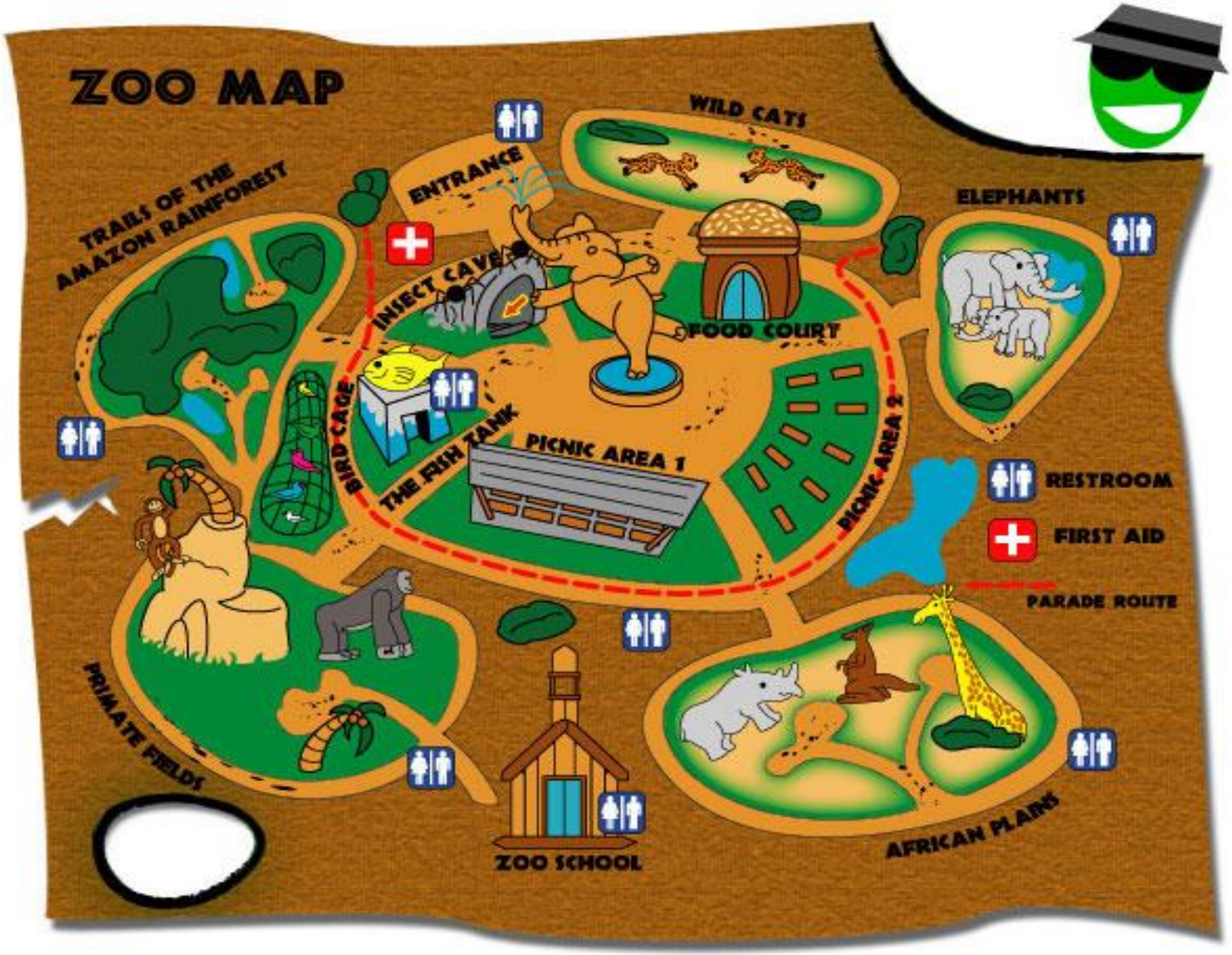
Even big squirrels have small teeth - about the malignant potential of vulvar lichen sclerosus

XXXVIII. Italian Meeting of Cutaneous Histopathology, Turin, March, 2013

I am aware that this meeting is about dermatopathology and not zoology. Nonetheless, let us pretend for a moment



that you were director of a zoo. You had many animals under your care, big and small ones, carnivores and herbivores,

Lynx

Puma

Tiger

Squirrel

Moose

Rabbit

with species such as lynx, pumas, and tigers, but also squirrels, moose, and rabbits. These are only six examples, but there are many more species,

Lynx

Lynx lynx

Puma

Cougar

Tiger

Panthera tigris

Squirrel

Sciurus vulgaris

Moose

Aces aces

Rabbit

Oryctolagus cuniculus

and each is known by different names, e.g. Cougar, Alces alces, and Oryctolagus cuniculus.

In brief, as director of a zoo you are confronted with hundreds of species and thousands of names. Clearly, life would be much easier with a simplified classification. How about the following suggestion?

~~Lynx~~

~~Lynx lynx~~

~~Puma~~

~~Cougar~~

~~Tiger~~

~~Panthera tigris~~

Squirrel

Sciurus vulgaris

Moose

Aces aces

Rabbit

Oryctolagus cuniculus

We expunge terms such as lynx, puma, and tiger from the vocabulary of zoology. Instead, we make a distinction, for practical purposes,

between dangerous and harmless animals, predators and prey.

dangerous

dangerous

dangerous

harmless

harmless

harmless

dangerous
small teeth

dangerous
medium teeth

dangerous
big teeth

harmless

harmless

harmless

In the group of predators we subclassify animals according to the size of their teeth, small, medium, and big.

dangerous
small teeth

dangerous
medium teeth

dangerous
big teeth

harmless
Squirrel

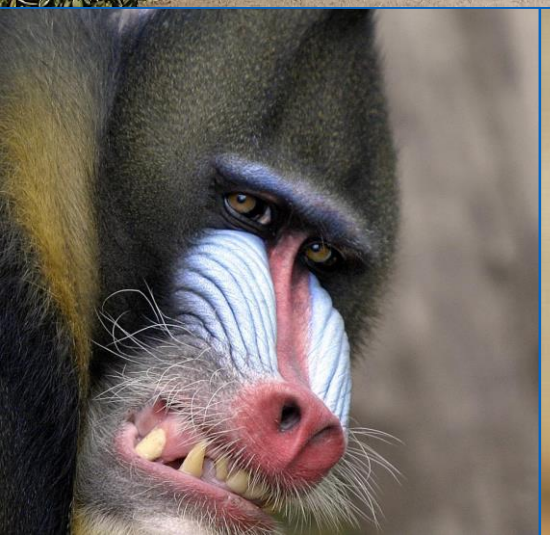
harmless
big animals

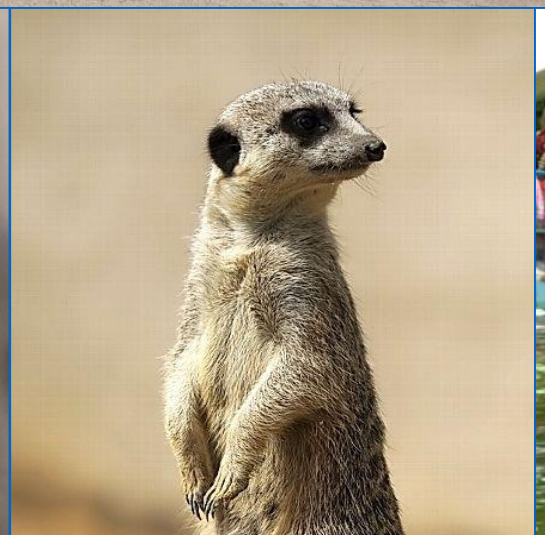
harmless
other creatures

In the group of prey, we distinguish between squirrels, big animals, and other creatures. The specific category of squirrels is maintained because they are so common in our zoo.

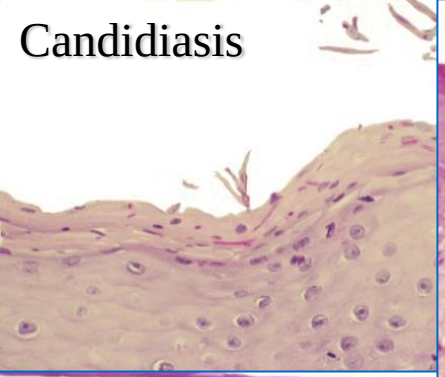
Of course, in regard to squirrels, we have to acknowledge that their size varies and that they are not only prey but also predators with sharp teeth.

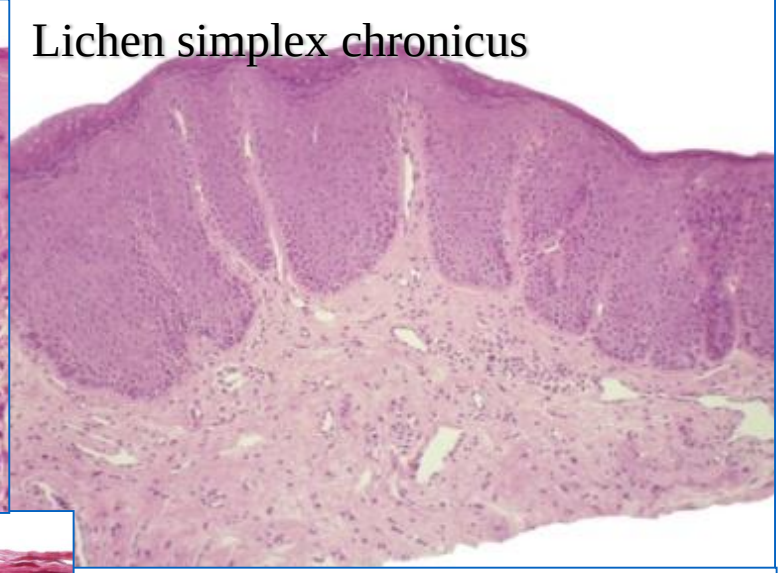
Hence, a combination should be possible, e.g., medium-sized squirrels with big teeth. And this would round up our classification.

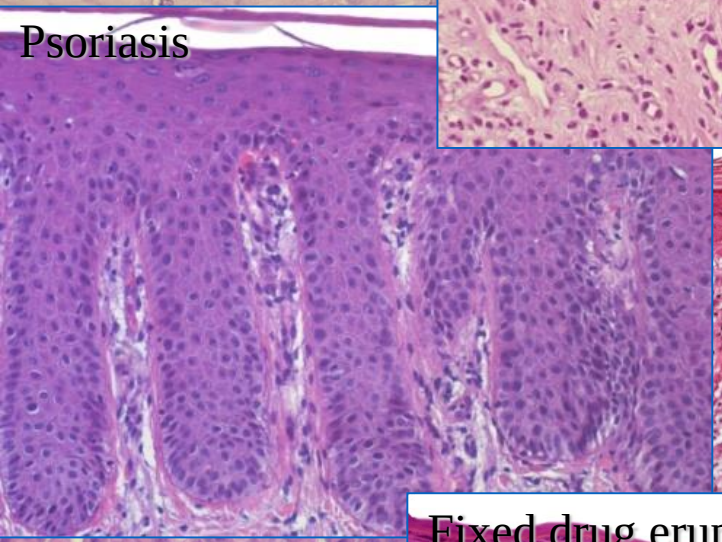


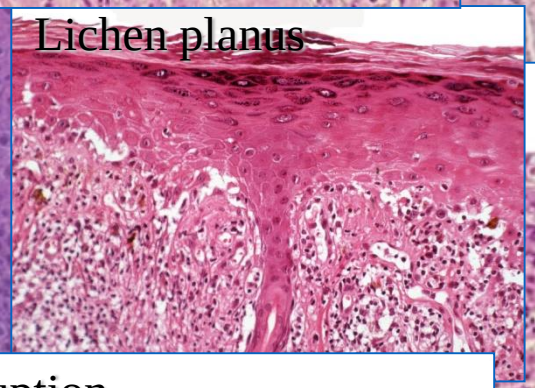


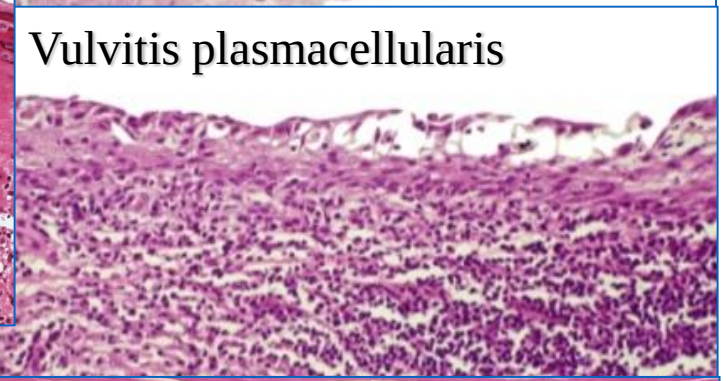
But would it attract visitors? Probably not. In zoology, such simplification would not be accepted because visitors presumably wanted to know the names of all the other animals.

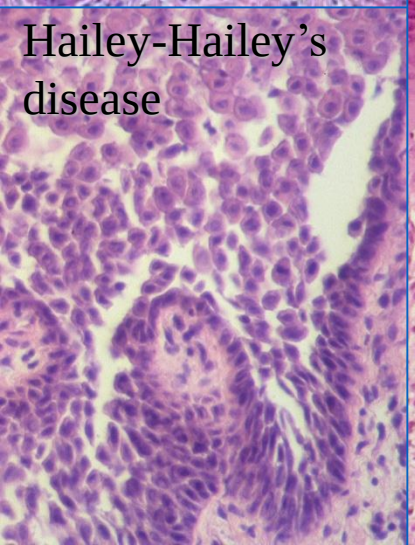


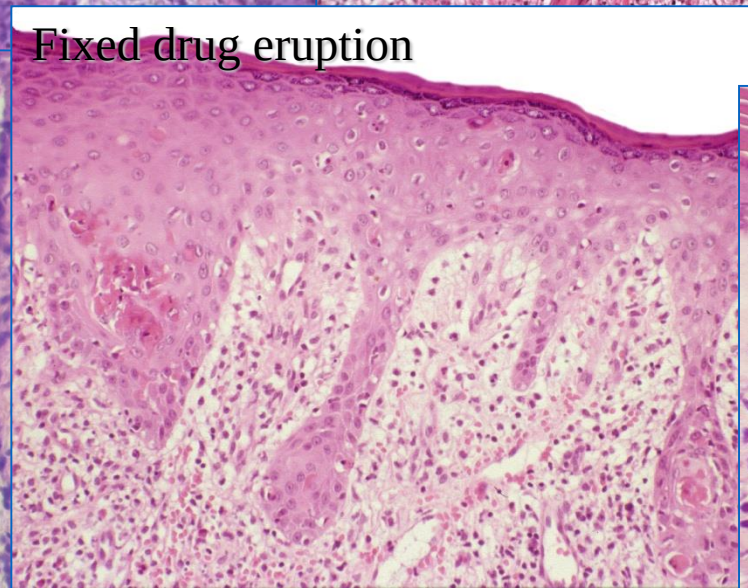


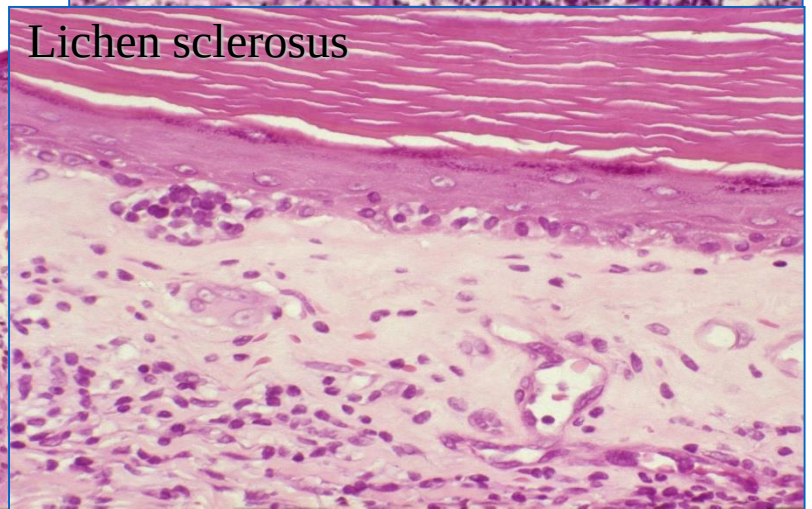












In vulvar pathology, acceptance is no problem. Who cares if there are diseases such as psoriasis, lichen planus, or fixed drug eruption? That is much too complicated.

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).

At the present time the diagnosis of many vulvar diseases is imprecise because of lack of a standard terminology, making the available data confusing and the experience nonadditive.

It is essential, therefore, that an international language be developed and employed in all future reports, and, insofar as possible, that all past publications be reviewed and reconsidered in the light of this new schema. Only by so doing can meaningful data be obtained.

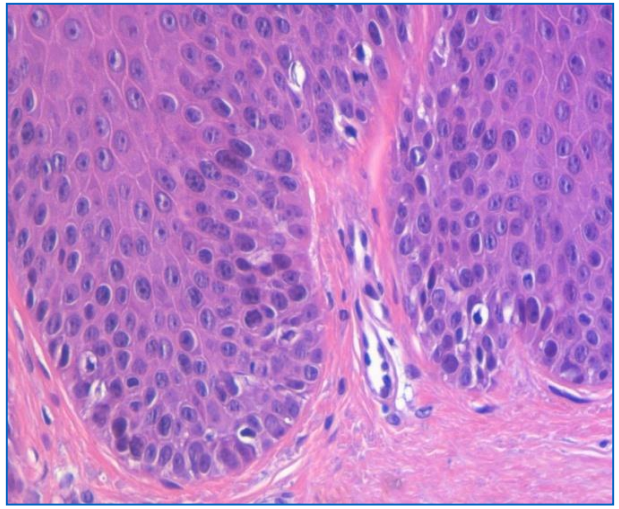
Use of the new nomenclature will permit simple and rapid grouping of cases. If a large enough number of cases in any single group show a unique pattern of biologic behavior different from other cases within the same group and identifiable as such, then further subdivision of the group may be warranted.

The following terms have been deleted from the vocabulary of vulvar diseases because of the confusion associated with their use:

Lichen sclerosus et atrophicus
Leukoplakia
Neurodermatitis
Leukeratosis
Bowen's disease
Erythroplasia of Queyrat
Carcinoma simplex
Leukoplakic vulvitis
Hyperplastic vulvitis
Kraurosis vulvae

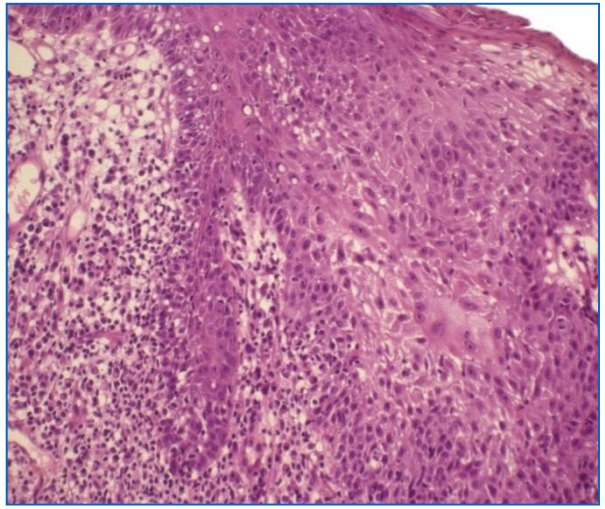
Obstet Gynecol 1976; 147: 122

In 1976, the International Society for the Study of Vulvar Diseases presented a new nomenclature for vulvar disease and declared that *"the following terms have been deleted from the vocabulary of vulvar diseases,"* among them common diagnoses such "neurodermatitis" and "Bowen's disease."



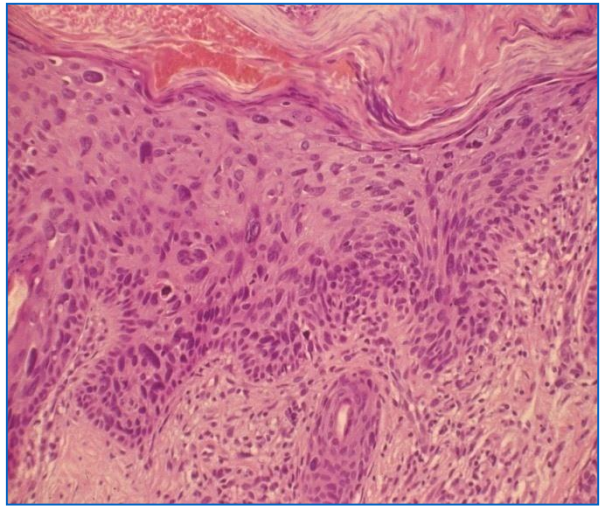
~~Condyloma acumin.~~

~~Genital wart~~



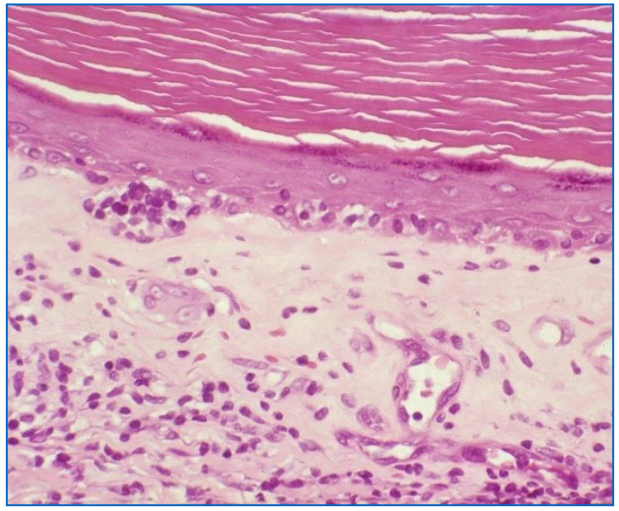
SCC in situ

~~Bowen's disease~~



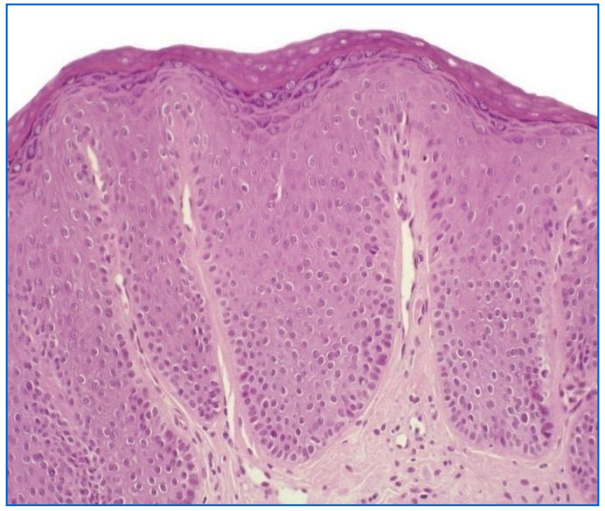
SCC in situ

~~Bowen's disease~~



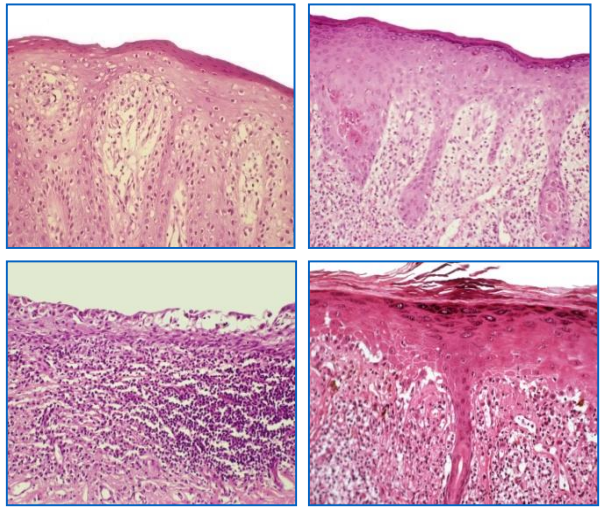
Lichen sclerosus

~~Kraurosis vulvae~~



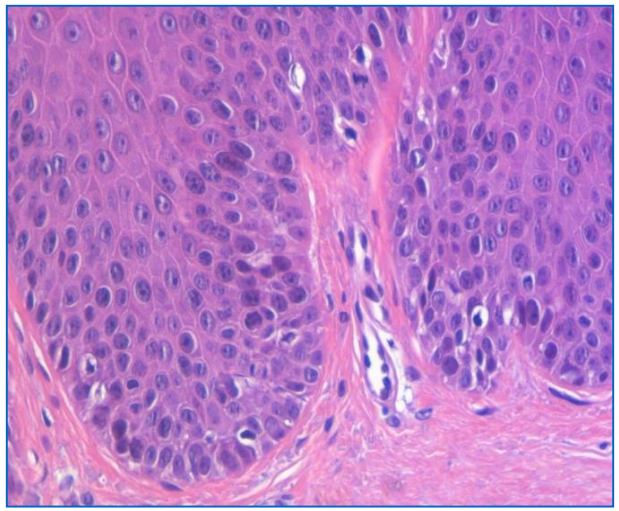
~~Atopic dermatitis~~

~~LSC~~, ~~Neurodermatitis~~

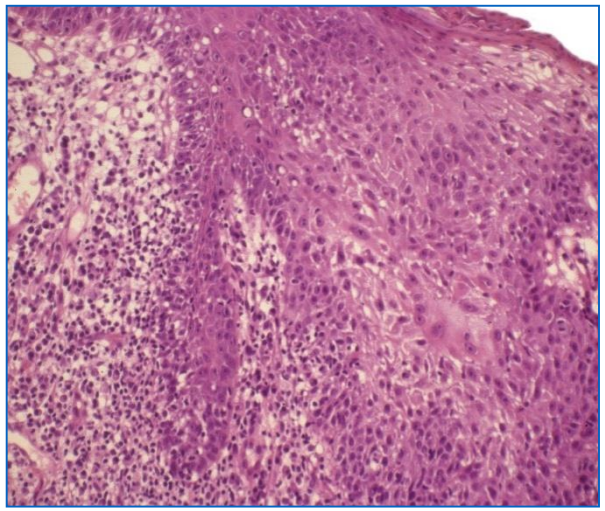


~~Psoriasis, Fixed drug eruption, Vulvitis Zoon, Lichen planus~~

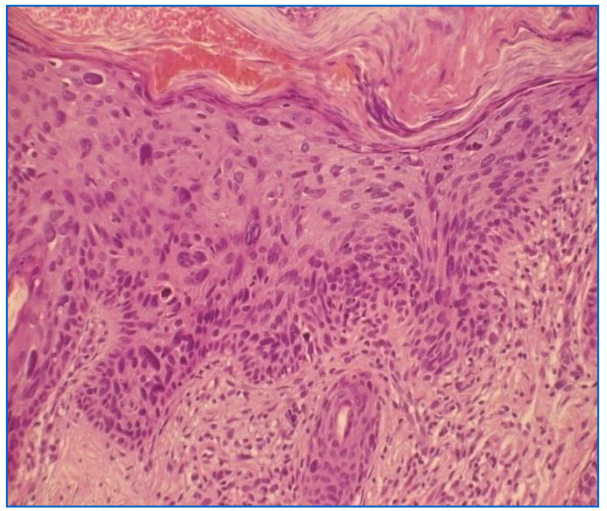
In addition to terms being struck from the vocabulary, many other diagnoses were not considered,



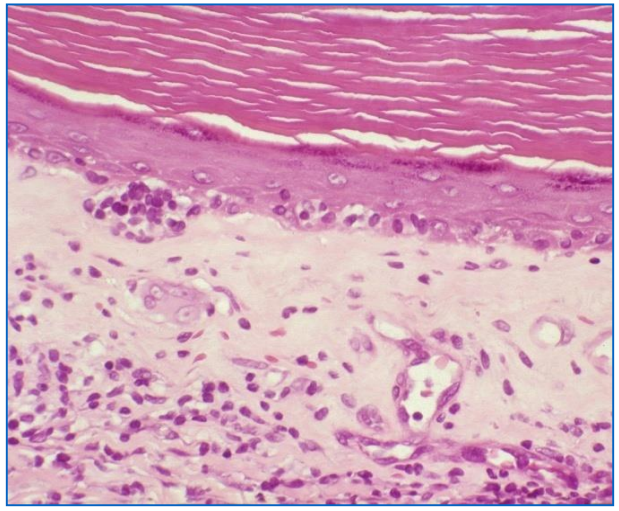
Neoplastic



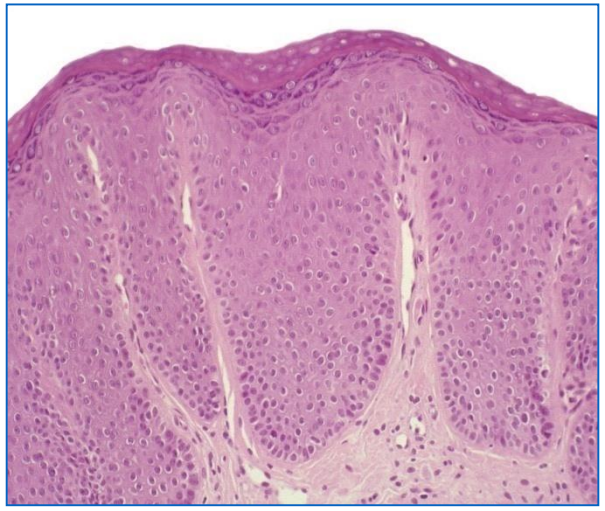
Neoplastic



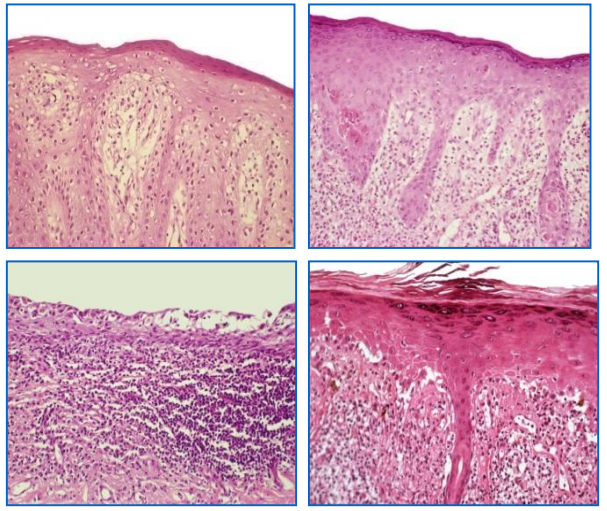
Neoplastic



Non-neoplastic

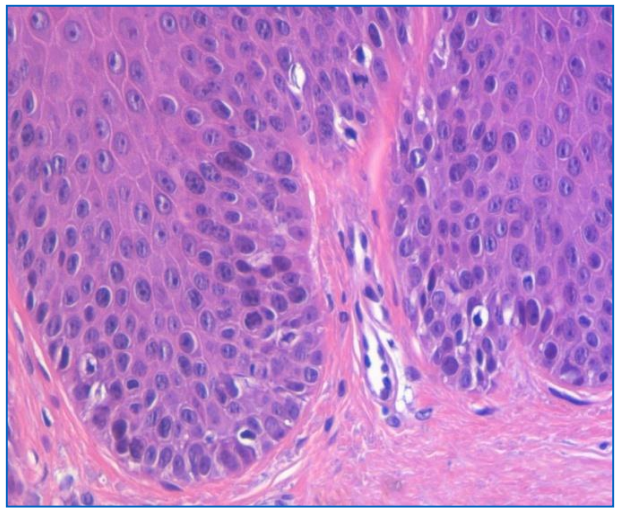


Non-neoplastic

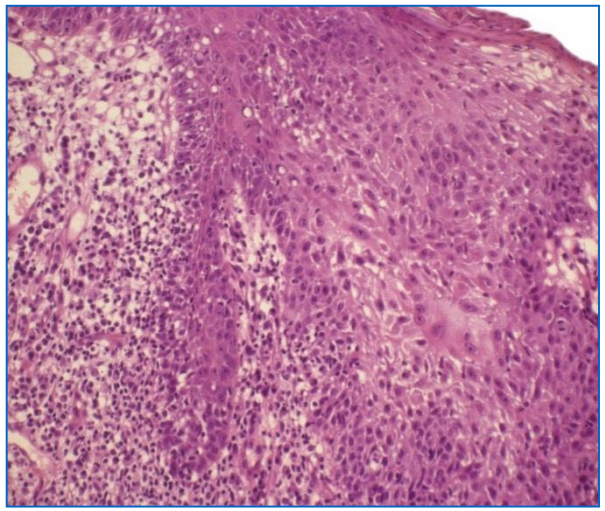


Non-neoplastic

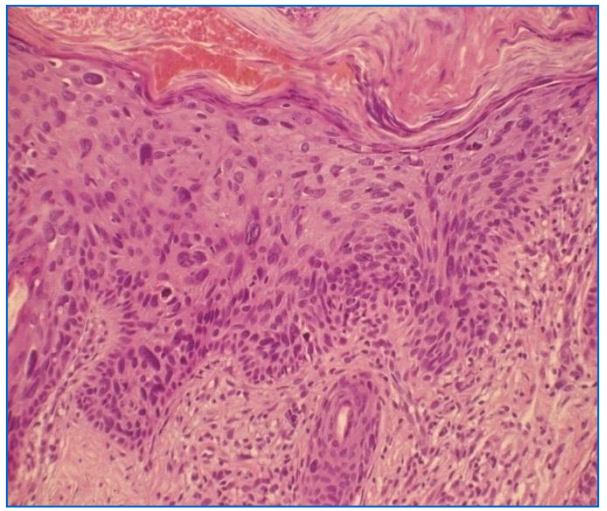
and, eventually, a classification was advanced that consisted of only six categories, three neoplastic and three non-neoplastic ones.



