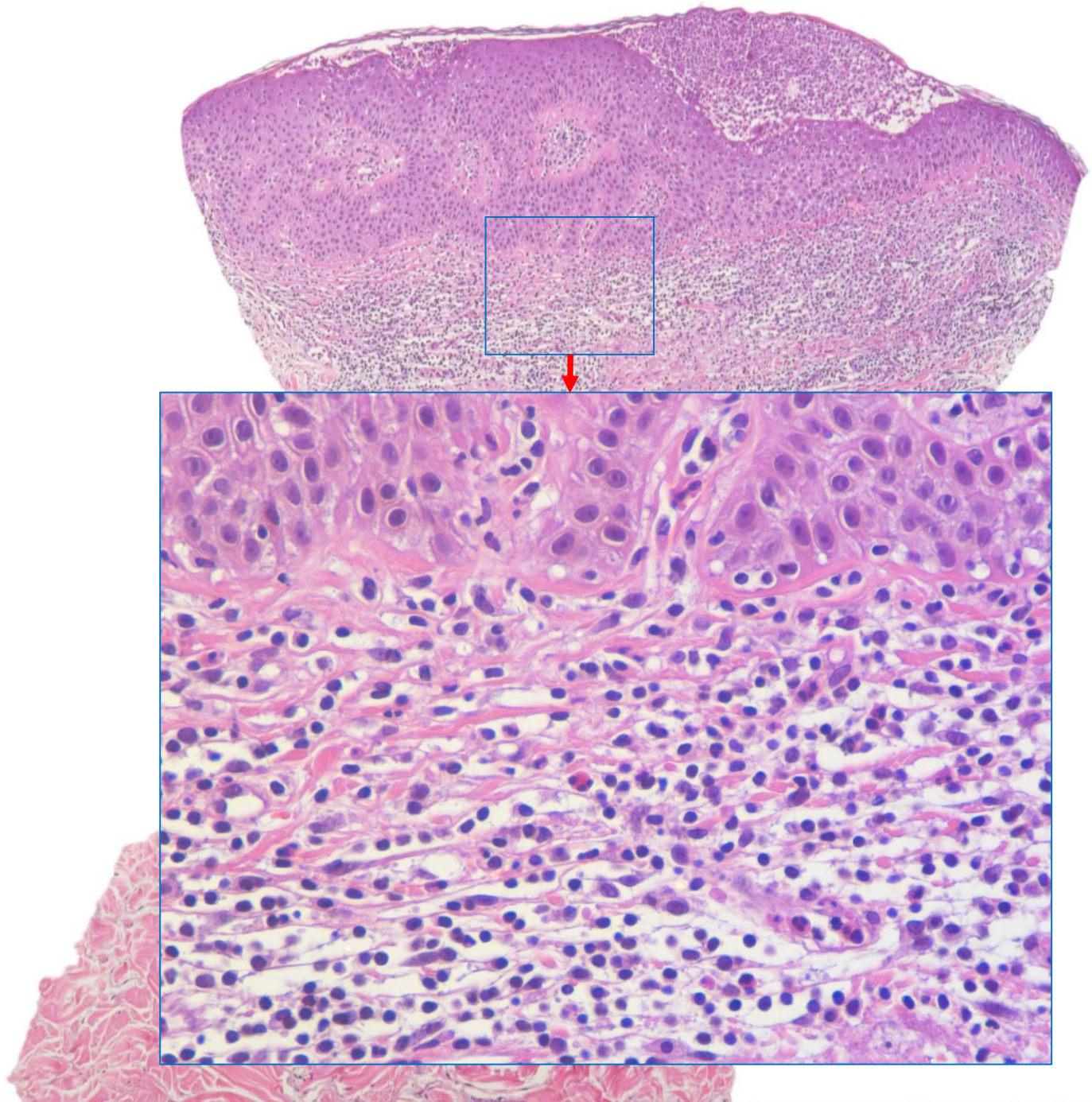
and is also the most challenging differential diagnosis histopathologically. In a larger retrospective study, *"the presence of eosinophils, the presence of keratinocytes, and mixed interstitial and mid-dermal perivascular infiltrate and absence of tortuous or dilated blood vessels"* were found to be *"in favor of AGEP."* However, the latter finding is often missing in pustular psoriasis, too, as a consequence of the acuity of the process, and so is psoriasiform hyperplasia of the epidermis.



By contrast, in this case of AGEP, there seems to be psoriasiform epidermal hyperplasia as a consequence of the section being cut tangentially.



The spongiform pustules are indistinguishable from those seen in psoriasis.



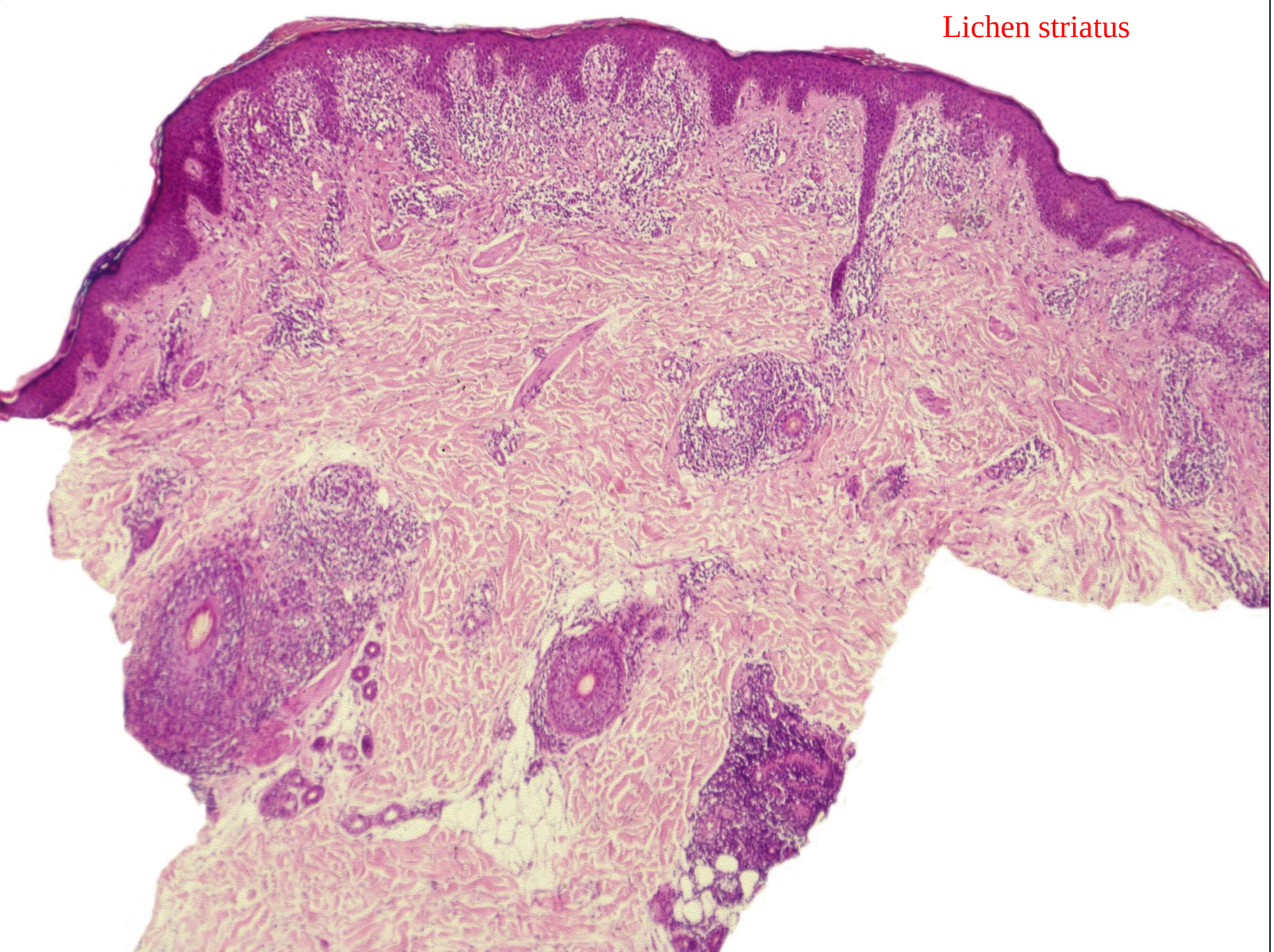
There are eosinophils in the infiltrate, but some eosinophils may be seen in pustular psoriasis, too. In this case, a helpful clue to the diagnosis of drug eruption are subtle vacuolar changes at the junction, but when there are conflicting criteria, diagnosis requires clinico-pathologic correlation.

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

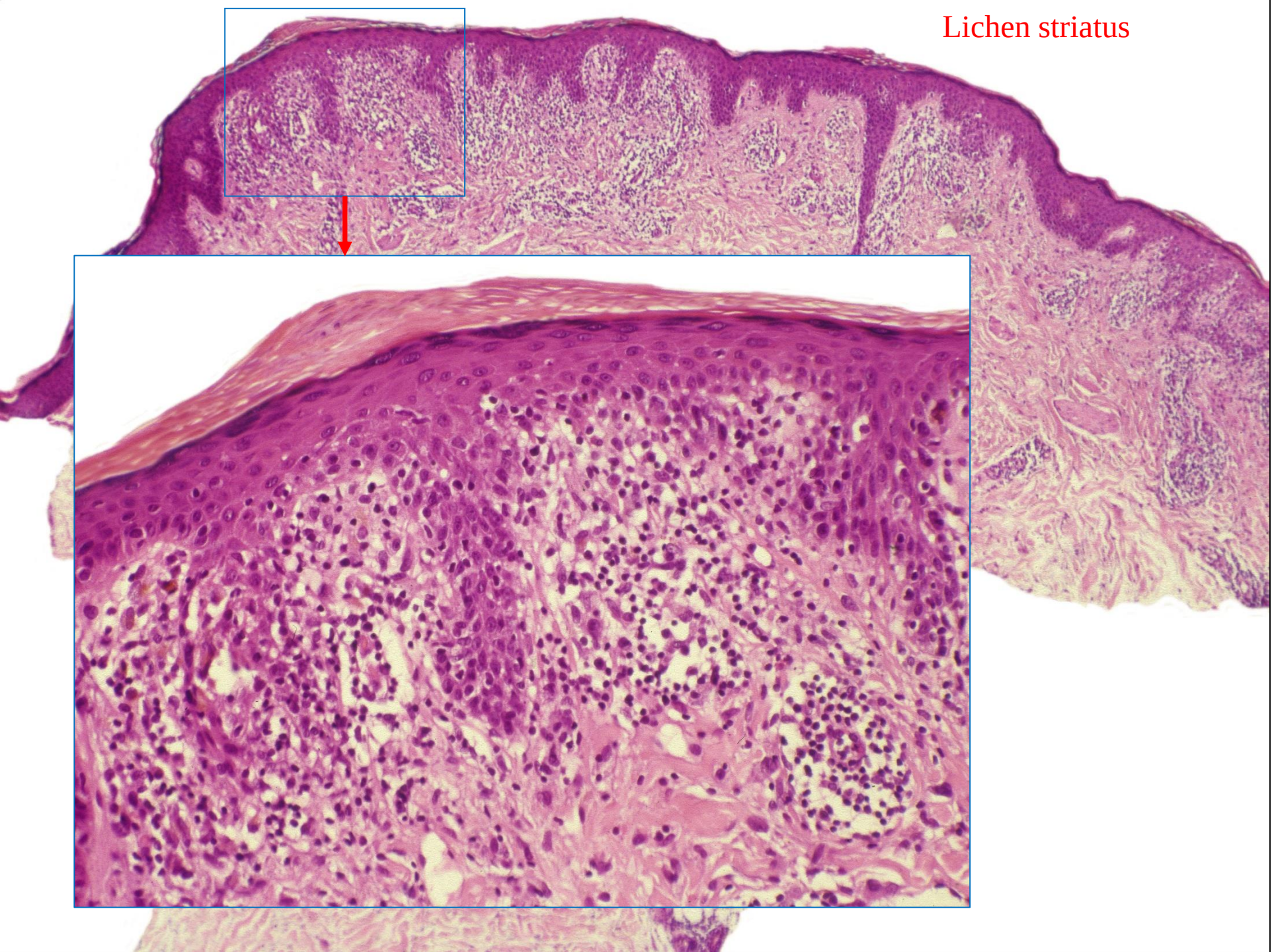
| | Pattern | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Lymphocytic dermal without epidermal Changes (n=12)* | *Superficial and deep dermal with eosinophils and neutrophils (n=12)* | *Severe vacuolar interface dermatitis (n=38)* | *Mild vacuolar interface dermatitis (n=83)* | *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 | | | | | | | 54 | 18 | 4 | 0 | 0 |
| Superficial and deep | | | | | | | 8 | 1 | 2 | 12 | 2 |
| Perivascular | | | | | | | 6 | 0 | 0 | 0 | 0 |
| Interstitial | | | | | | | 56 | 19 | 6 | 12 | 2 |
| Vacuolar | | | | | | | | | | | |
| + | | | | | | | 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 |

- lichen striatus
- lichen nitidus
- lichenoid sarcoidosis

An uncommon, but not exceptional, pattern of drug eruptions is granulomatous dermatitis. It is usually associated with lichenoid interface changes. Hence, the diseases most difficult to distinguish from granulomatous drug eruptions are those sharing that combination of findings, namely, a lichenoid granulomatous pattern, as it occurs in lichen striatus, lichen nitidus, and lichenoid sarcoidosis.

