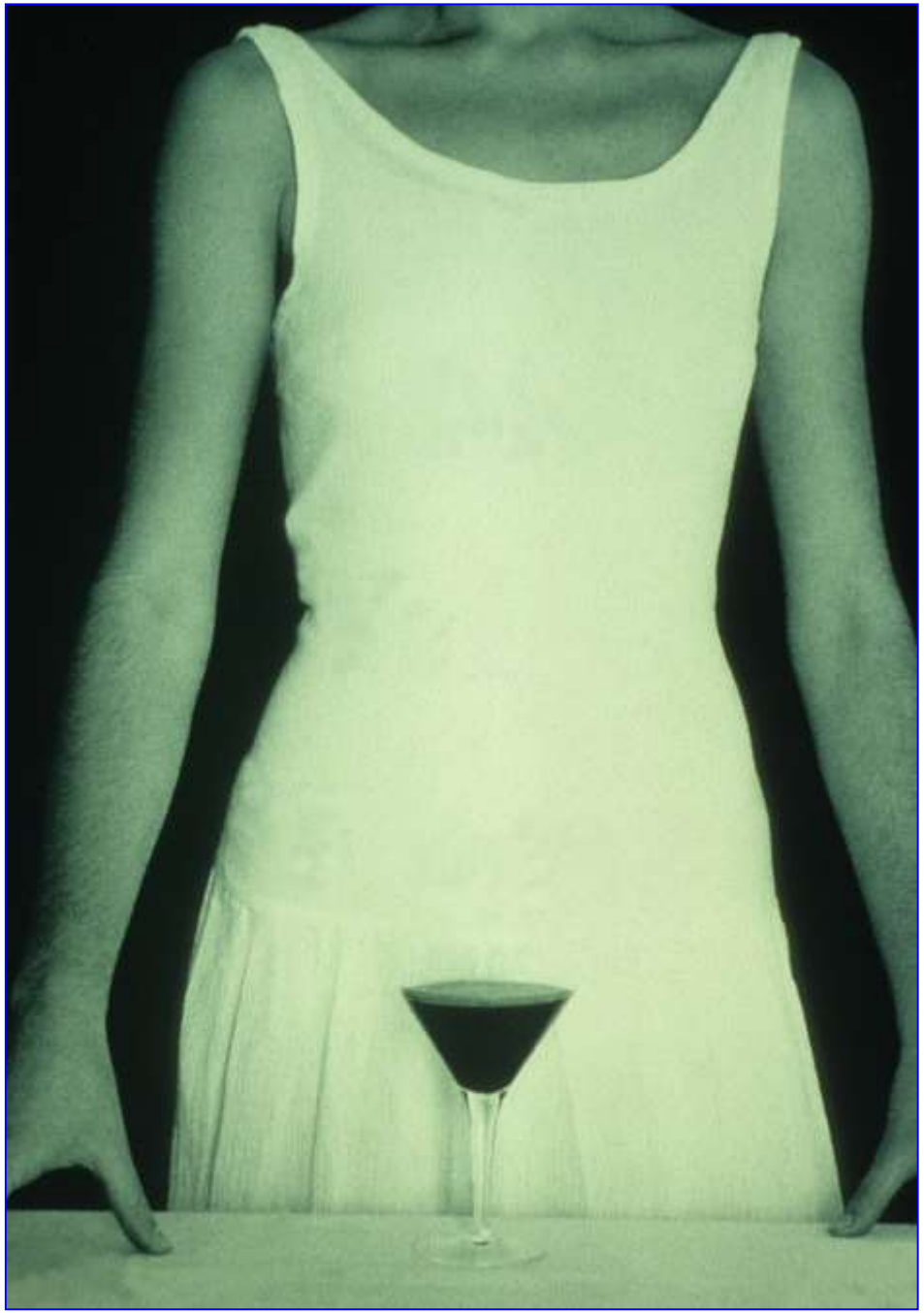


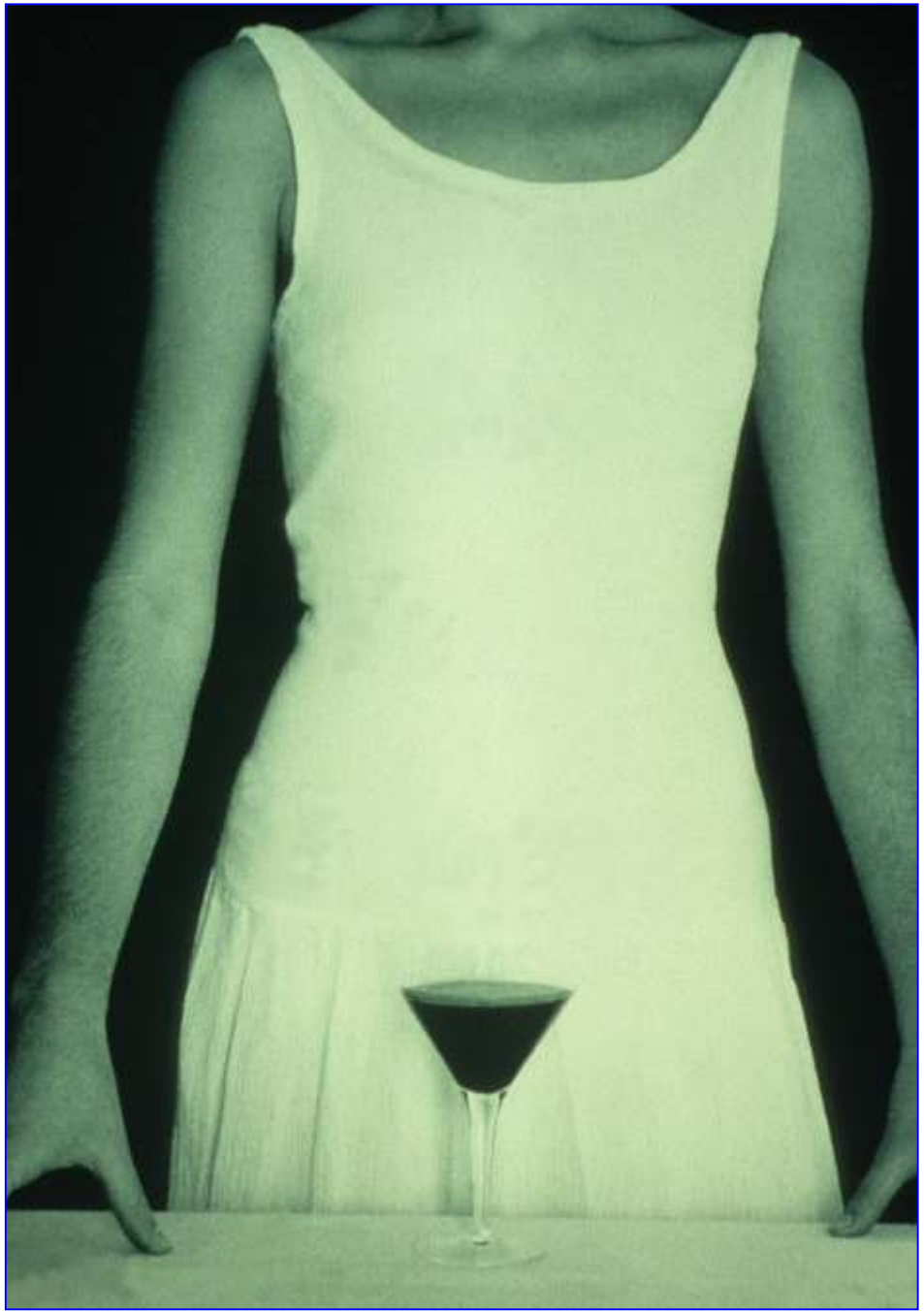
Inflammatory Diseases of the Vulva

W. Weyers
Center for Dermatopathology,
Freiburg, Germany

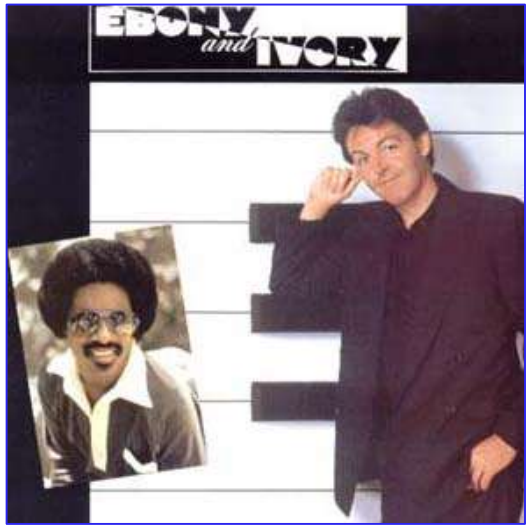
Inflammatory Diseases of the Vulva

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

"Inflammatory diseases of the vulva" is an odd subject because there is no such thing as an "inflammatory disease of the vulva." The vulva may be special in many ways but it is not so special as to possess its own diseases.



Inflammatory Diseases of the Vulva



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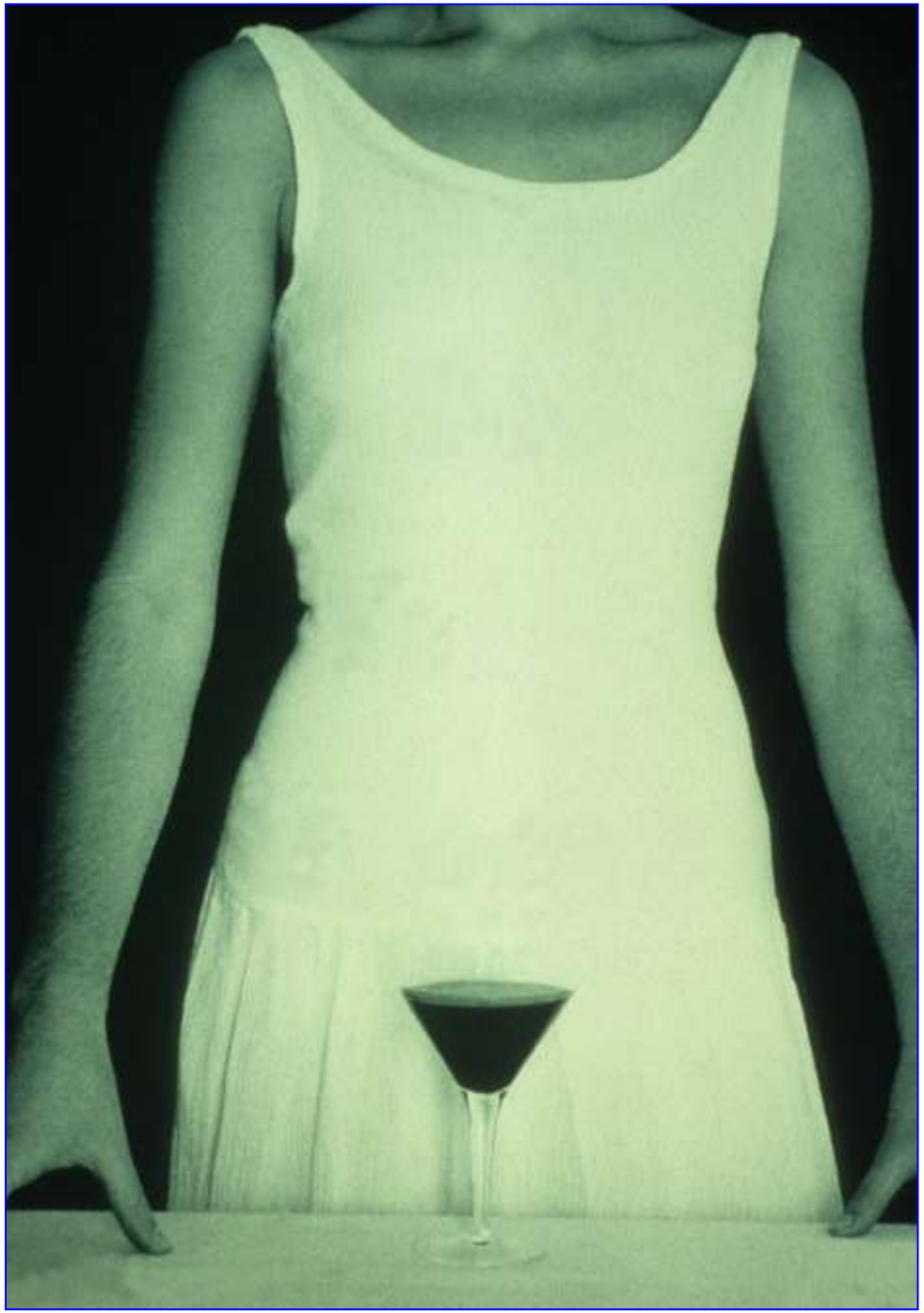
As Stevie Wonder and Paul McCartney noted in their song, “Ebony and Ivory,” *“People are the same wherever you go,”* and this is also true for the skin.



Inflammatory Diseases of the Vulva

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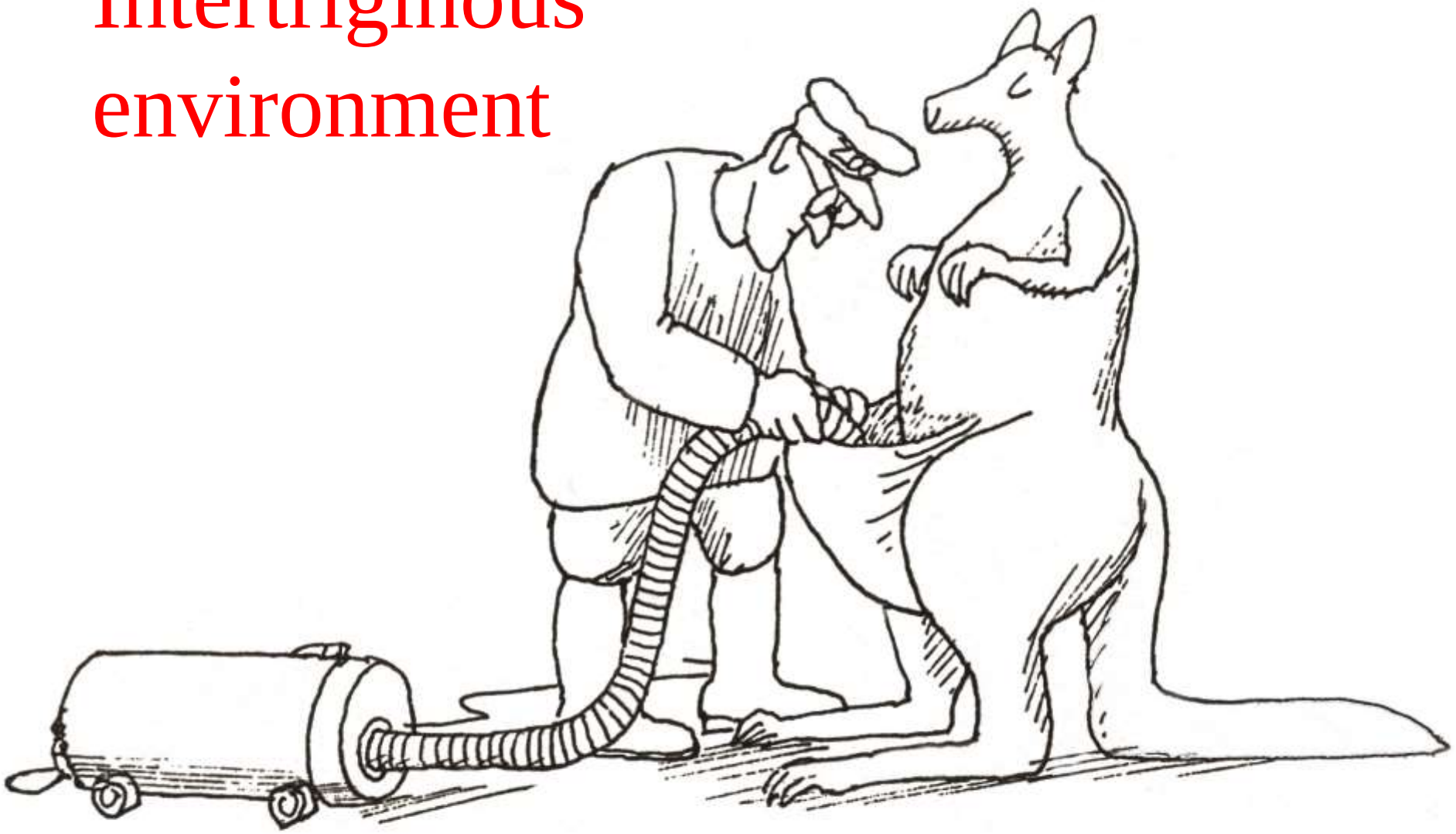
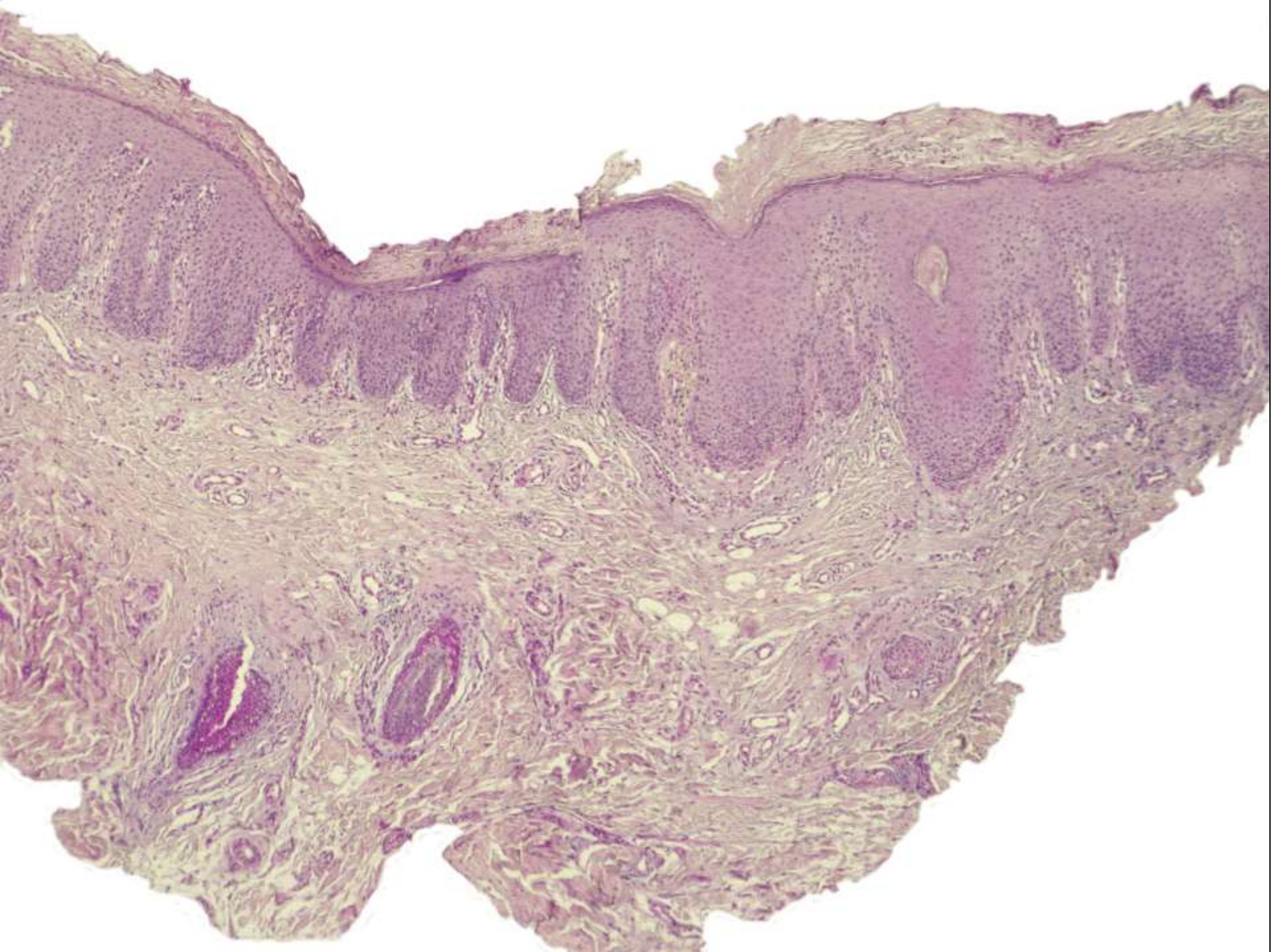
At the same time, one must admit that people in special regions, such as Switzerland, have peculiarities that are far from being universal, and so do different regions of skin.

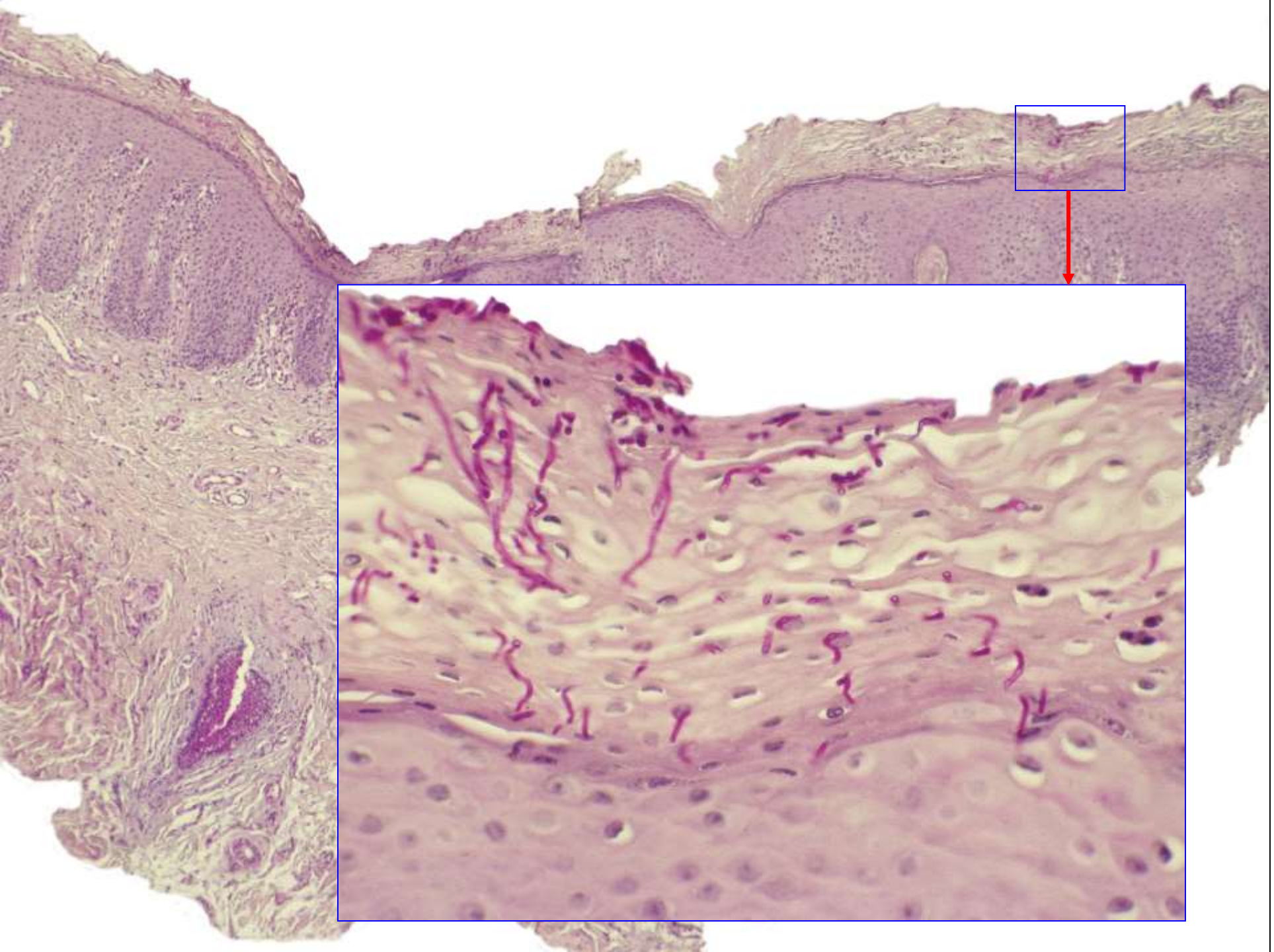
Intertriginous environment



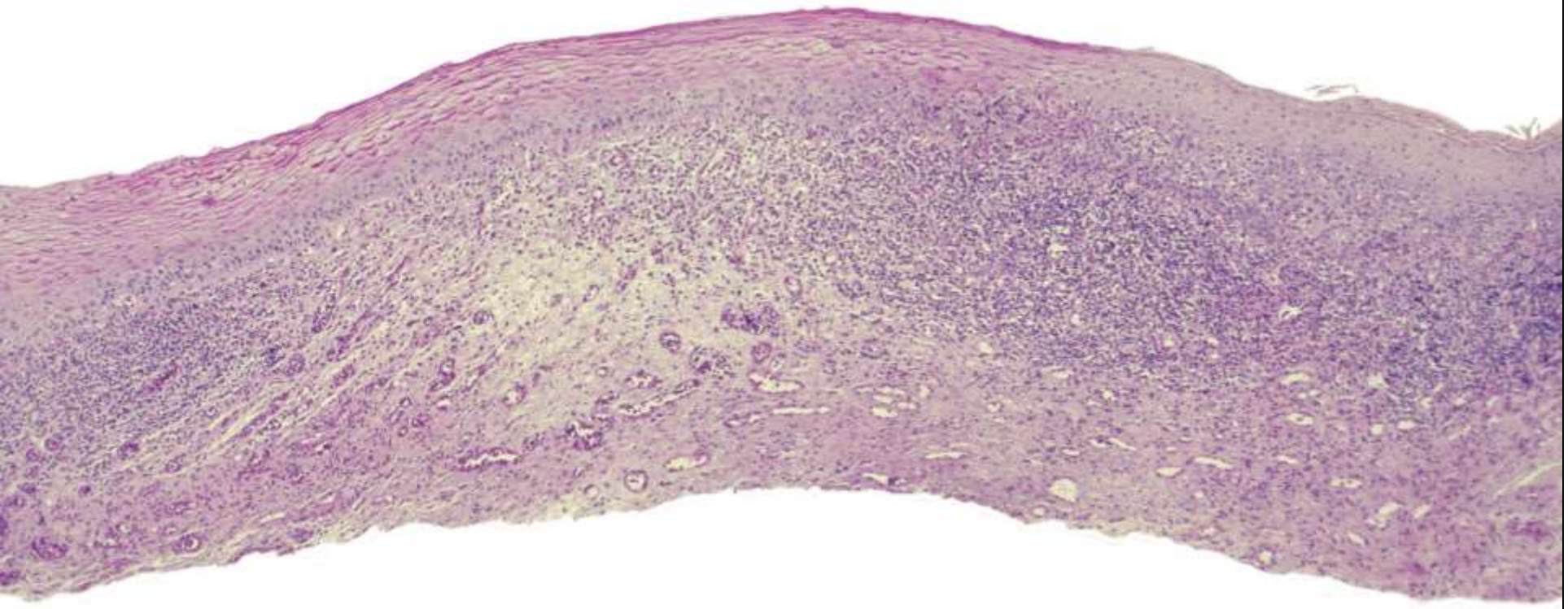
One peculiarity of the vulva is its intertriginous environment. The vulva is warm and moist, a climate cherished by microorganisms. Hence, the vulva is prone to infection,



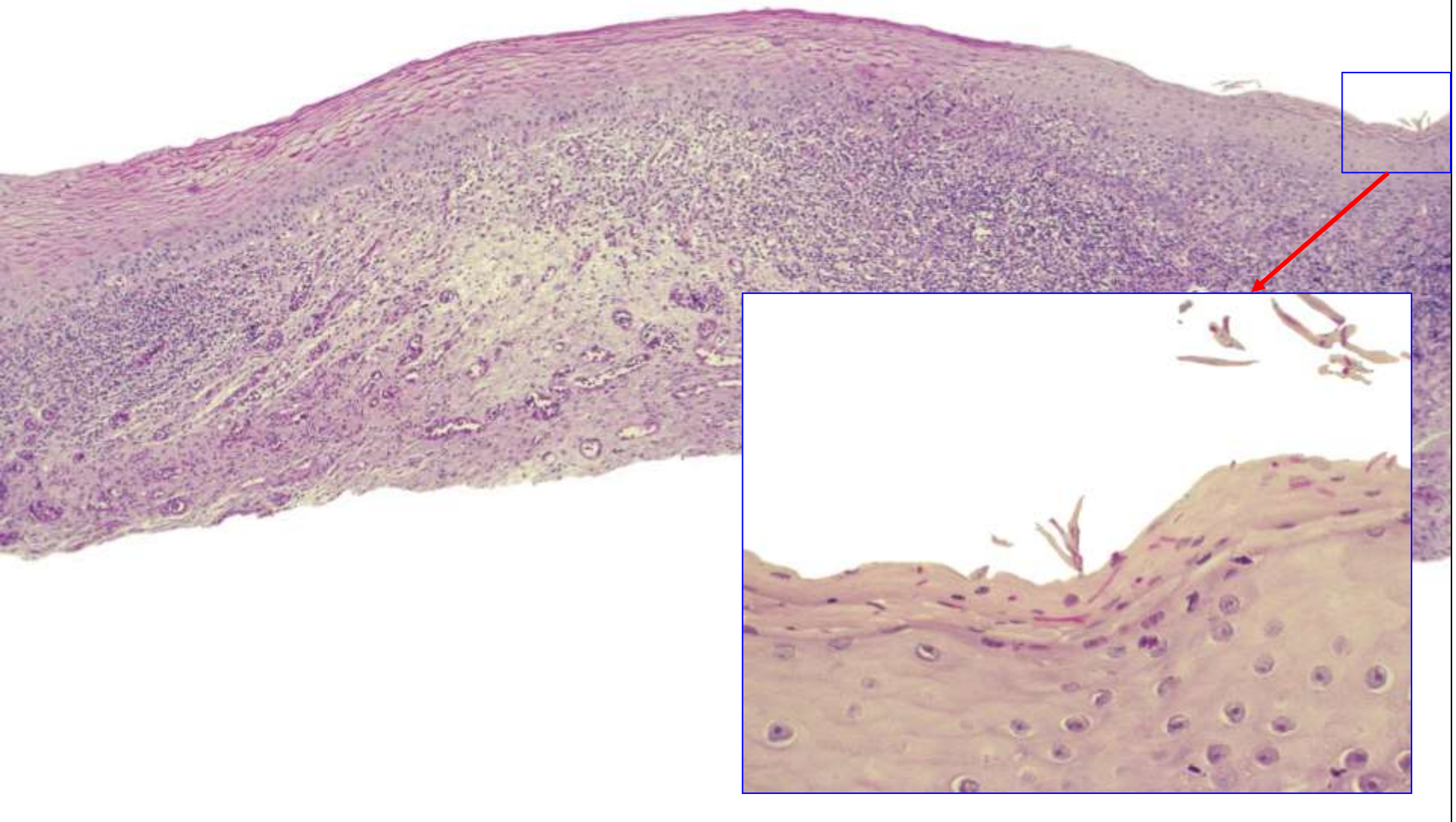
especially by candida. If the cornified layer is thick, as in this case from the labia maiora, fungi are normally detectable easily.



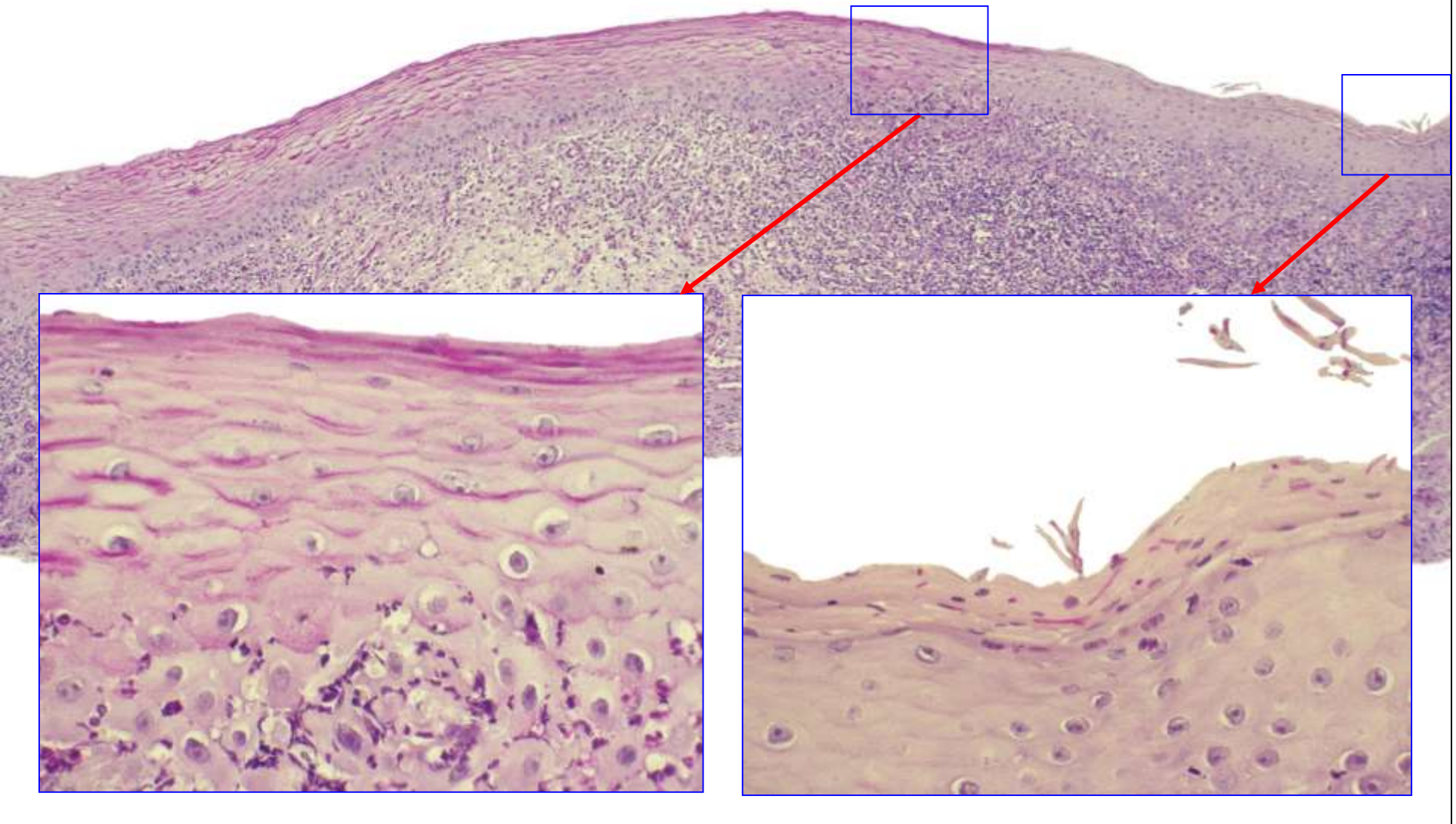
In contrast to dermatophytes, the hyphae of candida tend to be arranged mostly vertically, rather than horizontally.



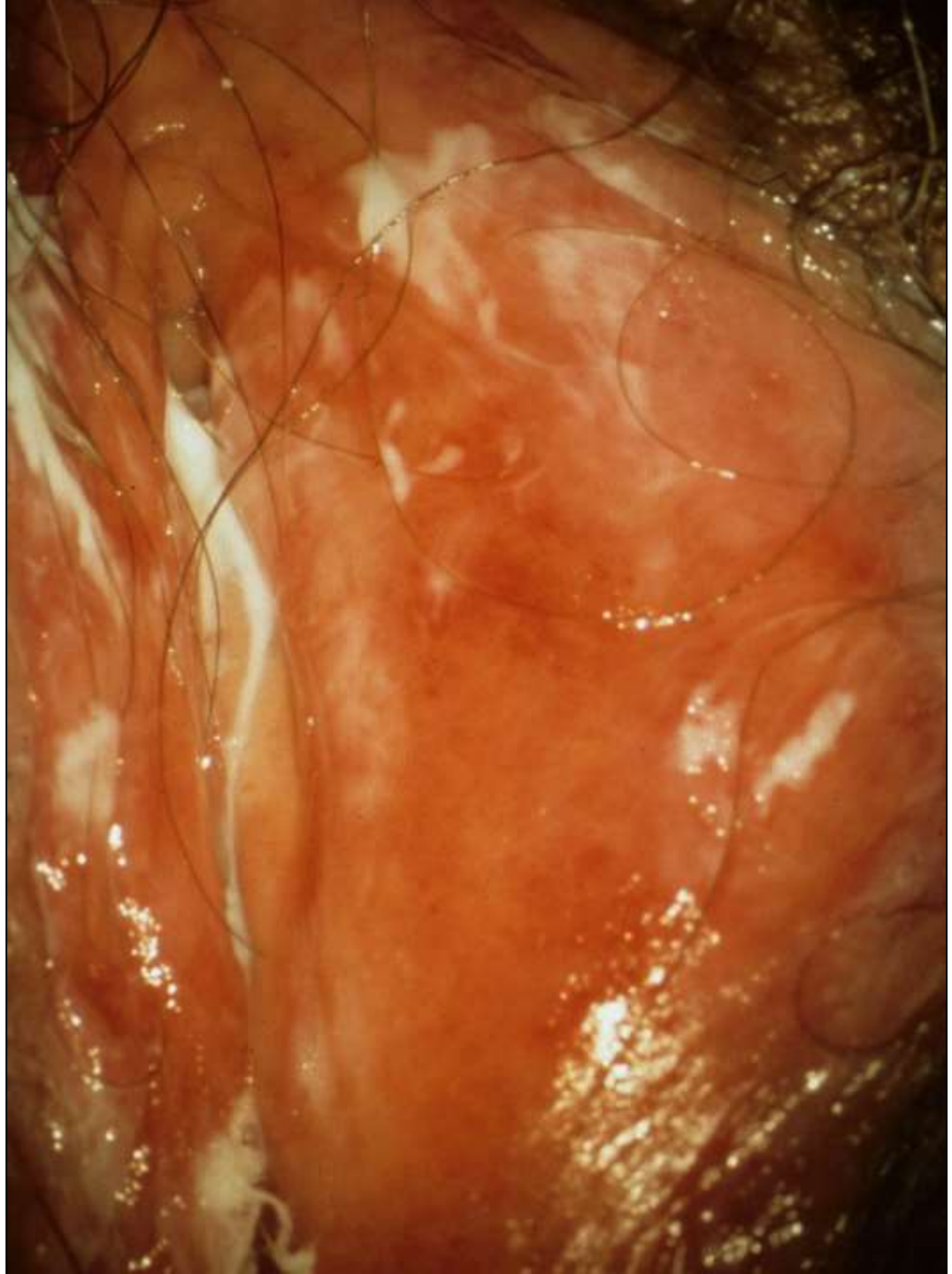
If the cornified layer is thin or absent, as on the labia minora, the diagnosis may be much more difficult. Here is an example: There is a dense lichenoid infiltrate in the upper dermis. Because of rich vascularity on the vulva, a perivascular infiltrate often appears patchy lichenoid.



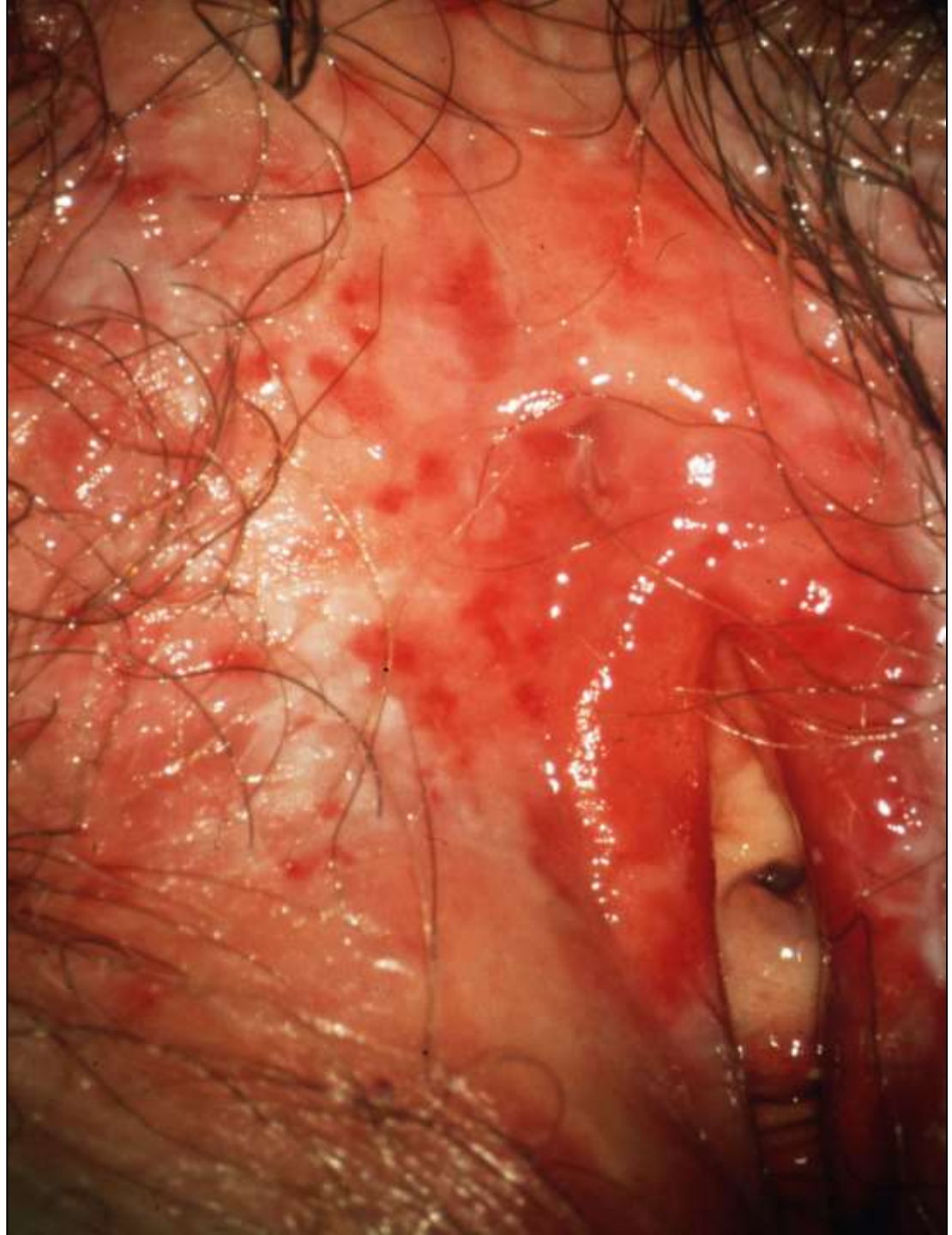
On the right, the epithelium is cornified and contains many fungal elements.



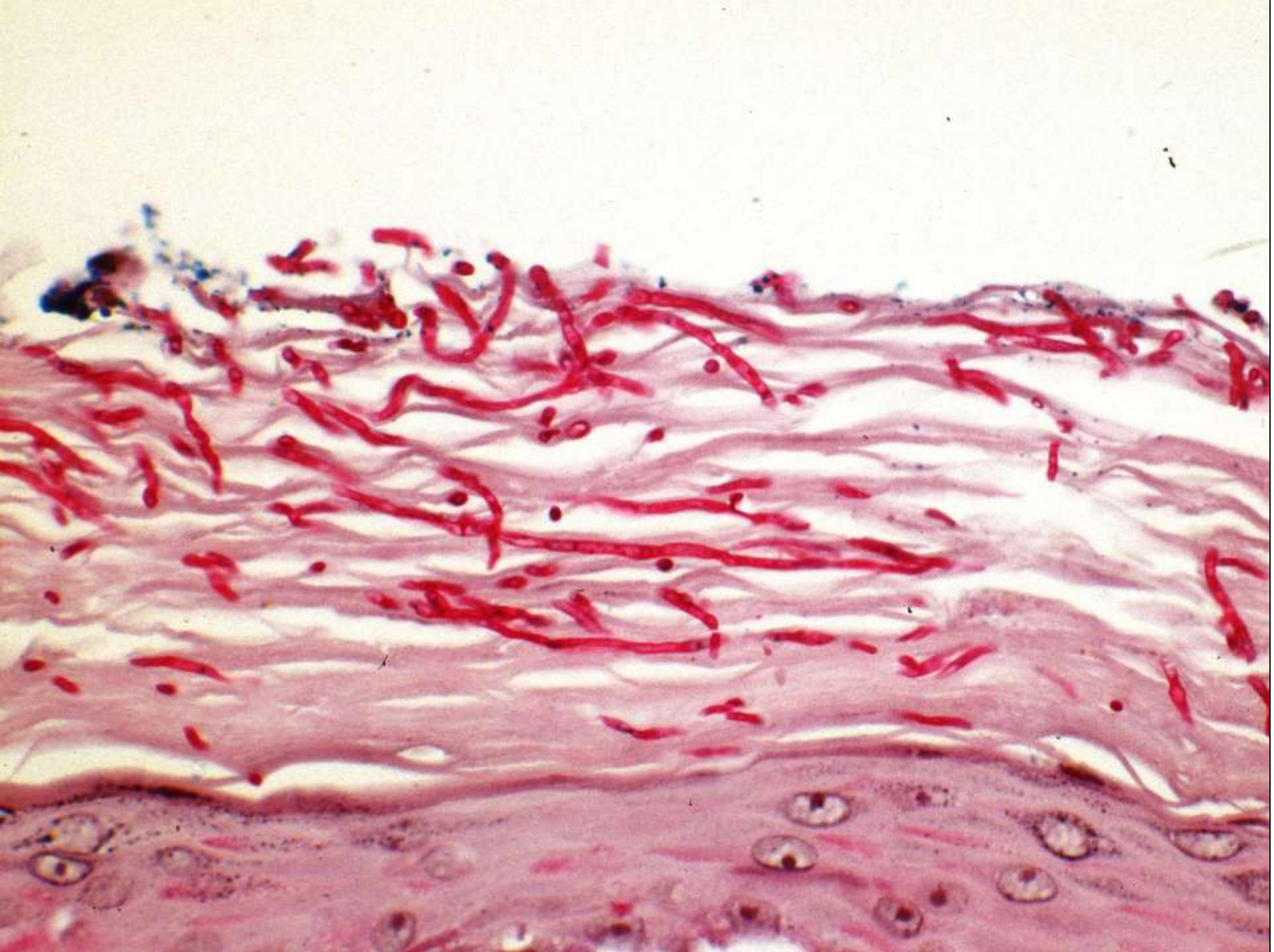
On the left, however, where there is no cornified layer, no fungi are visible. One clue to the diagnosis of candidiasis in the absence of fungal elements is numerous neutrophils in the epidermis. In such an instance, step sections stained by PAS are warranted, but even if they fail to reveal fungi,



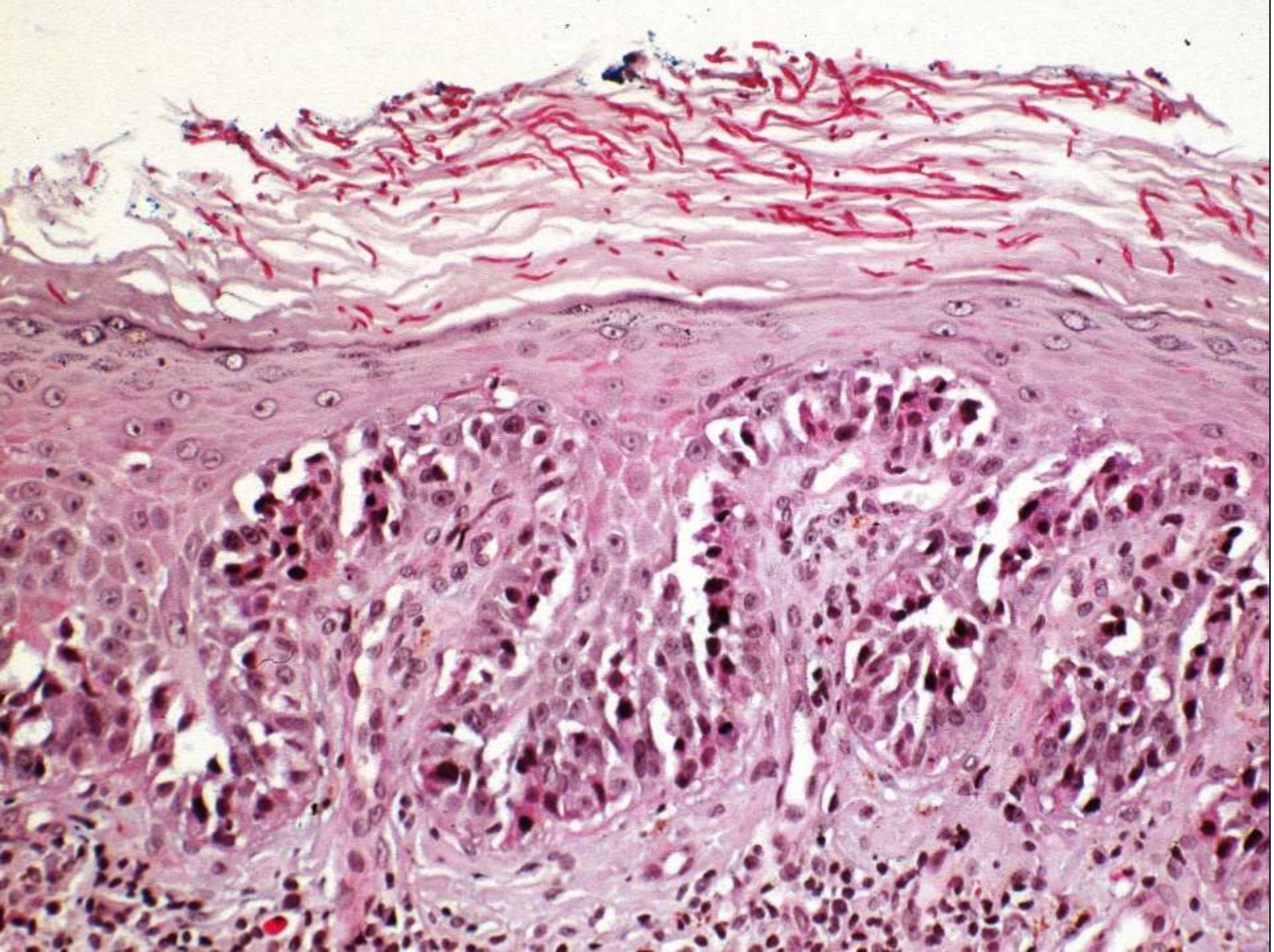
this does not exclude the diagnosis of candidiasis. Just as failure to detect fungal elements does not exclude candidiasis,



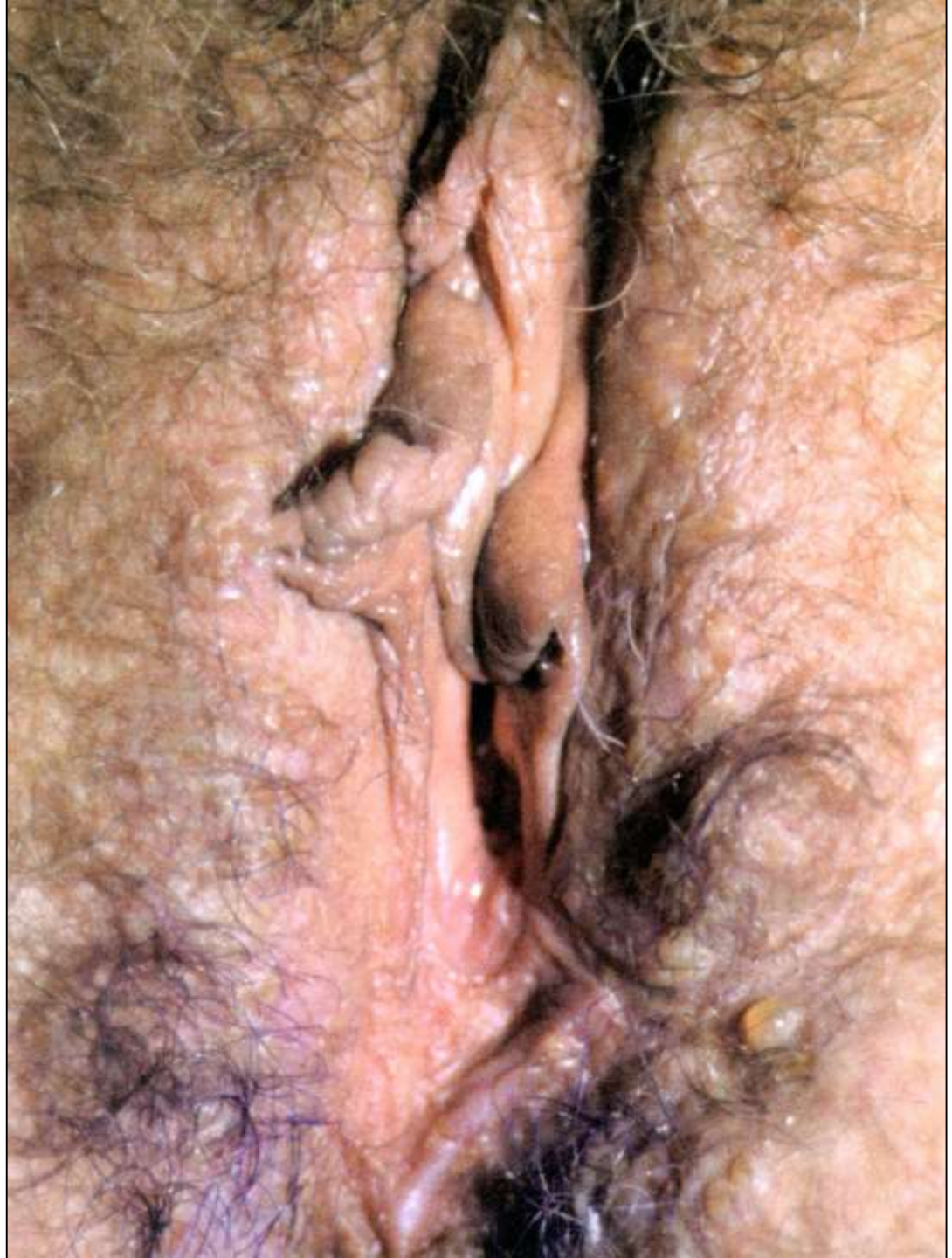
, detection of them does not imply that they are the chief pathologic alteration. Candida cherishes the warm and moist environment of the vulva and takes on any chance to grow. The latter is often provided by a decrease in resistance caused by another pathologic process.



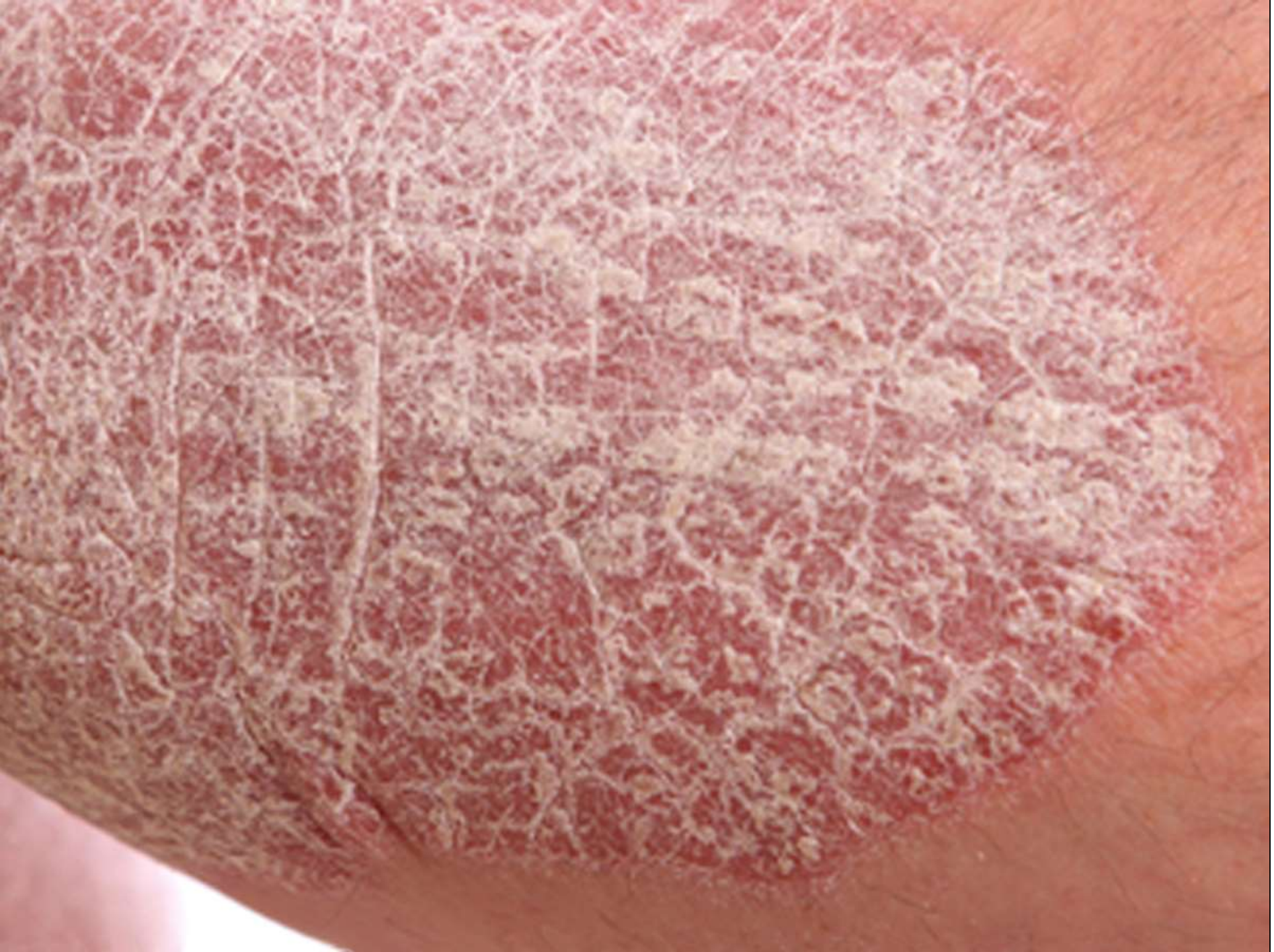
Here we have the case of a middle-aged women with chronic candidiasis. Candida had been cultivated from swabs repeatedly over years, and anti-mycotic treatment had led to some improvement, followed by aggravation of symptoms after cessation of therapy. In chronic vulvar candidiasis, this course is not uncommon because of re-infections from the gastro-intestinal tract or due to sexual intercourse. Nonetheless, because of the severity of the disease, a biopsy was finally taken and, not surprisingly, revealed hyphae in the cornified layer.



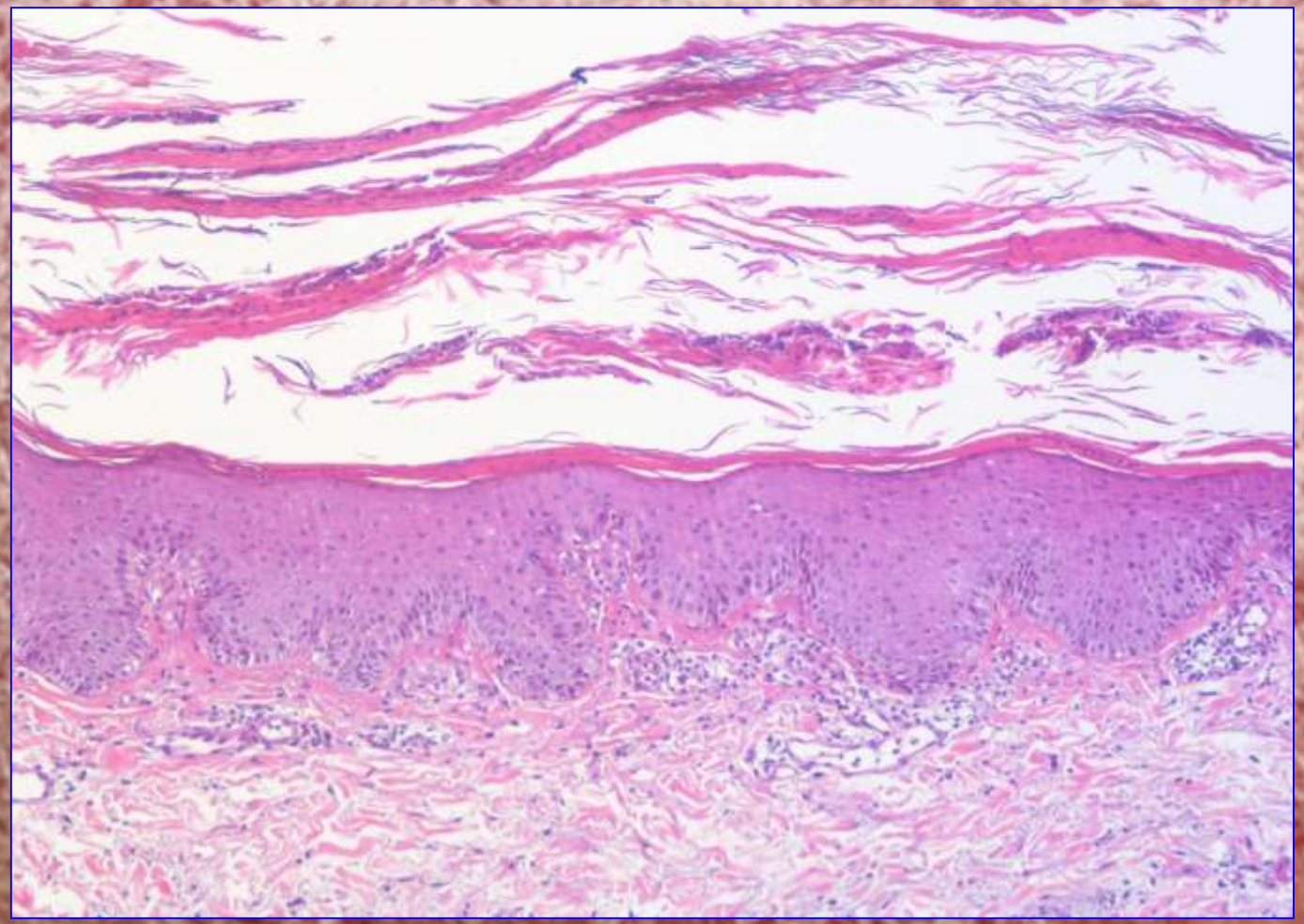
Beneath those hyphae, however, was the underlying pathologic process that allowed candida to grow, namely, extramammary Paget's disease.



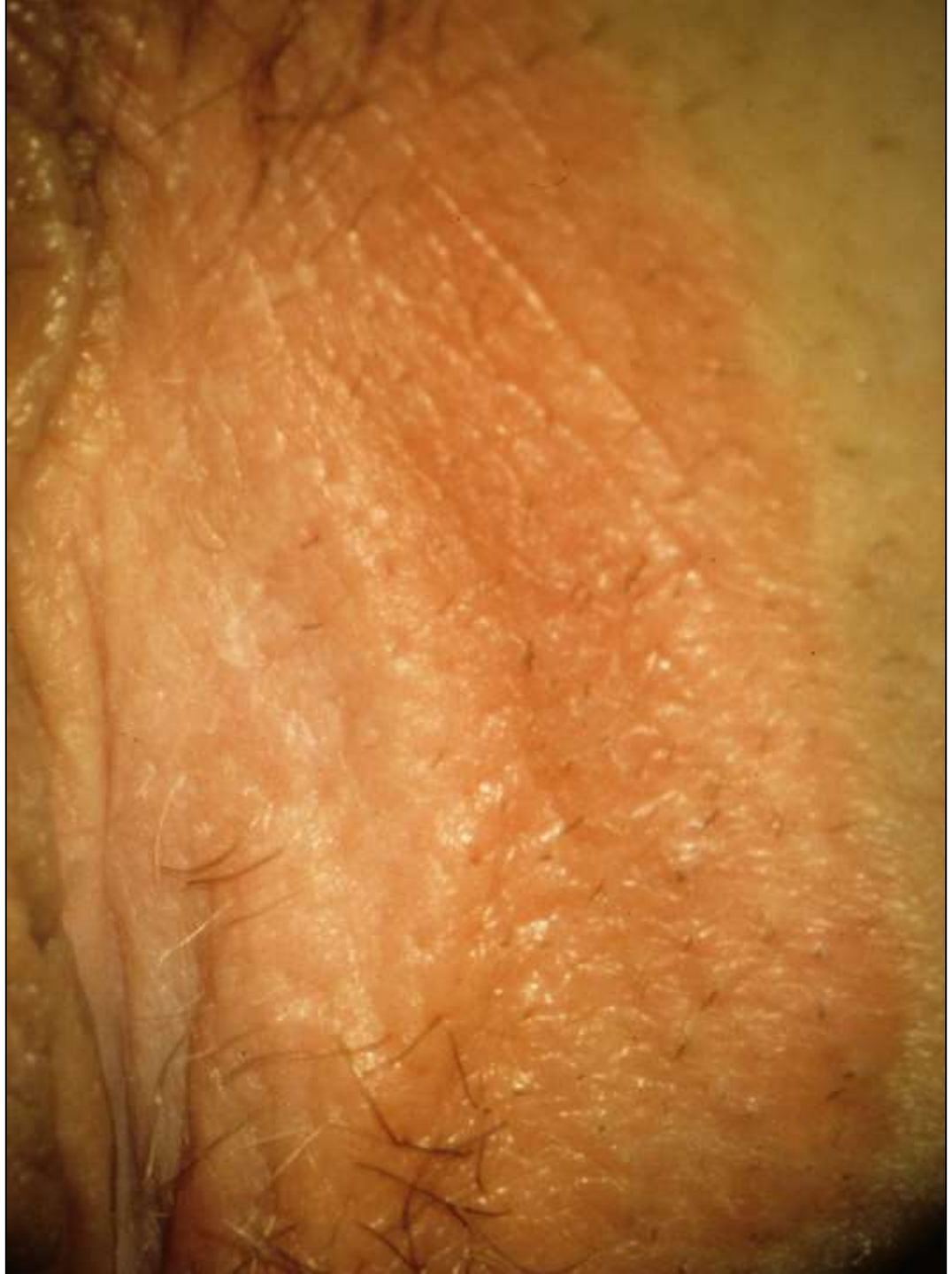
The moist environment of the vulva has some other consequences. One is that loose horny material is shed rapidly. For example, it is uncommon to see blisters with an intact roof; bullous dermatoses of the vulva usually presenting themselves with erosions only.



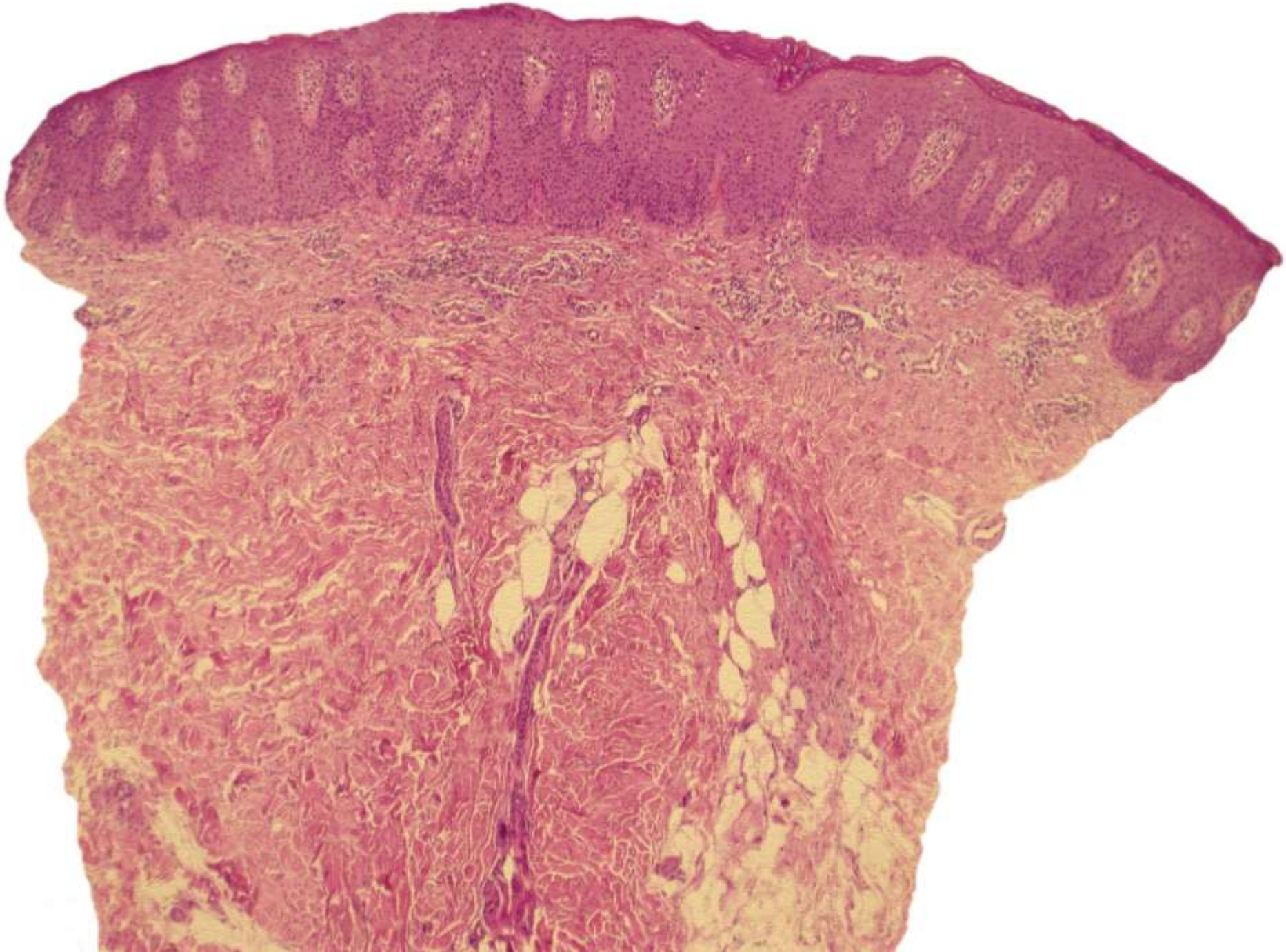
Likewise, squames tend to be shed. In psoriasis, one usually sees neither the typical white squames clinically,



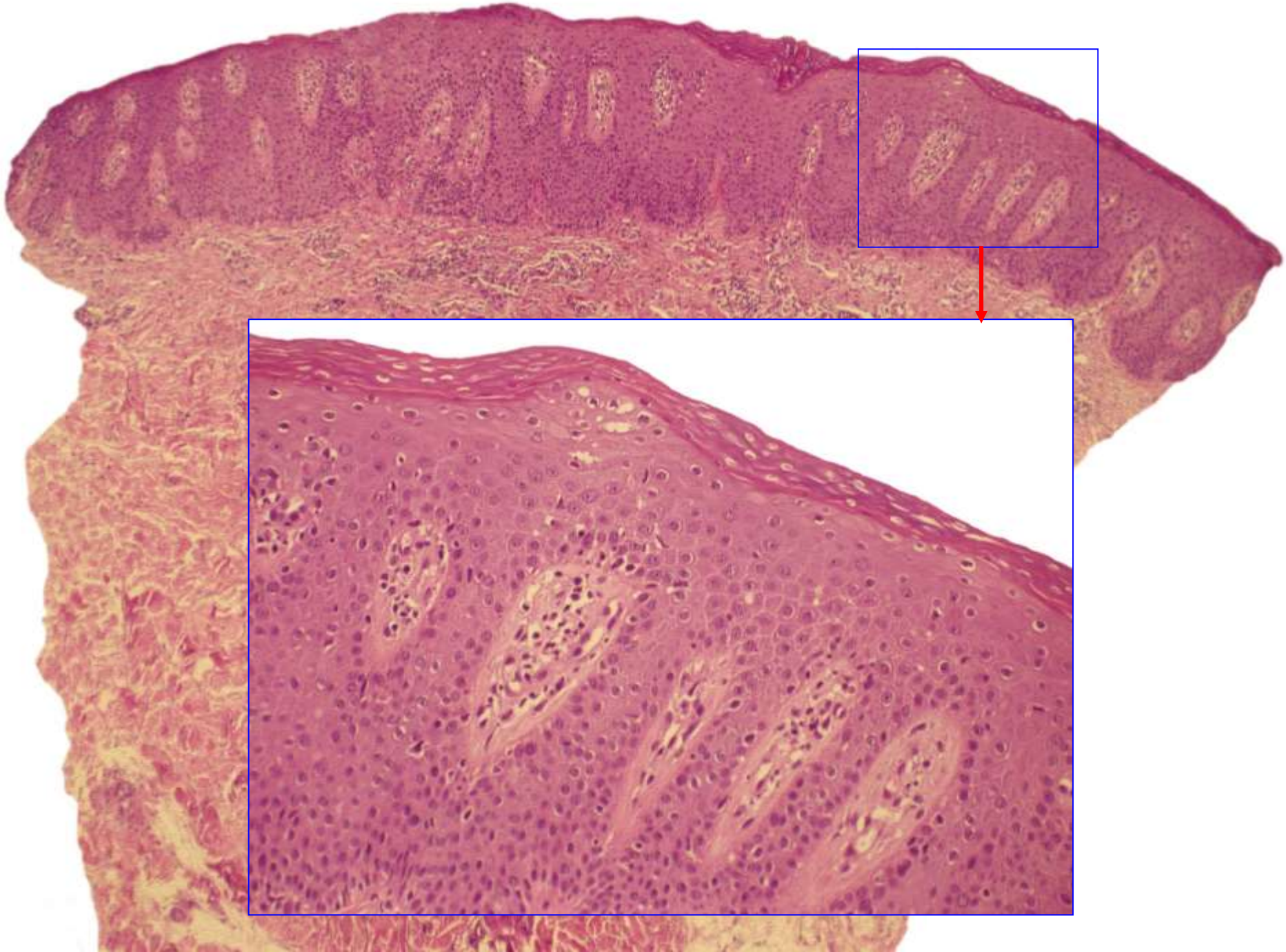
nor staggered mounts of parakeratosis histopathologically.



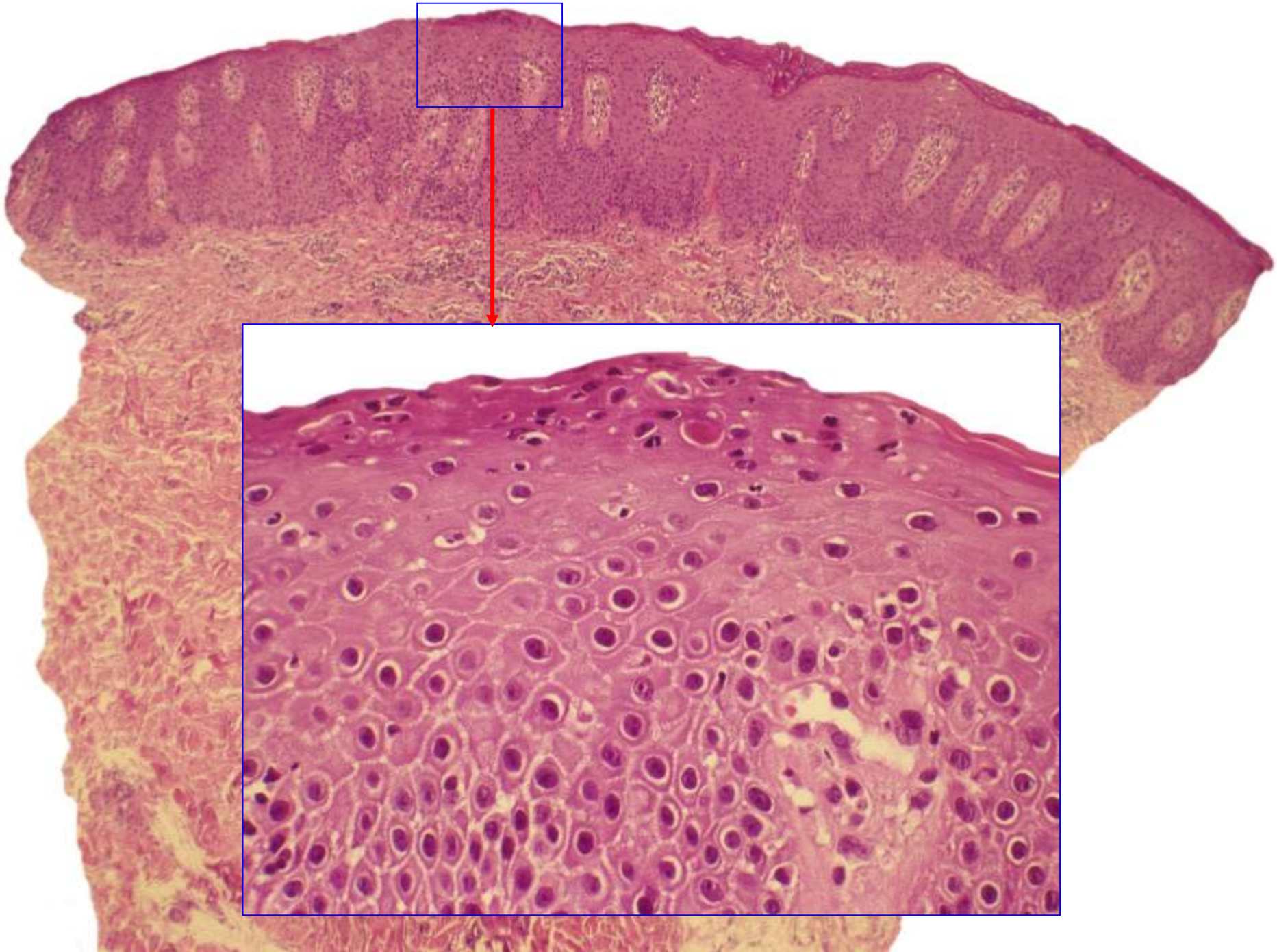
The typical clinical presentation of psoriasis of the vulva is that of sharply circumscribed erythematous patches.



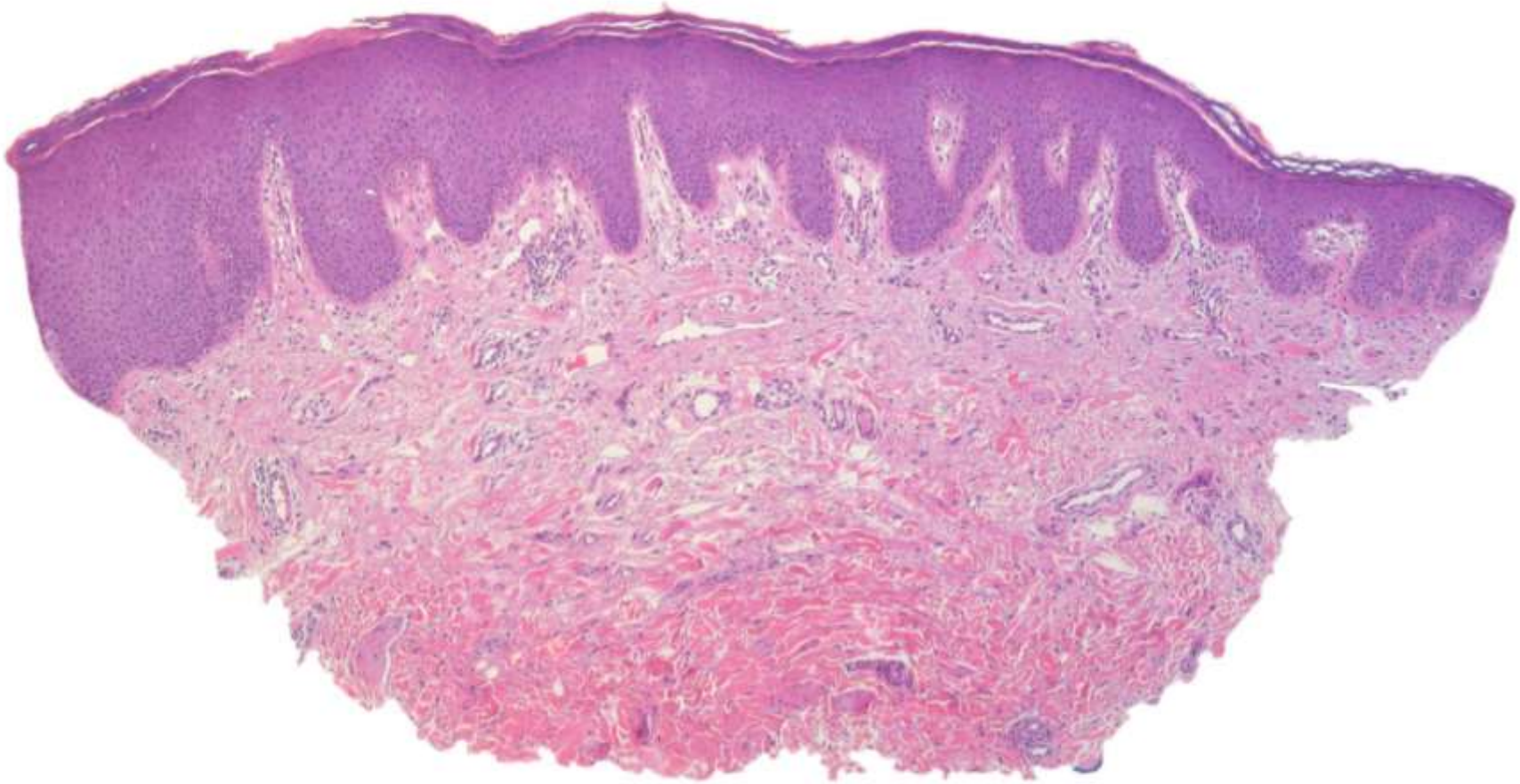
Histopathologically, the cornified layer may appear normal or even diminuished because of parakeratotic horn that has been shed. In other respects, findings are typical of psoriasis.



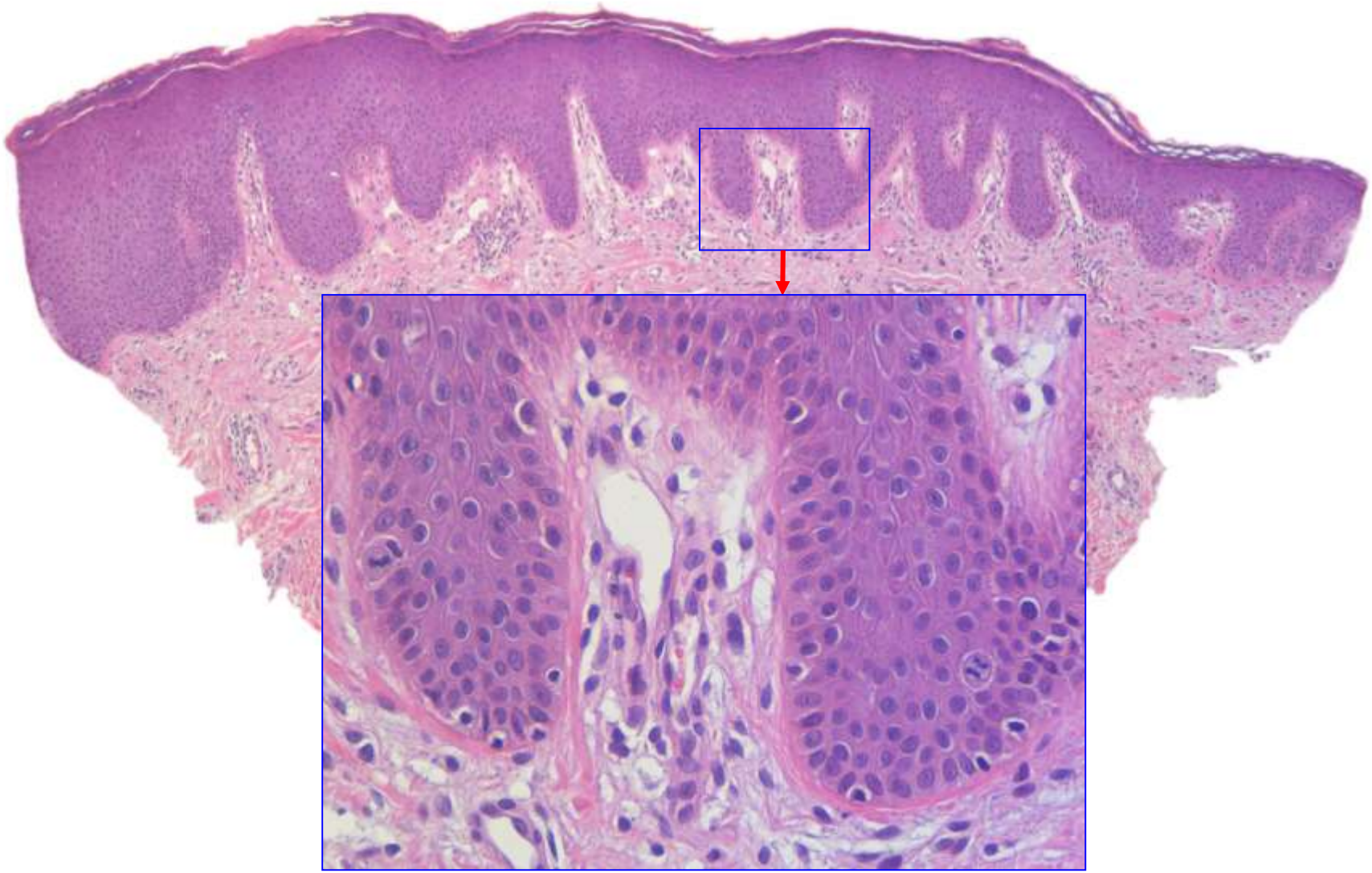
In this case, there no granular zone. The rete ridges are elongated markedly and are of approximately equal length and width. The papillae are elongated markedly and harbour dilated tortuous blood vessels. The association with elongated dermal papillae results in a very regular, monomorphous psoriasiform hyperplasia.



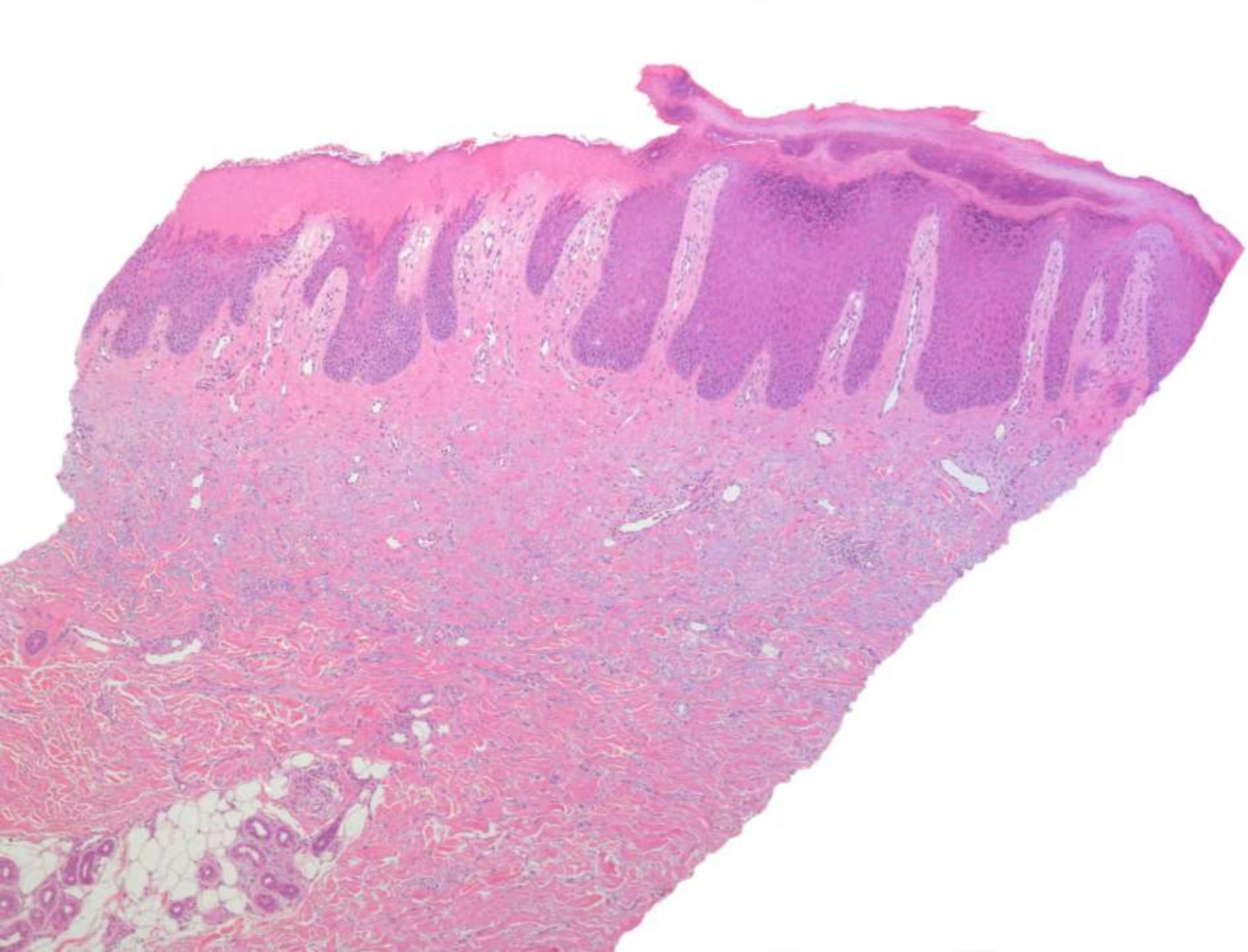
A helpful clue, if present, are neutrophils in the upper spinous zone.



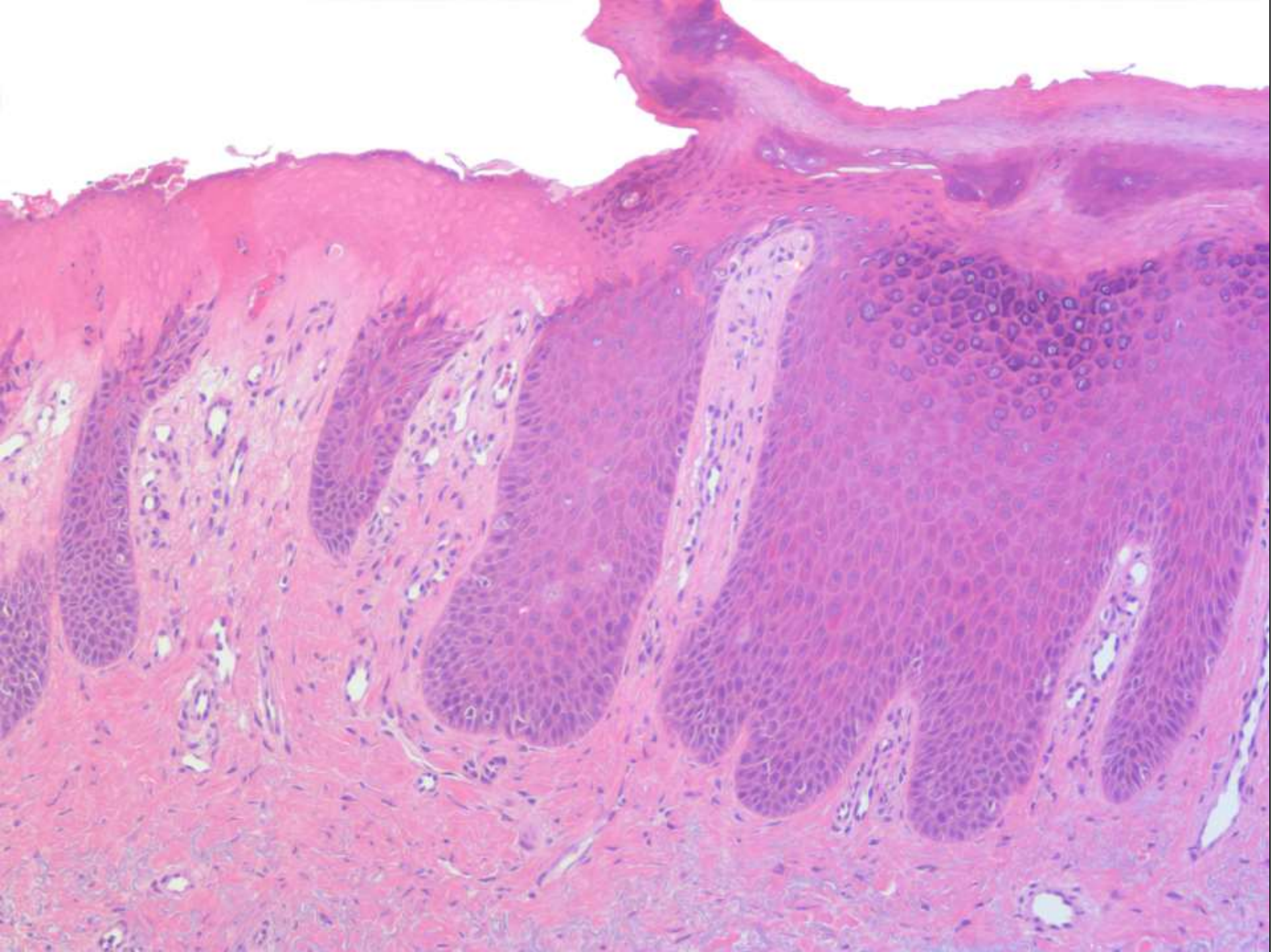
This is another example of psoriasis, again with a relatively regular psoriasiform hyperplasia. In this case, the granular zone is preserved, and the cornified layer is orthokeratotic, probably a result of lichen simplex chronicus superimposed on psoriasis.



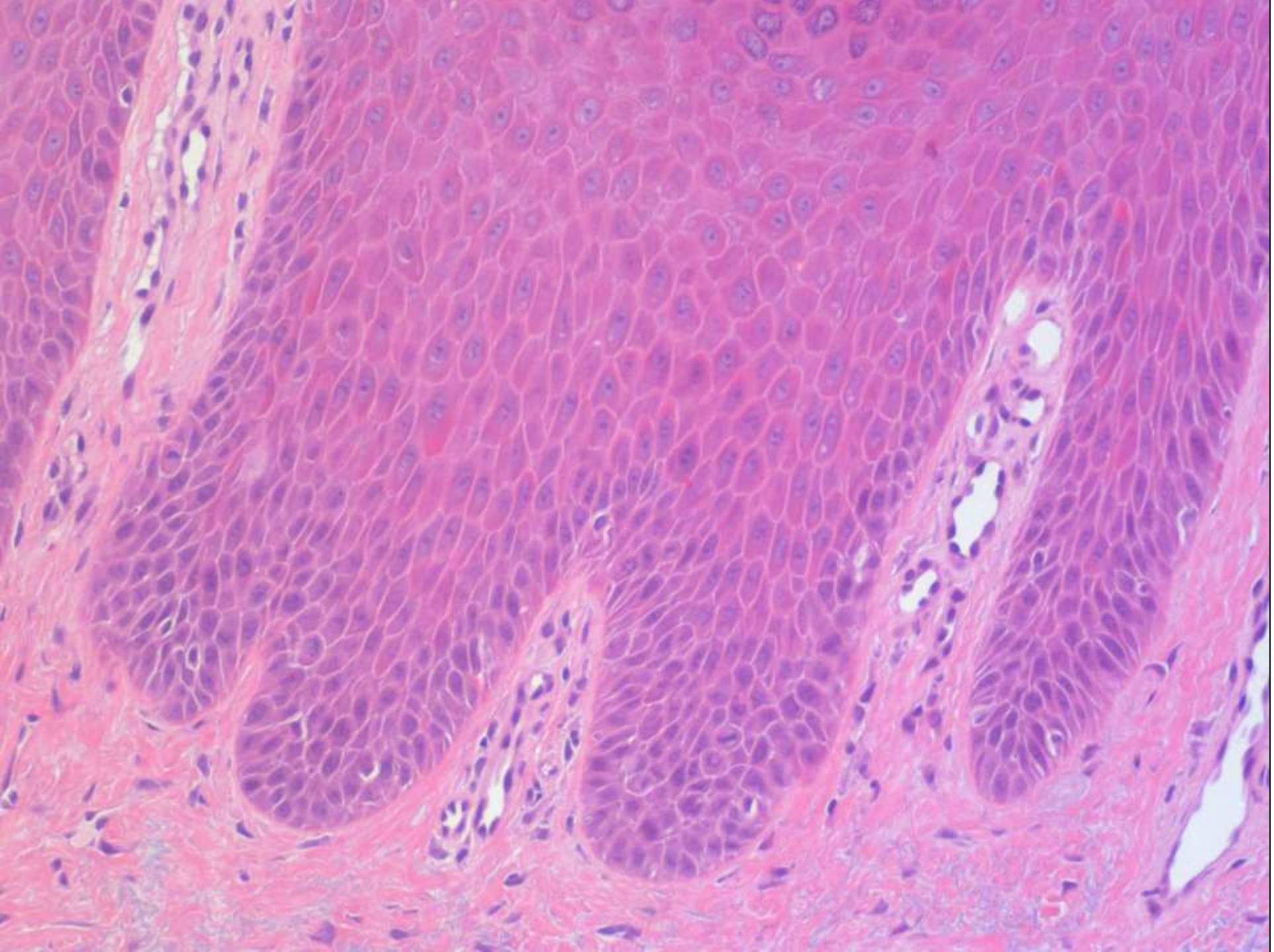
There are some mitotic figures in the basal and lower spinous zone, an expected finding in a disease characterized by enhanced epidermal proliferation. This lesion of psoriasis is difficult to distinguish from lichen simplex chronicus alone. However, the collagen fibres in dermal papillae are not thickened, and dilation and tortuousness of capillaries is more pronounced than usually seen in lichen simplex chronicus.



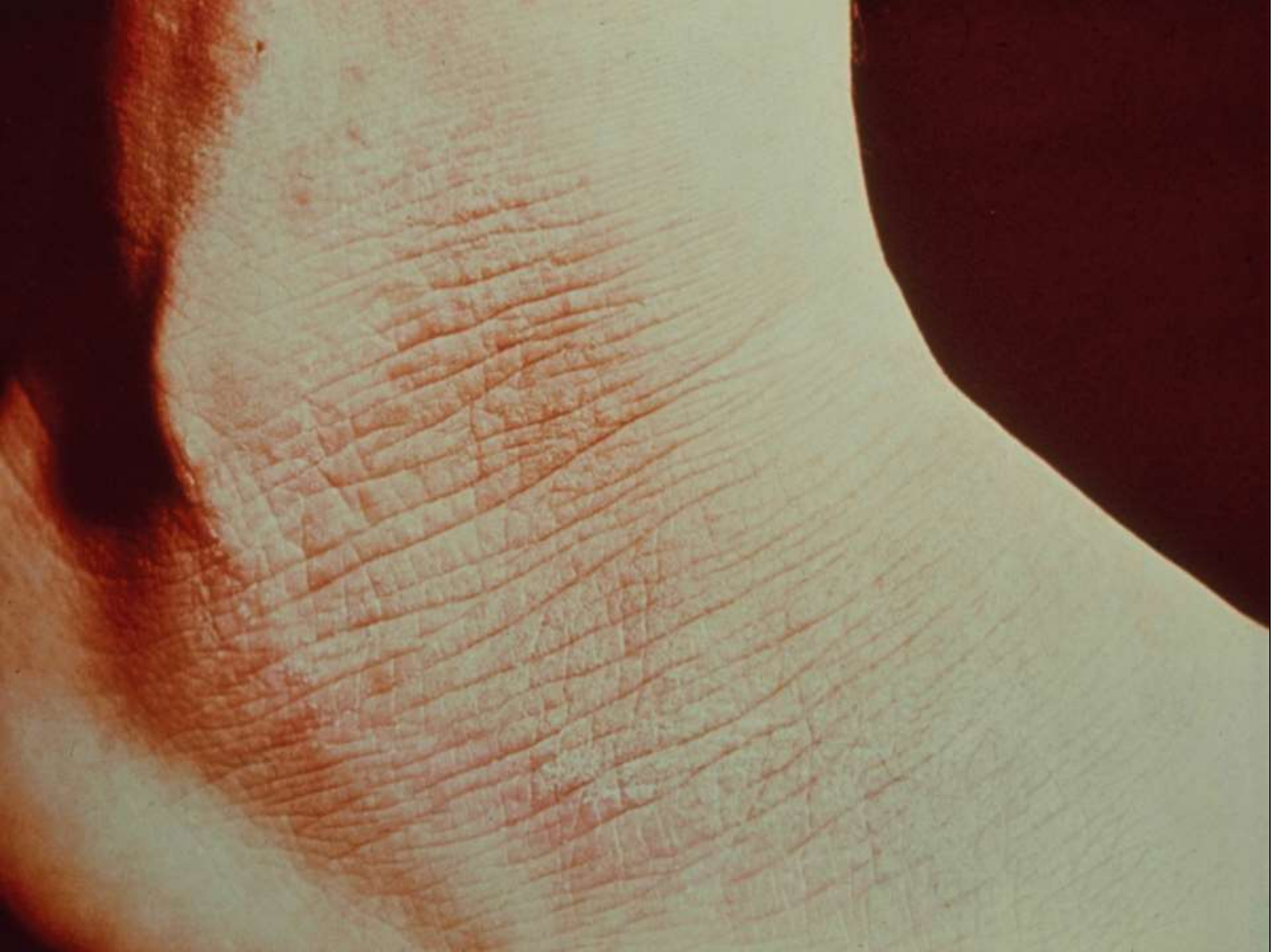
Lichen simplex chronicus may resemble psoriasis closely. Here you see the consequences of vigorous scratching: on the right, epithelial hyperplasia with a broad granular zone and marked compact orthokeratosis as an attempt to adapt to chronic mechanical trauma, and on the left, confluent necrosis of the upper layers of the epidermis where the attempt has failed because scratching was too vigorous. Typical of lesions induced solely by rubbing or scratching is the sparsity of the inflammatory-cell infiltrate.



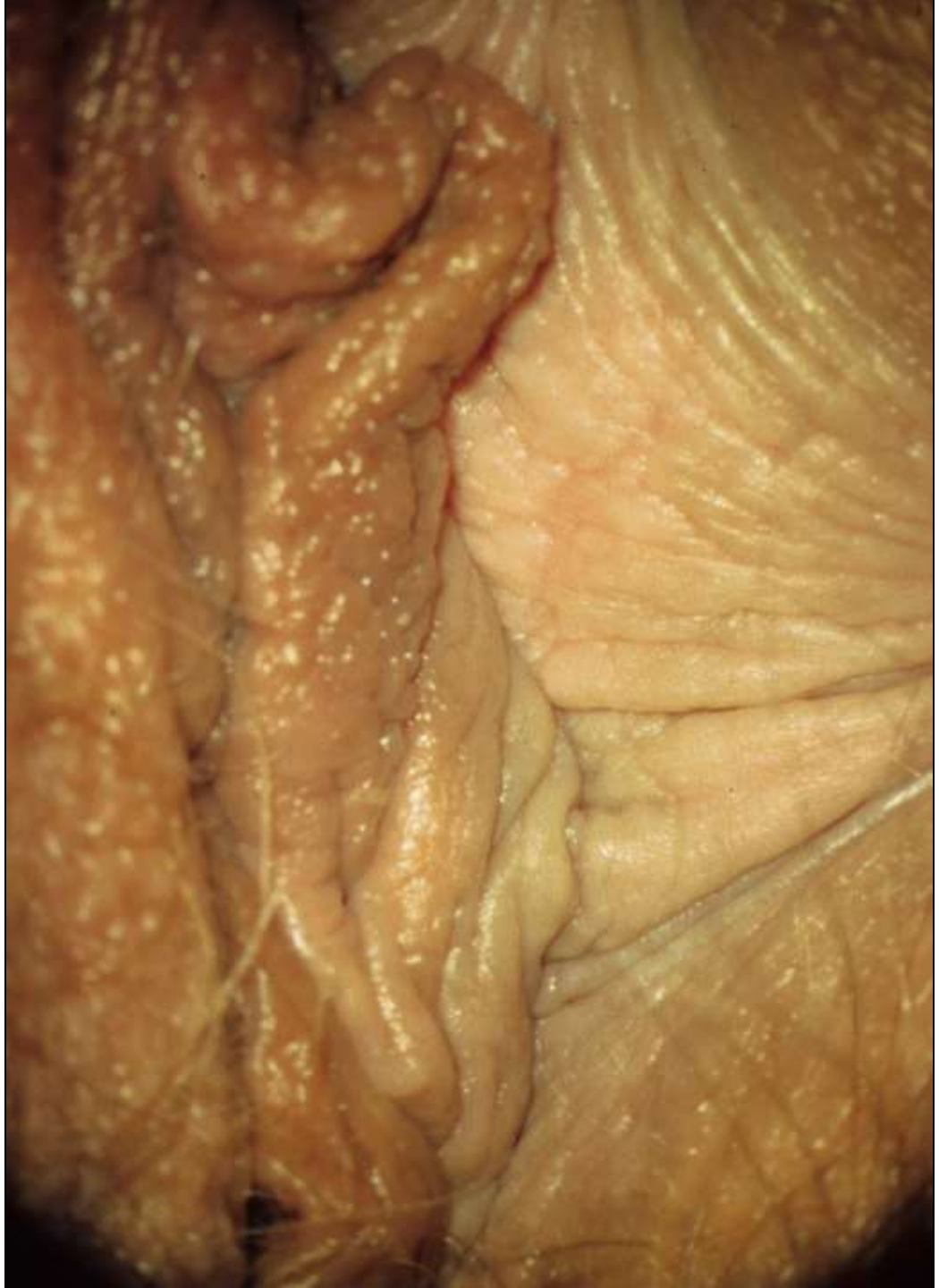
The epithelial hyperplasia is psoriasiform but, in this instance, an exaggeration of psoriasis, with rete ridges that are thicker and longer. The papillae are elongated markedly and harbour tortuous blood vessels.



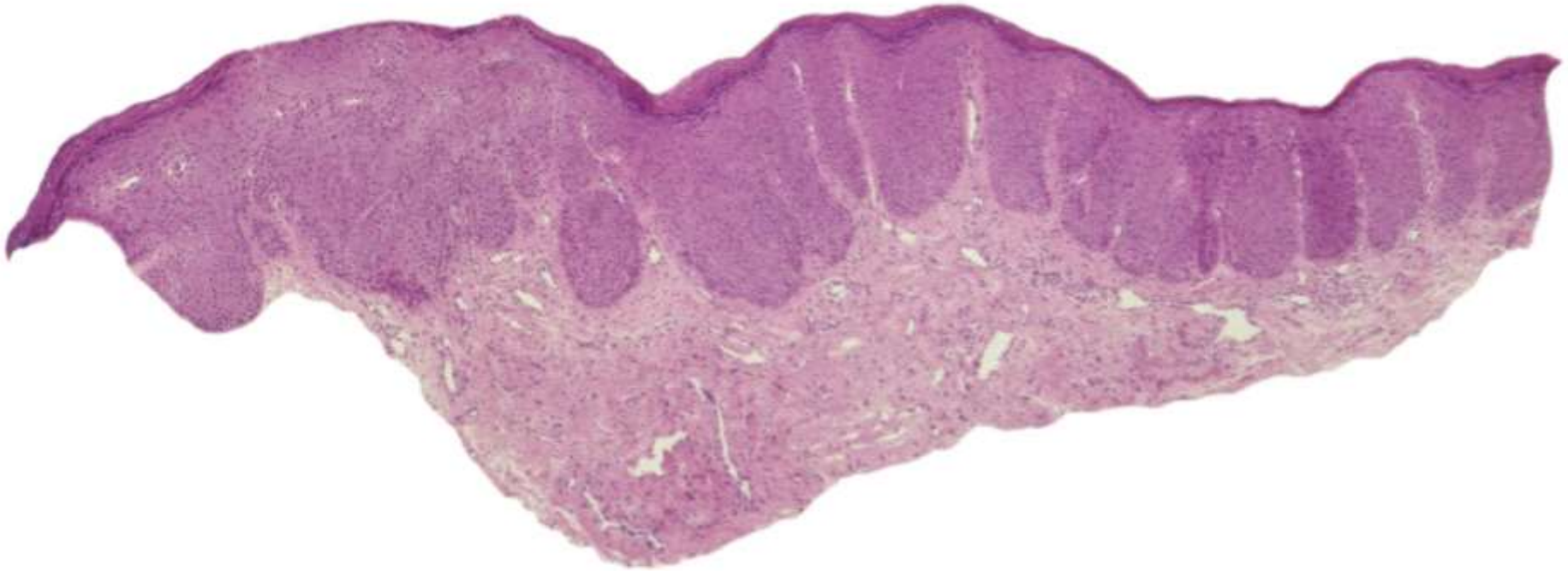
There are also some mitotic figures; the latter do not help to distinguish both processes from one another. A finding typical of lichen simplex chronicus and militating against psoriasis is thickened bundles of collagen in vertical array.



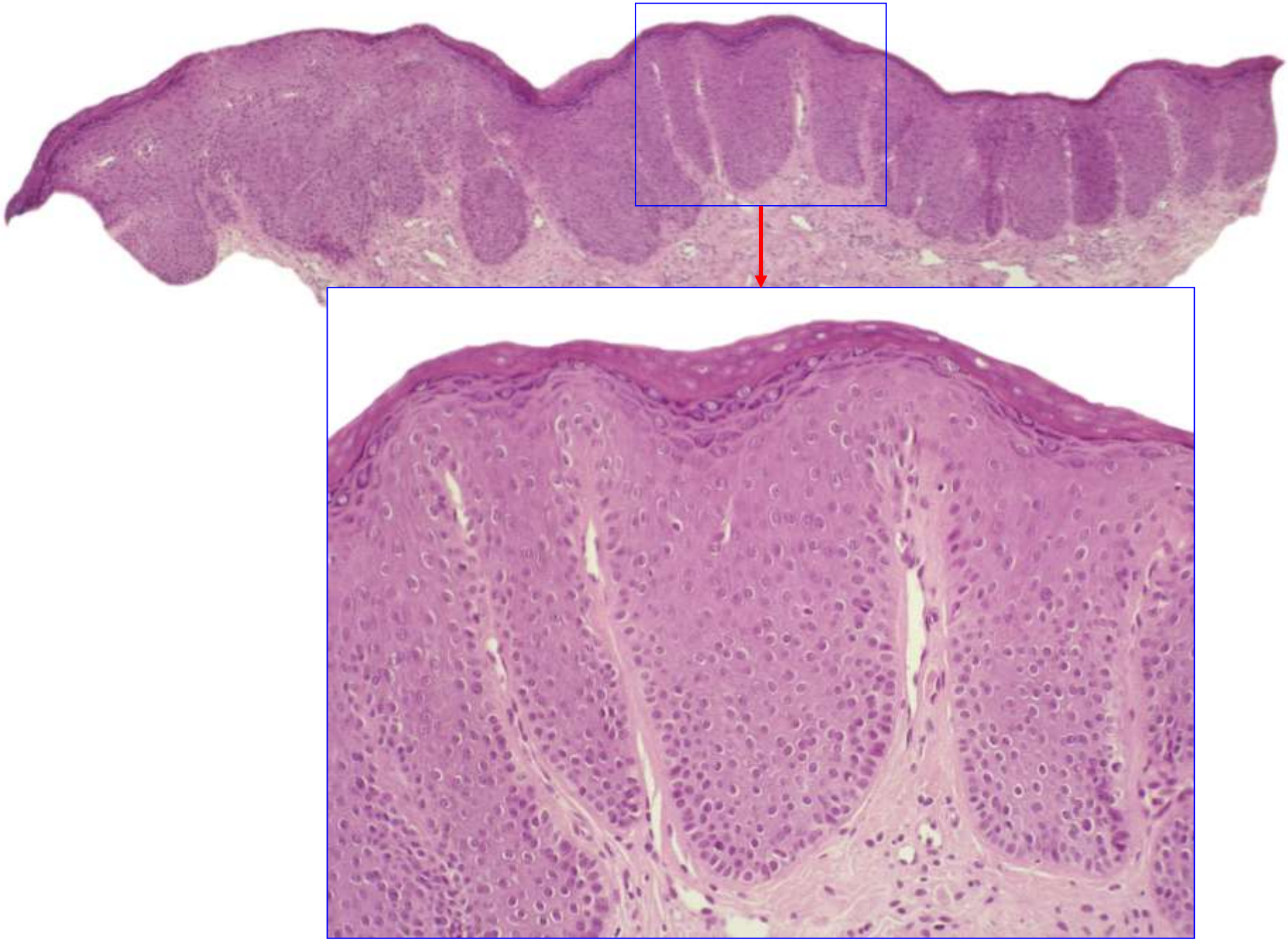
Clinically, those findings present themselves as lichenification: thickening of the skin with accentuation of skin furrows,



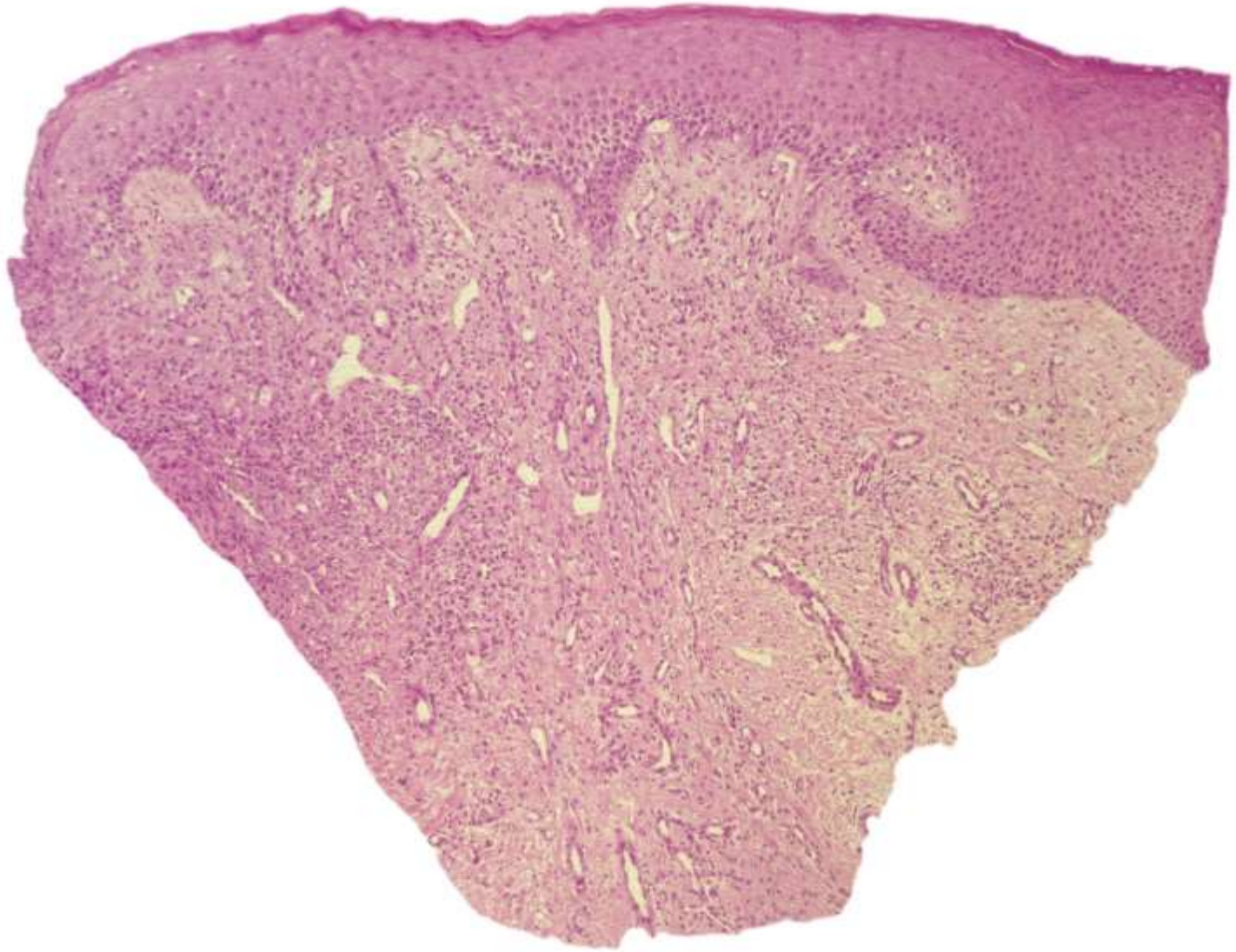
and the same can be seen on the vulva. The skin is thickened, whitish because of compact orthokeratosis that prevents blood vessels to shine through, and the furrows are deepened.



There is hardly any inflammation. The epidermal hyperplasia is psoriasiform, but very irregular with rete ridges varying in length and width.

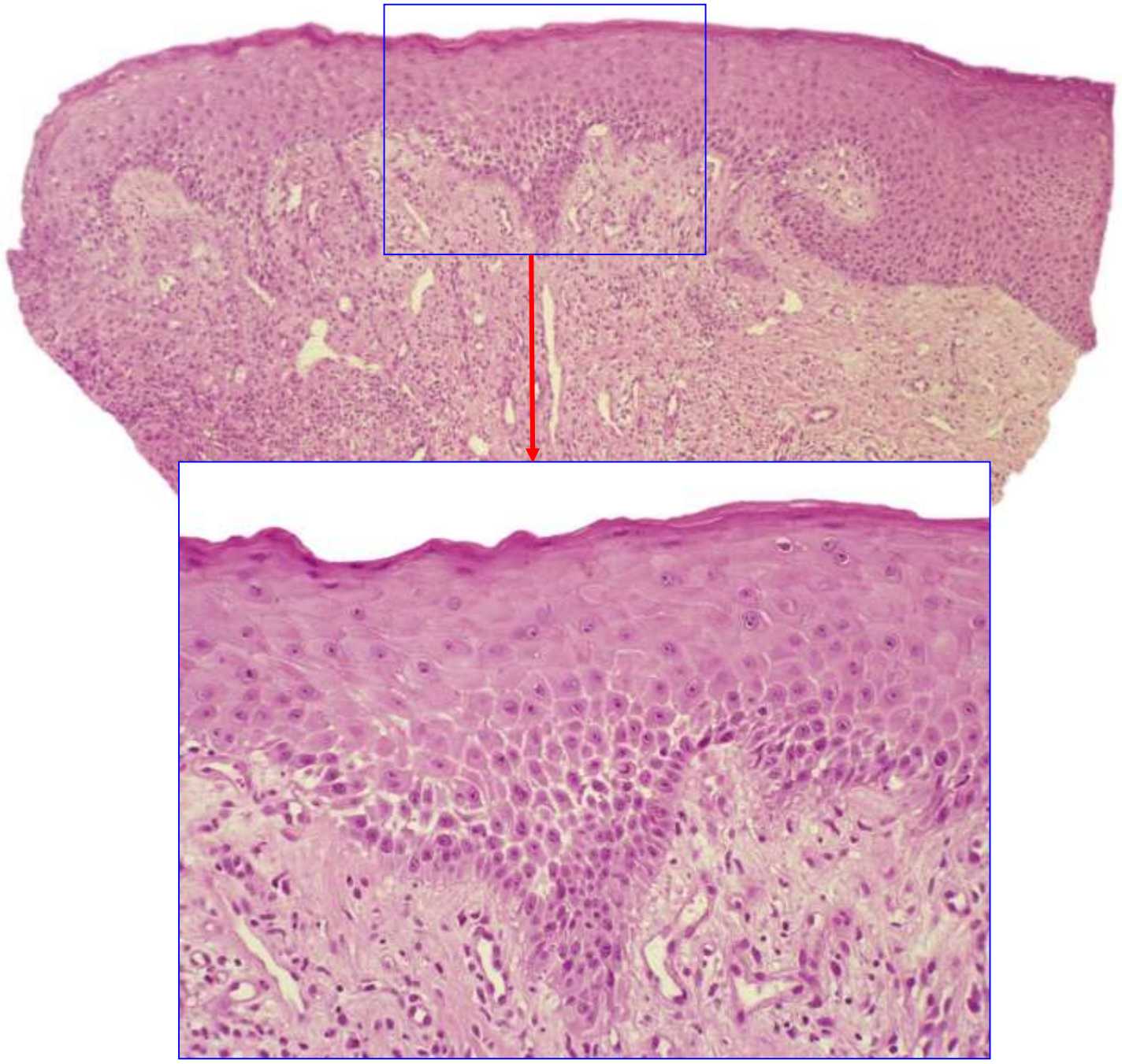


The granular zone is thickened across most of the specimen, and the orthokeratotic horny layer is thickened and compact, resembling the cornified layer of palms and soles. Note the thickened bundles of collagen in vertical array in elongated dermal papillae. Because all those findings result from rubbing and scratching, they can be found superimposed on any pruritic inflammatory process, modifying its presentation.



This, for example, is a case of allergic contact dermatitis of the vulva with superimposed lichen simplex chronicus. On the right, there are findings that we have just seen – epithelial hyperplasia with hypergranulosis and compact orthokeratosis –,

but in addition to those changes, there is a dense inflammatory-cell infiltrate in the dermis composed chiefly of lymphocytes and eosinophils.



Moreover, the epidermis is spongiotic, and this degree of spongiosis is already exceptional on the vulva. In general, spongiosis is only moderate, and one hardly ever sees spongiotic vesicles, the reason probably being the thin or absent cornified layer of the vulva that allows fluid to evaporate.