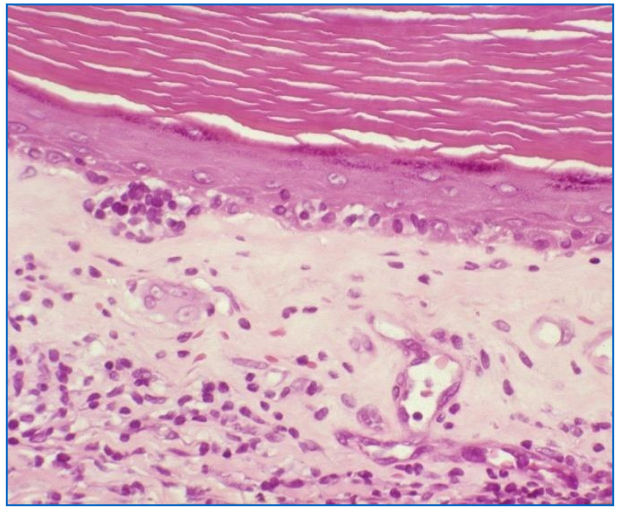
Neoplastic
VIN I



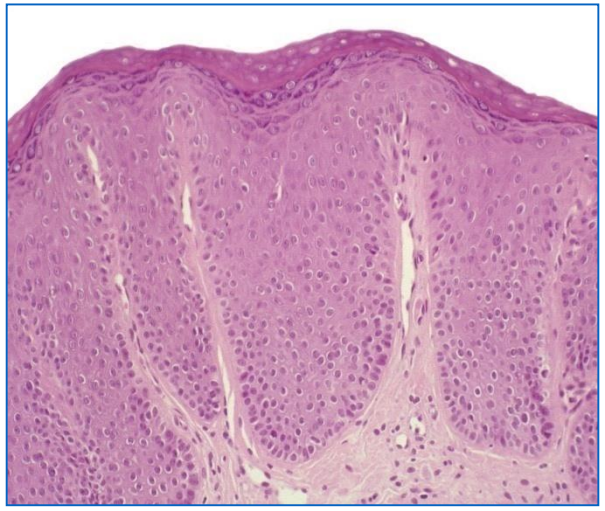
Neoplastic
VIN II



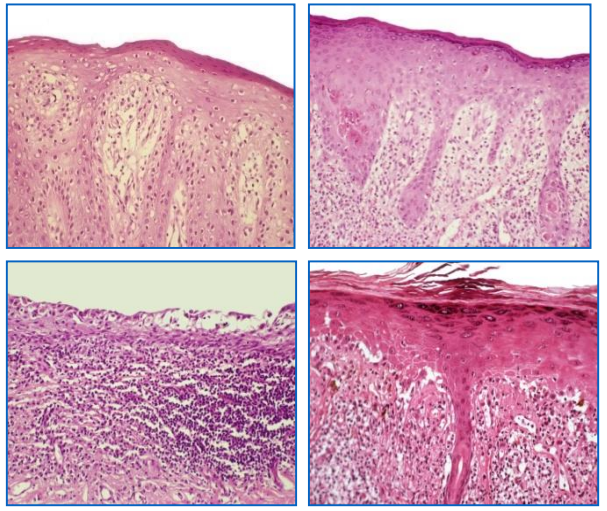
Neoplastic
VIN III



Non-neoplastic

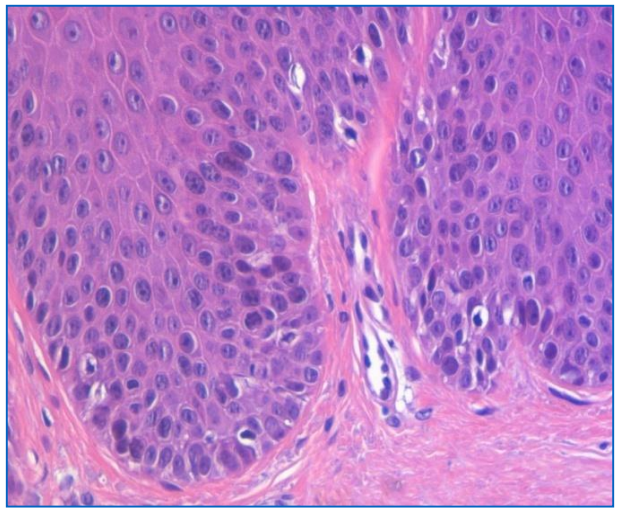


Non-neoplastic

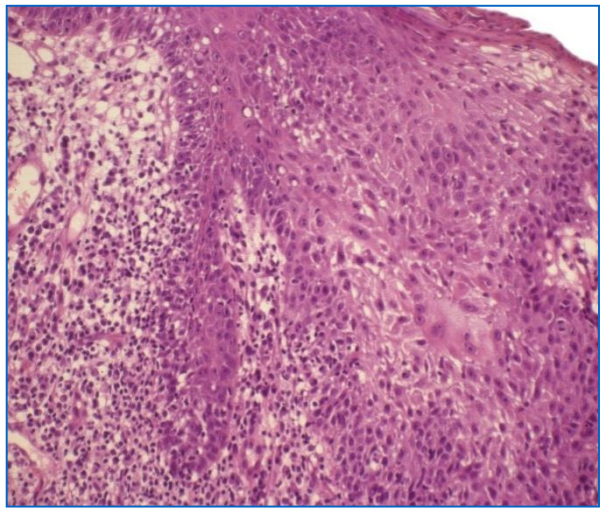


Non-neoplastic

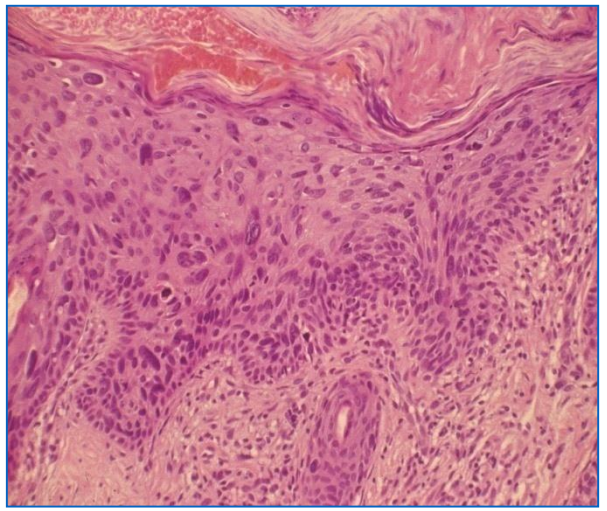
Neoplastic conditions were referred to as “vulvar intraepithelial neoplasia” and were subclassified according to the size of their teeth into VIN I, II, and III, corresponding to the level of involvement of the epidermis by atypical cells.



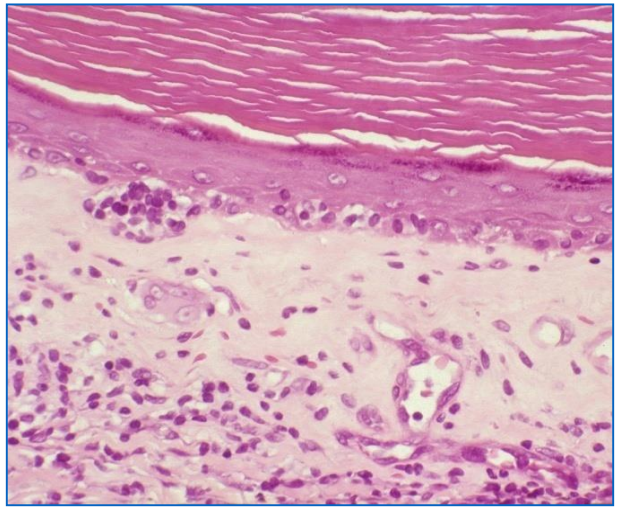
Neoplastic
VIN I



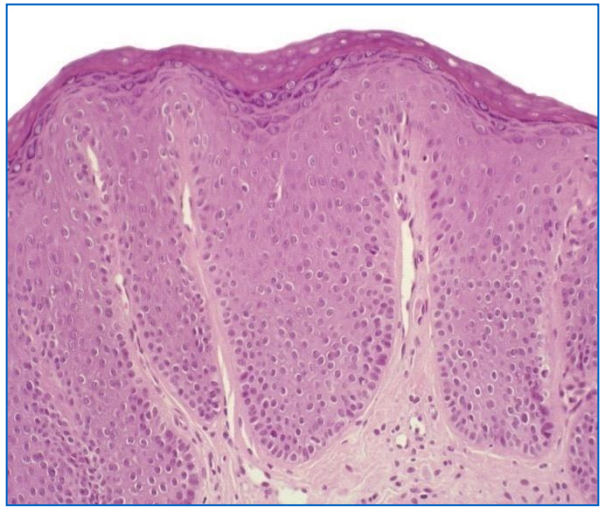
Neoplastic
VIN II



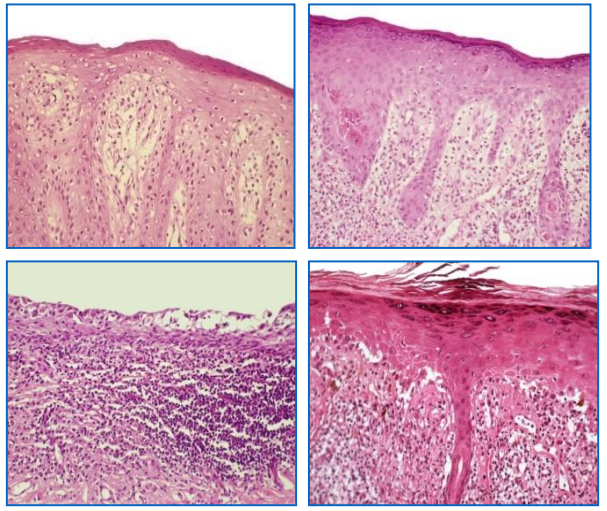
Neoplastic
VIN III



Non-neoplastic
Lichen sclerosus



Non-neoplastic
Squamous cell hyperplasia



Non-neoplastic
Other dermatoses

Among non-neoplastic conditions, only one specific disease was maintained, namely, lichen sclerosus, the other categories being “squamous cell hyperplasia” which may be seen in a wide variety of diseases, and “other dermatoses” which is even less meaningful.

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, recommendations 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.

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

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

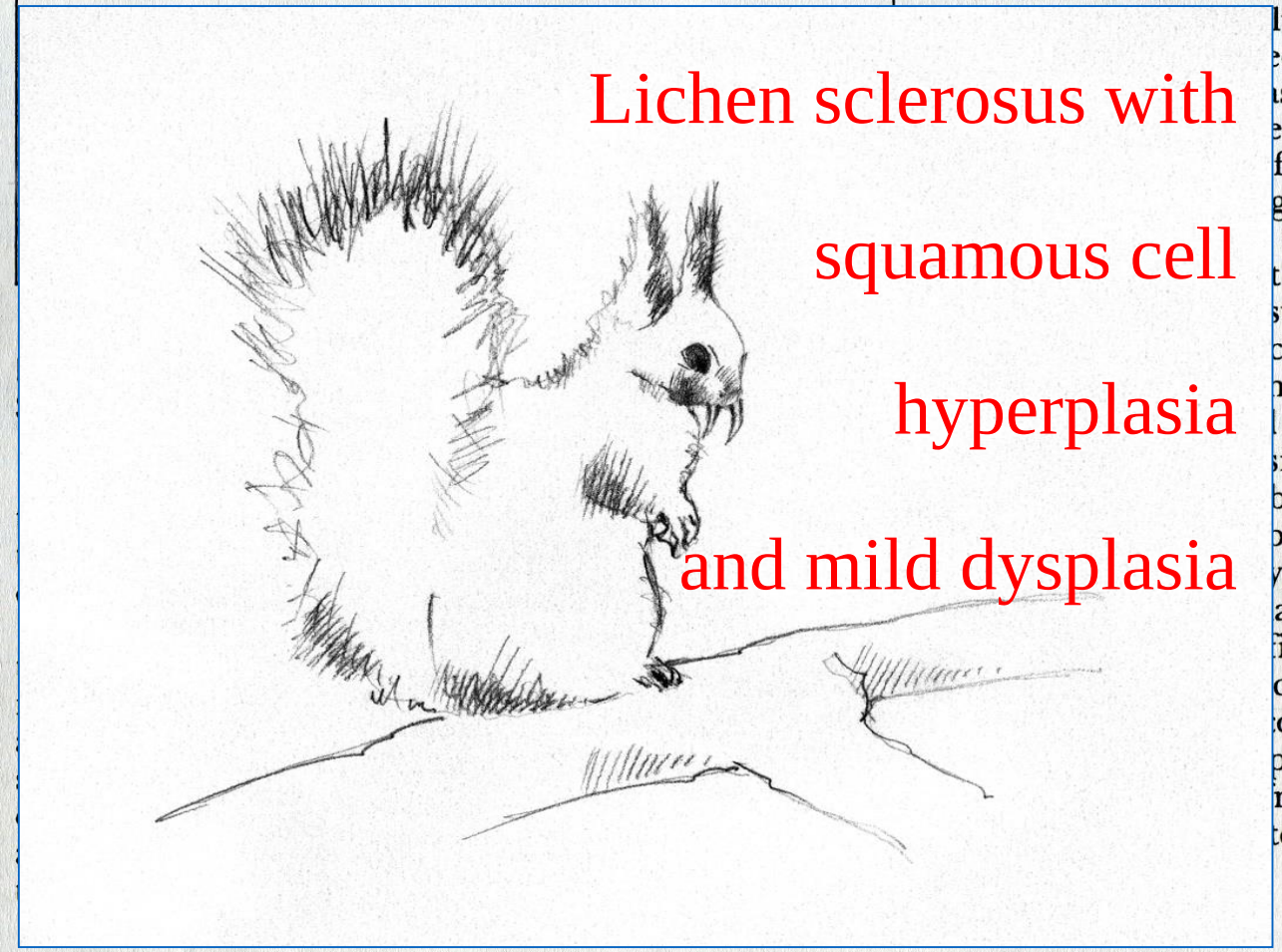
TABLE 2. Classification of Vulvar Intraepithelial Neoplasia

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]

Hum Pathol
1989; 20: 495

This was the entire “new nomenclature for vulvar disease,” but, in order to make up for the truncated classification,



Lichen sclerosus with squamous cell hyperplasia and mild dysplasia

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Hum Pathol 1989; 20: 495

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combinations were accepted, e.g., lichen sclerosus with squamous cell hyperplasia and mild dysplasia, and those combinations were said to bear special biologic significance.

J Reprod Med 1988 Jun;33(6):545-50.

Malignant potential of mixed vulvar dystrophy (lichen sclerosus associated with squamous cell hyperplasia).

Rodke G, Friedrich EG Jr, Wilkinson EJ.

Department of Obstetrics and Gynecology, University of Florida, Gainesville.

Abstract

Fifty women whose clinical vulvar appearance was compatible with that of hyperplastic or mixed vulvar dystrophy were evaluated in the Vulvovaginal Referral Unit, University of Florida, from 1980 through 1986. Histologic material from biopsies performed on these patients was reviewed. The histologic picture was consistent with the clinical diagnosis in 33 cases. Fifteen patients had lichen sclerosus with various degrees of hyperkeratosis, while one had human papillomavirus-associated vulvar intraepithelial neoplasia and another had only mild chronic inflammation. Three patients in the mixed dystrophy group developed squamous carcinoma of the vulva. Women with squamous cell hyperplasia occurring in a background of lichen sclerosus (mixed dystrophy) constitute a distinct group at higher risk of developing invasive cancer and require histologic assessment.

In 1988, Rodke and co-workers reported on the *"malignant potential of mixed vulvar dystrophy (lichen sclerosus associated with squamous cell hyperplasia)"* and suggested that *"women with squamous cell hyperplasia occurring in a background of lichen sclerosus (mixed dystrophy) constitute a distinct group at higher risk of developing invasive cancer and require histologic assessment."*

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-

This concept has prevailed to this date. 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."* But how risky is hypertrophic lichen sclerosus?

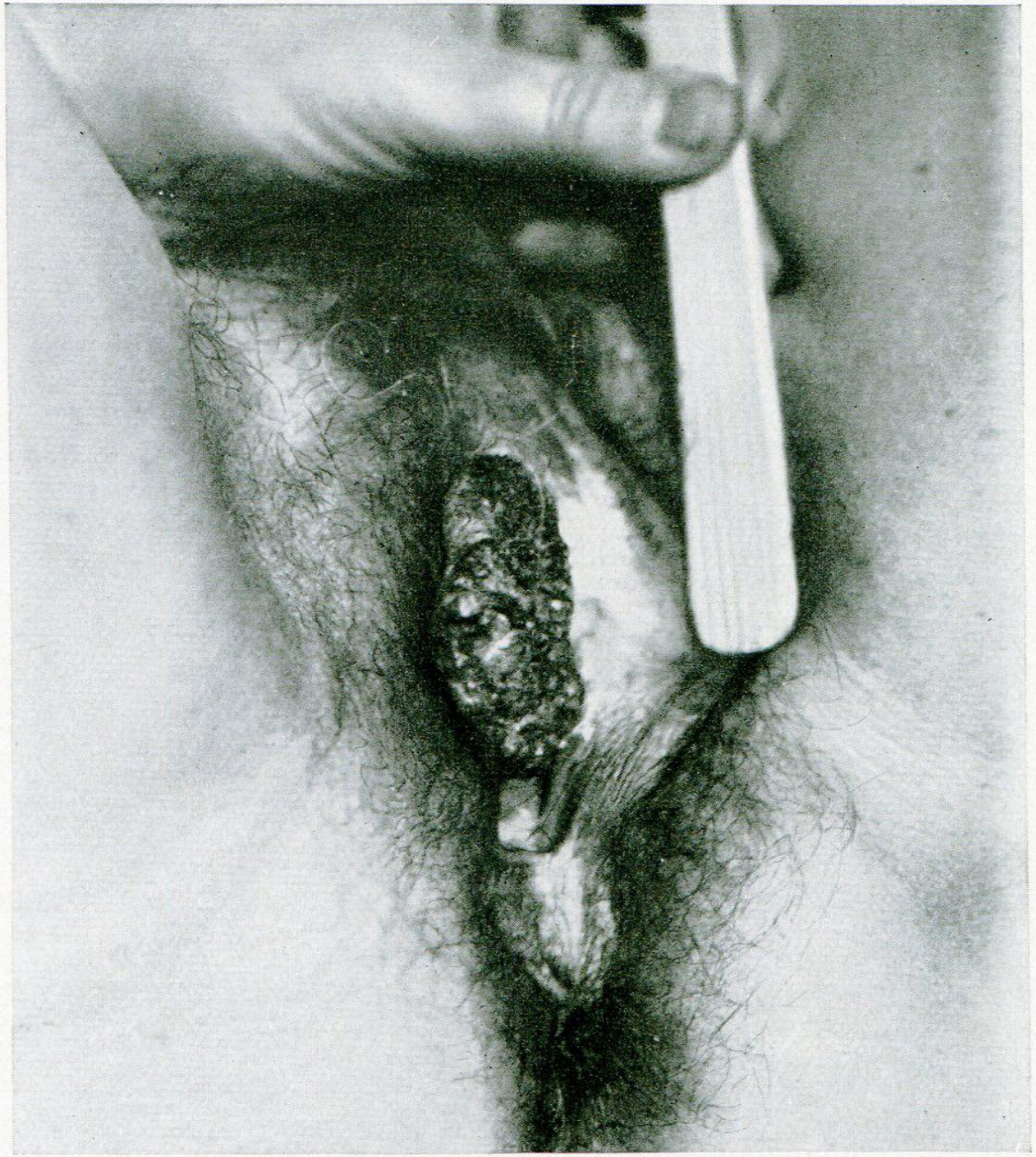

Abb. 20. Kraurosis vulvae, Leukoplakia. Blumenkohlähnliches Carcinom, das sich auf dem Boden einer Leukoplakie allmählich entwickelte. 70jährige Frau

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,

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,

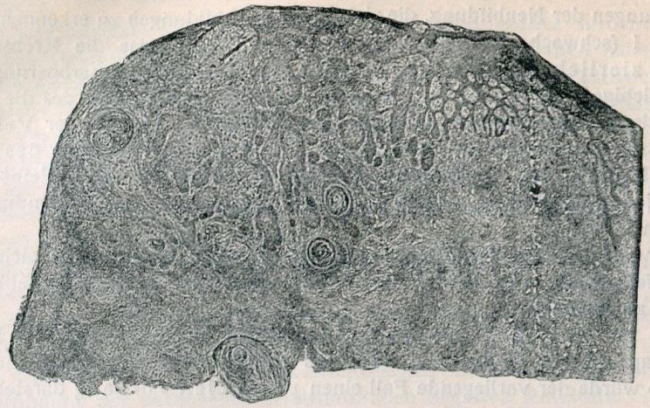

Fig. 1.

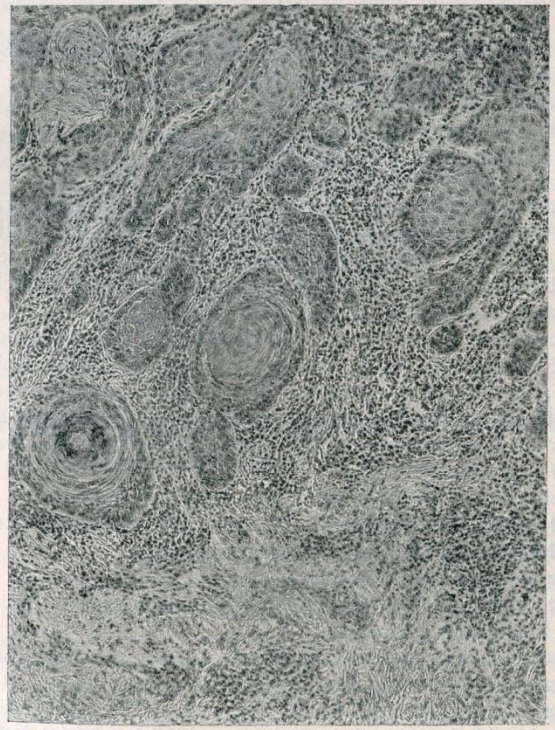

Fig. 2.

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-

*

it was confused commonly with early stages of squamous cell carcinoma known as “leukoplakia.” In many articles about “kraurosis” and cancer, there was evidence of cancer, but not of lichen sclerosus.

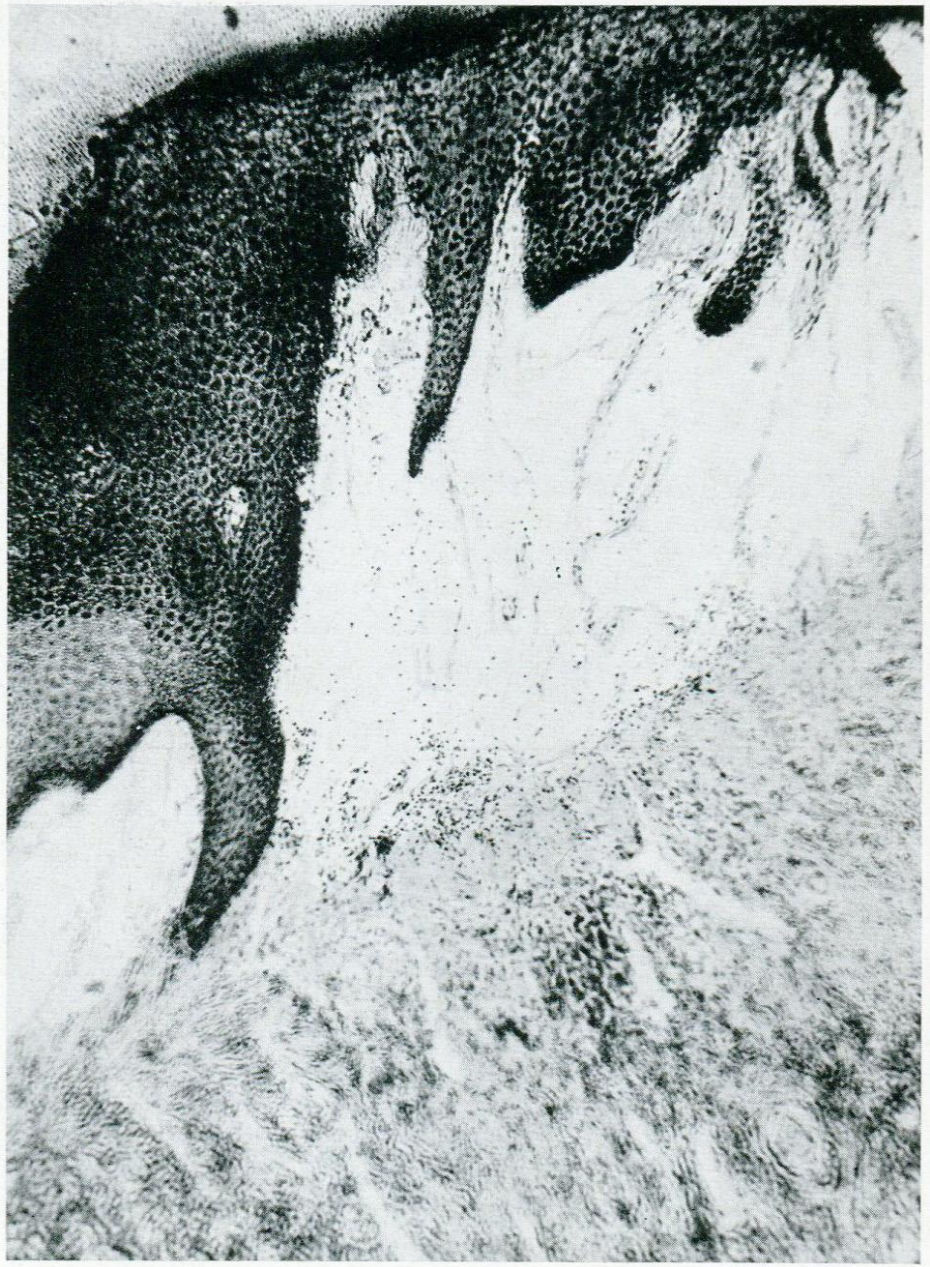

Abb. 2. Vulväre Leukoplakie mit beginnender epitheliomatöser Umwandlung bei Lichen sclerosus et atrophicus; bedeutendes Lymphödem in der oberen Cutis

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.”*

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

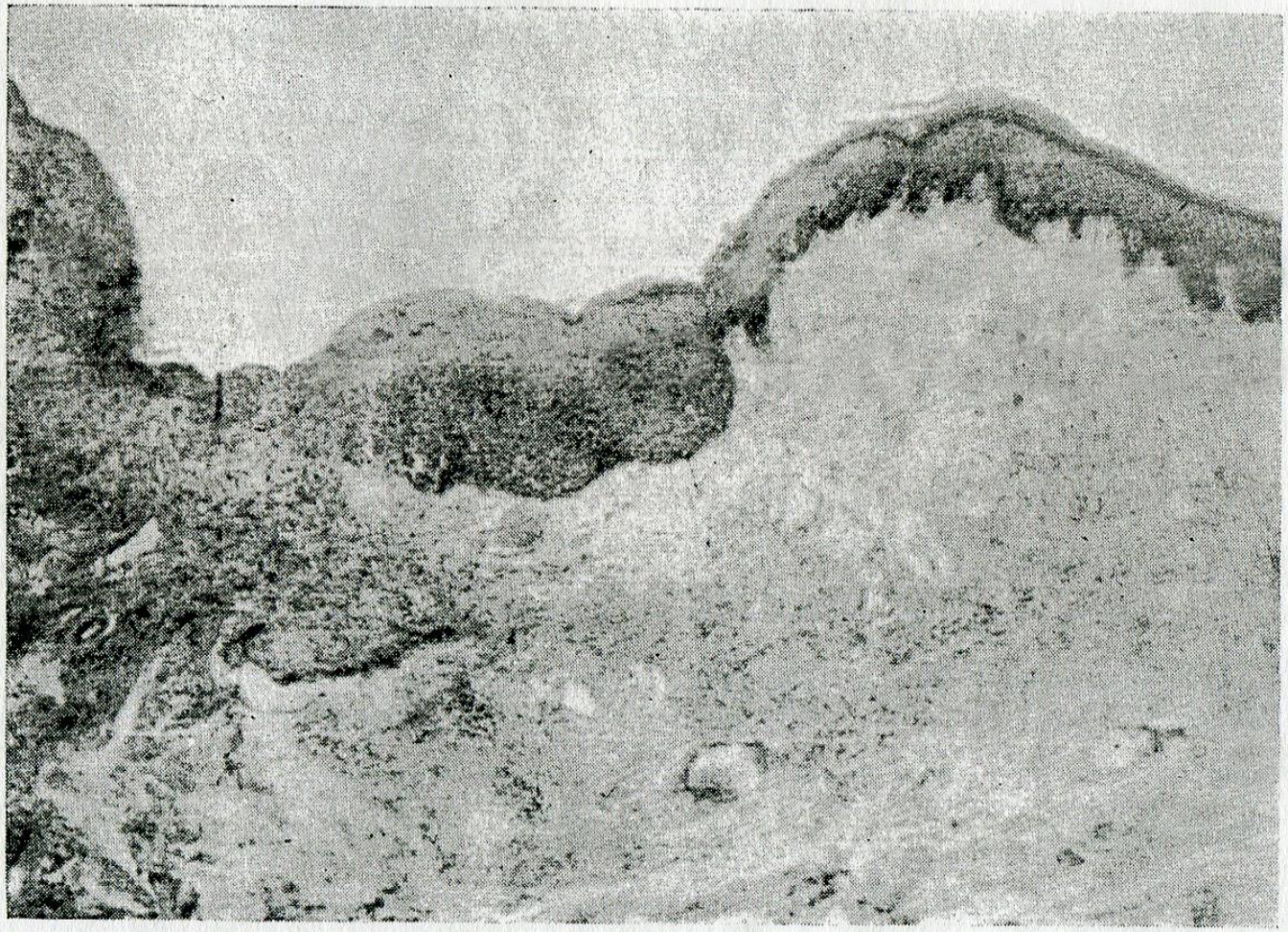

Fig. 7.—Sections of LSA of vulva with carcinoma in situ. Note leukoplakia changes in epidermis on the right of specimen, with homogenization of upper corium beneath. On the left is seen irregular proliferation of basal cells and mass of large prickle cells.

Arch Dermatol
1962; 85: 362

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,

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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.

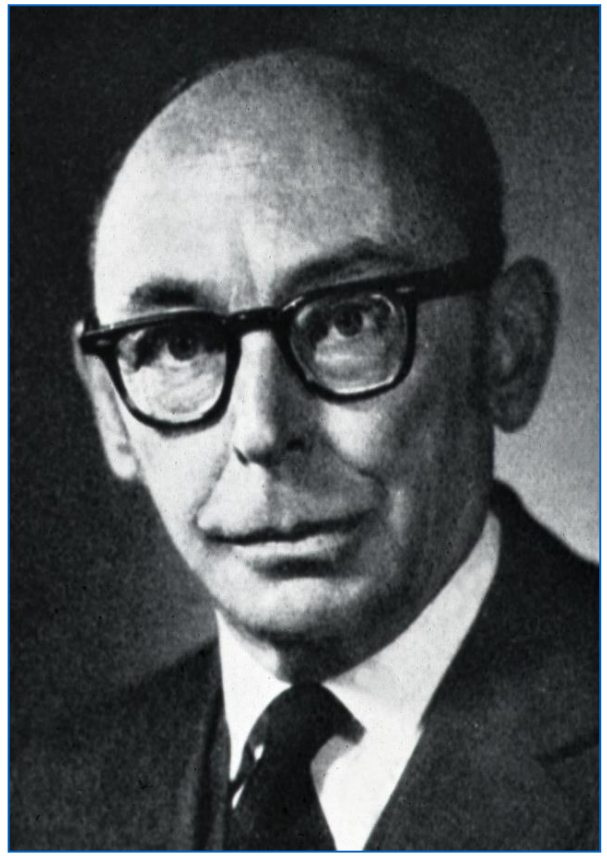
investigated.