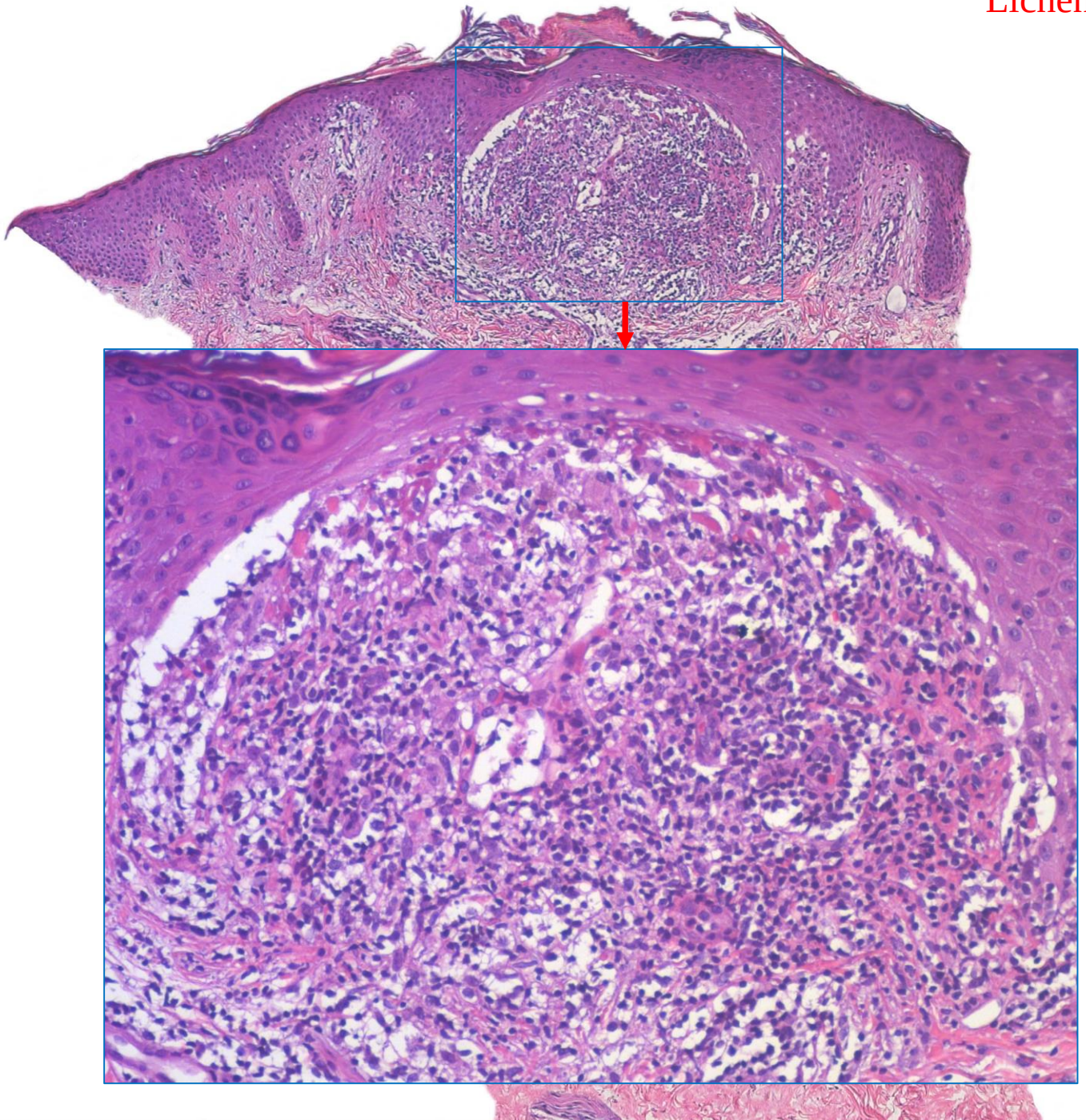



Lichen striatus usually shows psoriasiform epidermal hyperplasia and a superficial and deep infiltrate of lymphocytes that tends to be aggravated around eccrine structures.



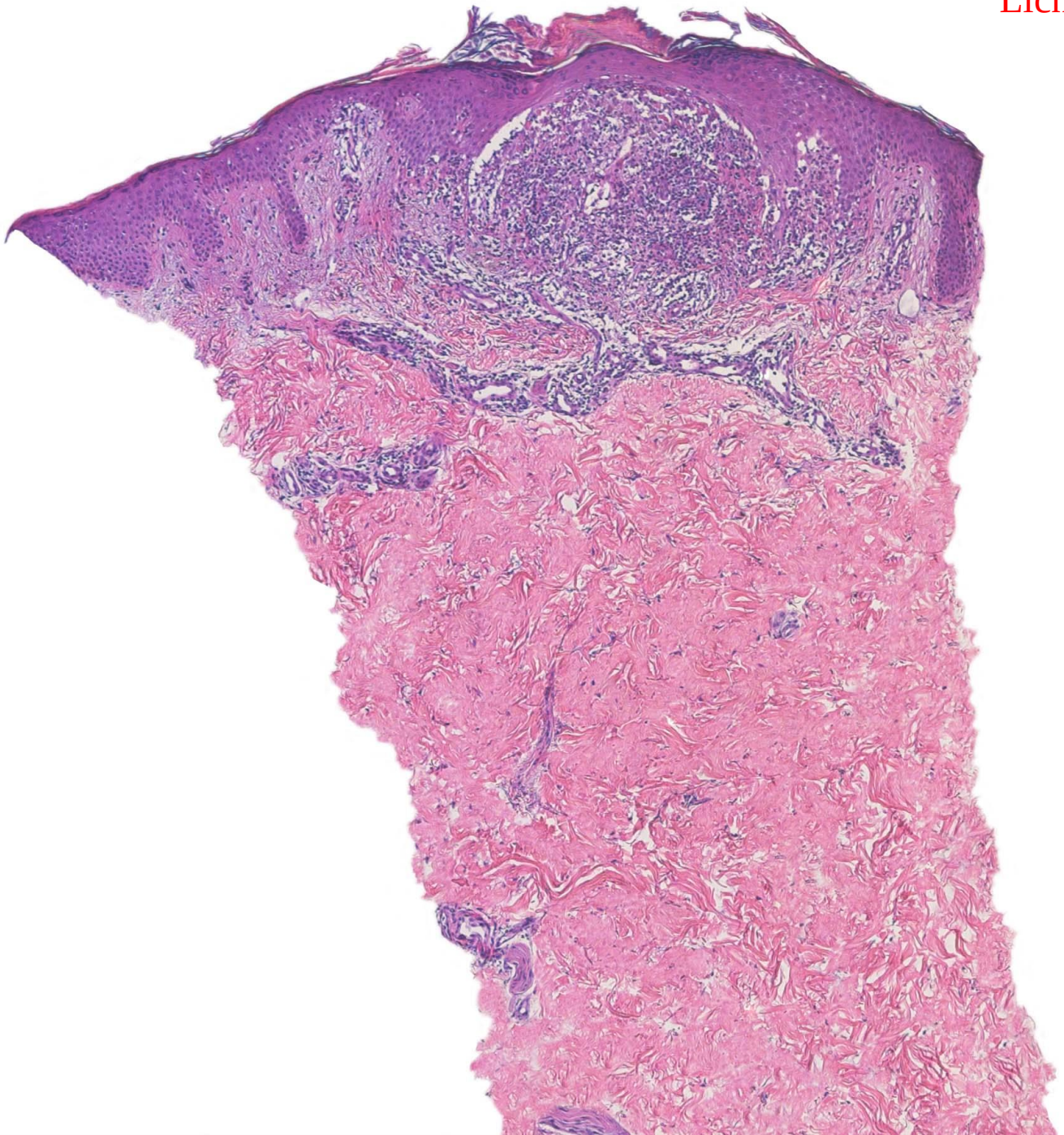

There are usually only few, if any, colloid bodies.

