Inflammatory Vulvar Pathology

[for surgical pathologists]

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UCLA Health

Where do we get vulvar biopsies from?

FAMILY PRACTITIONERS, DERMATOLOGISTS, PEDIATRICIANS, GYNECOLOGISTS, UROLOGISTS…

- Vulva is an anatomic location that many practitioners provide medical care for

- Our report should be written to be understood by physicians of any of these specialties

https://www.maimonidesmed.org/find-a-doctor/find-a-doctor

Who receives these biopsies?

ANATOMIC/SURGICAL PATHOLOGISTS, DERMATOPATHOLOGISTS, GYNECOLOGIC PATHOLOGISTS, GENITOURINARY PATHOLOGISTS…

https://ellenjdasilva.com/2014/05/05/givers-takers-matchers-and-favors/

Inflammatory vulvar pathology—a practical guide

https://www.pinterest.com/pin/746542075715042600/

Inflammatory vulvar pathology—a practical guide

1) How I approach inflammatory vulvar biopsies

2) Examples of common vulvar inflammatory lesions

How I approach vulvar biopsies

Q1) IS THERE A NEOPLASM (DYSPLASIA / CARCINOMA / MELANOCYTIC PROLIFERATION / PAGET)?

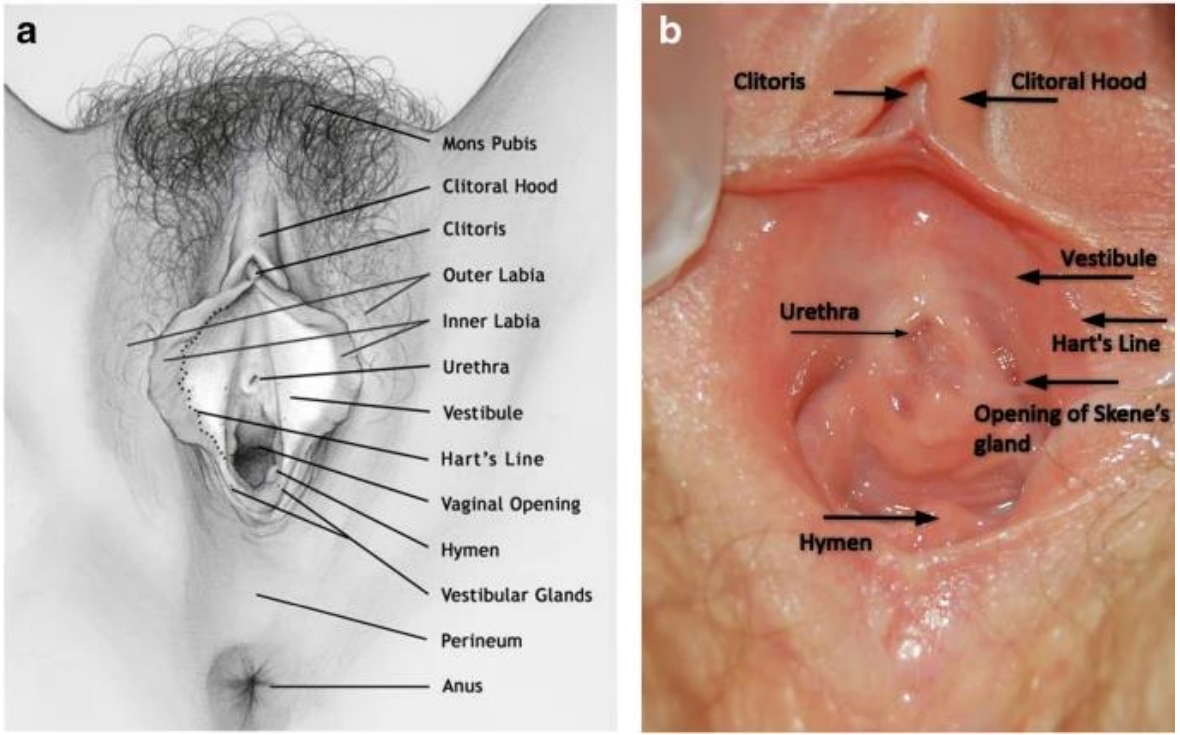
Q2) ARE THERE “BUGS” (INFECTION/INFESTATION)?

Q3) IS IT LICHEN SCLEROSUS?

Q4) …THEN WHAT IS IT?

Vulva is biopsied if the entity presents (or appears to present) only in the vulva, at the time of the biopsy

Vulvar anatomy



Lev-Sagie, A., Gilad, R. & Prus, D. The Vulvar Vestibule, a Small Tissue with a Central Position: Anatomy, Embryology, Pain Mechanisms, and Hormonal Associations. *Curr Sex Health Rep* **11,** 60–66

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Q1: IS THERE A NEOPLASM (DYSPLASIA / CARCINOMA / MELANOCYTIC PROLIFERATION / PAGET/ETC.)?

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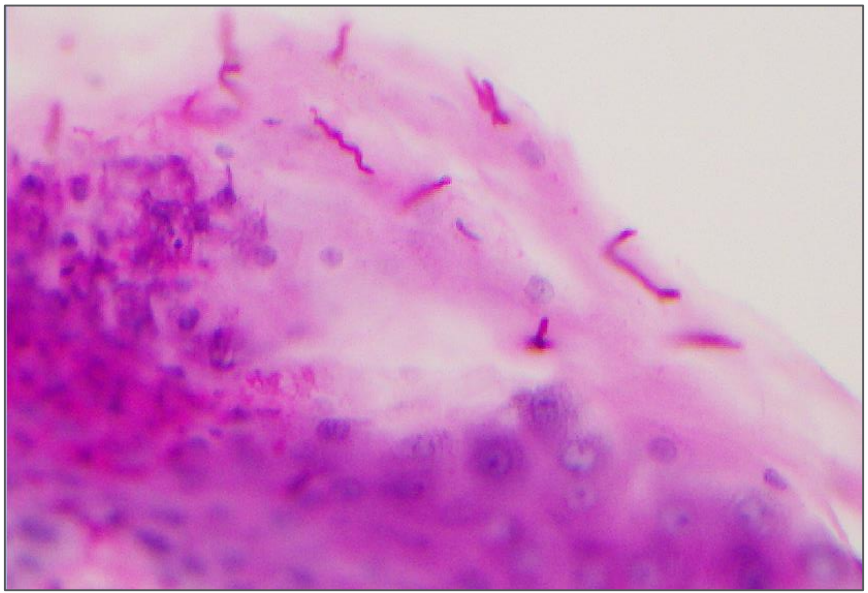
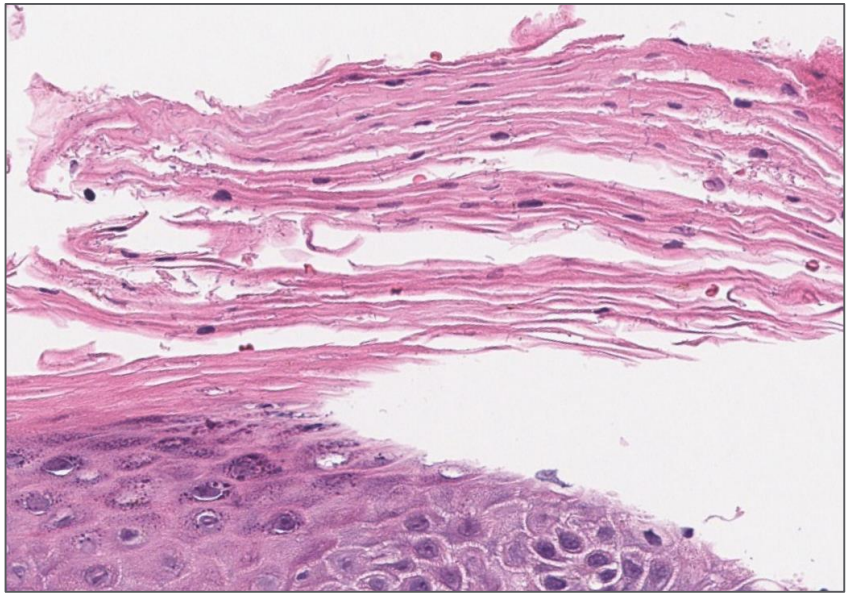
Q2: ARE THERE “BUGS”? (INFECTION/INFESTATION)

Are there bugs?



Superficial fungal infection

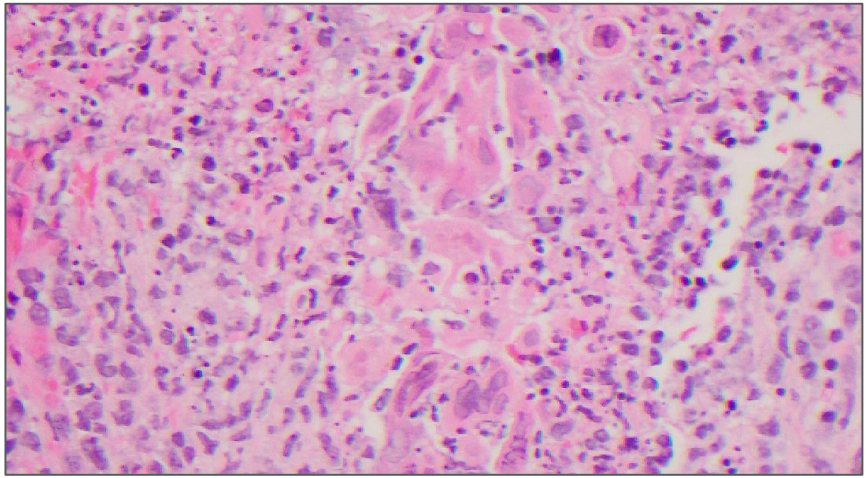
- Candida—yeasts, pseudohyphae
- Tinea (*Trichophyton rubrum,* etc.)—hyphae

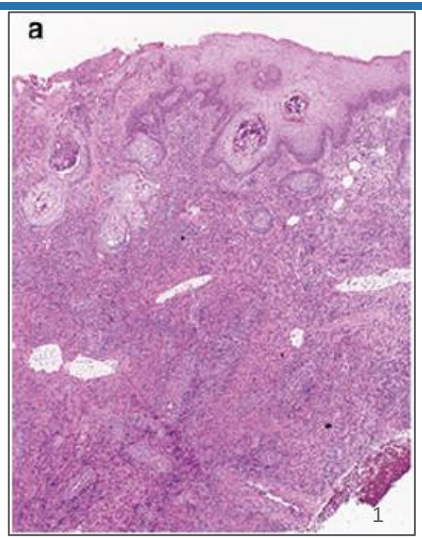


Erythrasma

- *Corynebacterium minutissimum* (Gram pos rods)

Are there bugs?





HSV/VZV

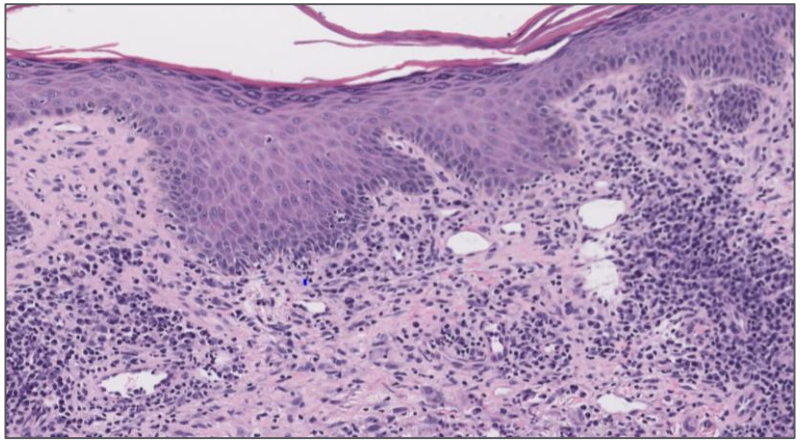
- DDX: SCC, nonspecific ulceration, EBV
- VZV more commonly shows vasculitis and follicular involvement

EBV

- Deep, necrotic ulcers with irregular borders and covered by a yellow adherent membrane.
- The mean age 14.5 years (range 2–51 years) [2]

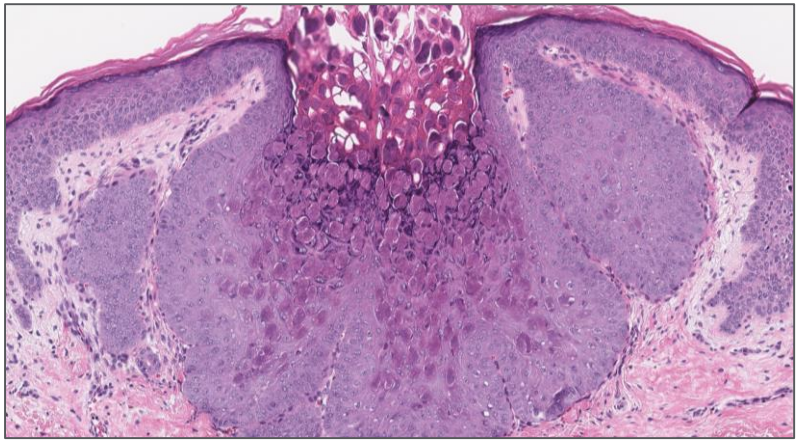
1. Hoang, M. and Selim, M., 2015. Vulvar Pathology. New York: Springer.
2. Halvorsen JA, et al. Genital ulcers as initial manifestation of Epstein-Barr virus infection: two new cases and a review of the literature. Acta Derm Venereol. 2006; 86(5):439–42.

Are there bugs?



Syphilis

- Primary: ulceration with mixed inflammation including plasma cells (nonspecific)
- Secondary: Lichenoid infiltrates with vacuolar changes and psoriasiform hyperplasia
- Tertiary: Necrosis, suppuration, granulomas



Molluscum

- Cup-shaped endophytic growth
- Intracytoplasmic eosinophilic viral inclusions (molluscum body or Henderson–Patterson body)

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Q3: IS IT LICHEN SCLEROSUS?

Is it lichen sclerosus (LS)?

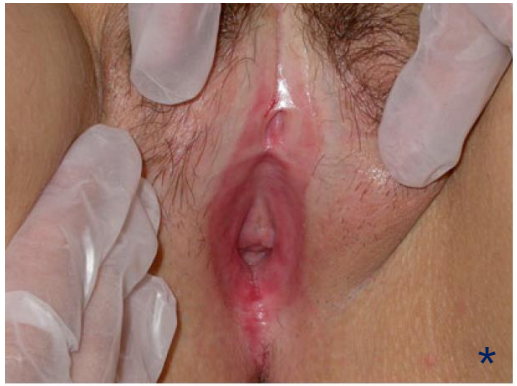


Fig. 5.11 Lichen sclerosus. The clitoris and interlabial sulcus showing erythema, mucosal thinning, focal pigmentation, and a small fissure (Courtesy of Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Badalona, Spain)

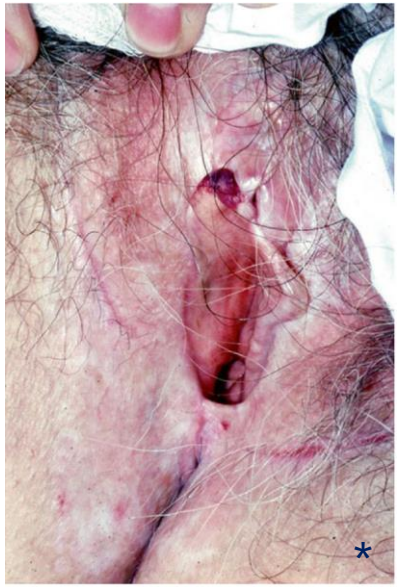


Fig. 5.14 Lichen sclerosus. Intense atrophy with indurated white-porcelain areas (Courtesy of Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Badalona, Spain)

CLINICAL PRESENTATION

- → Two peaks of incidence: prepubertal and postmenopausal
- → Itch is the most common symptom
- → Fissuring, pain
- → Some patients may be asymptomatic

* Hoang, M. and Selim, M., 2015. Vulvar Pathology. New York: Springer.