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

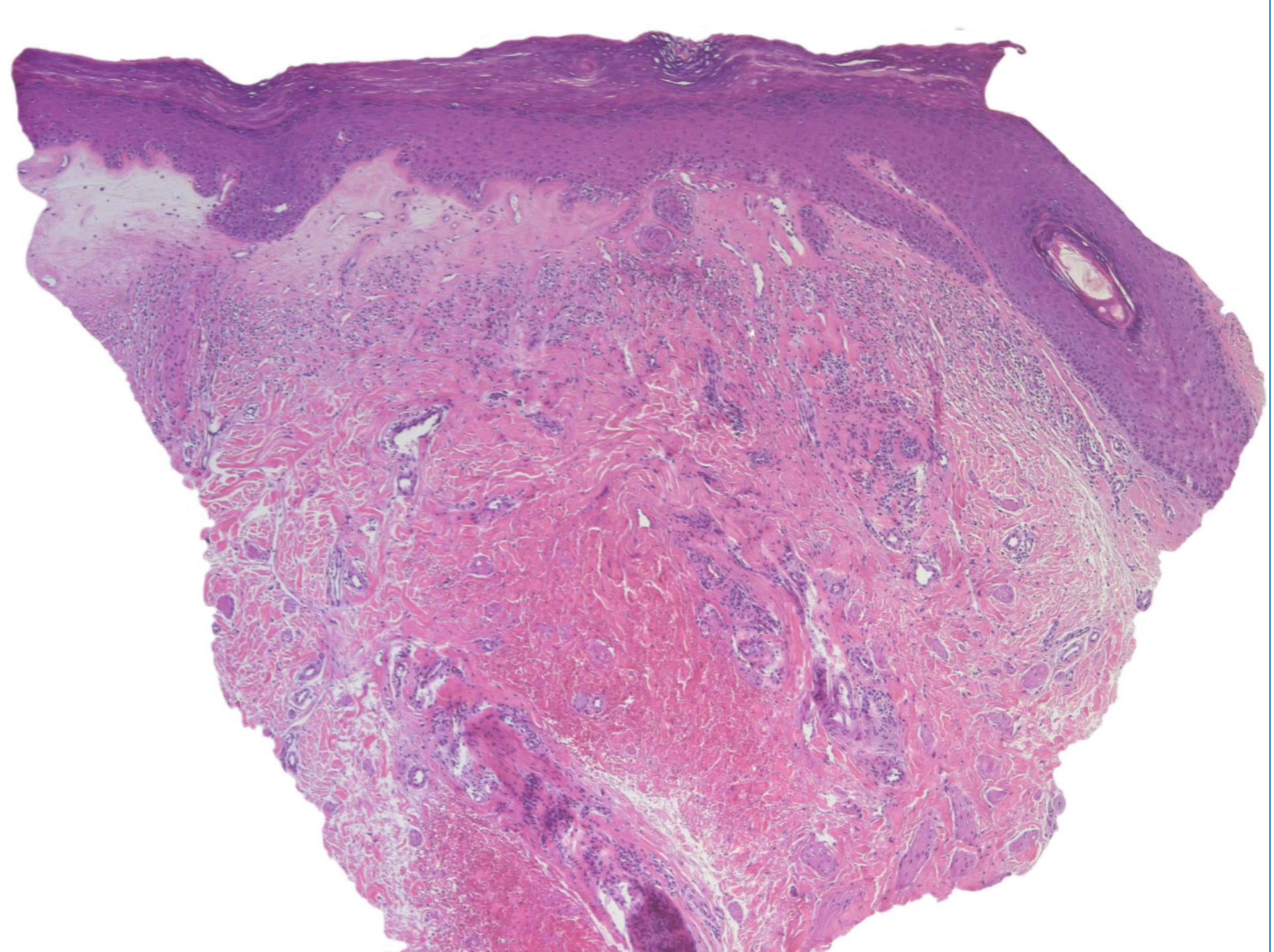
and although they observed cancer in but a single case, the authors concluded that *"the relationship between carcinoma of the vulva and LSA can no longer be discounted."*

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 …

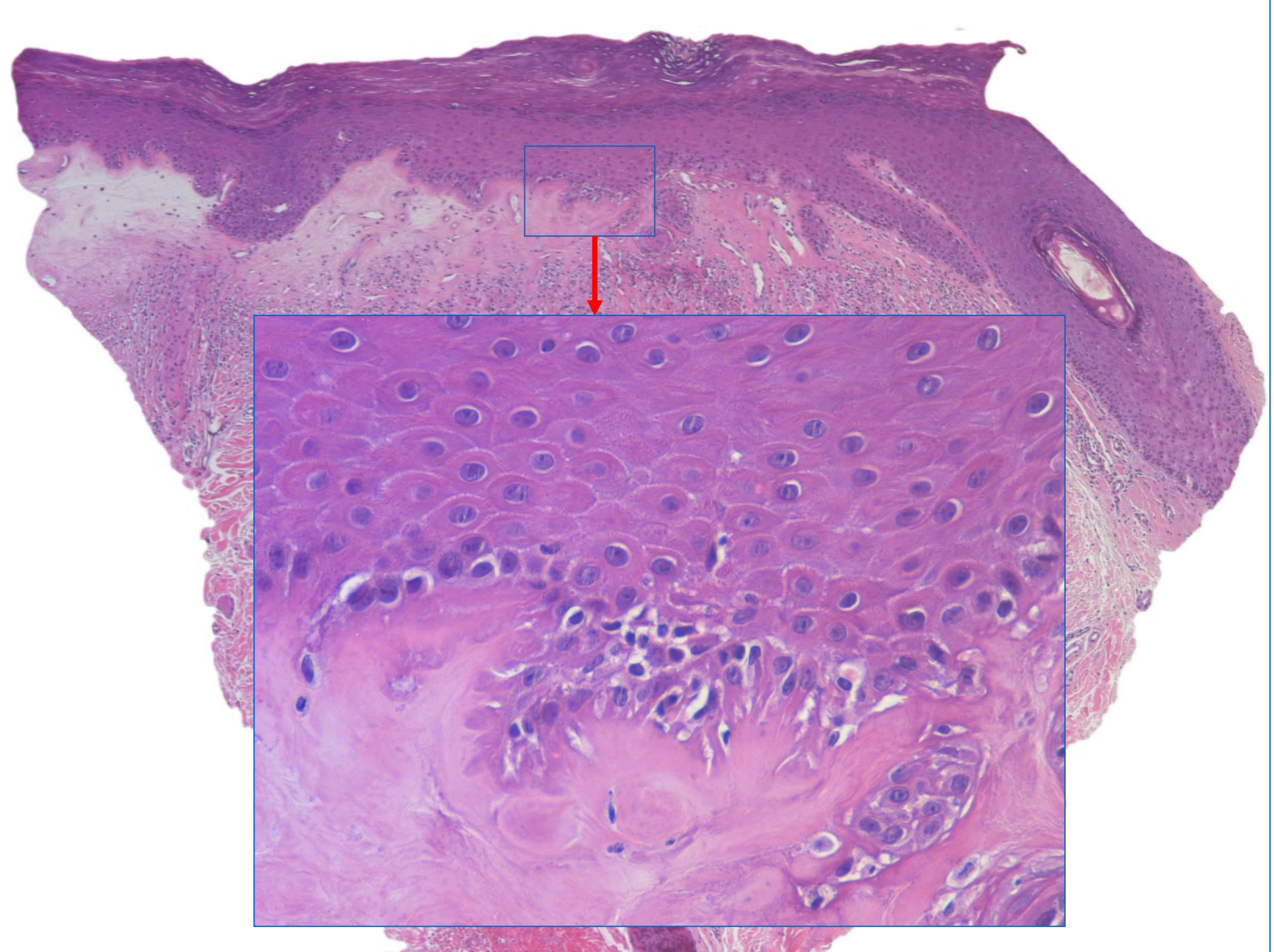


Walter Lever, Arch Dermatol 1962; 85: 371

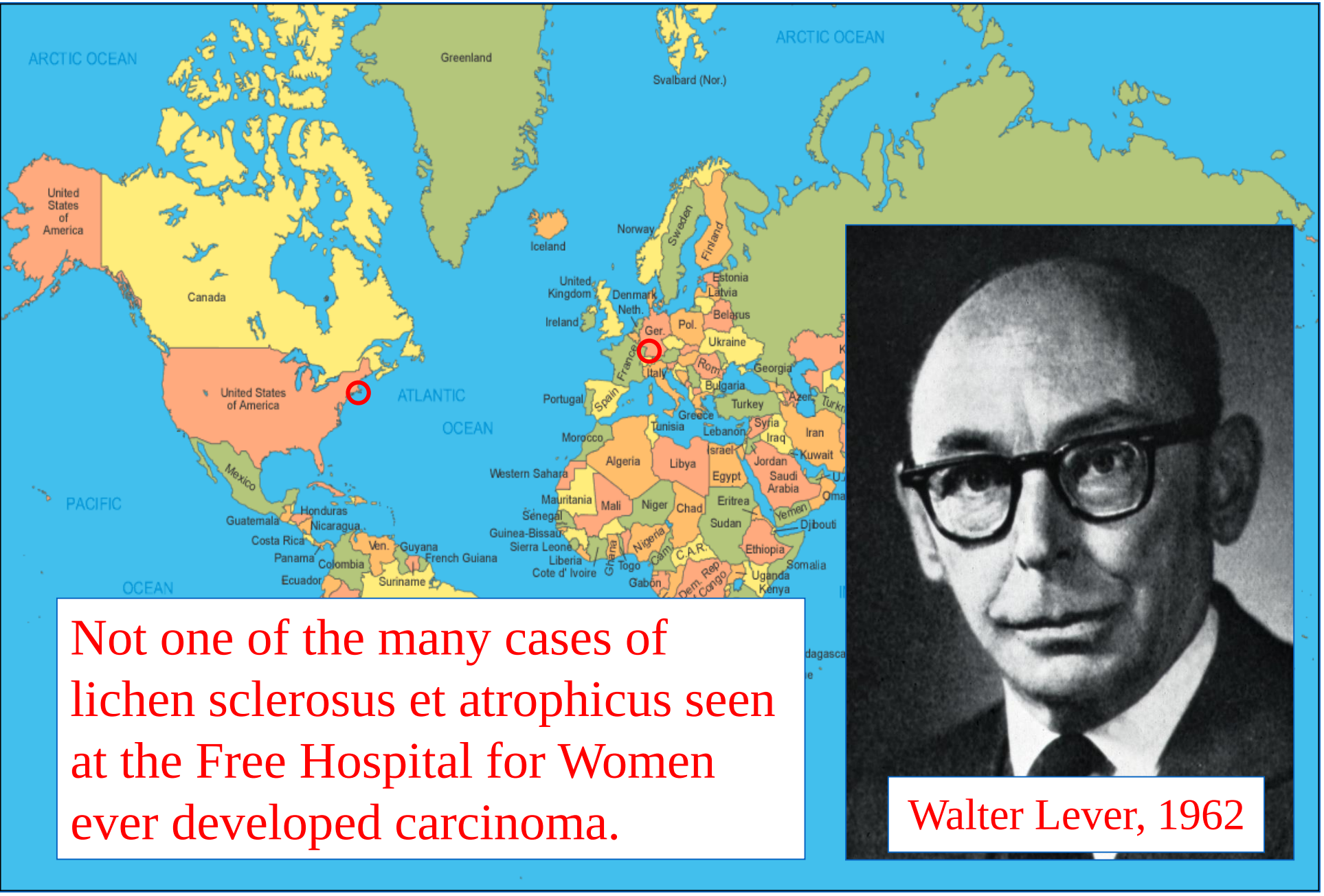
In a discussion of this paper, Walter Lever of Boston noted: *"I would caution against the concept of leukoplakia superimposed on lichen sclerosus et atrophicus. In cases of lichen sclerosus et atrophicus with a whitish, thickened skin one sees, on histologic examination, hyperkeratosis and irregular acanthosis, but no atypicality of the epidermal cells ..."*



This is what Lever described: Lichen sclerosus with hyperkeratosis and acanthosis. In vulvar lichen sclerosus, hyperplasia of the epidermis is the rule rather than the exception, and this is the reason why the extension “et atrophicus” has been discarded.



As an interface dermatitis, florid cases of lichen sclerosus are associated with vacuolar alterations at the junction and lymphocytes within the epidermis. As in all dermatitides with epidermal involvement, size and chromatism of keratocytes varies slightly, but there is no frank nuclear atypia, no crowding of nuclei, no evidence of a neoplastic process.



Not one of the many cases of lichen sclerosus et atrophicus seen at the Free Hospital for Women ever developed carcinoma.

Walter Lever, 1962

Lever stated in 1962 that *"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,

Not one of the many cases of lichen sclerosus et atrophicus seen at the Free Hospital for Women ever developed carcinoma.

we conducted a survey among leading dermatopathologists from Europe and the United States concerning the association of lichen sclerosus with cancer, the results of which were published in our journal “pink & blue.”

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

Some had seen a few cases, e.g., Helmut Kerl who estimated to have seen 5 cases in a professional career of more than 40 years. Most had not seen a single case in many years, including, for example, Zsolt Argenyi in Seattle, Heinz Kutzner in Friedrichshafen, 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.

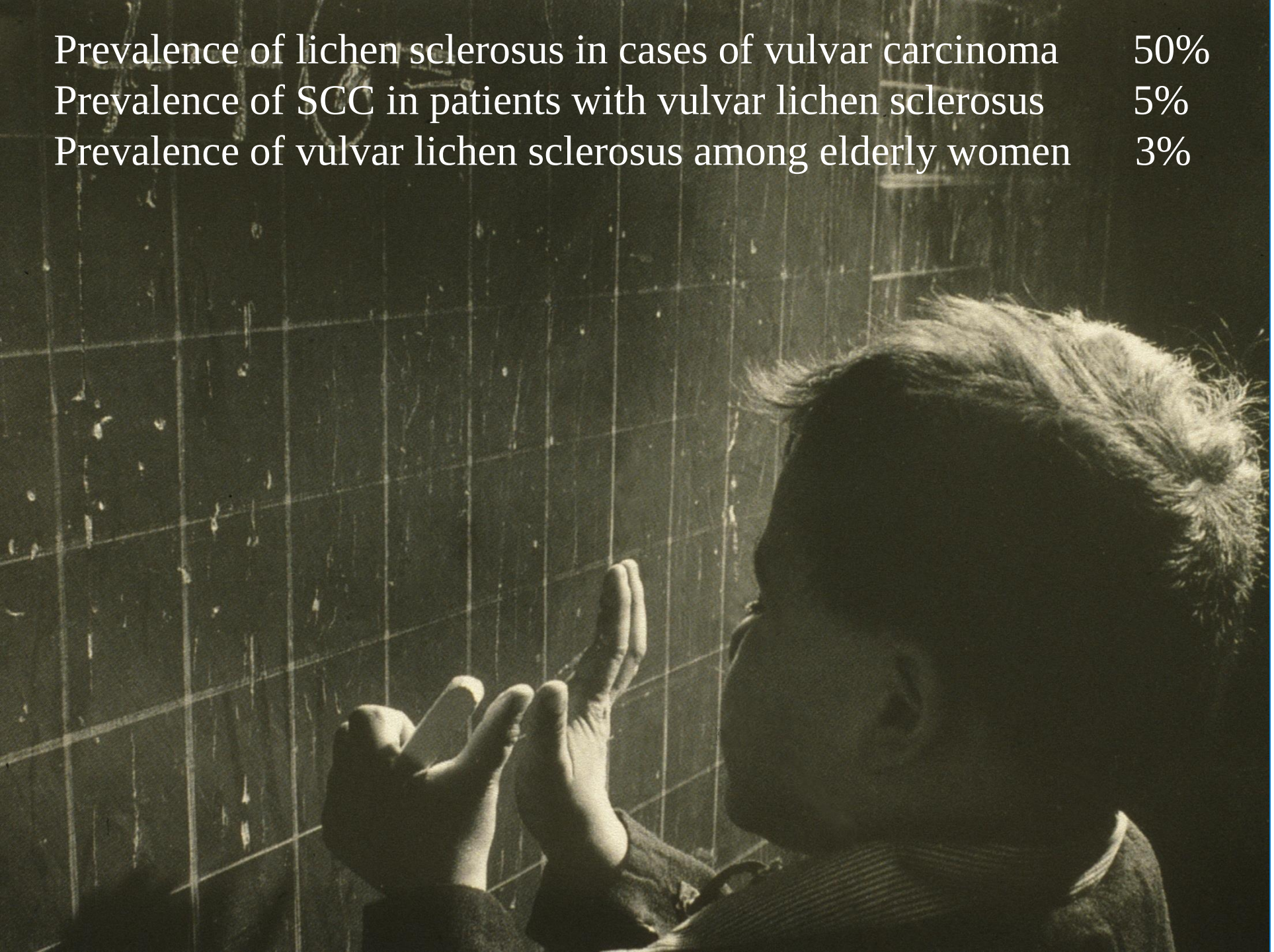
LS is a chronic inflammatory mucocutaneous disease most commonly affecting prepubertal girls and postmenopausal women. The etiology of LS is unknown; however, genetic factors and autoimmunity have been implicated. Alopecia areata, vitiligo, thyroid disorders, pernicious anemia, and diabetes

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.

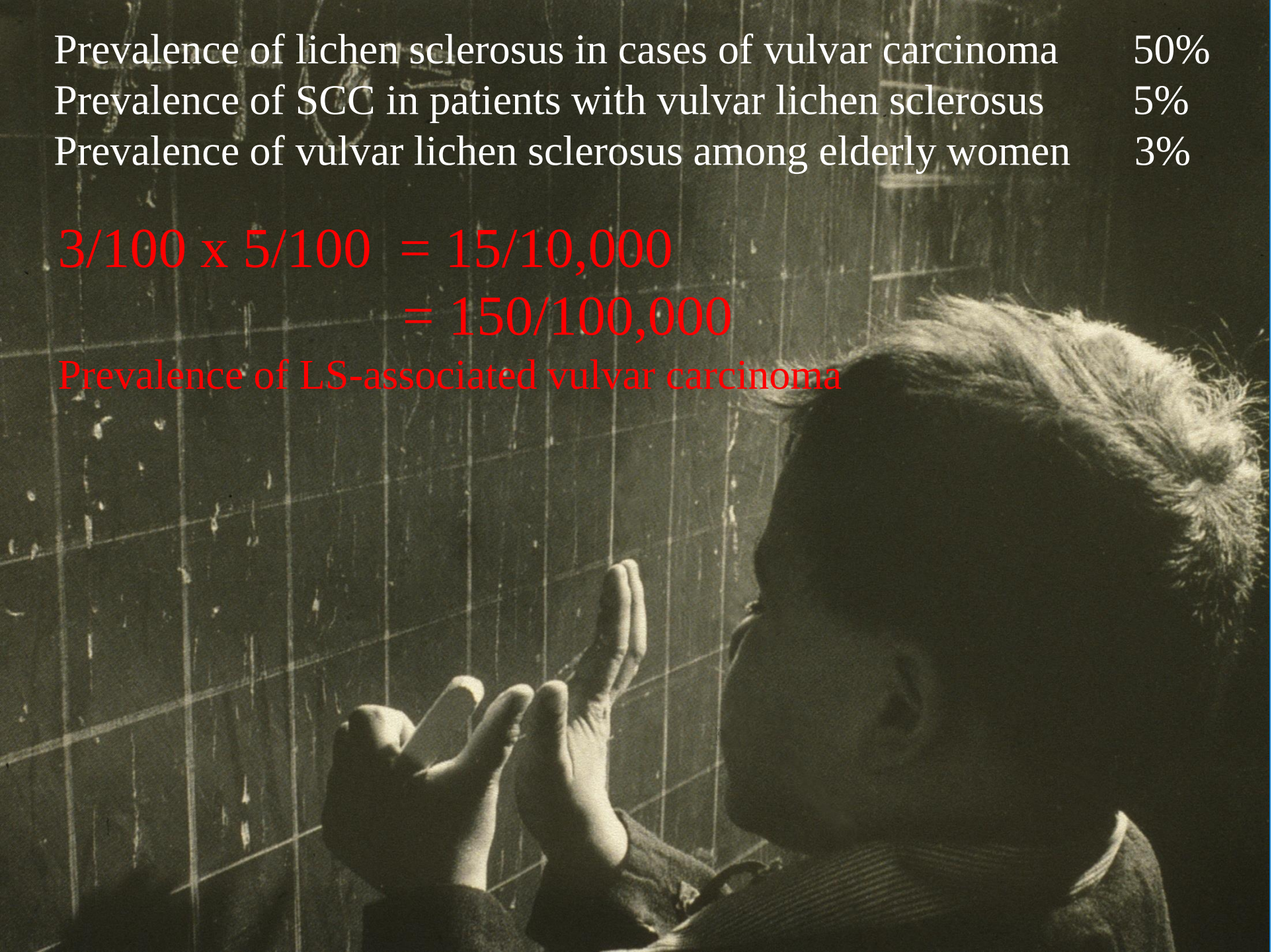
Patients with LS have a 4% to 6% risk of developing a vulvar squamous cell carcinoma (SCC).

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:

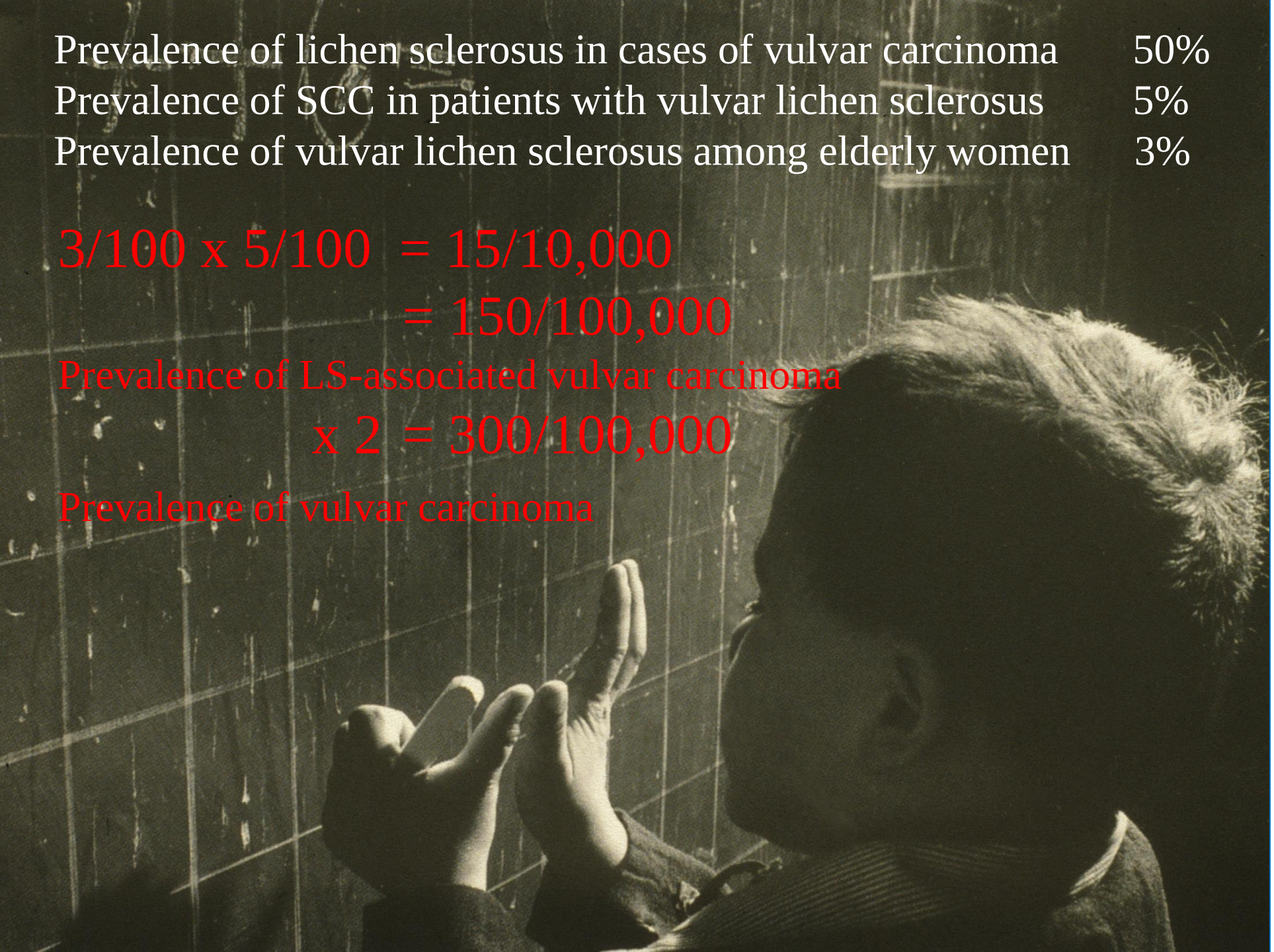
a prevalence of lichen sclerosus in cases of vulvar carcinoma of about 50% and a prevalence of SCC in patients with vulvar lichen sclerosus of about 5%.



If we also 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

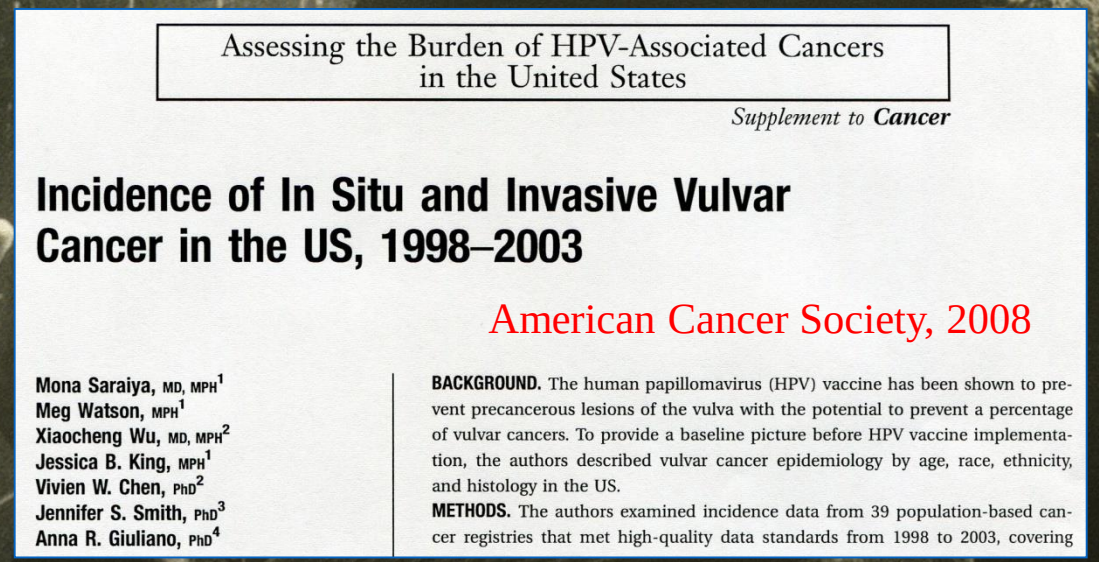
Prevalence of LS-associated vulvar carcinoma

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.

In brief, the incidence of lichen sclerosus-associated squamous cell carcinoma is exaggerated vastly. How can this be explained?

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

Lichen sclerosus (lichen sclerosus et atrophicus)
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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]

Hum Pathol
1989; 20: 495

There are many reasons, and one is the classification of the International Society for the Study of Vulvar Disease. With lichen sclerosus being the specific disease mentioned, this diagnosis came to be rendered excessively.

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

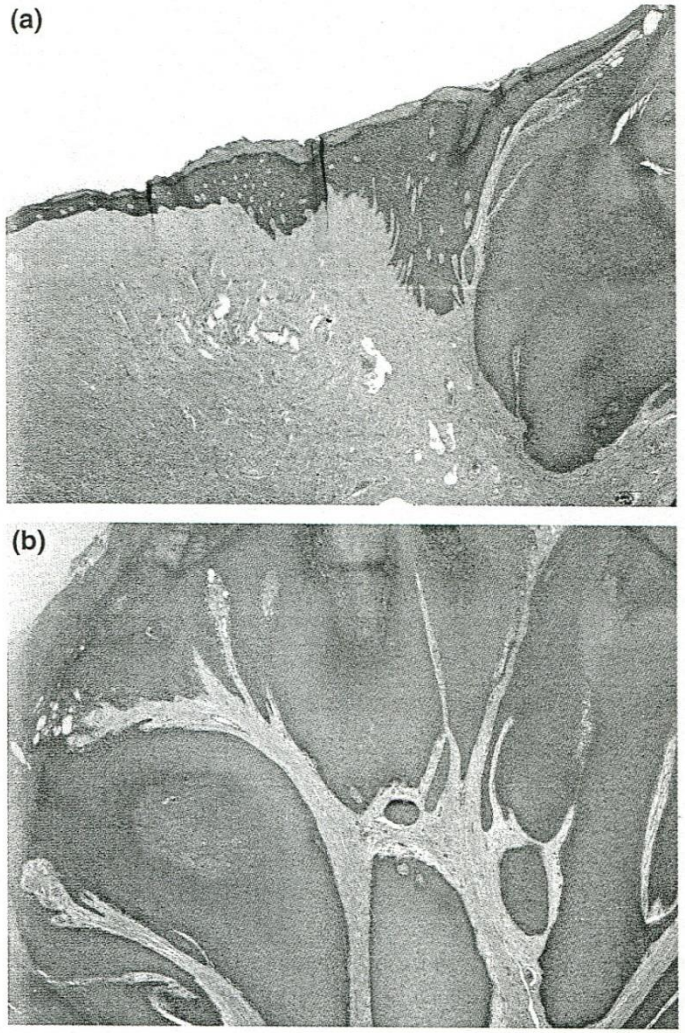


Figure 1 (a) Histopathological examinations showed verrucous carcinoma (right) with associated adjacent lichen sclerosus (left) manifested by atrophy of epidermis and homogenization of the dermis; (b) The verrucous carcinoma part showed hyperkeratotic warty endophytic growth of well-differentiated malignant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

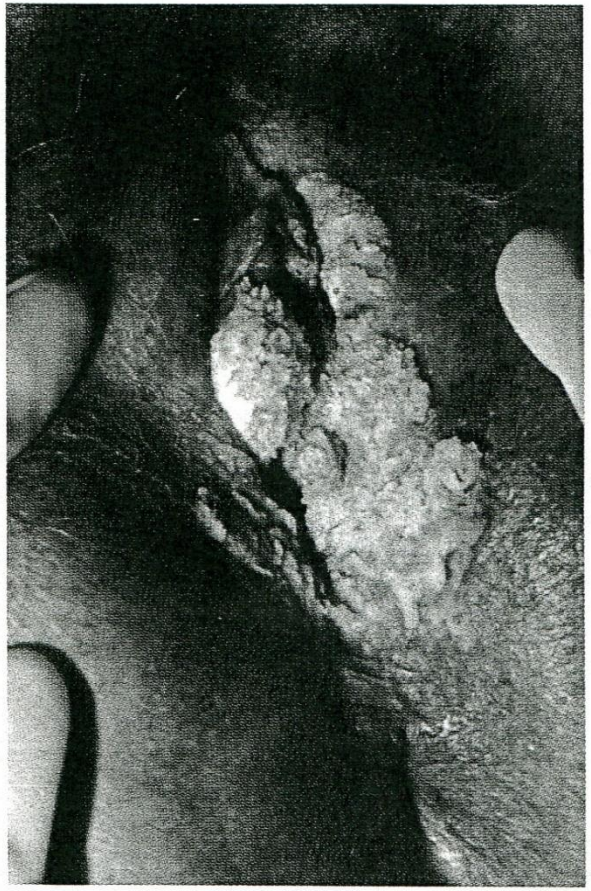


Figure 2 Extensive warty growths arising from both inner labia majora and extending into the introitus.

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

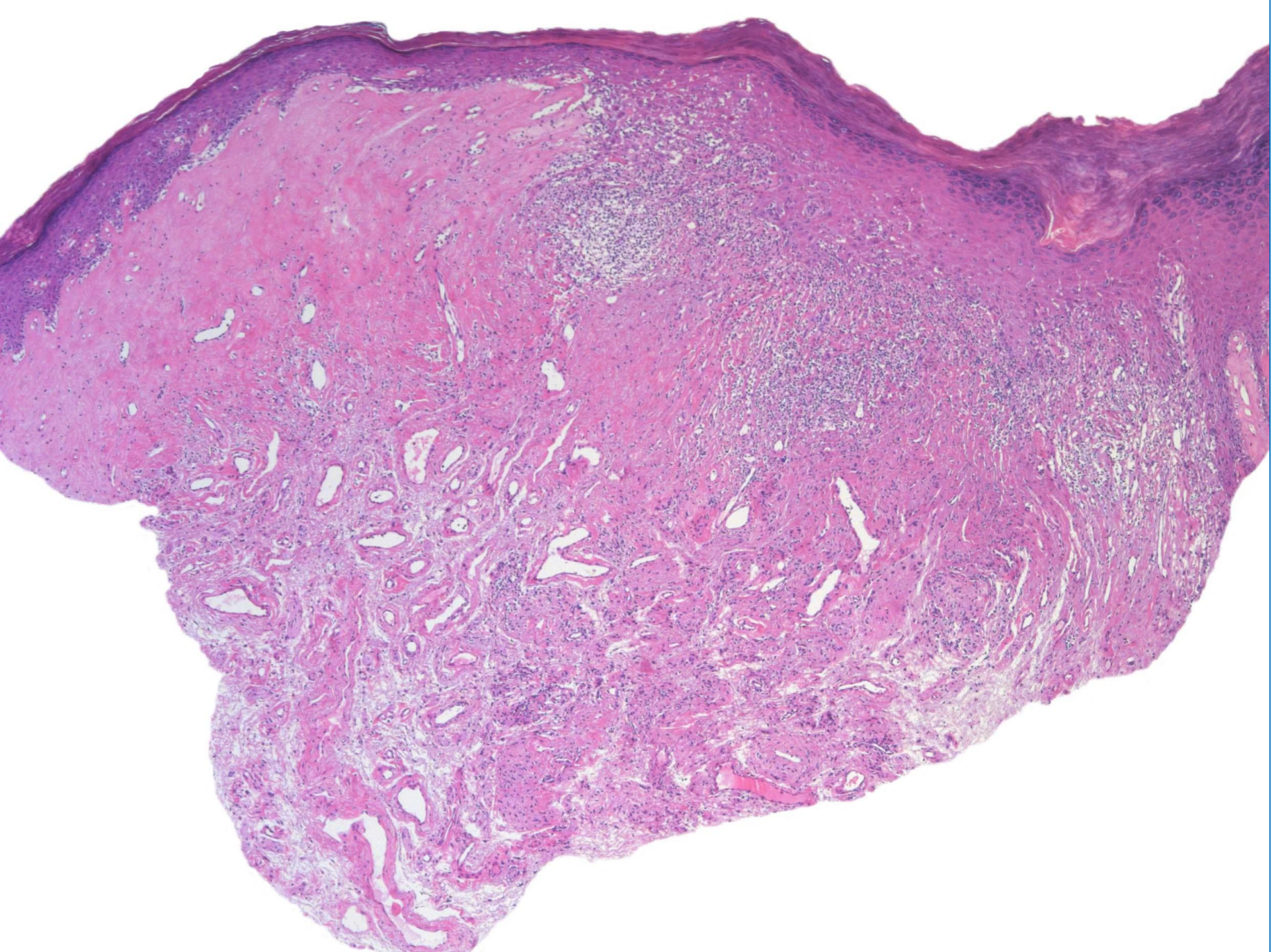
Hedwig P van de Nieuwenhof[1], Johan Bulten[2], Harrie Hollema[3], Rianne G Dommerholt[4], Leon FAG Massuger[1], Ate GJ van der Zee[5], Joanne A de Hullu[1] and Leon CLT van Kempen[2]

[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*

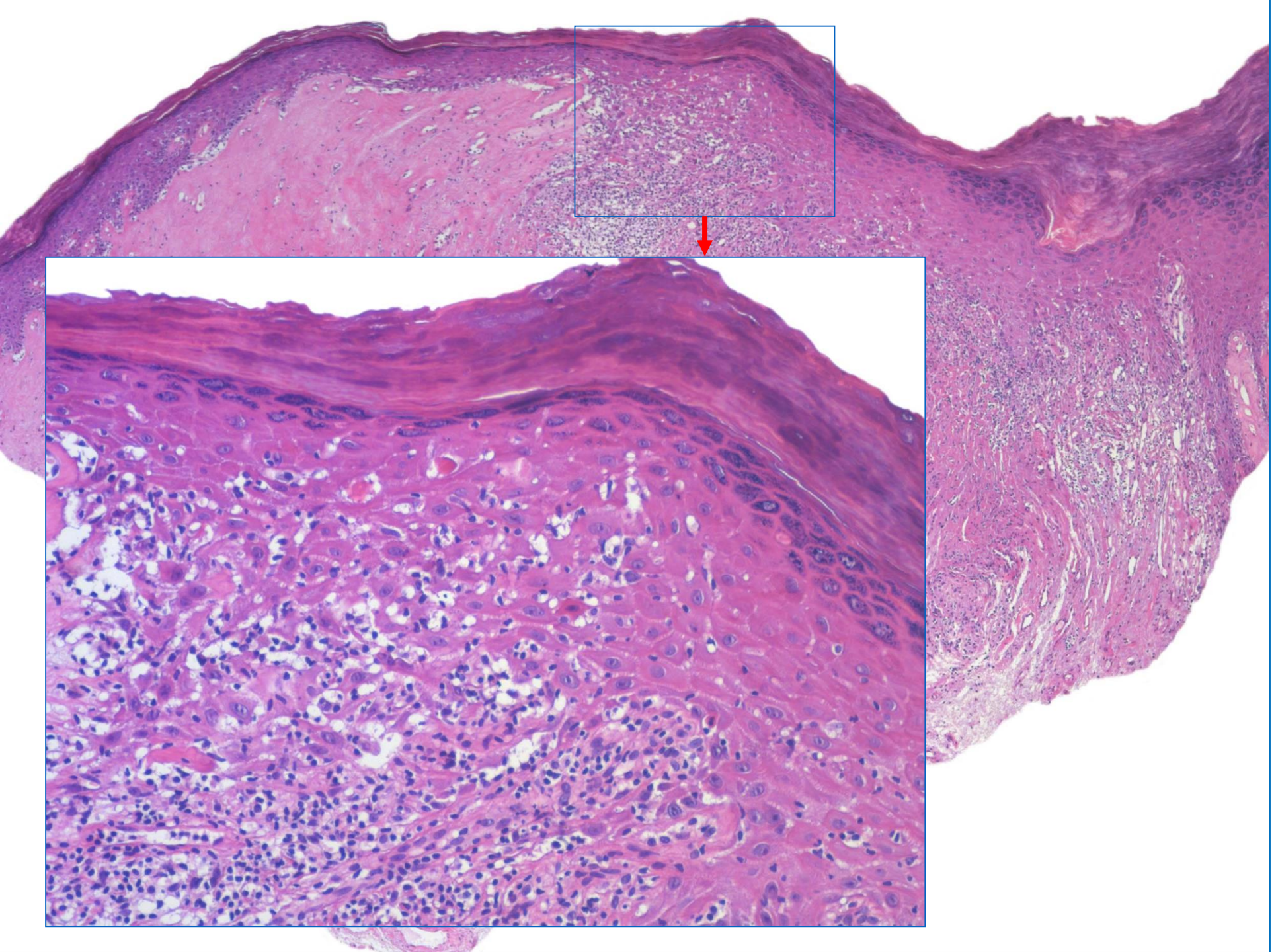
Lichen sclerosus is considered to be the precursor lesion of vulvar squamous cell carcinoma, of which only 2–5% progress to squamous cell carcinoma. Differentiated vulvar intraepithelial neoplasia (VIN) has been proposed to be the direct precursor lesion, but this is a recently recognized, and a difficult 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

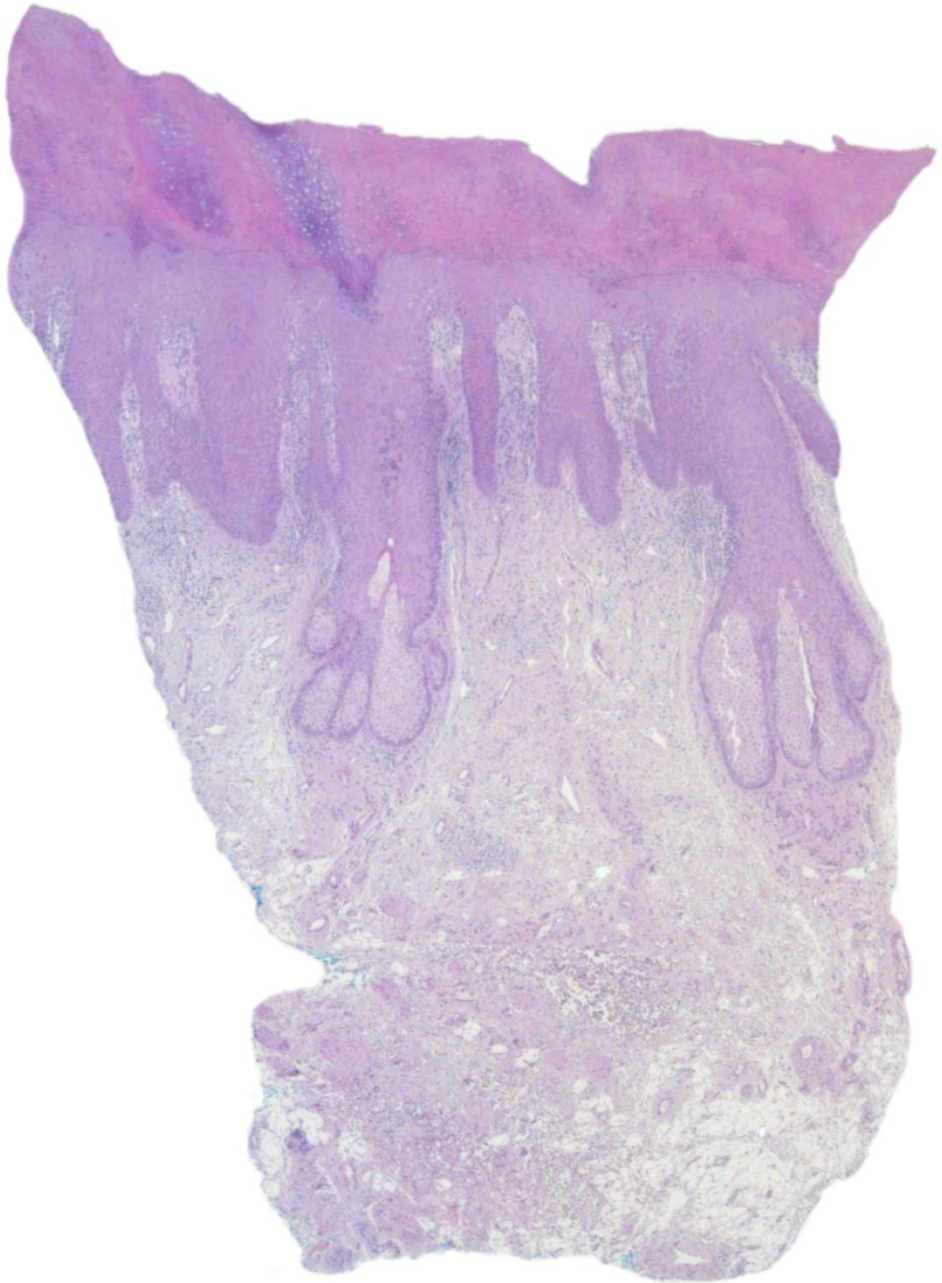
Three years ago, in a retrospective study of cases diagnosed as lichen sclerosus with progression to vulvar squamous cell carcinoma, revision of biopsies could confirm the diagnosis of lichen sclerosus in only 30% of cases.