Acta Derm Venereol 2013; 93: 242–245

CLINICAL REPORT

Characterization of Vulvar Skin of Healthy Thai Women: Influence of Sites, Age and Menopause

Tsutomu FUJIMURA[1], Noriko SATO[1], Suwirakorn OPHASWONGSE[2], Yutaka TAKAGI[1], Mitsuyuki HOTTA[1], Takashi KITAHARA[1], Yoshinori TAKEMA[1] and Piti PALUNGWACHIRA[2]

[1]Biological Science Laboratories, Kao Corp, Tochigi, and [2]Department of Skin Center, Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand

Although the physiological characteristics of vulvar skin have been characterized in Caucasians, little is known about the vulvar skin of Asian women. This study assessed the moisture content, transepidermal water loss (TEWL) and pH of vulvar skin of 99 healthy Asian women residing in Bangkok, aged 20–69 years, during their non-menstrual period, including 39 post-menopausal women. Skin pH was acidic at all sites, and the pH of the vulvar areas was significantly higher than the control sites (inner thigh, inner forearm). Skin moisture was slightly, but significantly, lower around the vulvar area and the thigh than around the forearm. TEWL was significantly higher in vulvar areas than control sites. Ageing and menopause did not cause notable alterations in most properties of vulvar skin. In conclusion, the vulvar skin of Asian women has similar properties to that of Caucasians. ***Key words: vulva; ageing; menopause; Asian; skin physiology.***

women, and those at different ages. Warren et al. (5) reported that there was no significant difference in the skin surface water loss (SSWL) of vulvar skin with age. Some effects of menopause on the percutaneous absorption of steroids by vulvar skin have also been reported (9).

Although it seems that the physiology of vulvar skin has been well investigated, the above studies have been conducted mainly with the Caucasian (white) ethnic population. Racial differences in skin are well known; for example, it has been reported that Japanese subjects show a higher tendency for skin irritation than do Caucasian subjects (10, 11). Hydration of the stratum corneum (SC) and/or TEWL are also different among ethnicities (12, 13).

The aim of this study was to investigate the vulvar skin properties of Thai women, focusing on functional properties of the SC.

Transepidermal water loss is much higher on the vulva than in other areas of skin.

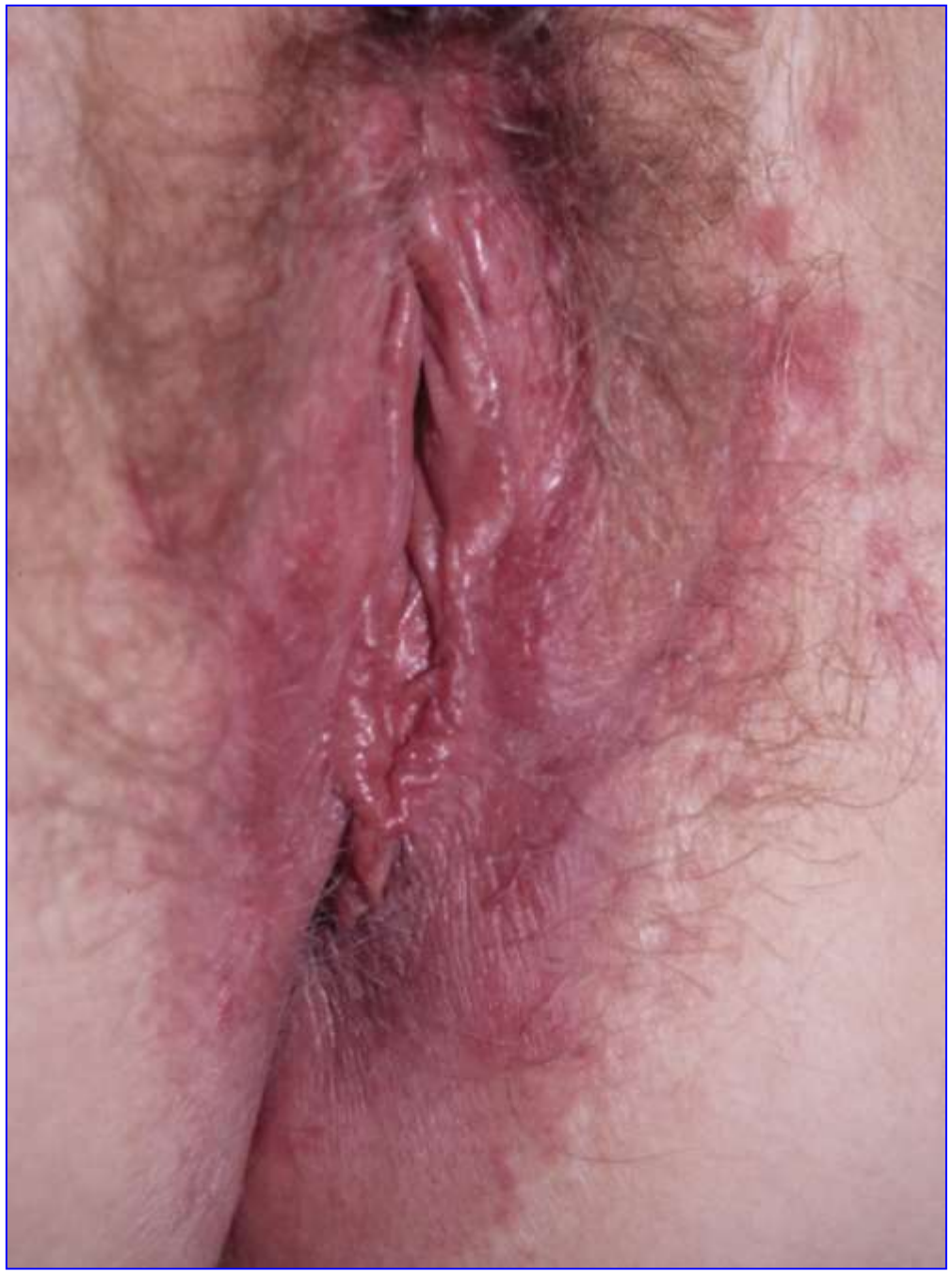
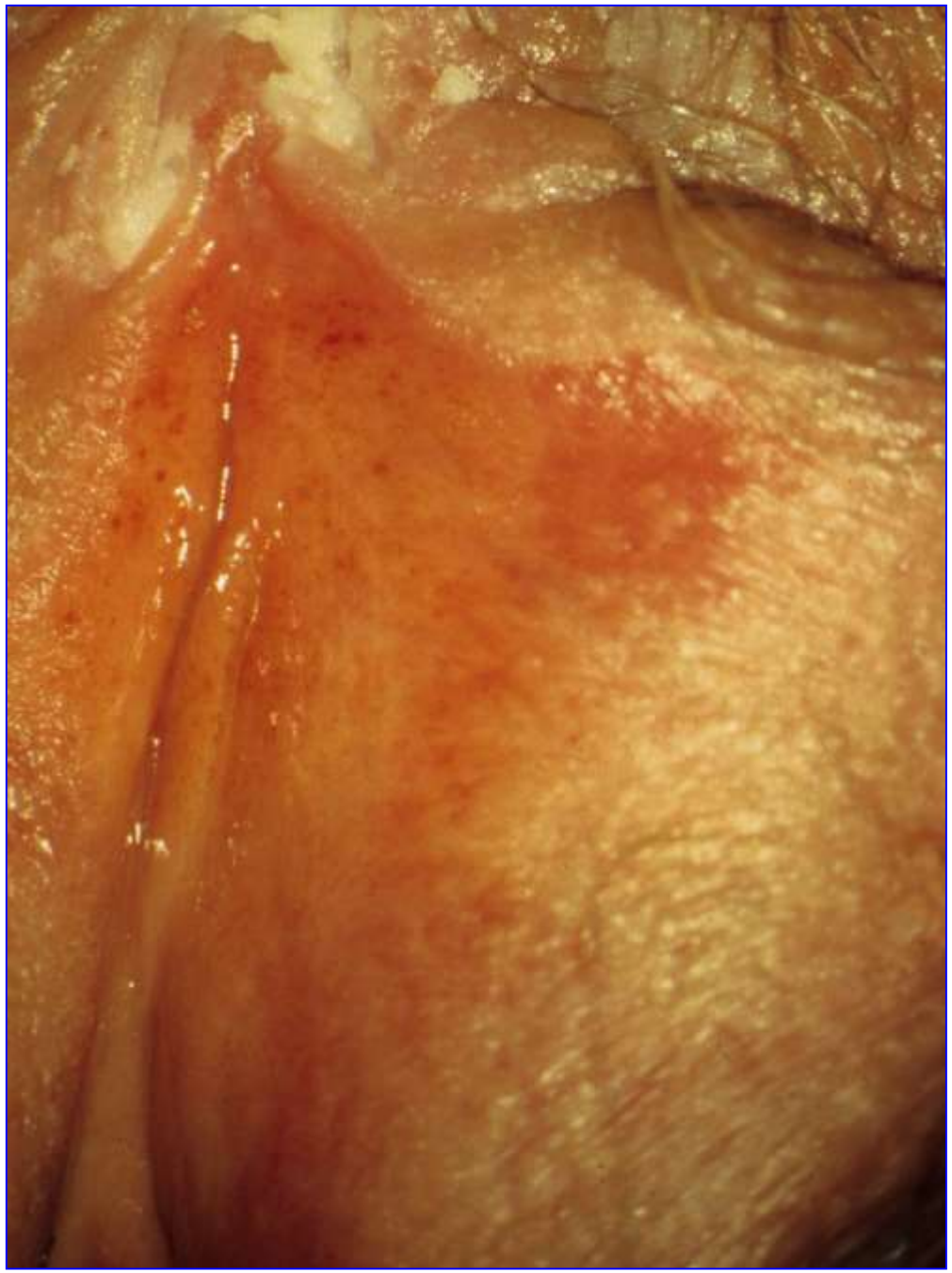


TABLE 3. Common Vulvar Allergens

Allergens
Antibiotics
Antifungals
Antiseptics
Fragrance
Nail polish
Nickel
Rubber
Irritants
Corticosteroids
Douches
Emollients
Sanitary napkins

The opposite traffic is also enhanced: external substances can penetrate much easier.
Hence, allergic and irritant contact dermatitis are very common, causes ranging from antibiotics and antifungals to corticosteroids, douches, emollients, and sanitary napkins.

This is the clinical picture corresponding to the biopsy specimen of allergic contact dermatitis just shown: Changes are not confined to the areas of contact but spread beyond it.



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By contrast, irritant contact dermatitis tends to be more sharply defined. Irritant contact dermatitis is by far the most common inflammatory disease of the vulva, the reason being the combined effects of tenuity of the cornified layer and moist environment.

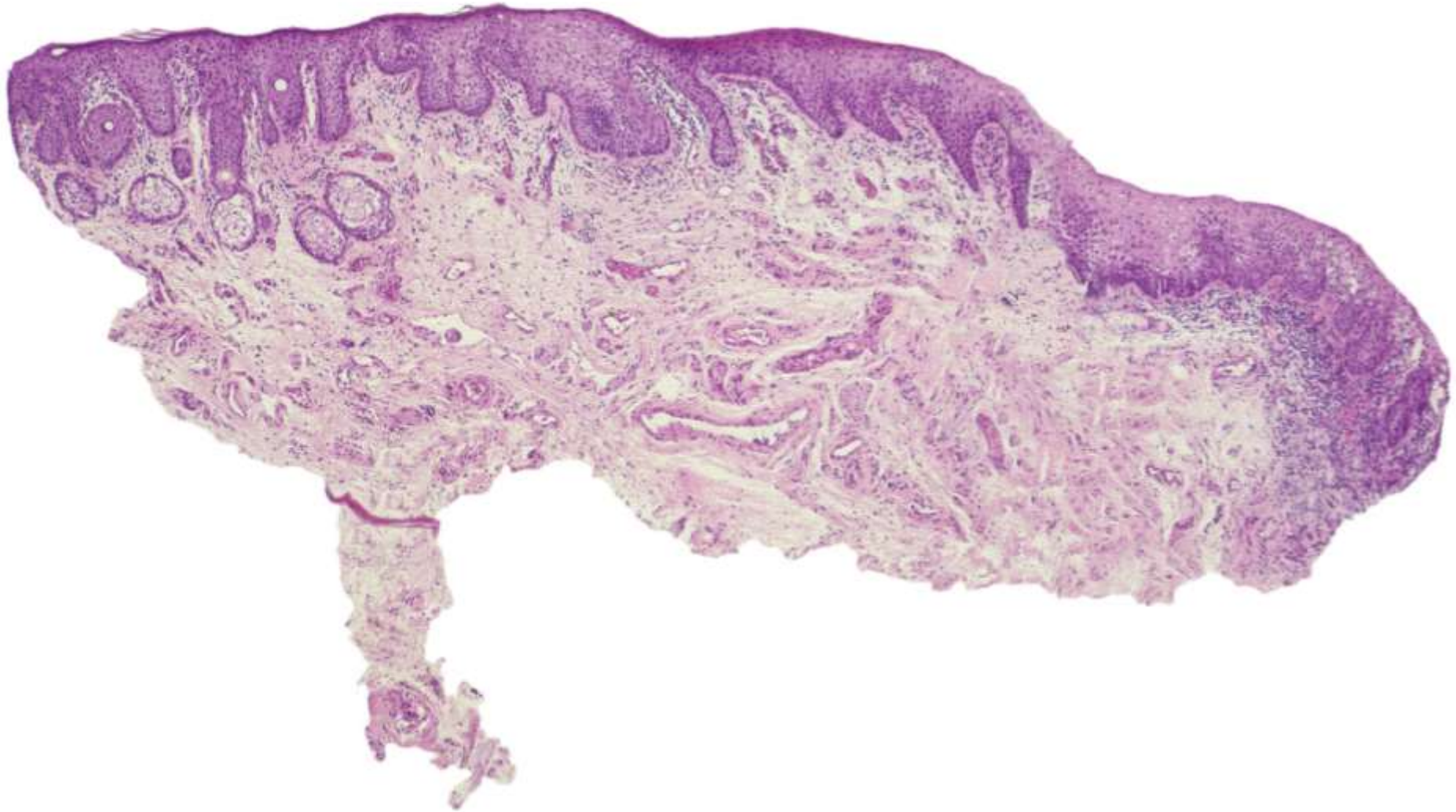
J Wound Ostomy Continence Nurs 2011;38(3): 233-41.

Moisture-associated skin damage: overview and pathophysiology

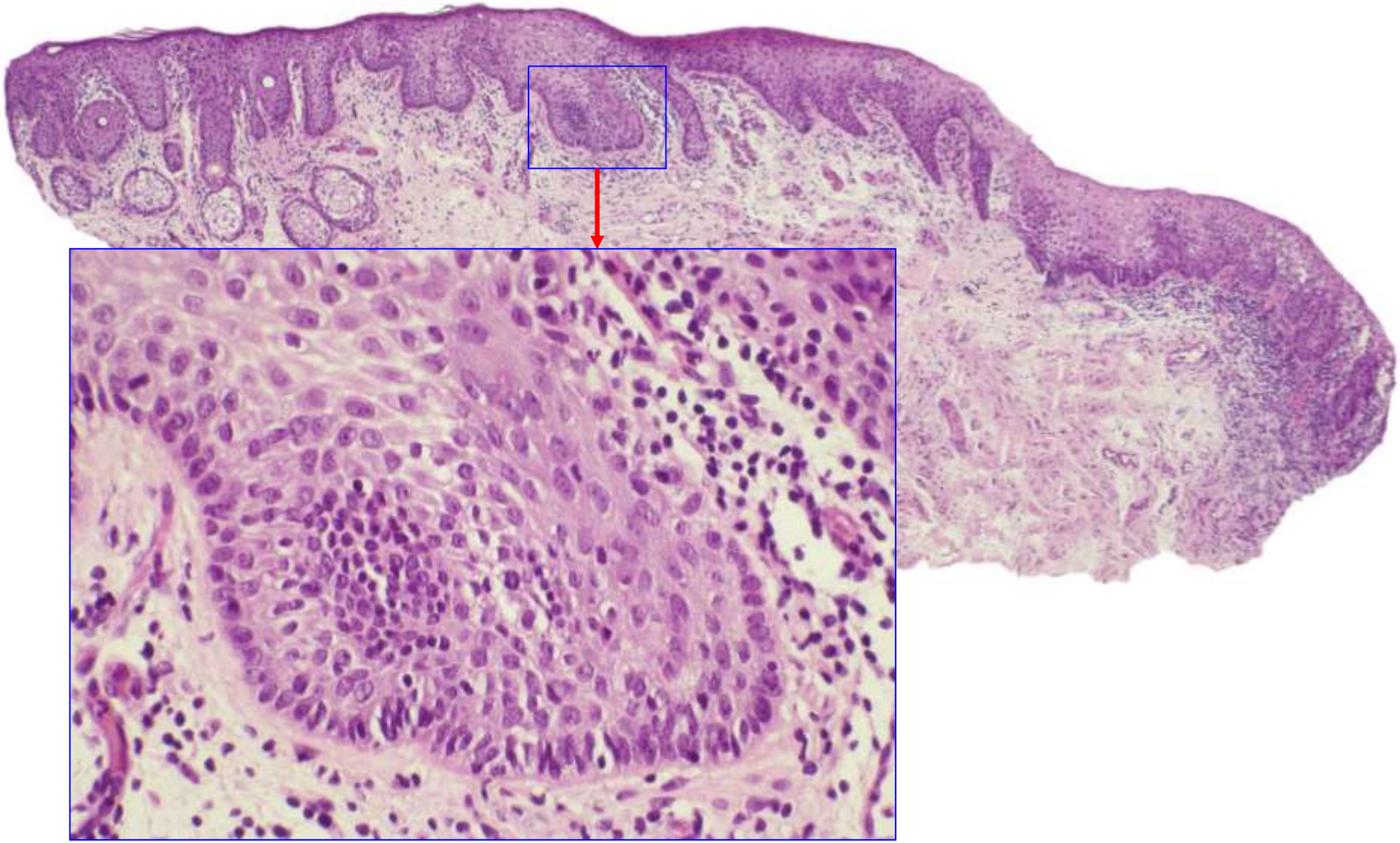
Mikel Gray , Joyce M Black, Mona M Baharestani, Donna Z Bliss, Janice C Colwell, Margaret Goldberg, Karen L Kennedy-Evans, Susan Logan, Catherine R Ratliff .

Moisture-associated skin damage (MASD) is caused by prolonged exposure to various sources of moisture, including urine or stool, perspiration, wound exudate, mucus, saliva, and their contents. MASD is characterized by inflammation of the skin, occurring with or without erosion or secondary cutaneous infection. Multiple conditions may result in MASD; 4 of the most common forms are incontinence-associated dermatitis, intertriginous dermatitis, periwound moisture-associated dermatitis, and peristomal moisture-associated dermatitis. Although evidence is lacking, clinical experience suggests that MASD requires more than moisture alone. Instead, skin damage is attributable to multiple factors, including chemical irritants within the moisture source, its pH, mechanical factors such as friction, and associated microorganisms. To prevent MASD, clinicians need to be vigilant both in maintaining optimal skin conditions and in diagnosing and treating minor cases of MASD prior to progression and skin breakdown.

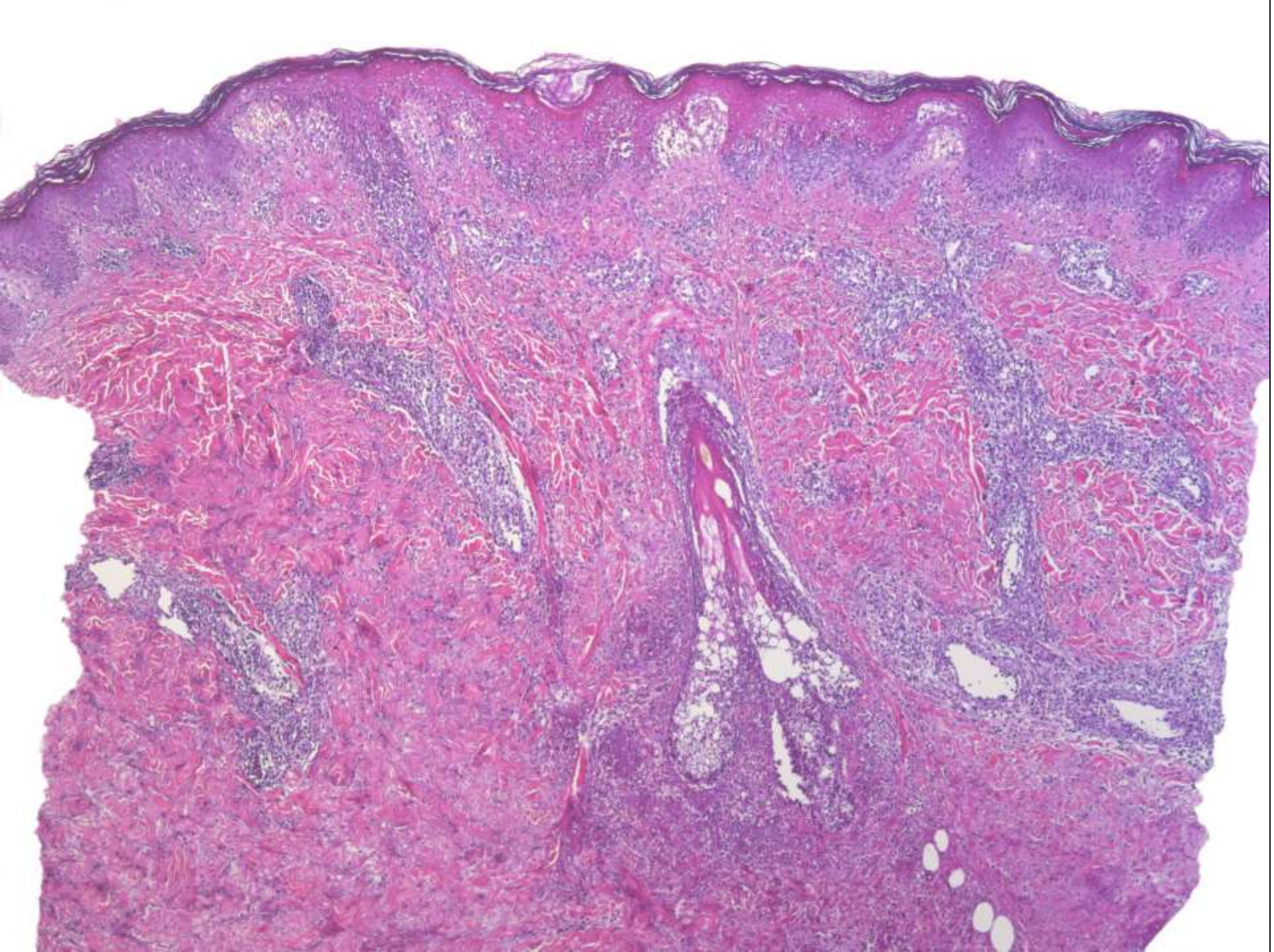
"Moisture-associated skin damage" has been attributed to *"multiple factors, including chemical irritants within the moisture source, its pH, mechanical factors such as friction, and associated microorganisms."* A moist surface enhances friction, and this alone may cause some irritation.



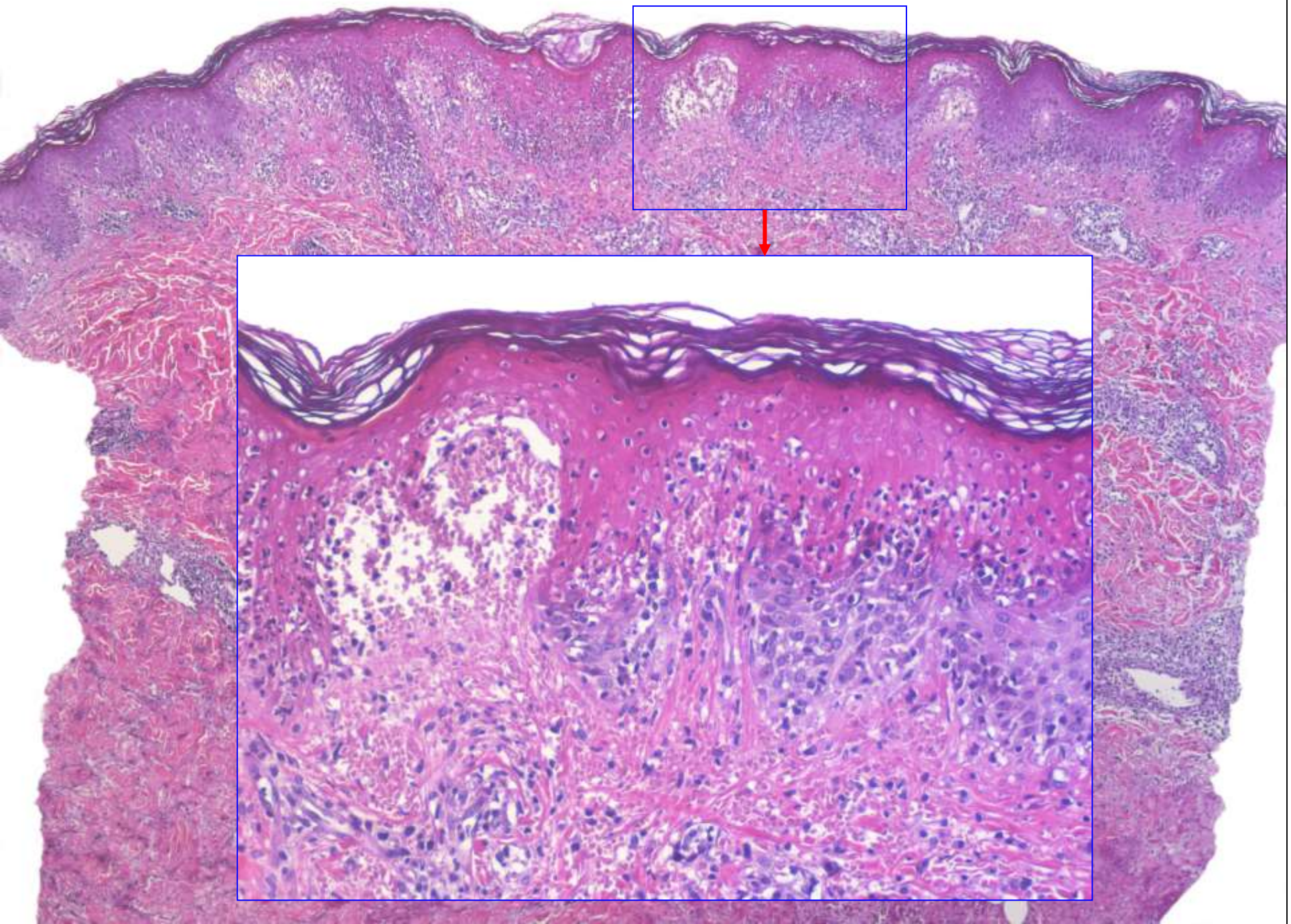
Histopathologically, one sees an irregular psoriasiform hyperplasia, usually associated with a relatively sparse infiltrate of lymphocytes.



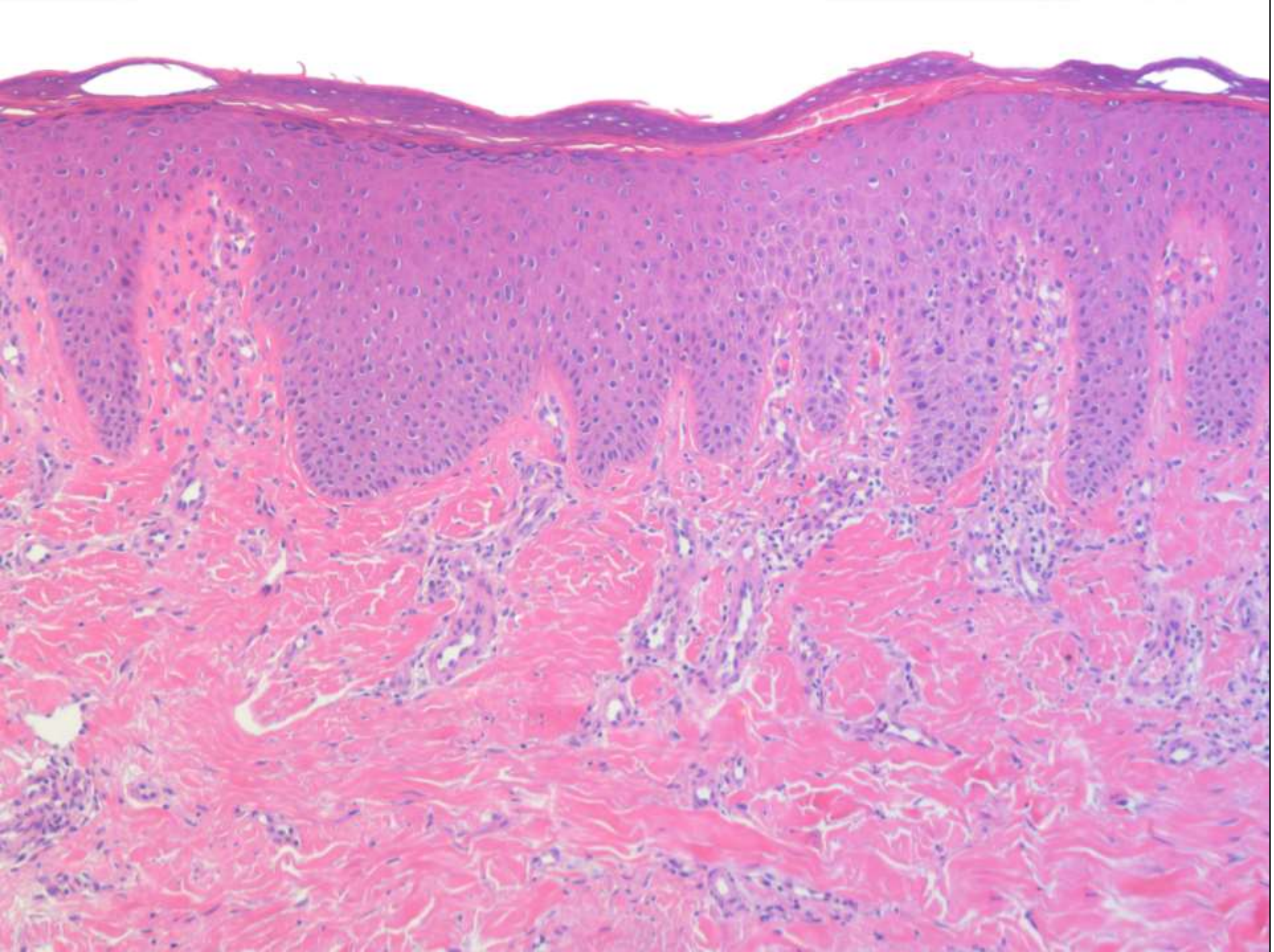
There are foci of parakeratosis and pallor of the epithelium secondary to intracellular edema. By contrast, spongiosis is only sparse, and only few lymphocytes are present within the epithelium.



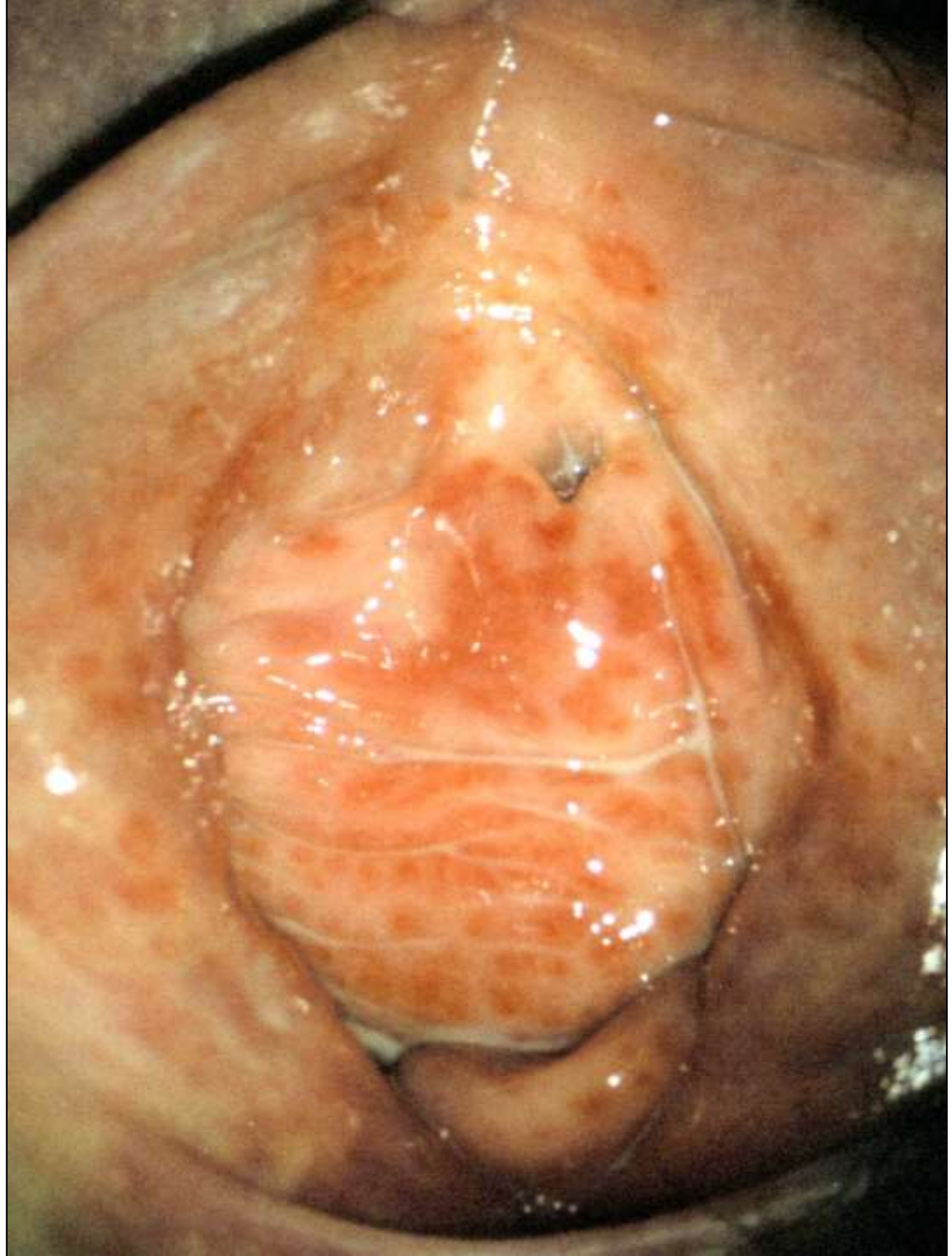
The degree of those changes, however, varies with the intensity of irritation. Strong irritants may induce a brisk infiltrate of inflammatory cells, including neutrophils. There may be edema of the papillary dermis with extravasation of erythrocytes.



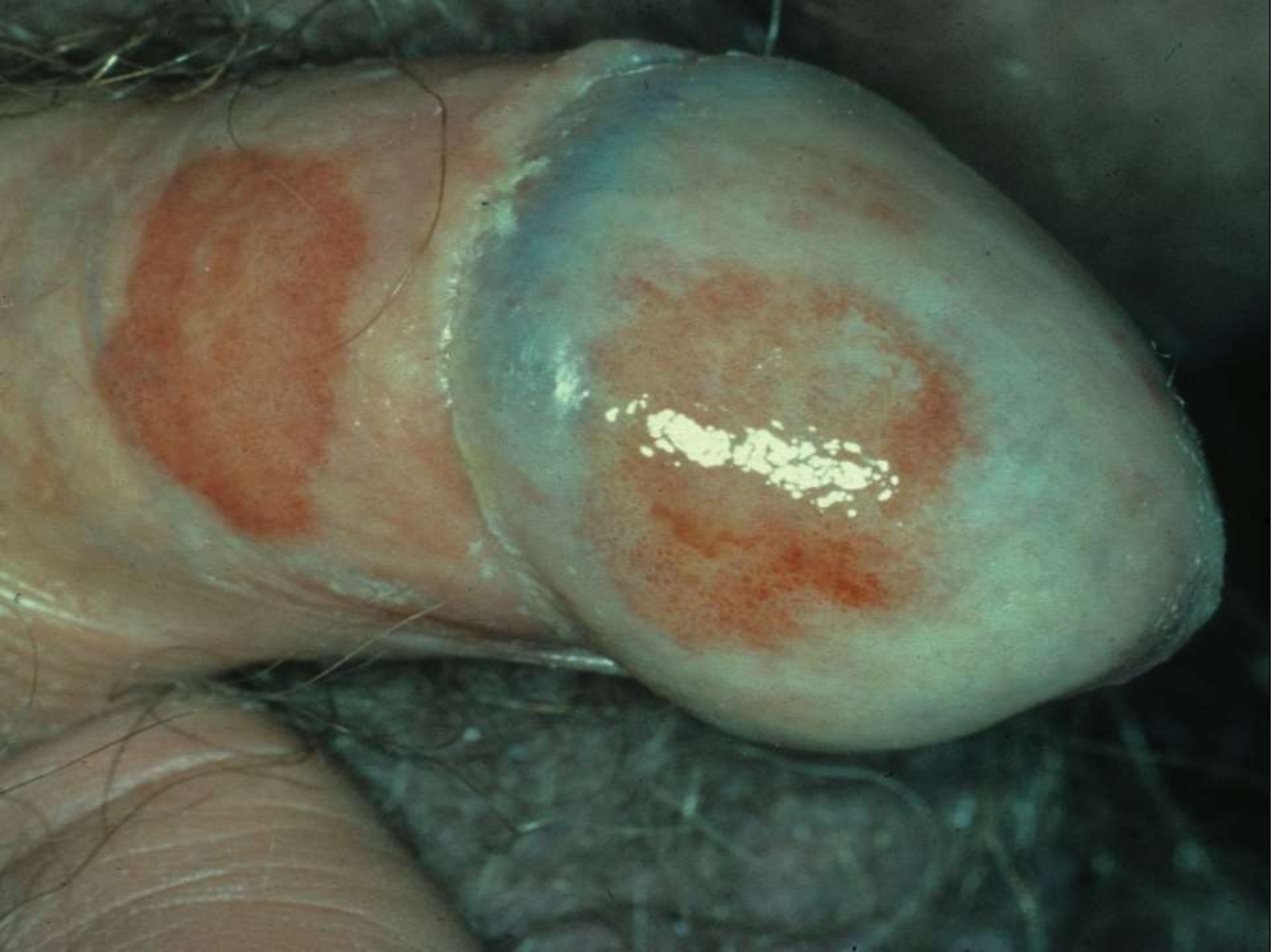
The upper layers of the spinous zone may become necrotic, whereas the lower layers often remain normal because they are affected less severely by the external irritant. The cornified layer also remains normal because of its greater resistance to external damage.



By contrast, weak irritants cause changes only after chronic exposure. The infiltrate, spongiosis, and parakeratosis remain minimal, and the chief finding may be lichen simplex chronicus caused by persistent rubbing. This is a common presentation of irritant contact dermatitis on cornified surfaces.



On the non-cornified surface on the introitus, minor chronic irritation leads to another type of alteration, namely, vulvitis of Zoon. Clinically, it presents itself as irregular red patches and erosions.



Its analogue on the penis is balanitis plasmacellularis

Travail de la clinique dermatologique de l'Université d'Utrecht
Directeur: Prof. Dr *J. J. Zoon*

Balanoposthite chronique circonscrite bénigne à plasmocytes

(contra érythroplasie de Queyrat)

Par J. J. ZOON

Depuis 1911, on connaît sous le nom d'érythroplasie du gland une affection décrite par *Queyrat* [1]. Il s'agit de taches d'une rougeur vive et nettement délimitées, situées au gland et à la face interne du prépuce. Ces efflorescences paraissent érosées, mais ne le sont pas à l'examen histologique. Elles ont un aspect velouté, ne sont pas ou très peu élevées au-dessus de la peau ou de la muqueuse normale qui les entoure. Le derme est légérement infiltré. La maladie fait peu de symptômes. Les taches sur le gland et à la face interne du prépuce sont souvent superposées. Le coït n'est pas gêné.

or "balanoposthite chronique circonscrite bénigne à plasmocytes," under which name the condition was described by J.J. Zoon who distinguished it from erythroplasia of Queryrat. When it became evident that Zoon's disease is not restricted to the penis, but may occur on or near all mucosal surfaces,

Idiopathic Lymphoplasmacellular mucositis-dermatitis

Background: In 1952, Zoon described a series of patients with dense plasma-cell infiltrates in the glans penis. Since then, similar Zoon-like lesions (ZLL) have been described on the external female genitalia and in the airways, for which over 20 designations currently exist.
Methods: Twenty-eight cases of ZLL, twenty-two cases of lichen planus, eight cases of plasmacytoma and two cases of syphilis were evaluated from the surgical pathology archive at the University of Virginia. Twenty-four histologic data points were tabulated in each case, including 12 epidermal and 12 dermal features.
Results: Histopathologic findings were similar in the majority of cases of ZLL, regardless of their location. They demonstrated superficial cutaneous erosions, basal vacuolar alteration and many showed lozenge-shaped keratinocytes in the epiderms. The dermis contained a dense inflammatory infiltrate composed predominantly of plasma cells, with scattered neutrophils and lymphocytes. Dense fibrosis was seen in the upper dermis.
Conclusions: A uniform nomenclature for ZLL does not exist. Based on the results of this analysis, we suggest that the generic term *idiopathic lymphoplasmacellular mucositis-dermatitis* be considered to encompass the lymphoplasmacellular infiltrates in the skin and mucosal surfaces considered herein. This designation is morphologically descriptive and can be applied regardless of anatomic location.

Brix WK, Nassau SR, Patterson JW, Cousar JB, Wick MR. Idiopathic lymphoplasmacellular mucositis-dermatitis.
J Cutan Pathol 2010; 37: 426–431. © 2009 John Wiley & Sons A/S.

William K. Brix, Sarah R. Nassau, James W. Patterson, John B. Cousar, and Mark R. Wick
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Accepted for publication May 27 2009

various other names have been suggested, including *"idiopathic lymphoplasmacellular mucositis-dermatitis."* However, plasma cells, although very common, are not required for the diagnosis, and the disease is not "idiopathic" but has a well recognized cause,

The American Journal of Dermatopathology 24(6): 459–467, 2002

Balanitis of Zoon

A Clinicopathologic Study of 45 Cases

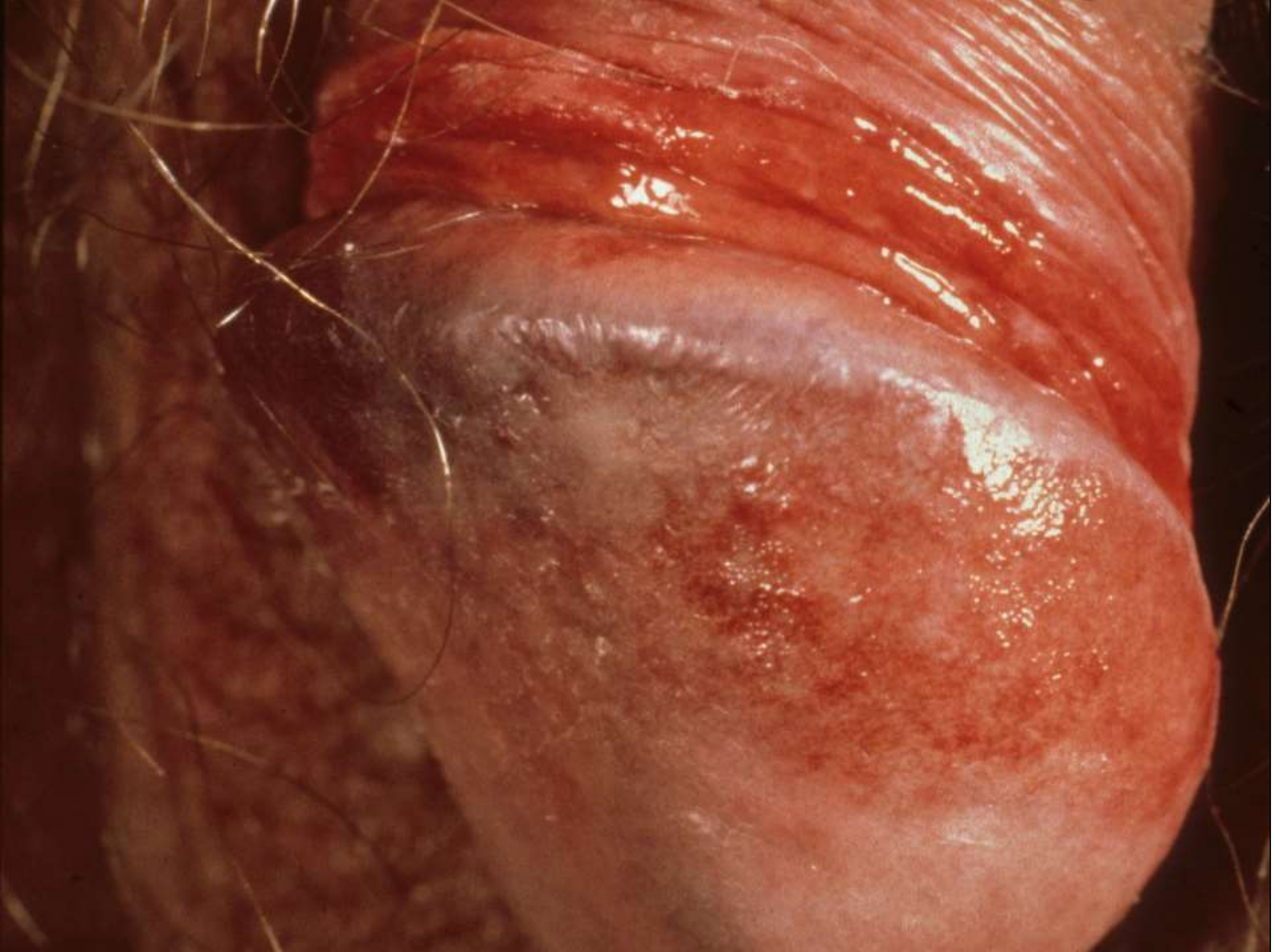
Wolfgang Weyers, M.D., Yvonne Ende, M.D., Wolfgang Schalla, M.D., and Carlos Diaz-Cascajo, M.D.

Balanitis of Zoon is a relatively common diagnosis in elderly men, although its nature is controversial and descriptions of its histopathologic features in current textbooks of dermatopathology vary considerably. We studied 45 cases of balanitis of Zoon clinically and histopathologically. The earliest histopathologic changes in cases diagnosed clinically as balanitis of Zoon were slight thickening of the epidermis, parakeratosis, and a patchy lichenoid infiltrate of lymphocytes and some plasma cells. More advanced cases showed atrophy of the epidermis, superficial erosions, a scattering of neutrophils in the upper reaches of the epidermis, scant spongiosis, extravasation of erythrocytes, and a much denser infiltrate with many plasma cells. Additional findings at even later stages were subepidermal clefts, sometimes with loss of the entire epidermis, marked fibrosis of the superficial dermis, and many siderophages. That sequence of histopathologic changes is compatible with the thesis that balanitis of Zoon results from irritation or mild trauma affecting barely keratinized skin in a moist environment. As a reaction to nonspecific stimuli, balanitis of Zoon may be found superimposed on lesions of other diseases and may modify the histopathologic presentation of those diseases to the extent that they are no longer recognizable. In the current study, several cases diagnosed originally as balanitis of Zoon turned out to be examples of allergic contact dermatitis, psoriasis, lichen planus, and squamous cell carcinoma in situ. It is important, therefore, to recognize balanitis of Zoon as a nonspecific pattern that may occur either as an isolated finding or may complicate other diseases affecting the glans penis or prepuce of uncircumcised men.

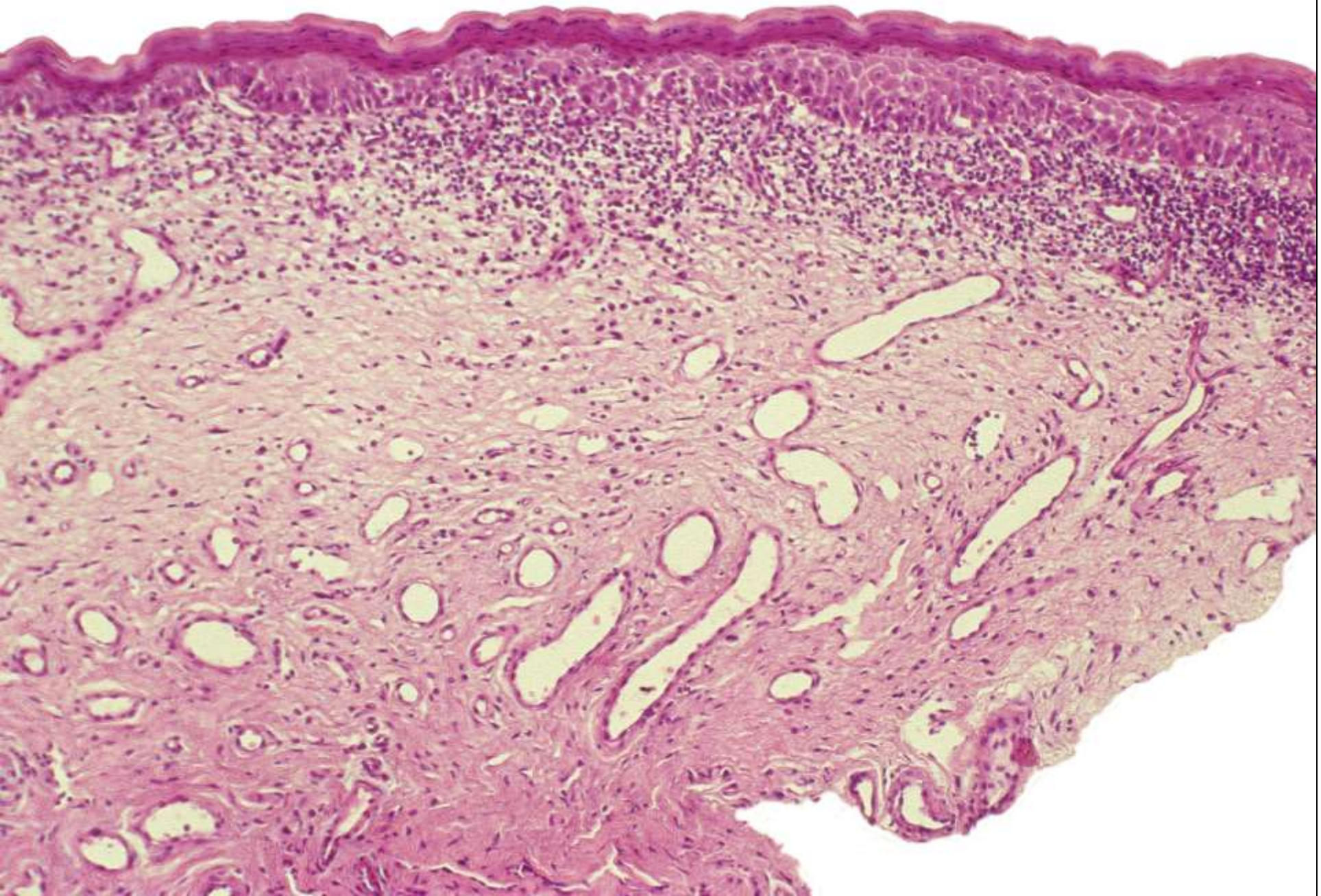
There are numerous diagnoses in dermatopathology that are rendered commonly and yet are highly controversial. Among those diagnoses is balanitis plasmacellularis of Zoon. In current textbooks of dermatopathology, the condition is either not mentioned at all (1), is said not to be an authentic disease (2), or is referred to as a distinct clinicopathologic process that may also afflict other mucocutaneous sites and thus has been given the more general designation of plasmacytosis mucosae (3,4). According to Nigel Kirkham, who wrote about balanitis of Zoon in the textbook by Elder (5), "the combination of histologic and clinical features seen in balanitis circumscripta plasmacellularis, and probably also vulvitis circumscripta plasmacellularis, is unique and deserves recognition as an entity."

Clinically, balanitis of Zoon is said to present consistently as a sharply demarcated, bright red, glistening patch on the glans penis, coronal sulcus, or inner surface of the prepuce that tends to erosion and bleeding. Histopathologically, however, the descriptions given in current textbooks of dermatopathology vary considerably. For example, in the textbook by Elder (5), the epidermis is said to be thinned, to show "absence of its upper layers," and to be "partially detached as a result of subepi-

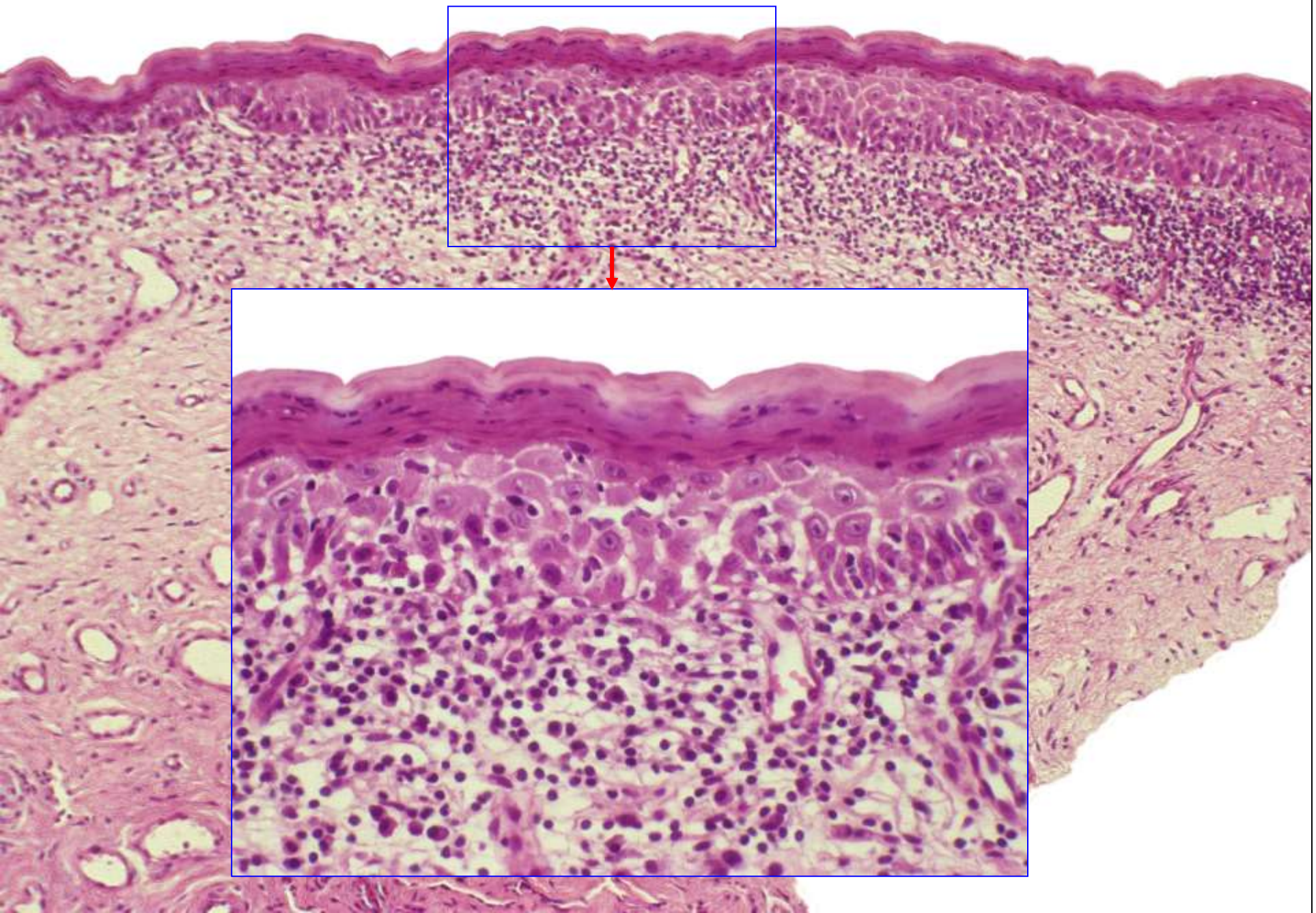
namely, *"irritation or mild trauma affecting barely keratinized skin in a moist environment"*.



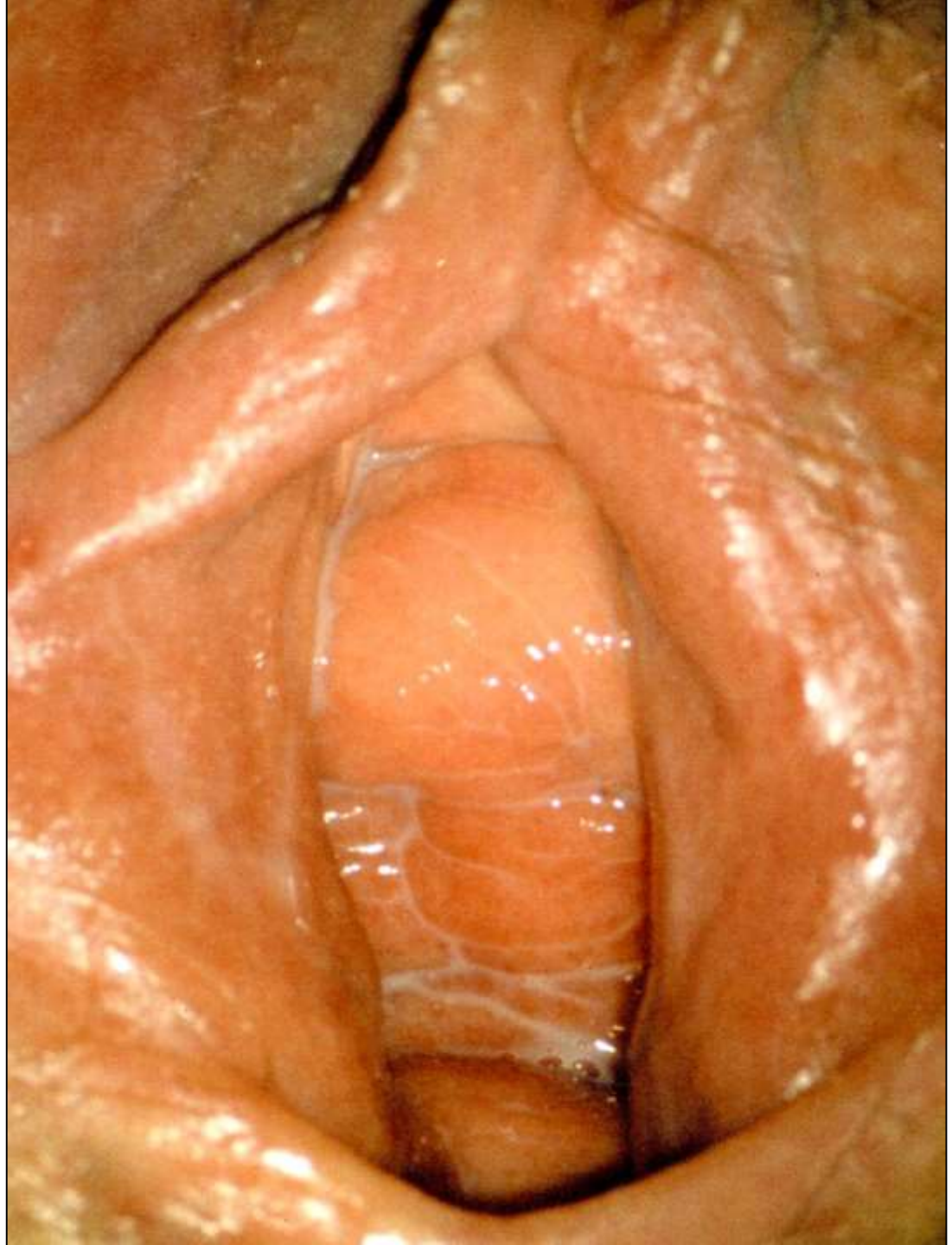
Balanitis of Zoon is most common in men with a long prepuce, and circumcision leads to prompt remission of all signs and symptoms because it removes the moist environment and allows a cornified layer to develop, conferring to the skin increased resistance to external damage.



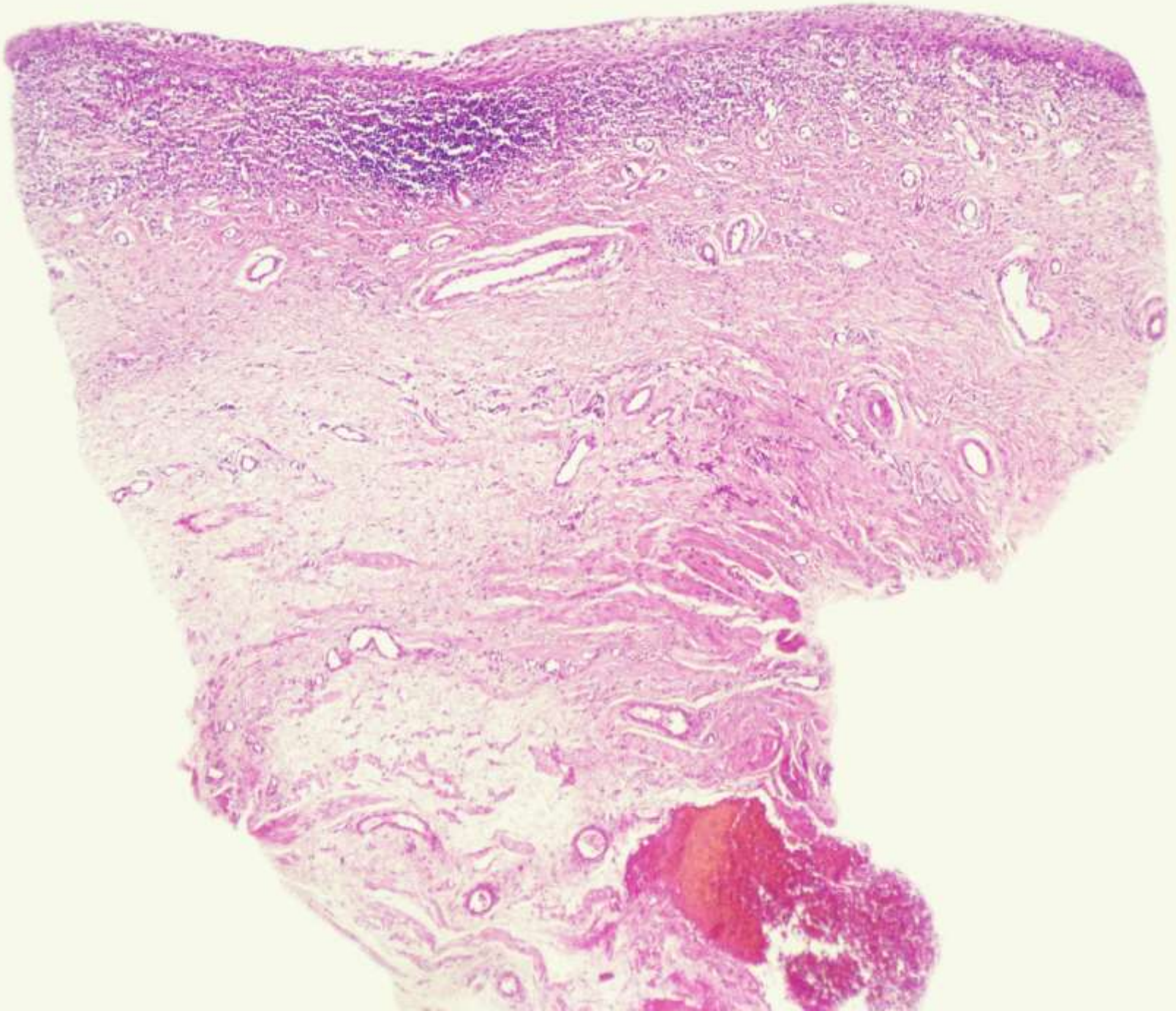
The sequence of histopathologic changes is the same on all sites. In the beginning, the skin tries to protect itself by developing a thin cornified layer, but the latter does not suffice. Inflammation ensues, and a perivascular inflammatory-cell infiltrate develops. As alread noted, the rich vascularity of genital skin confers a lichenoid aspect to all perivascular infiltrates as soon as they become a little denser.



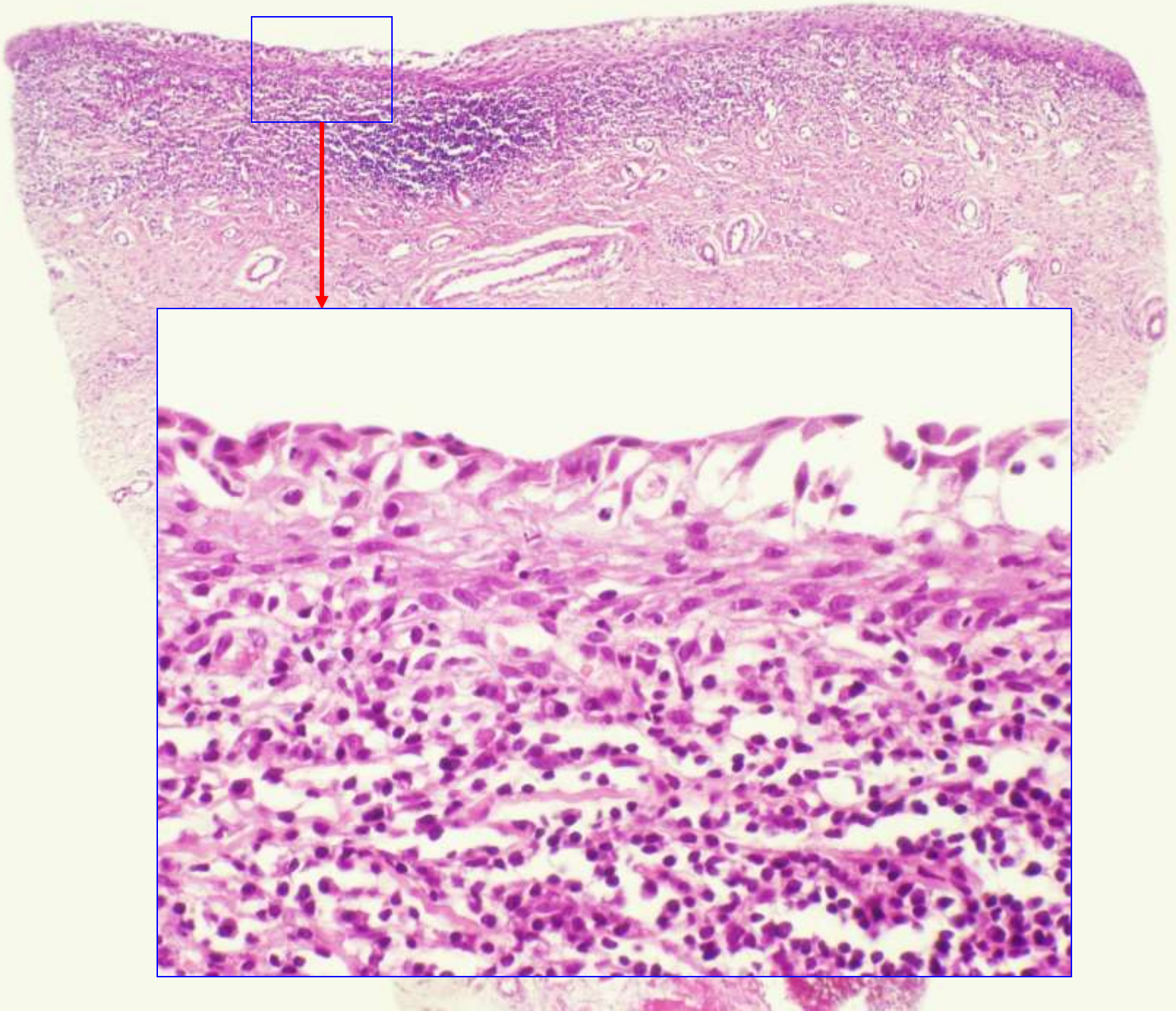
Some plasma cells may or may not be present at early stages. By contrast, neutrophils are seen almost invariably, and they enter the epithelium where there are found especially in the superficial portions. Spongiosis leads to detachment of keratocytes from one another, and the latter acquire what has been referred to as “lozenge shape”.



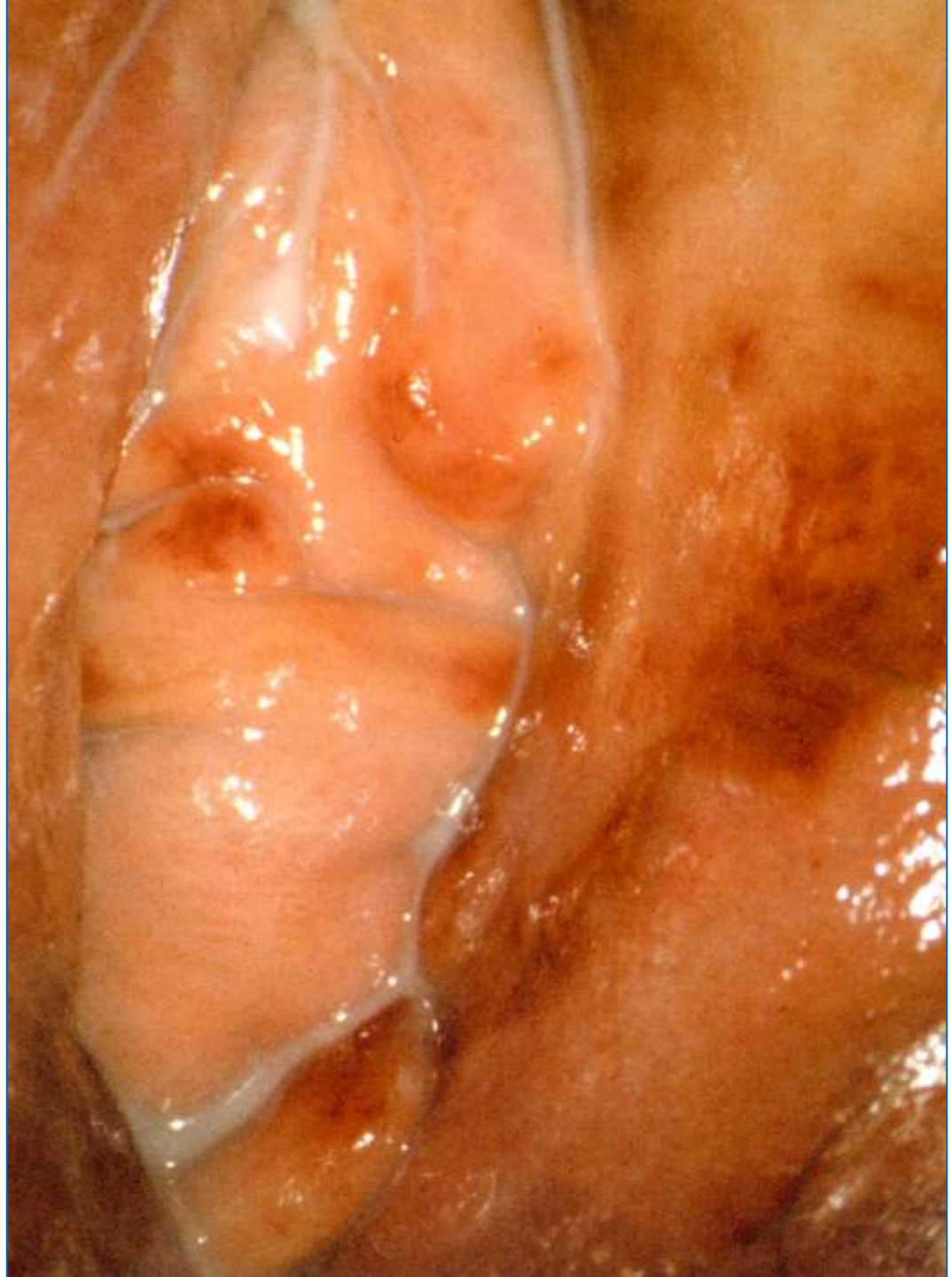
Clinically, changes are still mild, often consisting of nothing but erythema.



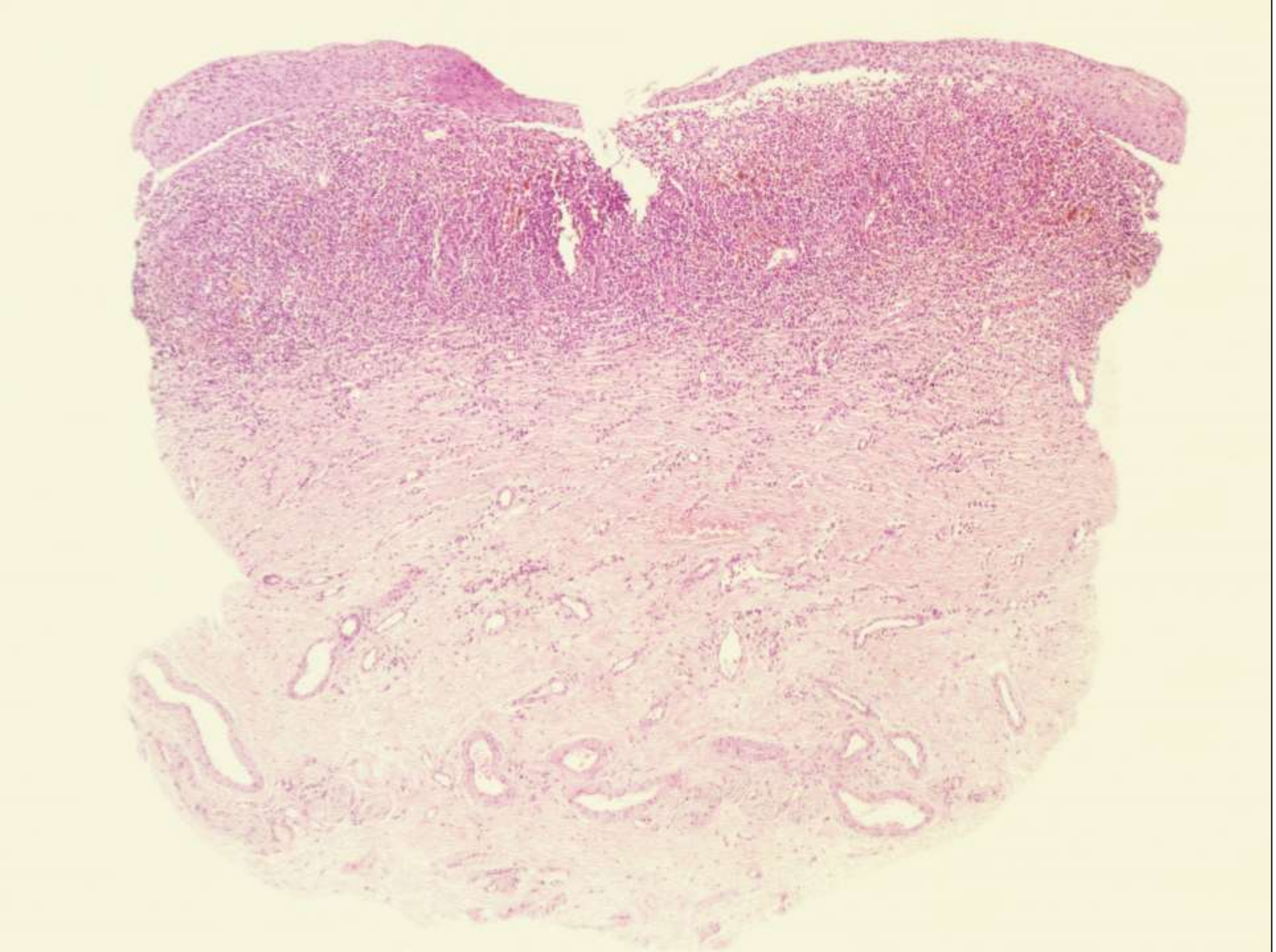
With increasing duration, the infiltrate becomes denser, and plasma cells may predominate.



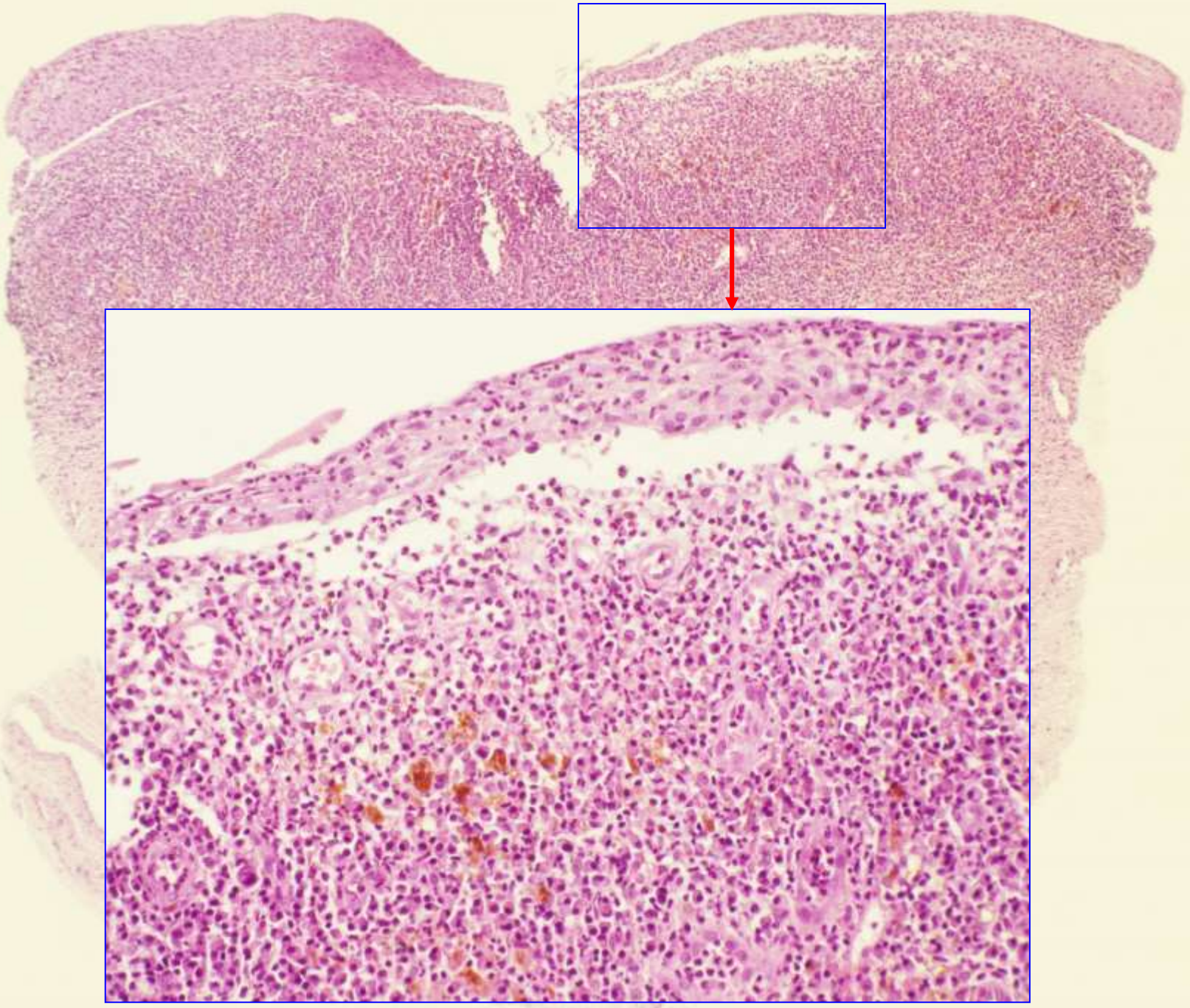
Plasma cells are a constituent of all long-standing inflammatory-cell infiltrates, but they are more common and numerous on or near mucosal surfaces than elsewhere. The superficial portions of the epithelium become acantholytic, probably because of the effects of proteolytic enzymes released by neutrophils.



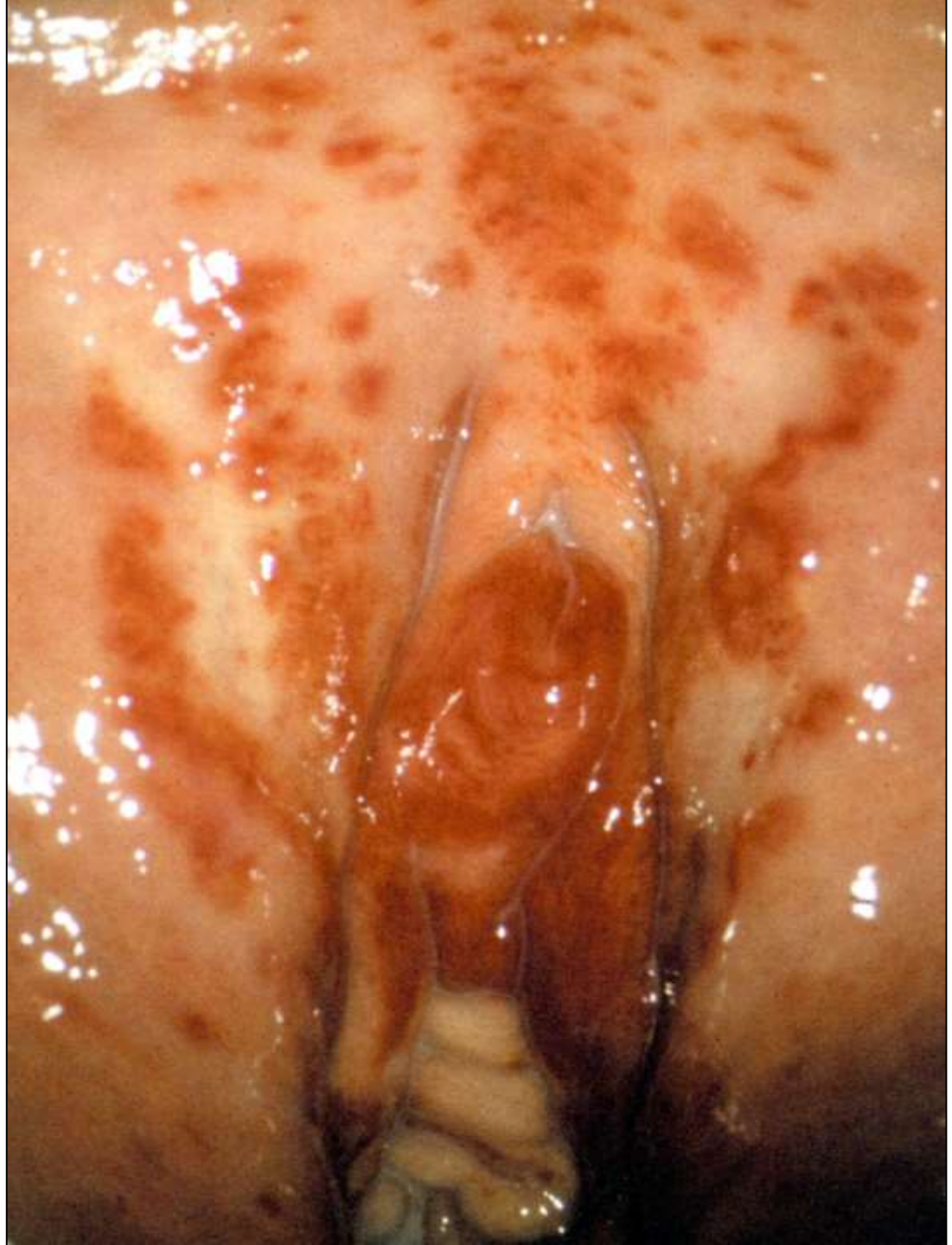
Clinically, one sees erosions and hemorrhage.



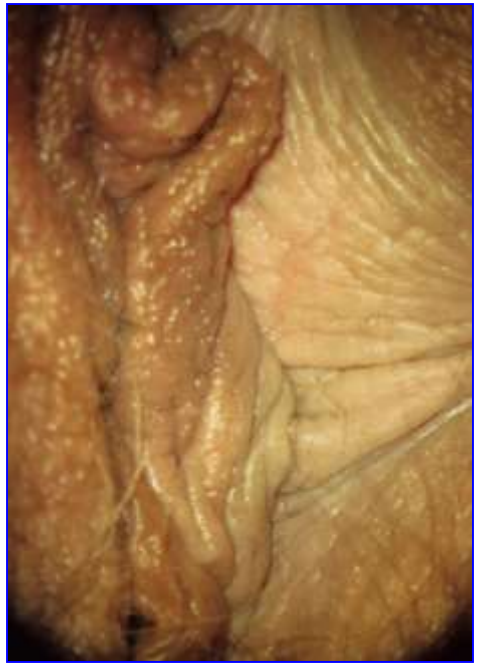
Eventually, subepidermal clefts develop, portions of the epithelium are lost, the superficial dermis becomes fibrotic,



and many siderophages may be seen in the midst of a dense lymphoplasmacellular infiltrate that is often associated with myriad neutrophils.

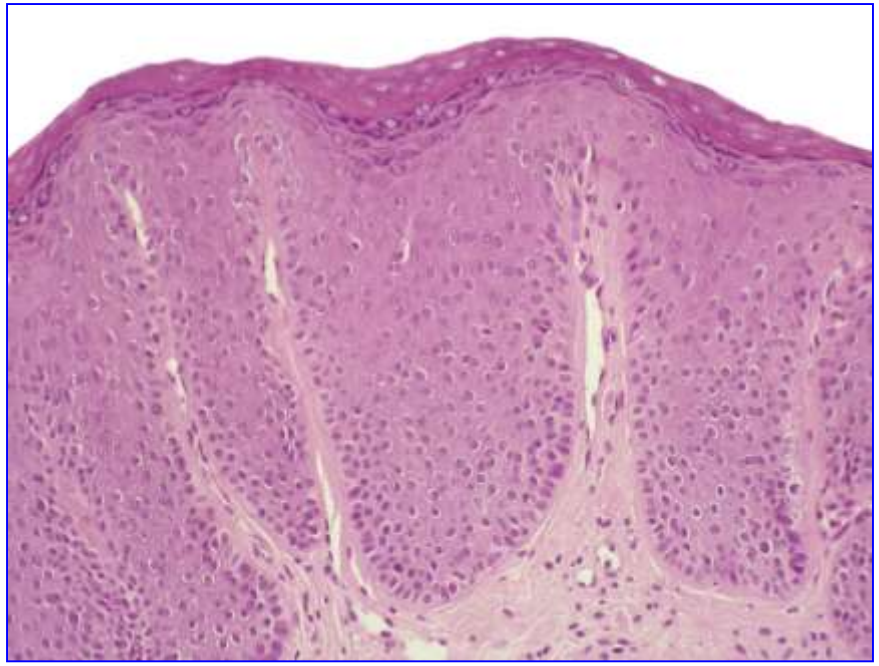


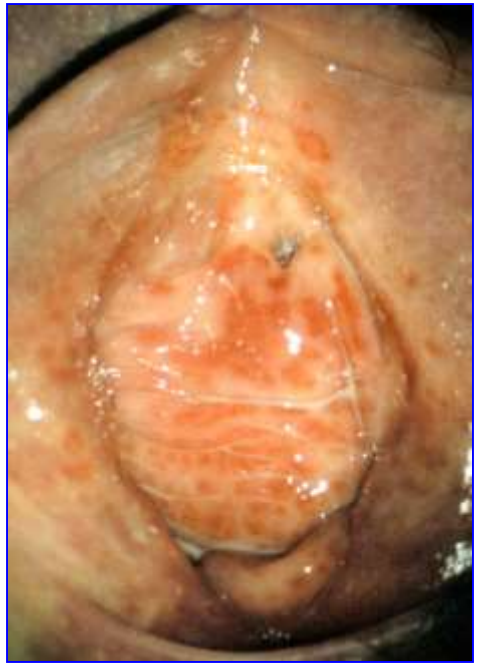
Treatment may be difficult. In contrast to men, circumcision is not an option. Local antinflammatory treatment with steroids or tacrolimus has been suggested, and has been successful, but it may cause irritation itself. Sometimes, cessation of any local treatment, supported by a brief course of steroids systemically, leads to resolution of lesions. Antibiotics such as clindamycin may also be successful, probably not only because of effects on a secondary infection but also because of anti-inflammatory properties. This case, for example, healed after a two-week-course of clindamycin.



Lichen simplex chronicus

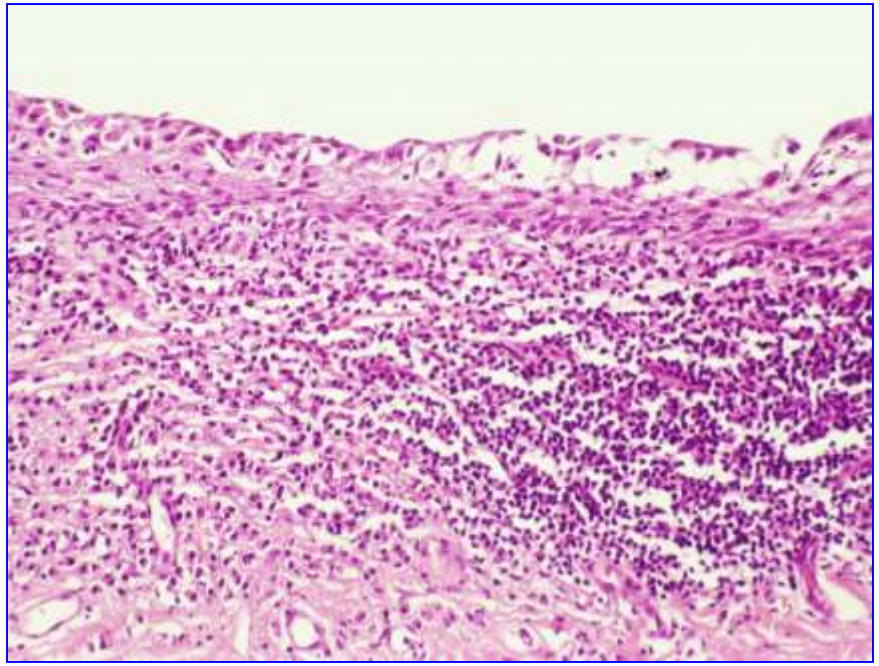
persistent rubbing and scratching



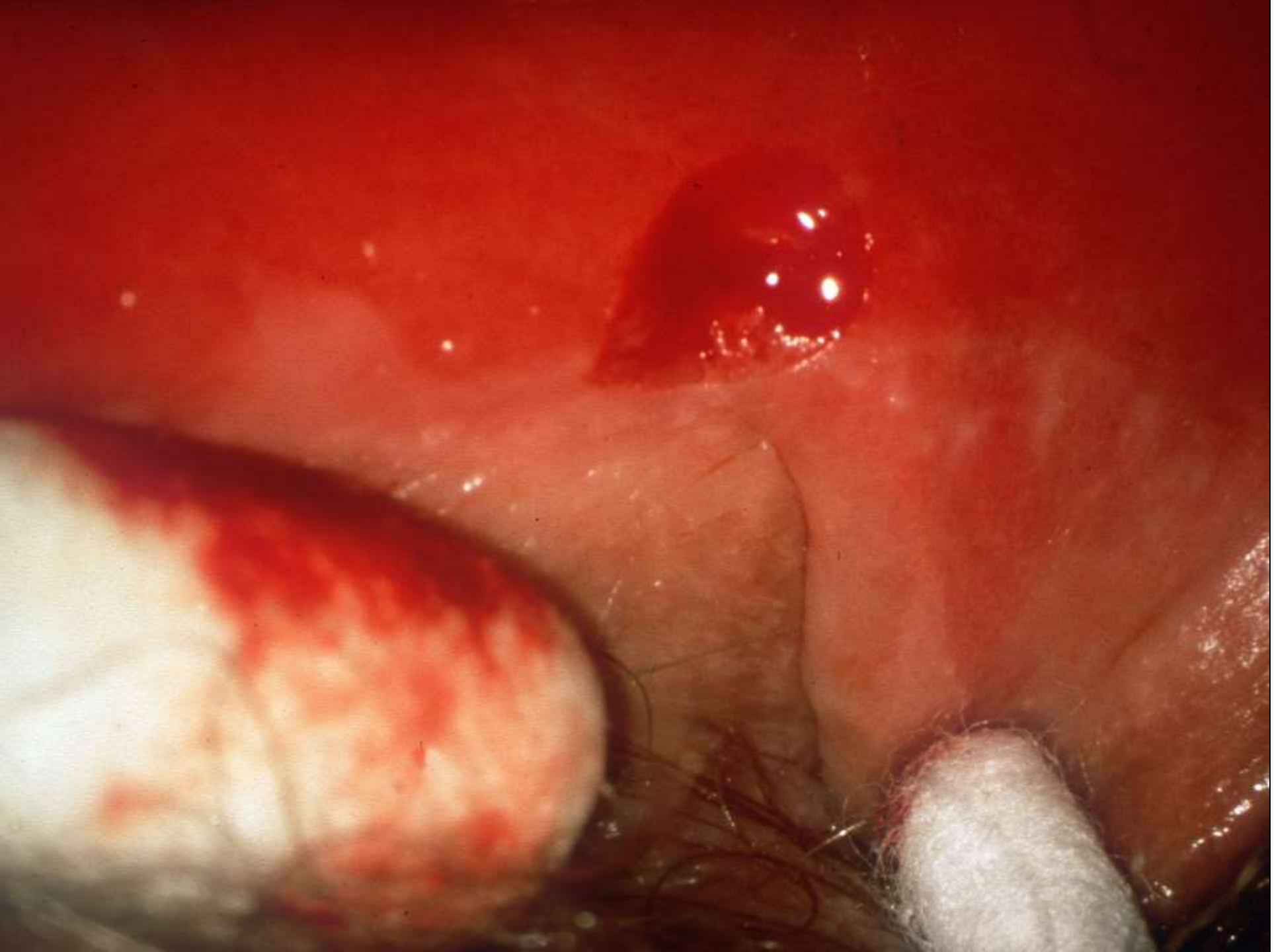


Vulvitis of Zoon

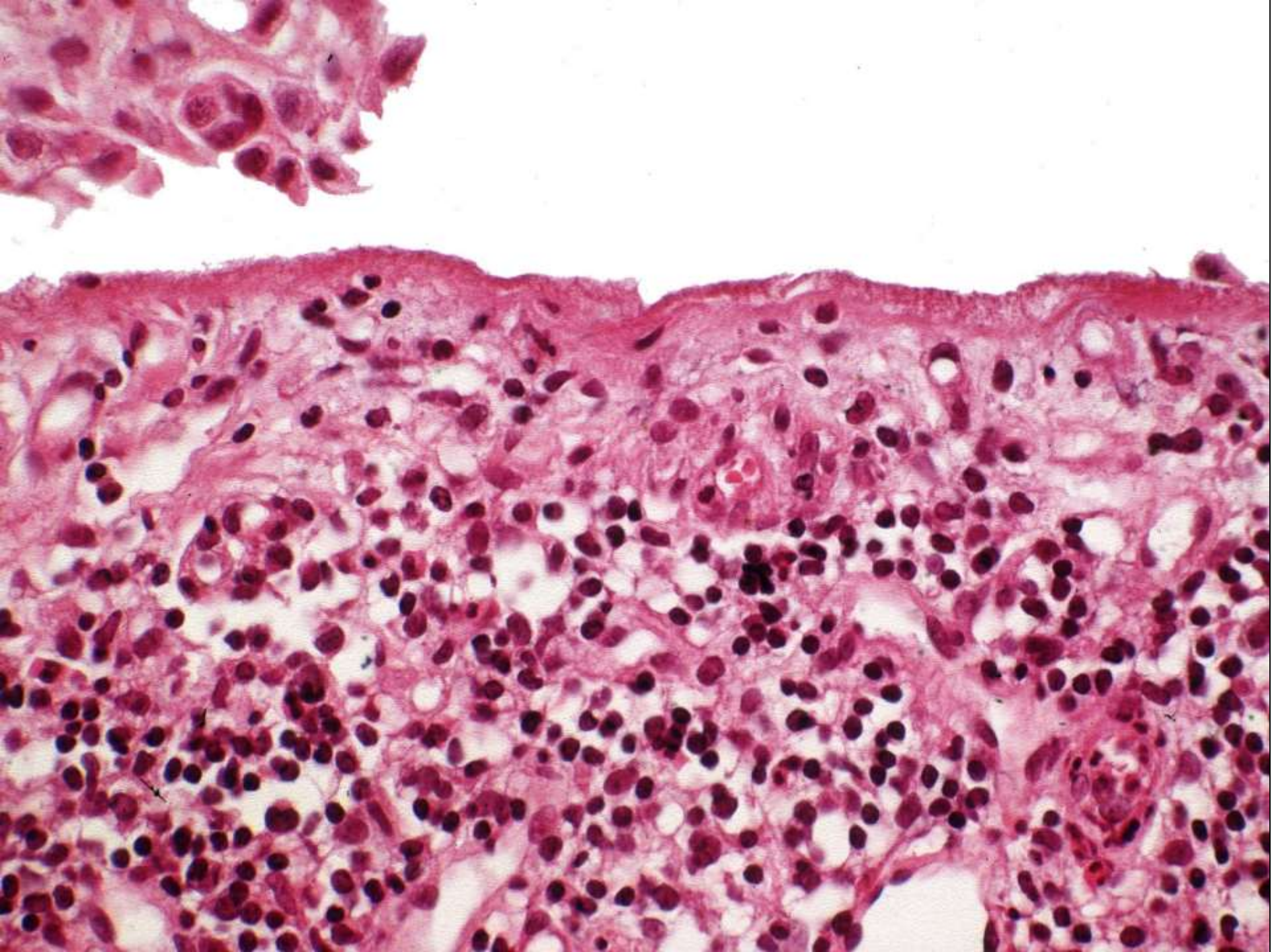
irritation of barely keratinized skin



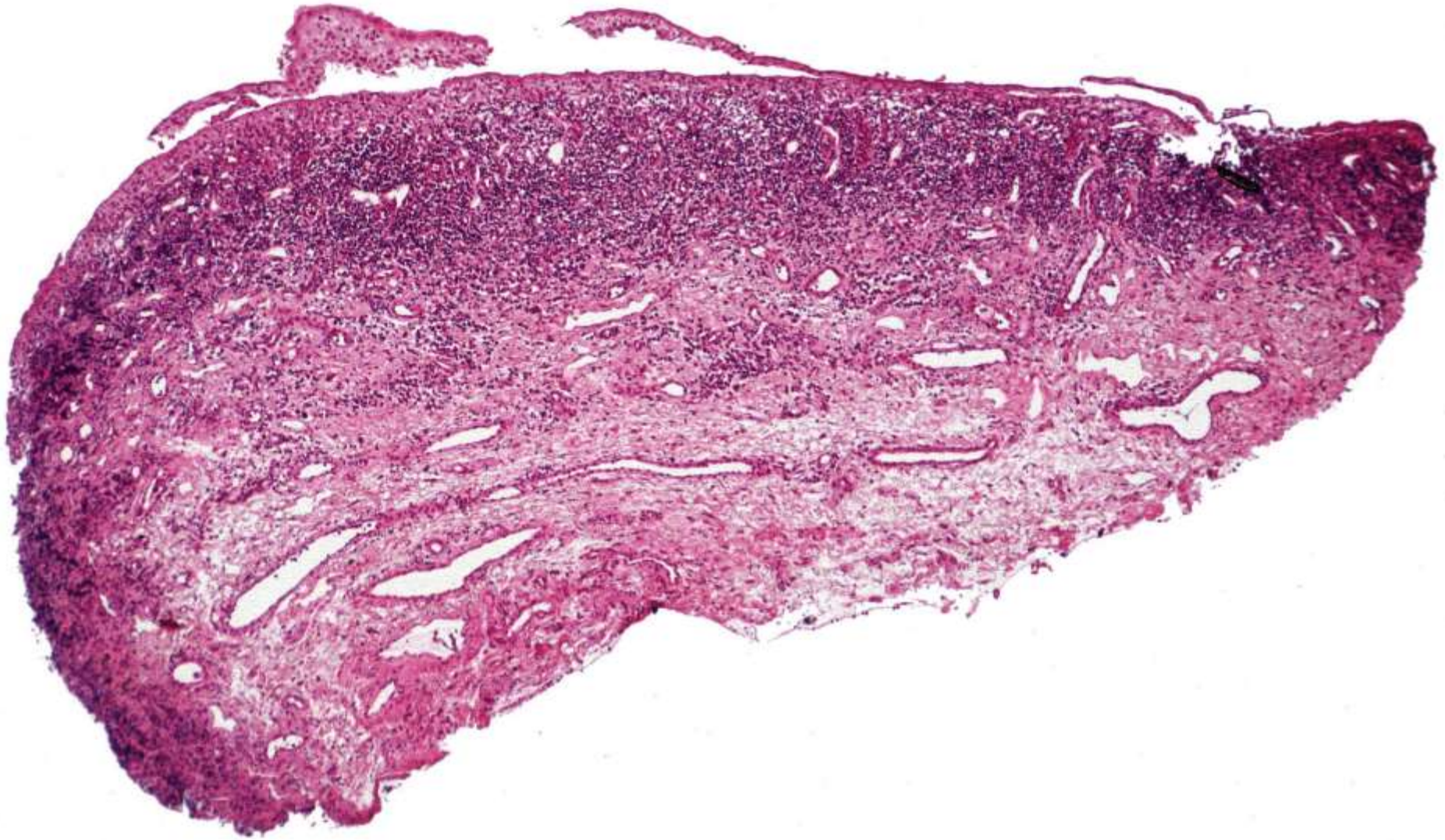
As a unique response to external damage, vulvitis of Zoon can be compared to lichen simplex chronicus. Both are non-specific, but distinctive reaction patterns. Lichen simplex chronicus is caused by persistent rubbing and scratching, vulvitis of Zoon by irritation of barely keratinized skin. Both conditions may occur alone but are often found superimposed on other pathologic processes.



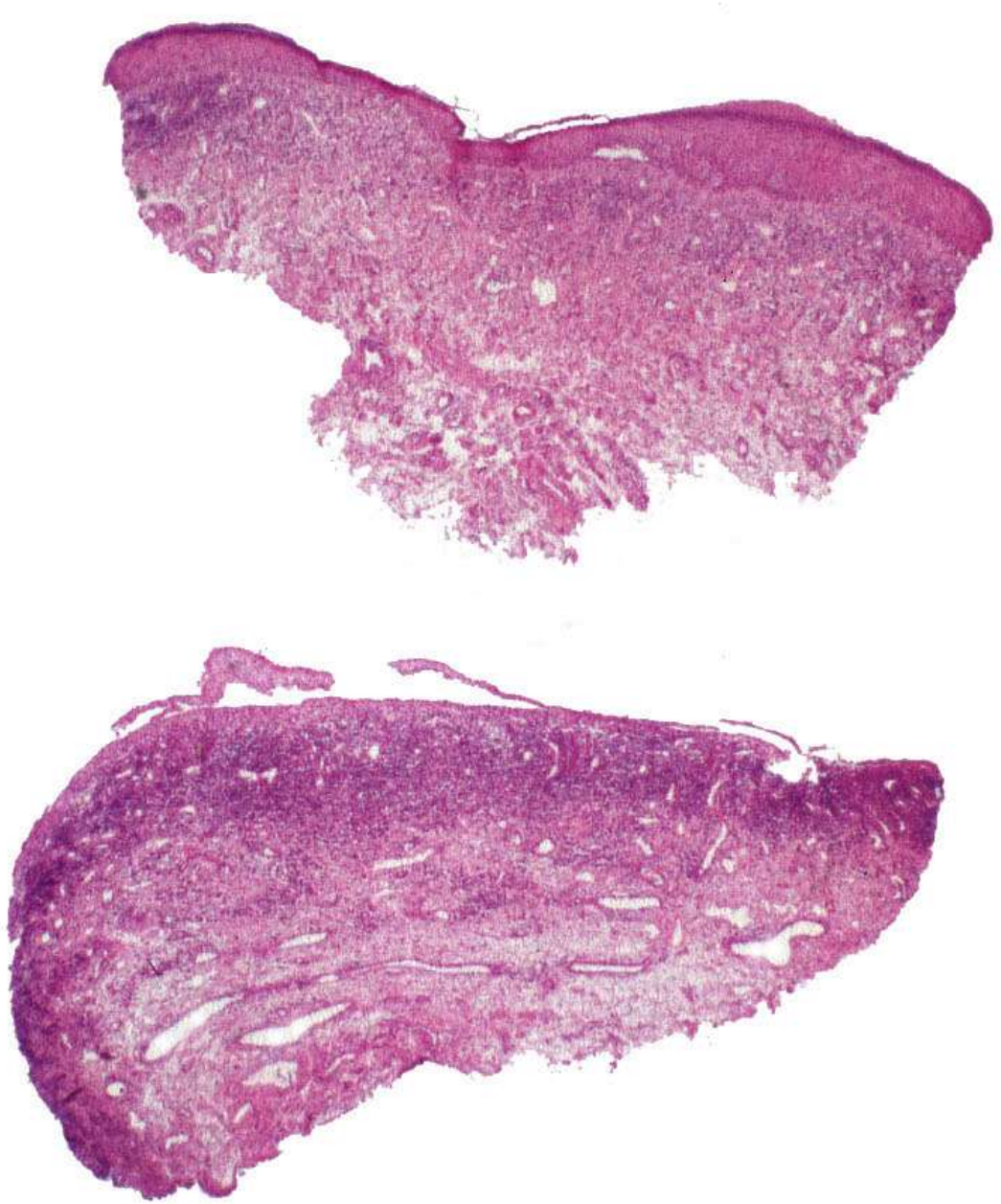
This is an example: a women with broad erosions on the vulva. A biopsy was taken at the border of eroded and non-eroded skin.



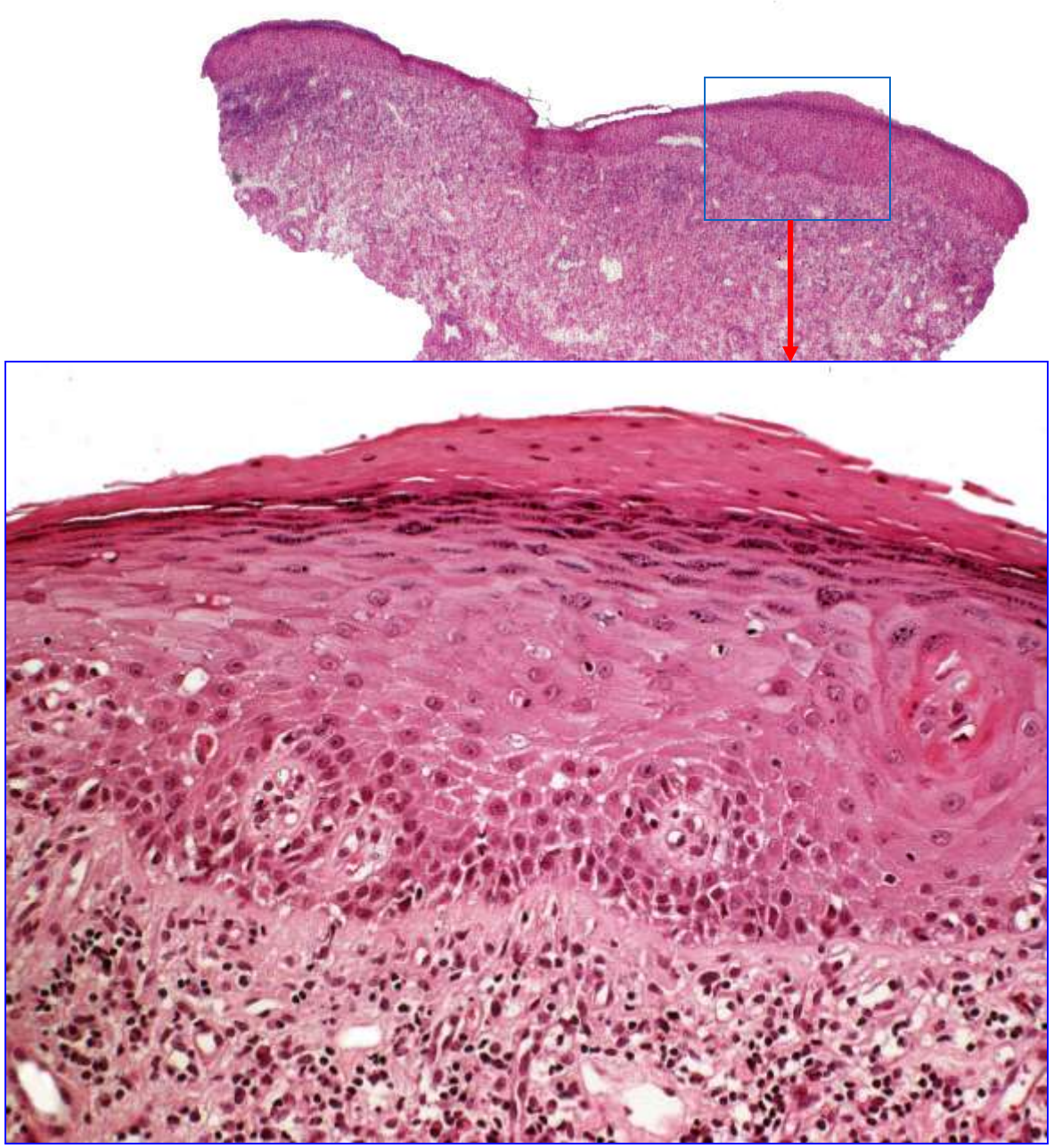
In the eroded portion, one sees nearly complete loss of the epithelium and a dense lichenoid lymphoplasmacellular infiltrate.



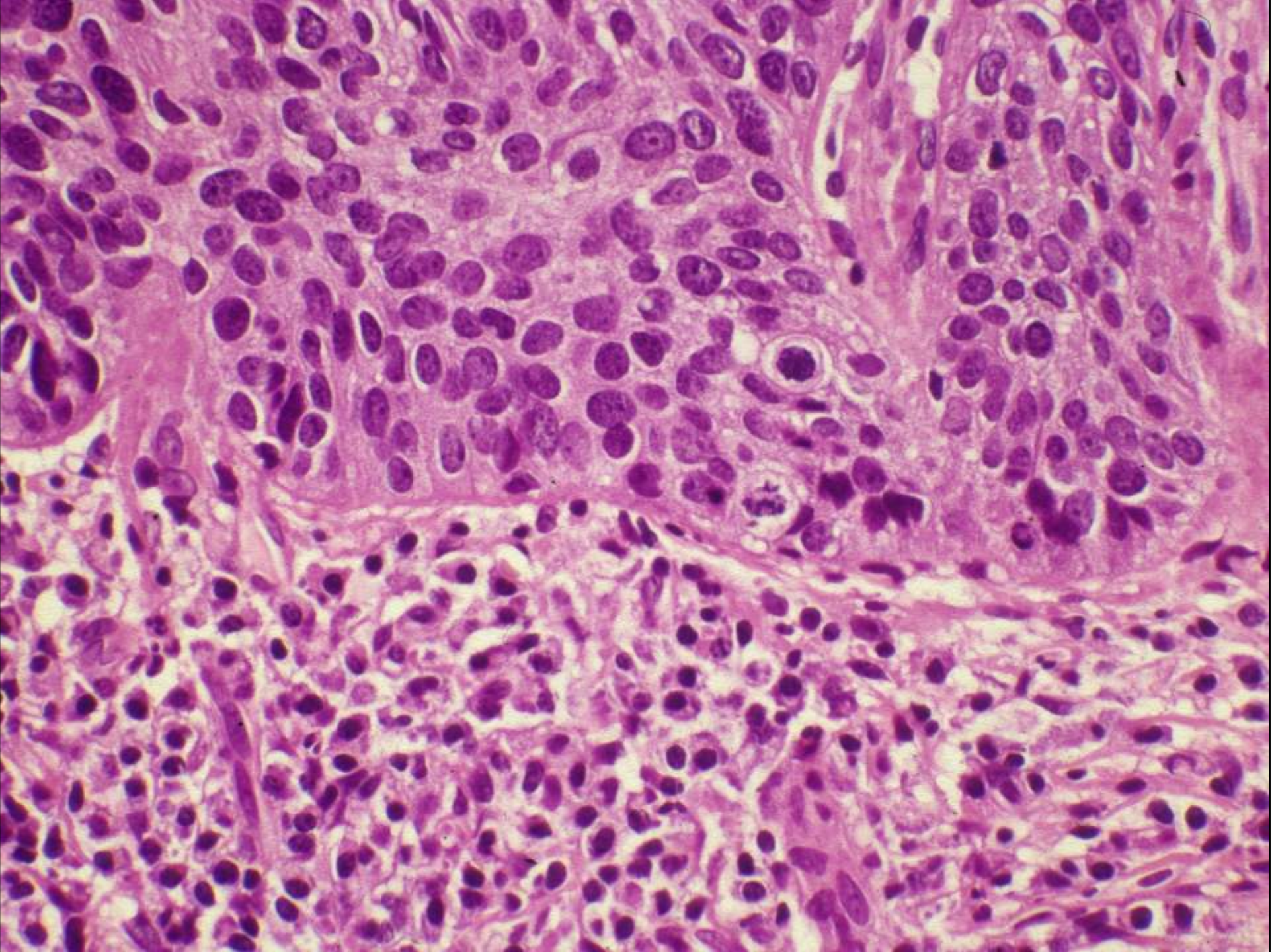
Those changes would have been diagnosed as vulvitis of Zoon,



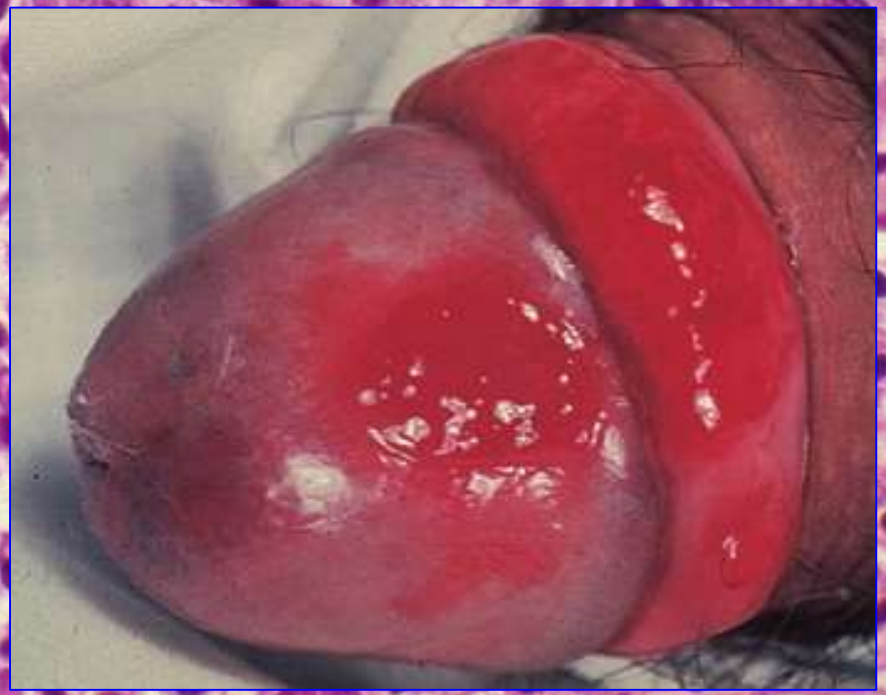
had there not been the other part of the specimen that shows



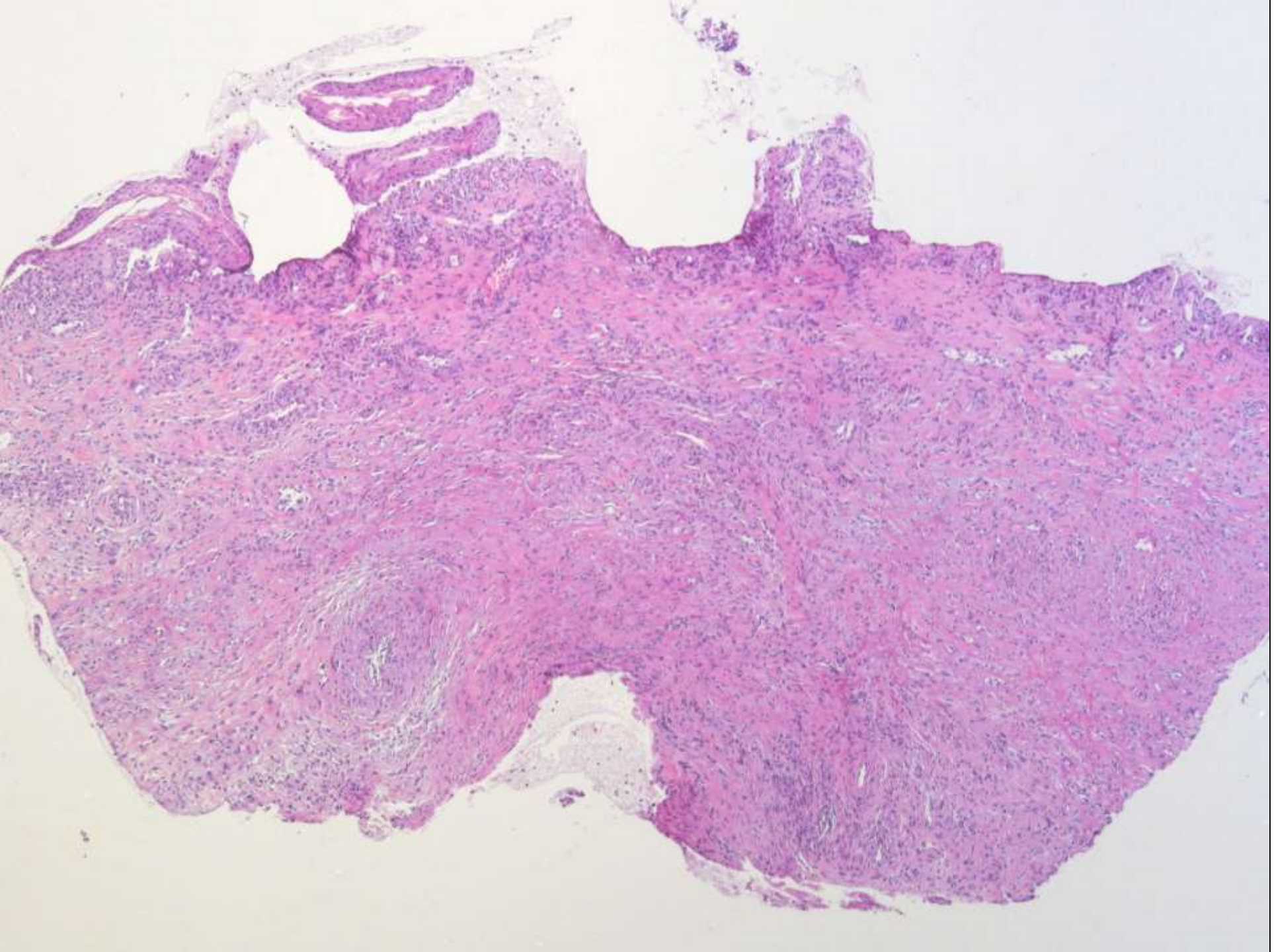
acanthosis of the epidermis with pointed rete ridges, vacuolar alteration at the junction, necrotic keratocytes, wedge-shaped zones of hypergranulosis and a thickened, compact cornified layer, changes suggestive of lichen planus. In brief, even when features of vulvitis of Zoon are present, one must always look for signs of an additional process,



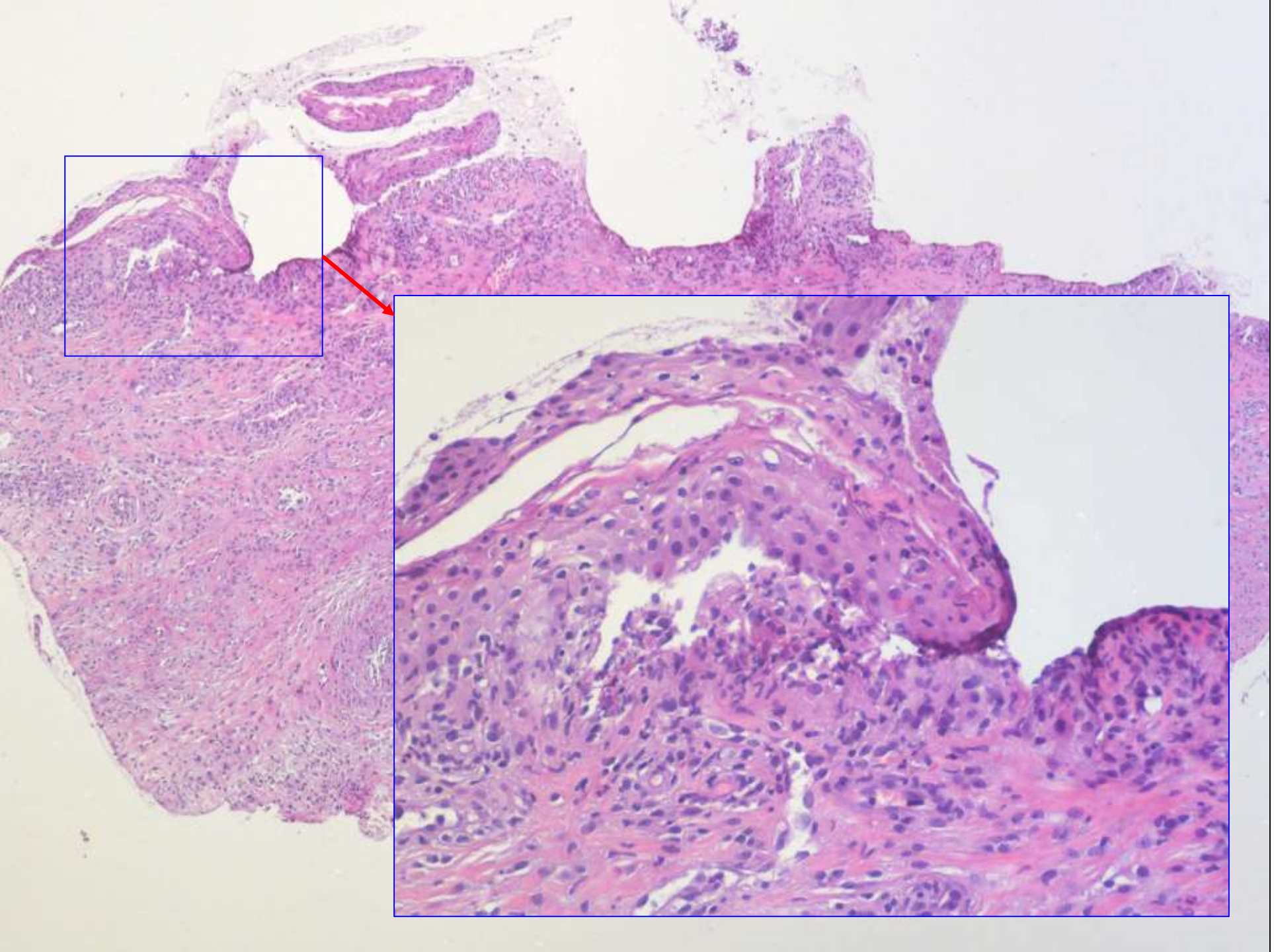
including nuclear atypia as evidence of carcinoma in situ with superimposed vulvitis of Zoon.