Is it lichen sclerosus (LS)?

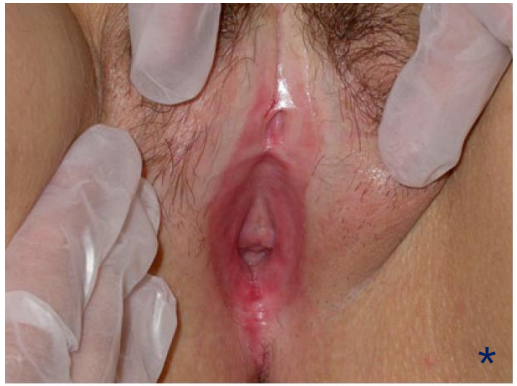


Fig. 5.11 Lichen sclerosus. The clitoris and interlabial sulcus showing erythema, mucosal thinning, focal pigmentation, and a small fissure (Courtesy of Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Badalona, Spain)

Usually begin around the clitoris→ labia minora/majora→ perineum → perianal skin (vaginal involvement is rare)

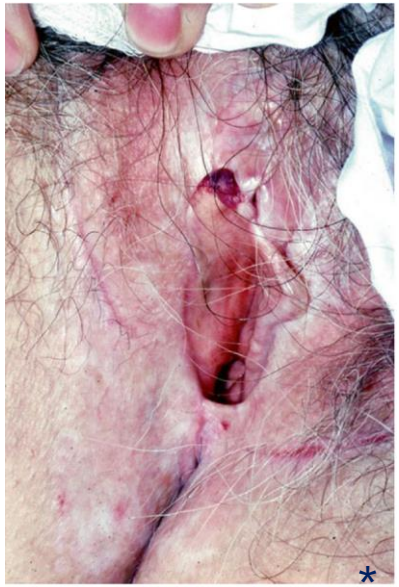


Fig. 5.14 Lichen sclerosus. Intense atrophy with indurated white-porcelain areas (Courtesy of Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Badalona, Spain)

CLINICAL EXAM

→ Early stage: erythema, mucosal thinning and wrinkling

→ Pallor, atrophy, hyperkeratosis, indurated papules/plaques

→ Advanced stages: lichenified, white/porcelein atrophic skin with hemorrhage

* Hoang, M. and Selim, M., 2015. Vulvar Pathology. New York: Springer.

Clinical significance of LS

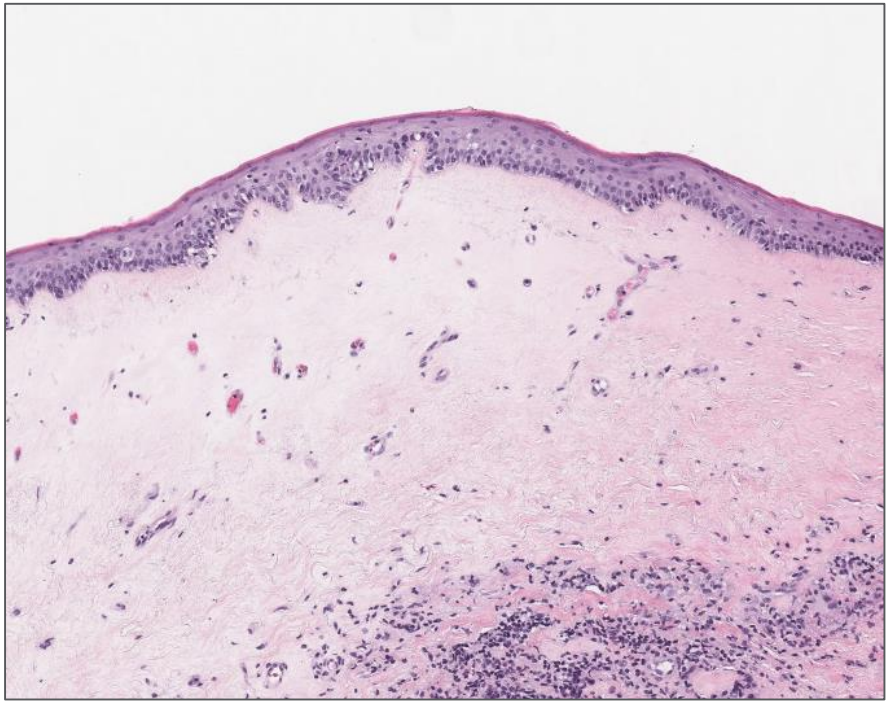
LS CAN CAUSE STENOSIS OF THE INTROITUS AFFECTING THE QUALITY OF LIFE

LS HAS BEEN CONSIDERED TO CARRY INCREASED RISK OF VULVAR SQUAMOUS CELL CARCINOMA (SCC)—LIFETIME RISK OF 2-6% FOR UNTREATED/INADEQUATELY TREATED LS

With intervention, these complications may be prevented*

*Lee A, Bradford J, Fischer G. Long-term management of adult vulvar lichen sclerosus: a prospective ccohort study of 507 women. JAMA Dermatol. 2015;151:1061–7.

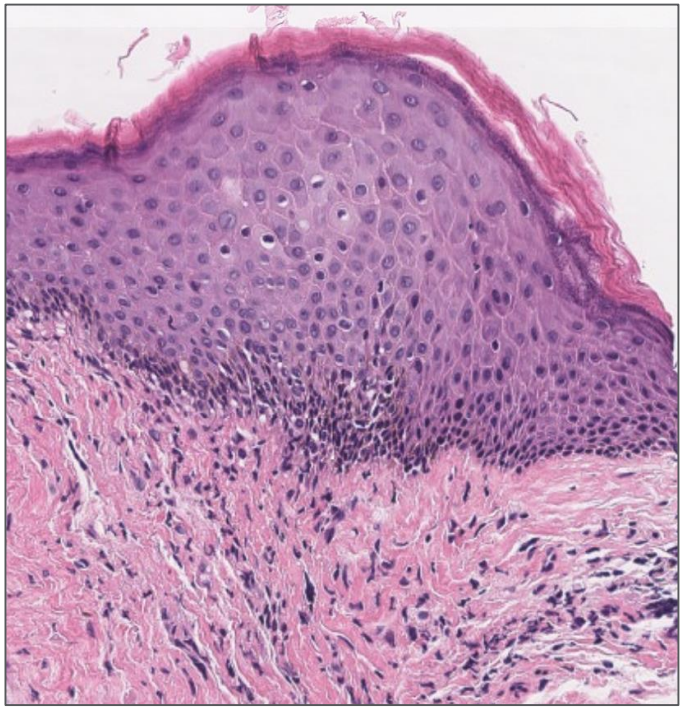
LS histopathology



WELL-DEVELOPED/ADVANCED STAGE

- Epidermal atrophy with vacuolar degeneration of the basal layer
- Superficial dermal edema/sclerosis/hyalinization is seen
- Band of lymphocyte-predominant inflammation below the sclerosis

LS histopathology

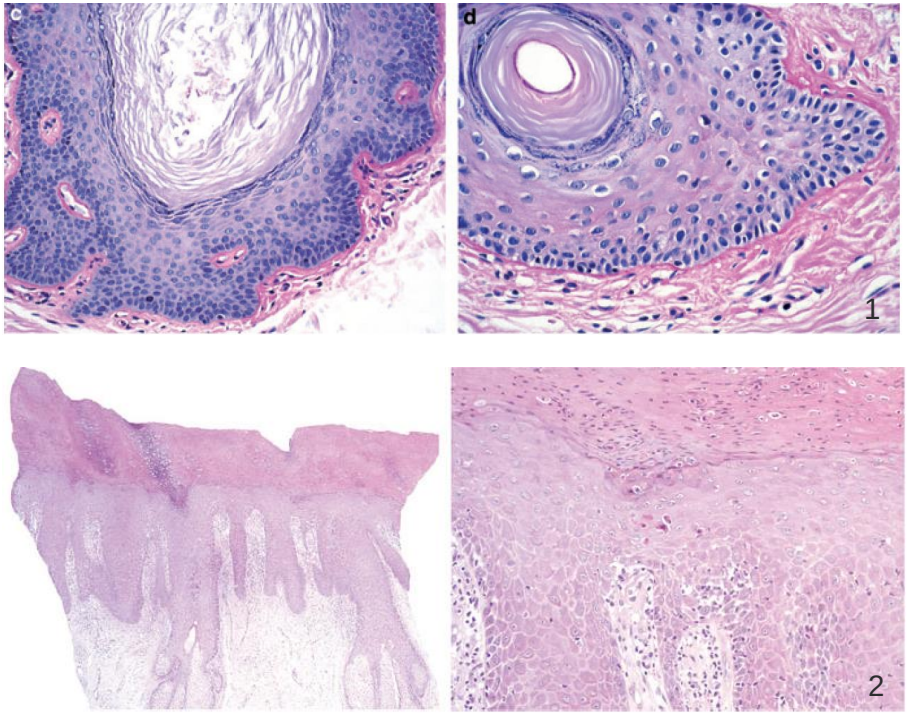


EARLY

Histopathologic findings may be subtle and nonspecific.

- Epithelium may be normal or acanthotic (thickened)
- Inflammation is usually lymphocyte-predominant, interstitial/lichenoid
- Lymphocyte epidermotropism, especially in the basal layer
- Basement membrane may be normal of thickened

LS histopathology



EARLY

Histopathologic findings may be subtle and nonspecific.

- **Follicular changes:**
  - **perifollicular basement membrane thickening**
  - **follicular plugging**
  - **follicular hyperkeratosis**

- **Vertical columns of parakeratosis[2]**

* 1 Regauer S, et al. Histopathology. 2005;47(4):340-347. 2. Weyers W. J Cutan Pathol. 2015;42(2)

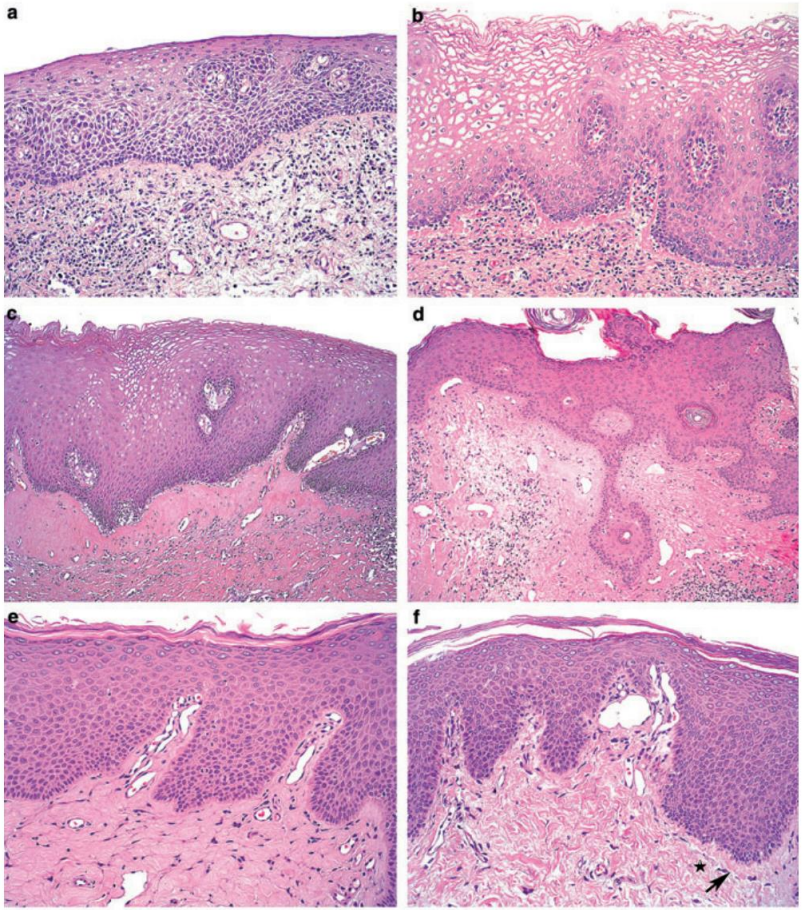
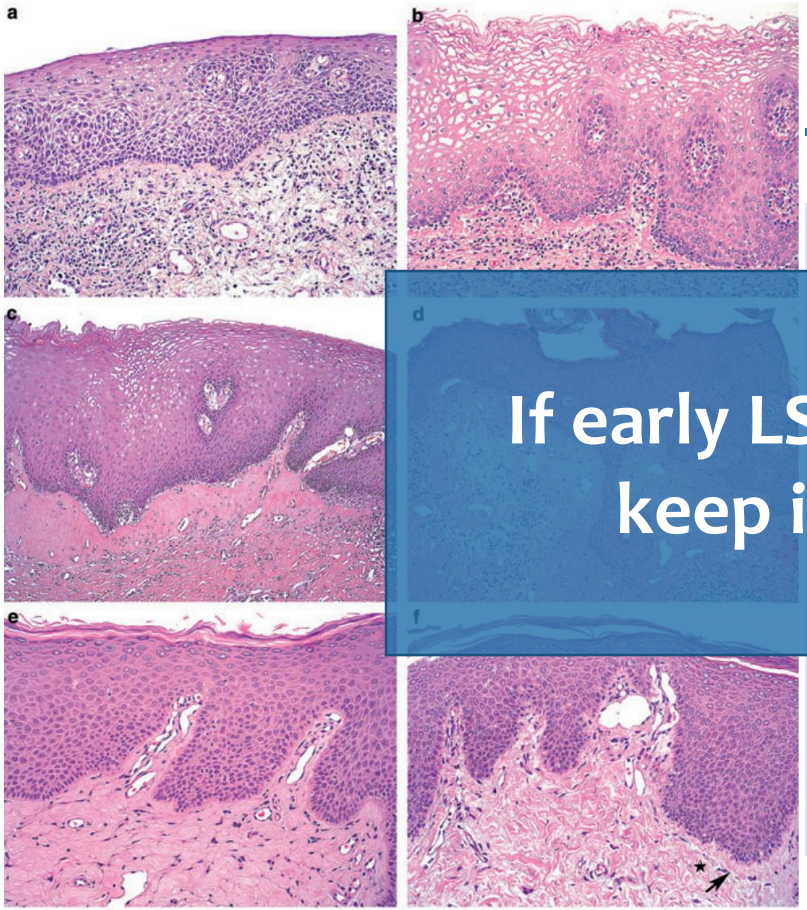


Table 1. Histological features of early lichen sclerosus

Epidermis	Normal thickness or
	Mild acanthosis with slightly irregular plump rete ridges
	Occasionally psoriasiform hyperplasia and mild hyperkeratosis
	Intraepithelial lymphocytes, mostly in basal or suprabasal location
	In the presence of intraepidermal lymphocytes: spongiosis
	Vacuolar basal keratinocyte and melanocyte degeneration
Basement membrane	Normal or focally thickened (periodic acid–Schiff reaction)
	May be obscured by band-like lichenoid lymphocytic infiltrate
Dermis	Homogenized collagen or oedema of papillary dermis
	Melanophages
	Interstitial lymphocytic infiltrate
Vessels	Normal numbers or slightly reduced
	Ectatic capillaries in dermal papillae, often located immediately beneath the basement membrane
	Hyalinized stiff vessel walls
	Perivascular lymphohistiocytic infiltrates
	Vasculitis: lymphocytic–lymphohistiocytic–rarely leukocytoclastic vasculitis
Inflammatory infiltrate	Intraepidermal lymphocyte exocytosis with epidermal spongiosis and keratinocyte vacuolization
	Dermal infiltrates: lichenoid with intraepidermal extension–interstitial–nodular perivascular
Hair/folliculo-sebaceous unit	Acanthosis of epithelium of follicular ostiae and sebaceous gland isthmus
	Luminal hyperkeratosis and hypergranulosis
	Perifollicular basement membrane thickening and sclerotic blood vessels
	Dystrophic hair shafts
Sweat glands	Acanthosis of acrosyringial epithelium with
	Luminal hyperkeratosis and hypergranulosis of ostiae
	Basement membrane thickening

Regauer S, et al. Histopathology. 2005;47(4):340-347.