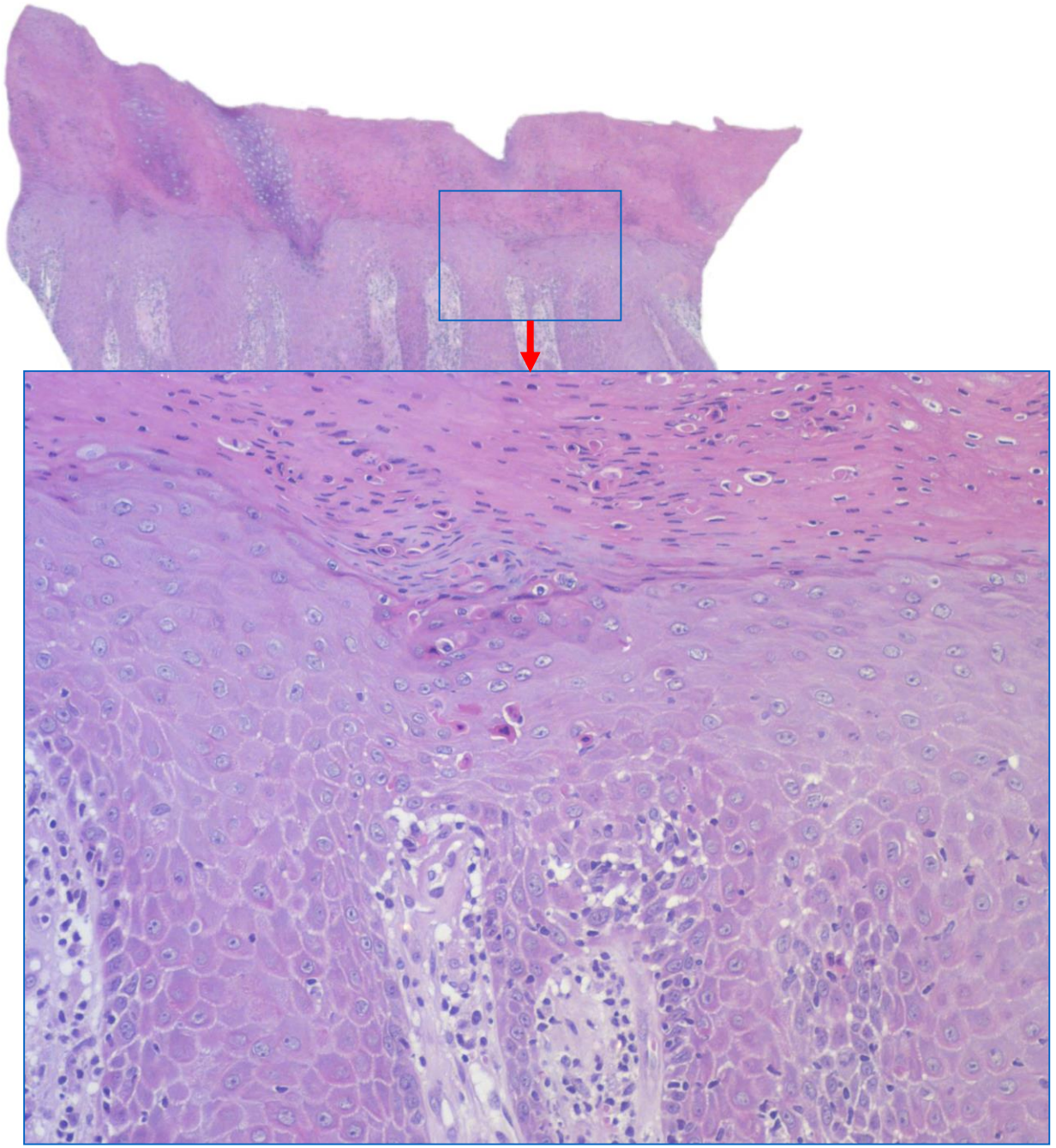
This should not be surprising. Although diagnosis of lichen sclerosus is usually straightforward in lesions with prominent subepidermal sclerosis, it may be difficult. In lesions with little or no sclerosis, lichen sclerosus often resembles lichen planus because of irregular epithelial hyperplasia with hypergranulosis and hyperkeratosis,



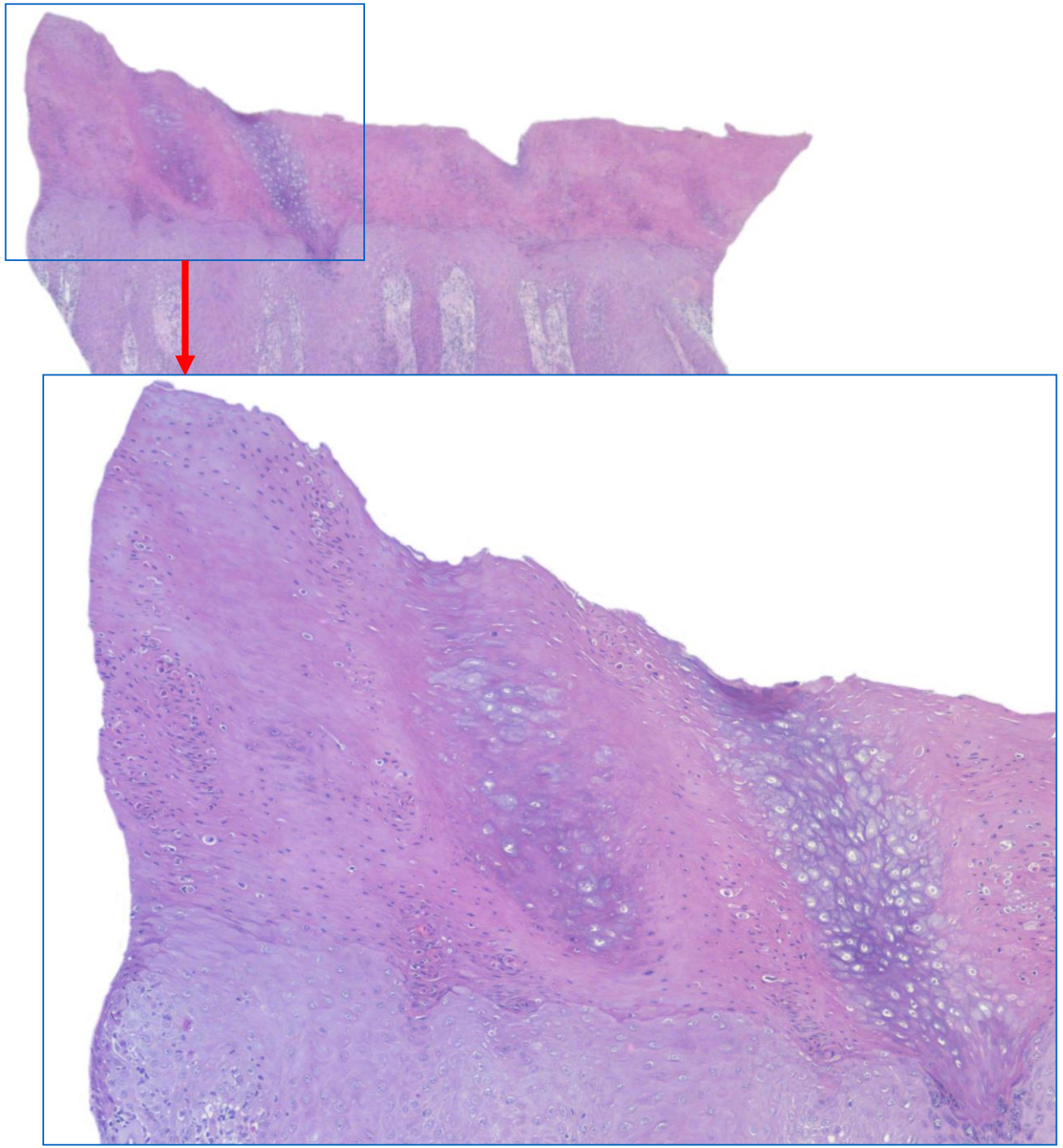
vacuolar changes at the junction, and necrotic keratocytes. Unlike lichen planus, lymphocytes are present not only in the lower epidermis, but pepper the epidermis in concert with scant spongiosis. The same is true for necrotic keratocytes that may be seen in all reaches of the epidermis.



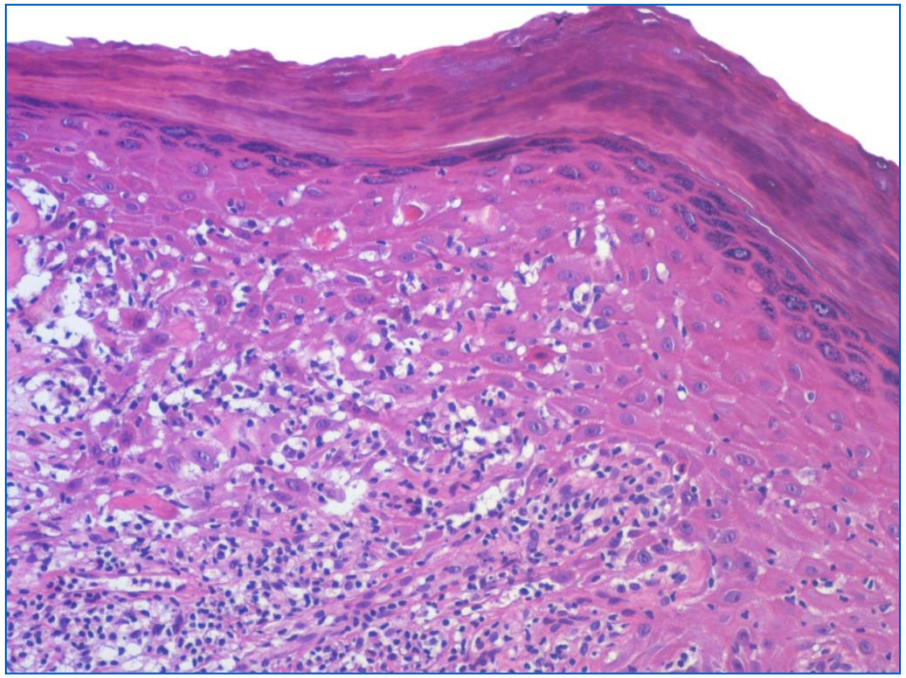
Moreover, epithelial hyperplasia in non-sclerotic lichen sclerosus is mostly psoriasiform with plump elongated rete ridges and papillomatosis.

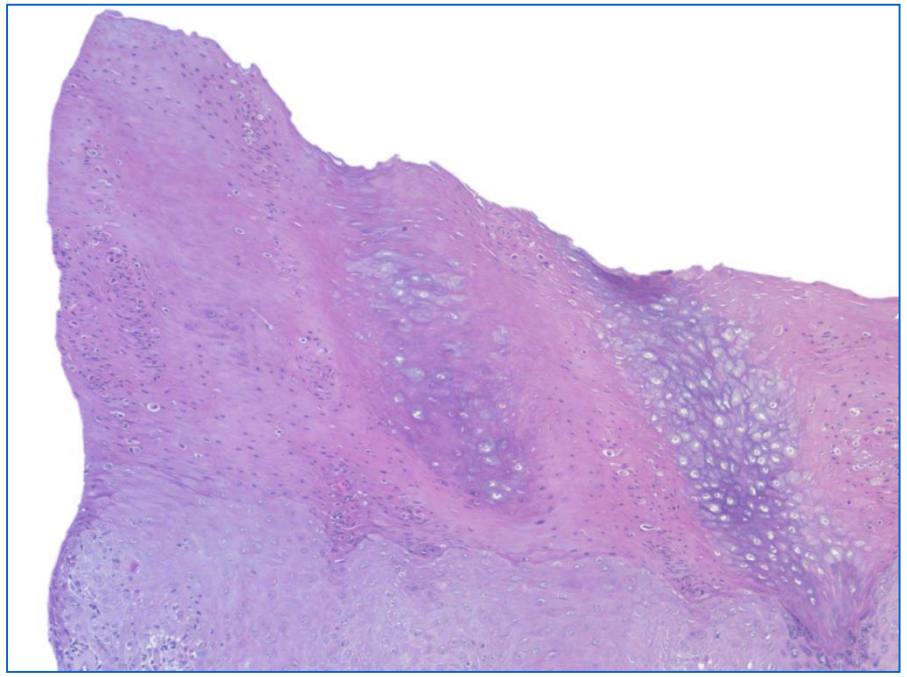


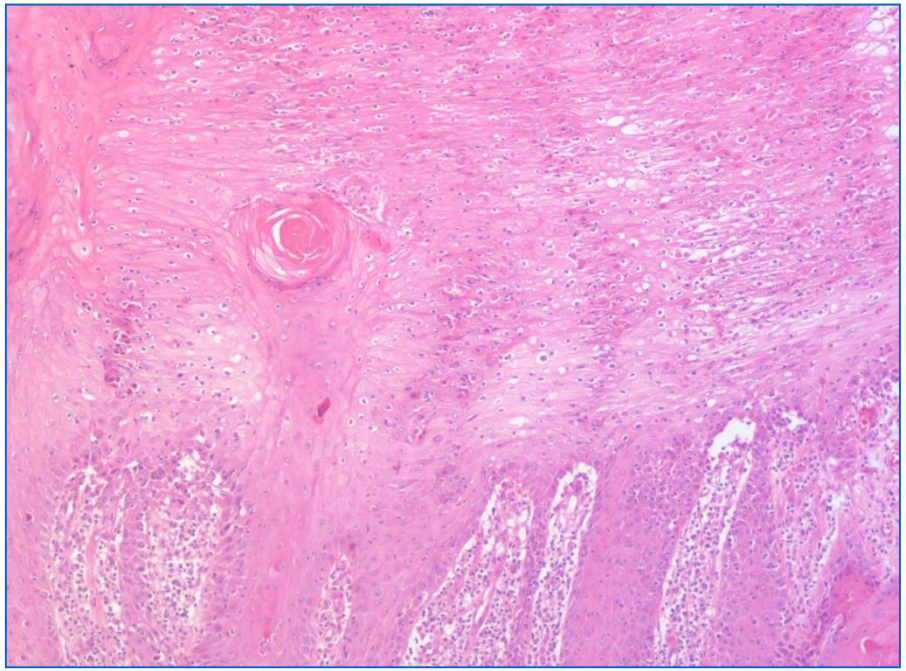
Also in this case, there are numerous lymphocytes in the epidermis in concert with scant spongiosis, necrotic keratocytes in the upper reaches of the epidermis, and parakeratosis with distinct dyskeratotic parakeratotic cells.

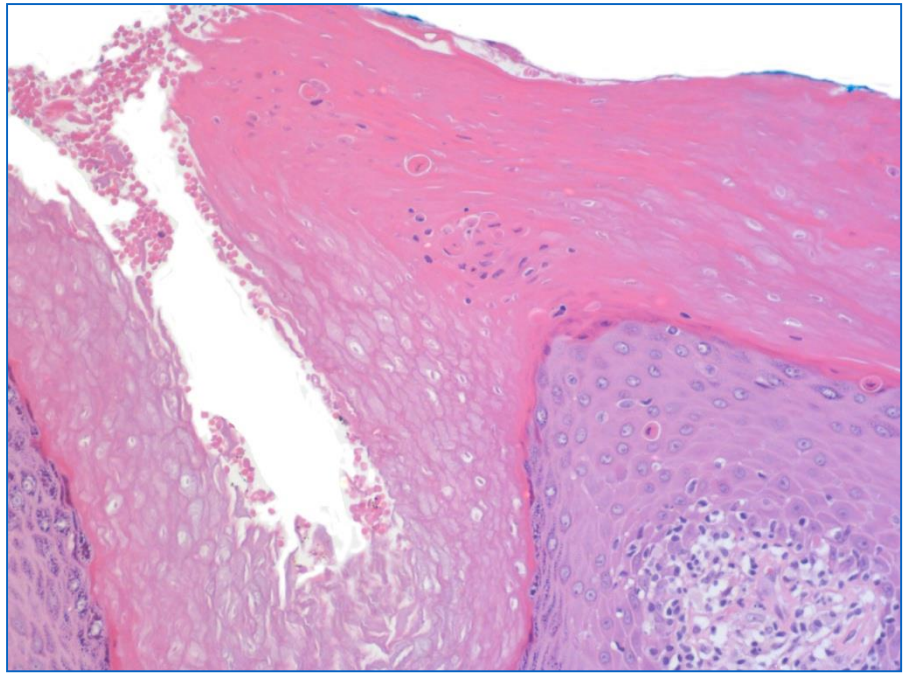


Those changes are accentuated above dermal papillae, the result being narrow, vertical columns of parakeratosis that are even more distinctive at the edge of the biopsy specimen.

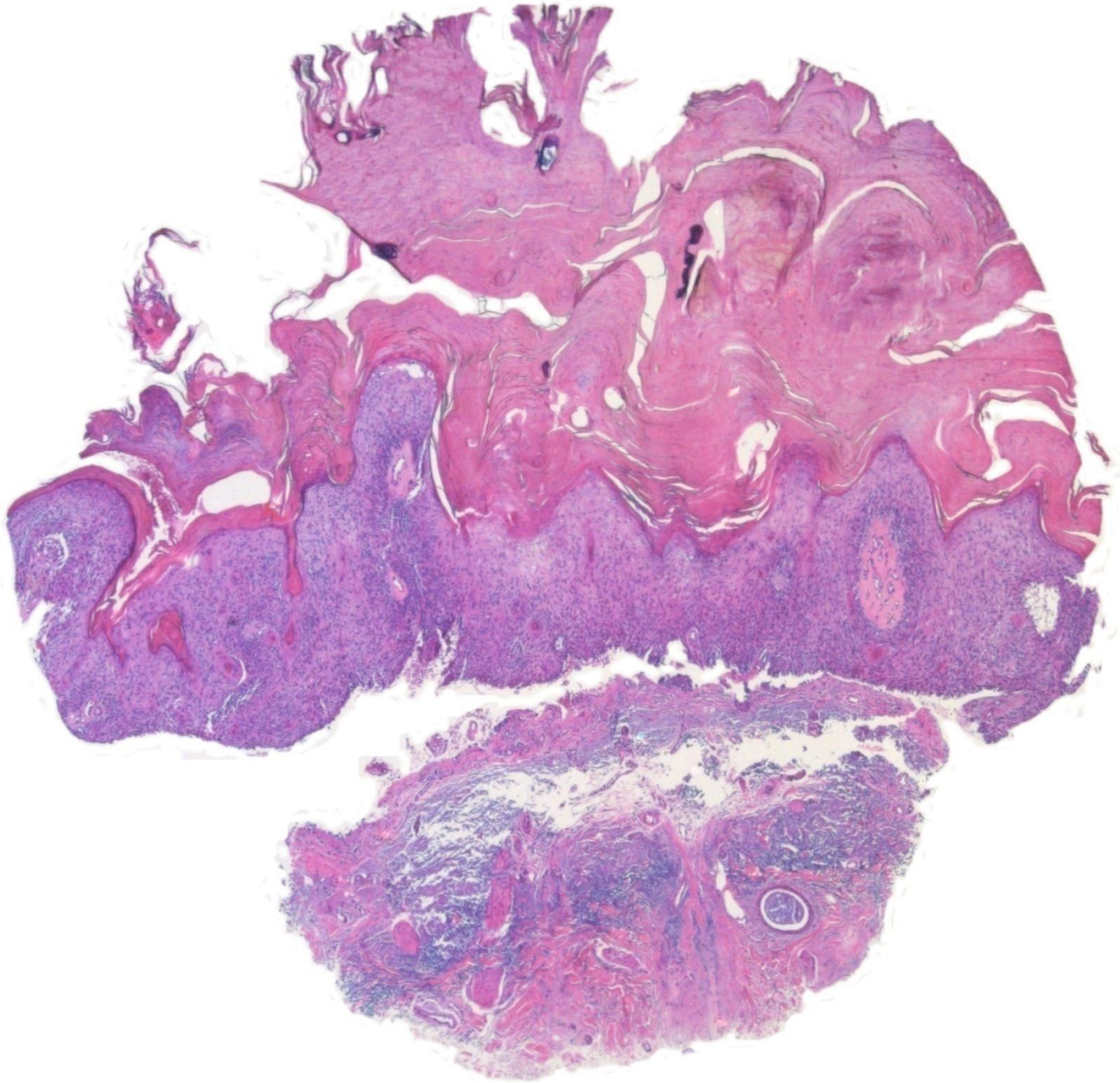




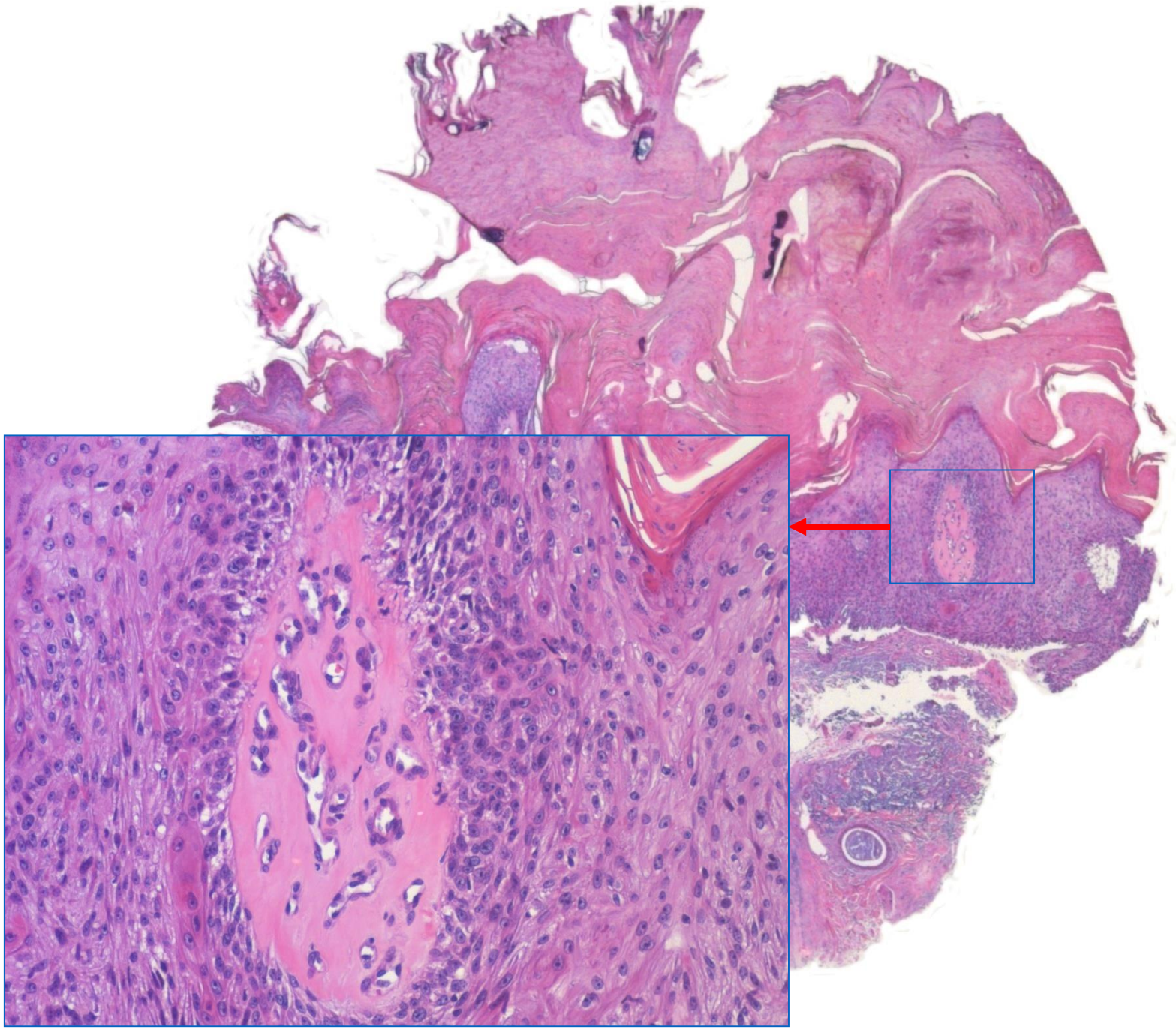




In brief, there are many criteria for histopathologic diagnosis of lichen sclerosus in the absence of sclerosis. However, diagnosis depends on a constellation of criteria because no single criterion is diagnostic, not even subepidermal sclerosis.



For example, foci of sclerosis may be seen in the stroma of squamous cell carcinoma, as in this carcinoma in situ from the scalp.



In the papillary dermis, the collagen appears homogenized; individual fibres cannot be distinguished. On the scalp, those findings are usually neglected, but on the vulva, they are likely to be interpreted as evidence of associated lichen sclerosus.

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

Hum Pathol
1989; 20: 495

Another effect of the classification of the International Society for the Study of Vulvar Disease was the tendency to interpret slight nuclear atypia as evidence of a neoplastic process. Once the category VIN I had been introduced, that diagnosis was given in a wide variety of diseases, ranging from inflammatory dermatoses to condylomata.

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Abstract

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

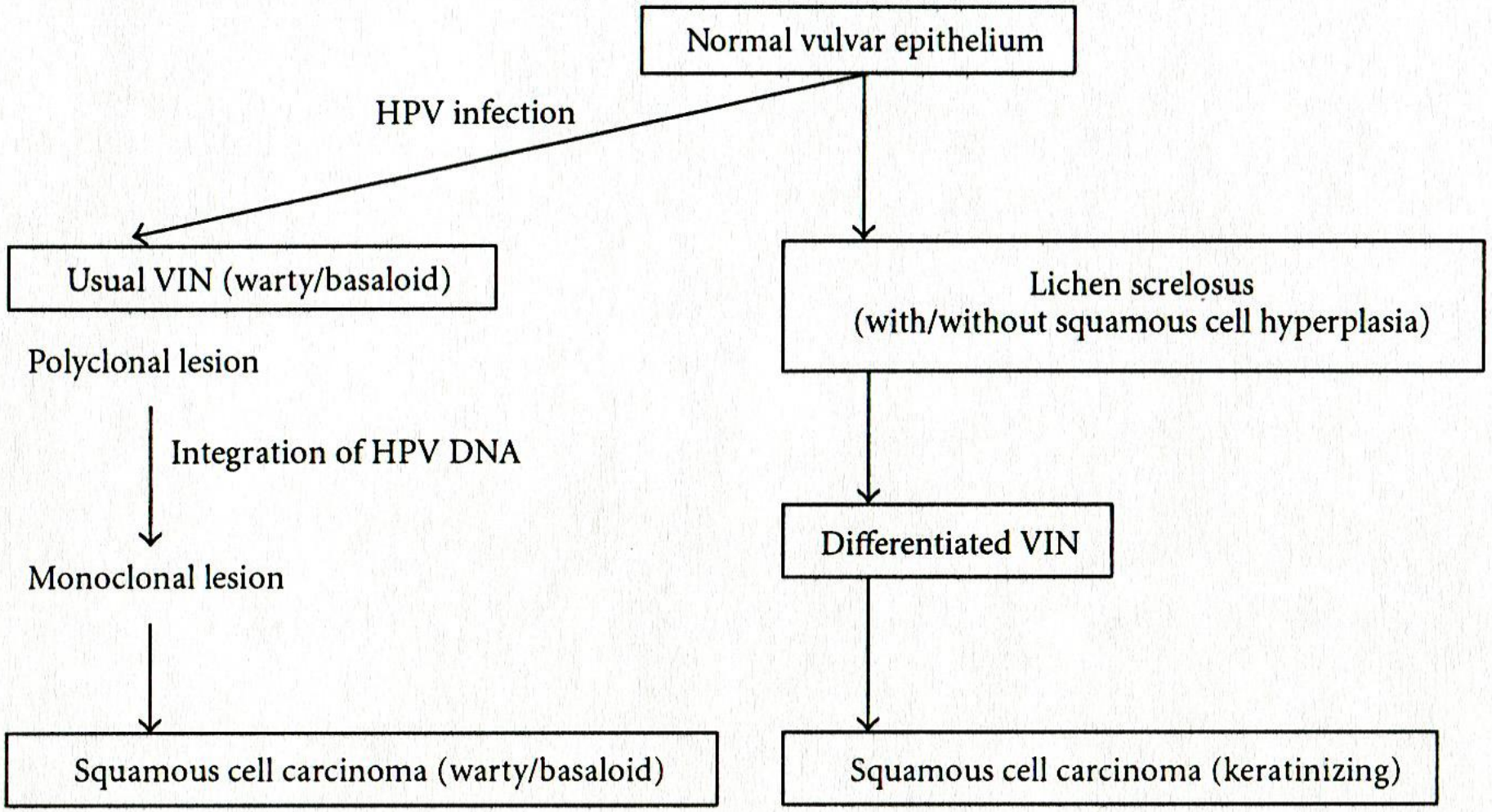
Authors: Mario Sideri, M.D., Ronald W. Jones, M.D., Edward J. Wilkinson, M.D., Mario Preti, M.D., Debra S. Heller, M.D., James Scurry, M.D., Hope Haefner, M.D., and Sallie Neill, M.D.