Lichen nitidus

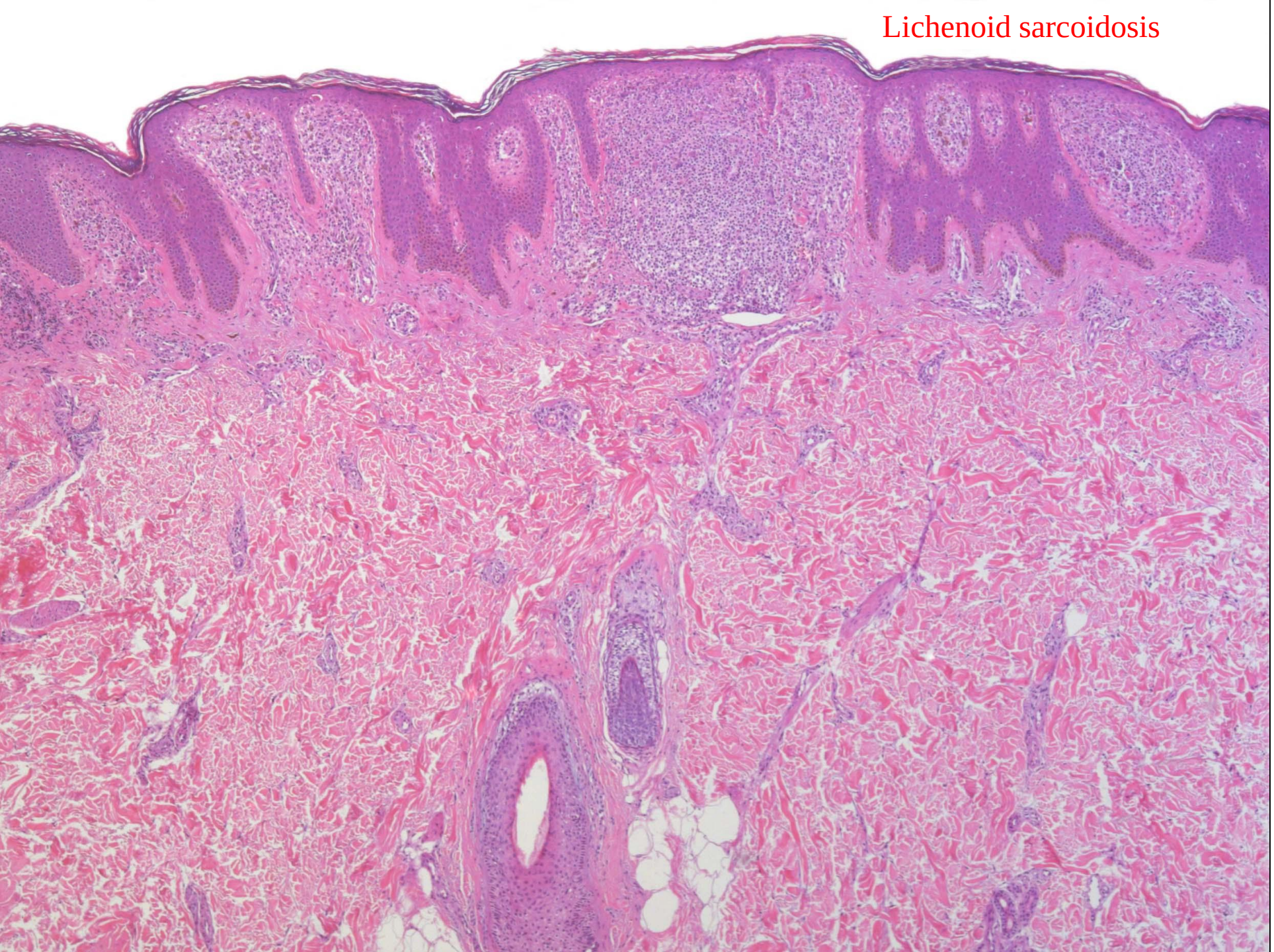


By contrast, the latter are often numerous in lichen nitidus,

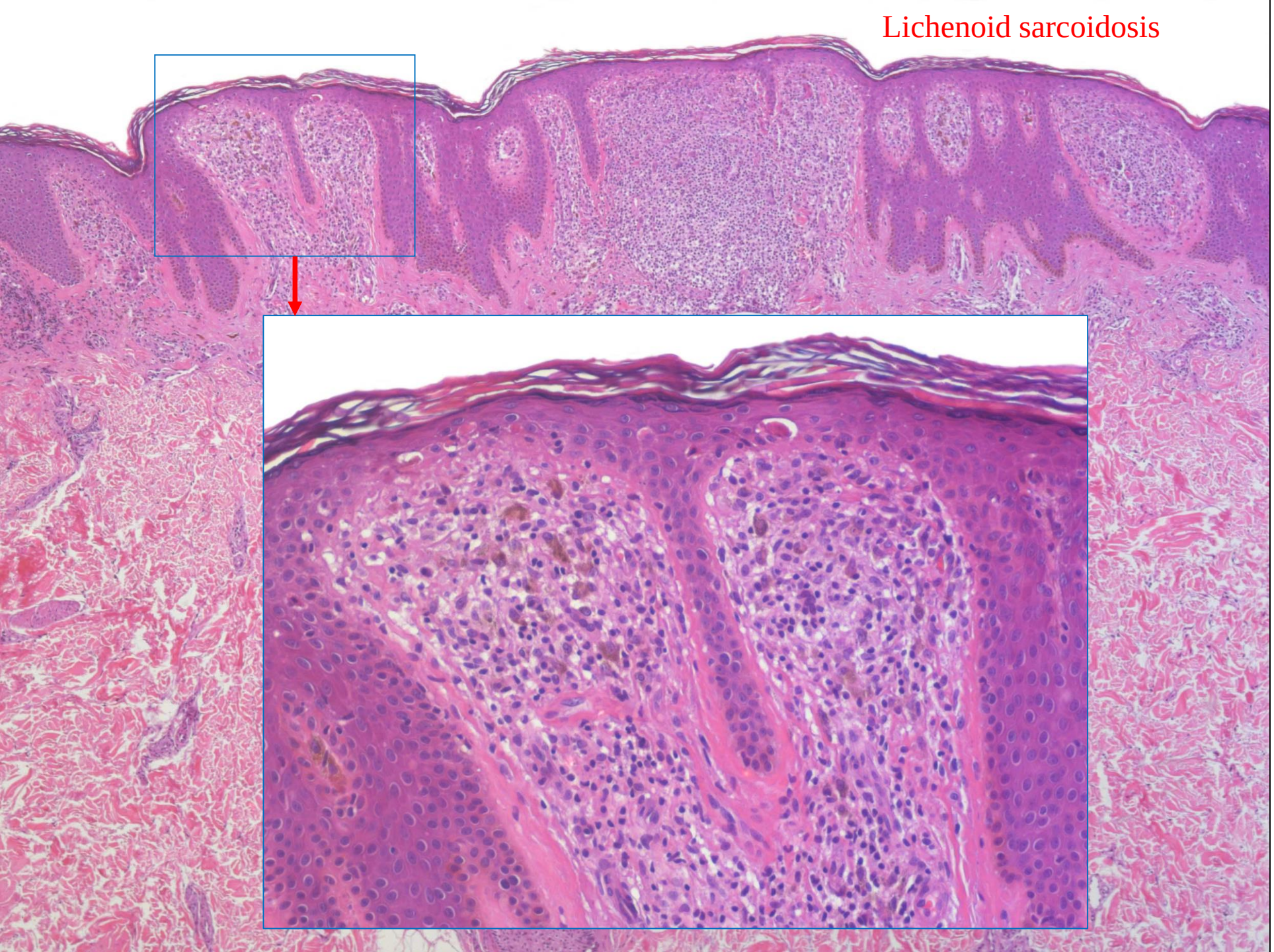
Lichen nitidus



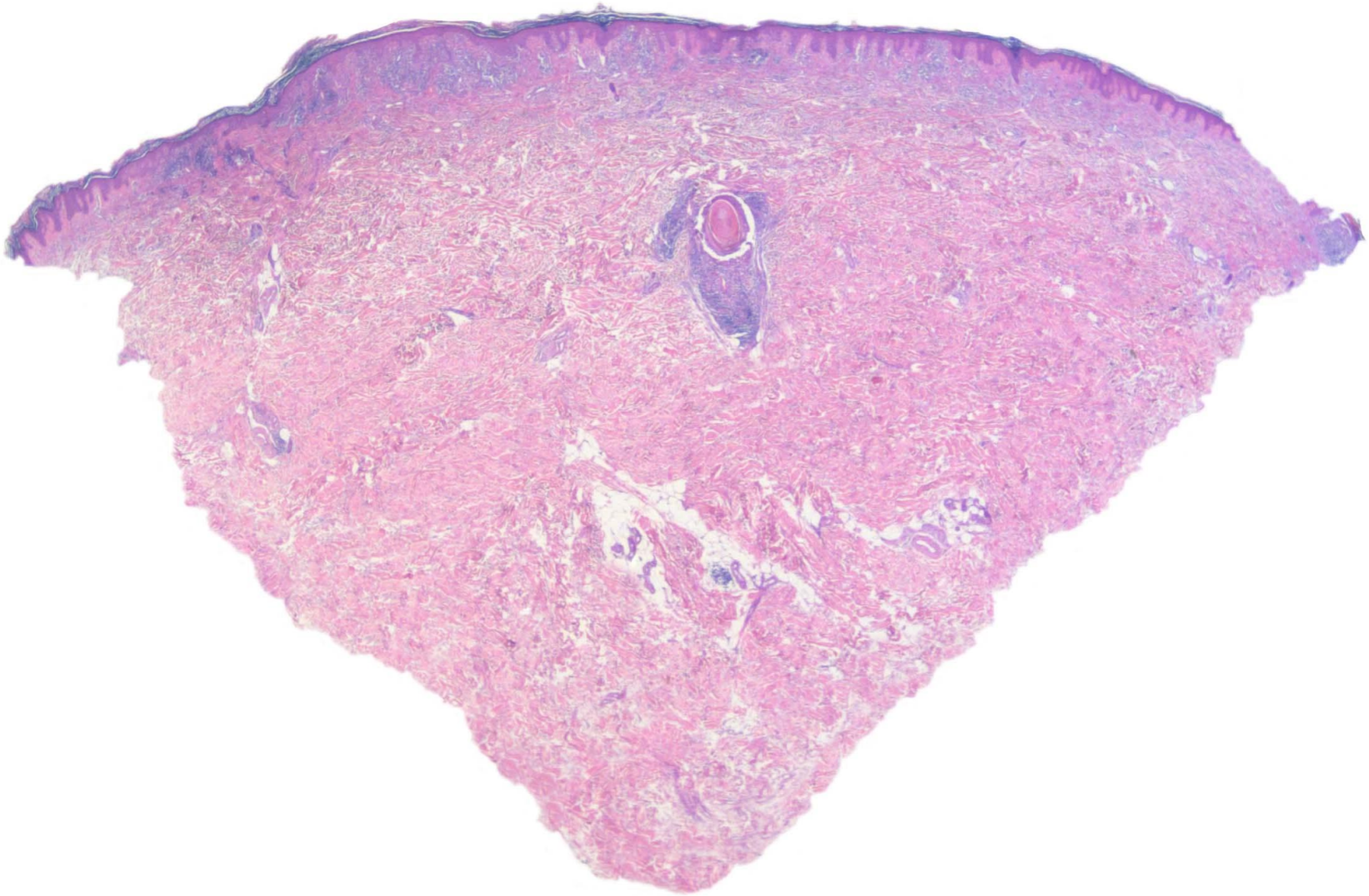
but the infiltrate is superficial only and very circumscribed, often being confined to a single widened dermal papilla.



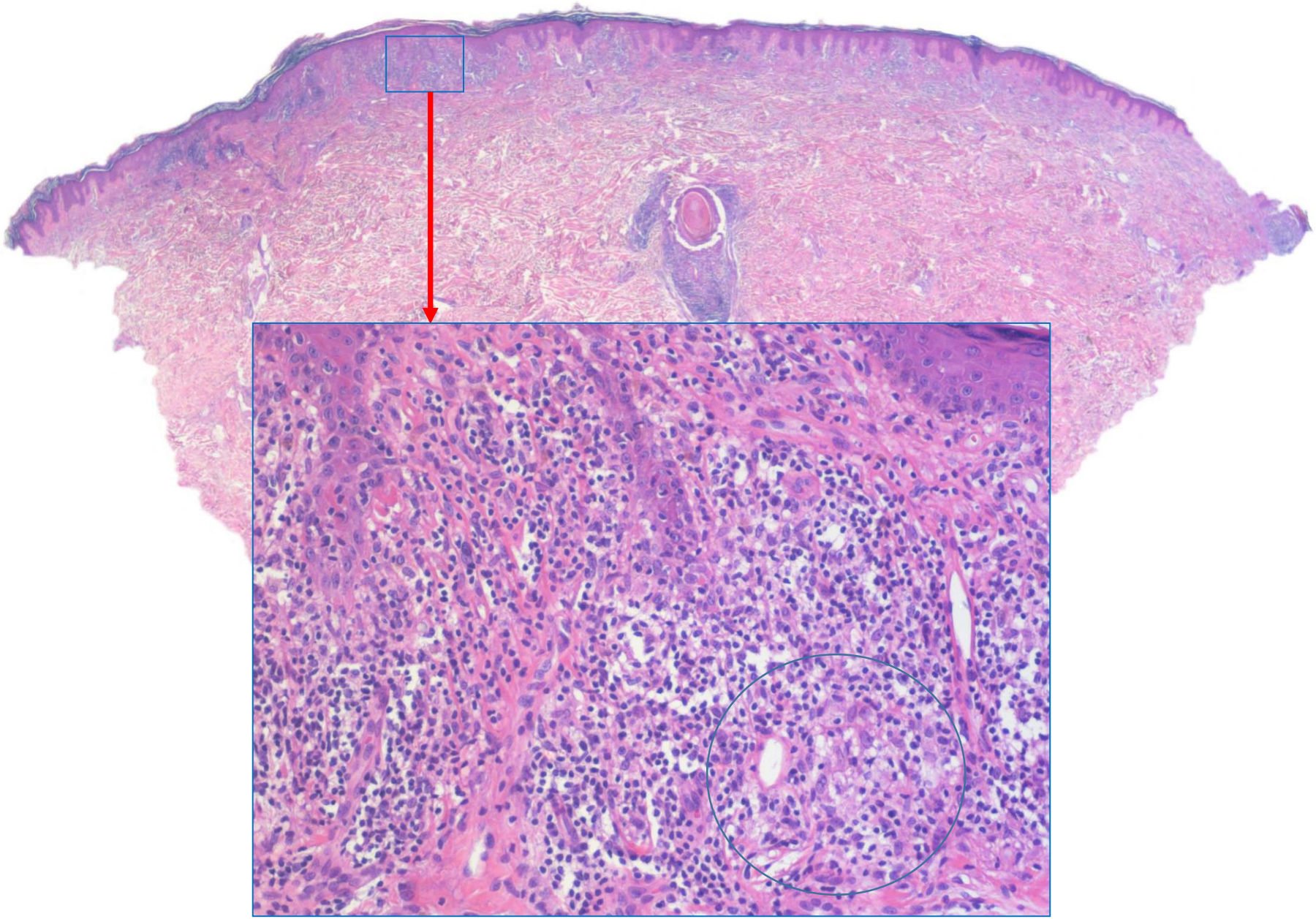

In lichenoid sarcoidosis, changes are similar but not confined to single foci.