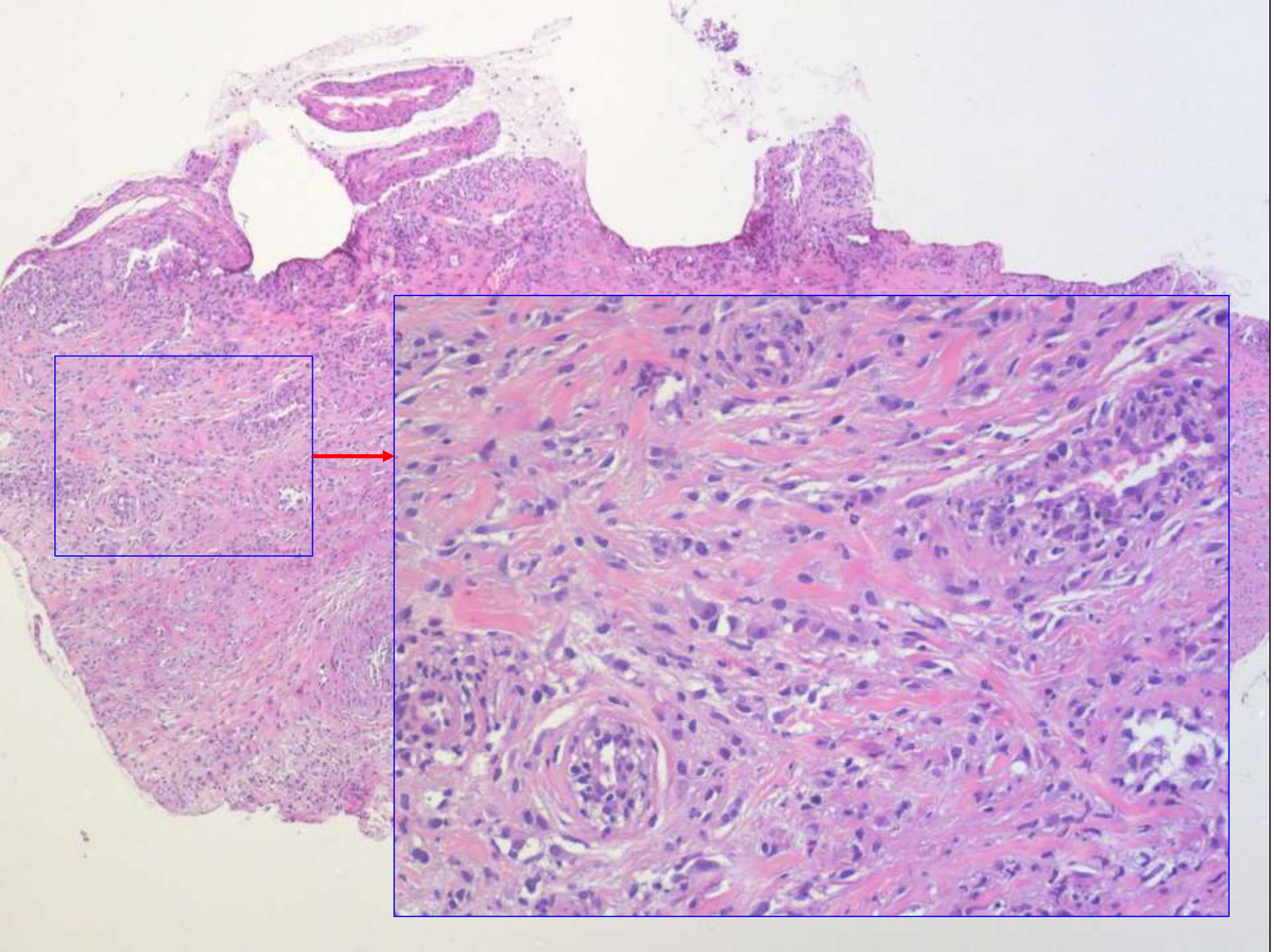
There is a reason why erythroplasia of Queyrat and balanitis of Zoon are look-alikes clinically, namely, balanitis of Zoon being superimposed on carcinoma in situ and conferring to it the red, glistening appearance not seen in other areas of skin.



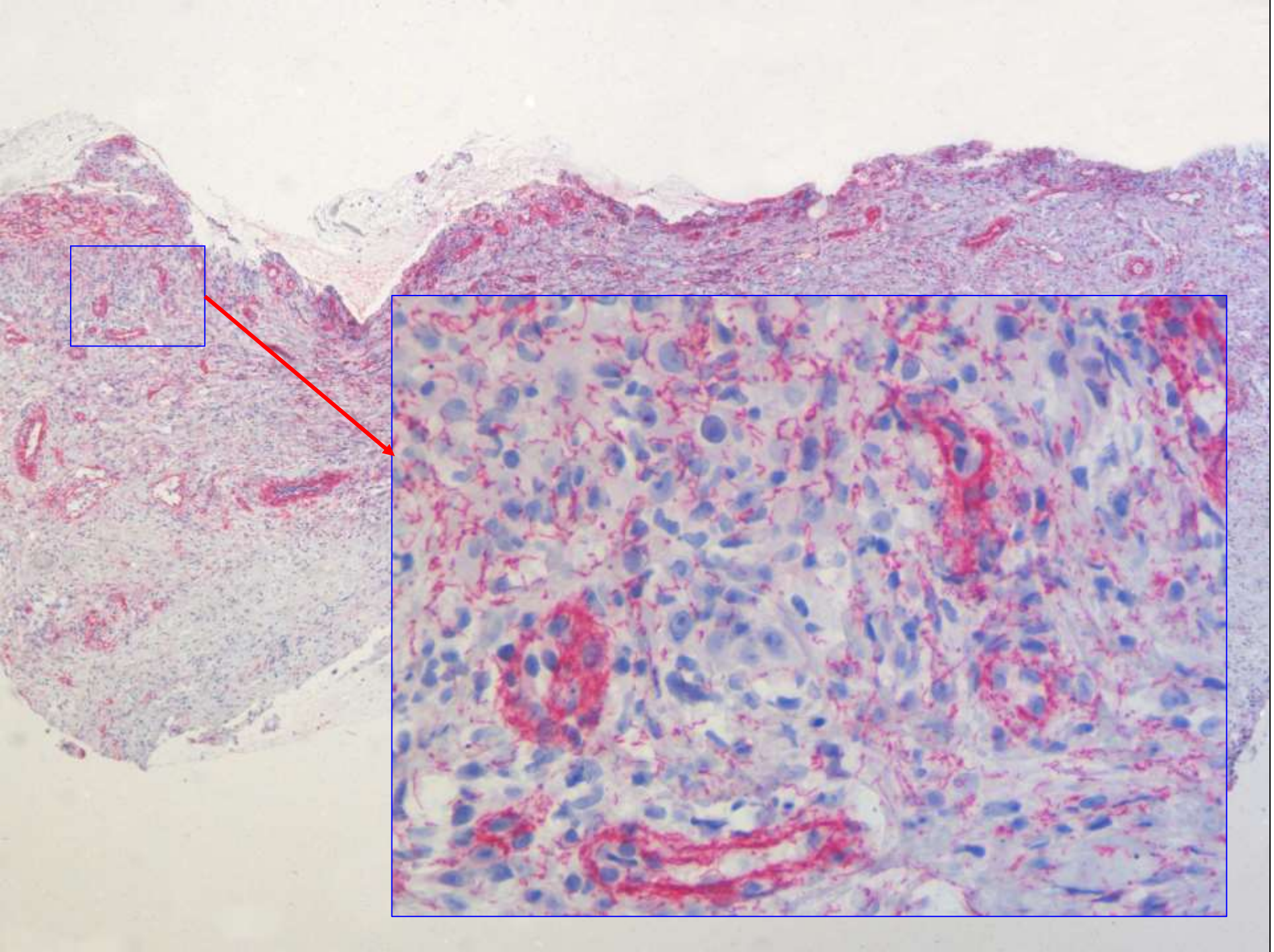
Of course, special care must be taken not to overlook associated processes that share cardinal features with balanitis or vulvitis of Zoon, such as fibrosis, a lymphoplasmocytic infiltrate,



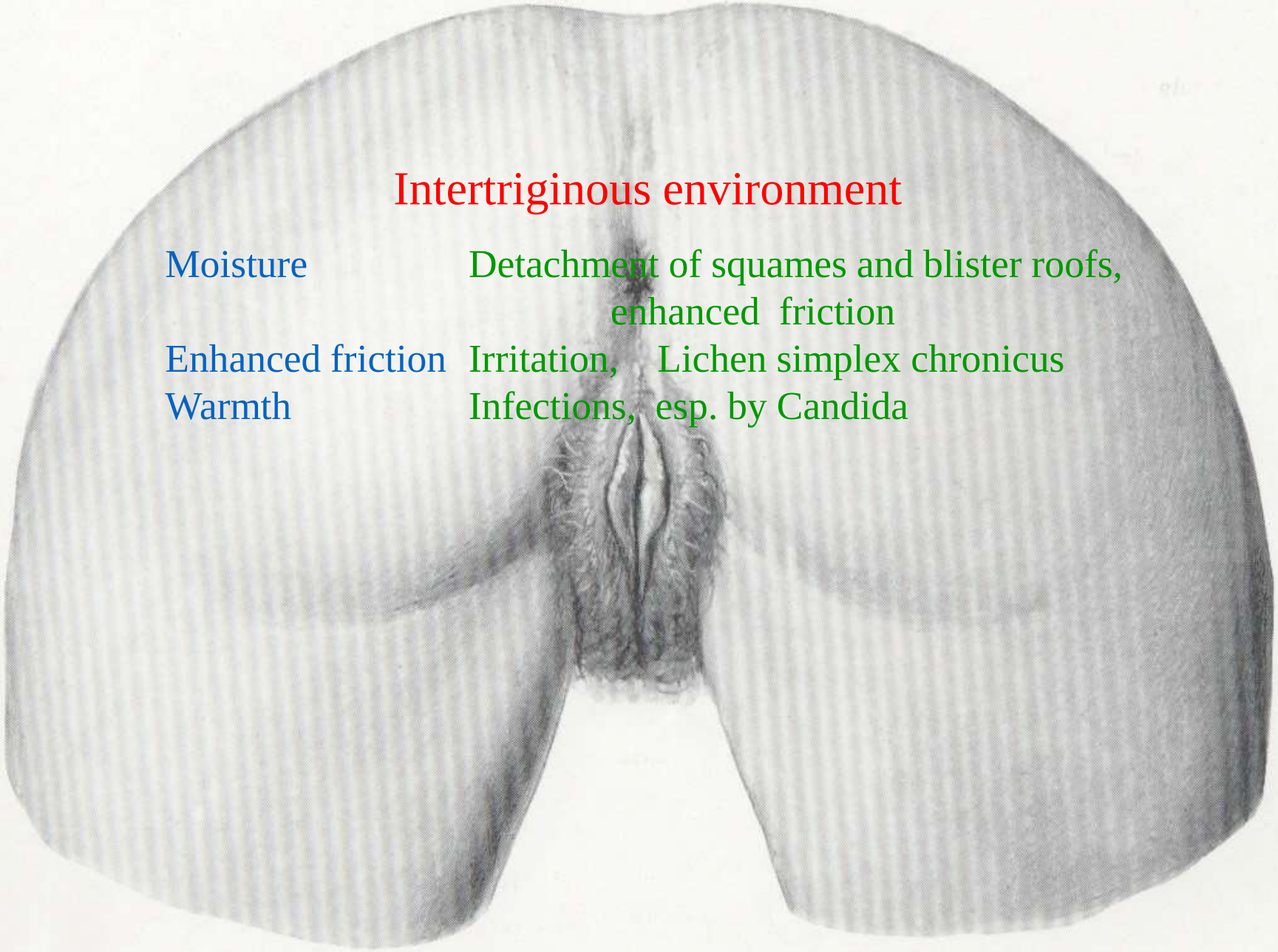
shedding of the epidermis, and neutrophils within the epidermis.



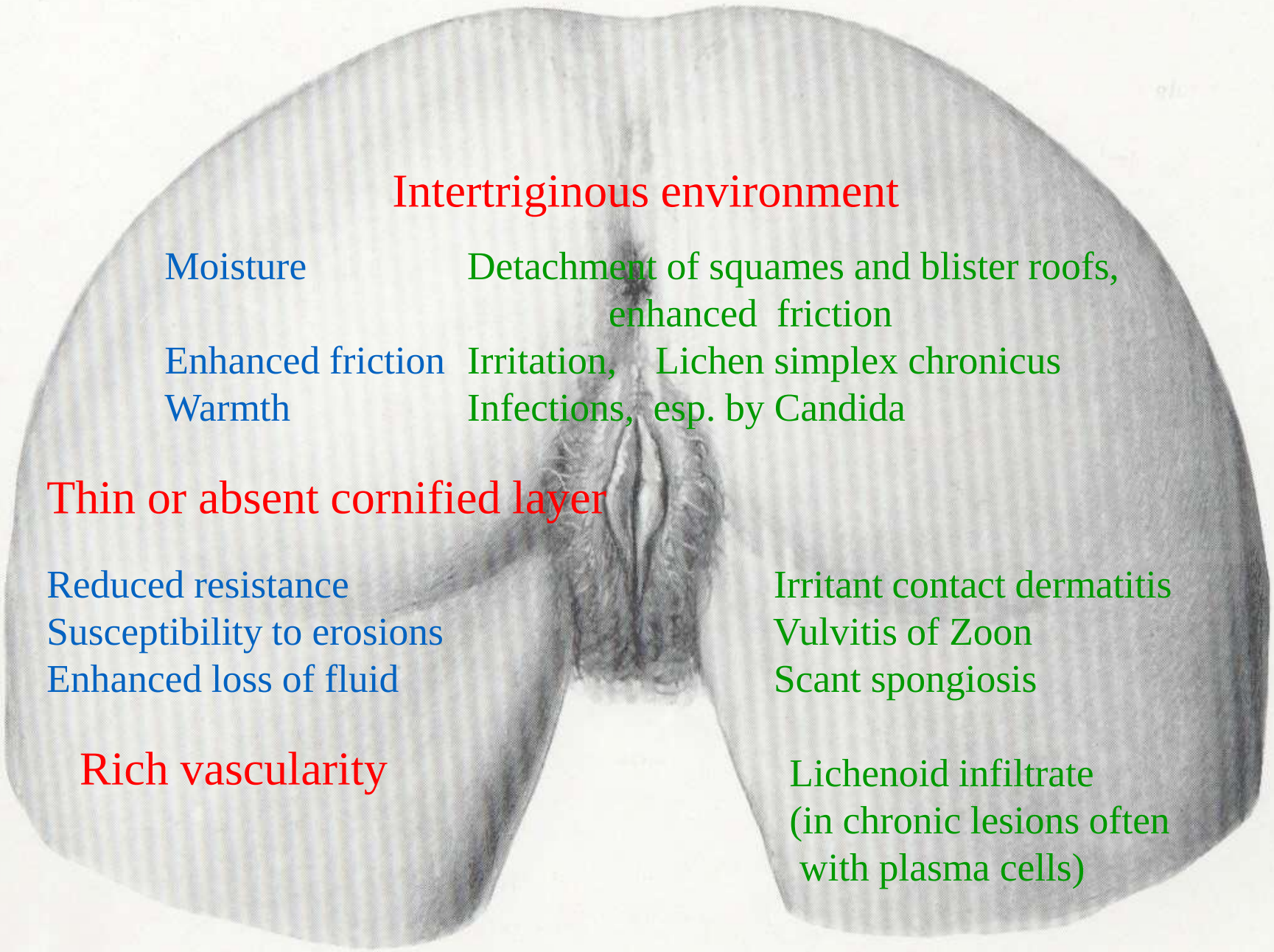
In this case, the infiltrate is also histiocytic, a feature not seen in vulvitis Zoon, and endothelial cells are swollen. This is primary syphilis,



and immunohistochemistry demonstrated scores of spirochetes especially in endothelia.



In sum, the vulva does not differ principally from other regions of skin, but some peculiarities should be kept in mind when dealing with diseases of the vulva and examining biopsy specimens from it: One is the intertriginous environment. Moisture leads to detachment of squames and blister roofs and to enhanced friction. The latter may cause irritation and provide the ground for lichen simplex chronicus, and warmth may further infections, especially by Candida.



The thin or absent cornified layer results in a reduced restistance of the skin to external damage, susceptibility to erosions, and enhanced transepidermal water loss, furthering the development of irritant contact dermatitis and vulvitis of Zoon and explaining why spongiosis is hardly ever pronounced on the vulva. Yet another peculiarity is the rich vascularity that explains why perivascular infiltrates tend to appear lichenoid on the vulva.

Intertriginous environment

Moisture

Enhanced friction
Warmth

Detachment of squames and blister roofs, enhanced friction

Irritation, Lichen simplex chronicus
Infections, esp. by Candida

Thin or absent cornified layer

Reduced resistance
Susceptibility to erosions
Enhanced loss of fluid

Irritant contact dermatitis
Vulvitis of Zoon
Scant spongiosis

Rich vascularity

Lichenoid infiltrate
(in chronic lesions often with plasma cells)

In brief, there are aspects that distinguish the vulva from other regions of skin, just as there are aspects that distinguish Switzerland from other regions, such as Northern Germany, e.g., mountains versus seaside, alphorn versus accordion. Nonetheless, people here and there are basically the same, and despite some differences, they understand one another because they speak more or less the same language. It is difficult to grasp why the much smaller differences between vulva and the rest of skin should warrant a different language.

2011 ISSVD Clinical Classification of Vulvar Dermatological Disorders (Lynch 2011)	2006 ISSVD Classification of Vulvar Dermatoses: Pathologic Subsets (Lynch 2011)
Skin-colored lesions	Spongiotic pattern
Red lesions: patches and plaques	Acanthotic pattern
Red lesions: papules and nodules	Lichenoid pattern
White lesions	Dermal homogenization/sclerosis pattern
Dark colored (brown, blue, gray, or black) lesions	Vesiculobullous pattern
Blisters	Acantholytic pattern
Erosions and ulcers	Granulomatous pattern
Edema (diffuse genital swelling)	Vasculopathic pattern

Nonetheless, the latter has been introduced by the International Society for the Study of Vulvovaginal Disease. In 2011, that society advanced a clinical classification of *"vulvar dermatological disorders"* in which lesions were referred to as *"skin colored"*, *"red"*, and *"white"*, and patches, plaques, papules, and nodules were only recognized among red lesions. To me, this nomenclature appears primitive and superfluous,

DESCRIPTION AND TREATMENT OF CUTANEOUS DISEASES.

ORDER I.

PAPULOUS ERUPTIONS ON THE SKIN.

BY

ROBERT WILLAN, M.D. F.A.S.

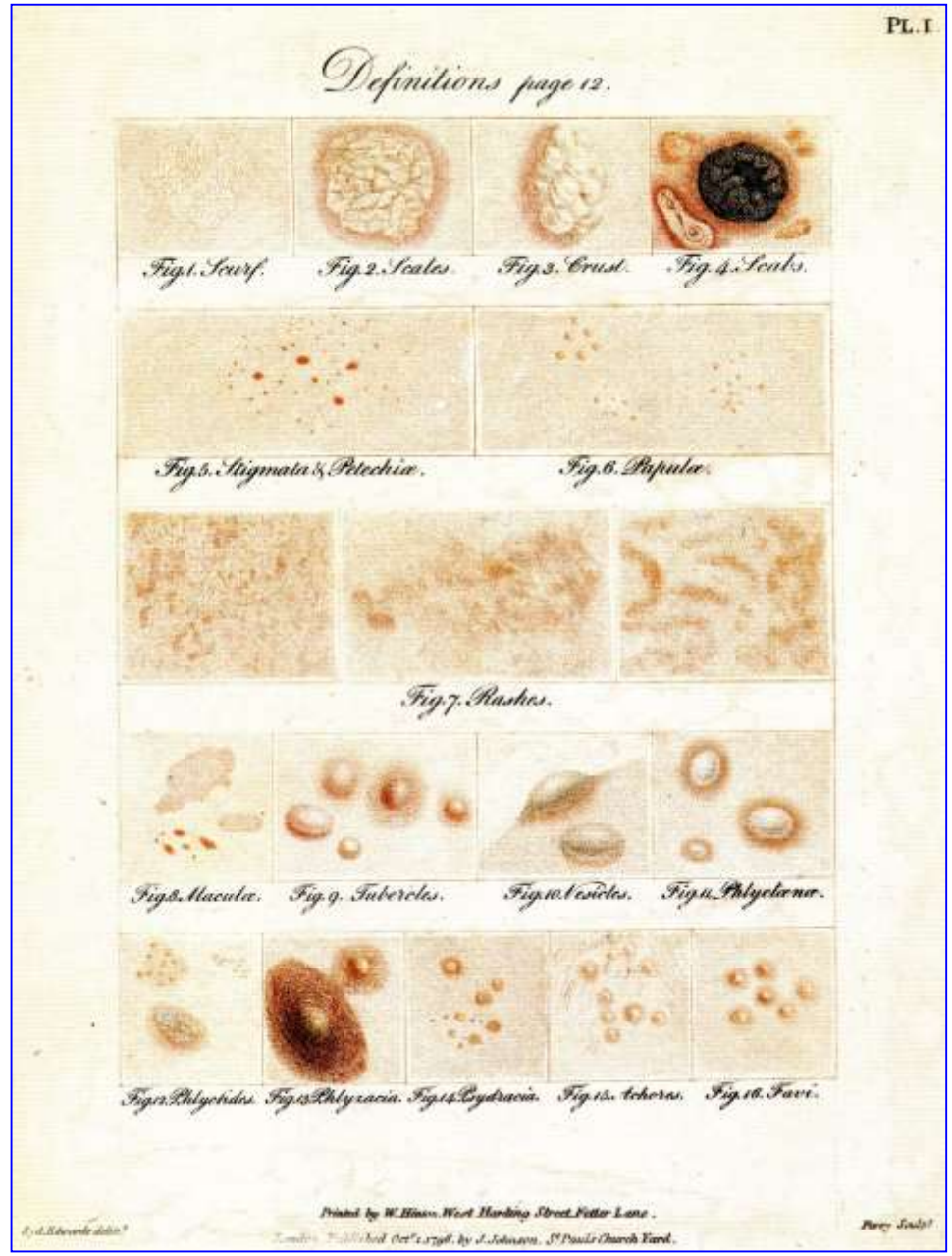
LONDON:

PRINTED FOR J. JOHNSON, ST. PAUL'S CHURCH-YARD.

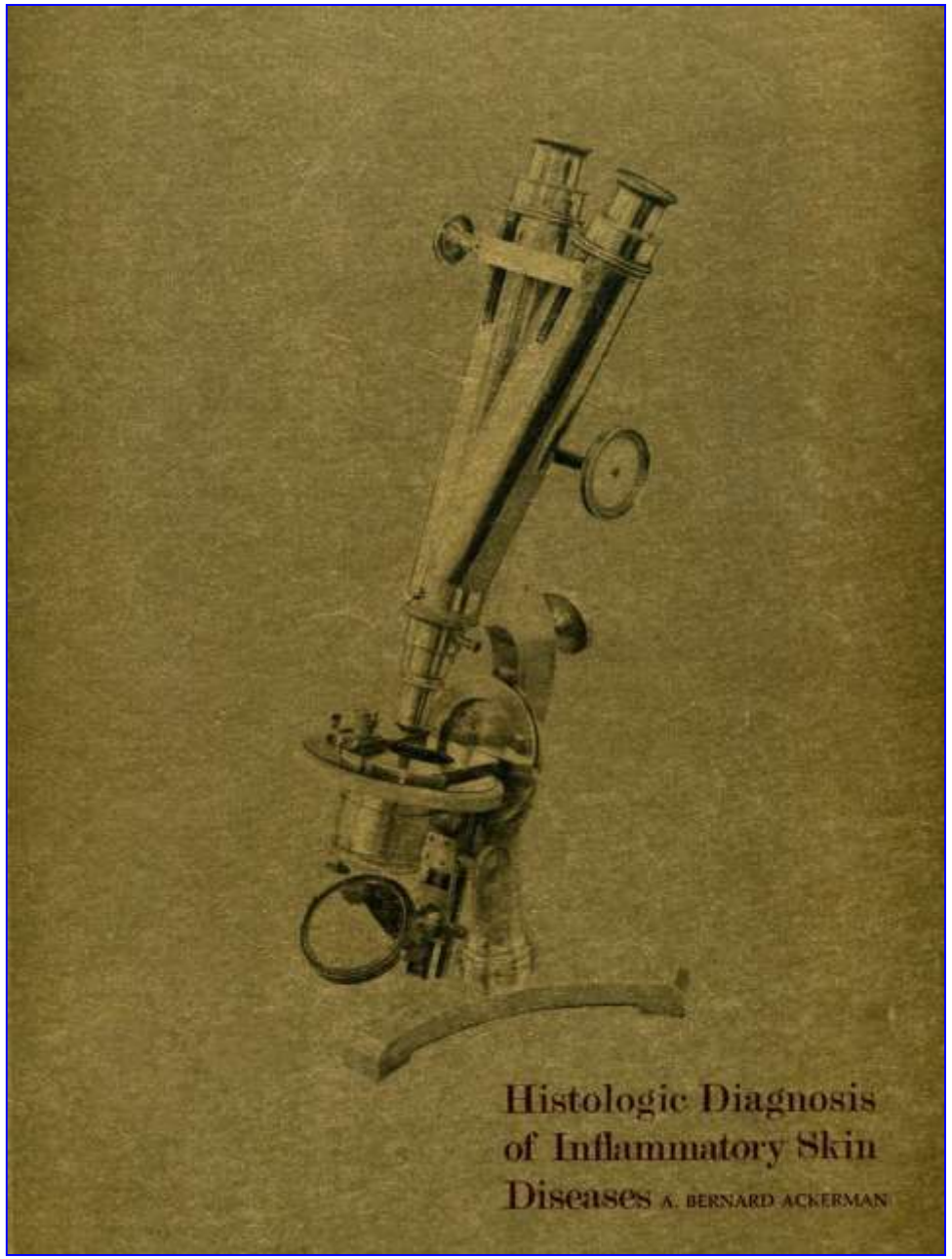
1798.

TO THE PUBLICK.

IN conducting the following Work, it is propoſed to publiſh the ſeven Orders, of which it conſiſts, ſeparately. The Orders, as ſtated Page 16, are characterized by the different Appearances



especially when considering that a much more elaborate nomenclature exists since more than 200 years and can be learned during a lunch break.



Diagnosis by Histopathologic Patterns

Recognition of Major Patterns

- Superficial perivascular dermatitis
- Superficial and deep perivascular dermatitis
- Vasculitis
- Nodular and diffuse dermatitis
- Intraepidermal vesicular and pustular dermatitis
- Subepidermal vesicular dermatitis
- Folliculitis and perifolliculitis
- Fibrosing dermatitis
- Panniculitis

Advantages of Pattern Method

Application of Pattern Method

Likewise, basic histopathologic patterns of cutaneous diseases have been defined in the 1970s.

2006 ISSVD Classification of Vulvar Dermatoses: Pathologic Subsets (Lynch 2011)

Spongiotic pattern

Acanthotic pattern

Lichenoid pattern

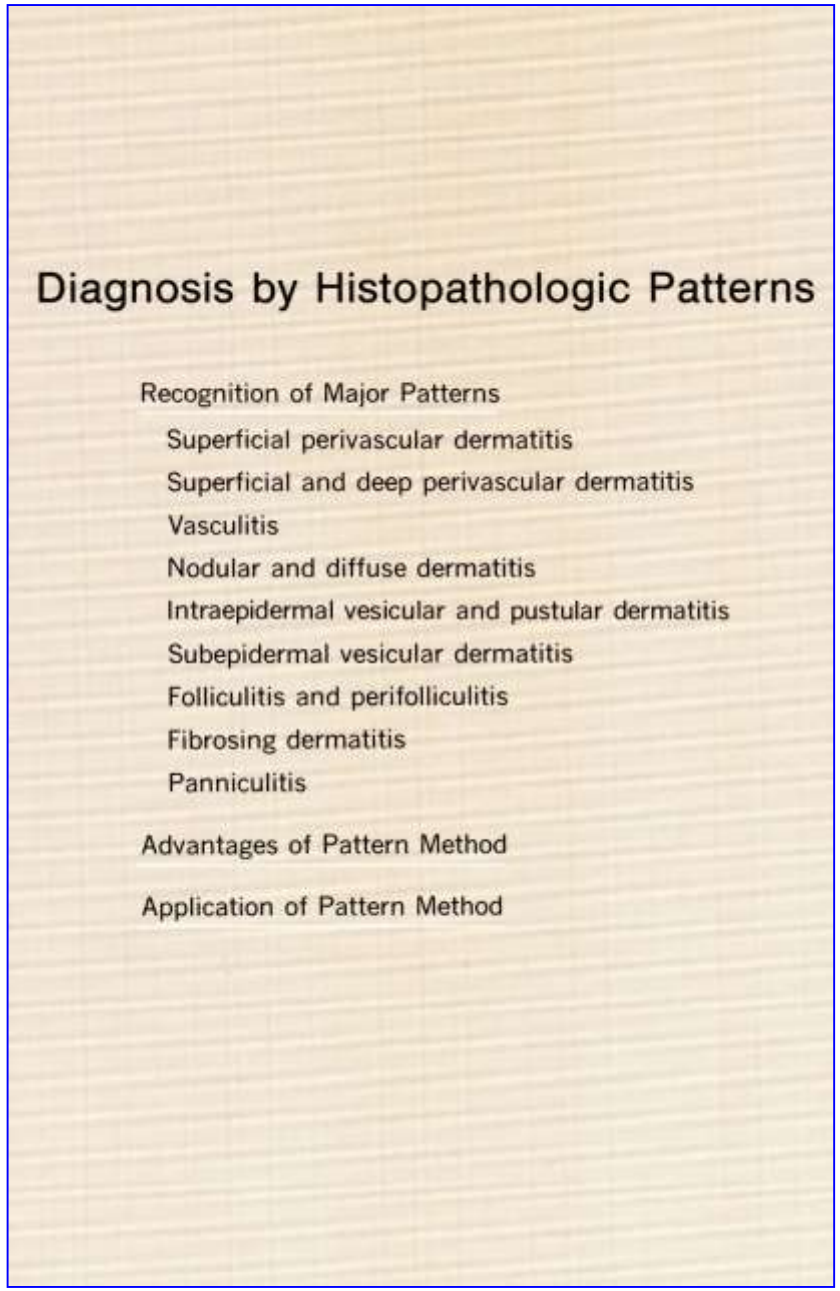
Dermal homogenization/sclerosis pattern

Vesiculobullous pattern

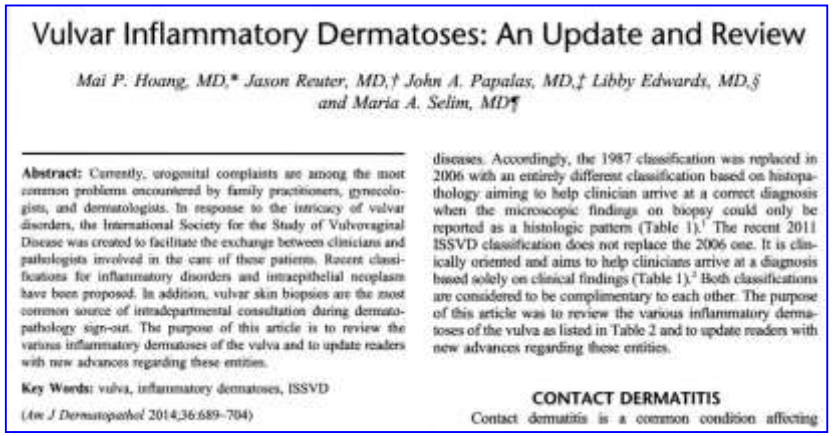
Acantholytic pattern

Granulomatous pattern

Vasculopathic pattern



The reasons why the International Society for the Study of Vulvovaginal Disease had to devise its own patterns – with overlapping categories such as *"vesiculobullous"* and *"acantholytic"* – are obscure.



Vulvar Inflammatory Dermatoses: An Update and Review

Mai P. Hoang, MD, Jason Reuter, MD,† John A. Papalas, MD,‡ Libby Edwards, MD,§ and Maria A. Selim, MD¶*

Abstract: Currently, urogenital complaints are among the most common problems encountered by family practitioners, gynecologists, and dermatologists. In response to the intricacy of vulvar disorders, the International Society for the Study of Vulvovaginal Disease was created to facilitate the exchange between clinicians and pathologists involved in the care of these patients. Recent classifications for inflammatory disorders and intraepithelial neoplasm have been proposed. In addition, vulvar skin biopsies are the most common source of intradepartmental consultation during dermatopathology sign-out. The purpose of this article is to review the various inflammatory dermatoses of the vulva and to update readers with new advances regarding these entities.

Key Words: vulva, inflammatory dermatoses, ISSVD

(*Am J Dermatopathol* 2014;36:689–704)

diseases. Accordingly, the 1987 classification was replaced in 2006 with an entirely different classification based on histopathology aiming to help clinician arrive at a correct diagnosis when the microscopic findings on biopsy could only be reported as a histologic pattern (Table 1).[1] The recent 2011 ISSVD classification does not replace the 2006 one. It is clinically oriented and aims to help clinicians arrive at a diagnosis based solely on clinical findings (Table 1).[2] Both classifications are considered to be complimentary to each other. The purpose of this article was to review the various inflammatory dermatoses of the vulva as listed in Table 2 and to update readers with new advances regarding these entities.

CONTACT DERMATITIS

Contact dermatitis is a common condition affecting

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TABLE 2. Outline of Review

Spongiotic pattern
- Contact dermatitis

Acanthotic pattern
- Psoriasis
- Amicrobial pustulosis of the folds
- Reiter syndrome

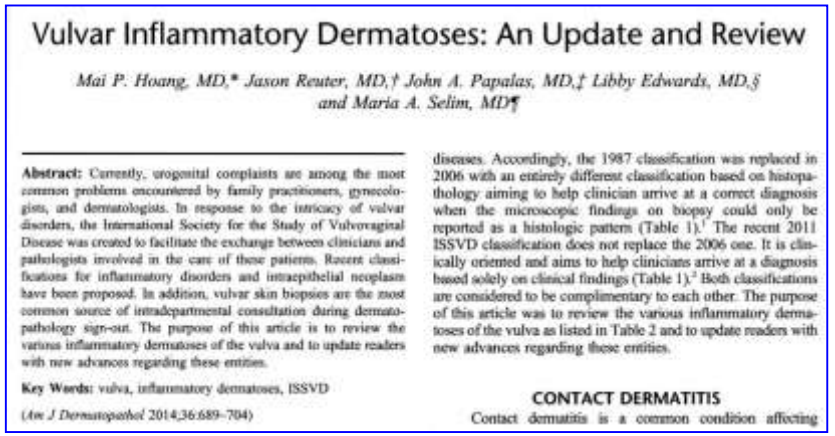
Lichenoid pattern
- Lichen sclerosus
- Lichen planus

Acantholytic pattern
- Papular genitocrural acantholysis
- Hailey–Hailey disease
- Darier disease
- Epidermolytic hyperkeratosis of the vulva
- Pemphigus vulgaris and pemphigus erythematosus
- Bullous pemphigoid and cicatricial pemphigoid
- Linear IgA disease

Granulomatous pattern
- Metastatic Crohn disease to the vulva

Vasculopathic pattern
- Behcet disease
- Plasma cell vulvitis (Zoon vulvitis)

Three years ago, an *"update and review"* of vulvar inflammatory dermatoses was published in the American Journal of Dermatopathology that was based on the *"2006 ISSDV classification of vulvar dermatoses"*. Starting from those *"pathologic subsets"*, various diseases were discussed, but what a hodgepodge! Under the designation of "acantholytic pattern", diseases such as Hailey-Hailey's disease and Darier's disease are listed along with diseases that never show acantholysis, such as epidermolytic hyperkeratosis and bullous pemphigoid, and why "Zoon vulvitis" is said to show a "vasculopathic pattern" is incomprehensible.



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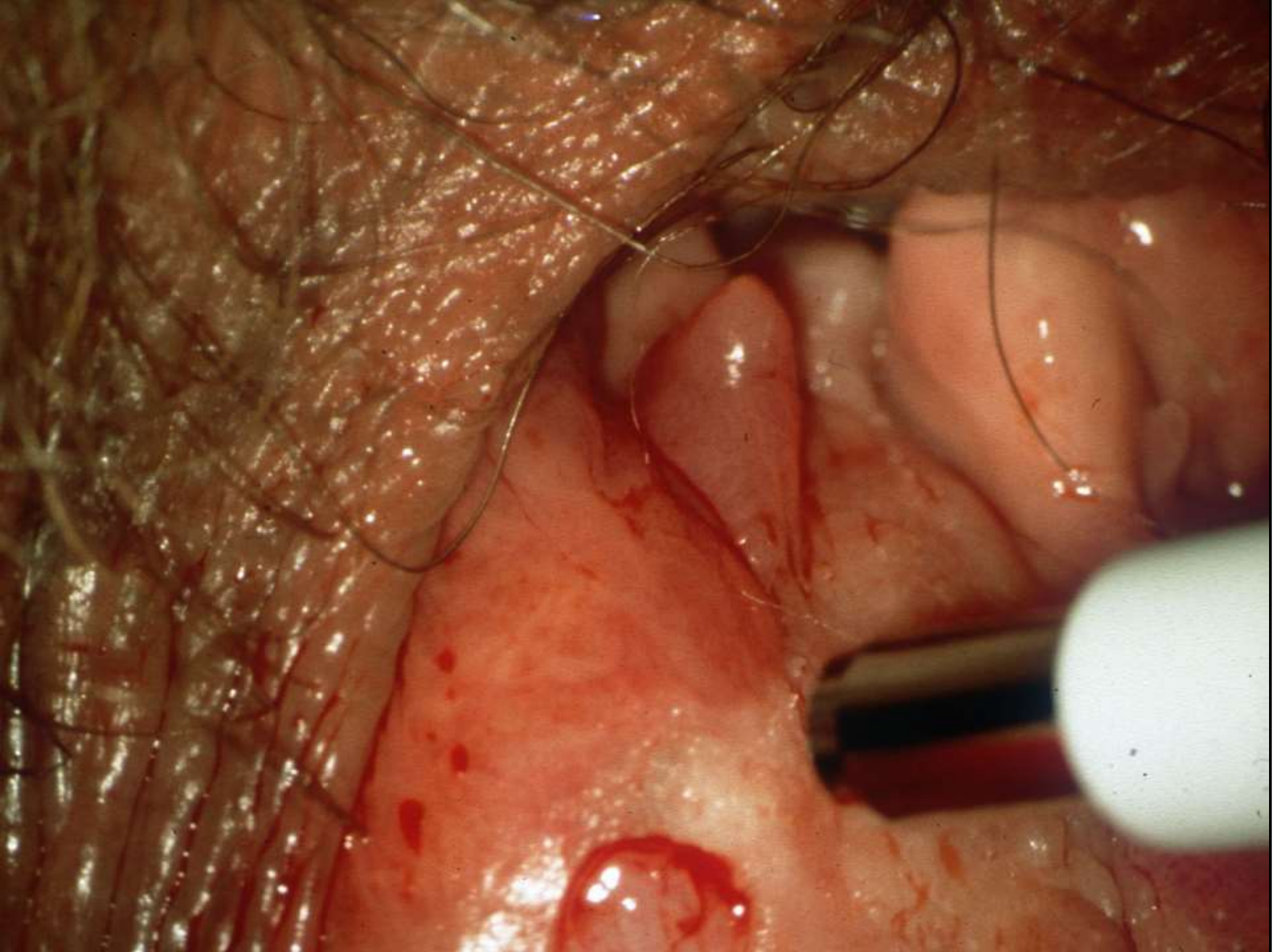
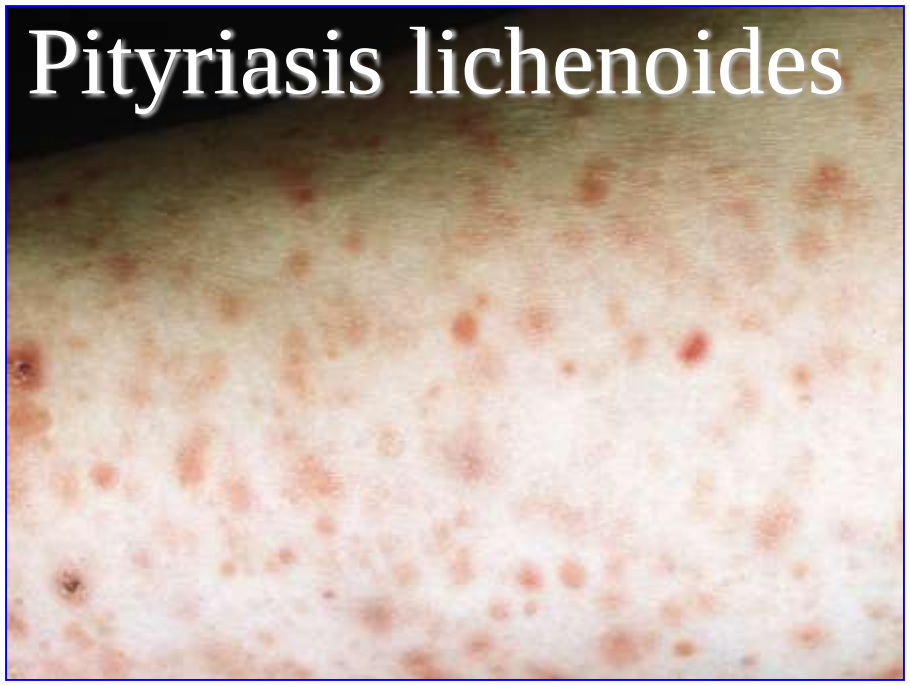
Granulomatous pattern
- Metastatic Crohn disease to the vulva

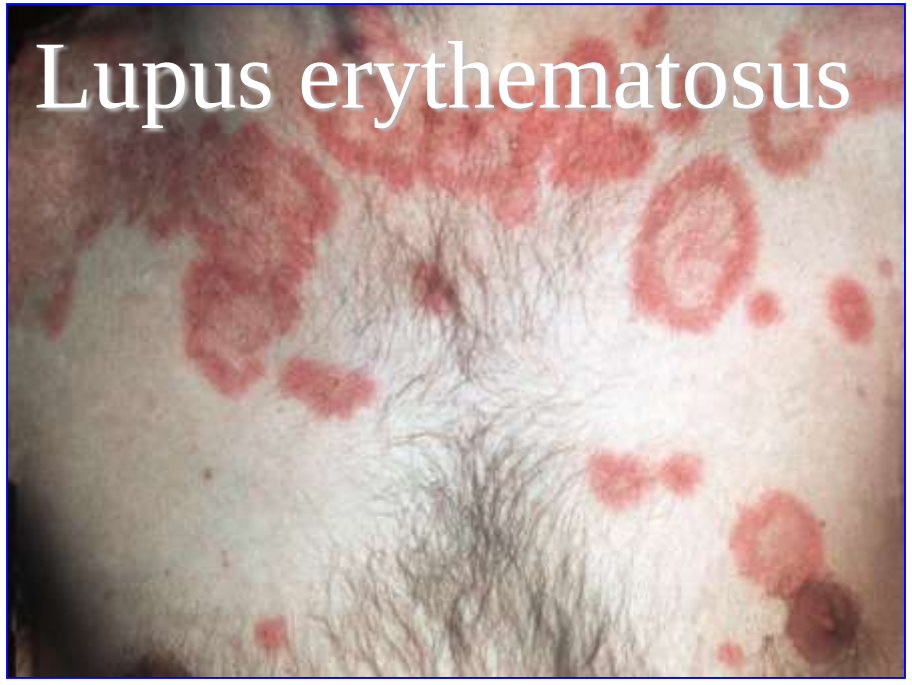
Vasculopathic pattern
- Behcet disease
- Plasma cell vulvitis (Zoon vulvitis)

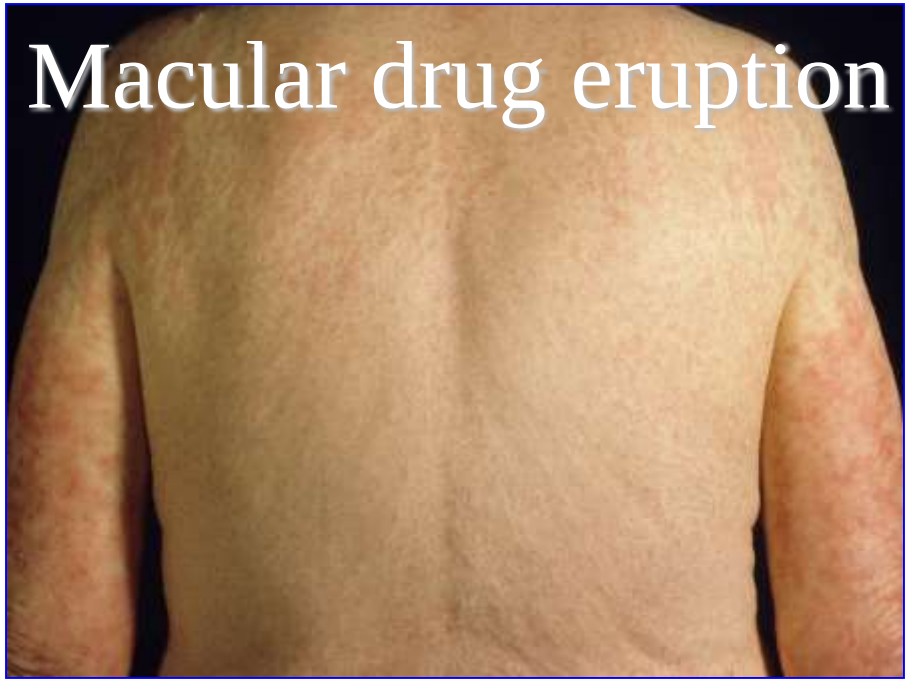
Moreover, common diseases that are important in the differential diagnosis are not mentioned at all, e.g., fixed drug eruption and genital herpes. It is a shame that this crap got published in the American Journal of Dermatopathology. The classifications of vulvar dermatoses advanced by gynecologists have been created for reasons of simplicity but, in reality, are simplifying and, thereby, complicate matters.



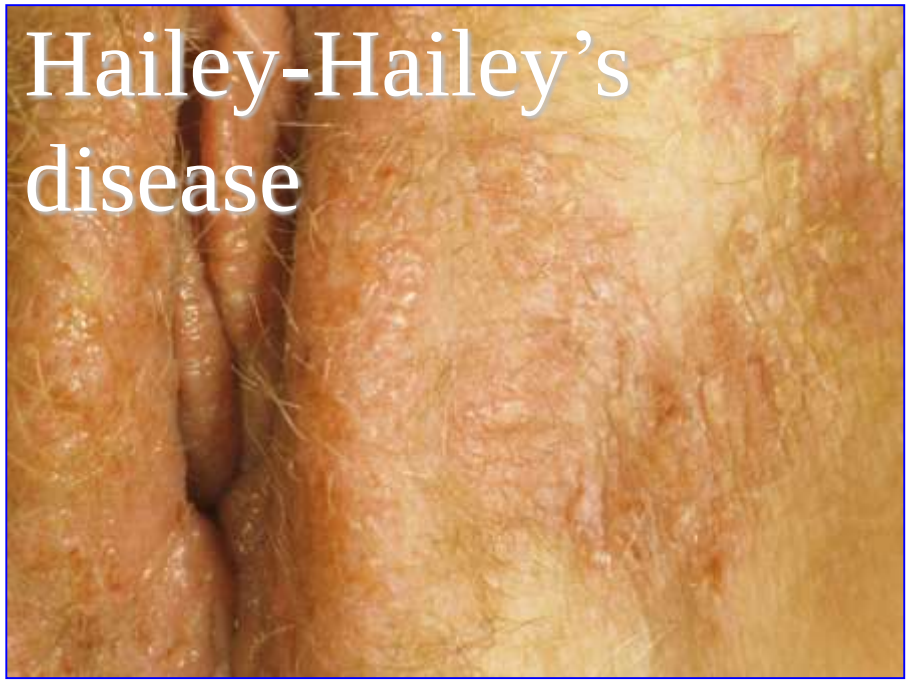
The vulva is skin and can be affected by any cutaneous disease.

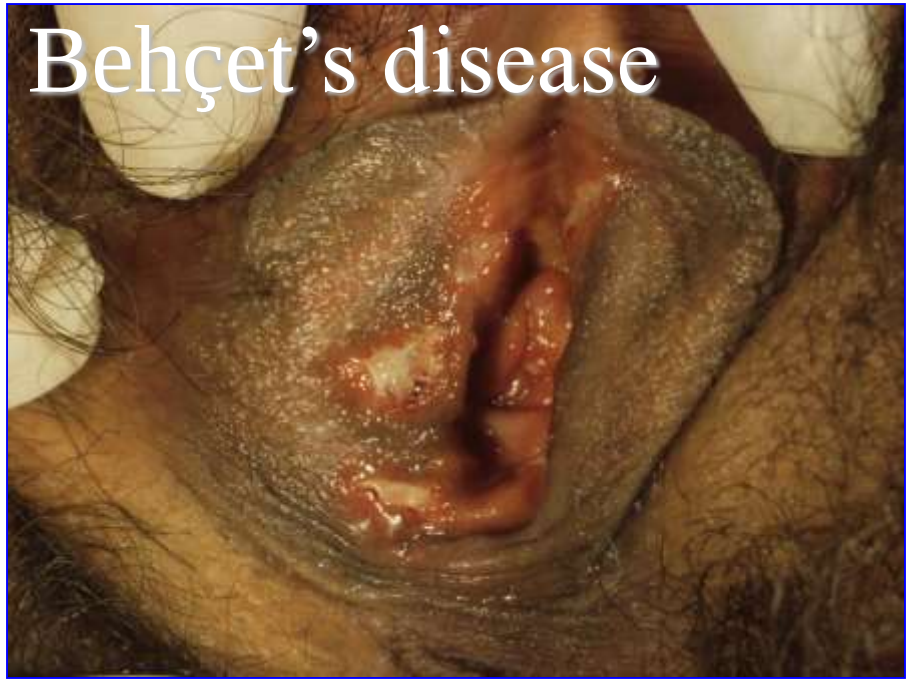




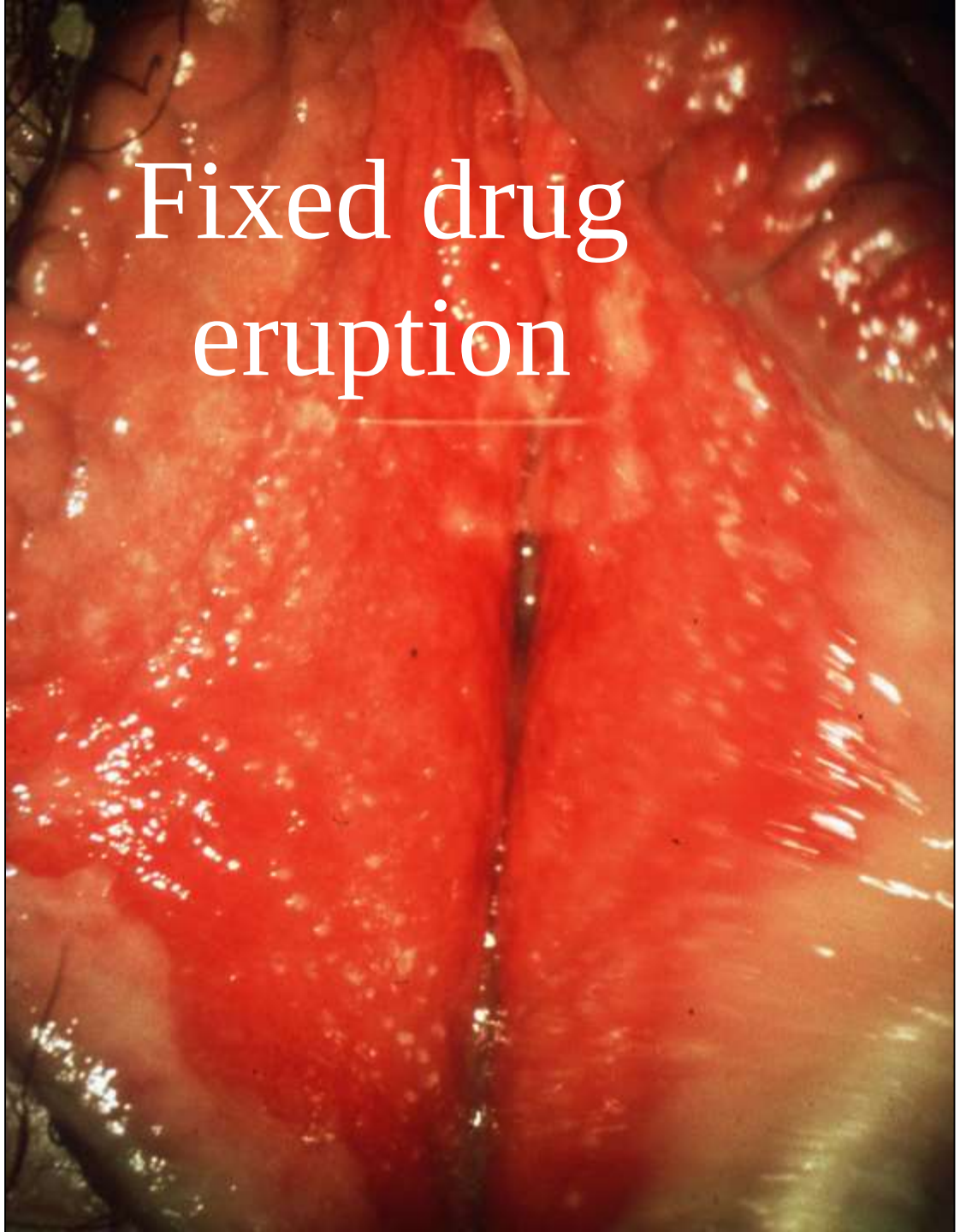


If some diseases are practically never encountered there by histopathologists, this is caused chiefly by the practices of biopsy. Nobody takes a biopsy from the vulva if there are widespead lesions on the rest of the body, as in pityriasis rosea, pityriasis lichenoides, lupus erythematosus, and macular drug eruption.

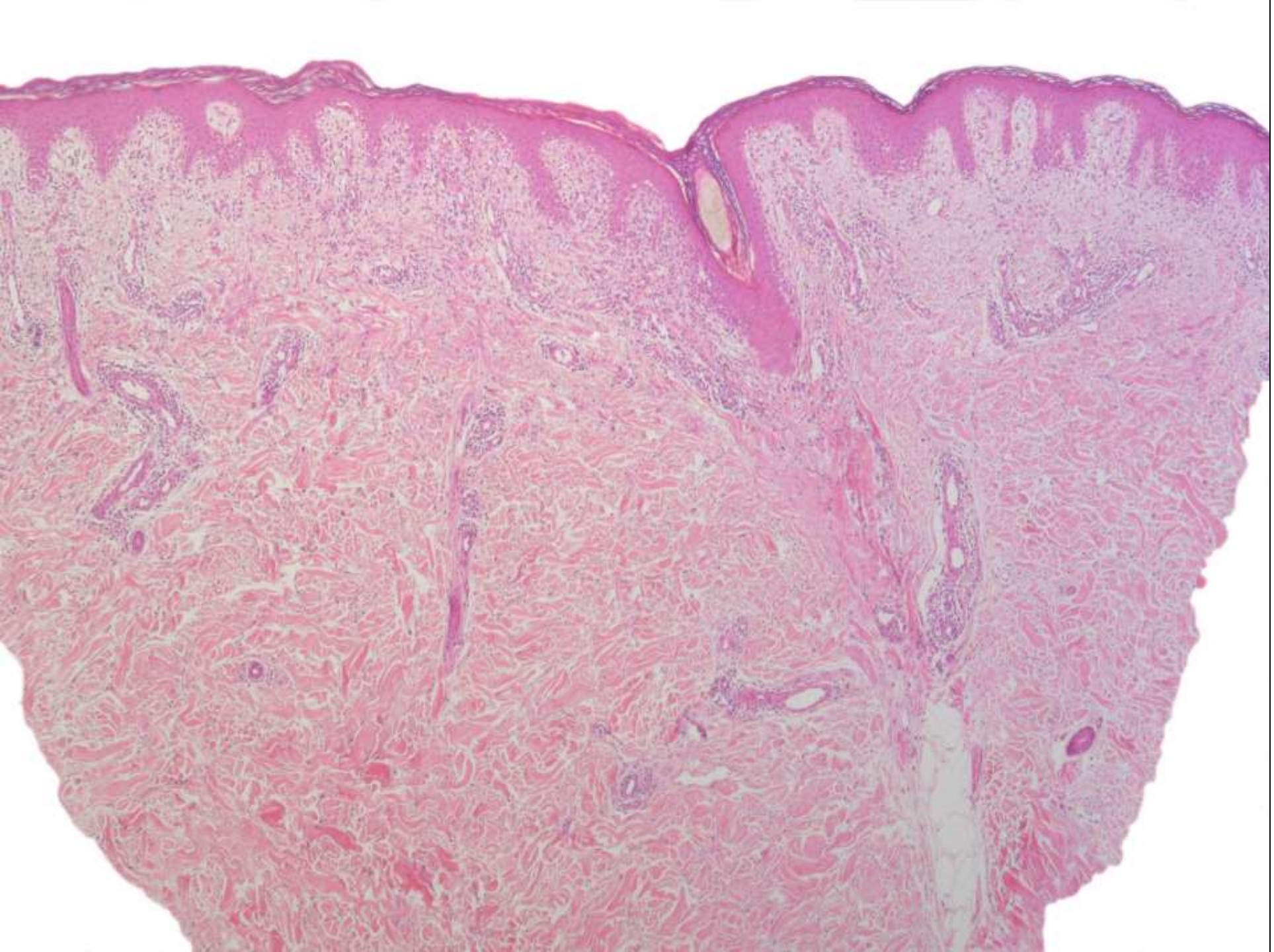




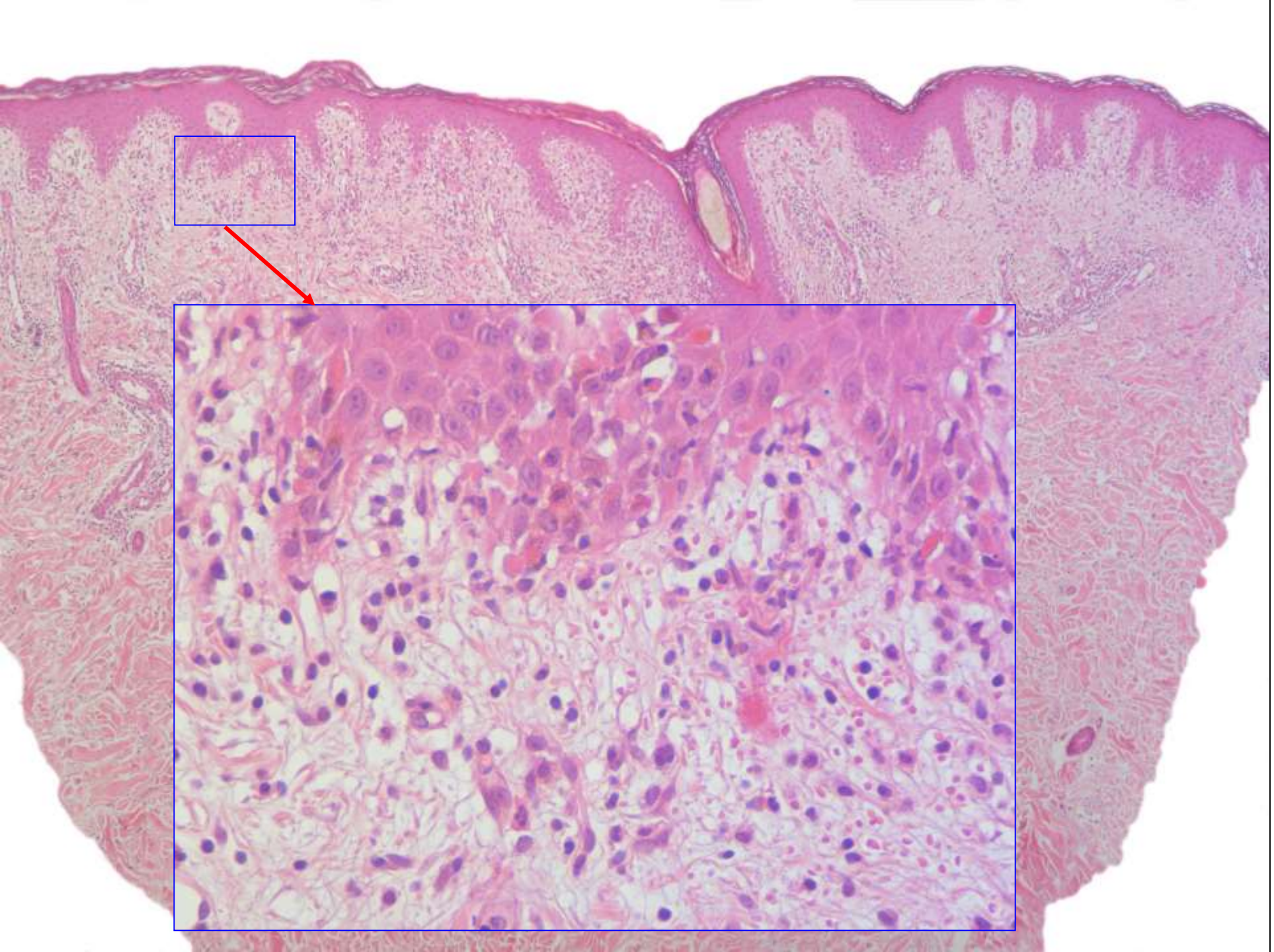
On the other hand, most cutaneous diseases have sites of predilection, and the vulva in among them. It may be affected chiefly by diseases such as fixed drug eruption, Hailey-Hailey's disease, Behçets disease, and pemphigus vegetans. Let's briefly look at some examples.



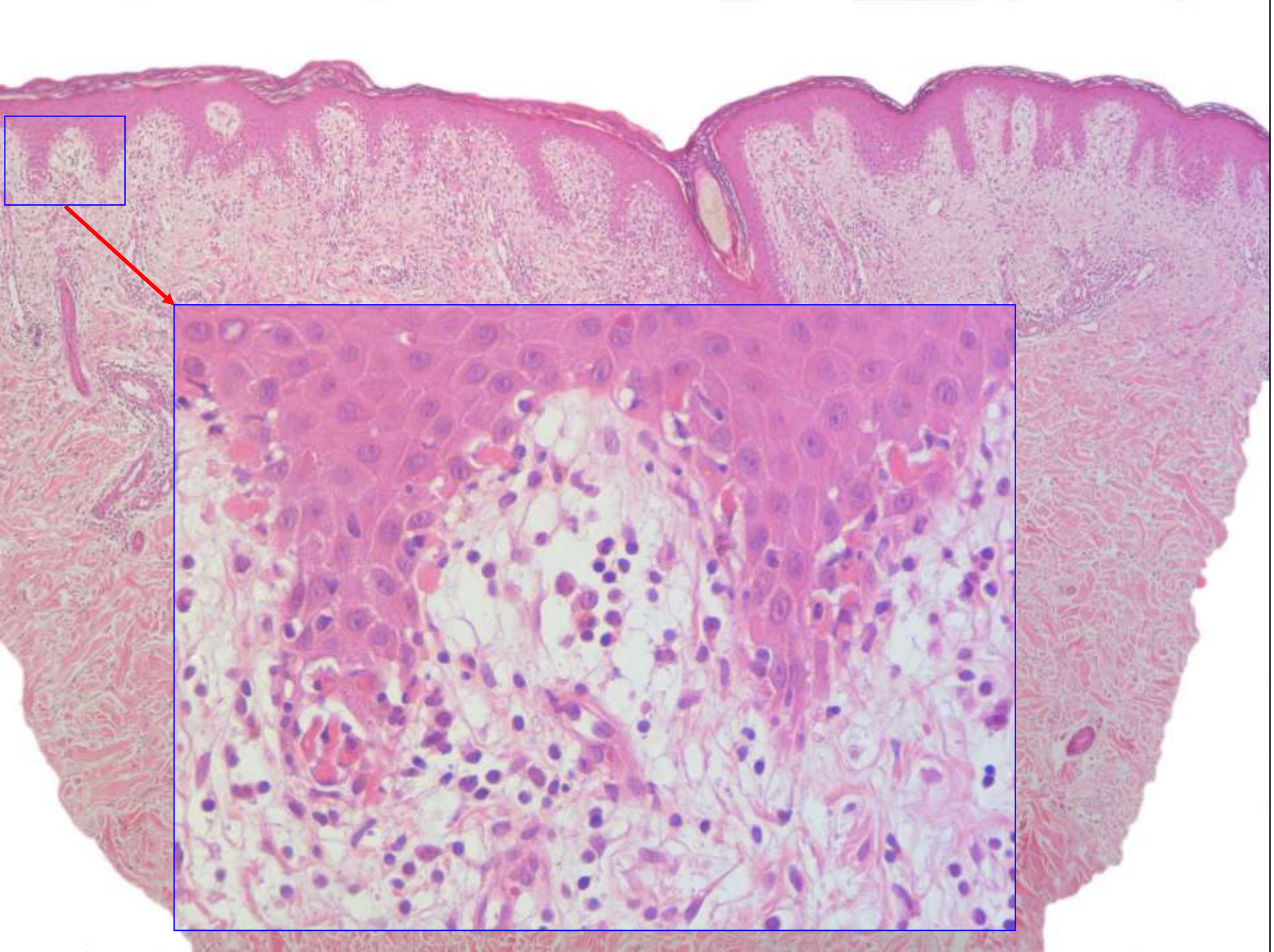
Fixed drug eruption presents itself clinically as a relatively sharply circumscribed erythema.



Histopathologically, lesions of the vulva show the same features as on other sites, namely, a superficial and often deep vacuolar interface dermatitis.

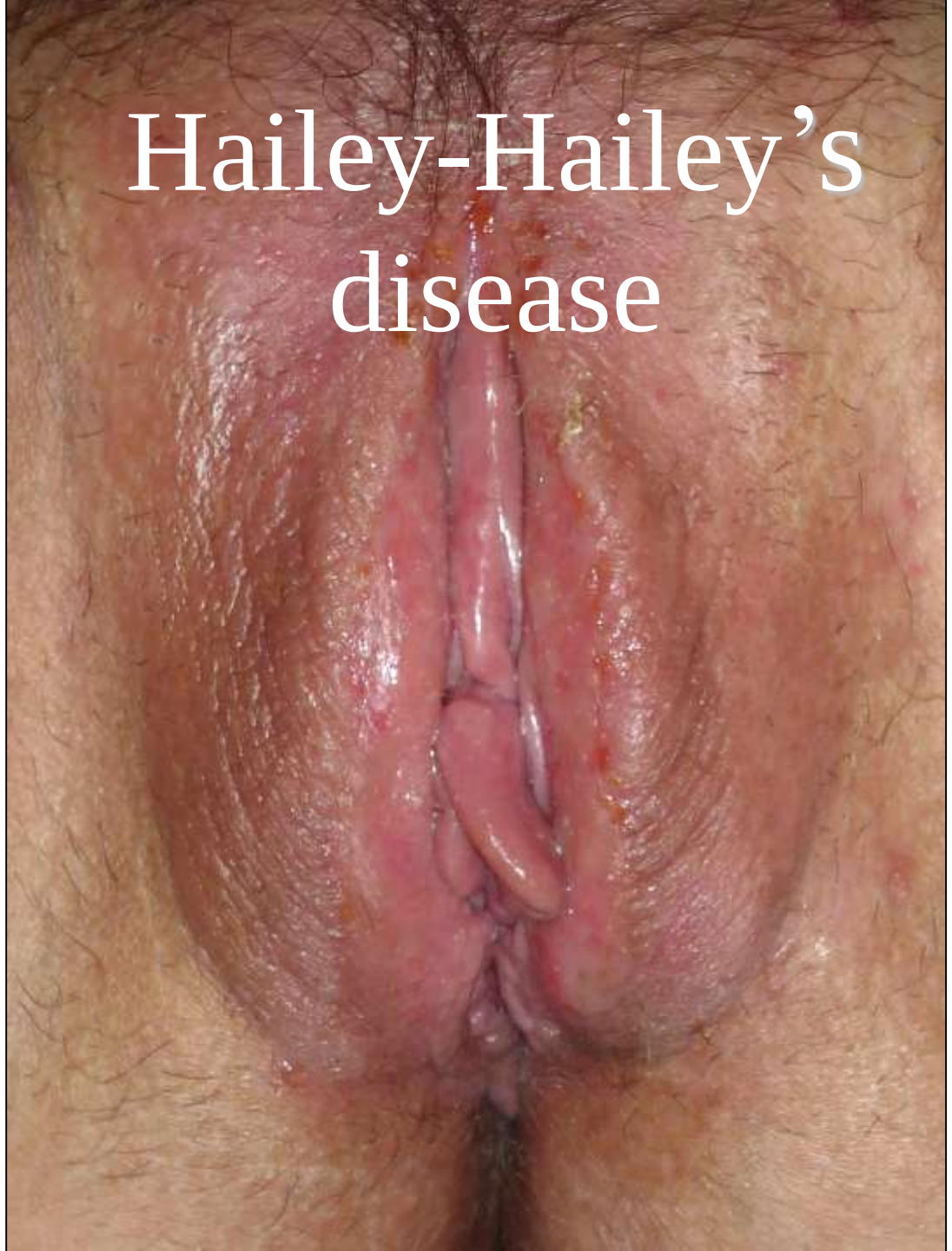


There is prominent vacuolar alteration at the junction in concert with many necrotic keratocytes. The latter are chiefly found at the junction but also above it.

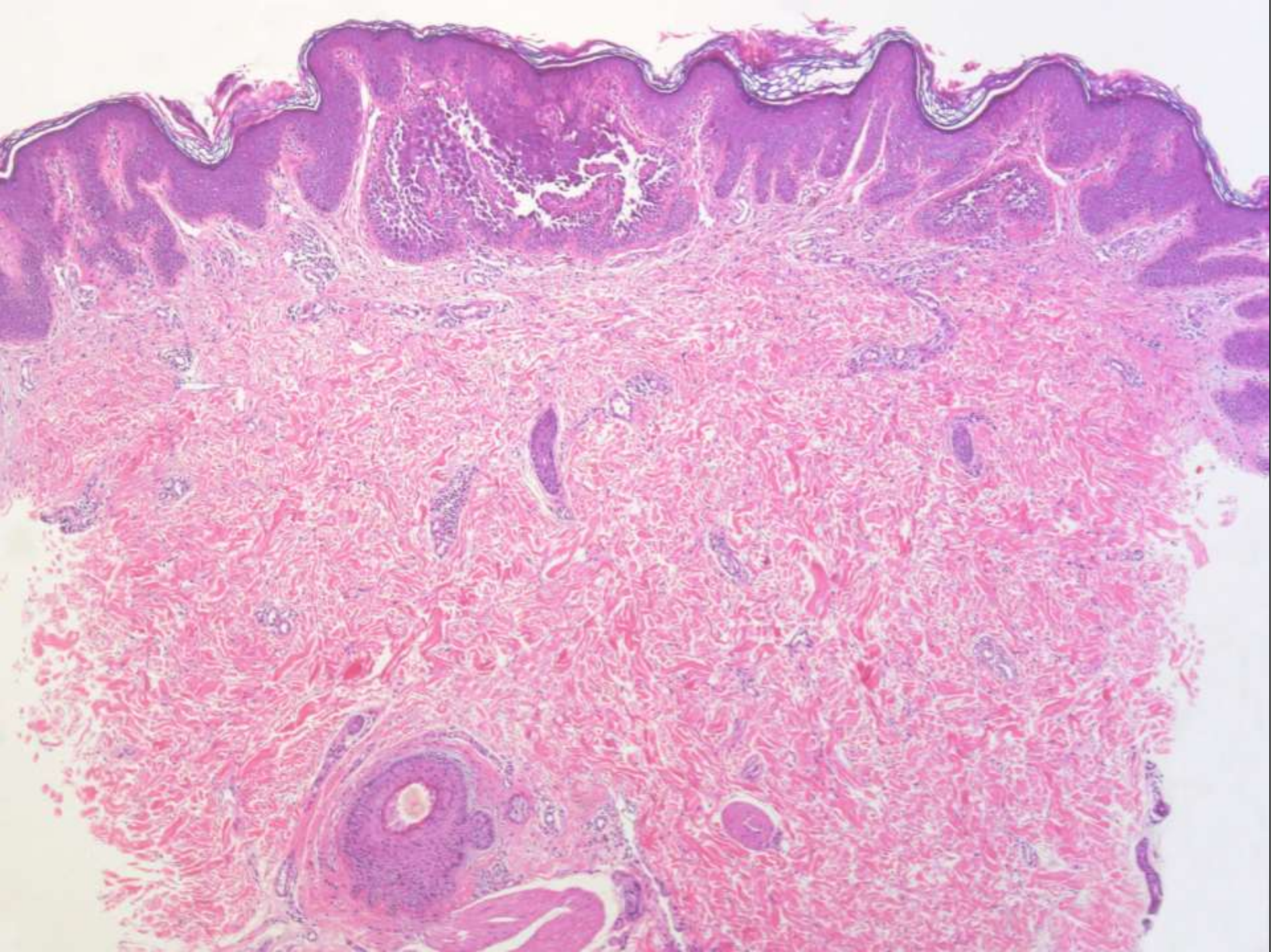


Necrotic keratocytes are found in many diseases but not in those numbers. Especially clusters of necrotic keratocytes at the junction indicate a drug eruption.

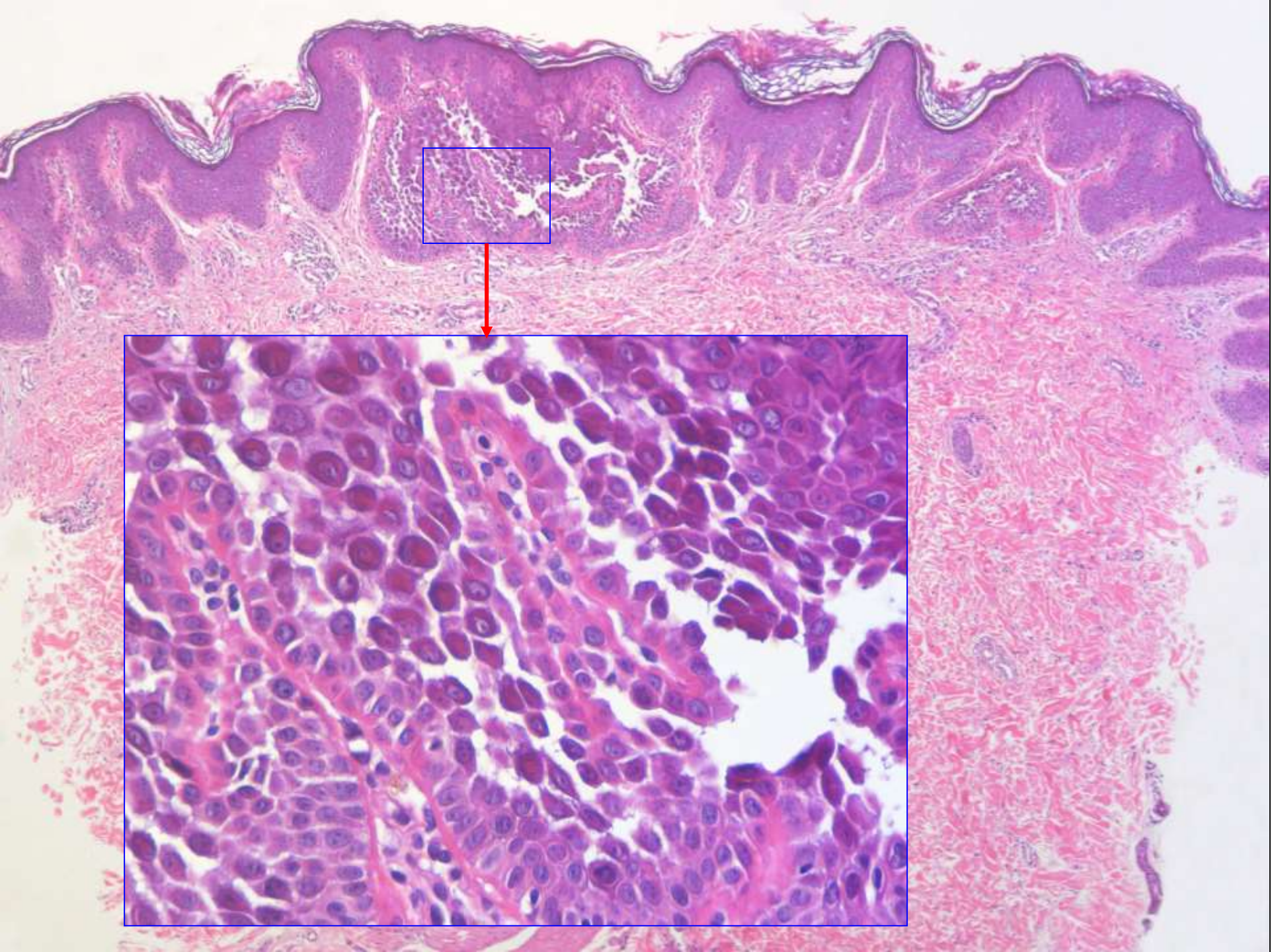
Hailey-Hailey’s disease



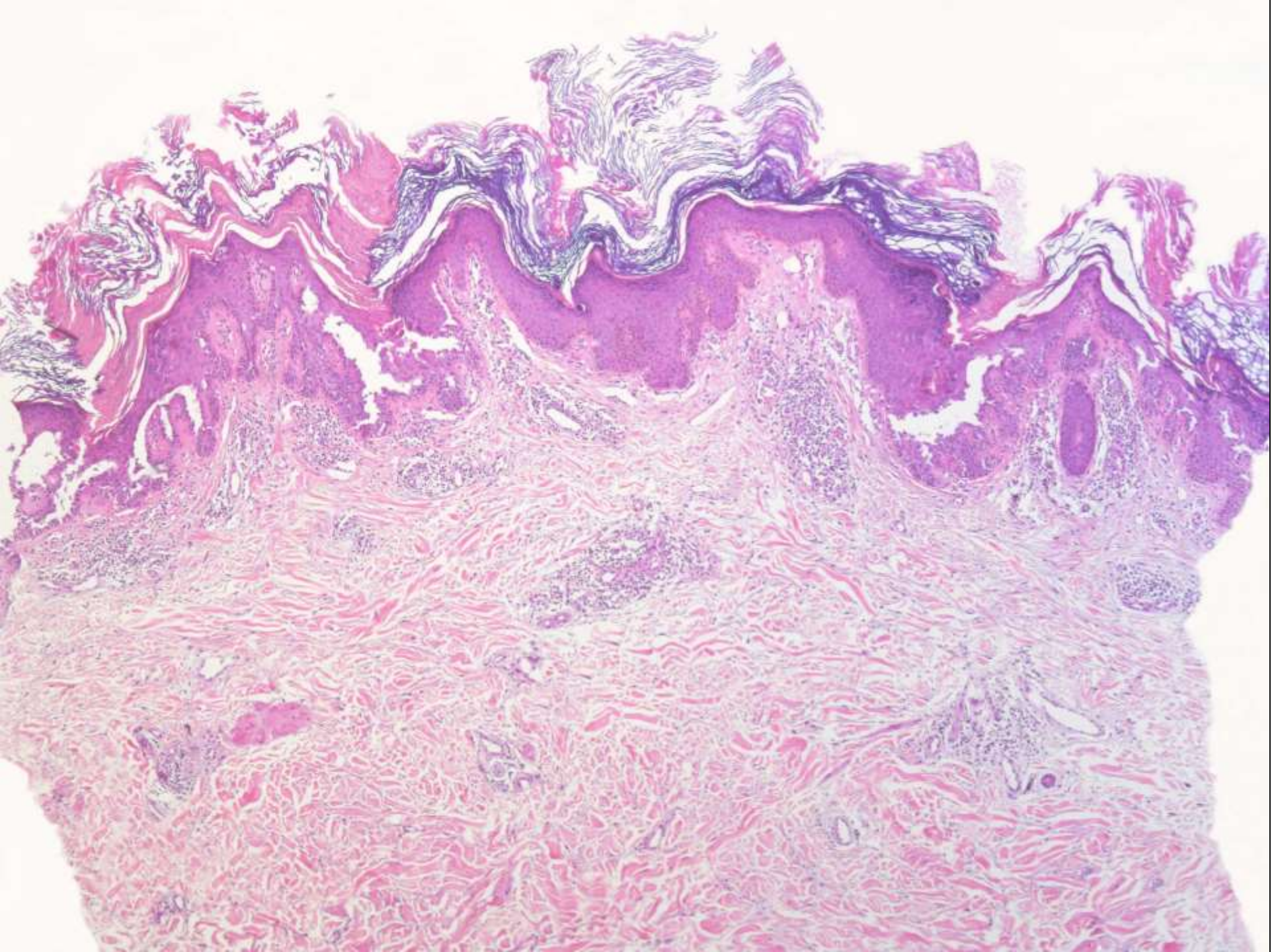
Hailey-Hailey’s disease affects chiefly the large folds and is common on the groin, but may be limited to the vulva.



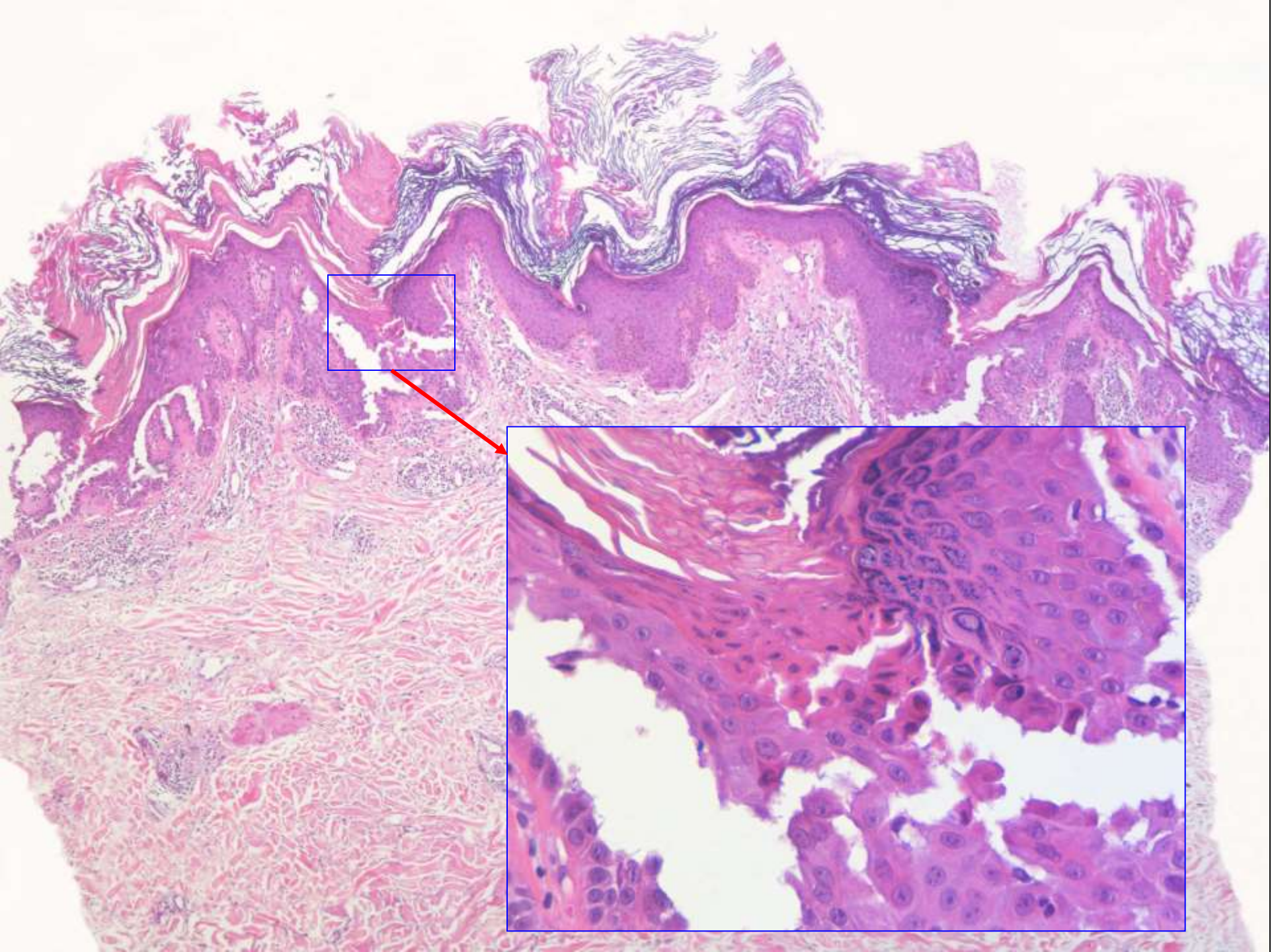
Its cause is a mutation resulting in malformation of desmosomes and, as a consequence, acantholysis affecting the entire thickness of the epidermis.



Because the actin filament system with adherens junctions remain intact, keratocytes often to not detach from one another completely, leading to a picture that Henry Haber once compared to a “delapidated brick wall”. Of course, some attachment of acantholytic cells to one another is also seen in other diseases at the beginning of acantholysis, but not across a broad front of the entire thickness of the epidermis. This picture is unique for Hailey-Hailey’s disease.



Similar changes can be caused by Darier’s disease which may also affect the vulva. Acantholysis in Darier’s disease is mostly suprabasilar but may be seen in all reaches of the epidermis. It is usually limited to discrete foci and,



unlike Hailey-Hailey's disease, it is associated with dyskeratosis, sometimes leading to columns of parakeratosis in a basket-woven cornified layer.

Pemphigus vegetans

Yet another acantholytic disease affecting the vulva preferentially is pemphigus vegetans. Being caused by antibodies against desmoglein-3, it is considered to be a variant of pemphigus vulgaris,

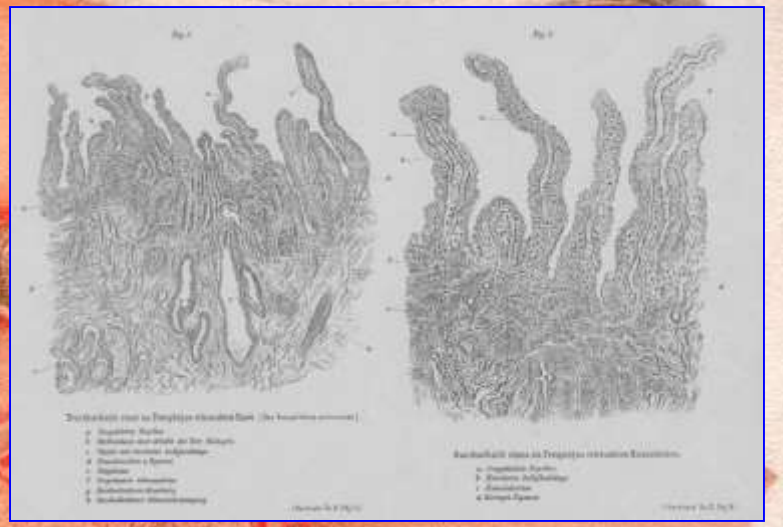
Beitrag zur Kenntniss des Pemphigus

Von Prof. **Isidor Neumann** in Wien.

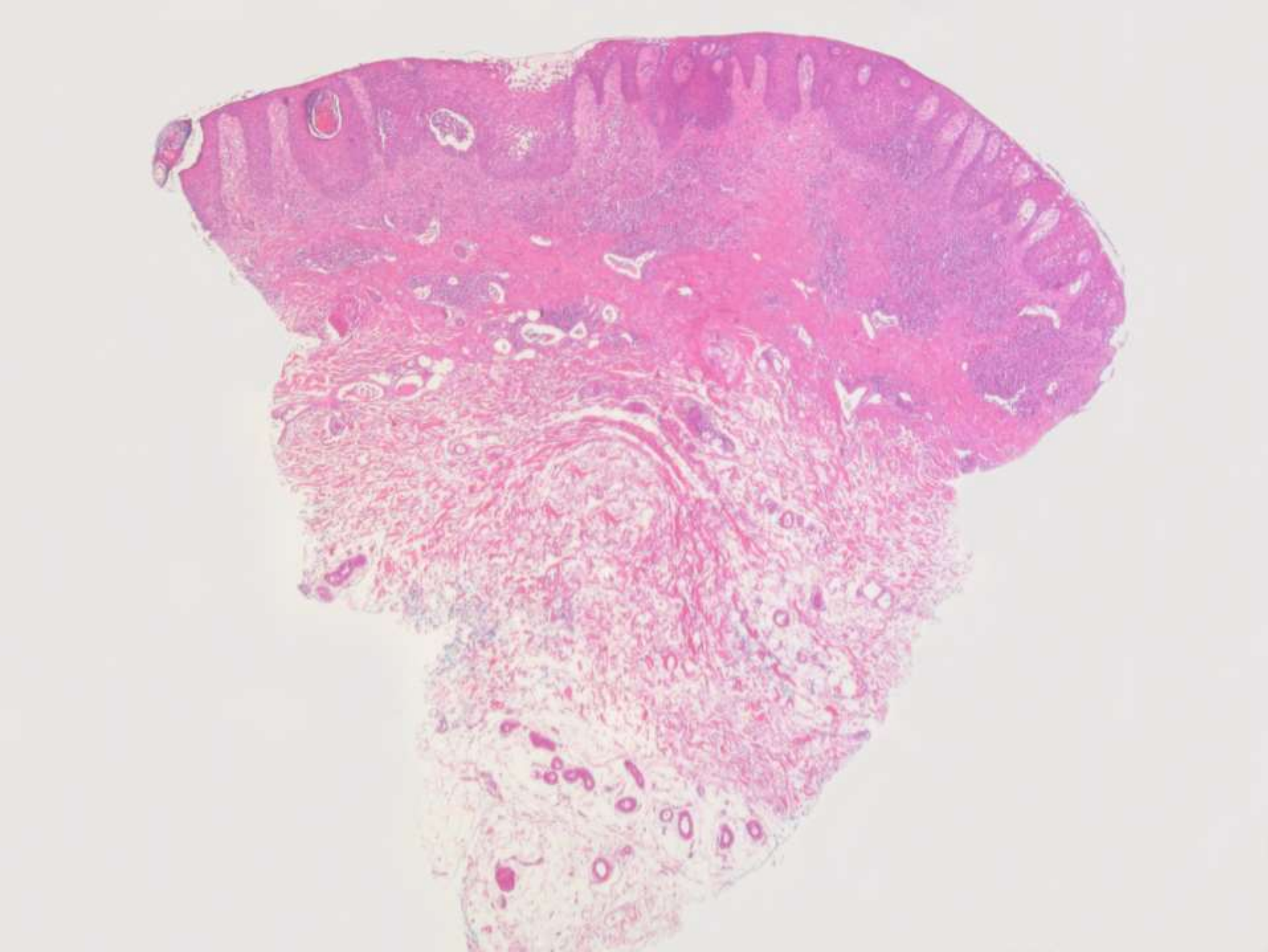
(Hierzu Tafel XIX.)

Es ist gewiss jedem Autor erwünscht, wenn er als Basis seiner Beobachtungen gleich eine grössere Reihe von Fällen anzuführen vermag. Es ist aber auch Pflicht, auf seltene Vorkommnisse aufmerksam zu machen, zumal dann, wenn weder eigene noch fremde Erfahrung über ähnliches Materiale verfügt. Von diesem Gesichtspunkte wolle man nachfolgende Mittheilungen beurtheilen, welche sowohl in ihrem klinischen Krankheitsbilde, gleich wie im mikroskopischen Befunde manches Neue enthalten:

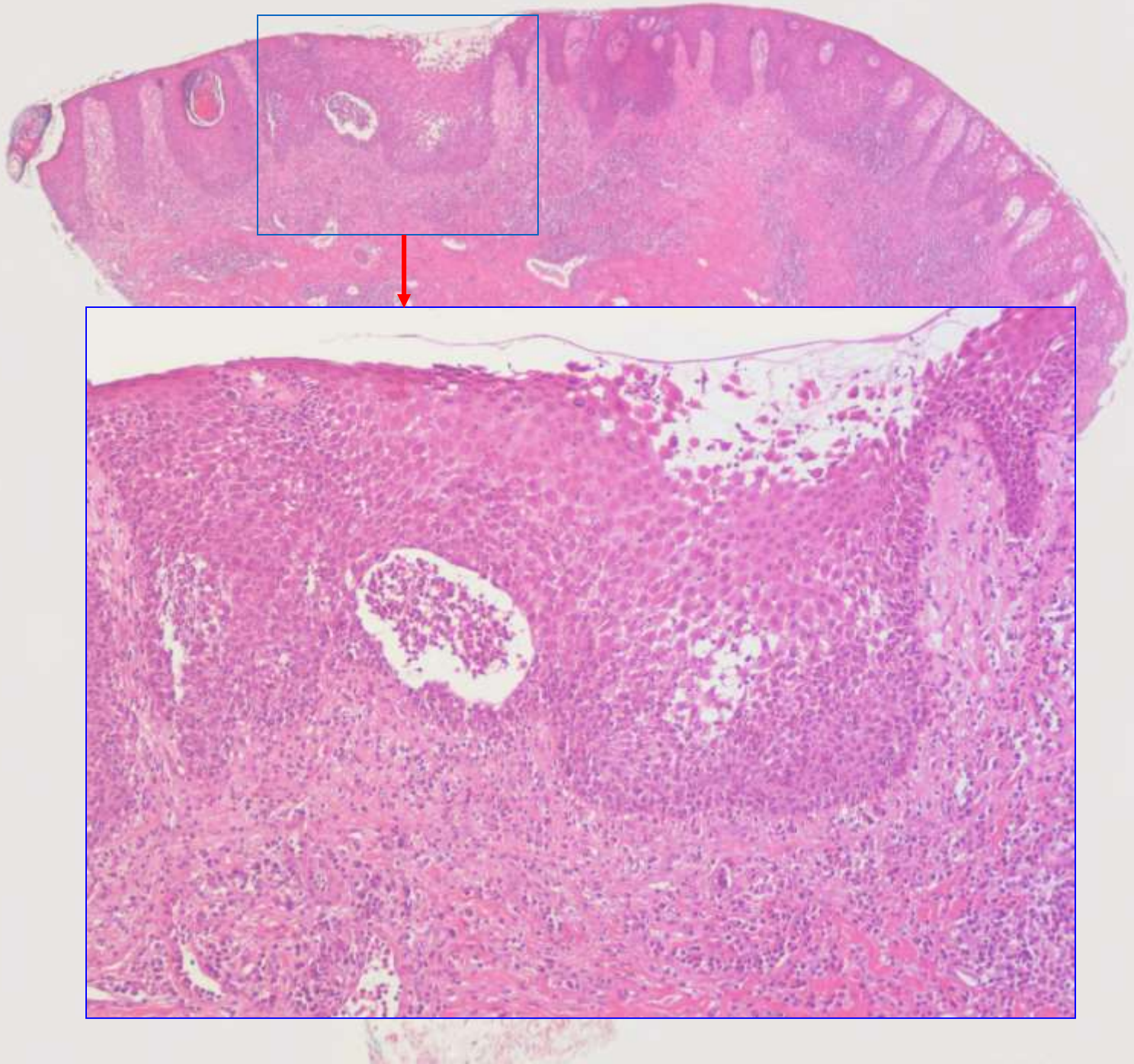
1876



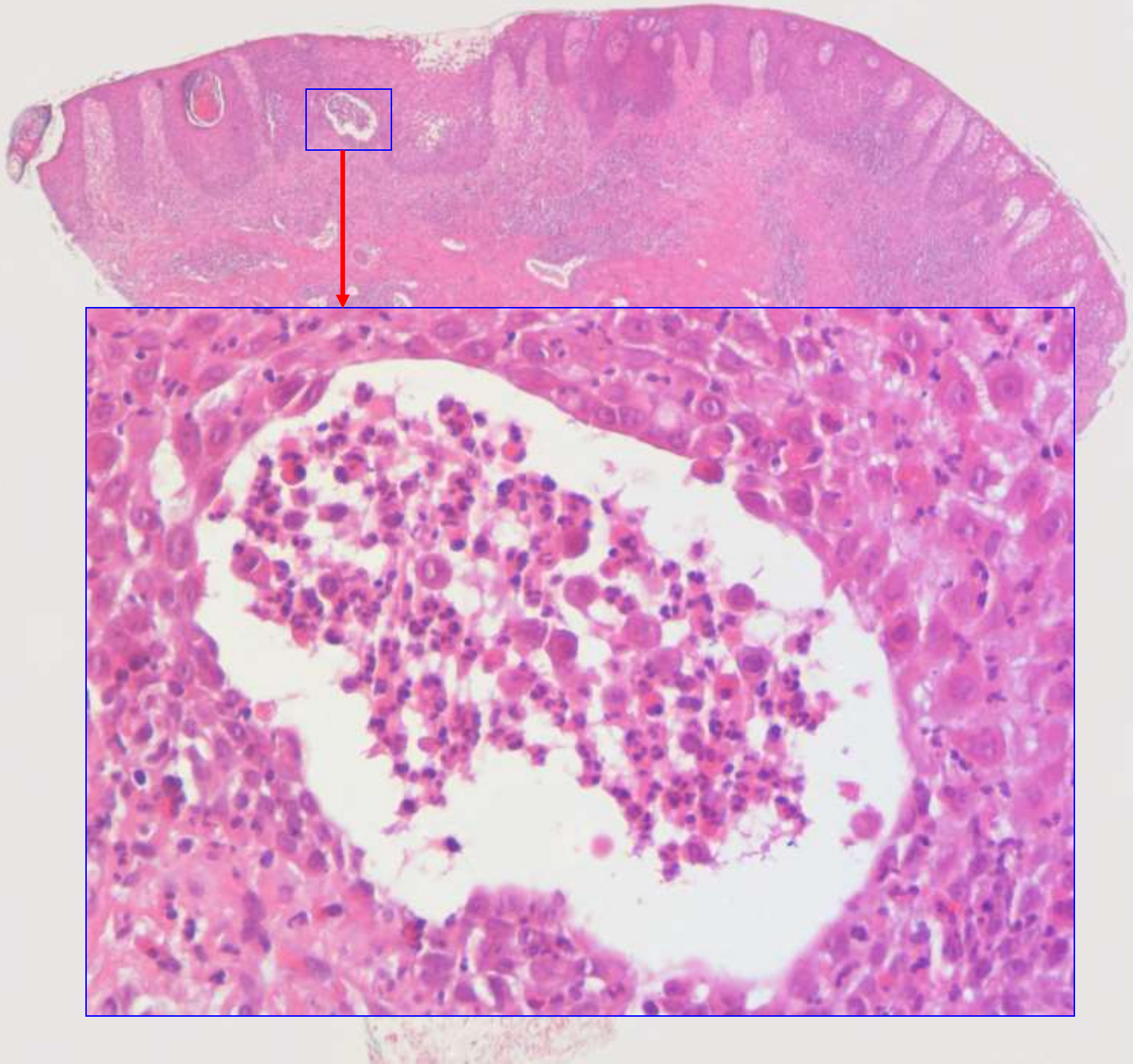
but differs from it by formation of “condylomatous excrescences,” as Isidor Neumann called them when he described the disease in 1876. Those excrescences seem to result chiefly from impaired healing of blisters in intertriginous areas because they are not seen in lesions from other areas of skin that may also be affected by the disease.



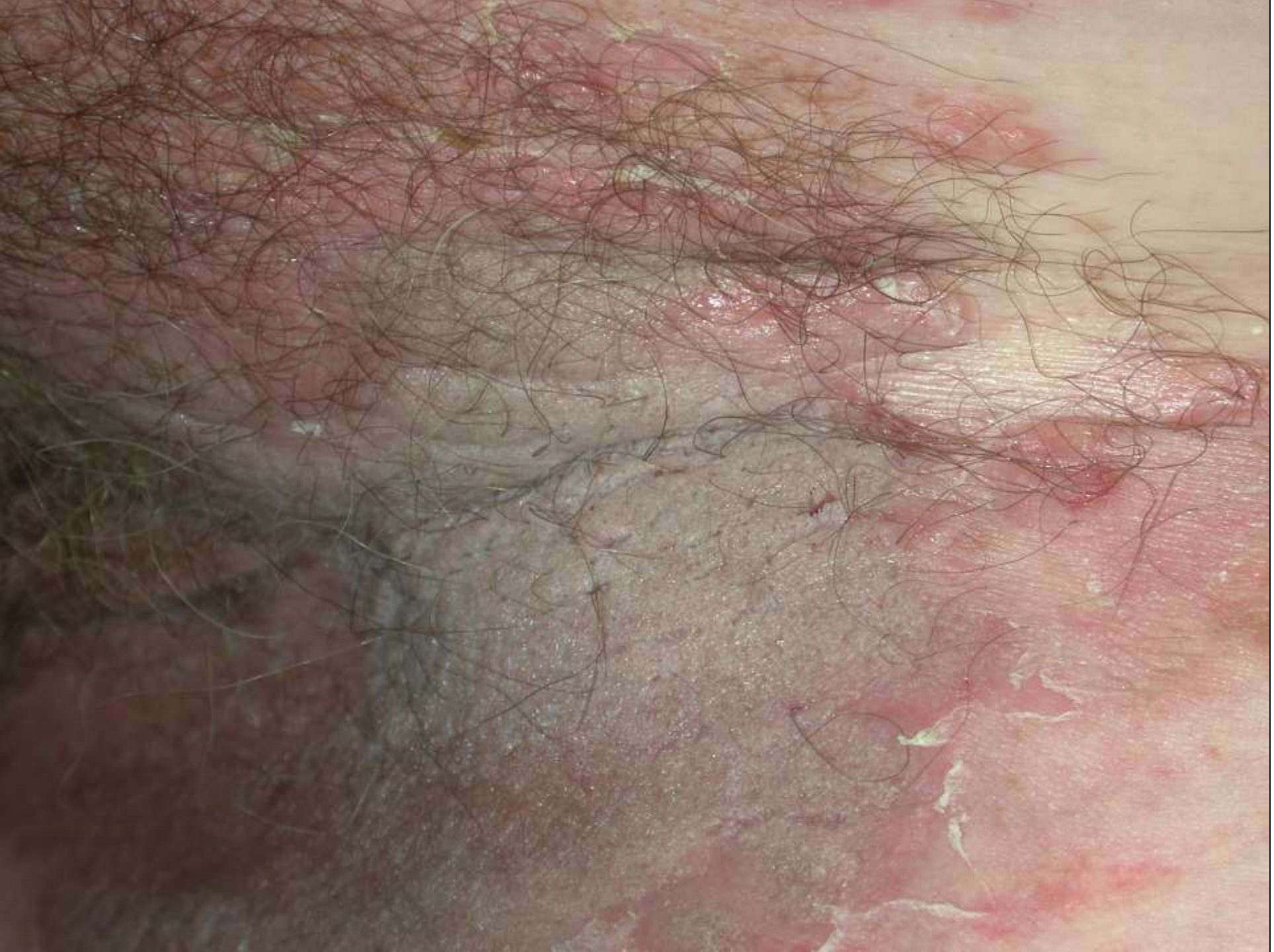
Nonetheless, they are not the only distinguishing feature between pemphigus vegetans and pemphigus vulgaris.



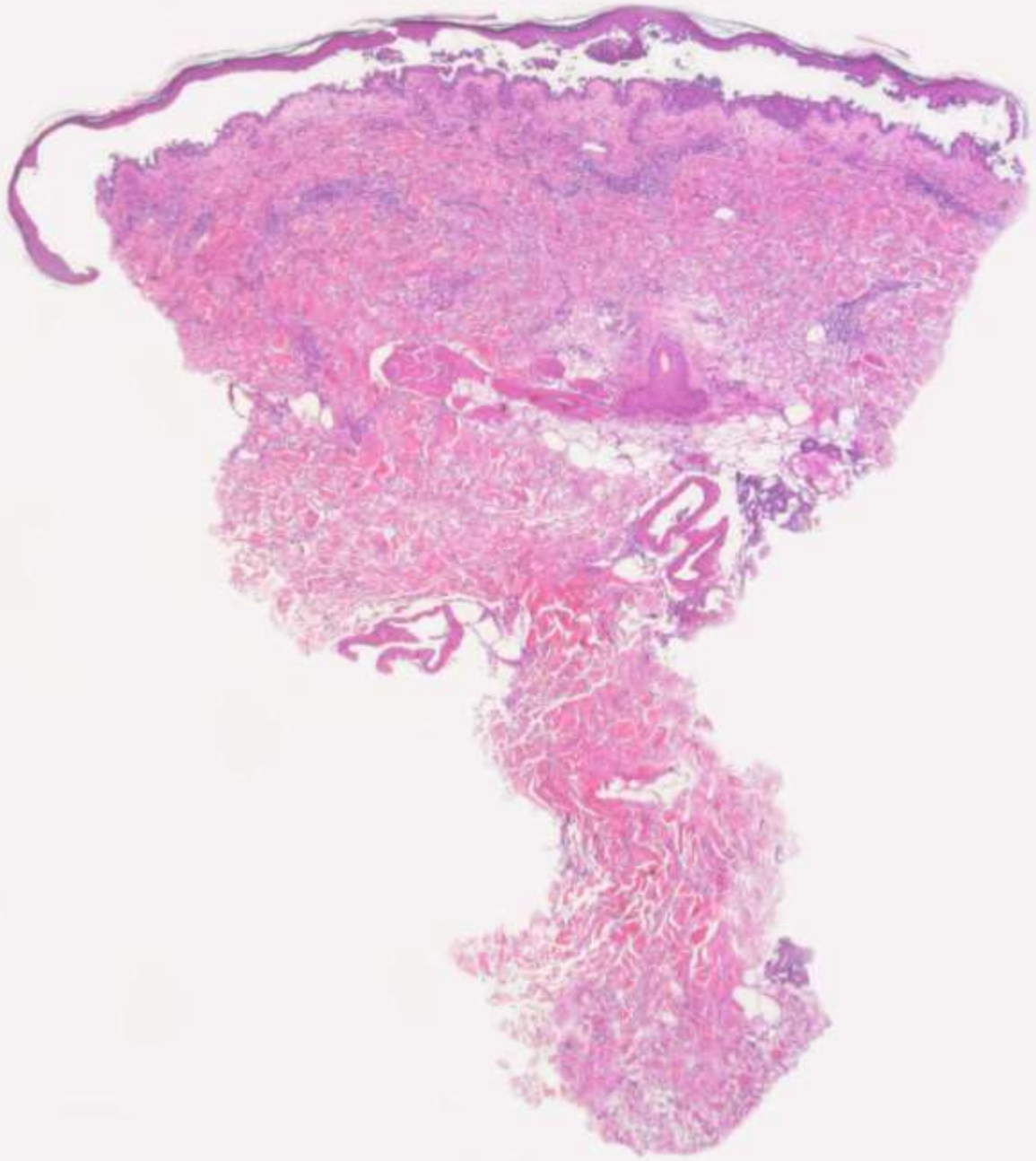
In pemphigus vegetans, acantholysis is often not limited to the suprabasal zone but may also affect the upper reaches of the epidermis.



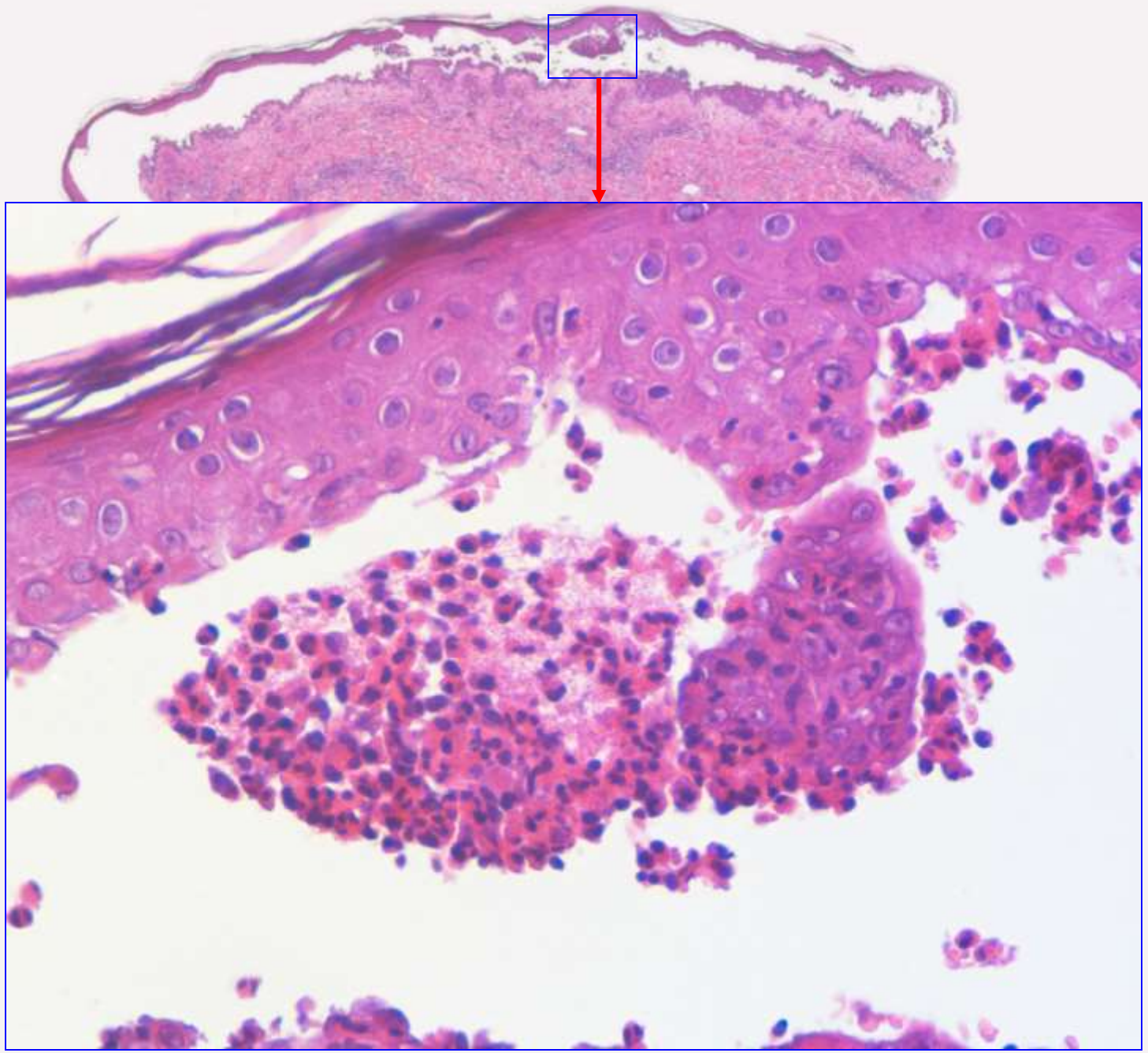
A common peculiar feature is intraepidermal abscesses of neutrophils and often myriad eosinophils.



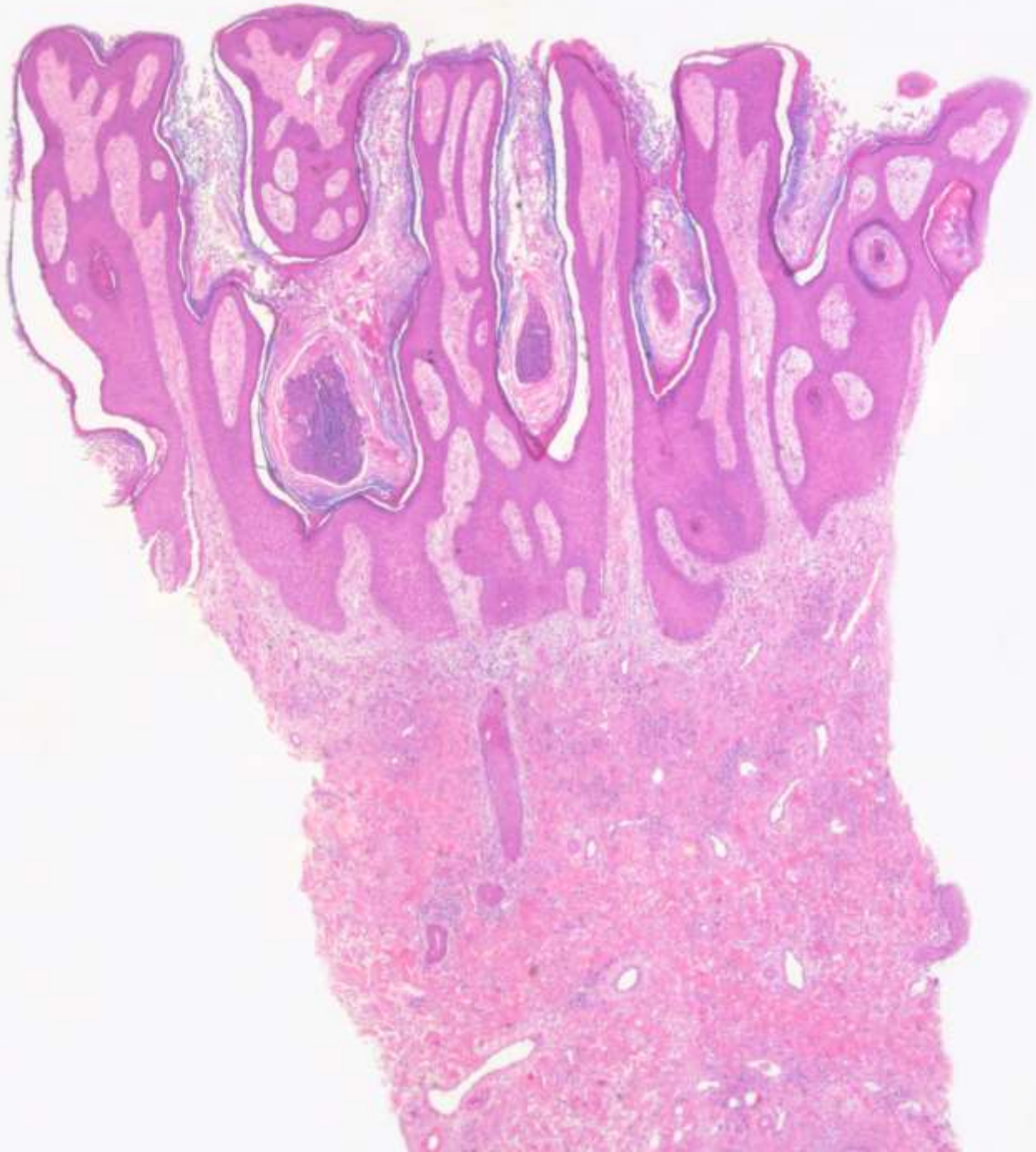
The histopathologic picture depends on where the biopsy is taken. If taken from the periphery of lesions,



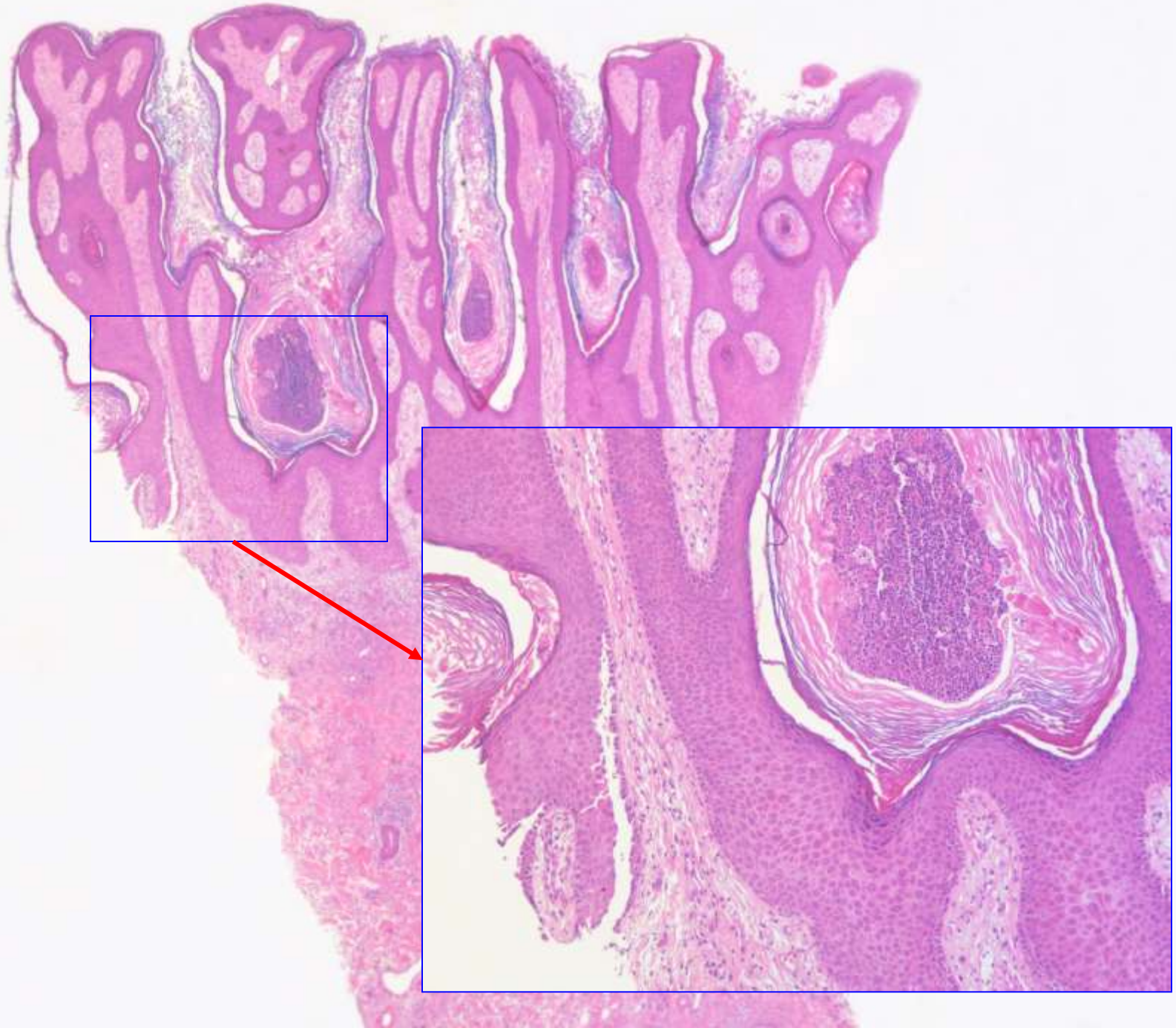
the presentation may be typical of pemphigus vulgaris with acantholysis above the basal zone,



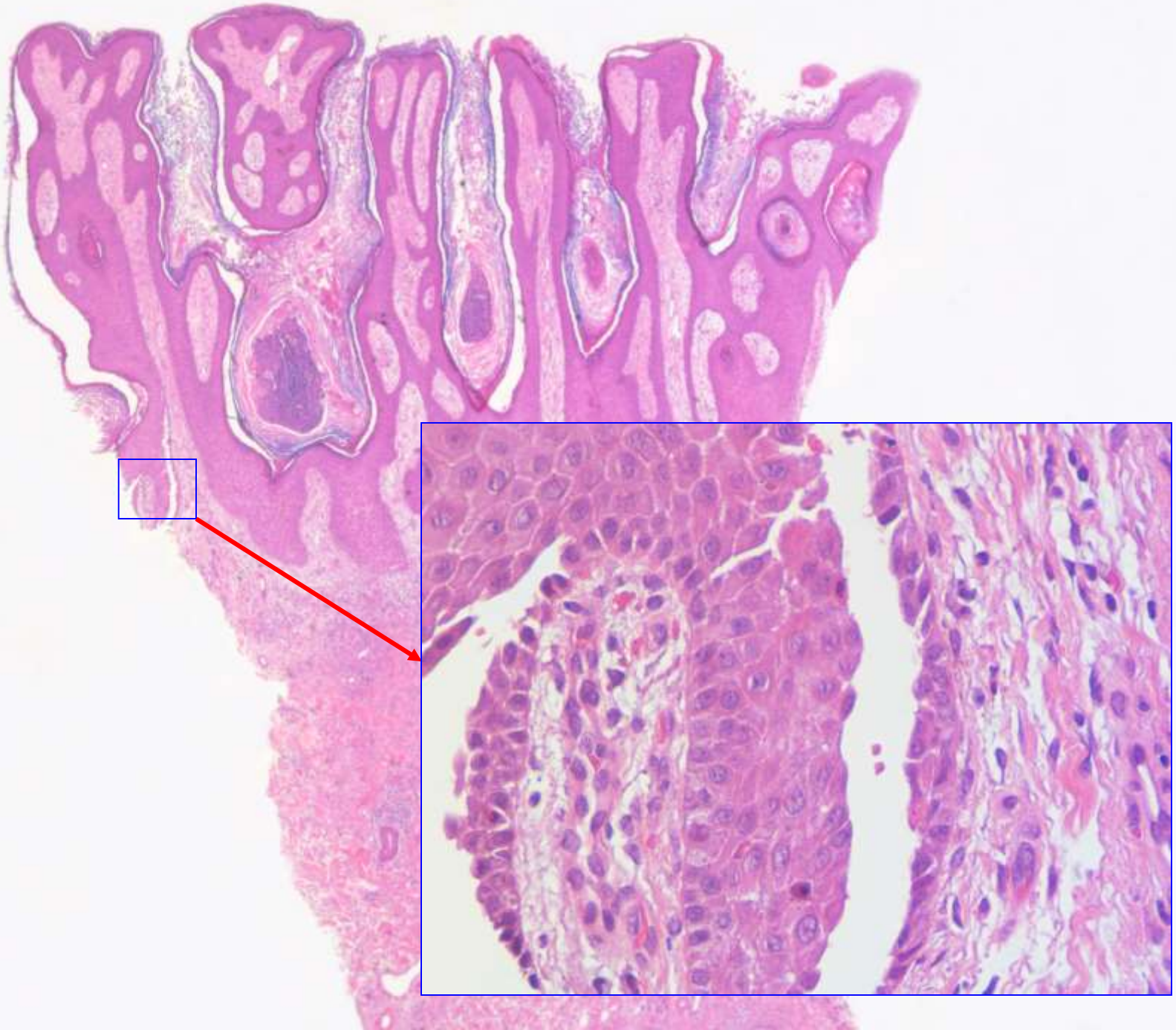
except for those intraepithelial abscesses of eosinophils.