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

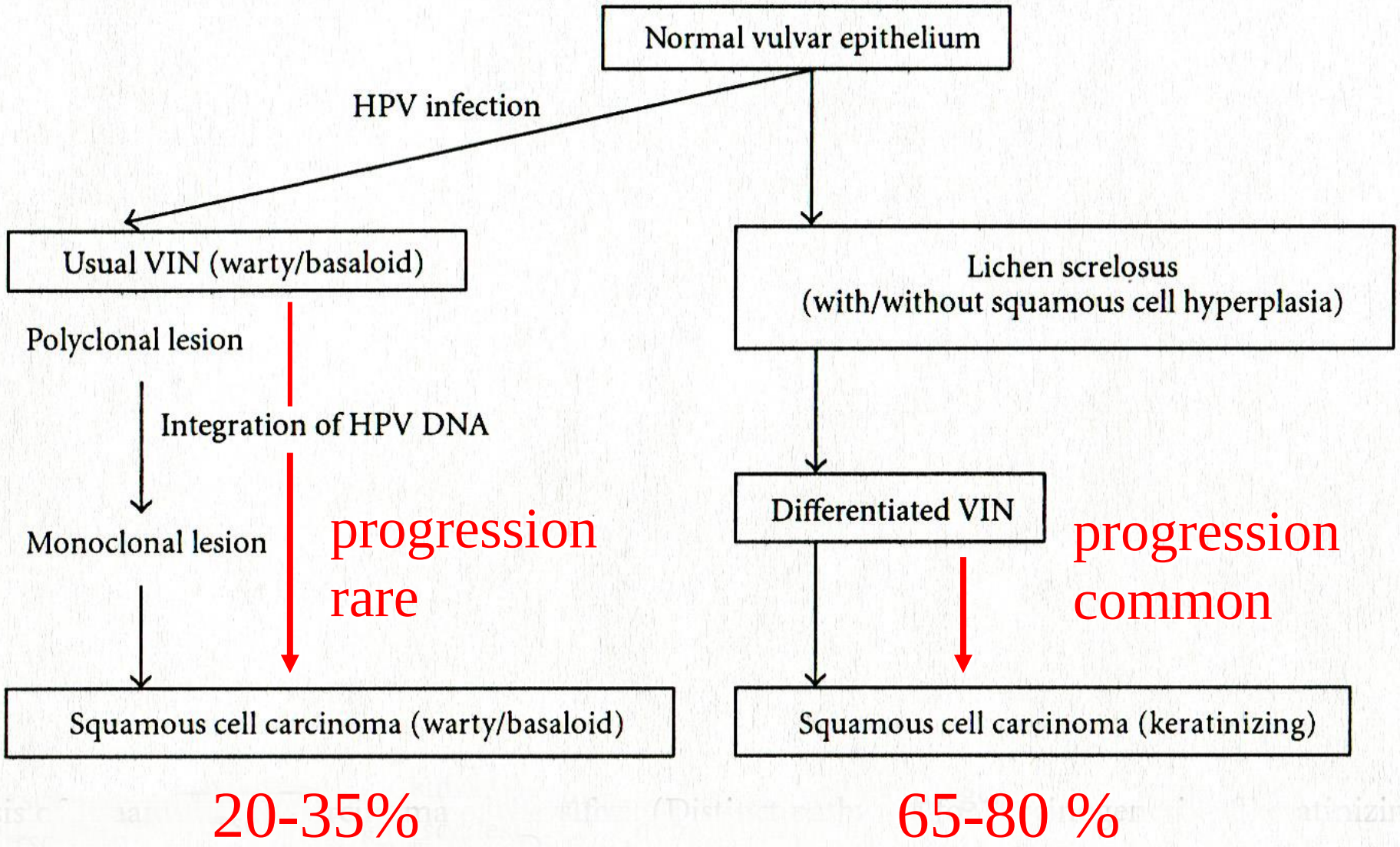
Eventually, this was recognized as a problem, and in 2004, the International Society for the Study of Vulvovaginal Disease proclaimed that *"the term VIN should apply only to histologically high grade suqamous lesions. … The term VIN 1 will no longer be used."* At the same time, a new classification was introduced that distinguished between *"VIN, usual type"* and *"VIN, differentiated type."*

Ueda Y et al.
J Skin Cancer, 2011



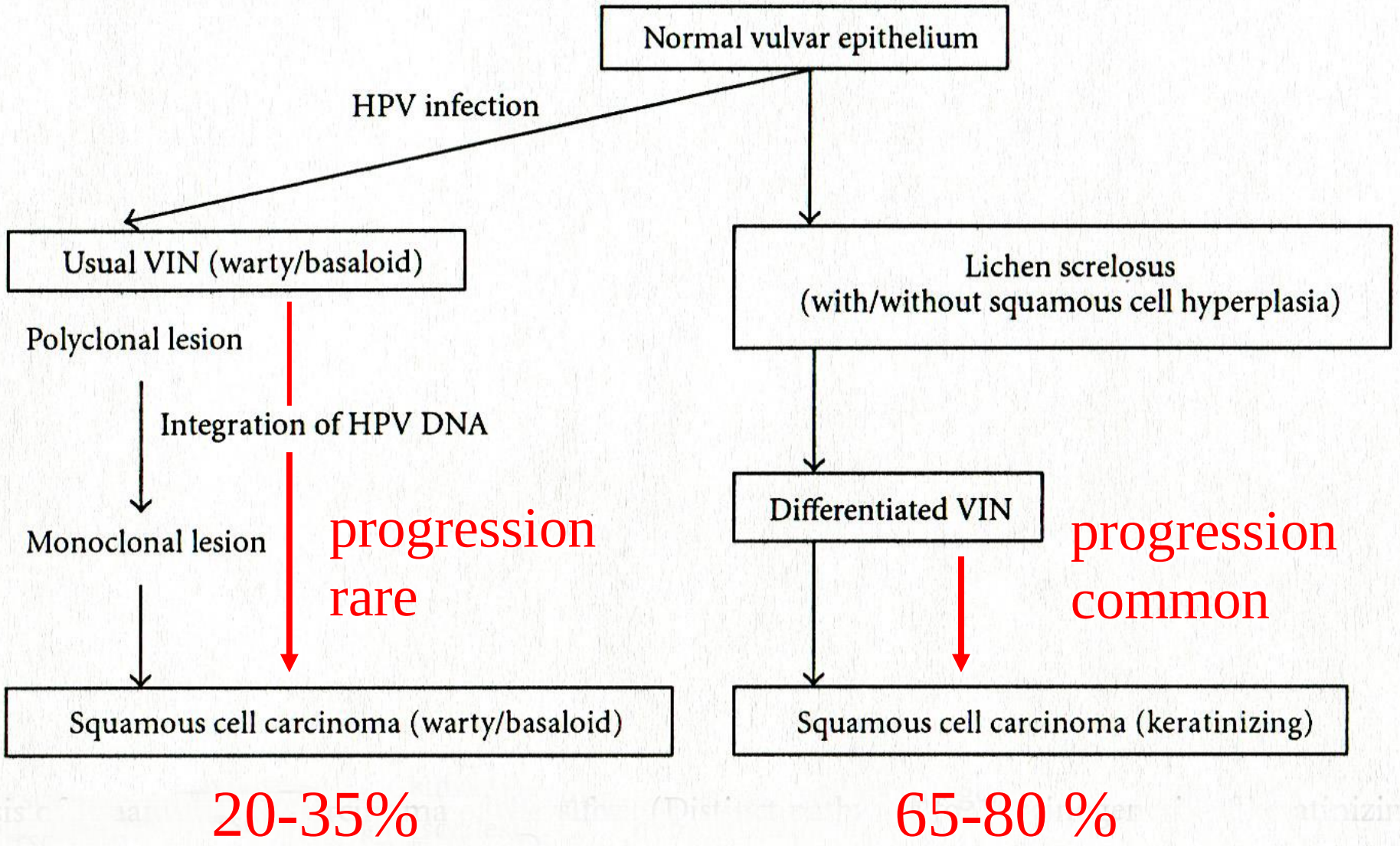
Those types were thought to reflect two distinct pathways of carcinoma formation. *"VIN, usual type"* was thought to be caused by human papilloma virus and to progress to warty or basaloid squamous cell carcinoma, whereas *"VIN, differentiated type"* was said to be associated with lichen sclerosus and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

Ueda Y et al.
J Skin Cancer, 2011



The warty or basaloid type 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.

Ueda Y et al.
J Skin Cancer, 2011



This two-tier classification of vulvar squamous cell carcinoma has the advantage of being elegant and the disadvantage of being incorrect on several grounds. 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

Correspondence to: Professor T J M Helmerhorst, Department of Gynaecology, Erasmus University Medical Centre, PO Box 2040, 3000 CA, Rotterdam, The Netherlands; t.helmerhorst@erasmusmc.nl

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. They also noted that *"HPV DNA was demonstrated in 31% of the lesions."*

The Journal of Reproductive Medicine®

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

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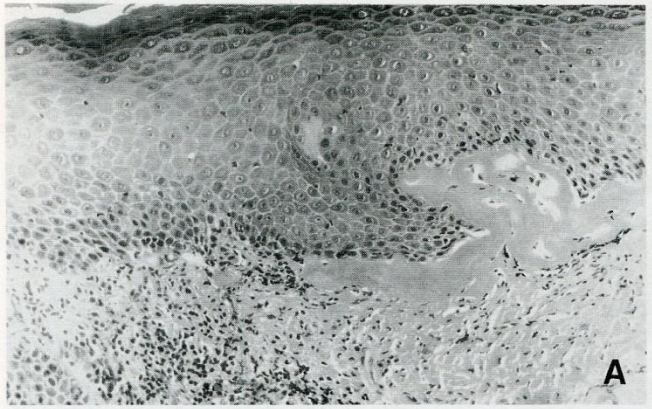
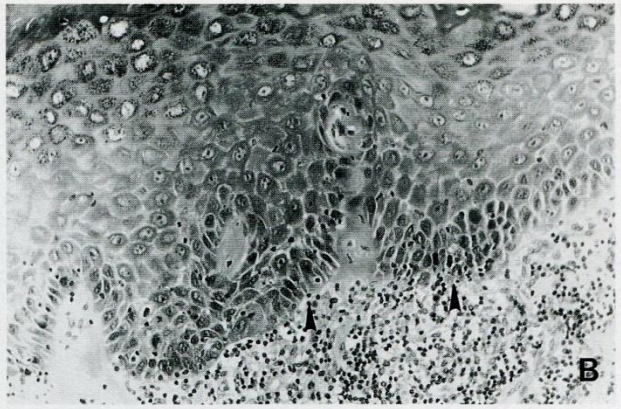
It was emphasized that *"the term 'differentiated' refers to … basal atypia in the context of a fully differentiated vulvar epithelium. …Its high degree of cellular differentiation and absence of widespread architectural disarray make it difficult to recognize this type of VIN."* This is not the description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





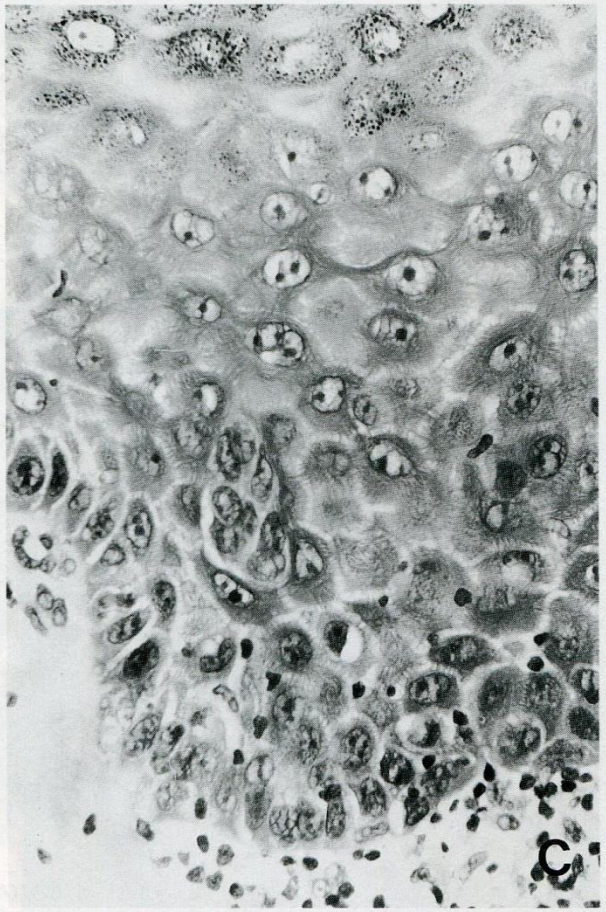


FIGURE 2. Morphological features of a specimen categorized as variant (differentiated) VIN associated with LS that was HPV negative. (A) Area of uninvolved LS without nuclear atypia. (B) Adjacent area with prominent maturation and conspicuous basal atypia (arrowheads). (C) Detail of parabasal epithelium 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."*

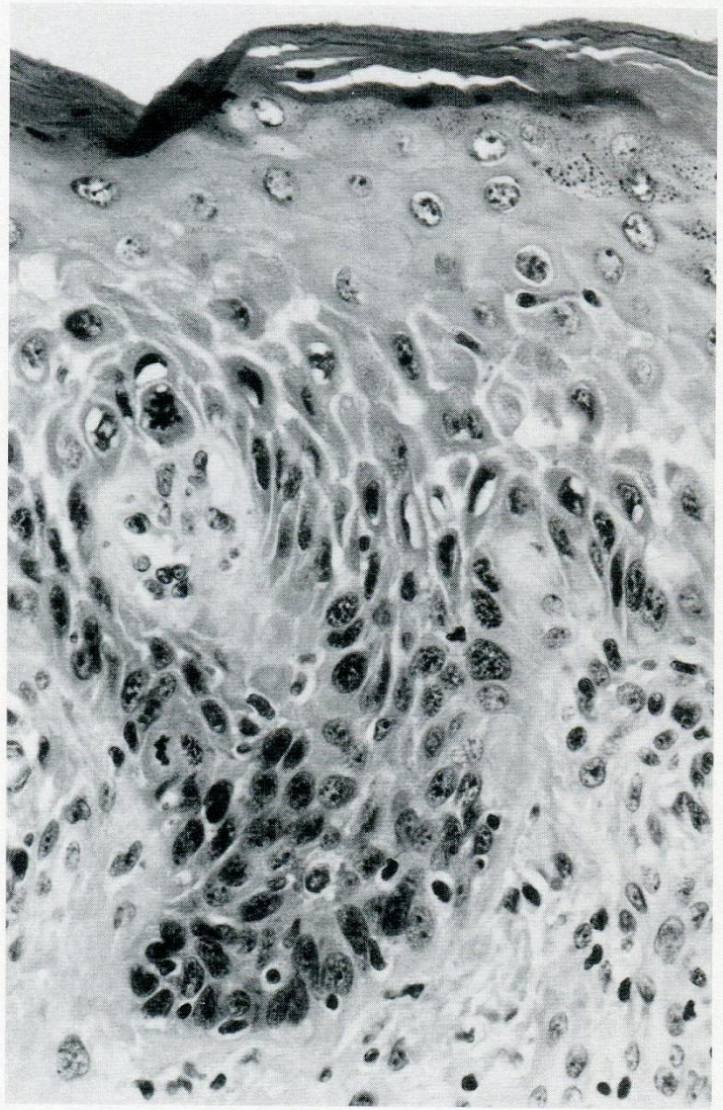


FIG. 11. Basilar cells and lower keratinocytes have irregular hyperchromatic nuclei and a mitotic figure. Although the dysplastic features of this example of simplex vulvar intraepithelial neoplasia (VIN) are marked, they are different distinctly than those of the "classic" (Bowen's) type of VIN.

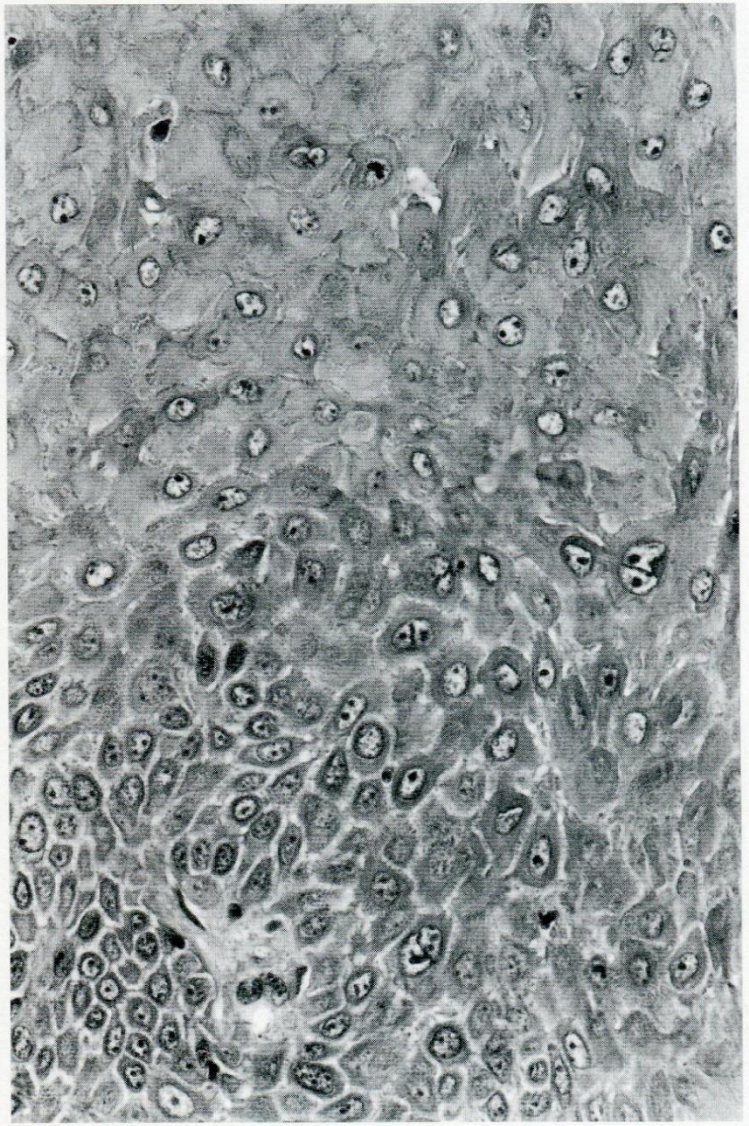
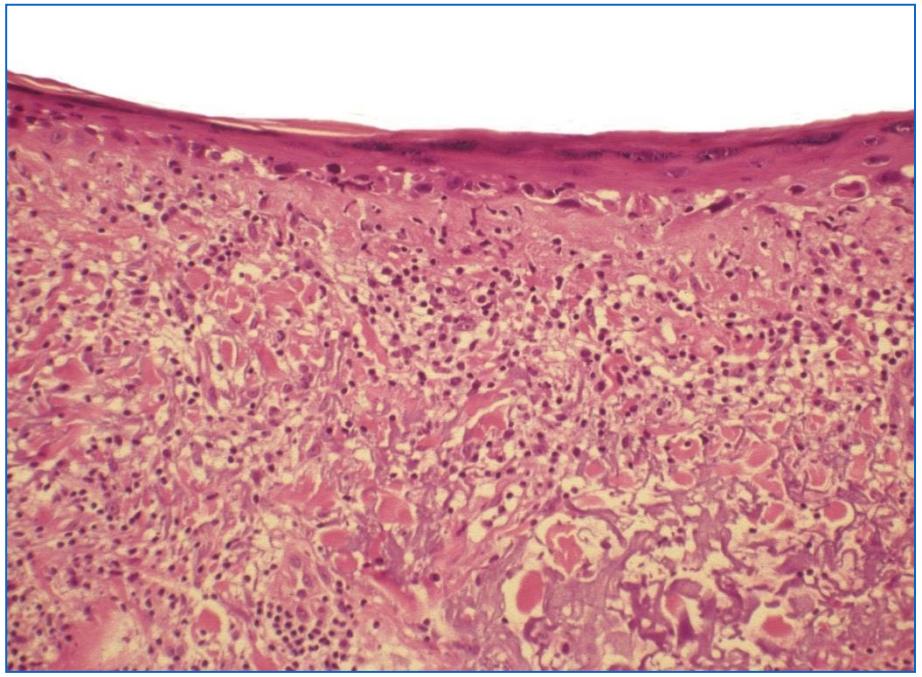
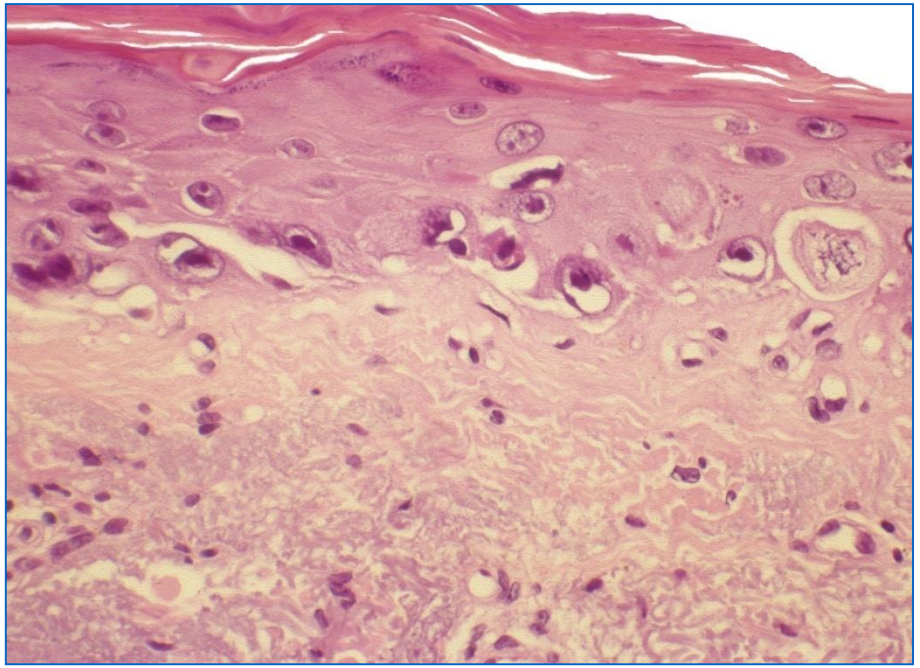


FIG. 4. Abnormal keratinocytes of simplex vulvar intraepithelial neoplasia have dense eosinophilic cytoplasm and enlarged nuclei with prominent nucleoli. Occasional cells are binucleated. Architectural differentiation of the abnormal cells is preserved in the superficial portions of the epidermis.

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."*





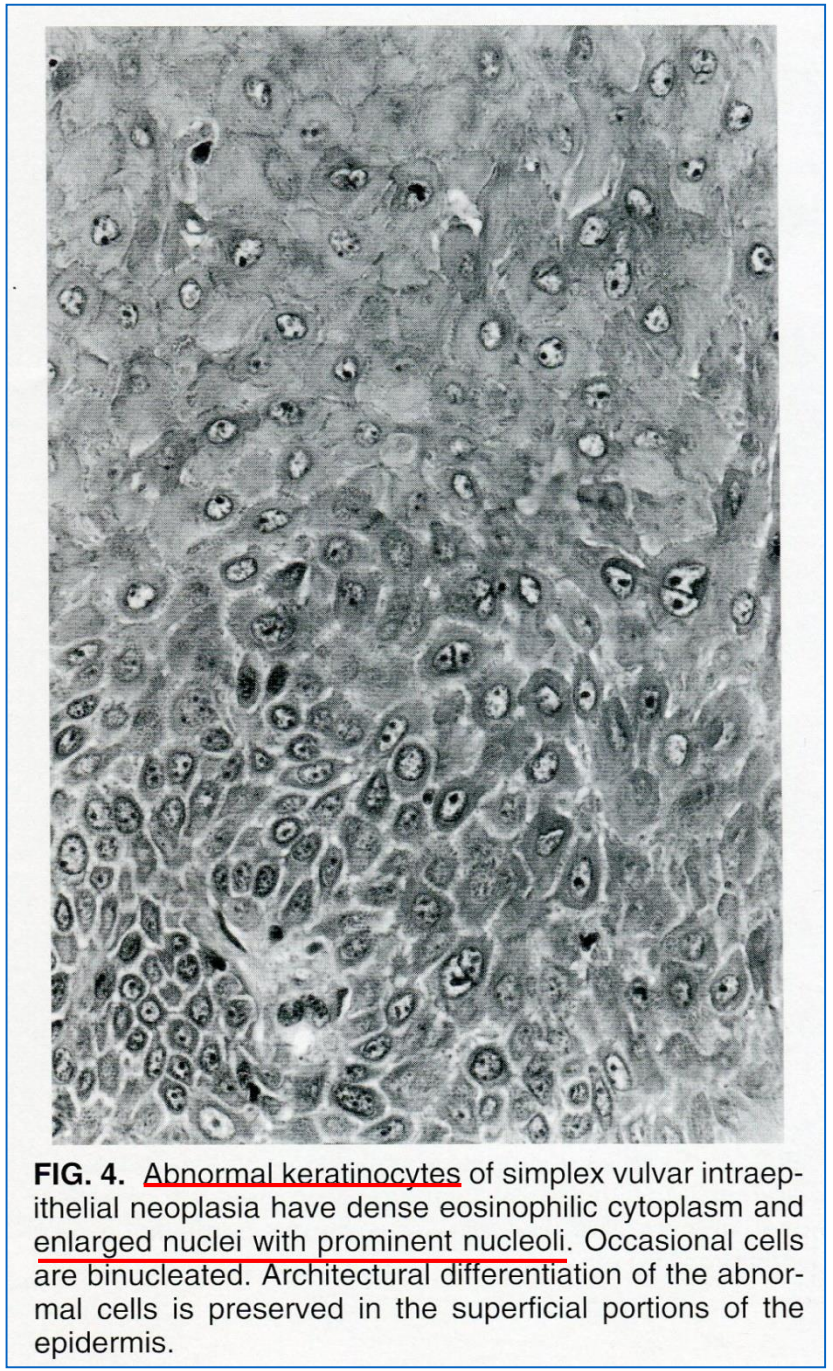
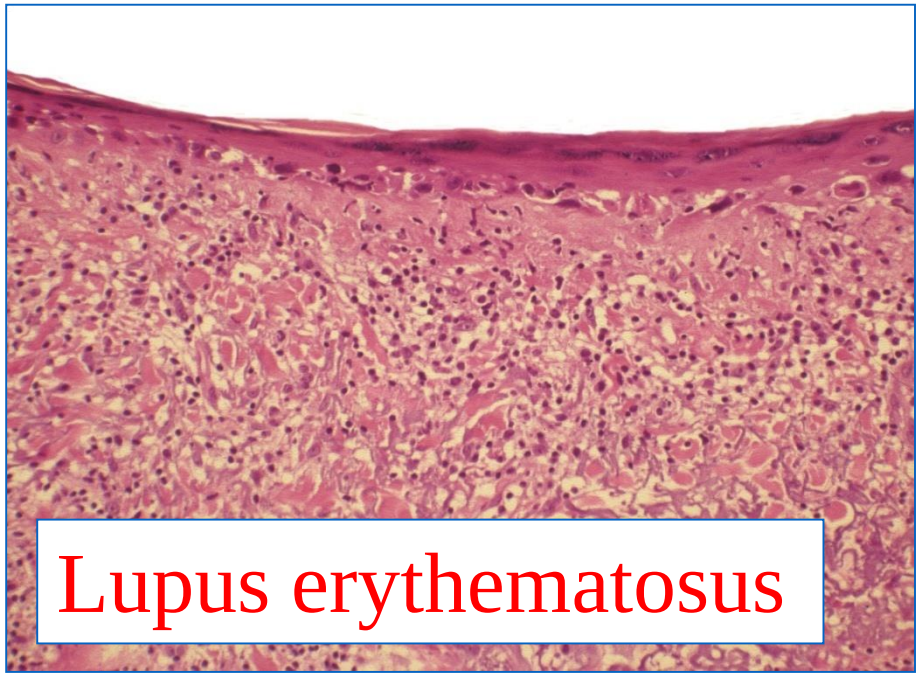


FIG. 4. Abnormal keratinocytes of simplex vulvar intraepithelial neoplasia have dense eosinophilic cytoplasm and enlarged nuclei with prominent nucleoli. Occasional cells are binucleated. Architectural differentiation of the abnormal cells is preserved in the superficial portions of the epidermis.

However, if those features suffice for diagnosis of a malignant neoplasm, how about these cells? They are much more atypical,



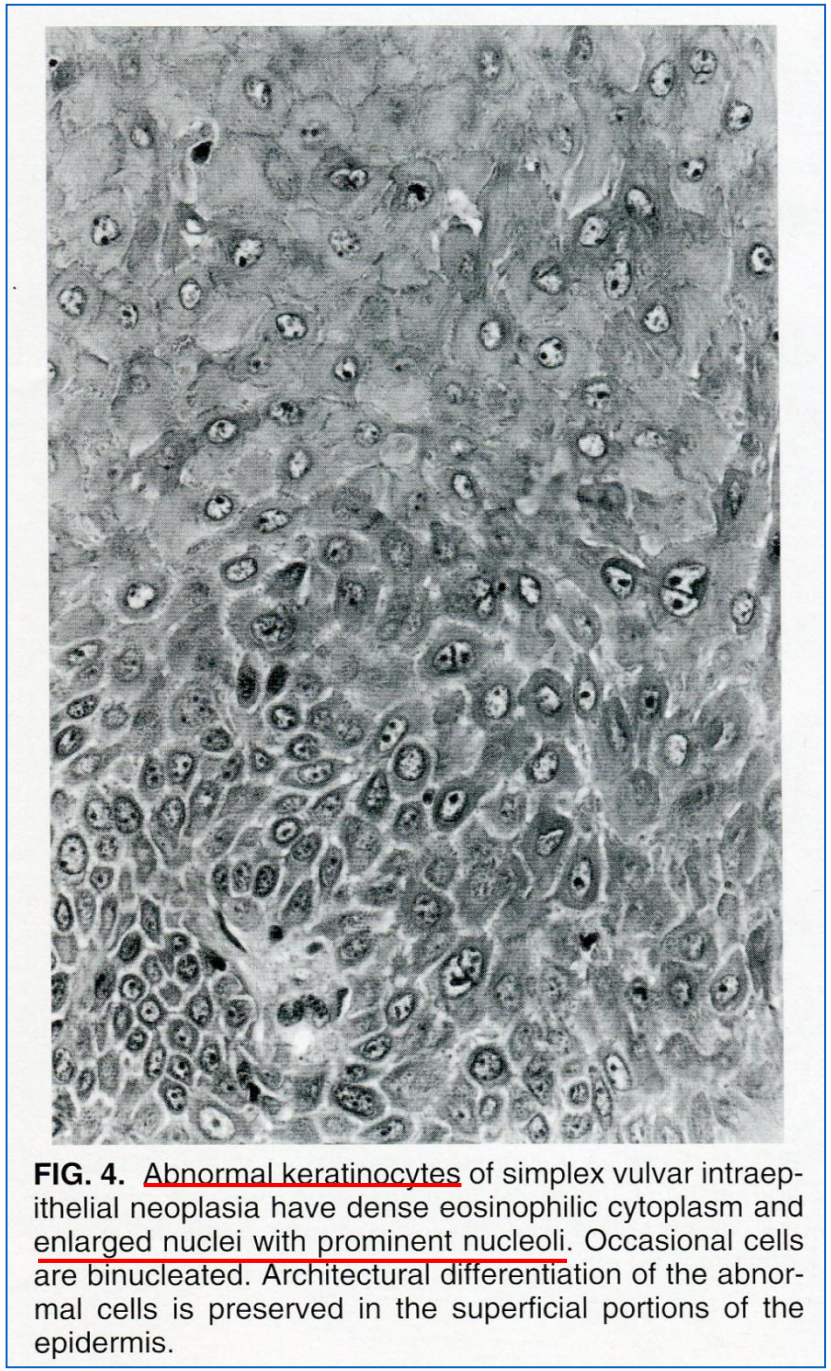


FIG. 4. Abnormal keratinocytes of simplex vulvar intraepithelial neoplasia have dense eosinophilic cytoplasm and enlarged nuclei with prominent nucleoli. Occasional cells are binucleated. Architectural differentiation of the abnormal cells is preserved in the superficial portions of the epidermis.

