Lichen sclerosus - histopathologic findings and risk factors for malignancy

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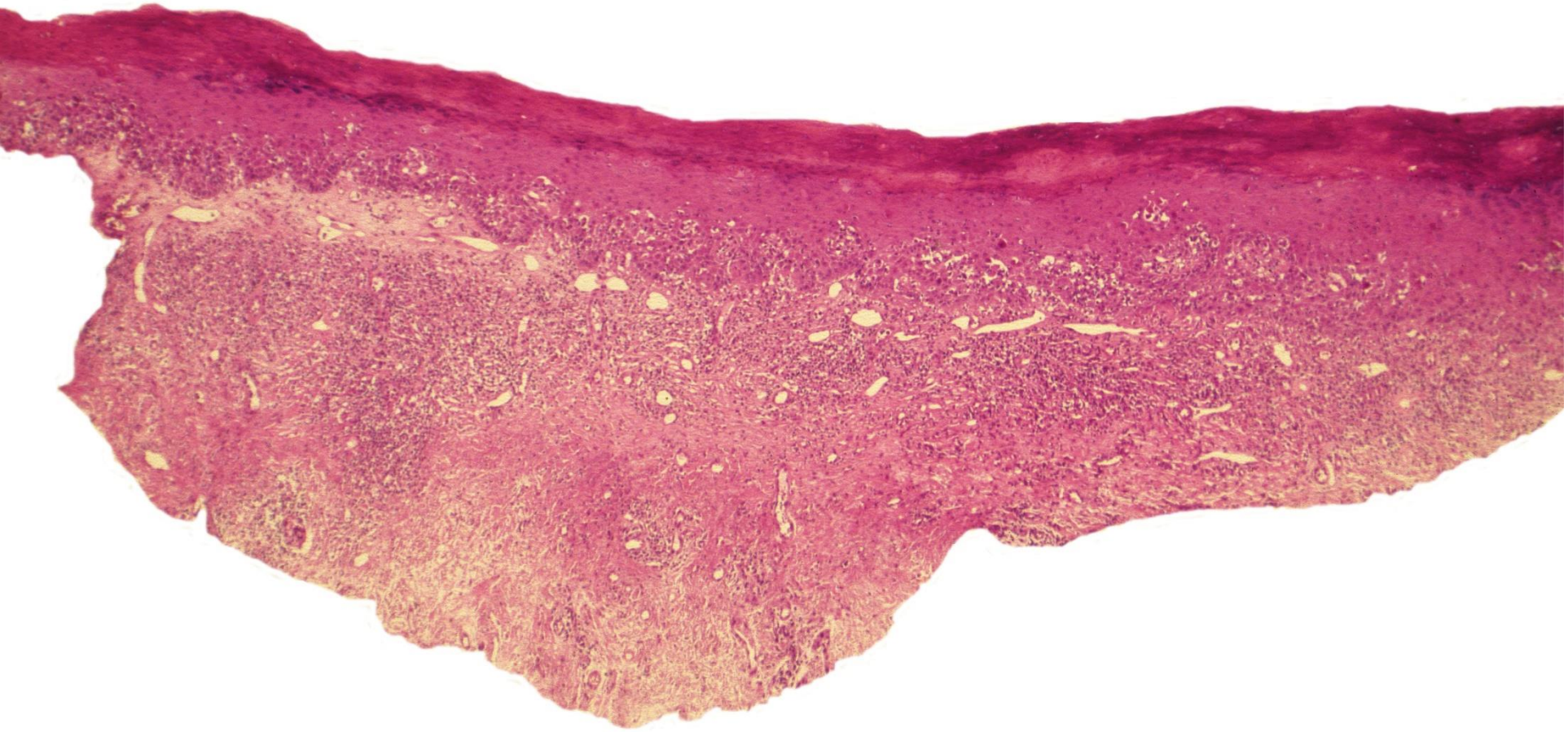
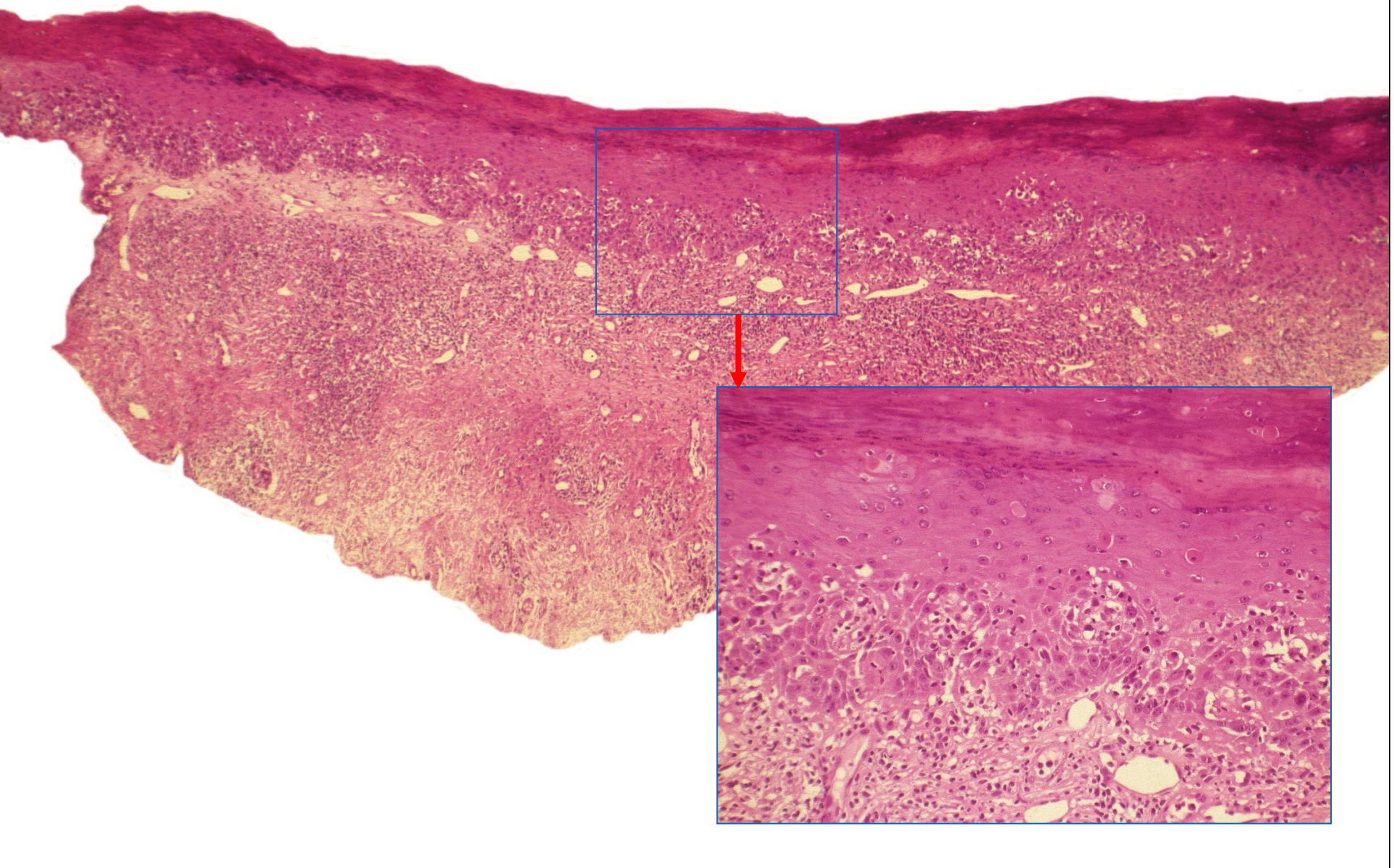
Lichen sclerosus is seldom addressed at meetings of dermatopathology, the reason being that diagnosis can usually be made at a glance and does not require more effort than the diagnosis of molluscum. However, there are always exceptions, and in lichen sclerosus, they are not uncommon. If the tell-tale sign of subepidermal sclerosis is missing,

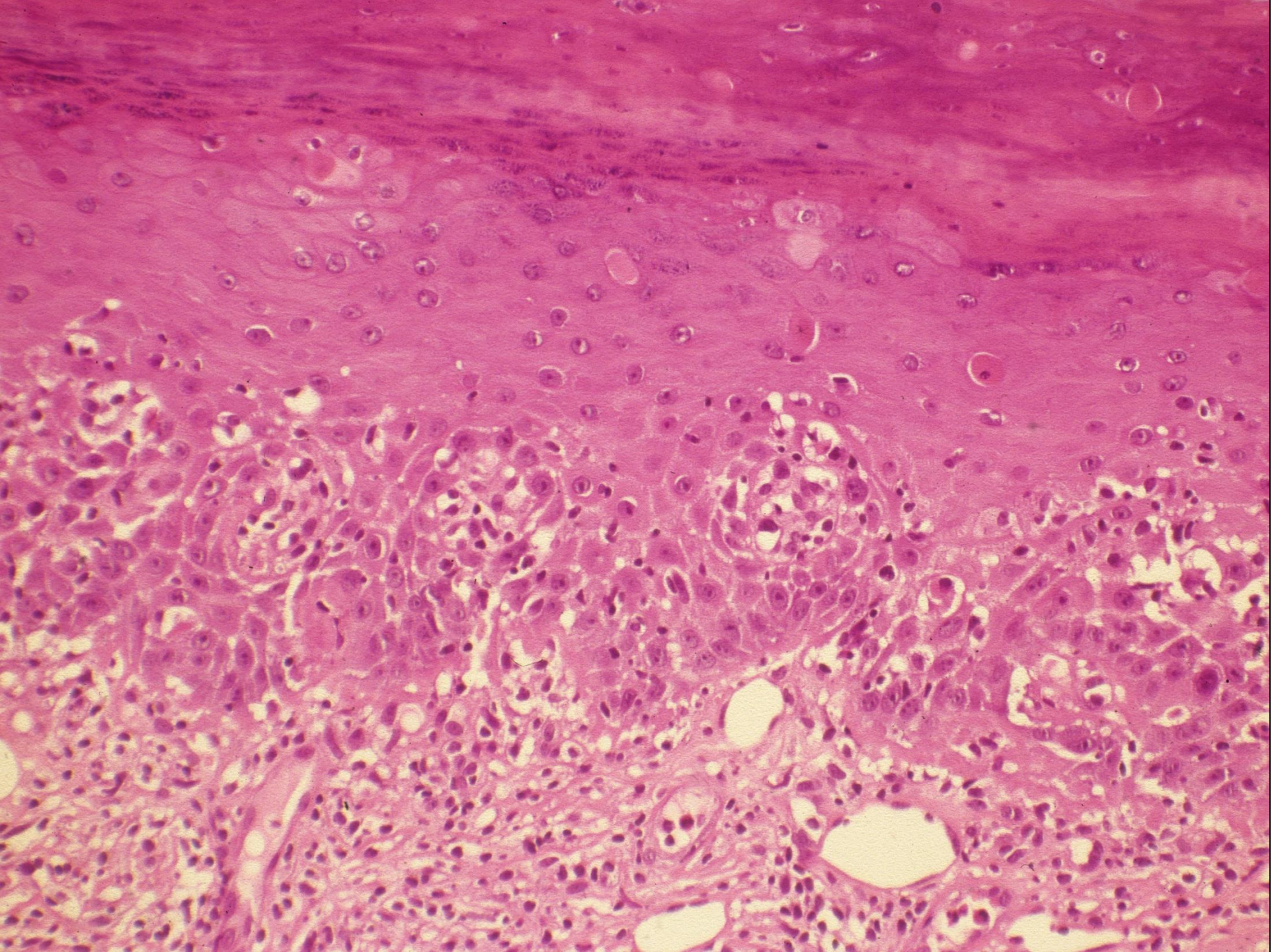


diagnosis become more challenging.

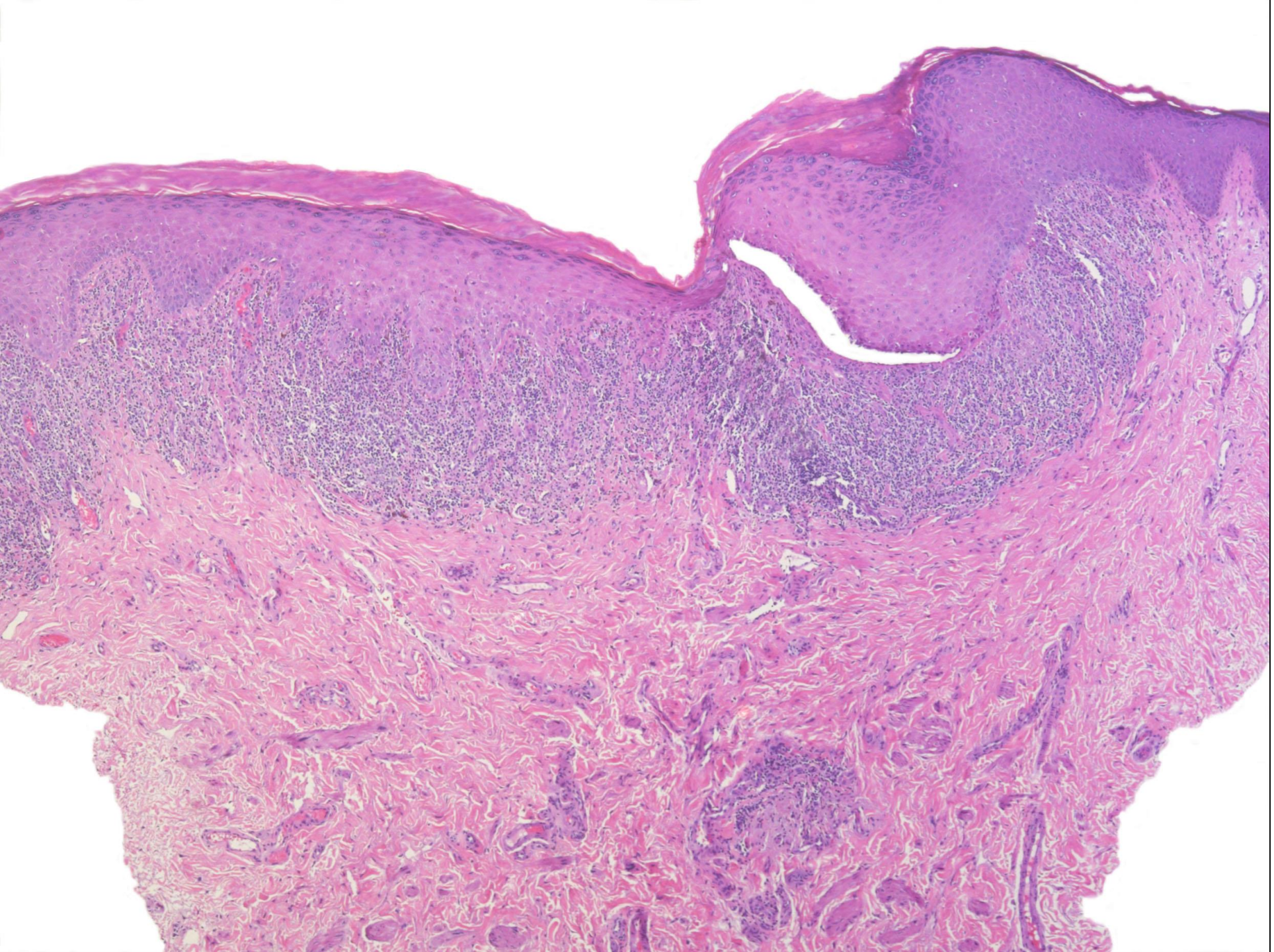
This is an example of a specimen showing both, areas with and without subepidermal sclerosis.
On the left, the diagnosis is straight forward, but on the right , there is only epithelial hyperplasia



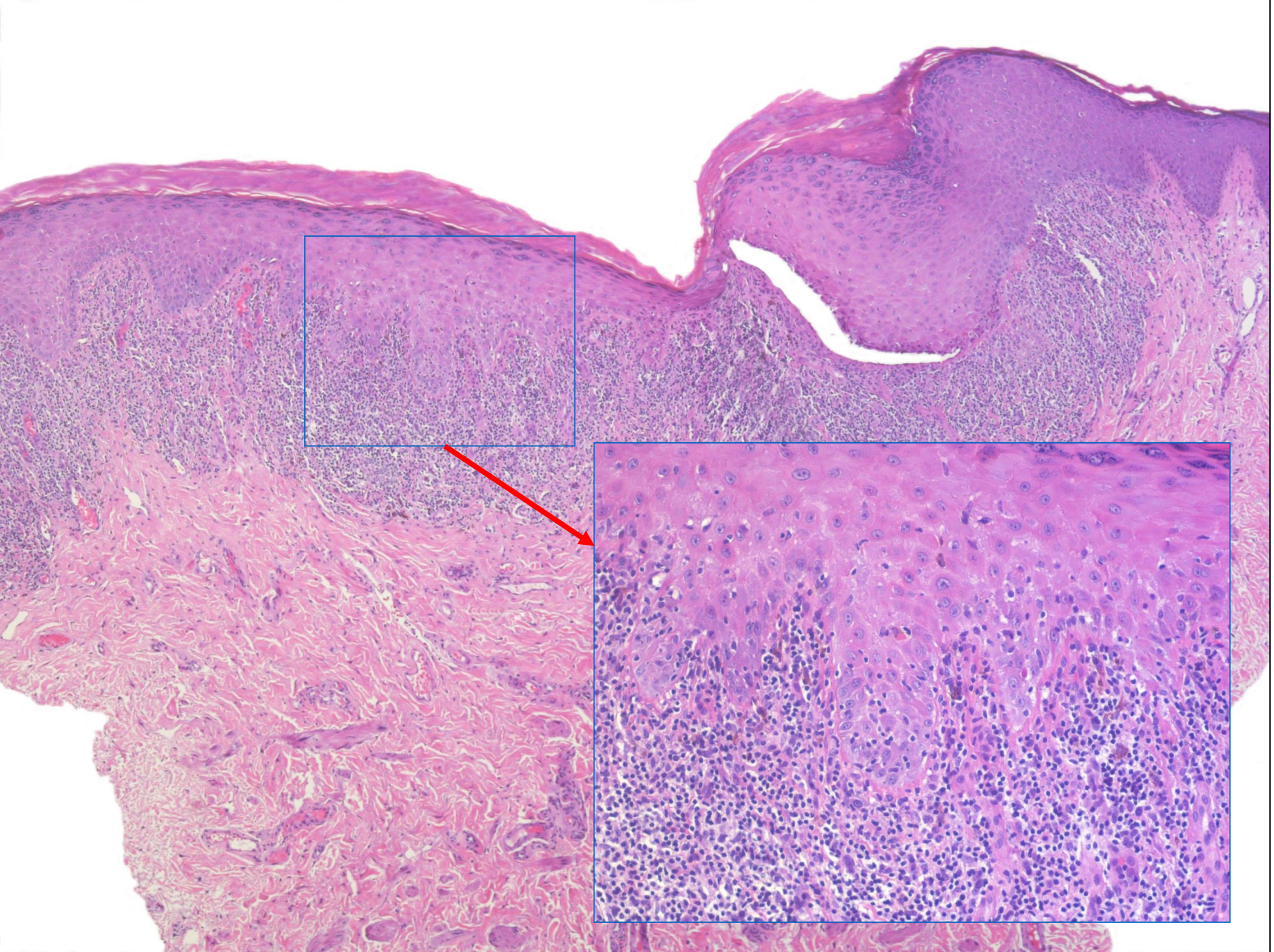
with wedge-shaped zones of hypergranulosis, compact orthokeratosis, a lichenoid infiltrate of lymphocytes, vacuolar changes at the junction, and necrotic keratocytes, i.e., changes reminiscent of lichen planus.



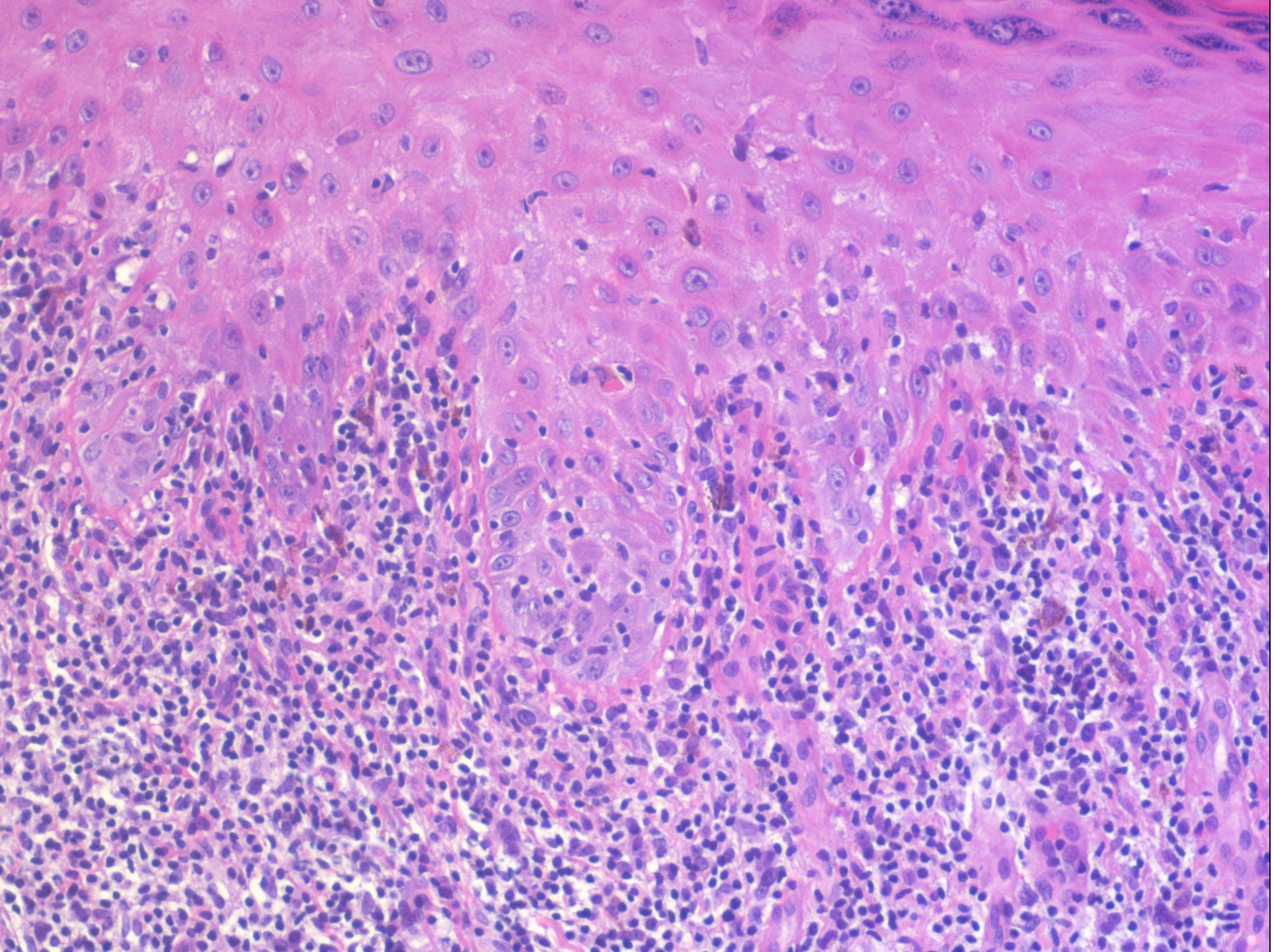
Findings militating against lichen planus are psoriasiform rete ridges and the presence of necrotic keratocytes not only at the junction, but in all reaches of the epidermis.



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 that differential diagnosis has prompted Fung and LeBoit to 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."

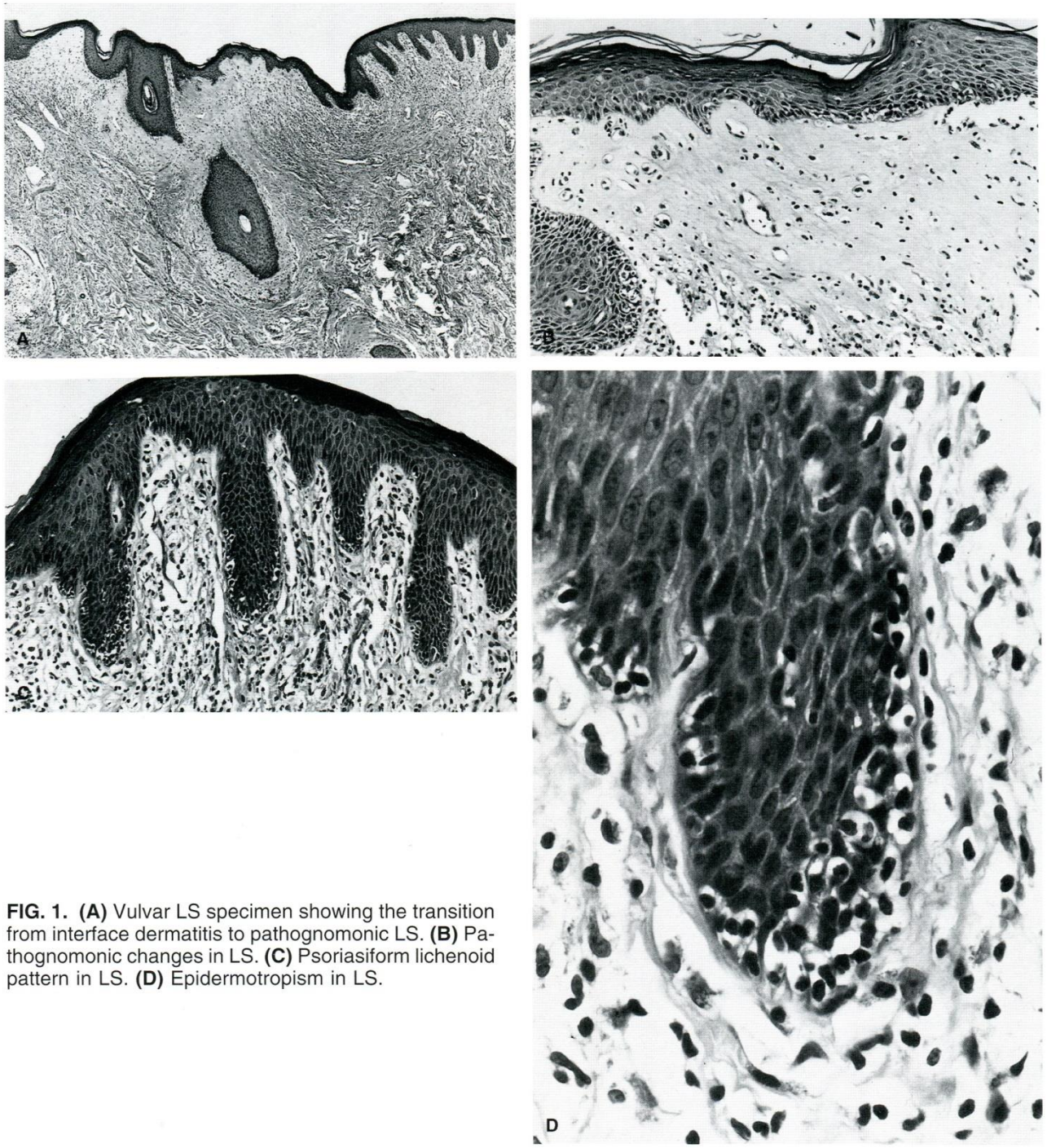
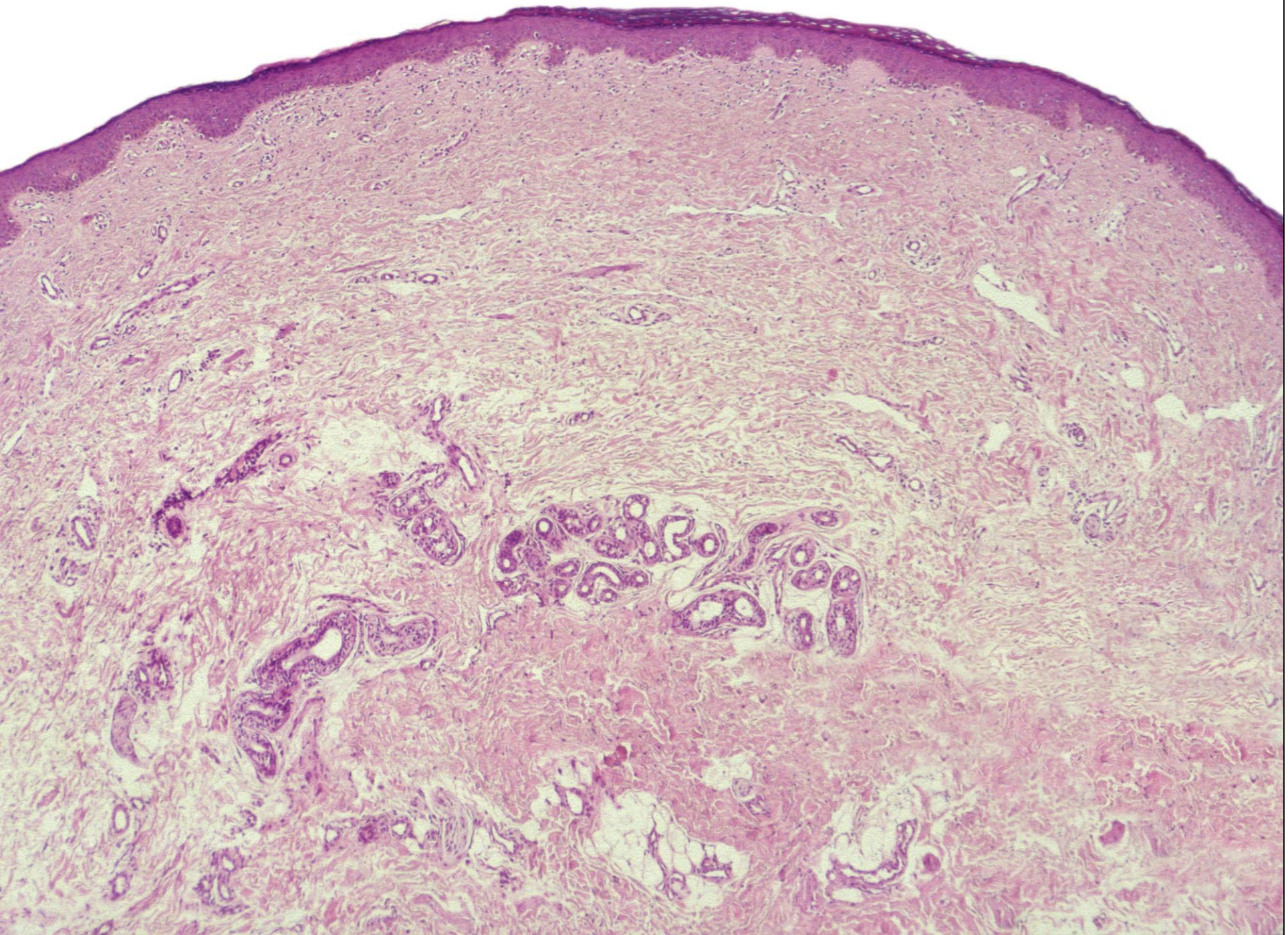
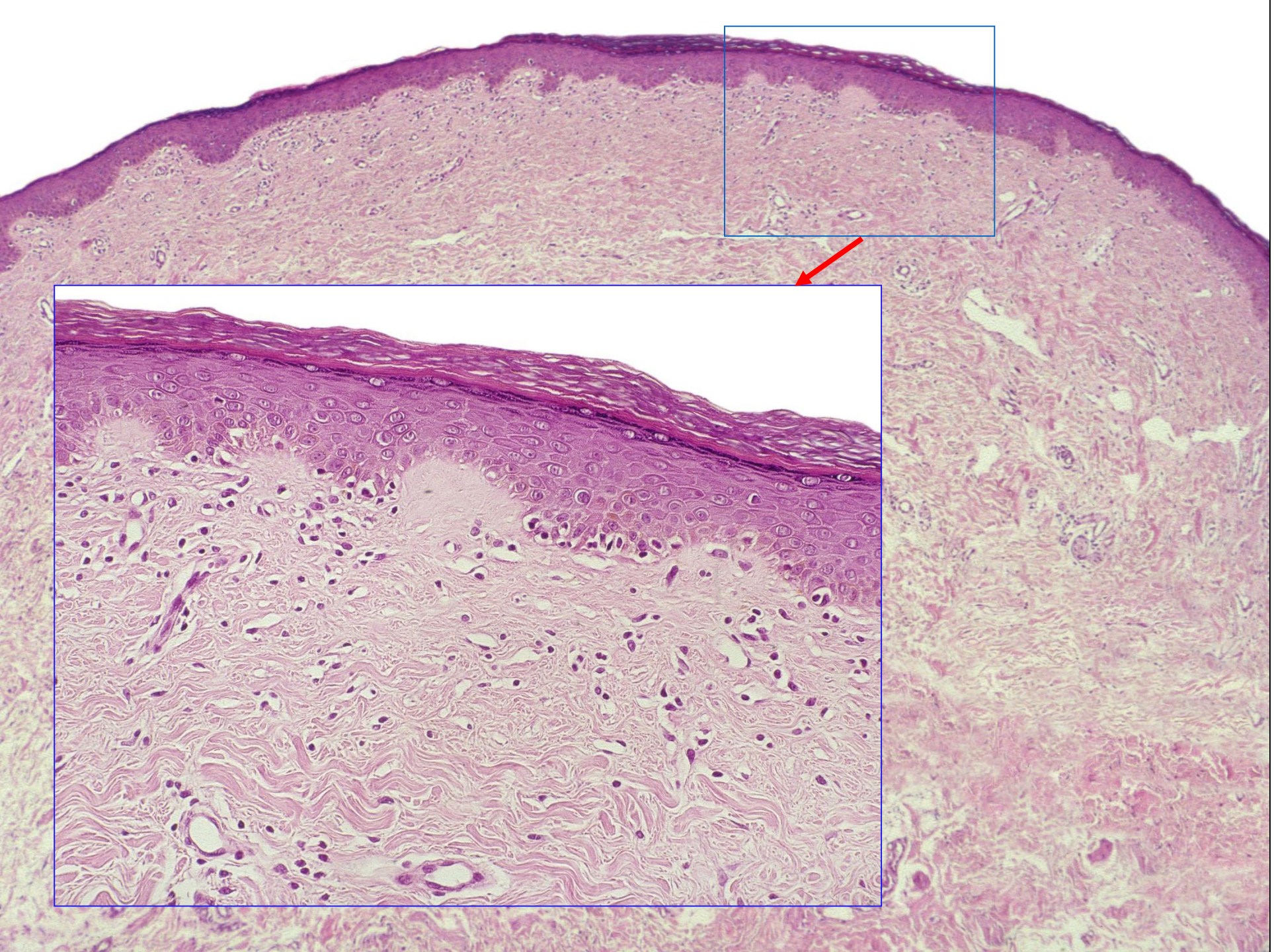


FIG. 1. **(A)** Vulvar LS specimen showing the transition from interface dermatitis to pathognomonic LS. **(B)** Pathognomonic changes in LS. **(C)** Psoriasiform lichenoid pattern in LS. **(D)** Epidermotropism in LS.