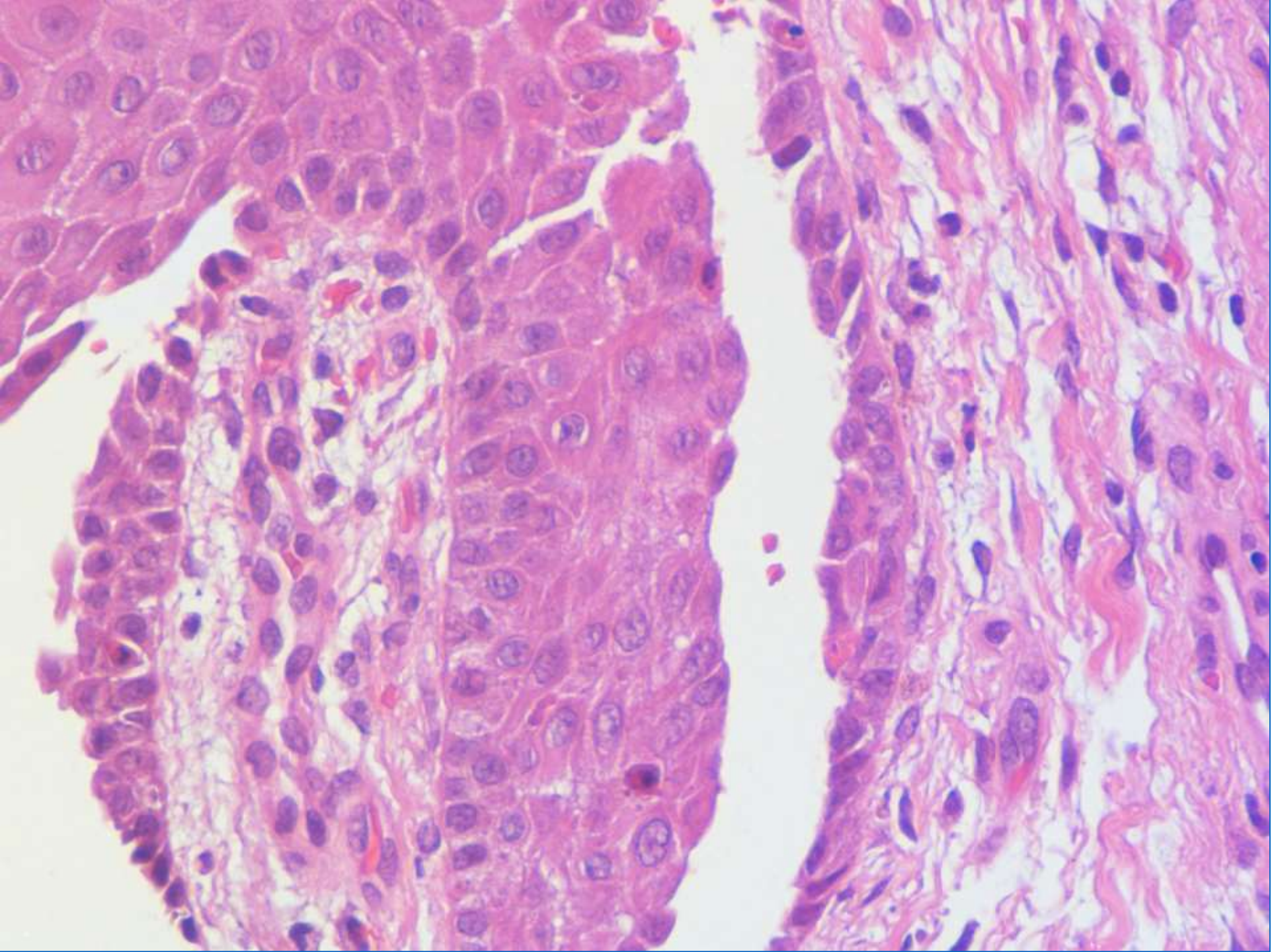
If the biopsy is taken from the papillations, i.e., blisters that have healed, acantholysis may be minimal or absent.



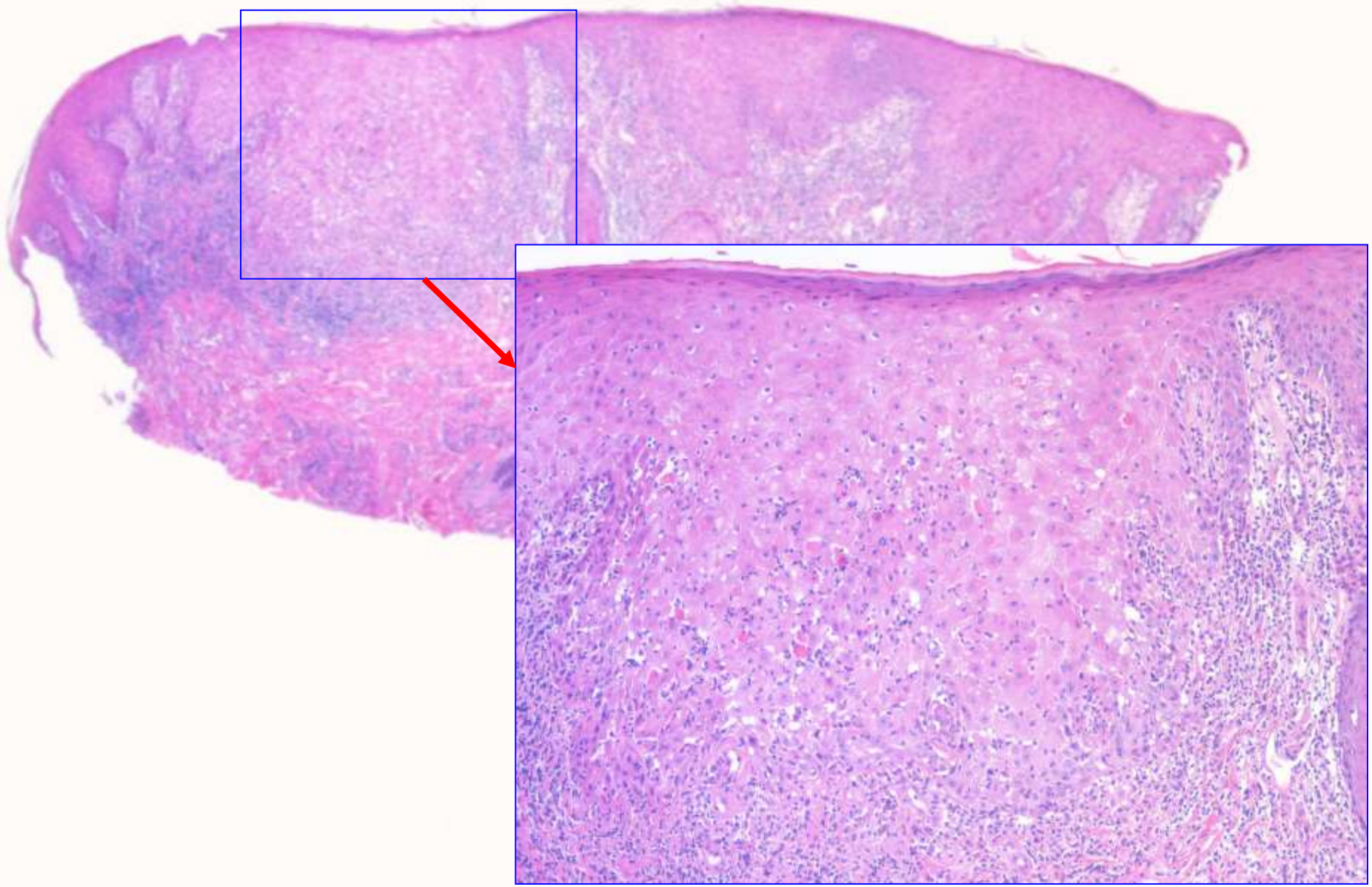
There are abscesses within the cornified layer,



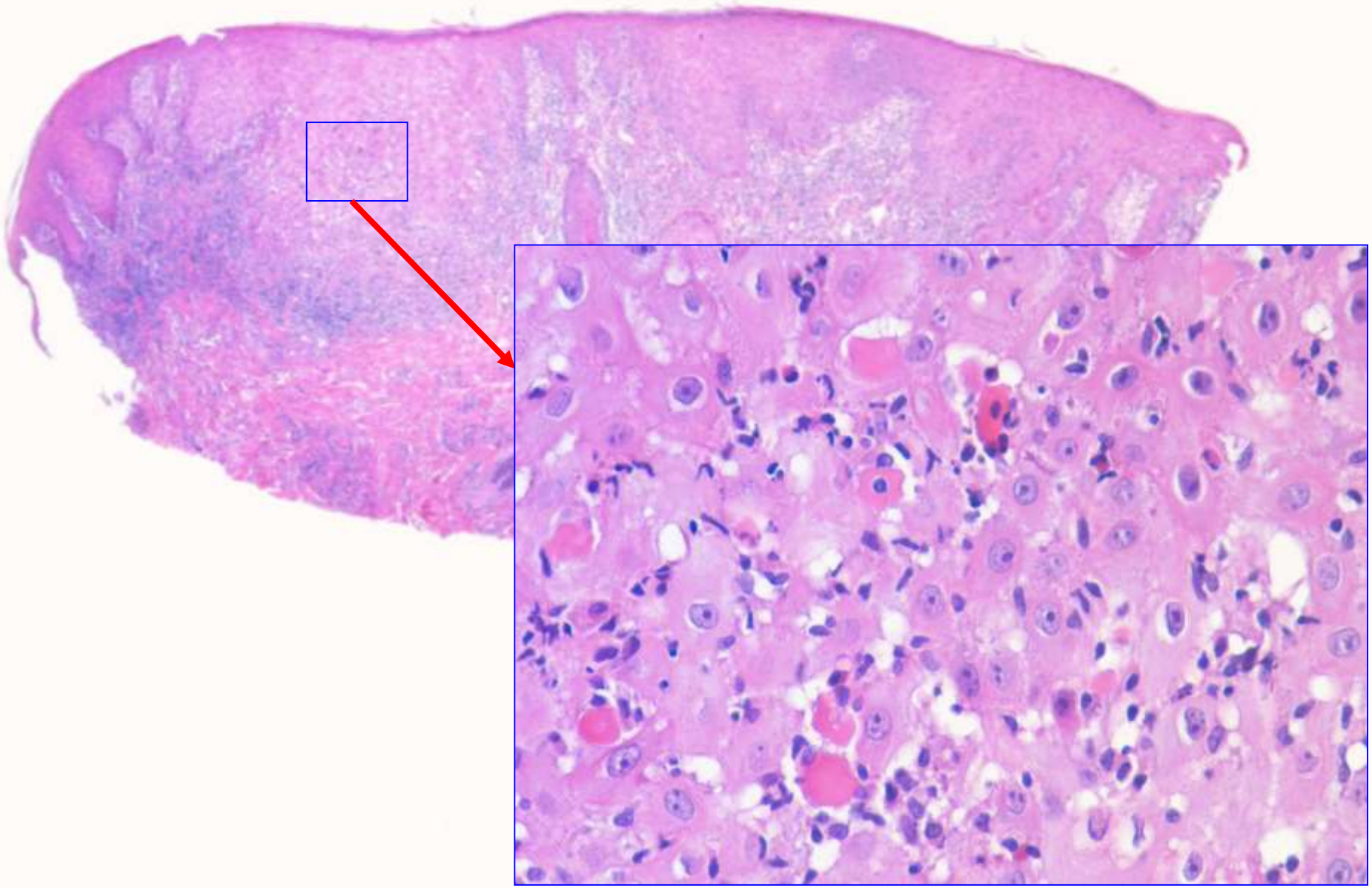
but acantholysis is limited to a tiny focus at the periphery of the specimen that was detectable in step sections only.



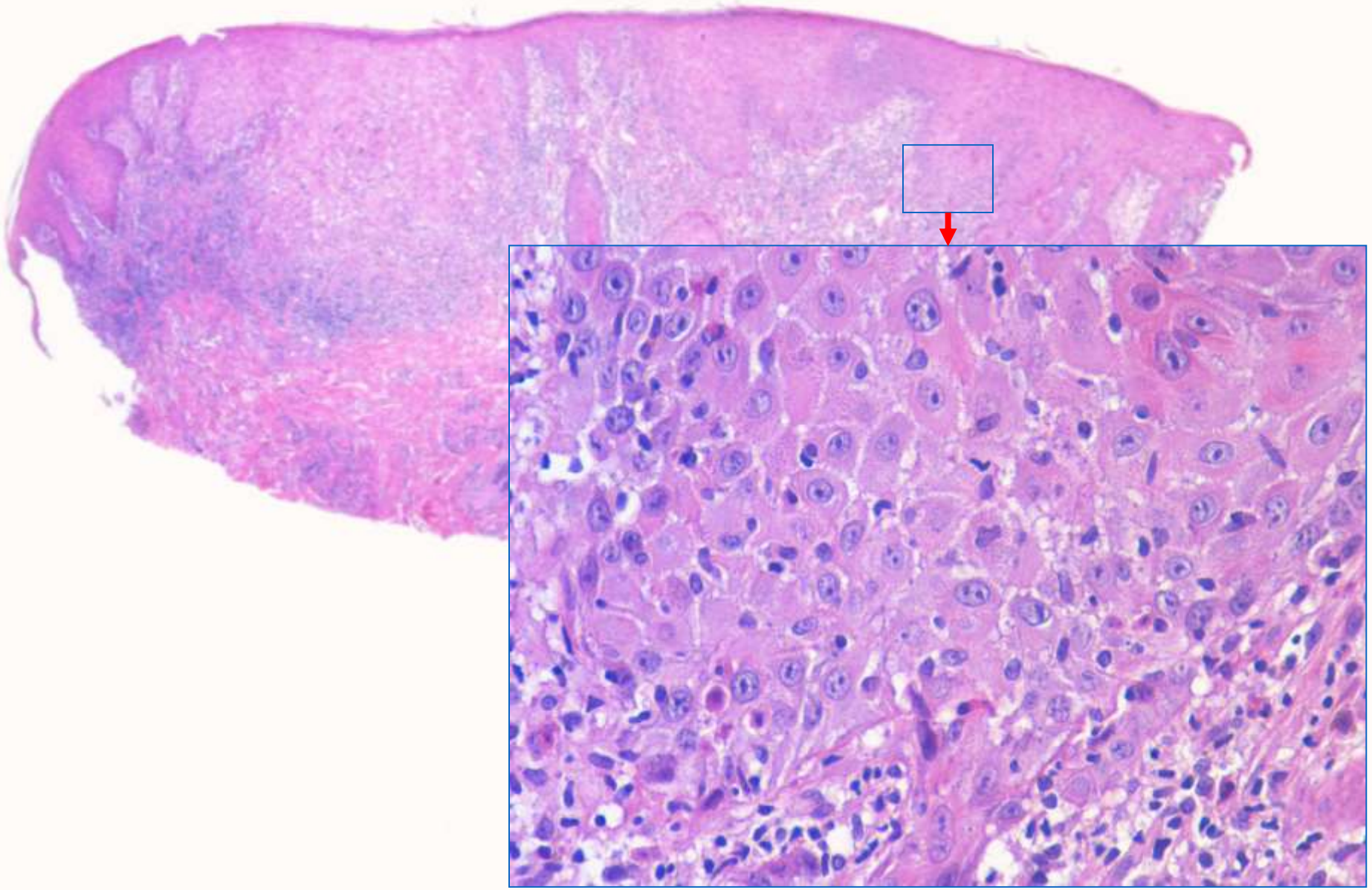
Note that there are also some necrotic keratocytes.



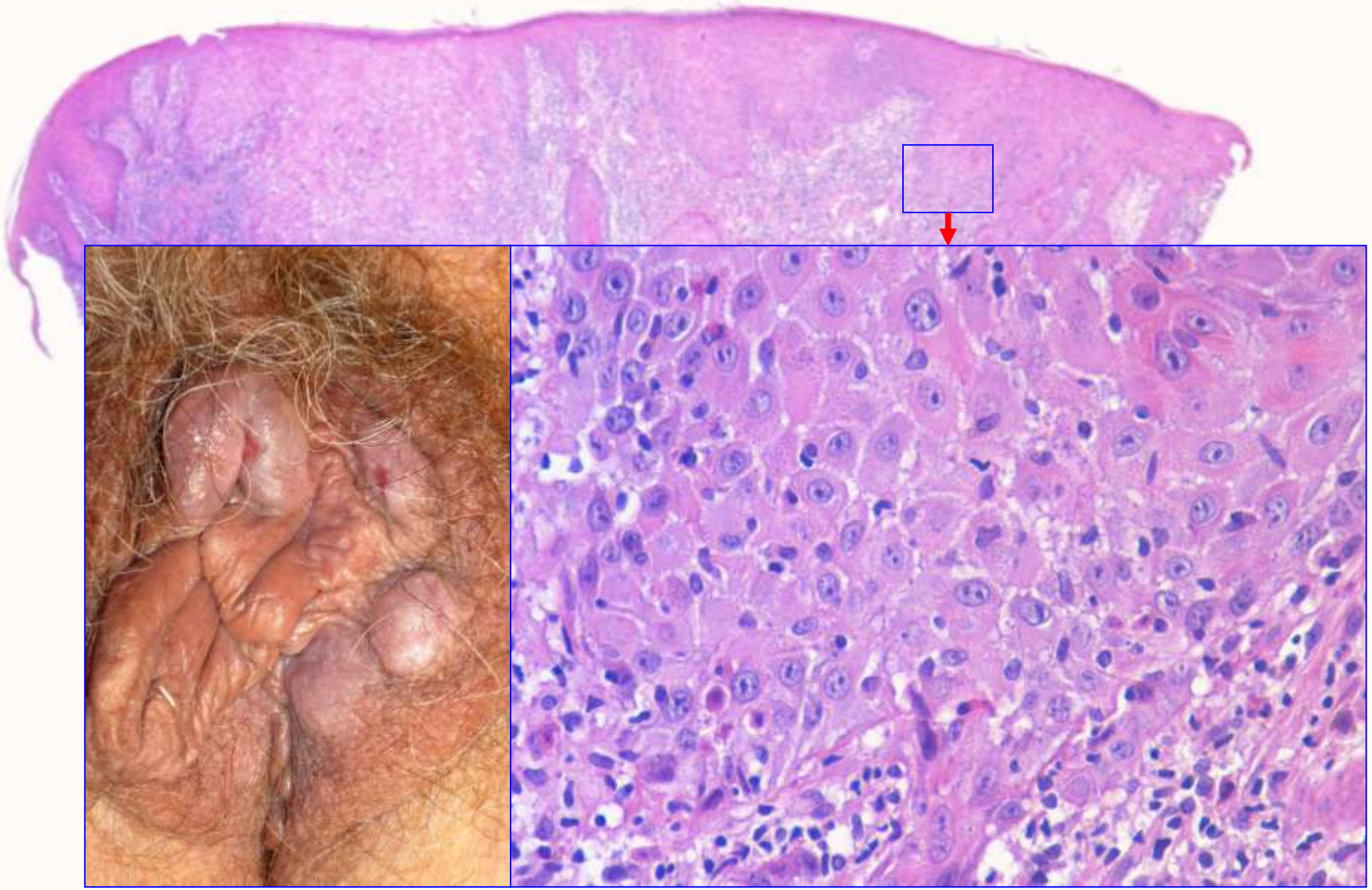
The latter may be seen in pemphigus vegetans and, if pronounced, represent a major histopathologic pitfall. For example, this case of pemphigus vegetans



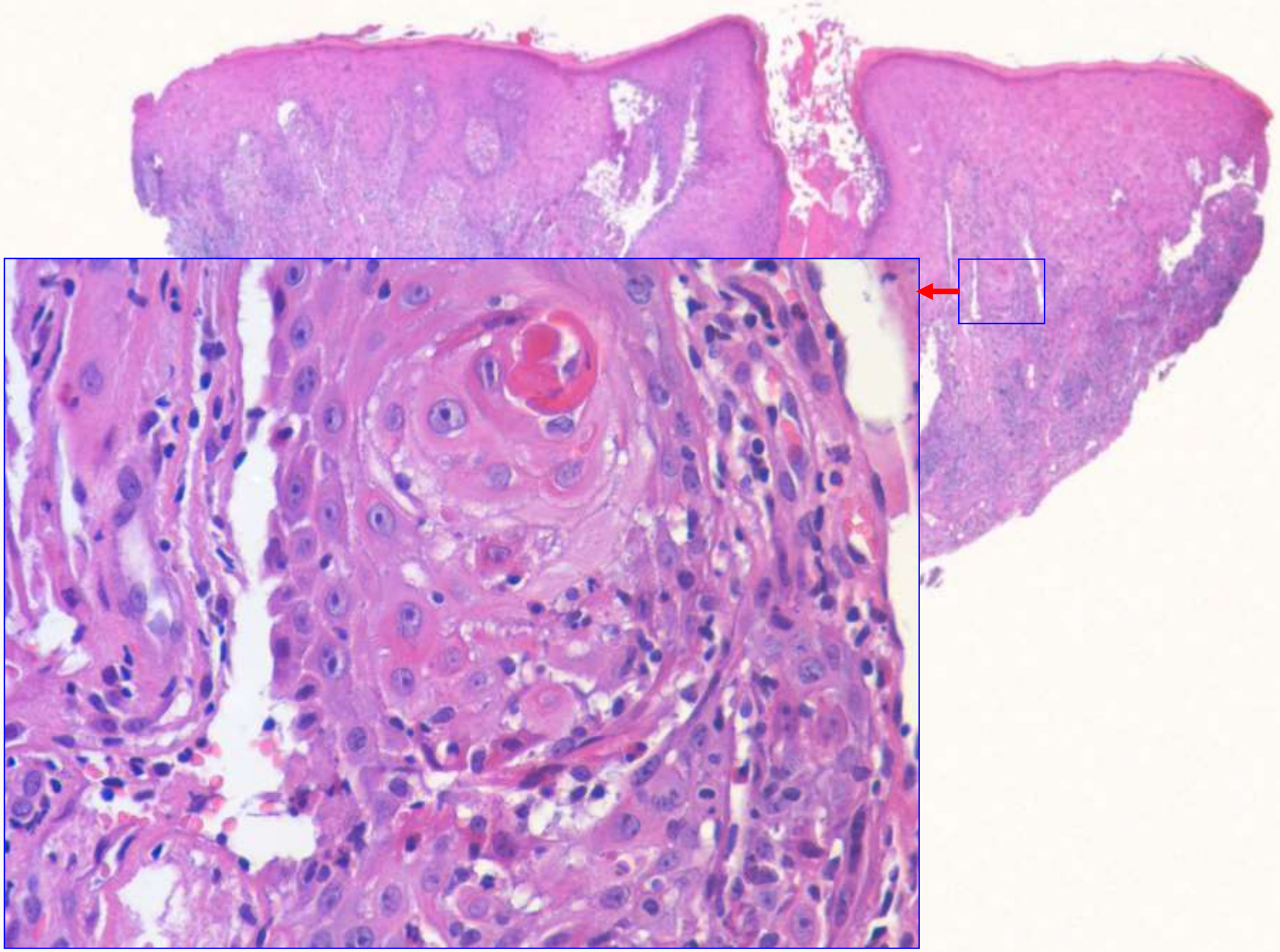
was originally misinterpreted as fixed drug eruption because of presence of many necrotic keratocytes in all reaches of the epidermis,



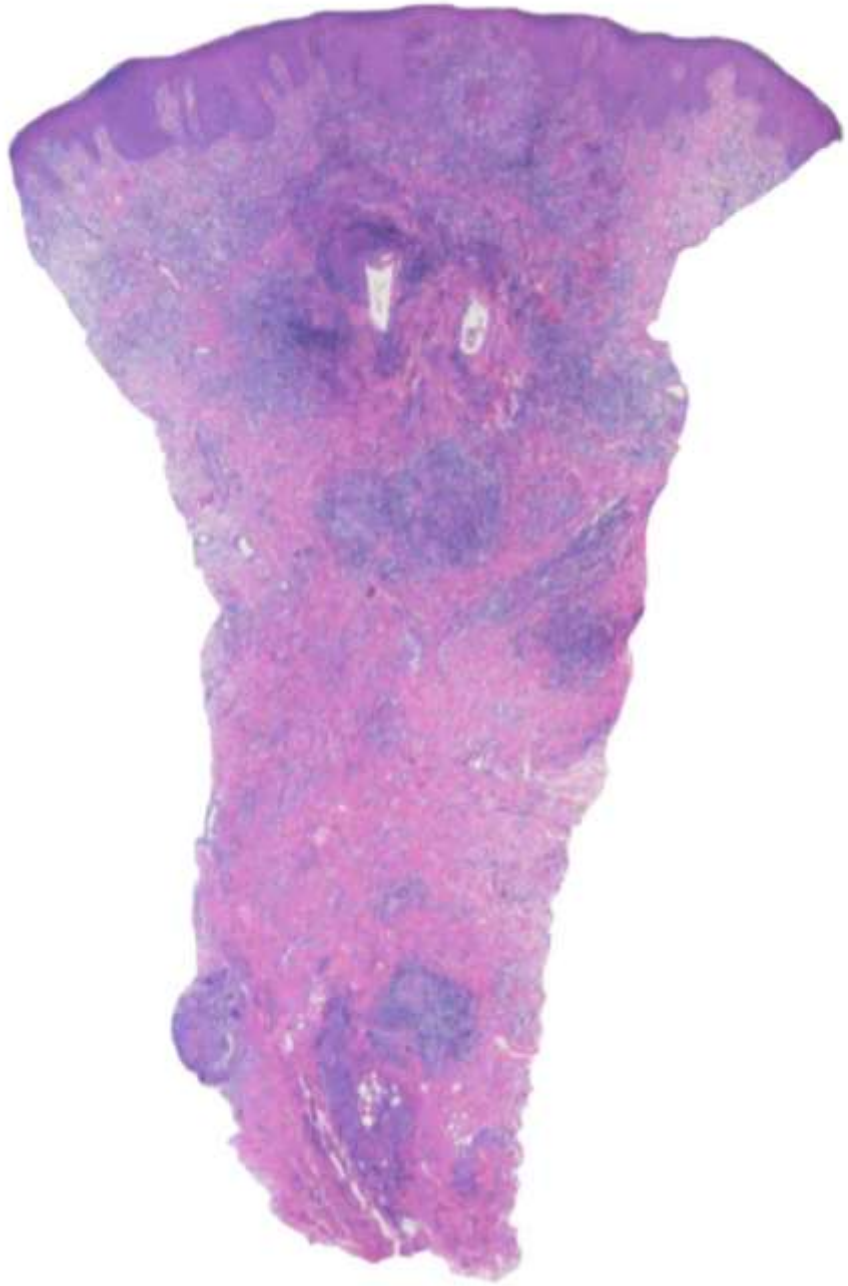
and so was loose scatter of neutrophils and eosinophils within the epidermis. The latter feature may also be seen in drug eruptions but, as a rule, not in relatively even distribution across a broad front.



At any rate, the clinical picture resolved any discussion,

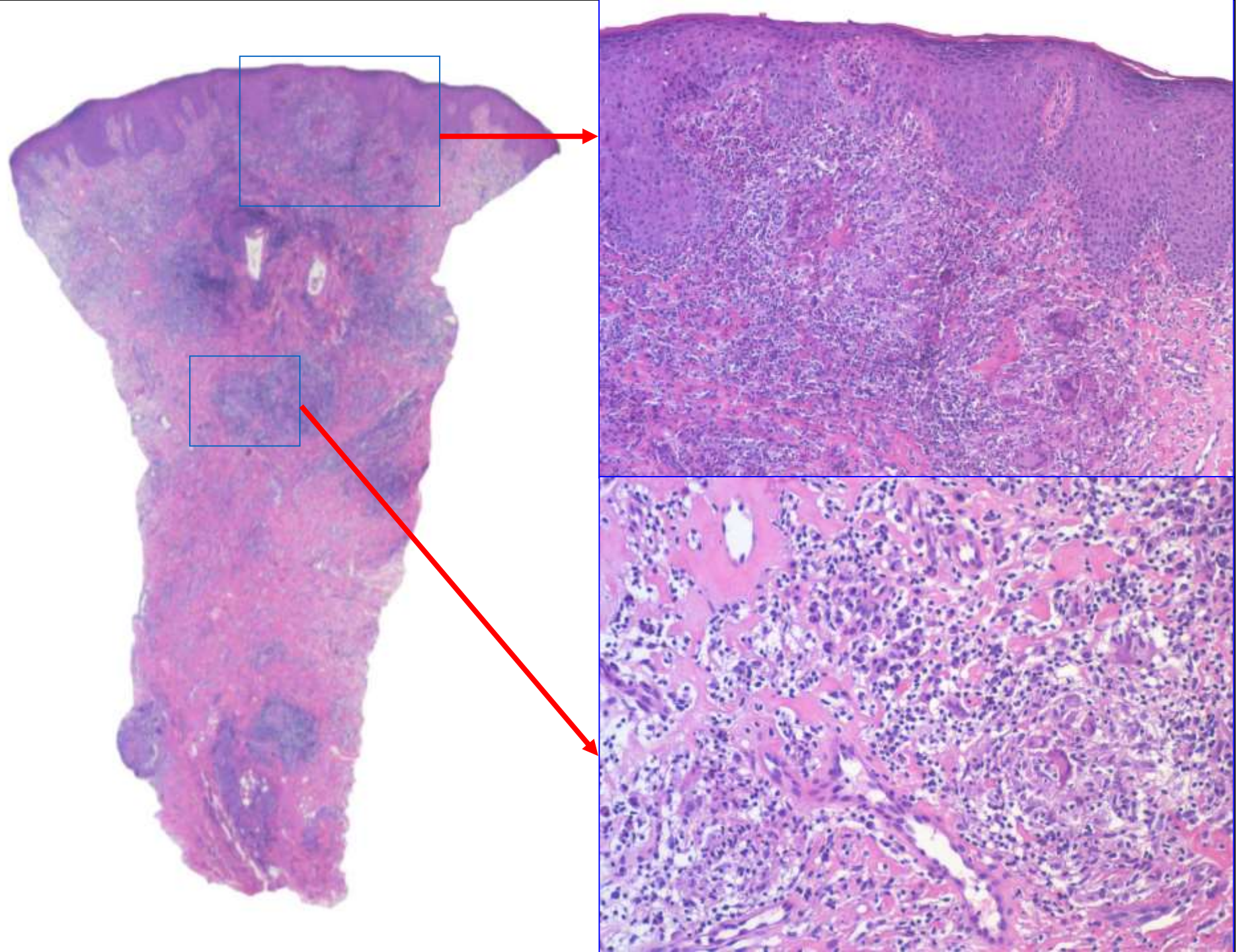


and an additional biopsy specimen showed more typical features of pemphigus vegetans with obvious suprabasilar acantholysis.

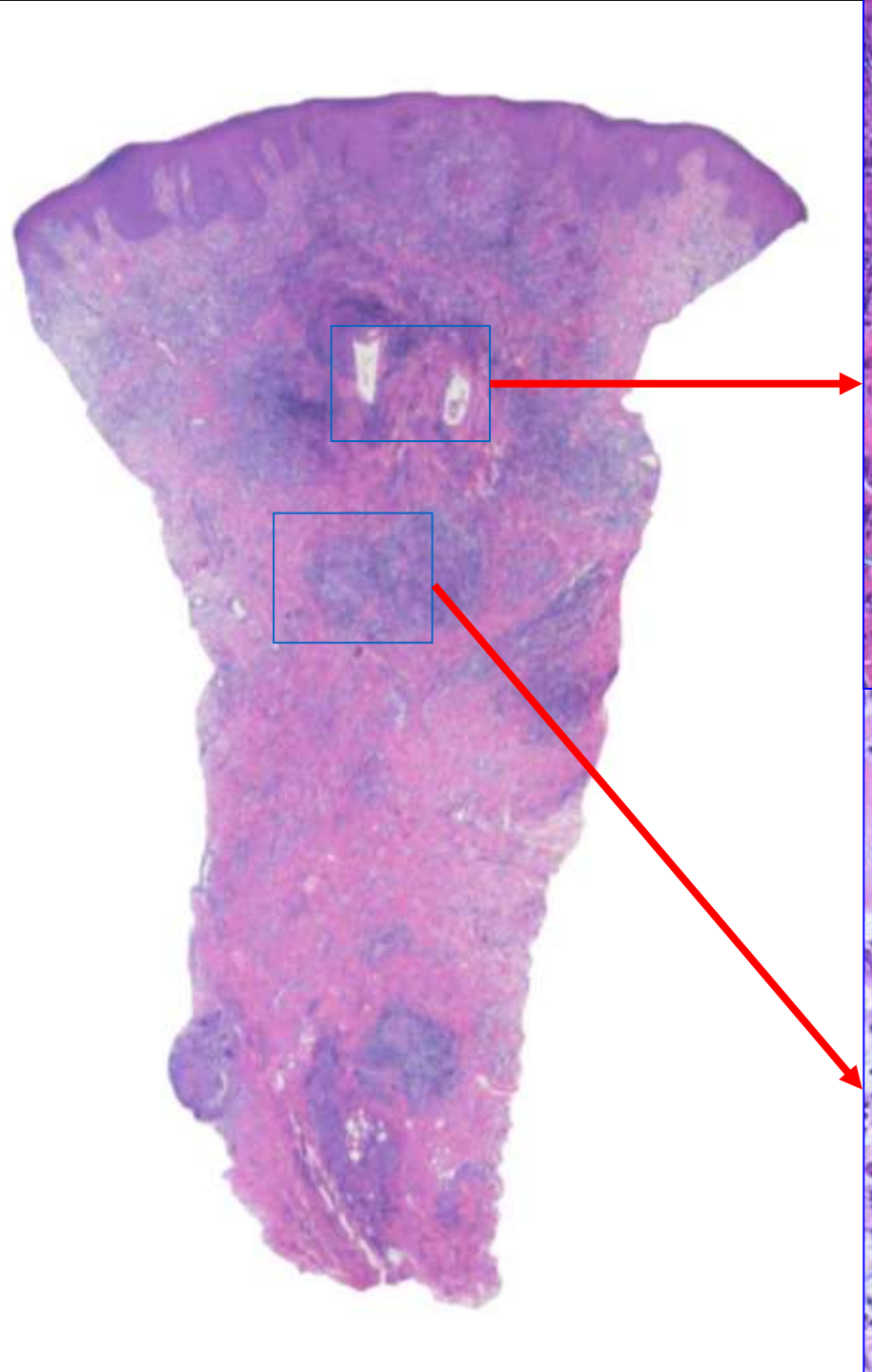


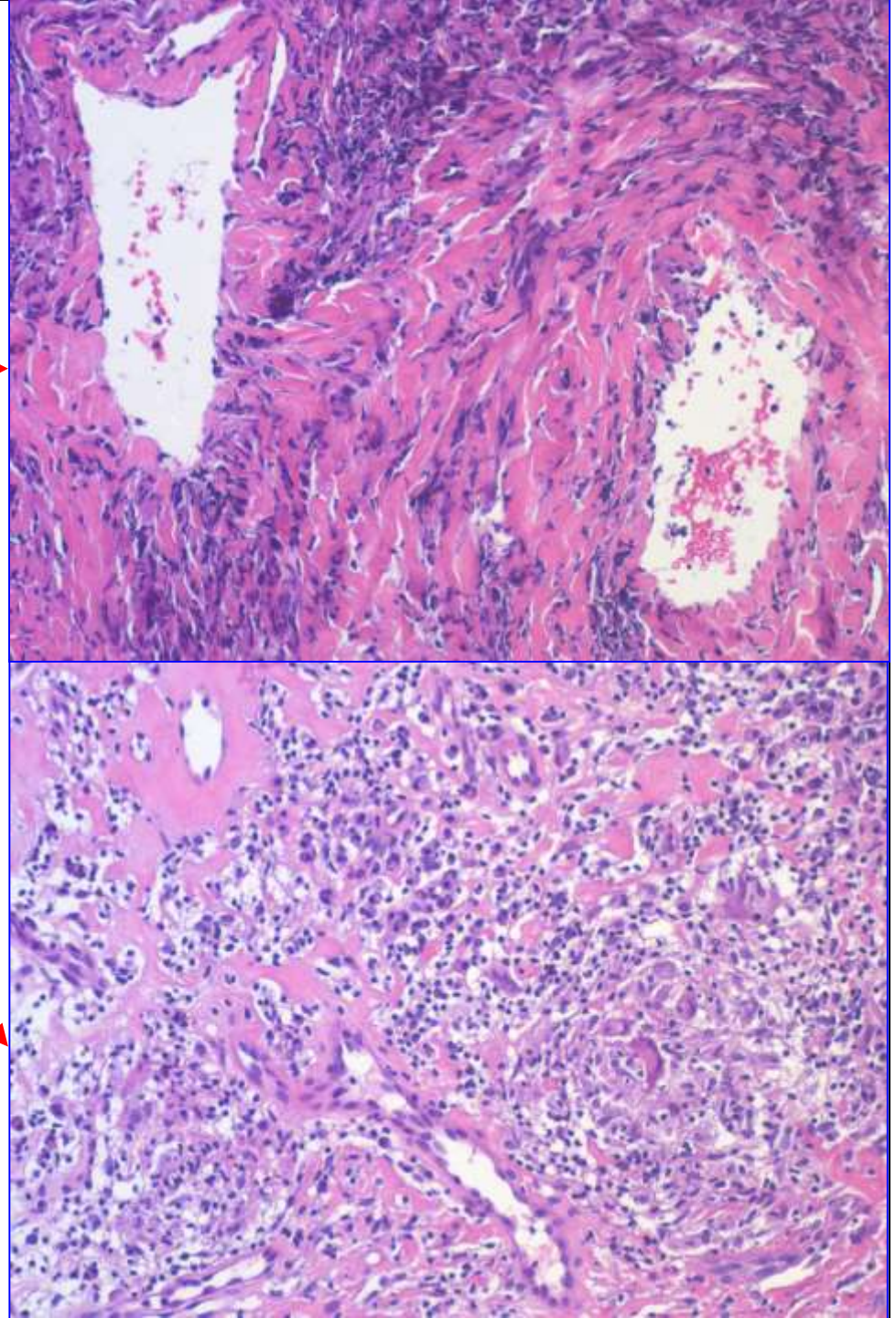
Crohn’s disease

Another disease affecting the genitalia preferentially is so-called “metastatic” extraintestinal Crohn’s disease.

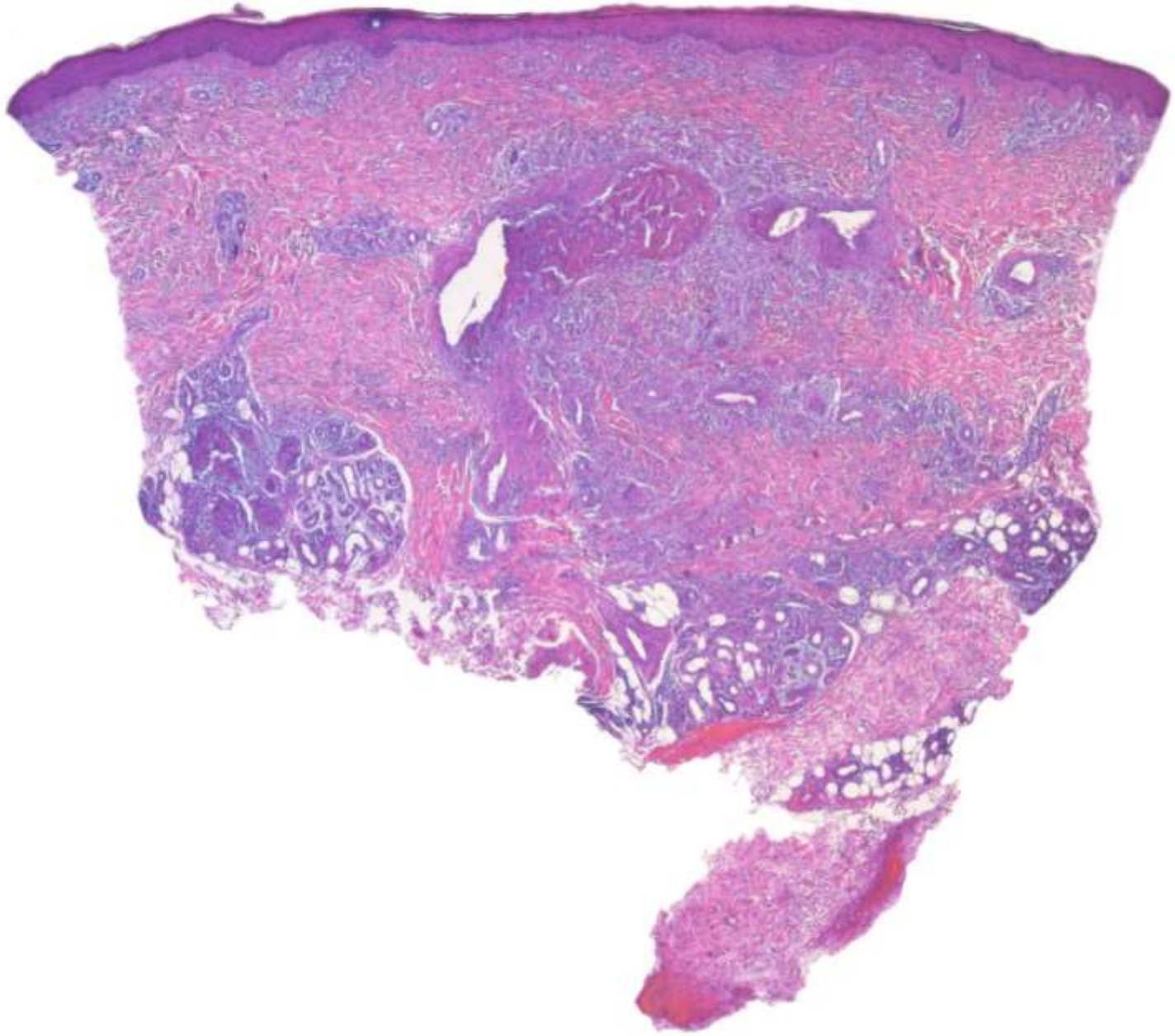


Like lesions in the bowel, it is characterized by granulomatous inflammation. Granulomas are usually small and poorly circumscribed, harbour many multinucleated giant cells, and are accompanied by a mixed inflammatory-cell infiltrate. In chronic lesions, such as this one, the dermis is fibrotic, and there are numerous plasma cells. The scatter of granulomas thoughout the superficial and deep dermis militates against the differential diagnosis of granulomatous folliculitis.

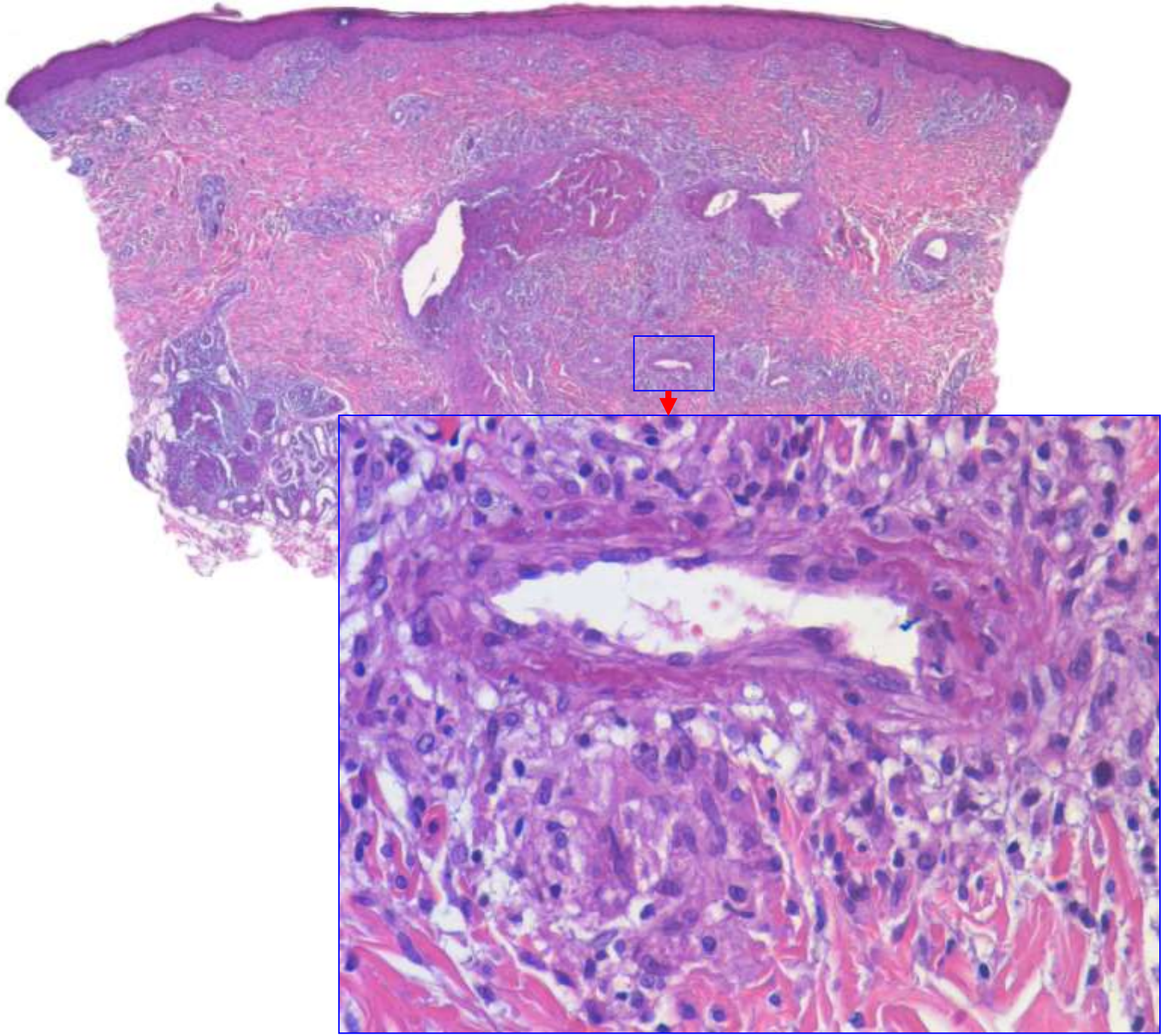




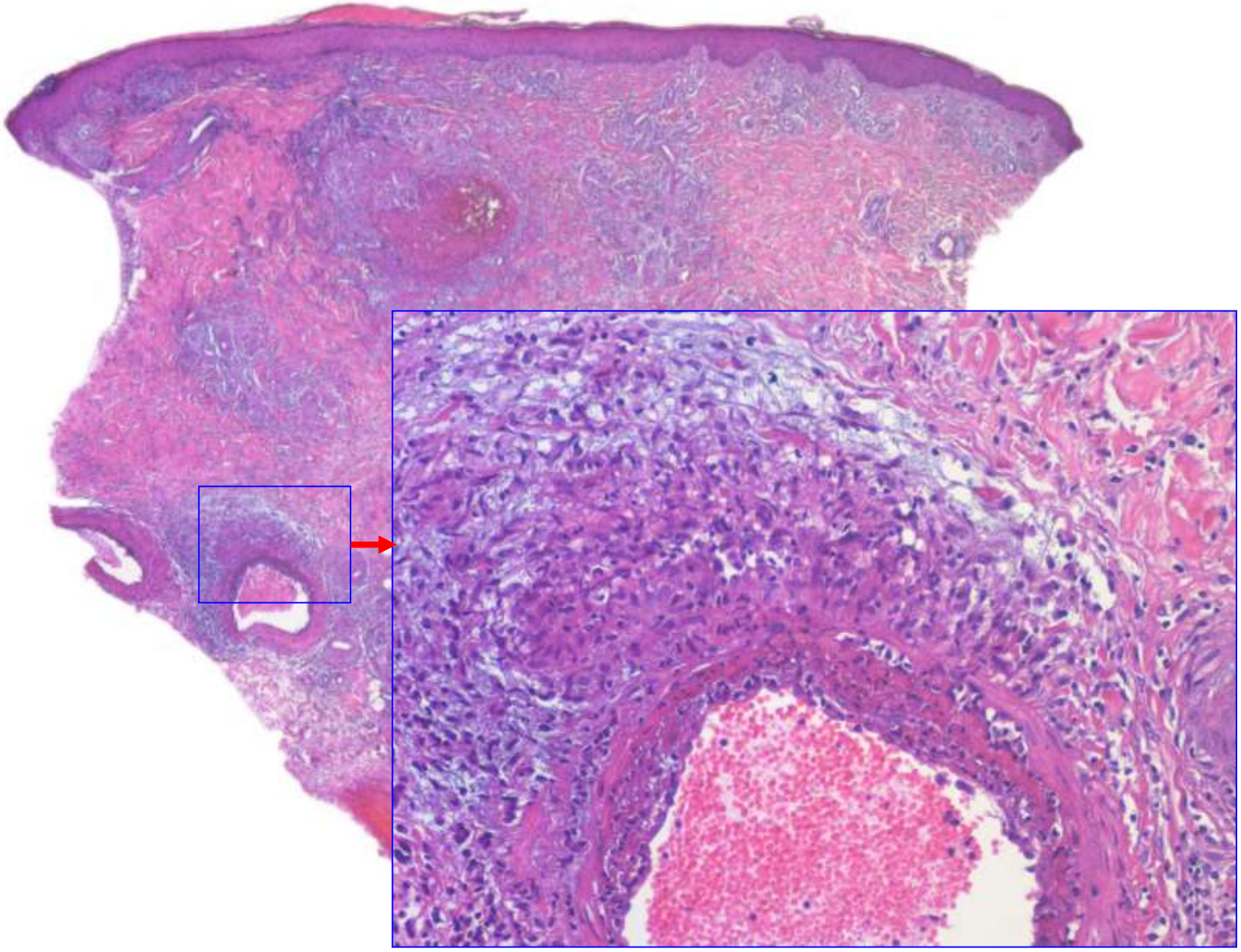
What, at first blush, seem to be lumina of ruptured follicles are, in reality, inflamed blood vessels. Extraintestinal Crohn's disease may show signs of vasculitis, granulomatous vasculitis being most distinctive.



This is an example: there are thrombi in the lumina of vessels, fibrin in vessel walls,



and granulomas form preferentially in the immediate vicinity of vessels.



Of course, the signs of vasculitis could be a consequence of the granulomatous inflammation, but in some foci one gets the impression that it is the other way round, namely, that granulomas form as a result of vasculitis.

Granulomatous vasculitis in Crohn's disease: a clinicopathologic correlate of two unusual cases

Cutaneous complications occur not uncommonly in patients with Crohn's disease (CD). Gastrointestinal CD often shows non-caseating granulomas and a rare cutaneous finding in CD is a sterile granulomatous infiltrate not contiguous with the GI tract, termed extraintestinal CD (ECD). The clinical presentation of ECD is diverse. The most common histopathological presentation is a superficial and deep granulomatous infiltrate that often accompanies a mixed perivascular infiltrate. Here we report two patients with CD and skin lesions characterized on microscopy by granulomatous vasculitis. A 29-year-old female presented with papules and ulcerated nodules above the ankle. The biopsy showed dermal and superficial subcutaneous involvement by a vasocentric infiltrate of mononuclear and multinucleated histiocytes as well as mural fibrin deposition. A 35-year-old male presented with two tender indurated erythematous plaques with punched-out centers on the lower leg. Histopathologically, a granulomatous vasculitis of small and medium-sized vessels in the dermis and subcutis was evident. These two cases represent the rarely described phenomenon of cutaneous granulomatous vasculitis in CD. Previously reported examples of this entity are reviewed.

Burns AM, Walsh N, Green PJ. Granulomatous vasculitis in Crohn's disease: a clinicopathologic correlate of two unusual cases. **J Cutan Pathol** 2010; 37: 1077–1083. © 2010 John Wiley & Sons A/S.

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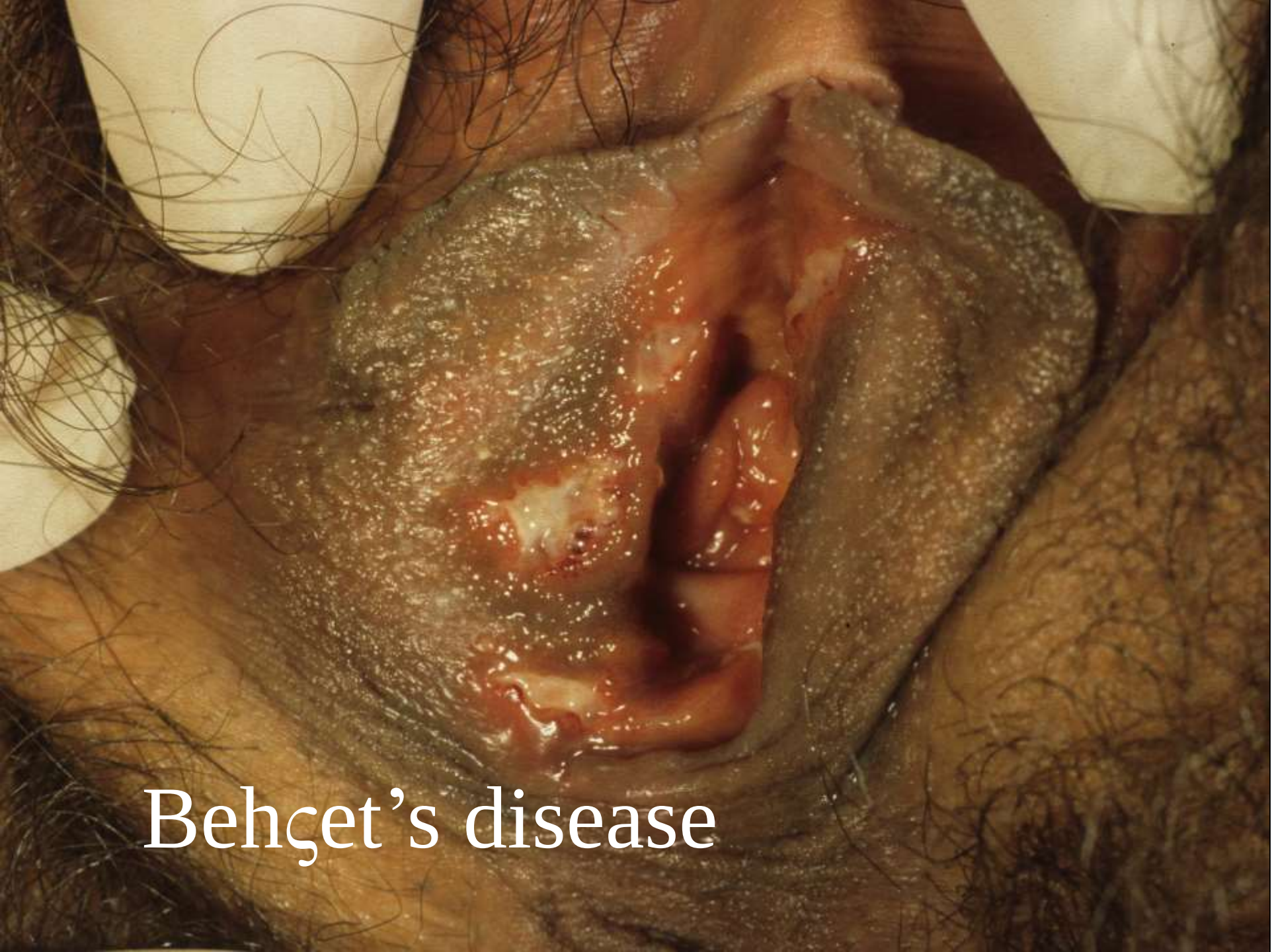
Accepted for publication February 28, 2010

At any rate, granulomatous vasculitis is a recognized feature of extraintestinal Crohn's disease and may serve as a diagnostic clue.



Behçet’s disease

Yet another disease affecting the genitalia preferentially is Behçet’s disease. It is characterized by recurrent ulcers on mucous membranes.

FOURTH EDITION

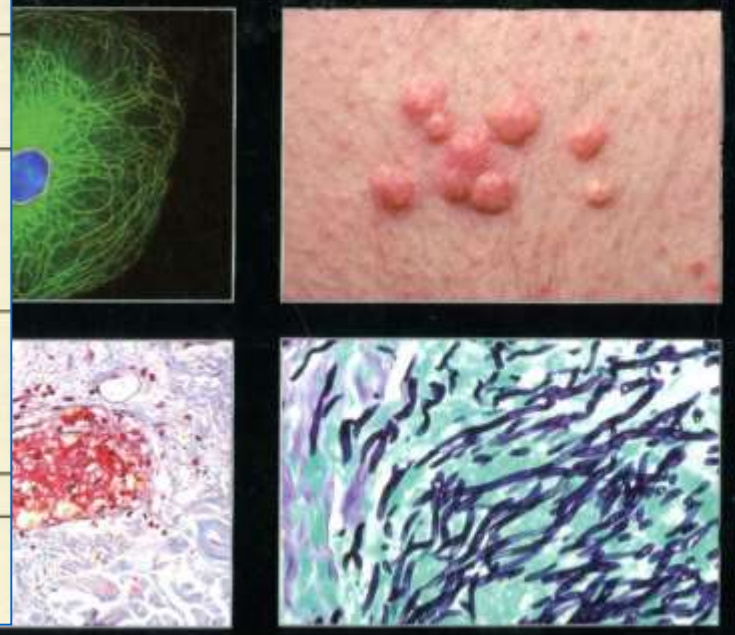
VOLUME ONE

McKee's PATHOLOGY of the SKIN

CORRELATIONS

Criterion	Definition
Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient, and recurrent at least three times in one 12-month period
Plus two of:	
Recurrent genital ulceration	Aphthous ulceration or scarring, observed by physician or patient
Eye lesions	Anterior uveitis, posterior uveitis or cells in vitreous on slit lamp examination or Retinal vasculitis observed by ophthalmologist
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions; or acneiform nodules observed by physician, patient not on corticosteroid treatment
Positive pathergy test	Read by physician at 24–48 hours

* Findings applicable only in the absence of other clinical explanations.
Reprinted with permission from Elsevier (International Study Group for Behçet's Disease (1990) Lancet, 335, 1078–1080).



The diagnosis is based on at least three episodes of recurrent oral ulceration in one 12-month period, together with at least two minor criteria, including genital ulcers.
No diagnostic role in accorded to histopathology; even major textbooks of dermatopathology, such as the one by McKee,

FOURTH EDITION

VOLUME ONE

McKEE'S PATHOLOGY of the SKIN

Criterion	Definition
Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient, and recurrent at least three times in one 12-month period
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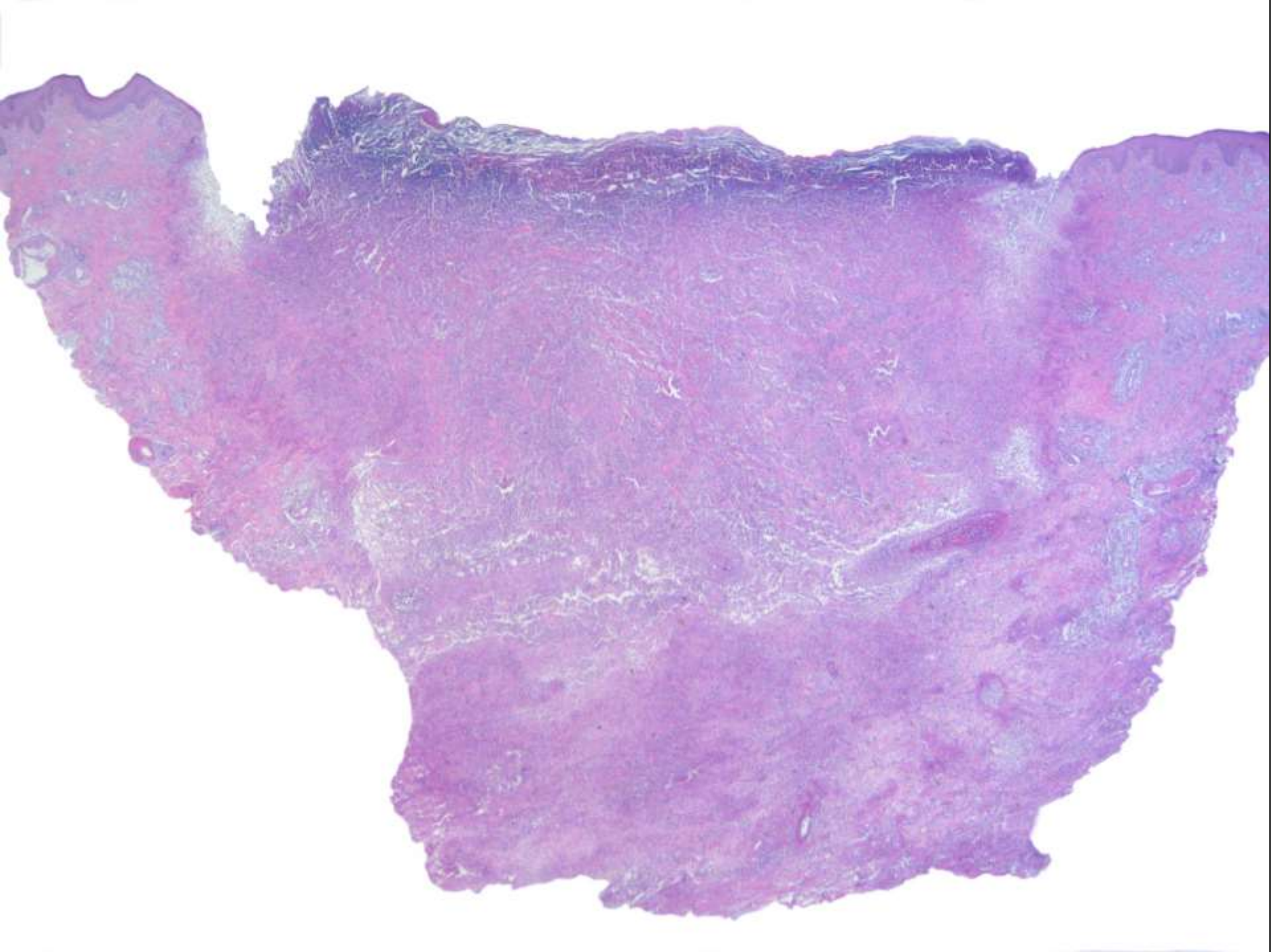
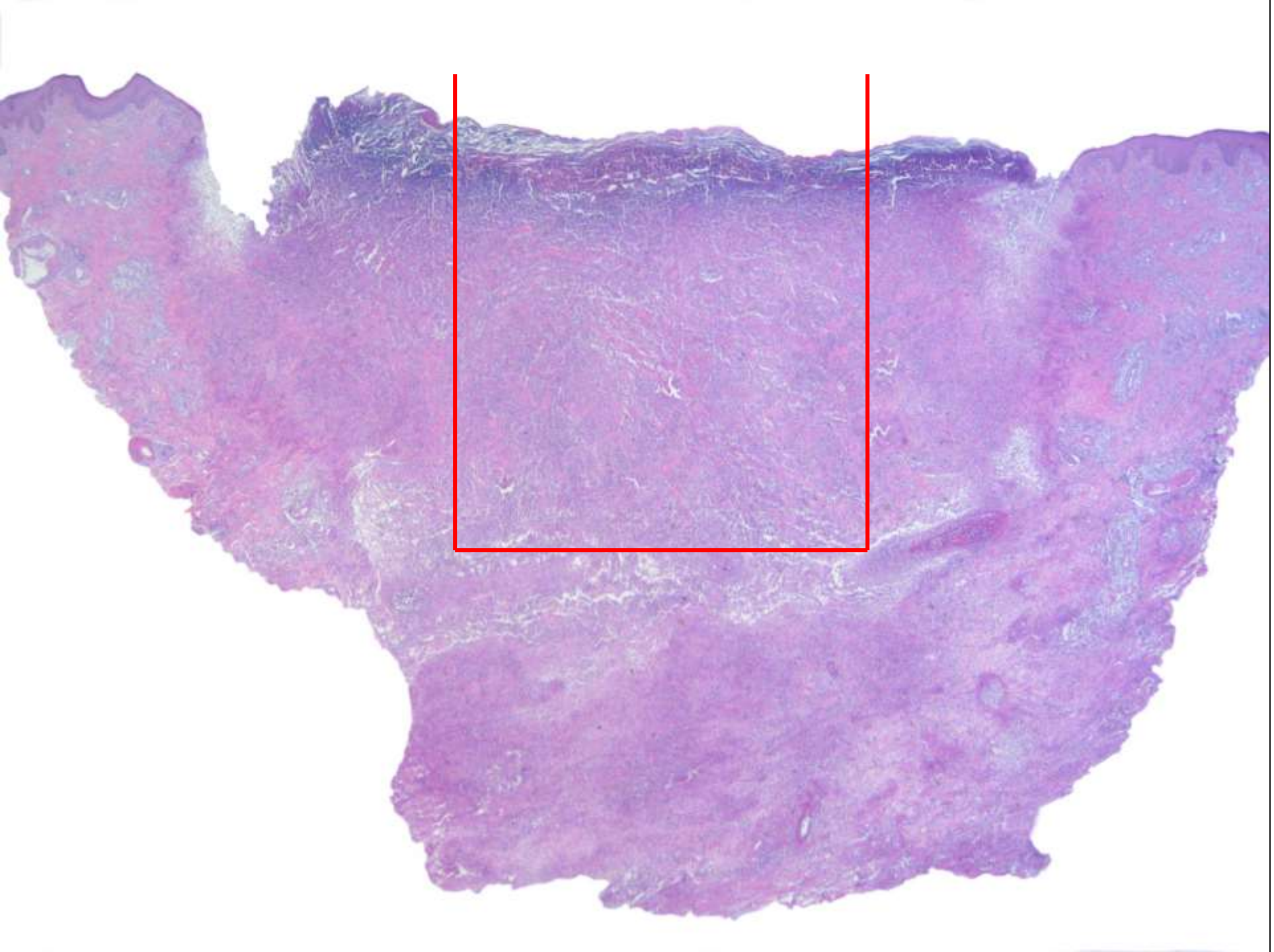
Reprinted with permission from Elsevier (International Study Group for Behçet's Disease (1990) Lancet, 335, 1078–1080).

The histopathologic features are in themselves largely non-specific. The diagnosis of Behçet's disease is essentially clinical.

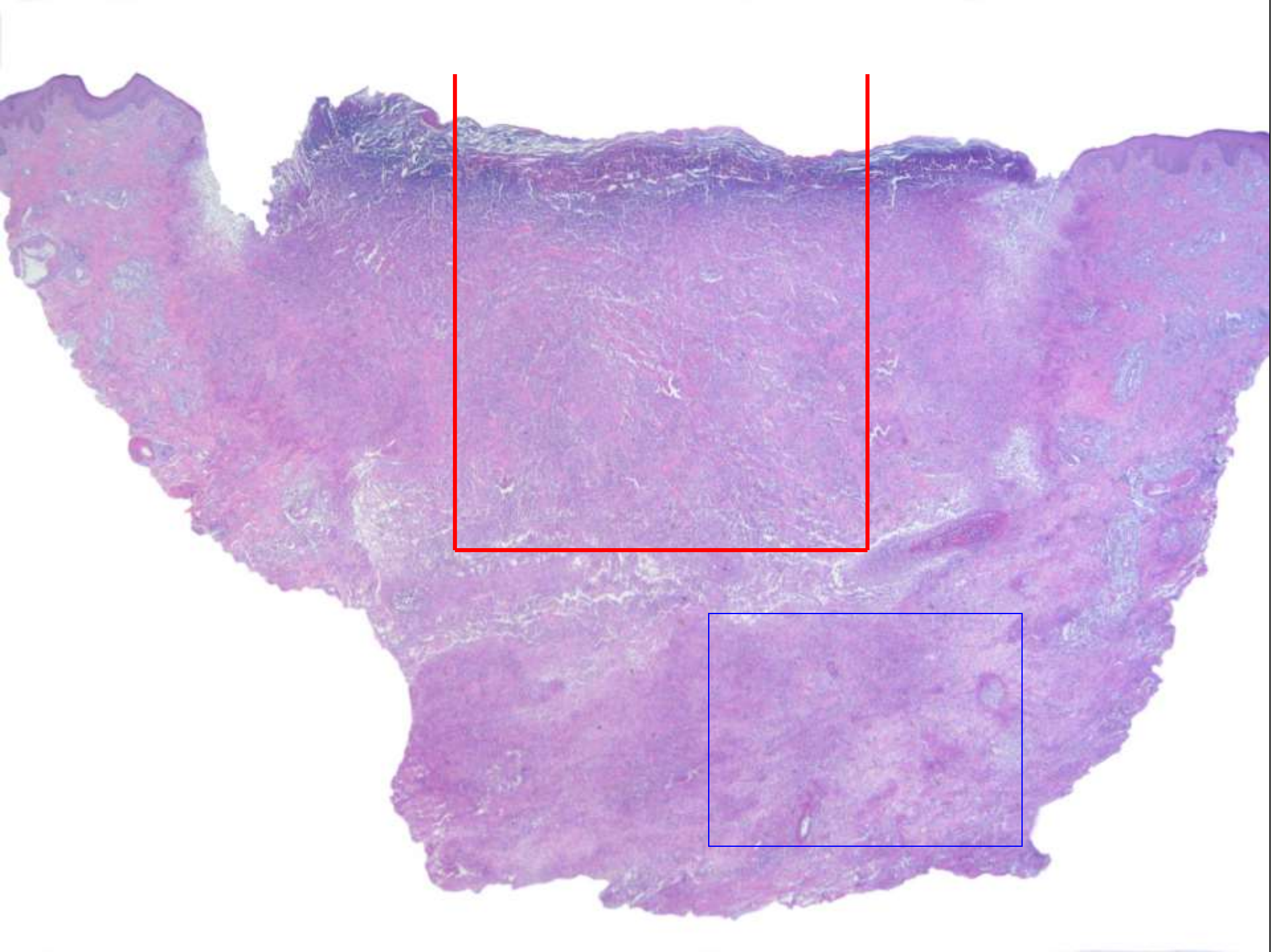
, concede that *"the histopathologic features are in themselves largely non-specific. The diagnosis of Behçet's disease is essentially clinical."* This, however, is not exactly true.



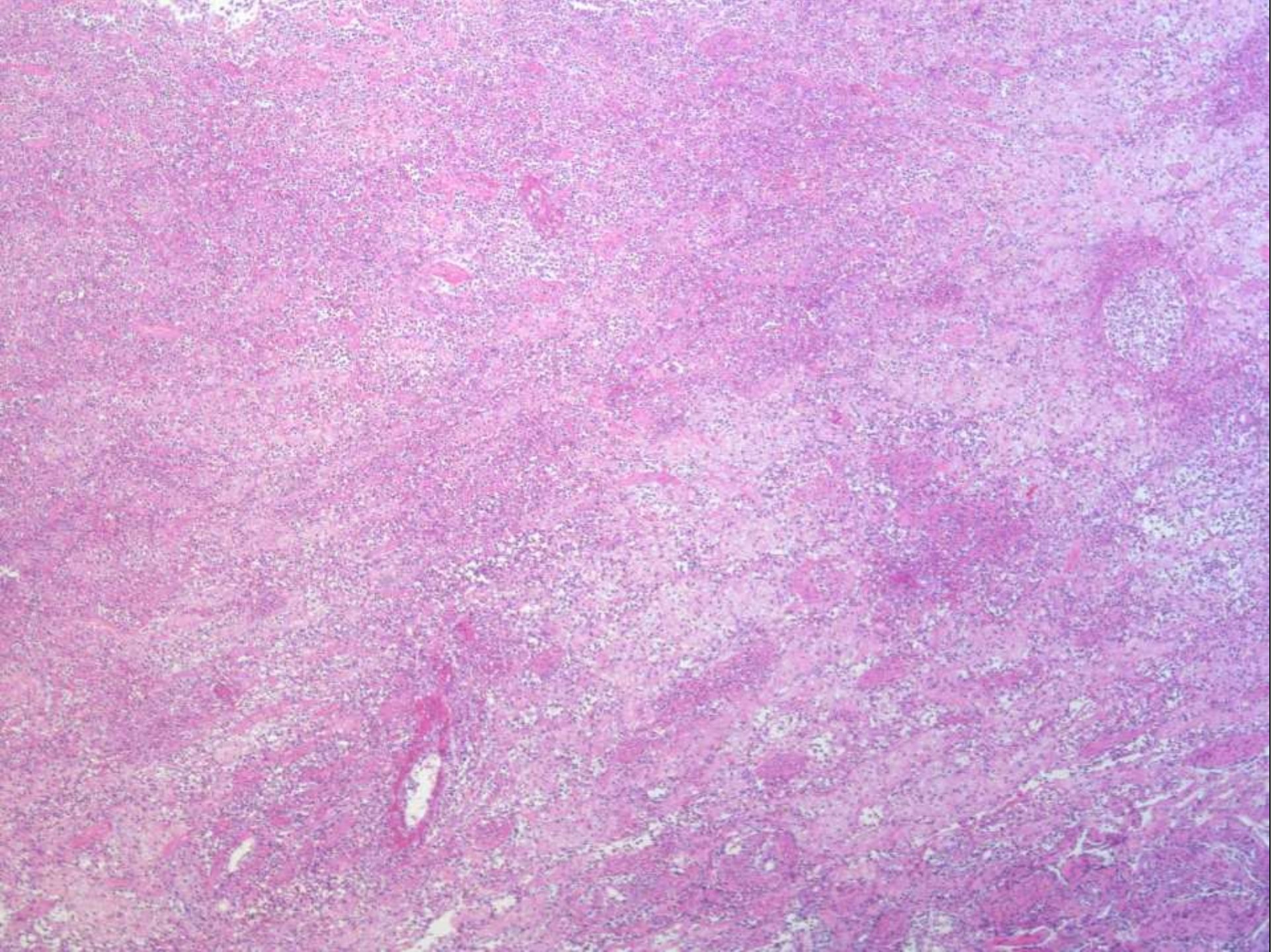
It applies only to the standard biopsy.



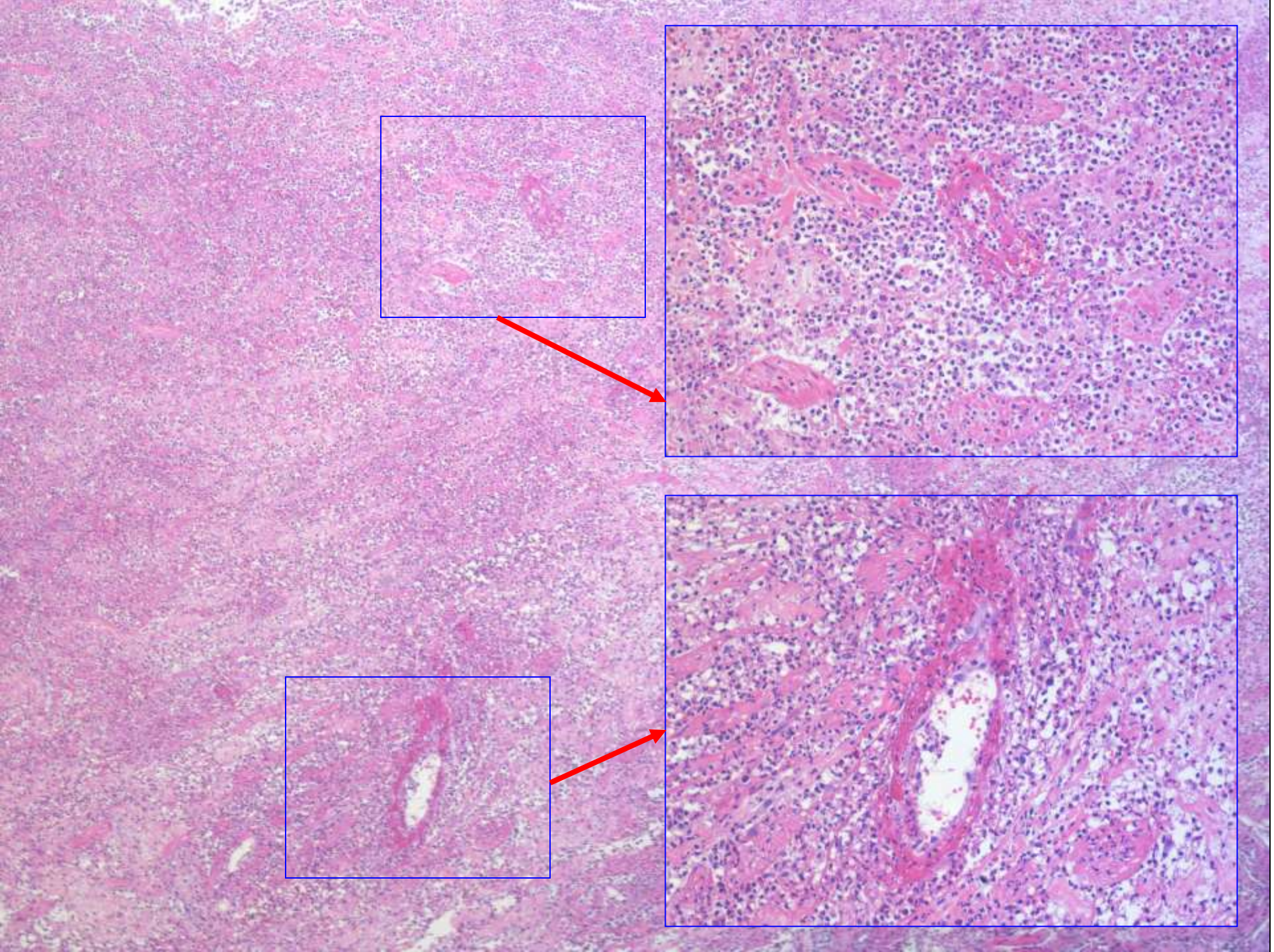
If a punch biopsy is performed in lesions such as this one, the changes found are non-specific, i.e., those of an ulcer with pronounced inflammation.



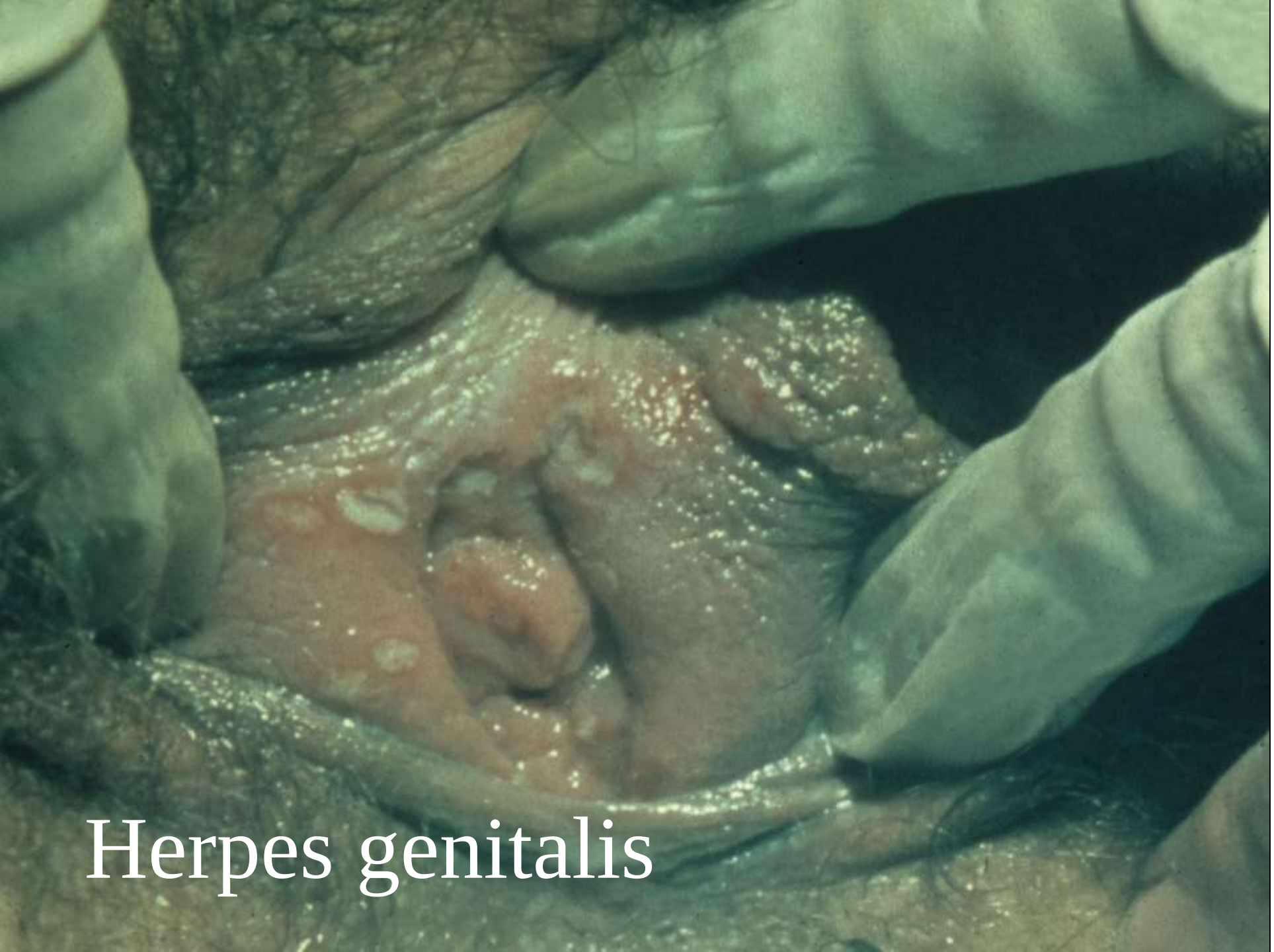
The changes typical of Behçet’s disease, and explaining the occurrence of ulcers, are found deeper down,



namely, vasculitis of medium-sized vessels.

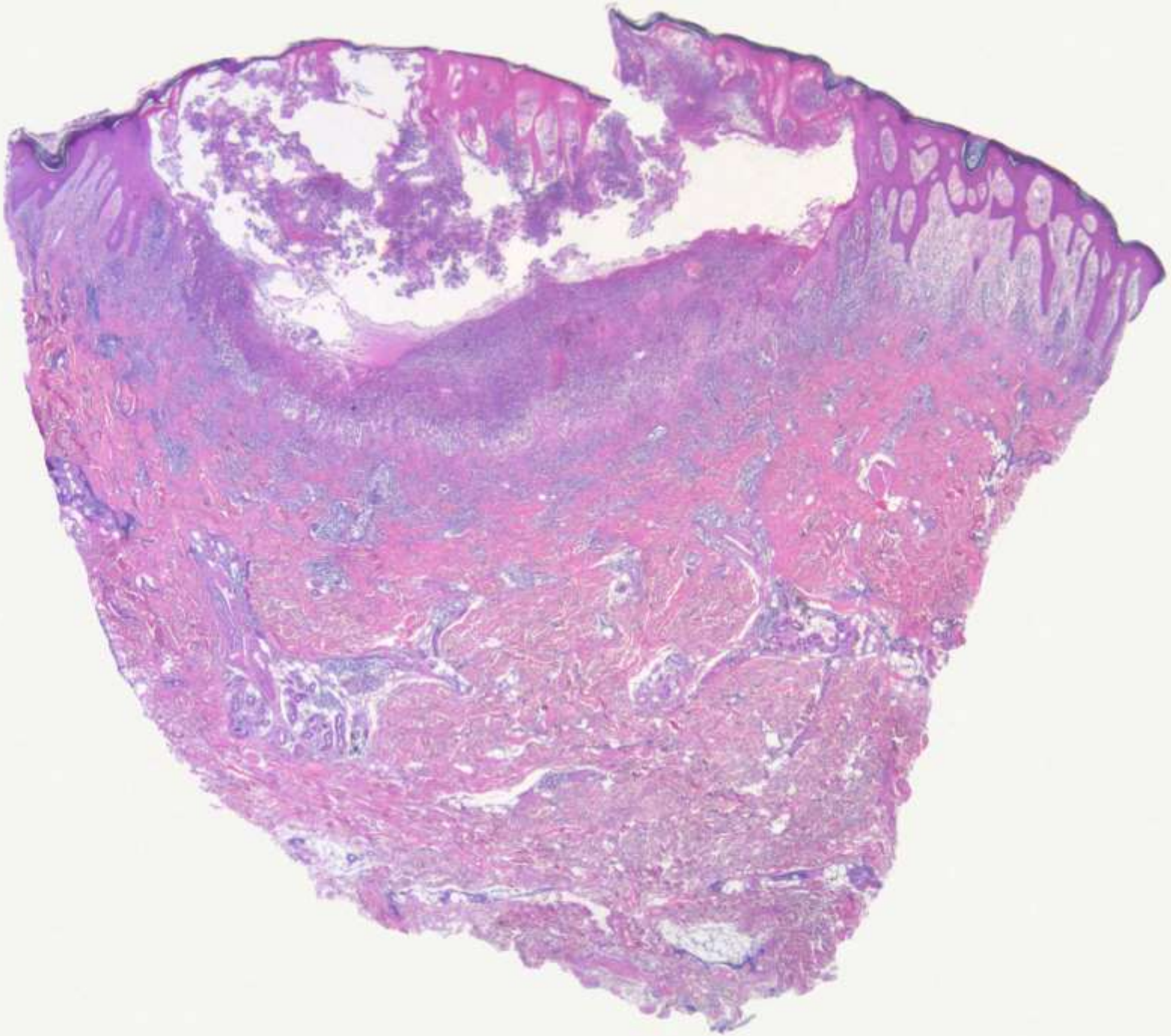


It requires a large and deep biopsy with a scalpel, however, to capture them.

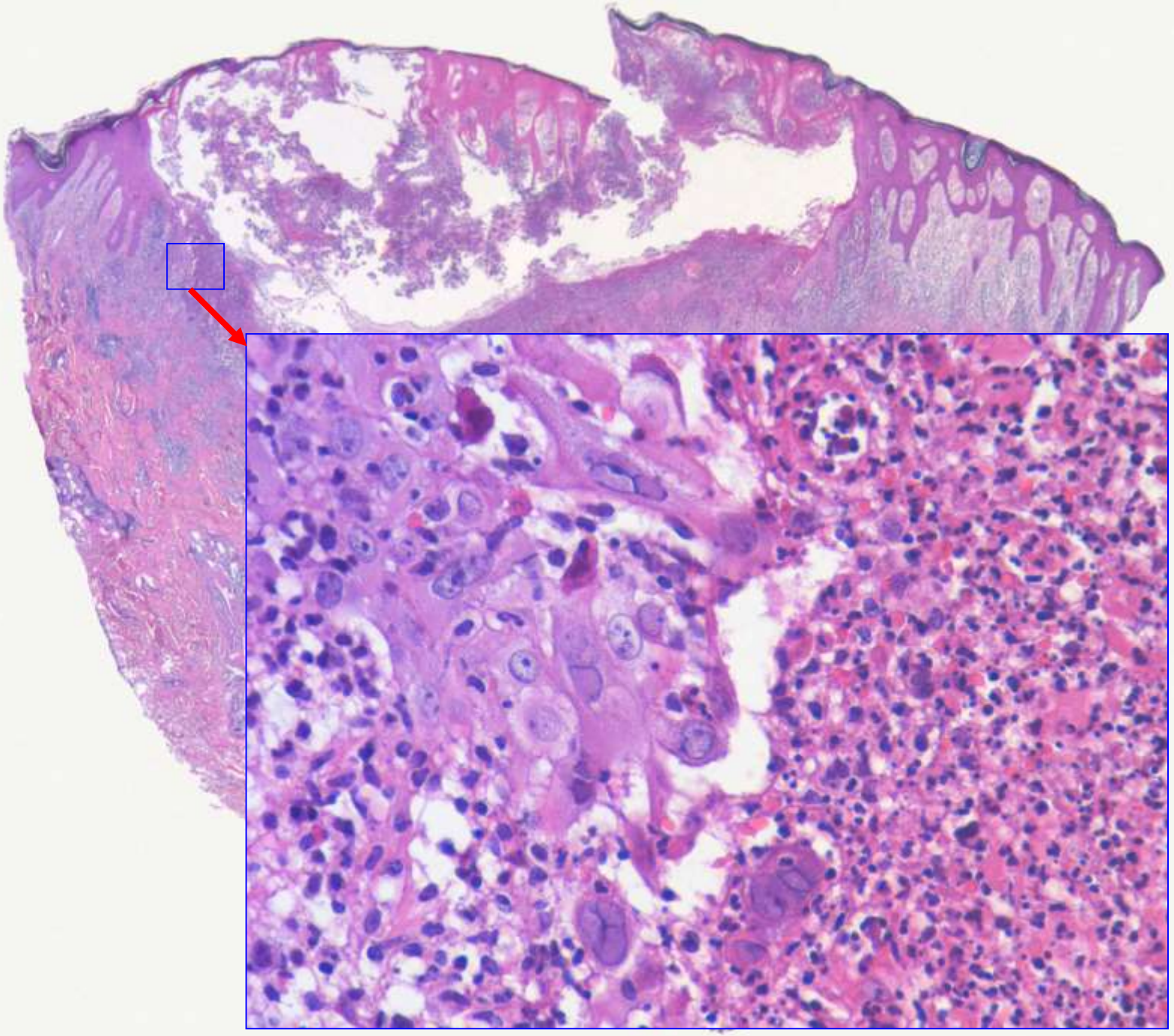


Herpes genitalis

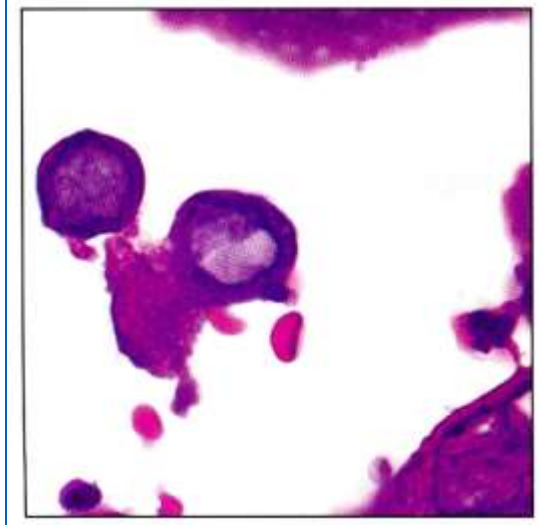
Among the differential diagnoses of Behçet's disease is one of the most common diseases of the vulva, namely, herpes genitalis. It is often, but not always, diagnostic clinically.



For example, this lesion came in as a cyst. It is unusually large but otherwise typical



and may serve to recapitulate the most essential histopathologic signs of infections by herpes viruses. One is ballooning of epithelial cells infected by the virus: they become large and have abundant pale cytoplasm. The nuclei acquire a steel-gray color with margination of the nucleoplasm.



Steel-gray nuclei and margination of nucleoplasm of keratinocytes are a clue to diagnosis of early infection by herpesvirus.

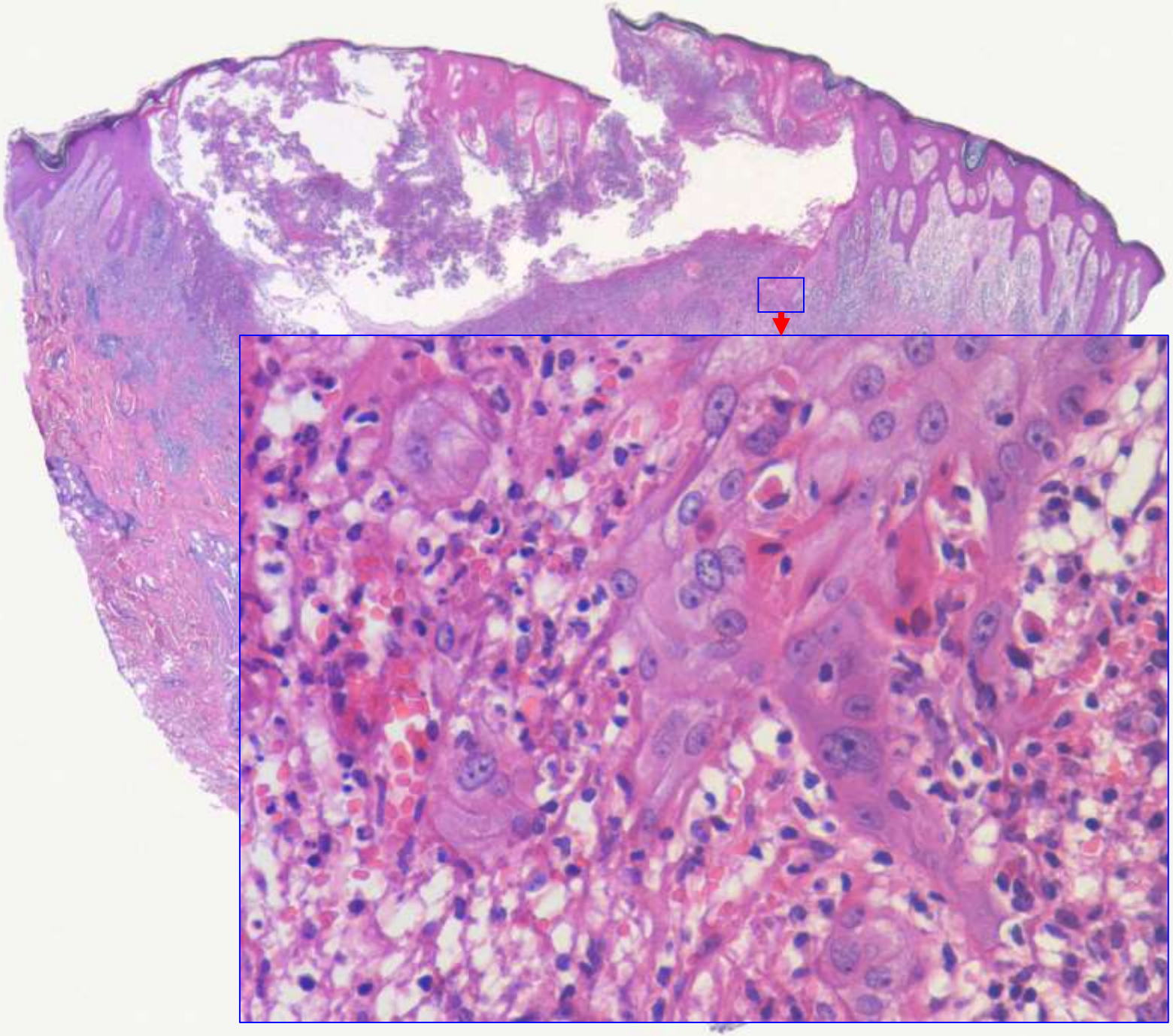
CLUES

To Diagnosis in Dermatopathology

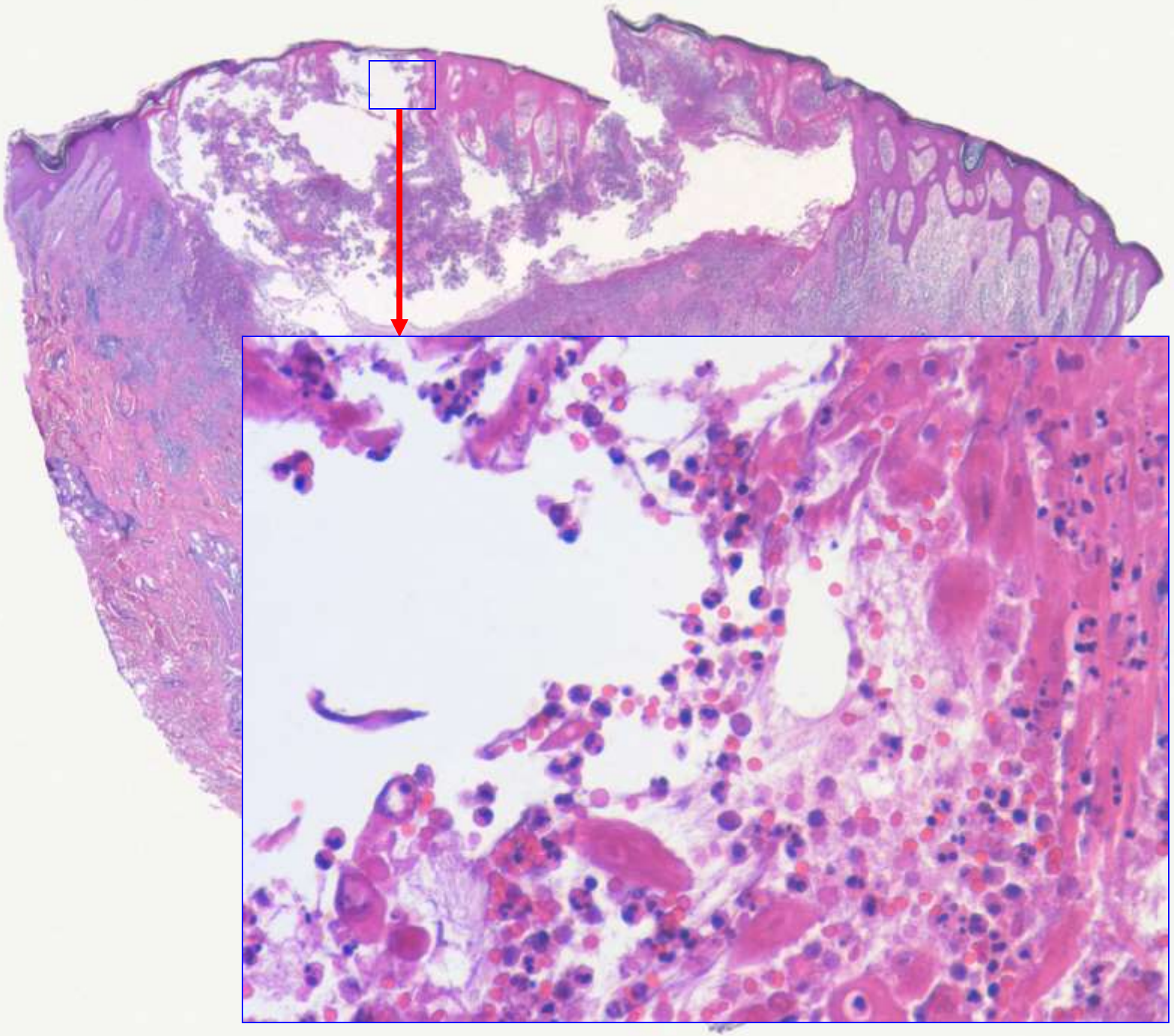
A. Bernard Ackerman

Mark Jacobson Patricia Vitale

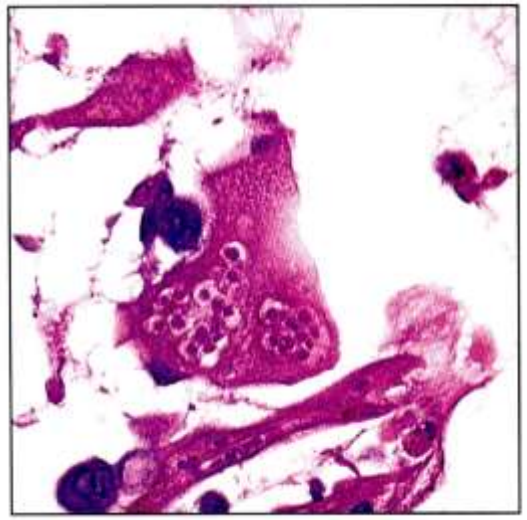
Those changes have been emphasized as a diagnostic clue by Bernard Ackerman: *“Steel-gray nuclei and margination of nucleoplasm of keratinocytes are a clue to diagnosis of early infection by herpesvirus.”*



Another cytopathic effect of herpesvirus infection is confluence of individual cells into multinucleated epithelial cells.



The latter eventually become necrotic, and those necrotic multinucleated epithelial cells may be the only indicator of herpesvirus infection in older lesions:



Ghosts of multinucleated epithelial giant cells are a clue to infection by herpesvirus.

CLUES

To Diagnosis in Dermatopathology

A. Bernard Ackerman

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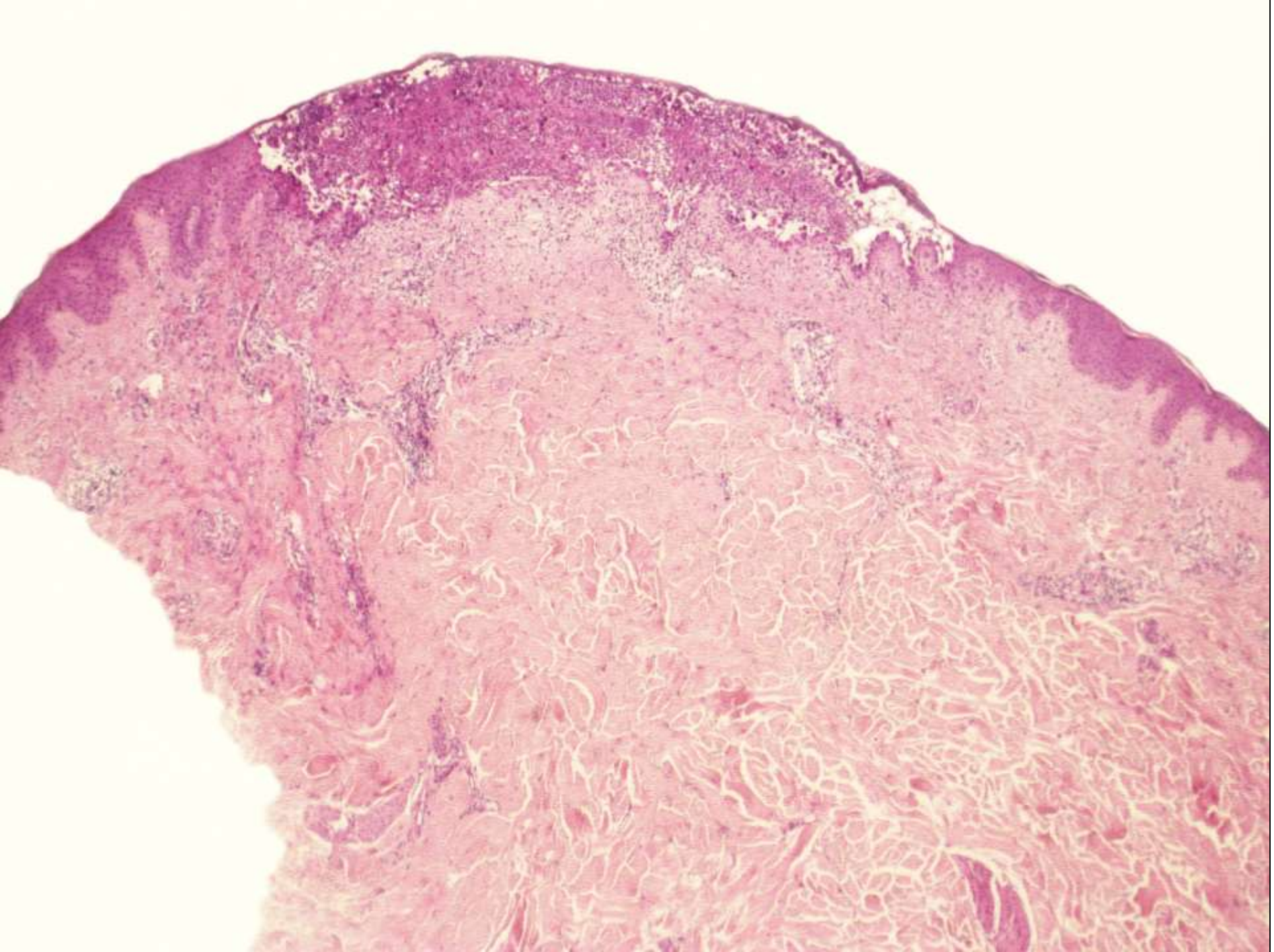
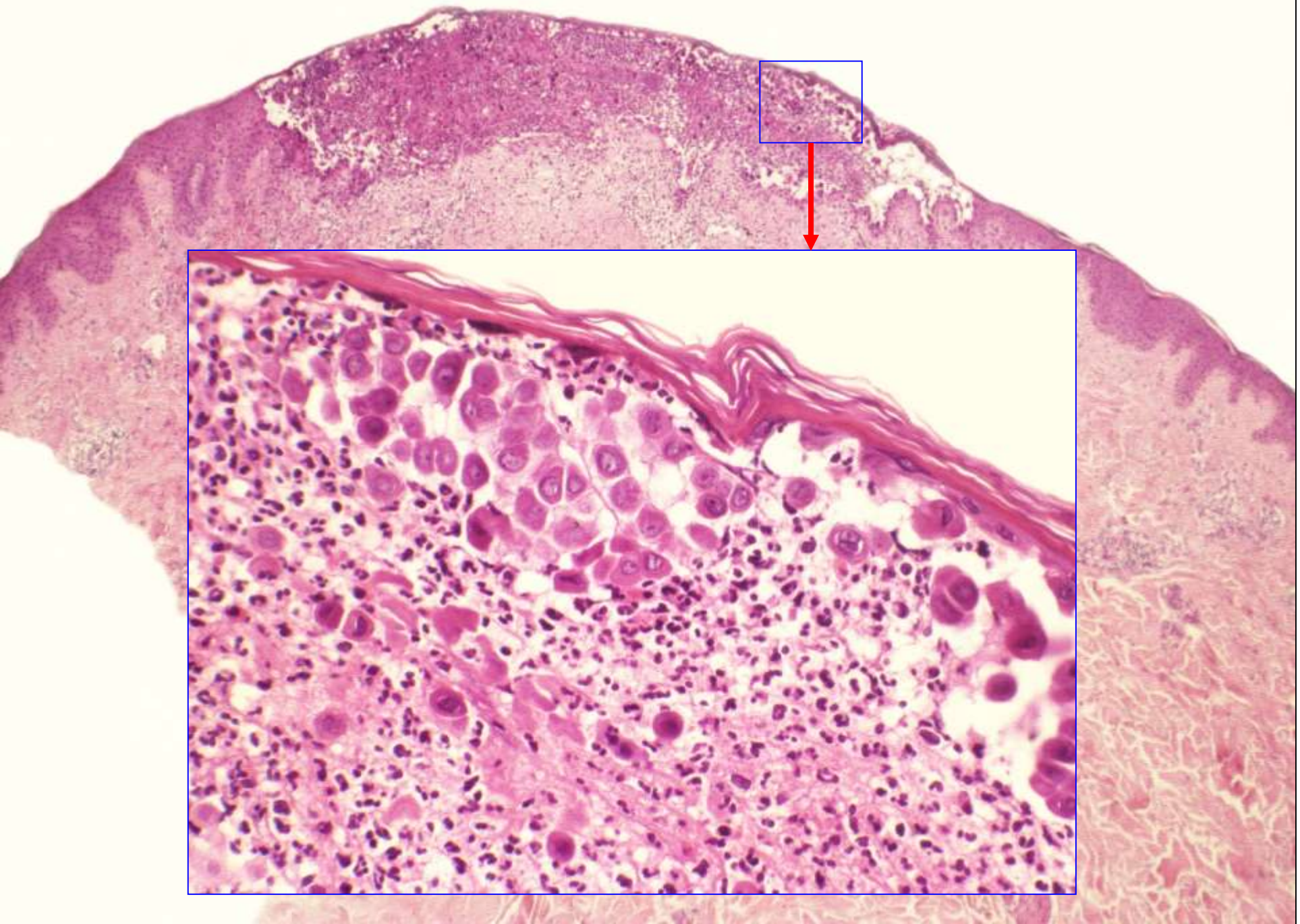
"Ghosts of multinucleated epithelial giant cells are a clue to infection by herpesvirus."



There are several other clues to infection by herpesvirus. One is myriad neutrophils within the cavity of a blister. That finding, a “busy blister,” can be appreciated already at scanning magnification.



It is helpful in cases such as this one that do not show diagnostic cytopathic features, or only hints of them. Moreover, there is prominent acantholysis that may be misconstrued as evidence of pemphigus or, especially, Grover's disease.

Pseudoherpetic Grover Disease: Report of 2 Cases and Review of the Literature

Ginger L. Wiersma, BS, Arturo P. Saavedra, MD, PhD, MBA,†‡§ F. Clarissa Yang, MD,‡ Tina R. Nandi, MD,‡ Danielle Levine, MD,¶ and George F. Murphy, MD†‖*

Abstract: Two cases of a pseudoherpetic variant of Grover disease are presented. The first patient was a 60-year-old woman who had high fevers in combination with right lower lobe pneumonia. She developed an itchy papulovesicular rash on her back and upper abdomen. The second patient was a 68-year-old woman who while bedridden developed an itchy papulovesicular rash on her back. Vesiculobullous forms of dermatitis were clinically suspected in both cases, and herpetic vesicles were the lead diagnosis in one case. Pathologically, lesions from both patients revealed intraepidermal fluid-filled vesicles that at scanning magnification raised the suspicion of herpetic lesions. At higher magnification, acantholytic cells, some seemingly multinucleated, could be ppreciated. However, immunohistochemistry for herpes simplex virus and varicella zoster virus antigens proved negative. Moreover, some of the lesional cells revealed dyskeratosis more typical of the spongiotic/vesicular variant of Grover disease, and accordingly, this diagnosis was eventually established in both patients. Recognition of the pseudoherpetic variant of spongiotic/vesicular Grover disease is important in determining correct treatment, and therefore, subtle clues to its diagnosis should be sought in evaluation of such lesions.

Key Words: Grover disease, acantholytic dermatosis, pseudoherpetic, vesicular variant, dyskeratosis

(*Am J Dermatopathol* 2014;36:746–750)

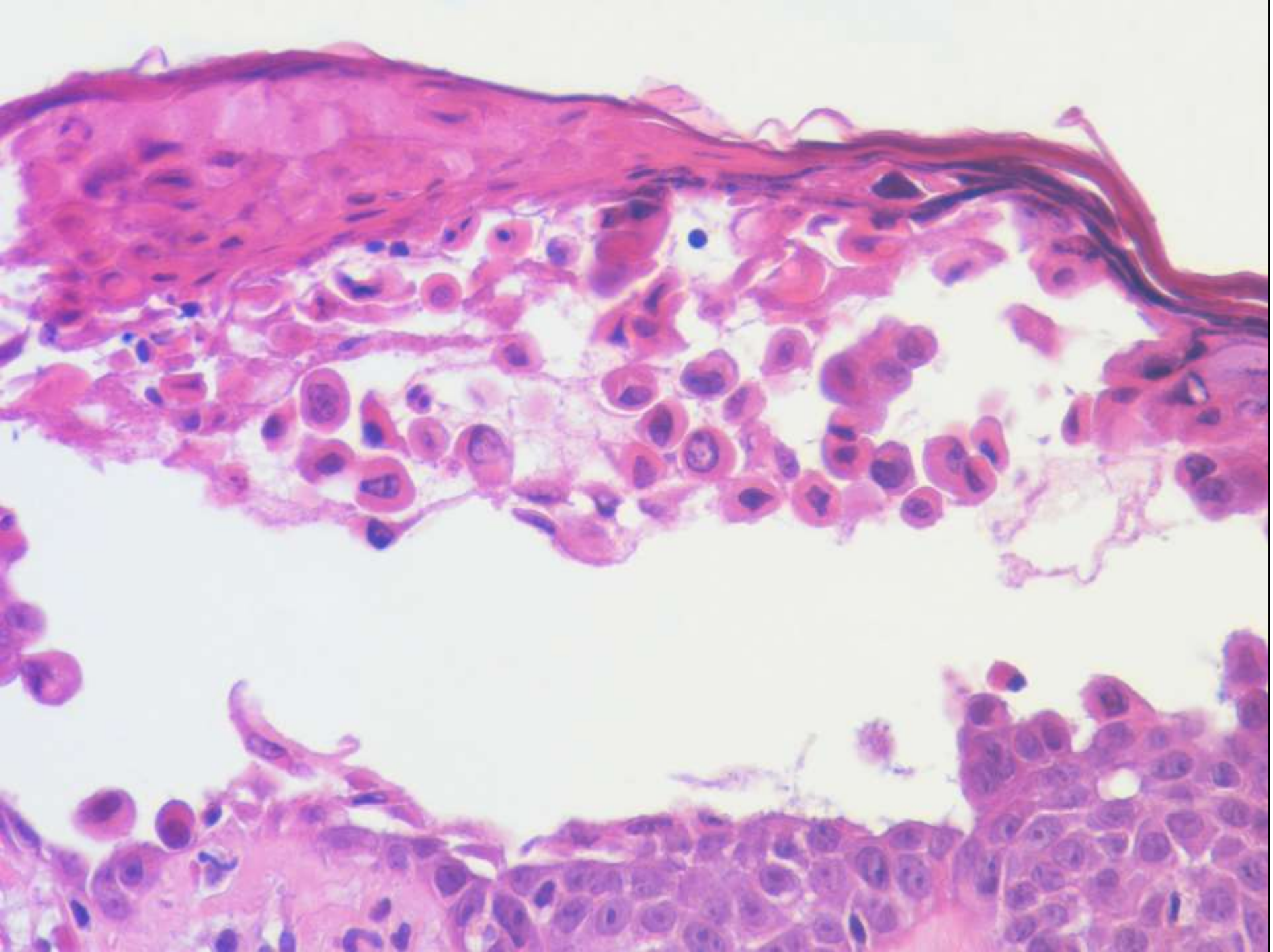
vesicles and even bullae are seen. The current diagnostic criteria for Grover disease involve both clinical and pathological features. Clinical lesions are pruritic, erythematous, nonfollicular crusted papules and papulovesicles located primarily on the trunk. Etiologic factors that have been hypothesized as either causal or precipitating include heavy sweat-inducing exercise, excessive sun exposure, heat exposure, or persistent fevers. Some cases have been reported with administration of ribavirin, cetuximab, IL-4, and sulfadoxine-pyrimethamine.[5–7] The histopathology reveals acantholysis, a variable degree of dyskeratosis and intraepidermal clefting.[1] The histological differential diagnosis for Grover disease is often broader than that of the clinical, as multiple variants have been described. Moreover, these variants may resemble other primary acantholytic diseases, including Darier disease, pemphigus vulgaris, pemphigus foliaceus, benign familial pemphigus (Hailey–Hailey disease), and various spongiotic conditions. When multiple intraepidermal patterns of acantholysis and dyskeratosis are seen in the same specimen focally, Grover disease is often diagnosed.[8,10–12]

Clinical Case Summary

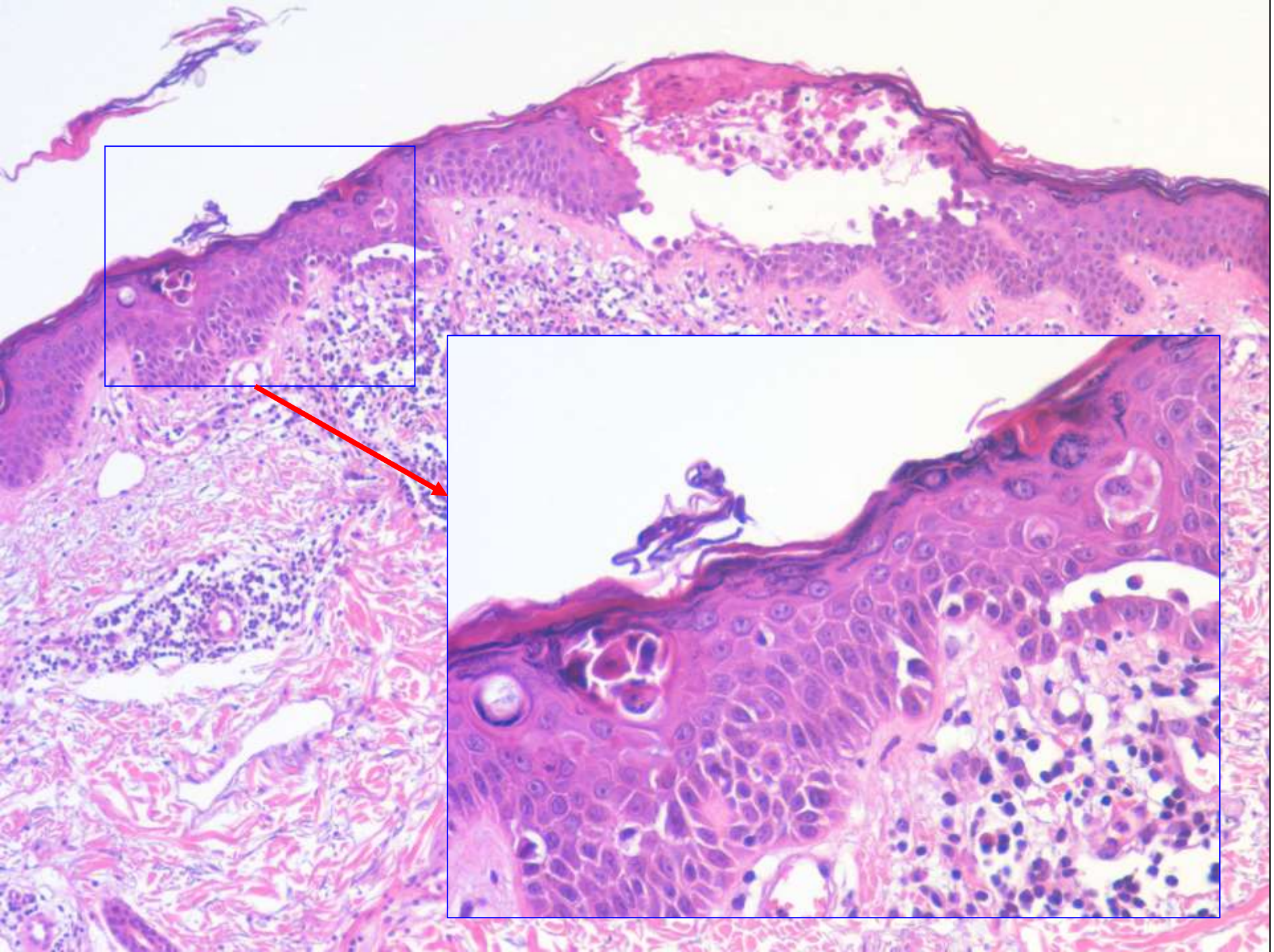
Patient 1

The first patient was a 60-year-old woman who developed a mildly pruritic rash on her back 2 days after initiation of treatment with azithromycin for right lower lobe

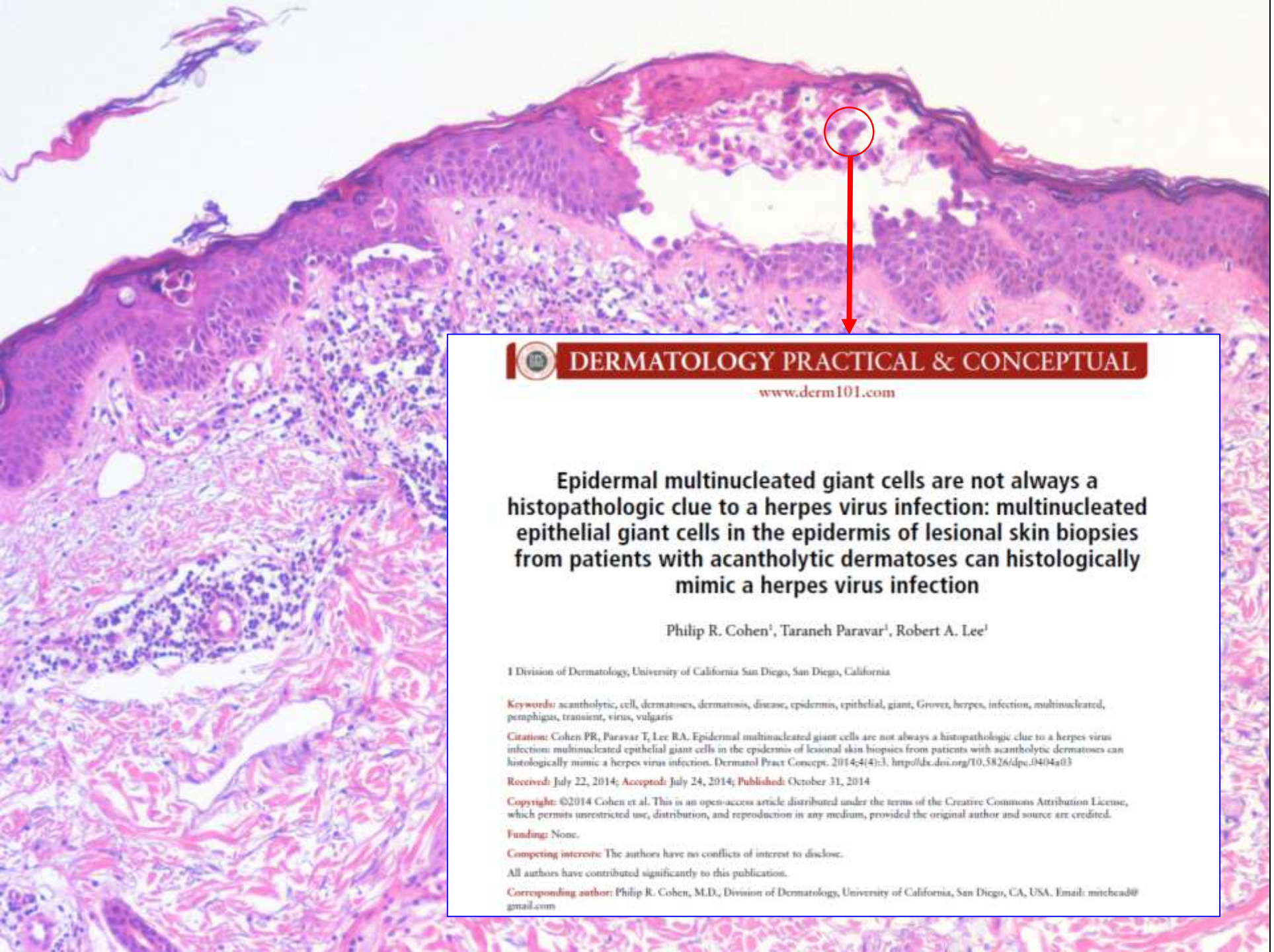
Vice versa, the latter may mimick infections by herpesvirus, a phenomenon described as “pseudoherpetic Grover disease.”