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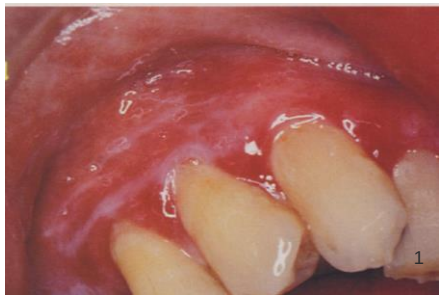
If early LS is a possibility, keep it in the DDX

Regauer S, et al. Histopathology. 2005;47(4):340-347.

DDX of LS—Lichen Planus (LP)



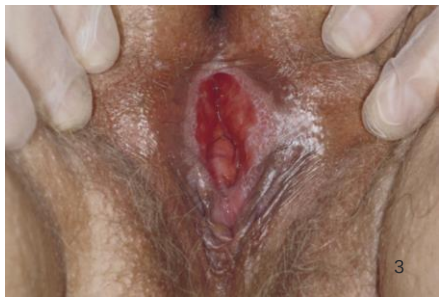


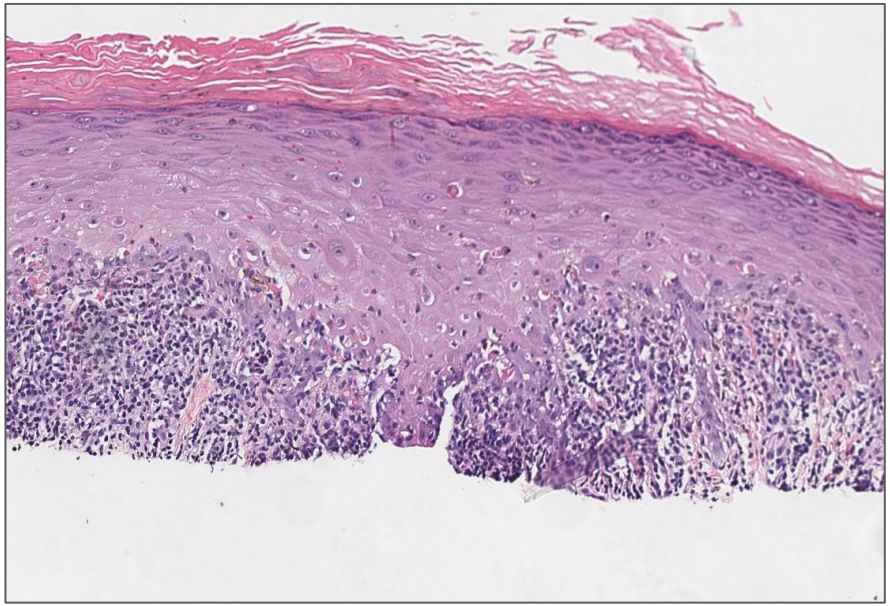
Fig. 5.2 Lichen planus. Whitish hyperkeratotic lesions with conspicuous Wickham striae (Courtesy of Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Badalona, Spain)

LP CLINICAL FEATURES

- Age: Rare in childhood, mostly 30-60 y
- ~1% incidence in women, with ~20% genital involvement.[4]
- Oral and extragenital involvement commonly seen
- Labia minora, vestibule and introitus ± vaginal erosion/ulceration
- Hyperkeratotic lesions with features of Wickham striae may be infrequently seen

1 Eisen D. The vulvovaginal-gingival syndrome of lichen planus. The clinical characteristics of 22 patients. Arch Dermatol. 1994 Nov;130(11):1379-82. PMID: 7979437.
2 Hoang, M. and Selim, M. (2015) Vulvar Pathology. New York: Springer.
3 Sand FL, Thomsen SF. Skin diseases of the vulva: inflammatory, erosive-ulcerating and apocrine gland diseases, zinc and vitamin deficiency, vulvodynia and vestibulodynia. J Obstet Gynaecol. 2018 Feb;38(2):149-160.
4. Eisen D. The evaluation of cutaneous, genital, scalp, nail, esophageal, and ocular involvement in patients with oral lichen planus. Oral surgery, oral medicine, oral pathology, oral radiology and endodontics 1999;88(4):431-436.

LP histopathology



- Hypergranulosis and hyperkeratosis
- Saw-toothing/serrated epidermis (pointed rete)
- Lichenoid (band-like) lymphocyte-predominant inflammation in the superficial dermis, obscuring the basal epidermis, with associated necrotic keratinocytes
- Subepidermal clefting may be present

LS versus LP

Table 5.1 Main clinical and histopathological differential features between lichen planus and lichen sclerosus

	Lichen planus	Lichen sclerosus
Clinical features		
Cutaneous involvement	Frequent	Infrequent
Vaginal involvement	Present, frequent in the erosive variant	Extremely rare
Perianal involvement	Rare	Frequent
Oral involvement	Frequent	Extremely rare
Nail involvement	Infrequent	Absent
Presenting symptoms	Sores and pain	Pruritus
Introital stenosis	Frequent	Only in the advanced stage
Clinical hallmarks	Keratosis and ulceration	Mucosal thinning and hemorrhage

	Lichen planus	Lichen sclerosus
Histologic features		
Serrated epidermis	Frequently focal	Extremely rare
Thickening of the basal membrane	Extremely rare	Frequent
Submucosal edema	Extremely rare	Frequent
Ectatic blood vessels	Extremely rare	Frequent
Hemorrhage or siderophages	Rare	Frequent
Collagen hyalinization	Rare	Frequent

Hoang, M. and Selim, M. (2015) Vulvar Pathology. New York: Springer.

LS versus LP

SAMPLE REPORT (IF LS IS CLINICALLY FAVORED BUT BX IS EQUIVOCAL)

VULVA (BIOPSY):

- Lichenoid interface dermatitis with superficial dermal lymphocyte-predominant inflammation
- Negative for dysplasia or malignancy

COMMENT:

The findings support the clinical impression of lichen sclerosus. Differential diagnosis includes lichen planus and correlation with total clinical information is suggested.

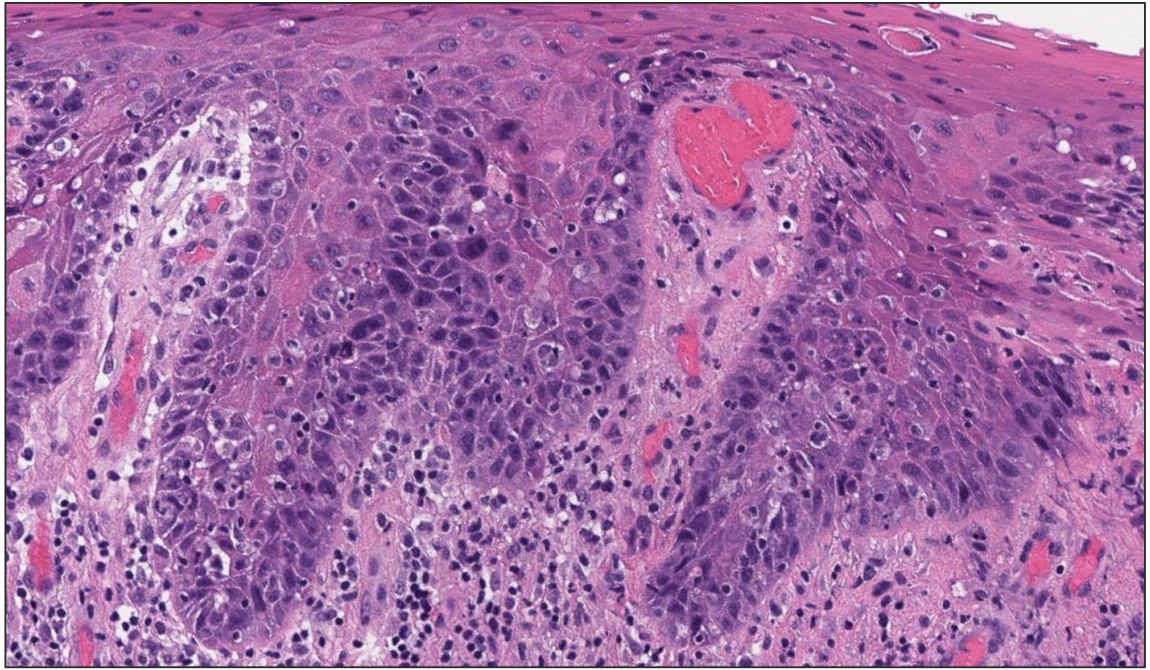
LS versus differentiated VIN (dVIN)

DIFFERENTIATED VULVAR INTRAEPITHELIAL NEOPLASIA (DVIN)

- May coexist with LS, but should be diagnosed when prominent basal atypia is present
- Development of dVIN is mediated by p53 mutation
- High-grade by definition, with apparently more rapid progression to SCC compared to HSIL

Differentiated VIN (dVIN) histopathology

HISTOPATHOLOGY



- Rete pegs are often elongated, branched/fused
- Most atypical cells confined to the basal and parabasal layers
  - Hyperchromatic, irregular and pleomorphic nuclei with macronucleoli
- “Paradoxical”maturation—premature keratinization and dysmaturation

LS versus differentiated VIN (dVIN)

IMMUNOHISTOCHEMISTRY—P53?

- p53 IHC patterns seen in dVIN:
  1) Null pattern
  2) Strong, uniform staining in ≥70% of basal cells, parabasal extension (>1/3 epithelial thickness) [1]
  3) Cytoplasmic positivity [2]

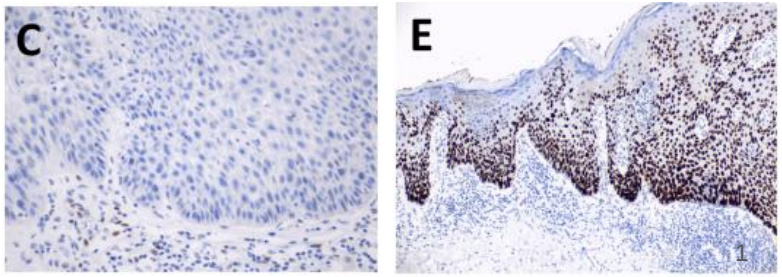


Table 1. Performance statistics of each p53 staining parameter for distinguishing dVIN from non-neoplastic vulvar squamous lesions.

Diagnosis	Parabasal extension		Basal intensity		Basal %		Consistency	
	>1/3	≤1/3	Strong	Weak-Mod	≥70%	<70%	Uniform	Patchy
dVIN*	9	3†	9	3	11	1	11	1
Non-neoplastic	3	43	7	39	12	34	3	43
Sensitivity	75%		75%		91%		92%	
Specificity	93%		85%		73%		93%	
p-value	<0.00001		<0.0001		<0.001		<0.0001	

*Excluding null/absent staining cases
†No dVIN had basal only staining

1

1. Liu, Y. A. et al. (2020). Comparison of p53 Immunohistochemical Staining in Differentiated Vulvar Intraepithelial Neoplasia (dVIN) to Inflammatory Dermatoses and Benign Squamous Lesions in the Vulva. Histopathology
2. Tessier-Cloutier B, et al. Major p53 immunohistochemical patterns in in situ and invasive squamous cell carcinomas of the vulva and correlation with TP53 mutation status. Mod Pathol. 2020;33(8):1595–605.

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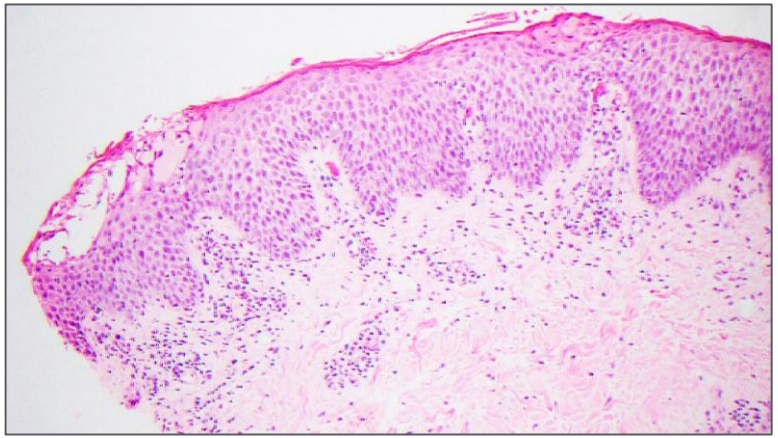
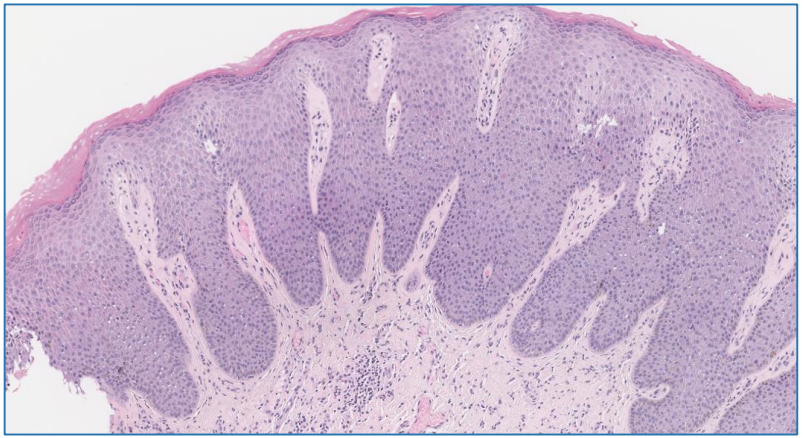
Q4: …THEN WHAT IS IT?