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

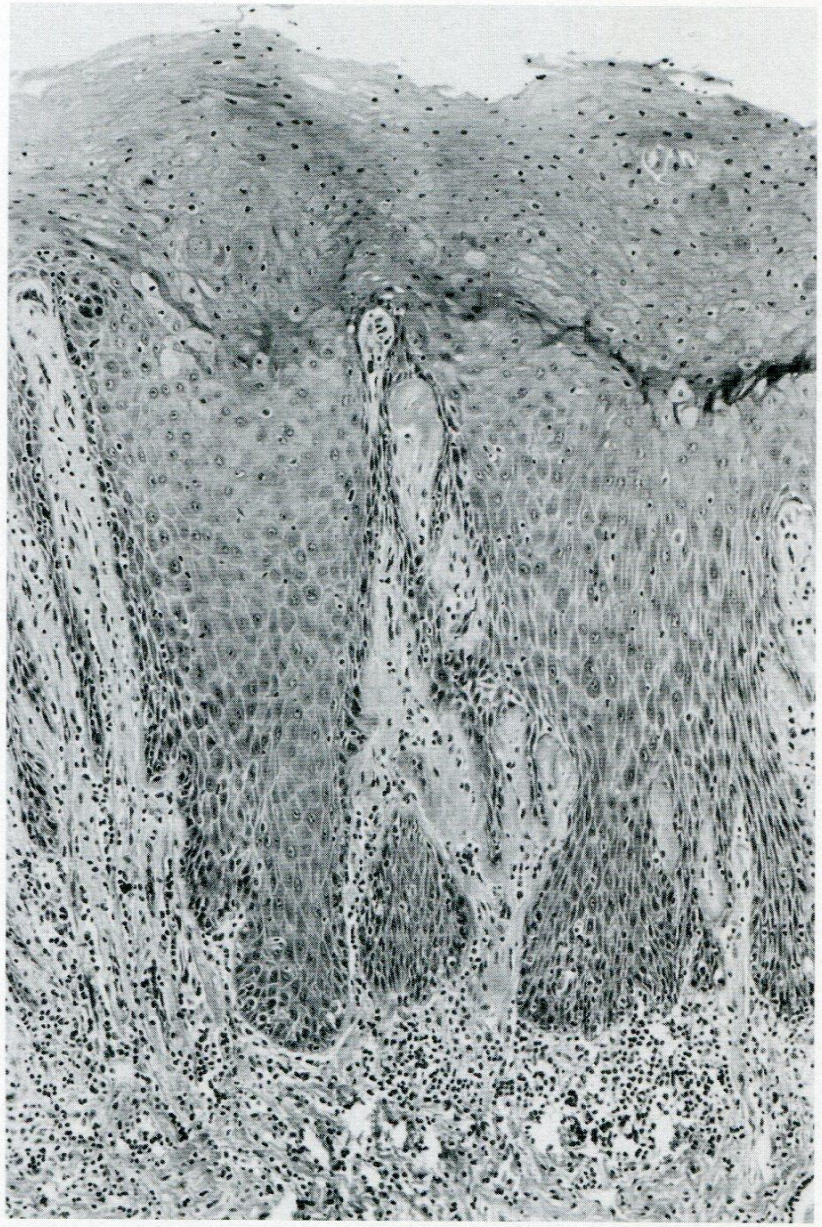
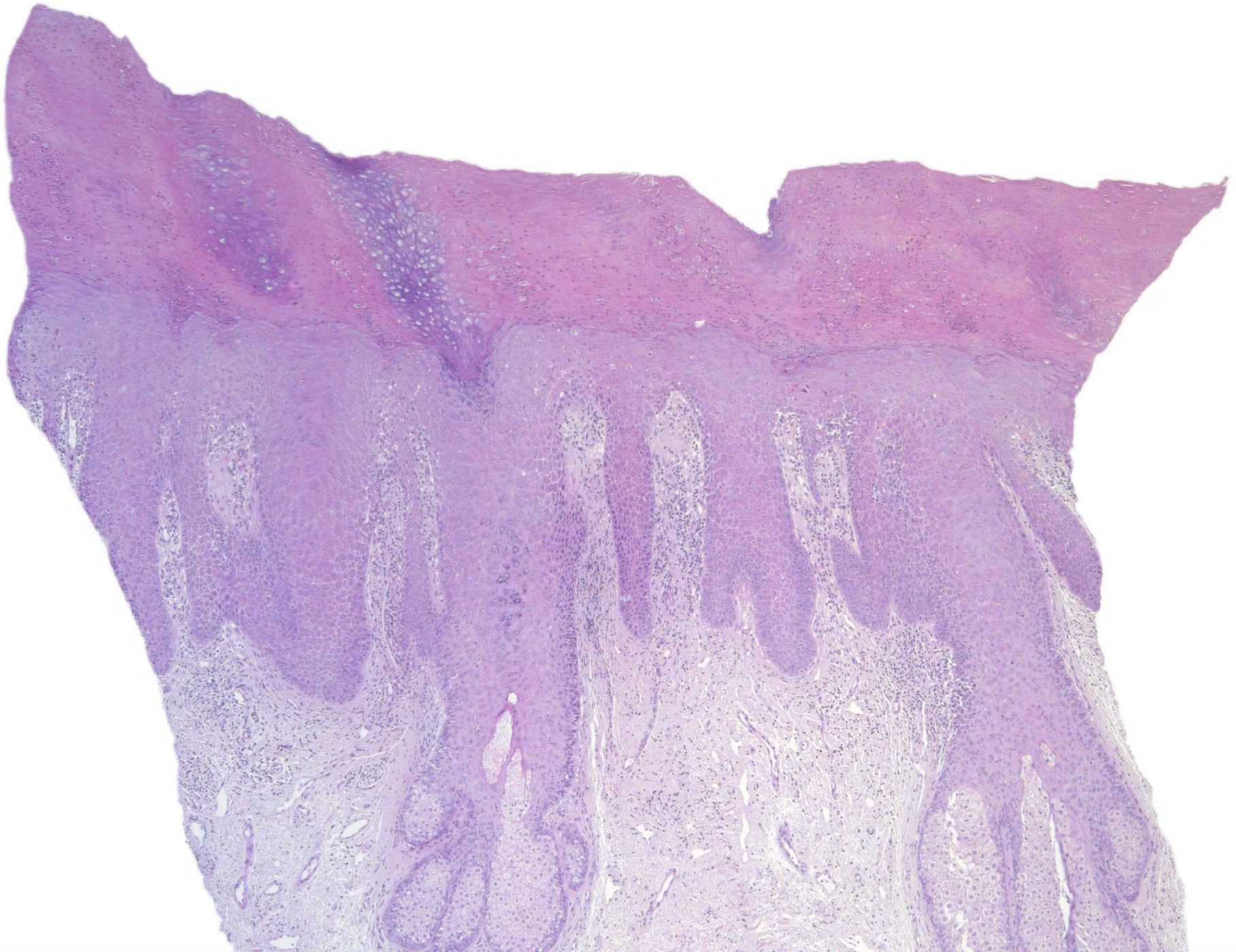
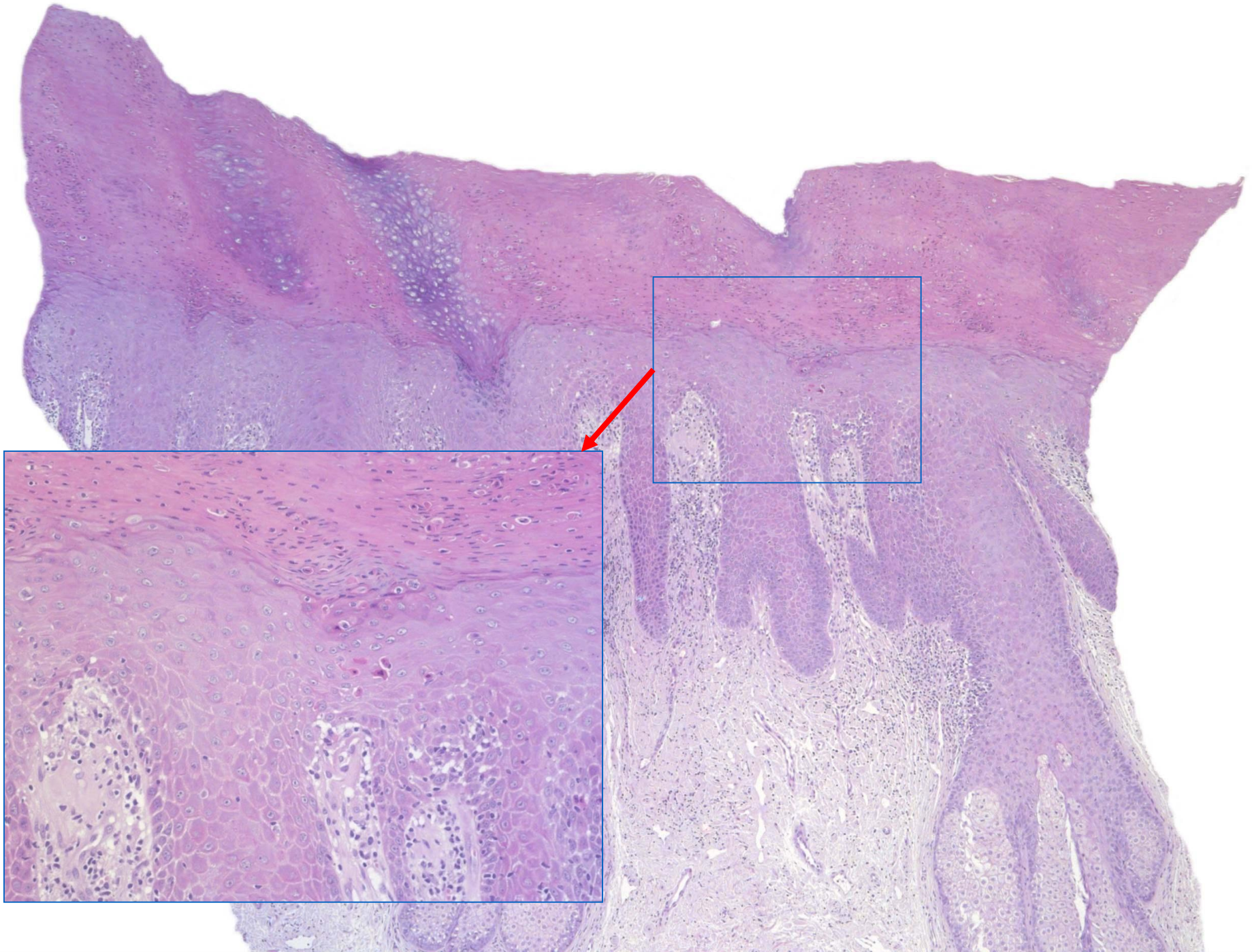


FIG. 1. Simplex vulvar intraepithelial neoplasia. The epidermis is thickened irregularly by a proliferation of abnormal, enlarged keratinocytes. The dermis contains chronic inflammatory cells. A thick parakeratotic surface reaction is present.

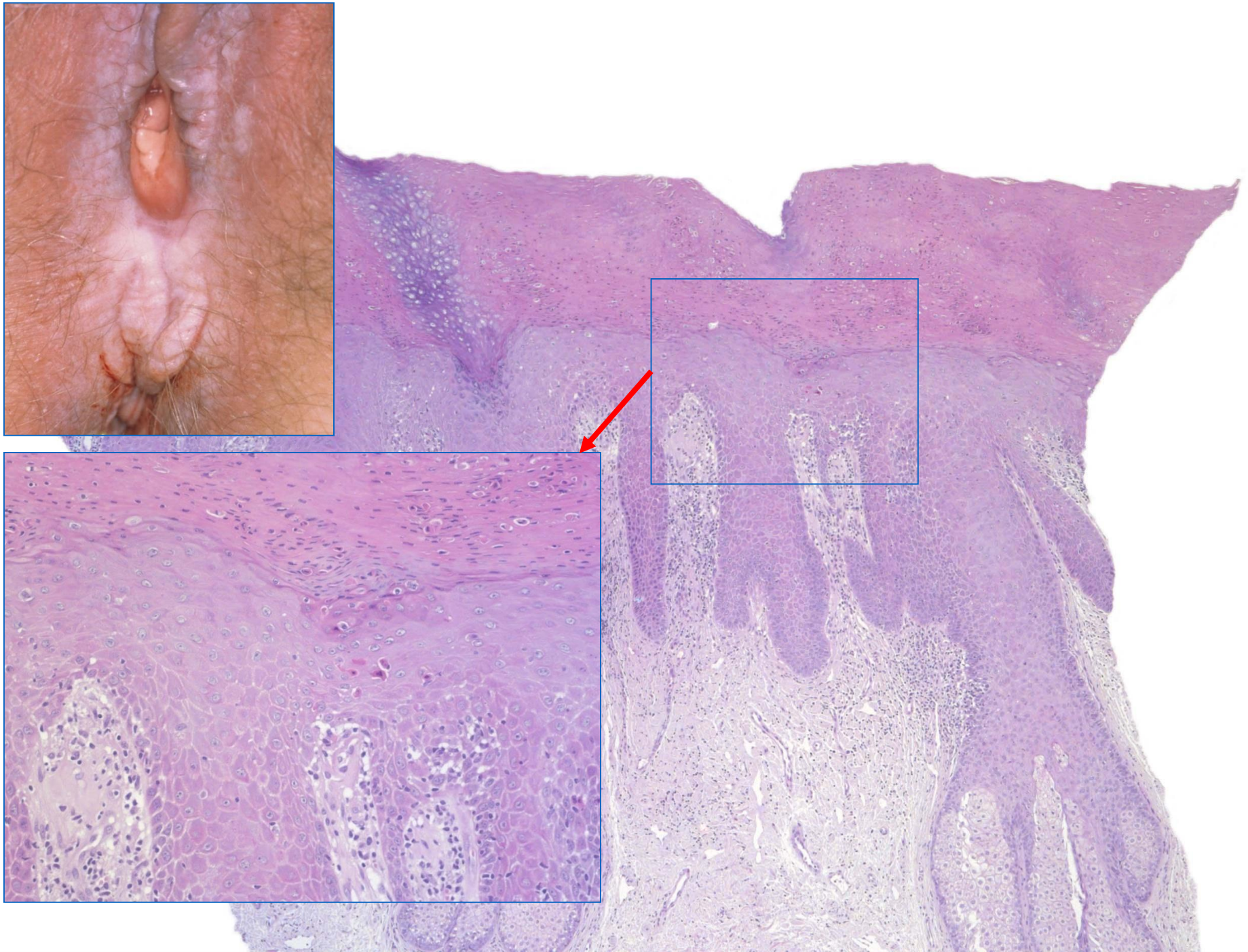
Another case from the same article: it is said to show *"simplex vulvar intraepithelial neoplasia"* characterized by a *"proliferation of abnormal enlarged keratinocytes,"* but where are those cells? These nuclei are small and monomorphous. To me, this is hypertrophic lichen sclerosus. There is a bandlike 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.



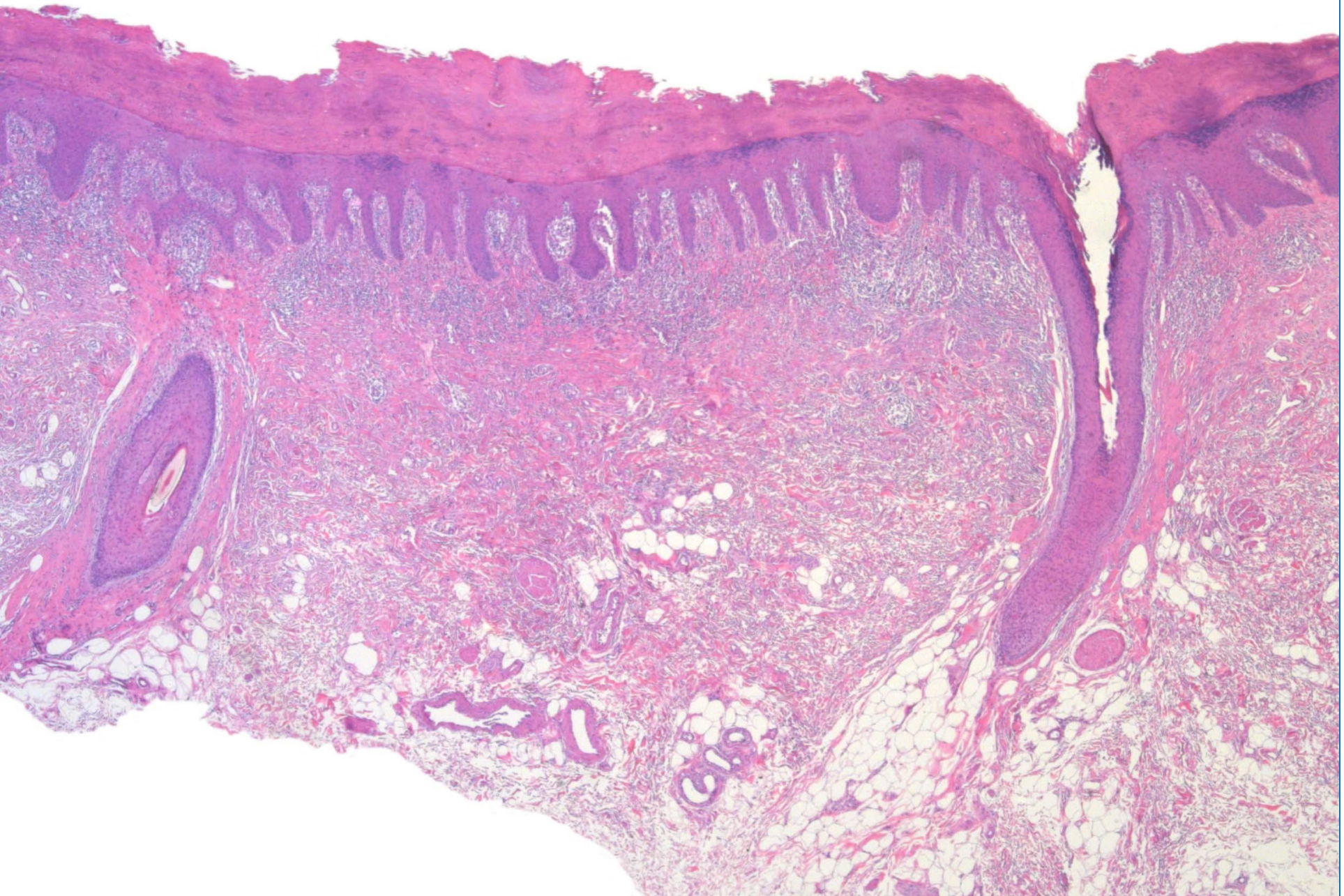
I have already shown a similar case: Lichen sclerosus with only small foci of sclerosis, psoriasiform epidermal hyperplasia,



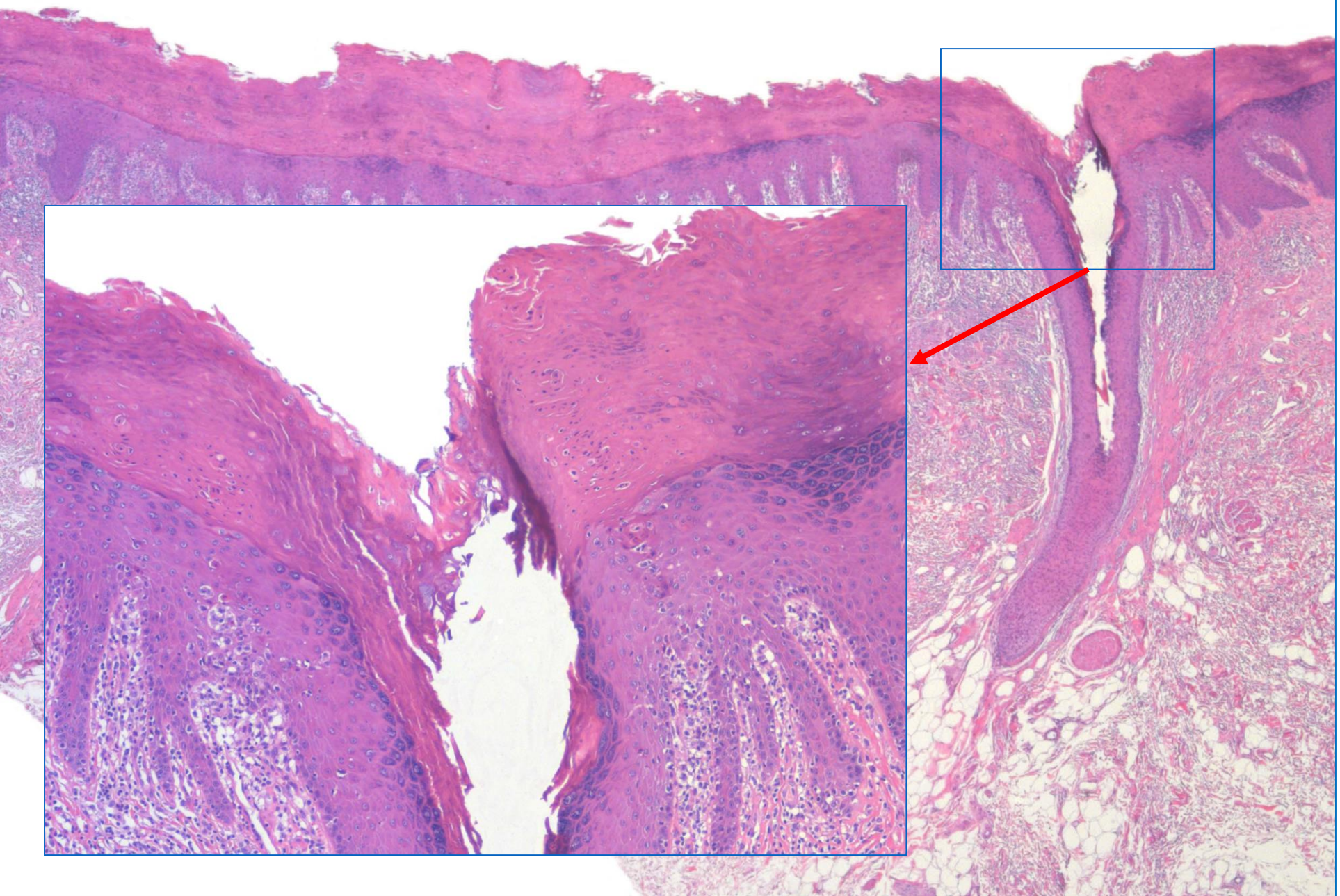
scant spongiosis above dermal papillae, necrotic keratocytes, and columns of parakeratosis. This presentation of lichen sclerosus is found, in more or less pronounced fashion, in about 5 to 10% of our cases of lichen sclerosus. There are no atypical nuclei,



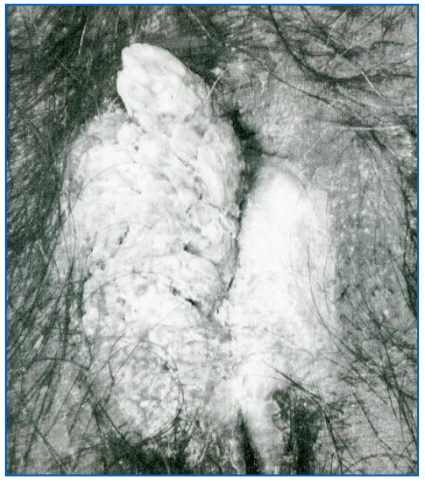
and this is the clinical picture: an exceedingly chronic lesion of lichen sclerosus with accentuation of skin furrows as a consequence to superimposed lichen simplex chronicus.



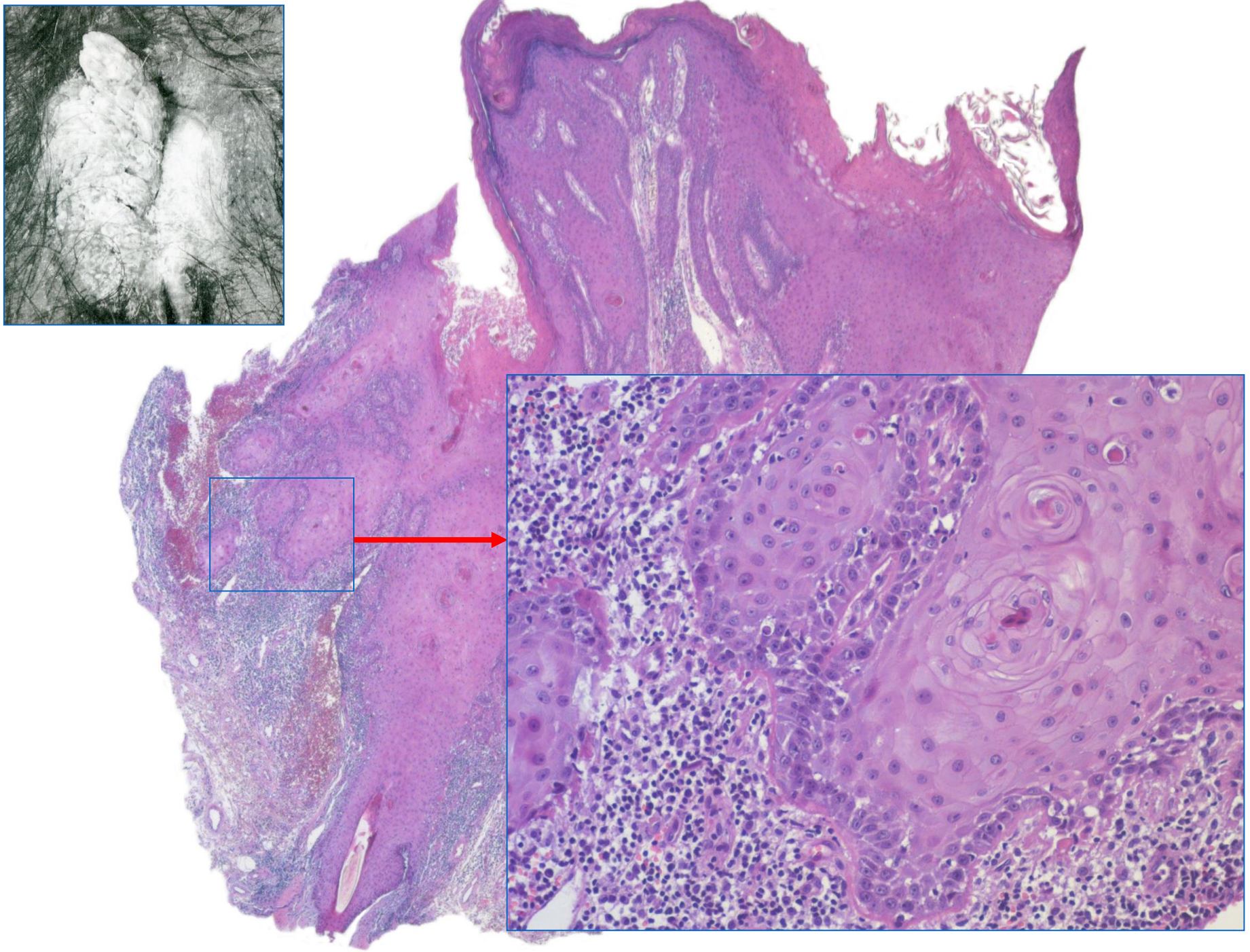
Another example: Note the psoriasiform epithelial hyperplasia. It is irregular but, in general, rete ridges have approximately the same length. There is a dense lichenoid infiltrate, marked hyperkeratosis,



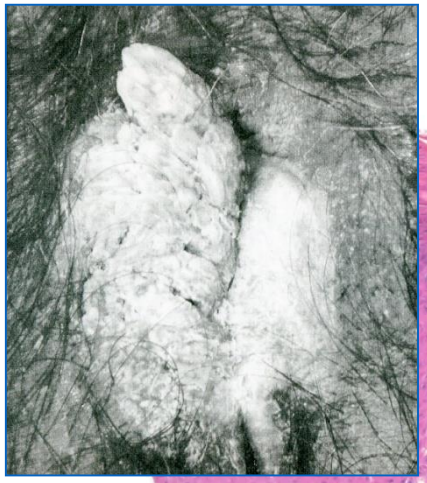
and, again, foci of spongiosis above dermal papillae with individual necrotic keratocytes and vertical columns of parakeratosis.



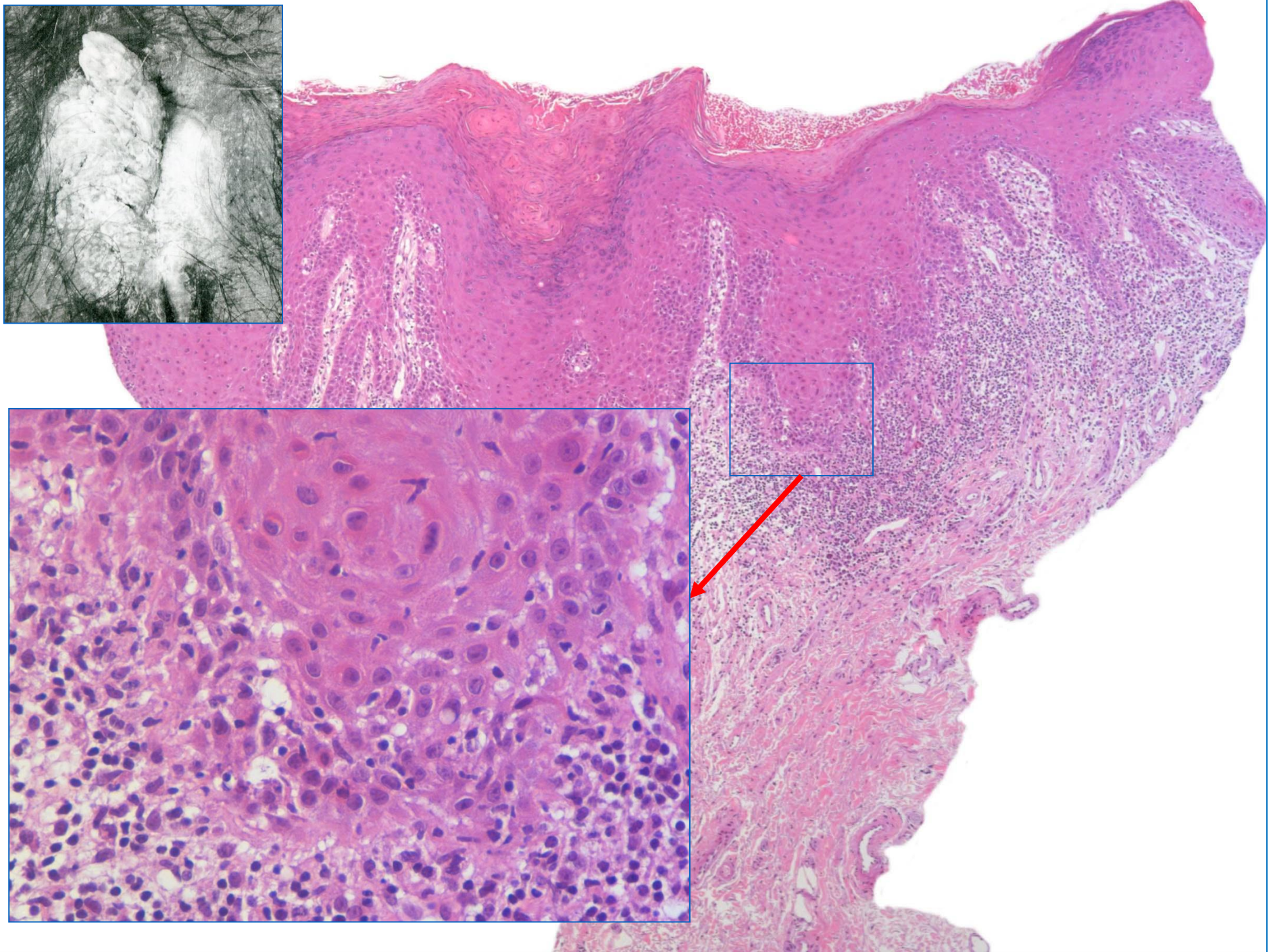
Although those findings are relatively distinctive, they may be simulated by squamous cell carcinomas. In this squamous cell carcinoma, the epithelial hyperplasia is much more pronounced, more irregular and deeper reaching. However, there is also a lichenoid infiltrate of lymphocytes,



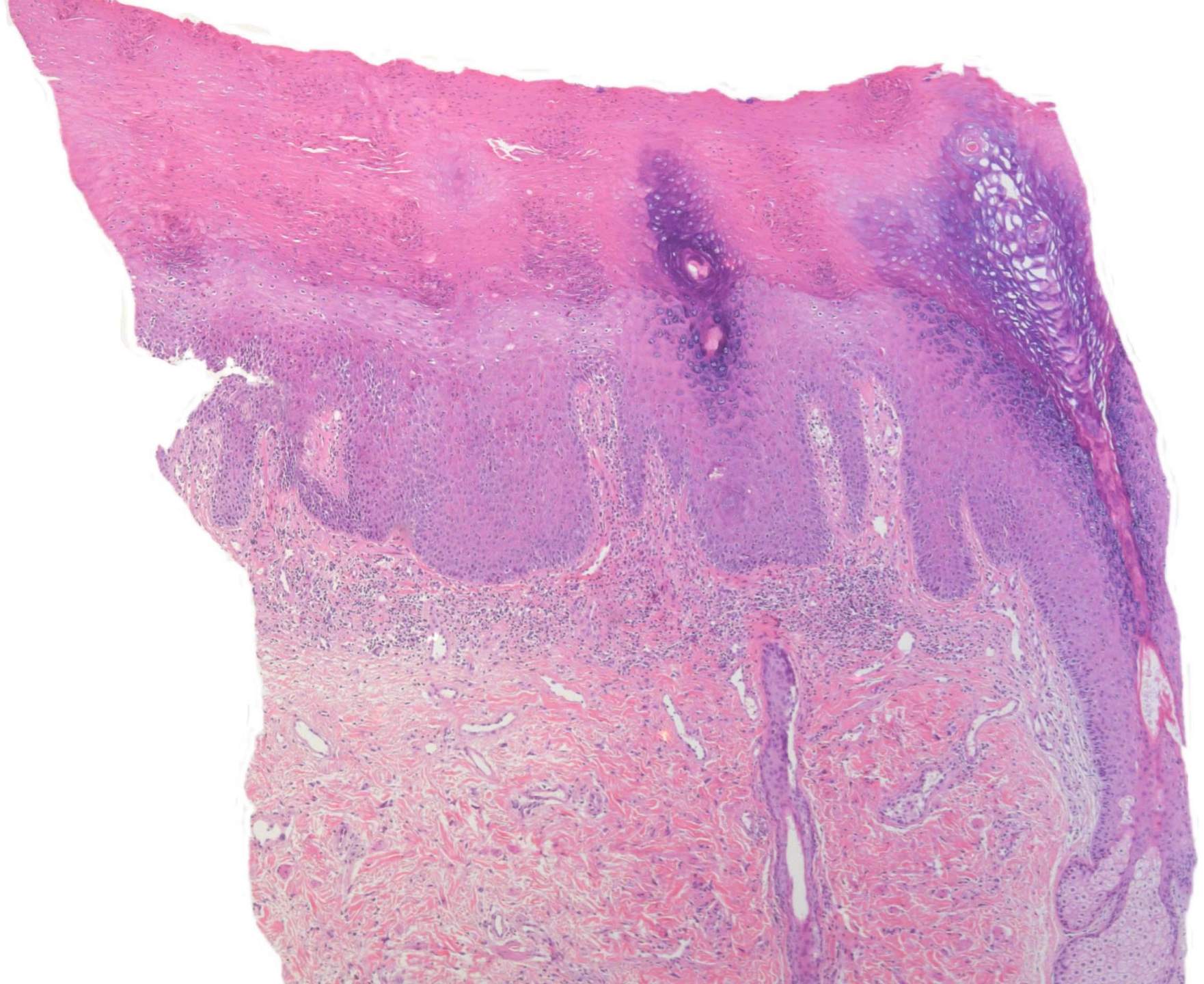
individual necrotic keratocytes are present in haphazard array, and there is no significant nuclear atypia. Note that keratocytes are crowded in the basal and suprabasal layers and that there are hints of acantholysis. Together, this leads to a relatively sharp demarcation of the lower layers from the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



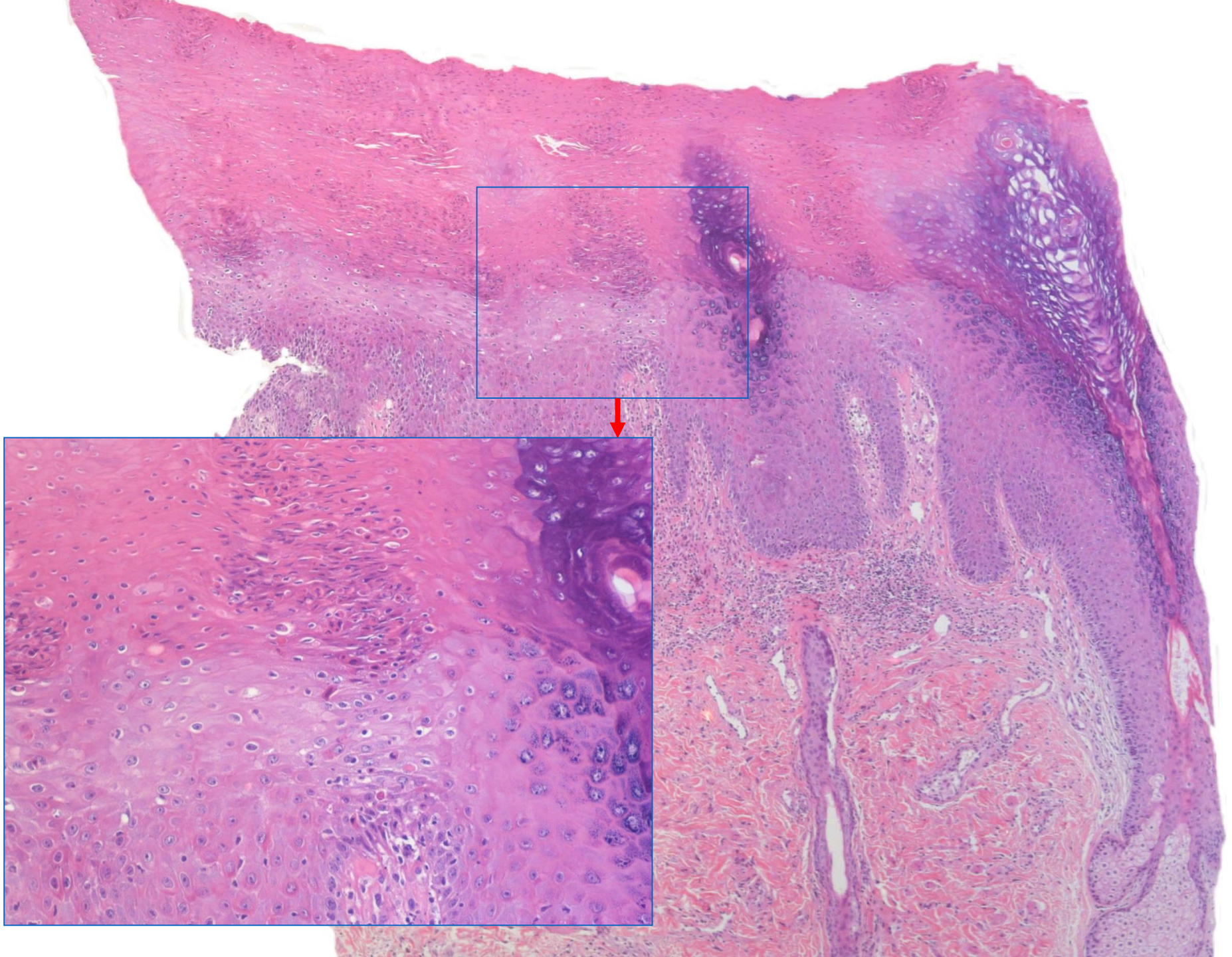
In an earlier biopsy from the same lesion, distinction from hypertrophic lichen sclerosus is even more difficult. Again, however, the epithelial hyperplasia is more irregular than usually seen in hypertrophic lichen sclerosus,



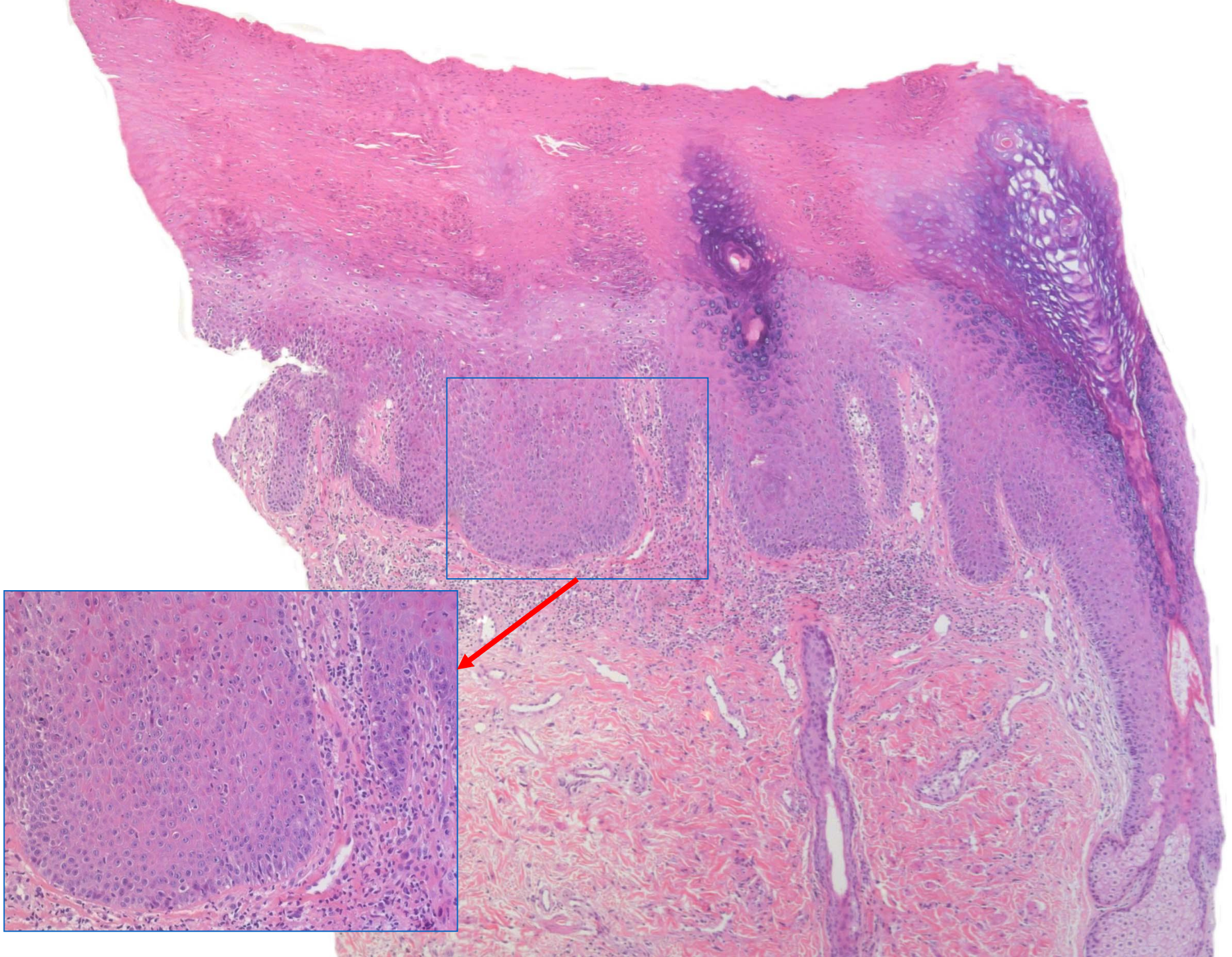
nuclei are crowded focally, and there are hints of acantholysis in the lower spinous zone.