This is an example: an acantholytic blister with cells that resemble, to some degree, the cytopathic effects seen in infections by herpesvirus. There are even some multinucleated epithelial cells. Nonetheless, this is not a herpetic blister but Grover’s disease,



and more typical signs of focal acantholytic dyskeratosis are seen right next to the blister. Hence, if there are no cells with steel-gray nuclei and margination of nucleoplasm, one must be cautious not to overcall herpesvirus infections.



DERMATOLOGY PRACTICAL & CONCEPTUAL

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Epidermal multinucleated giant cells are not always a histopathologic clue to a herpes virus infection: multinucleated epithelial giant cells in the epidermis of lesional skin biopsies from patients with acantholytic dermatoses can histologically mimic a herpes virus infection

Philip R. Cohen[1], Taraneh Paravar[1], Robert A. Lee[1]

1 Division of Dermatology, University of California San Diego, San Diego, California

Keywords: acantholytic, cell, dermatoses, dermatosis, disease, epidermis, epithelial, giant, Grover, herpes, infection, multinucleated, pemphigus, transient, virus, vulgaris

Citation: Cohen PR, Paravar T, Lee RA. Epidermal multinucleated giant cells are not always a histopathologic clue to a herpes virus infection: multinucleated epithelial giant cells in the epidermis of lesional skin biopsies from patients with acantholytic dermatoses can histologically mimic a herpes virus infection. Dermatol Pract Concept. 2014;4(4):3. http://dx.doi.org/10.5826/dpc.0404a03

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All authors have contributed significantly to this publication.

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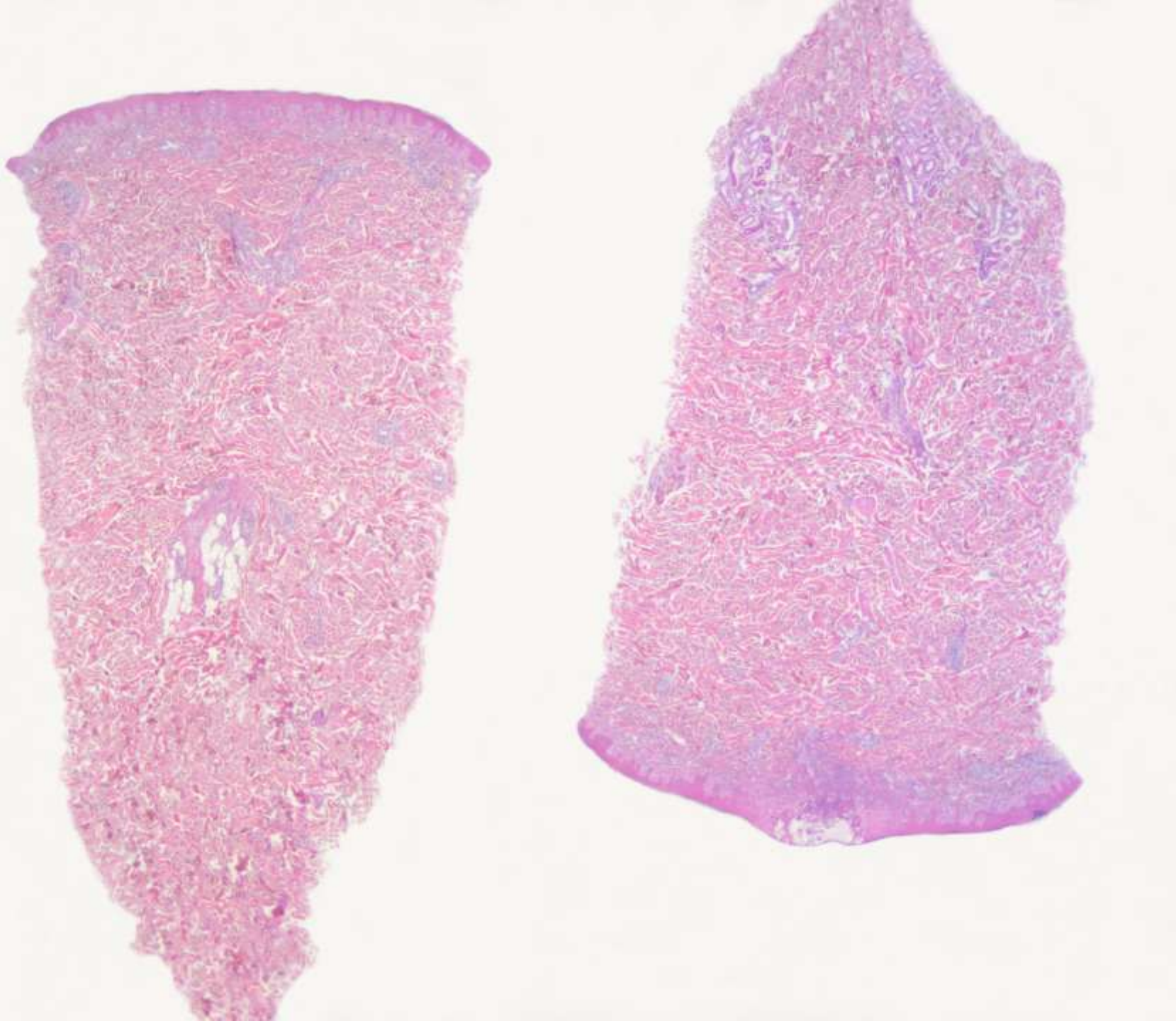
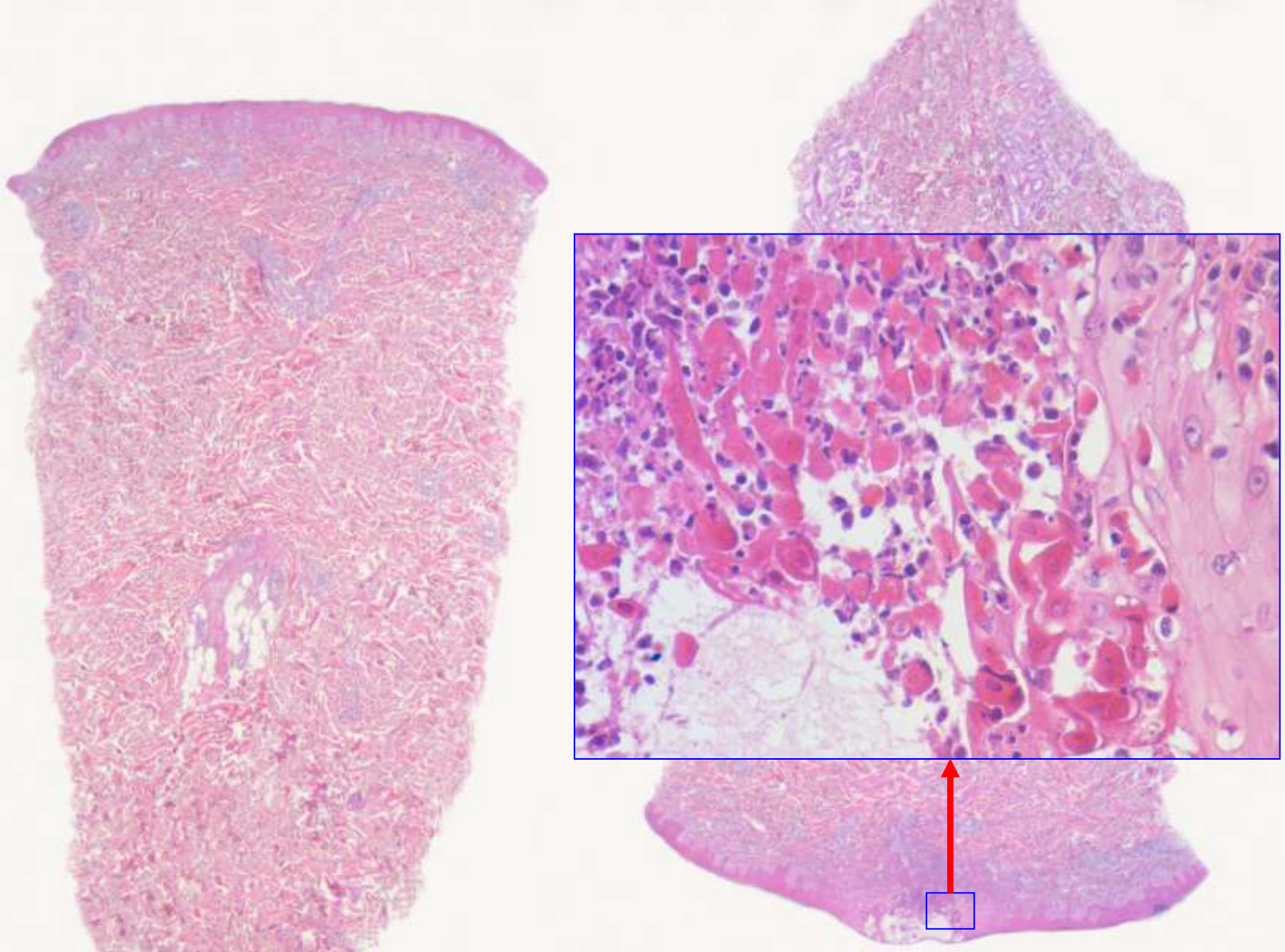
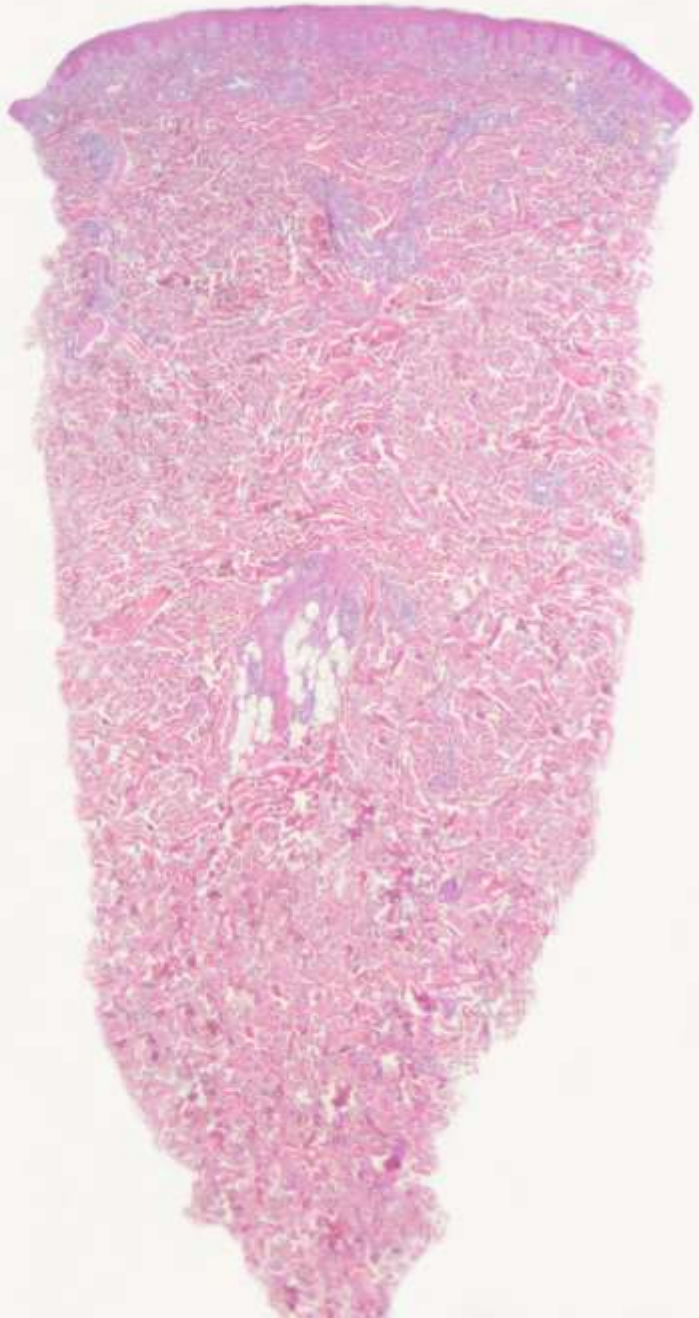
As emphasized recently, even multinucleated epithelial cells are *“not always a histopathologic clue to a herpes virus infection”* but may be seen occasionally in other acantholytic dermatoses *“histologically mimicking a herpes virus infection.”* As emphasized recently, even multinucleated epithelial cells are *“not always a histopathologic clue to a herpes virus infection”* but may be seen occasionally in other acantholytic dermatoses *“histologically mimicking a herpes virus infection.”*



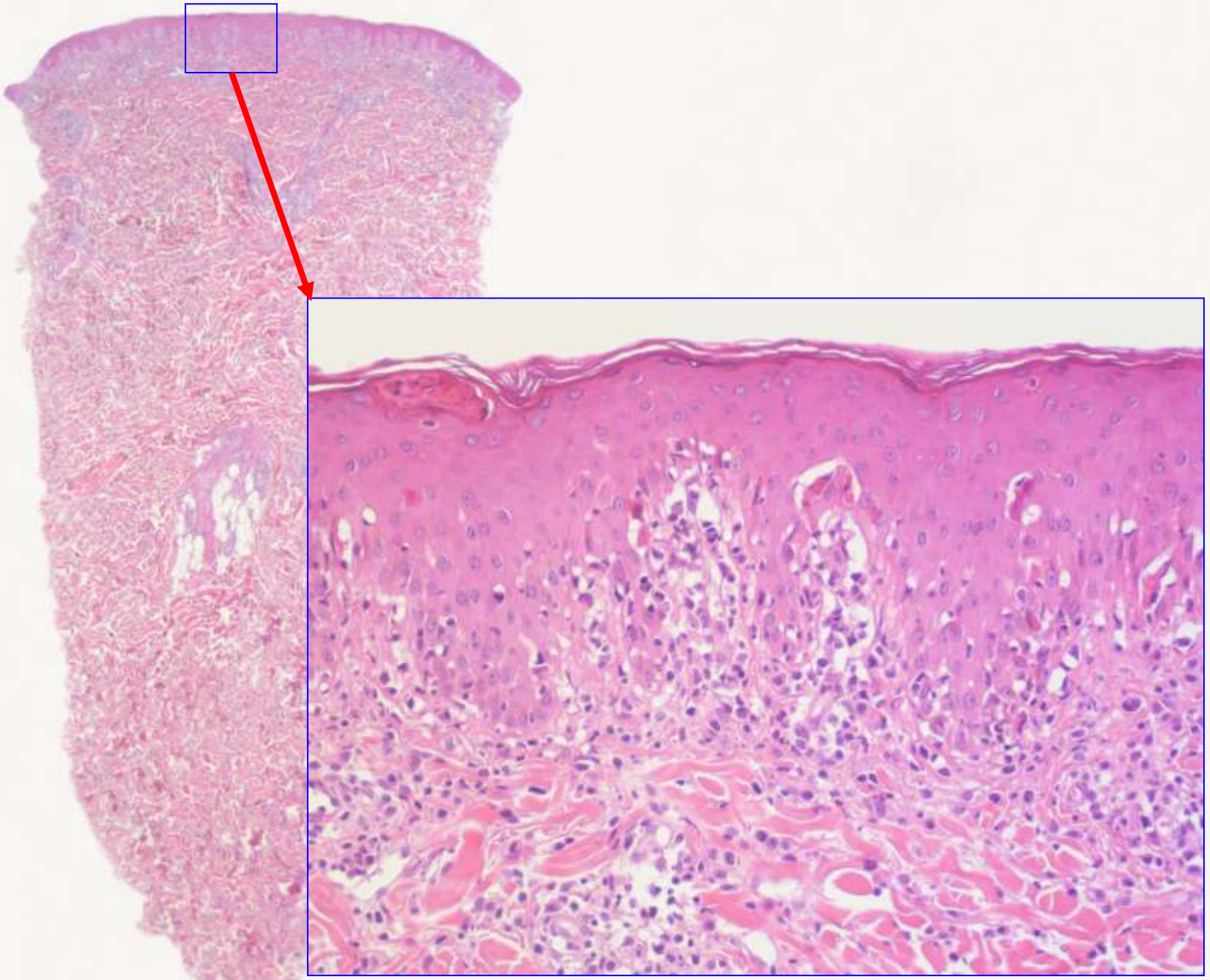
The typical histopathologic features of herpesvirus infection are often limited to small foci. In this bisectioned specimen,



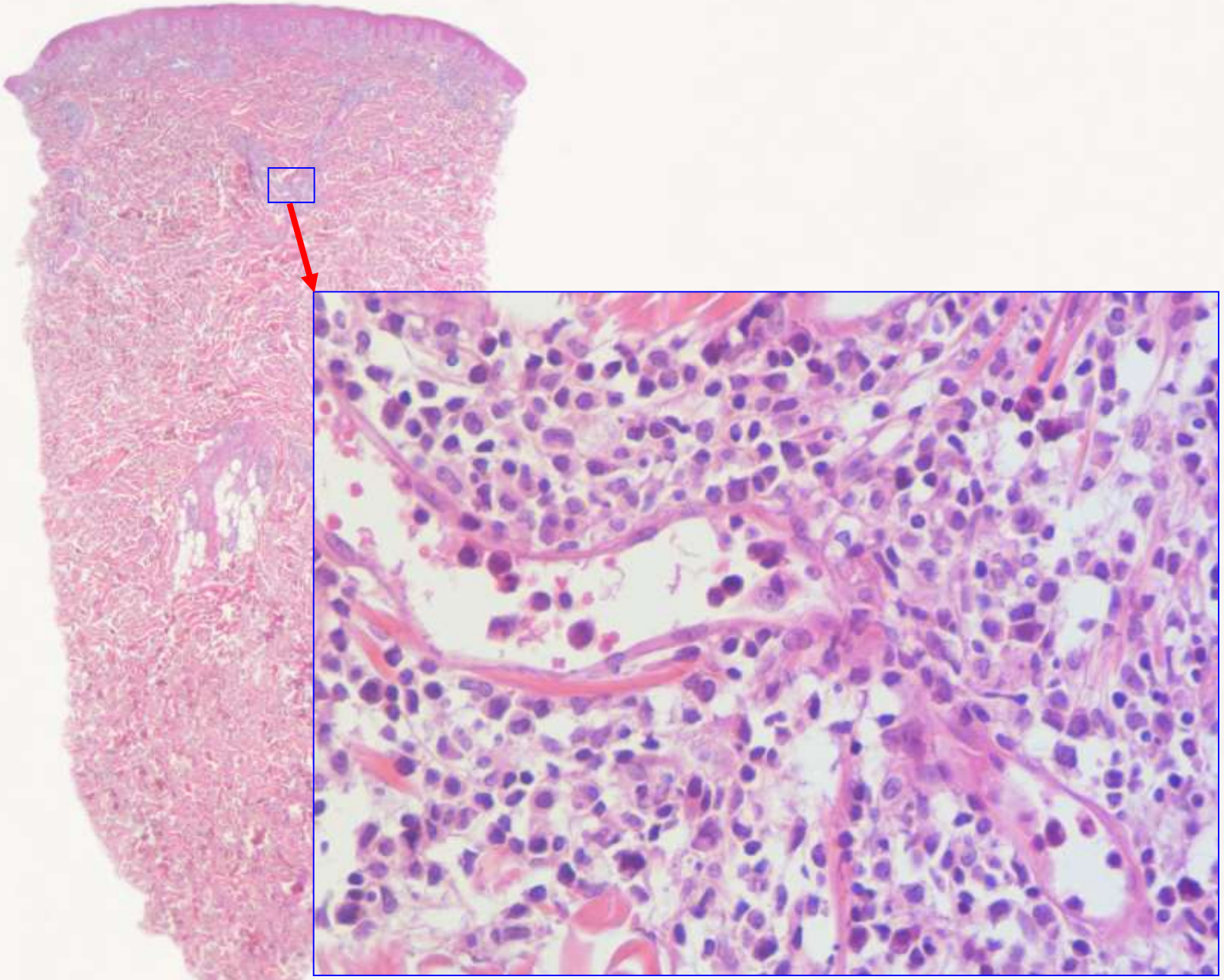
they are only present in the center of one cut. Here one sees numerous necrotic multinucleated giant cells,



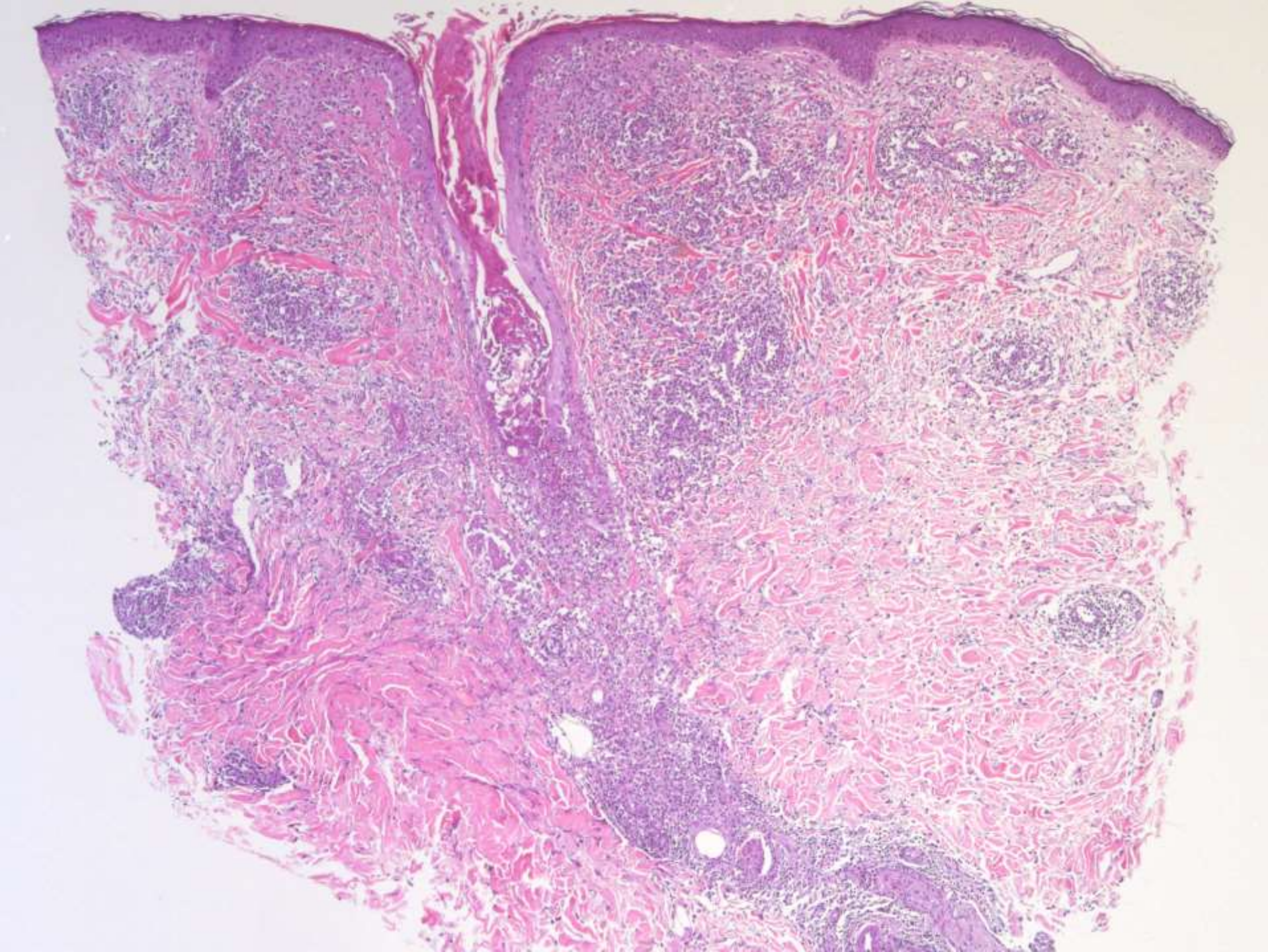
but the other section shows no such findings. There is a superficial and deep wedge-shaped infiltrate



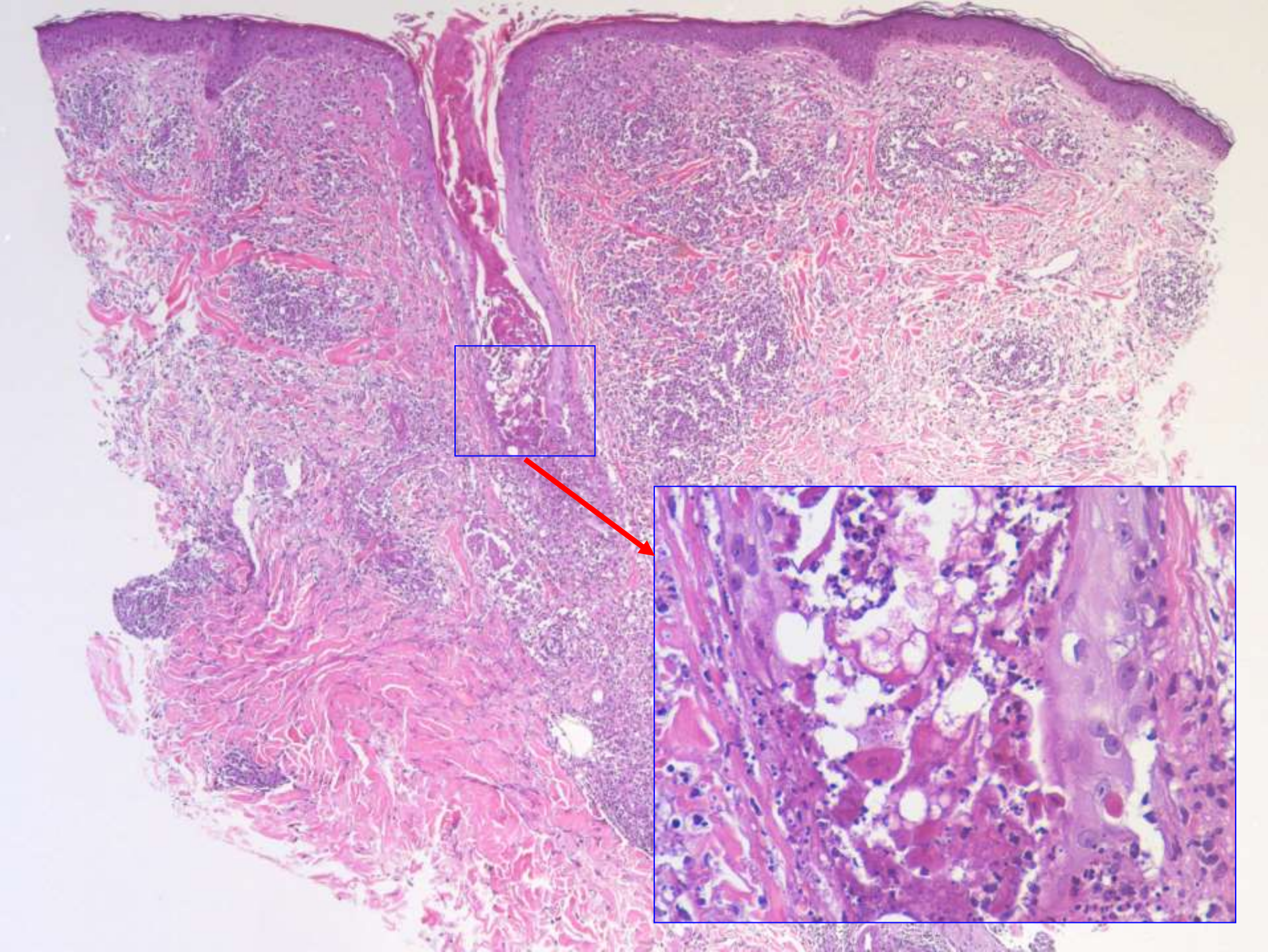
in concert with vacuolar changes at the junction and numerous necrotic keratocytes, changes that may be confused with acute pityriasis lichenoides. The pattern of vacuolar interface dermatitis, however, is seen commonly in the early stage of infections by herpesvirus.



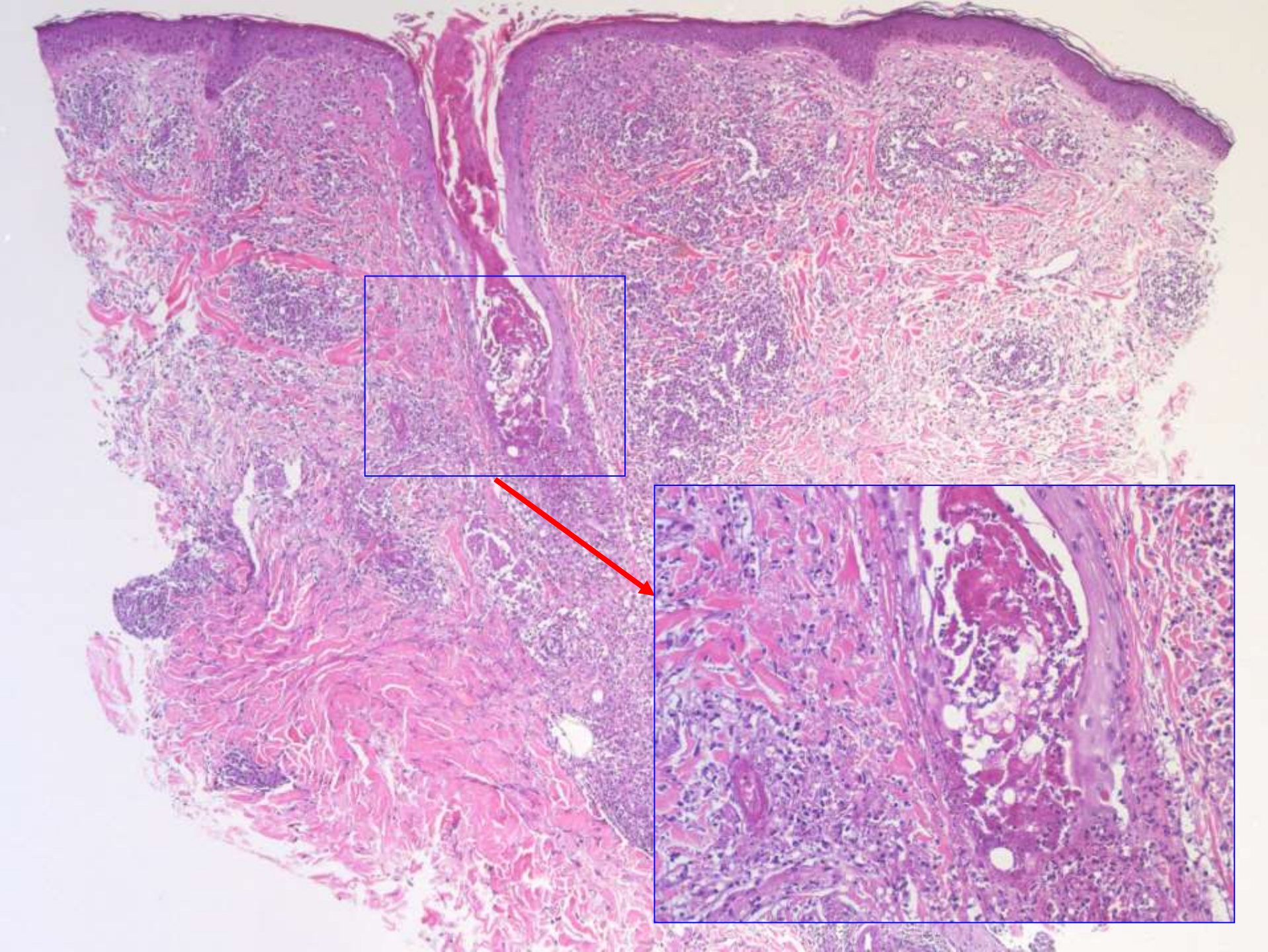
The infiltrate is composed of lymphocytes only, and many of those lymphocytes have large and somewhat atypical nuclei, findings that may be seen in pityriasis lichenoides – but also in infections by herpesvirus.



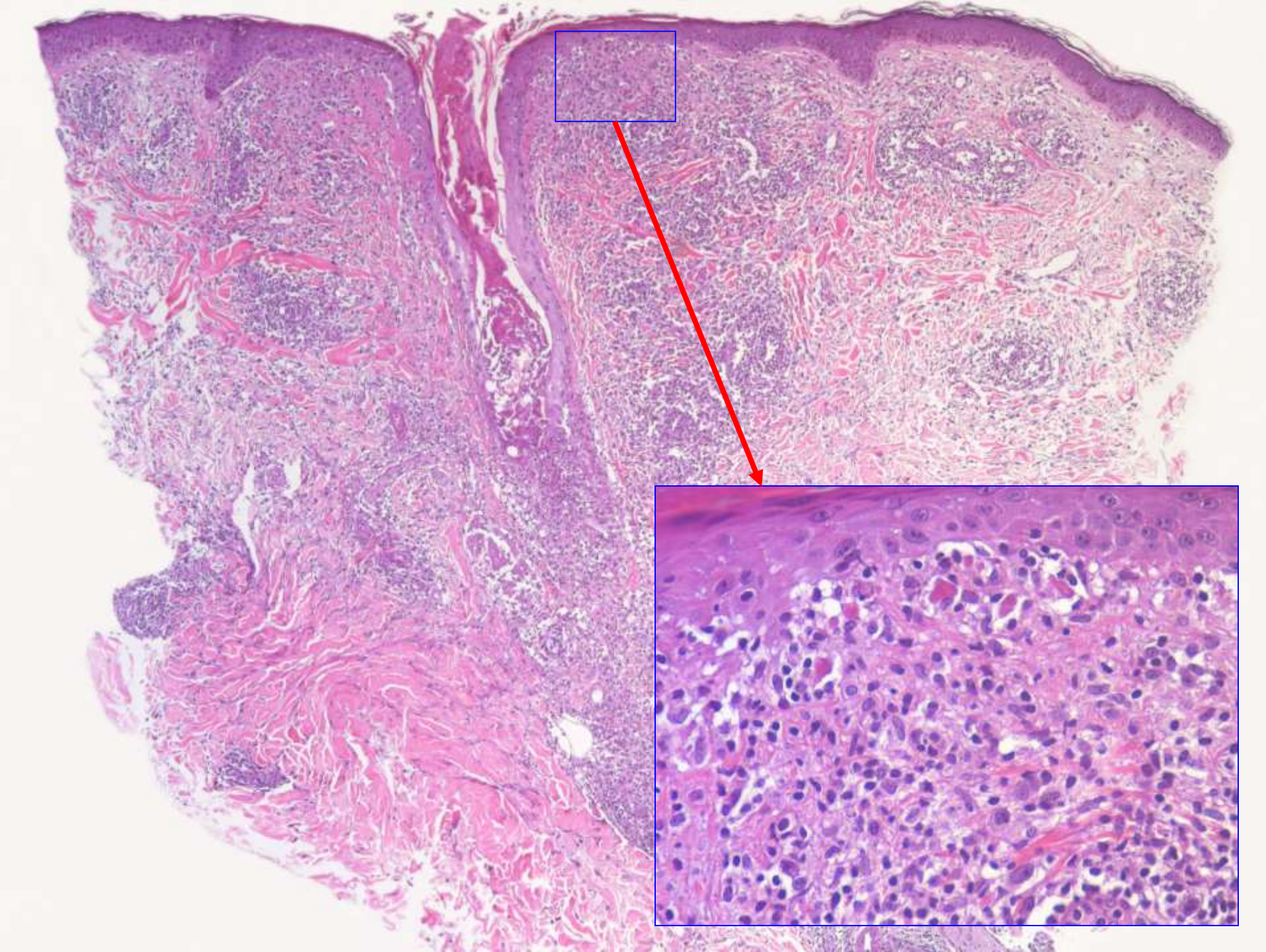
A distinctive feature of infections by herpesvirus is preferential involvement of follicles. In this lesion, the epidermis is nearly normal, and the cytopathic changes induced by herpesvirus are restricted to an infundibulum



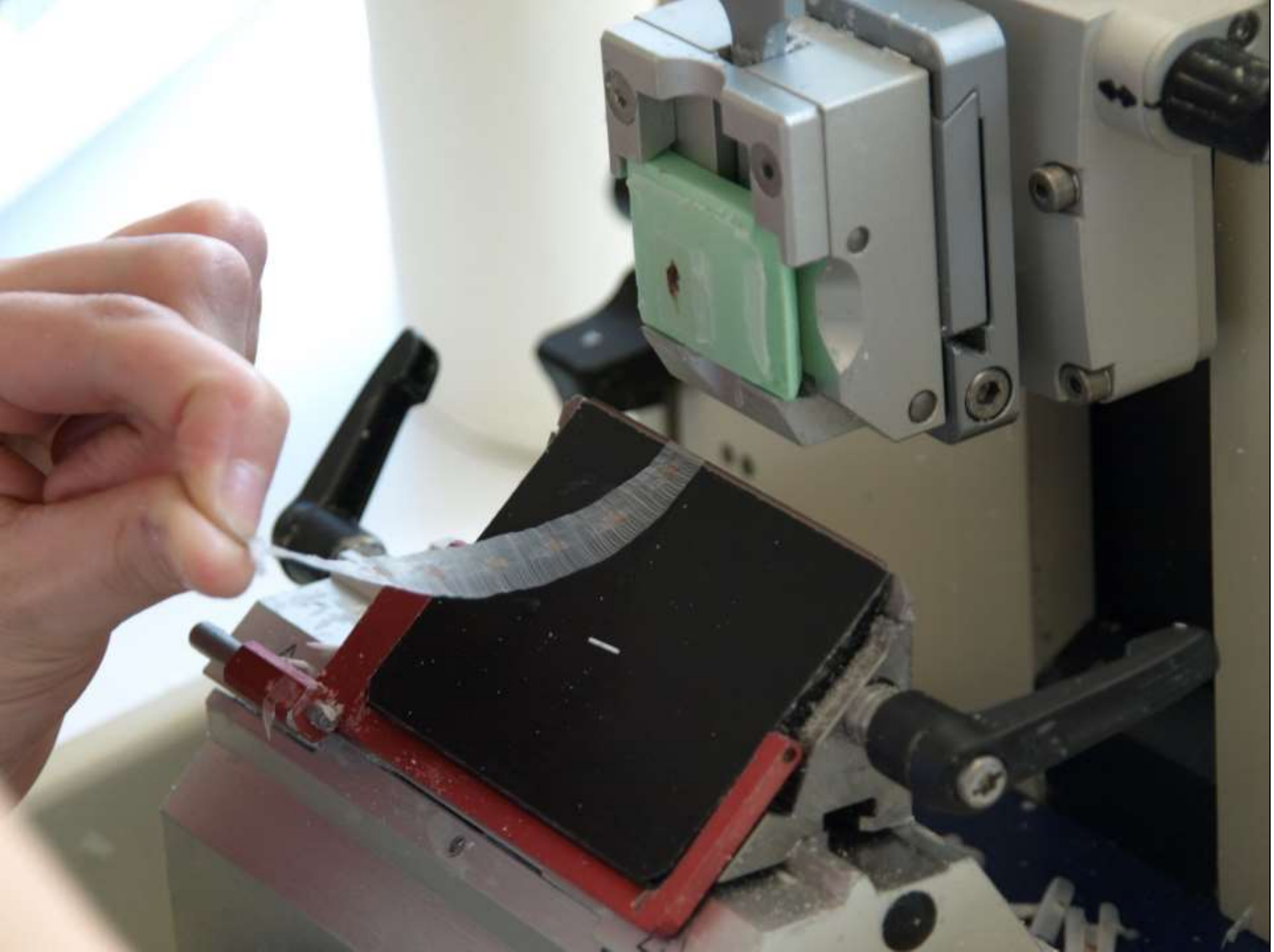
that also shows necrosis of keratocytes and sebocytes. Especially necrosis of sebocytes, sometimes involving an entire sebaceous lobule, is pathognomonic of herpesvirus.



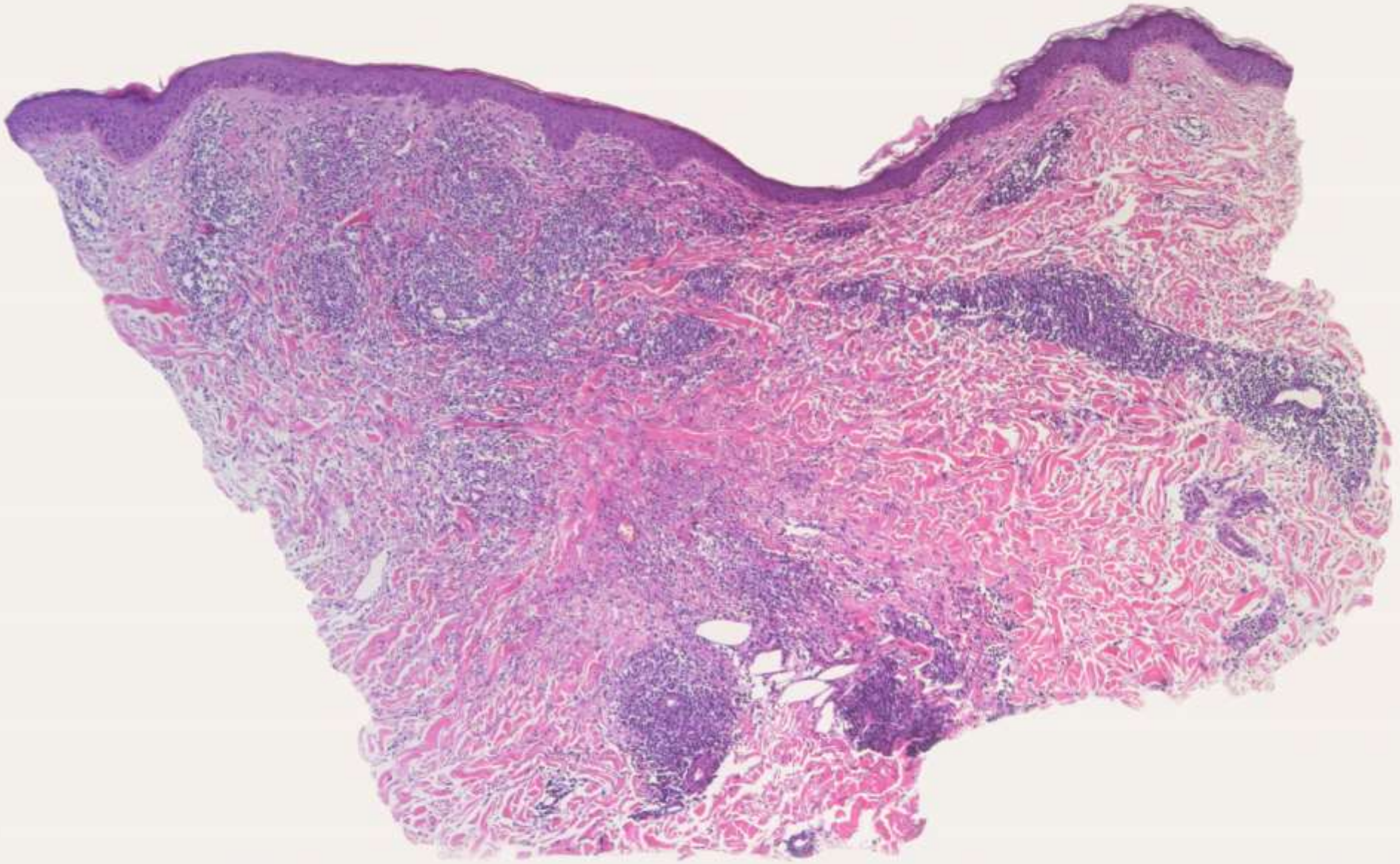
Two other subtle clues are present in this specimen, namely, focal vasculitis with fibrin in the wall of blood vessels



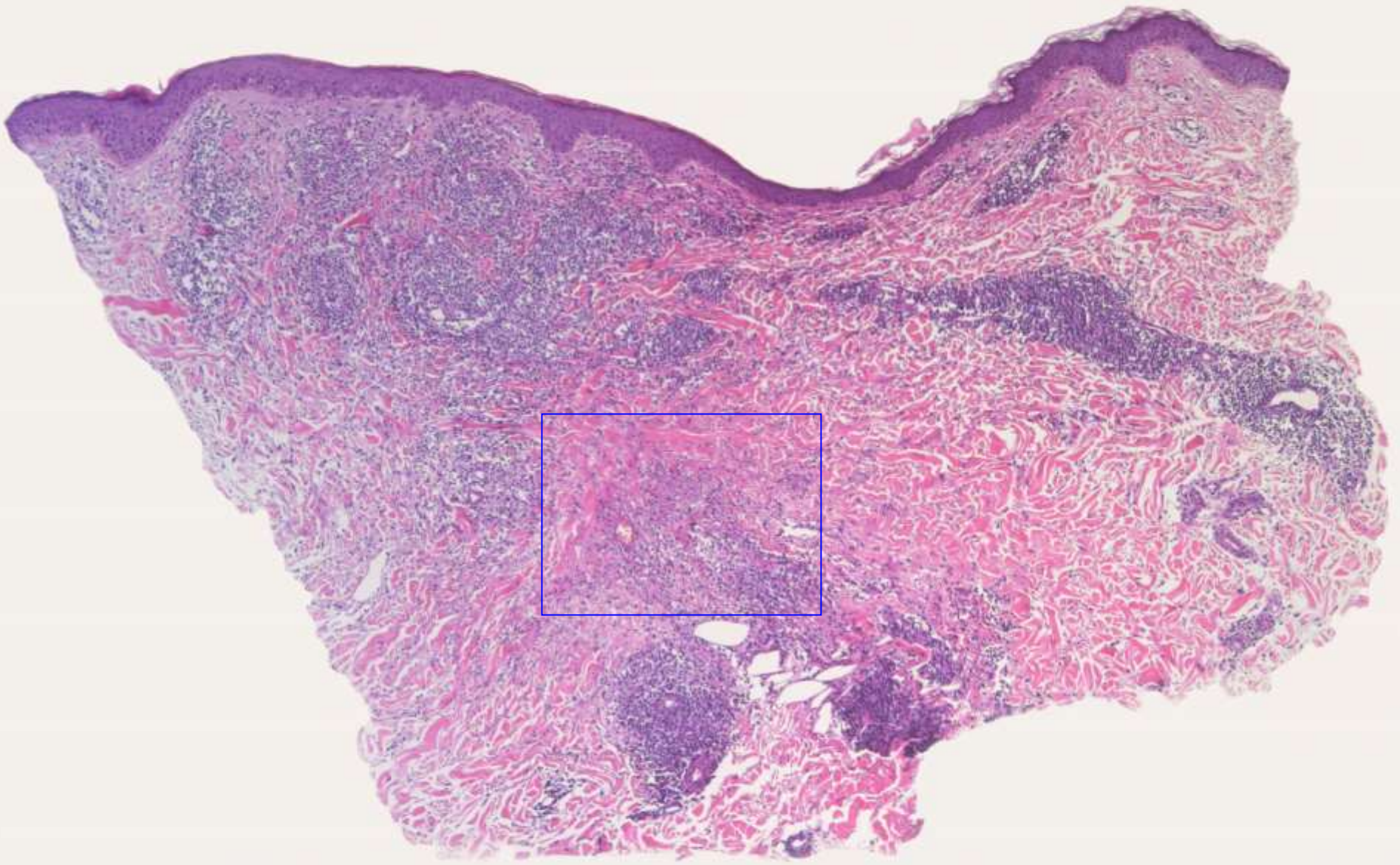
and focal signs of vacuolar interface dermatitis. Of course, those clues are not needed in the presence of all other findings, but they may alert to the possibility of a herpesvirus infection in cases not immediately diagnostic.



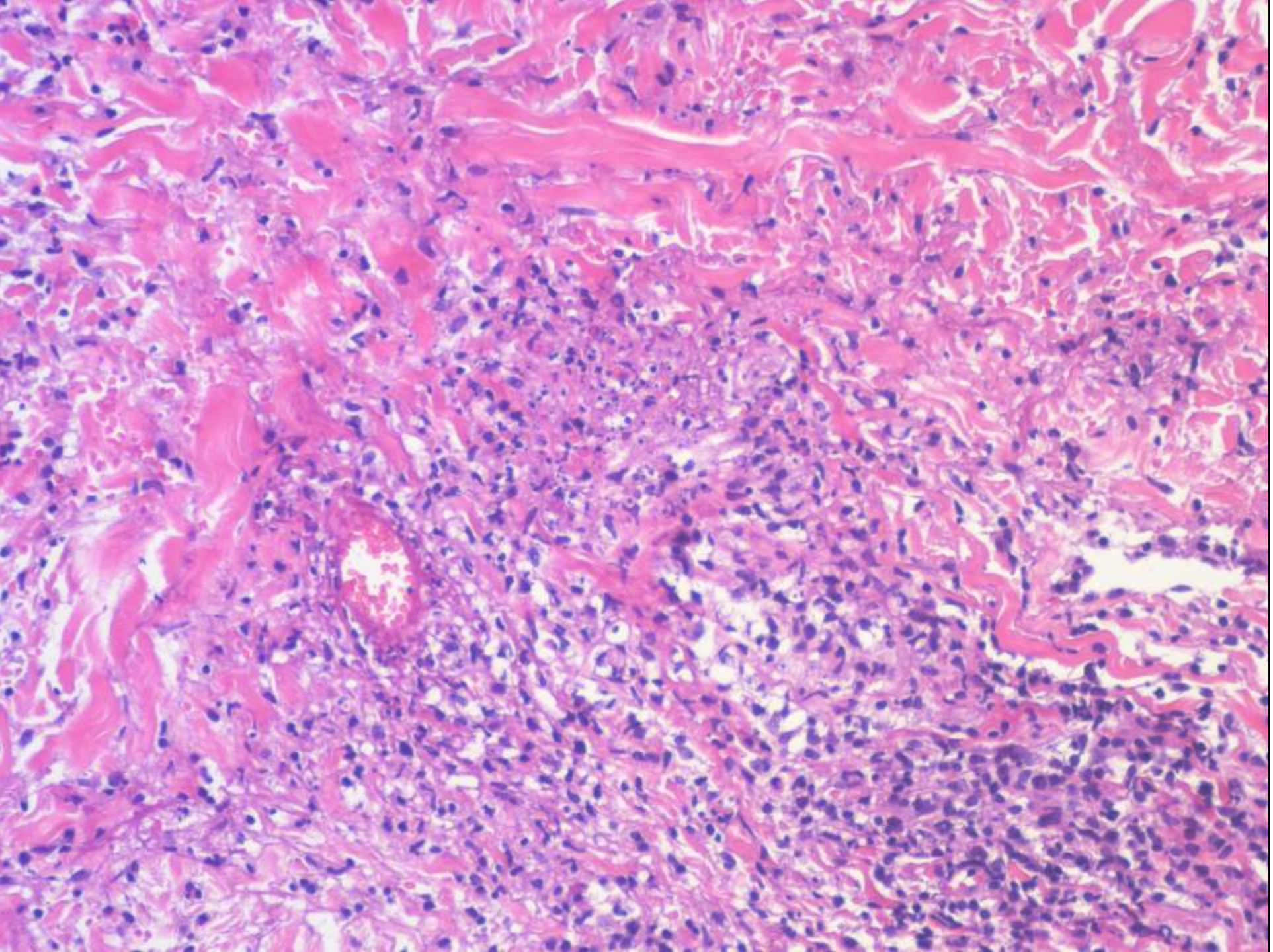
This can be demonstrated by cutting a few step sections through this specimen.



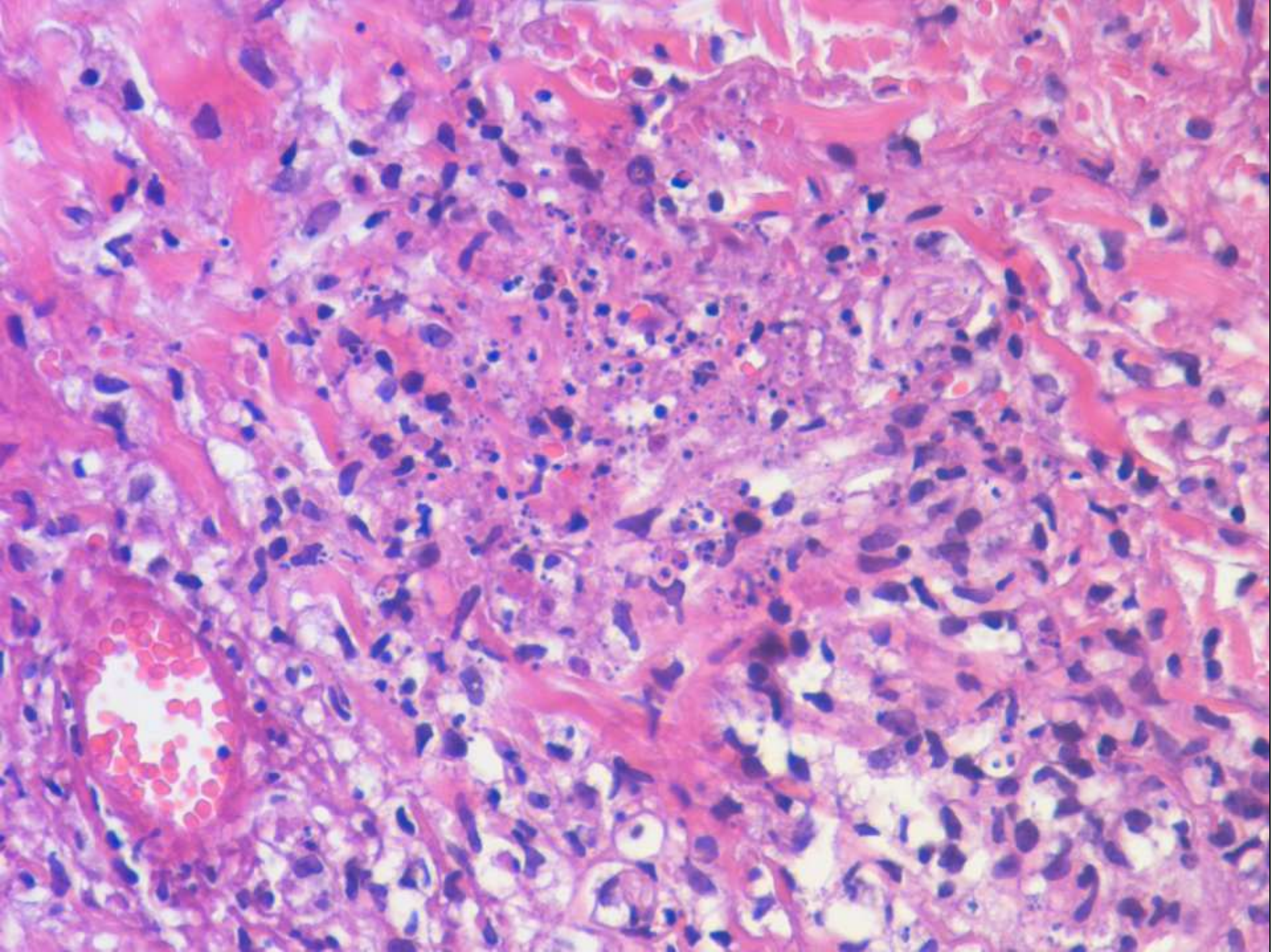
Only a few levels further down, the follicle is no longer present, and, in its stead, one sees a vertically oriented zone of fibrosis reflecting the orientation of the neighbouring follicle,



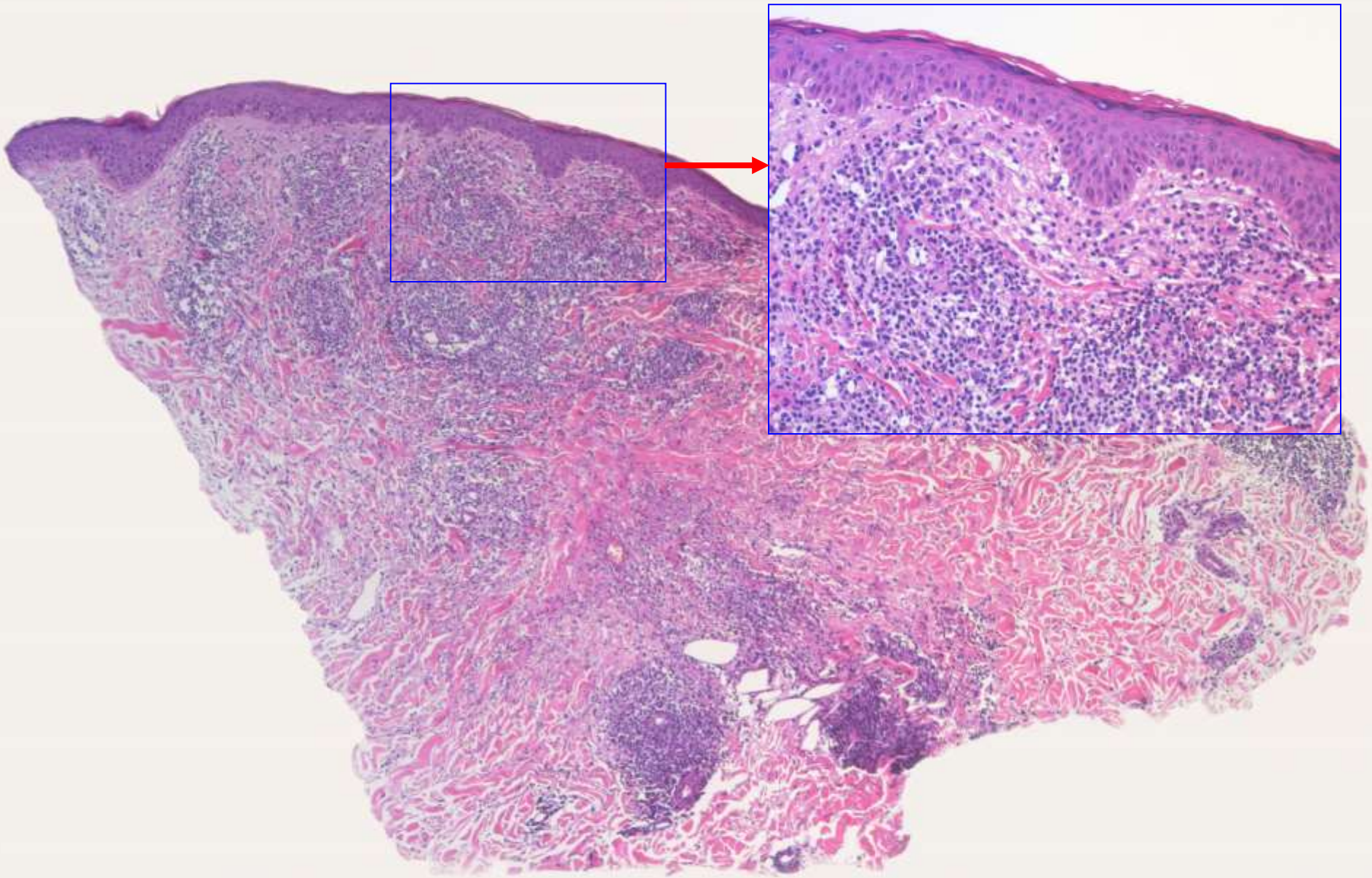
reflecting the orientation of the neighbouring follicle,



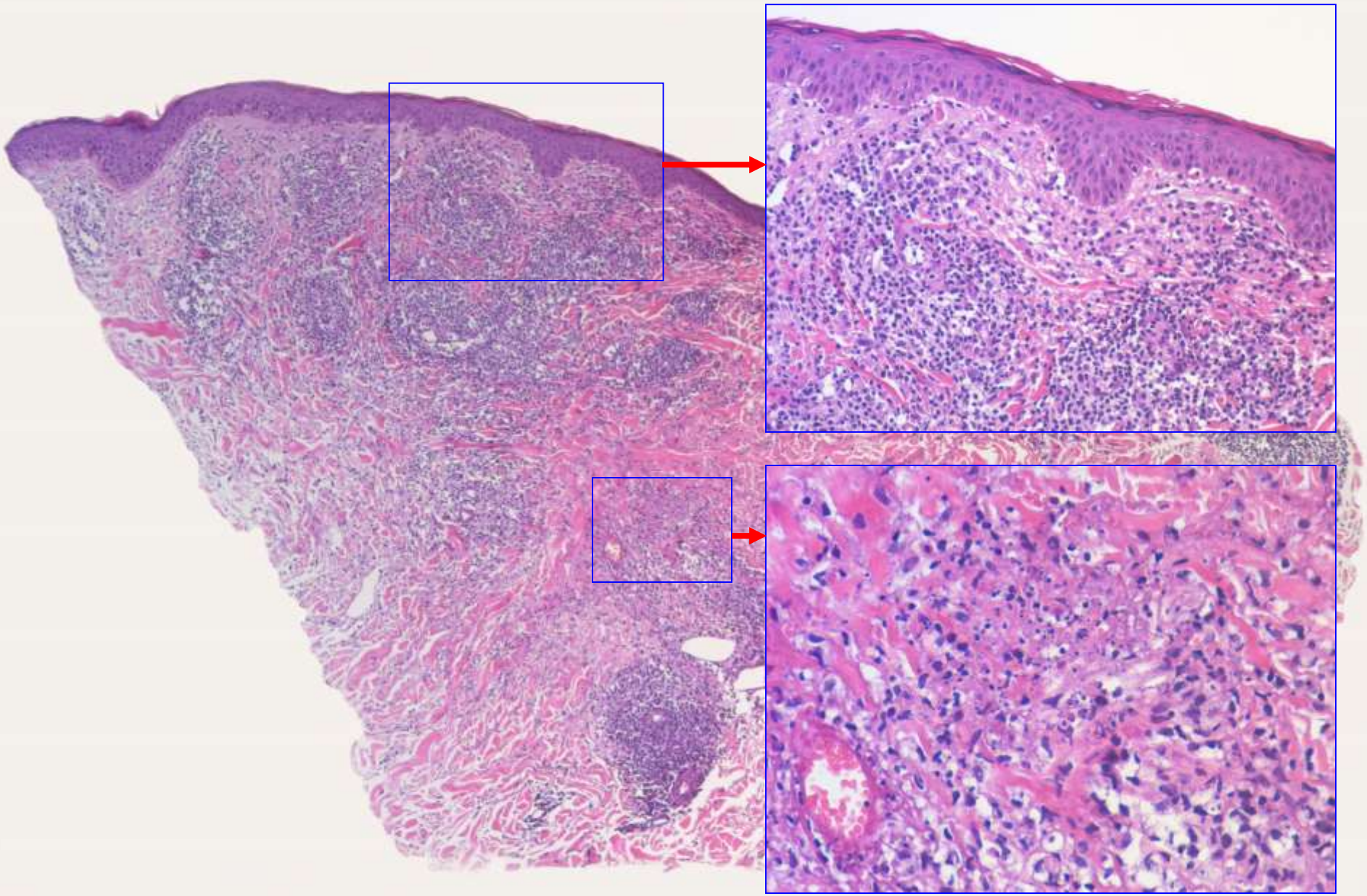
with a dense infiltrate of largish lymphocytes and neutrophils



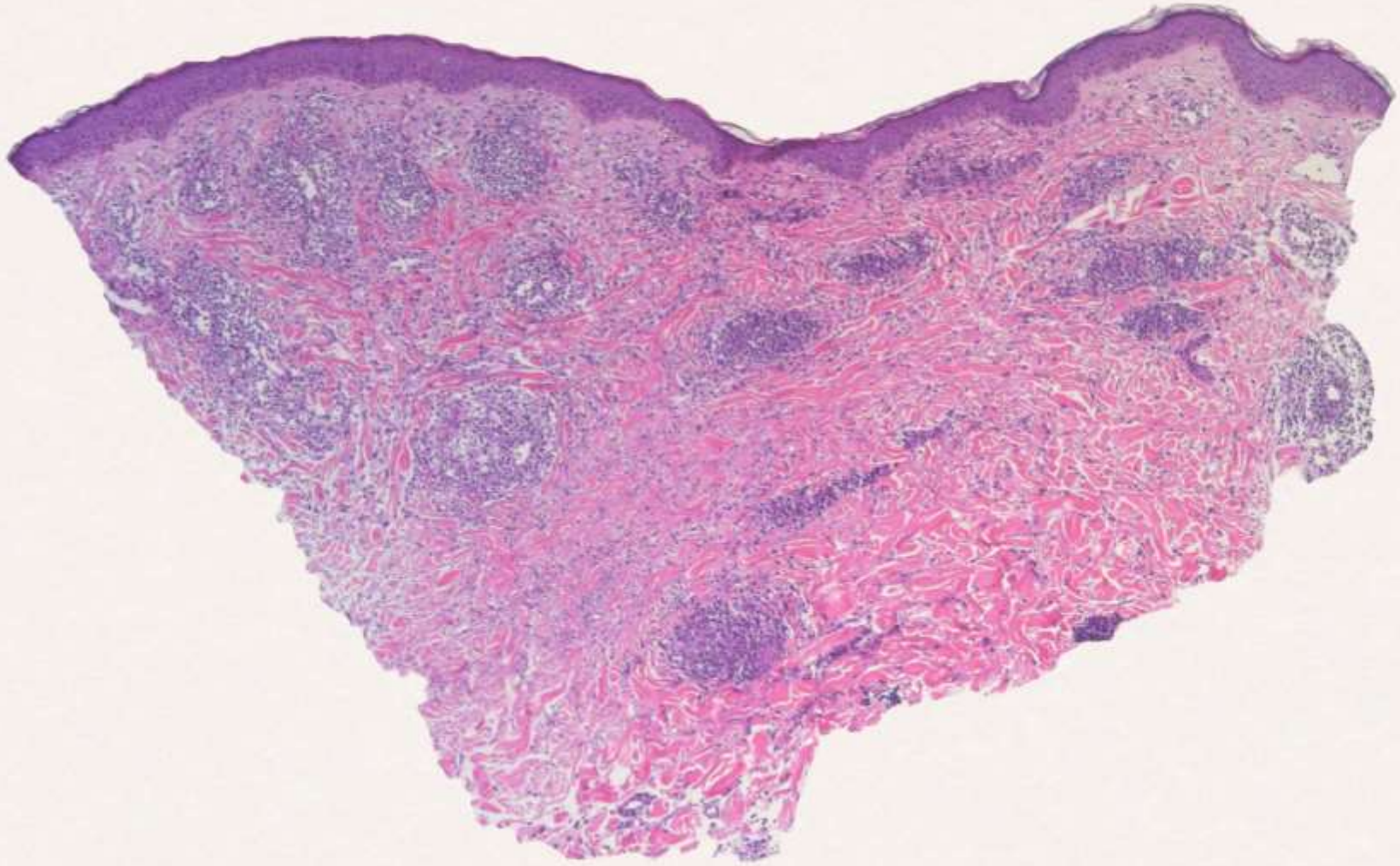
with abundant neutrophilic nuclear dust.



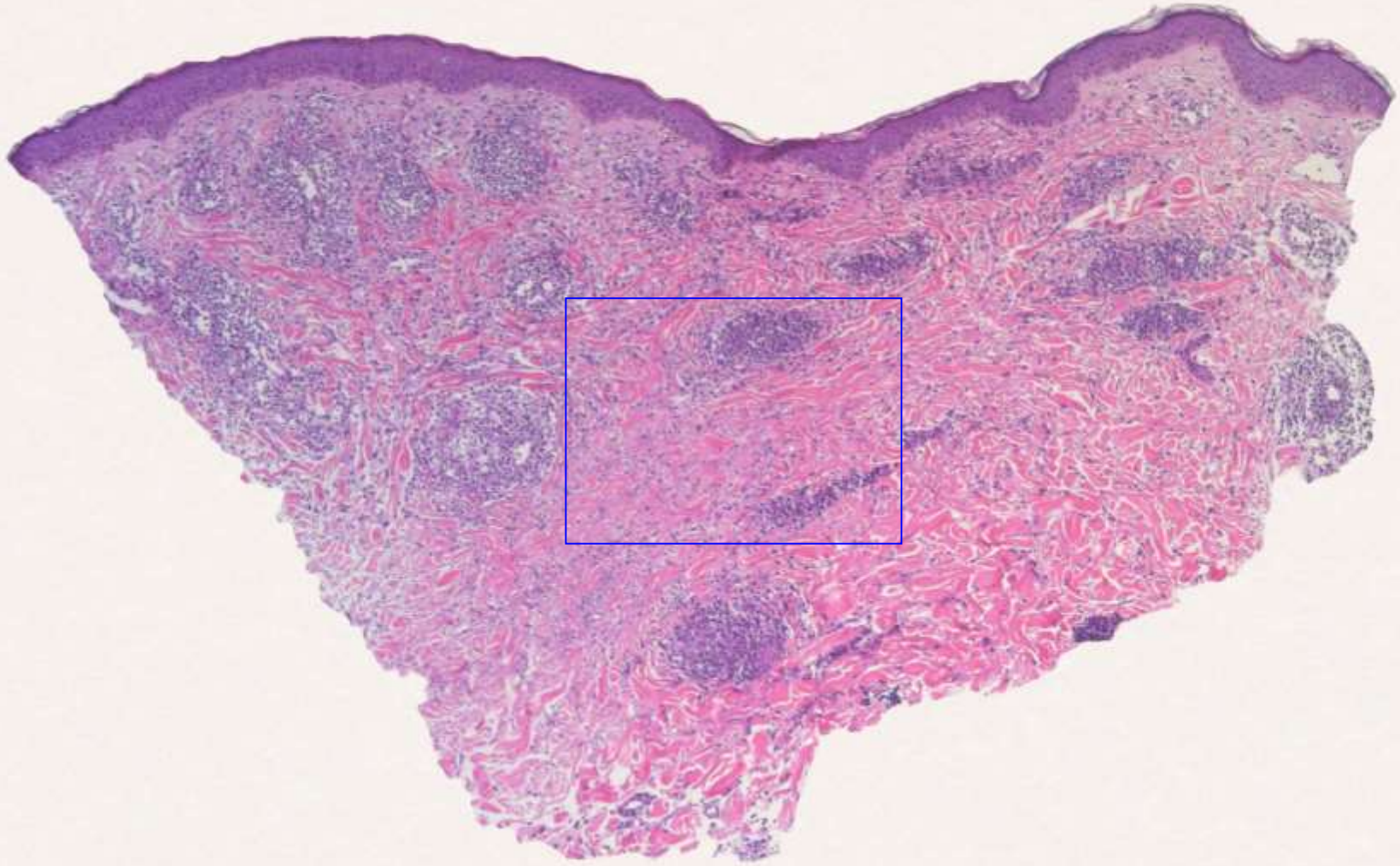
The other two clues can still be encountered, namely, fibrin in the wall of this venule and subtle signs of interface dermatitis.



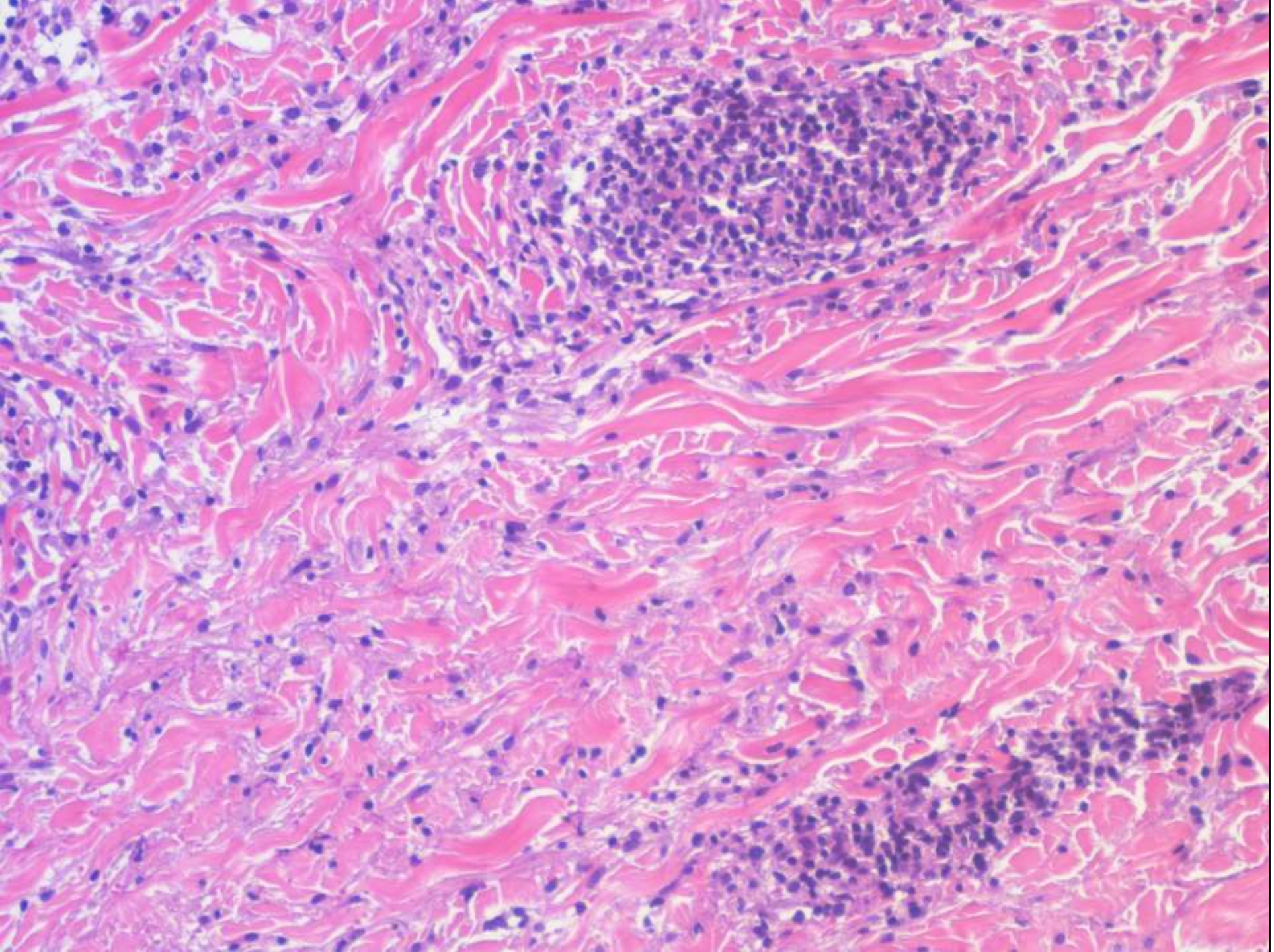
Of course, those findings are no longer diagnostic but, together, they are strongly suggestive of an infection by herpesvirus.



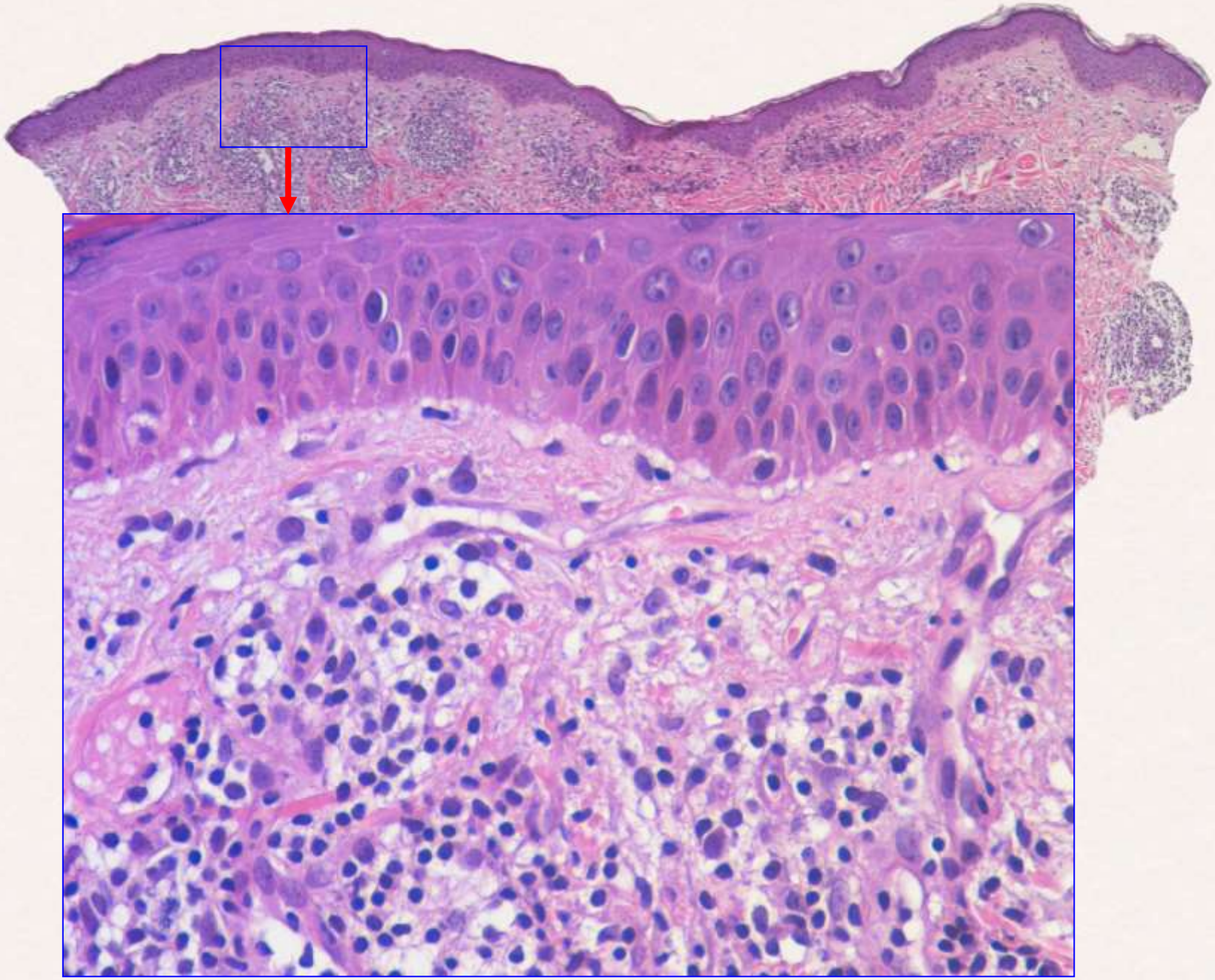
If we get even further away from the follicle,



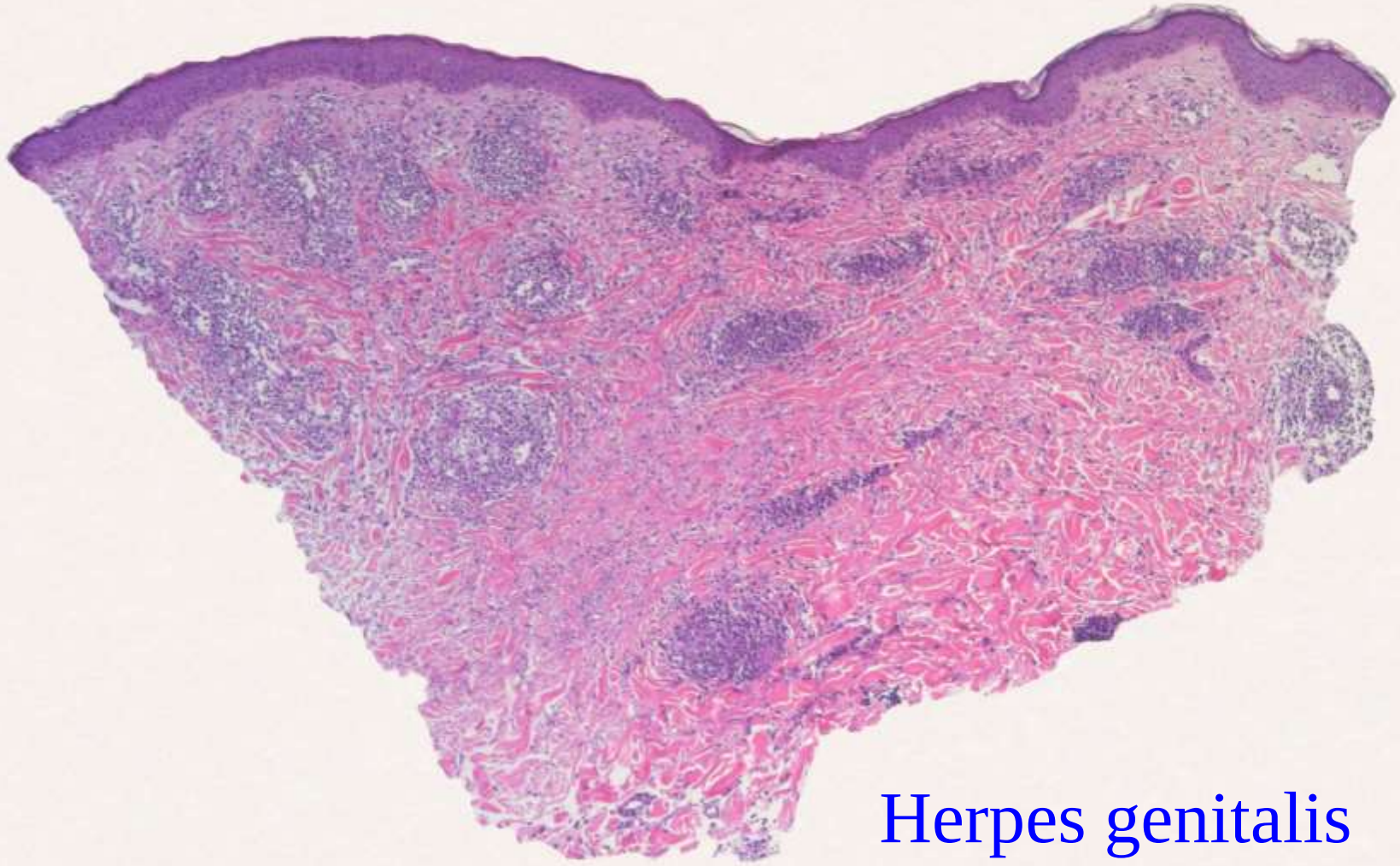
there is still the vertically oriented zone of fibrosis



with some neutrophils,
but no nuclear dust

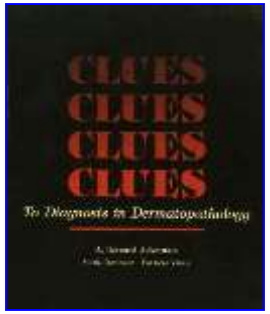


and only minimal vacuolar changes at the dermoepidermal junction – no longer diagnostic but, as we have seen,



Herpes genitalis

a manifestation of herpes genitalis. In sum, not every biopsy specimen of herpesvirus infection gives away the diagnosis easily. One may be in need of subtle clues

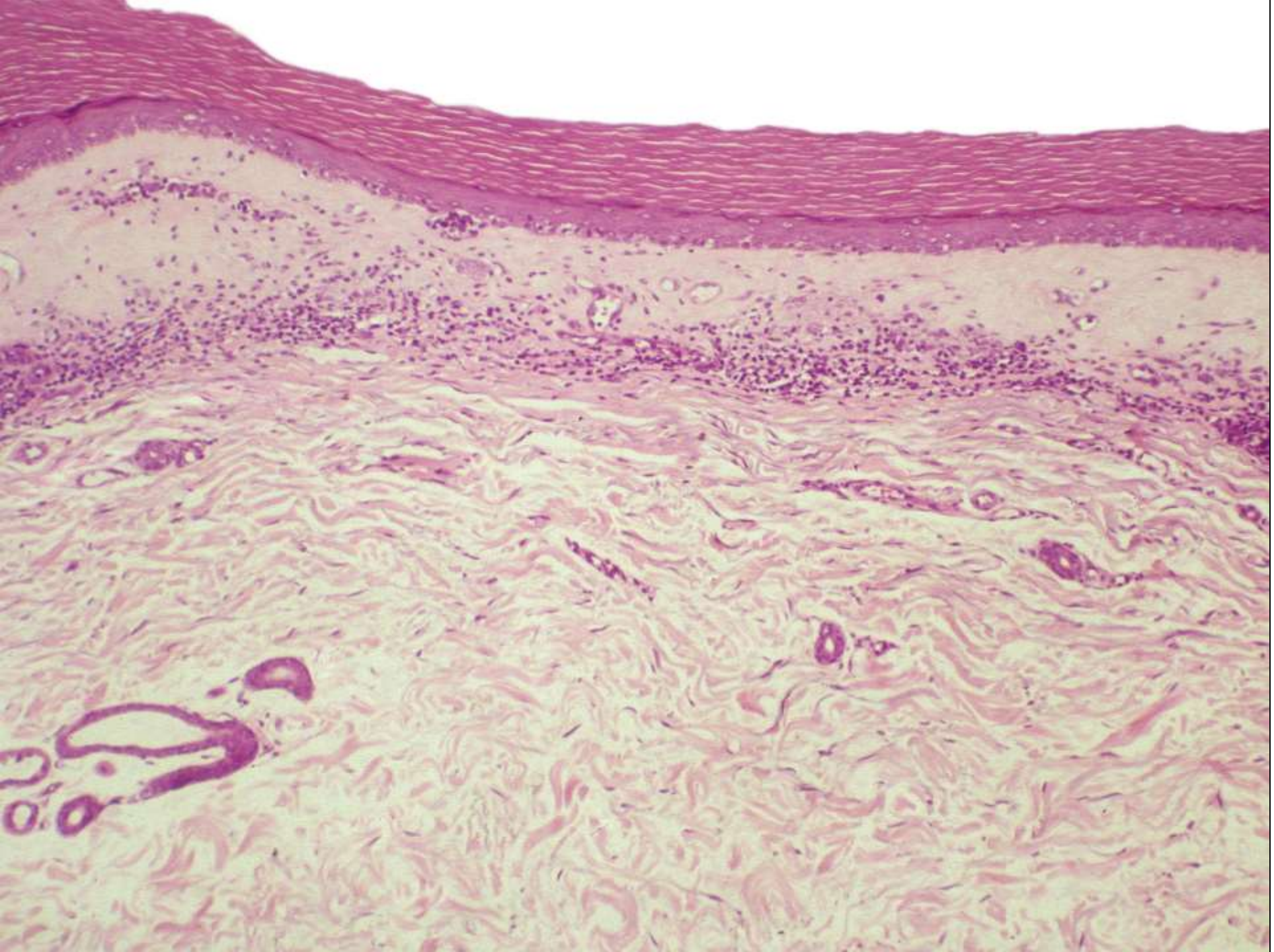


Clues to the diagnosis of infections by herpes viruses

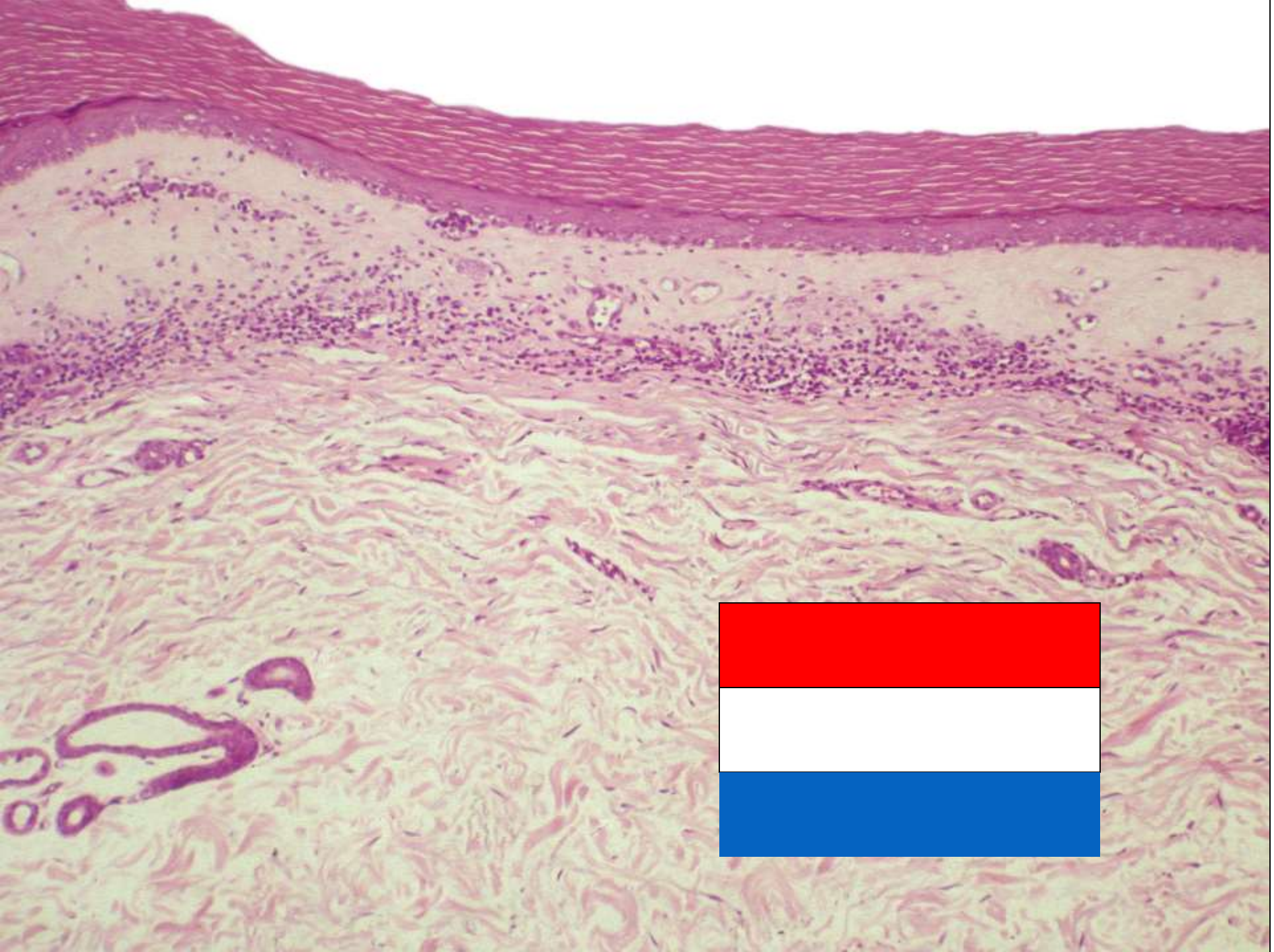
- Keratocytes with steel-gray nuclei and margination of nucleoplasm
- (Necrotic) epithelial giant cells
- Swollen keratocytes with large, pale nuclei
- Acantholysis
- Intraepidermal blister with myriad inflammatory cells ("busy blister")
- Vacuolar interface dermatitis with large lymphocytes
- Necrosis of follicles and sebaceous glands
- Dense, vertically oriented infiltrates of neutrophils with neutrophilic nuclear dust
- Vasculitis

In addition to those mentioned in the books by Bernard Ackerman, namely, keratocytes with steel-gray nuclei and margination of nucleoplasm and necrotic epithelial giant cells, one may see swollen keratocytes with large, pale nuclei, acantholysis, an intraepithelial blister with myriad inflammatory cells, vacuolar interface dermatitis with large lymphocytes, necrosis of follicles and sebaceous glands, dense, vertically oriented infiltrates of neutrophils with neutrophilic nuclear dust, and vasculitis.
Herpes genitalis is extremely common and, therefore, important.

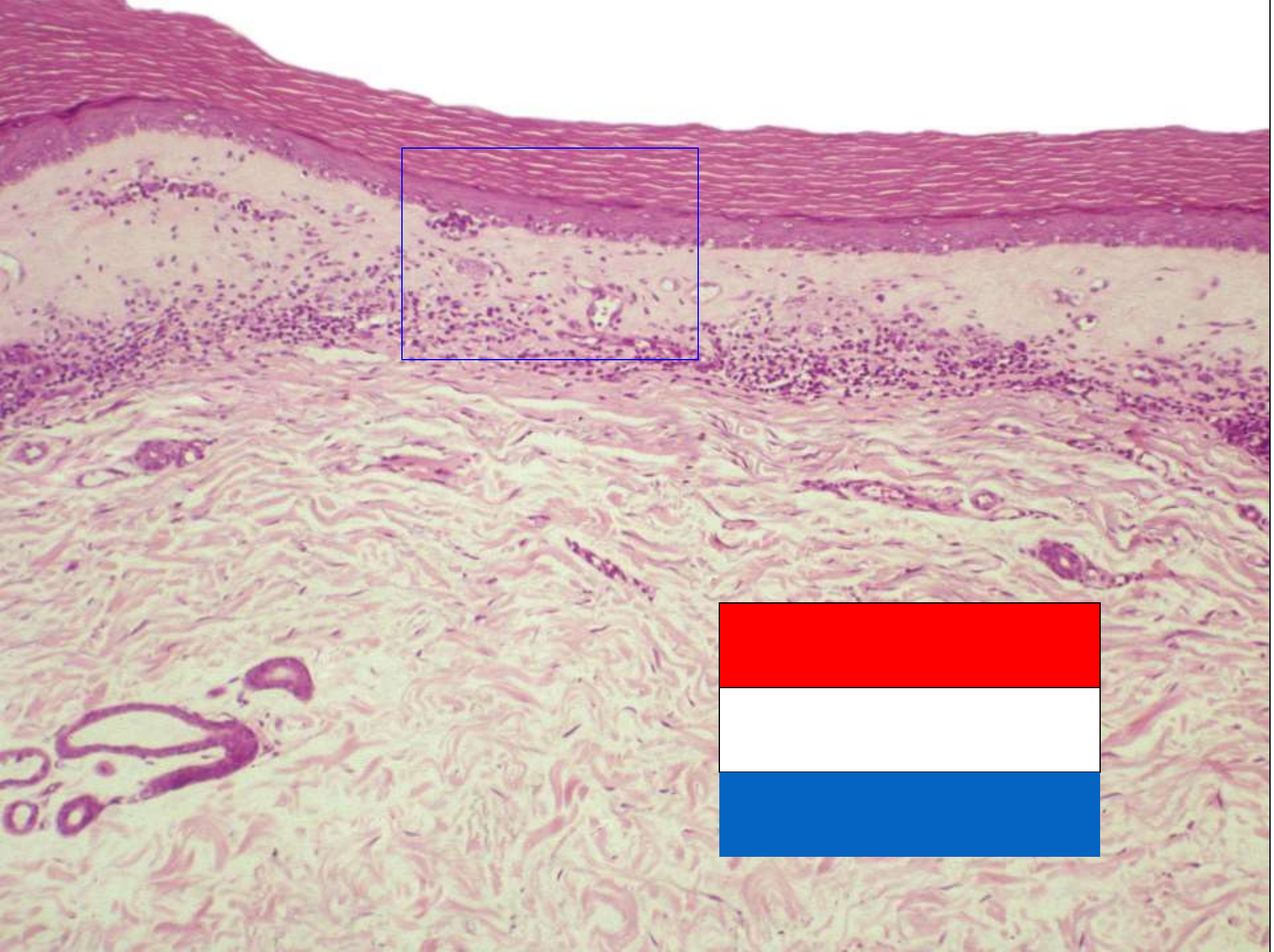
This is also true for another disease affecting the vulva prefentially, lichen sclerosus. As in infections by herpes viruses, the diagnosis is usually easy, clinically as well as



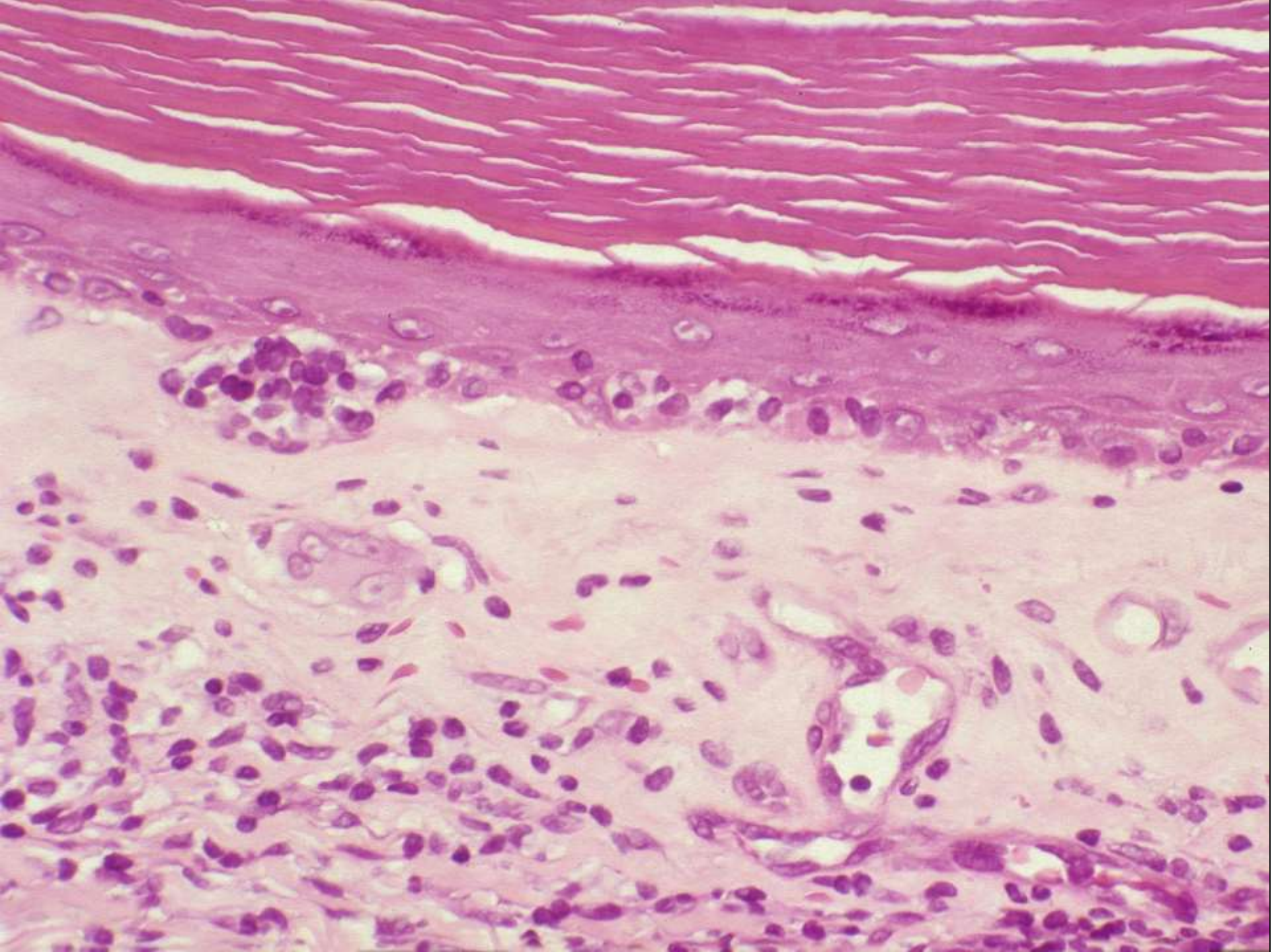
histopathologically, because of a characteristic constellation of findings: a thin epidermis with thickened red cornified layer, a pale subepidermal zone of sclerosis, and a blue bandlike-infiltrate of lymphocytes beneath it



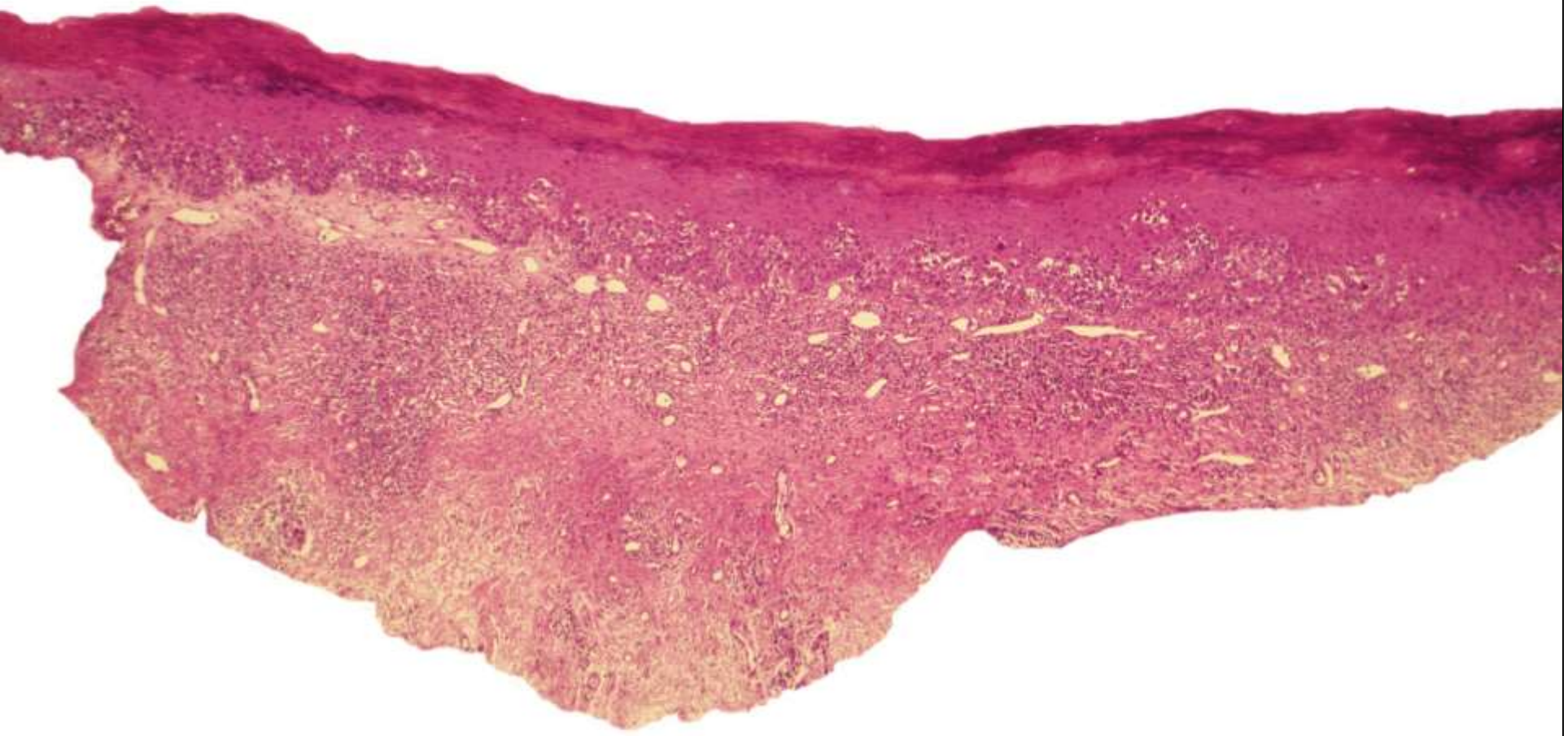
– red above white above blue, reminiscent of the ensign of the Netherlands.



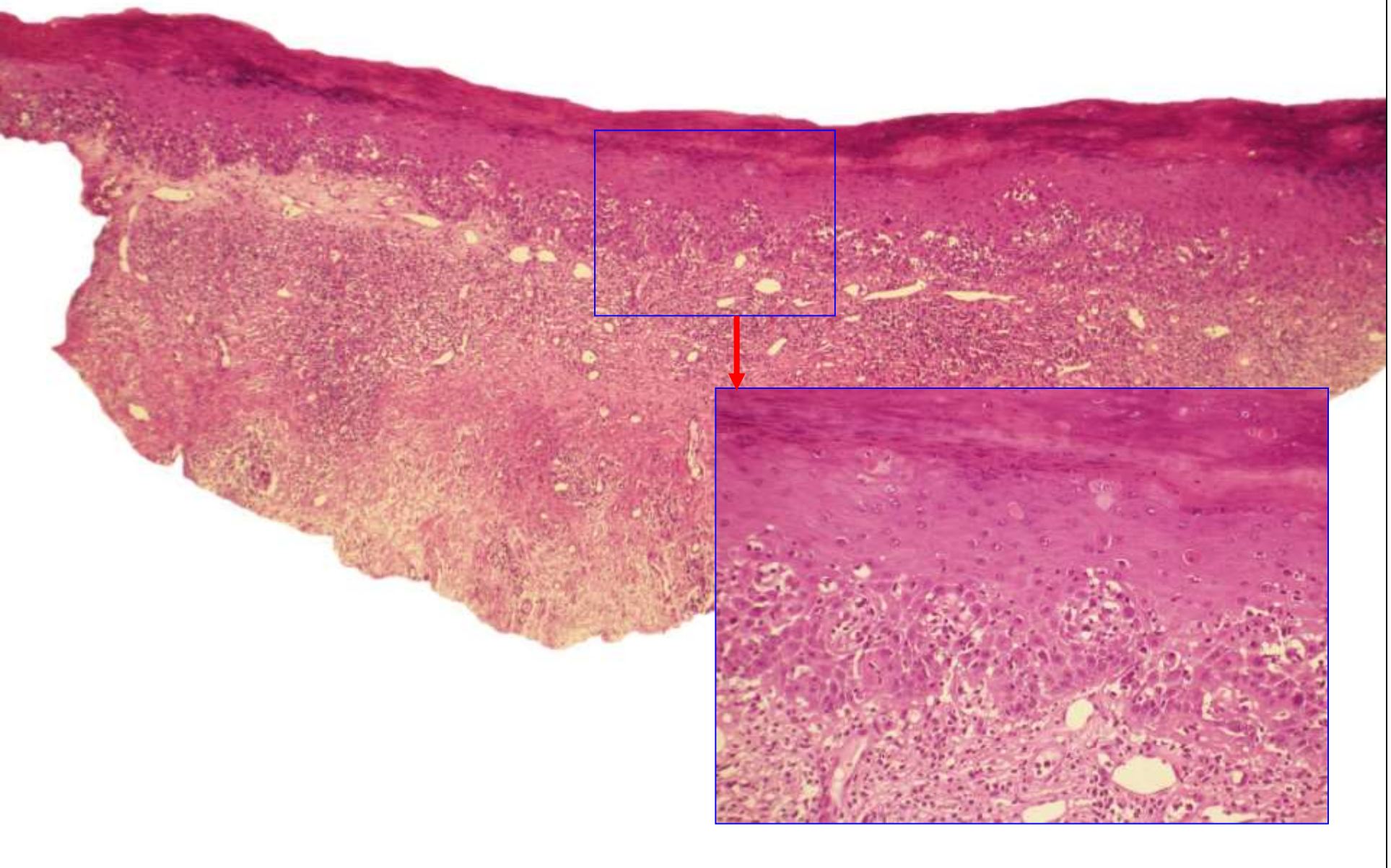
Moreover, lichen sclerosus is an interface dermatitis



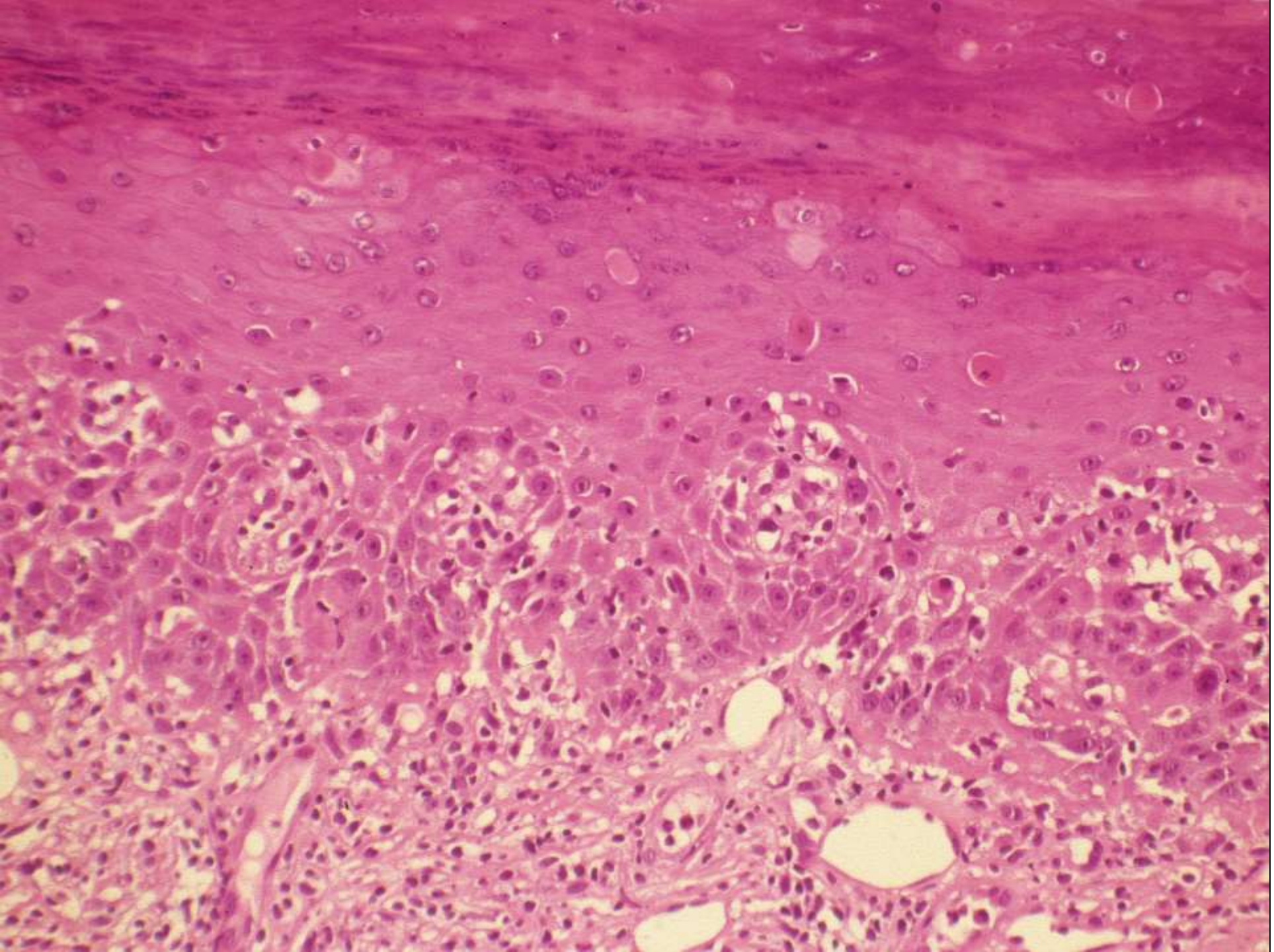
with vacuolar changes and lymphocytes at the dermo-epidermal junction. When all those features are present, the diagnosis can be made at a glance.



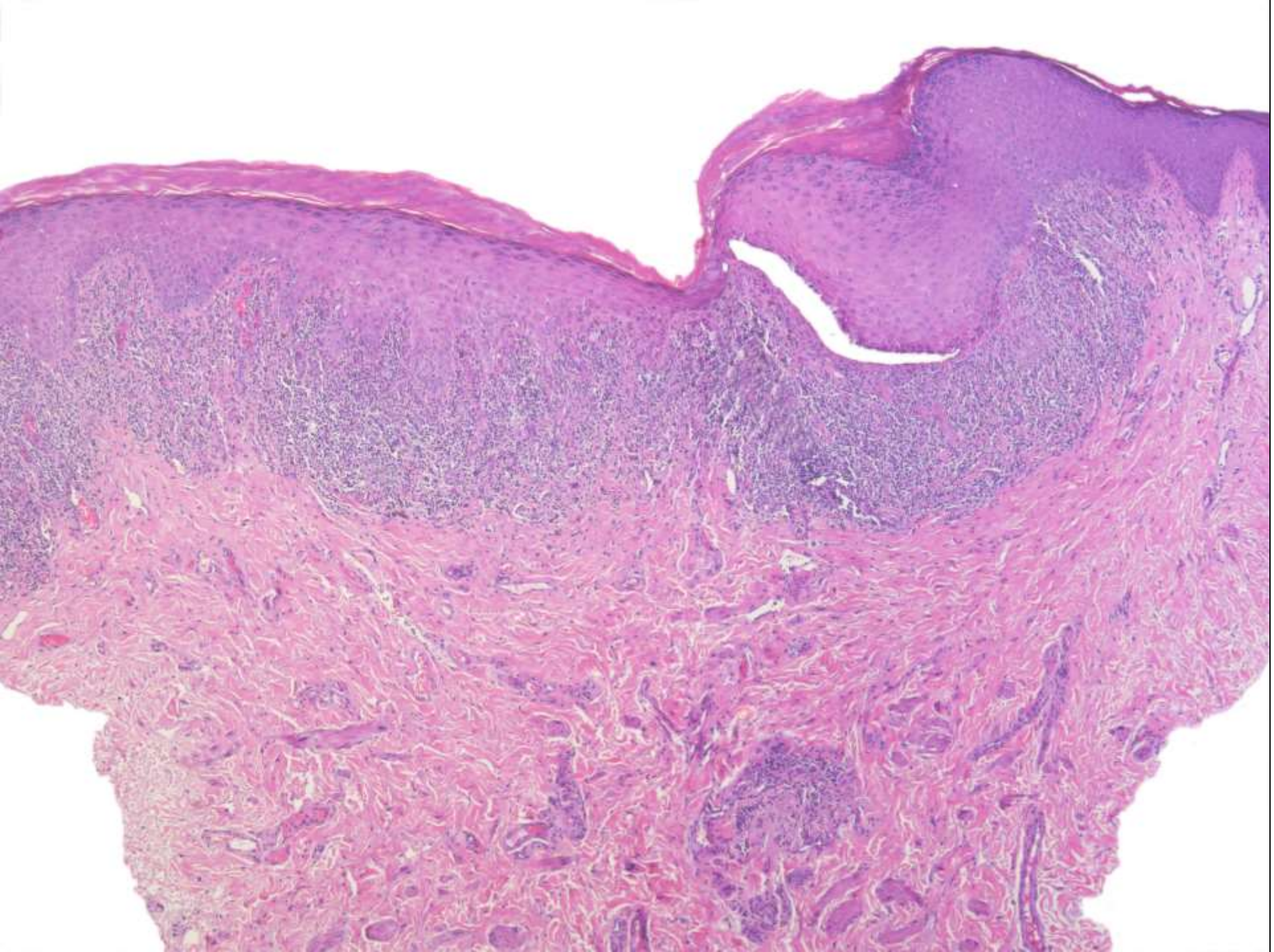
However, in the absence of subepidermal sclerosis, it is more difficult. On the left of this specimen, it is fairly easy because of subepidermal sclerosis,



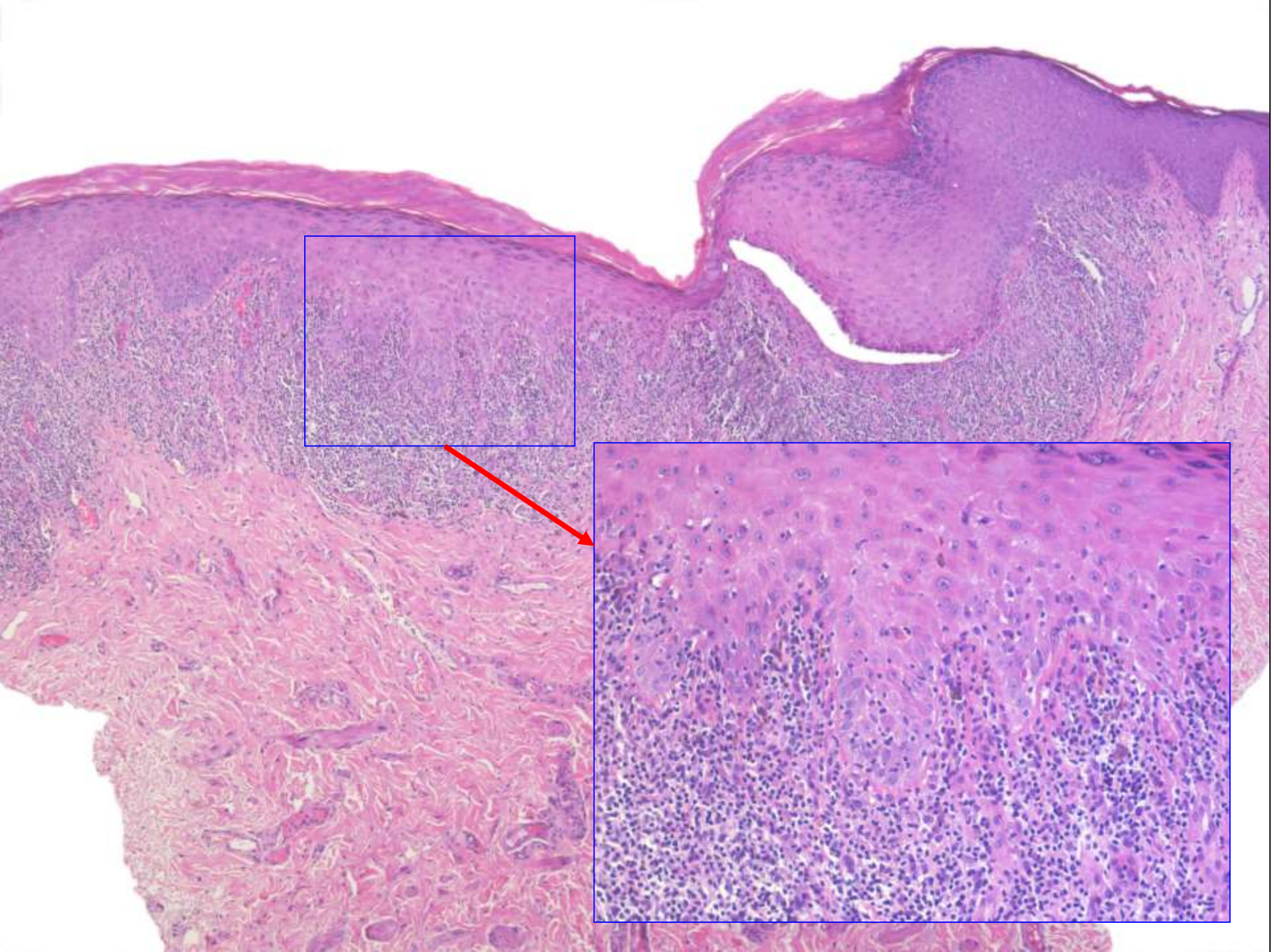
but not on the right. Here one sees only epithelial hyperplasia with wedge-shaped zones of hypergranulosis, compact orthokeratosis,



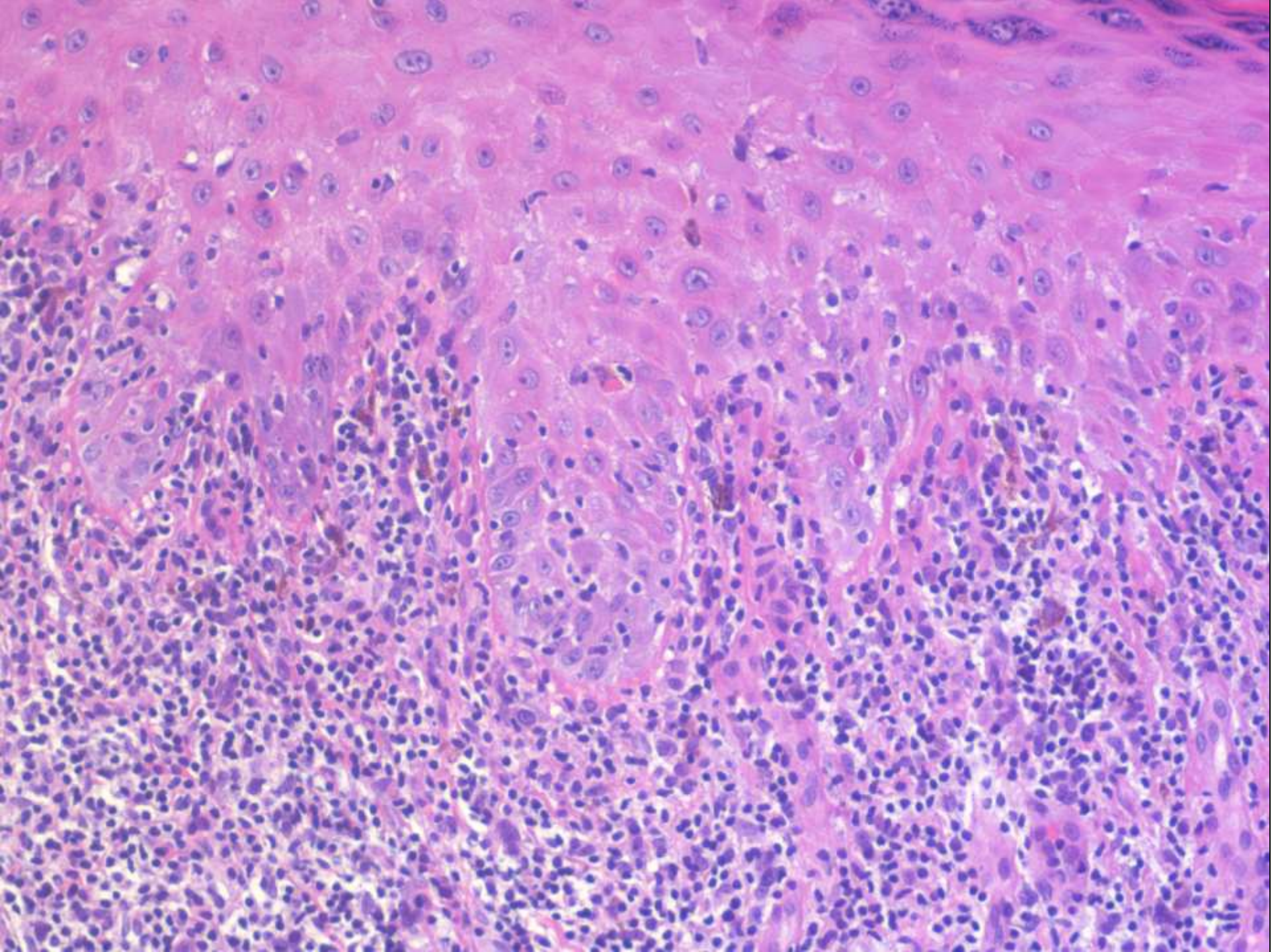
a lichenoid infiltrate of lymphocytes, vacuolar changes at the junction, and necrotic keratocytes, i.e., changes reminiscent of lichen planus. Findings militating against lichen planus are psoriasiform rete ridges and the presence of necrotic keratocytes not only at the junction, but in all reaches of the epidermis.