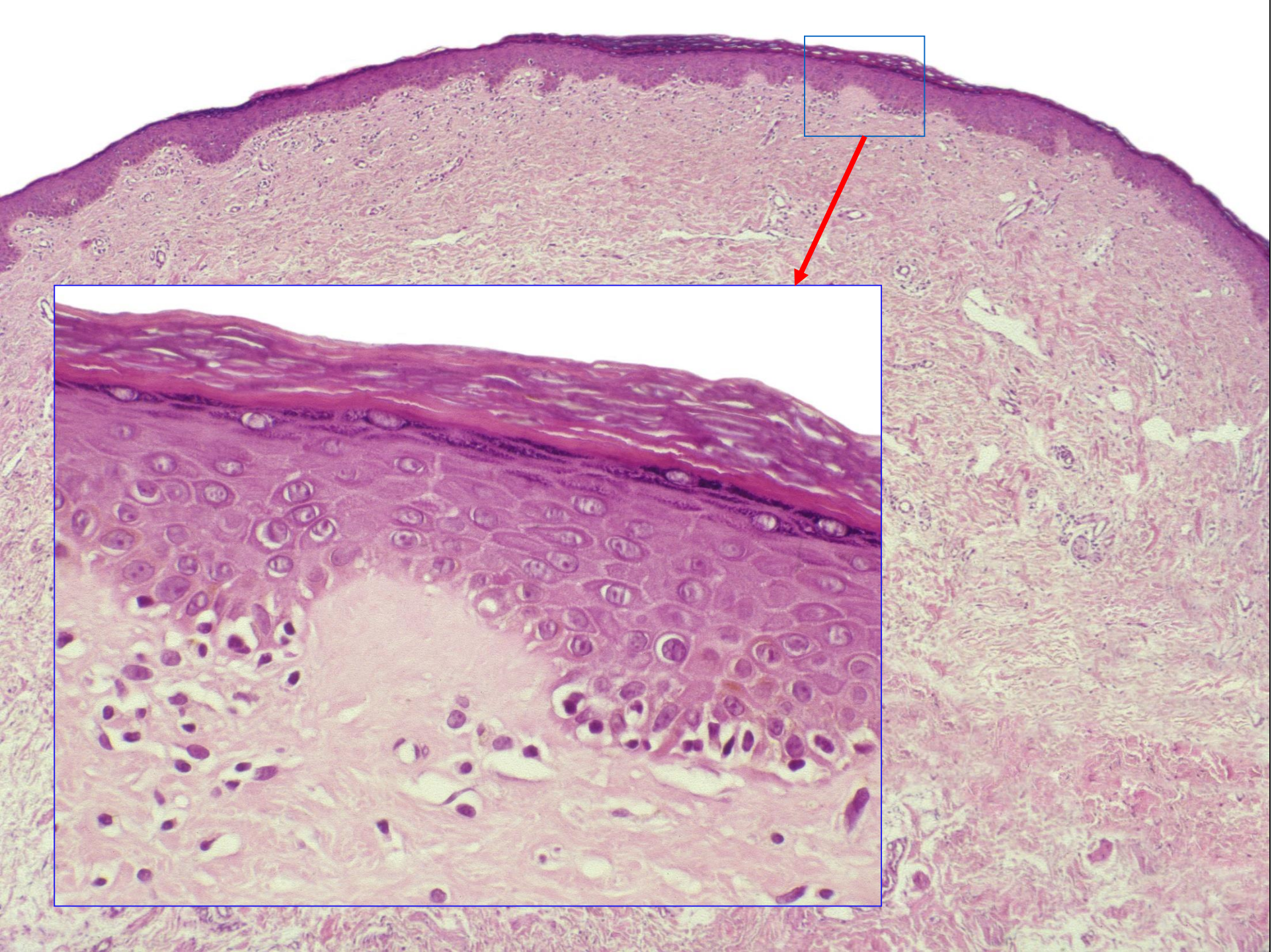
This is what Fung and LeBoit saw: a psoriasiform hyperplasia of the epidermis with many lymphocytes in elongated rete ridges in concert with only scant spongiosis. Those features facilitate distinction of lichen sclerosus from lichen planus but are criteria also of mycosis fungoides.



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

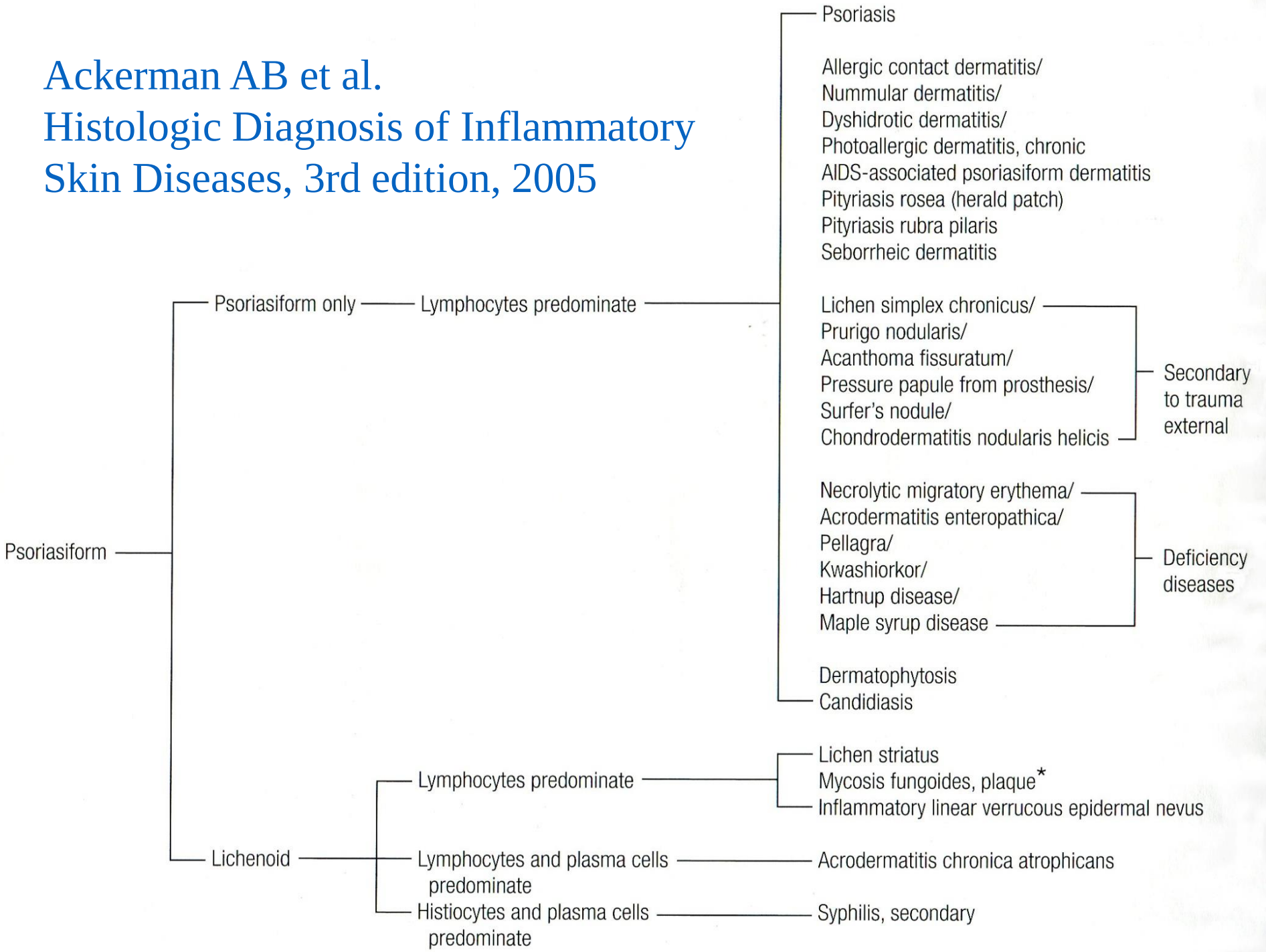
In every case histopathologic examination of the biopsy specimen was performed on sections of tissue stained with hematoxylin and eosin. Molecular analysis of the T-cell receptor-γ (TCR-γ) gene rearrangement was performed in all cases with a standard PCR technique described previously.[11]

RESULTS

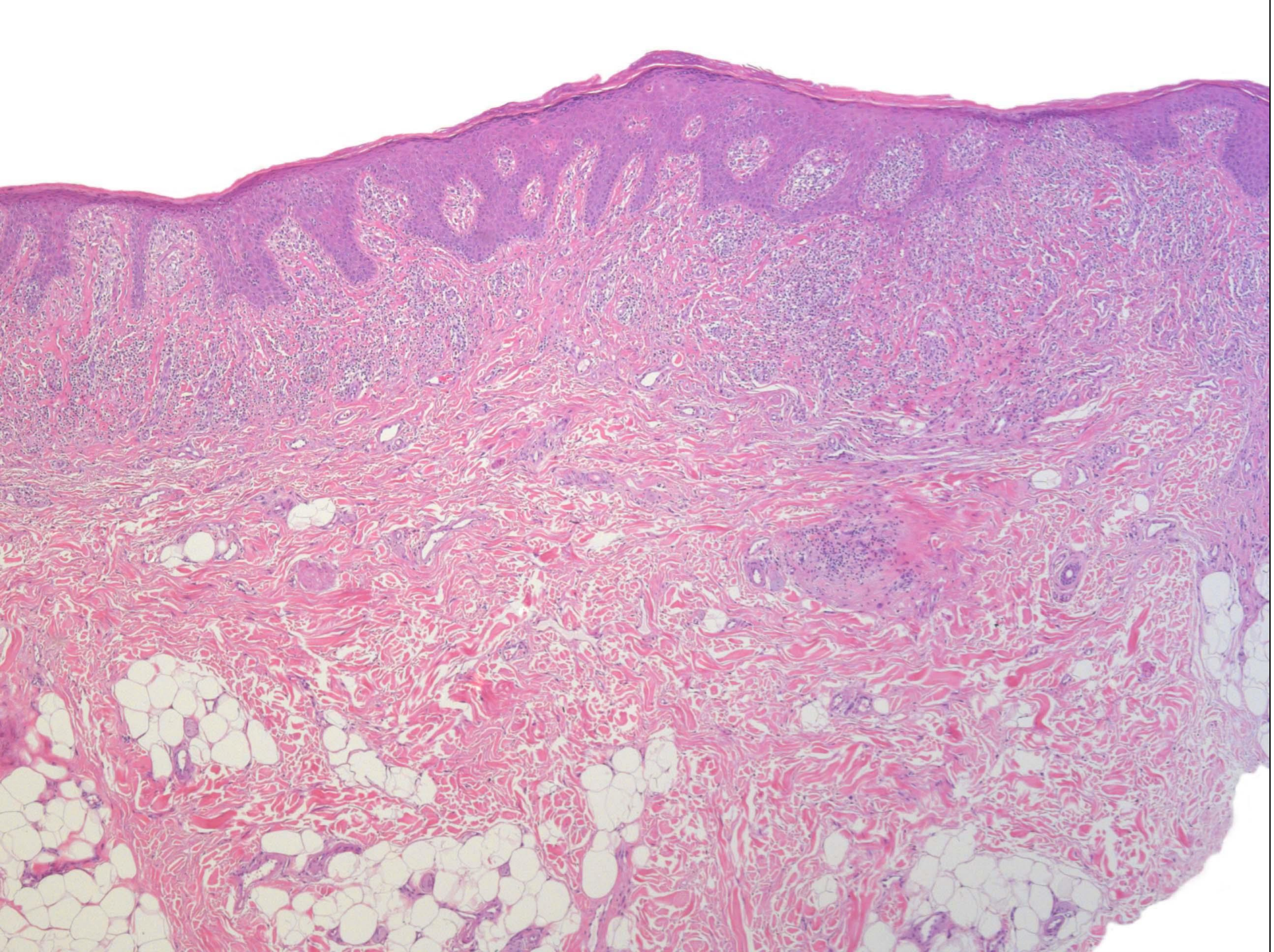
All patients had lesions clinically diagnostic of LS characterized by itching, atrophic, partly whitish, partly erythematous patches. In 6 patients the lesions were located on the

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

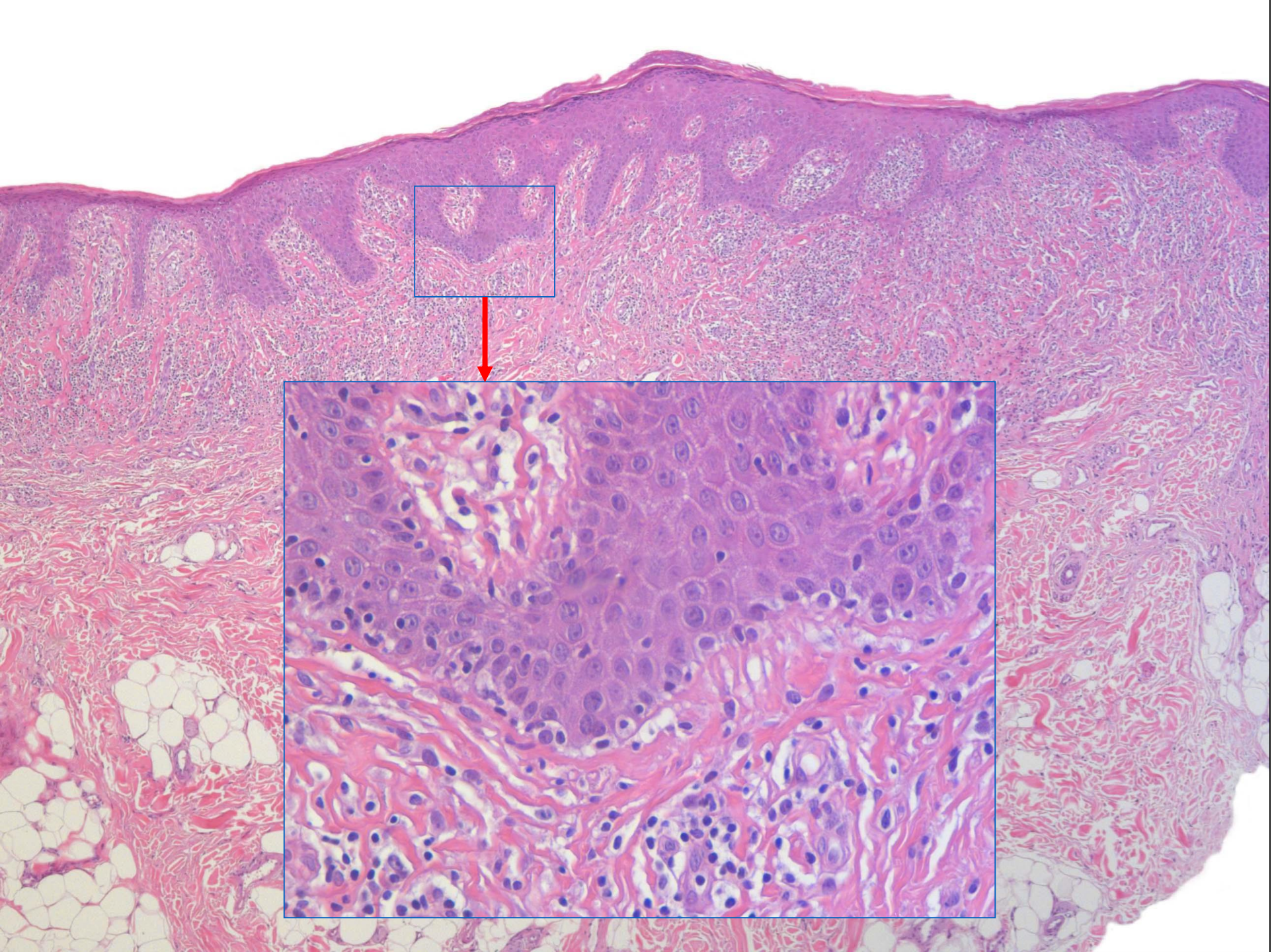
Ackerman AB et al. Histologic Diagnosis of Inflammatory Skin Diseases, 3rd edition, 2005



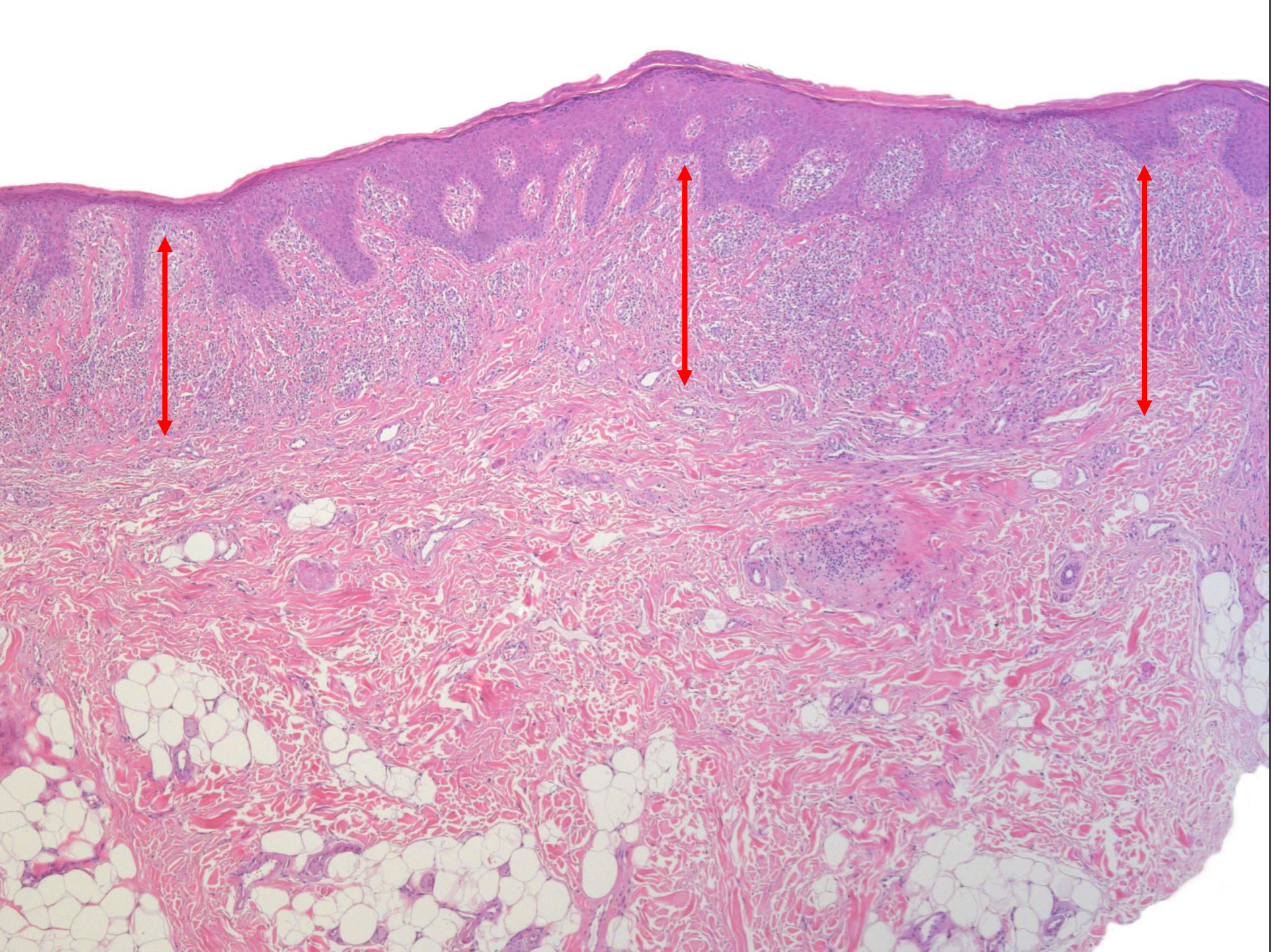
If one studies the 3rd edition of Ackerman's book, "Histologic Diagnosis of Inflammatory Skin Diseases," and looks for the pattern of psoriasiform lichenoid dermatitis with predominance of lymphocytes, only lichen striatus, mycosis fungodies, and ILVEN are mentioned. That pattern, however, is also common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



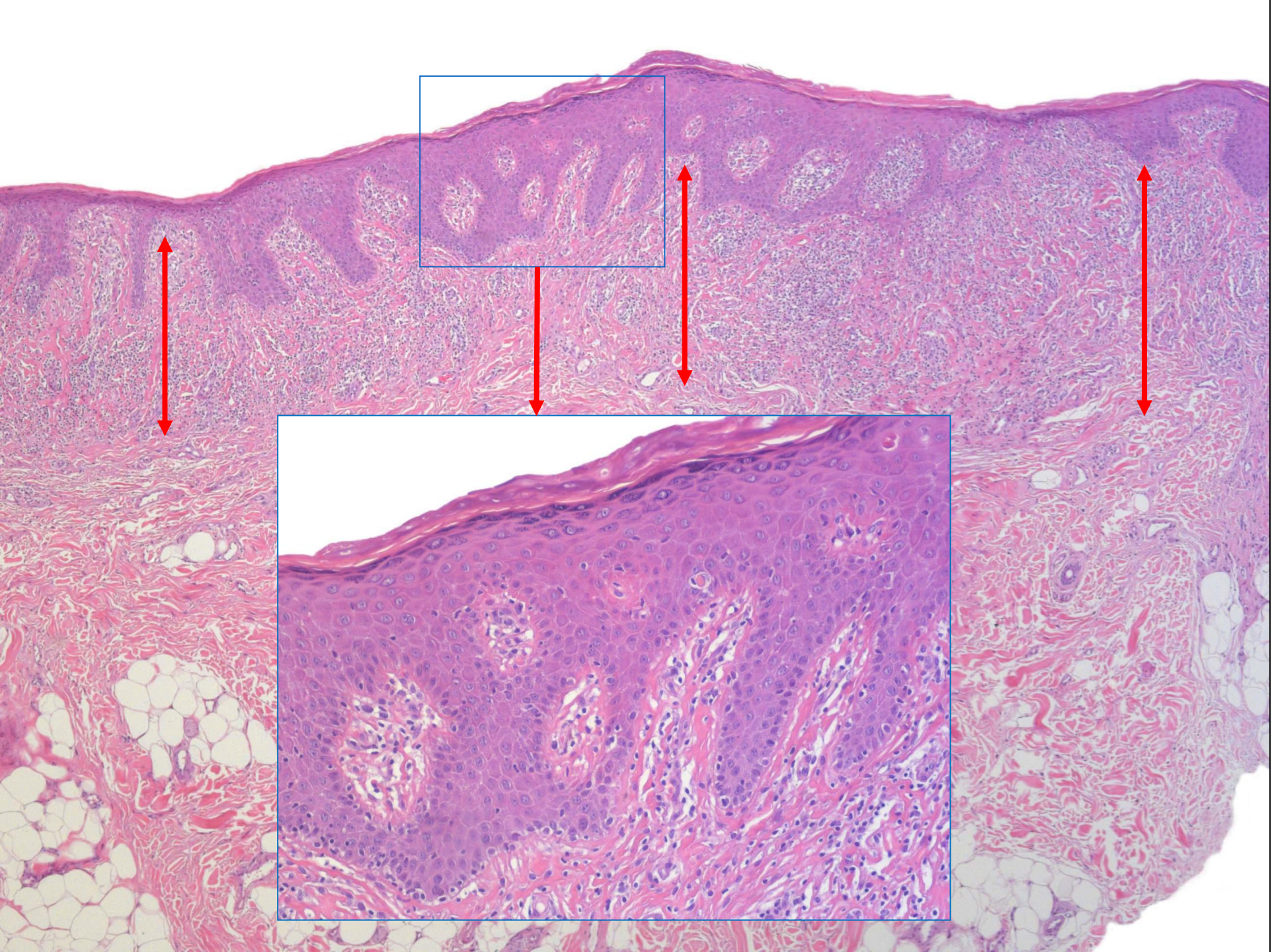
This is an example: A psoriasiform epidermal hyperplasia associated with a dense lichenoid infiltrate of lymphocytes,



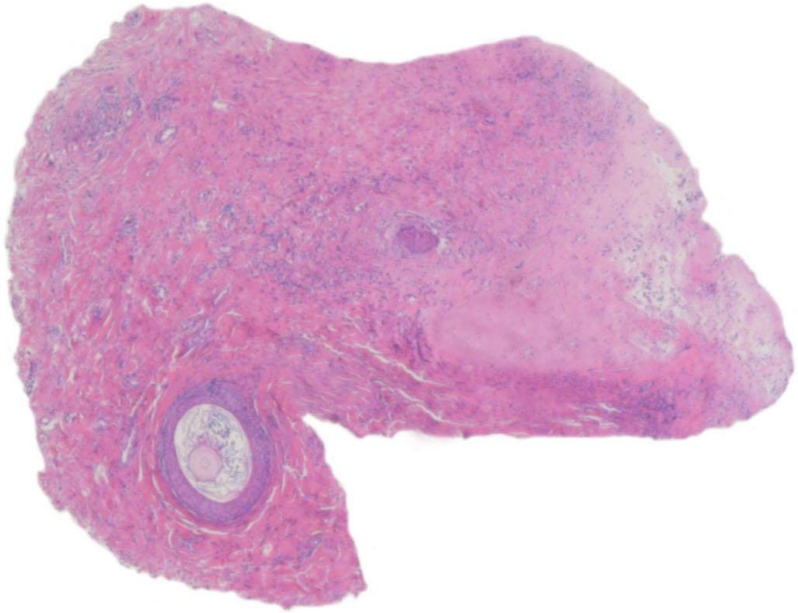
coarse bundles of collagen in the papillary dermis, and lymphocytes aligned in the basal layer. This is not mycosis fungoides, however, because lymphocytes in the basal layer are small

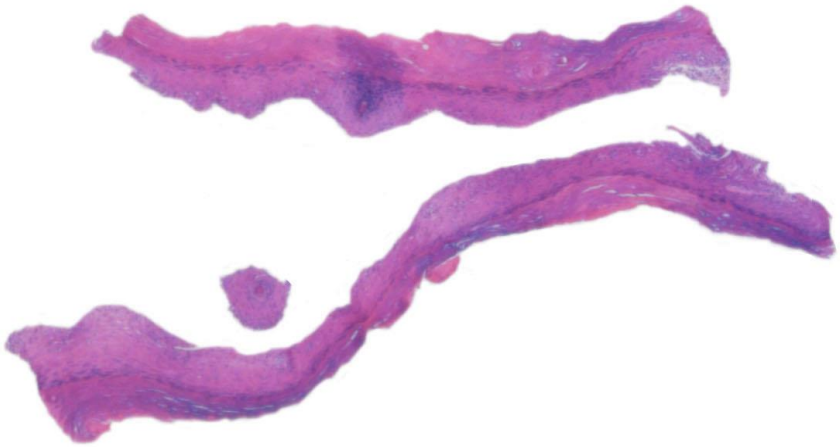


and the papillary dermis is far too thick. This is a clue to lichen sclerosus. The papillary dermis may be thickened in mycosis fungoides, too, but not to that extent.

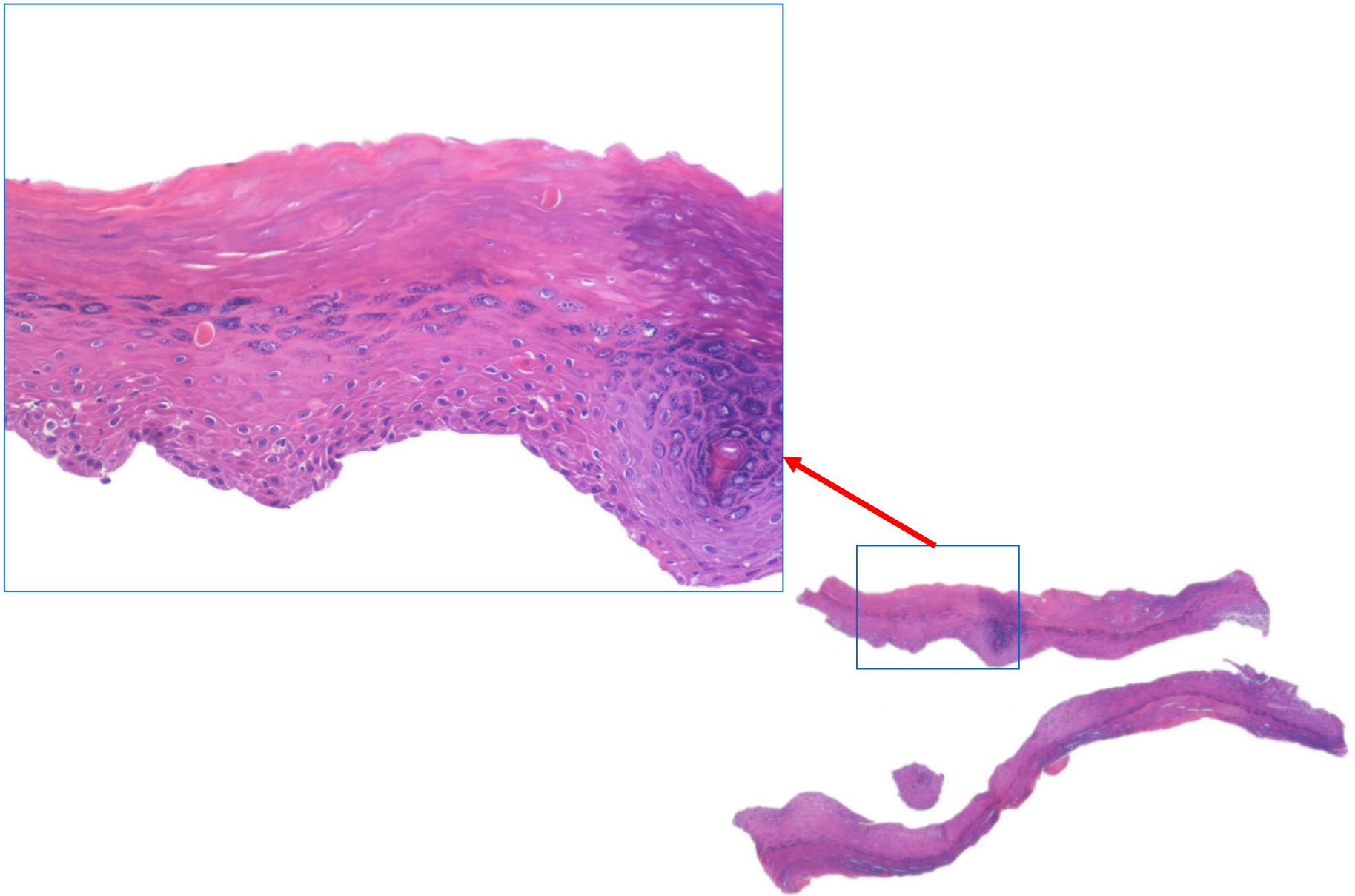


Another feature suggestive of lichen sclerosus is presence of necrotic keratocytes in all reaches of the epidermis. Of course, that finding is not specific, but an extremely helpful clue.