Spongiotic dermatitis





- Spongiosis=intercellular edema
- Acute: Prominent spongiosis +/- spongiotic vesicles containing Langerhans cells
- Subacute/chronic: epidermal acanthosis (thickening) with hyperkeratosis, parakeratosis. Spongiosis may be minimal
- Dermal inflammation, often containing eosinophils

Spongiotic dermatitis—DDX

SPONGIOTIC DERMATITIS DDX	CLUES
Allergic/irritant contact dermatitis or eczema	Superficial dermal inflammation, often with eosinophils
Fungal infection/erythrasma	GMS or PAS shows organisms
Insect bite reaction/infestation	May show deep dermall inflammation containing eosinophils
Drug reaction	May show deep dermal inflammation, additional patterns of interface changes may be present
Seborrheic dermatitis	Parakeratosis around the hair follicles, neutrophil/lymphocyte exocytosis
Psoriasis (differential diagnosis of subacute spong)	Neutrophils in the stratum corneum, regular elongation of rete ridges, diminished granular layer, prominent parakeratosis
Early immunobullous disorder (i.e. pemphigus/pemphigoid)	Often with extragenital involvement. DIF is clinically suspected

Spongiotic dermatitis

SAMPLE REPORT:

VULVA (BIOPSY):

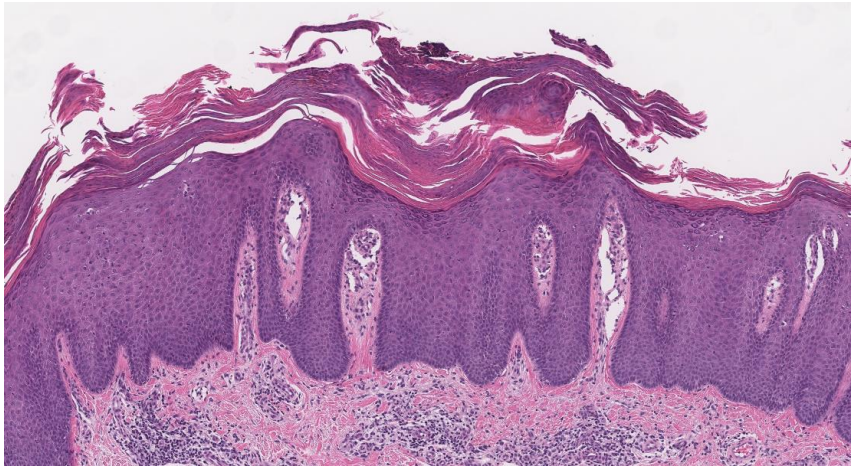
- Spongiotic dermatitis with superficial dermal inflammation +/-containing eosinophils
- GMS/PAS stain is negative for pathogenic fungal organisms
- No dysplasia or malignancy in the sections examined

COMMENT:

The microscopic differential diagnosis for spongiotic dermatitis includes contact dermatitis, eczema and drug reaction. Correlation with total clinical information is necessary.

Psoriasis

- Well-demarcated red plaques with thickening and silver scaling
- When flexural folds and anogenital region are involved, referred to as “inverse psoriasis.” commonly seen with involvement of non-genital region



- Regular acanthosis, confluent parakeratosis, hypogranulosis, thinned suprapapillary plate with tortuous blood vessels
- Neutrophilic microabscesses in the stratum corneum /epidermis
- Lymphocyte-predominant inflammation (usually without eos)

* Sand FL, Thomsen SF. Skin diseases of the vulva: inflammatory, erosive-ulcerating and apocrine gland diseases, zinc and vitamin deficiency, vulvodynia and vestibulodynia. J Obstet Gynaecol. 2018 Feb;38(2):149-

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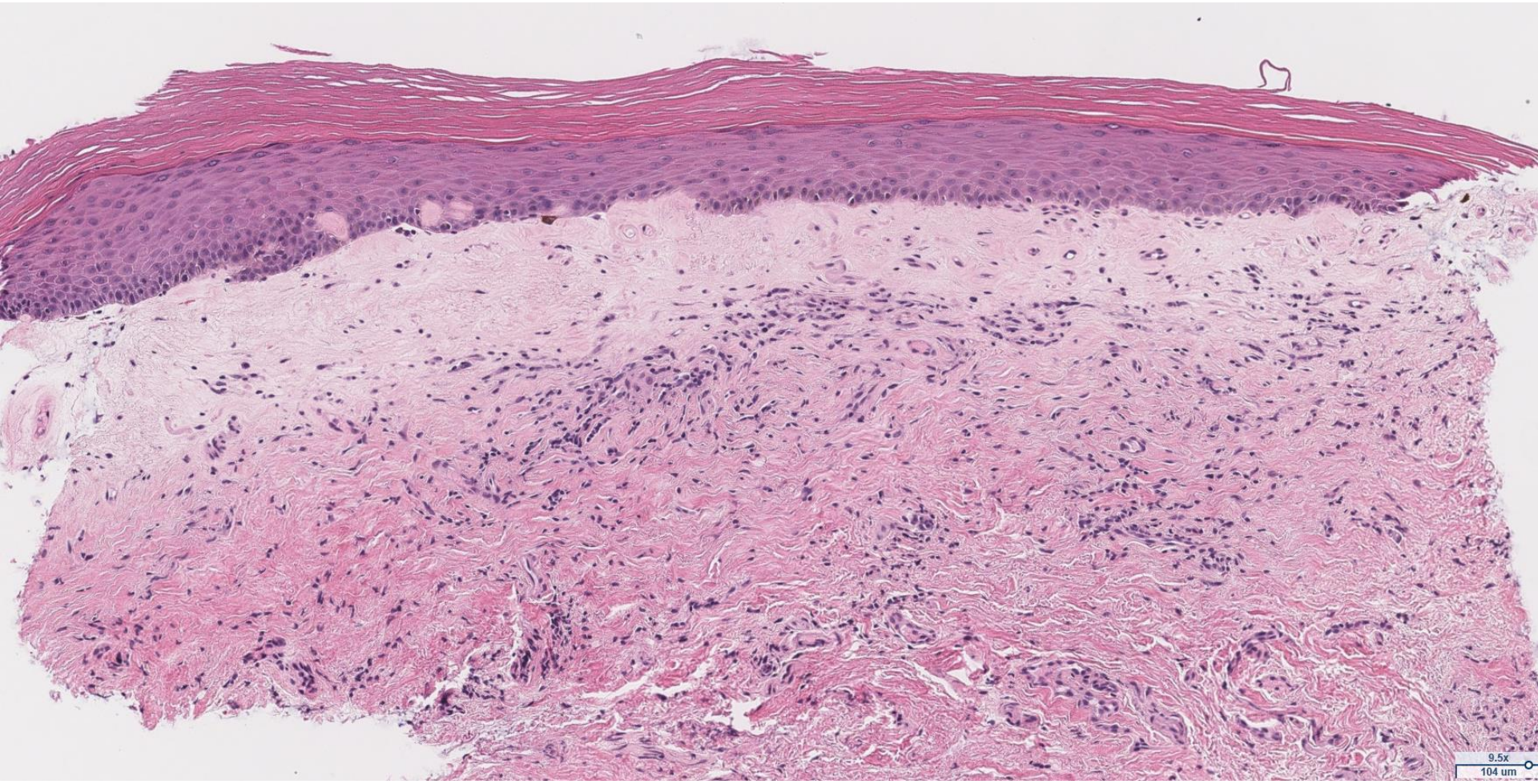
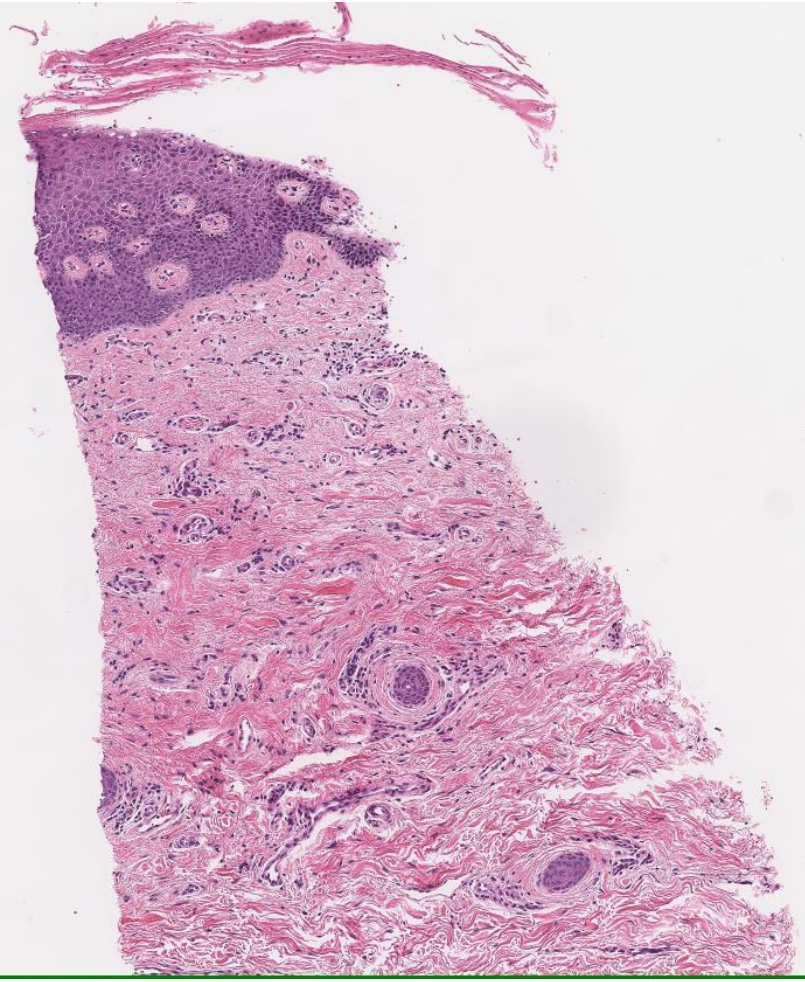
CASE 1
“53F, rule out LS versus LSC”