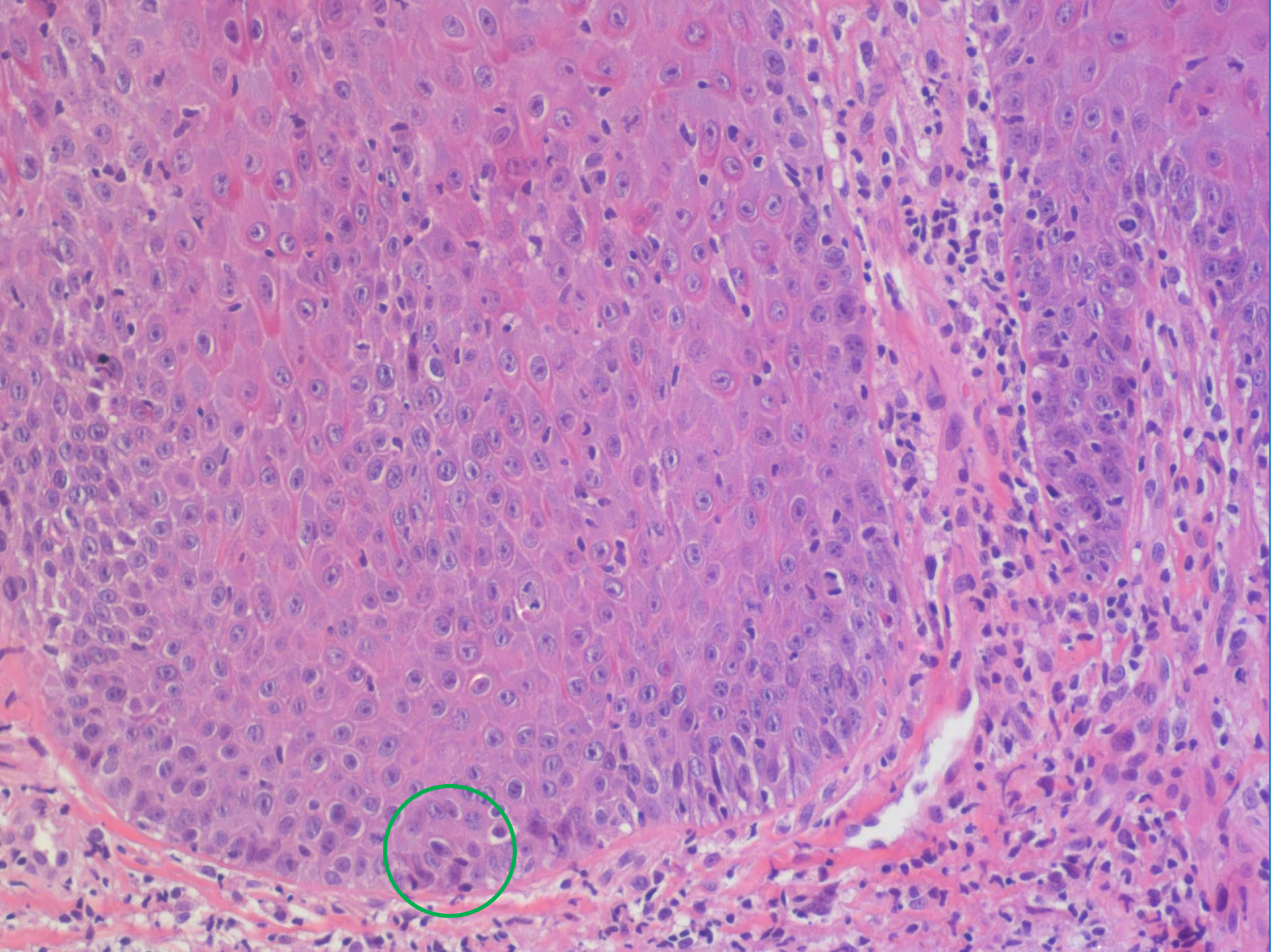
For comparison, another case of hypertrophic lichen sclerosus: The epidermis is thickened markedly, and the rete ridges are of uneven thickness but of approximately equal length.



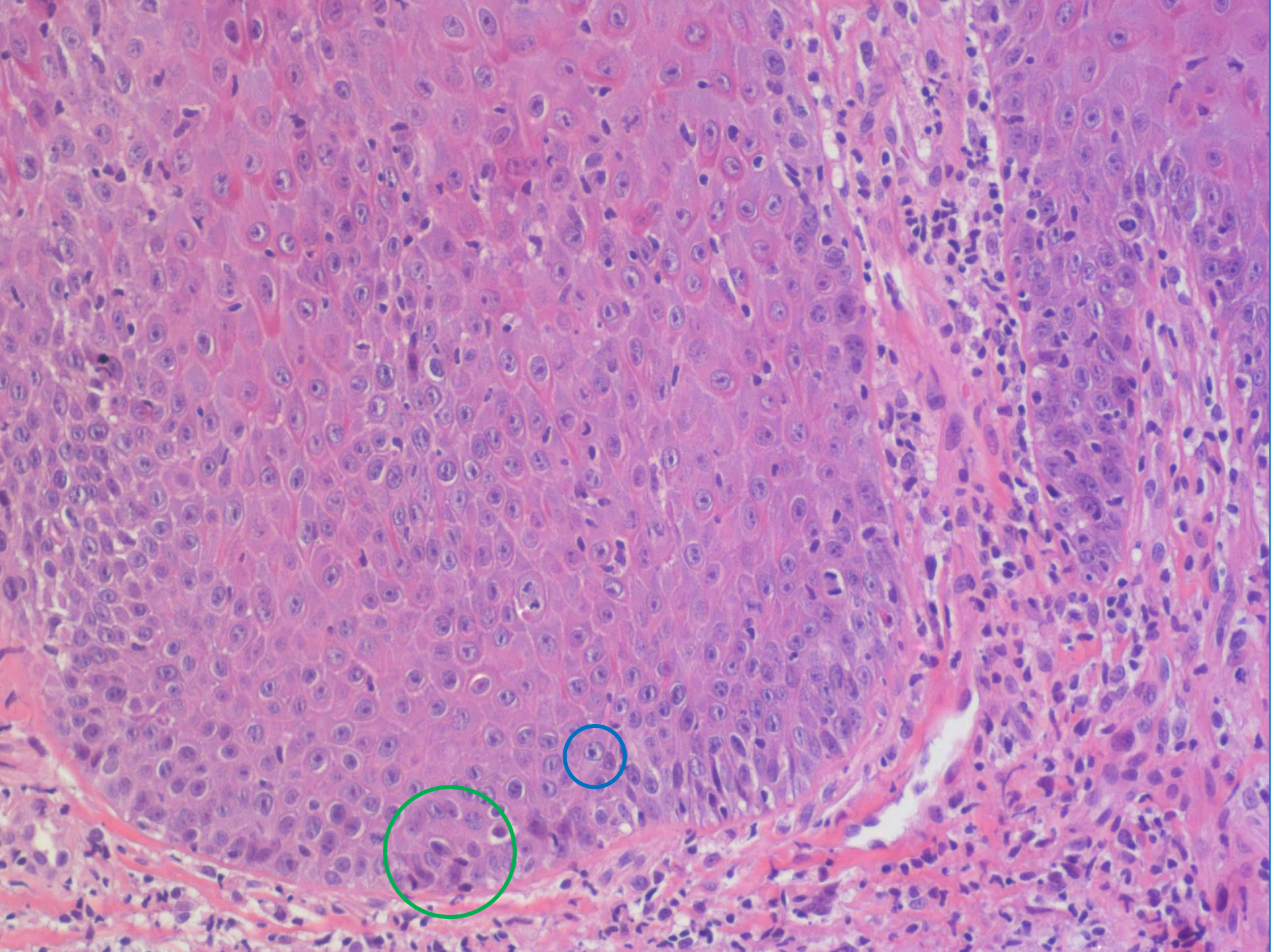
There are foci of sclerosis in the tips of dermal papillae, and chiefly above those tips, one sees slight spongiosis, individual necrotic keratocytes, and columns of parakeratosis with parakeratotic dyskeratotic cells, somewhat resembling the grains of Darier’s disease.



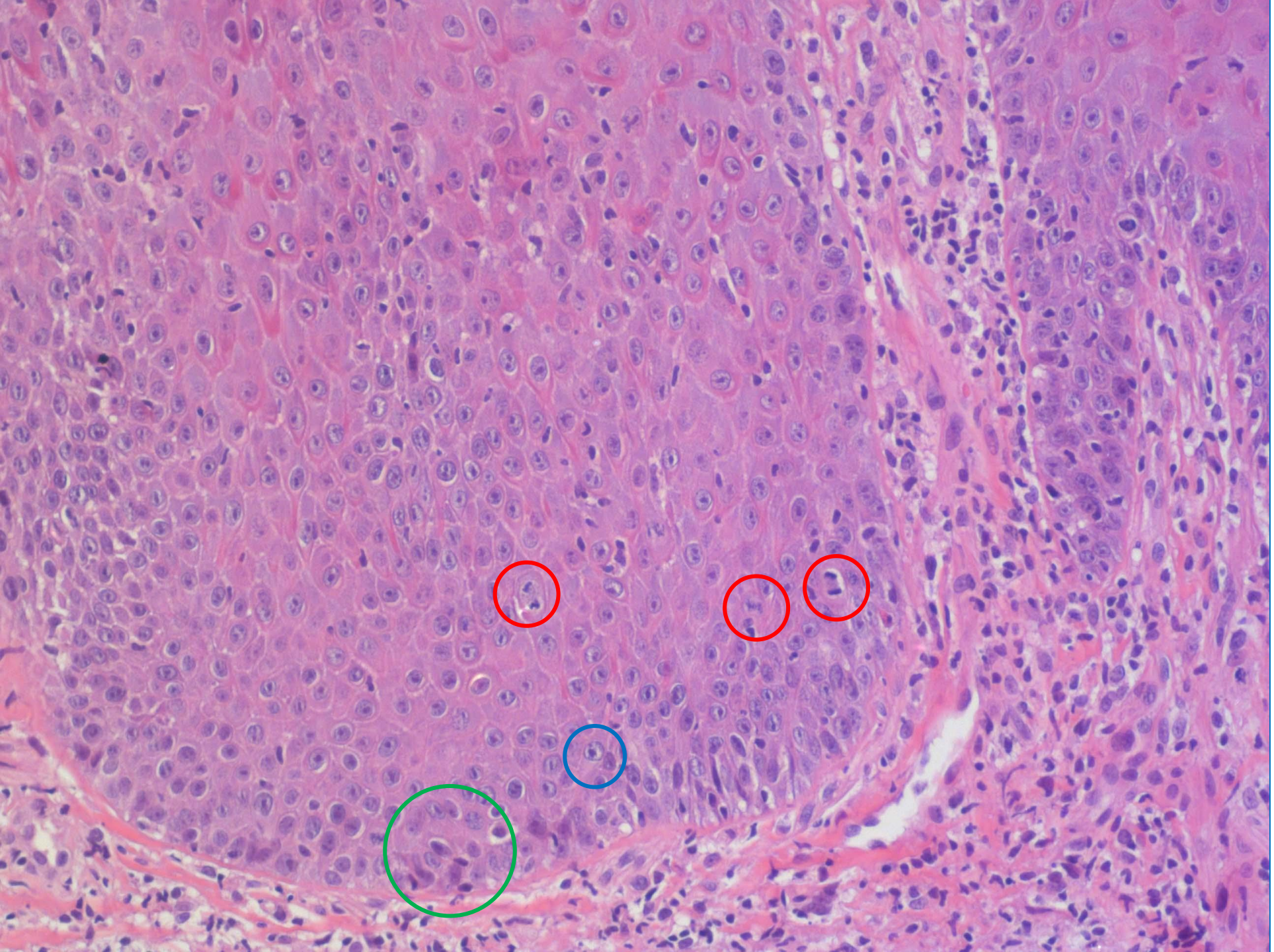
There is no crowding of nuclei and no acantholysis.



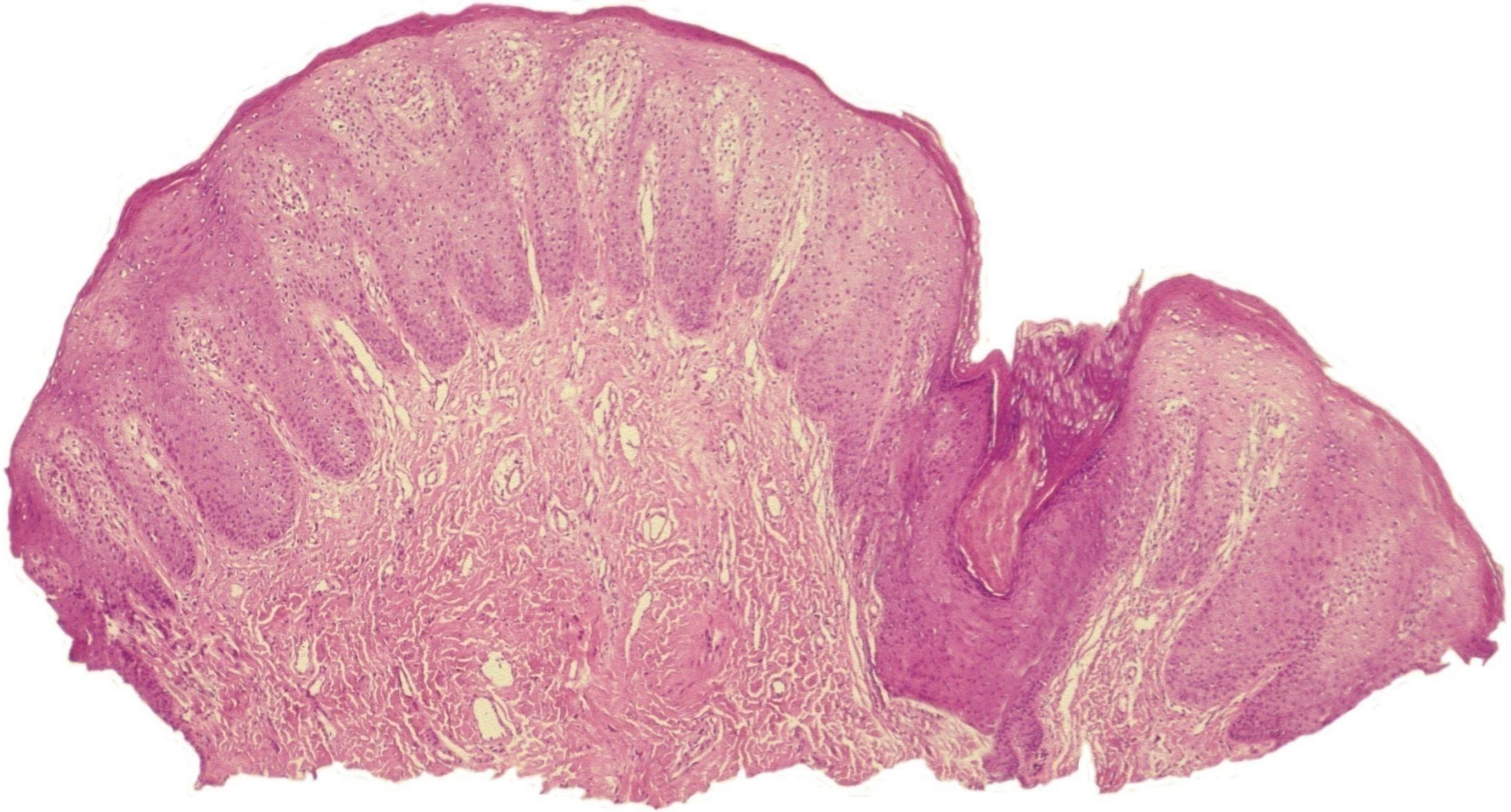
Of course, there is some variation in the size and staining quality of nuclei of keratocytes



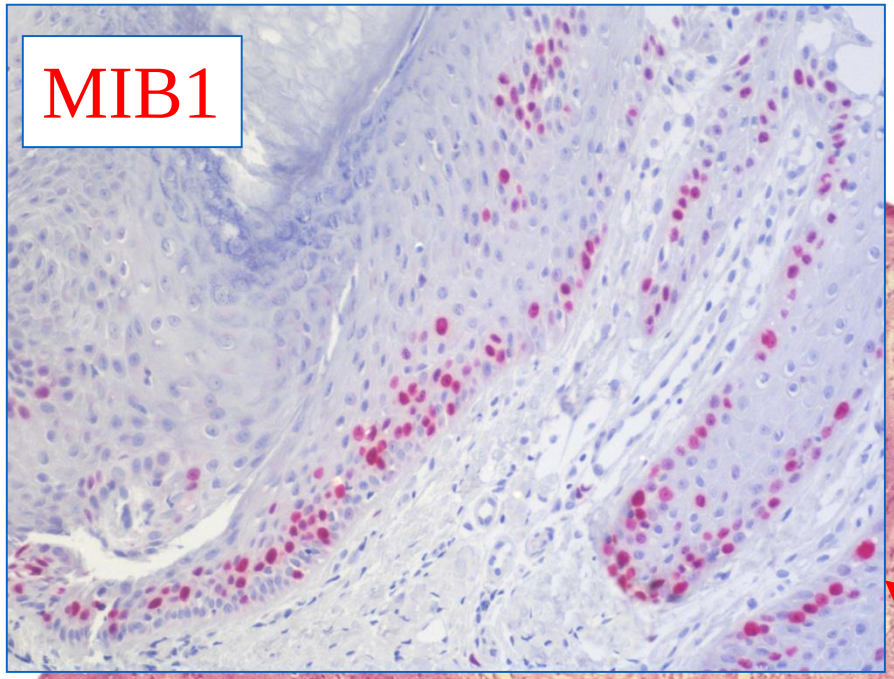
and some have prominent nucleoli, but this is within the range of normal.

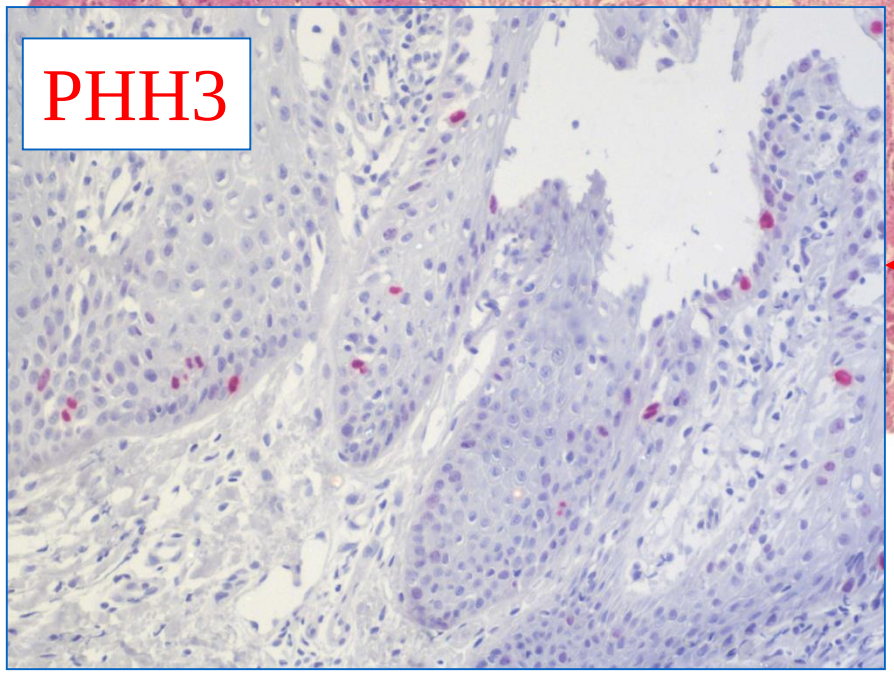


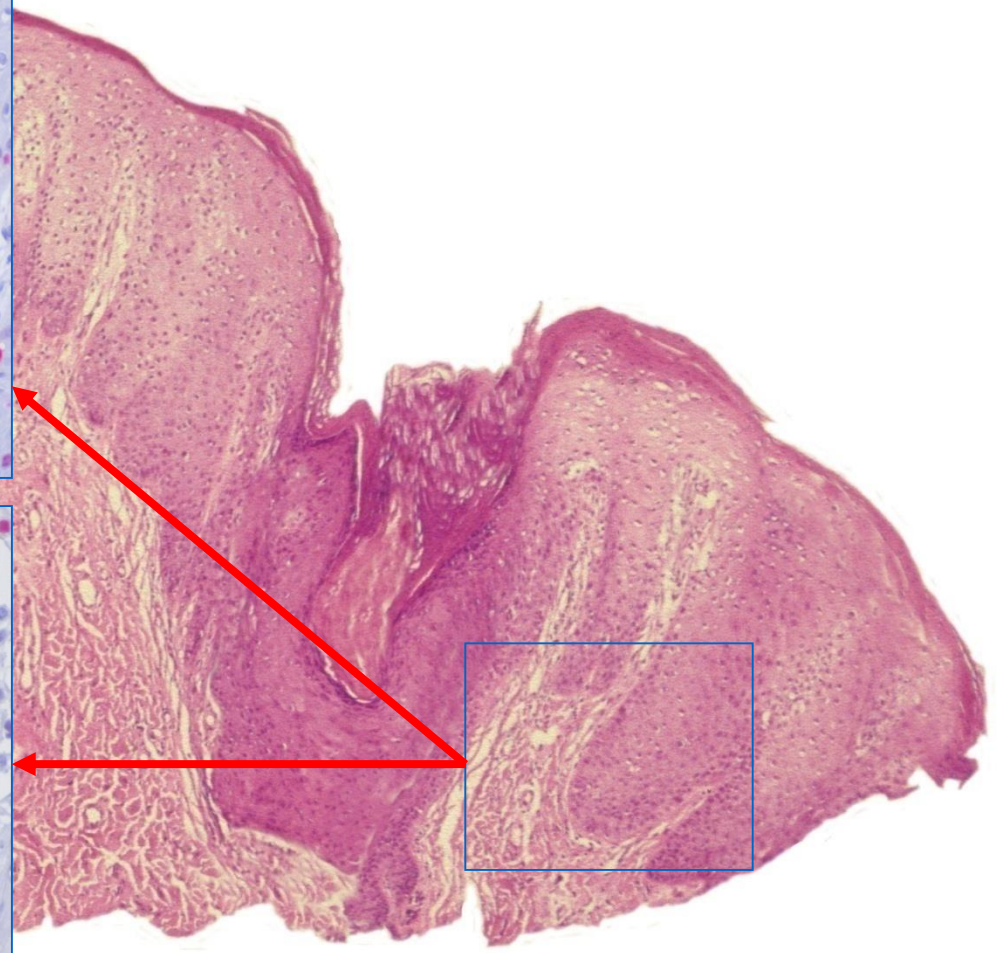
There are some mitotic figures in the lower spinous zone, but this is an expected finding in any inflammatory disease associated with epidermal hyperplasia. Somehow, the hyperplasia must come into being.



This is a biopsy of vulvar psoriasis.







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

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[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.

Hautarzt 2008 · 59:77–78
DOI 10.1007/s00105-008-1471-9

B. Korge
Hautarztpraxis Düren

Genitaler Lichen sclerosus et atrophicans: eine obligate Präkarzinose?

Der anogenitale Lichen sclerosus et atrophicans (LSA) ist eine chronische entzündliche und fibrosierende Dermatose. Das Auftreten von Plattenepithelkarzinomen nach längerem Krankheitsverlauf ist wiederholt beschrieben worden. Chronische Entzündungsreaktionen scheinen generell das Risiko für die Entstehung von Krebserkrankungen zu fördern. Dies ist bereits für die ulzerierende Kolitis und dem

figkeit von SBS in zwei der drei am häufigsten modifizierten Codons von TP53 in Plattenepithelkarzinomen der Vulva und in einem Codon des Kirsten-ras-Gens (KRAS), welches als wichtiges Gen im Prozess der Karzinogenese betrachtet wird und häufig mutiert in Hauttumoren vorgefunden wurde, untersucht. Hierzu wurden 55 anogenitale LSA-Gewebeproben von 37 Patientinnen mit normaler ge-

pansion, Tumorprogression und schließlich die Manifestation eines genitalen Plattenepithelkarzinoms.

Chronische Entzündungen verbunden mit Proliferation und Vernarbung scheinen die Selektion von TP53-Onkomutationen zu fördern

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

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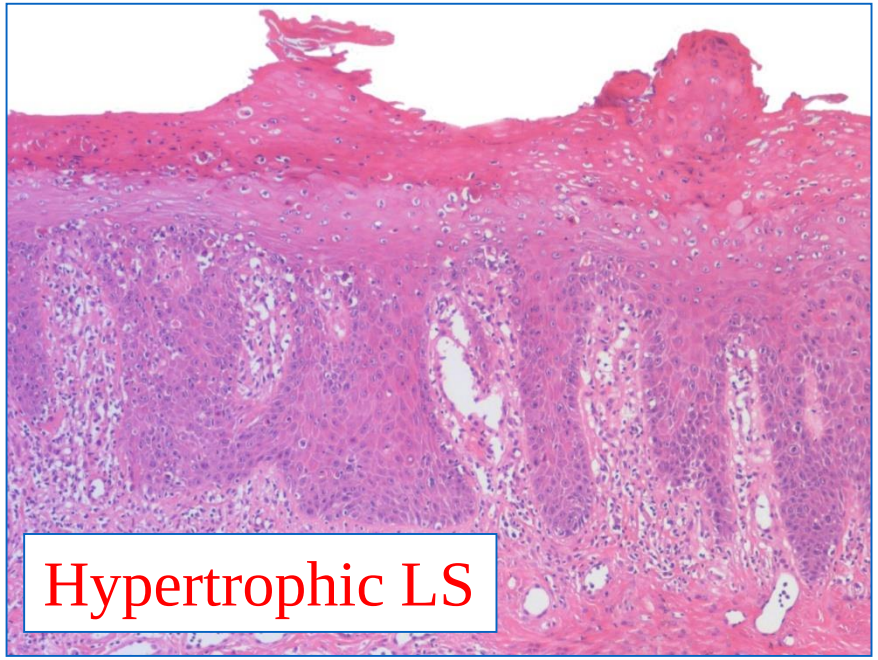
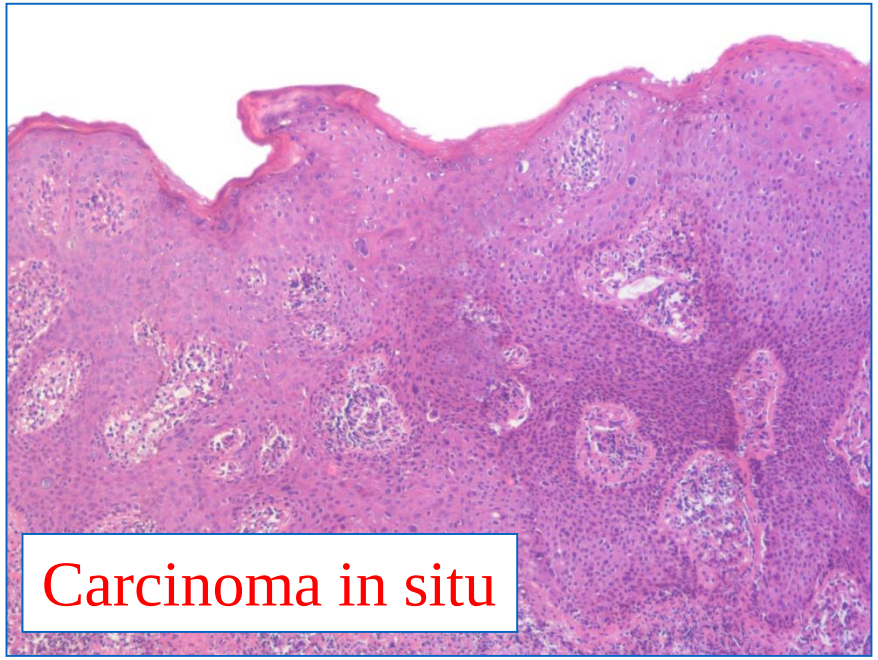
*Trescowthick Research Laboratories, Peter MacCallum Cancer Institute, Melbourne, Australia; †Department of Pathology, Mercy Hospital for Women, East Melbourne, Australia; ‡Statistical Center, Peter MacCallum Cancer Institute, Melbourne, Australia

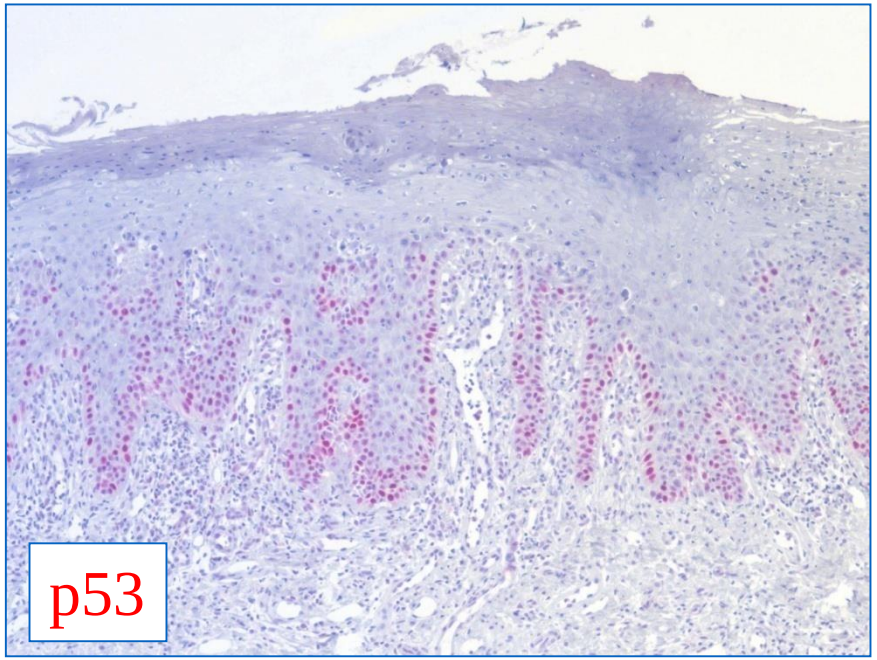
Human papillomavirus is a risk factor for vulvar cancer, whereas human papillomavirus-negative late onset vulvar carcinoma is associated with the dermatologic condition, lichen sclerosus. Human papillomavirus E6 protein targets TP53 for degradation and by inference it has been assumed that human papillomavirus-negative 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.