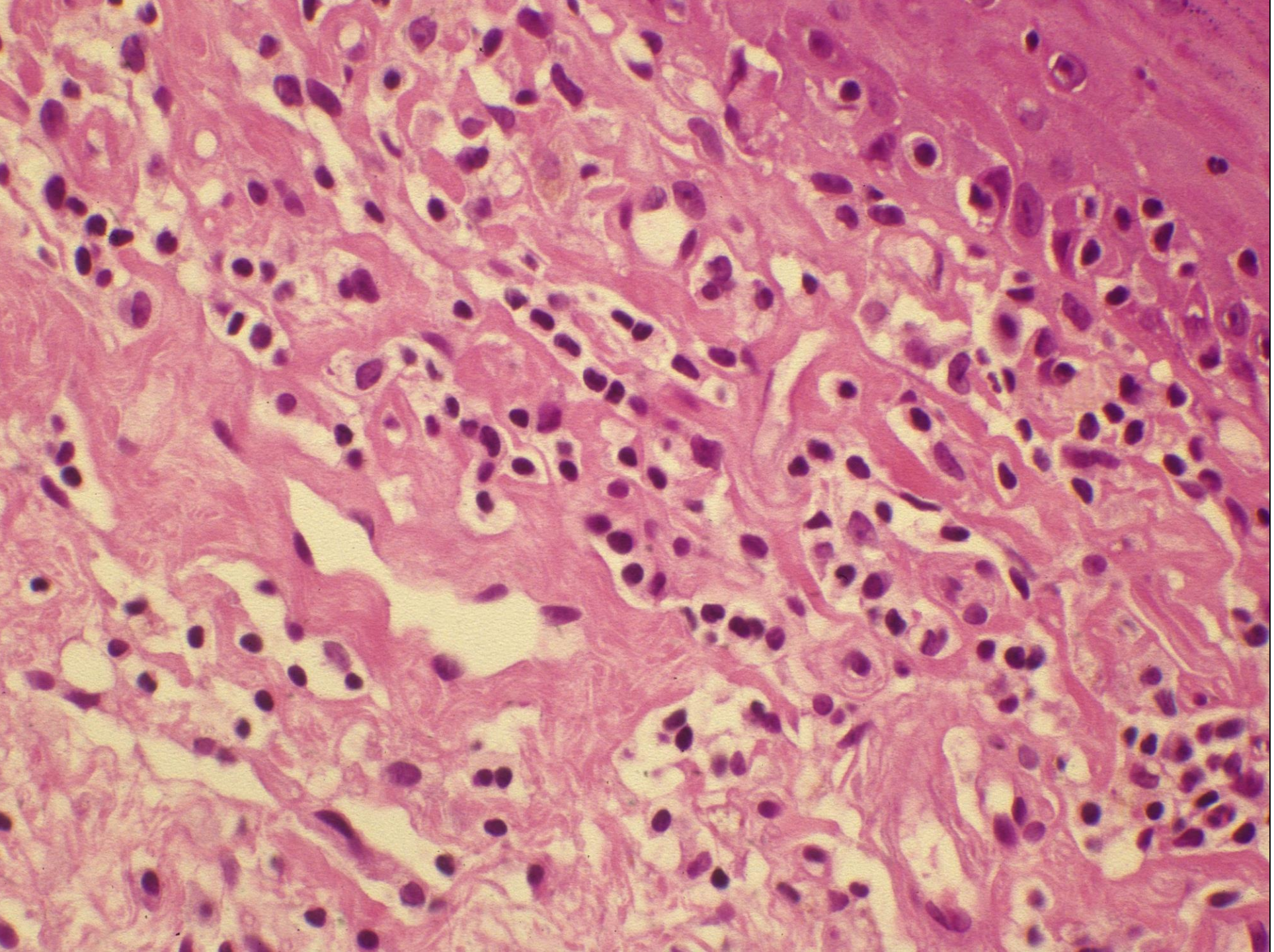




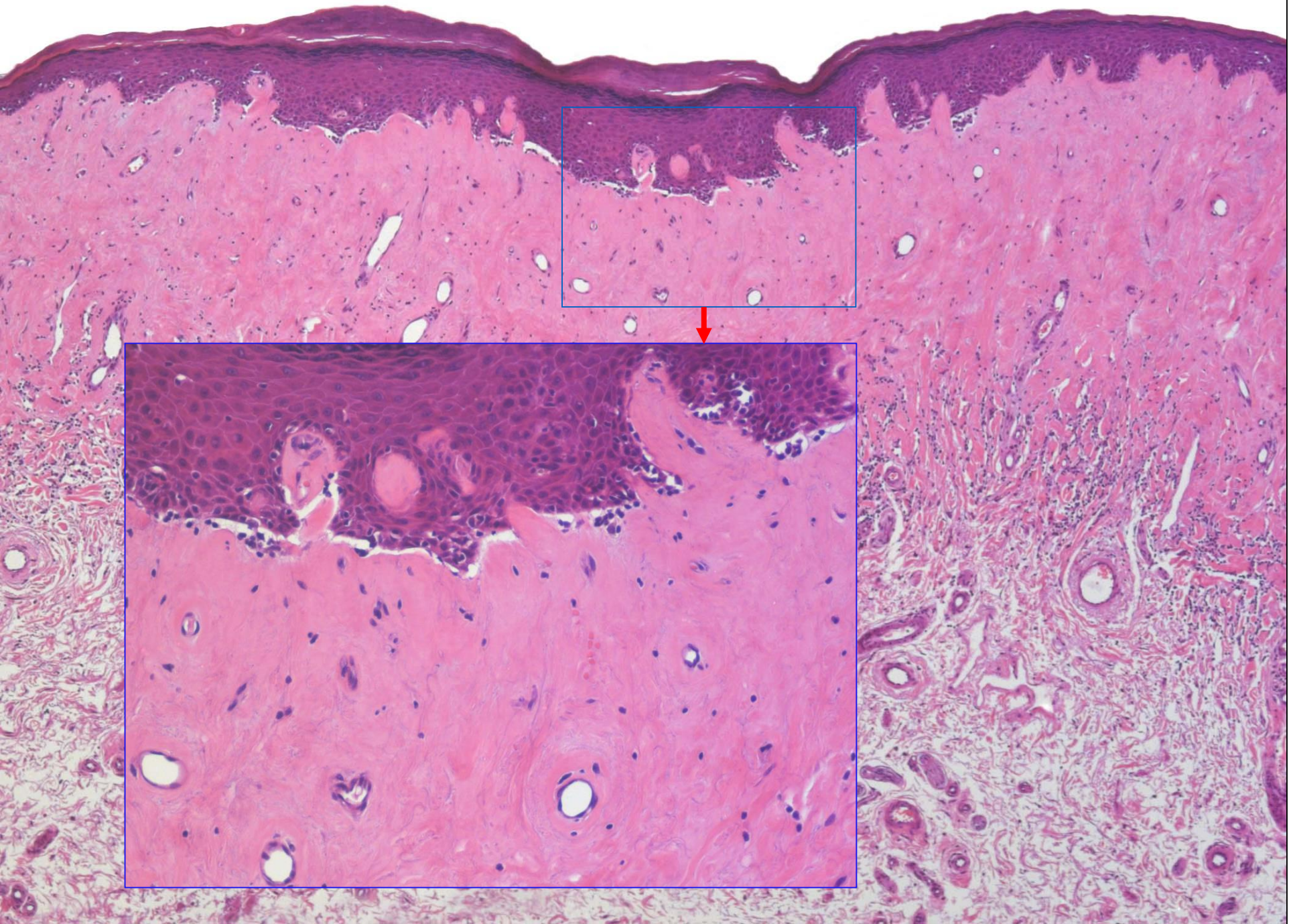
It is not needed in cases with subepidermal sclerosis, but sometimes specimens from the genitalia are very superficial,



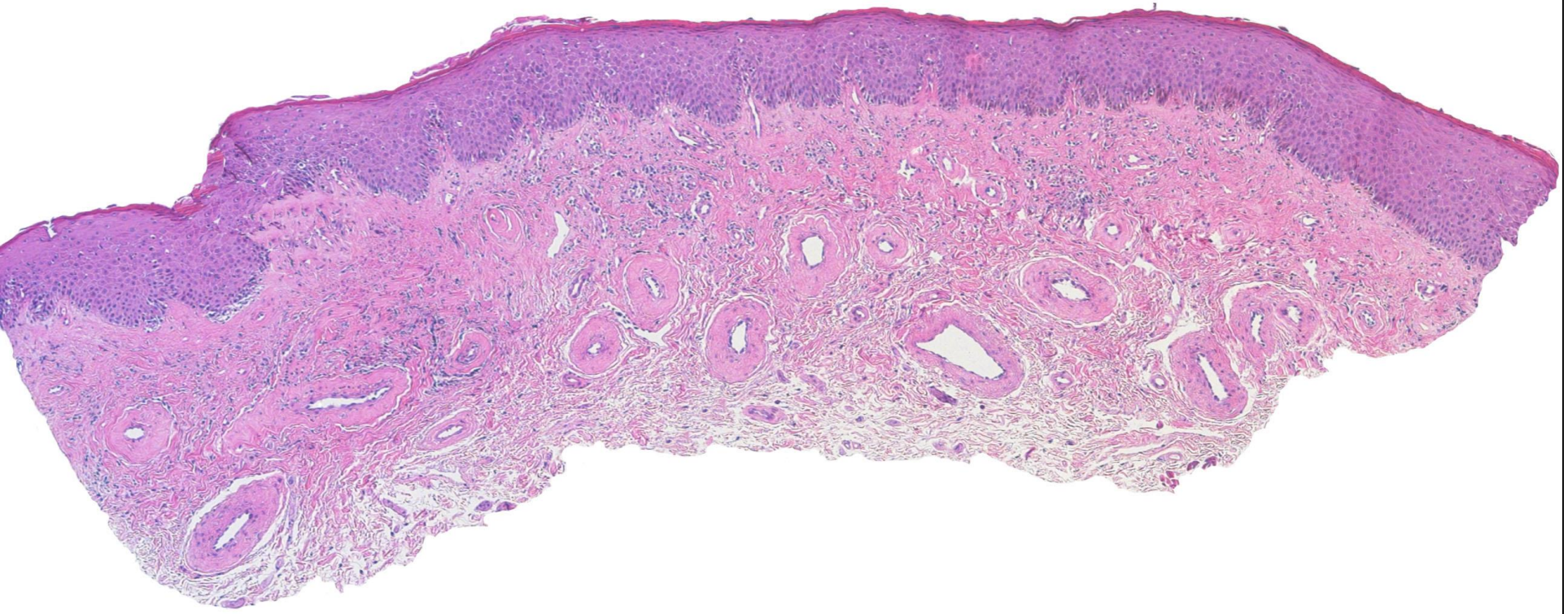
and if the dermis is not included, individual necrotic keratocytes throughout the spinous and cornified layer allow a presumptive diagnosis of lichen sclerosus to be made.



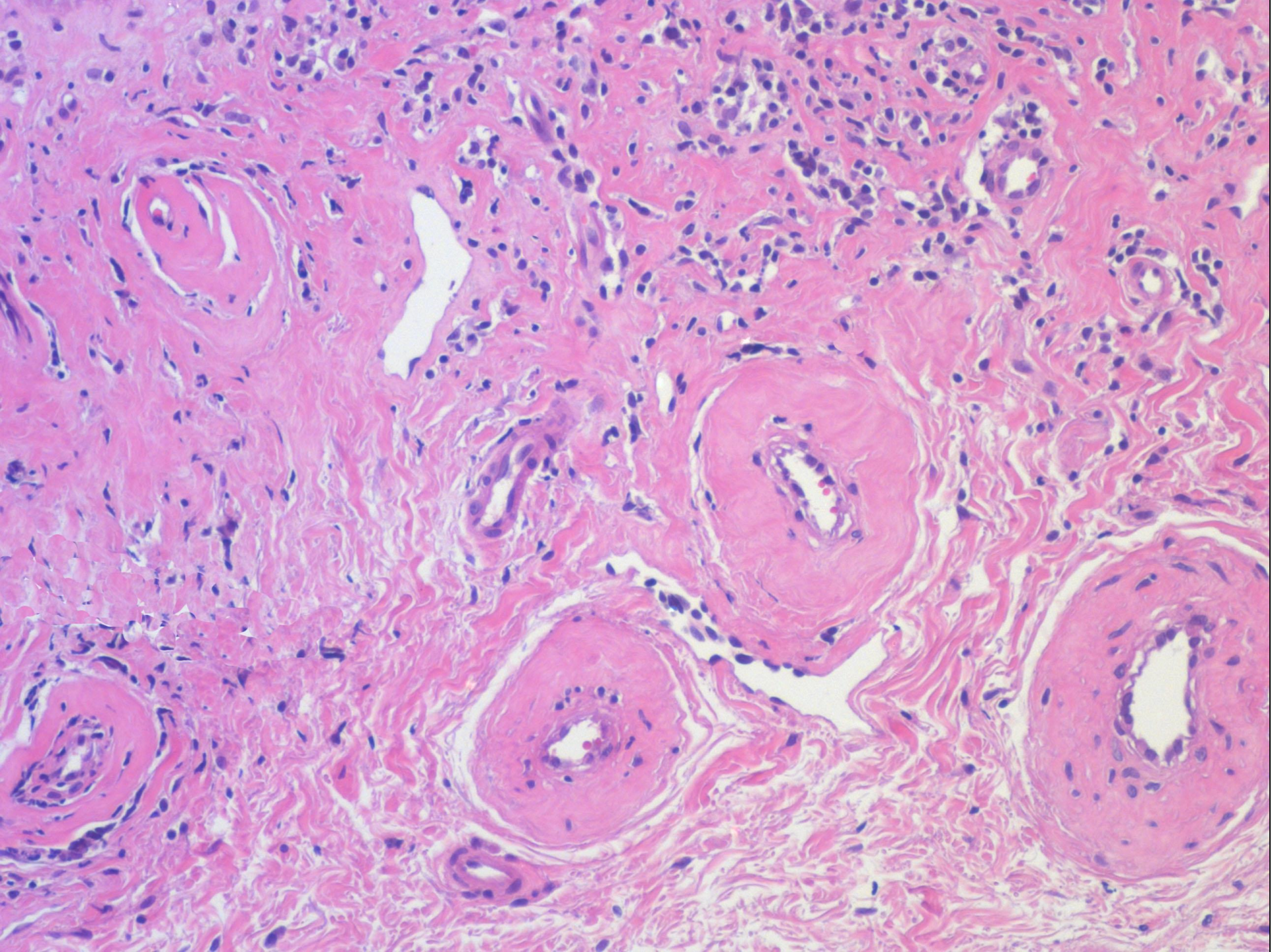
In the absence of sclerosis, the papillary dermis of lesions of lichen sclerosis nearly always shows fibrosis which is usually marked, and files of lymphocytes may be seen between thickened collagen fibres, a finding recently referred to as *“lymphocyte entrapment.”*



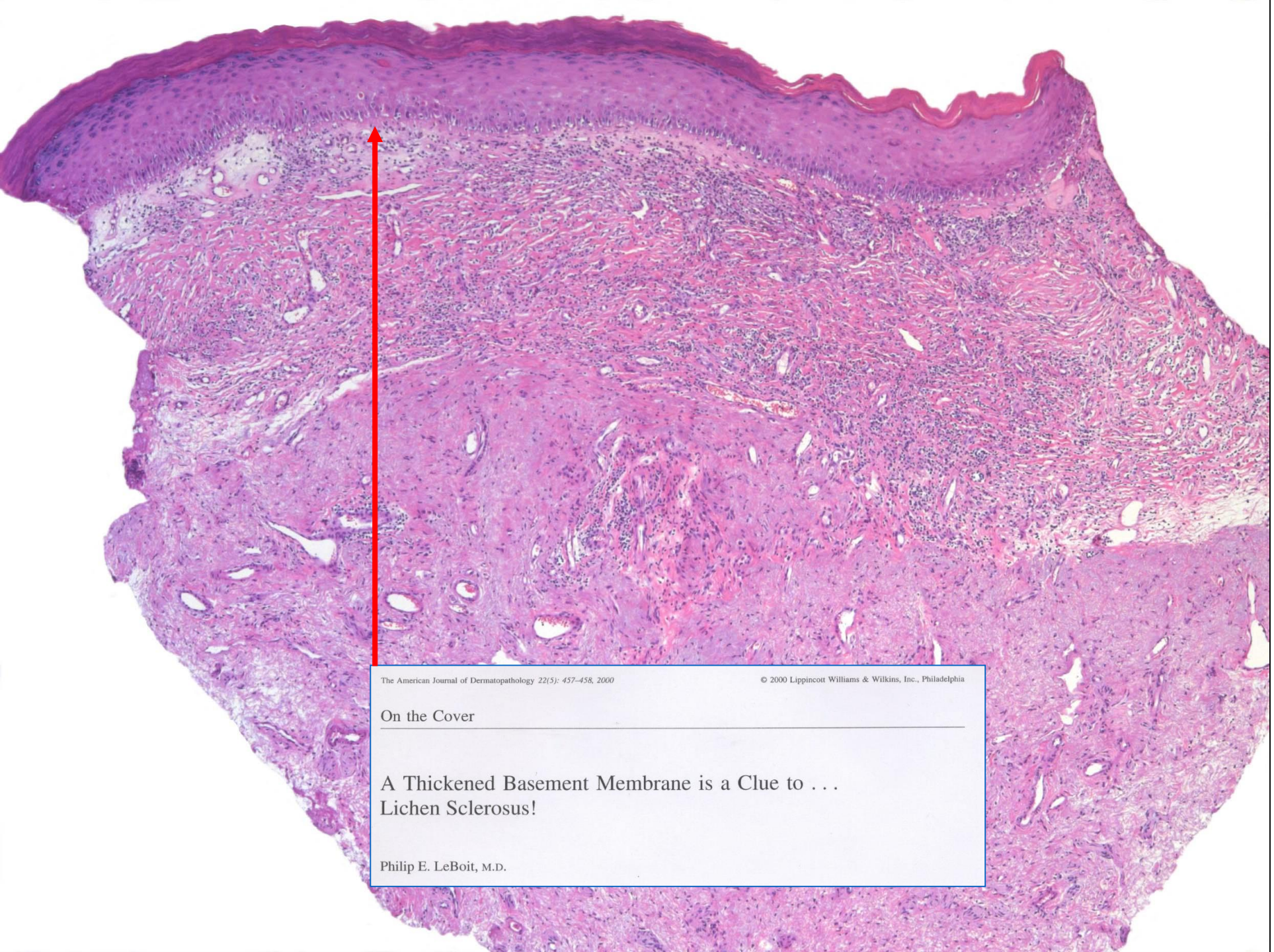
Another distinctive finding is concentric collagen cuffs around venules in the upper dermis. If one looks closely, those rings of collagen around vessels are a common finding in sclerotic lesions,



but they may also be observed in areas without sclerosis. In that instance, they are a helpful diagnostic clue



because they are not seen in diseases entering the differential diagnosis, such as lichen planus or mycosis fungoides.



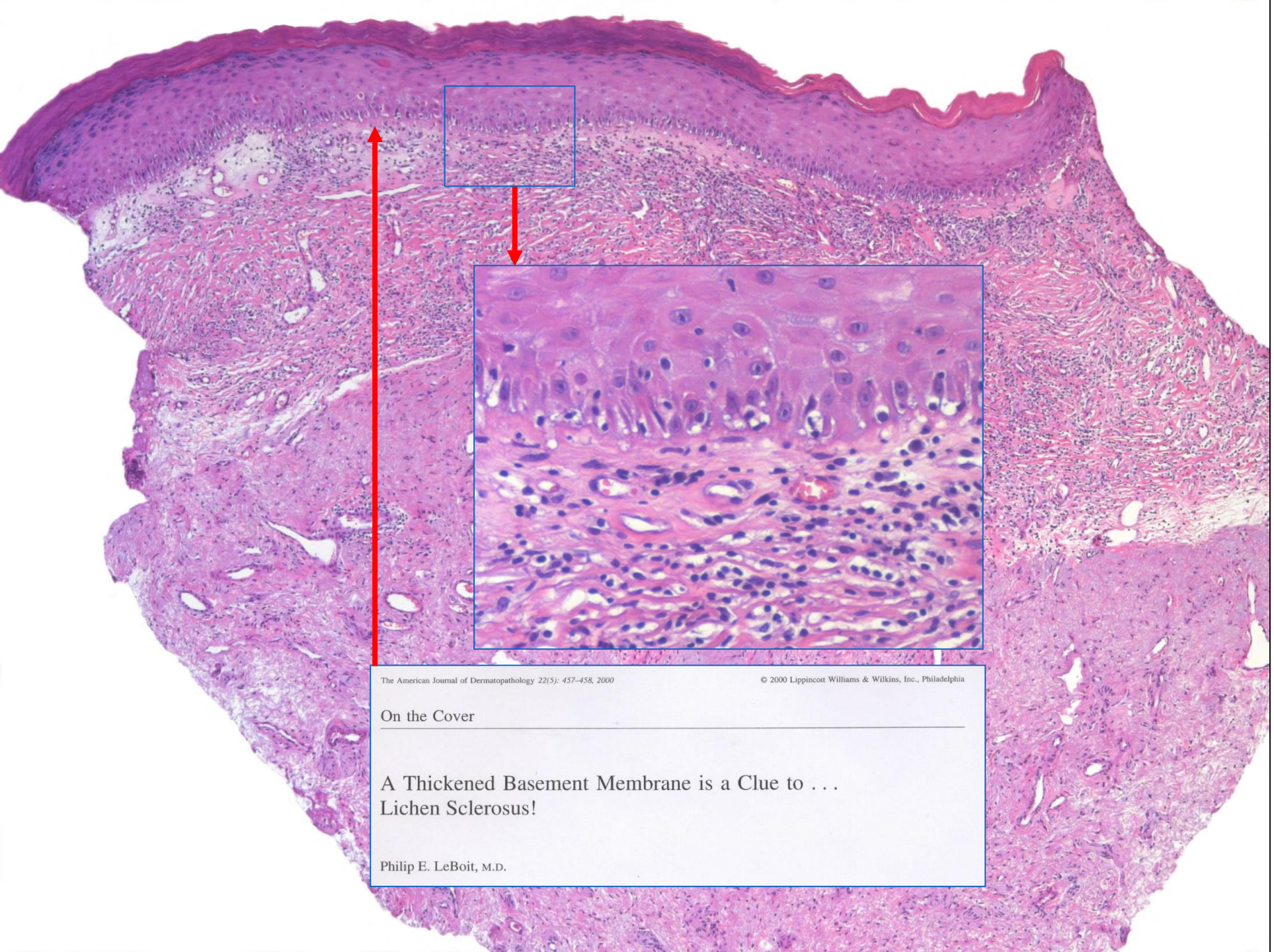
The American Journal of Dermatopathology 22(5): 457–458, 2000

On the Cover

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

Philip E. LeBoit, M.D.

Another clue to the diagnosis of lichen sclerosus is a thickened basement membrane. The utility of that clue, however, is limited because thickening of the basement membrane is usually confined to sclerotic areas,



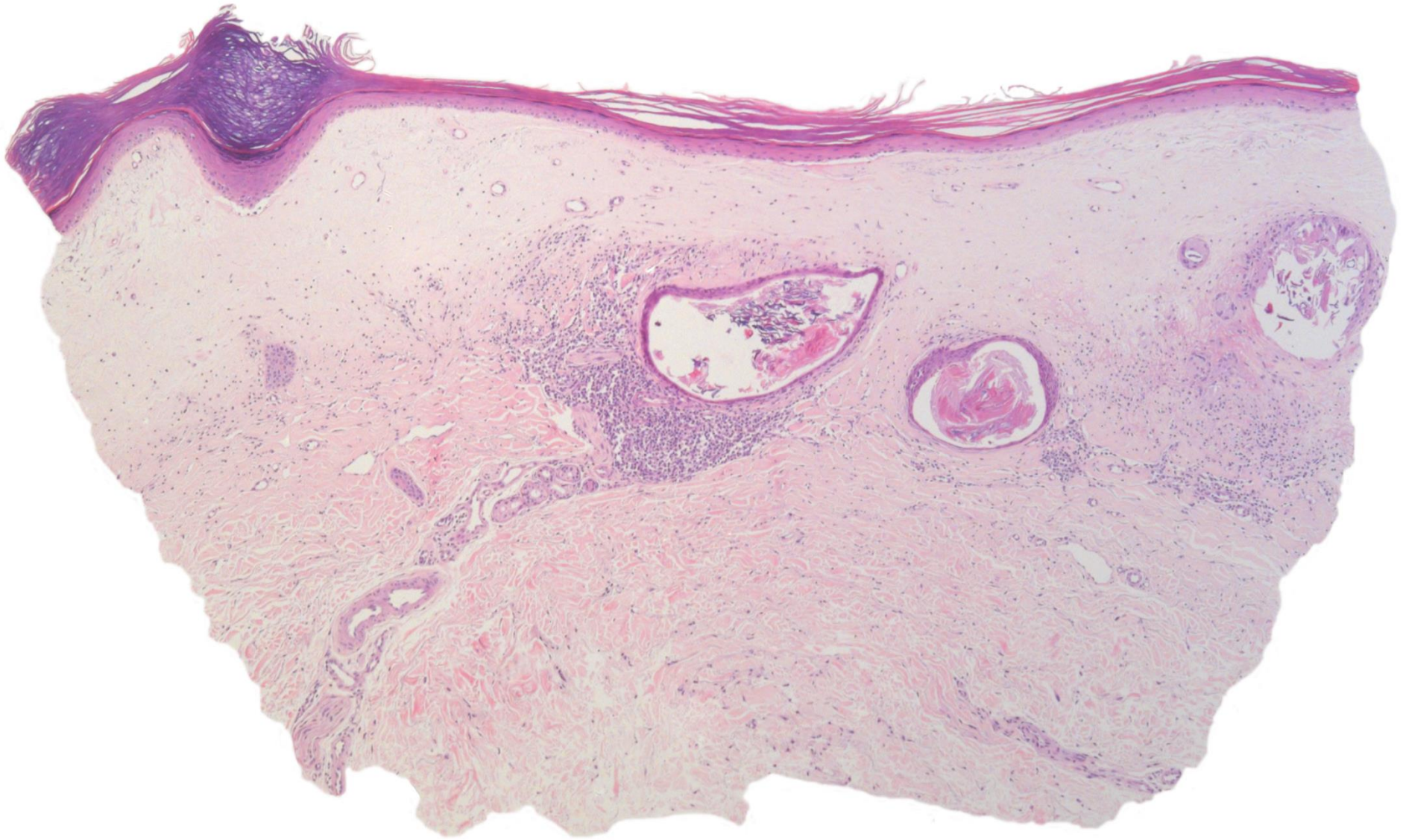
The American Journal of Dermatopathology 22(5): 457–458, 2000

On the Cover

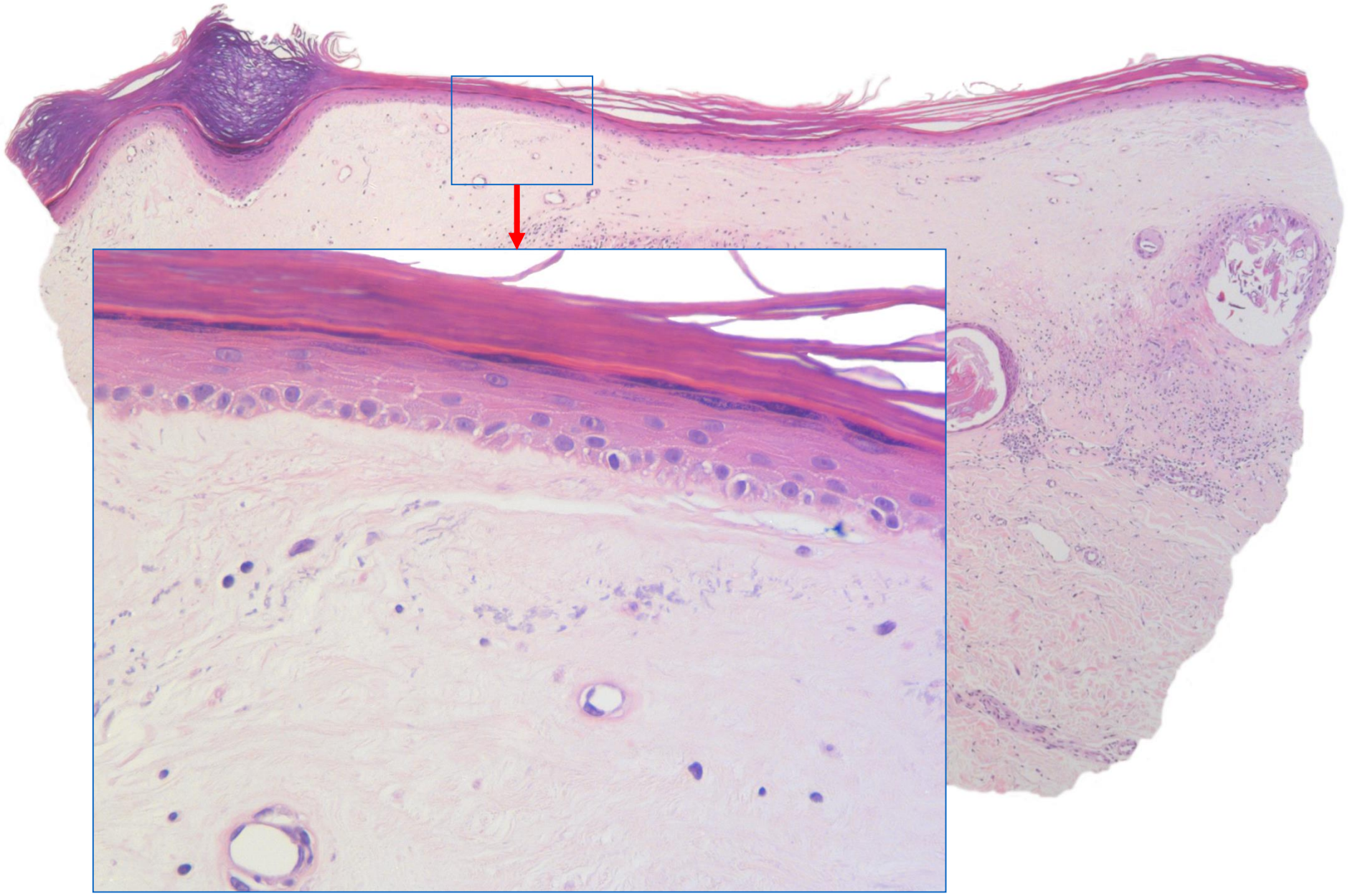
A Thickened Basement Membrane is a Clue to . . . Lichen Sclerosus!

Philip E. LeBoit, M.D.

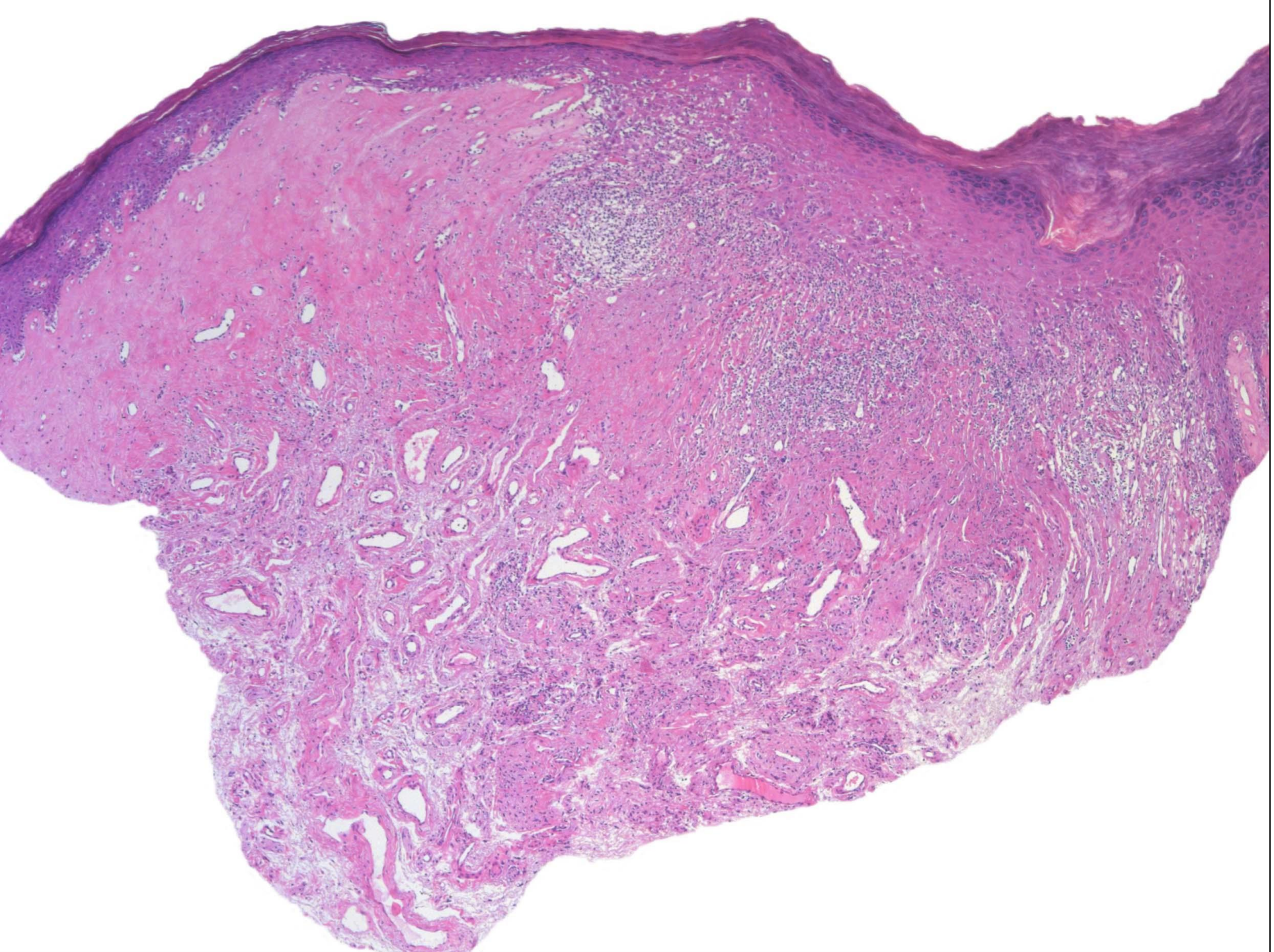
and if one leaves them, the basement membrane turns to normal.