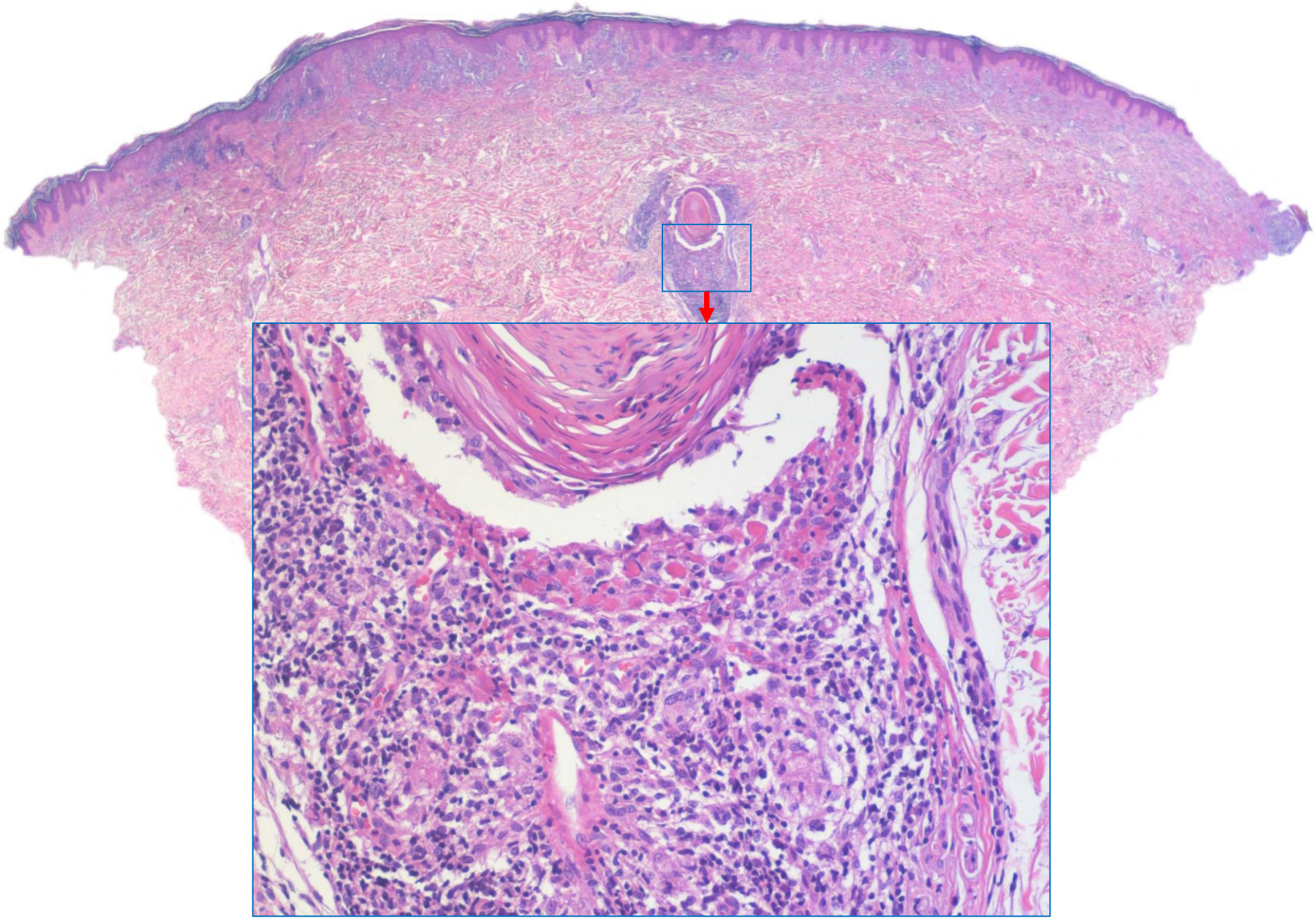

There are usually no eosinophils and only few colloid bodies.



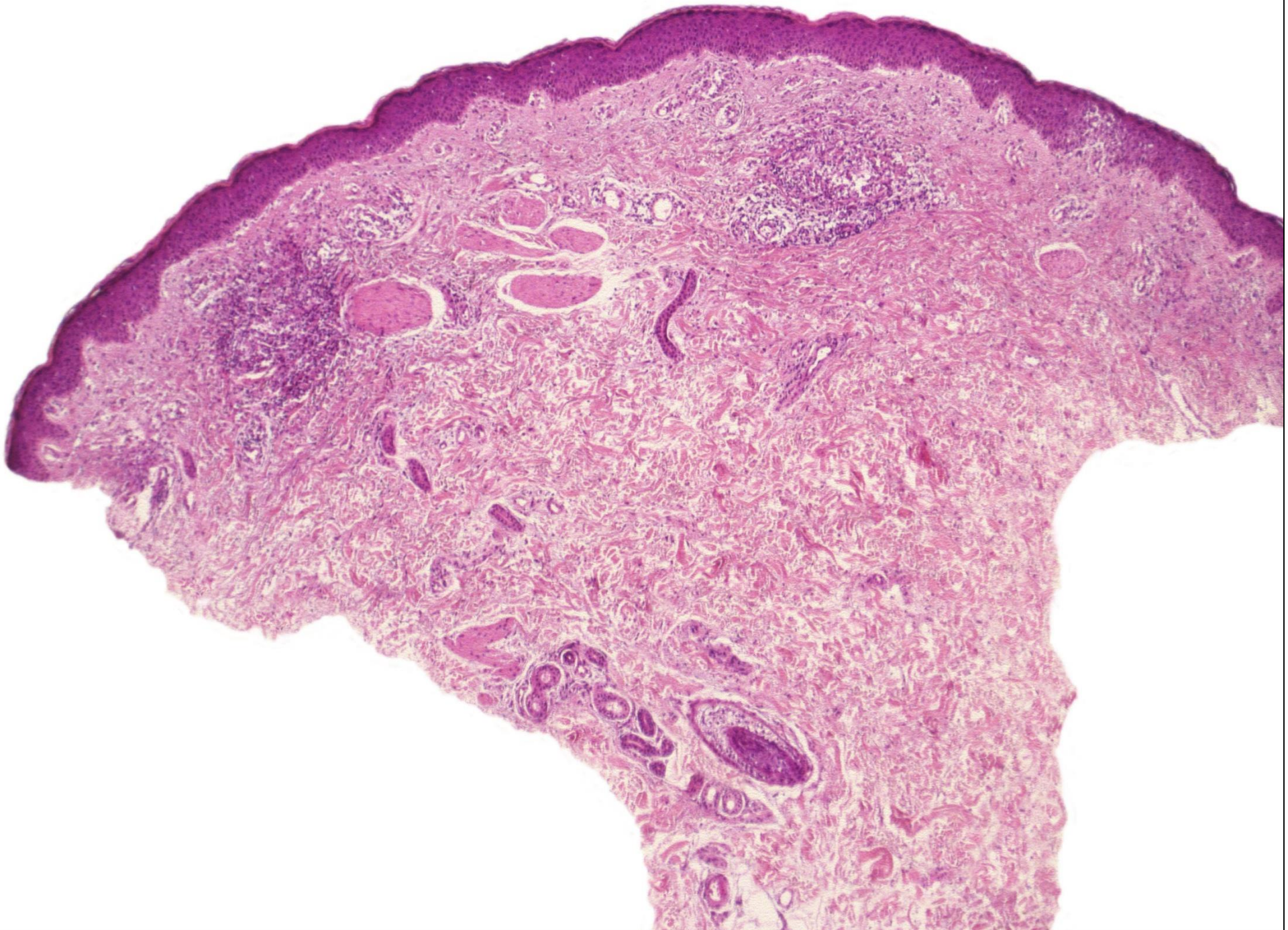
By contrast, the infiltrate in granulomatous drug eruptions may contain eosinophils.



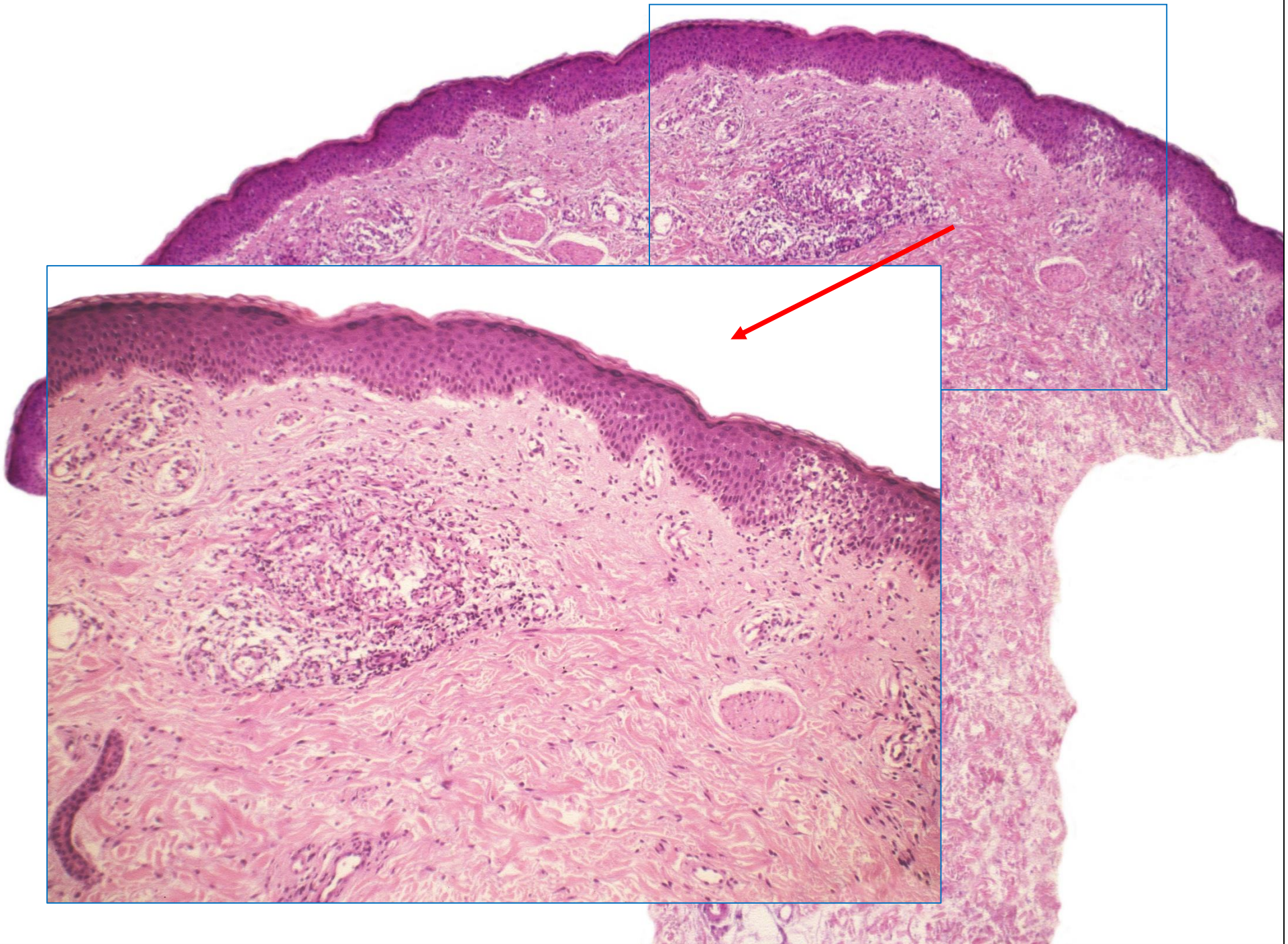
The granulomas are usually small and poorly circumscribed, an incidental finding rather than the most prominent one.