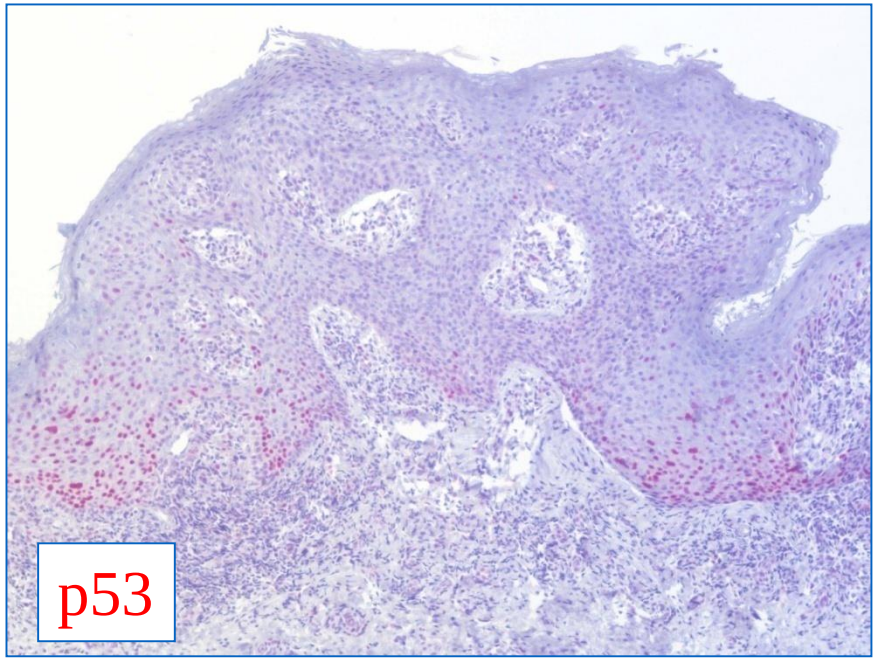
Key words: lichen sclerosus/loss of heterozygosity/mutation analysis/p53/tumor suppressor gene/vulvar carcinoma. J Invest Dermatol 119:1027–1033, 2002

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

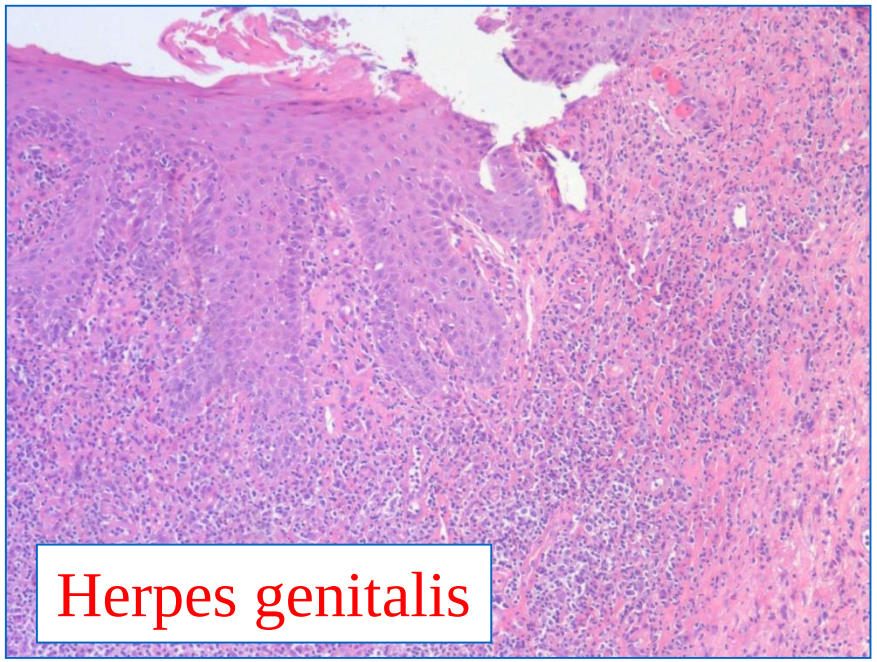


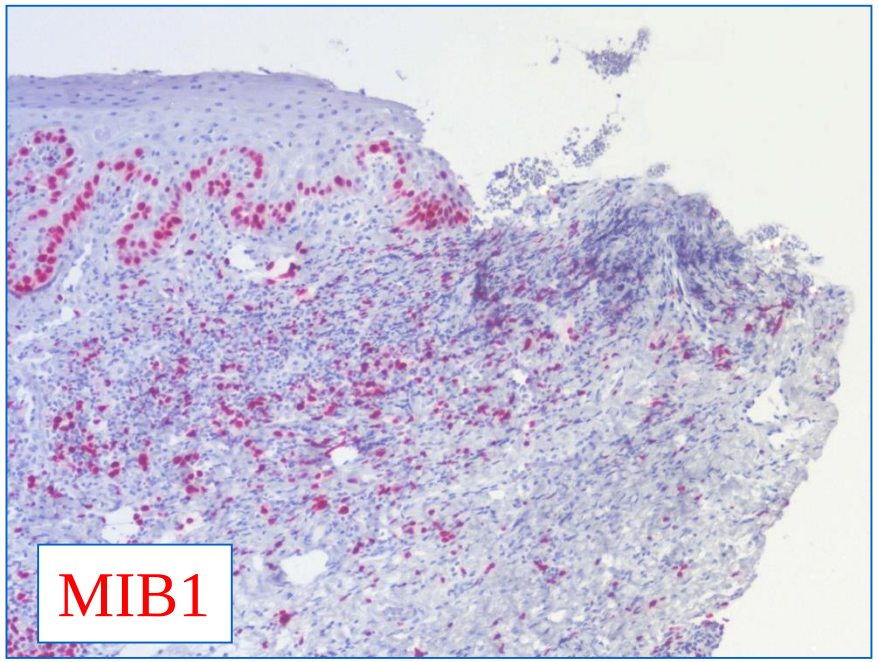


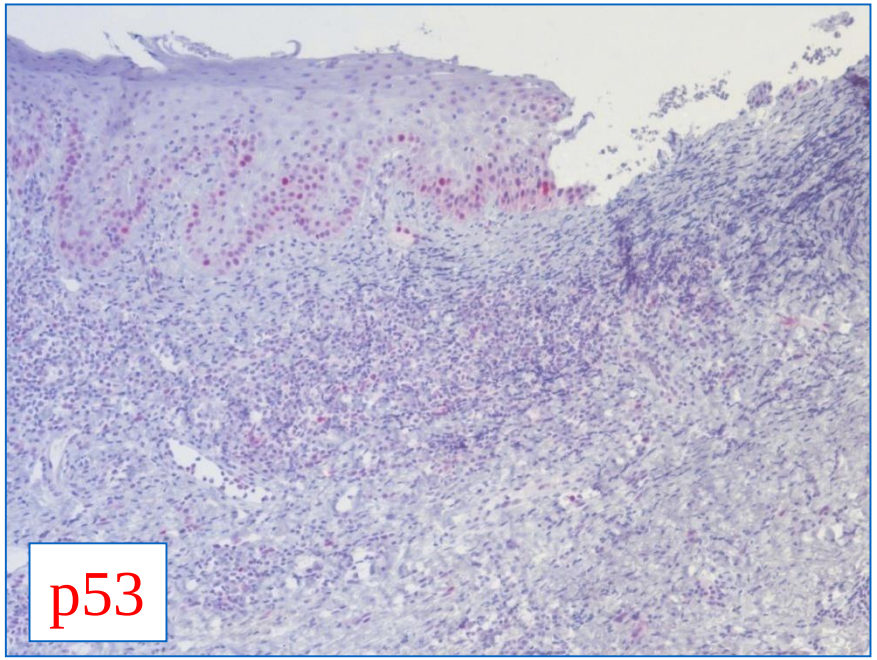


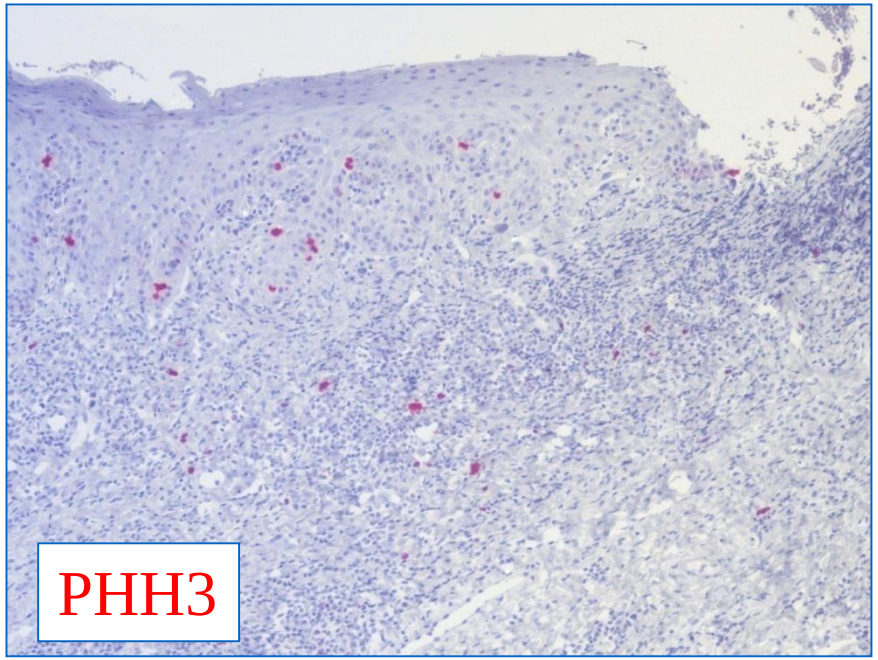


Indeed, p53 expression in lichen sclerosus may be just as strong as in squamous cell carcinoma in situ. However, it may also be over-expressed in other inflammatory diseases, such as genital herpes. In herpes, there may also be enhanced proliferation adjacent to the ulcer, with strong expression of Mib-1 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
(2) Nationales Referenzzentrum für Papilloma- und Polyomaviren, Institut für Virologie, Universität Köln

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 3 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

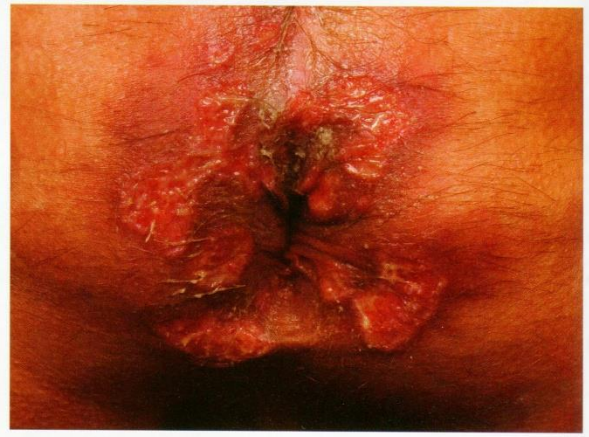
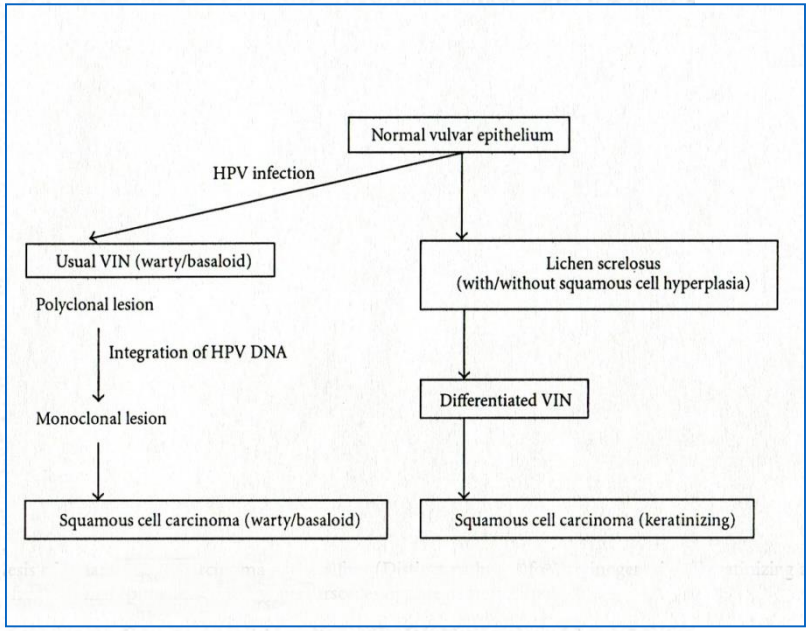


Abbildung 1: Klinische Präsentation der Hautveränderungen. Im Bereich der Perianalregion imponieren multiple, oberflächliche Ulzerationen mit zum Teil fibrinösen Belägen. Der Analkanal ist nicht betroffen.

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

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

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



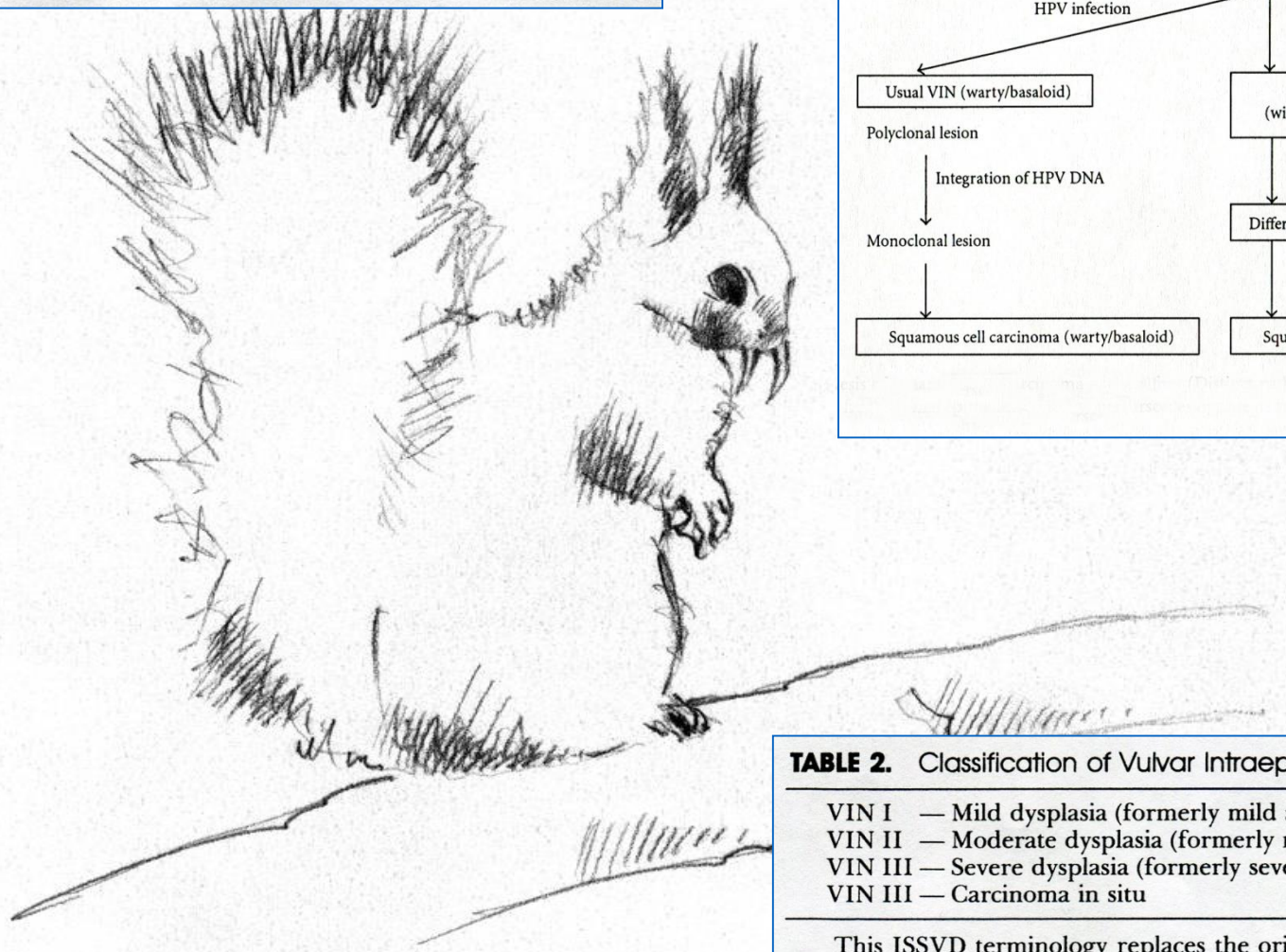


TABLE 2. Classification of Vulvar Intraepithelial Neoplasia

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]

Of all inflammatory diseases of the vulva, only lichen sclerosus is said to have big teeth, and this is chiefly a consequence of those caricatures of classification that have anchored firmly the concept of a malignant potential of lichen sclerosus.

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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[1], 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 V-associated types from non–HPV-associated types of vulvar can- **008;113(10 suppl):2865–72.** *Published 2008 by the American Can-*

ilvar 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."* 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."*

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Those are impressive numbers, 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,

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

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

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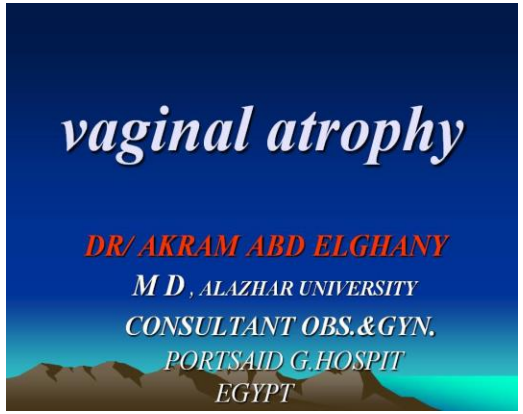
"had been affected … by cervical carcinoma, which had been treated with hysterectomy and radiotherapy." Obviously, that clinical history prohibits inclusion of the patient in a study concerning risk of malignancy in lichen sclerosus, and without this patient, those data, calculated up to the first number 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.

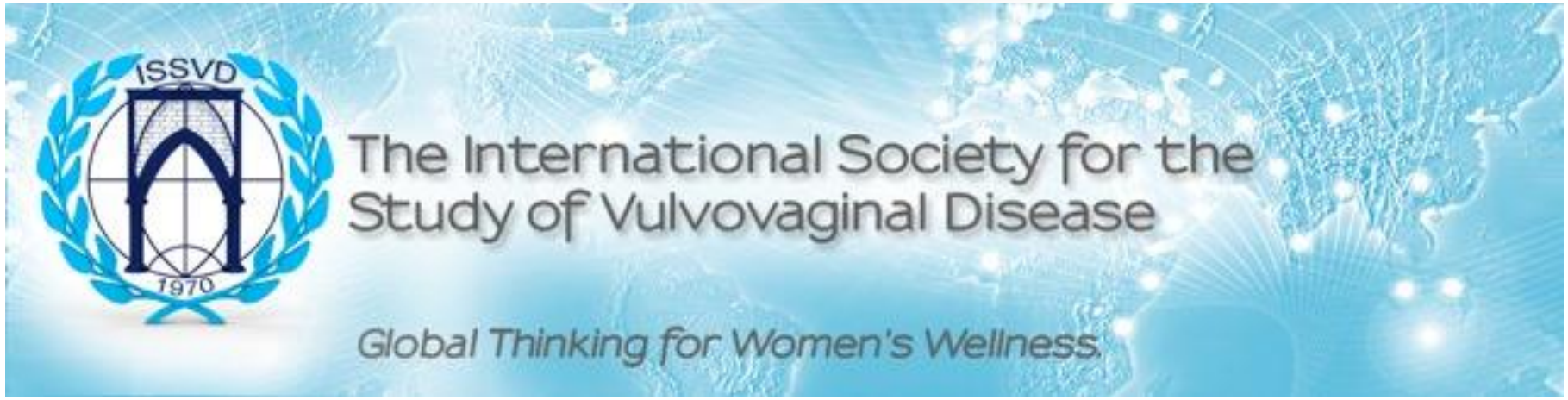


The British Association for the Study of Vulval Disease

ISSVD 1970

Arizona Vulva Clinic

ANZ Vulvovaginal Society



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.

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 connections 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

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

"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."

ist 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

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

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 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

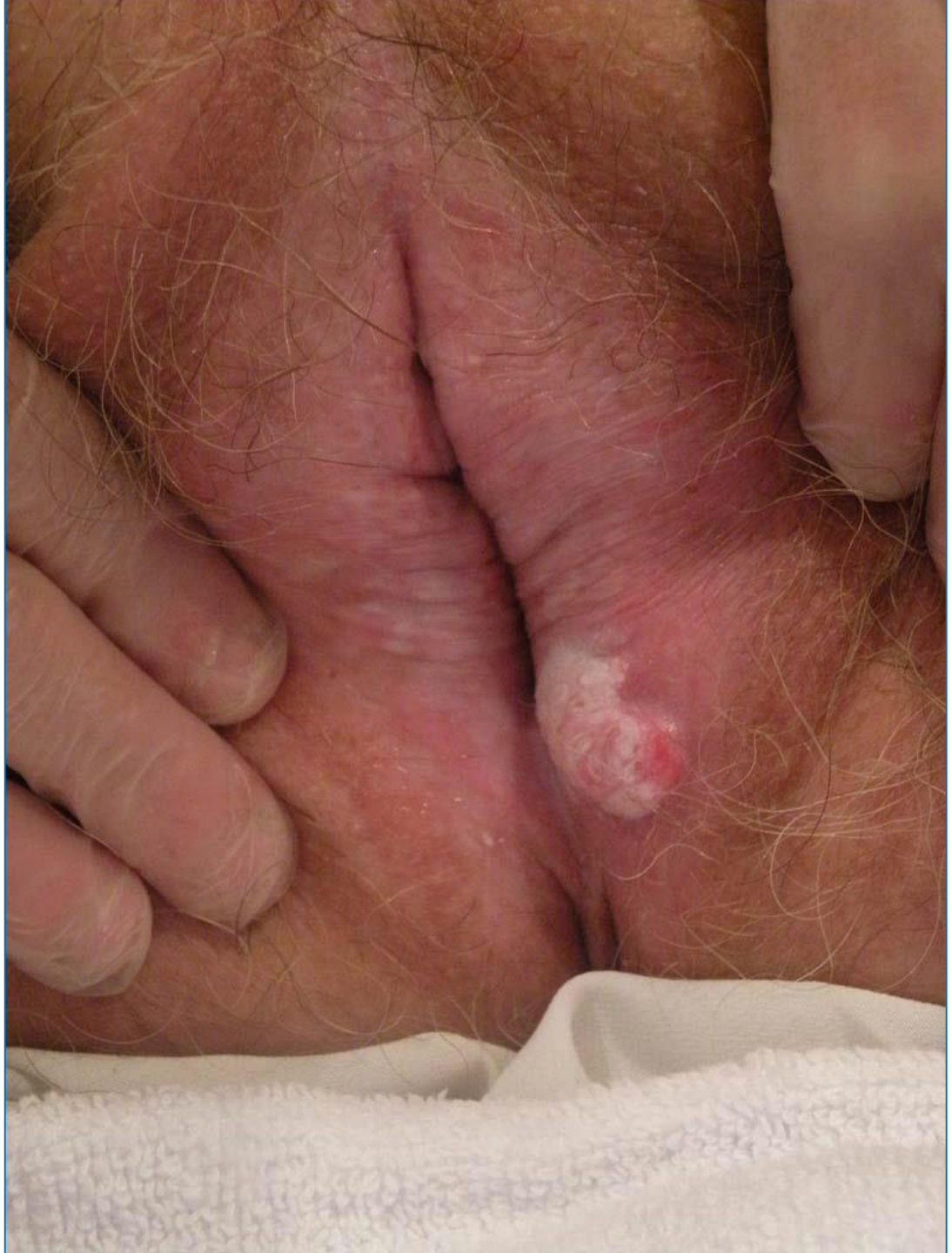
Hedwig P van de Nieuwenhof[1], Johan Bulten[2], Harrie Hollema[3], Rianne G Dommerholt[4], Leon FAG Massuger[1], Ate GJ van der Zee[5], Joanne A de Hullu[1] and Leon CLT van Kempen[2]

[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*

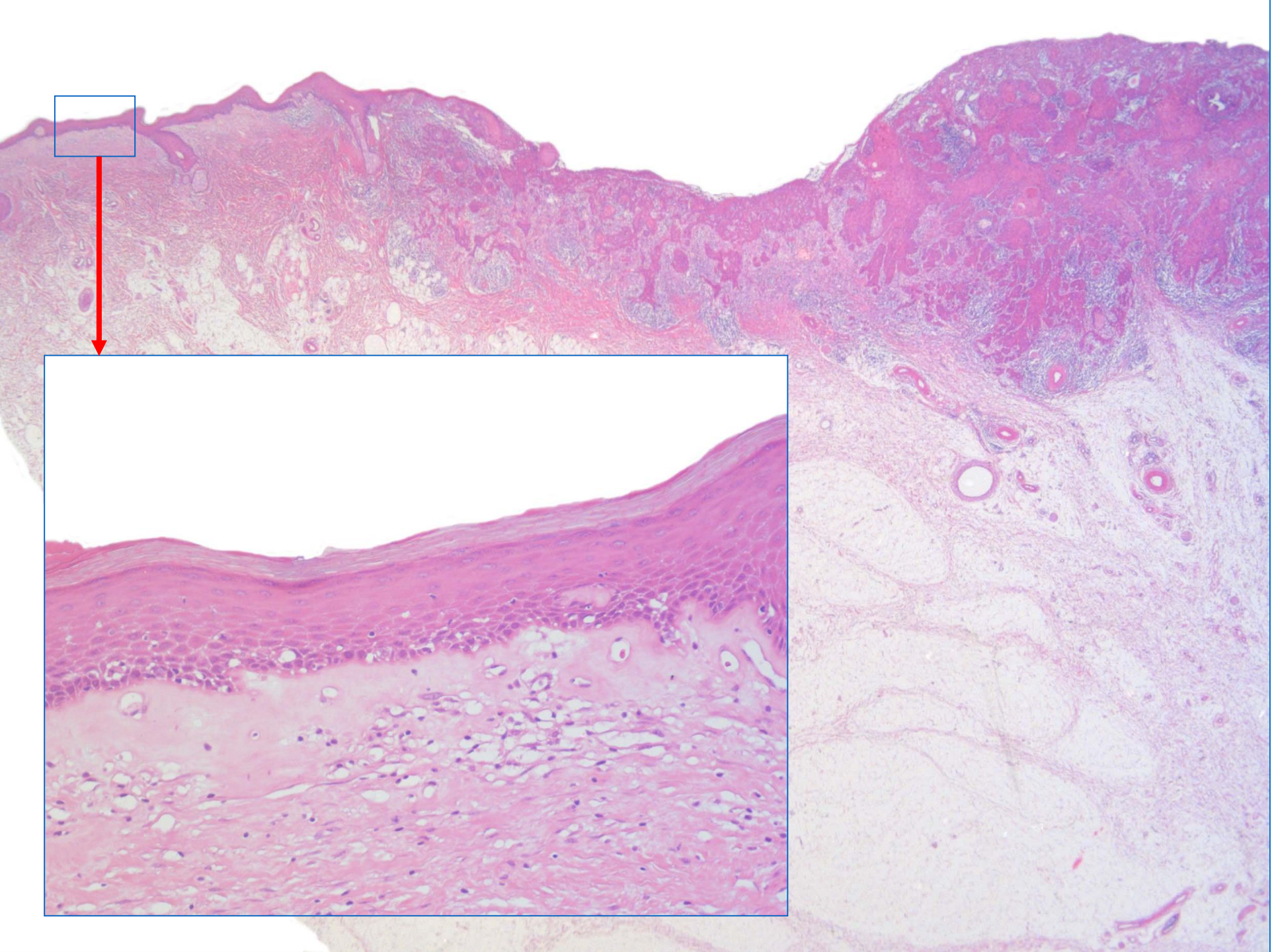
Lichen sclerosus is considered to be the precursor lesion of vulvar squamous cell carcinoma, of which only 2–5% progress to squamous cell carcinoma. Differentiated vulvar intraepithelial neoplasia (VIN) has been proposed to be the direct precursor lesion, but this is a recently recognized, and a difficult 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.



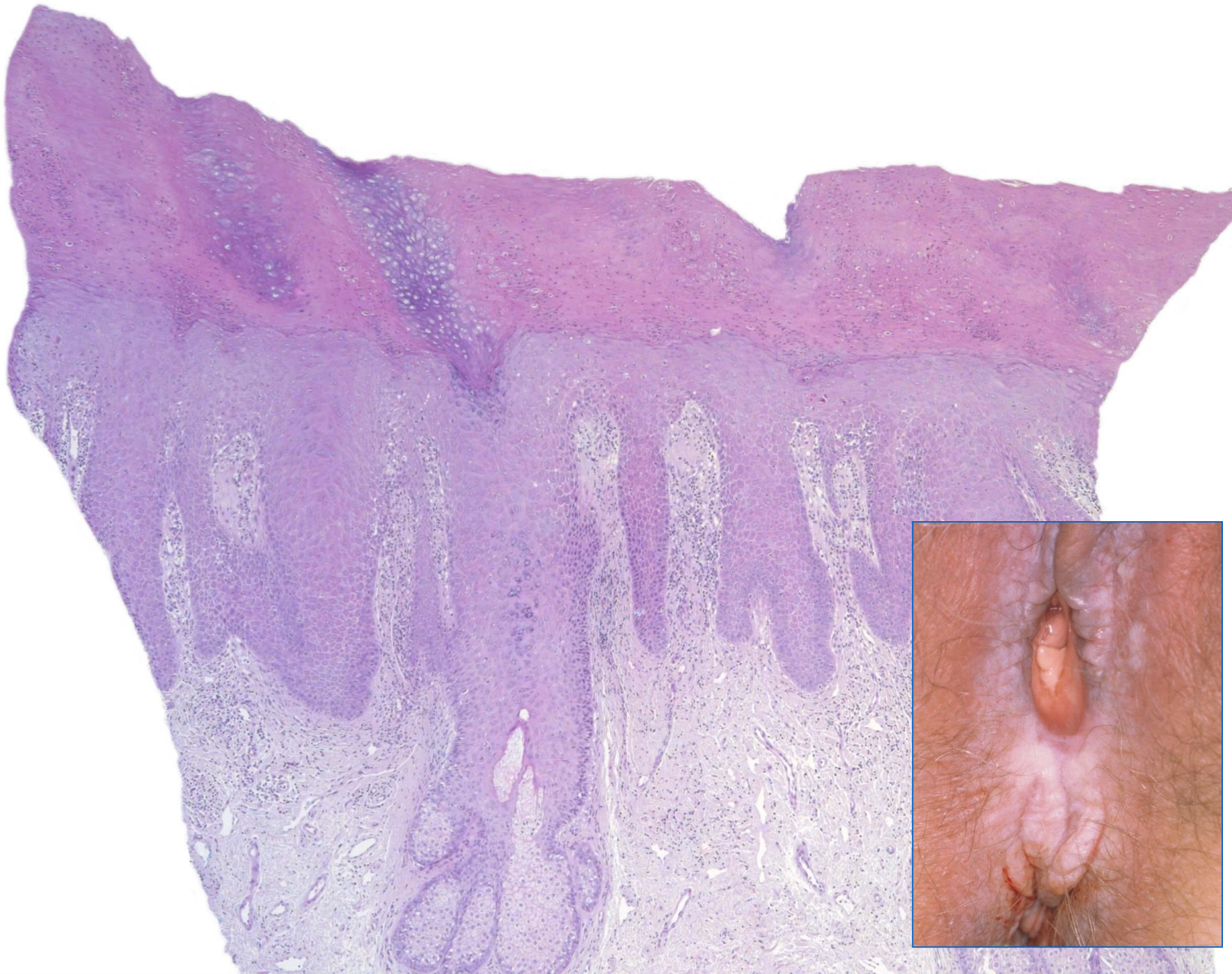
Maybe chronic inflammation and sclerosis has really some carcinogenic potential. If this is the case, it is minimal because the association is so rare. Maybe the existing risk can be reduced slightly by close surveillance, but excessive care bears risks of its own.

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

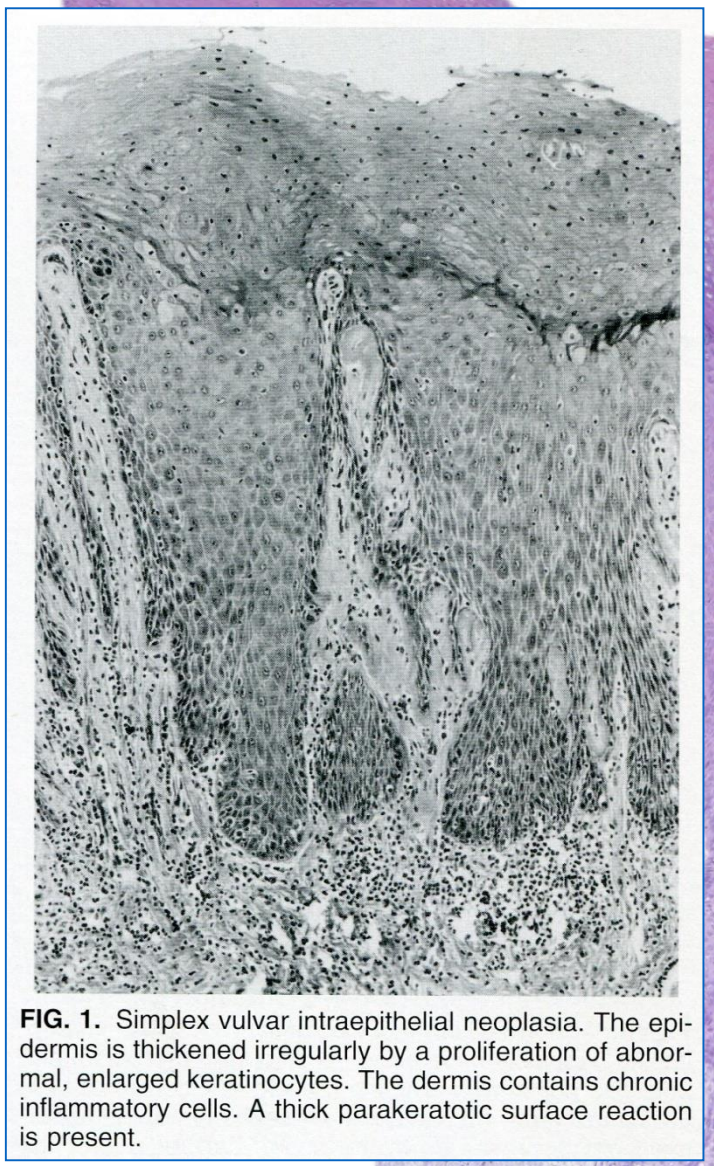
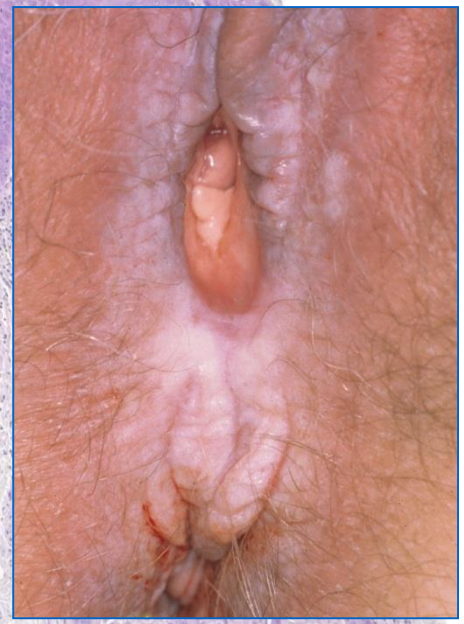


FIG. 1. Simplex vulvar intraepithelial neoplasia. The epidermis is thickened irregularly by a proliferation of abnormal, enlarged keratinocytes. The dermis contains chronic inflammatory cells. A thick parakeratotic surface reaction is present.



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

GENERAL GYNECOLOGY

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

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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

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 specialist clinicians (a specialist is a gynecologist in 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-

Differentiated VIN requires excision.

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.

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

Even big squirrels have small teeth.