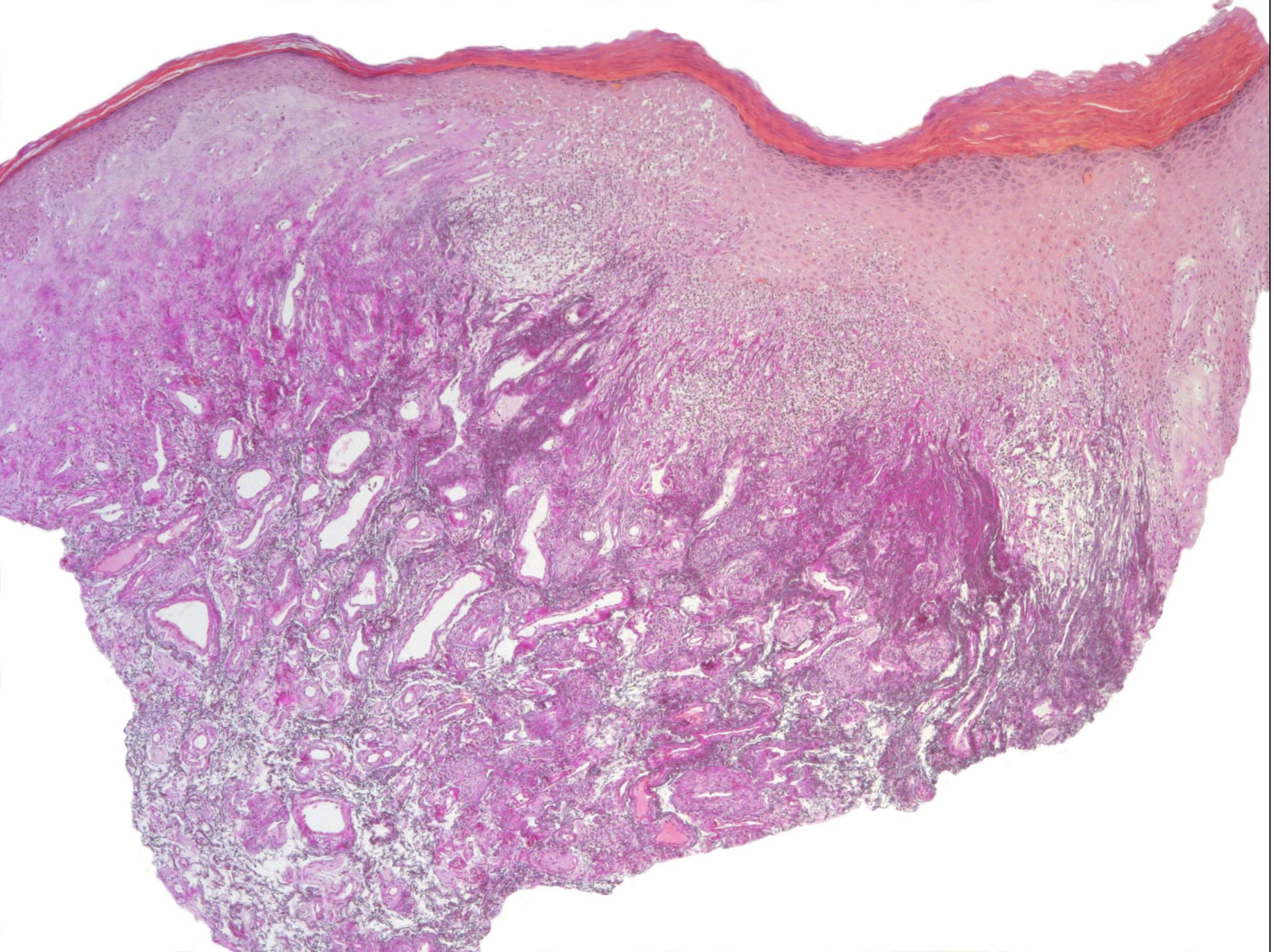
Likewise, follicular hyperkeratoses may be striking in lichen sclerosus, reminiscent of findings sometimes encountered in lupus erythematosus, but this is only the case in advanced stages with prominent sclerosis.



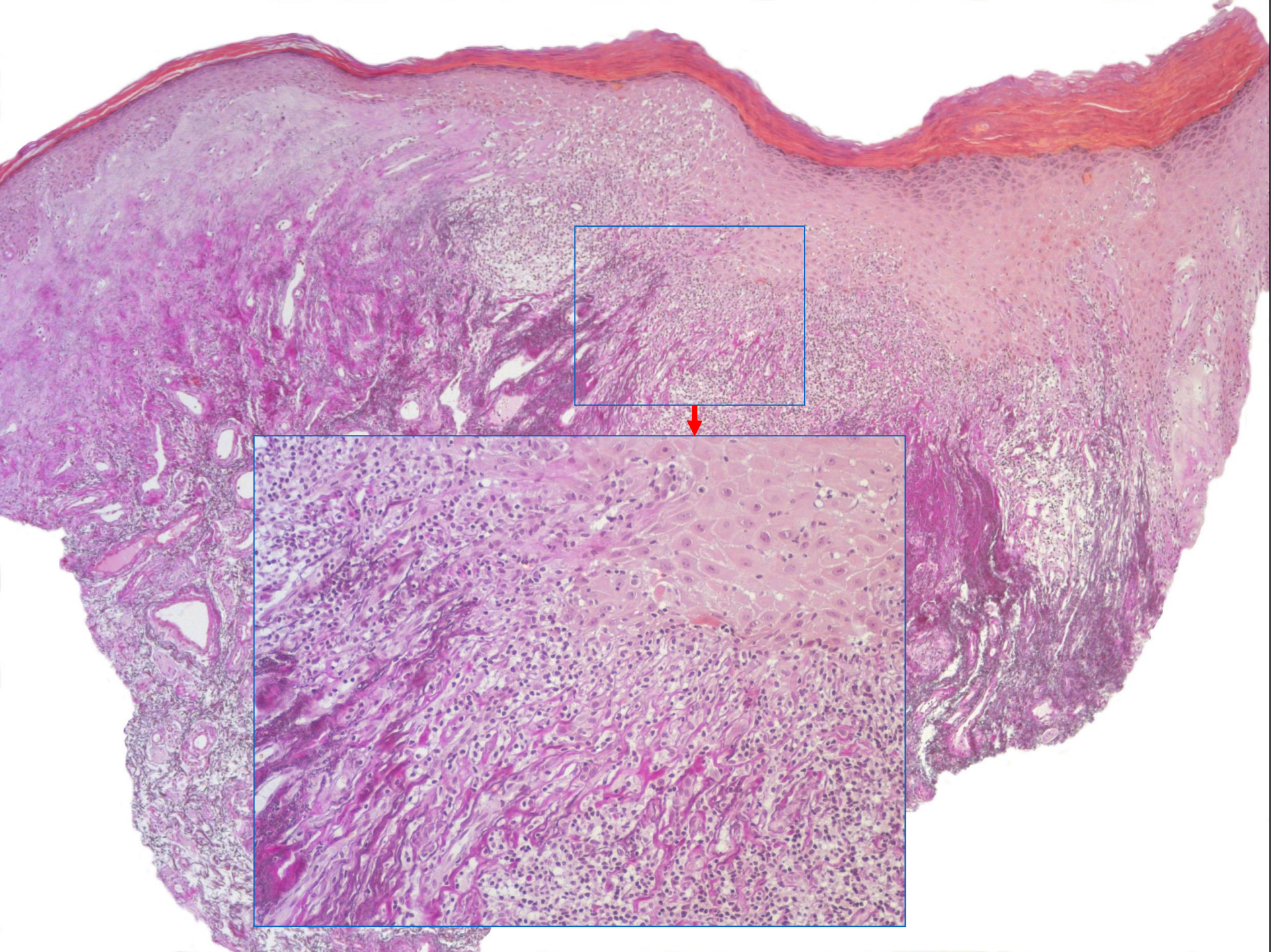
Another finding typical of lichen sclerosus is loss of elastic fibres that are diminuished markedly in zones of sclerosis, and the few that have remained are bluish and fragmented. Those changes, however, are practically never seen in diagnostically challenging cases without subepidermal sclerosis.



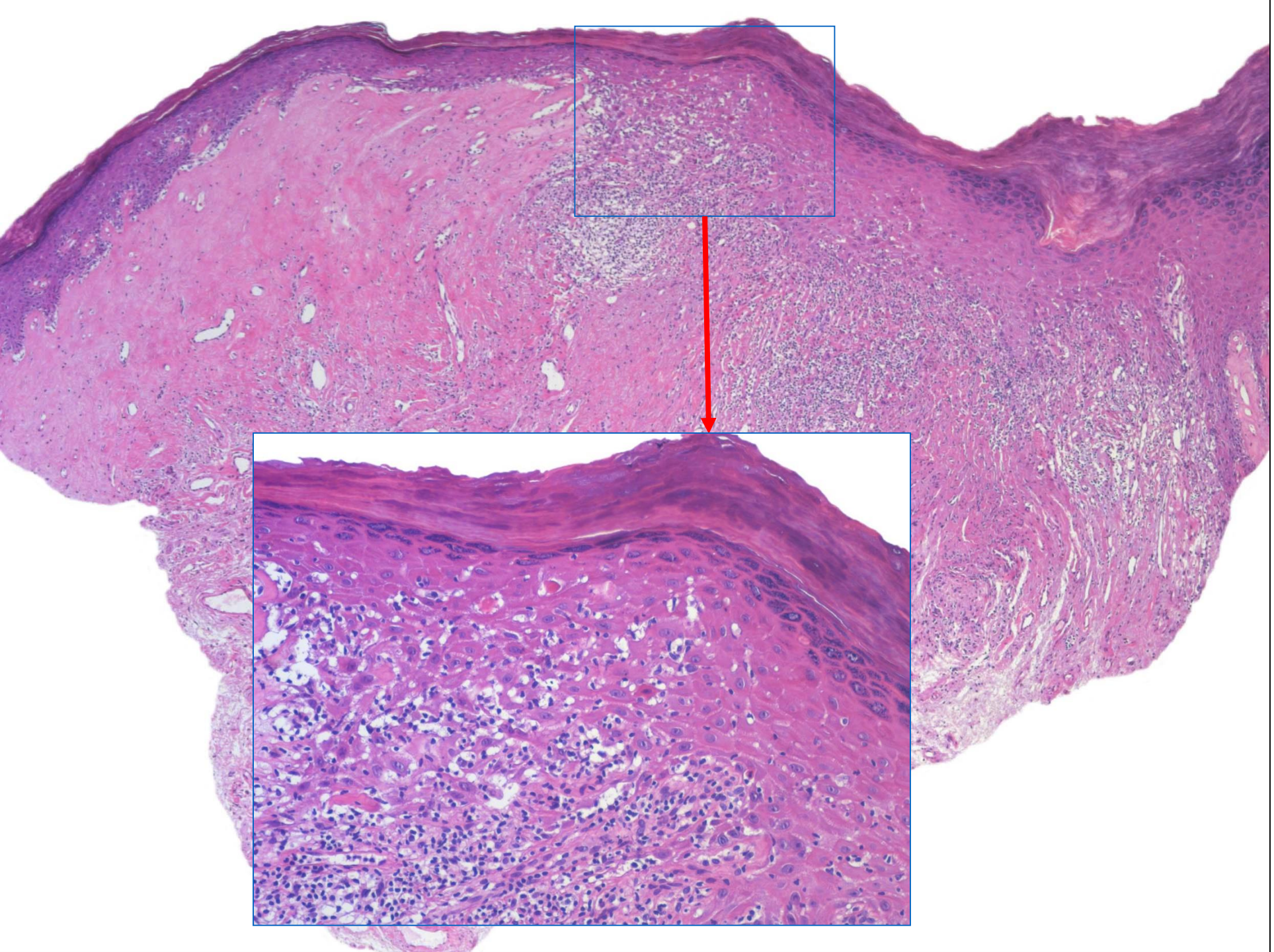
Here is an example of a case that shows both, zones with and without sclerosis.



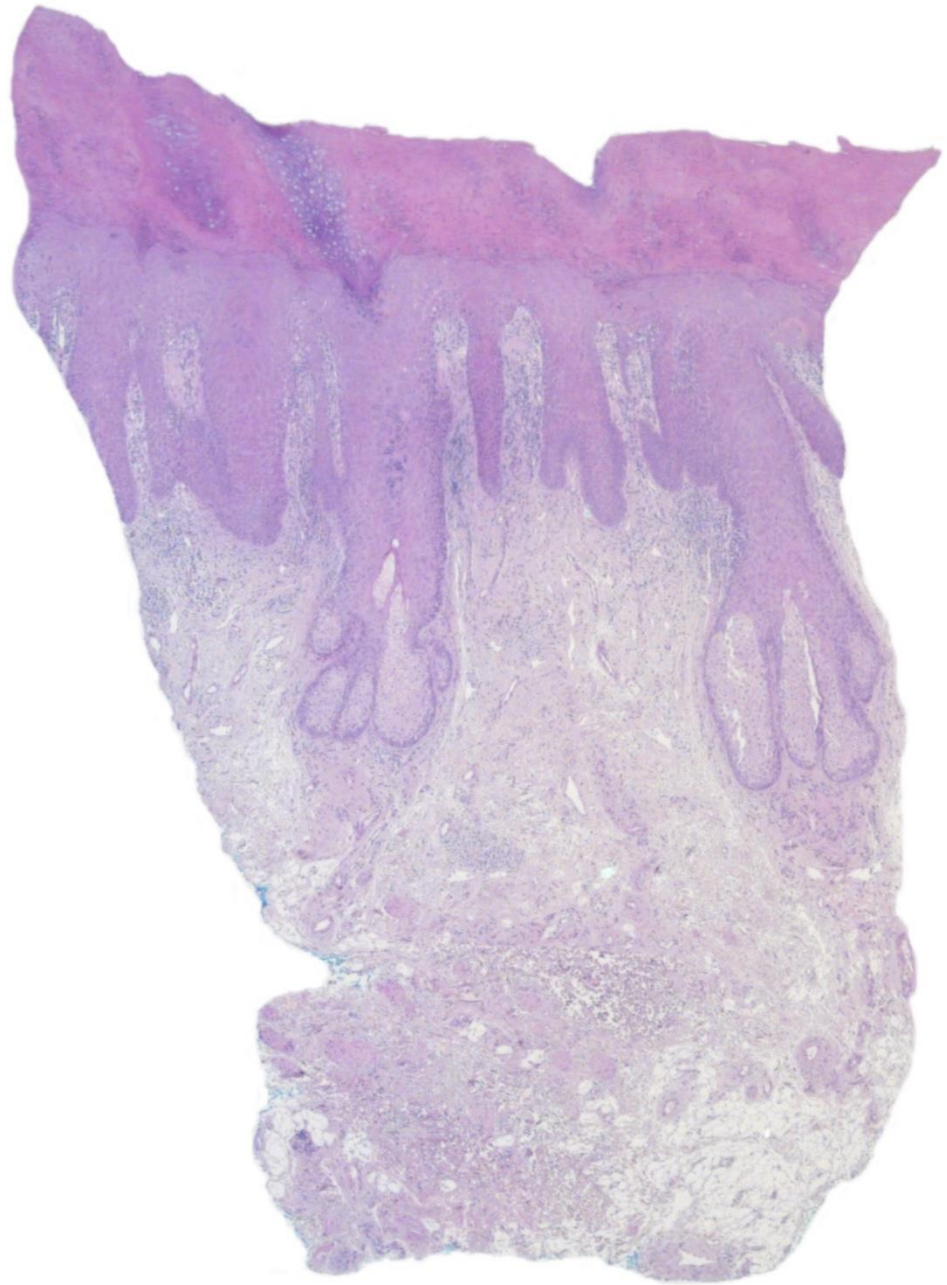
In the sclerotic area, elastic fibres are gone,



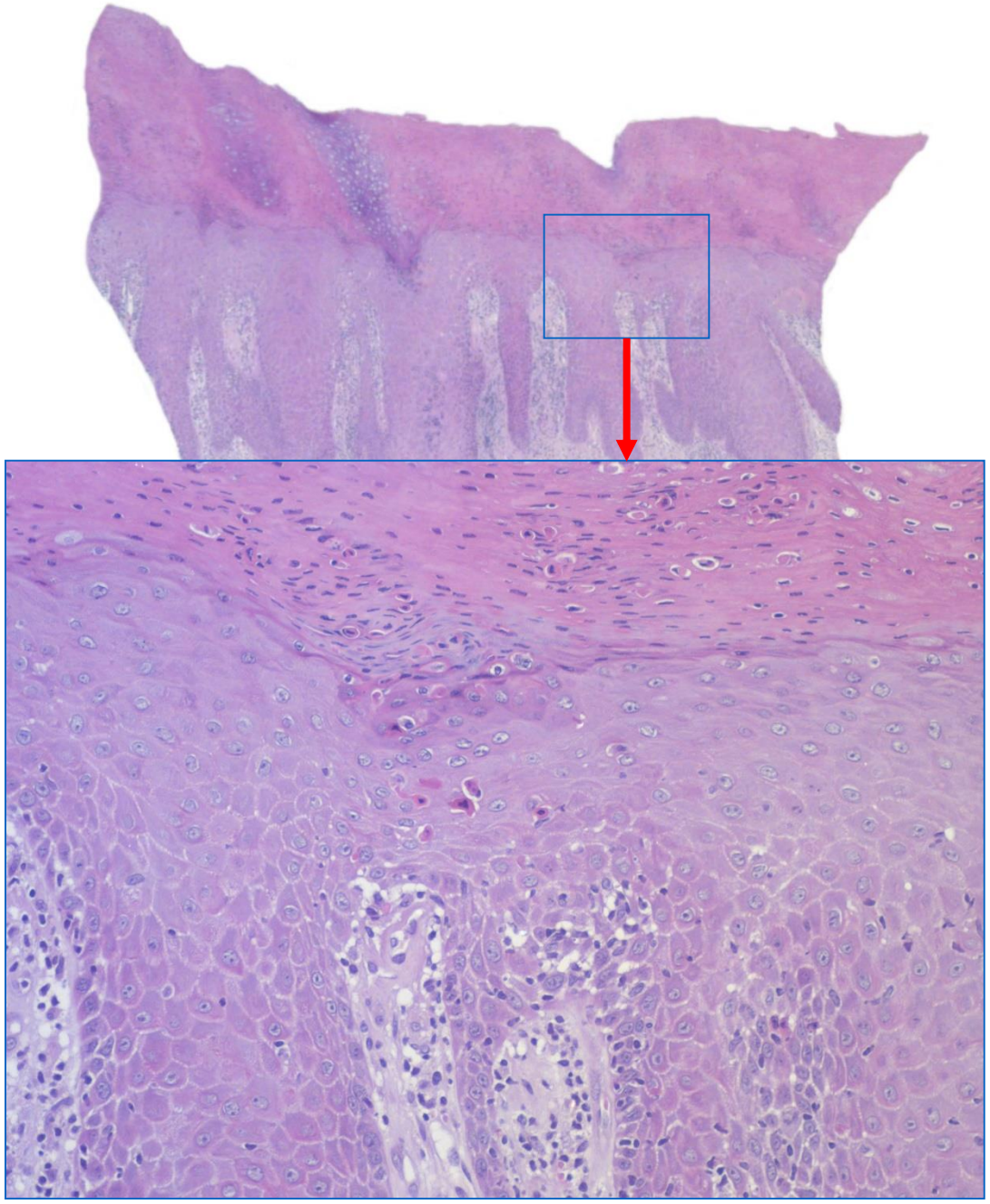
but they are preserved in the zone without sclerosis. In such cases, one relies on other clues,



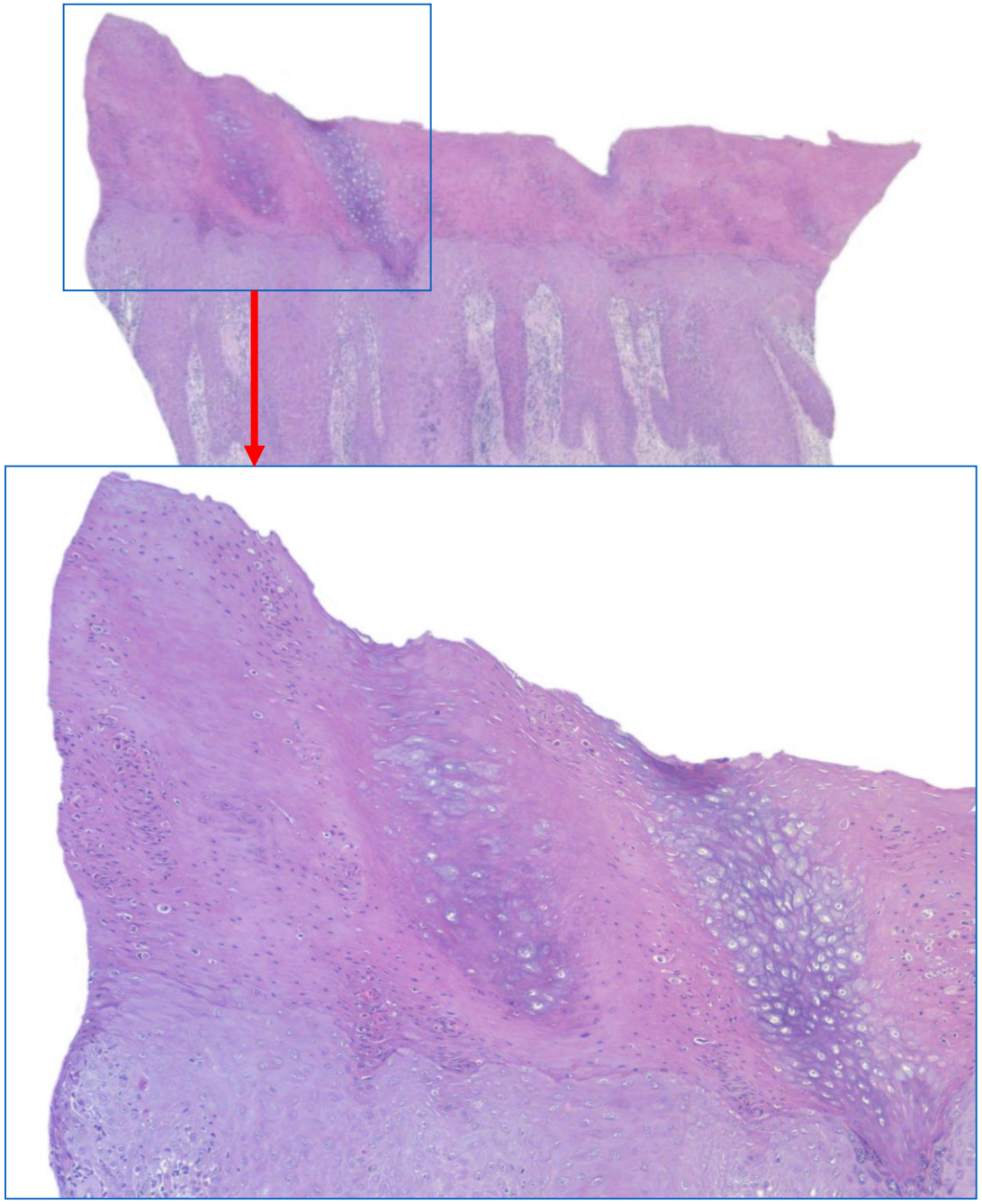
such as lymphocytes scattered through the lower half of the spinous zone – a finding militating against lichen planus – and necrotic keratocytes in all reaches of the epidermis.



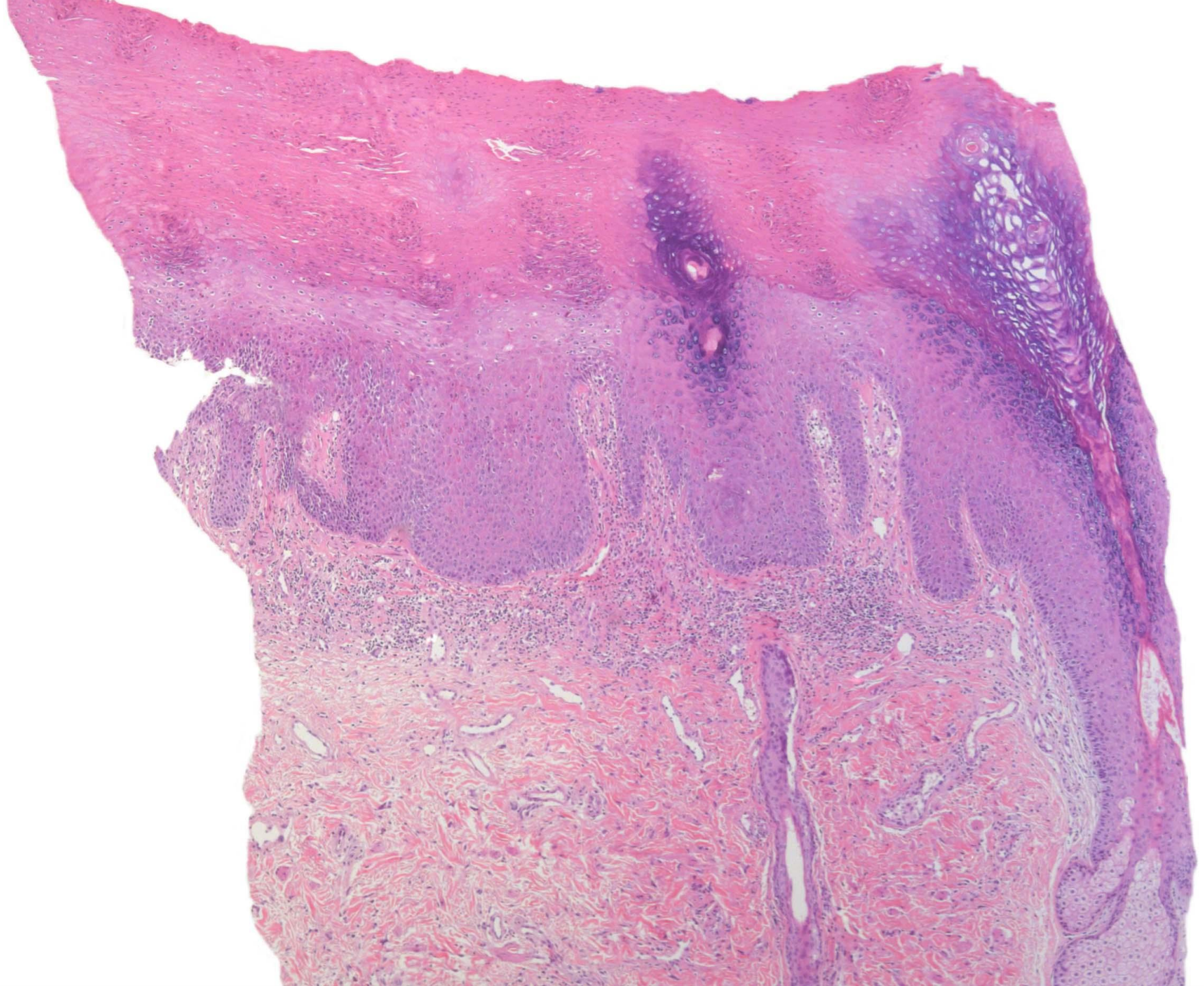
A finding that is both, distinctive and of high diagnostic value in cases without sclerosis, is accentuation of pathologic changes in suprapapillary plates. In this case with pronounced psoriasiform hyperplasia,



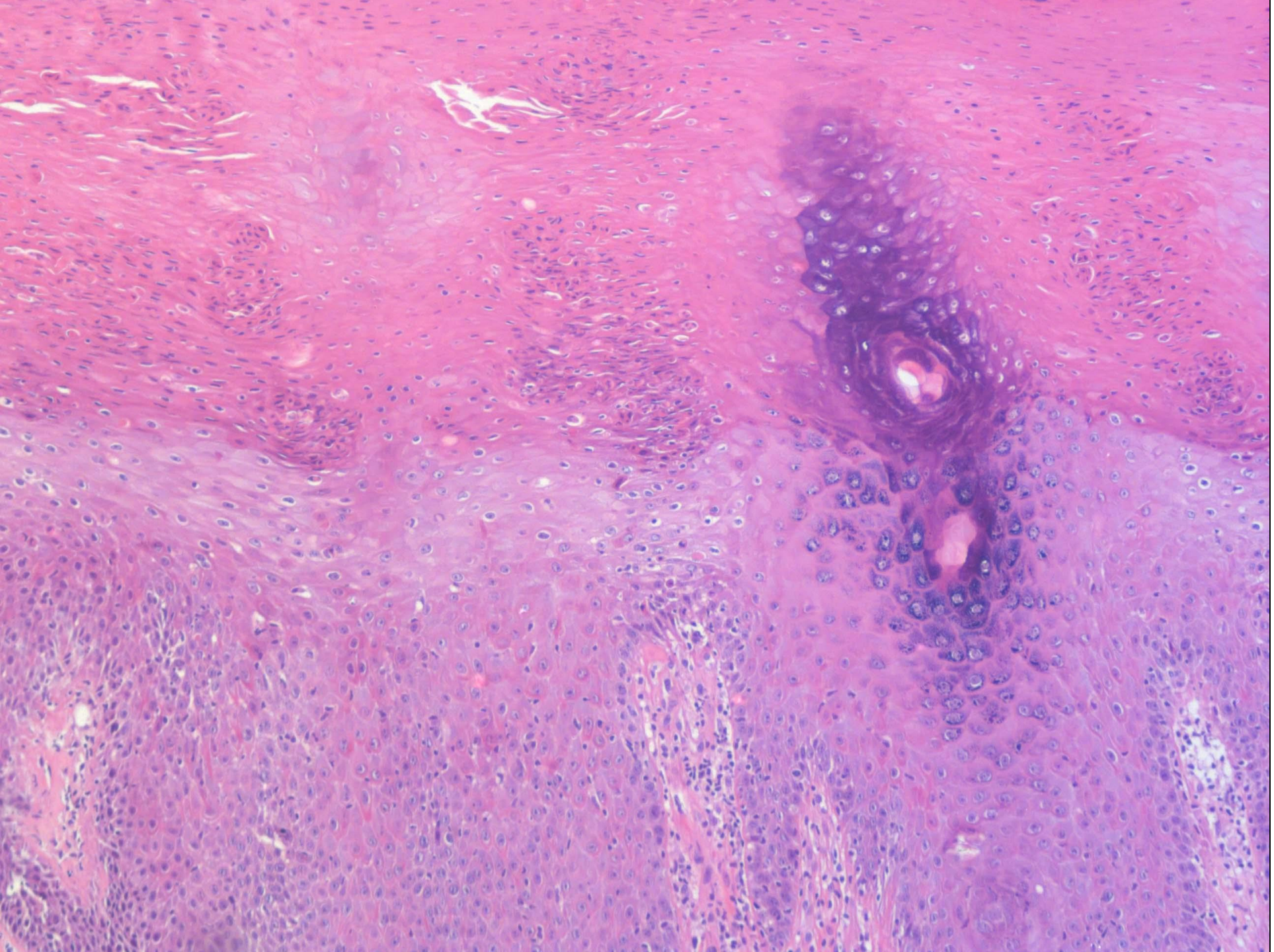
necrotic keratocytes and lymphocytes with some spongiosis are seen especially above the tips of dermal papillae, giving rise to narrow columns of parakeratosis in which individual necrotic keratocytes are still discernible.