Cytoid bodies are often numerous, as in other lichenoid drug eruptions.



Yet another clue to a granulomatous drug eruptions is a more complex combination of patterns,

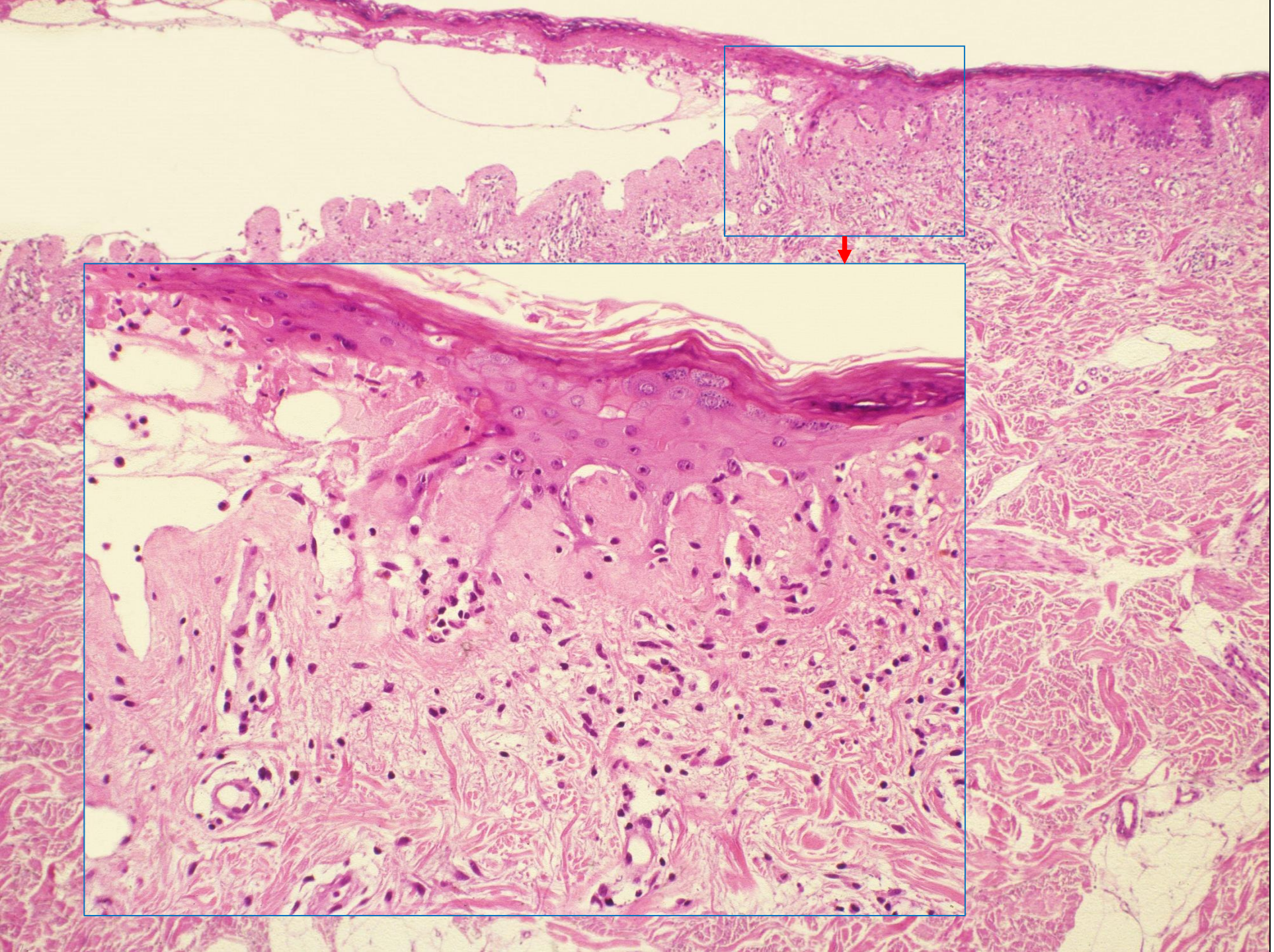


e.g., not only granulomatous with vacuolar interface changes, but also spongiotic.

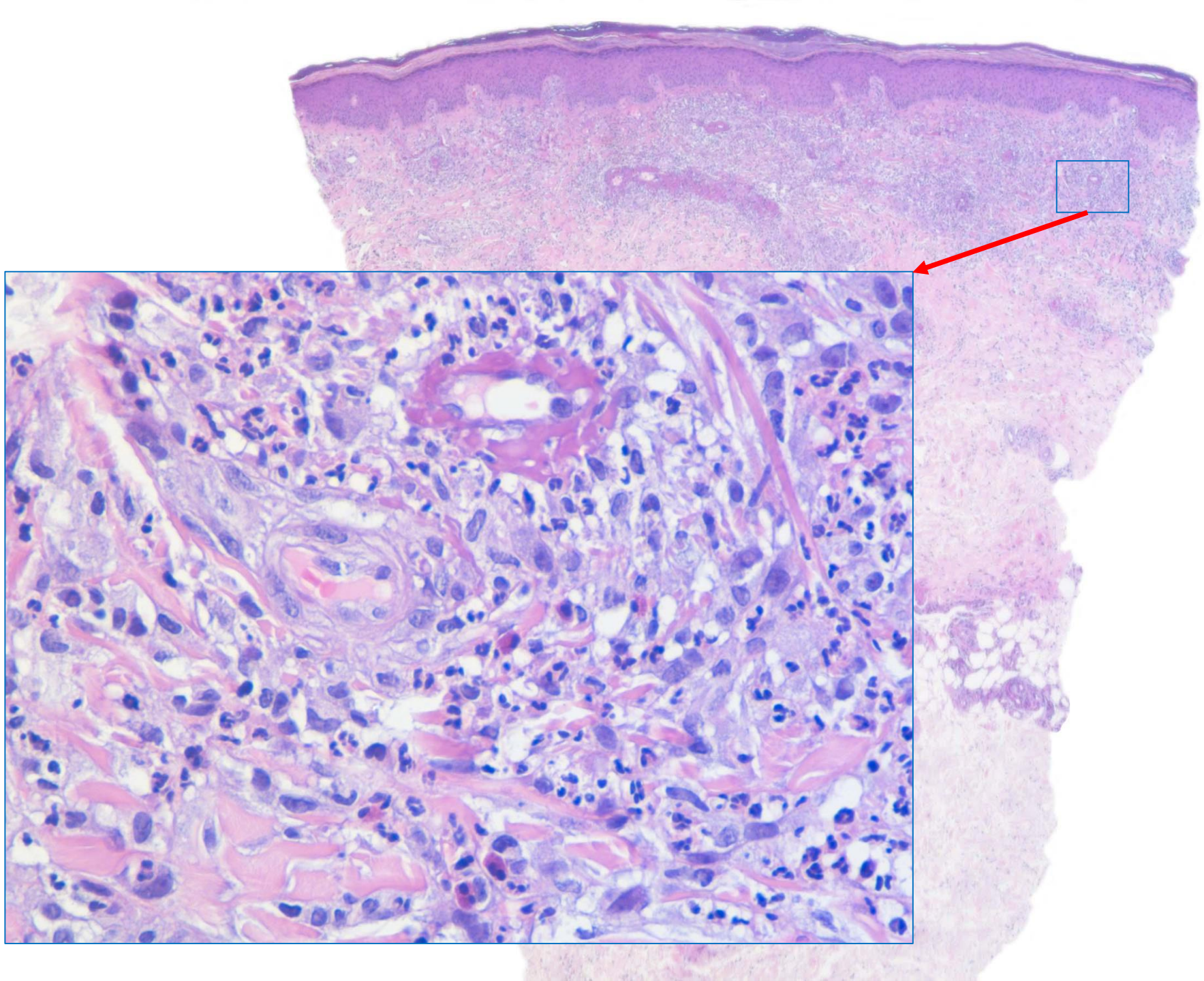
Table 1: Histopathologic findings in 300 cases with the clinical and histopathologic diagnosis of drug eruption

| | Pattern | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Lympho-cytic dermal without epidermal Changes (n=12)* | *Superficial and deep dermal with eosino-phils and neutrophils (n=12)* | *Severe vacuolar interface dermatitis (n=38)* | *Mild vacuolar interface dermatitis (n=83)* | *Lichenoid dermatitis (n=36)* | *Lichenoid pso-riasiform dermatitis (n=18)* | *Spongiotic dermatitis (n=62)* | *Pustular dermatitis (n=19)* | *Subepi-dermal bullous dermatitis (n=6)* | *Granulo-matous dermatitis (n=12)* | *Leukocy-toklastic 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 |

Subepidermal bullous dermatitis and leukocytoclastic vasculitis were only rarely seen in our study of drug eruptions.



A bullous drug eruption should be suspected whenever there are prominent interface changes adjacent to a subepidermal blister.



Drug-induced leukocytoklastic vasculitis does not differ from other leukocytoklastic vasculitides, except for their tendency of being associated with numerous eosinophils.

STUDY

# Tissue Eosinophilia as an Indicator of Drug-Induced Cutaneous Small-Vessel Vasculitis

*Soon Bahrami, MD; Janine C. Malone, MD; Kelli G. Webb, MD; Jeffrey P. Callen, MD*

**Objective:** To determine whether tissue eosinophilia is a reliable indicator of a drug-induced etiology in biopsy samples demonstrating leukocytoclastic vasculitis.

**Design:** Retrospective medical record review with concurrent histopathologic analysis.

**Setting:** University-affiliated dermatology practice.

**Patients:** Sixty-three patients with cutaneous small-vessel vasculitis meeting specific inclusion criteria were divided into drug-induced (n=16) and non–drug-induced (n=47) groups.