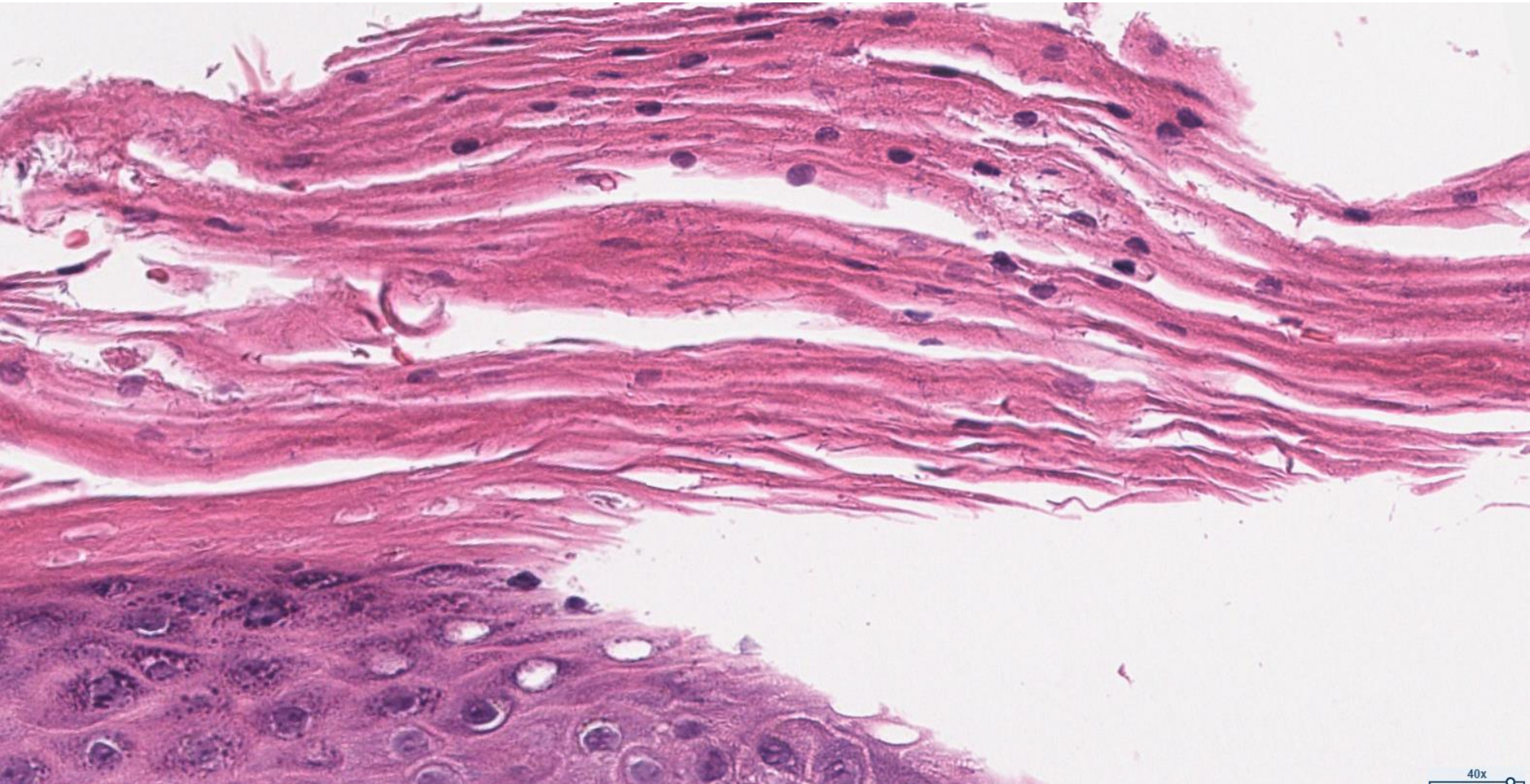
CASE 1-1



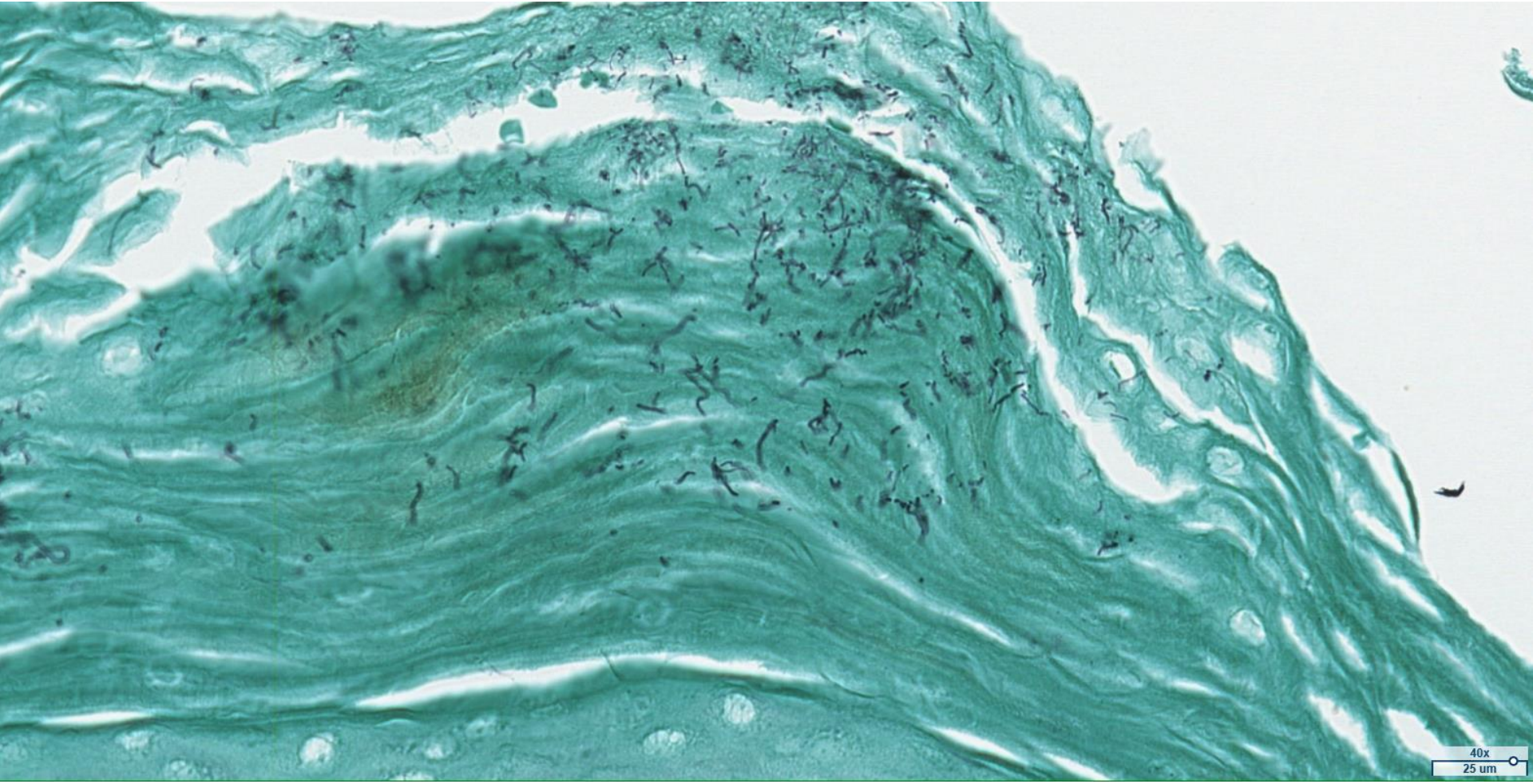
CASE 1-2



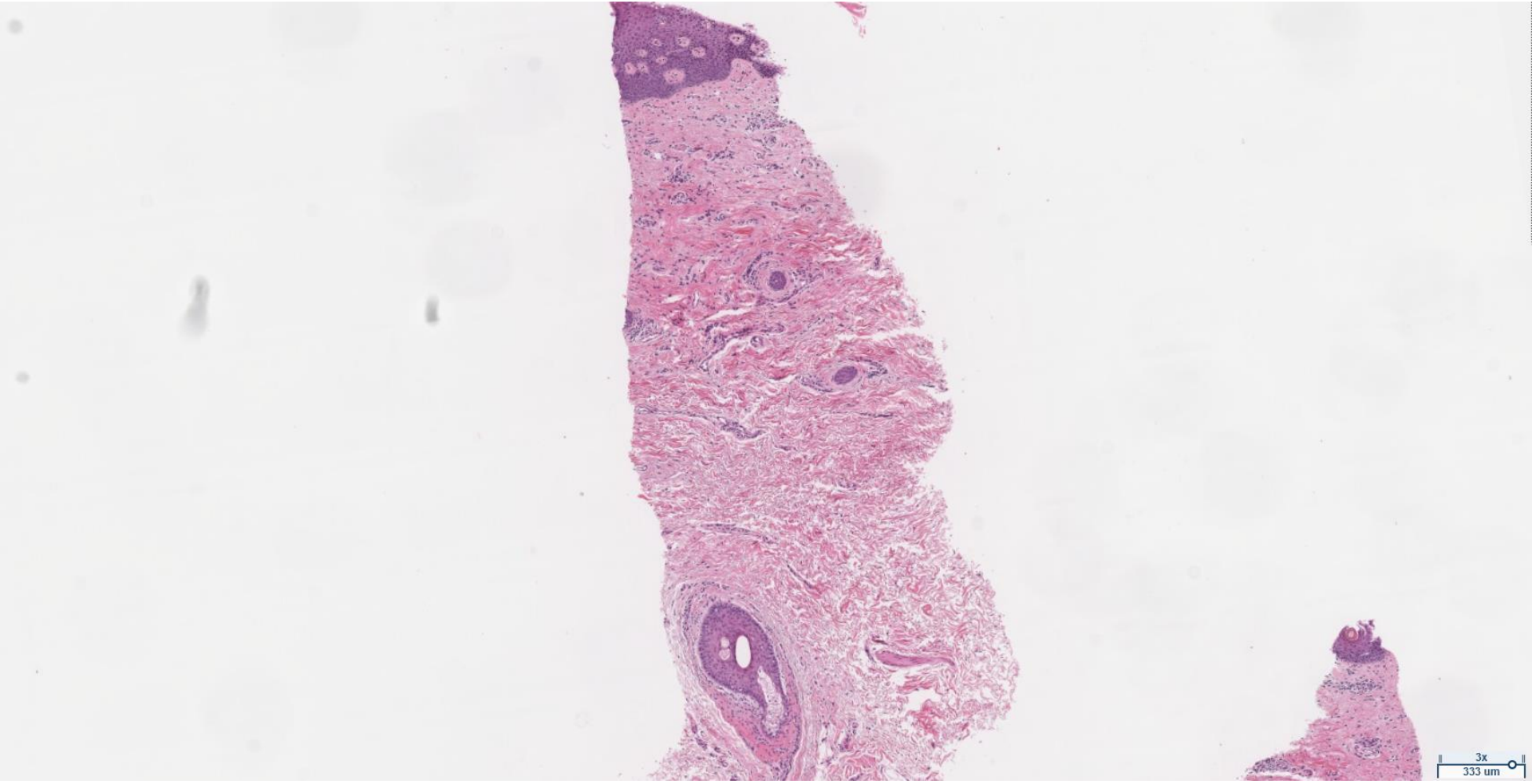
CASE 1-2



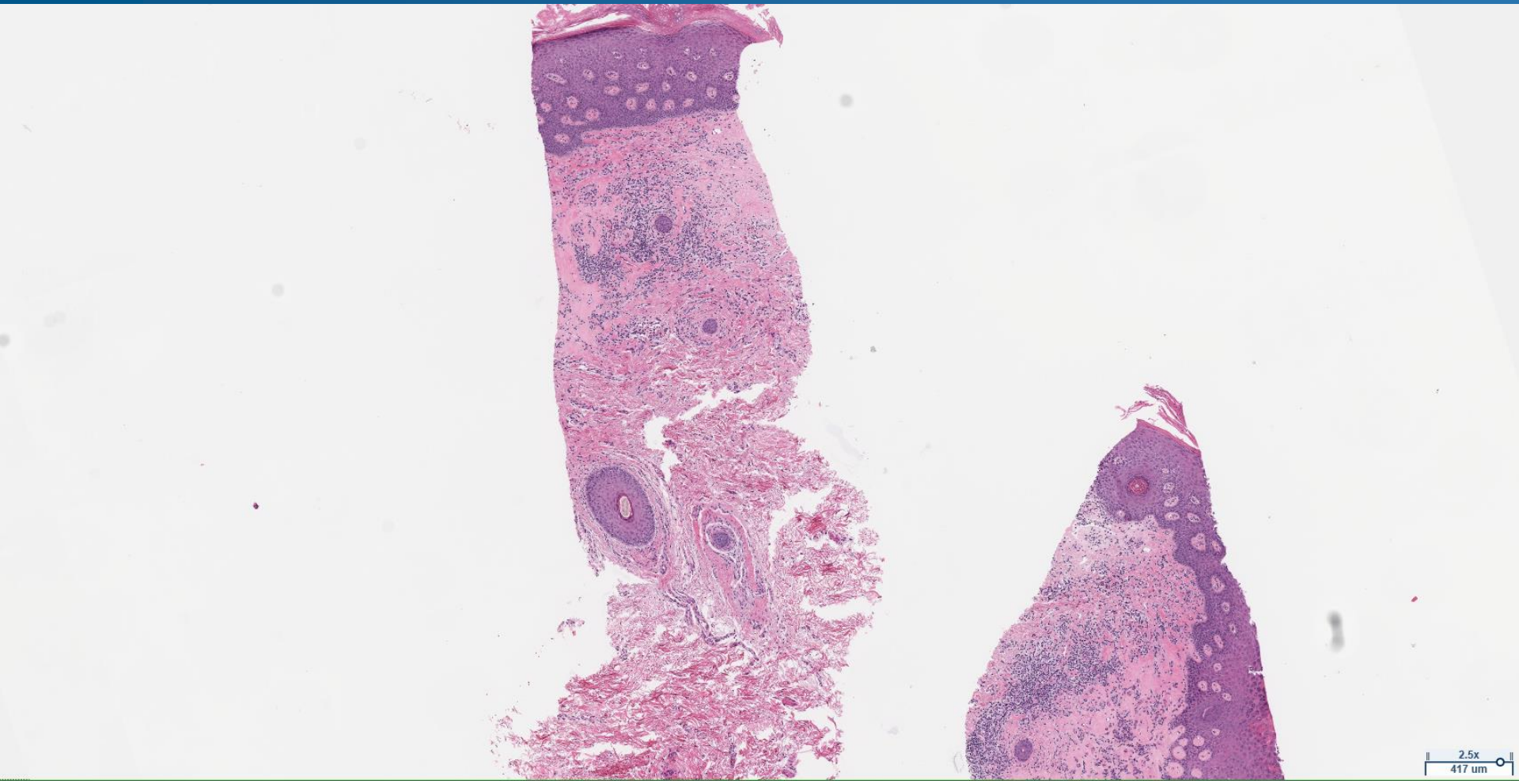
CASE 1-2



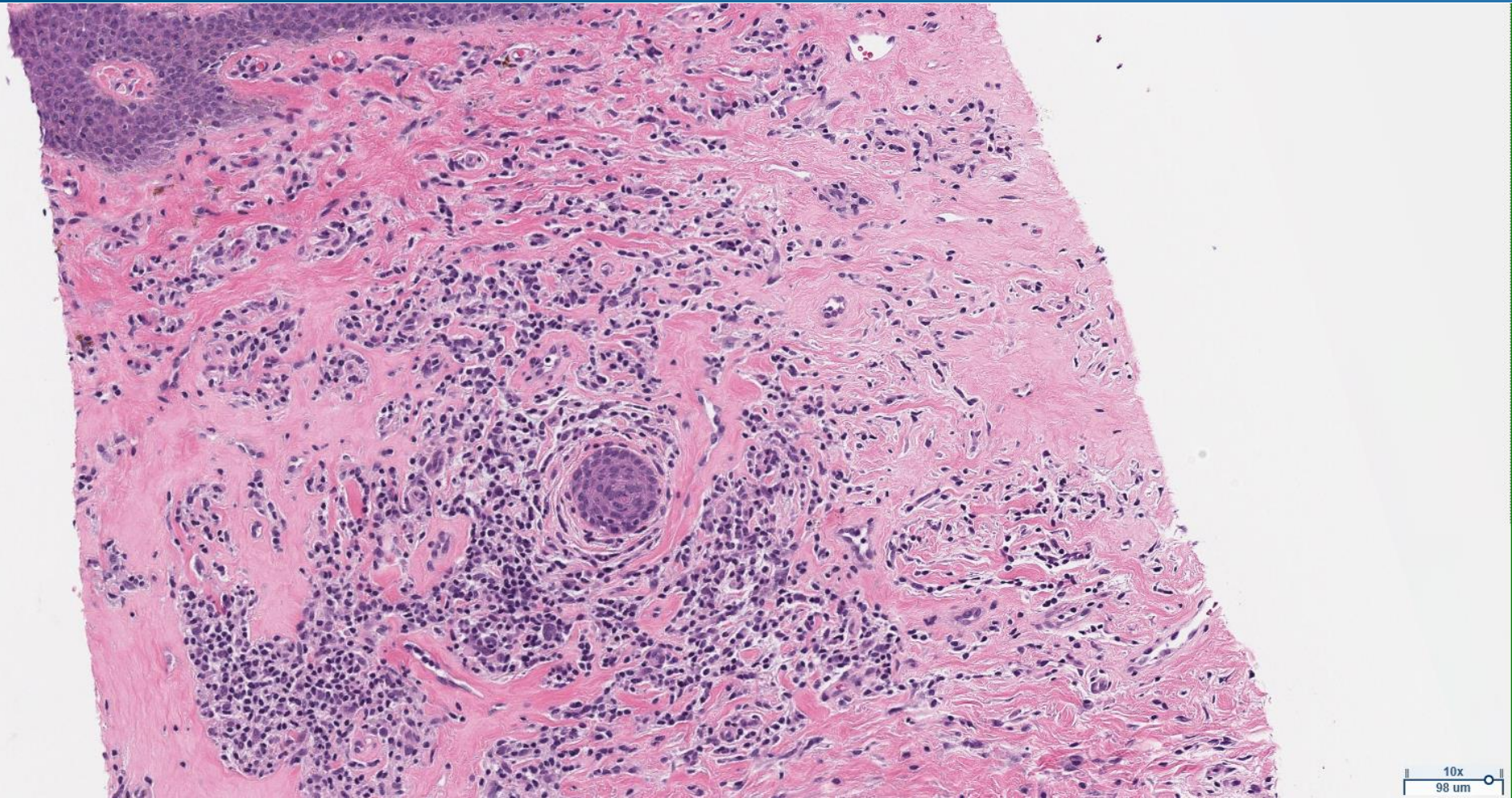
CASE 1-2



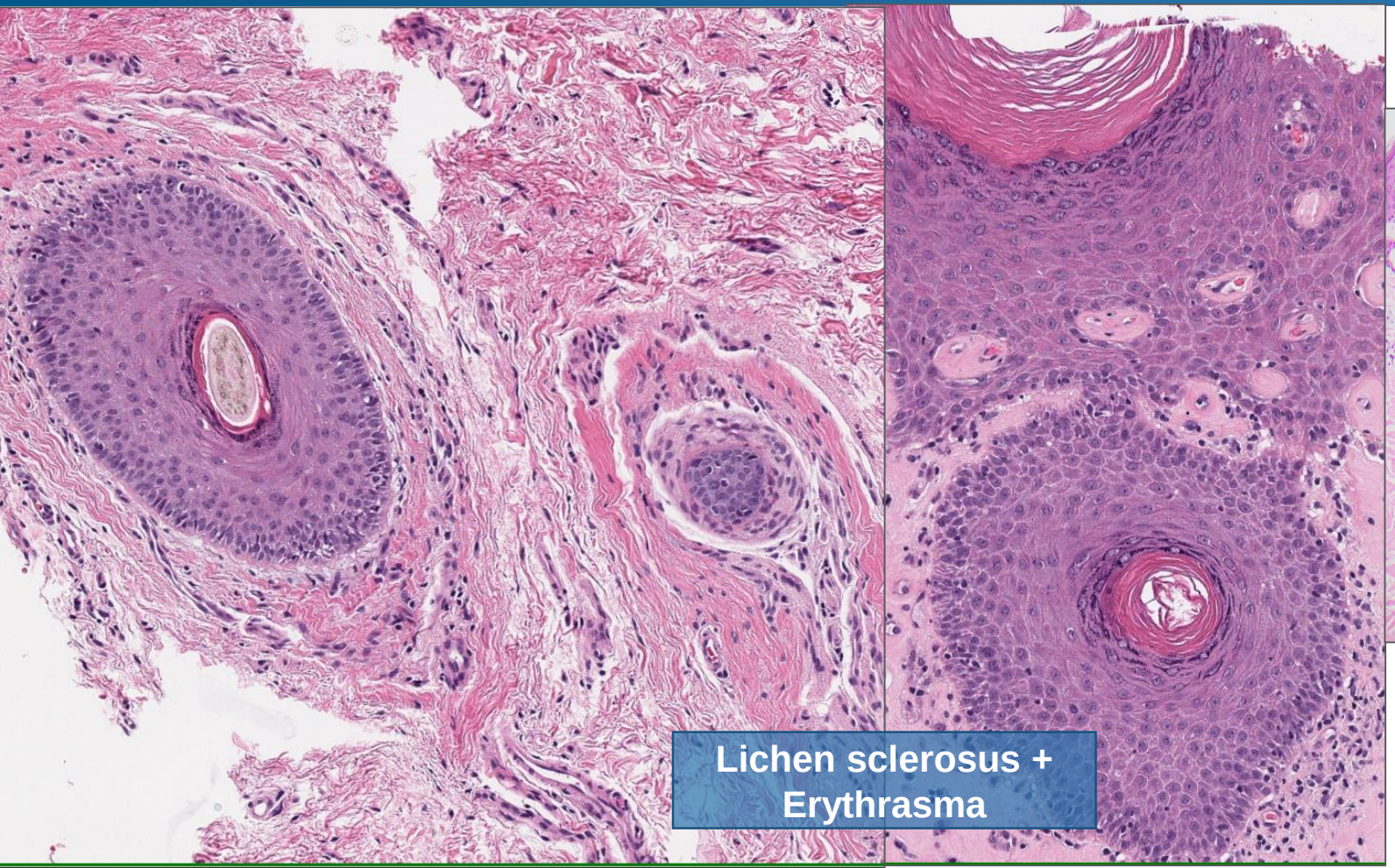
CASE 1-2



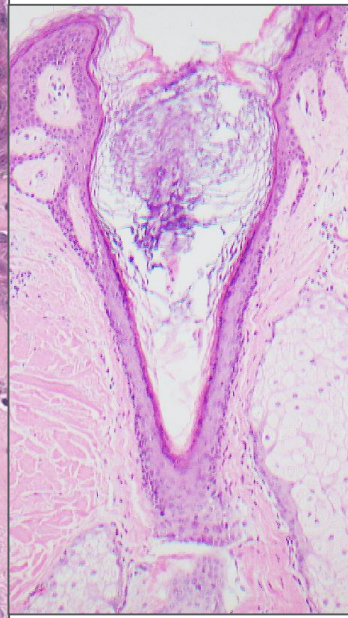
CASE 1-2



CASE 1-2



Lichen sclerosus + Erythrasma