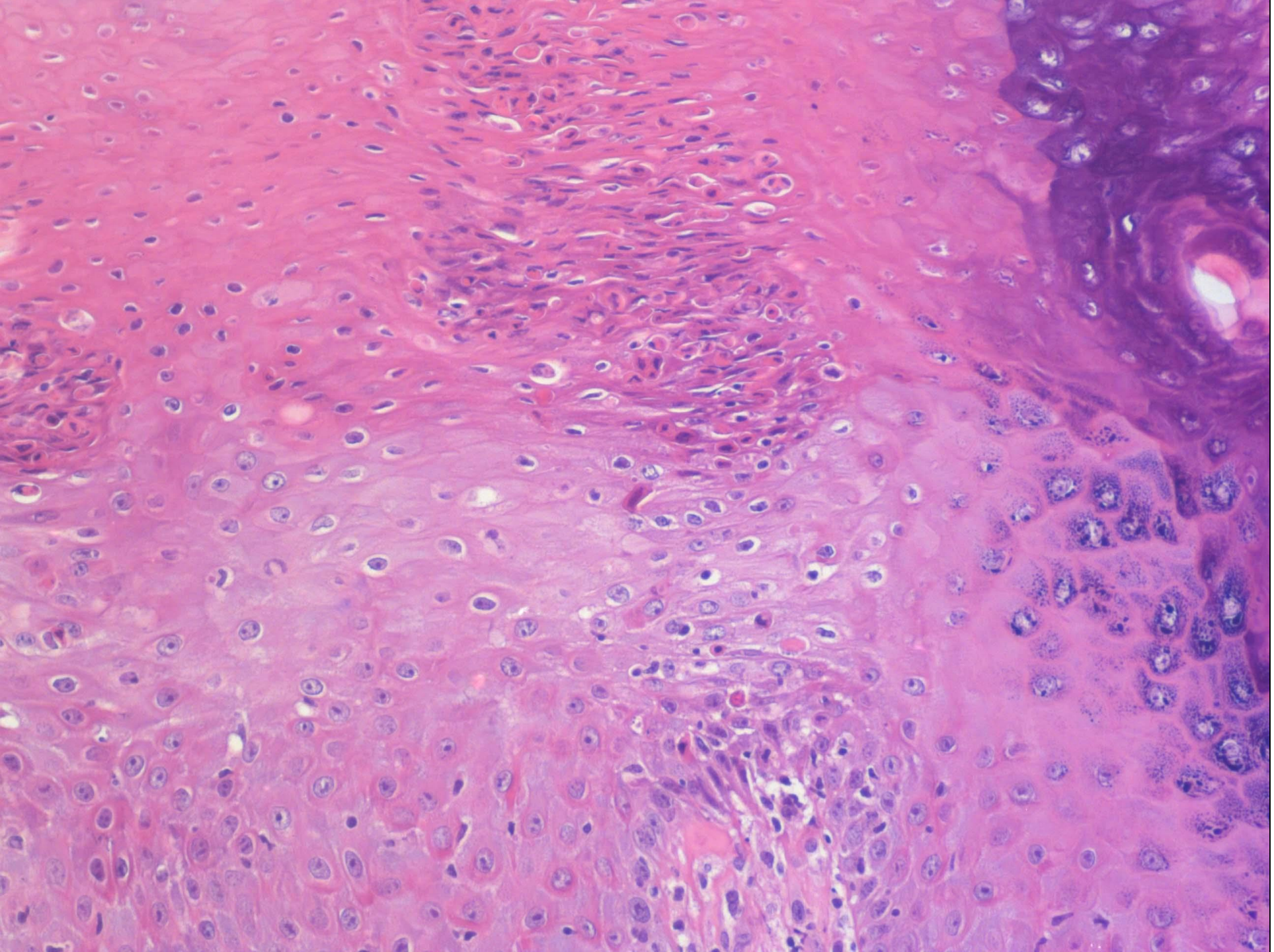
Those vertical columns of parakeratosis are a very helpful clue to the diagnosis of hypertrophic, non-sclerotic lichen sclerosus.



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 “corps ronds” of Darier’s disease.



Moreover, necrotic keratocytes are scattered in the spinous zone above dermal papillae. In the latter, 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.

Wolfgang Weyers

Center for Dermatopathology, Freiburg, Germany

Wolfgang Weyers, MD
Center for Dermatopathology
Engelbergerstr. 19, 79106 Freiburg, Germany
Tel: +01149 761 31696
Fax: +01149 761 39772
e-mail: ww@dzdpf.de

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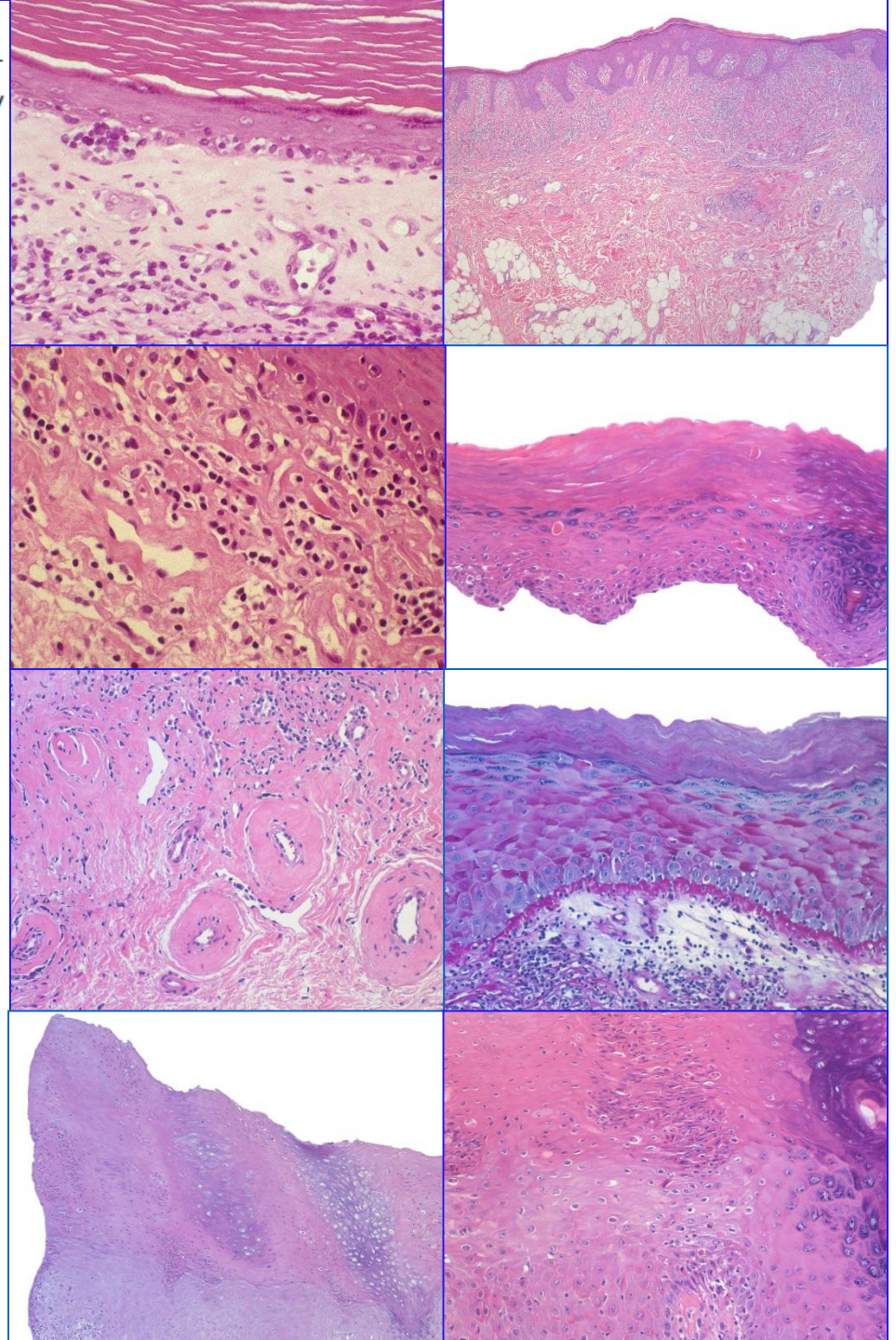
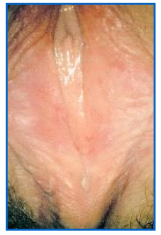


In sum, there are many histopathologic clues that enable the diagnosis of lichen sclerosus to be made even in difficult cases. I have summarized them in a review in the Journal of Cutaneous Pathology two years ago.

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 a number of criteria of somewhat decreasing importance, namely,



Clues to the diagnosis of lichen sclerosus

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

tiny foci of sclerosis at the tips of dermal papillae, marked subepidermal fibrosis with thickening of the papillary dermis, necrotic keratocytes in all reaches of the epidermis, foci of spongiosis with necrotic keratocytes above the tips of dermal papillae and beneath columns of parakeratosis, lymphocytes aligned in the basal layer, lymphocytes scattered through the lower half of the spinous zone in concert with scant spongiosis, files of lymphocytes between thickened collagen bundles, “concentric collagen cuffs” around vessels, a thickened basement membrane, bluish, fragmented, and diminuished elastic fibres, follicular hyperkeratoses, and hypergranulosis and compact hyperkeratosis.

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-

Knowledge of those findings is not only important for establishing the diagnosis of lichen sclerosus in cases without sclerosis, but also to avoid the overdiagnosis of cancer in such lesions. As you know, lichen sclerosus is reputed to carry an enhanced risk of malignancy which is said to be even higher in lesions with epithelial hyperplasia. In current *"guidelines for the follow-up of women with vulvar lichen sclerosus,"* the *"association between LS and squamous cell cancer of the vulva"* is emphasized, particularly in the case of *"localized skin thickening."*

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.

According to literature of gynecopathology, about half of the cases of vulvar carcinoma are associated with lichen sclerosus, 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.)

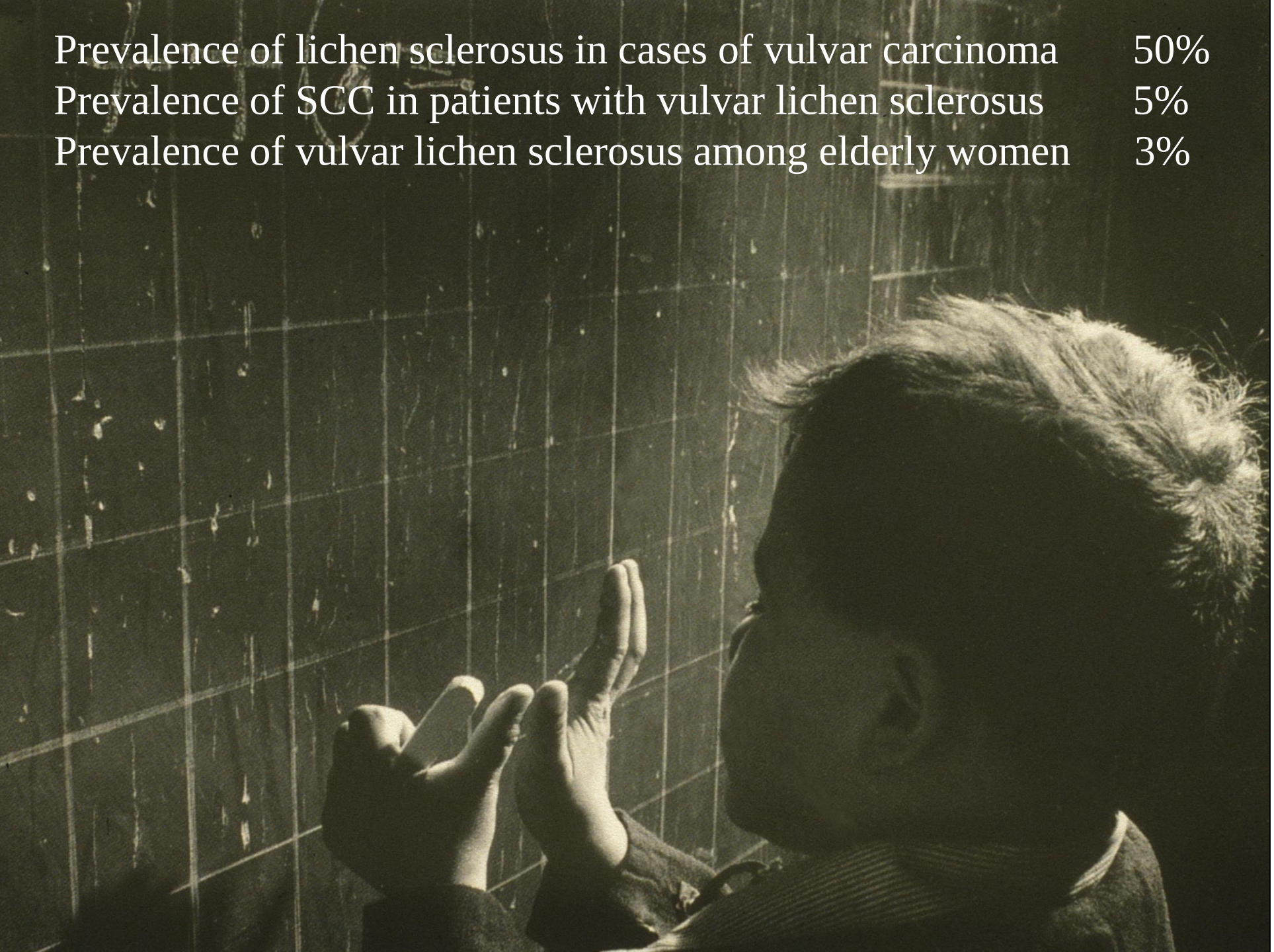
Vulvar disorders are among the most recalcitrant, frustrating, and burdensome conditions that adversely affect a woman's quality of life. In this dialogue, Dr Margesson offers many suggestions on how to examine and treat patients with a host of diseases that involve the vulva, including herpes simplex, 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

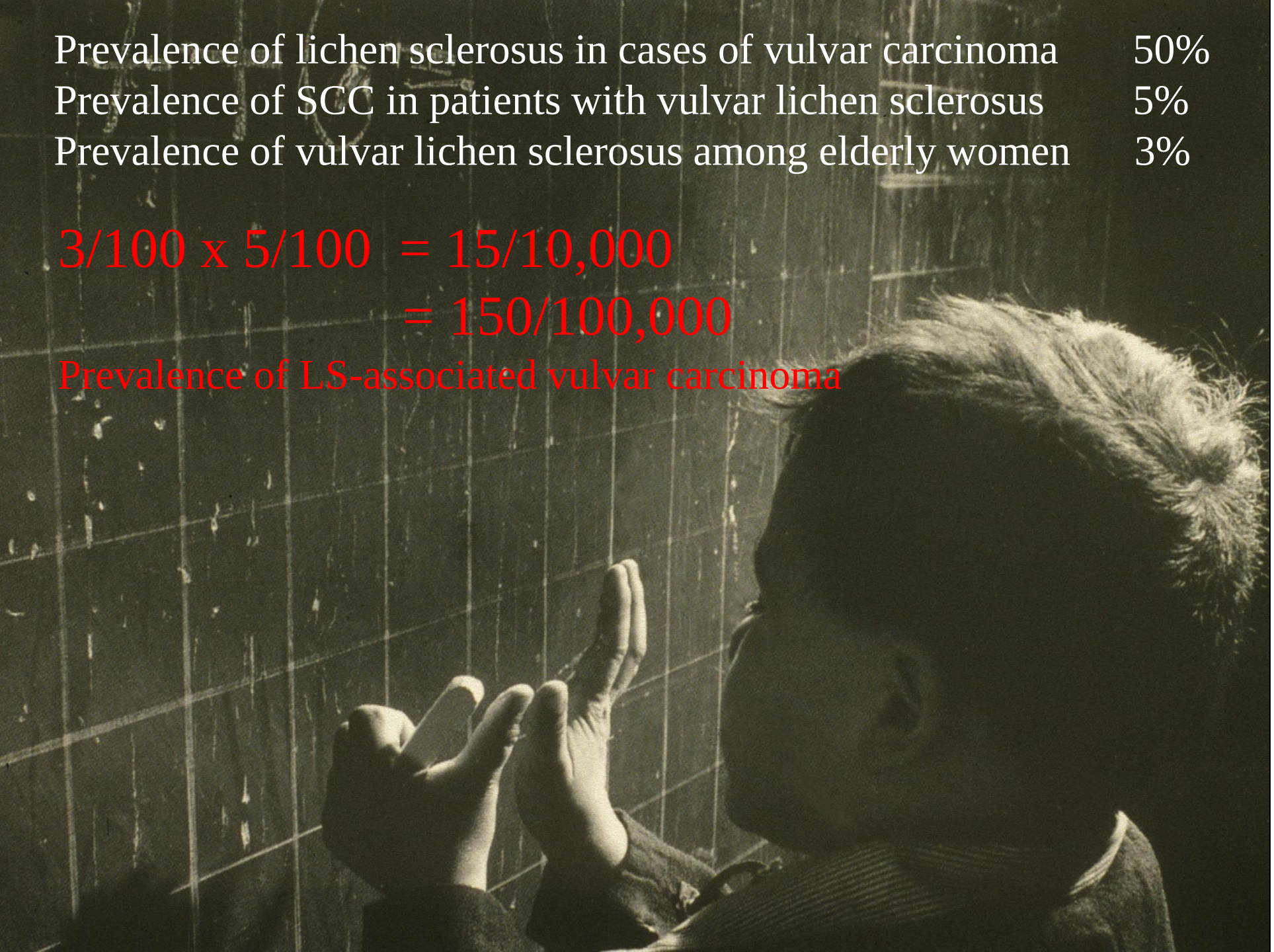
interferon gamma, tumor necrosis factor–alpha, interleukin-1, interferon gamma receptor, CD25, CD11a, and ICAM-1. Sander et al[5] compared vulvar LS tissue from 16 patients with tissue from 16 vulvar control samples and found a significant increase of lipid peroxidation products, particularly within 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).

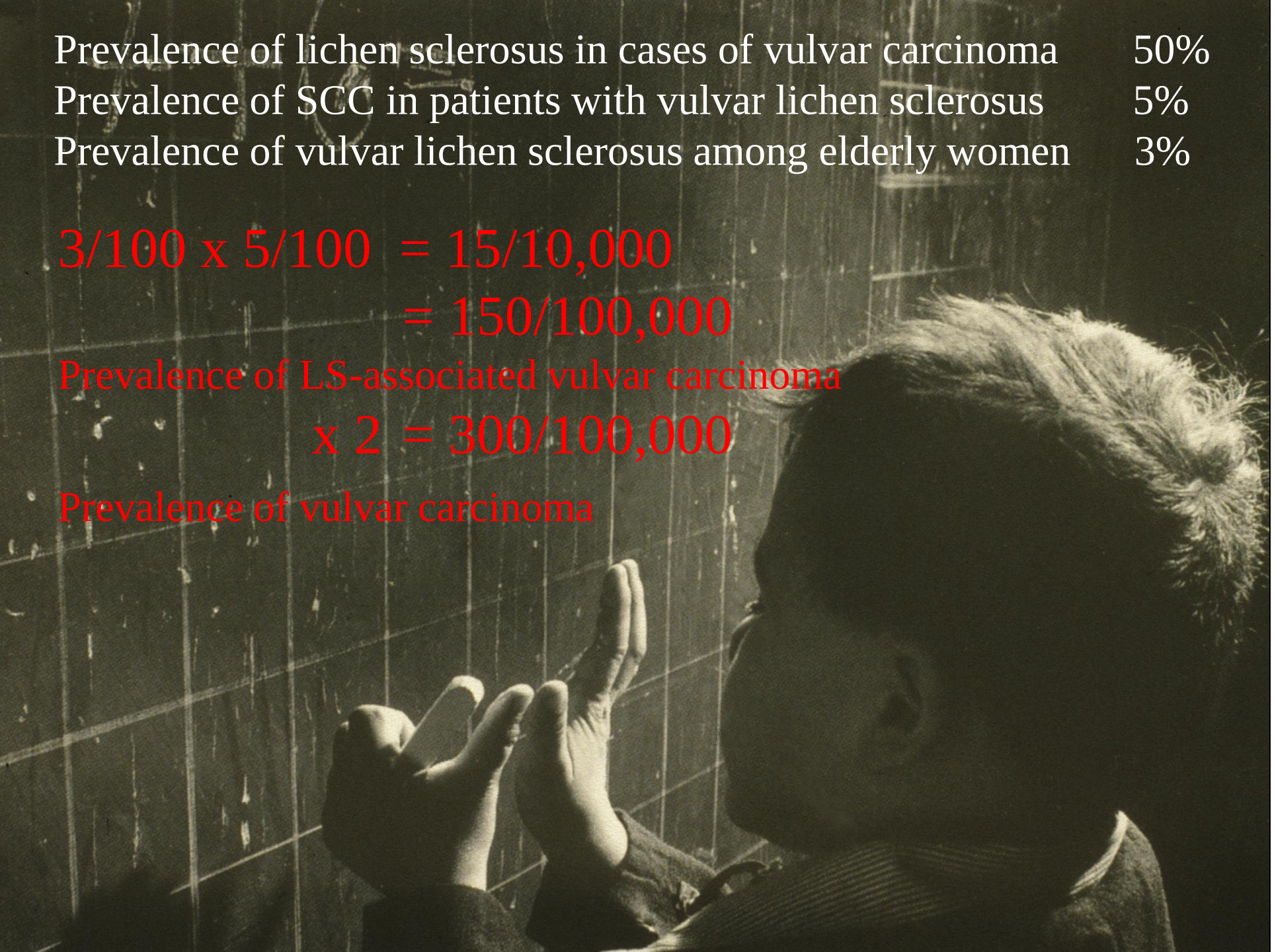
Vice versa, patients with lichen sclerosus are said to have *"a 4% to 6% risk of developing a vulvar squamous cell carcinoma."* Let's assume for a moment that these data are correct:



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. 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

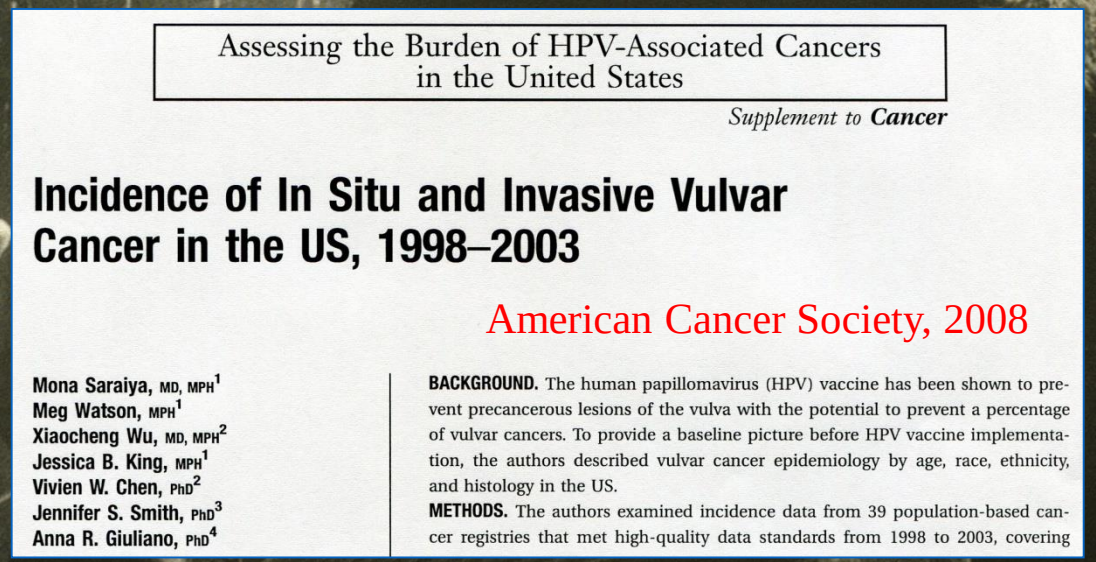
Prevalence of LS-associated vulvar carcinoma

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.

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

The risk of malignancy is said to be especially high 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."*

Hypertrophic Lichen Sclerosus With Dyskeratosis and Parakeratosis—A Common Presentation of Vulvar Lichen Sclerosus Not Associated With a Significant Risk of Malignancy

Wolfgang Weyers, MD

Abstract: Epithelial hyperplasia, individual necrotic keratocytes, and parakeratosis are common findings in lichen sclerosus. When those changes are prominent, they may pose diagnostic problems, especially because such lesions often show no or only minimal sclerosis. Necrotic keratocytes are often numerous and are found in all reaches of the epidermis, presenting themselves as eosinophilic globules with or without remnants of pyknotic nuclei. Because those changes tend to be accentuated focally above dermal papillae, they often give rise to narrow columns of parakeratosis in the overlying cornified layer. Within those columns, individual necrotic keratocytes with pyknotic nuclei are preserved as distinct dyskeratotic parakeratotic cells. That constellation of findings is fairly characteristic of hypertrophic lichen sclerosus. It was found, at least subtle and focally, in 14 of 70 consecutive biopsy specimens of lichen sclerosus, most of which came from the vulva of elderly women. Although similar cases have been described as differentiated vulvar intraepithelial neoplasia (VIN) in the literature, there was no significant nuclear atypia, no crowding of nuclei, and no significant mitotic activity in any of those lesions. Follow-up of at least 5 years in 8 patients revealed no development of squamous cell carcinoma. Hypertrophic lichen sclerosus with dyskeratosis and parakeratosis seems to be a relatively common presentation of vulvar lichen sclerosus not associated with a significant risk of malignancy.

Key Words: vulva, lichen sclerosus, dyskeratosis, parakeratosis, vulvar intraepithelial neoplasia, differentiated VIN

(*Am J Dermatopathol* 2013;35:713–721)

often have a long clinical history.[1] In the absence of sclerosis, the lichenoid infiltrate is situated immediately beneath the epidermis, and lymphocytes may "pepper" the epidermis in concert with scant spongiosis, findings reminiscent of mycosis fungoides.[2,3] Necrotic (dyskeratotic) keratocytes are often seen in the upper reaches of the epidermis, sometimes in number, and lesions may show prominent parakeratosis.

Those findings pose problems in 2 respects. First, if not recognized as one presentation of lichen sclerosus, diagnosis may be missed easily in cases with little or no sclerosis. Second, because of classification of lichen sclerosus as a "premalignant" dermatosis, unusual changes in the epidermis are often regarded as evidence of progression toward malignancy.

We recently observed an unusual case of hypertrophic lichen sclerosus with prominent dyskeratosis and parakeratosis. Two similar cases were retrieved from our teaching collection. To assess the frequency of those findings, we re-examined 70 consecutive cases from the year 2005 in which the diagnosis of lichen sclerosus had been made both clinically and histopathologically. In this group, we found 5 additional cases that shared the constellation of marked epithelial hyperplasia with numerous necrotic keratocytes and prominent parakeratosis. All biopsy specimens came from the vulva or perineum of elderly women. Moreover, 9 cases from the vulva or perineum showed similar findings that were less pronounced or present only in foci. Epithelial hyperplasia with dyskeratosis and parakeratosis, therefore, is a relatively common finding in vulvar lichen sclerosus.

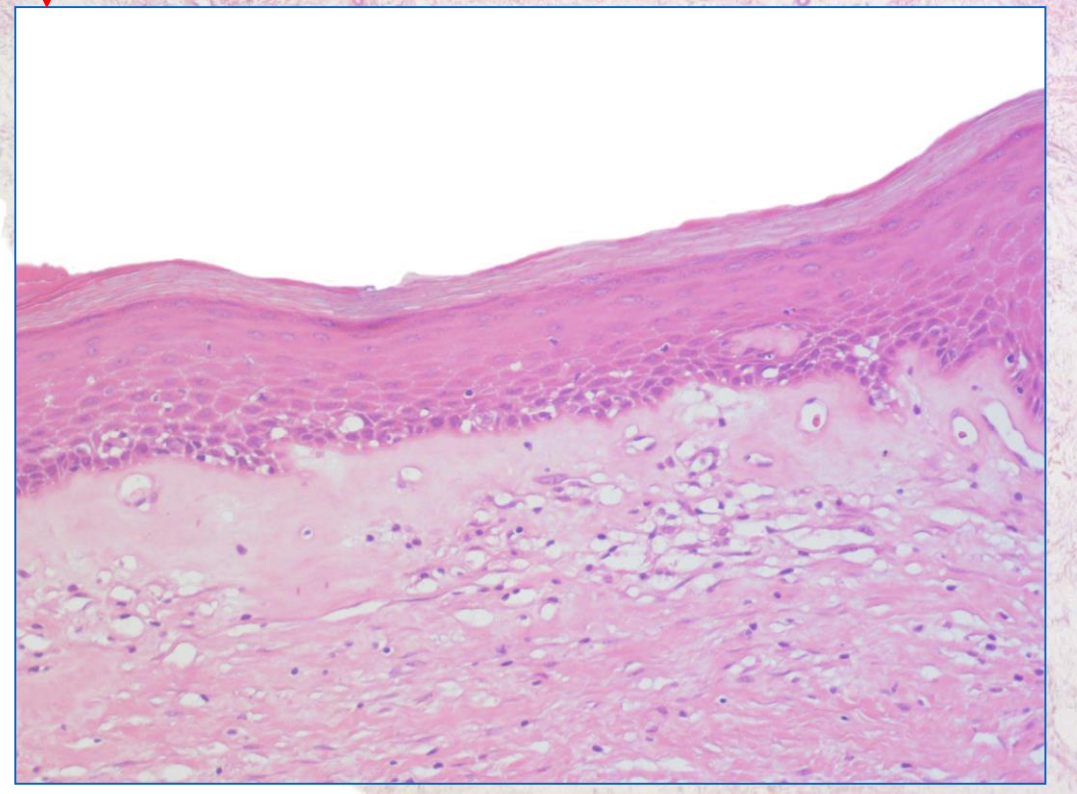
A few years ago, we conducted a study of that type of lesions and found that they were *"not associated with a significant risk of malignancy"*: none of our patients developed squamous-cell carcinoma during a follow-up period between 6 months and 7 years.

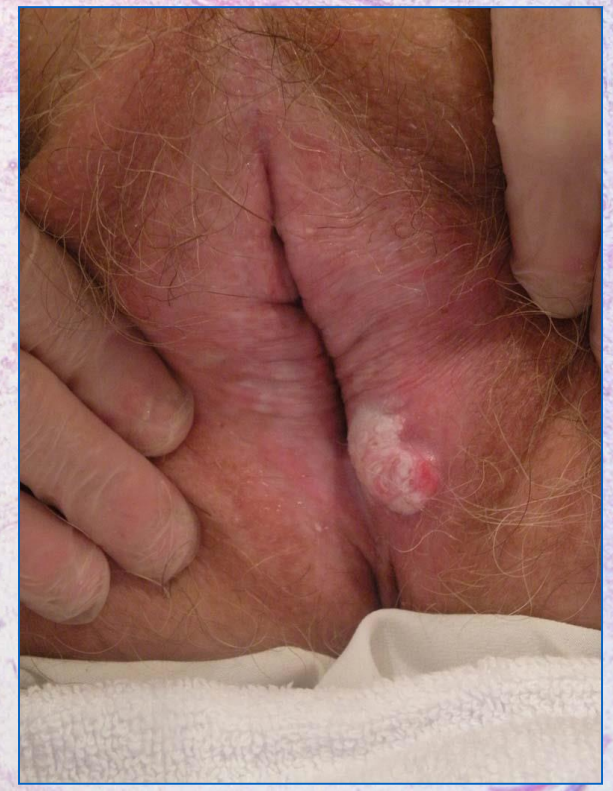
We also conducted a survey concerning the alleged “white danger” emanating from lichen sclerosus. Leading dermatopathologists from Europe and the United States were asked how often they had seen the association of lichen sclerosus with cancer in their regular material.

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 five cases in a professional career of more than 40 years. 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. There may be some bias in that survey because larger carcinomas of the vulva are probably sent chiefly to gynaecopathologists.





However, dermatopathologists also see scores of biopsies performed by dermatologists and gynaecologists to rule out malignancy in lesions of lichen sclerosus, and those biopsies performed for screening purposes may reflect the true risk of lichen sclerosus better than data derived from pathology units associated with departments for gynaecological surgery. Although squamous-cell carcinoma may develop in lesions of lichen sclerosus, this is a rare event, and the risk is exaggerated vastly.