For comparison, a lesion of vulvar lichen planus: Rete ridges are not psoriasiform but pointed. The infiltrate is denser at the junction. There are subepidermal clefts, so-called “Max Joseph spaces” which are practically never seen in lichen sclerosus.



Melanophages tend to be more common. Necrotic keratocytes in the upper reaches of the epidermis may be seen occasionally in lichen planus,



but this is hardly ever a pronounced feature.

Light Microscopic Criteria for the Diagnosis of Early Vulvar Lichen Sclerosus

A Comparison With Lichen Planus

Maxwell A. Fung, M.D., and Philip E. LeBoit, M.D.

Lichen sclerosus (LS) and lichen planus (LP) are two conditions frequently affecting genital skin whose clinical and histologic distinction can be difficult. Both diseases can feature solitary genital lesions with bandlike lymphocytic infiltrates. We reviewed 68 cases of vulvar LS to find sections that contained a transition from a lichenoid interface reaction to pathognomonic LS (i.e., marked papillary dermal sclerosis or edema), and in these nine cases we studied routinely and specially stained sections, as well as sections stained with a panel of antisera to lymphoid antigens, and compared the findings with those in six cases of genital LP. We assumed that changes at the periphery of a lesion of LS mirror findings seen in early lesions. The features that we found more commonly in the inflammatory phase of LS included a psoriasiform lichenoid pattern (100% LS, 0% LP), basilar epidermotropism (78% LS, 0% LP), loss of papillary dermal elastic fibers (100% LS, 33% LP), basement membrane thickening (44% LS, 0% LP), and epidermal atrophy (33% LS, 0% LP). Features found more commonly in LP included many cytoid bodies (0% LS, 100% LP), wedge-shaped hypergranulosis (11% LS, 100% LP), basal squamatization (22% LS, 100% LP), and pointed rete ridges (11% LS, 83% LP). We did not detect any significant differences in the immunohistochemical features of the infiltrates. Taken together, these histologic features comprise light microscopic criteria for the diagnosis of early vulvar LS and its differentiation from LP.

Key Words: Lichen sclerosus—Lichen planus—Balanitis xerotica obliterans—Kraurosis vulvae—Vulvar—Genitals—Lichenoid dermatitis—TIA-1—OPD-4—CD8—p53—MIB-1.

Am J Surg Pathol 22(4): 473–478, 1998.

by creamy white plaques, and LP is characterized by violaceous plaques with a reticulated white surface (Wickham's striae). However, the clinical morphology of lesions on genital skin is often obscured by erosion or lichenification. Furthermore, the histologic distinction between LS and LP can be difficult if the pathognomonic changes of edema, homogenization, and sclerosis in the papillary dermis of LS are not present. In light of this problem, we examined what we believe are the early inflammatory changes in vulvar LS and compared them with LP using routinely stained sections and immunohistochemical methods. We demonstrate that although both fully developed changes of LP and the early changes of LS on genital skin are characterized by a lymphocytic, lichenoid interface dermatitis, there exist light microscopic criteria that can be used to distinguish them.

MATERIALS AND METHODS

To identify the early changes in LS, we examined 68 specimens of vulvar LS diagnosed between 1983 and 1993 from the archives of the Department of Pathology at the University of California, San Francisco. We identified nine cases (in patients 24–79 years of age), mostly

The difficulty of differential diagnosis has prompted Fung and LeBoit study the issue in 1998. They referred to non-sclerotic cases of lichen sclerosis as “early lichen sclerosus”, but lack of sclerosis may also be seen in lesions of long standing. The most important findings favouring lichen sclerosus were found to be “a psoriasiform lichenoid pattern” and “basilar epidermotropism.”

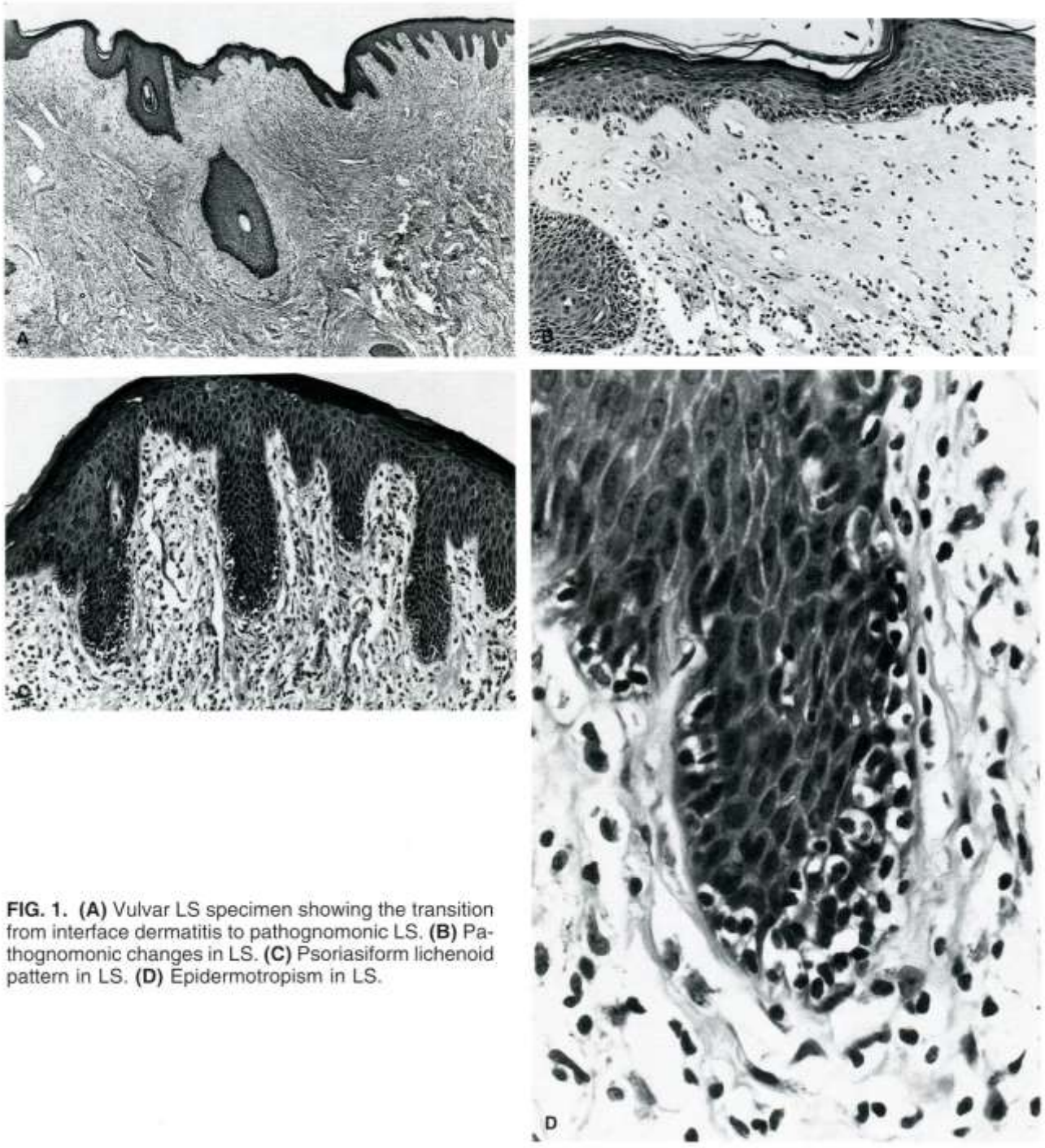
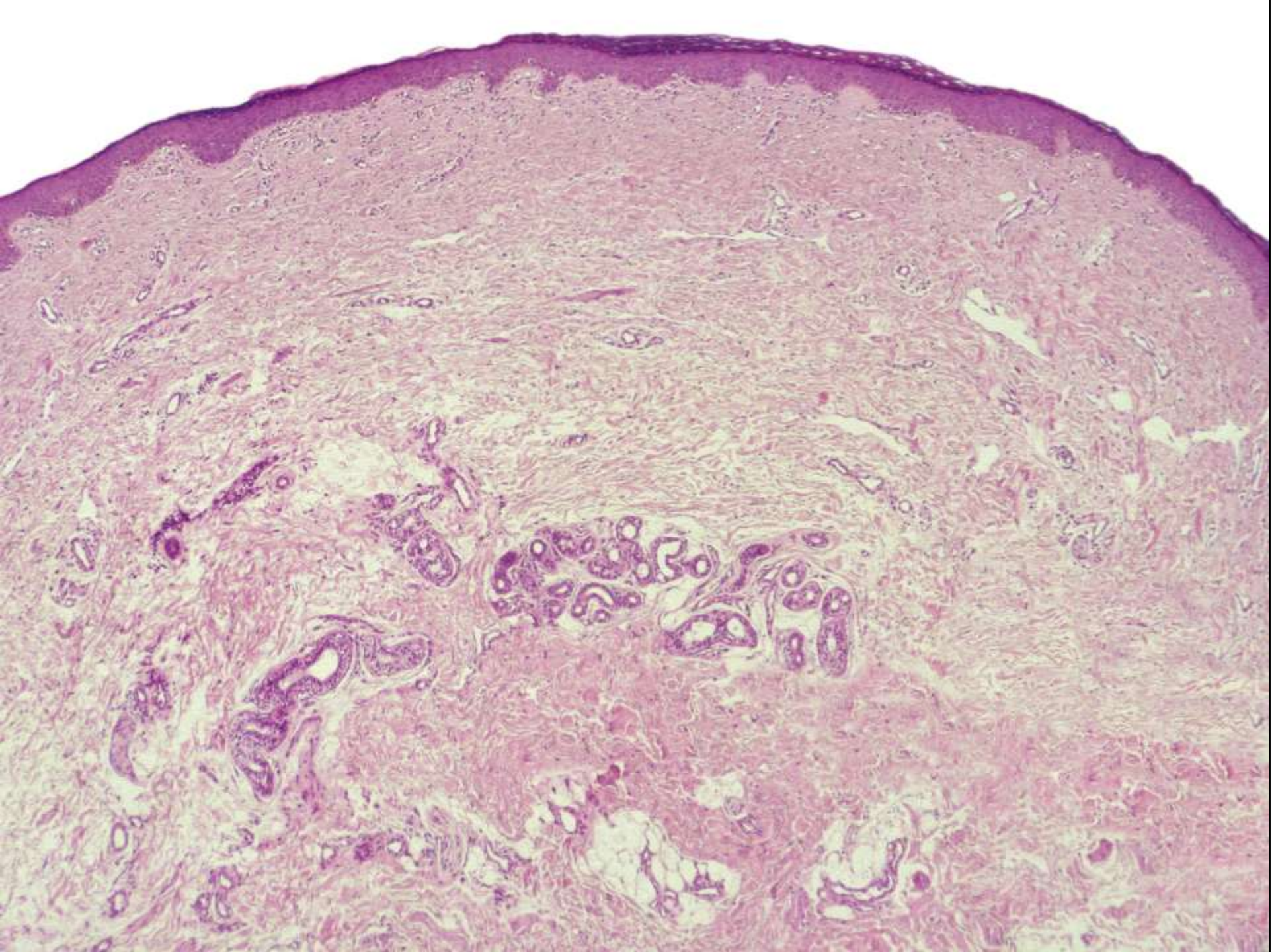
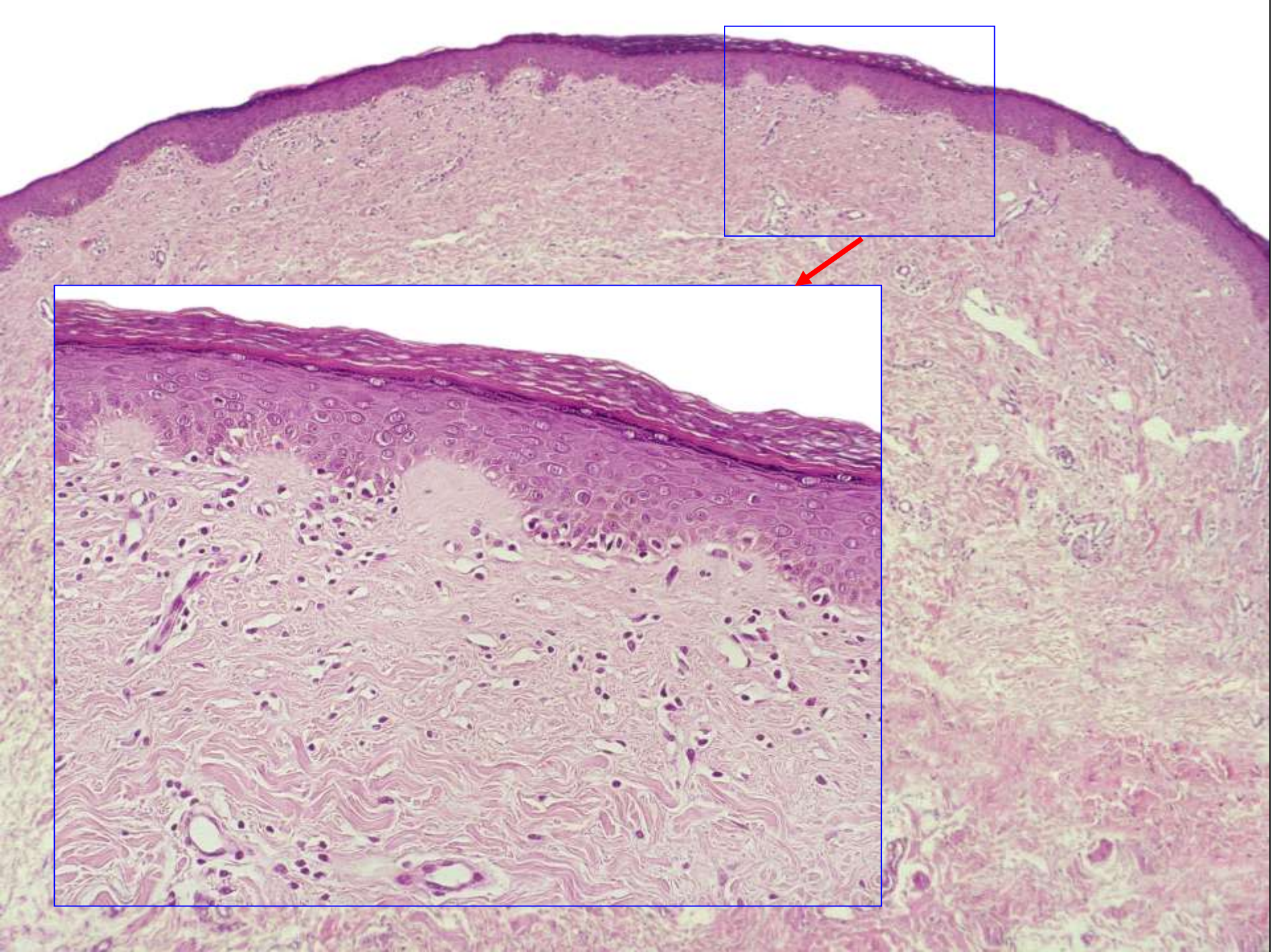


FIG. 1. **(A)** Vulvar LS specimen showing the transition from interface dermatitis to pathognomonic LS. **(B)** Pathognomonic changes in LS. **(C)** Psoriasiform lichenoid pattern in LS. **(D)** Epidermotropism in LS.

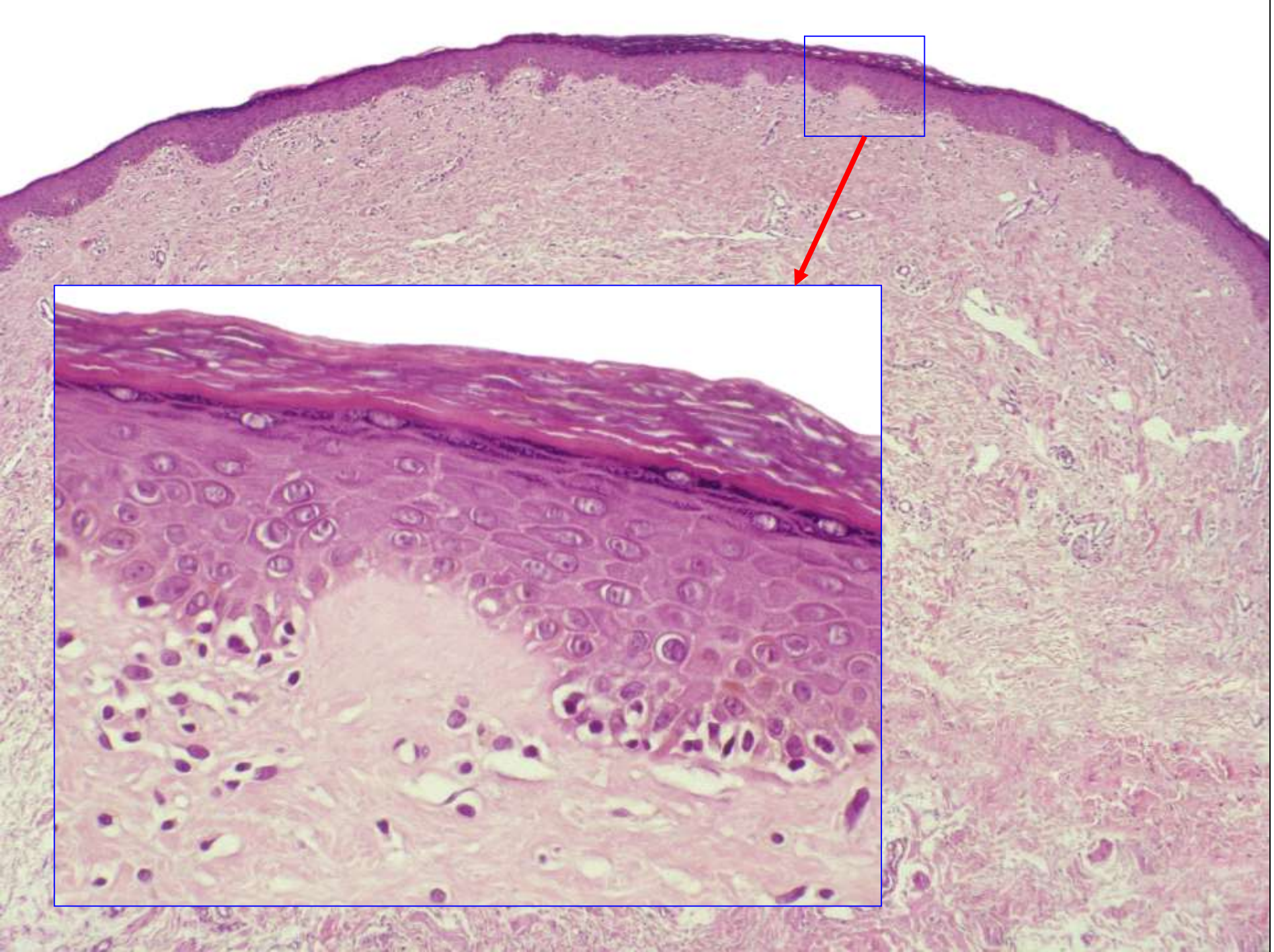
This is what Fung and LeBoit saw: a psoriasiform hyperplasia of the epidermis with many lymphocytes in elongated rete ridges in concert with only scant spongiosis. Those features facilitate distinction of lichen sclerosus from lichen planus but are criteria also of mycosis fungoides.



In this case of lichen sclerosus, the infiltrate is sparse and patchy lichenoid,



there are coarse collagen bundles in haphazard array in the papillary dermis, and lymphocytes are aligned as solitary units in the basal layer, as in the patch stage of mycosis fungoides.



Were it not for a tiny zone of subepidermal sclerosus and, of course, the clinical diagnosis, it would be difficult not to invoke the patch stage of mycosis fungoides in a case like this one.

Lichen Sclerosus with Histopathologic Features Simulating Early Mycosis Fungoides

Luigi Citarella, MD, Cesare Massone, MD, Helmut Kerl, MD, and Lorenzo Cerroni, MD

Abstract: Mycosis fungoides (MF) is a cutaneous T-cell lymphoma characterized in its early stages by a superficial band-like infiltrate with epidermotropism of lymphocytes without particularly atypical cytologic features. Even though clinicopathologic presentation is diagnostic in typical cases, some inflammatory skin disorders can simulate the histopathologic features of early MF. In this study we present data on 9 patients affected by lichen sclerosus (LS) (M:F ratio 8:1; age range 7–75 years; mean age 31.3 years; median age 13 years), who presented with histopathologic features simulating early lesions of MF. The histopathologic picture was characterized in all cases by a dense, band-like infiltrate of lymphocytes within the superficial dermis, with exocytosis of lymphocytes within the lower part of the epidermis. The papillary dermis was expanded and showed focally coarse bundles of collagen simulating MF. The typical signs of LS were either absent or present only focally. Molecular analyses of the TCRγ gene rearrangement performed with the polymerase chain reaction (PCR) technique revealed a polyclonal smear in eight cases, and a monoclonal band in one. Our study shows that LS can present with histopathologic features simulating early MF. Especially in cases revealing a monoclonal population of T lymphocytes by PCR, the correct diagnosis may be overlooked without proper clinical information and clinicopathologic correlation. Lichen sclerosus should be added to the list of cutaneous T-cell pseudolymphomas.

Key Words: histopathologic simulator, mycosis fungoides, lichen sclerosus, pseudolymphoma

(*Am J Dermatopathol* 2003;25:463–465)

one of the most vexing problems in dermatopathology.[1,2] The best known among these benign cutaneous diseases are actinic reticuloid,[3–5] lymphomatoid contact dermatitis,[2,6] lymphomatoid drug eruption, T-cell type,[7,8] and lymphomatoid keratosis.[9,10]

We report on 9 patients with lichen sclerosus (LS) showing histopathologic features simulating early MF.

PATIENTS AND METHODS

Nine patients (M:F ratio 8:1; age range 7–75 years; mean age 31.3 years; median age 13 years) presenting with LS that showed histopathologic features simulating MF have been included in our study (Table 1).

Histology and Molecular Biology

In every case histopathologic examination of the biopsy specimen was performed on sections of tissue stained with hematoxylin and eosin. Molecular analysis of the T-cell receptor-γ (TCR-γ) gene rearrangement was performed in all cases with a standard PCR technique described previously.[11]

RESULTS

All patients had lesions clinically diagnostic of LS characterized by itching, atrophic, partly whitish, partly erythematous patches. In 6 patients the lesions were located on the

The problem is aggravated by the occasional finding of monoclonality in the infiltrate of lichen sclerosus,

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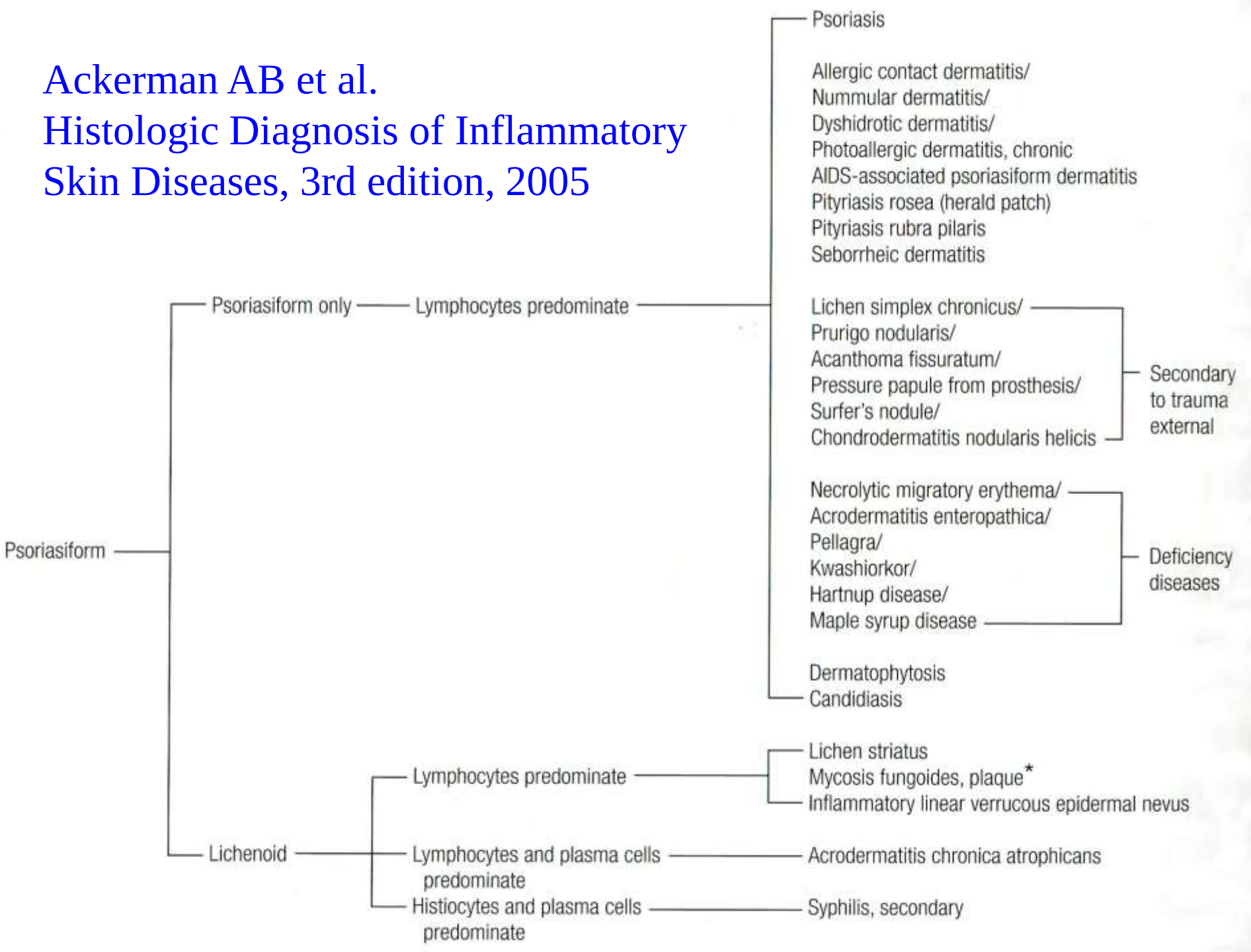
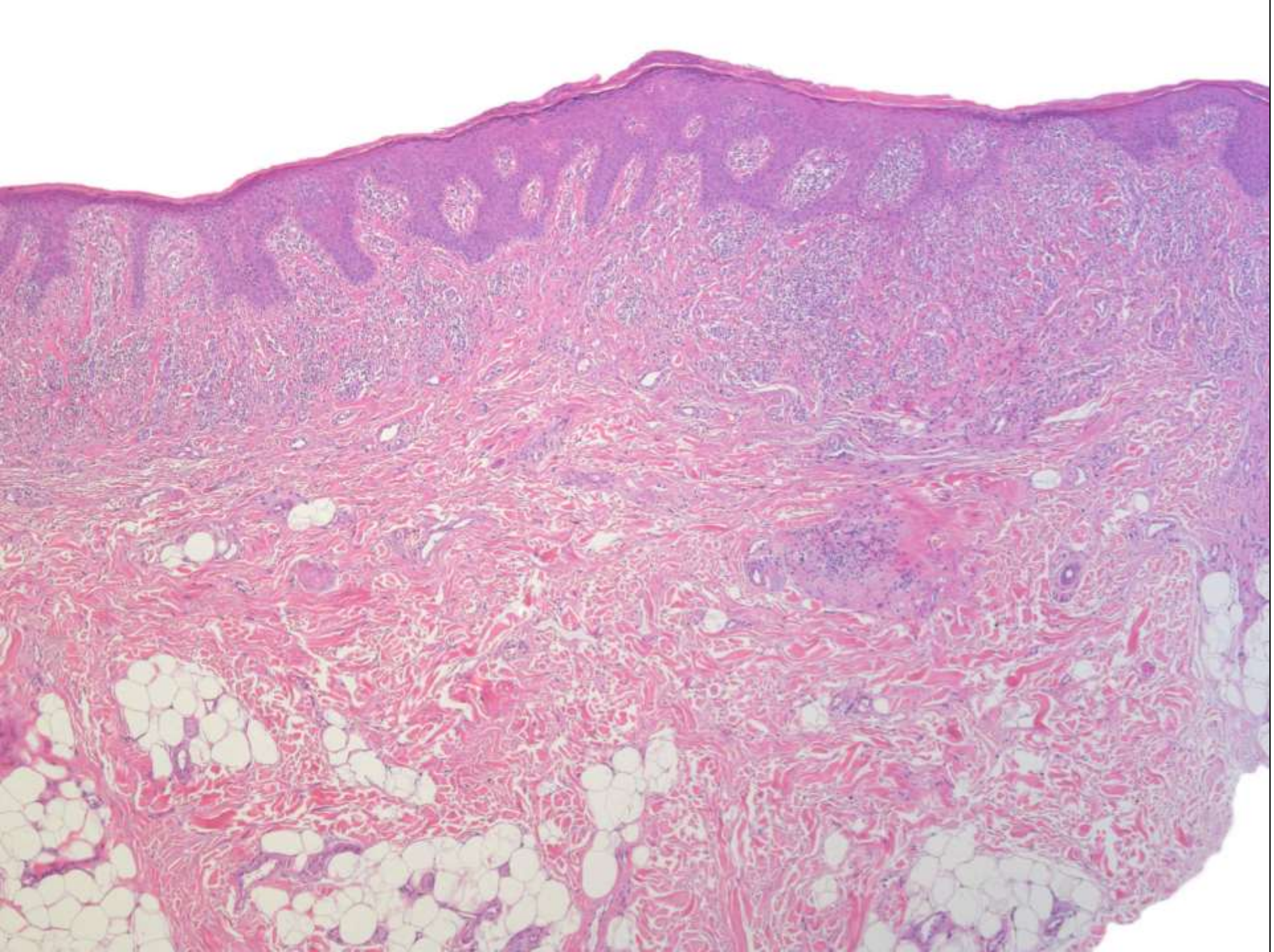
and those combined features prompted the Graz group to suggest in 2003 that *"lichen sclerosus should be added to the list of cutaneous T-cell pseudolymphomas."*

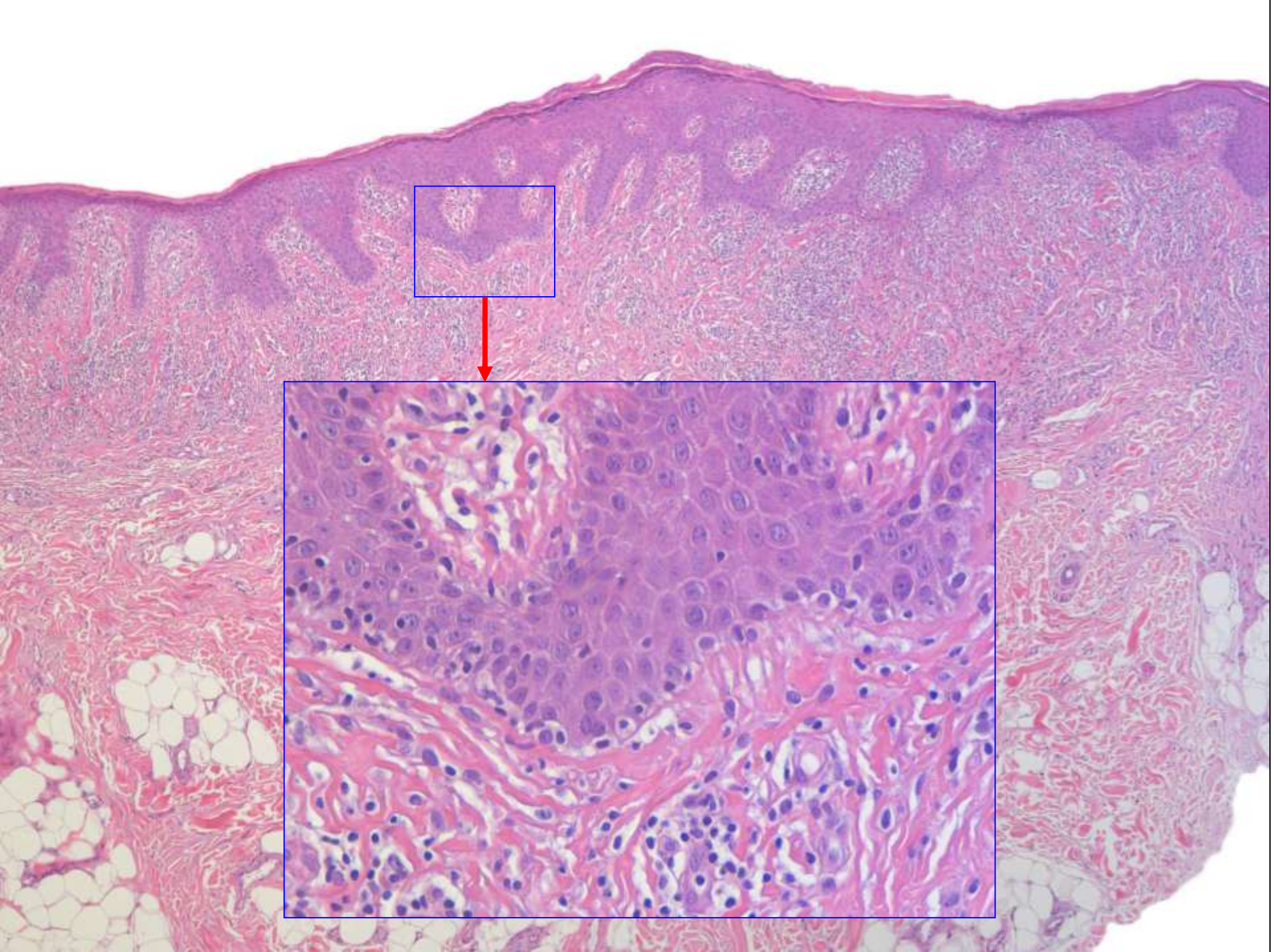
Ackerman AB et al. Histologic Diagnosis of Inflammatory Skin Diseases, 3rd edition, 2005



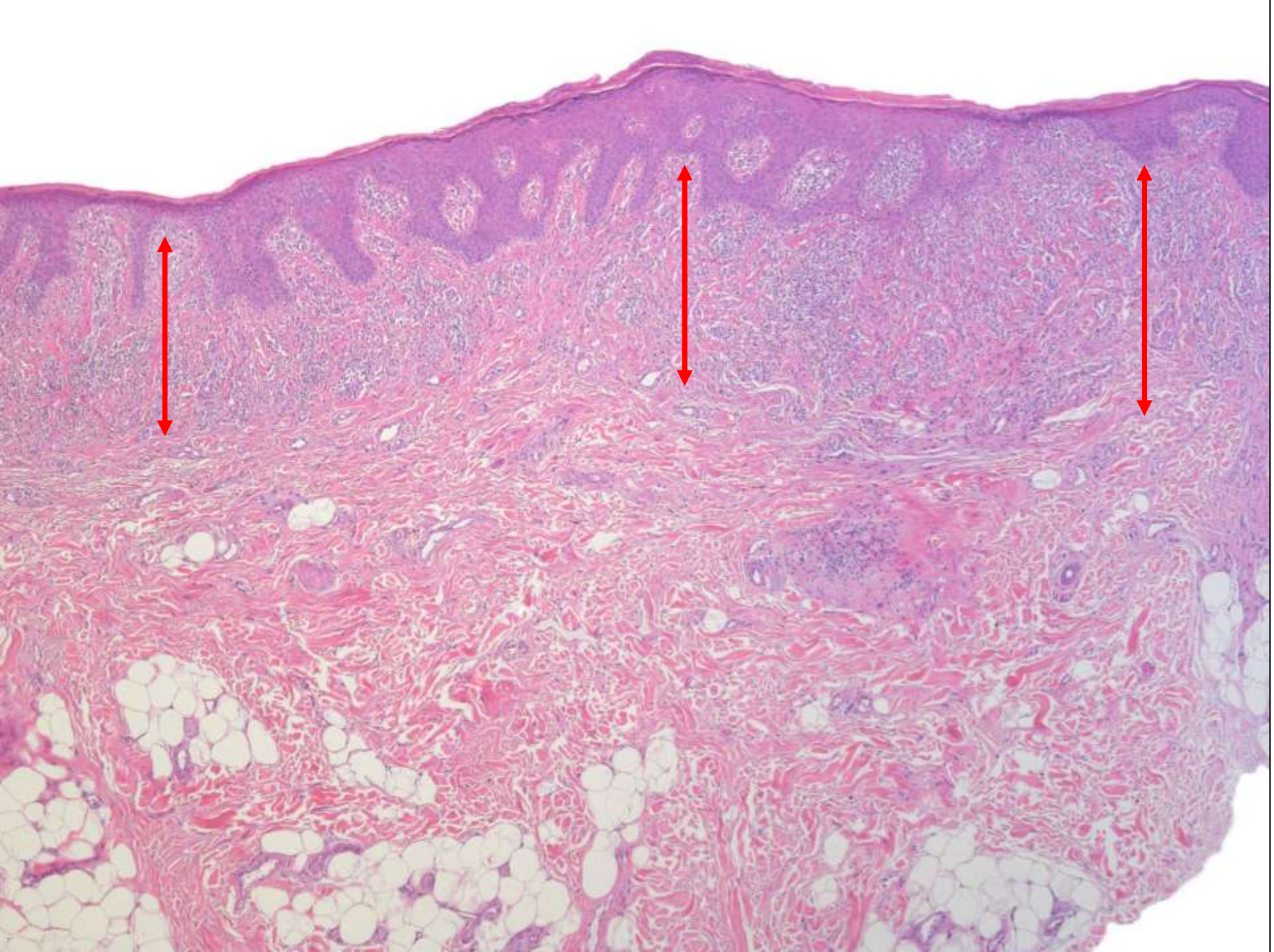
If one studies the 3rd edition of Ackerman's "Histologic Diagnosis of Inflammatory Skin Diseases" and looks for the pattern of a psoriasiform lichenoid dermatitis with predominance of lymphocytes, only lichen striatus, mycosis fungodies, and ILVEN are mentioned. That pattern, however, is also common in lichen sclerosus.



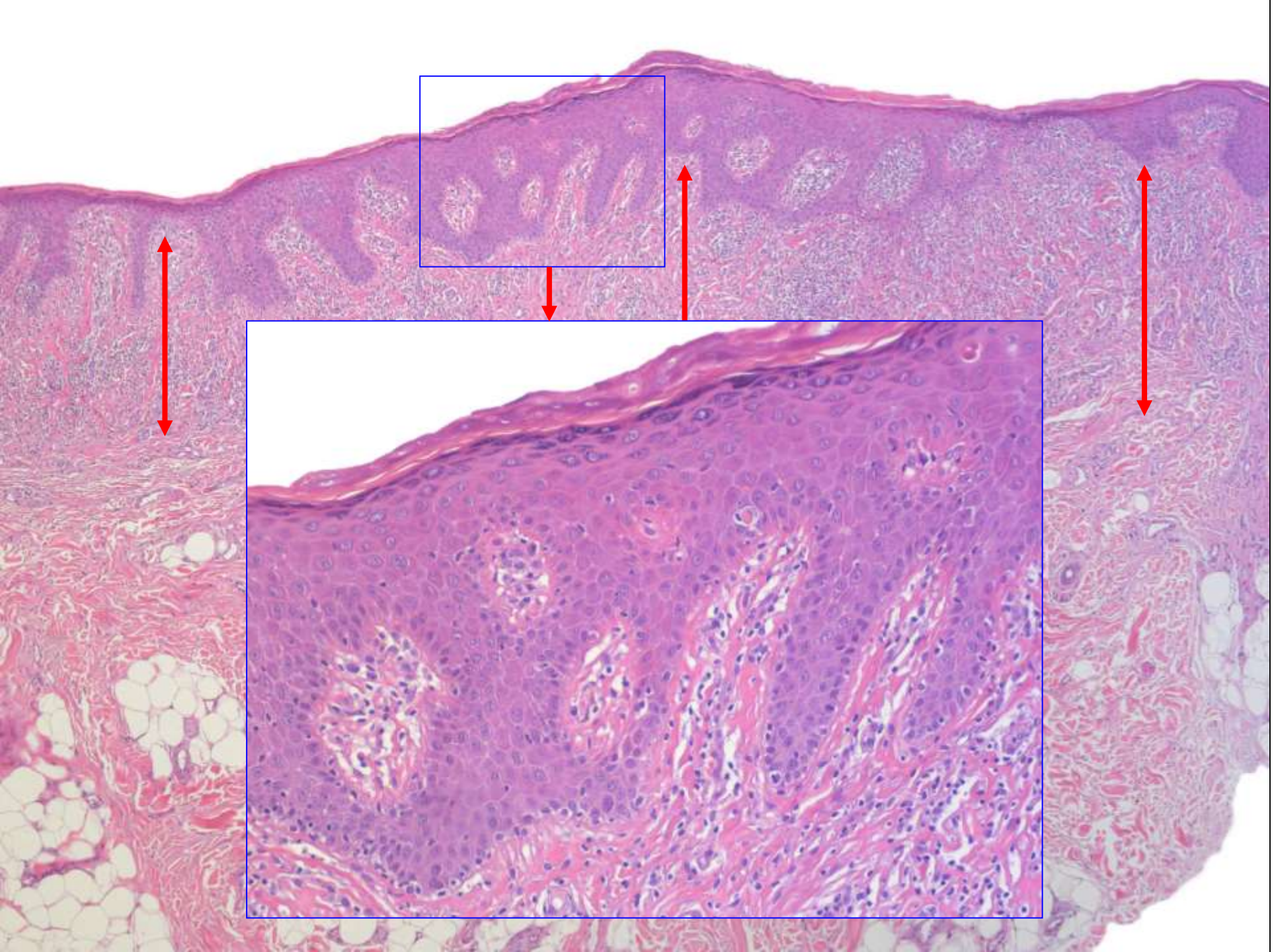
This is an example: A psoriasiform epidermal hyperplasia associated with a dense lichenoid infiltrate of lymphocytes, coarse bundles of collagen in the papillary dermis,



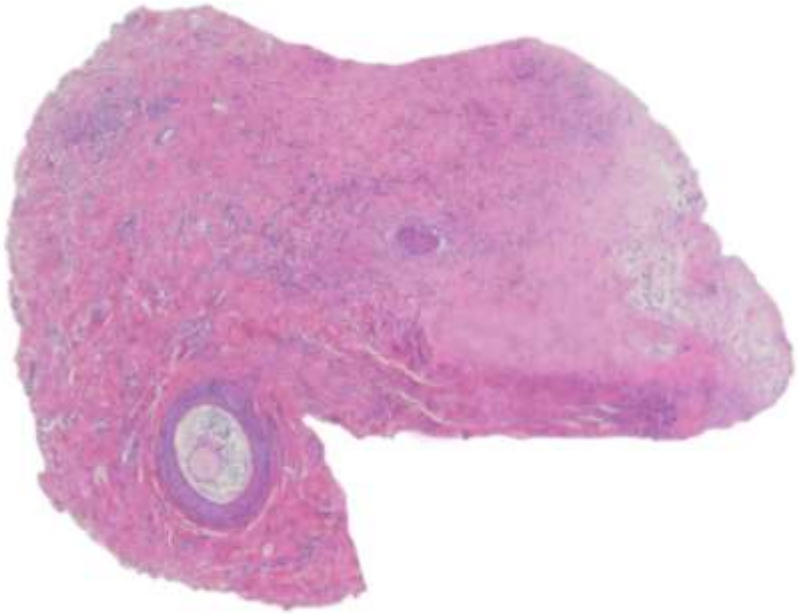
and lymphocytes aligned in the basal layer. This is not mycosis fungoides, however, because lymphocytes in the basal layer are small

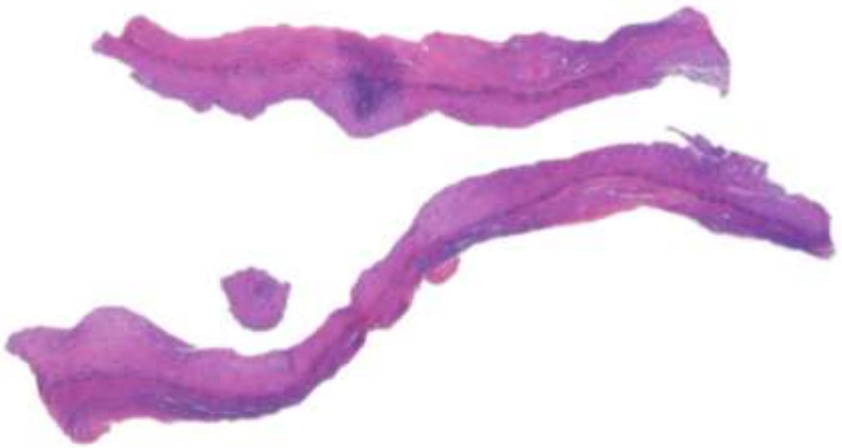


and the papillary dermis is far too thick. This is a clue to lichen sclerosus. The papillary dermis may be thickened in mycosis fungoides, too, but not to that extent.

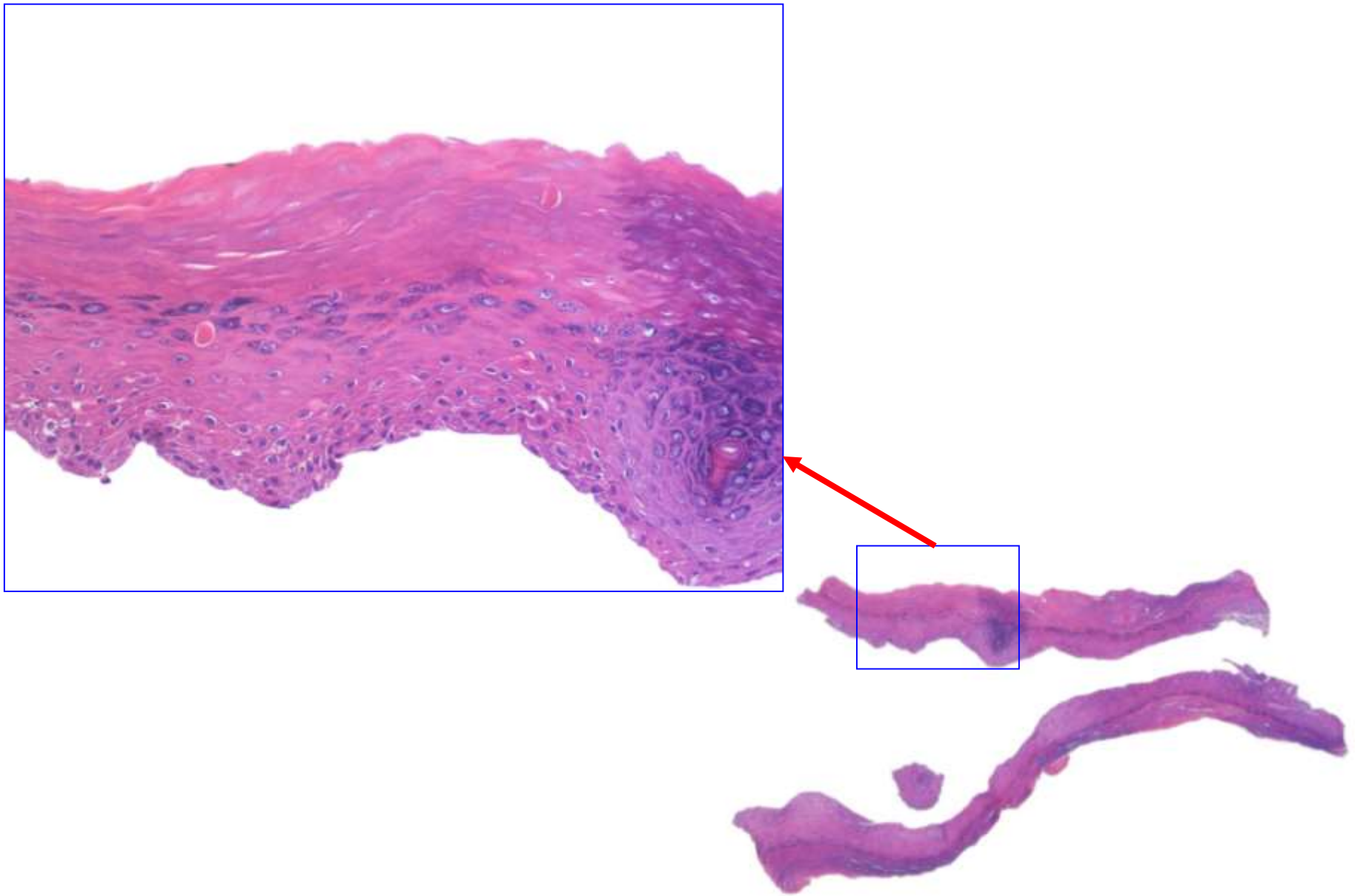


Another feature suggestive of lichen sclerosus is presence of necrotic keratocytes in all reaches of the epidermis. Of course, that finding is not specific, but an extremely helpful clue.

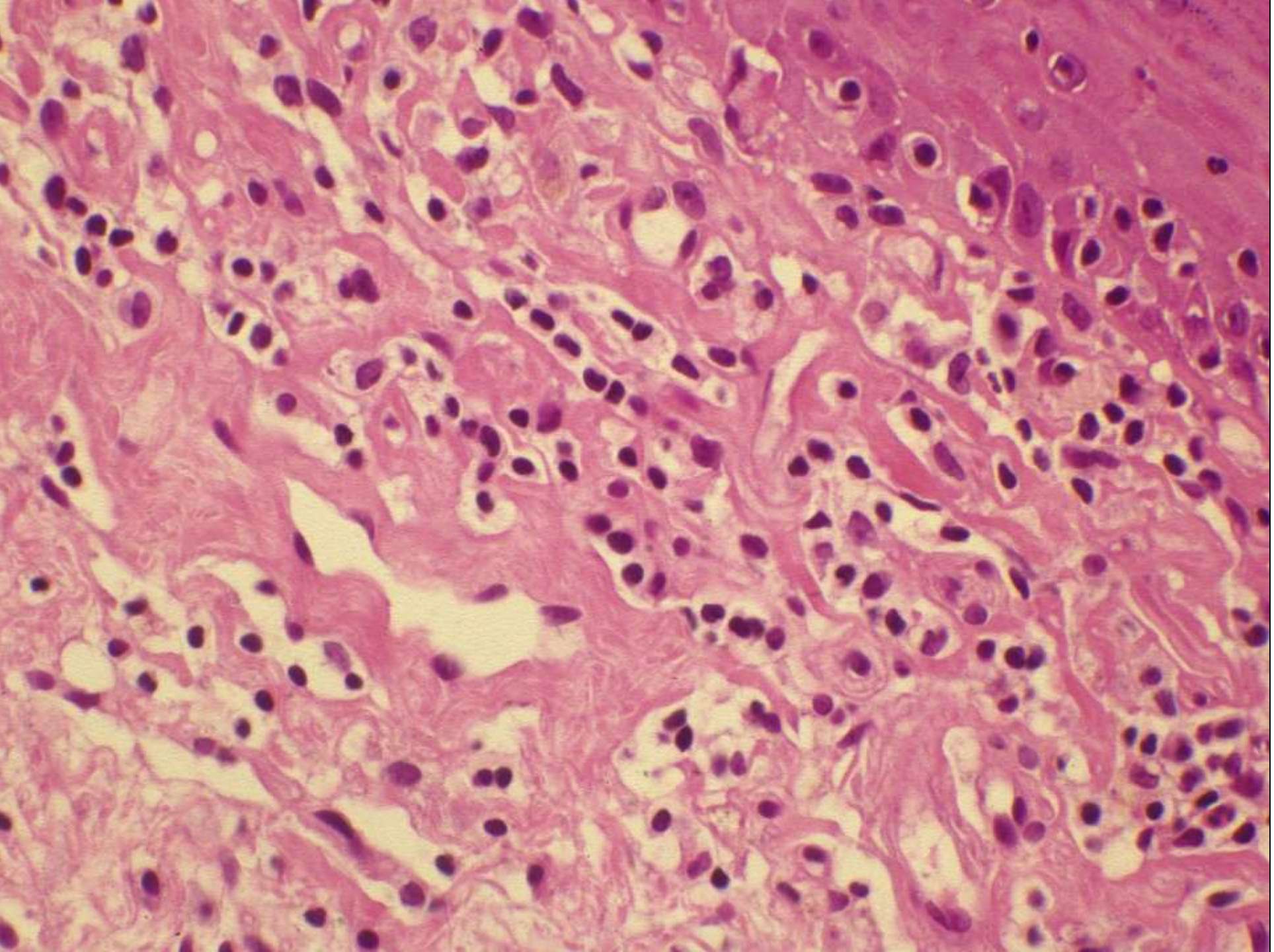




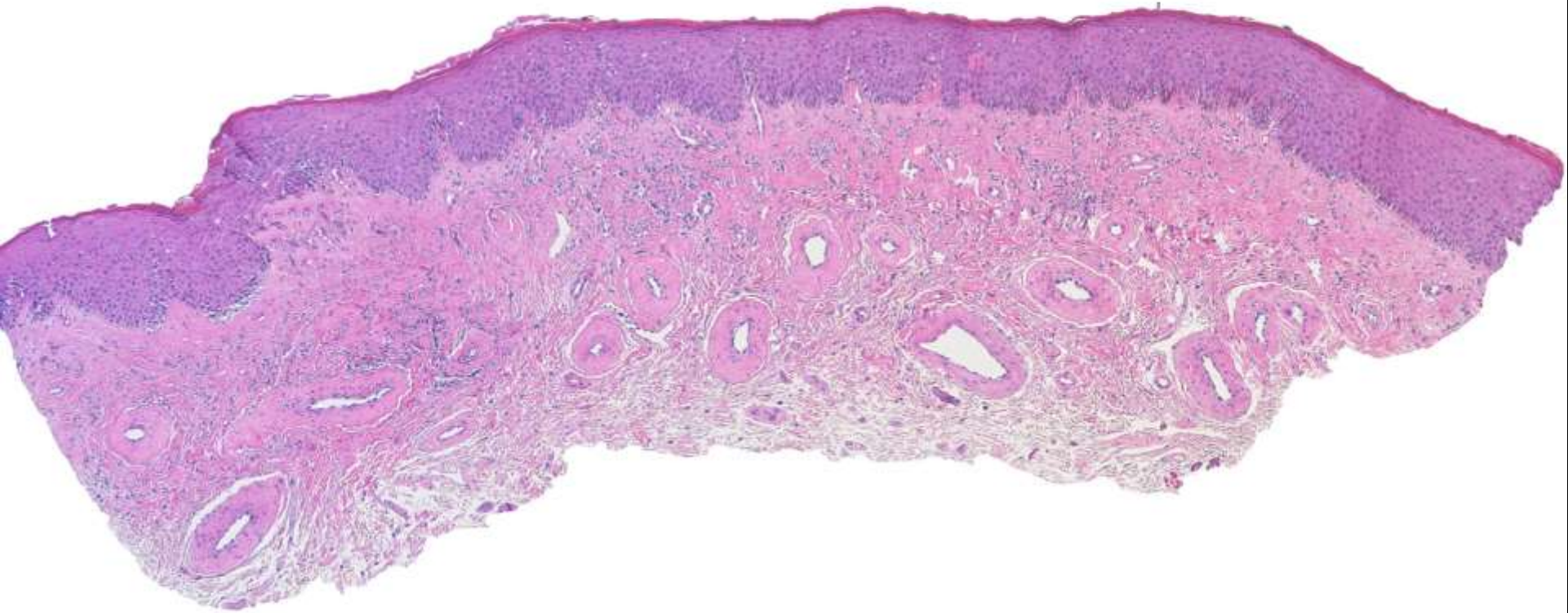
It is not needed in cases with subepidermal sclerosis,



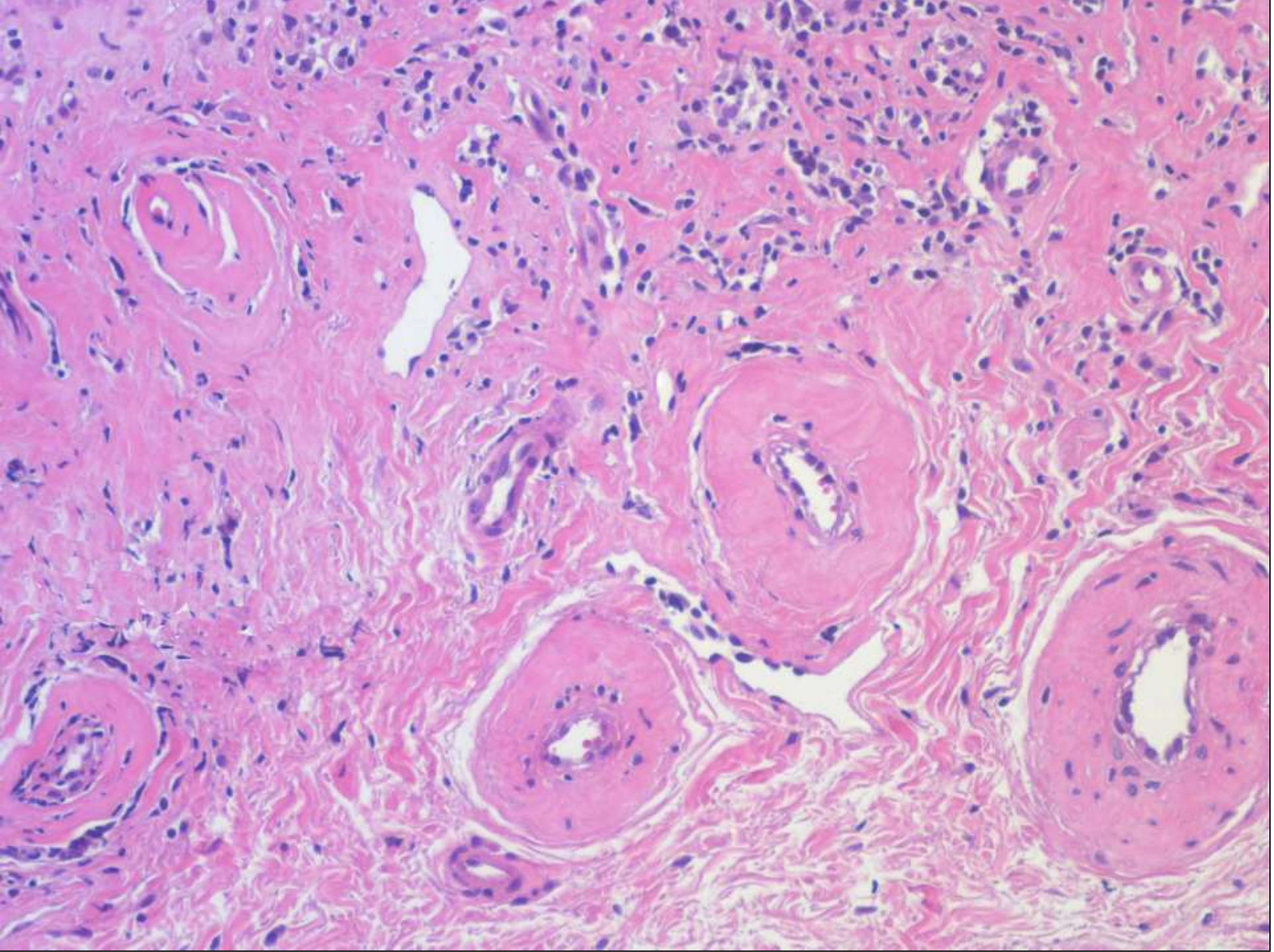
but sometimes specimens from the genitalia are very superficial, and if the dermis is not included, individual necrotic keratocytes throughout the spinous and cornified layer allow a presumptive diagnosis of lichen sclerosus to be made.



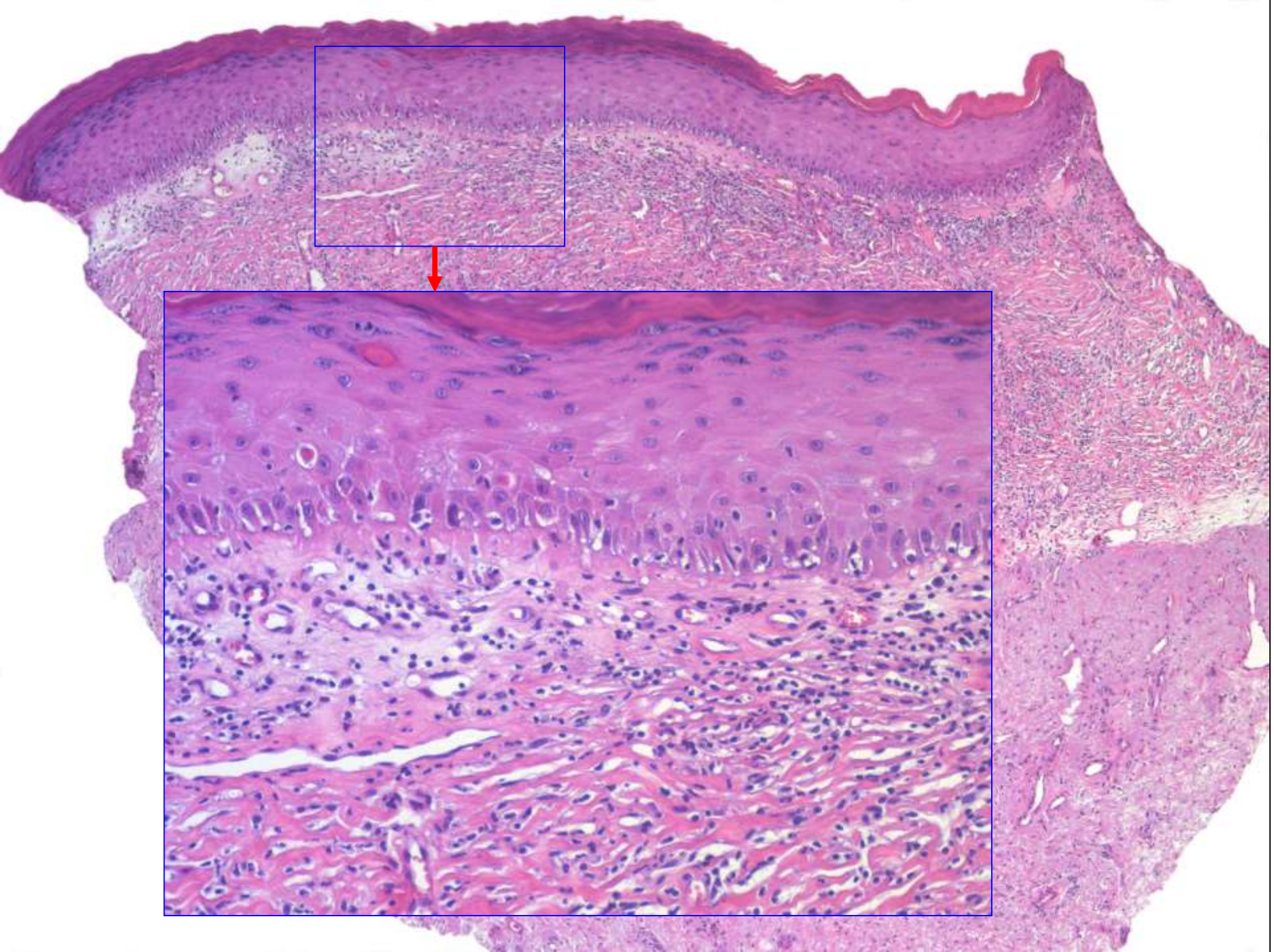
In the absence of sclerosis, the papillary dermis of lesions of lichen sclerosis nearly always shows fibrosis which is usually marked, and files of lymphocytes may be seen between thickened collagen fibres.



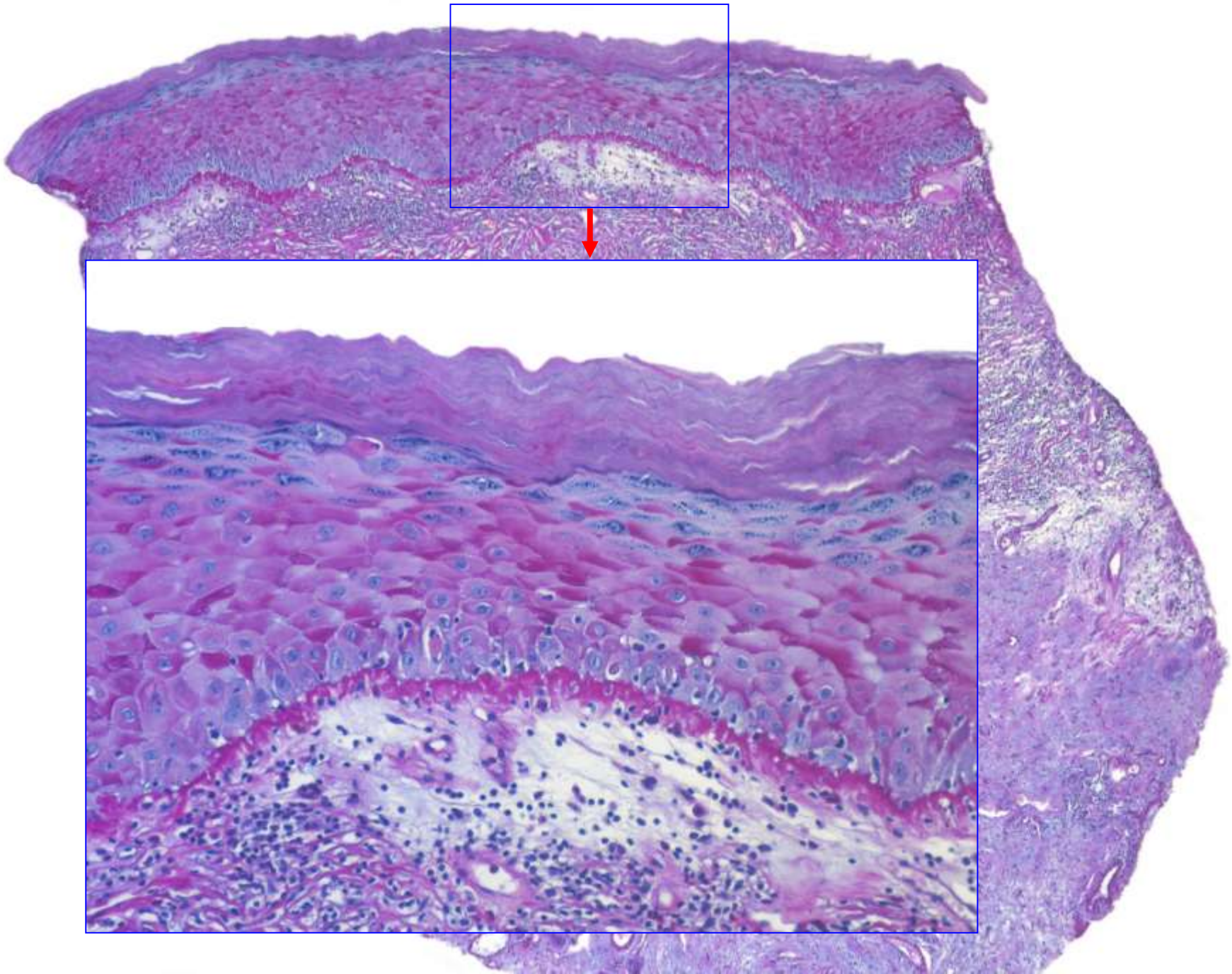
Another distinctive finding is concentric collagen cuffs around venules in the upper dermis. It is relatively uncommon and mostly seen in cases with subepidermal sclerosis in which the diagnosis can be made on other grounds.



Nonetheless, it is helpful occasionally because it is not seen in diseases entering the differential diagnosis, such as lichen planus or mycosis fungoides.



The same is true for thickening of the basement membrane. It resembles the changes seen in lupus erythematosus



and can be appreciated better in the PAS stain. A thickened basement membrane

The American Journal of Dermatopathology 22(5): 457–458, 2000

On the Cover

A Thickened Basement Membrane is a Clue to . . . Lichen Sclerosus!

Philip E. LeBoit, M.D.

Key Words: Basement membrane—Dermatopathology—Interface dermatitis—Lichen sclerosus—Lupus erythematosus

There are many microscopic signs that are emblematic of diseases, but few are pathognomonic. Flame figures, initially believed to be a sign of eosinophilic cellulitis or Well's syndrome, occur in diverse conditions in which there are many eosinophils in the dermis (1). Ghost cells, at one time regarded as signifying pilomatricoma, can occur in any neoplasm in which there is differentiation toward the follicular matrix (2). Eosinophilic pustules in follicular infundibula occur not only in Ofuji's disease, but in a recalcitrant folliculitis in immunocompromised patients and even in some patients with dermatophytic folliculitis (3). Diseases seem to conspire to defeat microscopists who try to diagnose them based on a single finding. On the other hand, all is not lost, as nonspecific findings can be vehicles to specific diagnoses, because they usually are present in circumscribed groups of conditions (4).

Among the few specific findings that seem to have stood the test of time is that of a thickened basement membrane. The result of excess secretion of basement membrane material and deposits of immunoglobulin, the thick basement membrane of lupus erythematosus is known to even first year residents in pathology and dermatology as indicating lupus erythematosus. More sophisticated trainees learn that it can occur in dermatomyositis as well, and that it usually takes months to appear. Thus, it is a finding to be sought in older lesions but not in fresh ones. The repeatability of this association and its significance was noted by Ackerman, who wrote that "there are only two diseases associated repeatedly with a thickened epidermal (and adnexal epithelial) basement membrane, namely discoid lupus erythematosus and dermatomyositis. When a histopathologist sees a thickened basement membrane immediately beneath the epidermis and often along the upper part of follicular infundibula and eccrine ducts, the diagnosis must be either lupus erythematosus or dermatomyositis" (5).

It is startling to find a thickened basement membrane in lichen sclerosus. Unlike the thin band of eosinophilic collagen just beneath the real (and thin) basement membrane in severely sun damaged skin, which entraps beginners in dermatopathology into making the diagnosis of lupus, the thickened basement membrane in the case of lichen sclerosus depicted on the cover of this issue is the "real deal" (Fig. 1). It is more deeply eosinophilic than the pallid and homogeneous appearing papillary dermis beneath it, and bright pink with a digested peri-

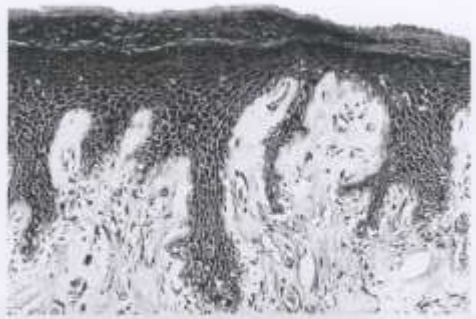
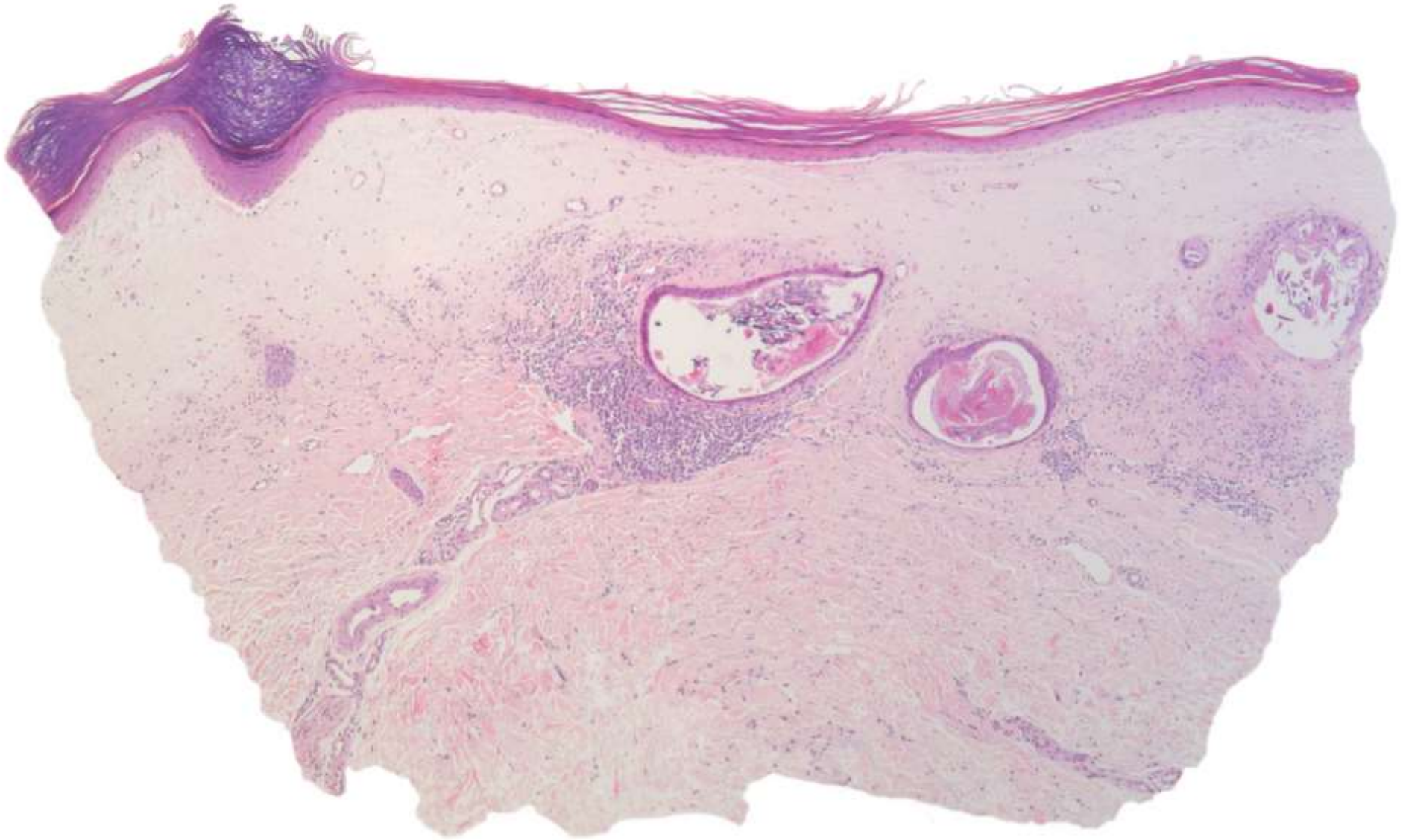


FIG. 1. In this portion of an incisional specimen of lichen sclerosus, also shown on the cover, the papillary dermis is pallid and homogeneous in appearance. A thickened epidermal basement membrane can be discerned along most of the junctional zone.

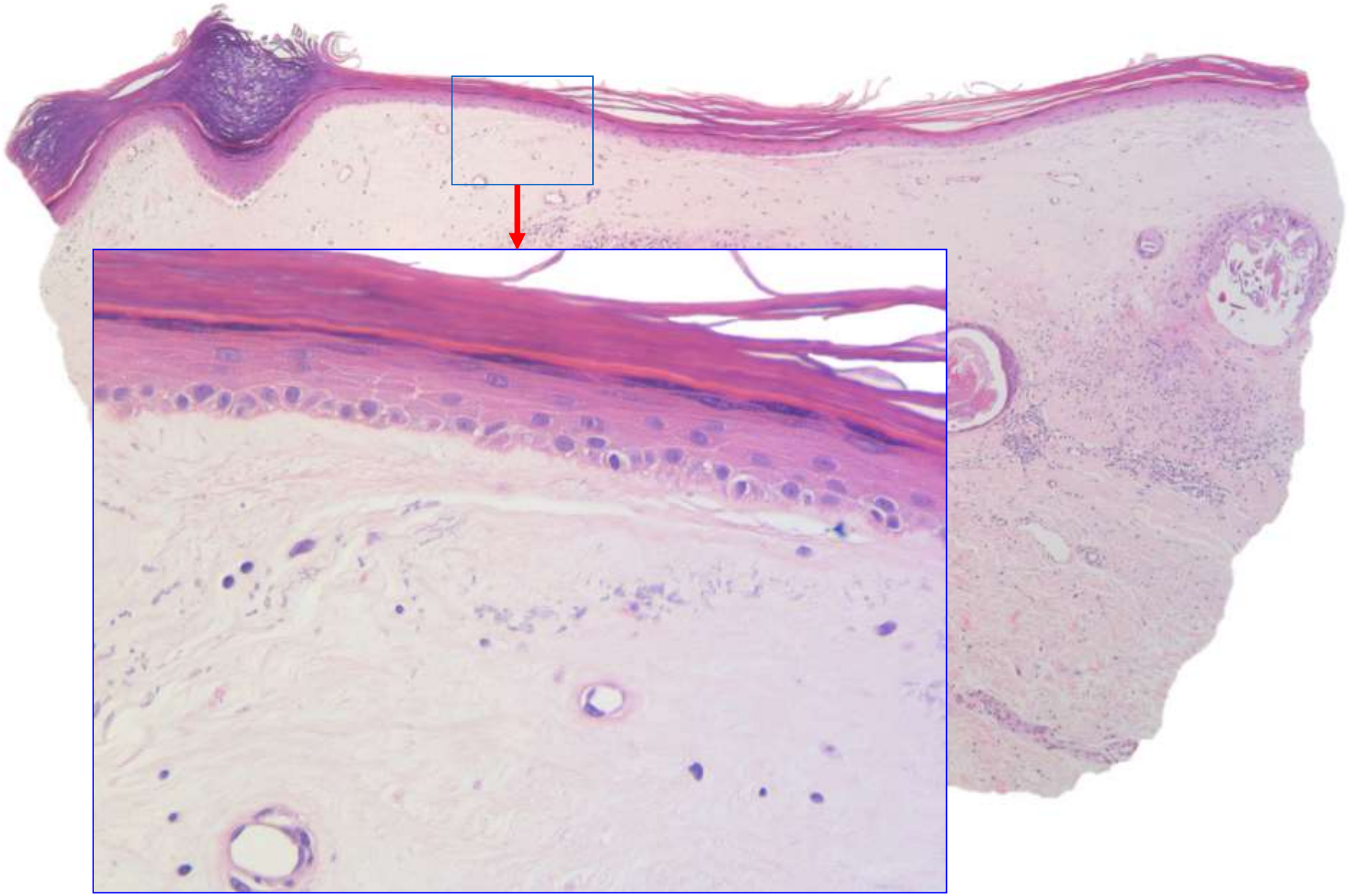
From the Dermatopathology Section, University of California, San Francisco, California.

Address correspondence to Philip E. LeBoit, M.D., Dermatopathology Section, University of California, San Francisco, California, San Francisco, 1701 Divisadero Street, Room 335, San Francisco, CA 94115.

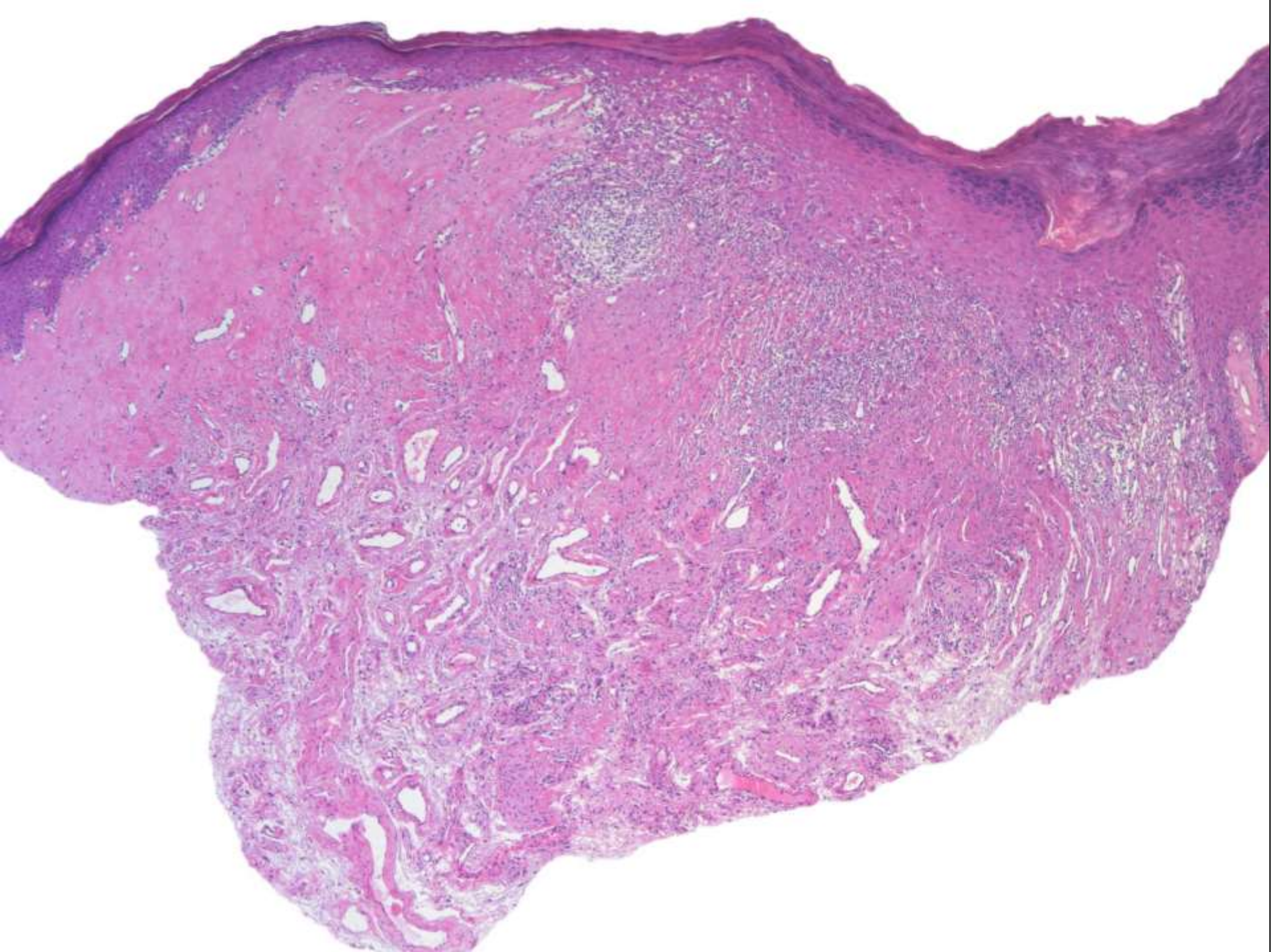
has been emphasized as a clue to lichen sclerosus. However, its utility is limited because there is nearly always the tell-tale sign of subepidermal sclerosis associated with it, whereas the basement membrane tends to be normal in areas without sclerosis.



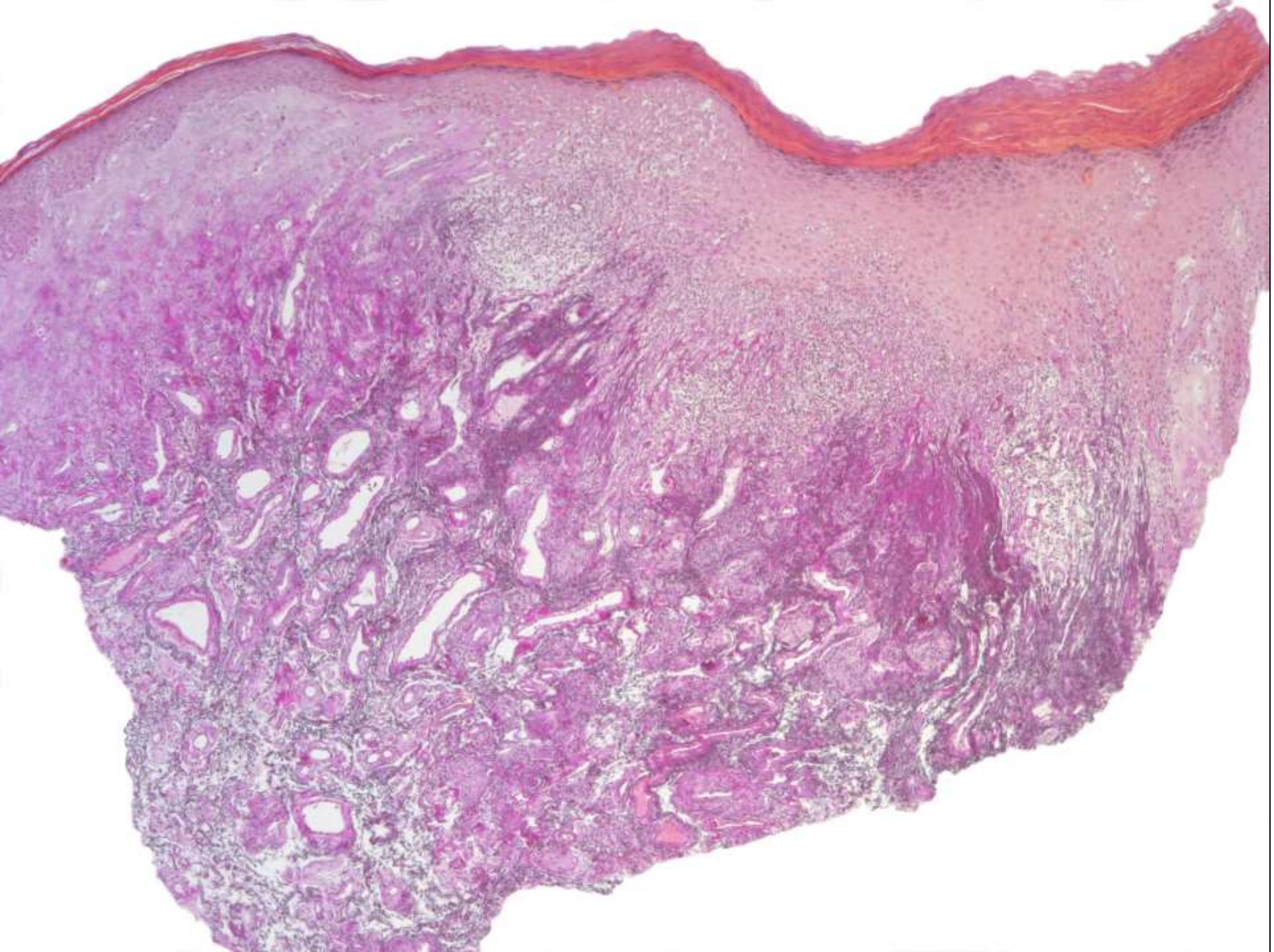
The same applies to other findings, such as follicular hyperkeratosis and loss of elastic fibres. Follicular hyperkeratosis may be striking, reminiscent of findings sometimes encountered in lupus erythematosus, but this is only seen in advanced stages with prominent sclerosis.



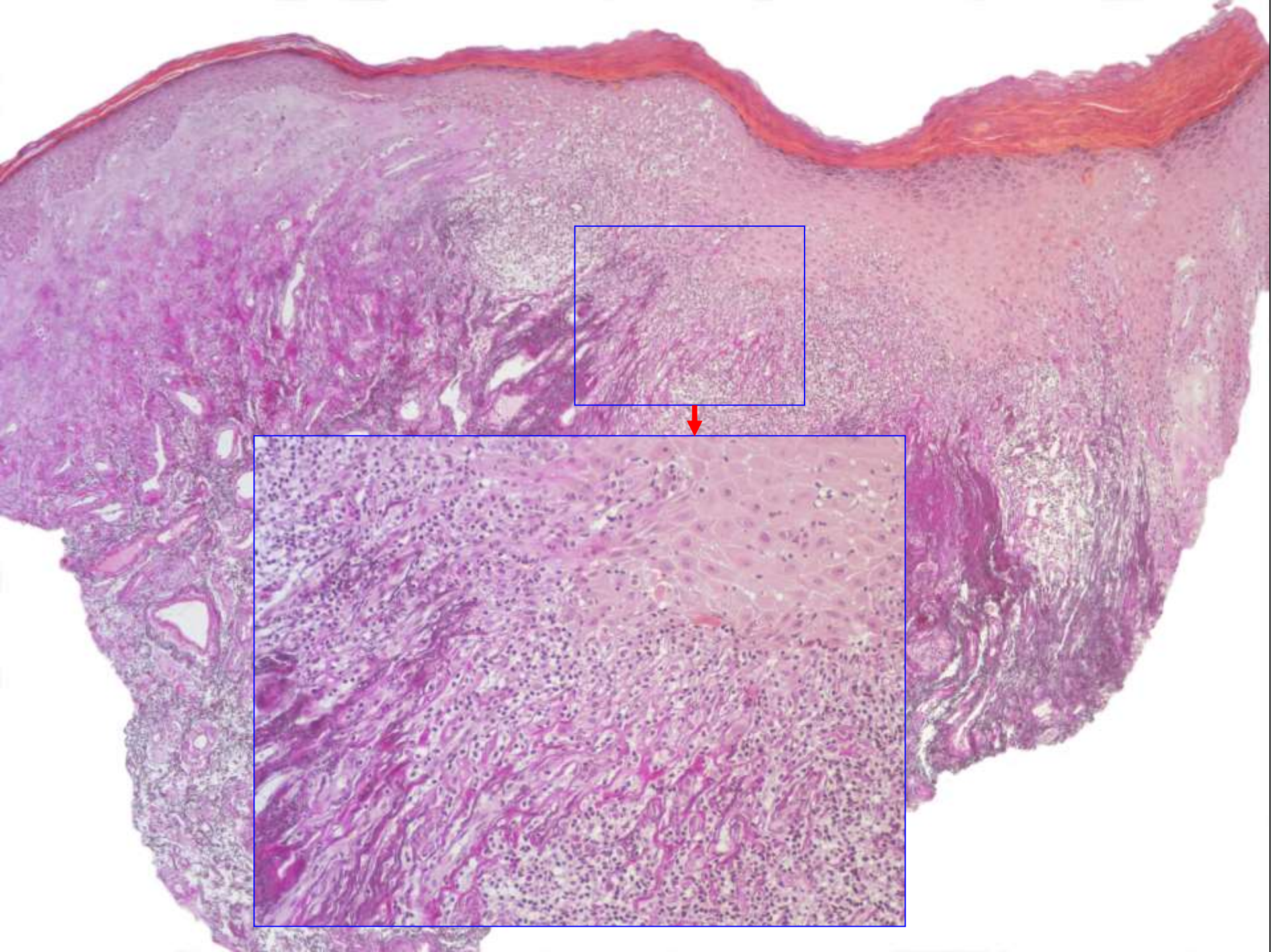
In zones of sclerosis, elastic fibres are diminuished markedly, and the few that have remained are bluish and fragmented. Although typical of lichen sclerosus, those changes are practically never seen in diagnostically challenging cases without subepidermal sclerosis, limiting their diagnostic value.



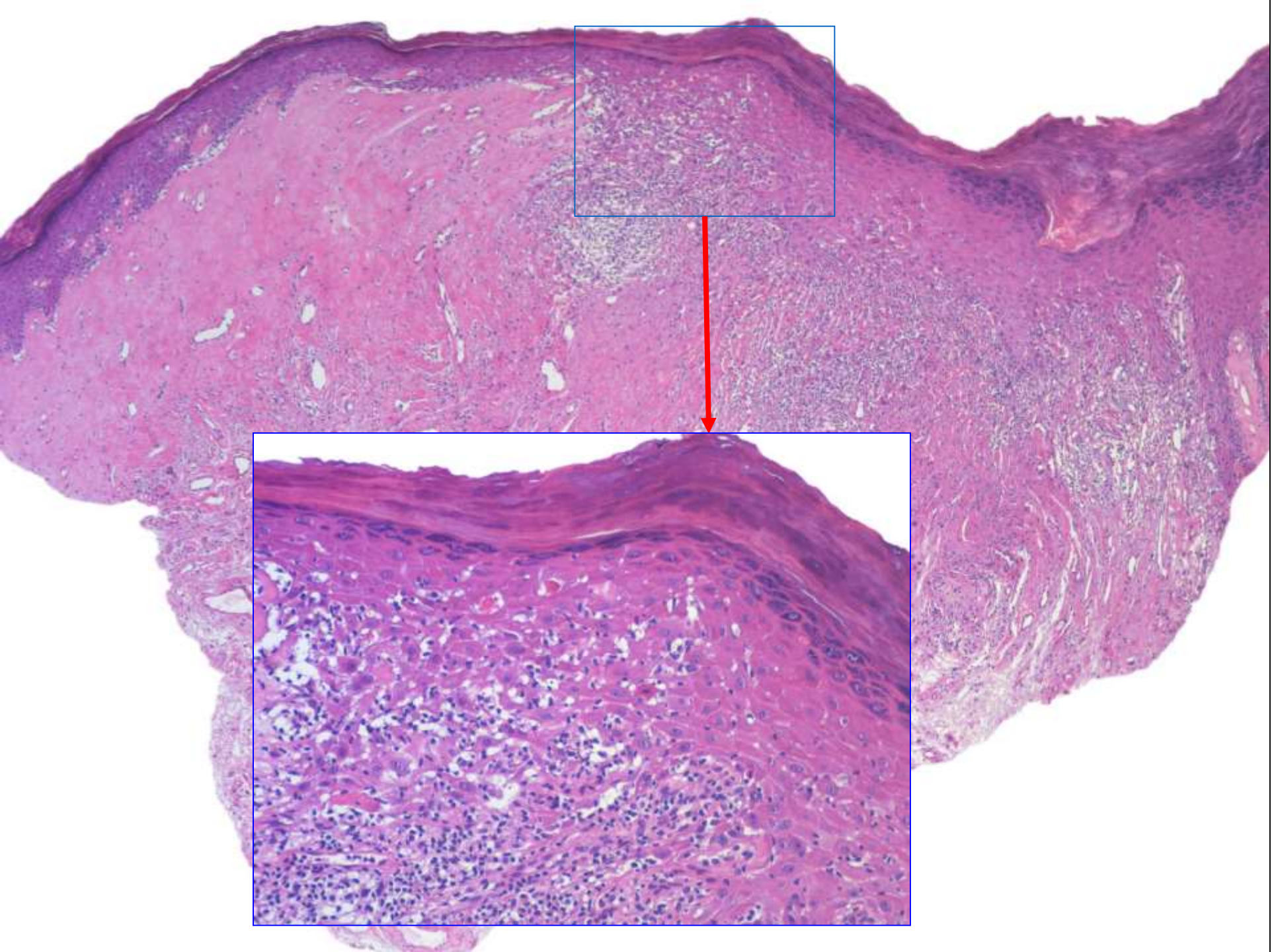
Here is an example of a case that shows both, zones with and without sclerosis.



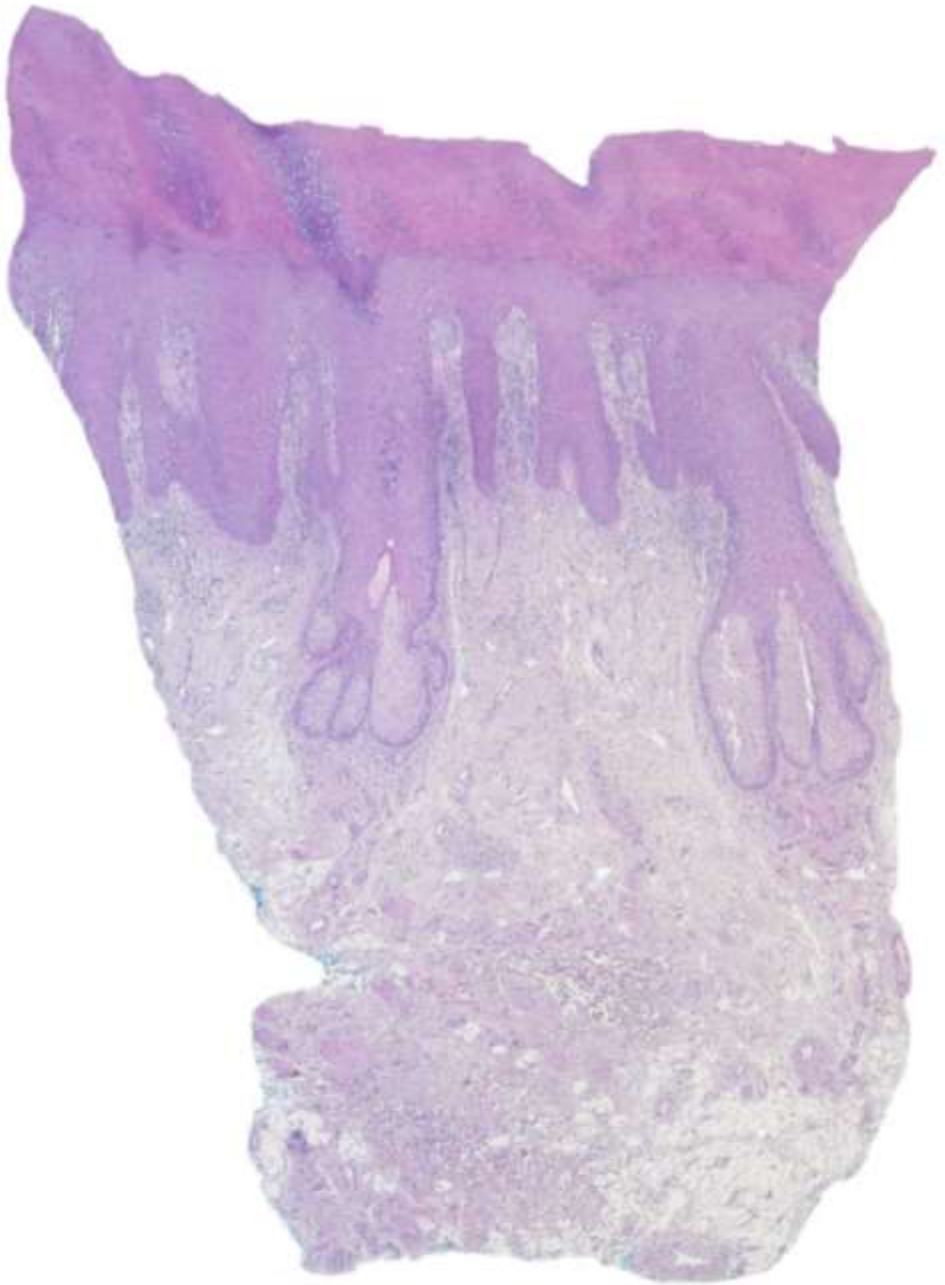
but they are preserved in the zone without sclerosis.



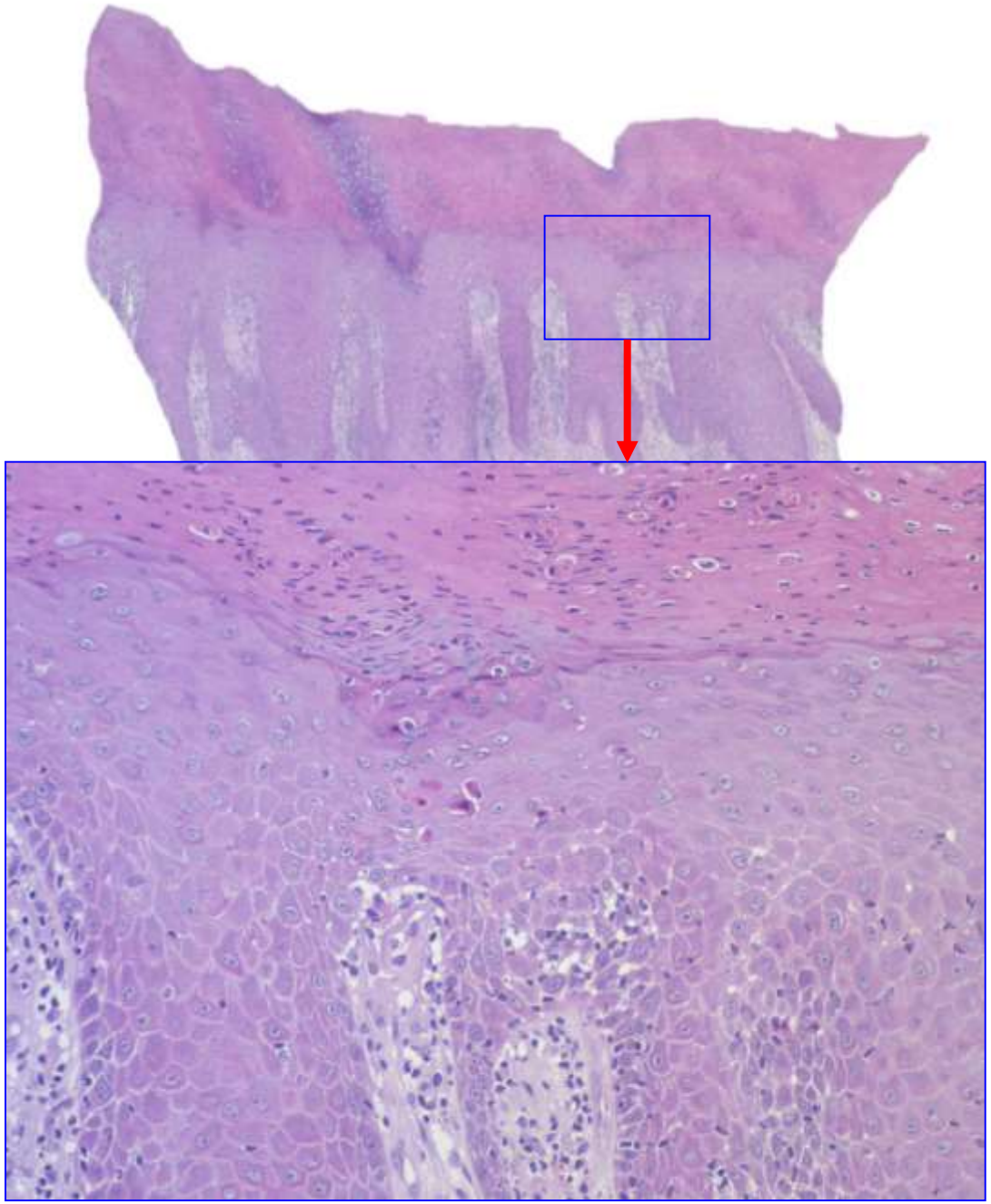
If confronted only with the latter changes, one has to rely on other clues,



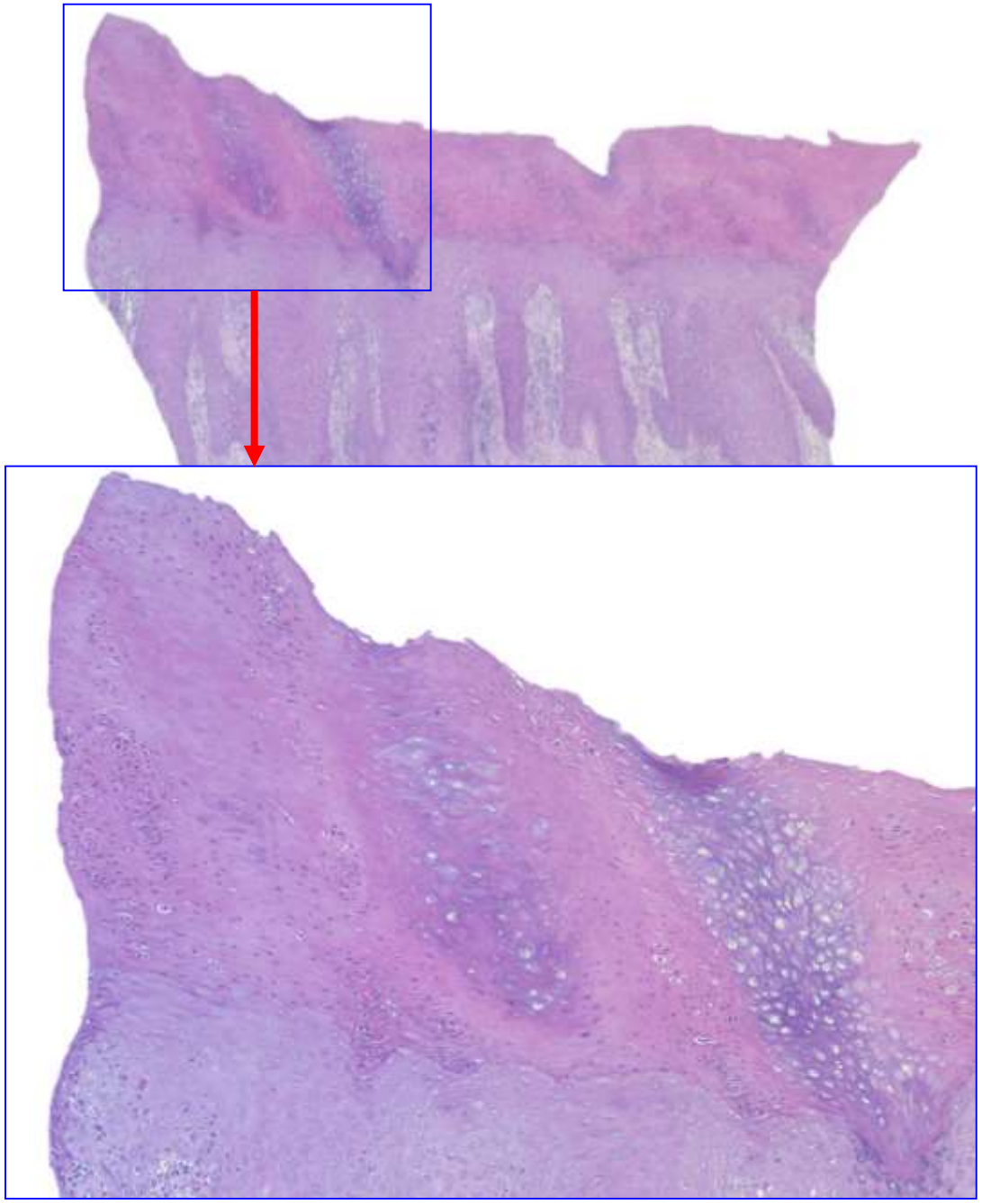
such as lymphocytes scattered through the lower half of the spinous zone – a finding militating against lichen planus – and necrotic keratocytes in all reaches of the epidermis.



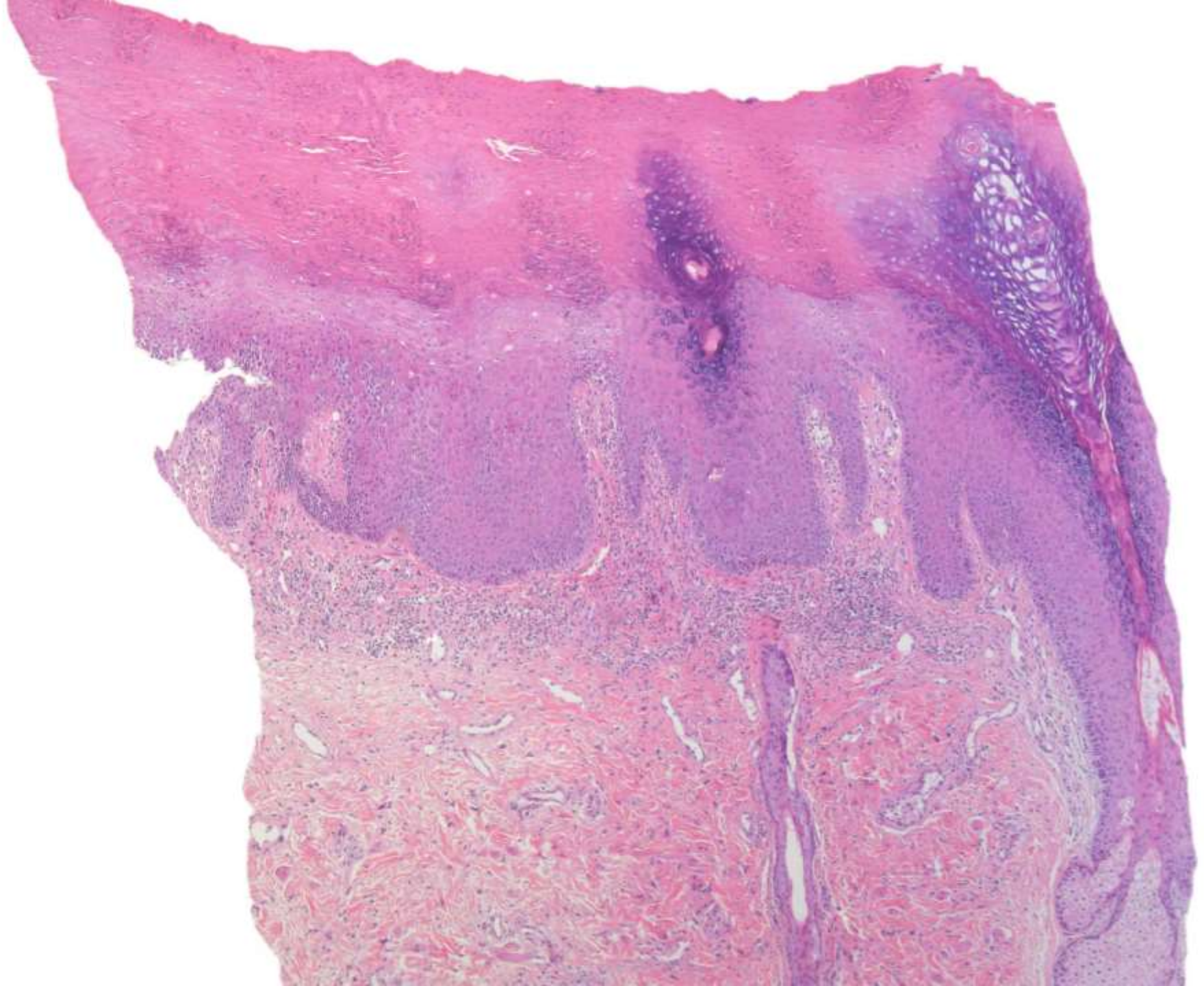
A finding that is distinctive and of high diagnostic value in cases of lichen sclerosus without sclerosis is restriction of those changes to the suprapapillary plates. In this case with pronounced psoriasiform hyperplasia,



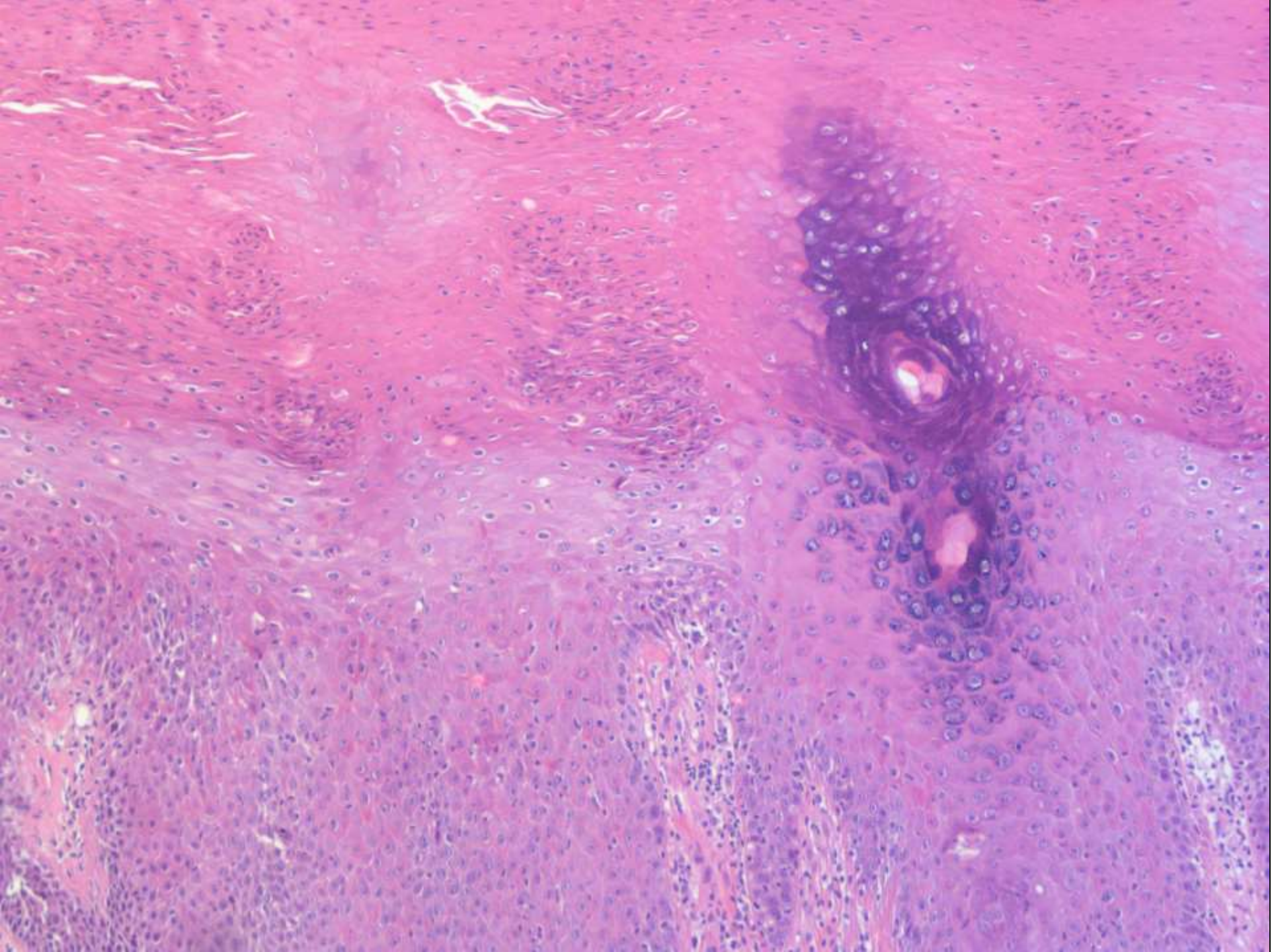
necrotic keratocytes and lymphocytes with some associated spongiosis are seen especially above the tips of dermal papillae,



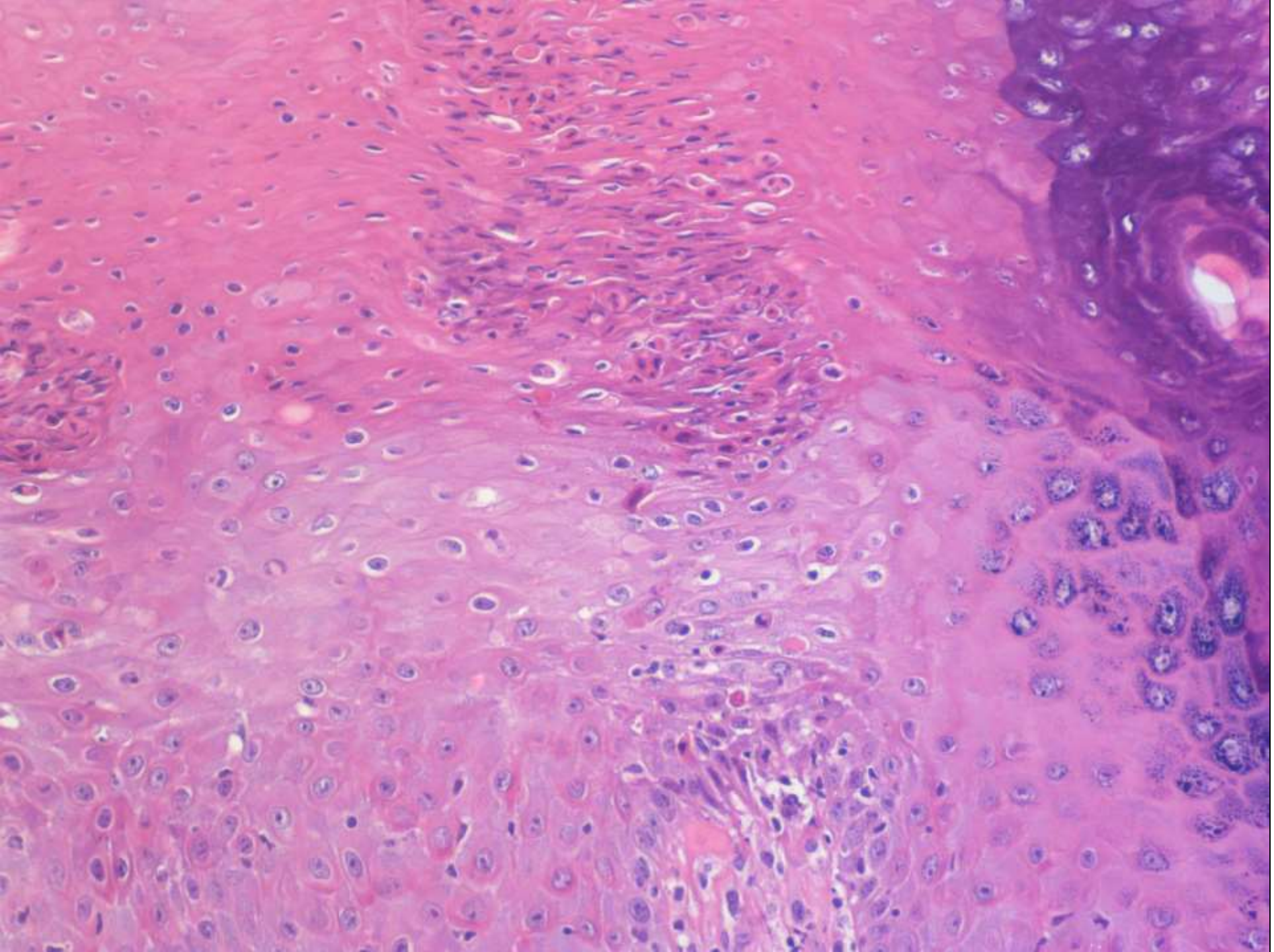
giving rise to narrow columns of parakeratosis in which individual necrotic keratocytes are still discernible. Those vertical columns of parakeratosis are a very helpful clue to the diagnosis of hypertrophic, non-sclerotic lichen sclerosus.



They are fairly common and can be appreciated at scanning magnification.



In contrast to cornoid lamellae, there are individual necrotic keratocytes in those columns, somewhat resembling the so-called “grains” of Darier’s disease.



Moreover, necrotic keratocytes are scattered in the spinous zone above dermal papillae in which one may see tiny foci of sclerosis which, of course, are another clue to the diagnosis.

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Journal of
Cutaneous Pathology

Hypertrophic lichen sclerosus sine sclerosis: clues to histopathologic diagnosis when presenting as psoriasiform lichenoid dermatitis

Background: The histopathologic diagnosis of lichen sclerosus (LS) is usually facilitated by a subepidermal zone of sclerosis. In the absence of sclerosis, LS mostly presents itself as a psoriasiform lichenoid dermatitis that may be difficult to distinguish from other diseases.

Objective: We sought to assess histopathologic findings that allow recognition of LS in the absence of sclerosis.

Methods: We studied 28 criteria in 100 biopsy specimens of LS from genital or perianal skin, including 55 cases with marked sclerosis, 16 cases with mild sclerosis confined to foci of the papillary dermis and 29 cases without sclerosis. Fifteen cases each of the early plaque stage of mycosis fungoides, lichen planus and lichen simplex chronicus were studied for comparison.