*normal for comparison

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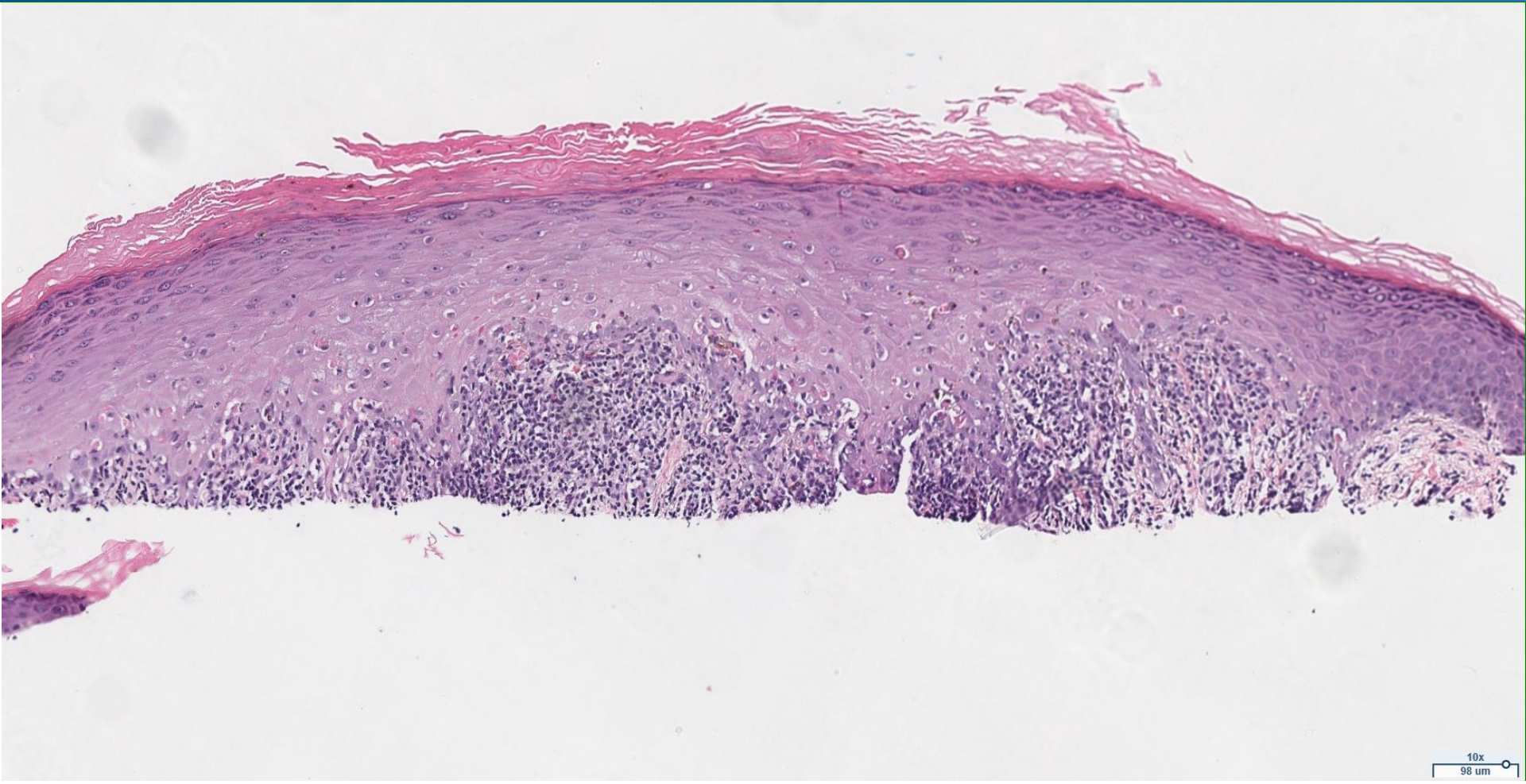
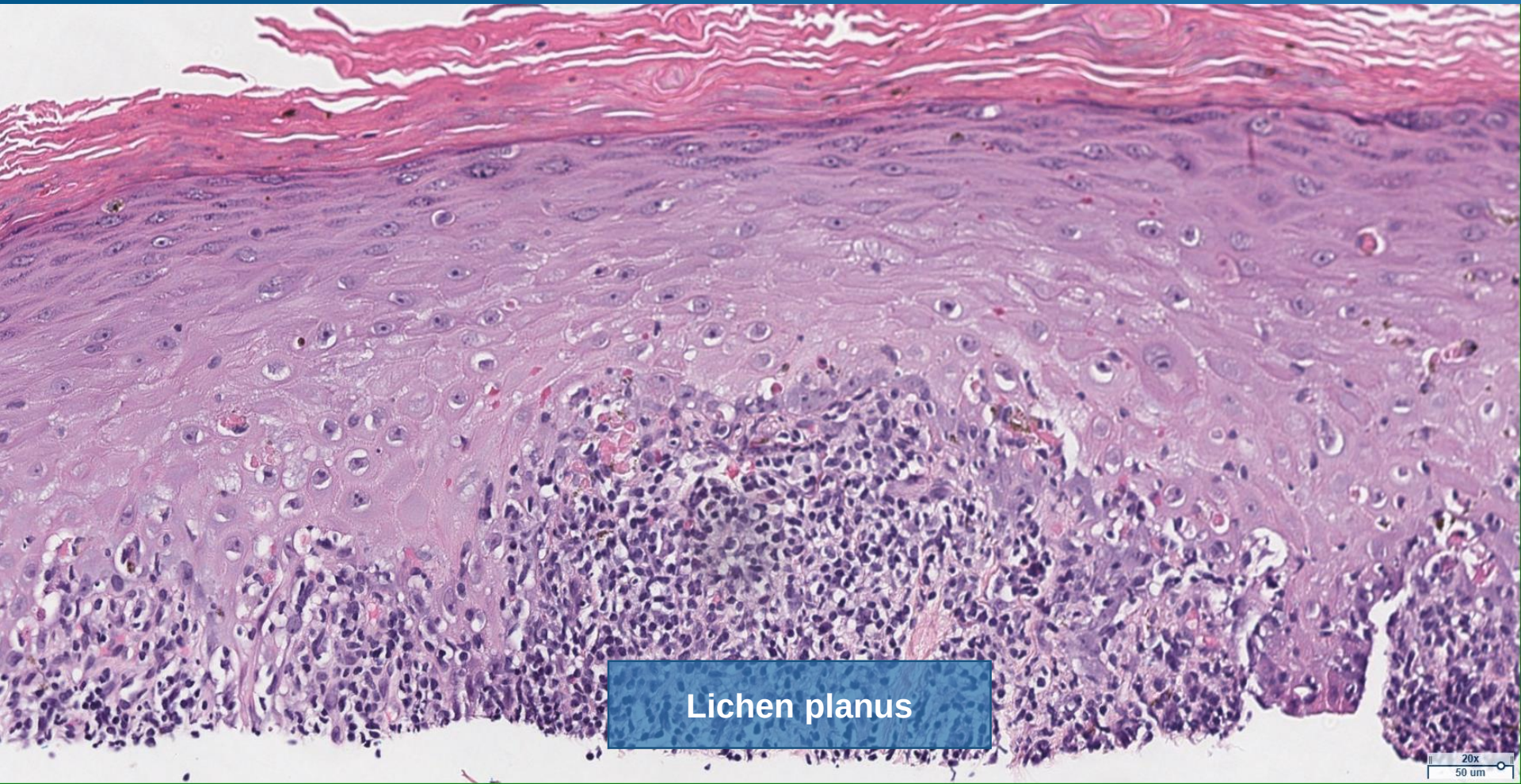
CASE 2

“51F, lacy patches along the buccal mucosa and vulvar lesion”

CASE 2



CASE 2



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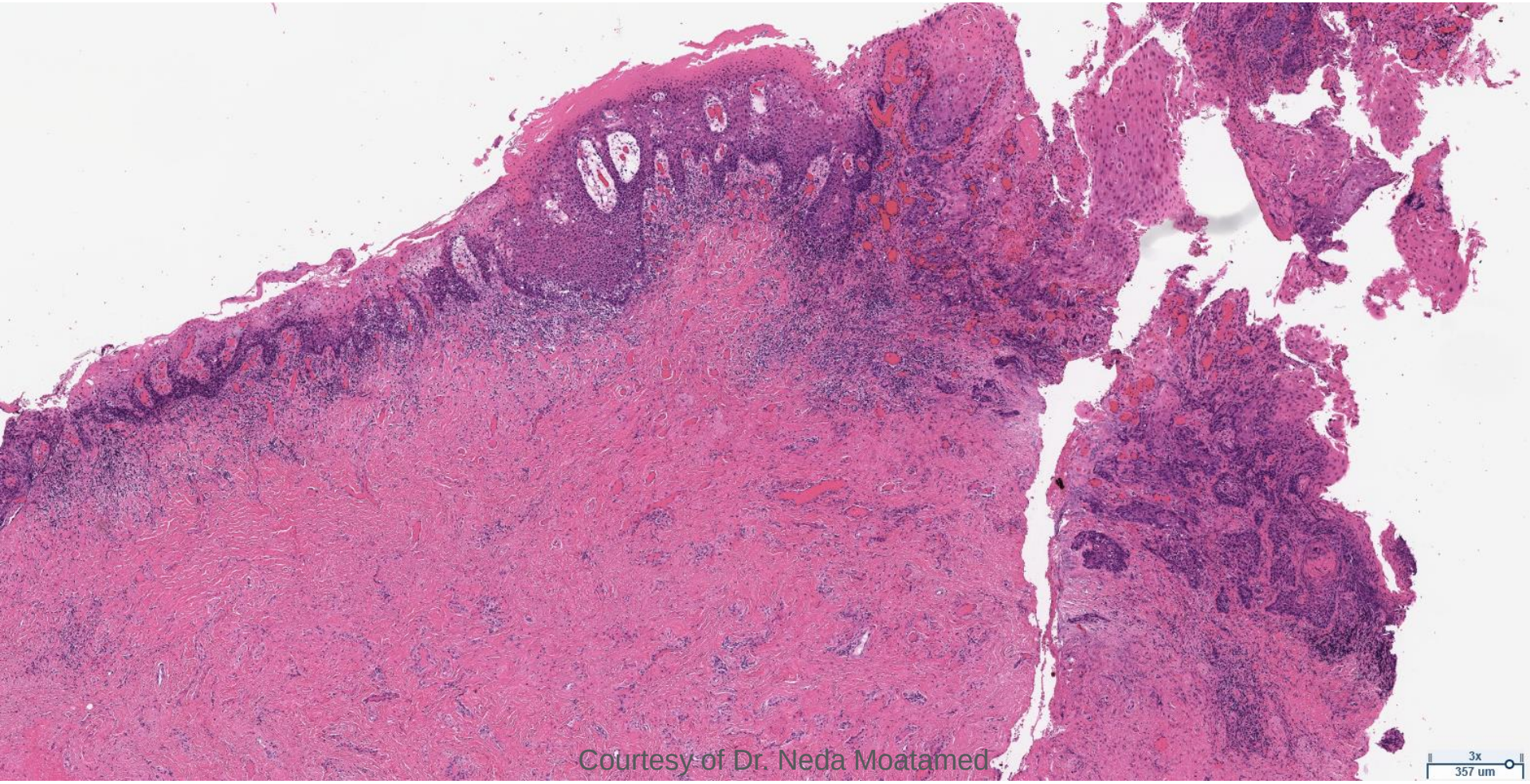
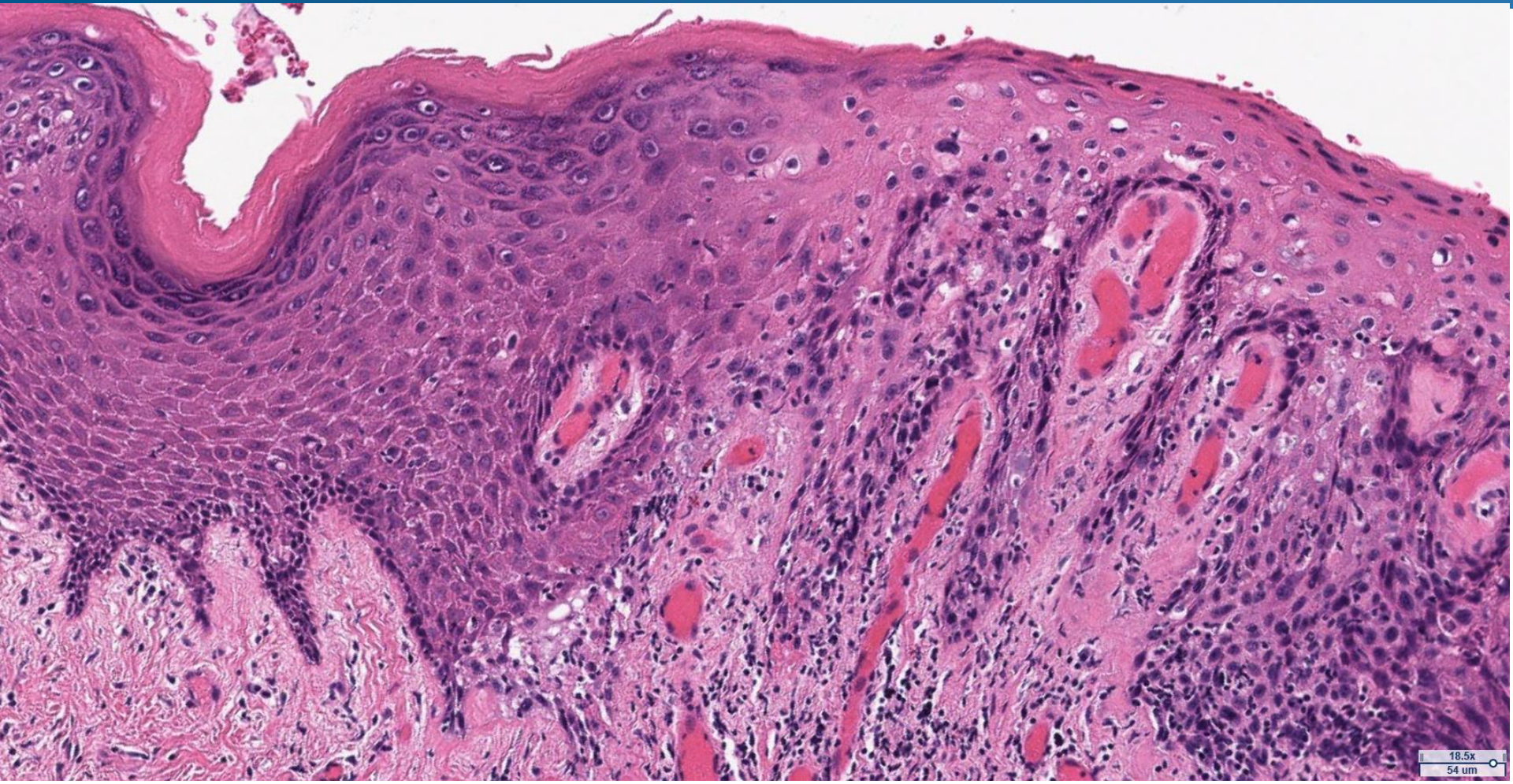
CASE 3
“54F, rule out SCC”