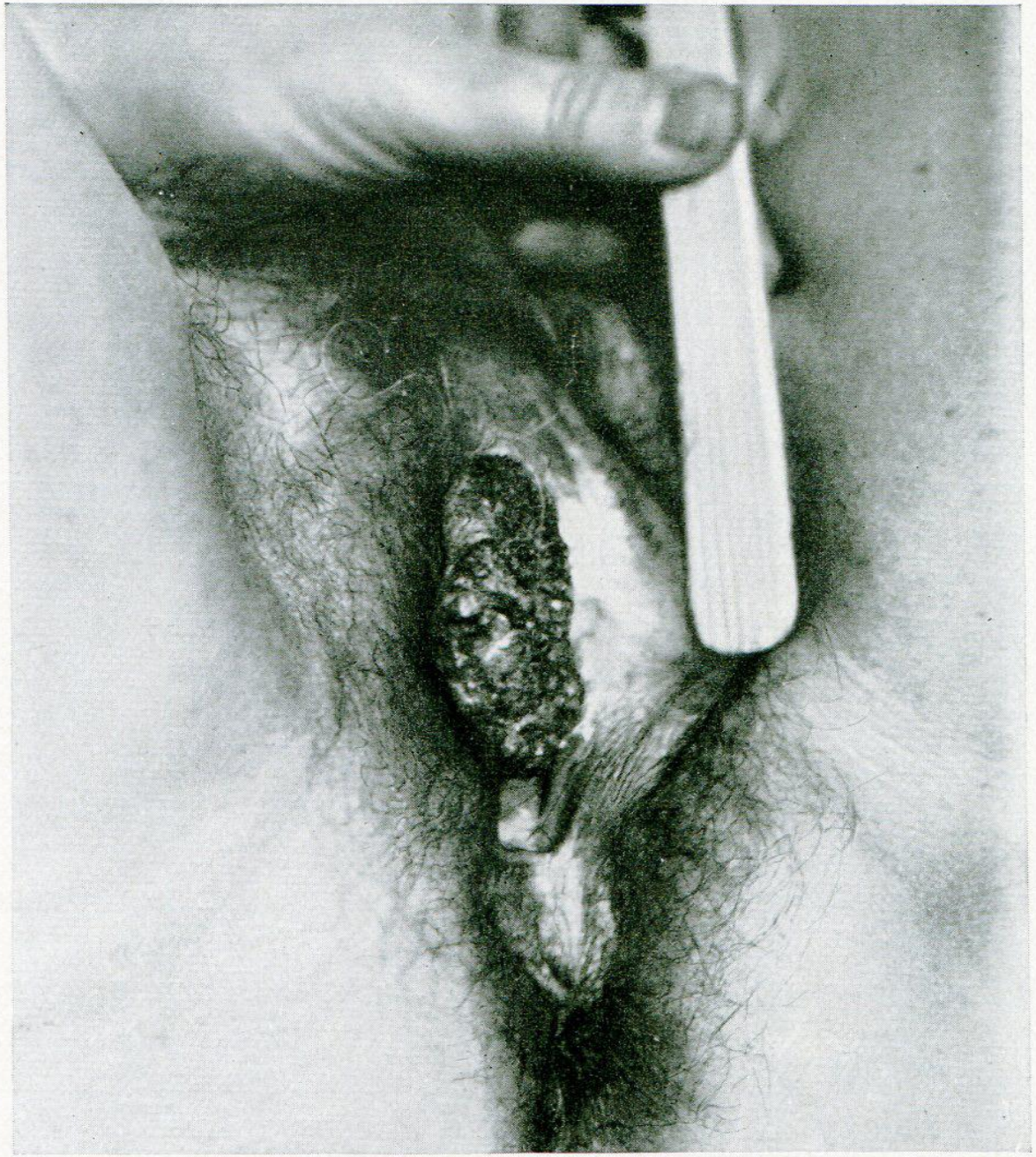


Abb. 20. Kraurosis vulvae, Leukoplakia. Blumenkohlähnliches Carcinom, das sich auf dem Boden einer Leukoplakie allmählich entwickelte. 70jährige Frau

The reasons for that exaggeration are in part historical. In the early 20th century when vulvar lichen sclerosus was still known as “kraurosis vulvae,” the whitish lesions of it were confused 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,

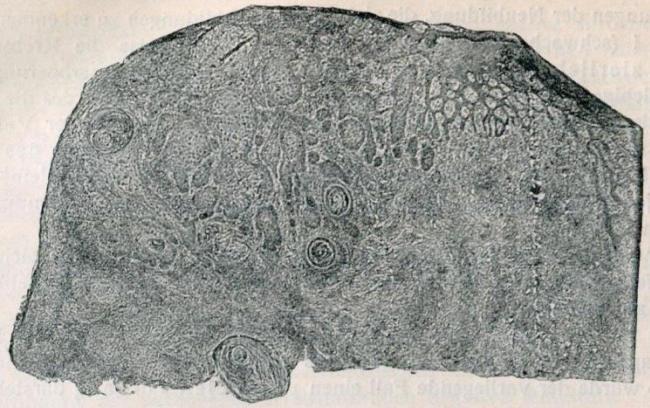


Fig. 1.

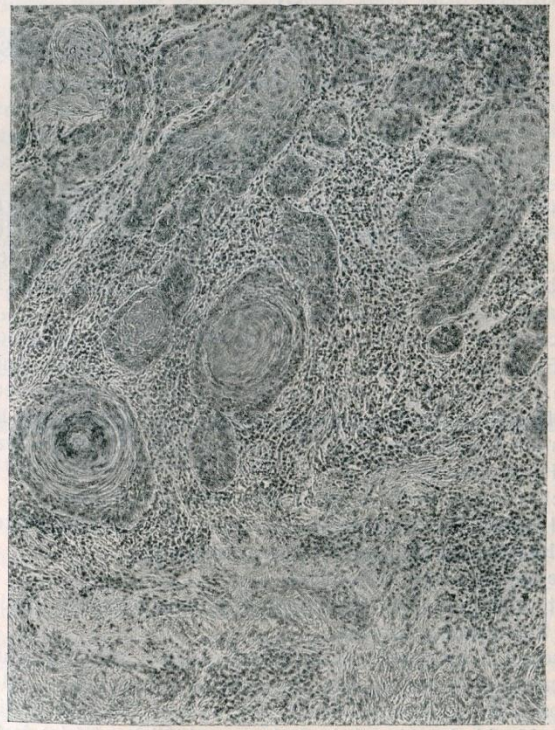


Fig. 2.

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.

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

Arch Dermatol
1962; 85: 362

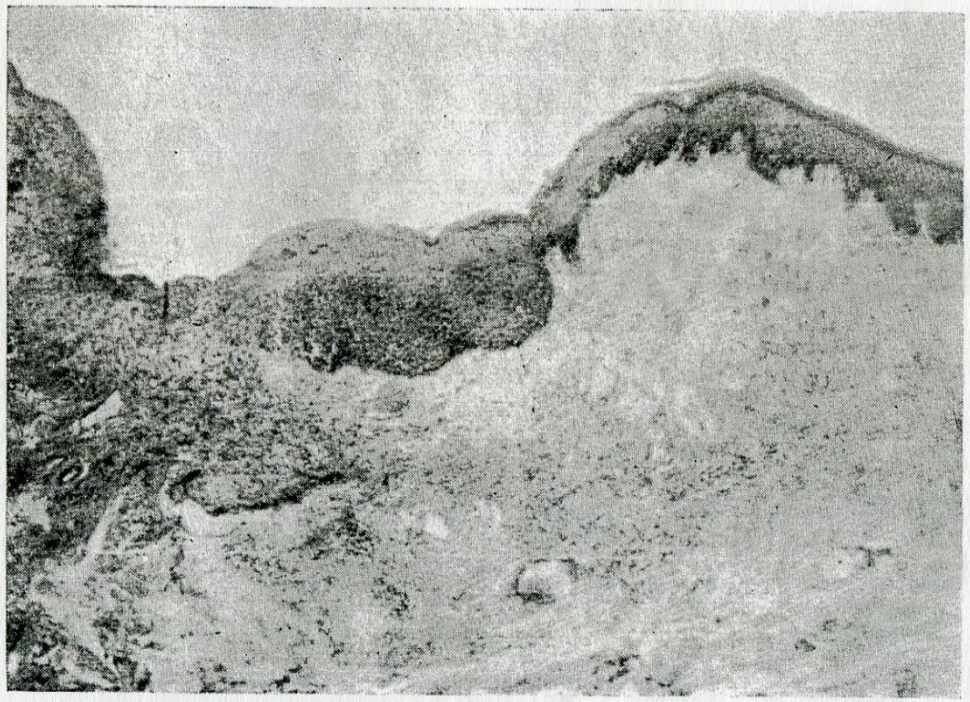


Fig. 7.—Sections of LSA of vulva with carcinoma in situ. Note leukoplakia changes in epidermis on the right of specimen, with homogenization of upper corium beneath. On the left is seen irregular proliferation of basal cells and mass of large prickle cells.

Since Hal s. Hence,
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lichen scler teria for
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dermatitis,
card-like sc ission of
and many o is outline
(1934), Mo ase as it
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specific clini

the criteria for a classification of LSA were finally clarified.

General Characteristics of Lichen Sclerosus et Atrophicus

Subsequently, cases of squamous-cell carcinoma within lesions of lichen sclerosus were described, but at that time,

Lichen Sclerosus et Atrophicus of the Female Genitalia

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1962; 85: 362

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

lichen sclerosus was treated routinely with radiotherapy which may have been a contributing factor.

GRADUATE EDUCATION

NEW NOMENCLATURE FOR VULVAR DISEASE

Report of the Committee on Terminology

THE ONLY PURPOSE for a uniform terminology of any group of diseases is to enable a physician to diagnose a condition using a term which indicates the biologic behavior of the disease and characterizes its clinical significance. Such prediction of behavior and significance is based on the documented experience of others and will have validity and reliability in proportion to the uniformity, comparability, and volume of that documentation.

Proposal of the International Society for the Study of Vulvar Disease.

Adopted by the ISSVD at the 2nd International Congress, January 10, 1975, Key Biscayne, Florida. The Committee on Terminology consisted of R. H. Kaufman, MD, Chairman, G. R. DiPaola, MD, E. G. Friedrich, Jr., MD, and J. D. Woodruff, MD.

Submitted for publication July 25, 1975.

The illustration at the top of the page depicts Galen lecturing at the Temple de la Paix (The Bettmann Archive).

VULVAR DYSTROPHIES

The term *dystrophy* characterizes the many disorders of epithelial growth and nutrition which result in otherwise unclassified alterations of the surface architecture. Included within the general classification of the vulvar dystrophies are those vulvar changes variously described in the past as leukoplakia, kraurosis, atrophic dystrophy, hyperplastic vulvitis, leukoplakic vulvitis, neurodermatitis. The gross changes seen on the vulva may be diffuse or localized and may be seen as thickened or thinned. White or red color changes may be evident. These lesions should be specifically classified according to their microscopic features as follows:

I. Hyperplastic dystrophy
   A. Without atypia
   B. With atypia
II. Lichen sclerosus
III. Mixed dystrophy (lichen sclerosus with foci of epithelial hyperplasia)
   A. Without atypia
   B. With atypia

Friedrich EG Jr.
Obstet Gynecol
1976; 47: 122-124

Another cause for the exaggeration is the simplistic classification of vulvar dermatoses advanced by gynecopathologists. In the first classification by the International Society for the Study of Vulvar Disease, lichen sclerosus was the only specific disease mentioned and, therefore, that diagnosis was given excessively.

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

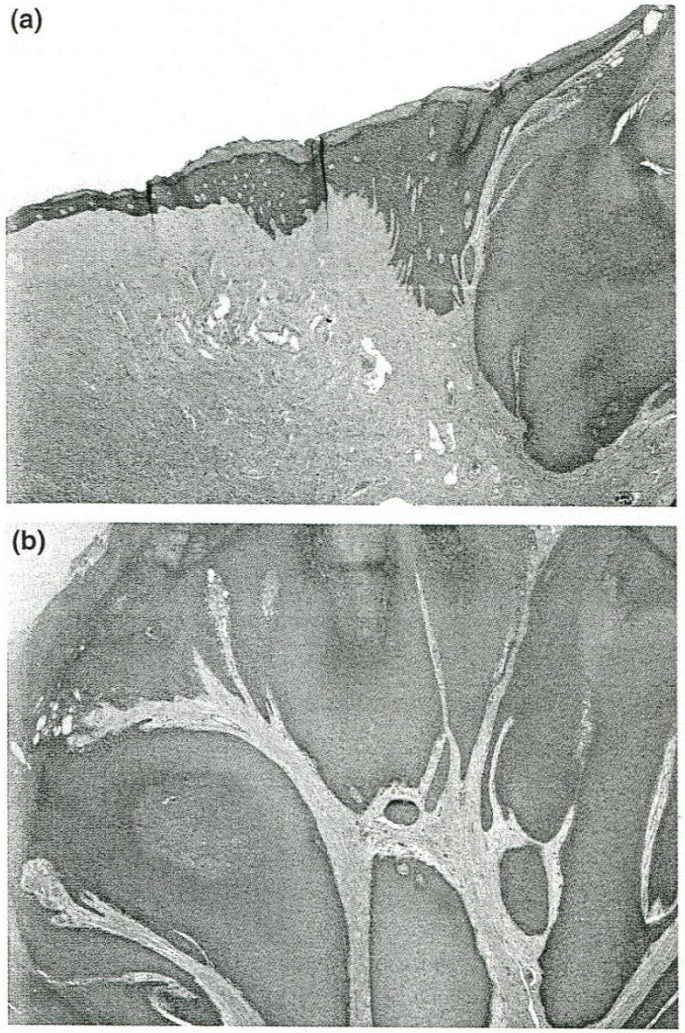


Figure 1 (a) Histopathological examinations showed verrucous carcinoma (right) with associated adjacent lichen sclerosus (left) manifested by atrophy of epidermis and homogenization of the dermis; (b) The verrucous carcinoma part showed hyperkeratotic warty endophytic growth of well-differentiated malignant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

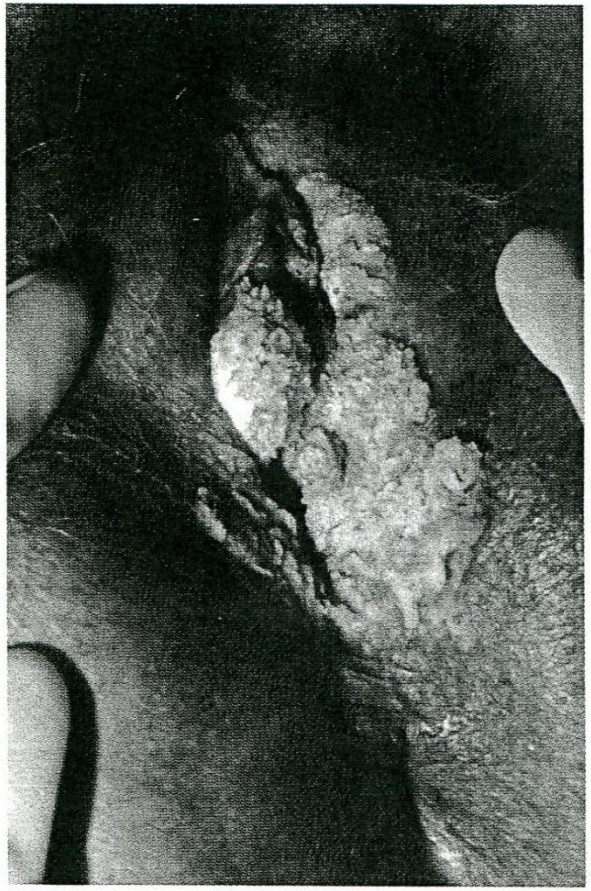
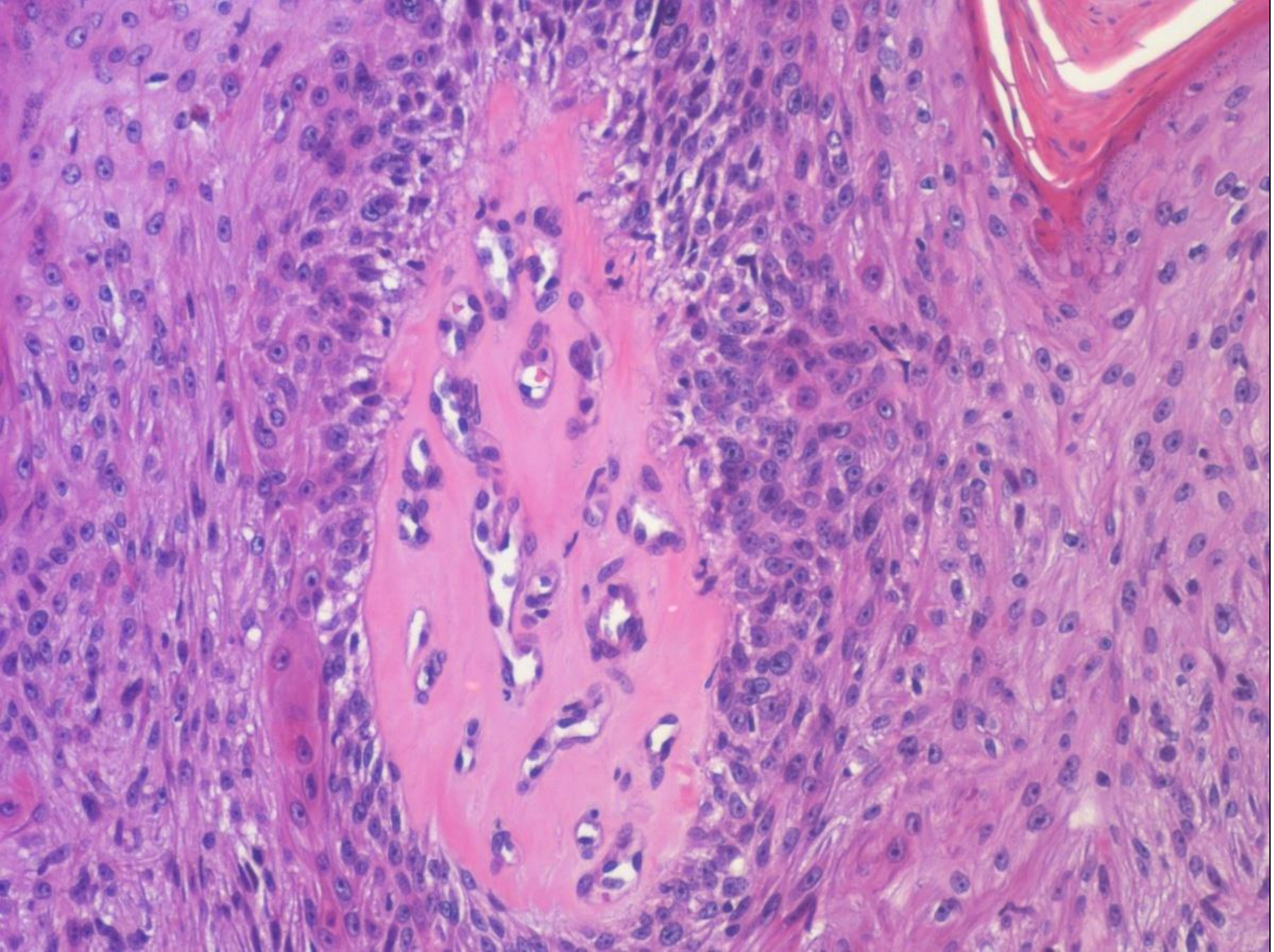


Figure 2 Extensive warty growths arising from both inner labia majora and extending into the introitus.

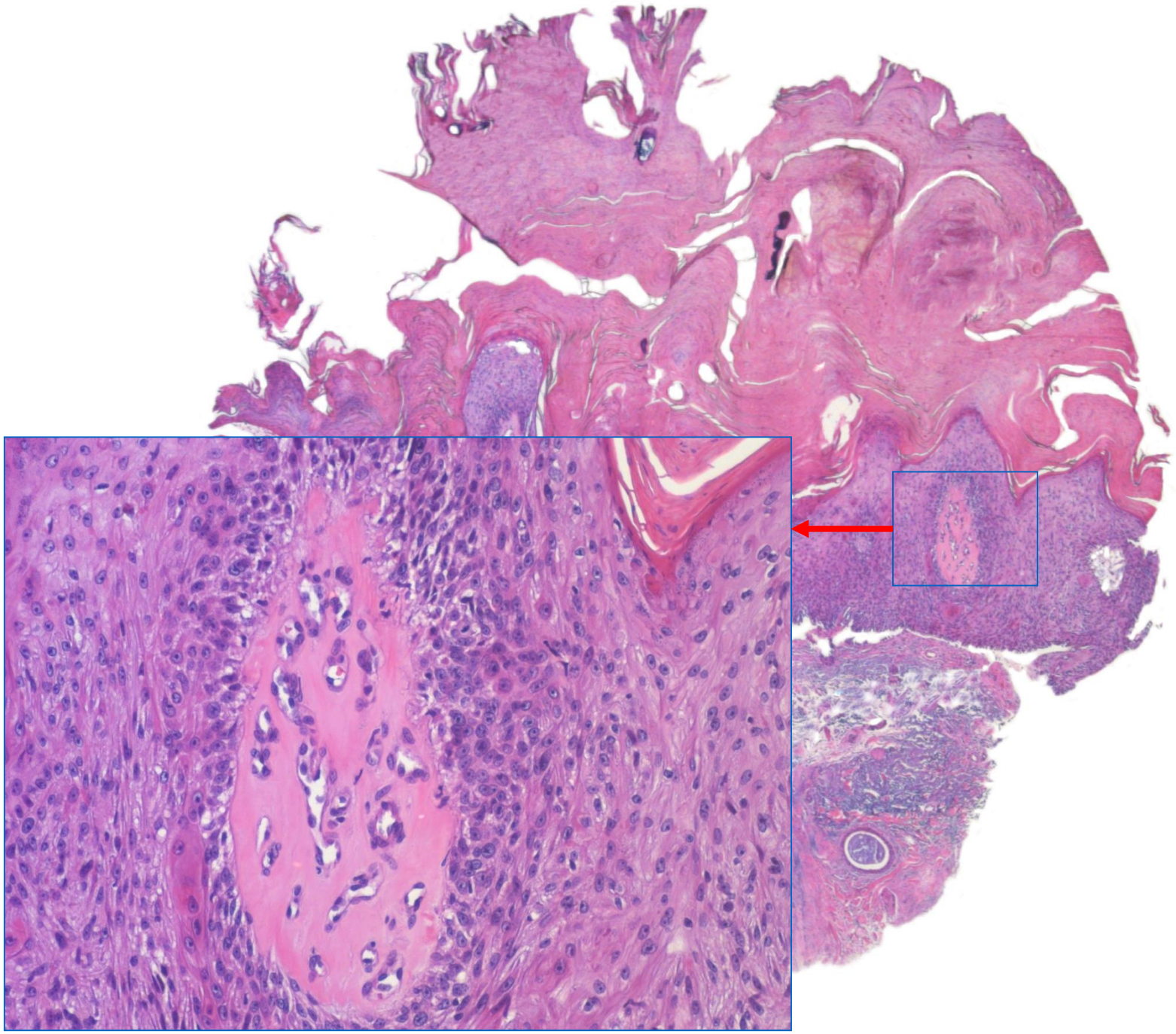
including HPV infection, altered p53 expression, chronic inflammation and oxidative stress, may contribute to this association (Fig. 3).

Verrucous carcinoma is thought to be related to HPV infection

Well into recent years, reports have been published of *"carcinoma associated with lichen sclerosus"* in which there is no evidence of lichen sclerosus in photomicrographs.



But even the presence of undubitable sclerosis beneath a squamous-cell carcinoma 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.

The Journal of Reproductive Medicine®

Abstract

Title: **Squamous Vulvar Intraepithelial Neoplasia: 2004 Modified Terminology, ISSVD Vulvar Oncology Subcommittee**

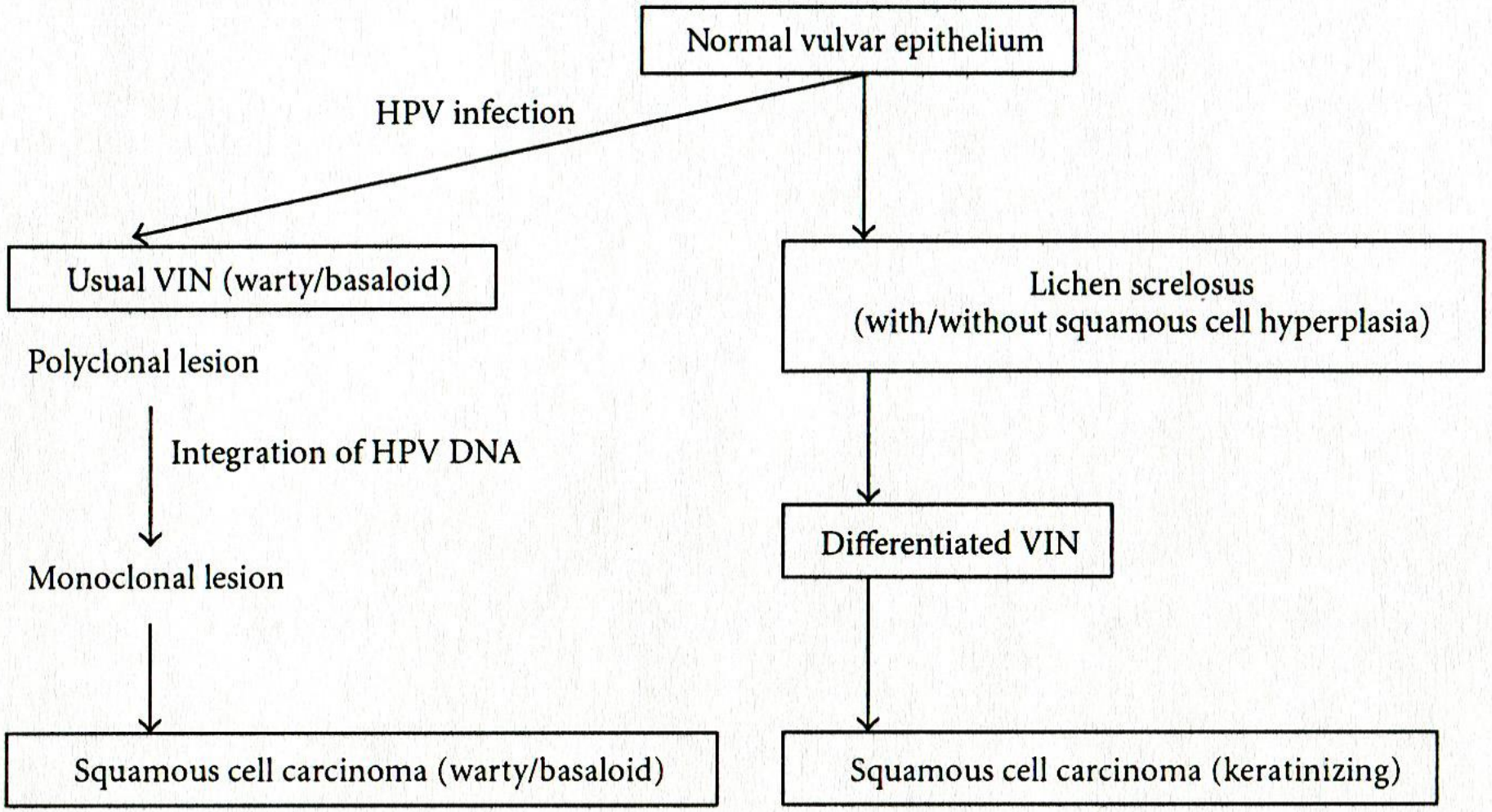
Authors: Mario Sideri, M.D., Ronald W. Jones, M.D., Edward J. Wilkinson, M.D., Mario Preti, M.D., Debra S. Heller, M.D., James Scurry, M.D., Hope Haefner, M.D., and Sallie Neill, M.D.

In the current classification, squamous vulvar intraepithelial neoplasia (VIN) is categorized as VIN 1, 2 and 3 according to the degree of abnormality. There is neither evidence that the VIN 1-3 morphologic spectrum reflects a biologic continuum nor that VIN 1 is a cancer precursor. The VIN 2 and 3 category includes 2 types of lesion, which differ in morphology, biology and clinical features. VIN, usual type (warty, basaloid and mixed), is HPV related in most cases. Invasive squamous carcinomas of warty or basaloid type is associated with VIN, usual type. VIN, differentiated type, is seen particularly in older women with lichen sclerosus and/or squamous cell hyperplasia in some cases. Neither VIN, differentiated type, nor associated keratinizing squamous cell carcinoma is HPV related. The term VIN should apply only to histologically high grade squamous lesions (former terms, VIN 2 and VIN 3 and differentiated VIN 3). The term VIN 1 will no longer be used. Two categories should describe squamous VIN: VIN, usual type (encompassing former VIN 2 and 3 of warty, basaloid and mixed types) and VIN, differentiated type (VIN 3, differentiated type). (J Reprod Med 2005;50:807-810)

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

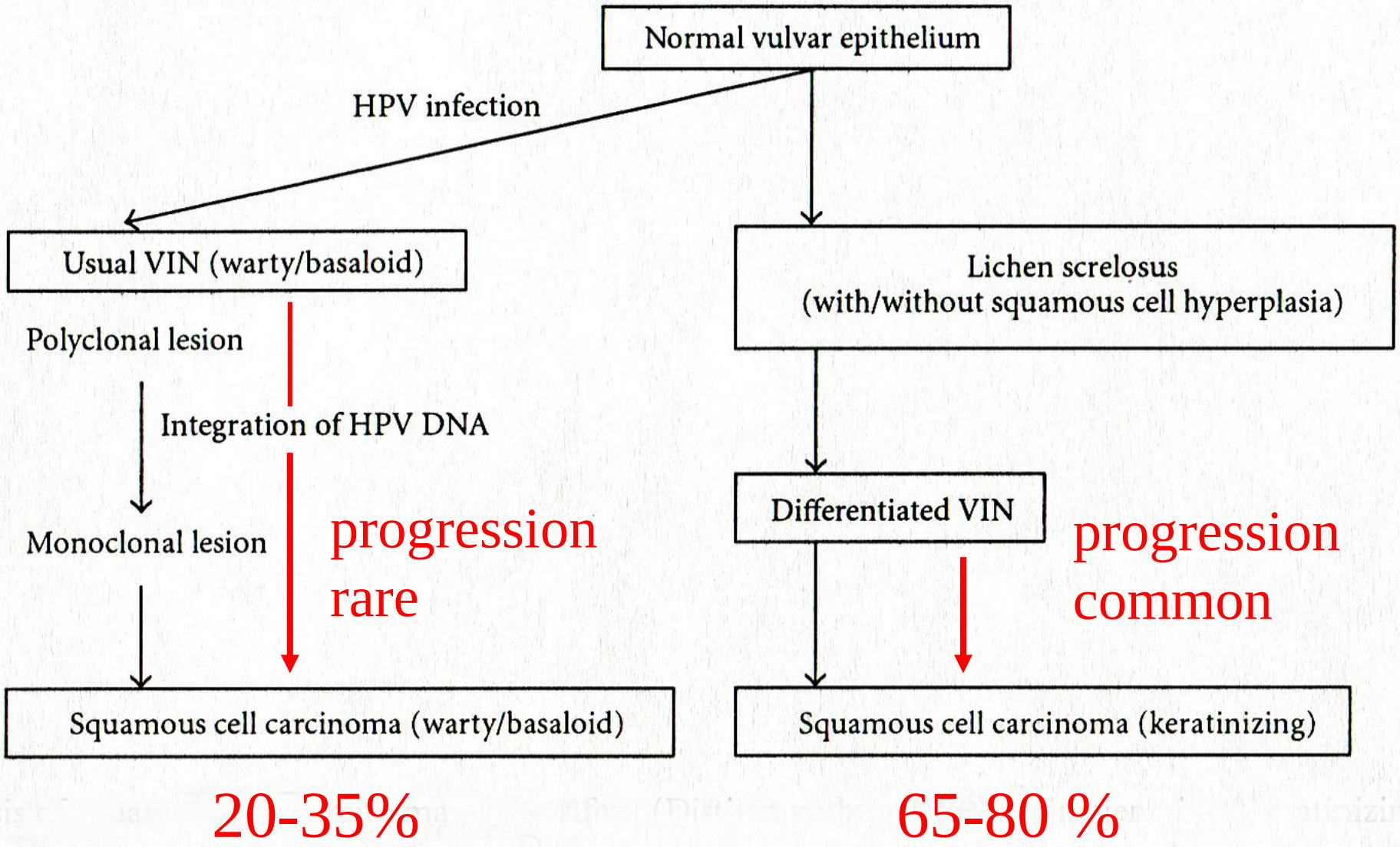
Exaggeration of the risk of malignancy is caused not only by overdiagnosis of lichen sclerosus but also by overdiagnosis of malignancy. This trend has been furthered by the new classification of so-called "vulvar intraepithelial neoplasia" advanced by the International Society for the Study of Vulvovaginal Disease in 2004. It distinguished between *"VIN, usual type"* and *"VIN, differentiated type."*

Ueda Y et al.
J Skin Cancer, 2011

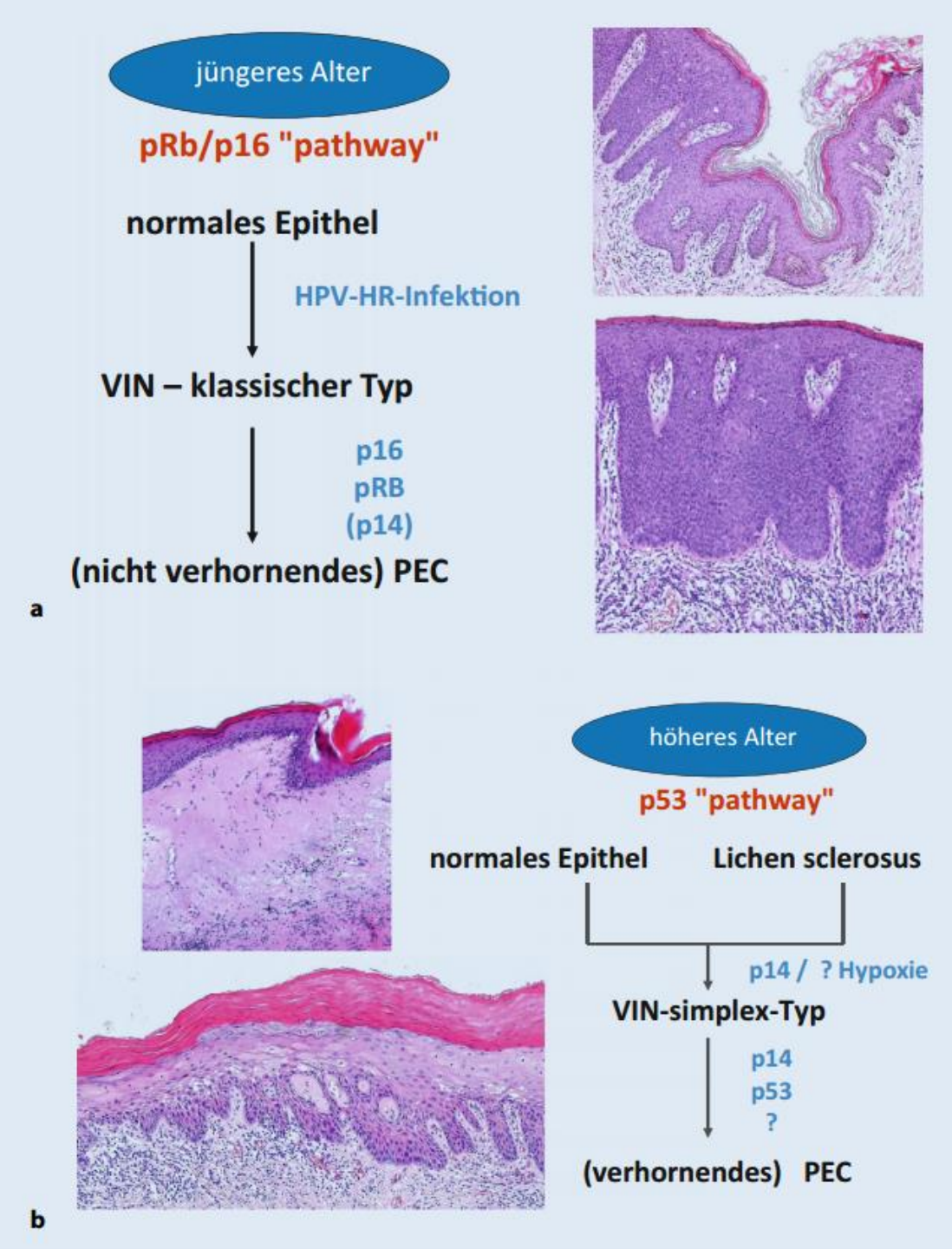


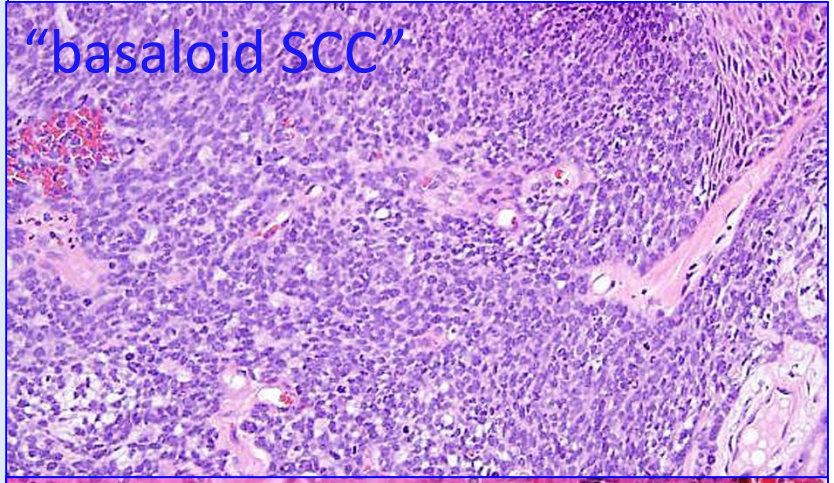
The former was claimed to be caused by human papilloma virus and to progress to warty or basaloid squamous cell carcinoma, whereas the latter was said to be associated with lichen sclerosus and to progress to keratinizing squamous cell carcinoma.