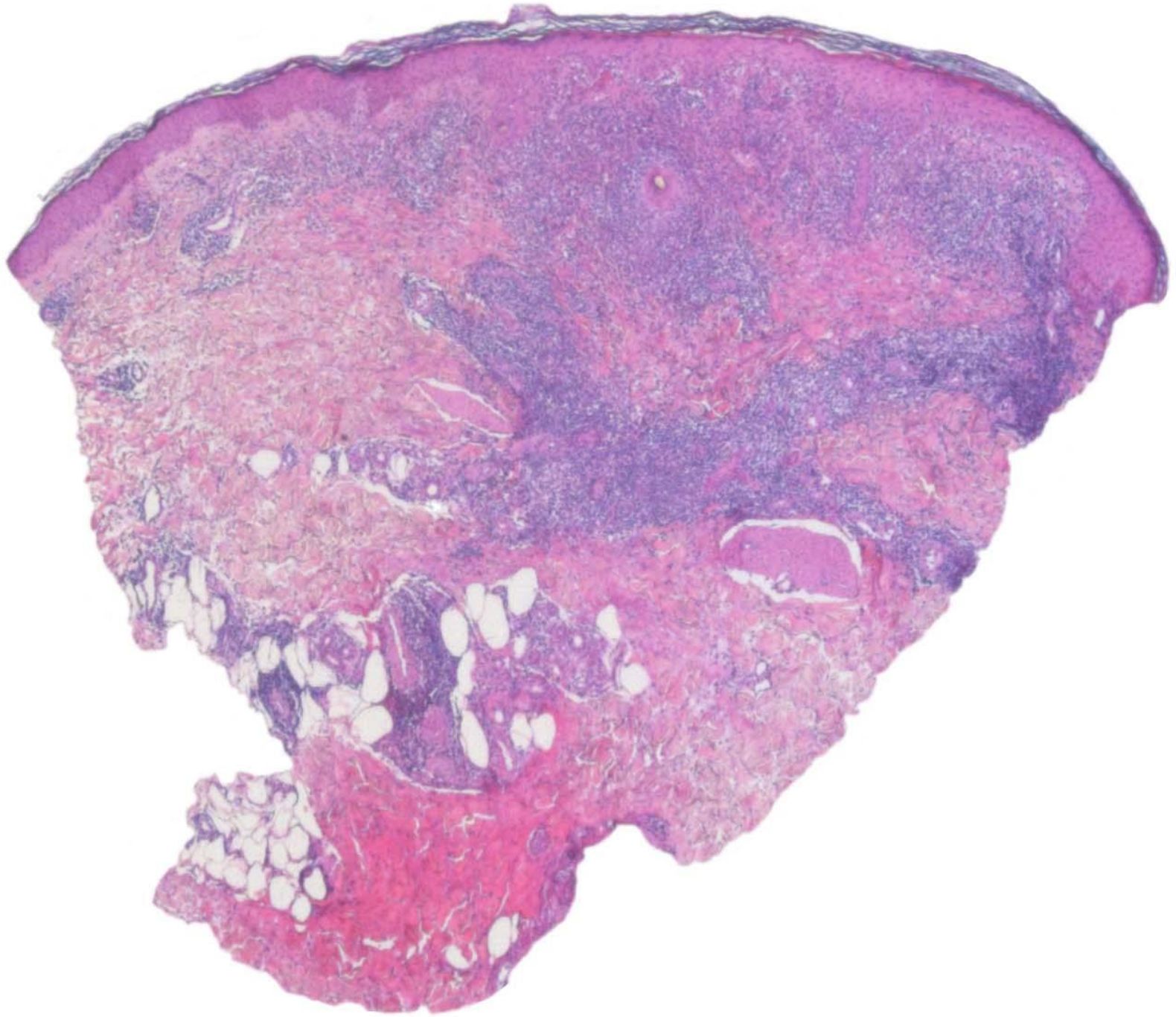
**Main Outcome Measures:** Corresponding histopathologic material was reviewed by a dermatopathologist masked to the etiologic associations. An eosinophil ratio was calculated for each patient, derived from the mean eosinophil score (averaging eosinophil counts from 10 high-power histologic fields), and expressed in relation to the intensity of inflammation in the histopathologic slides examined. Eosinophilia ratios were compared for both groups using the Mann-Whitney test.

**Results:** A significant difference was found in mean eosinophil ratios in the drug-induced vs non–drug-induced groups (5.20 vs 1.05; $P=.01$). Vascular fibrin deposition was present in both groups and was not found to be significantly different ($P=.78$). Clinical evidence of systemic vasculitis was present in 2 patients (13%) in the drug-induced group vs 15 (32%) in the non–drug-induced group. Fourteen patients (88%) in the drug-induced group had a short-term disease course vs 27 (57%) in the non–drug-induced group.

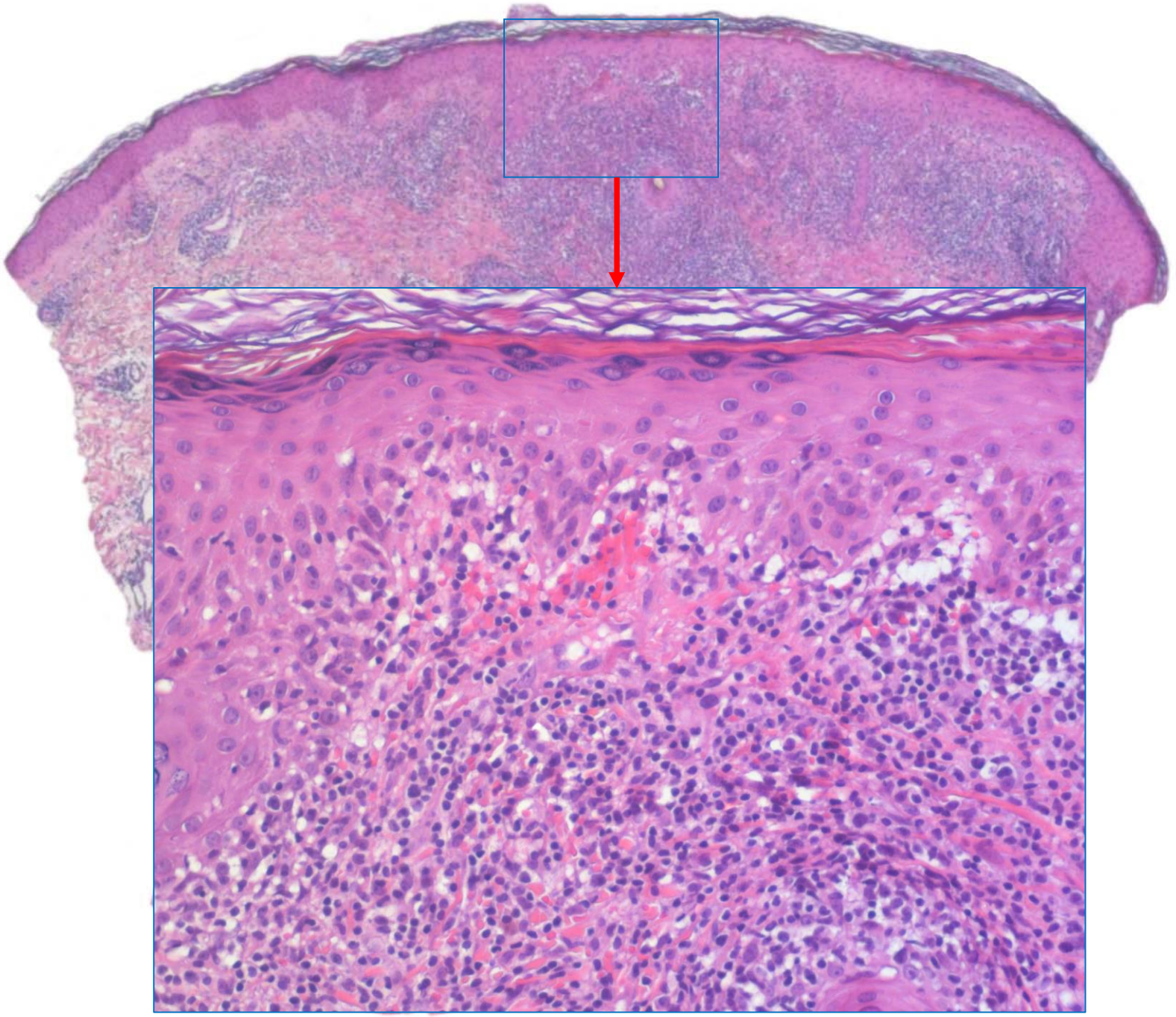
**Conclusions:** Tissue eosinophilia is established as a reliable indicator of drug induction in cutaneous small vessel vasculitis. Drug-induced small-vessel vasculitis generally follows a short-term disease course without development of systemic involvement. This information may be useful for guiding management decisions, especially when the etiology is unclear.

*Arch Dermatol. 2006;142:155-161*

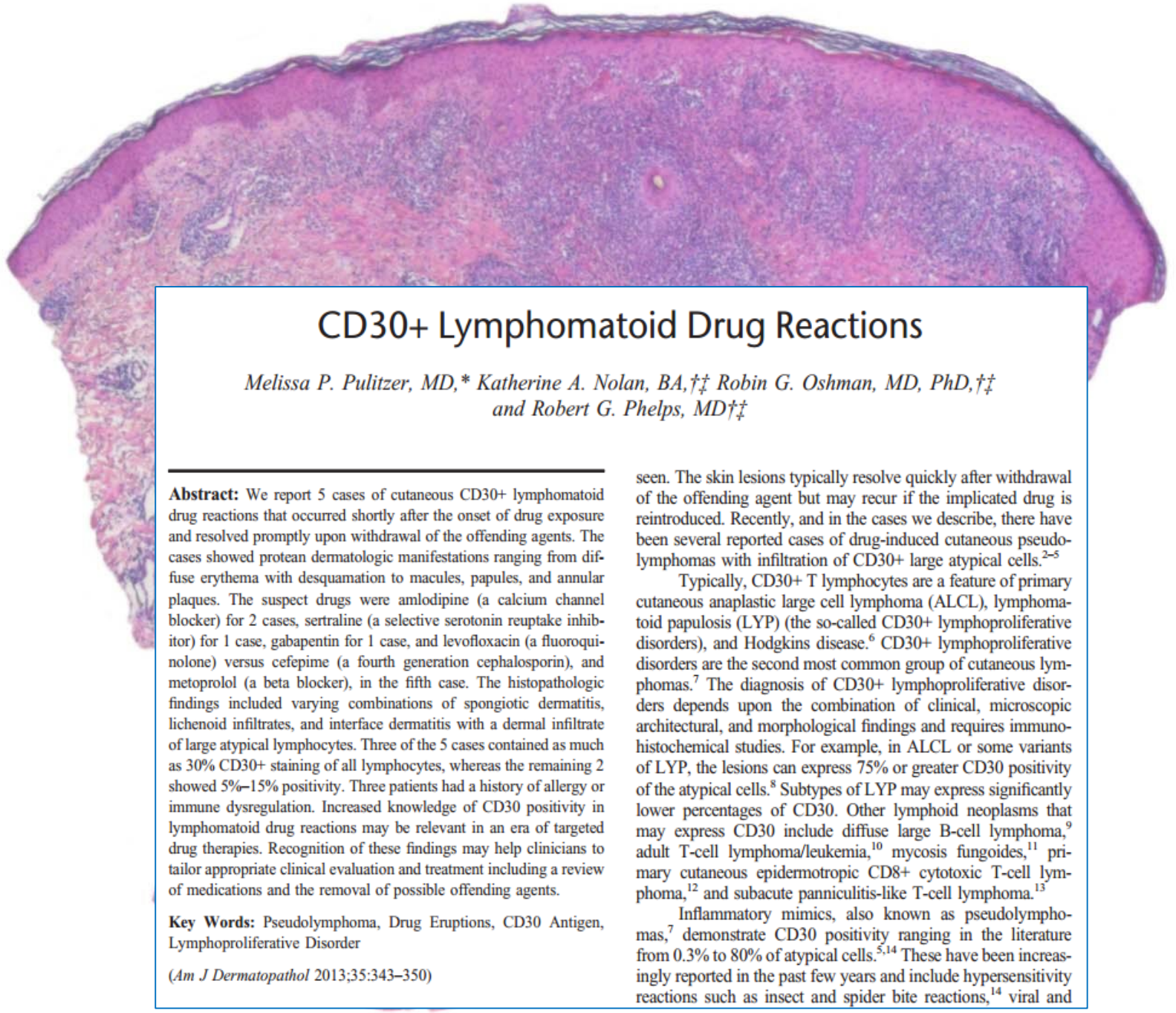
*"Tissue esosinophilia"* has been emphasized as *"an indicator of drug-induced cutaneous small-cessel vasculitis,"* and this is also my experience.



A pattern not observed in our study of 300 consecutive cases of drug eruption, but not exceptional, is nodular dermatitis. The infiltrate is dense



and often associated with interface changes or spongiosis with exocytosis of lymphocytes into the epidermis. As in other drug eruptions, there are often signs of acuteness, such extravasation of erythrocytes, and lymphocytes are often on the large side.