Results: Some histopathologic hallmarks of LS were seen chiefly in sclerotic lesions and, therefore, did not contribute to the diagnosis of difficult cases, such as dissolution of elastic fibers. Others were seen rarely in non-sclerotic lesions but might be helpful in individual cases, including follicular hyperkeratosis and thickening of the basement membrane. Findings that were more common and may be utilized as clues to the histopathologic diagnosis of non-sclerotic LS include tiny foci of homogenized tissue in dermal papillae, marked fibrosis with thickening of the papillary dermis, marked thickening of individual collagen fibers, lymphocytes aligned in rows between those fibers, necrotic keratinocytes, often with preserved pyknotic nuclei, in all reaches of the epidermis, including the cornified layer, clustering of necrotic keratinocytes above elongated dermal papillae and vertical columns of parakeratosis with distinct dyskeratotic parakeratotic cells.

Conclusion: In the absence of sclerosis, histopathologic diagnosis of LS depends on findings that are less distinctive. Nonetheless, a constellation of those findings allows a specific diagnosis to be made.

Keywords: histopathology, lichen sclerosus, psoriasiform lichenoid dermatitis, vulva

Weyers W Hypertrophic lichen sclerosus sine sclerosis: clues to histopathologic diagnosis when presenting as psoriasiform lichenoid dermatitis.

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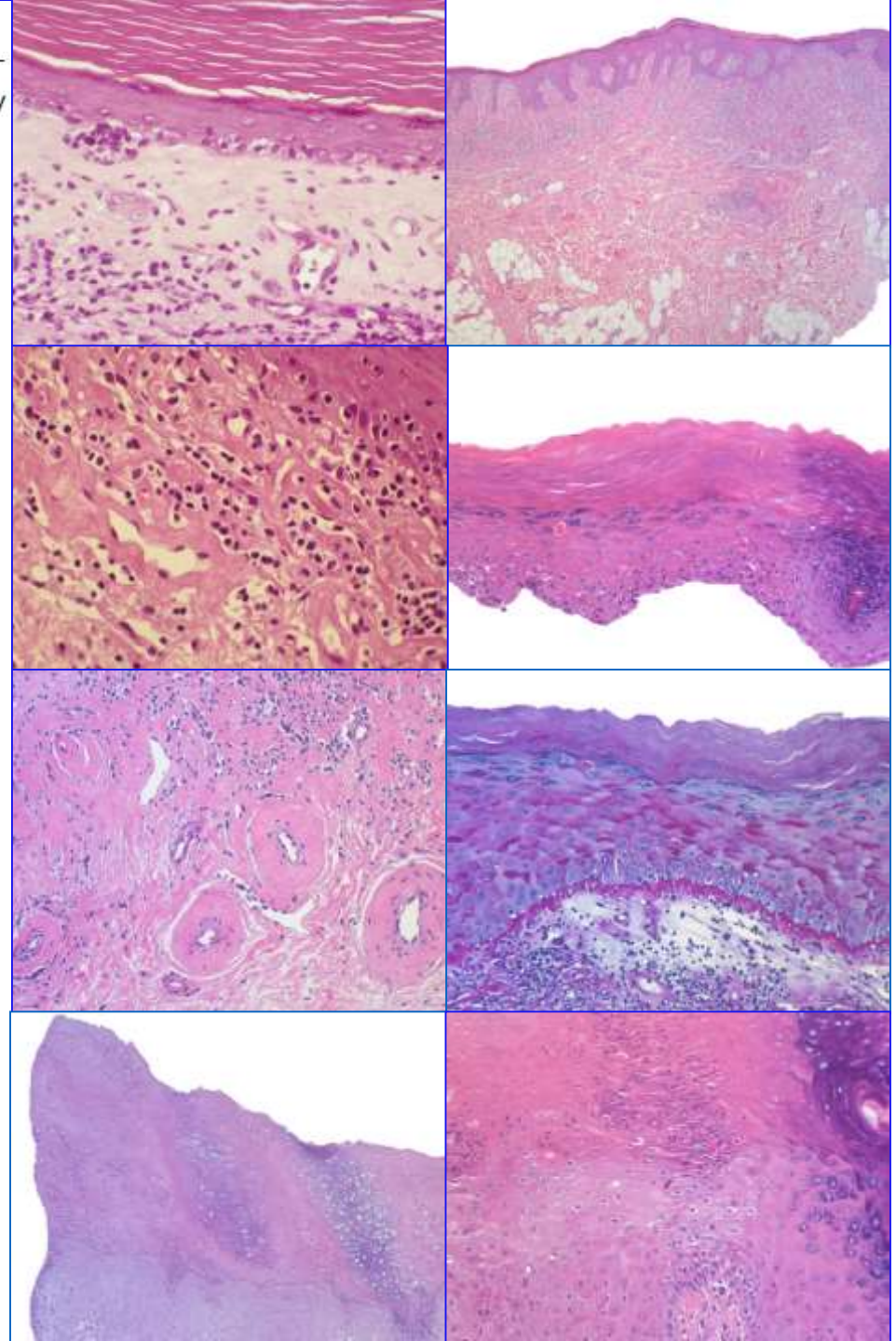
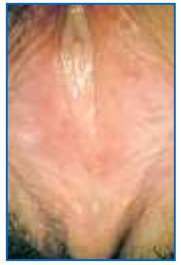


In sum, there are many histopathologic clues that enable the diagnosis of lichen sclerosus to be made even in difficult cases. I have summarized them in a review in the Jouunal of Cutaneous Pathology two years ago.



Clues to the diagnosis of lichen sclerosus

- Poorly cellular zone of sclerosis between epidermis and a superficial lichenoid infiltrate (“flag of the Netherlands”)
- Marked subepidermal fibrosis with thickening of papillary dermis
- Tiny foci of sclerosis at the tips of dermal papillae
- Lymphocytes scattered through the lower half of the spinous zone in concert with scant spongiosis
- Lymphocytes aligned in the basal layer
- Files of lymphocytes between thickened collagen bundles
- Hypergranulosis and compact orthokeratosis
- Follicular hyperkeratosis
- Thickened basement membrane
- Bluish, fragmented, and diminuished elastic fibres
- “Collagen cuffs” around vessels
- Necrotic keratocytes in all reaches of the epidermis
- Columns of parakeratosis

In the absence of the tell-tale sign of a poorly cellular zone of sclerosis between the epidermis and a superficial lichenoid infiltrate, the diagnosis can be made on the basis of marked subepidermal fibrosis with thickening of the papillary dermis, tiny zones of sclerosis at the tips of dermal papillae, lymphocytes scattered through the lower half of the spinous zone in concert with scant spongosis, lymphocytes aligned in the basal layer, files of lymphocytes between thickened collagen bundles, hypergranulosis and compact hyperkeratosis, follicular hyperkeratosis, a thickened basement membrane, bluish, fragmented, and diminuished elastic fibres, “collagen cuffs” around vessels, necrotic keratocytes in all reaches of the epidermis, and columns of parakeratosis.

GENERAL GYNECOLOGY

Guidelines for the follow-up of women with vulvar lichen sclerosus in specialist clinics

Ronald W. Jones, FRCOG; James Scurry, FRCPA; Sallie Neill, FRCP; Allan B. MacLean, FRCOG

It is recommended that women with vulvar lichen sclerosus be followed in specialist clinics where difficulty exists with symptom control or where there is clinical evidence of localized skin thickening. Follow-up is also recommended for women who have previously been treated for squamous cell carcinoma of the vulva (arising in lichen sclerosus or vulvar intraepithelial neoplasia) or where the pathologist expresses concern and is unable to make a definitive diagnosis of differentiated vulvar intraepithelial neoplasia.

Key words: cancer risk, specialist clinics, vulvar lichen sclerosus

Cite this article as: Jones RW, Scurry J, Neill S, et al. Guidelines for the follow-up of women with vulvar lichen sclerosus in specialist clinics. Am J Obstet Gynecol 2008;198:496.e1-496.e3.

There is no consensus with respect to the follow-up of women with vulvar lichen sclerosus (LS). The overall efficacy of modern therapy, the inconvenience of "routine" clinic visits, and the increasing burden of health care costs support the establishment of guidelines for the follow-up of women with vulvar LS by specialists. We define a specialist in this context as a consultant dermatologist or gynecologist (and outside the United States, a genitourinary physician) who has had additional and dedicated training in managing vulvar disease; a specialist clinic is provided by 1 or more of the above in a dedicated setting.

LS is a non-neoplastic chronic lymphocyte-mediated inflammatory dermatosis with distinctive dermal sclerosis and with a predilection for the anogenital skin in women. The true prevalence is not known. One study suggests that 1 in 30 elderly women have LS.[1]

An association between LS and squamous cell cancer of the vulva (SCCV) has long been recognized and thought to be the result of chronic inflammation and scarring. Much of the available evidence of the relationship between LS and SCCV is based on historical studies and retrospective case-series. Risk has never

CLINICAL
Symptoms

The introduction of potent topical steroids has revolutionized the management of LS, resulting in straightforward symptom control/maintenance therapy for the majority of women—and specialist follow-up is usually not warranted. Guidelines for the management of LS are available.[3] These women should regu-

Let me finish with some remarks about the impact of the diagnosis of lichen sclerosus. This is important because current *"guidelines for the follow-up of women with vulvar lichen sclerosus"* emphasize the *"association between LS and squamous cell cancer of the vulva,"*

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particularly in the case of *"localized skin thickening."* But how risky is hypertrophic lichen sclerosus?

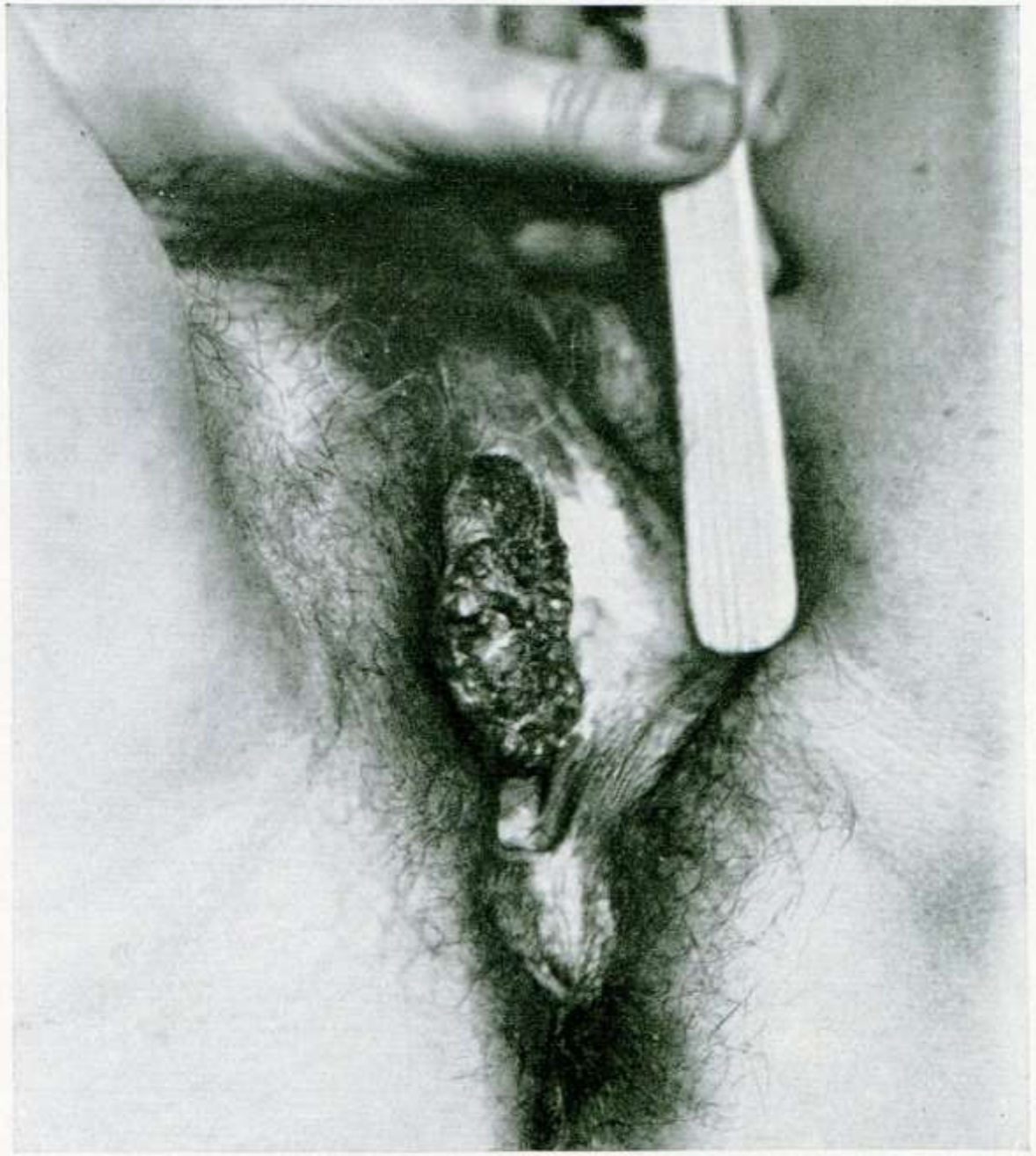

Abb. 20. Kraurosis vulvae, Leukoplakia. Blumenkohlähnliches Carcinom, das sich auf dem Boden einer Leukoplakie allmählich entwickelte. 70jährige Frau

There is no question that lichen sclerosus may be associated with squamous cell carcinoma. Such cases have been documented abundantly in the literature, beginning in the early 20th century when vulvar lichen sclerosus was known as “kraurosis vulvae.” However, because “kraurosis vulvae” was associated with whitish lesions, it was confused commonly with early stages of squamous cell carcinoma known as “leukoplakia.”

Es ist also wahrscheinlich, für bestimmte Fälle ist es sicher, daß Placentabrei oder Placentasaft mehr proteoplastische als proteolytische Wirkung entfaltet. Hieraus ersieht man, wie ungenügend begründet die Versuche von Bumm und Liepmann waren, die Placentasaft bei bösartigen Geschwülsten einspritzten (Zeitschrift für Geburtshilfe Bd. LXI. 1908. p. 417).

Liepmann stützt sich auf Ergebnisse seiner Untersuchungen mit P. Bergell (M. m. W. 1905, Nr. 46), welche mit Hilfe chemischer Methoden die menschliche Placenta auf ihren Gehalt an Fermenten studierten. Daß aus diesen Untersuchungen etwas Unerwartetes herauskam, kann nicht behauptet werden; denn der Beweis, daß die Fermente der Placenta etwas anderes darstellen, als die gewöhnlichen autolytischen, beinahe in allen Organen anzutreffenden Fermente, wird nicht erbracht. Das einzige Neue scheint uns die Bemerkung zu sein, daß sich in der Placenta »wahrscheinlich auch synthetisierende Prozesse abspielen«. Indessen blieb dies vollkommen unbeachtet, als es galt, Krebsgeschwülste mit Placentasaft zu behandeln.

Auffallend war der hohe Gehalt der letzten Placenta an löslichen und unkoagulablen Eiweißstoffen. Dieselbe Beobachtung konnten wir machen an einer Reihe von Eklampsieplacenten, die uns freundlichst durch Herrn Dr. Warnekros aus der Universitäts-Frauenklinik zu Berlin (Geheimrat Bumm) geschickt wurden.

Normale Placenten hatten uns (für 2 g) Werte ergeben von löslichem Eiweißstoff von 28, 25, 10 mg, von unkoagulablem Eiweißstoff von 10, 10, 9 mg, Eklampsieplacenten bzw. Werte von 34, 49, 44, 44 und 26, 27, 27, 25.

Höchst interessant schien es uns in diesen Fällen, genau dem Gang der Autolyse bzw. Autoplastie nachzugehen. Kontrollversuche lehrten uns leider, daß die Einpackung der Placenten in Formoltüchern (zum Übersenden) auf den späteren Gang der Autolyse einen störenden Einfluß ausübte und zwangen uns, diese Untersuchungen den größeren, an Eklampsiefällen reichen Kliniken zu überlassen.

II.

Kraurosis und Cancroid.

Von

R. Teuffel in Stuttgart.

Die neueren Veröffentlichungen über die Karzinombehandlung haben mich an einen Fall aus meiner Chemnitzer Praxis (1899) erinnert, bei dem gleichzeitig Kraurosis und Cancroid bestand, und der einen Beitrag zur Kenntnis der Wirkung von Entzündung auf maligne Neubildung zu liefern geeignet scheint.

Als Kraurosis war die über Clitoris, kleine und zum Teil große Labien verbreitete Hautaffektion charakterisiert, sowohl durch die subjektiven Beschwerden als durch die eigentümlich mattweiße Verfärbung, das plumpe Aussehen und die derbe Beschaffenheit der befallenen Teile; seichte Risse, deren Grund dunkel bläulichrot durchschimmerte, zogen sich über die pigmentlosen Stellen hin.

Einige Zeit später konnte ich im Gebiet der Erkrankung oberflächliche und tiefere Geschwüre beobachten, sowie deutliche Anschwellung der Inguinaldrüsen. Aus einem von mir in diesem späteren Stadium exzidierten Gewebsstück wurden im Chemnitzer pathologischen Institut (Prof. Nauwerck) Schnitte hergestellt, die den beiden Mikrophotogrammen zugrunde liegen.

Die von den tieferen Schichten der Epidermis, bei noch intakter Hornschicht,

Fig. 1.

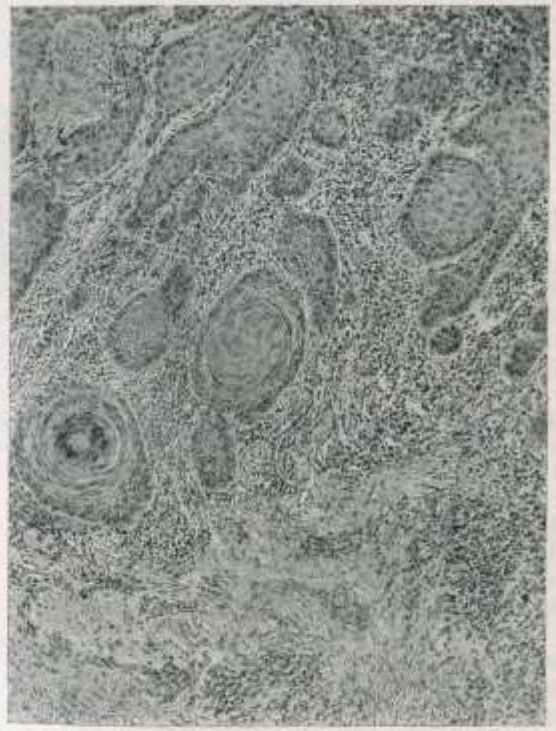

Fig. 2.

ausgehende cancroide Neubildung läßt sich deutlich als solche erkennen; ebenso der in der Hauptsache das Corium betreffende, durch massenhafte Plasmazellen und Schwund der drüsigen und Gefäßelemente charakterisierte Entzün-

In many articles about “kraurosis” and cancer, there was evidence of cancer, but not of lichen sclerosus.

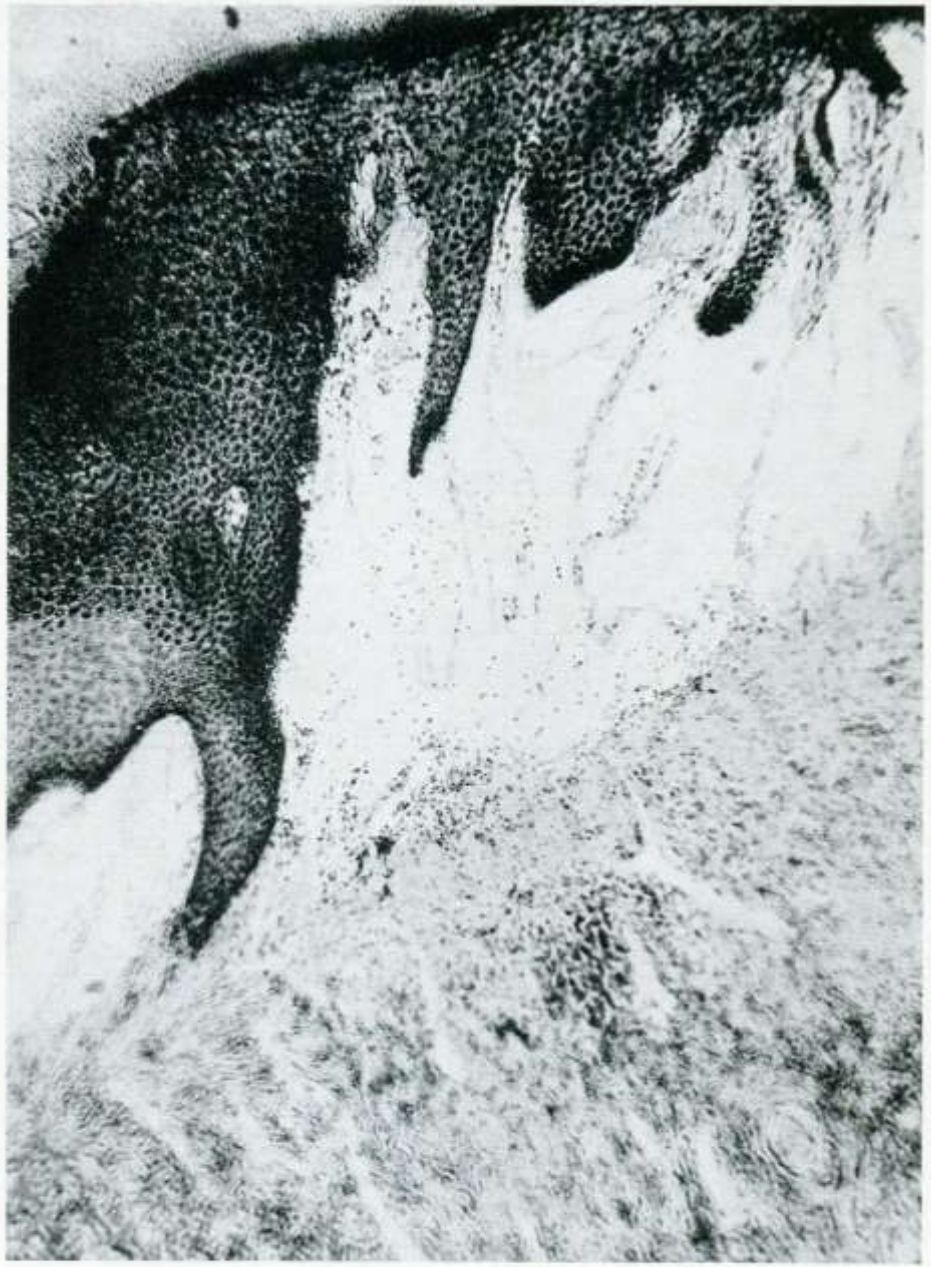

Abb. 2. Vulväre Leukoplakie mit beginnender epitheliomatöser Umwandlung bei Lichen sclerosus et atrophicus; bedeutendes Lymphödem in der oberen Cutis

Vice versa, pictures of lichen sclerosus with alleged *“epitheliomatous transformation”* showed no clear signs of a malignant process.

Băluş L ,
Hautarzt 1971;
22: 199

Lichen sclerosus et atrophicus der Vulvagegend als präcanceröser Zustand

L. Bălus
Dermato-venerologisches Zentrum des Gesundheitsministeriums (Rumänien)

Die Epitheliome der Vulvagegend stellen infolge ihrer raschen Ausbreitung, ihrer frühen Metastasierung und ihres Widerstands gegenüber den uns heute zur Verfügung stehenden Behandlungsverfahren besonders bösartige Tumoren dar [2, 4, 10, 17, 32]. Daher sind möglichst wirksame vorbeugende Maßnahmen notwendig, in deren Rahmen die Kenntnis und Behandlung der präcancerösen Erkrankungen der Vulvagegend einen wichtigen Platz einnehmen. Zu diesen Präcancerosen gehört der Lichen sclerosus et atrophicus der Vulvagegend (LSAV), eine Dermatose, deren carcinogenes Potential noch wenig bekannt ist.

Krankengut und Arbeitsmethode

Unser Krankengut umfaßt eine Anzahl von 83 Frauen und 12 Männern mit LSA. Bei allen Patienten wurden je 1—3 Biopsien der Haut- und Schleimhautschäden in verschiedenen Zeitabständen durchgeführt. Die histologischen Schnitte wurden in üblicher Weise gefärbt, und zwar Hämatoxylin-Eosin, van Gieson, Trichrom nach Masson, Orcein für das elastische Gewebe usw.

Klinisches und histologisches Bild der LSAV-Veränderungen

Wir beabsichtigen nicht, hier eine eingehende Beschreibung der Vulvaveränderungen beim LSA zu geben. Wir möchten bloß auf einige Merkmale hinweisen, die eine Erkennung der Dermatose erleichtern und das Verständnis des Cancerisierungsvorgangs fördern.

Tabelle 1

Lokalisation	Anzahl der Fälle
Vulva	12
Vulva, Damm, Perianalgegend	36
Vulva, Damm, Perianalgegend, Haut	27
Haut	8
Insgesamt	83

Perianalgegend ergriffen ist, eine Lokalisation, die wegen ihrer großen Häufigkeit einen wichtigen richtungweisenden Punkt für die klinische Diagnose des LSA bei der Frau darstellt. Der LSA ist eine Dermatose des vorgeschrittenen Alters, da die Mehrzahl der Fälle sowohl bei Frauen als auch bei Männern nach dem 45. Lebensjahr beobachtet wird (Tabelle 2).

Tabelle 2

	Alter (Jahre)						
	unter 30	30—40	40—50	50—60	60—70	70—80	über 80
Anzahl der Fälle	2	4	13	24	23	12	5

Nonetheless, those cases served to reconfirm the concept of lichen sclerosus of the vulva as a *“precancerous state.”*

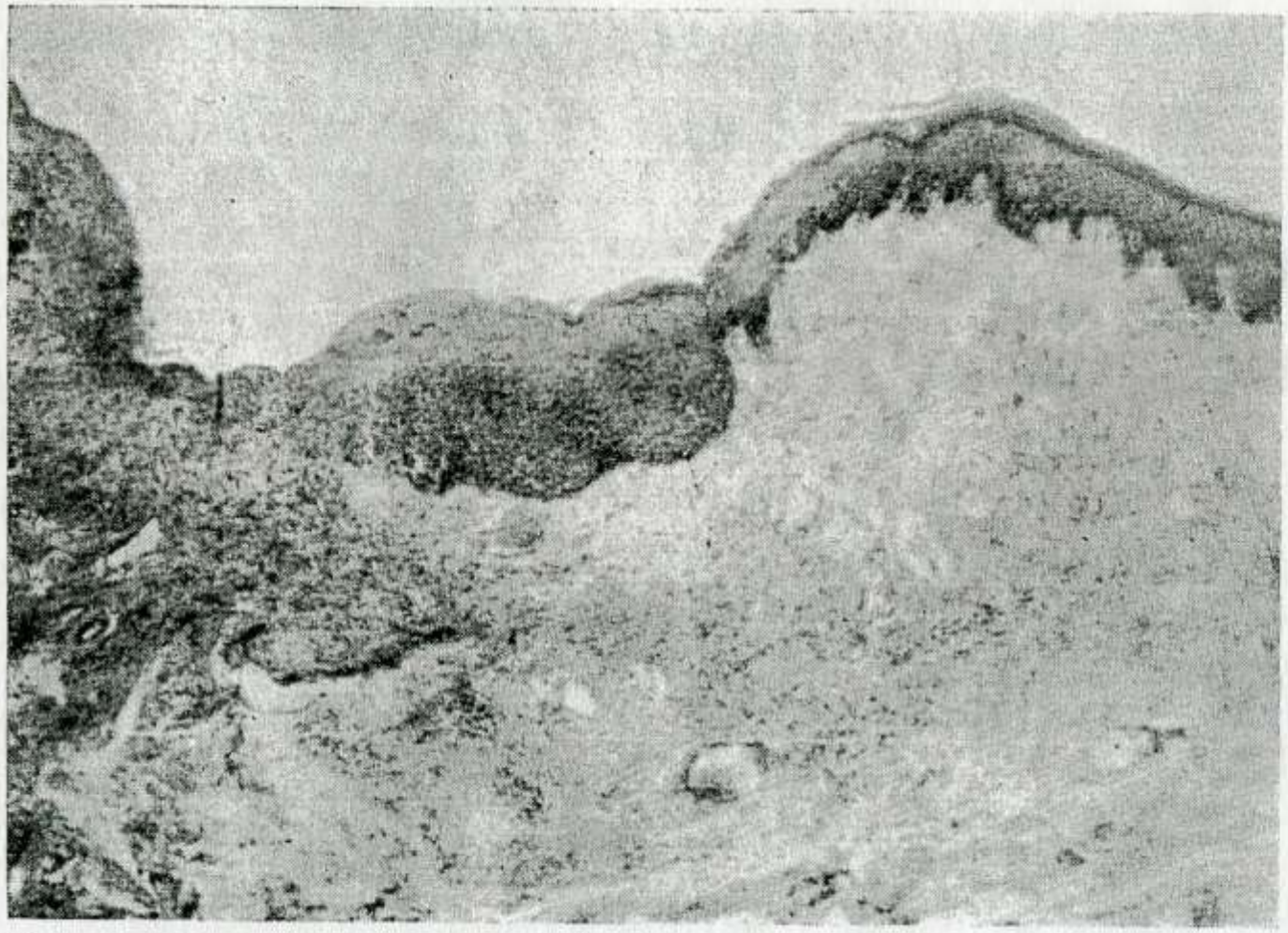

Fig. 7.—Sections of LSA of vulva with carcinoma in situ. Note leukoplakia changes in epidermis on the right of specimen, with homogenization of upper corium beneath. On the left is seen irregular proliferation of basal cells and mass of large prickle cells.

Arch Dermatol
1962; 85: 362

And then there were pictures showing an undubitable association of lichen sclerosus and cancer, as in this article by Barker and Gross in 1962.

Lichen Sclerosus et Atrophicus of the Female Genitalia

A Clinical Study and Diagnostic Guide

LESLIE PAXTON BARKER, M.D.
AND
PAUL GROSS, M.D.
NEW YORK

For the keratotic lesions of the vulva, weekly or semi-monthly applications of thorium X were used.

card-like scleroderma, morphea guttata—and many others. It was not until Kogoj [3,4] (1934), Montgomery and Hill,[5] (1940) and subsequent contributors brought out its specific clinical and histological features that the criteria for a classification of LSA were finally clarified.

As a background for the discussion of LSA of the female genitalia, let us outline briefly such features of the disease as it affects other parts of the integument.

General Characteristics of Lichen Sclerosus et Atrophicus

However, the authors acknowledged that, in their clinic, keratotic lesions of lichen sclerosus were routinely treated with radiotherapy. Although that treatment may have contributed to carcinogenesis, and although they observed cancer in but a single case,

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The Malignancy Potential.—The relationship between carcinoma of the vulva and LSA can no longer be discounted.

dermatitis, white-spot disease, lichen albus, card-like scleroderma, morphea guttata—and many others. It was not until Kogoj [3,4] (1934), Montgomery and Hill,[5] (1940) and subsequent contributors brought out its specific clinical and histological features that the criteria for a classification of LSA were finally clarified.

investigated.

As a background for the discussion of LSA of the female genitalia, let us outline briefly such features of the disease as it affects other parts of the integument.

General Characteristics of Lichen Sclerosus et Atrophicus

the authors concluded that *"the relationship between carcinoma of the vulva and LSA can no longer be discounted."*

Lichen Sclerosus et Atrophicus of the Female Genitalia

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I would caution against the concept of leukoplakia superimposed on lichen sclerosus et atrophicus. In cases of lichen sclerosus et atrophicus with a whitish, thickened skin one sees, on histologic examination, hyper-keratosis and irregular acanthosis, but no atypicality of the epidermal cells … Not one of the many cases of lichen sclerosus et atrophicus seen at the Free Hospital for Women ever developed carcinoma.

Walter Lever, Arch Dermatol 1962; 85: 371

were finally clarified.

Sclerosus et Atrophicus

In a discussion of this paper, Walter Lever of Boston noted: *"I would caution against the concept of leukoplakia superimposed on lichen sclerosus et atrophicus. In cases of lichen sclerosus et atrophicus with a whitish, thickened skin one sees, on histologic examination, hyperkeratosis and irregular acanthosis, but no atypicality of the epidermal cells ... not one of the many cases of lichen sclerosus et atrophicus seen at the Free Hospital for Women ever developed carcinoma."*

This is also my experience. Because it is unlikely that things in Boston and Freiburg are different from the rest of the world,

we conducted a survey in 2012 concerning the alleged “white danger” emanating from lichen sclerosus. Leading dermatopathologists from Europe and the United States were asked how often they had seen the association of lichen sclerosus with cancer in their regular material.

Zsolt Argenyi	Seattle	USA	P	>30	k.A.	0
Susanna Borghi	Freiburg	D	D	15	ca. 1.000*	0
Walter Burgdorf	Tutzing	D	D	>20	k.A.	0
Lorenzo Cerroni	Graz	A	D	>20	3-4 pro Monat	0
Carlos Diaz	Freiburg	D	P	30	ca. 3.000*	0
Angel Fernandez Flores	Ponferrada	E	P	19	k.A.	0
Markus Hantschke	Friedrichshafen	D	D	17	ca. 1.200*	2
Stefan Hörster	Freiburg	D	D	14	ca. 1.200*	0
Jean Kanitakis	Lyon	F	D	30	k.A.	0
Werner Kempf	Zürich	CH	D	>20	ca. 2.000*	1
Helmut Kerl	Graz	A	D	>40	k.A.	5
Heinz Kutzner	Friedrichshafen	D	D	>30	k.A.	0
Phil LeBoit	San Francisco	USA	D	27	500	0
Tim McCalmont	San Francisco	USA	D	21	k.A.	3
Thomas Mentzel	Friedrichshafen	D	P	>20	k.A.	0
Dieter Metze	München	D	D	> 20	100 pro Jahr	2
Francois Milette	Longueuil	CAN	P	22	k.A.	0
Jochen Möckel	Freiburg	D	P	8	40 pro Jahr	0
Bruno Paredes	Friedrichshafen	D	D,P	15	ca. 1.200*	0
Luis Requena	Madrid	E	D	25	k.A.	1
Christian Rose	Lübeck	D	D,P	20	ca. 2500*	2
Arno Rütten	Friedrichshafen	D	D	25	ca. 1.500*	0
Omar Sangüeza	Winston Salem	USA	D	>25	ca. 2.000*	0
Leo Schärer	Friedrichshafen	D	D	8	ca.2.000*	0
Michael Tronnier	Hildesheim	D	D	>20	ca. 1.000*	0
Noreen Walsh	Halifax	CAN	D	>20	k.A.	0
Wolfgang Weyers	Freiburg	D	D	22	ca. 4000*	0
Mirjana Ziemer	Leipzig	D	D	8	ca. 800*	0

* im Berufsleben (sehr grobe Schätzung) | ** D = Dermatologe, P = Pathologe | k.A. = keine Angabe

The highest number was given by Helmut Kerl who estimated to have seen 5 cases in a professional career of more than 40 years.

Zsolt Argenyi	Seattle	USA	P	>30	k.A.	0
Susanna Borghi	Freiburg	D	D	15	ca. 1.000*	0
Walter Burgdorf	Tutzing	D	D	>20	k.A.	0
Lorenzo Cerroni	Graz	A	D	>20	3-4 pro Monat	0
Carlos Diaz	Freiburg	D	P	30	ca. 3.000*	0
Angel Fernandez Flores	Ponferrada	E	P	19	k.A.	0
Markus Hantschke	Friedrichshafen	D	D	17	ca. 1.200*	2
Stefan Hörster	Freiburg	D	D	14	ca. 1.200*	0
Jean Kanitakis	Lyon	F	D	30	k.A.	0
Werner Kempf	Zürich	CH	D	>20	ca. 2.000*	1
Helmut Kerl	Graz	A	D	>40	k.A.	5
Heinz Kutzner	Friedrichshafen	D	D	>30	k.A.	0
Phil LeBoit	San Francisco	USA	D	27	500	0
Tim McCalmont	San Francisco	USA	D	21	k.A.	3
Thomas Mentzel	Friedrichshafen	D	P	>20	k.A.	0
Dieter Metze	München	D	D	> 20	100 pro Jahr	2
Francois Milette	Longueuil	CAN	P	22	k.A.	0
Jochen Möckel	Freiburg	D	P	8	40 pro Jahr	0
Bruno Paredes	Friedrichshafen	D	D,P	15	ca. 1.200*	0
Luis Requena	Madrid	E	D	25	k.A.	1
Christian Rose	Lübeck	D	D,P	20	ca. 2500*	2
Arno Rütten	Friedrichshafen	D	D	25	ca. 1.500*	0
Omar Sangüeza	Winston Salem	USA	D	>25	ca. 2.000*	0
Leo Schärer	Friedrichshafen	D	D	8	ca.2.000*	0
Michael Tronnier	Hildesheim	D	D	>20	ca. 1.000*	0
Noreen Walsh	Halifax	CAN	D	>20	k.A.	0
Wolfgang Weyers	Freiburg	D	D	22	ca. 4000*	0
Mirjana Ziemer	Leipzig	D	D	8	ca. 800*	0

* im Berufsleben (sehr grobe Schätzung) | ** D = Dermatologe, P = Pathologe | k.A. = keine Angabe

Most had not seen a single case in many years, including, for example, Lorenzo Cerroni in Graz, Heinz Kutzner in Friedrichshafen, Phil LeBoit in San Francisco, Omar Sangüeza in Winston Salem, and Noreen Walsh in Halifax. Altogether there were maybe a dozen carcinomas among several ten thousand cases of lichen sclerosus.

British Journal of Obstetrics and Gynaecology
December 1990, Vol. 97, pp. 1135–1139

The epithelial changes associated with squamous cell carcinoma of the vulva: a review of the clinical, histological and viral findings in 78 women

MICHELE LEIBOWITCH, SALLIE NEILL,
MONIQUE PELISSE, MICHELINE MOYAL-BARACCO

Summary. Seventy-eight excised specimens of squamous cell carcinoma of the vulva were reviewed retrospectively for the presence of lichen sclerosus or vulvar intraepithelial neoplasia (VIN) at sites proximal to the tumour or more distant. Lichen sclerosus was evident in 61% and VIN alone in 31%. VIN III (differentiated) was associated with over 50% of the specimens with lichen sclerosus. HPV 16 was found in six of the 11 VIN lesions, investigated but in none of the six with lichen sclerosus.

Compare this to data from the literature. In series of squamous cell carcinoma of the vulva, lichen sclerosus has been claimed to be present in about half of the cases, e.g., in 61% in this study of 1990.

Lichen sclerosus

Warren R. Heymann, MD
Based on the dialogue "Challenging vulvar problems"
with Lynette J. Margesson, MD, as interviewed by Stuart Brown, MD

Dialogues in Dermatology, a monthly audio program from the American Academy of Dermatology, contains discussions between dermatologists on timely topics. Commentaries from *Dialogues* Editor-in-Chief Warren R. Heymann, MD, are provided after each discussion as a topic summary and are provided here as a special service to readers of the *Journal of the American Academy of Dermatology*. (J Am Acad Dermatol 2007;56:683-4.)

Vulvar disorders are among the most recalcitrant, frustrating, and burdensome conditions that adversely affect a woman's quality of life. In this dialogue, Dr Margesson offers many suggestions on how to examine and treat patients with a host of diseases that involve the vulva, including herpes simplex, Candidiasis, irritant and allergic contact dermatitis, lichen planus, and lichen sclerosus (LS). This commentary will focus on recent insights into the pathogenesis of lichen sclerosus and the risk of associated malignancy.

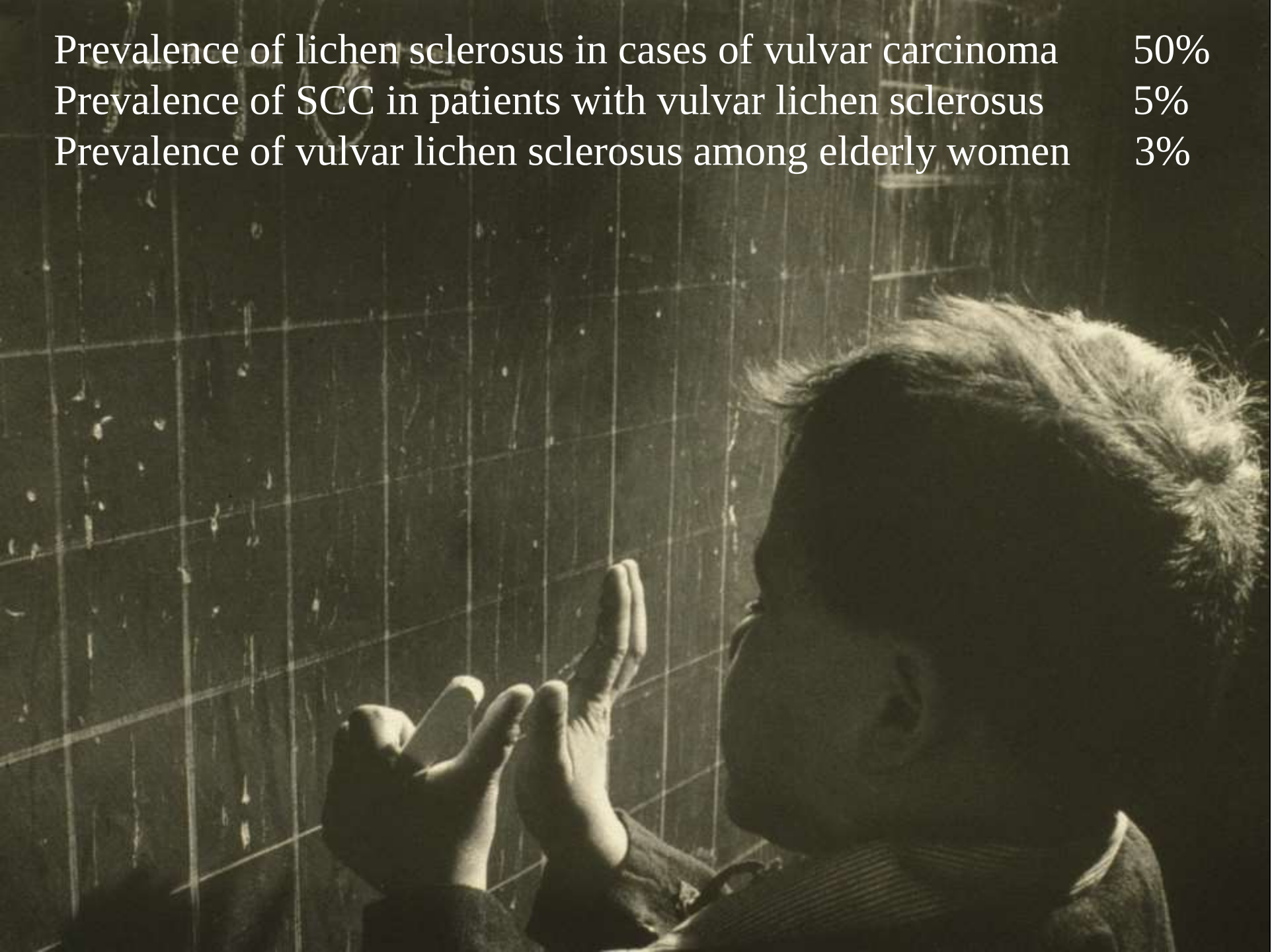
LS is a chronic inflammatory mucocutaneous disease most commonly affecting prepubertal girls and postmenopausal women. The etiology of LS is unknown; however, genetic factors and autoimmunity have been implicated. Alopecia areata, vitiligo, thyroid disorders, pernicious anemia, and diabetes

interferon gamma, tumor necrosis factor–alpha, interleukin-1, interferon gamma receptor, CD25, CD11a, and ICAM-1. Sander et al[5] compared vulvar LS tissue from 16 patients with tissue from 16 vulvar control samples and found a significant increase of lipid peroxidation products, particularly within epidermal basal cells, thus co-localizing with ECM-1. The authors also demonstrated a significantly reduced expression of manganese superoxide dismutase, a mitochondrial enzyme that catalyzes the reaction from superoxide anions to hydrogen peroxide. The enhanced oxidative stress caused by reduced enzyme expression could be a pathogenic factor in the autoimmune or neoplastic associations observed in some patients with LS.

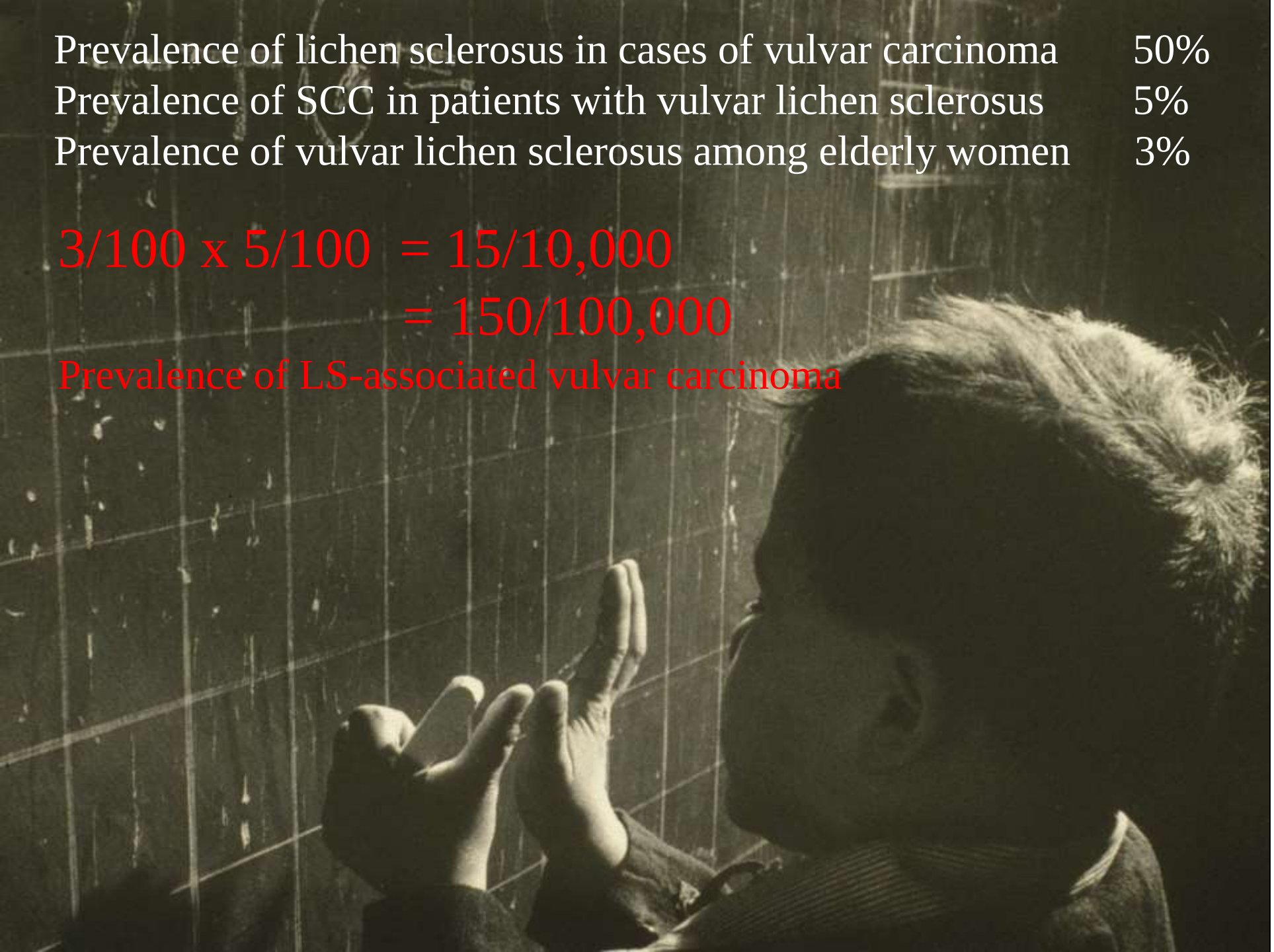
Patients with LS have a 4% to 6% risk of developing a vulvar squamous cell carcinoma (SCC).

Vice versa, patients with lichen sclerosus are said currently to have *"a 4% to 6% risk of developing a vulvar squamous cell carcinoma."*

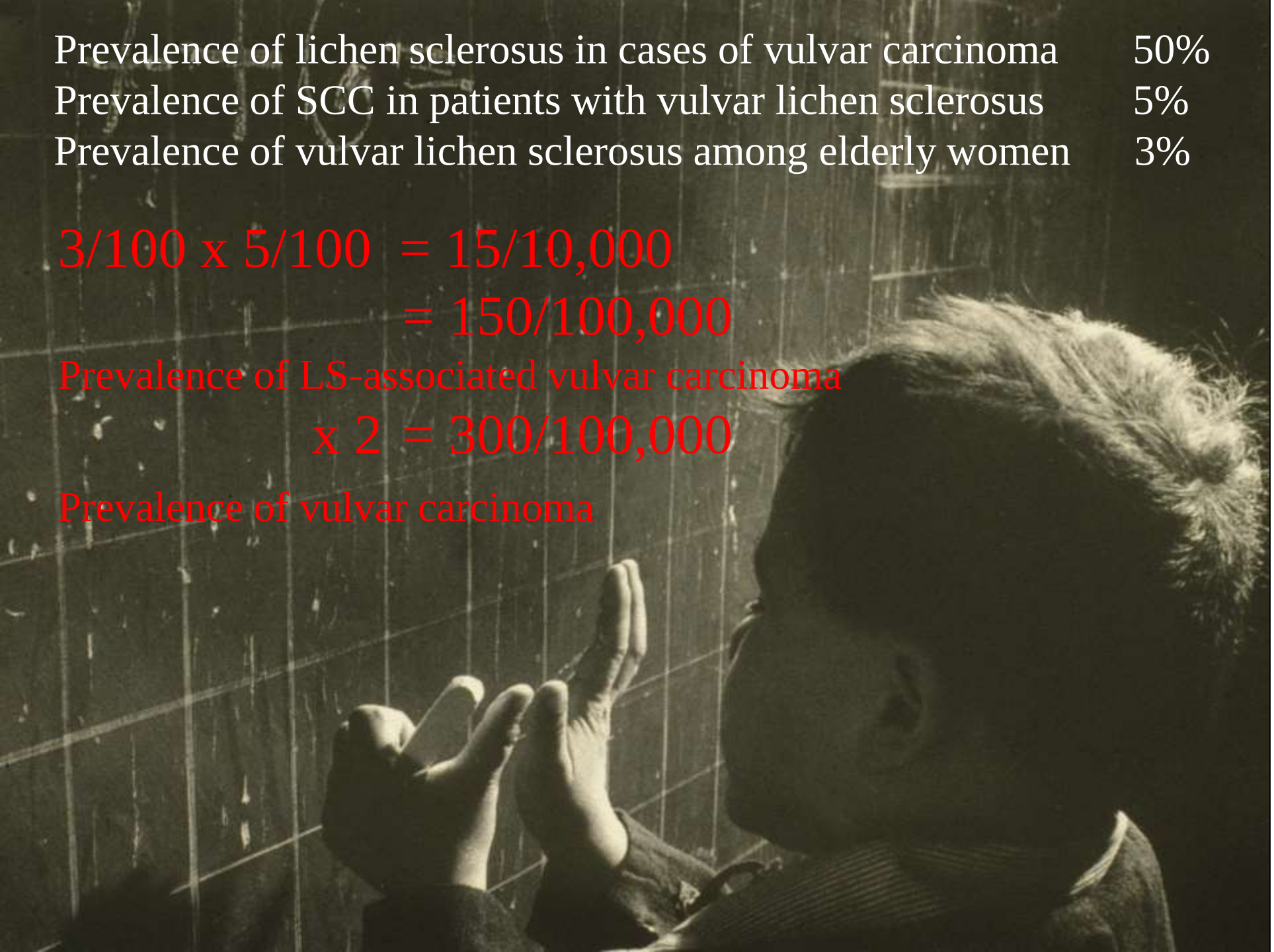
Let’s assume for a moment that these data are correct: a prevalence of lichen sclerosus in cases of vulvar carcinoma of about 50% and a prevalence of SCC in patients with vulvar lichen sclerosus of about 5%.



If we take into account the high prevalence of vulvar lichen sclerosus among elderly women that has been estimated to be about 3%, a simple computation can be done:



3% times 5% equals 15 in 10,000 or 150 in 100,000 patients. This would be the prevalence of vulvar squamous cell carcinoma associated with lichen sclerosus.



Prevalence of lichen sclerosus in cases of vulvar carcinoma 50%
Prevalence of SCC in patients with vulvar lichen sclerosus 5%
Prevalence of vulvar lichen sclerosus among elderly women 3%

3/100 x 5/100 = 15/10,000
= 150/100,000

Prevalence of LS-associated vulvar carcinoma
x 2 = 300/100,000

Prevalence of vulvar carcinoma

Because only one half of vulvar squamous cell carcinomas are said to be associated with vulvar lichen sclerosus, this number must be doubled in order to calculate the prevalence of vulvar squamous cell carcinoma on the basis of those data.

Prevalence of lichen sclerosus in cases of vulvar carcinoma 50%
Prevalence of SCC in patients with vulvar lichen sclerosus 5%
Prevalence of vulvar lichen sclerosus among elderly women 3%

3/100 x 5/100 = 15/10,000
= 150/100,000

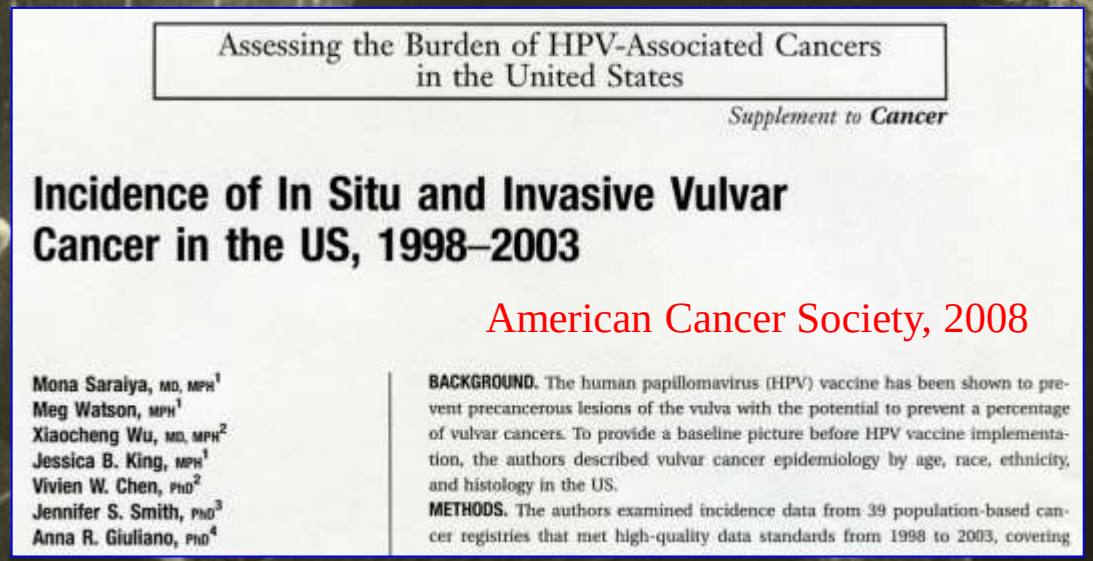
Prevalence of LS-associated vulvar carcinoma

x 2 = 300/100,000

Prevalence of vulvar carcinoma

Carcinoma in situ
1.3/100,000

Invasive SCC
1.8/100,000



Assessing the Burden of HPV-Associated Cancers in the United States

Supplement to ***Cancer***

Incidence of In Situ and Invasive Vulvar Cancer in the US, 1998–2003

American Cancer Society, 2008

Mona Saraiya, MD, MPH[1]
Meg Watson, MPH[1]
Xiaocheng Wu, MD, MPH[2]
Jessica B. King, MPH[1]
Vivien W. Chen, PhD[2]
Jennifer S. Smith, PhD[3]
Anna R. Giuliano, PhD[4]

BACKGROUND. The human papillomavirus (HPV) vaccine has been shown to prevent precancerous lesions of the vulva with the potential to prevent a percentage of vulvar cancers. To provide a baseline picture before HPV vaccine implementation, the authors described vulvar cancer epidemiology by age, race, ethnicity, and histology in the US.

METHODS. The authors examined incidence data from 39 population-based cancer registries that met high-quality data standards from 1998 to 2003, covering

In actuality, according to a study by the American Cancer Society in 2008, the incidence of vulvar squamous cell carcinoma is 1.3 per 100.000 for carcinoma in situ and 1.8 for invasive SCC. These numbers differ by a factor of 100.

Guidelines for Letters

Letters to the Editor will be published at the discretion of the editor as space permits and are subject to editing and abridgement. They should be typewritten, double-spaced, and submitted in triplicate. They should be limited to 500 words or less and to no more than five pertinent references.

New Nomenclature for Vulvar Disease: International Society for the Study of Vulvar Disease

To the Editor:—In 1976, Friedrich[1] gave an account of the proposed nomenclature for vulvar disease arising out of the Second International Congress of the International Society for the Study of Vulvar Disease (ISSVD) in 1975.

Since that time, discussion has continued, in conjunction with representatives of the International Society of Gynecological Pathologists (ISGYP), with a view to developing and improving this scheme. The desirability of such a scheme, which will be accepted by gynecologists, dermatologists, and pathologists, is self-evident in that it will encourage standardization and comparability of reports on an international and interdisciplinary basis.

At the Ninth Congress of the ISSVD in 1987, recom-

TABLE 1. Non-Neoplastic Epithelial Disorders of Skin and Mucosa

Lichen sclerosus (lichen sclerosus et atrophicus)
Squamous cell hyperplasia (formerly hyperplastic dystrophy)
Other dermatoses

on terminology of the ISGYP is in agreement with these conclusions, which will be incorporated by them into their wider recommendations on the histologic classification of vulvar disorders, including tumors. It will be recalled that there is already agreement on the classification of vulvar intraepithelial neoplasia.[2] The new classification noted here will appear under the pathologic heading of non-neoplastic epithelial disorders of skin and mucosa and replaces the old dystrophy terminology (see parentheses, Table 1).

Mixed epithelial disorders may occur. In such cases, it is recommended that both conditions be reported. For example, lichen sclerosus with associated squamous cell hyperplasia (formerly classified as mixed dystrophy) should be reported as lichen sclerosus with squamous cell hyperplasia. Squamous cell hyperplasia with associated vulvar intraepithelial neoplasia (formerly hyperplastic dystrophy with atypia) should be diagnosed as vulvar intraepithelial neoplasia (VIN) (Table 2).

Squamous cell hyperplasia is used for those instances in which the hyperplasia is not attributable to a more specific tissue process. Specific lesions or dermatoses involving the vulva (eg, psoriasis, lichen planus, lichen simplex chronicus, Candida infection, condylo
squamous cell hyperplasia, b
ically and excluded from thi
thognomonic characteristics.

Hum Pathol
1989; 20: 495

TABLE 2. Classification of Vulvar Intraepithelial Neoplasia

VIN I — Mild dysplasia (formerly mild atypia)
VIN II — Moderate dysplasia (formerly moderate atypia)
VIN III — Severe dysplasia (formerly severe atypia)
VIN III — Carcinoma in situ

This ISSVD terminology replaces the original ISSVD atypia-carcinoma in situ terminology.[2]

In brief, the incidence of lichen sclerosus-associated squamous cell carcinoma is exaggerated vastly. How can this be explained? There are many reasons, and one is a “New Nomenclature for Vulvar Disease” introduced by the International Society for the Study of Vulvar Disease in 1989. In this grotesquely simplyfying classification, all non-neoplastic diseases were reduced to three categories: lichen sclerosus, so-called “squamous-cell hyperplasia,” and “other dermatoses.” With lichen sclerosus being the only specific disease mentioned, this diagnosis came to be rendered excessively.

Wang SH et al., JEADV 2010; 24: 815

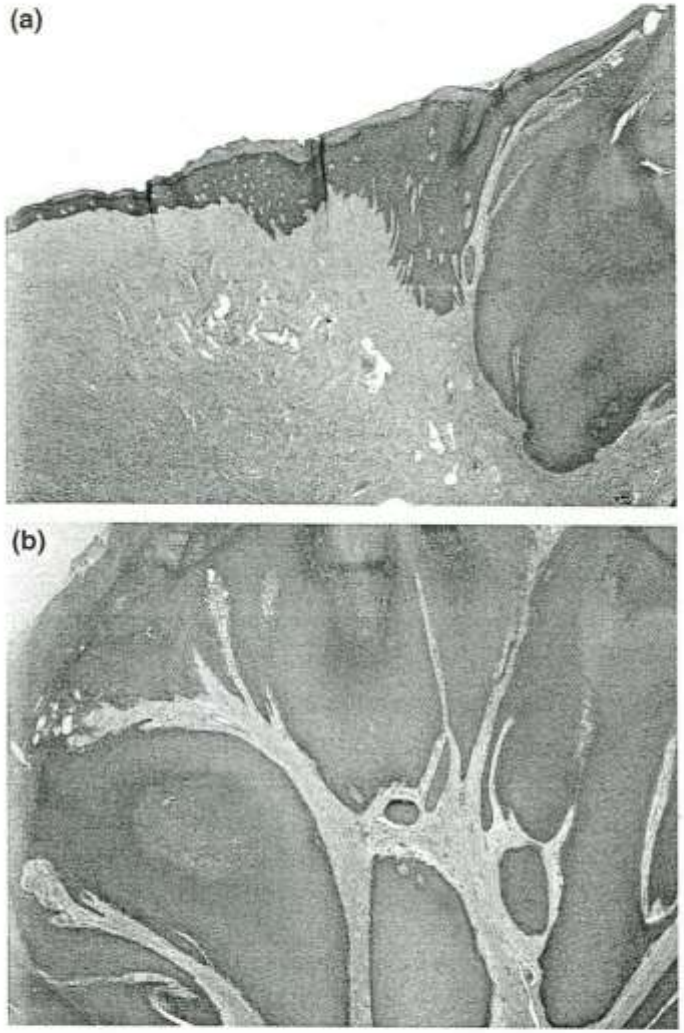


Figure 1 (a) Histopathological examinations showed verrucous carcinoma (right) with associated adjacent lichen sclerosus (left) manifested by atrophy of epidermis and homogenization of the dermis; (b) The verrucous carcinoma part showed hyperkeratotic warty endophytic growth of well-differentiated malignant squamous cells (both haematoxylin and eosin, ×40).

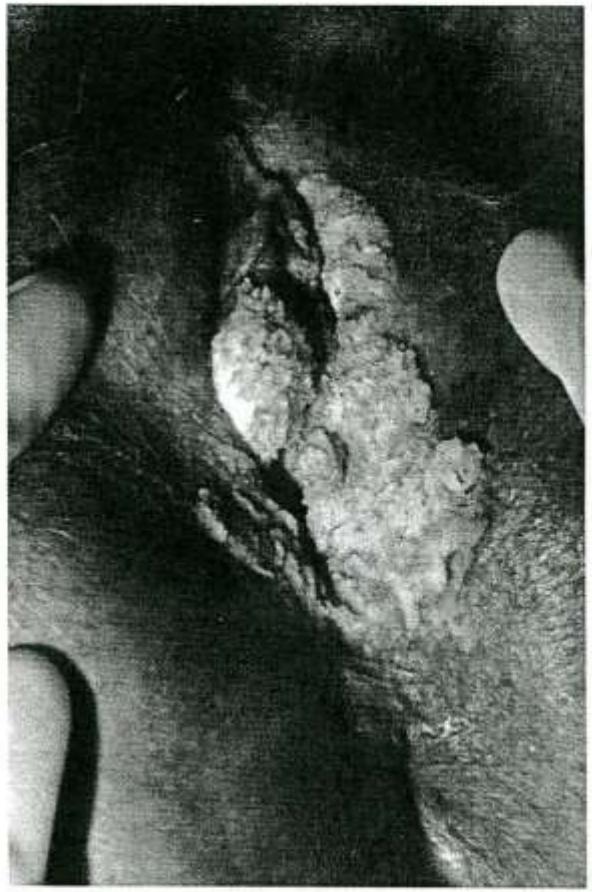


Figure 2 Extensive warty growths arising from both inner labia majora and extending into the introitus.

including HPV infection, altered p53 expression, chronic inflammation and oxidative stress, may contribute to this association (Fig. 3).

Verrucous carcinoma is thought to be related to HPV infection

In the literature, there are reports, well into recent years, of *"vulvar cell carcinoma associated with lichen sclerosus*" in which there is no evidence of lichen sclerosus in photomicrographs.

Differentiated vulvar intraepithelial neoplasia is often found in lesions, previously diagnosed as lichen sclerosus, which have progressed to vulvar squamous cell carcinoma

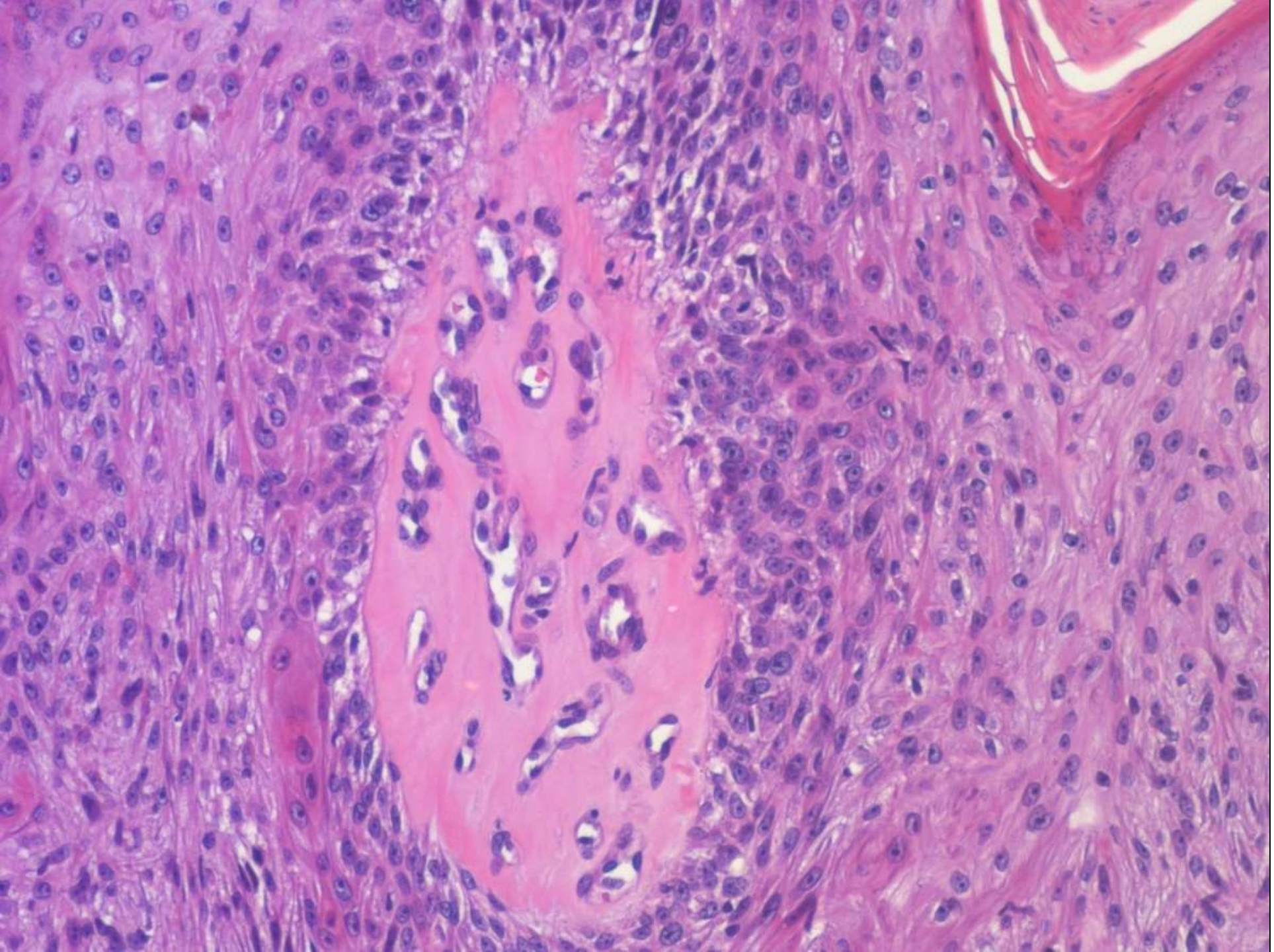
Hedwig P van de Nieuwenhof[1], Johan Bulten[2], Harrie Hollema[3], Rianne G Dommerholt[4], Leon FAG Massuger[1], Ate GJ van der Zee[5], Joanne A de Hullu[1] and Leon CLT van Kempen[2]

[1]Department of Obstetrics and Gynecology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [2]Department of Pathology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [3]Department of Pathology, University Medical Centre Groningen, Groningen, The Netherlands; [4]Department of Obstetrics and Gynecology, Jeroen Bosch Hospital, 's Hertogenbosch, The Netherlands and [5]Department of Obstetrics and Gynecology, University Medical Centre Groningen, Groningen, The Netherlands

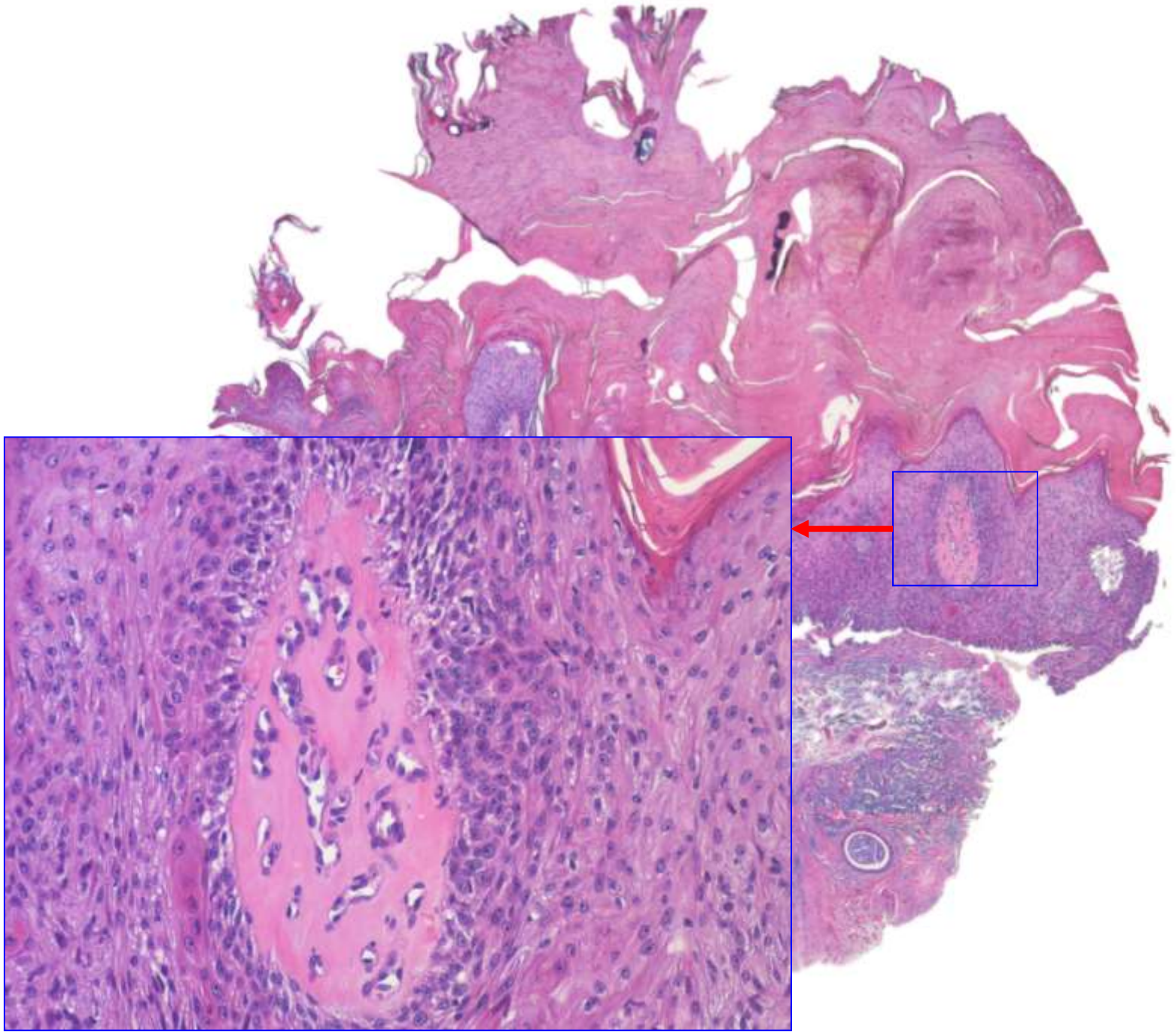
Lichen sclerosus is considered to be the precursor lesion of vulvar squamous cell carcinoma, of which only 2–5% progress to squamous cell carcinoma. Differentiated vulvar intraepithelial neoplasia (VIN) has been proposed to be the direct precursor lesion, but this is a recently recognized, and a difficult to diagnose, entity, which may easily be mistaken for a benign dermatosis. The aim of this study was to test the hypothesis that of all lesions that have been diagnosed as lichen sclerosus in the past, a part might currently be diagnosed as differentiated VIN, and to identify histopathological differences between lichen sclerosus lesions with and without progression to vulvar squamous cell carcinoma. All lichen sclerosus slides were revised by two expert gynecopathologists and histopathological characteristics were documented. After revision of lichen sclerosus biopsies without progression ($n=61$), 58 were reclassified as lichen sclerosus. Revision of lichen sclerosus biopsies with progression yielded concordant diagnoses in 18 of 60 cases (30%). Of 60 lesions, 25 (42%) were reclassified as differentiated VIN. The median time from differentiated VIN to vulvar squamous cell carcinoma was shorter (28 months) than that from lichen sclerosus to vulvar squamous cell carcinoma (84 months) ($P<0.001$). Lichen sclerosus that progressed to squamous cell carcinoma, but did not meet the criteria for differentiated VIN, more often showed parakeratosis ($P=0.004$), dyskeratosis ($P<0.001$), hyperplasia ($P=0.048$) and basal cellular atypia ($P=0.009$) compared with lichen sclerosus without progression. In conclusion, differentiated VIN diagnosis has been frequently missed and is associated with rapid progression to squamous cell carcinoma. Patients with lichen sclerosus with dyskeratosis and parakeratosis, hyperplasia and/or basal cellular atypia should be kept under close surveillance as these lesions also tend to progress to squamous cell carcinoma.

Modern Pathology (2011) **24,** 297–305; doi:10.1038/modpathol.2010.192; published online 5 November 2010

In 2011, in a retrospective study of cases diagnosed as lichen sclerosus with progression to vulvar squamous cell carcinoma, revision of biopsies could confirm the diagnosis of lichen sclerosus in only 30% of cases. This is not surprising because, as we have seen, histopathologic diagnosis may be difficult, especially in cases without sclerosis.



But even if there is undubitable sclerosis beneath a squamous-cell carcinoma, this does not necessarily mean that the patient has lichen sclerosus. This is a lesion from the face;



it is a hypertrophic solar keratosis, and the sclerosis is an incidental finding. Had this lesion come from the vulva, it probably would have been interpreted as incipient squamous-cell carcinoma associated with lichen sclerosus.

Guidelines for Letters

Letters to the Editor will be published at the discretion of the editor as space permits and are subject to editing and abridgement. They should be typewritten, double-spaced, and submitted in triplicate. They should be limited to 500 words or less and to no more than five pertinent references.

New Nomenclature for Vulvar Disease: International Society for the Study of Vulvar Disease

To the Editor:—In 1976, Friedrich[1] gave an account of the proposed nomenclature for vulvar disease arising out of the Second International Congress of the International Society for the Study of Vulvar Disease (ISSVD) in 1975.

Since that time, discussion has continued, in conjunction with representatives of the International Society of Gynecological Pathologists (ISGYP), with a view to developing and improving this scheme. The desirability of such a scheme, which will be accepted by gynecologists, dermatologists, and pathologists, is self-evident in that it will encourage standardization and comparability of reports on an international and interdisciplinary basis.

At the Ninth Congress of the ISSVD in 1987, recom-

TABLE 1. Non-Neoplastic Epithelial Disorders of Skin and Mucosa

Lichen sclerosus (lichen sclerosus et atrophicus)
Squamous cell hyperplasia (formerly hyperplastic dystrophy)
Other dermatoses

on terminology of the ISGYP is in agreement with these conclusions, which will be incorporated by them into their wider recommendations on the histologic classification of vulvar disorders, including tumors. It will be recalled that there is already agreement on the classification of vulvar intraepithelial neoplasia.[2] The new classification noted here will appear under the pathologic heading of non-neoplastic epithelial disorders of skin and mucosa and replaces the old dystrophy terminology (see parentheses, Table 1).

Mixed epithelial disorders may occur. In such cases, it is recommended that both conditions be reported. For example, lichen sclerosus with associated squamous cell hyperplasia (formerly classified as mixed dystrophy) should be reported as lichen sclerosus with squamous cell hyperplasia. Squamous cell hyperplasia with associated vulvar intraepithelial neoplasia (formerly hyperplastic dystrophy with atypia) should be diagnosed as vulvar intraepithelial neoplasia (VIN) (Table 2).

Squamous cell hyperplasia is used for those instances in which the hyperplasia is not attributable to a more specific tissue process. Specific lesions or dermatoses involving the vulva (eg, psoriasis, lichen planus, lichen simplex chronicus, Candida infection, condylo
squamous cell hyperplasia, b
ically and excluded from thi
thognomonic characteristics.

Hum Pathol
1989; 20: 495

TABLE 2. Classification of Vulvar Intraepithelial Neoplasia

VIN I — Mild dysplasia (formerly mild atypia)
VIN II — Moderate dysplasia (formerly moderate atypia)
VIN III — Severe dysplasia (formerly severe atypia)
VIN III — Carcinoma in situ

This ISSVD terminology replaces the original ISSVD atypia-carcinoma in situ terminology.[2]

The "New Nomenclature for Vulvar Disease" in 1989 also introduced the VIN classification. Different grades of so-called "dysplasia" were distinguished, from "mild" to "severe" and to frank "carcinoma in situ," as if there was continuum between hyperplasia and malignant neoplasia. Before long, condylomas or inflammatory diseases with some hyperchromatic cells or a few mitotic figures were said to exhibit "mild dysplasia," with the implication of being considered en route to cancer.

The Journal of Reproductive Medicine®

Abstract

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Keywords: vulvar cancer, vulvar neoplasms, vulvar intraepithelial neoplasia, terminology

When this problem was recognized in 2004, the International Society for the Study of Vulvovaginal Disease proclaimed that *“the term VIN should apply only to histologically high grade suqamous lesions. … The term VIN 1 will no longer be used.”*

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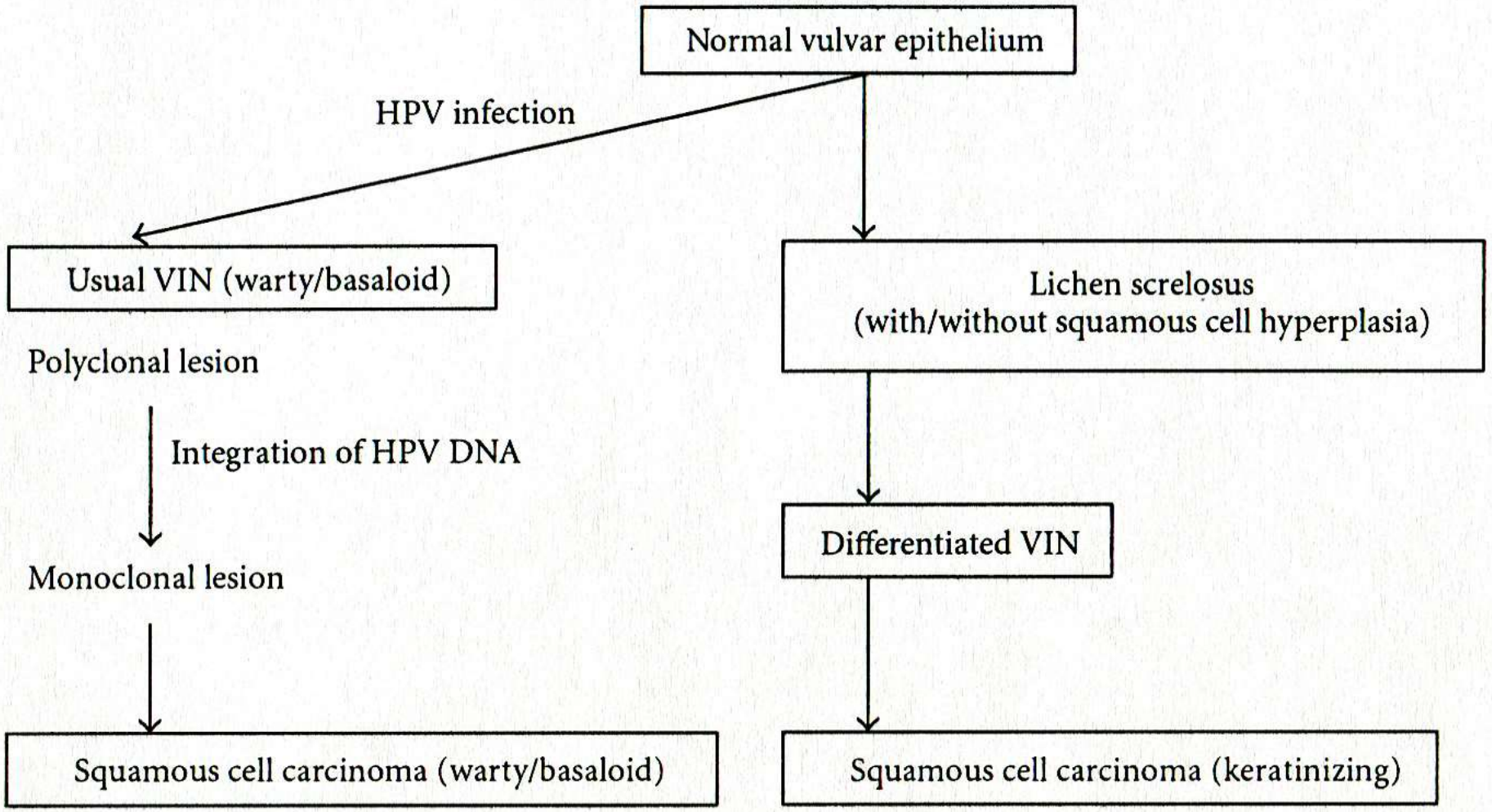
Keywords: vulvar cancer, vulvar neoplasms, vulvar intraepithelial neoplasia, terminology

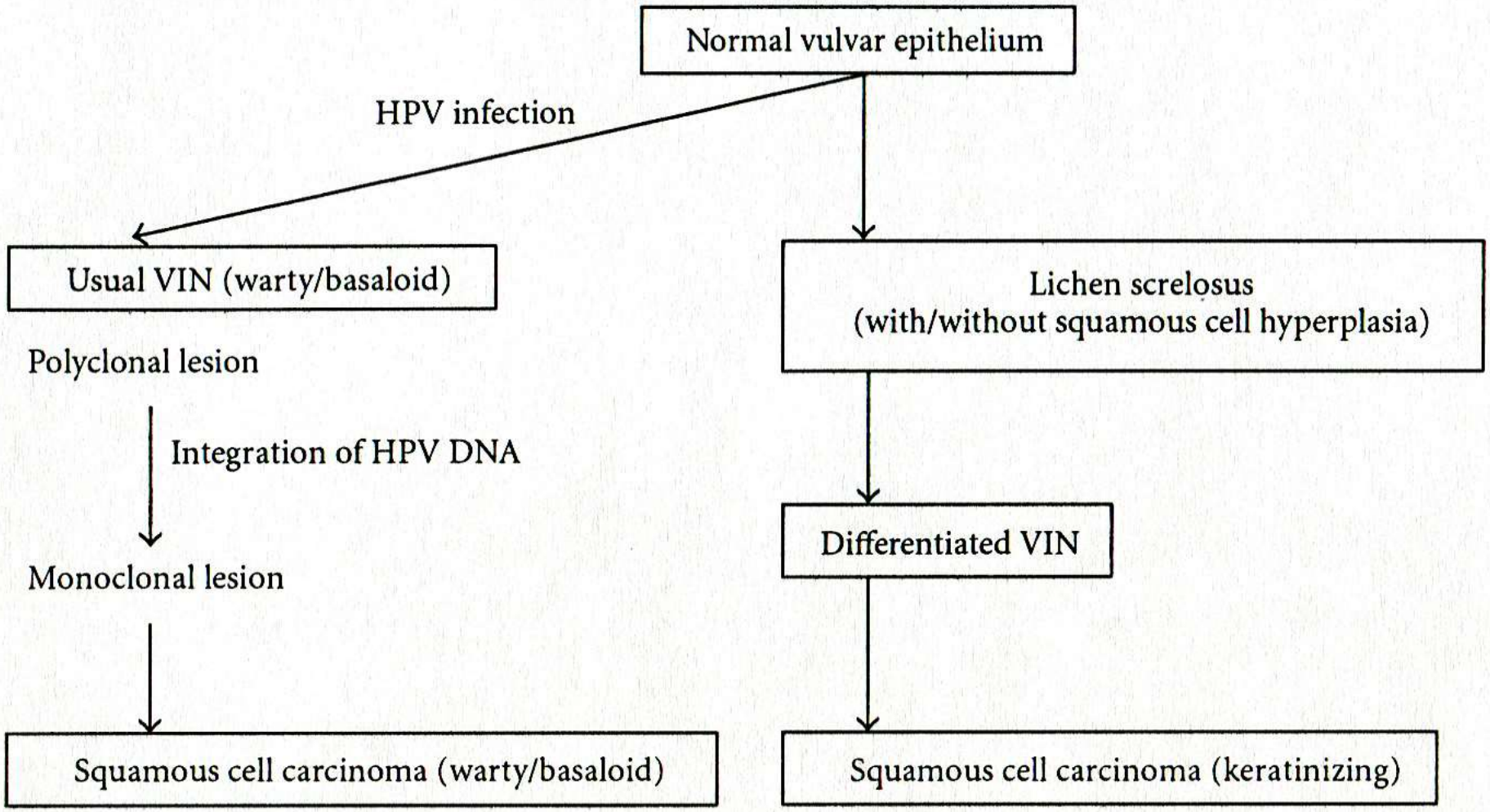
At the same time, a new classification was introduced that distinguished between *“VIN, usual type”* and *“VIN, differentiated type.”*

Ueda Y et al.
J Skin Cancer, 2011



Those types were thought to reflect two distinct pathways of carcinoma formation. *"VIN, usual type"* was thought to be caused by human papilloma virus and to progress to warty or basaloid squamous cell carcinoma, whereas *"VIN, differentiated type"* was said to be associated with lichen sclerosus and to progress to keratinizing squamous cell carcinoma.

Ueda Y et al.
J Skin Cancer, 2011

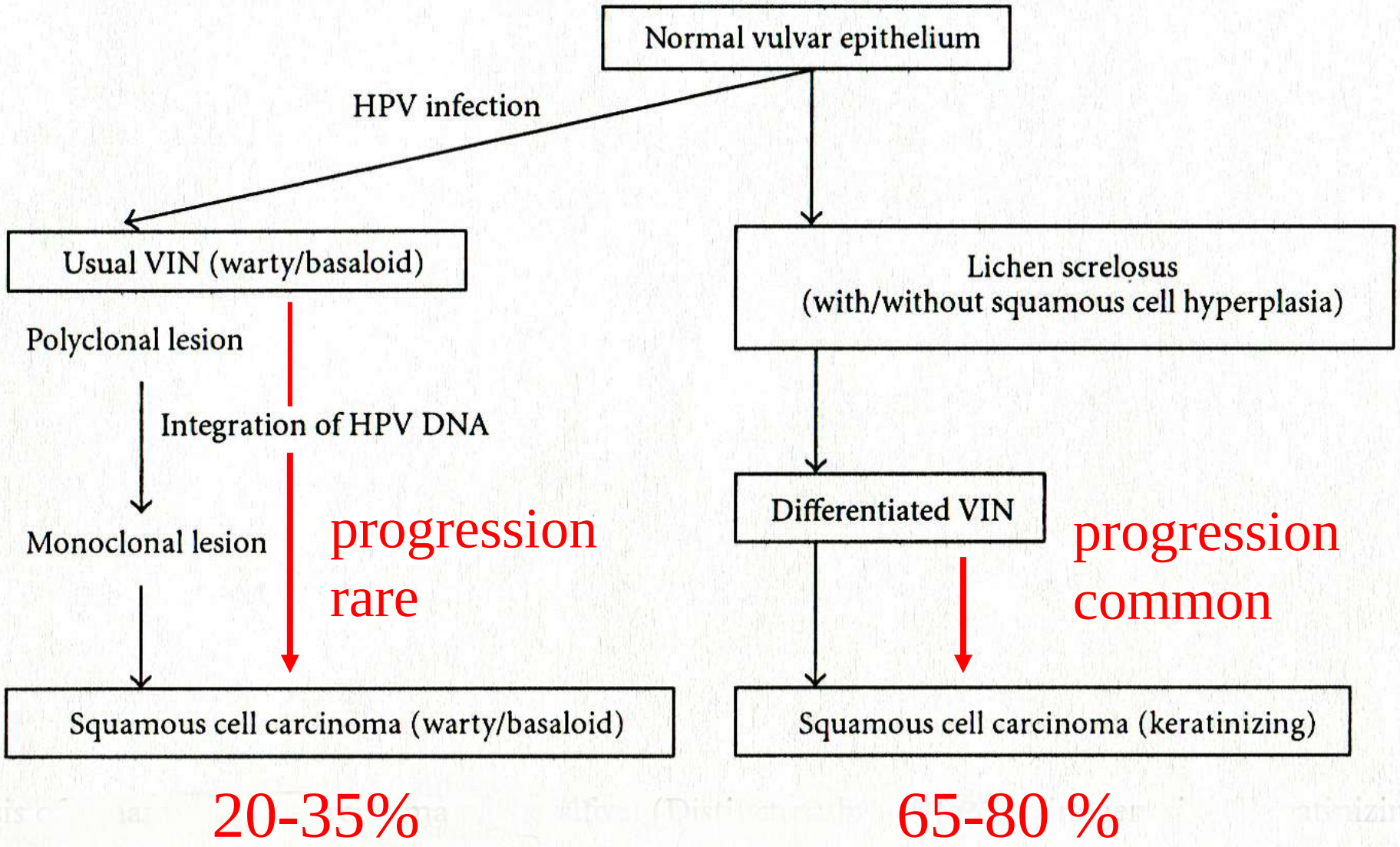


20-35%

65-80 %

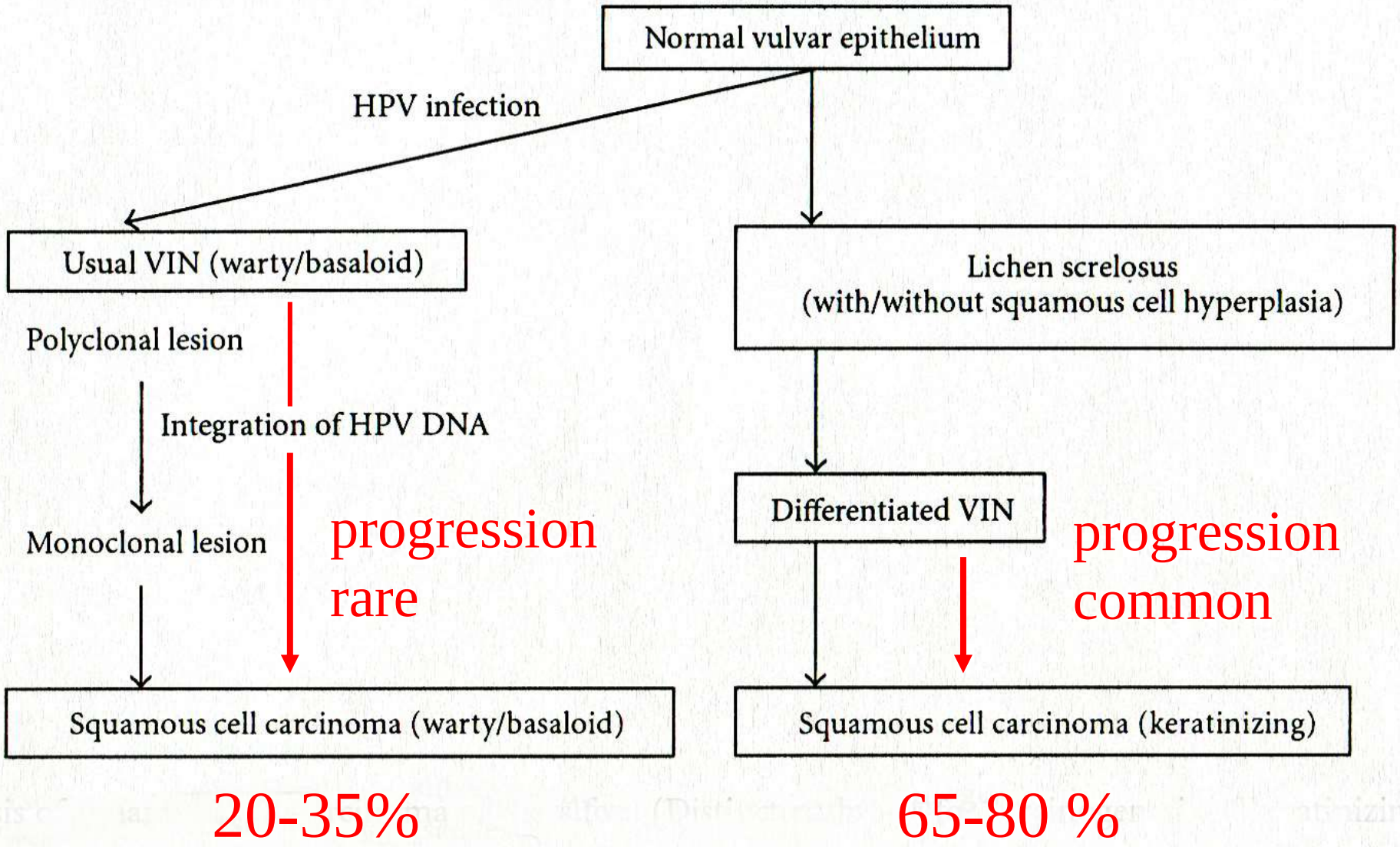
The warty or basaloid type was said to be much rarer than the keratinizing one,

Ueda Y et al.
J Skin Cancer, 2011



and progression of *"usual VIN"* was said to be rare in comparison to progression of *"differentiated VIN"*. With this new classification, lichen sclerosus suddenly became associated conceptually with the most dangerous type of vulvar intraepithelial neoplasia and the most common type of squamous cell carcinoma. This two-tier classification of vulvar squamous cell carcinoma has the advantage of being elegant and the disadvantage of being incorrect on several grounds.

Ueda Y et al.
J Skin Cancer, 2011



First, so-called *"warty," "basaloid,"* and *"keratinizing squamous-cell carcinomas"* are not distinct lesions, all kinds of transitions are possible. Second, the concept that one type of carcinoma is associated with HPV infection and *"usual, undifferentiated VIN"* and another type with lichen sclerosus and *"differentiated VIN"* has been refuted in numerous studies.

ORIGINAL ARTICLE

In the absence of (early) invasive carcinoma, vulvar intraepithelial neoplasia associated with lichen sclerosus is mainly of undifferentiated type: new insights in histology and aetiology

M van Seters, F J W ten Kate, M van Beurden, R H M Verheijen, C J L M Meijer, M P M Burger, T J M Helmerhorst

J Clin Pathol 2007;**60**:504–509. doi: 10.1136/jcp.2005.031989

Background: Differentiated vulvar intraepithelial neoplasia (VIN) is presumed to be the precursor of invasive squamous cell carcinoma (SCC) of the vulva. It is commonly assumed that differentiated VIN is related to lichen sclerosus (LS). However, evidence for this is limited to a small number of studies describing epithelial alterations adjacent to vulvar SCC.
Aim: To study the histology and human papillomavirus (HPV) status in patients with a history of both LS and VIN without coexistent SCC.
Methods: Original biopsy specimens and surgical specimens of patients retrieved from the pathology files were revised for the presence of LS, VIN and (early) invasive SCC, specifically focused on the two different types of VIN: differentiated and undifferentiated. Thereafter, VIN lesions were tested for the presence of HPV DNA.
Results: Twenty-seven patients fulfilled the criteria for LS and VIN without SCC. In all 27 patients, LS was found to be related to undifferentiated VIN. Grading yielded the following results: VIN 1 (n = 10), VIN 2 (n = 11) and VIN 3 (n = 6). Additionally, VIN lesions from 26 patients could be tested for the presence of HPV DNA. HPV DNA, predominantly type 16, was present in 8 (31%) of them. Seven of these eight patients had VIN 2 or 3. During follow-up, three patients progressed to (early) invasive carcinoma. In two of these patients, differentiated VIN was observed overlying early invasive SCC.
Conclusions: VIN related to LS without coexisting SCC is likely to be undifferentiated, in contrast to what was previously thought. HPV DNA was demonstrated in 31% of the lesions, and was strongly related to high-grade VIN.

See end of article for authors' affiliations

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Accepted 11 April 2006
Published Online First 19 May 2006

For example, van Seters and co-workers found in 2007 that *"vulvar intraepithelial neoplasia associated with lichen sclerosus is mainly of the undifferentiated type,"* rather than the differentiated one, as claimed in the classification.

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They also noted that *"HPV DNA was demonstrated in 31% of the lesions."* In other words, there was evidence of concomitant infection with human papilloma virus in nearly one third of carcinomas claimed to be associated with lichen sclerosus.

The Journal of Reproductive Medicine®

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Keywords: vulvar cancer, vulvar neoplasms, vulvar intraepithelial neoplasia, terminology

Last, with its new classification, the Society violated its own rule that *"the term VIN should apply only to histologically high grade squamous lesions."*

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The term "differentiated" refers to … basal atypia in the context of a fully differentiated vulvar epithelium. …Its high degree of cellular differentiation and absence of widespread architectural disarray make it difficult to recognize this type of VIN.

Preti et al., Clin Obstet Gynecol 2005; 48:845

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It was emphasized that *"the term 'differentiated' refers to … basal atypia in the context of a fully differentiated vulvar epithelium. …Its high degree of cellular differentiation and absence of widespread architectural disarray make it difficult to recognize this type of VIN."* This is not the description of a *"histologically high grade squamous lesion,"* the only criterion for diagnosis being *"basal atypia."*

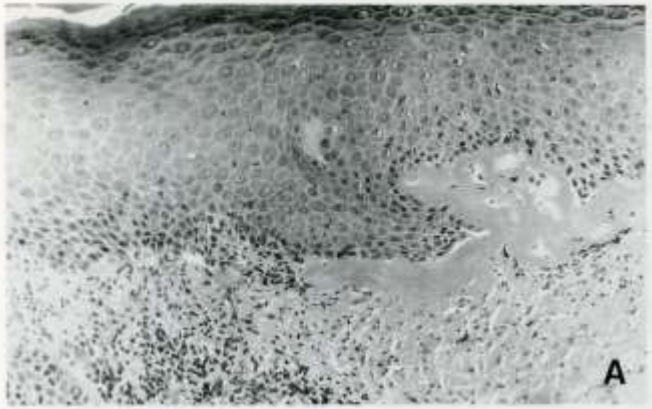


FIGURE 2. Morphological features of a specimen categorized as variant (differentiated) VIN associated with LS that was HPV negative. (A) Area of uninvolved LS without nuclear atypia. (B) Adjacent area with prominent maturation and conspicuous basal atypia (arrowheads). (C) Detail of parabasal epithelium composed of cells with enlarged and hyperchromatic nuclei with anisokaryosis. (HE stain; original magnifications A ×100, B ×100, C ×300.)

Haefner et al.,
Hum Pathol 1995; 26:147

And what is *"basal atypia"*? Let's look at some pictures. This is said to be *"differentiated VIN associated with LS,"* but is it really diagnostic of a neoplastic transformation of an inflammatory disease?

The American Journal of Surgical Pathology 24(3): 429–441, 2000

Vulvar Intraepithelial Neoplasia of the Simplex (Differentiated) Type

A Clinicopathologic Study Including Analysis of HPV and p53 Expression

Bin Yang, M.D., Ph.D., and William R. Hart, M.D.

The simplex (differentiated) variant of vulvar intraepithelial neoplasia (VIN) has not been well characterized. The authors studied the clinicopathologic features of 12 cases of simplex VIN and obtained follow-up data to assess its relationship to vulvar invasive squamous cell carcinoma (InvSCC). Expression of p53 protein was analyzed immunohistochemically and compared with adjacent non-neoplastic epidermal lesions. Assessment of human papilloma virus (HPV) deoxyribonucleic acid was done by polymerase chain reaction amplification and in situ hybridization. All patients were of postmenopausal age (mean age, 66.8 years). Three patients had a history of prior vulvar InvSCC and one had a separate synchronous vulvar InvSCC. Squamous hyperplasia was present in the adjacent epidermis in 10 patients and lichen sclerosus (LS) was present in four patients. Histologically, simplex VIN differed from "classic" VIN by its highly differentiated features. The characteristic features included parakeratosis, thickened epidermis with elongated and anastomosing rete ridges, enlarged abnormal keratinocytes with premature eosinophilic cytoplasmic differentiation extending deeply within the epidermis, whorling of enlarged keratinocytes or keratin pearl formation within rete ridges, prominent intercellular bridges, and dysplastic basilar cells. One patient had minimal microinvasion (0.6 mm). Ten of 12 patients had positive p53 immunostaining staining with suprabasilar extension of p53 positive cells in each patient. The labeling index (LI) of basilar cells ranged from 0% to 99% (median, 94.5%). Non-neoplastic lesions in the adjacent epidermis had p53-positive basal cells in nine of 11 evaluable cases. The LI was significantly lower in these lesions, with a median of 4% in squamous hyperplasia and 7.5% in LS; none had suprabasilar extension of p53-positive cells. HPV (type 31/35/51) was identified in only one simplex VIN—a p53-negative lesion. Staining for p53 often delineated sharply the junction between simplex VIN and squamous hyperplasia. Four patients subsequently developed vulvar InvSCC at 5, 6, 9, and 55 months. All four InvSCCs were of the conventional keratinizing type and were HPV negative, as were the one synchronous and two prior InvSCCs. The authors conclude that (1) simplex VIN has a strong association with vulvar InvSCC and is a probable precursor lesion of HPV-negative vulvar InvSCCs, (2) HPV is very uncommon in simplex VIN and probably does not play an important role in its genesis, (3) alteration of the p53 gene appears to be involved in the development of simplex VIN, and (4) immunostaining for p53 protein may be helpful in the differential diagnosis of simplex VIN.

Key Words: Vulva—Vulvar intraepithelial neoplasia—VIN—Simplex—Differentiated—Squamous cell carcinoma—Carcinoma in situ—p53—Human papilloma virus—HPV—Polymerase chain reaction—PCR—In situ hybridization—Immunohistochemistry.

Am J Surg Pathol 24(3): 429–441, 2000.

In a series of reports in the 1960s, Abell and his associates[1,18] described a highly differentiated form of vulvar squamous cell carcinoma in situ (CIS). Abell designated it "intraepithelial carcinoma of simplex type" to distinguish it from Bowen's disease.[1] It is relatively infrequent in its pure form, but is often seen adjacent to or overlying superficially invasive squamous cell carcinoma (InvSCC).[18,22] Abell[1,18] stated that the simplex type was the most subtle and least readily recognized form of CIS because the neoplastic squamous cells were well differentiated and often did not extend throughout the entire thickness of the epidermis whereas the Bowen's type corresponded to the easily recognized, typical (or so-called "classic"[19]) form of CIS.

Another example from an article about *"vulvar intraepithelial neoplasia of the simplex (differentiated) type."*

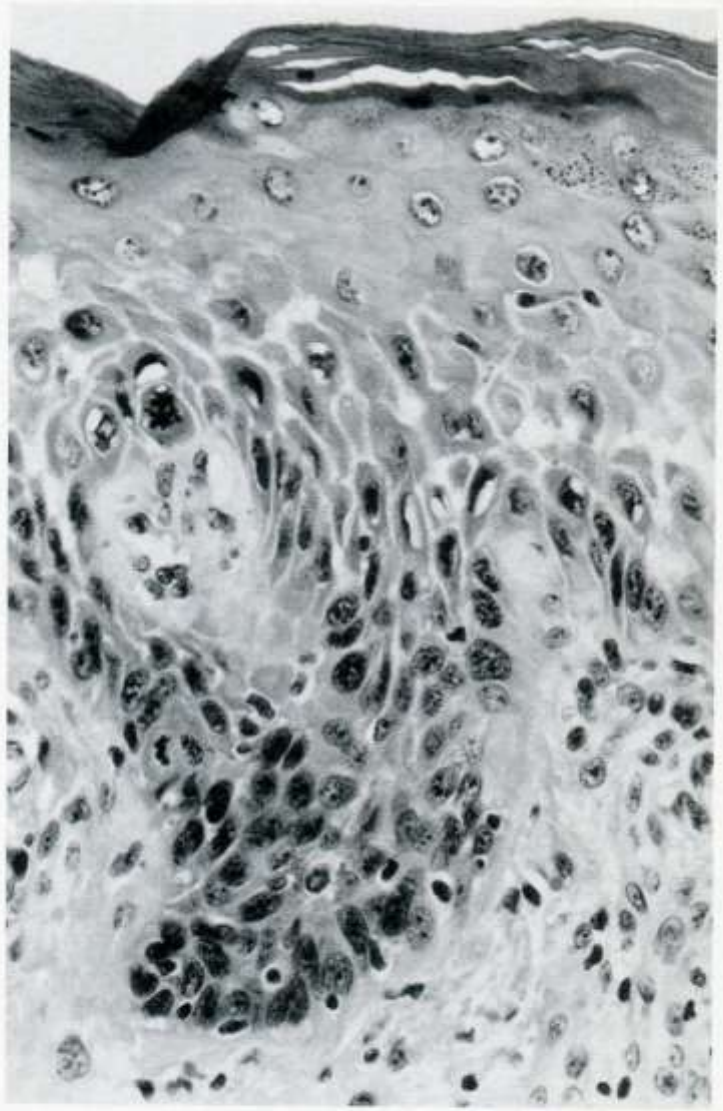


FIG. 11. Basilar cells and lower keratinocytes have irregular hyperchromatic nuclei and a mitotic figure. Although the dysplastic features of this example of simplex vulvar intraepithelial neoplasia (VIN) are marked, they are different distinctly than those of the "classic" (Bowen's) type of VIN.

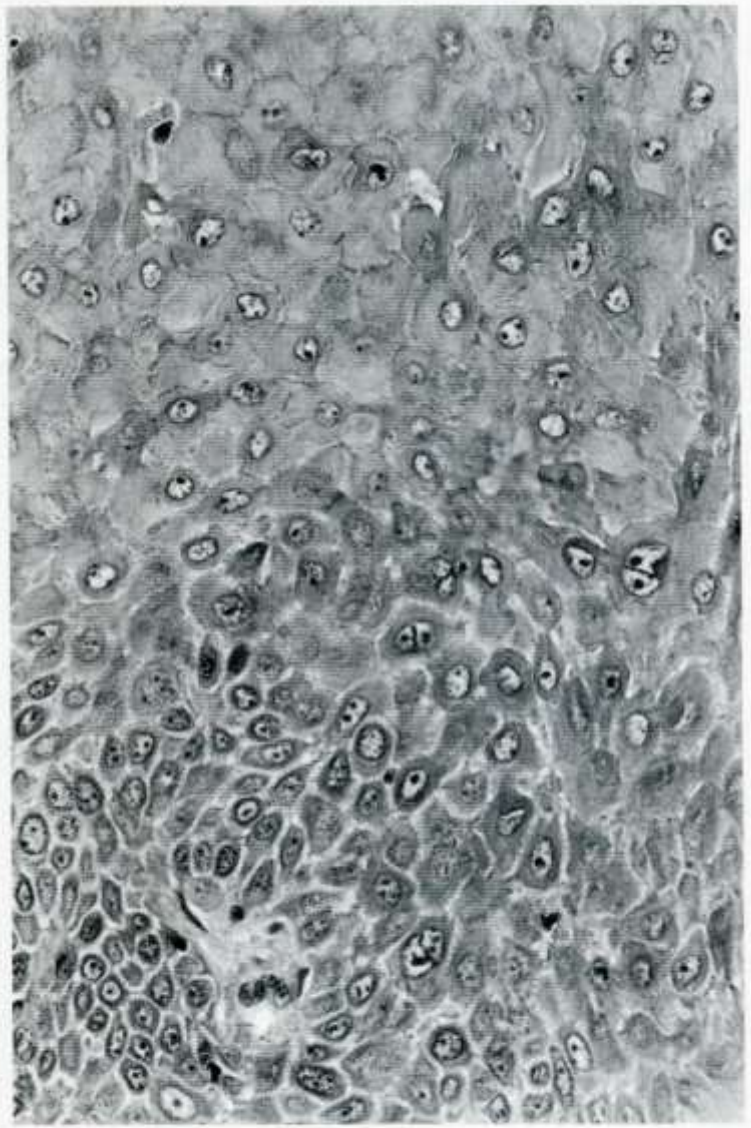
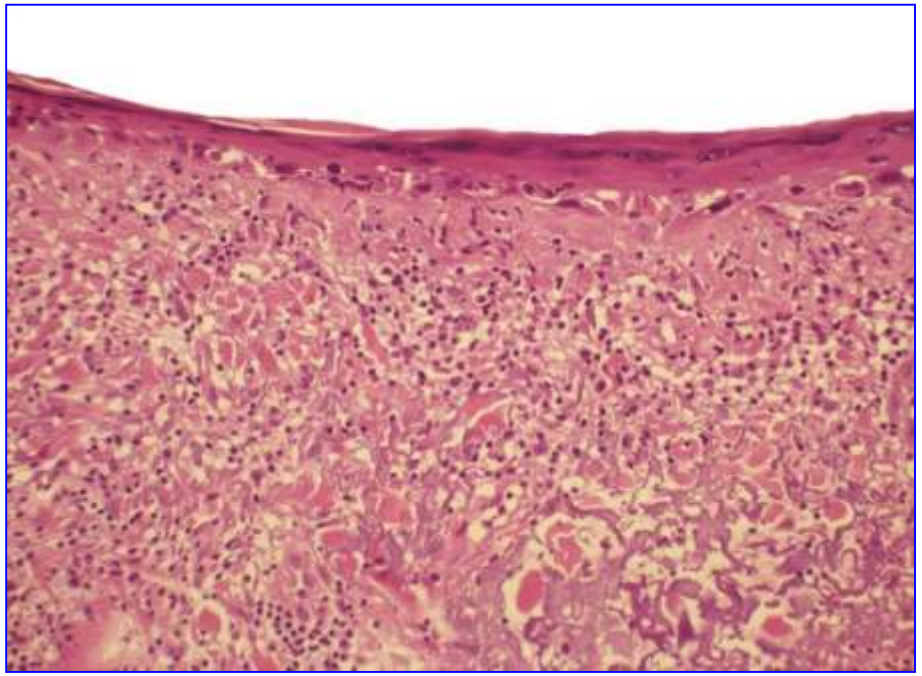
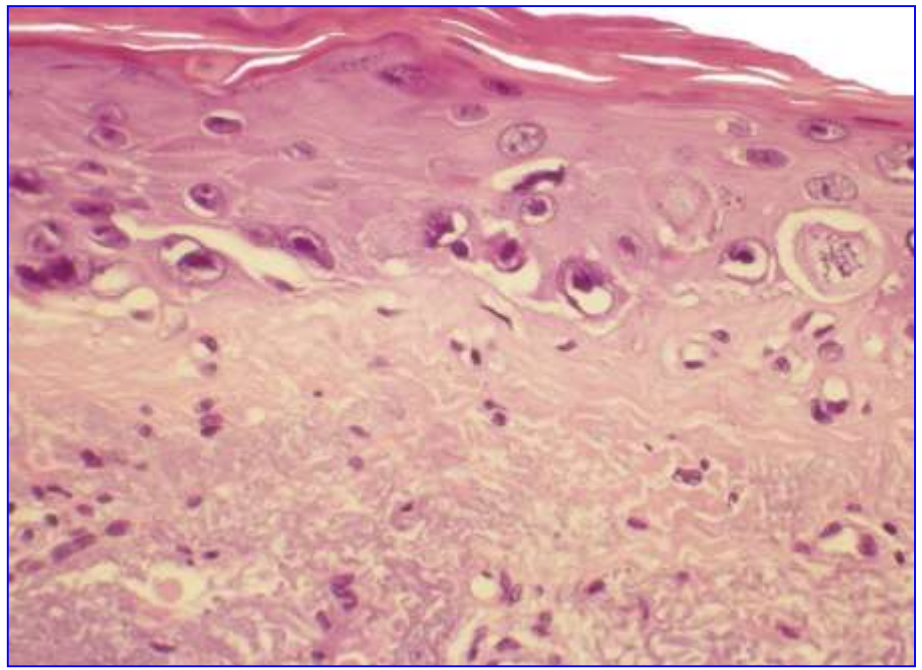


FIG. 4. Abnormal keratinocytes of simplex vulvar intraepithelial neoplasia have dense eosinophilic cytoplasm and enlarged nuclei with prominent nucleoli. Occasional cells are binucleated. Architectural differentiation of the abnormal cells is preserved in the superficial portions of the epidermis.

By this term, the authors refer to lesions of indubitable squamous cell carcinoma in situ, but also to lesions with only minimal nuclear atypia. According to the authors, these are *"abnormal keratinocytes"* with *"enlarged nuclei with prominent nucleoli."* However, if those features suffice for diagnosis of a malignant neoplasm,





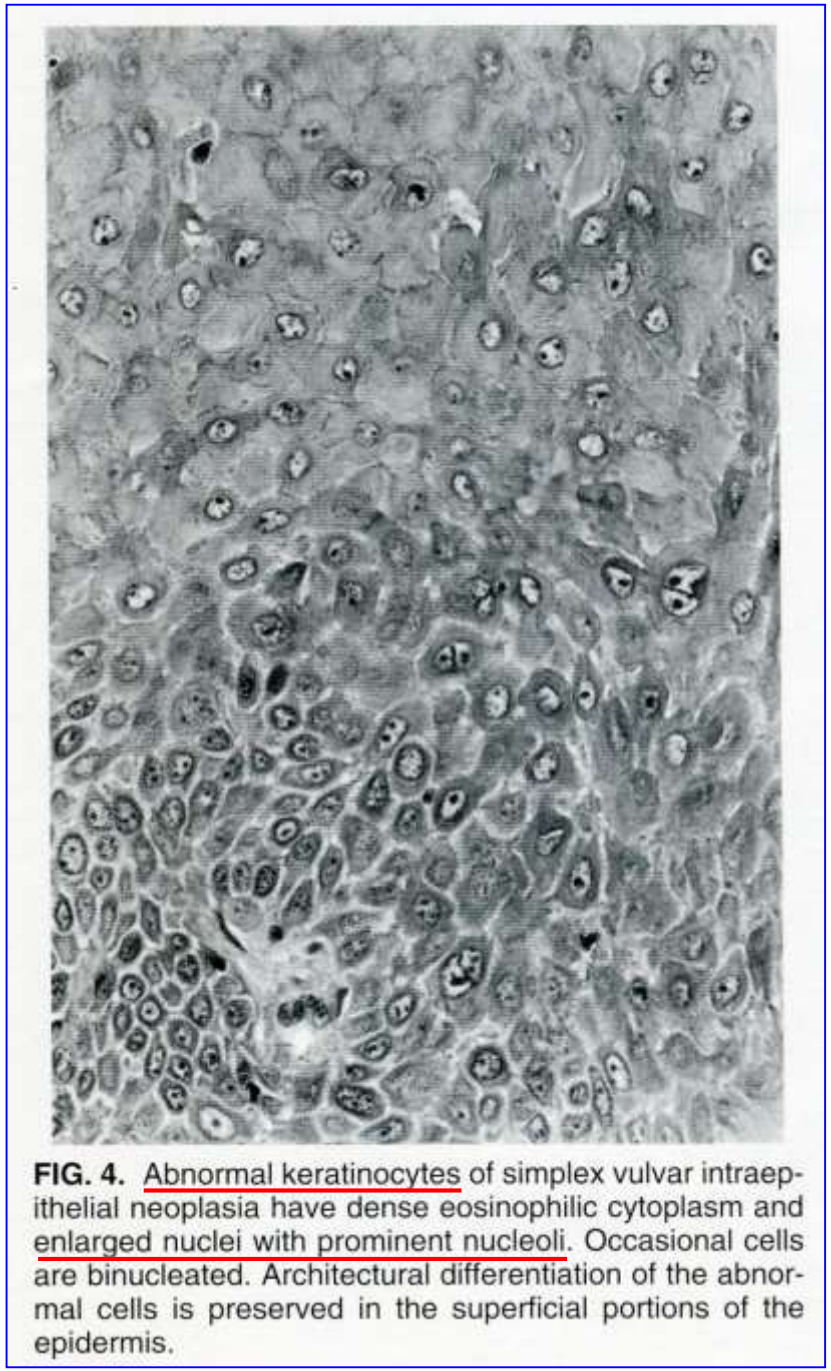
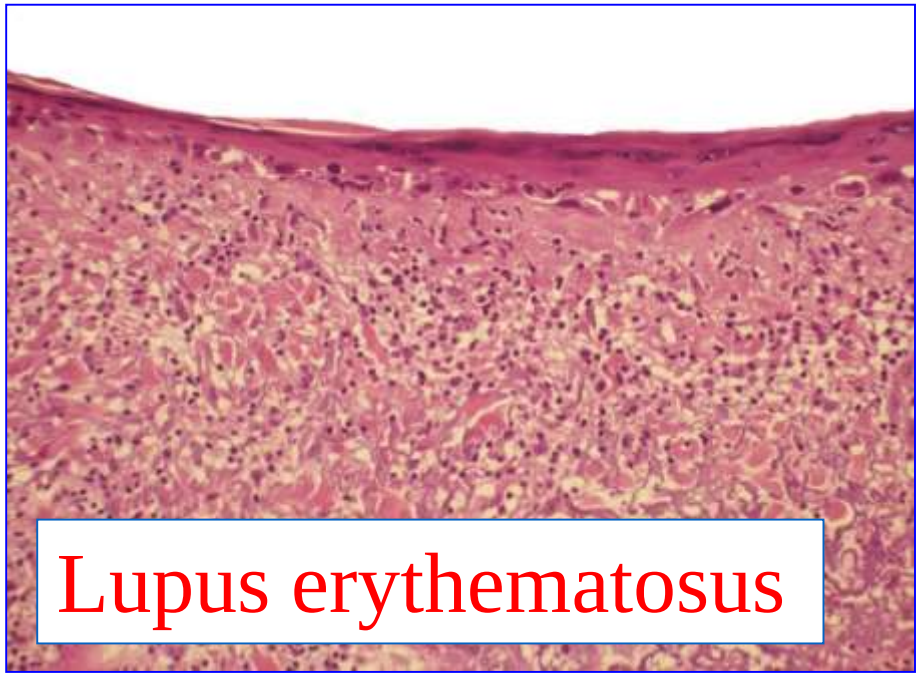


FIG. 4. Abnormal keratinocytes of simplex vulvar intraepithelial neoplasia have dense eosinophilic cytoplasm and enlarged nuclei with prominent nucleoli. Occasional cells are binucleated. Architectural differentiation of the abnormal cells is preserved in the superficial portions of the epidermis.

how about these cells? They are much more atypical,



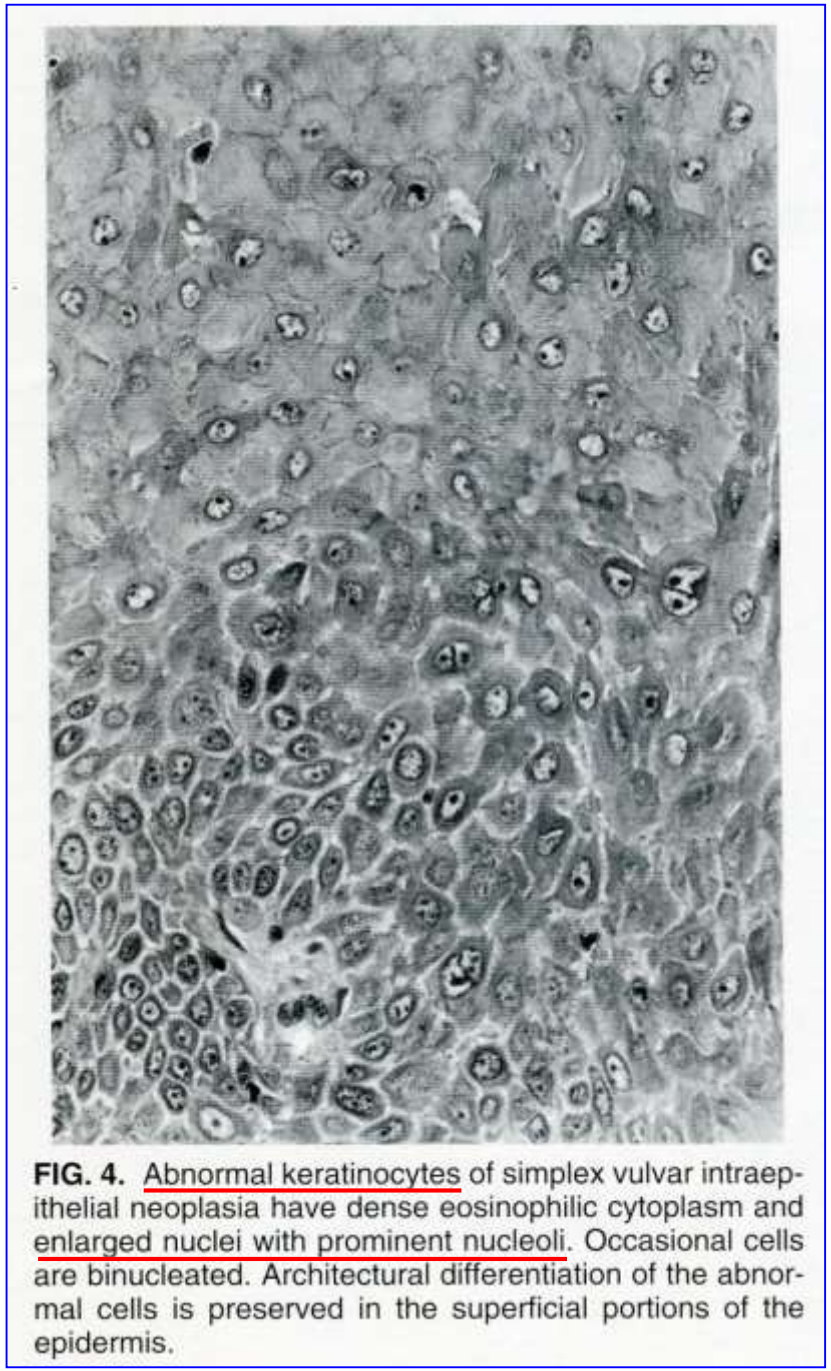


FIG. 4. Abnormal keratinocytes of simplex vulvar intraepithelial neoplasia have dense eosinophilic cytoplasm and enlarged nuclei with prominent nucleoli. Occasional cells are binucleated. Architectural differentiation of the abnormal cells is preserved in the superficial portions of the epidermis.

but the biopsy specimens came from lesions of lupus erythematosus and a drug eruption.