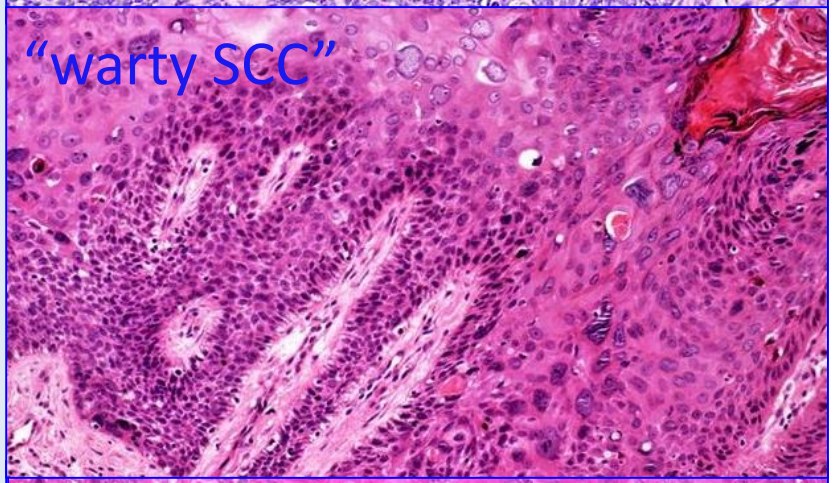
Ueda Y et al.
J Skin Cancer, 2011

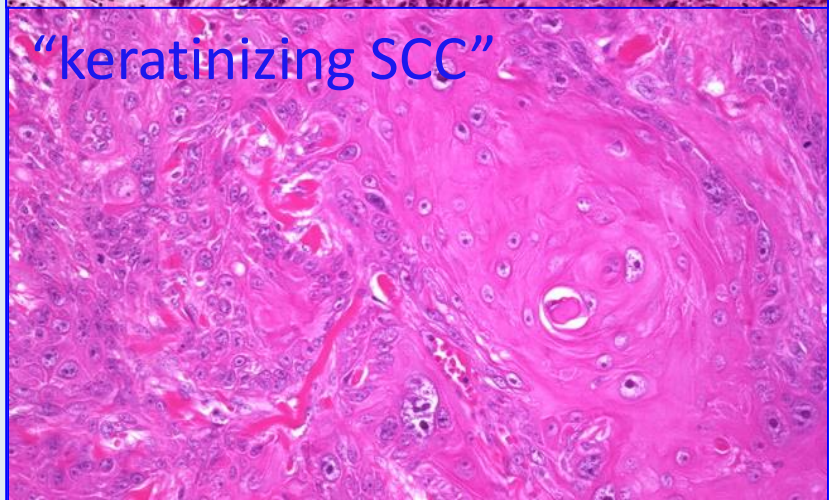


The warty or basaloid type of carcinoma was said to be much rarer than the keratinizing one, and progression of *"usual VIN"* was said to be rare in comparison to progression of *"differentiated VIN"*. With this new classification, lichen sclerosus suddenly became associated conceptually with the most dangerous type of vulvar intraepithelial neoplasia and the most common type of squamous cell carcinoma.



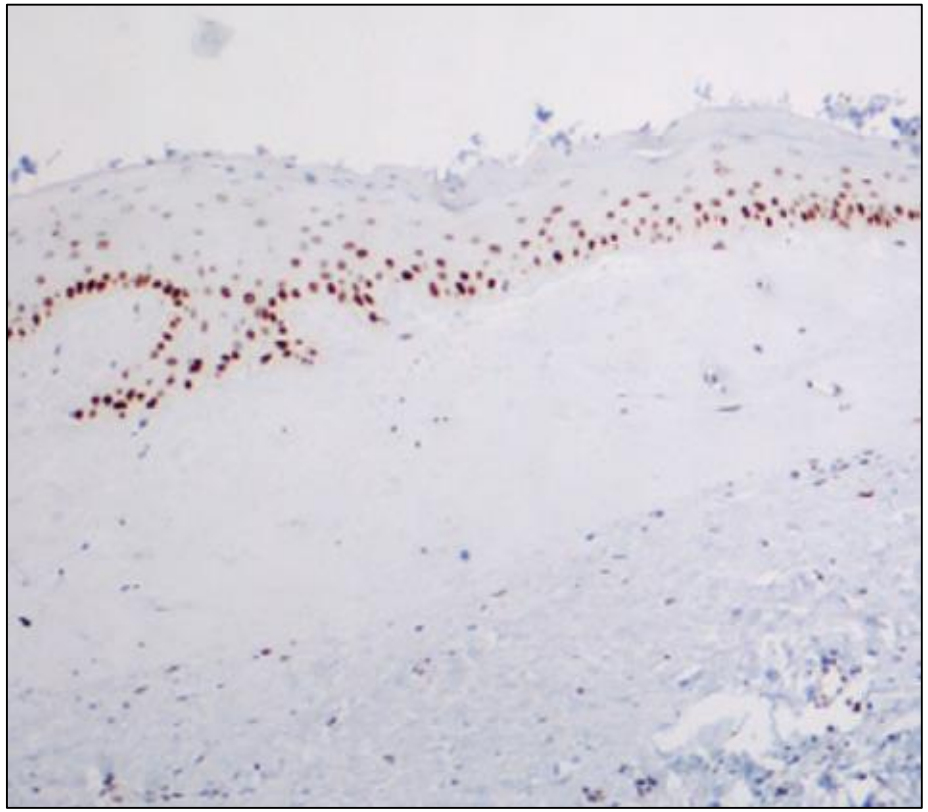


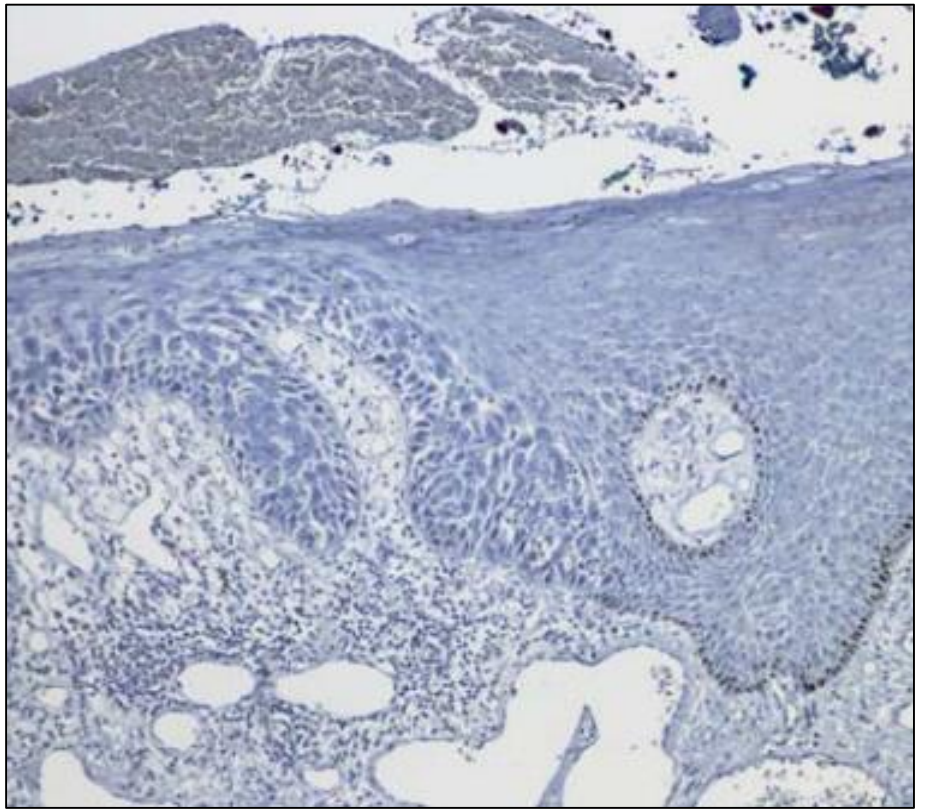




This classification has become widely accepted and is reputed to reflect two distinct pathways of carcinogenesis caused by distinct types of molecular alterations, the “p16 pathway” and the “p53 pathway.” That concept, however, violates many observations. For example, the purported types of squamous-cell carcinoma are not distinct – all types of transitions are possible, and they are common. Human papilloma virus is commonly detected in carcinomas with marked keratinization,

Immunohistochemical staining pattern (% positive cells)	Mutational analysis						
	Wild type	*Nucleotide deletion*	*Nucleotide insertion*	*Missense mutation*	*Nonsense mutation*	*Known TP53 polymorphism*	*Changes in intron region*
Negative ($n=17$)	2	7	1	1	2	2	2
≤10% ($n=8$)	6	—	—	2	—	—	—
20–50% ($n=2$)	2	—	—	—	—	—	—
60–80% ($n=11$)	2	1	—	5	—	2	1
90–100% ($n=19$)	1	1	1	14	1	1	—
Total ($n=57$)	13	9	2	22	3	5	3





and p53 is neither a sensitive nor a specific marker. Different types of mutations have been described for squamous cell carcinoma: missense mutations with overexpression of p53 and nonsense mutations with complete loss of it.

Histopathology 2006, **48**, 268–274. DOI: 10.1111/j.1365-2559.2005.02321.x

p53 immunostaining in lichen sclerosus is related to ischaemic stress and is not a marker of differentiated vulvar intraepithelial neoplasia (d-VIN)

B Liegl & S Regauer
Institute of Pathology, Medical University of Graz, Graz, Austria

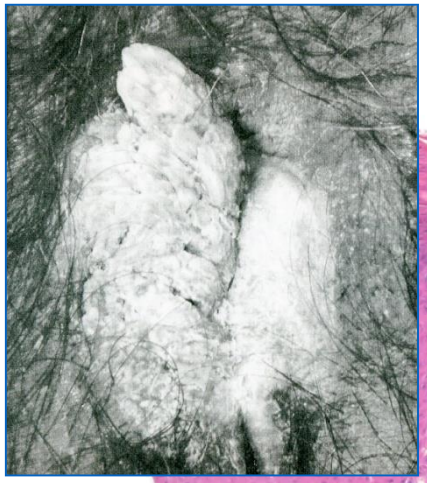
Date of submission 2 May 2005
Accepted for publication 9 May 2005

Liegl B & Regauer S
(2006) *Histopathology* **48**, 268–274

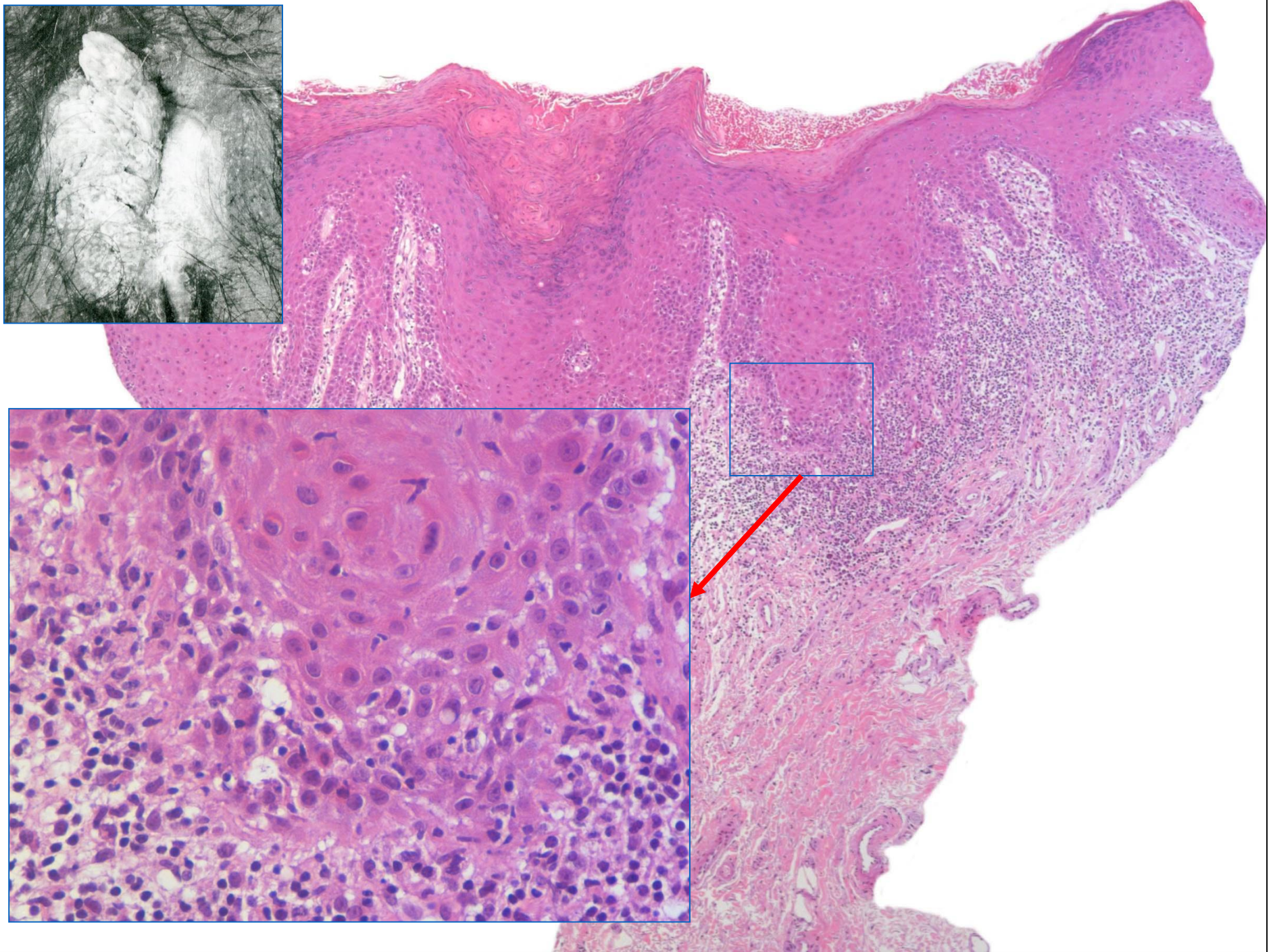
p53 immunostaining in lichen sclerosus is related to ischaemic stress and is not a marker of differentiated vulvar intraepithelial neoplasia (d-VIN)

Aim: To analyse p53 immunoreactivity in 207 biopsy specimens of lichen sclerosus (LS) and 'differentiated vulvar intraepithelial neoplasia' (d-VIN), a postulated precursor lesion for LS-associated vulvar squamous cell carcinoma (SCC), which is characterized by atypical basal keratinocyte proliferations with p53+ basal/suprabasal keratinocyte nuclei.
Methods and results: Forty early, 78 classic, 30 hypertrophic vulvar LS, 26 paediatric vulvar and penile LS, 33 vulvar LS-associated SCC and 30 vulvar/penile control specimens were examined for p53 expression and the presence of d-VIN. Nuclear p53 staining was observed in 175/207 LS biopsy specimems. Eighty percent of early and 69% of paediatric LS showed discontinuous/continous p53 staining in basal keratinocytes. Classic LS showed no p53 staining in 17%, discontinuous basal keratinocyte staining in 20%, continuous basal keratinocyte staining in 58%, basal/suprabasal staining in 5%. Hypertrophic LS revealed basal keratinocyte staining in 32% and basal/suprabasal staining in 61%. p53 staining was associated with sclerosis of blood vessels and dermis, lymphoid infiltrates, vasculitis and hypertrophic LS. d-VIN was seen in 2% of LS alone and in 24% of LS-associated SCC.
Conclusion: d-VIN in LS is rare, while p53 staining is common and best explained as an ischaemic stress response due to poor oxygenation, vasculitis and inflammation rather than as a marker of a precancerous lesion in LS.

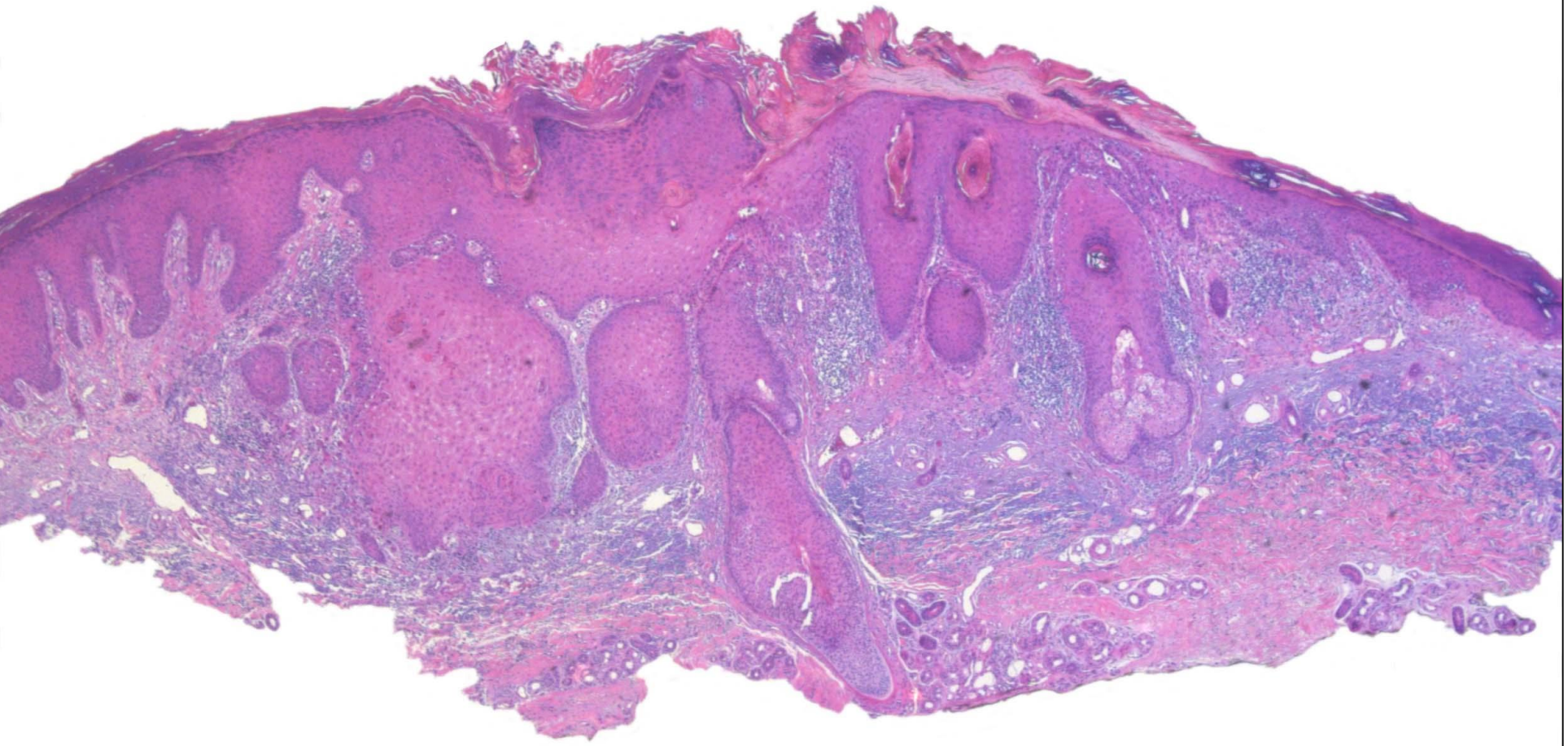
The same spectrum – from complete loss to overexpression of p53 – has also been described for lichen sclerosus and has been attributed to "ischaemic stress," rather than impending malignancy.
In brief, p53 staining does not resolve the problem of distinguishing between lichen sclerosus and incipient carcinoma.



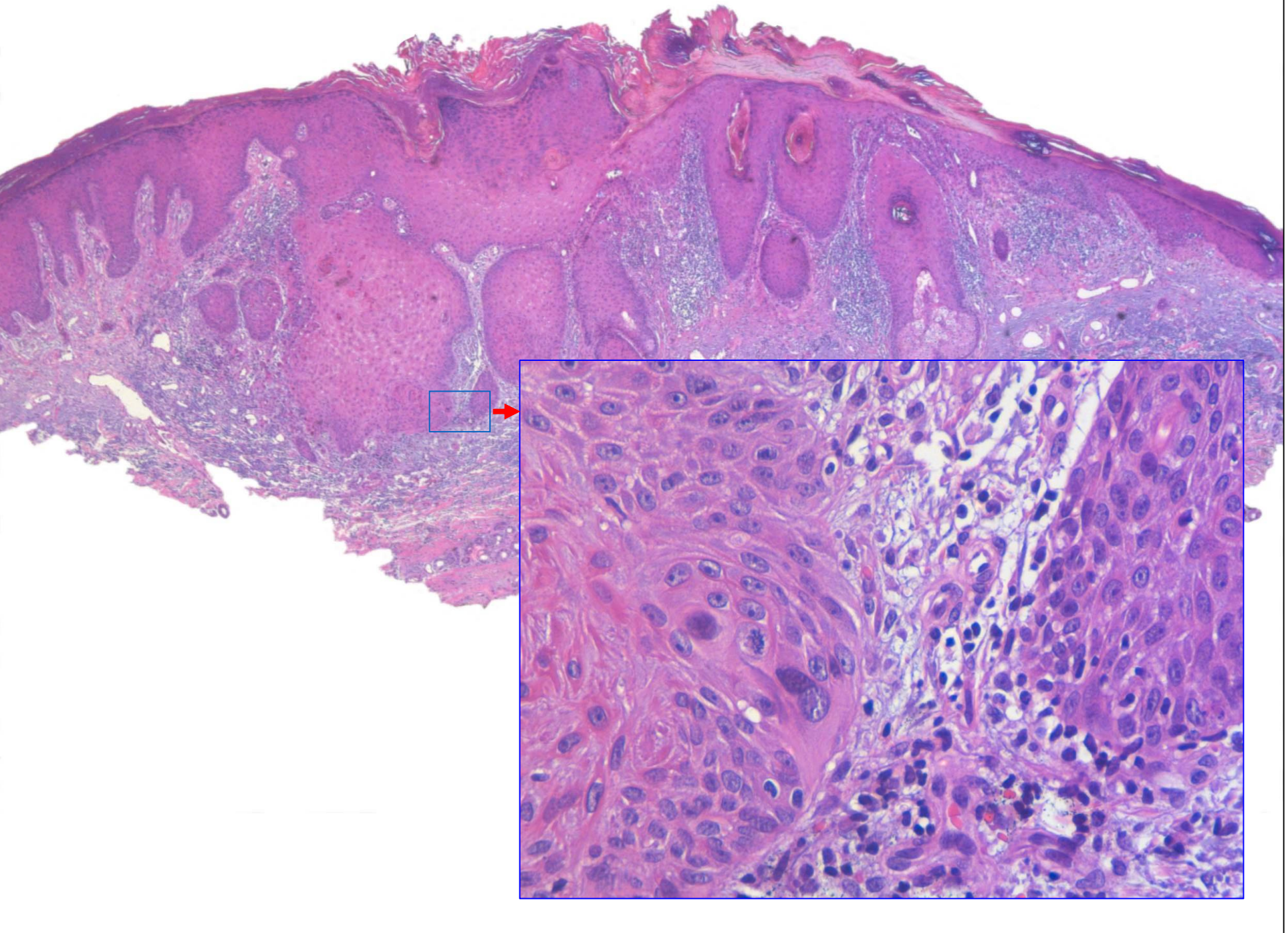
That problem is caused by lack of significant nuclear atypia in early lesions of carcinoma. In such cases, the diagnosis is made on the basis of irregular growth and bizarre configuration of the epithelium.



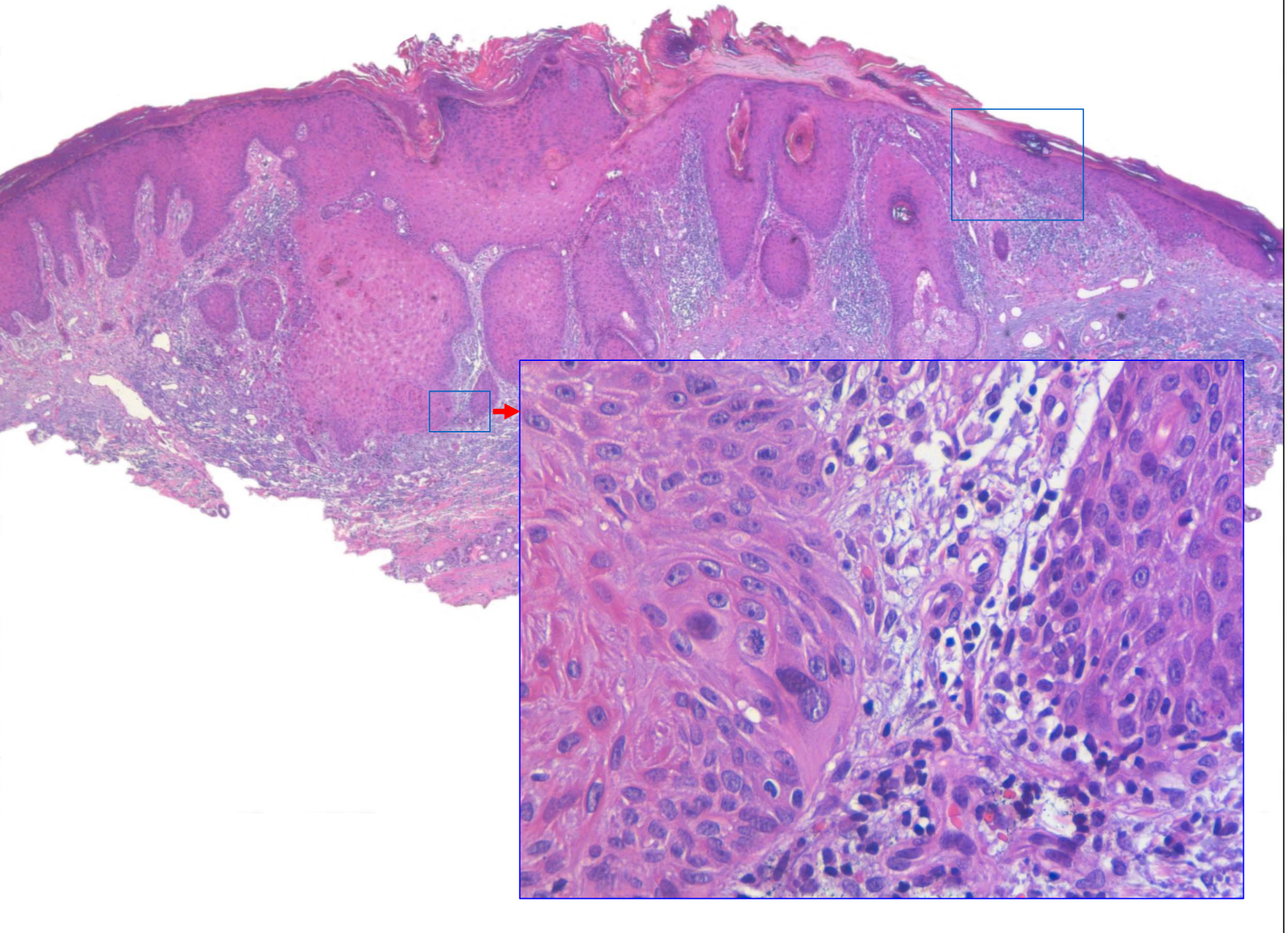
Epithelial cells may be closely crowded, and there may be foci of suprabasilar acantholysis that are not seen in lichen sclerosus. By contrast, nuclear atypia and mitotic figures may not be more common or pronounced than in hypertrophic lichen sclerosus, and both types of lesions may share findings such as a lichenoid infiltrate of lymphocytes and individual necrotic keratocytes.