# CD30+ Lymphomatoid Drug Reactions

*Melissa P. Pulitzer, MD,* Katherine A. Nolan, BA,†‡ Robin G. Oshman, MD, PhD,†‡ and Robert G. Phelps, MD†‡*

**Abstract:** We report 5 cases of cutaneous CD30+ lymphomatoid drug reactions that occurred shortly after the onset of drug exposure and resolved promptly upon withdrawal of the offending agents. The cases showed protean dermatologic manifestations ranging from diffuse erythema with desquamation to macules, papules, and annular plaques. The suspect drugs were amlodipine (a calcium channel blocker) for 2 cases, sertraline (a selective serotonin reuptake inhibitor) for 1 case, gabapentin for 1 case, and levofloxacin (a fluoroquinolone) versus cefepime (a fourth generation cephalosporin), and metoprolol (a beta blocker), in the fifth case. The histopathologic findings included varying combinations of spongiotic dermatitis, lichenoid infiltrates, and interface dermatitis with a dermal infiltrate of large atypical lymphocytes. Three of the 5 cases contained as much as 30% CD30+ staining of all lymphocytes, whereas the remaining 2 showed 5%–15% positivity. Three patients had a history of allergy or immune dysregulation. Increased knowledge of CD30 positivity in lymphomatoid drug reactions may be relevant in an era of targeted drug therapies. Recognition of these findings may help clinicians to tailor appropriate clinical evaluation and treatment including a review of medications and the removal of possible offending agents.

**Key Words:** Pseudolymphoma, Drug Eruptions, CD30 Antigen, Lymphoproliferative Disorder

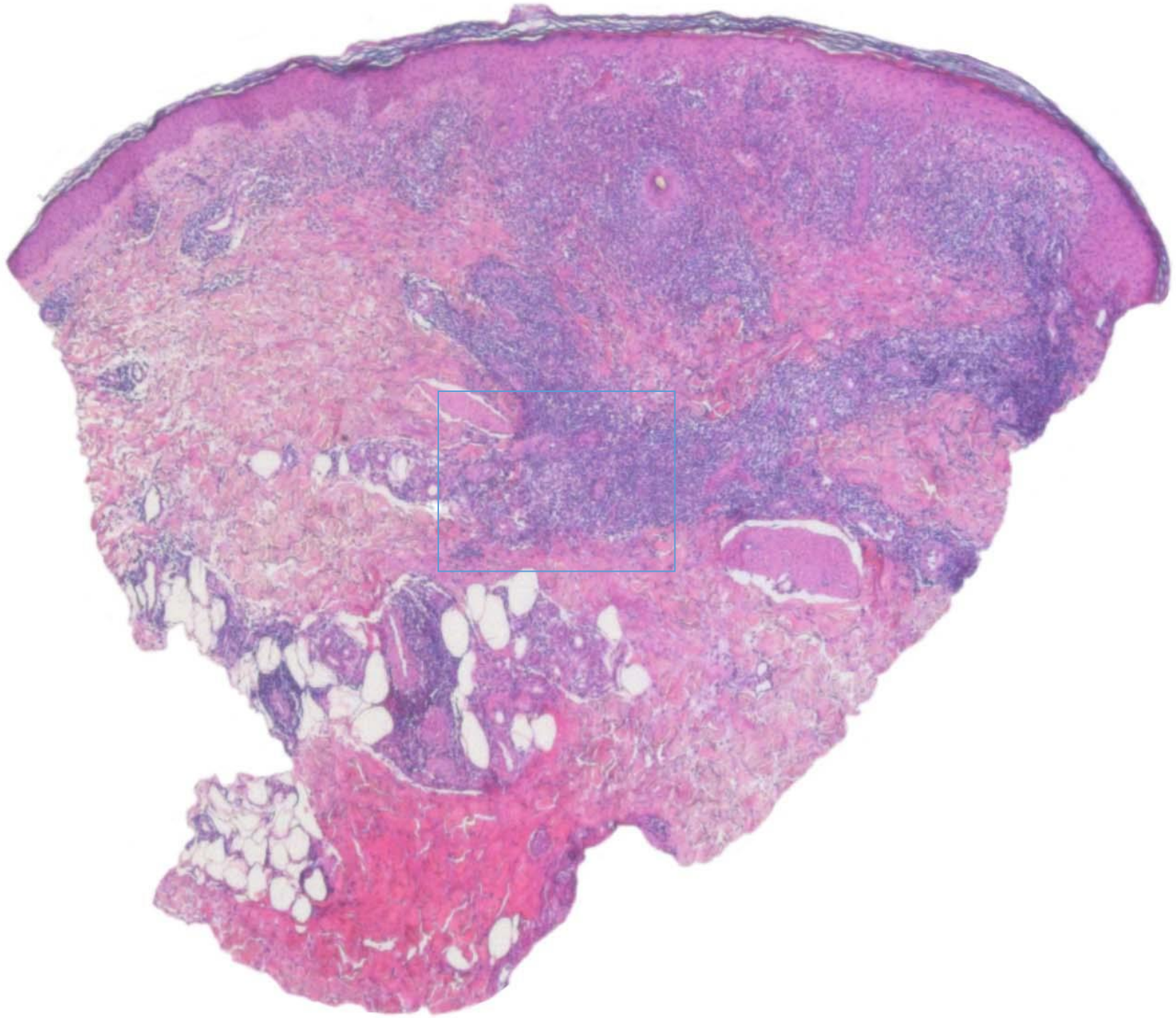
(*Am J Dermatopathol* 2013;35:343–350)

seen. The skin lesions typically resolve quickly after withdrawal of the offending agent but may recur if the implicated drug is reintroduced. Recently, and in the cases we describe, there have been several reported cases of drug-induced cutaneous pseudolymphomas with infiltration of CD30+ large atypical cells.[2–5]

Typically, CD30+ T lymphocytes are a feature of primary cutaneous anaplastic large cell lymphoma (ALCL), lymphomatoid papulosis (LYP) (the so-called CD30+ lymphoproliferative disorders), and Hodgkins disease.[6] CD30+ lymphoproliferative disorders are the second most common group of cutaneous lymphomas.[7] The diagnosis of CD30+ lymphoproliferative disorders depends upon the combination of clinical, microscopic architectural, and morphological findings and requires immunohistochemical studies. For example, in ALCL or some variants of LYP, the lesions can express 75% or greater CD30 positivity of the atypical cells.[8] Subtypes of LYP may express significantly lower percentages of CD30. Other lymphoid neoplasms that may express CD30 include diffuse large B-cell lymphoma,[9] adult T-cell lymphoma/leukemia,[10] mycosis fungoides,[11] primary cutaneous epidermotropic CD8+ cytotoxic T-cell lymphoma,[12] and subacute panniculitis-like T-cell lymphoma.[13]

Inflammatory mimics, also known as pseudolymphomas,[7] demonstrate CD30 positivity ranging in the literature from 0.3% to 80% of atypical cells.[5,14] These have been increasingly reported in the past few years and include hypersensitivity reactions such as insect and spider bite reactions,[14] viral and

They may express CD30, a constellation referred to as *"CD30+ lymphomatoid drug reactions,"* and distinction from lymphomatoid papulosis may be difficult because, in both conditions, the infiltrate is dense and wedge-shaped, and spongiosis and presence of eosinophils and neutrophils are expected findings.



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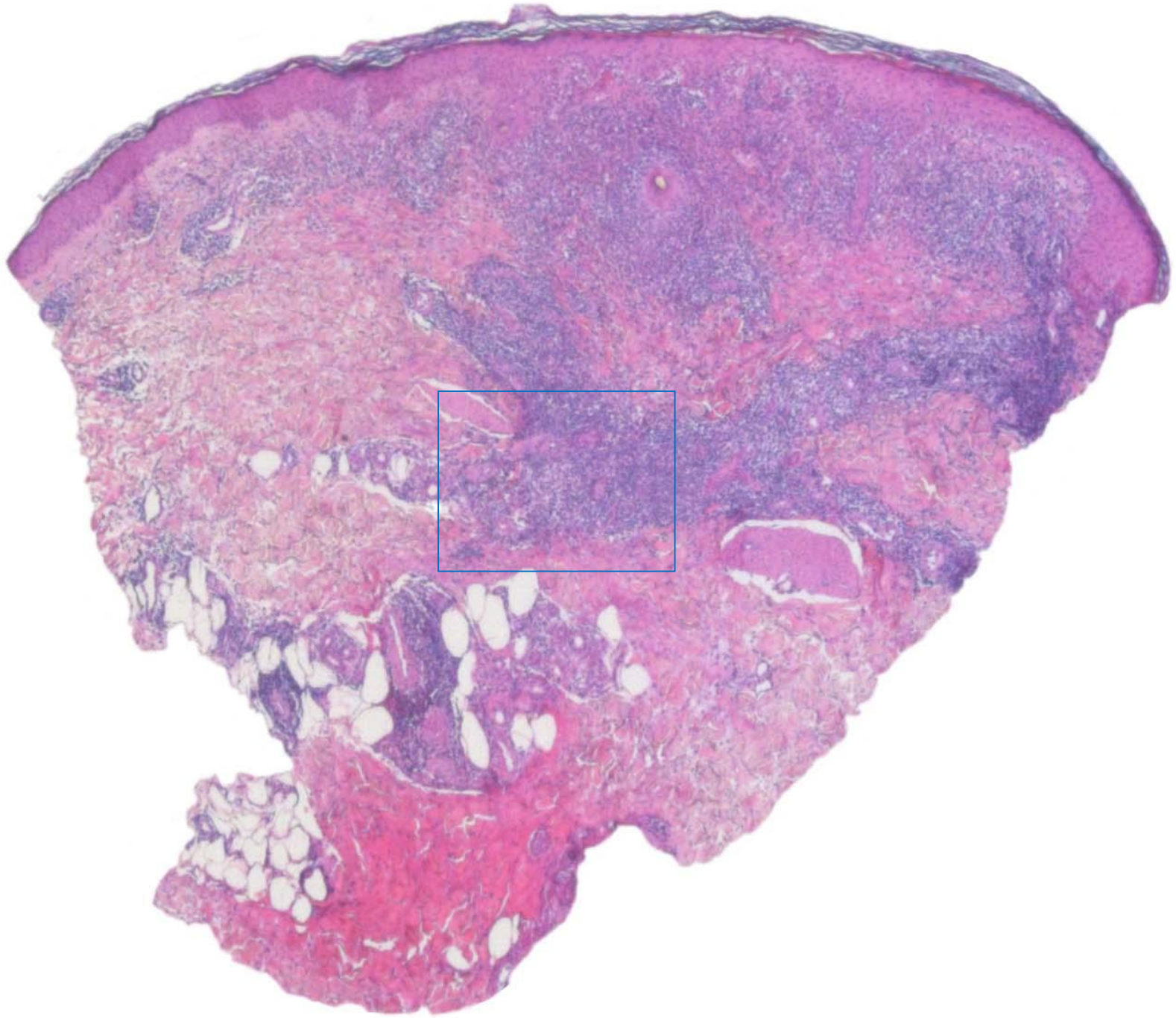
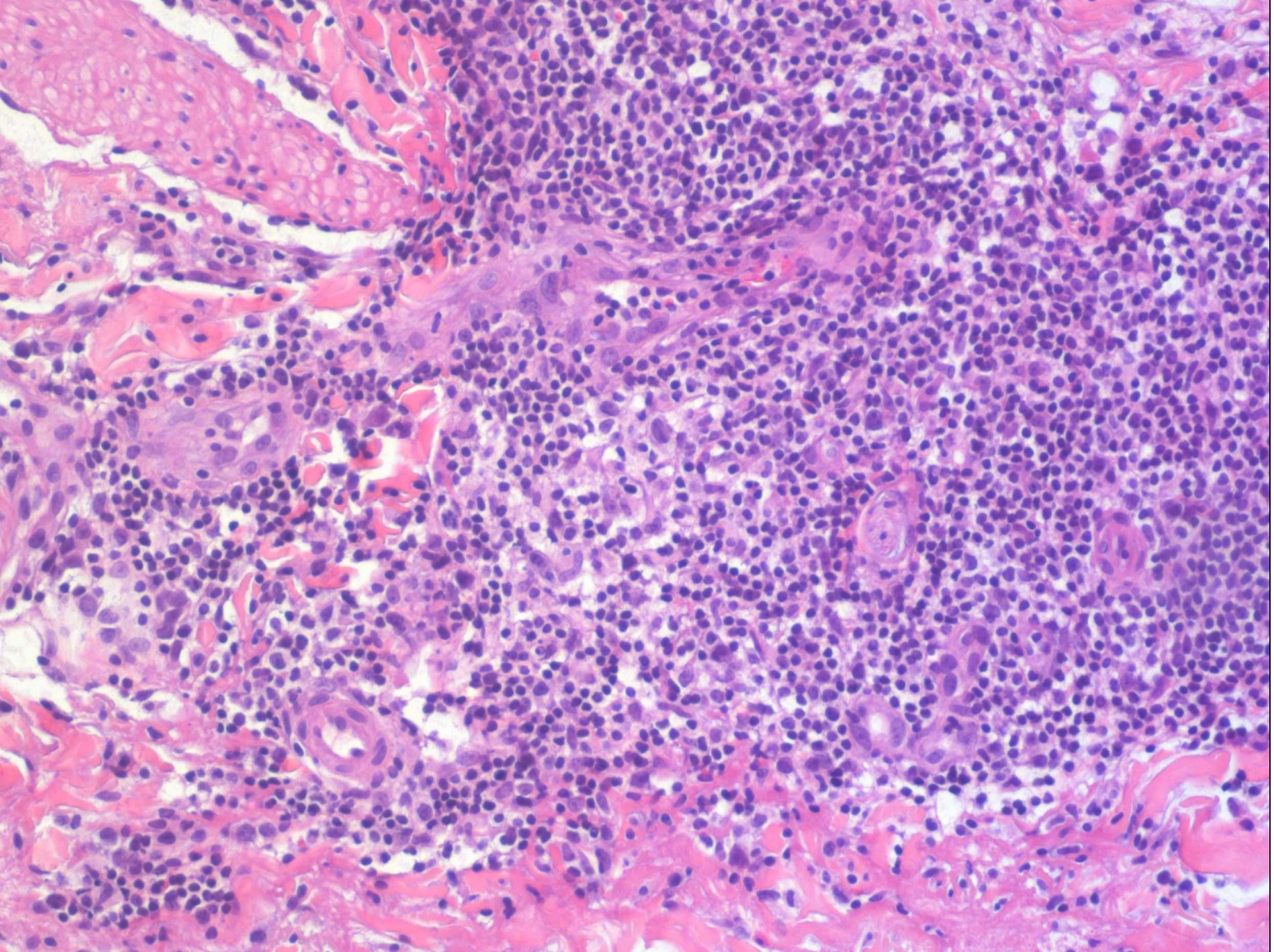