CASE 3-1

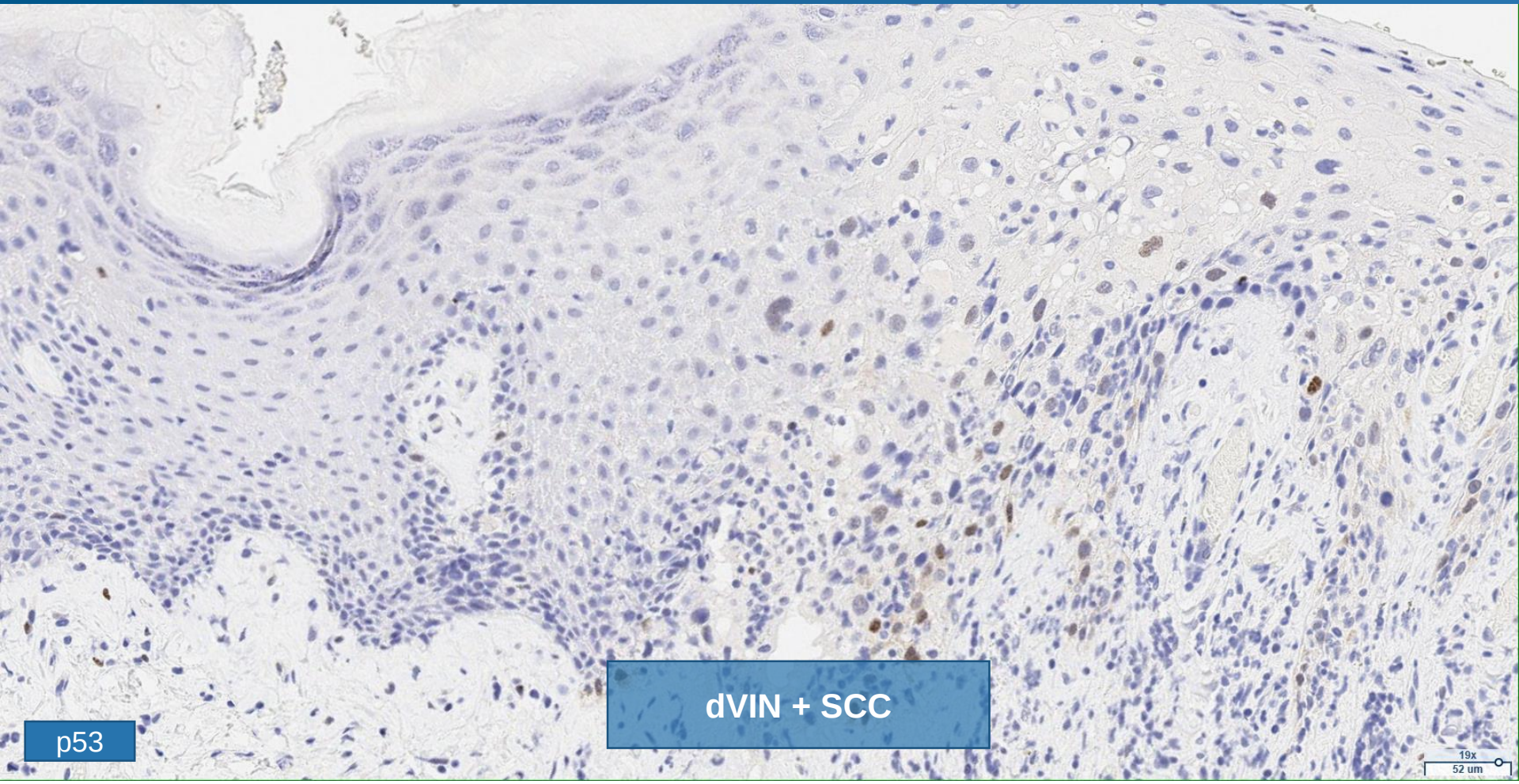


Courtesy of Dr. Neda Moatamed

CASE 3-1



CASE 3-1



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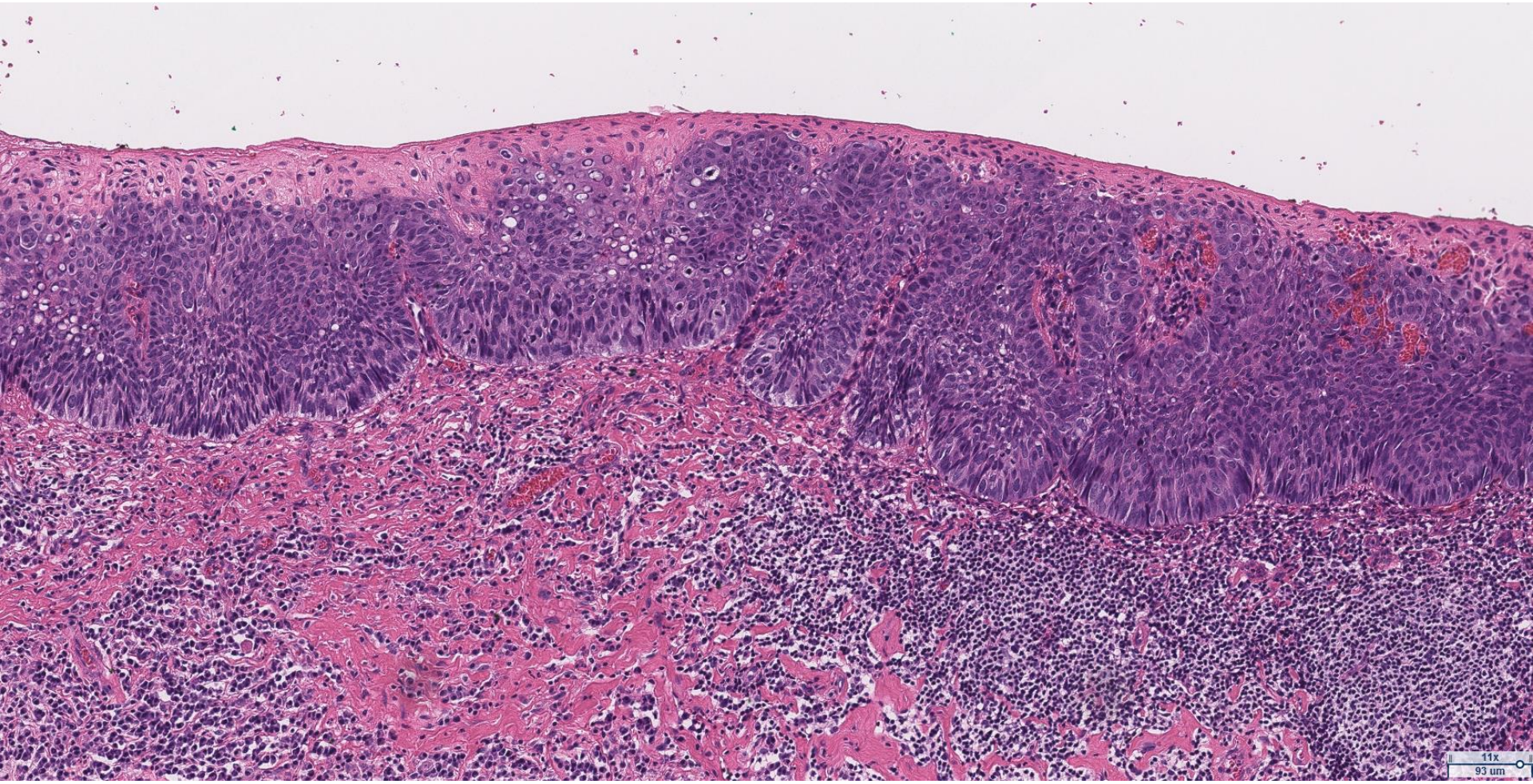
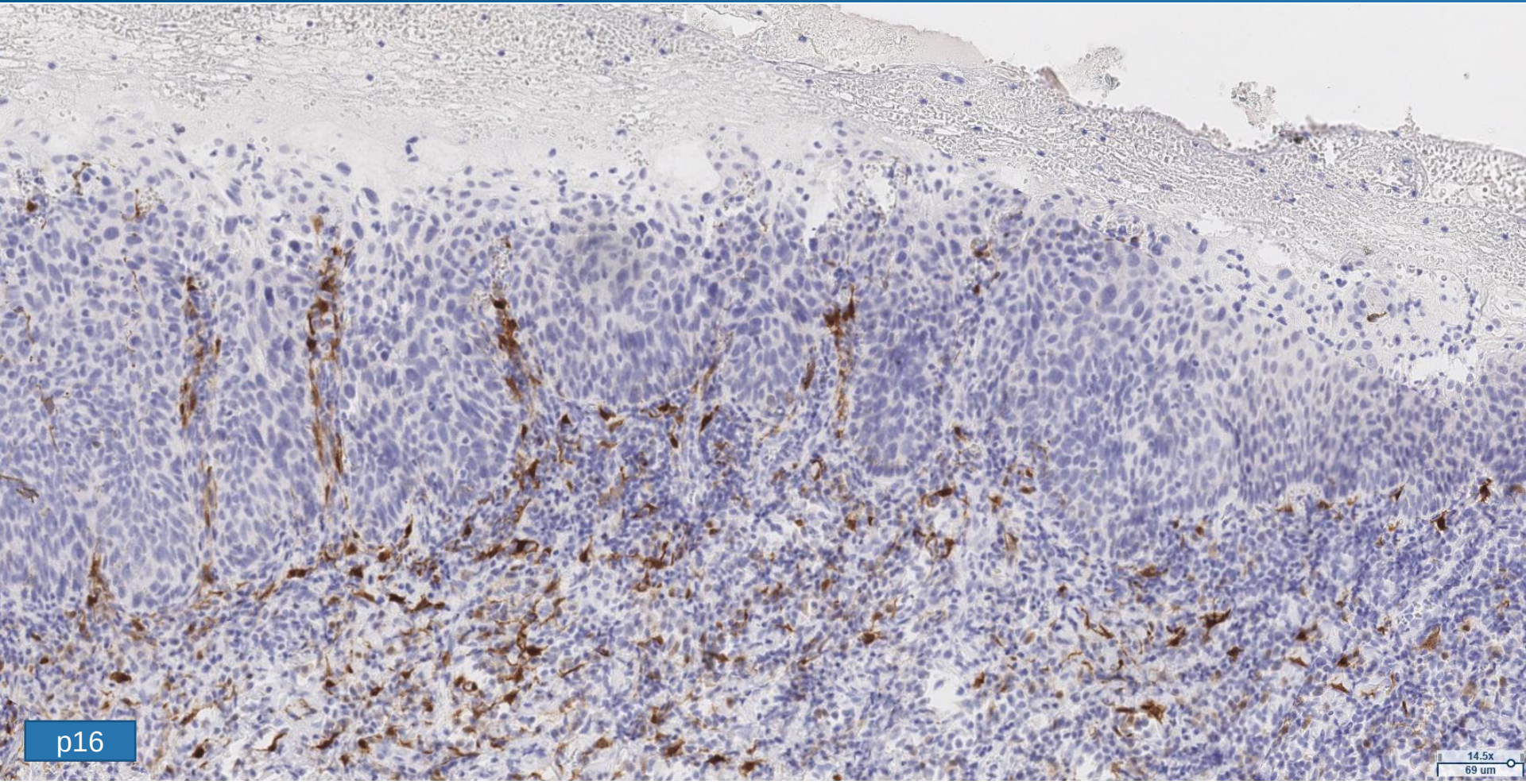
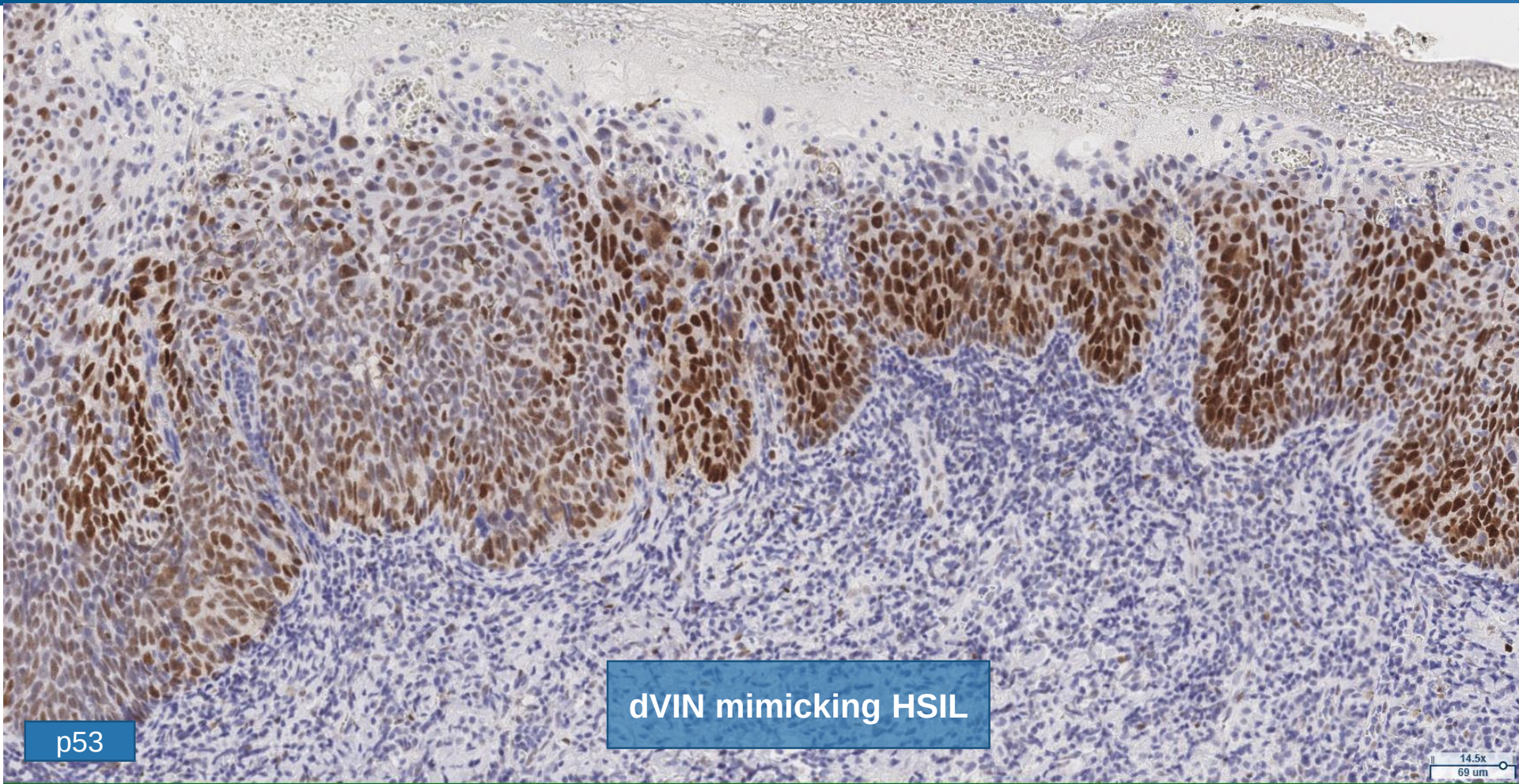
CASE 3-2: 70F, “prior history of HSIL”