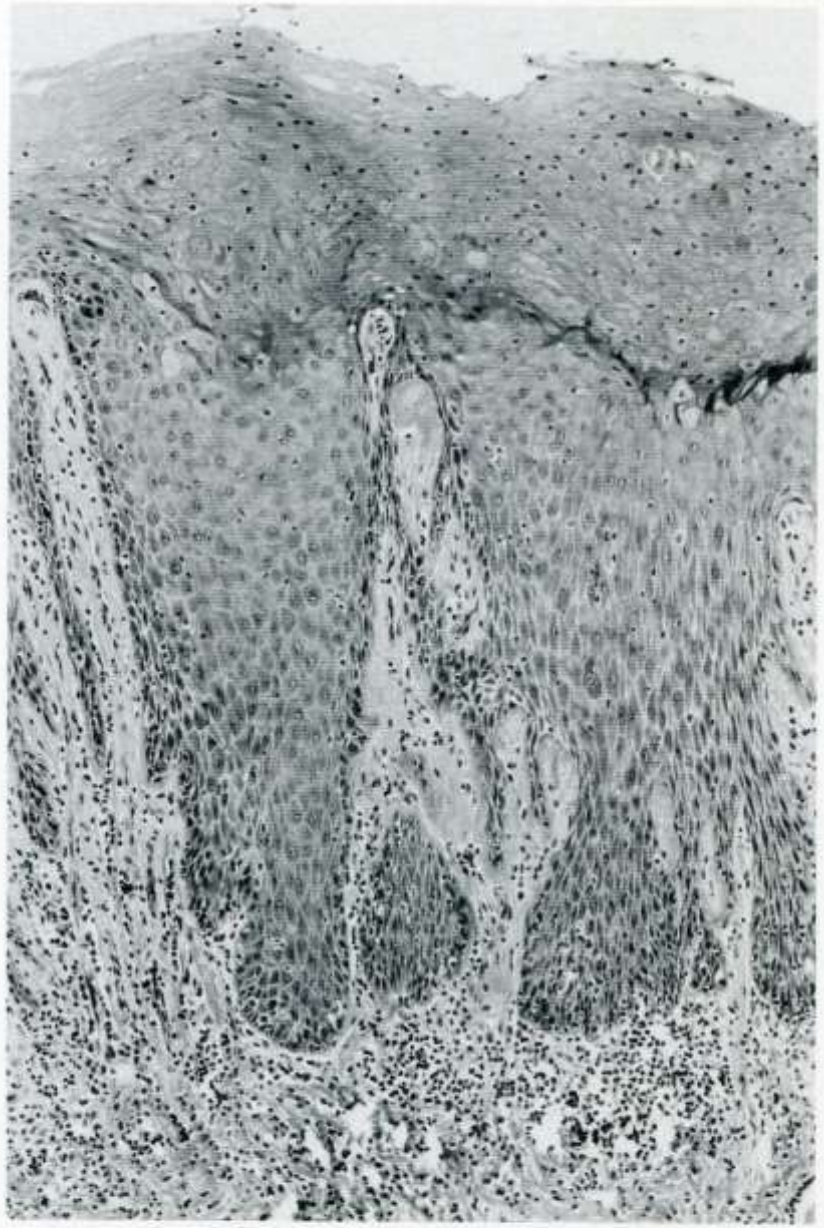
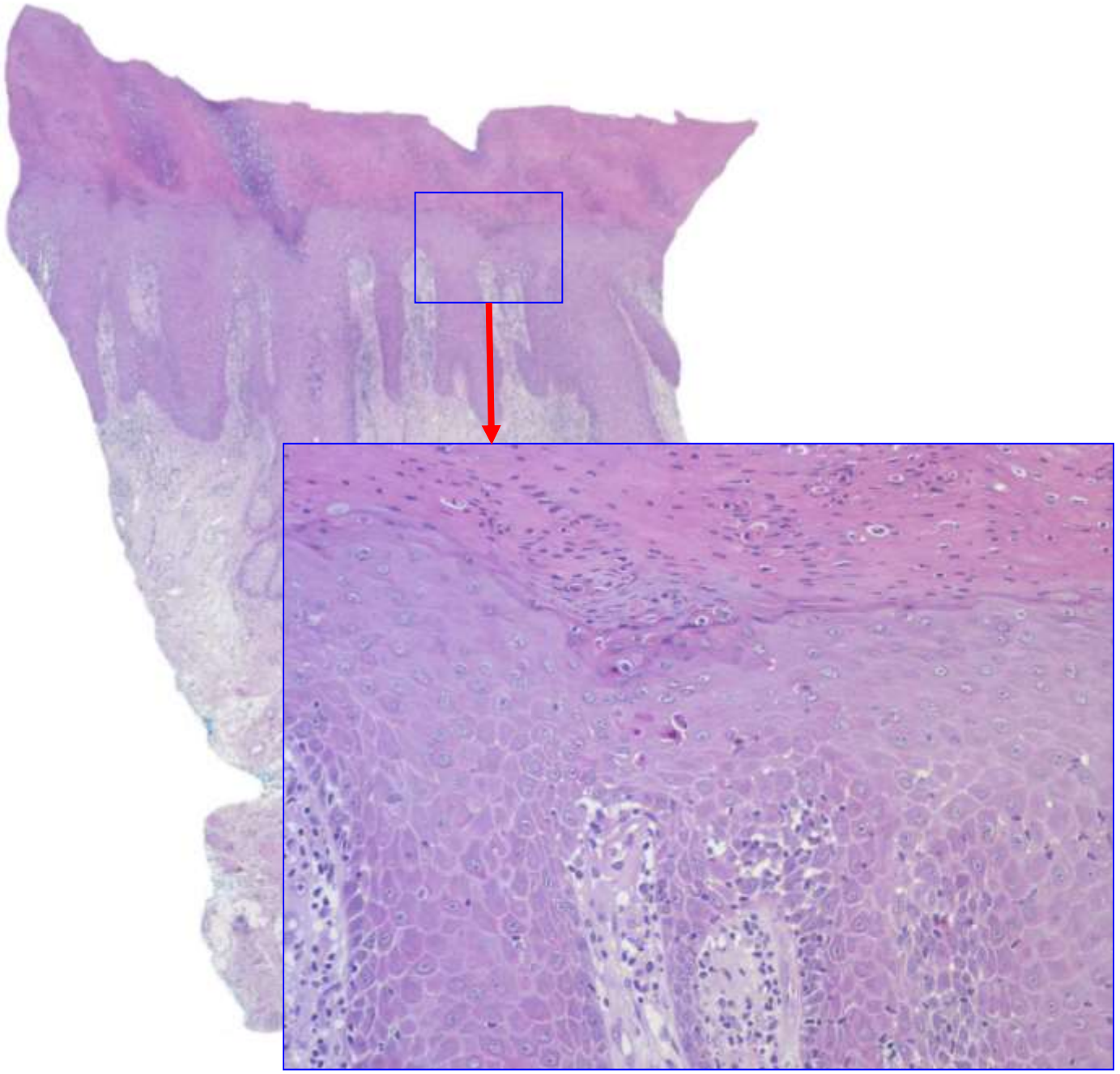
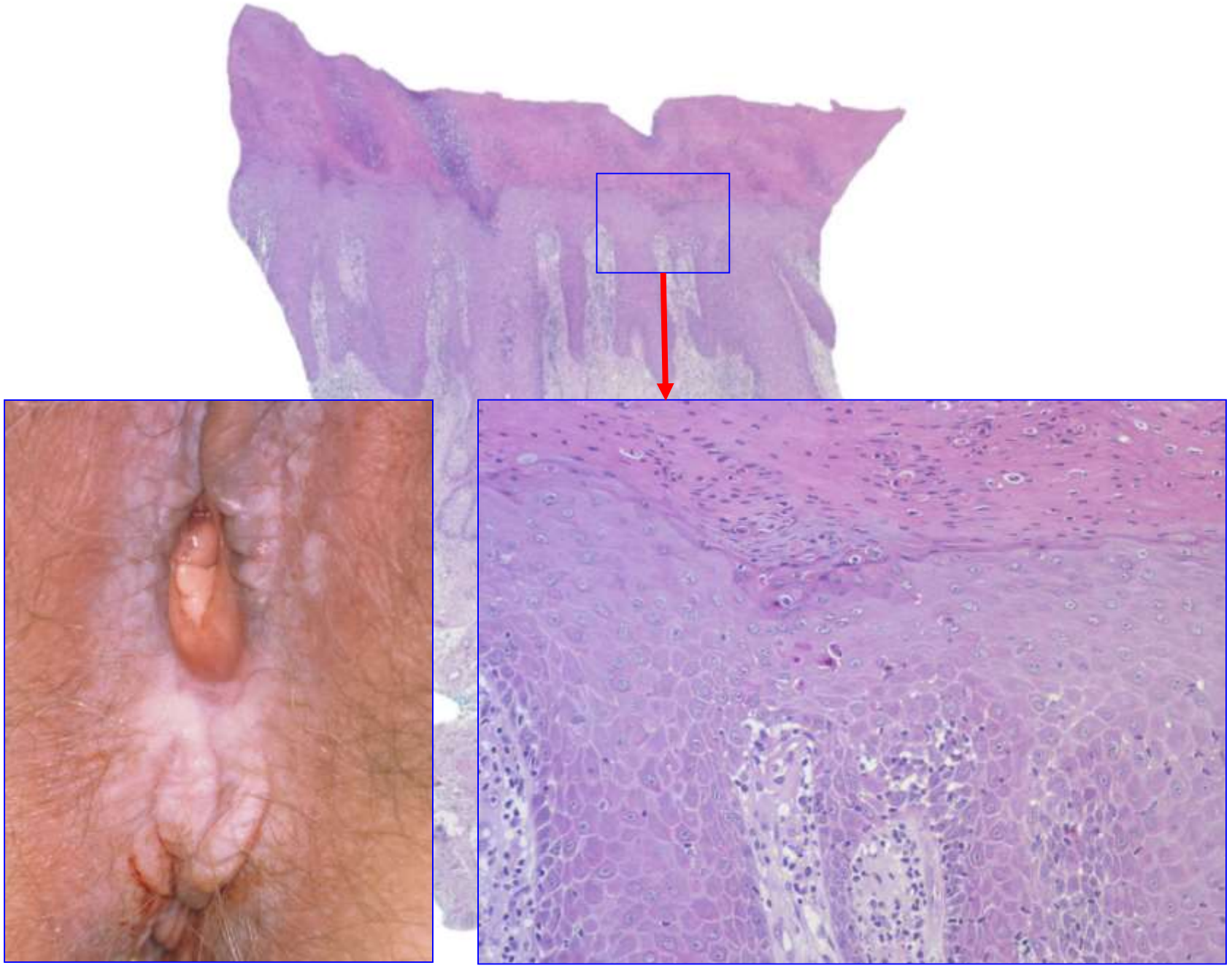


FIG. 1. Simplex vulvar intraepithelial neoplasia. The epidermis is thickened irregularly by a proliferation of abnormal, enlarged keratinocytes. The dermis contains chronic inflammatory cells. A thick parakeratotic surface reaction is present.

Another case from the same article: it is said to show *"simplex vulvar intraepithelial neoplasia"* characterized by a *"proliferation of abnormal enlarged keratinocytes,"* but where are those cells? These nuclei are small and monomorphous. To me, this is hypertrophic lichen sclerosus. There is a bandlike infiltrate of lymphocytes impinging on the epidermis and associated with foci of sclerosis in dermal papillae. The epidermis shows irregular psoriasiform hyperplasia and parakeratosis that seems to be arranged in vertical columns.

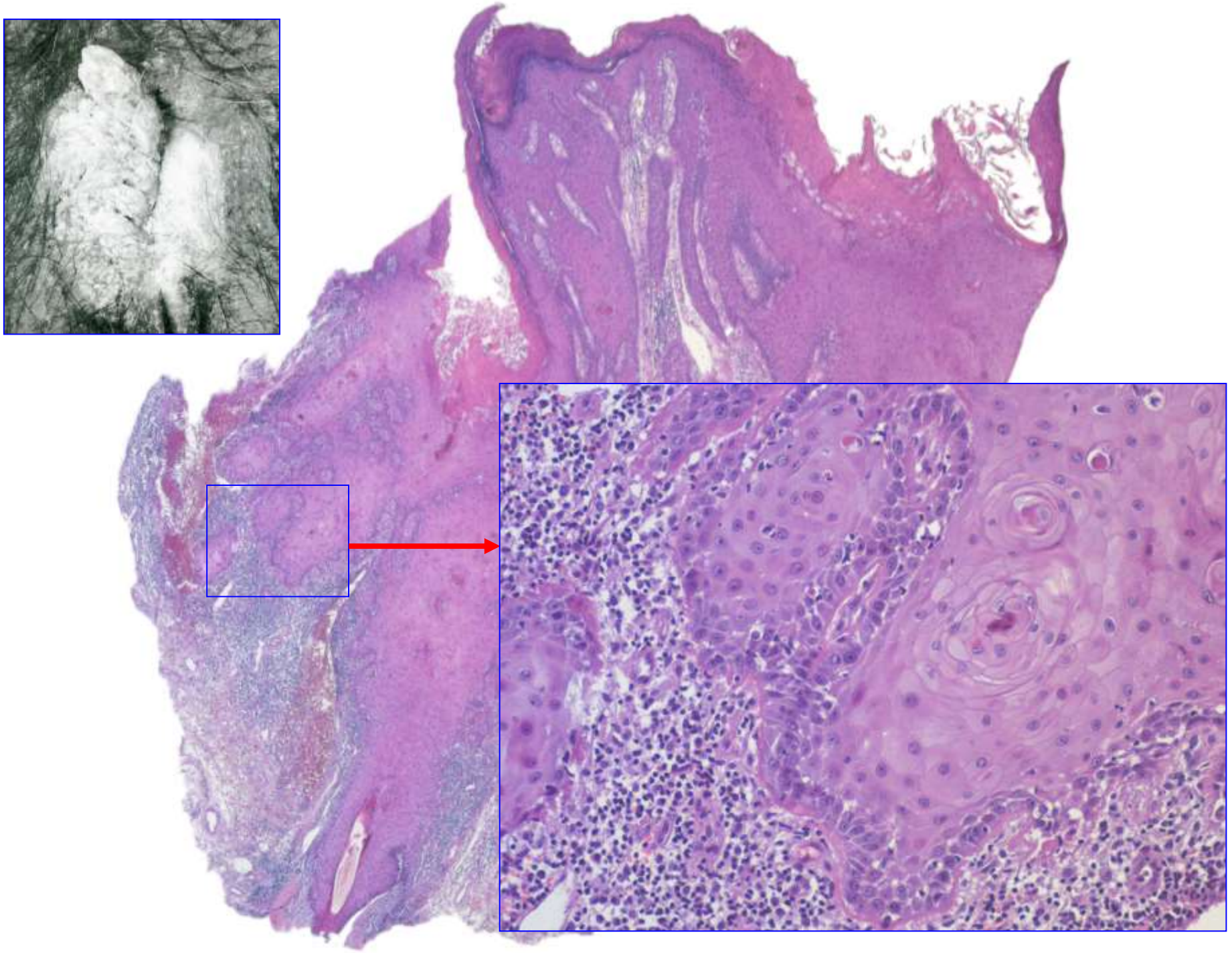


By now, we are familiar with those cases of lichen sclerosus with only small foci of sclerosis, psoriasiform epidermal hyperplasia, scant spongiosis above dermal papillae, necrotic keratocytes, and columns of parakeratosis. In more or less pronounced fashion, that presentation of lichen sclerosus is found in about 5 to 10% of our cases of lichen sclerosus. There are no atypical nuclei,



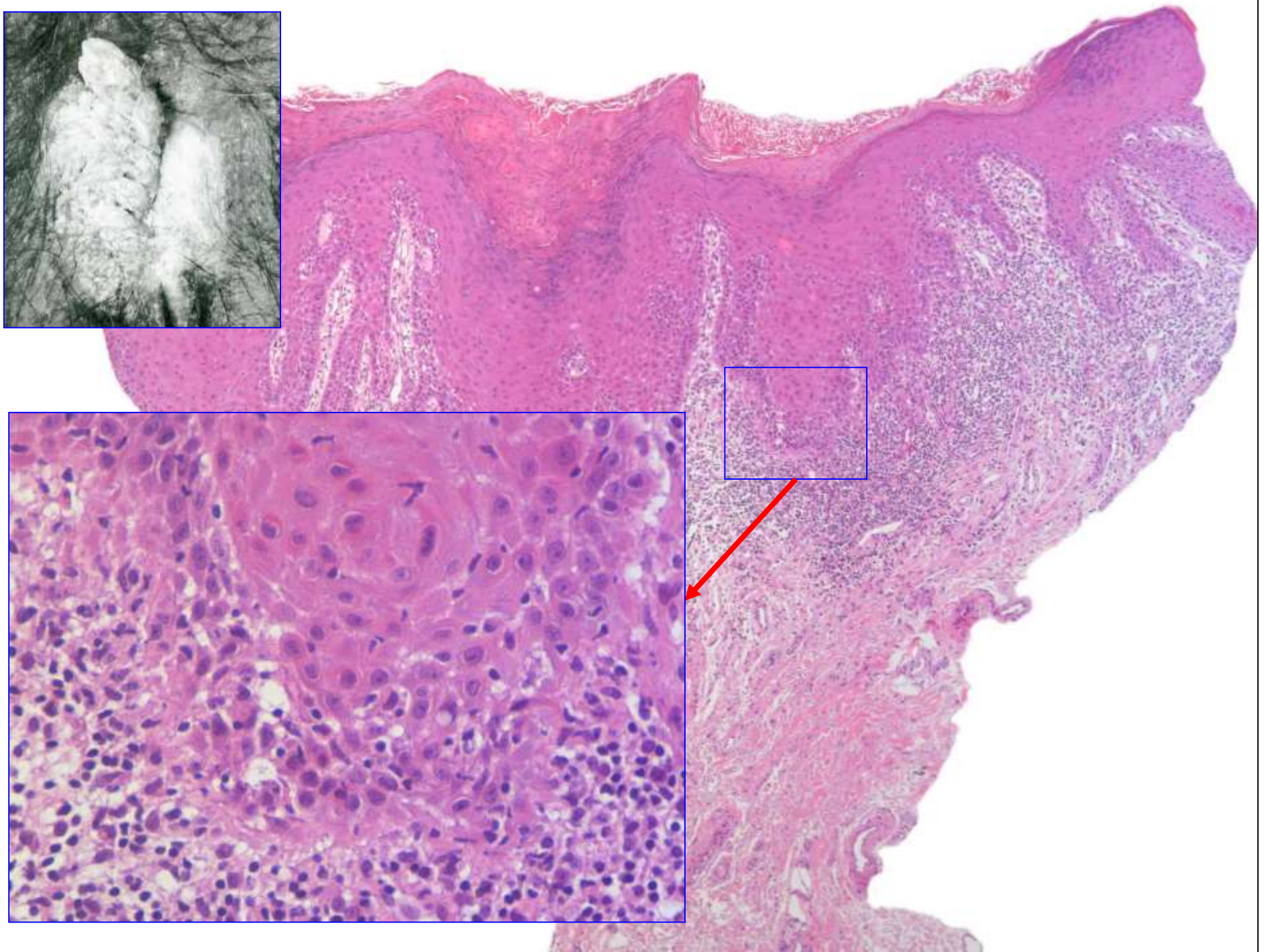
and this is the clinical picture: an exceedingly chronic lesion of lichen sclerosus with accentuation of skin furrows as a consequence to superimposed lichen simplex chronicus.

Although those findings are distinctive, they may be simulated by squamous cell carcinomas. In this lesion of squamous cell carcinoma, the epithelial hyperplasia is much more pronounced, more irregular and deeper reaching.

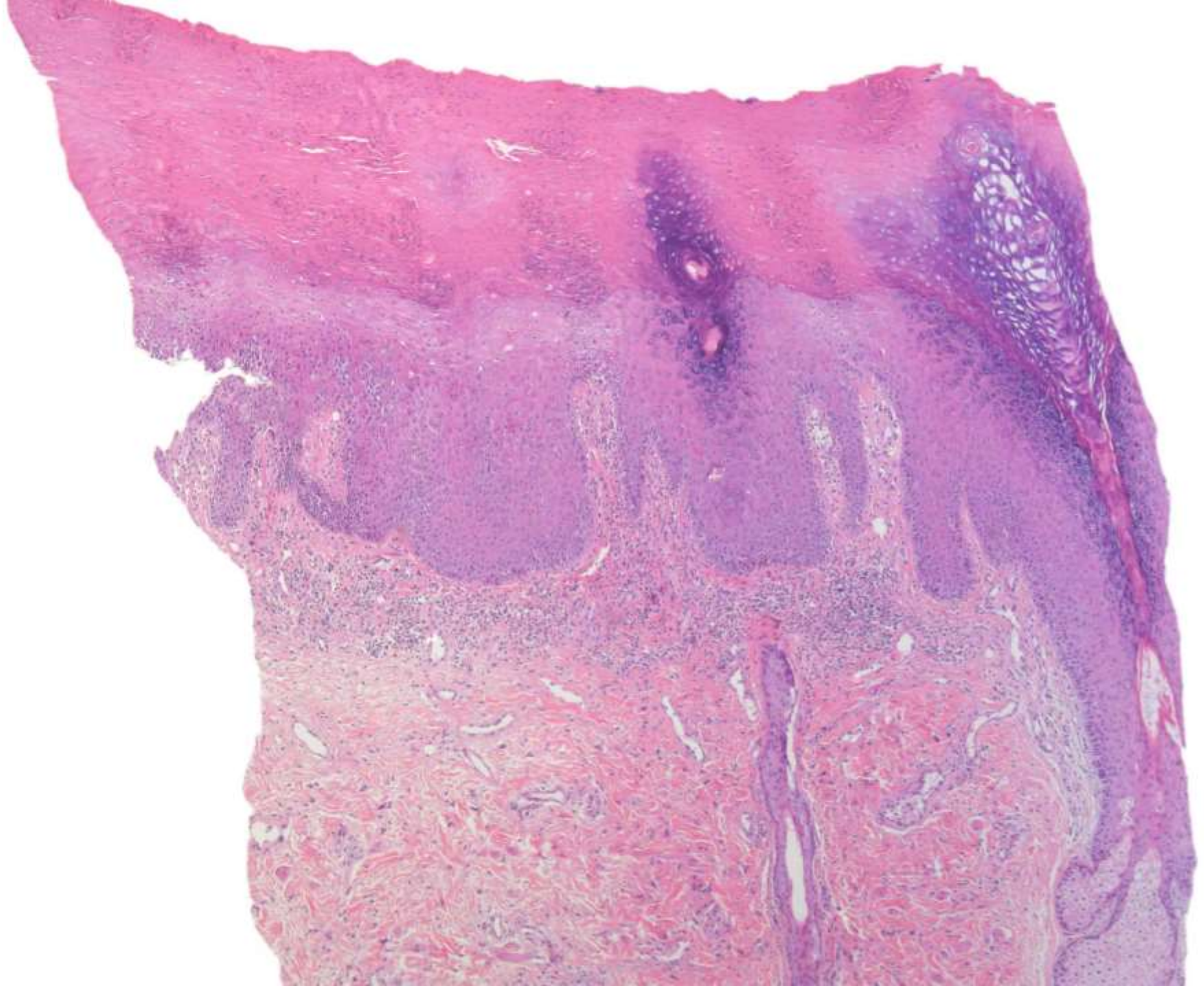


However, there is also a lichenoid infiltrate of lymphocytes, individual necrotic keratocytes are present in haphazard array, and there is no significant nuclear atypia. Note that keratocytes are crowded in the basal and suprabasal layers and that there are hints of acantholysis. Together, this leads to a relatively sharp demarcation of the lower layers from the mid spinous zone.

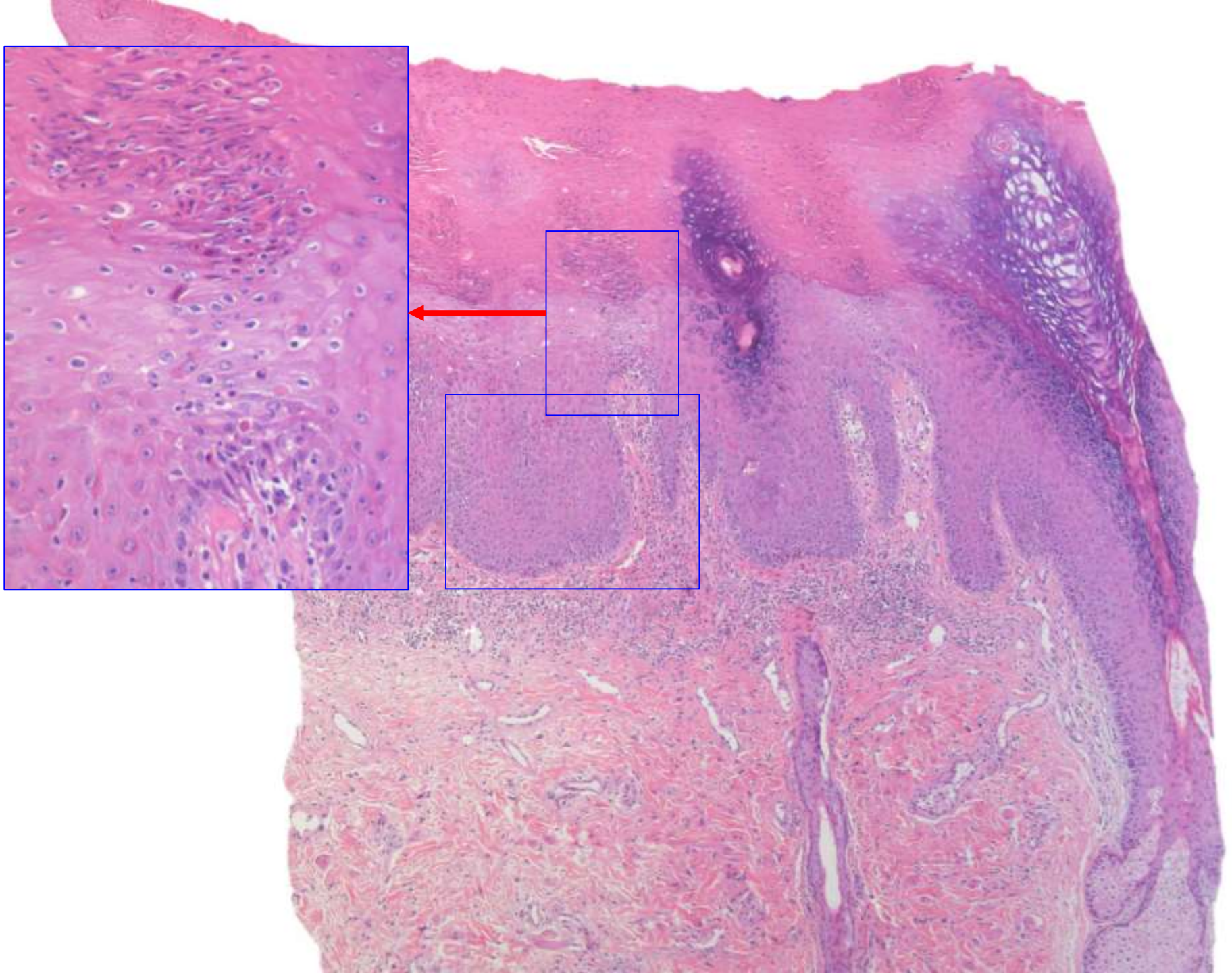
In an earlier biopsy from the same lesion, distinction from hypertrophic lichen sclerosus is even more difficult. Again, however, the epithelial hyperplasia is more irregular than usually seen in hypertrophic lichen sclerosus,



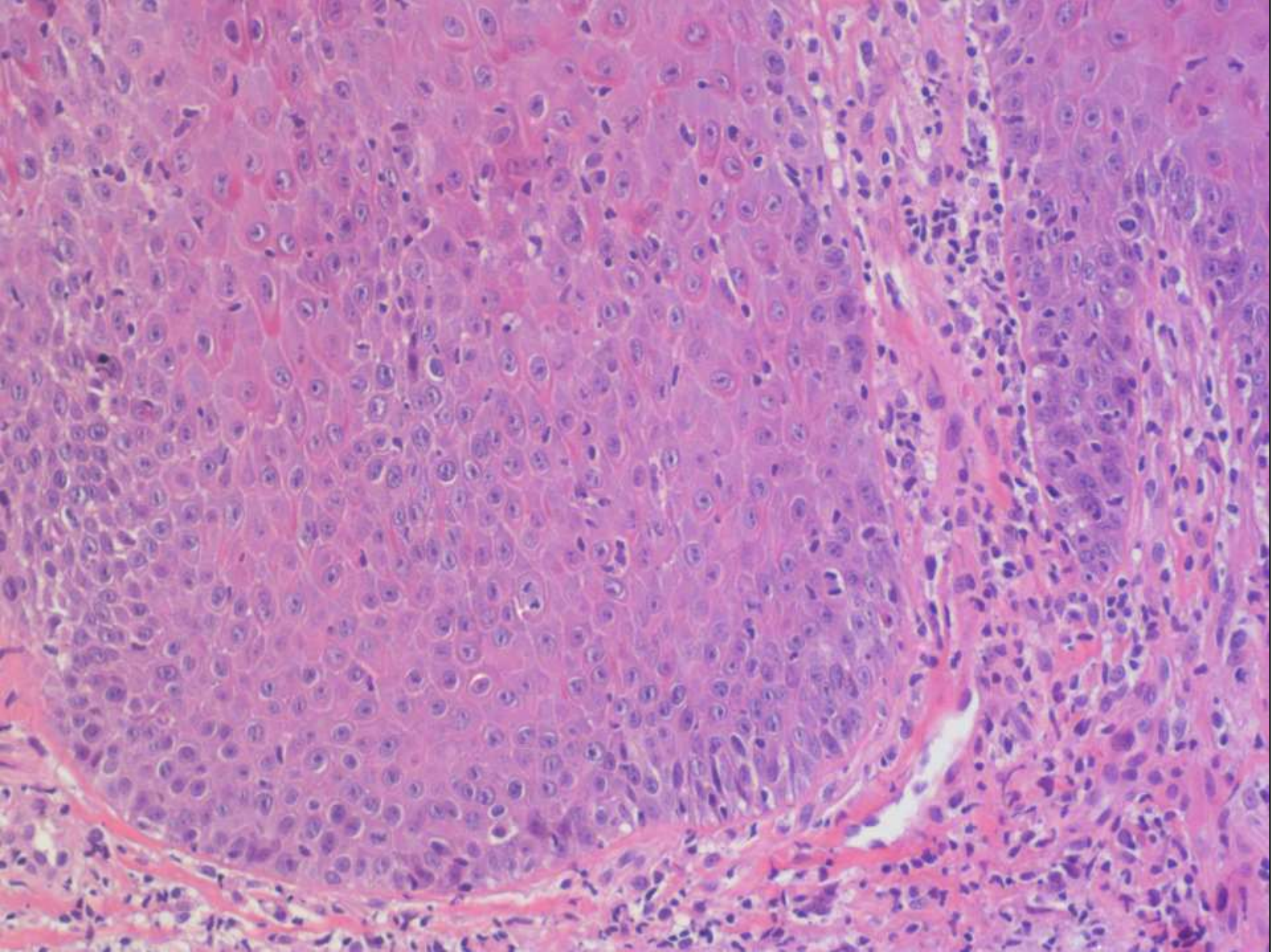
nuclei are crowded focally, and there are hints of acantholysis in the lower spinous zone.



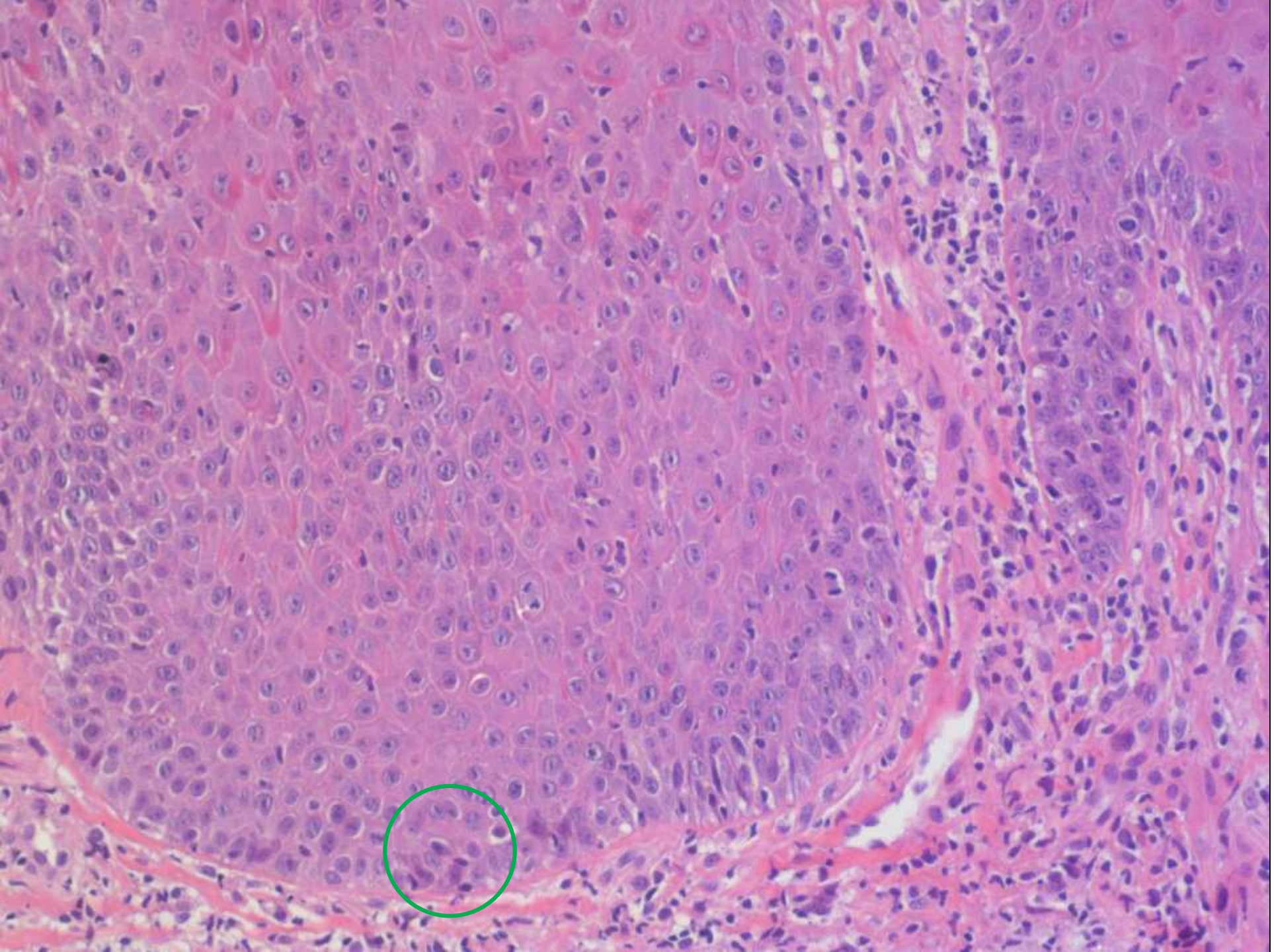
For comparison, another case of hypertrophic lichen sclerosus: The epidermis is thickened markedly, and the rete ridges are of uneven thickness but of approximately equal length.



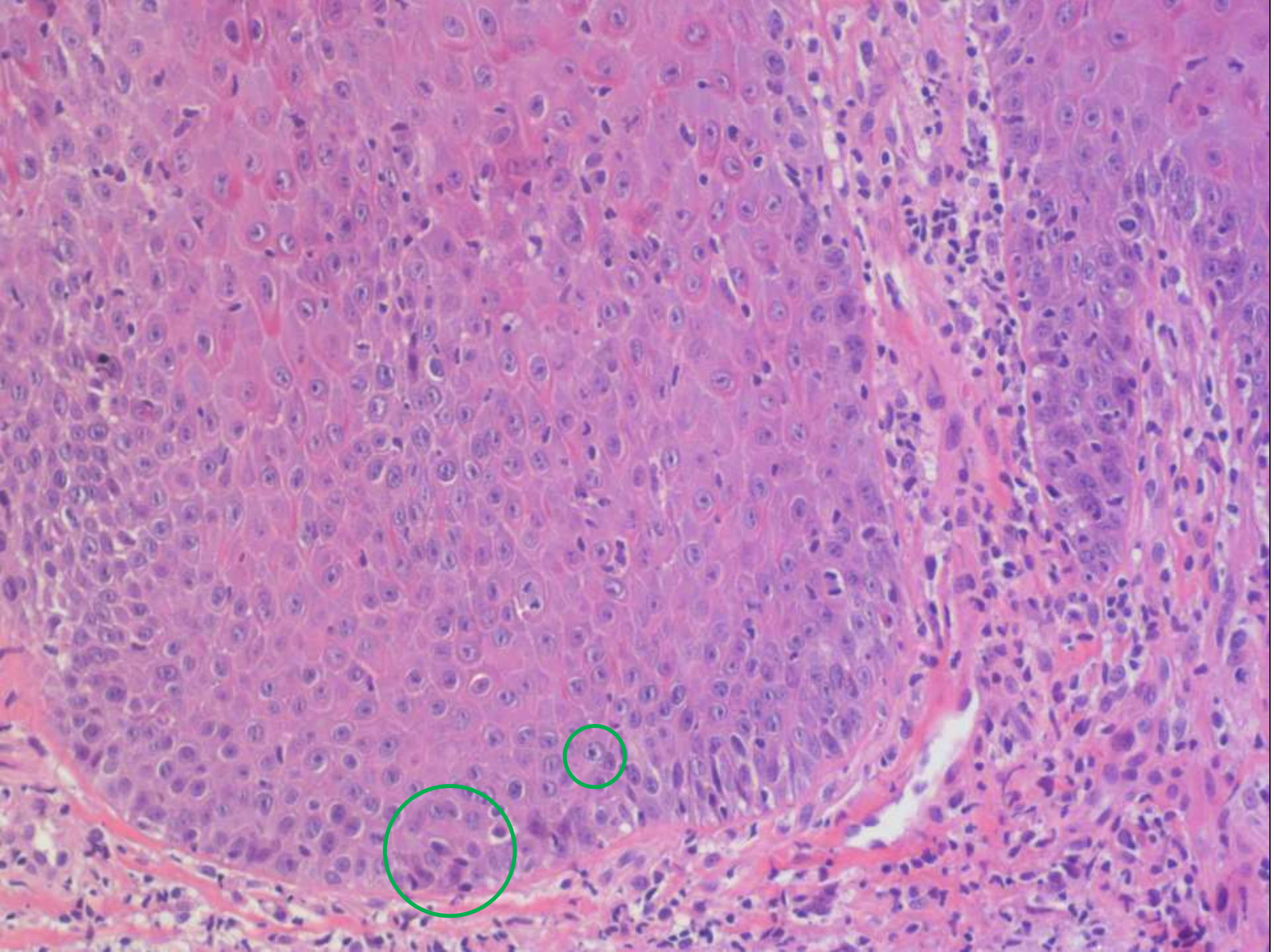
There are foci of sclerosis in the tips of dermal papillae, and chiefly above those tips, one sees slight spongiosis, individual necrotic keratocytes, and columns of parakeratosis with parakeratotic dyskeratotic cells, somewhat resembling the grains of Darier’s disease.



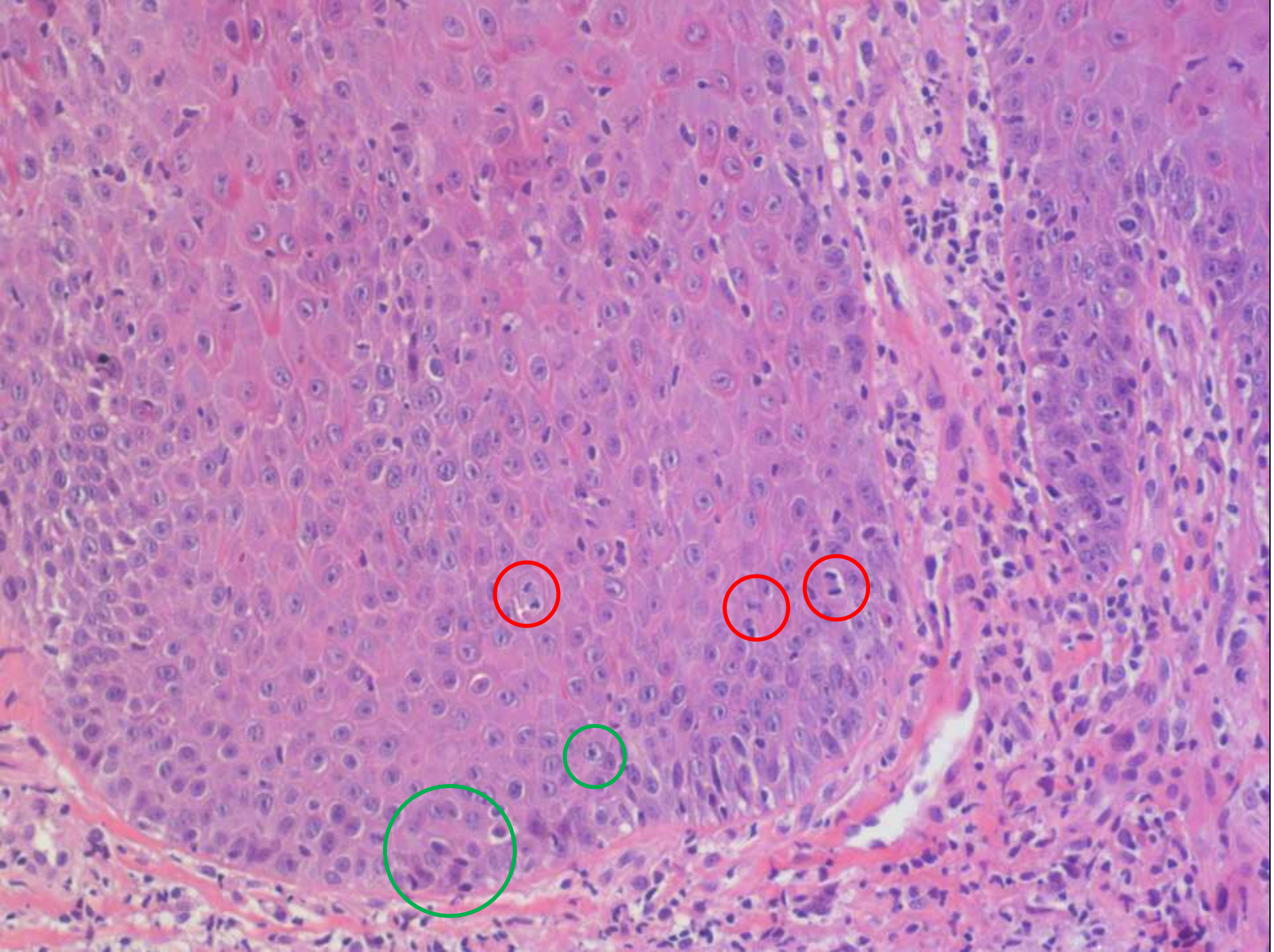
There is no crowding of nuclei and no acantholysis.



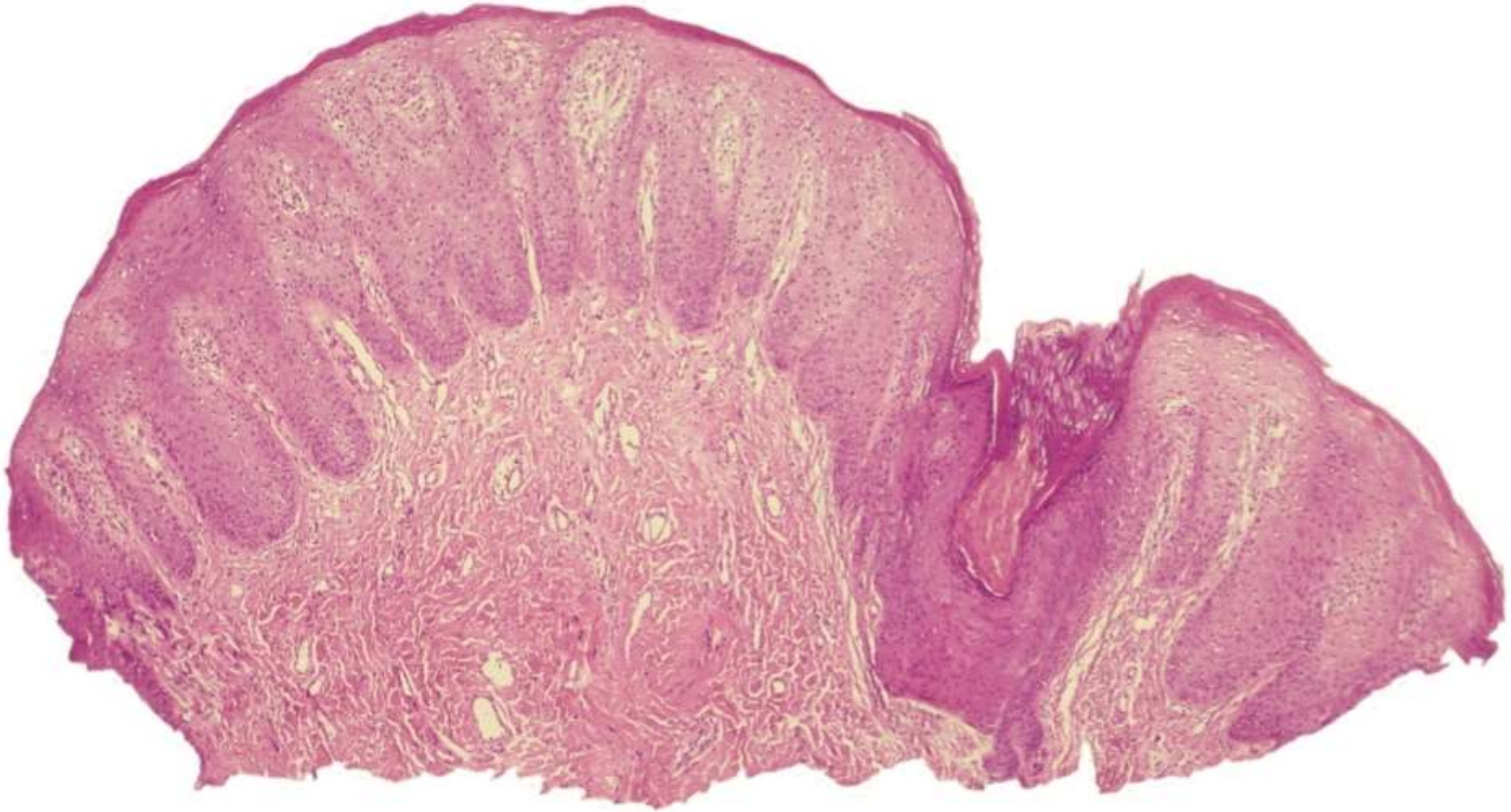
Of course, there is some variation in the size and staining quality of nuclei of keratocytes



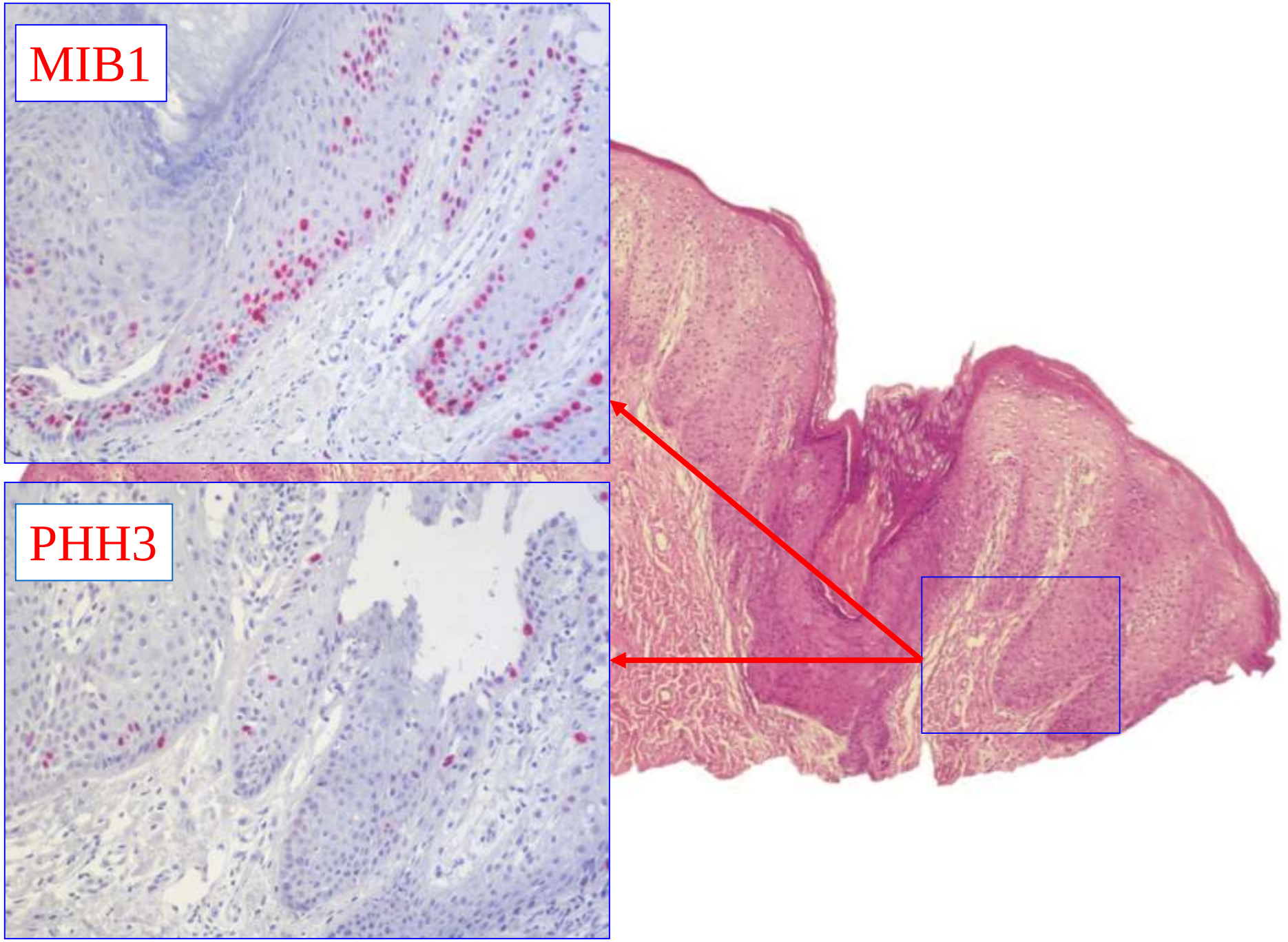
and some have prominent nucleoli, but this is within the range of normal.



There are some mitotic figures in the lower spinous zone, but this is an expected finding in any inflammatory disease associated with epidermal hyperplasia. Somehow, the hyperplasia must come into being.



This is a biopsy of vulvar psoriasis, an inflammatory disease charactzerized by an enhanced proliferation of keratocytes.



Many cells are stained by the proliferation marker Mib-1, and there are numerous mitotic figures highlighted by the pHH3 antibody. These are expected findings.

Modern Pathology (2007) 20, 770–778

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MIB1 expression in basal cell layer: a diagnostic tool to identify premalignancies of the vulva

Irene AM van der Avoort[1], Jeroen AWM van der Laak[2], Ard Paffen[1], Johanna MM Grefte[2], Leon FAG Massuger[1], Peter CM de Wilde[2], Joanne A de Hullu[1] and Johan Bulten[2]

[1]*Department of Obstetrics & Gynaecology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands and* [2]*Department of Pathology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands*

Lichen sclerosus, high-grade usual vulvar intraepithelial neoplasia (VIN) and differentiated VIN have a different malignant potential. The objective of this study was to quantify the proliferative activity in the basal region of the epithelium of vulvar premalignancies. Furthermore, we investigated whether MIB1 expression in the basal region of vulvar epithelium can be helpful in diagnosing differentiated VIN, which may be hard to discern from normal epithelium. MIB1 was used to immunohistochemically visualise proliferating cells within formalin-fixed, paraffin-embedded, archival tissue sections of different vulvar premalignancies ($N=48$) and normal vulvar epithelium ($N=16$). Automatic digital image analysis software was developed to quantify the proliferating fraction in different parts of the epithelium (MIB1 positivity index). MIB1 expression differed among the various vulvar premalignancies; a MIB1-negative basal cell layer was a distinct feature of normal vulvar epithelium. No MIB1-negative basal cell layer was noted in differentiated VIN or other vulvar premalignancies. Owing to this negative cell layer, the MIB1 proliferation index in normal vulvar epithelium was significantly lower than in vulvar premalignancies. In conclusion, MIB1 expression can be a helpful tool in diagnosing a premalignancy and has additional value especially to distinguish differentiated VIN neoplasia from normal vulvar epithelium, but cannot explain the differences in malignant potential.
Modern Pathology (2007) **20**, 770–778; doi:10.1038/modpathol.3800796; published online 27 April 2007

Keywords: MIB1; differentiated VIN; usual VIN; lichen sclerosus; diagnostic tool; vulvar cancer

Nonetheless, in gynecopathology, enhanced proliferation is interpreted commonly as a sign of incipient malignant transformation. The authors of this study found that *"the MIB1 proliferation index in normal vulvar epithelium was significantly lower than in vulvar premalignancies"* and they recommended this as *"a diagnostic tool to identify premalignancies of the vulva."* Proliferation was enhanced in lichen sclerosus, but the authors did not examine other inflammatory dermatoses with epithelial hyperplasia for comparison.

ORIGINAL ARTICLE

Single Base Instability Is Promoted in Vulvar Lichen Sclerosus

Ronald A. Tapp[1], Jingtao Feng[2], J. Wesley Jones[2], J. Andrew Carlson[3] and Vincent L. Wilson[1,2,4]

Single base substitution mutations in codons 248 and 273 of *TP53* and codon 12 Kirsten-*ras* (*KRAS*) are commonly found in human carcinomas. To determine whether these mutations also occur in normal and inflamed tissues from which carcinomas arise, we utilized the ultra-sensitive polymerase chain reaction/restriction endonuclease/ligase chain reaction mutation assay. Ninety samples of genital skin, including lichen sclerosus (LS) affected skin, adjacent normal and non-adjacent normal, were assayed. Mutations were detected in 103 of 349 assays and consisted of *KRAS* G34A, G34T, G35A, and *TP53* C742T, G818C, C817T, and G818A mutations. Mutant prevalence varied from 1 to 20 per 10^6 wild-type cells. Mutations occurred significantly more frequently in LS (78/224 (35%)) than adjacent normal (20/88 (23%)) and non-adjacent normal genital skin (5/38 (13%)). *KRAS* G34A mutation was relatively common to all classes of specimen, whereas *TP53* gene C742T and G818C mutations were significantly more frequent in LS than normal genital skin. In matched samples, immunohistochemistry evaluation of p53 protein expression revealed the presence of epidermal p53 clones in LS whose presence and number significantly correlated with the presence of *TP53* C742T and G818C mutations. Based on these results, it appears oncogenic point mutations occur in normal genital skin, and are selected for in LS.

Journal of Investigative Dermatology (2007) **127,** 2563–2576; doi:10.1038/sj.jid.5700889; published online 7 June 2007

This is a cardinal failure in nearly all articles addressing the malignant potential of lichen sclerosus. For example, Tapp and co-workers assessed single base instability in vulvar lichen sclerosus and found that *"mutations occurred significantly more frequently in LS … than adjacent normal … and non-adjacent normal genital skin."* They did not assess other inflammatory dermatosis. Nonetheless, on the basis of this study, lichen sclerosus has been referred to not only as a *"precancerosis,"* but an *"obligatory precancerosis."*

Overexpression of Wild-type p53 in Lichen Sclerosus adjacent to Human Papillomavirus-negative Vulvar Cancer

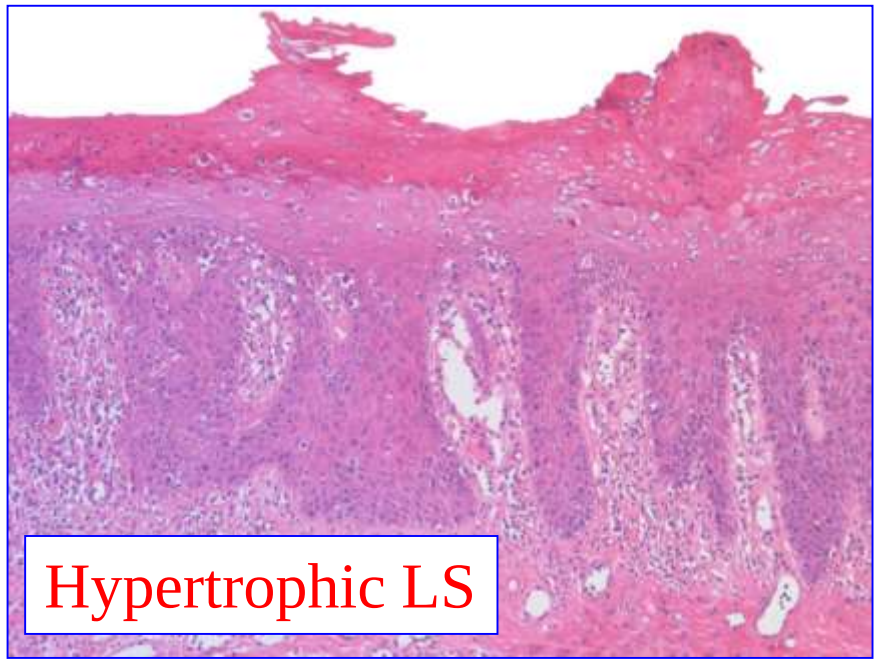
Katrina Vanin,*† James Scurry,† Heather Thorne,* Kally Yuen,‡ and Robert G. Ramsay*

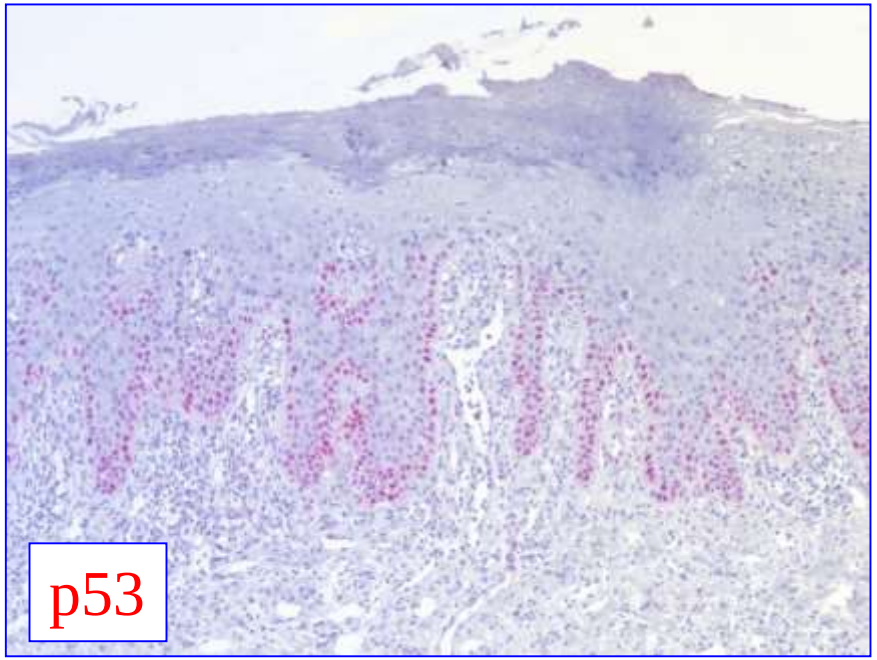
*Trescowthick Research Laboratories, Peter MacCallum Cancer Institute, Melbourne, Australia; †Department of Pathology, Mercy Hospital for Women, East Melbourne, Australia; ‡Statistical Center, Peter MacCallum Cancer Institute, Melbourne, Australia

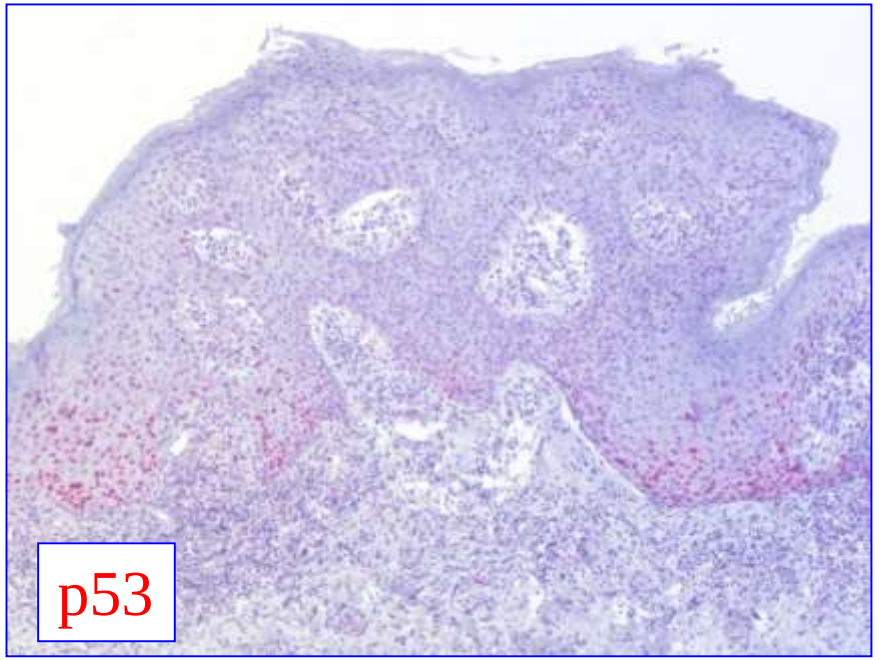
Human papillomavirus is a risk factor for vulvar cancer, whereas human papillomavirus-negative late onset vulvar carcinoma is associated with the dermatologic condition, lichen sclerosus. Human papillomavirus E6 protein targets TP53 for degradation and by inference it has been assumed that human papillomavirus-negative vulvar cancer is dependent upon the acquisition of p53 somatic mutations and subsequent allelic loss. To investigate this, TP53 expression, loss of heterozygosity, and p53 genomic sequence were examined in 29 cases of human papillomavirus-negative vulvar carcinoma with adjacent lichen sclerosus. We examined 37 cases of lichen sclerosus without vulvar carcinoma, 10 cases of nongenital lichen sclerosus, and 12 cases of normal vulvar epithelium served as controls. TP53 was evident in 72% of vulvar carcinoma, 48% in epithelium adjacent to vulvar carcinoma, but was minimal in normal samples. When lichen sclerosus cases were selected to exclude samples with absolutely no TP53 expression through probable failed antigen retrieval or homozygous p53 loss the number of epithelial cells expressing TP53 increased progressively from nongenital lichen sclerosus to lichen sclerosus without vulvar carcinoma, then to lichen sclerosus with vulvar carcinoma ($p < 0.0001$). These data suggest elevated TP53 is a feature of vulvar lichen sclerosus. Seventy-four percent of vulvar carcinoma had chromosome 17p-linked loss of heterozygosity, whereas 47% of adjacent lichen sclerosus featured loss of heterozygosity, but only 31% of vulvar carcinoma had p53 mutations, a frequency less than reported previously. Seven percent of adjacent lichen sclerosus had mutations, showing for the first time the presence of an identical mutation to the matched vulvar carcinoma. These data, however, implicate p53 mutations as a later event in vulvar carcinoma and in marked contrast to the original expectation, our loss of heterozygosity data are consistent with loss of another locus (not p53) on 17p operating as a tumor suppressor in lichen sclerosus destined to develop vulvar carcinoma.

Key words: lichen sclerosus/loss of heterozygosity/mutation analysis/p53/tumor suppressor gene/vulvar carcinoma. J Invest Dermatol 119:1027–1033, 2002

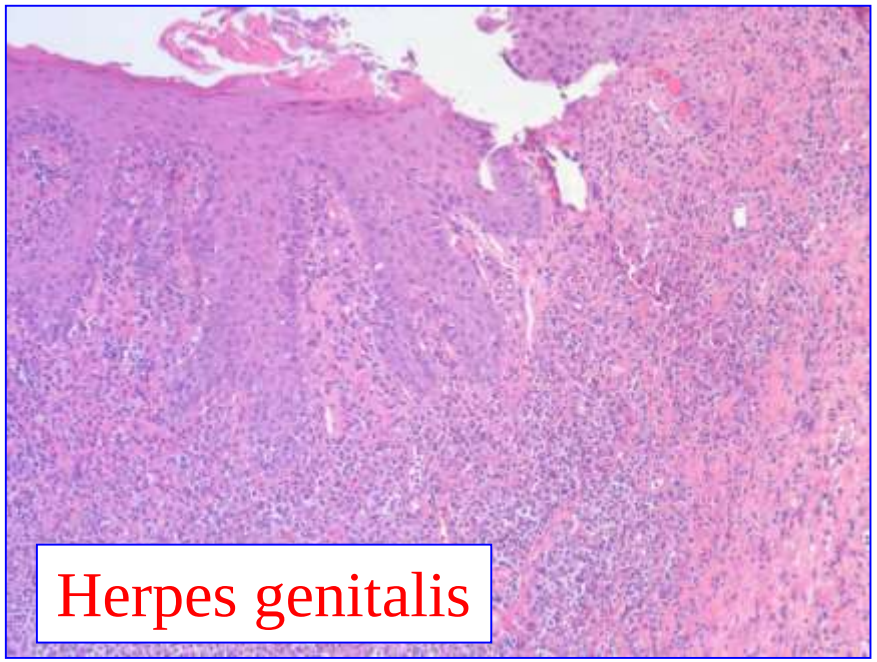
Several groups examined p53 expression and found that p53 is overexpressed in lichen sclerosus adjacent to vulvar cancer.

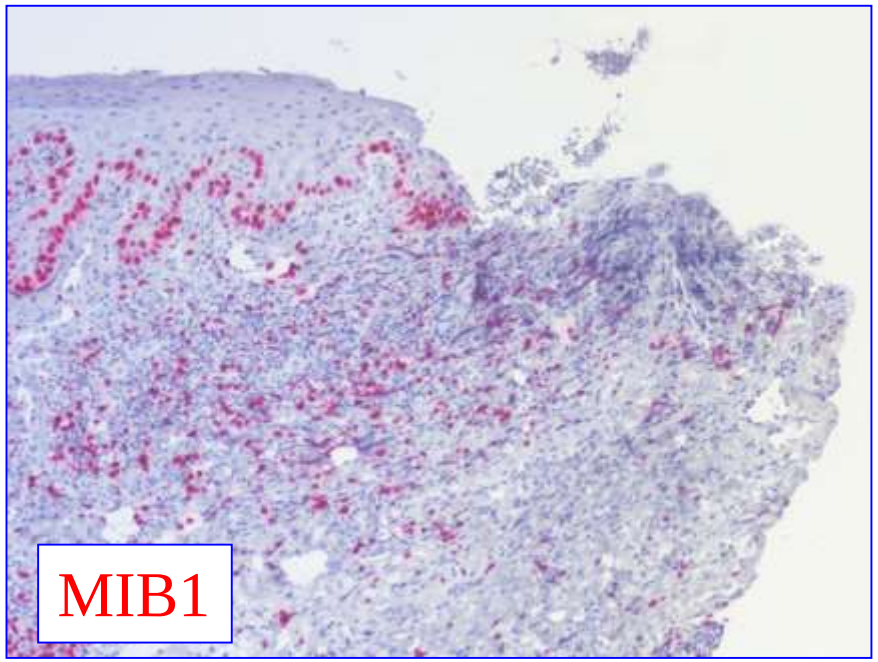


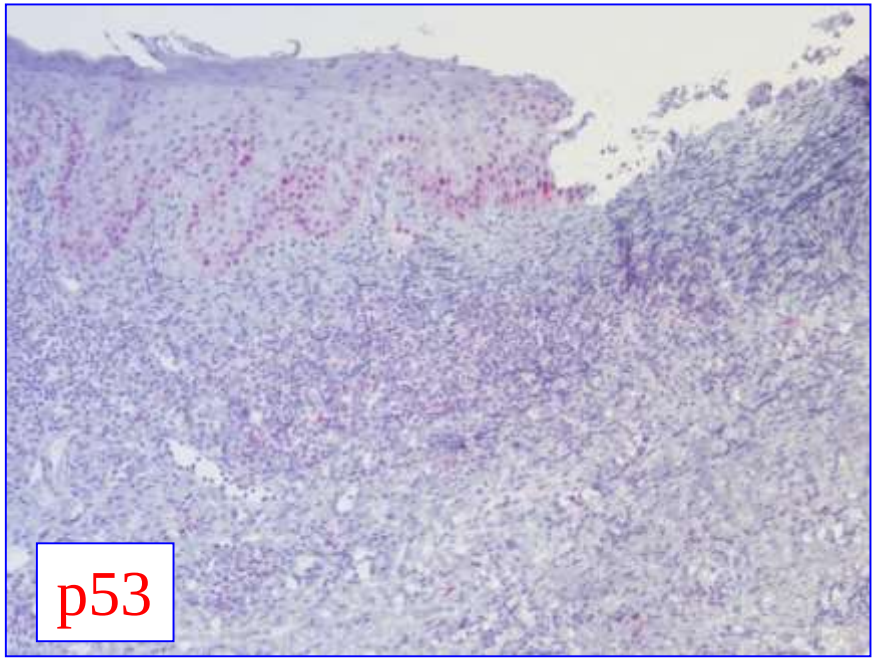


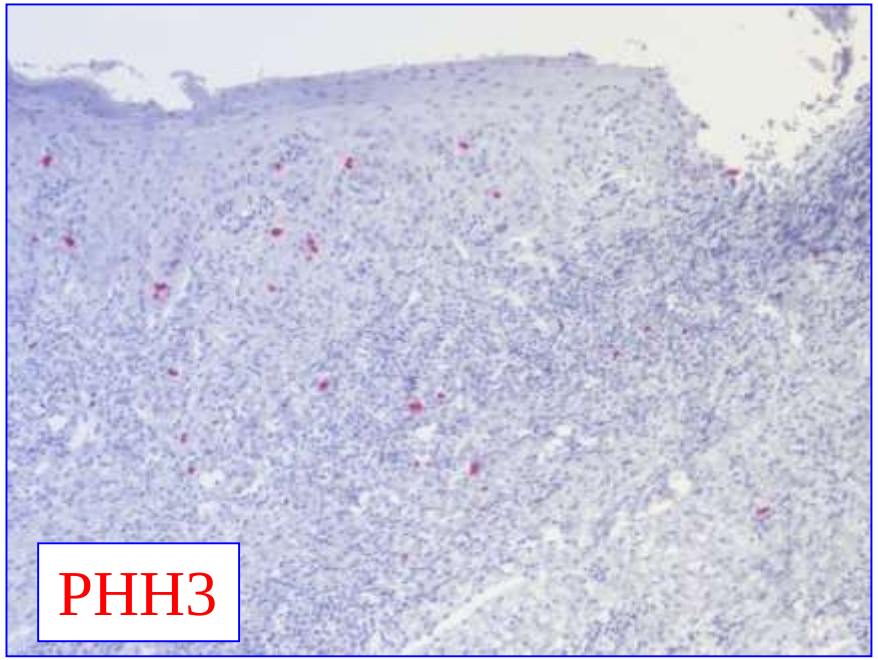


Indeed, p53 expression in lichen sclerosus may be just as strong as in squamous cell carcinoma in situ. However, it may also be over-expressed in other inflammatory diseases,









such as genital herpes. In herpes, there may also be enhanced proliferation adjacent to the ulcer, with strong expression of Mib-1 and numerous mitotic figures.

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Clinical Letter

HPV73 und HPV82 positives Analrandkarzinom mit sekundärer Überlagerung durch eine ulzerierende Herpes simplex Virus Typ 2 Infektion

HPV-73- and HPV-82 positive anal margin carcinoma with secondary ulcerating Herpes simplex-virus 2 infection

Alexander Kreuter[1], Anja Potthoff[1], Norbert Brockmeyer[1], Markus Stücker[1], Ulrike Wieland[2] für das Deutsche Kompetenznetzwerk HIV/AIDS
(1) Klinik für Dermatologie, Venerologie und Allergologie, Ruhr-Universität Bochum
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Analkarzinome und deren potentielle Vorläuferläsionen, die so genannten analen intraepithelialen Neoplasien (AIN), stellen eine zunehmendes medizinisches Problem in der Langzeitbehandlung von HIV-positiven Patienten dar [1]. Insbesondere für HIV-positive Männer, die Sex mit Männern haben (MSM), wurden dramatisch erhöhte AIN- und Analkarzinom-Inzidenzen beobachtet [2]. Der Beginn einer hochaktiven antiretroviralen Therapie (HAART) scheint dabei keinen wesentlichen Einfluss auf die Entstehung bzw. Verhinderung von AIN- und Analkarzinomen zu haben [3]. Ähnlich wie beim Zervixkarzinom werden Analkarzinome durch Infektionen mit high-risk humanen Papillomviren (HPV), insbesondere HPV16 und HPV18, verursacht [4]. Im Folgenden wird über den Fall eines durch seltene high-risk HPV-Typen verursachten Analrandkarzinoms bei HIV berichtet, das durch eine ulzerierende Herpes simplex-Infektion überlagert und somit maskiert wurde.

Ein 60-jähriger Patient stellte sich wegen seit einigen Wochen zunehmenden Missempfindungen und Schmerzen im Bereich der Perianalregion in unserer interdisziplinären immunologischen Ambulanz vor. Zwei Jahre zuvor war die Diagnose einer HIV-Infektion (Stadium B3 nach CDC/WHO) gestellt worden. Zeitgleich war eine HAART mit Efavirenz, Emtricitabin und Tenofovir initiiert worden, diese wurde jedoch von dem Patienten nur unregelmäßig eingenommen. Zum Zeitpunkt der aktuellen Vorstellung lag die CD4+ Zellzahl des Patienten bei 6/µl (normal: 300–1400/µl), die CD8+ Zellzahl bei 277/µl (normal: 200–900/µl), die CD4/CD8-ratio bei 0.0 (normal: 2–3), die Absolutzahl der Leukozyten bei 2540/µl (normal: 4600–9500/µl), und die die HIV-RNA bei 431 000 Kopien/ml. Klinisch imponierten multiple, oberflächliche, schmierig belegte Ulzerationen in der gesamten Zirkumferenz der Perianalregion (Abbildung 1). Aufgrund des klinischen Verdachtes auf das Vorliegen einer ulzerierenden Herpes-simplex Infektion bei fortgeschrittener Immundefizienz erfolgte die stationäre Aufnahme zur Einleitung einer intravenösen Therapie mit Aciclovir. Zum Ausschluss eines zusätzlich bestehenden Malignoms erfolgte die Entnahme mehrerer Probebiopsien. Hierbei zeigte sich bei 5 Uhr perianal in Steinschnittlage ein ulzerierendes, hochdifferenziertes Plattenepithelkarzinom mit einer Tumordicke von 1,1 mm (Abbildung 2 und 3). Die virologische Analyse der Plattenepithelkarzinom-Biopsie mittels Polymerase-Ketten-Reaktion (PCR) [5] erbrachte den Nachweis der HPV-Typen HPV73 und HPV82. Zusätzlich bestand eine Infektion mit Herpes simplex Virus Typ 2. Eine Zytomegalievirus Infektion konnte mittels

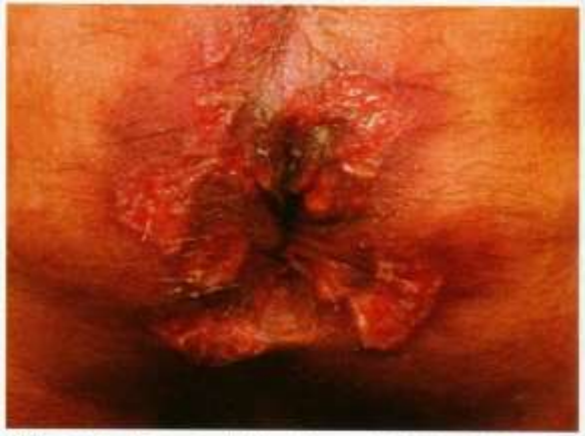
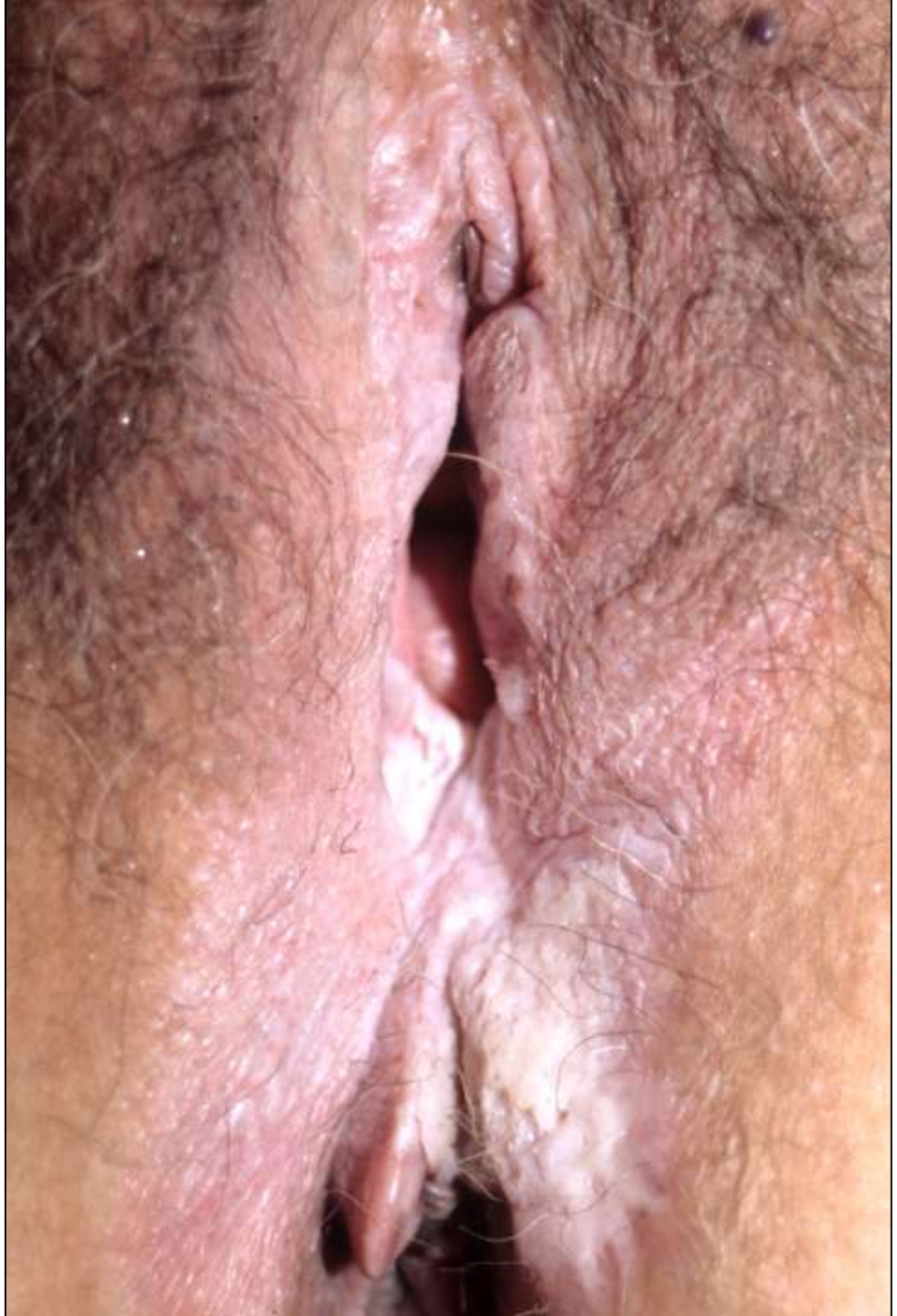


Abbildung 1: Klinische Präsentation der Hautveränderungen. Im Bereich der Perianalregion imponieren multiple, oberflächliche Ulzerationen mit zum Teil fibrinösen Belägen. Der Analkanal ist nicht betroffen.

Moreover, squamous cell carcinoma has been reported in association with herpes genitalis. Nonetheless, nobody considers herpes to be a *“precancerosis.”*



Of all inflammatory diseases of the vulva, only lichen sclerosus is said to be dangerous,

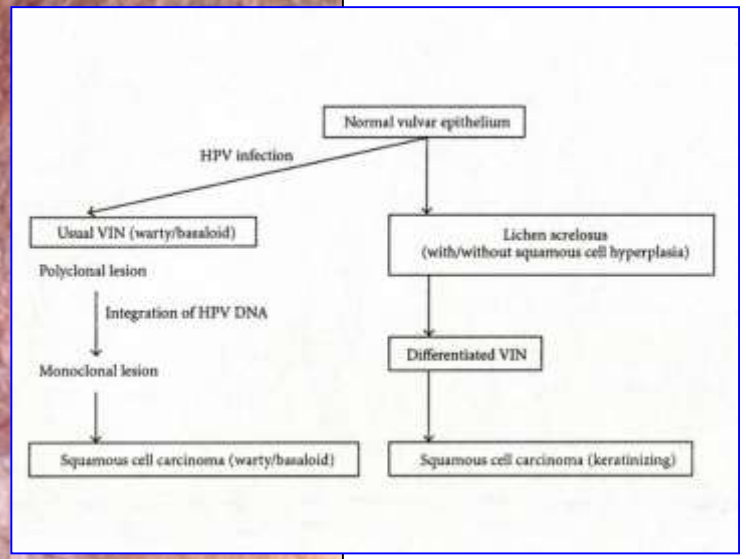
TABLE 1. Non-Neoplastic Epithelial Disorders of Skin and Mucosa

Lichen sclerosus (lichen sclerosus et atrophicus)
Squamous cell hyperplasia (formerly hyperplastic dystrophy)
Other dermatoses

TABLE 2. Classification of Vulvar Intraepithelial Neoplasia

VIN I — Mild dysplasia (formerly mild atypia)
VIN II — Moderate dysplasia (formerly moderate atypia)
VIN III — Severe dysplasia (formerly severe atypia)
VIN III — Carcinoma in situ

This ISSVD terminology replaces the original ISSVD atypia-carcinoma in situ terminology.[2]



and this is chiefly a consequence of those caricatures of classification that have anchored firmly the concept of a malignant potential of lichen sclerosus.

Modern Pathology (2007) 20, 770–778

www.modernpathology.org

MIB1 expression in basal cell layer: a diagnostic tool to identify premalignancies of the vulva

Irene AM van der Avoort[1], Jeroen AWM van der Laak[2], Ard Paffen[1], Johanna MM Grefte[2], Leon FAG Massuger[1], Peter CM de Wilde[2], Joanne A de Hullu[1] and Johan Bulten[2]

[1]Department of Obstetrics & Gynaecology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands and [2]Department of Pathology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Lichen sclerosus, high-grade usual vulvar intraepithelial neoplasia (VIN) and differentiated VIN have a different malignant potential. The objective of this study was to quantify the proliferative activity in the basal region of the epithelium of vulvar premalignancies. Furthermore, we investigated whether MIB1 expression in the basal region of vulvar epithelium can be helpful in diagnosing differentiated VIN, which may be hard to discern from normal epithelium. MIB1 was used to immunohistochemically visualise proliferating cells within formalin-fixed, paraffin-embedded, archival tissue sections of different vulvar premalignancies ($N=48$) and normal vulvar epithelium ($N=16$). Automatic digital image analysis software was developed to quantify the proliferating fraction in different parts of the epithelium (MIB1 positivity index). MIB1 expression differed among the various vulvar premalignancies; a MIB1-negative basal cell layer was a distinct feature of normal vulvar epithelium. No MIB1-negative basal cell layer was noted in differentiated VIN or other vulvar premalignancies. Owing to this negative cell layer, the MIB1 proliferation index in normal vulvar epithelium was significantly lower than in vulvar premalignancies. In conclusion, MIB1 expression can be a helpful tool in diagnosing a premalignancy and has additional value especially to distinguish differentiated VIN neoplasia from normal vulvar epithelium, but cannot explain the differences in malignant potential.
Modern Pathology (2007) **20**, 770–778; doi:10.1038/modpathol.3800796; published online 27 April 2007

Keywords: MIB1; differentiated VIN; usual VIN; lichen sclerosus; diagnostic tool; vulvar cancer

Overexpression of Wild-type p53 in Lichen Sclerosus adjacent to Human Papillomavirus-negative Vulvar Cancer

Katrina Vanin,*† James Scurry,† Heather Thorne,* Kally Yuen,‡ and Robert G. Ramsay*

*Trescowthick Research Laboratories, Peter MacCallum Cancer Institute, Melbourne, Australia; †Department of Pathology, Mercy Hospital for Women, East Melbourne, Australia; ‡Statistical Center, Peter MacCallum Cancer Institute, Melbourne, Australia

Human papillomavirus is a risk factor for vulvar cancer, whereas human papillomavirus-negative late onset vulvar carcinoma is associated with the dermatologic condition, lichen sclerosus. Human papillomavirus E6 protein targets TP53 for degradation and by inference it has been assumed that human papillomavirus-negative vulvar cancer is dependent upon the acquisition of p53 somatic mutations and subsequent allelic loss. To investigate this, TP53 expression, loss of heterozygosity, and p53 genomic sequence were examined in 29 cases of human papillomavirus-negative vulvar carcinoma with adjacent lichen sclerosus. We examined 37 cases of lichen sclerosus without vulvar carcinoma, 10 cases of nongenital lichen sclerosus, and 12 cases of normal vulvar epithelium served as controls. TP53 was evident in 72% of vulvar carcinoma, 48% in epithelium adjacent to vulvar carcinoma, but was minimal in normal samples. When lichen sclerosus cases were selected to exclude samples with absolutely no TP53 expression through probable failed antigen retrieval or homozygous p53 loss the number of epithelial cells expressing TP53 increased progressively from nongenital lichen sclerosus to lichen sclerosus without vulvar carcinoma, then to lichen sclerosus with vulvar carcinoma ($p<0.0001$). These data suggest elevated TP53 is a feature of vulvar lichen sclerosus. Seventy-four percent of vulvar carcinoma had chromosome 17p-linked loss of heterozygosity, whereas 47% of adjacent lichen sclerosus featured loss of heterozygosity, but only 31% of vulvar carcinoma had p53 mutations, a frequency less than reported previously. Seven percent of adjacent lichen sclerosus had mutations, showing for the first time the presence of an identical mutation to the matched vulvar carcinoma. These data, however, implicate p53 mutations as a later event in vulvar carcinoma and in marked contrast to the original expectation, our loss of heterozygosity data are consistent with loss of another locus (not p53) on 17p operating as a tumor suppressor in lichen sclerosus destined to develop vulvar carcinoma.
***Key words:** lichen sclerosus/loss of heterozygosity/mutation analysis/p53/tumor suppressor gene/vulvar carcinoma. J Invest Dermatol 119:1027–1033, 2002*

Single Base Instability Is Promoted Sclerosus

Ronald A. Tapp[1], Jingtao Feng[2], J. Wesley Jones[2], J. Andrew Carlson[3] and Vincent L. Wilson[1,2,4]

Single base substitution mutations in codons 248 and 273 of *TP53* and codon 12 Kirsten-*ras* (*KRAS*) are commonly found in human carcinomas. To determine whether these mutations also occur in normal and inflamed tissues from which carcinomas arise, we utilized the ultra-sensitive polymerase chain reaction/restriction endonuclease/ligase chain reaction mutation assay. Ninety samples of genital skin, including lichen sclerosus (LS) affected skin, adjacent normal and non-adjacent normal, were assayed. Mutations were detected in 103 of 349 assays and consisted of *KRAS* G34A, G34T, G35A, and *TP53* C742T, G818C, C817T, and G818A mutations. Mutant prevalence varied from 1 to 20 per 10^6 wild-type cells. Mutations occurred significantly more frequently in LS (78/224 (35%)) than adjacent normal (20/88 (23%)) and non-adjacent normal genital skin (5/38 (13%)). *KRAS* G34A mutation was relatively common to all classes of specimen, whereas *TP53* gene C742T and G818C mutations were significantly more frequent in LS than normal genital skin. In matched samples, immunohistochemistry evaluation of p53 protein expression revealed the presence of epidermal p53 clones in LS whose presence and number significantly correlated with the presence of *TP53* C742T and G818C mutations. Based on these results, it appears oncogenic point mutations occur in normal genital skin, and are selected for in LS.

Journal of Investigative Dermatology (2007) **127**, 2563-2576; doi:10.1038/sj.jid.5700889; published online 7 June 2007

rd lower than for their counterparts (white women and non-His- respectively). For women aged <50 years, the age-specific rates of vere approximately the same among whites and blacks. Increases ge 50 years, however, were noted to be more rapid among white ack women.

Distinct age-specific incidence rate patterns of invasive vulvar nd ethnicity and the higher incidence rates observed among white red with women of other races and ethnicities were opposite to for cervical cancer. Underestimations of the burden of in situ vul- re a result of the inability to examine VIN 3 in the authors' data. t of cancer registries to report and submit VIN 3 data and more ata quality will allow a thorough assessment of the impact of y providing a basis for examining the true burden and quality of erous vulvar tumors. Increased documentation of histologic sub- logy reports and in cancer registry data can help differentiate the /-associated types from non–HPV-associated types of vulvar can- **008;113(10 suppl):2865–72.** *Published 2008 by the American Can-*

lvar cancer, human papillomavirus, HPV vaccine, cancer registries.

overnment work and, as main in the United States

Received April 14, 2008; revision received May 7, 2008; accepted May 22, 2008.

Eventually, that concept has resulted in studies concerning mechanisms of carcinogenesis, and if one looks for findings destined to support a preconceived concept, one is likely to find something, be it enhanced proliferation, p53 expression, or single base instability. These are self-fulfilling prophecies.

European Journal of Cancer Prevention 1995, 4, 491–495

Squamous cell carcinoma arising in vulval lichen sclerosus: a longitudinal cohort study

P Carli[1], A Cattaneo[1], A De Magnis[1], A Biggeri[2], G Taddei[3], B Giannotti[3]

Histological changes of lichen sclerosus (LS)—a chronic inflammatory disease—are frequently found in association with squamous cell carcinoma (SCC) of the vulva, suggesting that women with this disorder are at increased risk. However, follow-up studies have been less convincing, showing that the vast majority of these patients do not go on to develop cancer. In this study, a series of 211 women affected by histologically demonstrated vulval LS were treated with topical therapy (testosterone, clobetasol) and followed prospectively by repetitive vulval examination. Three patients developed SCC of the vulva (two invasive, one *in situ*) at the sites affected by LS during an average follow-up period of 1 year and 8 months. Compared with the reference population, the number of cases of invasive SCC detected significantly exceeded the number estimated to occur in a comparable age-matched group. The standardized incidence rate of vulval SCC in the LS cohort was 317 (95% CI 35.7–1146.2). Cumulative risk was 14.8% (0.06% in the general female population), with a relative risk of 246.6. In conclusion, these data support the view that LS is a precursor of SCC, although characterized by slight tendency to evolve to carcinoma. Medical treatment of LS, although useful in the control of severity of disease, did not seem to be able to prevent the evolution to malignancy.

Another consequence of the firm belief in the malignant potential of lichen sclerosus is an amazingly uncritical attitude concerning statistical data. Take this *"longitudinal cohort study"* about *"squamous cell carcinoma arising in vulvar lichen sclerosus."*

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The *"cumulative risk"* in the lichen sclerosus cohort was calculated to be 14.8% versus 0.06% in the general population, *"with the relative risk being 246.6."* Those are impressive numbers,

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but they were based on detection of only three carcinomas, two invasive and one in-situ. Because no pictures were shown, the legitimacy of diagnoses cannot be assessed, but the authors remarked that one of the patients, more than a decade before,

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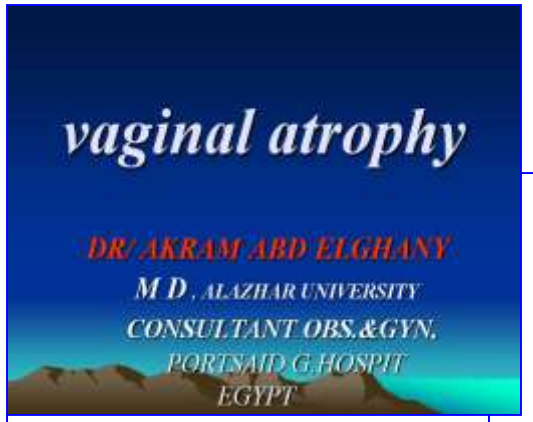
"had been affected … by cervical carcinoma, which had been treated with hysterectomy and radiotherapy." Obviously, that clinical history prohibits inclusion of the patient in a study concerning risk of malignancy in lichen sclerosus, and without this patient, those data, calculated up to the first number behind the decimal point, would already have been much different. Nonetheless, despite its weaknesses, this paper is one of the most frequently cited studies concerning the malignant potential of lichen sclerosus.



The British Association for the Study of Vulval Disease

ISSVD 1970

Arizona Vulva Clinic

ANZ Vulvovaginal Society

ISSVD 1970

The International Society for the Study of Vulvovaginal Disease

Global Thinking for Women's Wellness

Yet another factor contributing to the perception of lichen sclerosus as a premalignant disease, and one not to be underestimated, is self-promotion by physicians and medical societies. Nothing is worse for a medical society than a disease without serious consequences,

but as soon as “cancer” is invoked, one is on war, and “war” means public funding. This applies to all aspects of society.

For example, if you tell the public that you are engaged in the defense against squirrels, you will not earn much attention. If you insist that those squirrels are not harmless rodents

but dangerous predators,

maybe even with ties to the mafia, you may raise concern and get support.

Lichen sclerosus

This is also true for the defense against lichen sclerosus. Accordingly, the risk is emphasized.

GENERAL GYNECOLOGY

Guidelines for the follow-up of women with vulvar lichen sclerosus in specialist clinics

Ronald W. Jones, FRCOG; James Scurry, FRCPA; Sallie Neill, FRCP; Allan B. MacLean, FRCOG

There is no consensus with respect to the follow-up of women with vulvar lichen sclerosus (LS). The overall efficacy of modern therapy, the inconvenience of "routine" clinic visits, and the increasing burden of health care costs support the establishment of guidelines for the follow-up of women with vulvar LS by specialists. We define a specialist in this context as a consultant dermatologist or gynecologist (and outside the United States, a genitourinary physician) who has had additional and dedicated training in managing vulvar disease; a specialist clinic is provided by 1 or more of the above in a dedicated setting.

LS is a non-neoplastic chronic lymphocyte-mediated inflammatory dermatosis with distinctive dermal sclerosis and with a predilection for the anogenital skin in women. The true prevalence is not known. One study suggests that 1 in 30 elderly women have LS.[1]

It is recommended that women with vulvar lichen sclerosus be followed in specialist clinics where difficulty exists with symptom control or where there is clinical evidence of localized skin thickening. Follow-up is also recommended for women who have previously been treated for squamous cell carcinoma of the vulva (arising in lichen sclerosus or vulvar intraepithelial neoplasia) or where the pathologist expresses concern and is unable to make a definitive diagnosis of differentiated vulvar intraepithelial neoplasia.

Key words: cancer risk, specialist clinics, vulvar lichen sclerosus

Cite this article as: Jones RW, Scurry J, Neill S, et al. Guidelines for the follow-up of women with vulvar lichen sclerosus in specialist clinics. Am J Obstet Gynecol 2008;198:496.e1-496.e3.

An association between LS and squamous cell cancer of the vulva (SCCV) has long been recognized and thought to be the result of chronic inflammation and scarring. Much of the available evidence of the relationship between LS and SCCV is based on historical studies and retrospective case-series. Risk has never

CLINICAL
Symptoms

The introduction of potent topical steroids has revolutionized the management of LS, resulting in straightforward symptom control/maintenance therapy for the majority of women—and specialist follow-up is usually not warranted. Guidelines for the management of LS are available.[3] These women should regu-

In the current ISSDV *"guidelines for the follow-up of women with vulvar lichen sclerosus in specialist clinics,"* the warning is uttered

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that *"vulvar cancer can arise with surprising rapidity in women with LS … Where cancer risk exists, women should be followed at least every 3-6 months."*

Differentiated vulvar intraepithelial neoplasia is often found in lesions, previously diagnosed as lichen sclerosus, which have progressed to vulvar squamous cell carcinoma

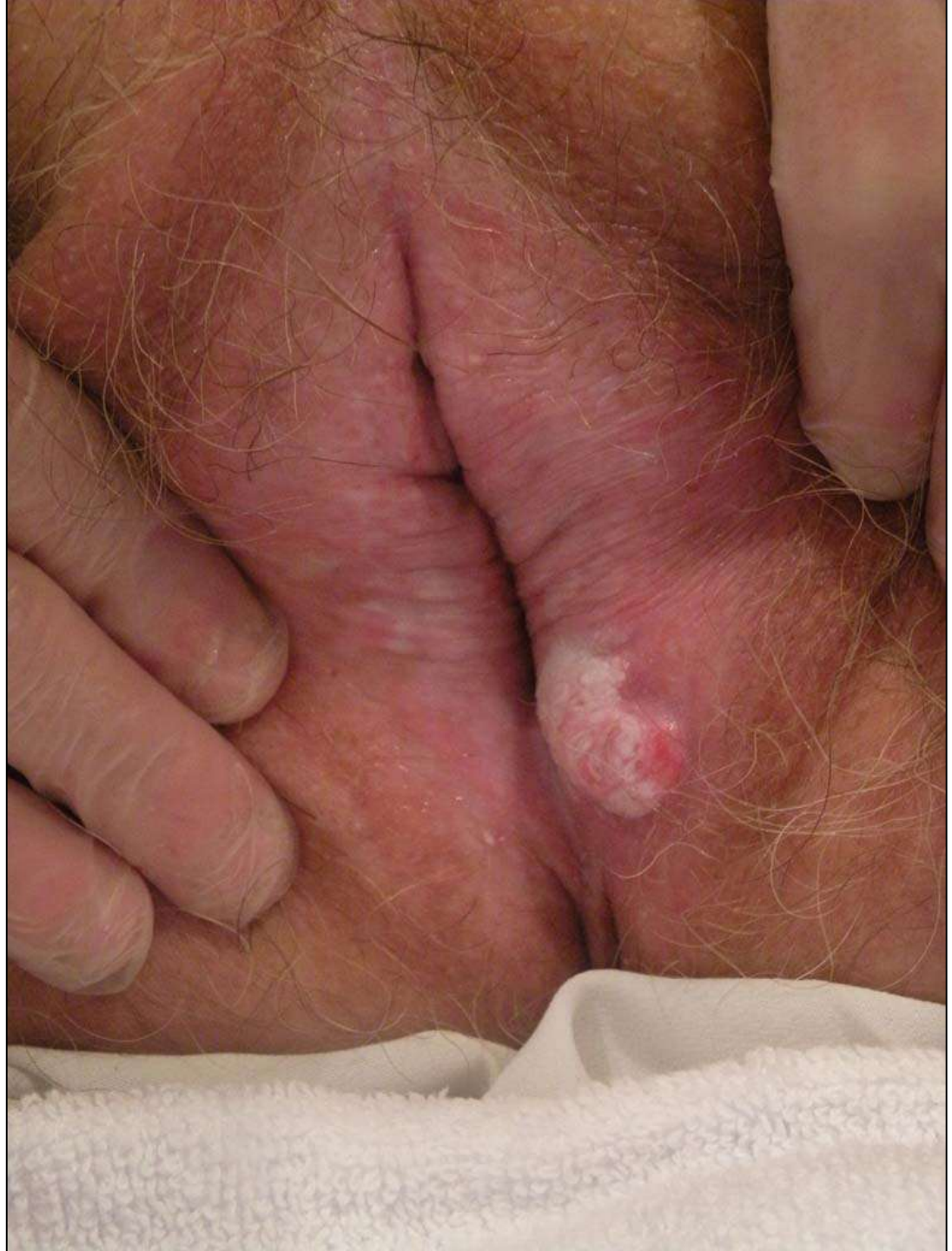
Hedwig P van de Nieuwenhof[1], Johan Bulten[2], Harrie Hollema[3], Rianne G Dommerholt[4], Leon FAG Massuger[1], Ate GJ van der Zee[5], Joanne A de Hullu[1] and Leon CLT van Kempen[2]

[1]Department of Obstetrics and Gynecology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [2]Department of Pathology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [3]Department of Pathology, University Medical Centre Groningen, Groningen, The Netherlands; [4]Department of Obstetrics and Gynecology, Jeroen Bosch Hospital, 's Hertogenbosch, The Netherlands and [5]Department of Obstetrics and Gynecology, University Medical Centre Groningen, Groningen, The Netherlands

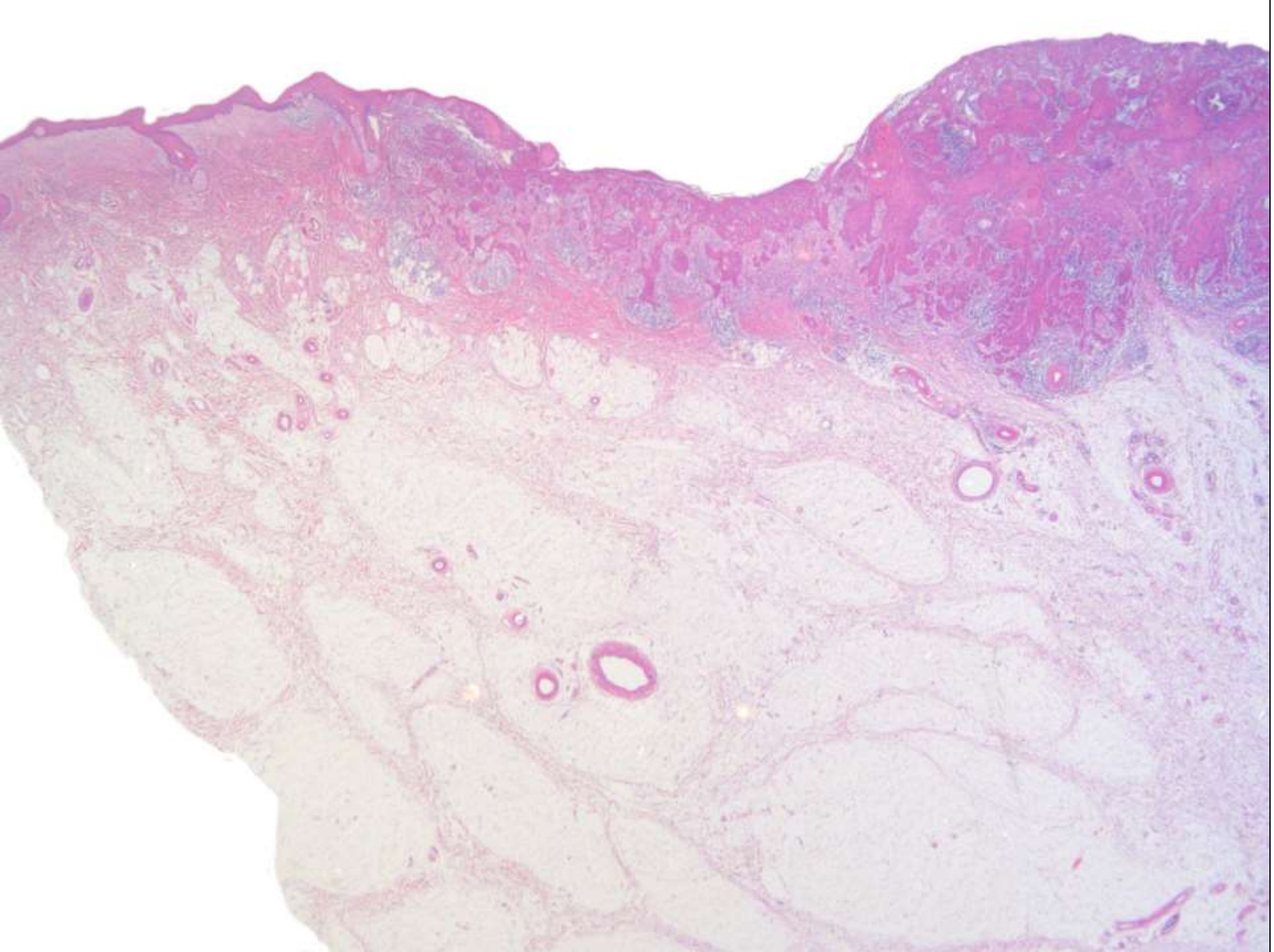
Lichen sclerosus is considered to be the precursor lesion of vulvar squamous cell carcinoma, of which only 2–5% progress to squamous cell carcinoma. Differentiated vulvar intraepithelial neoplasia (VIN) has been proposed to be the direct precursor lesion, but this is a recently recognized, and a difficult to diagnose, entity, which may easily be mistaken for a benign dermatosis. The aim of this study was to test the hypothesis that of all lesions that have been diagnosed as lichen sclerosus in the past, a part might currently be diagnosed as differentiated VIN, and to identify histopathological differences between lichen sclerosus lesions with and without progression to vulvar squamous cell carcinoma. All lichen sclerosus slides were revised by two expert gynecopathologists and histopathological characteristics were documented. After revision of lichen sclerosus biopsies without progression ($n=61$), 58 were reclassified as lichen sclerosus. Revision of lichen sclerosus biopsies with progression yielded concordant diagnoses in 18 of 60 cases (30%). Of 60 lesions, 25 (42%) were reclassified as differentiated VIN. The median time from differentiated VIN to vulvar squamous cell carcinoma was shorter (28 months) than that from lichen sclerosus to vulvar squamous cell carcinoma (84 months) ($P<0.001$). Lichen sclerosus that progressed to squamous cell carcinoma, but did not meet the criteria for differentiated VIN, more often showed parakeratosis ($P=0.004$), dyskeratosis ($P<0.001$), hyperplasia ($P=0.048$) and basal cellular atypia ($P=0.009$) compared with lichen sclerosus without progression. In conclusion, differentiated VIN diagnosis has been frequently missed and is associated with rapid progression to squamous cell carcinoma. Patients with lichen sclerosus with dyskeratosis and parakeratosis, hyperplasia and/or basal cellular atypia should be kept under close surveillance as these lesions also tend to progress to squamous cell carcinoma.

Modern Pathology (2011) **24,** 297–305; doi:10.1038/modpathol.2010.192; published online 5 November 2010

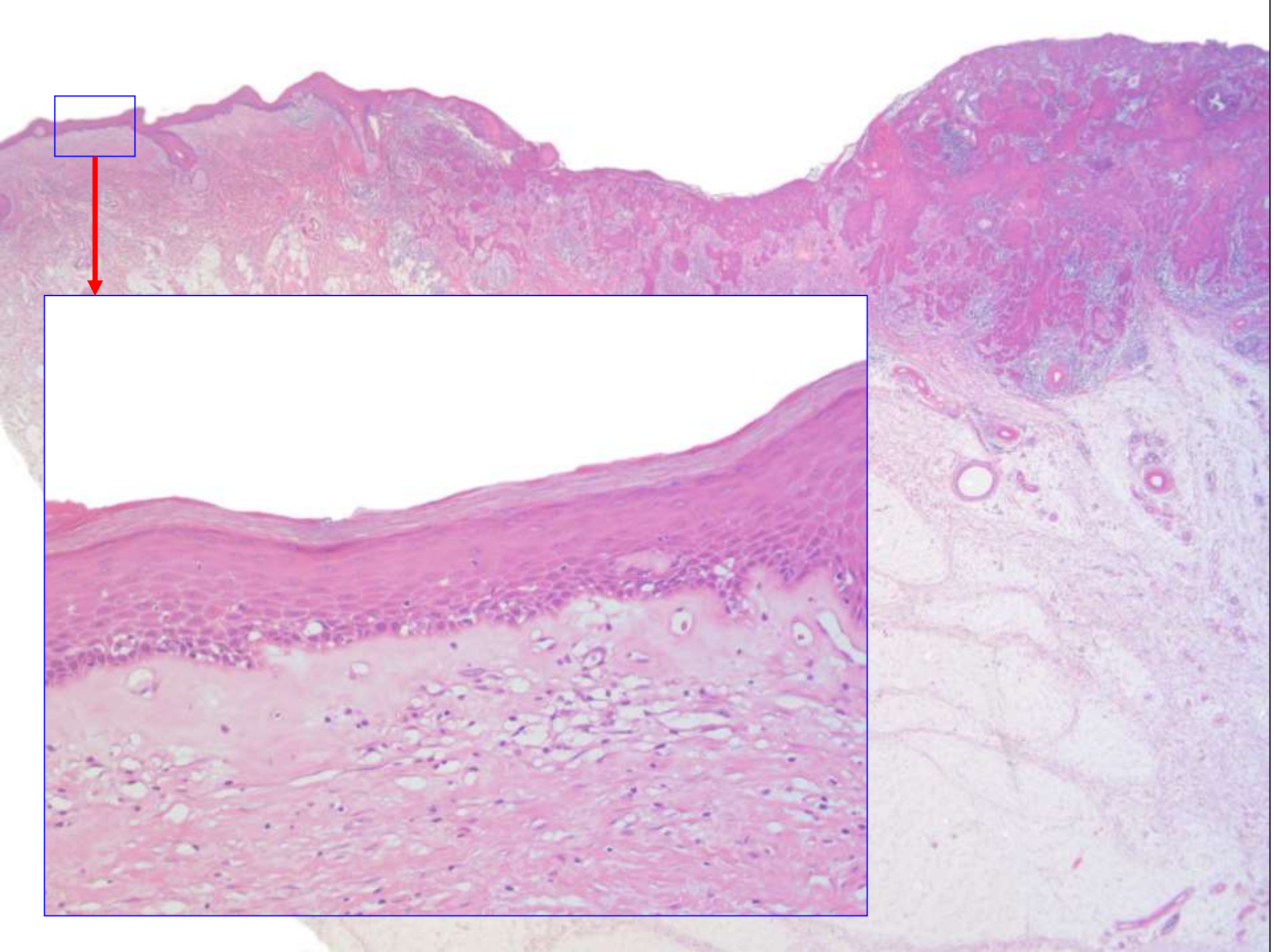
Cancer risk is said to exist especially in hypertrophic lesions: *"Patients with lichen sclerosus with dyskeratosis and parakeratosis, hyperplasia and/or basal cellular atypia should be kept under close surveillance as these lesions also tend to progress to squamous cell carcinoma."*



Admittedly, it is wise to be careful, and squamous cell carcinomas may develop in lesions of lichen sclerosus.



Maybe this is co-incidence, maybe it is caused by independent carcinogenic factors, such as previous radiation therapy or carcinogenic human papilloma viruses.



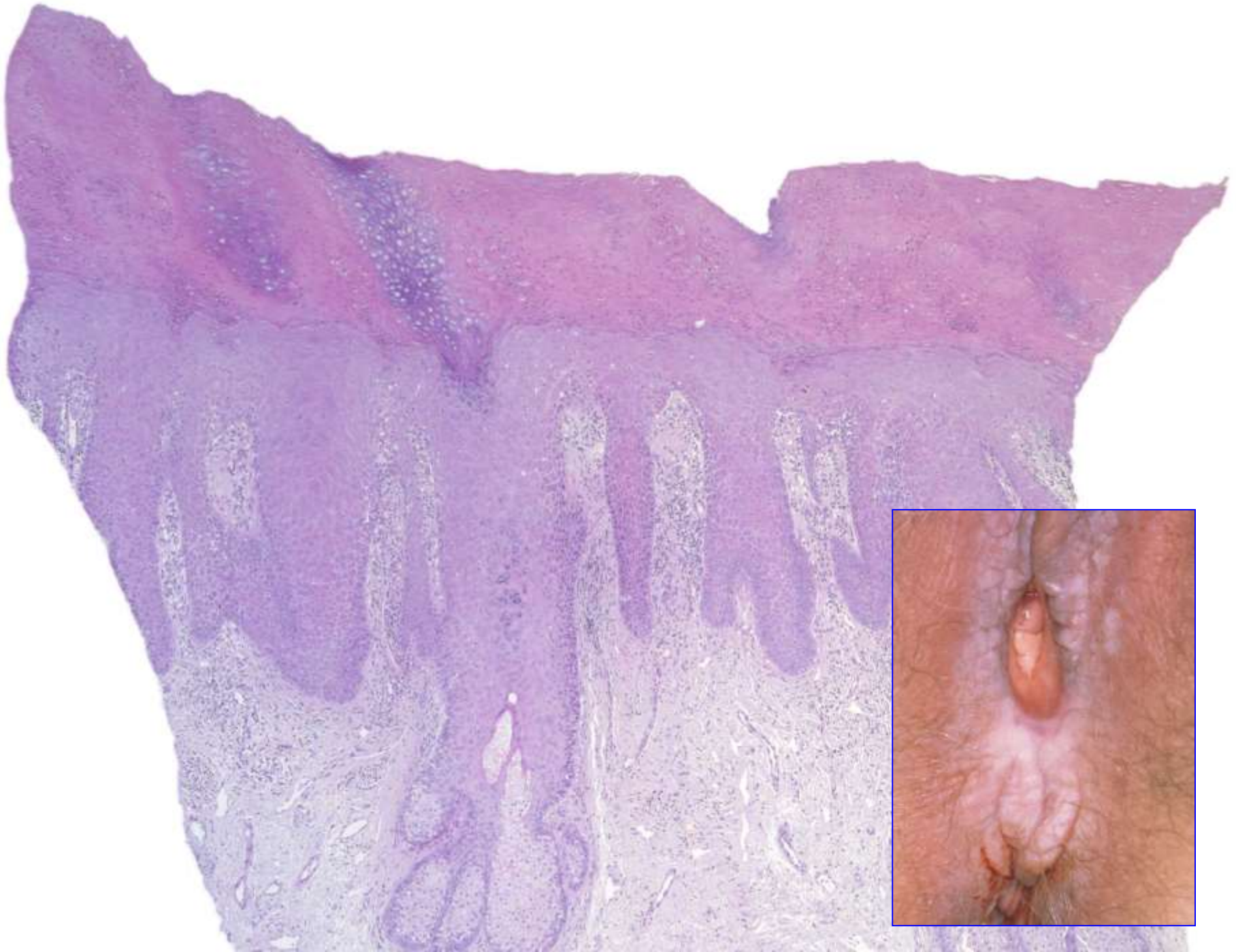
Maybe chronic inflammation and sclerosis really have some carcinogenic potential. If this is the case, it is minimal because the association is so rare. Maybe the existing risk can be reduced slightly by close surveillance, but excessive care bears risks of its own.

For example, the white danger in the mountains are avalanches, and if one gets into one,

presence of an avalanche rescue dog can be life saving.

However, when queing at a ski lift, the risk of being struck by an avalanche is minimal, and if, for purposes of safety,

every skier was accompanied by a rescue dog, crowding on the slopes with the increased risk of accidents would outweigh by far any potential benefits.



The same is true for lichen sclerosus. When women with lichen sclerosus are controlled regularly and subjected to biopsies every three to six months, it is only a question of time until some pathologist

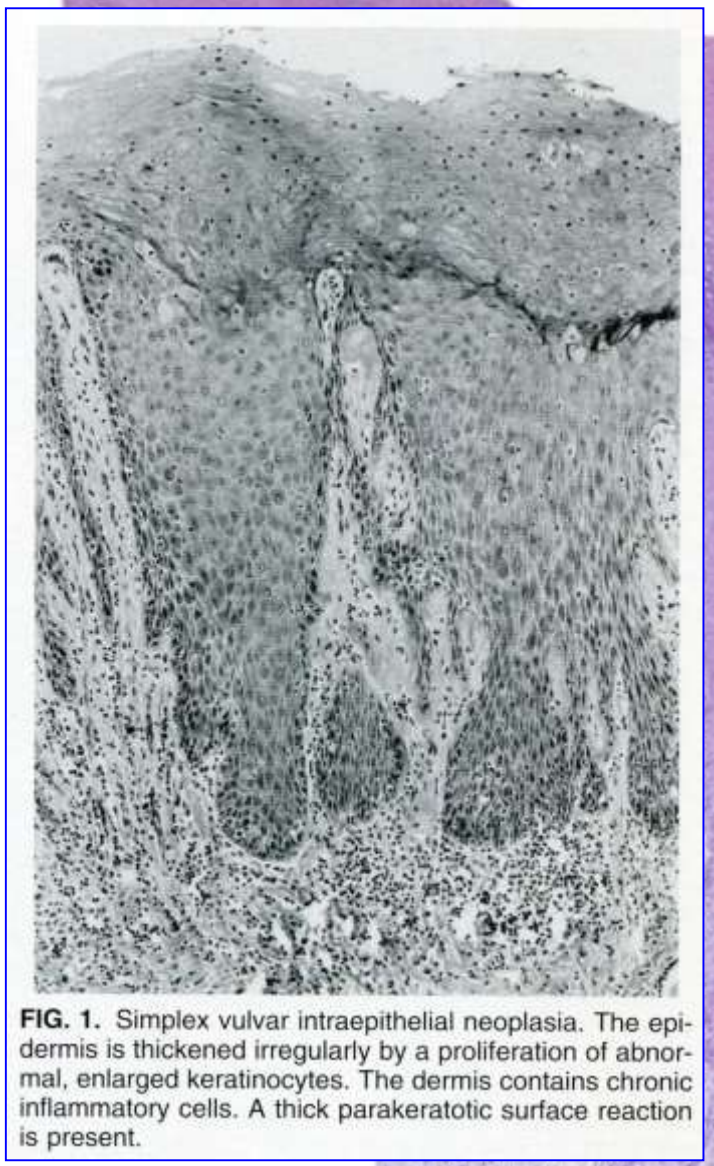
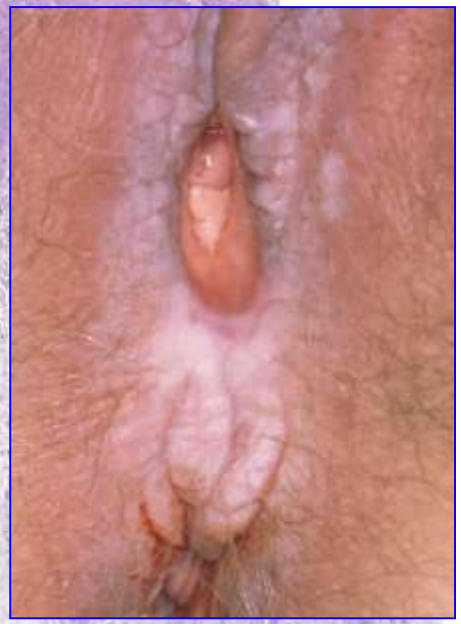


FIG. 1. Simplex vulvar intraepithelial neoplasia. The epidermis is thickened irregularly by a proliferation of abnormal, enlarged keratinocytes. The dermis contains chronic inflammatory cells. A thick parakeratotic surface reaction is present.



will give the diagnosis of *"simplex or differentiated vulvar intraepithelial neoplasia"* because of minimal cytologic variation and some mitotic figures.

GENERAL GYNECOLOGY

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not known. One study suggests that 1 in 30 elderly women have LS.[1]

An association between LS and squa-

Clinical

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Differentiated VIN requires excision.

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According to current guidelines of the International Society for the Study of Vulvovaginal Disease, *"differentiated VIN requires excision."* Hence, there is a great chance that an inflammatory skin disease will end up to be treated surgically, surely not to the advantage of the patient.

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It is time, therefore, to remind of the fact that vampire squirrels are a fiction.