Clues to a lymphomatoid drug eruption are vacuolar interface changes and, as in this case, foci of granulomatous inflammation. However, none of those findings is specific, and clinico-pathologic is essential for distinction of both conditions.



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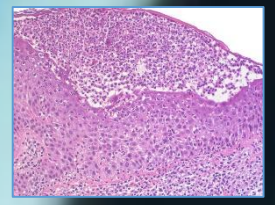
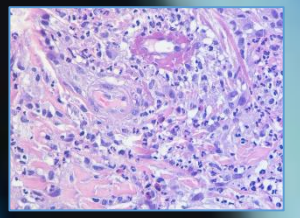
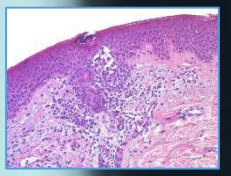
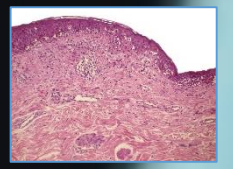
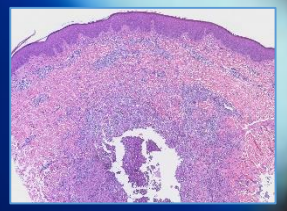
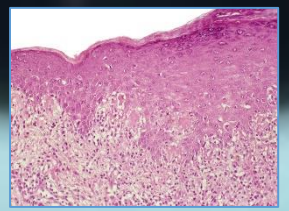
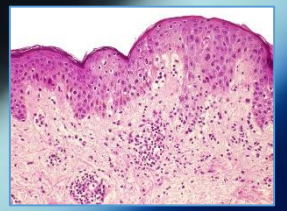





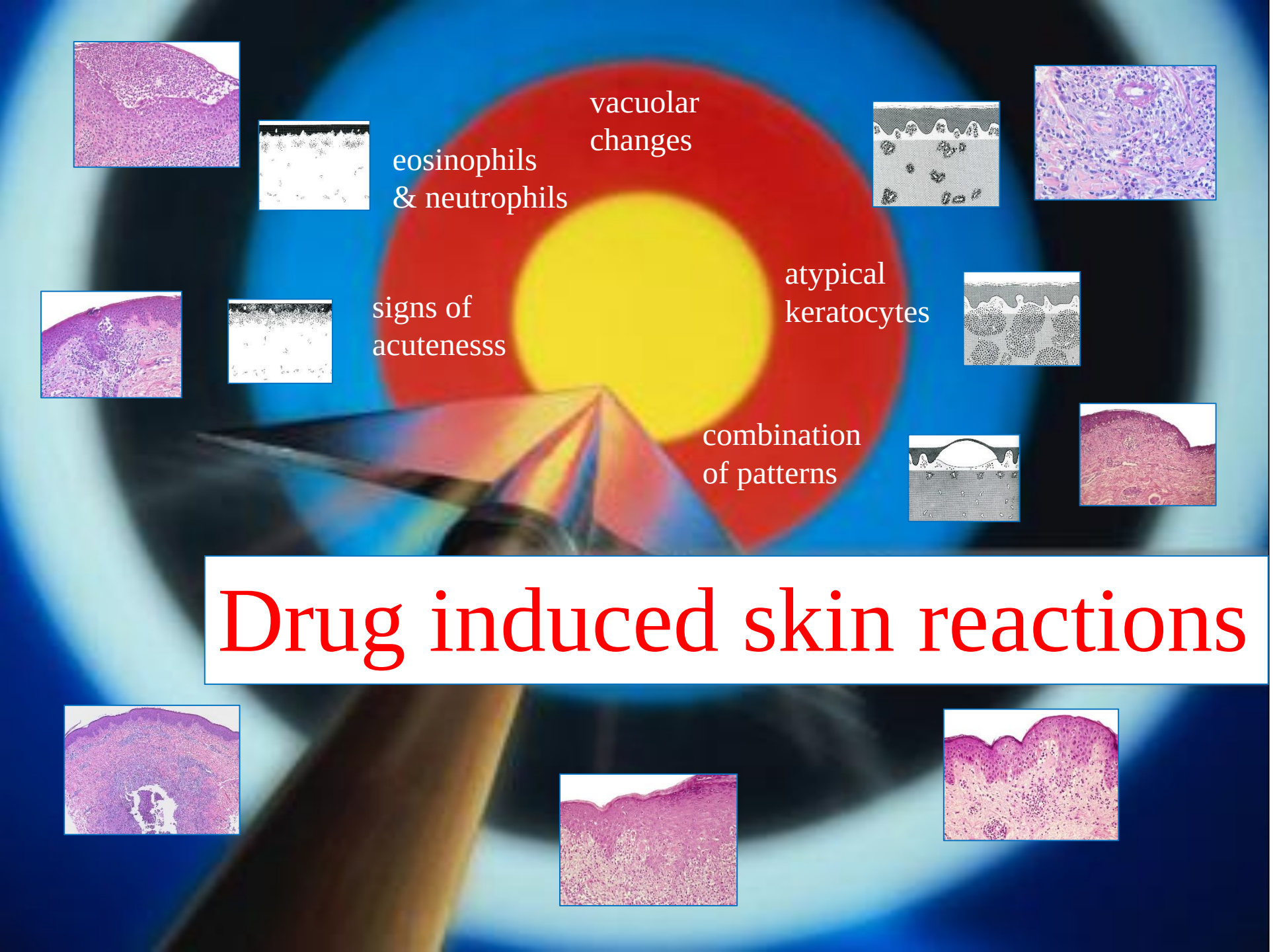
# Drug induced skin reactions

In sum, the histopathologic presentation of drug-induced skin reactions is extremely variable, and histopathologic diagnosis may be difficult. Nonetheless, it is possible in the majority of cases.

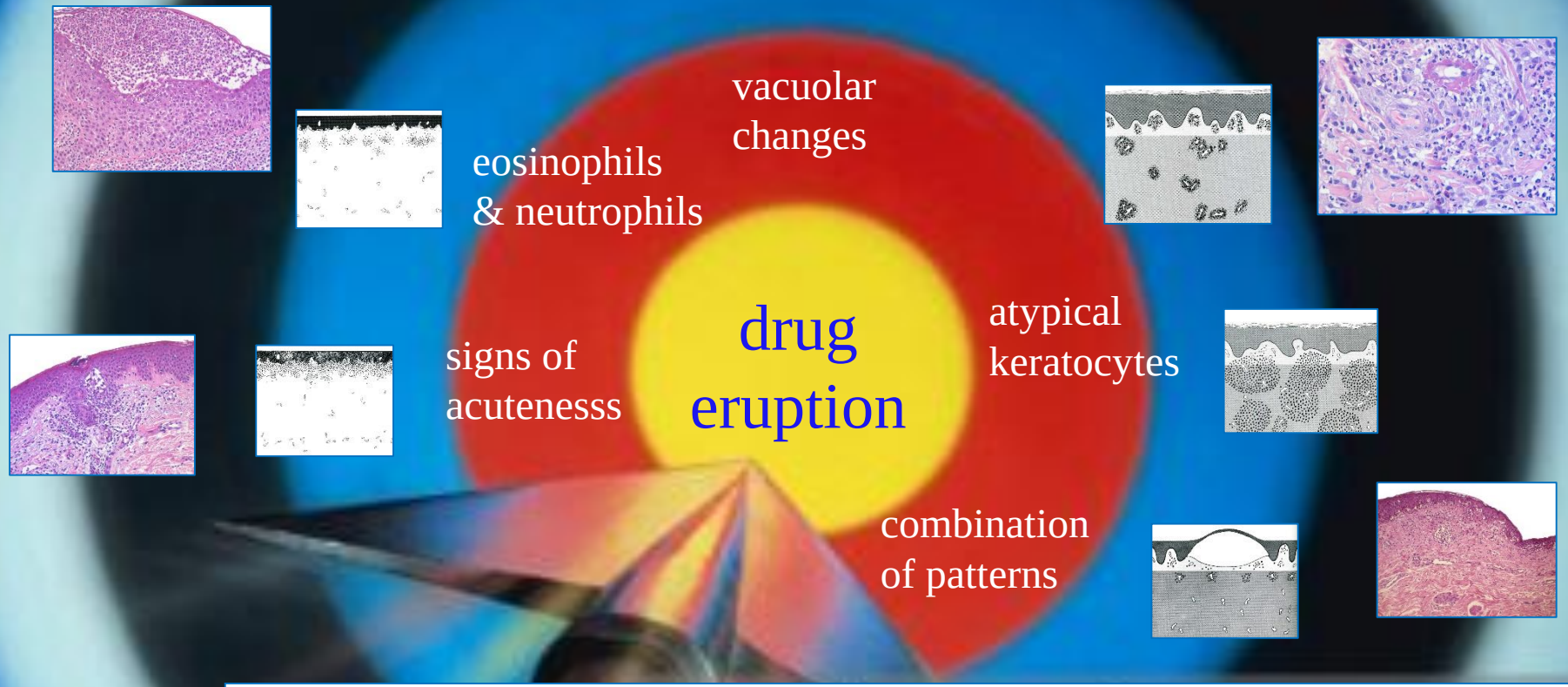
# Drug induced skin reactions

In general, recognition of distinct patterns of inflammation, followed by consideration of the respective differential diagnoses,




# Drug induced skin reactions

and of the relatively large number of clues to the diagnosis of drug eruption, such as vacuolar changes at the dermo-epidermal junction, eosinophils and neutrophils in the infiltrate, signs of acuteness, atypical keratocytes, and a combination of patterns, allow a presumptive histopathologic diagnosis




# Drug induced skin reactions

of drug eruption to be made with the same degree of confidence as in any other inflammatory disease of the skin.