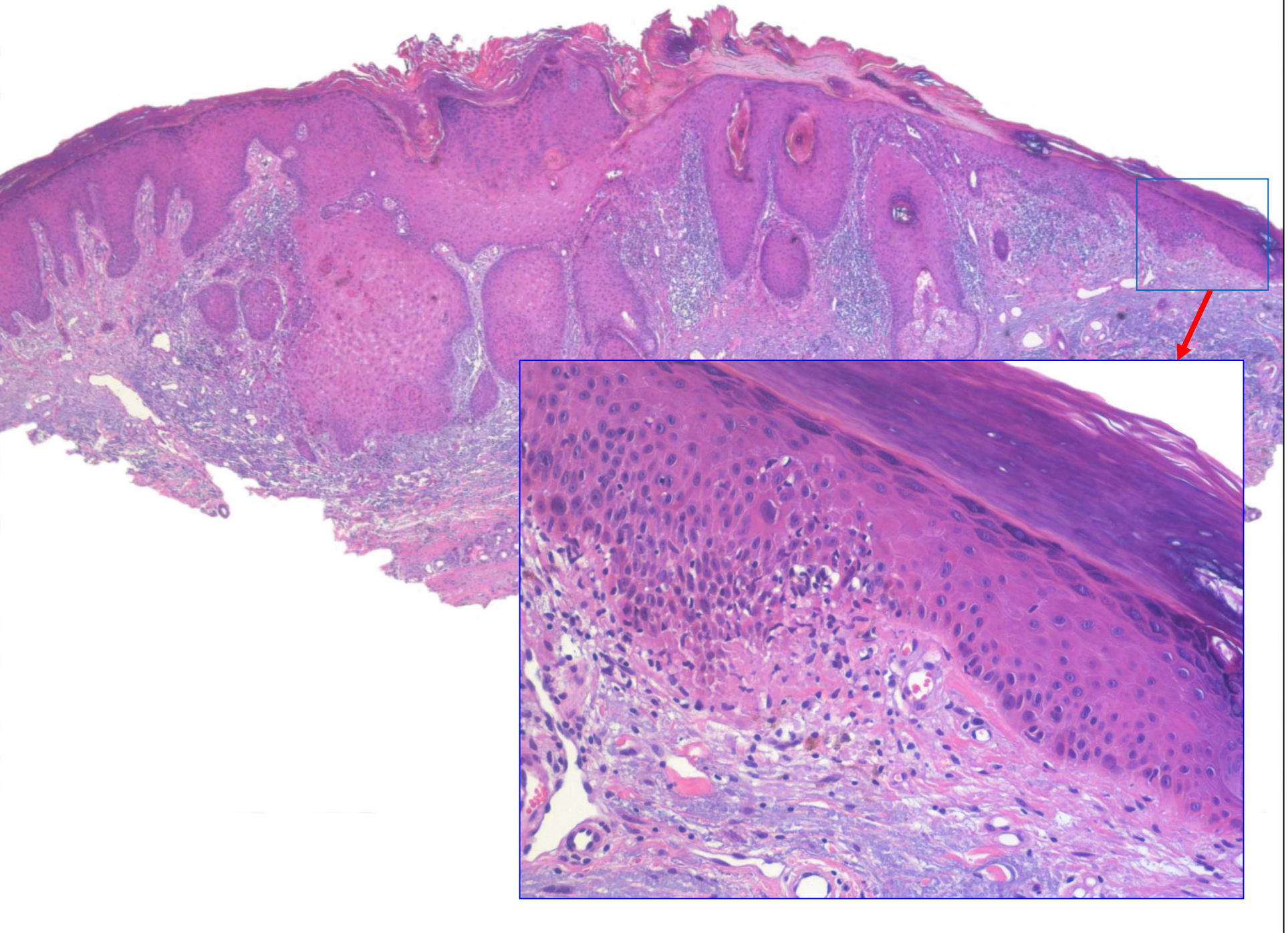
In other words, it may be exceedingly difficult to distinguish incipient carcinoma from epithelial hyperplasia in an inflammatory disease such as hypertrophic lichen sclerosus. This is not only true for the vulva but for all regions of skin.



Often pronounced nuclear atypia and mitotic figures are confined to advanced areas, whereas cytologic changes at the edges of the carcinoma are minimal.



This zone still allows the diagnosis of incipient carcinoma to be made,



but in this zone, it is no longer possible if one does not know the entire picture of the lesion.

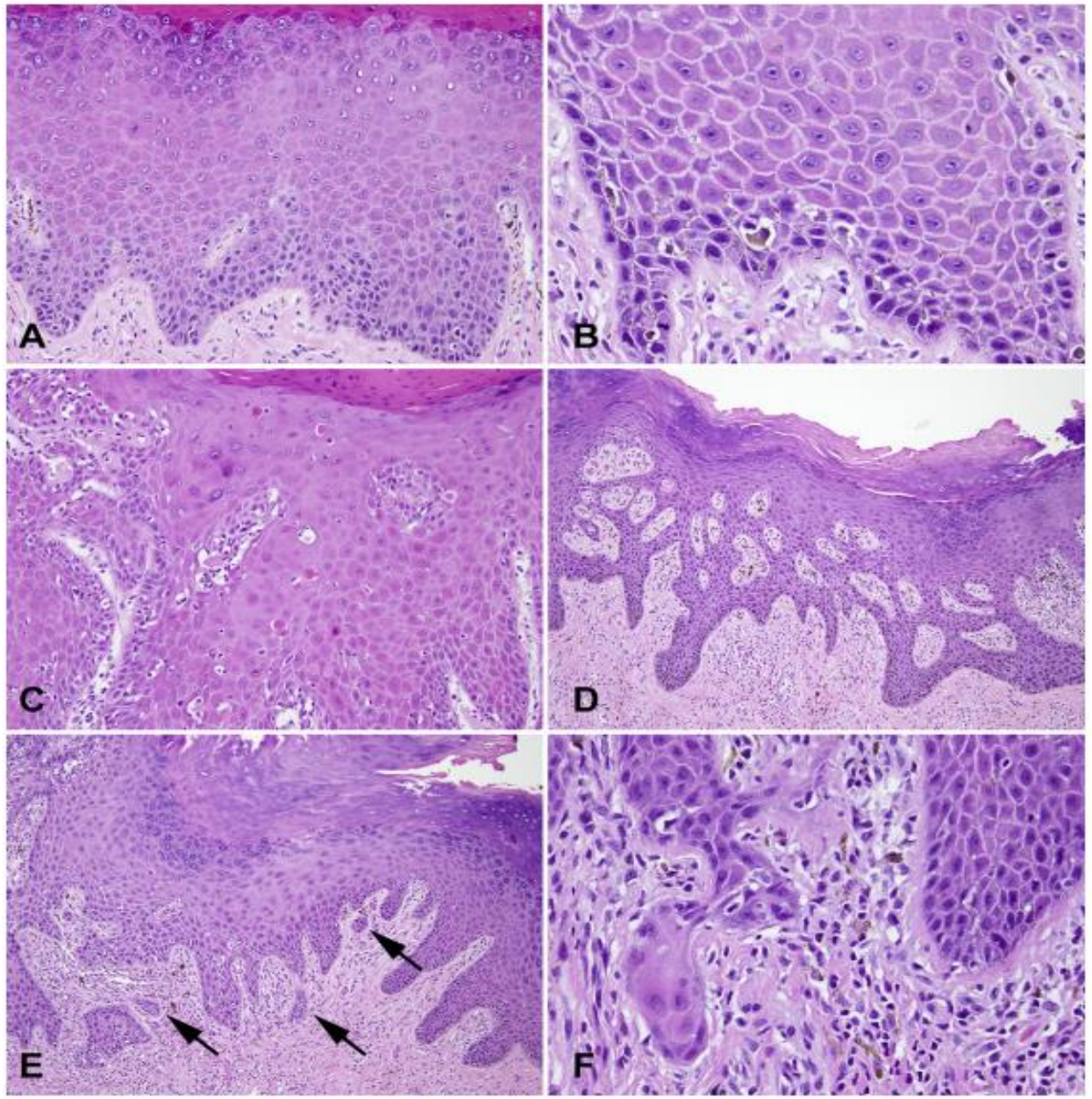


Fig. 3 Vulvar intraepithelial neoplasia, differentiated type (dVIN). (A) Partial thickness dysplasia with retention of keratohyaline granules; (B) basal atypia, nuclei with prominent nucleoli and intercellular bridges; (C) hypereosinophilia and premature keratinisation; (D) irregular branching and anastomoses of rete ridges; (E) pseudoinvasion, regular spacing of nests with rounded contours (arrows); (F) paradoxical maturation suggestive of early invasion.

And if one tries to recognize incipient carcinoma at that early stage – even if referring to it by the evasive term “vulvar intraepithelial neoplasia” – overdiagnoses are inevitable.

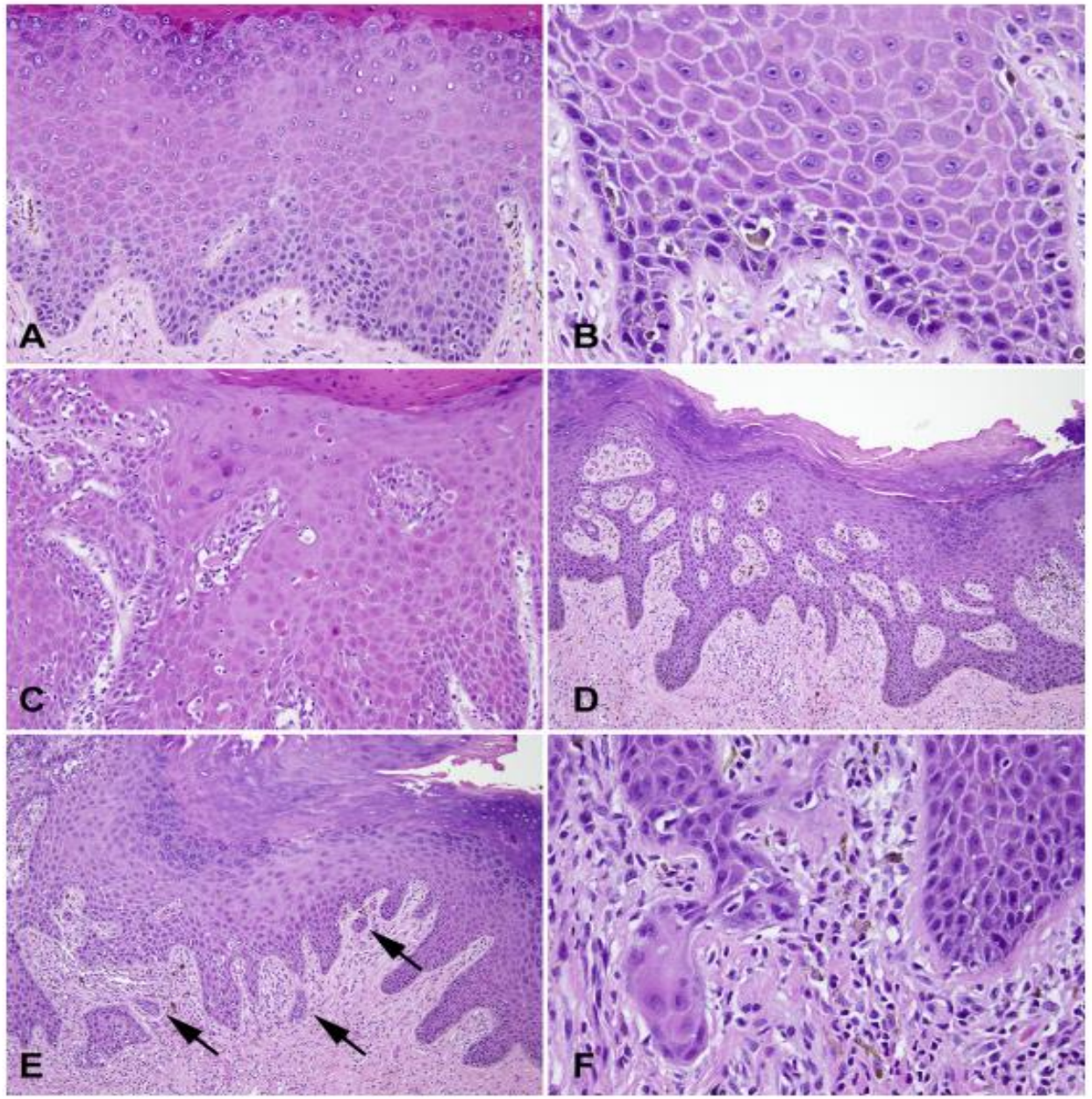


Fig. 3 Vulvar intraepithelial neoplasia, differentiated type (dVIN). (A) Partial thickness dysplasia with retention of keratohyaline granules; (B) basal atypia, nuclei with prominent nucleoli and intercellular bridges; (C) hypereosinophilia and premature keratinisation; (D) irregular branching and anastomoses of rete ridges; (E) pseudoinvasion, regular spacing of nests with rounded contours (arrows); (F) paradoxical maturation suggestive of early invasion.

In those pictures, the diagnosis is probably correct,

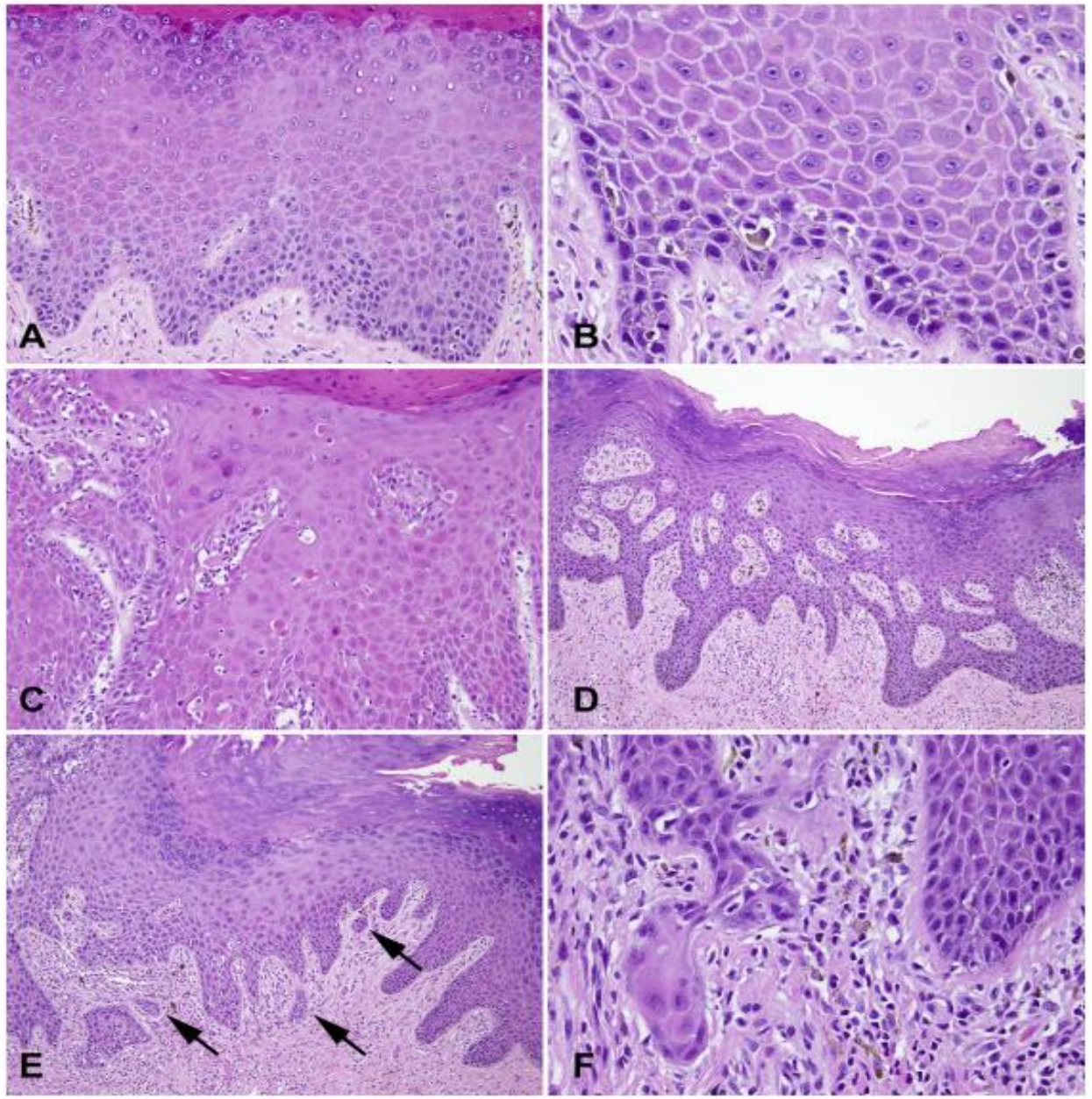


Fig. 3 Vulvar intraepithelial neoplasia, differentiated type (dVIN). (A) Partial thickness dysplasia with retention of keratohyaline granules; (B) basal atypia, nuclei with prominent nucleoli and intercellular bridges; (C) hypereosinophilia and premature keratinisation; (D) irregular branching and anastomoses of rete ridges; (E) pseudoinvasion, regular spacing of nests with rounded contours (arrows); (F) paradoxical maturation suggestive of early invasion.

but, in my view, these pictures show only epithelial hyperplasia or, at most, changes that cannot be distinguished reliably from it.

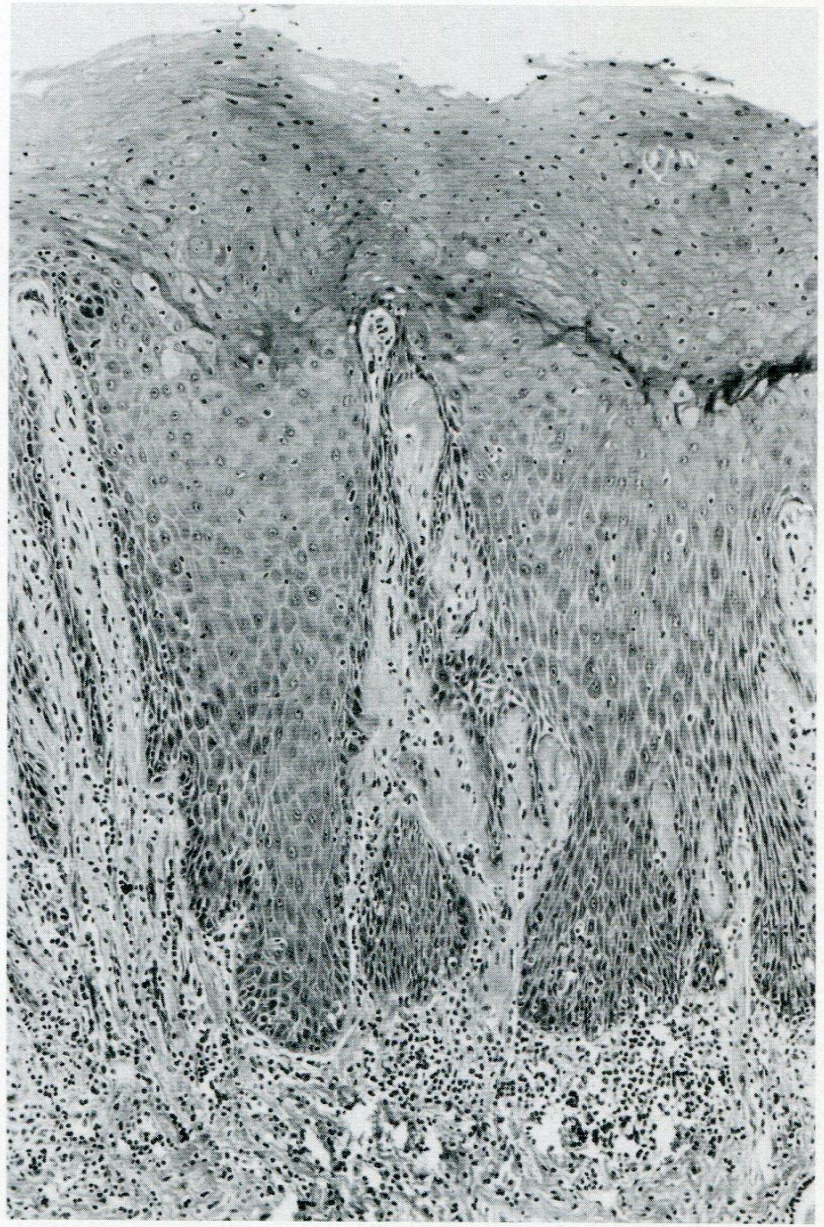
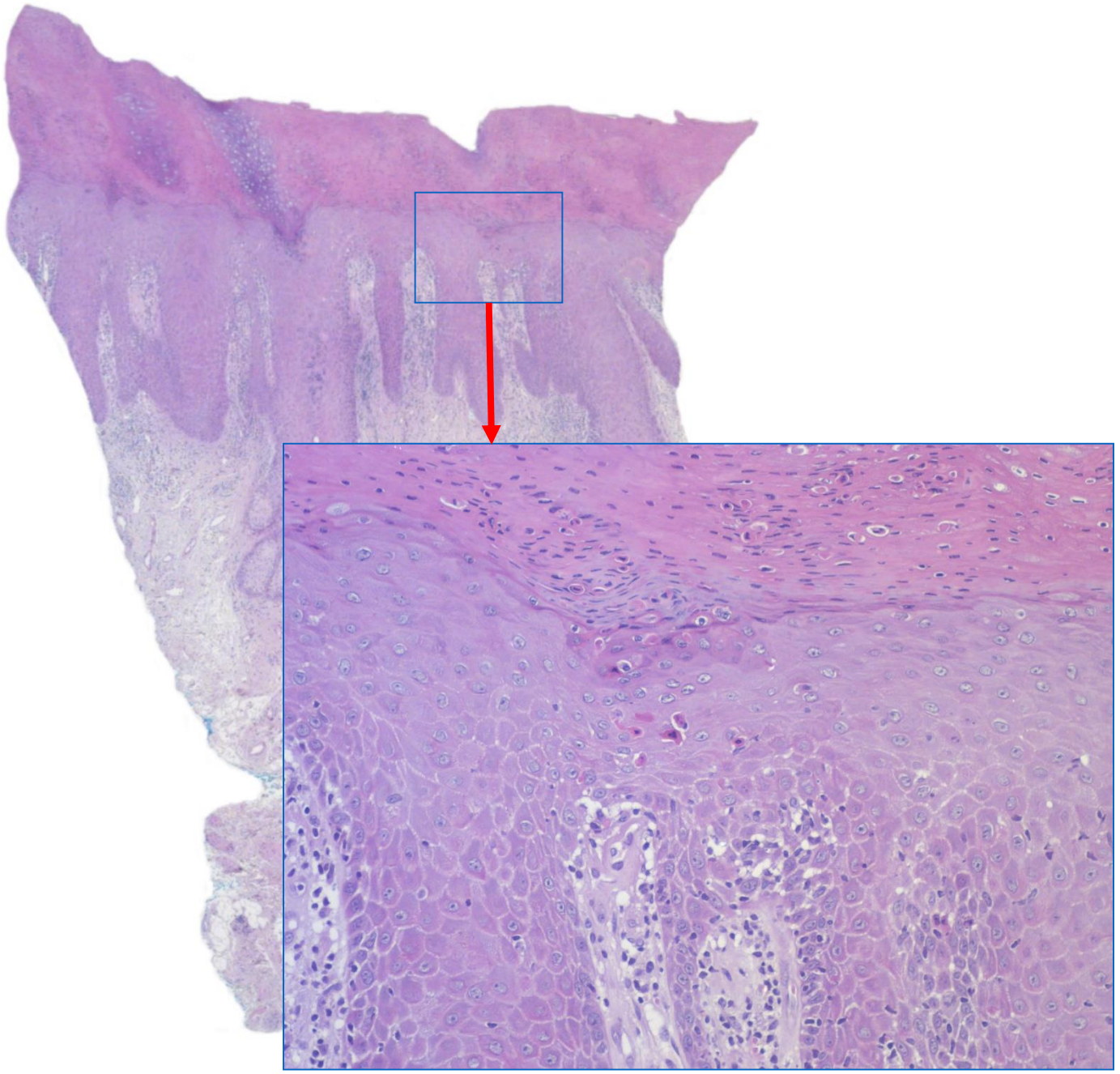


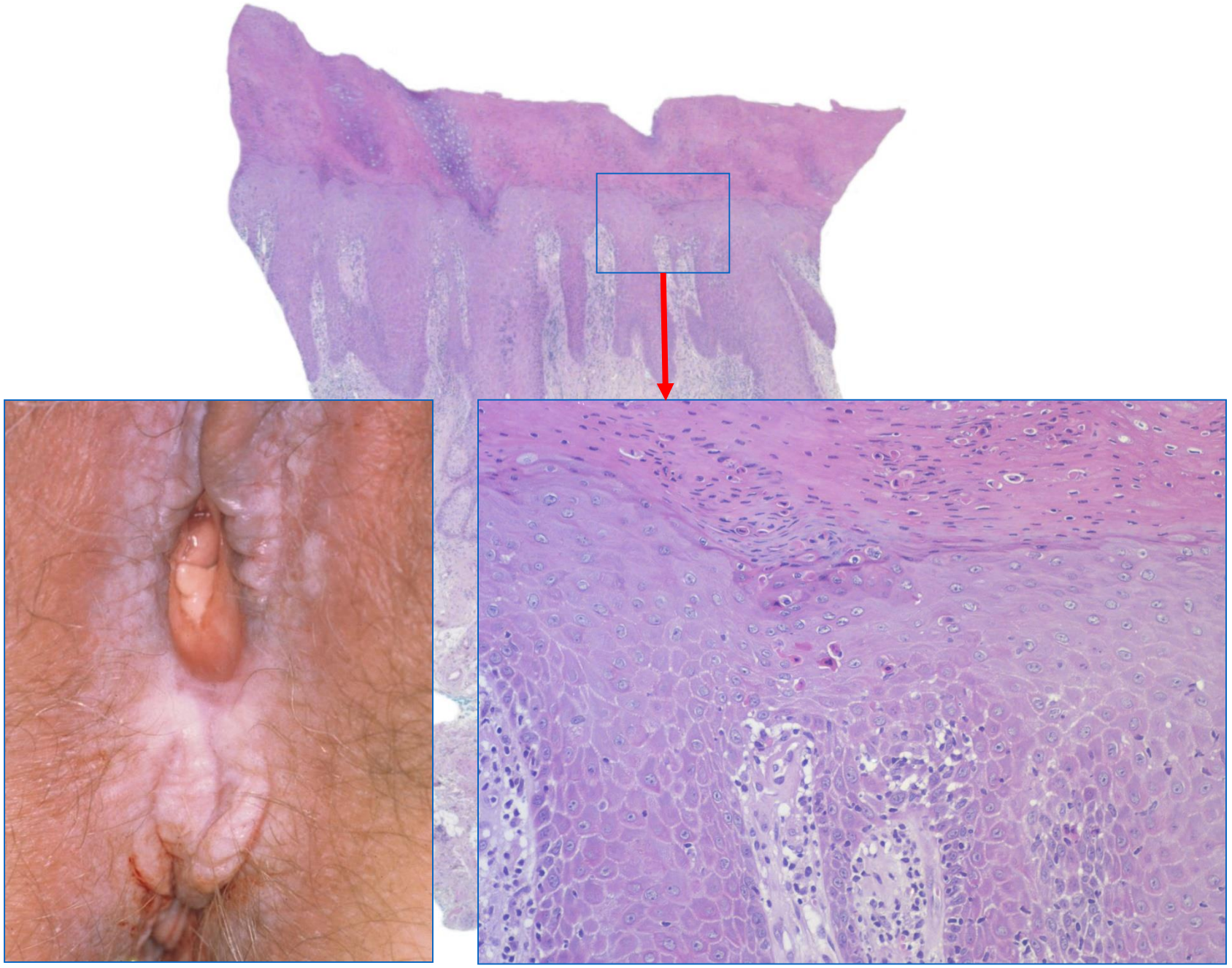
FIG. 1. Simplex vulvar intraepithelial neoplasia. The epidermis is thickened irregularly by a proliferation of abnormal, enlarged keratinocytes. The dermis contains chronic inflammatory cells. A thick parakeratotic surface reaction is present.

Thickening of the epidermis with slightly irregular keratocytes cannot be equated with incipient malignancy, and interpretation of such minimal changes as “vulvar intraepithelial neoplasia” is an overdiagnosis.

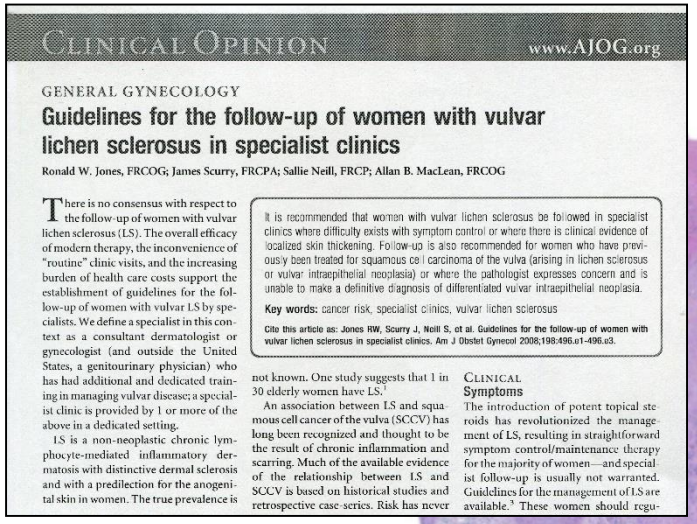
In my view, this picture shows hypertrophic lichen sclerosus. There are even small foci of sclerosis at the tips of dermal papillae. The findings do not differ



from those in cases of lichen sclerosus already shown: there is epidermal hyperplasia, but the latter is rather regular with rete ridges of similar lenght and width.



This is the corresponding clinical picture: a lesion of long-standing lichen sclerosus without evidence of a malignant process.



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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

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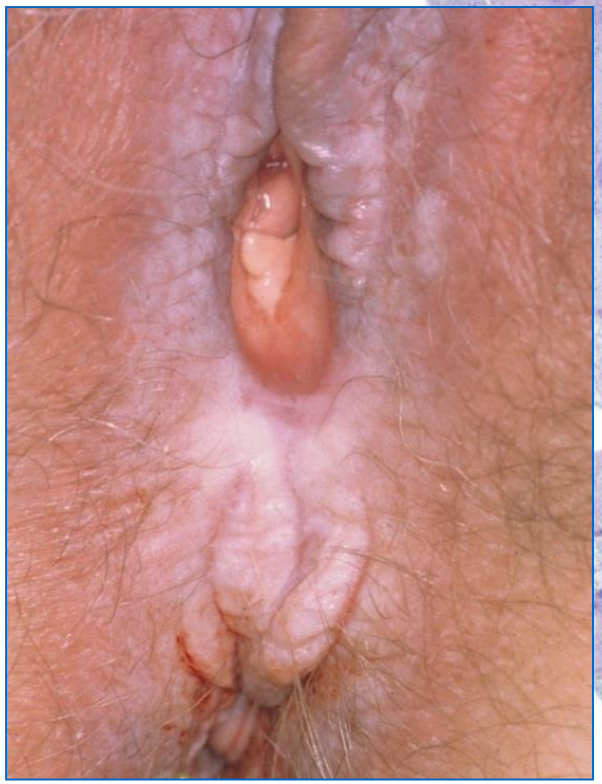
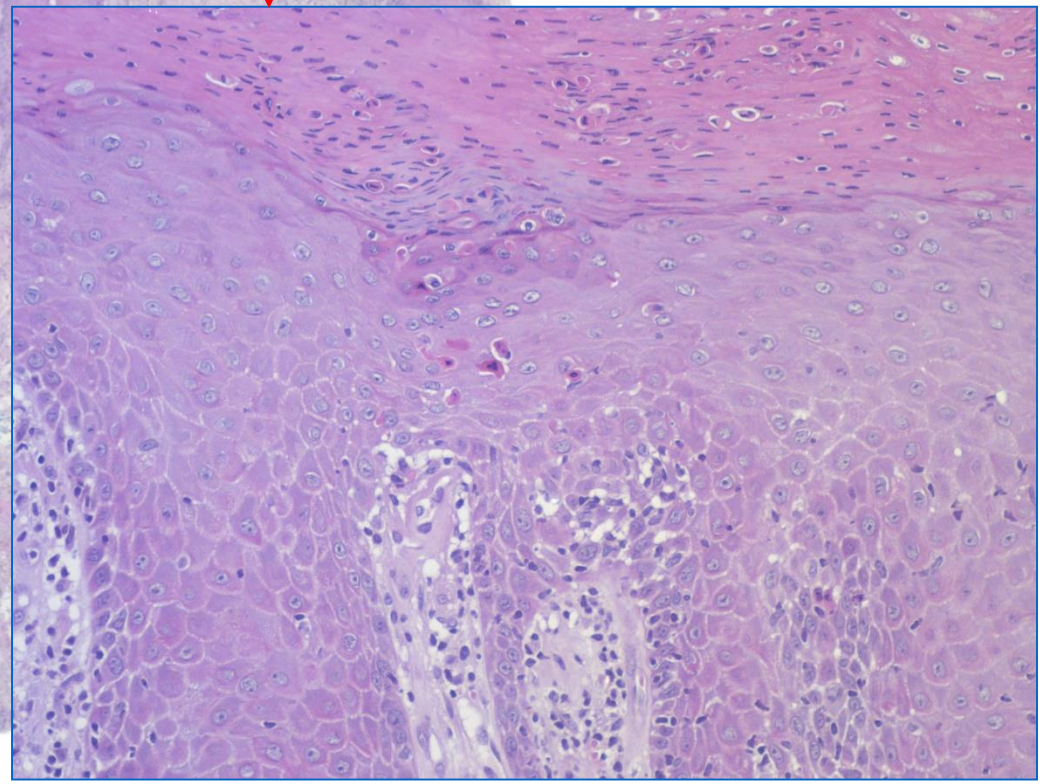
An association between LS and squamous cell cancer of the vulva (SCCV) has long been recognized and thought to be the result of chronic inflammation and scarring. Much of the available evidence of the relationship between LS and SCCV is based on historical studies and retrospective case-series. Risk 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-





"Differentiated VIN requires excision."

According to current guidelines of gynecology, *"differentiated VIN requires excision."* If patients with lichen sclerosus are followed closely for the risk of malignancy, as demanded by current guidelines, and if biopsies are performed repeatedly, there is a considerable risk of overdiagnosis as *"differentiated VIN"* in hypertrophic lesions. It is important, therefore, to know the entire spectrum of changes in lichen sclerosus in order to prevent an inflammatory disease from being treated surgically.