CASE 3-2



CASE 3-2



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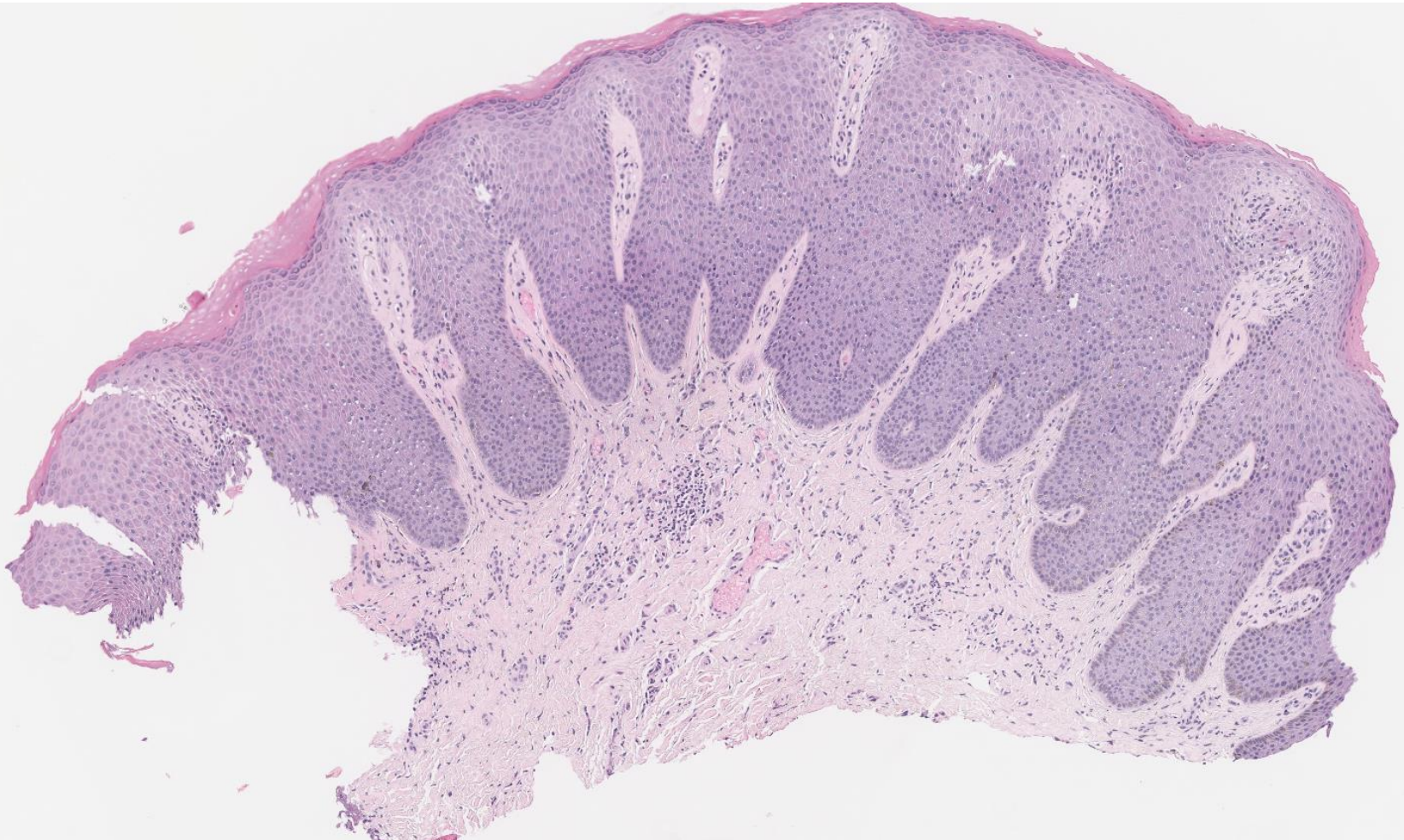
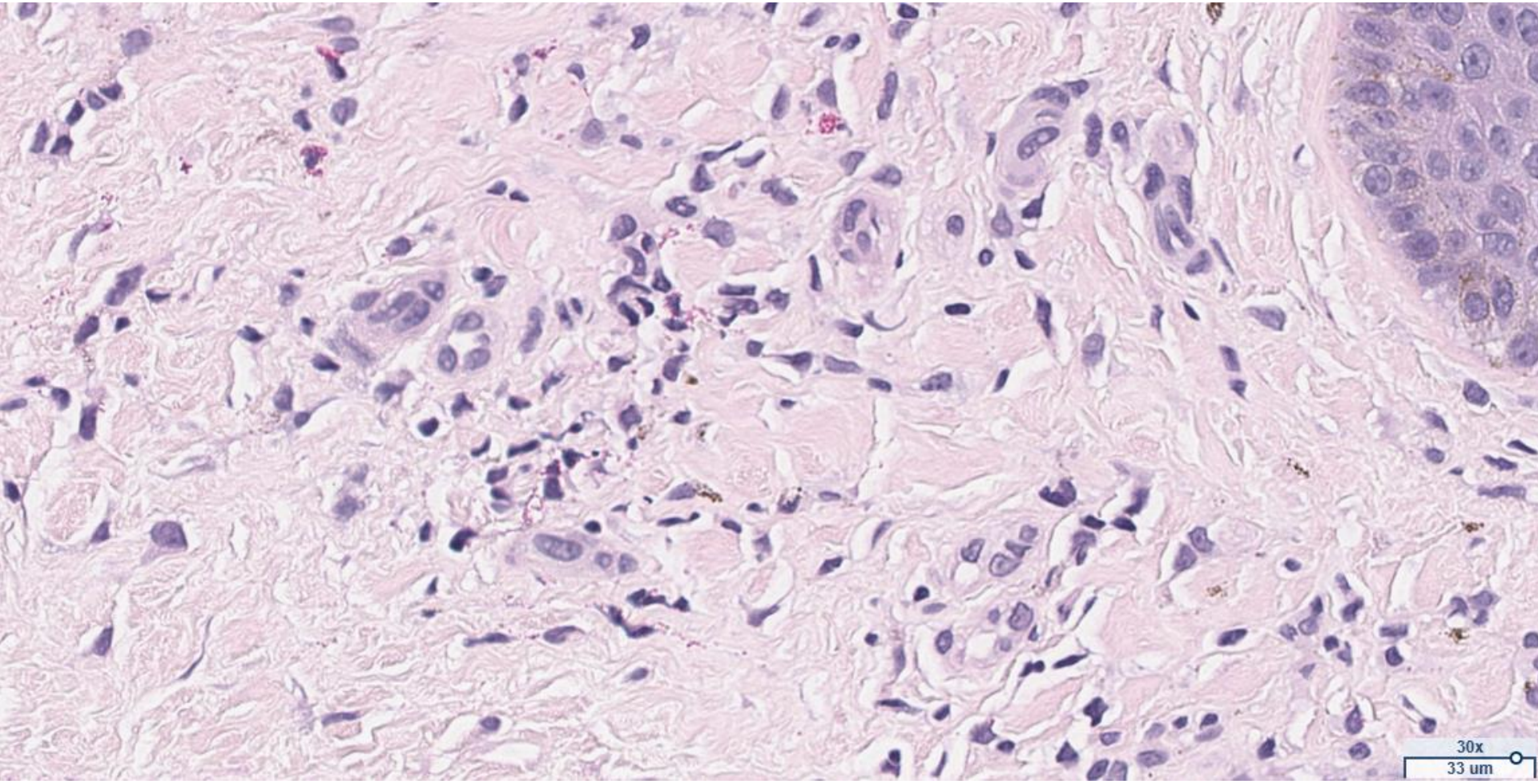
CASE 4

"37F, vulvar irritation in the R vulva and leukoplakia, labium majus biopsy"

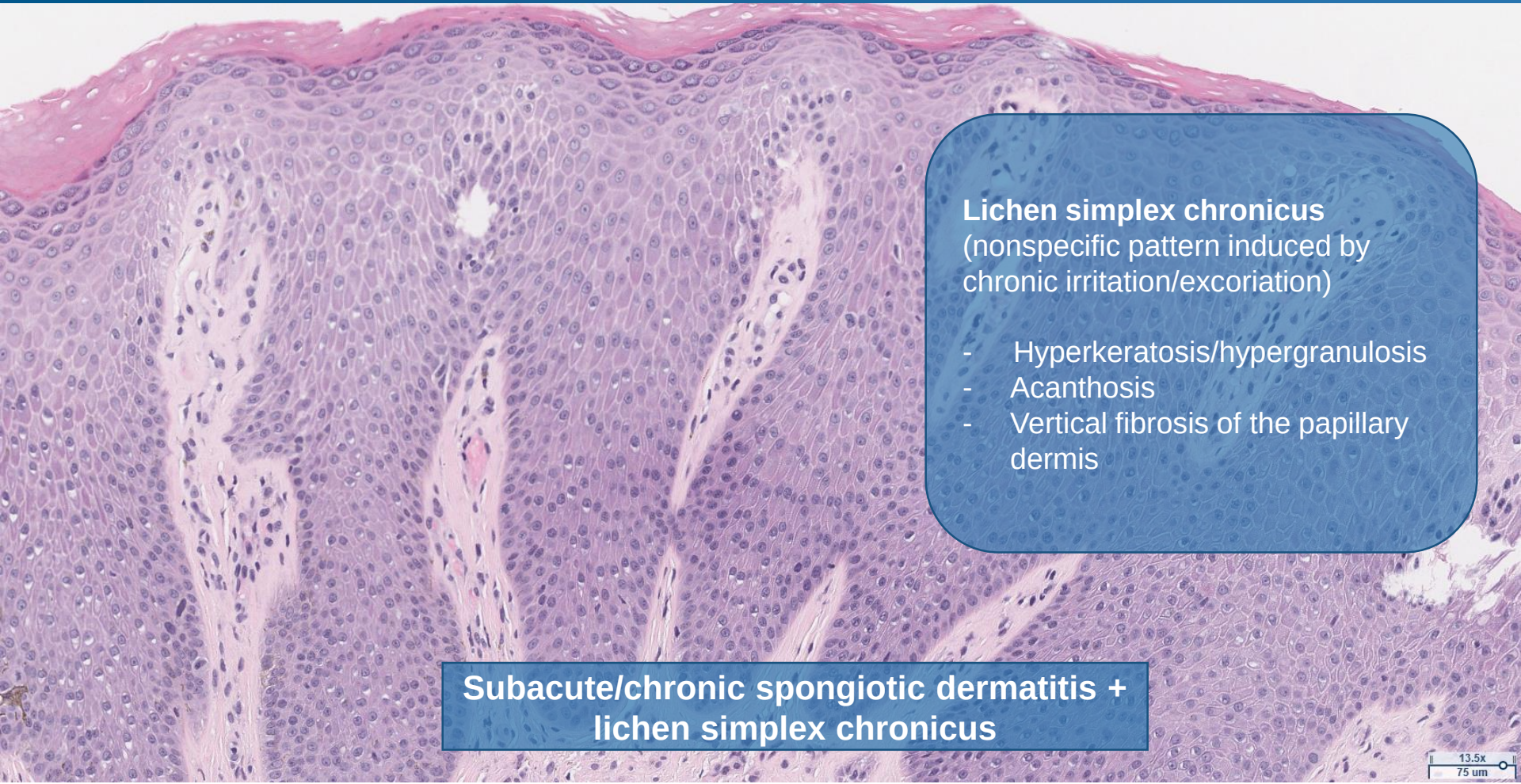
CASE 4-1



CASE 4-1



CASE 4-1

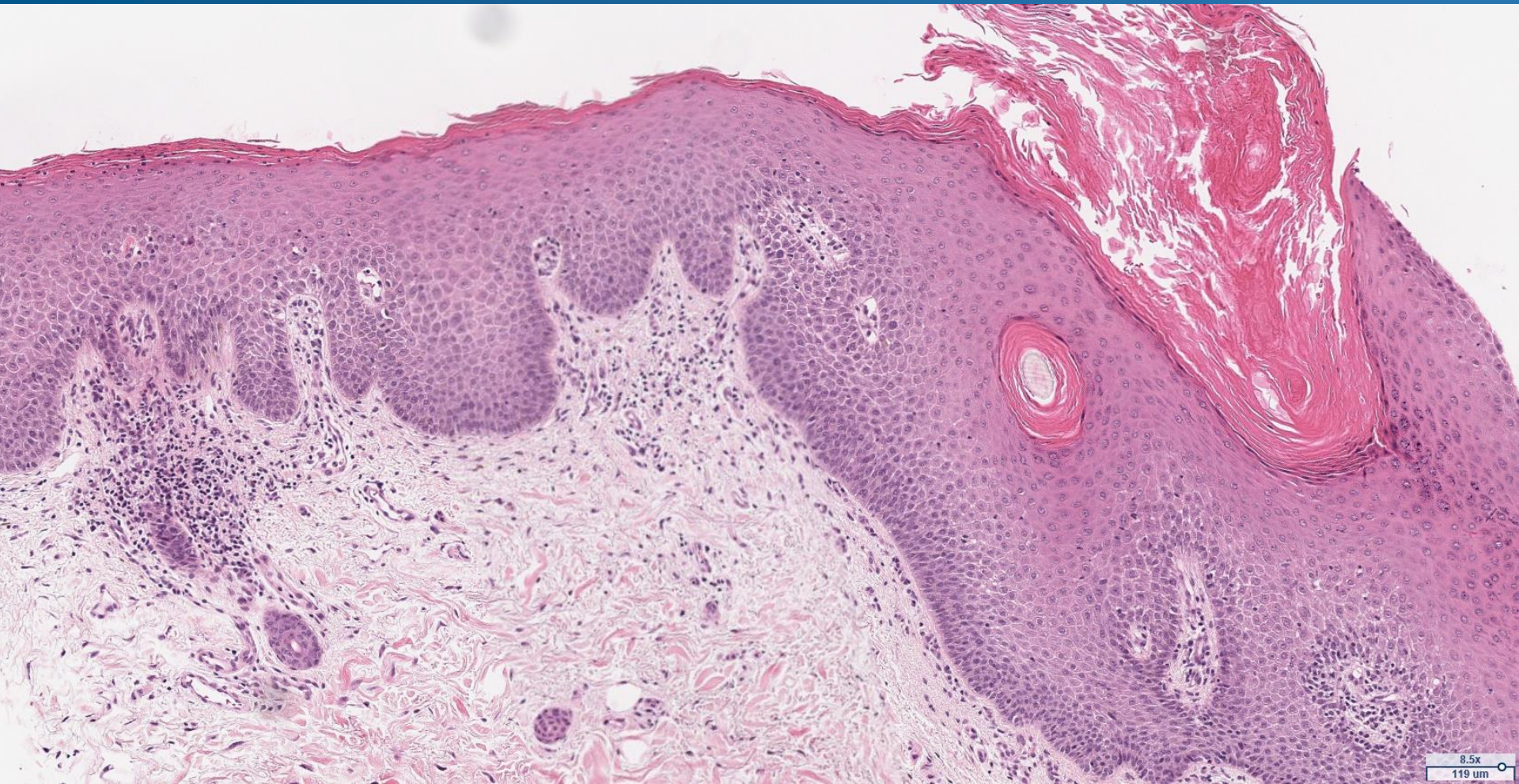


Lichen simplex chronicus
(nonspecific pattern induced by chronic irritation/excoriation)

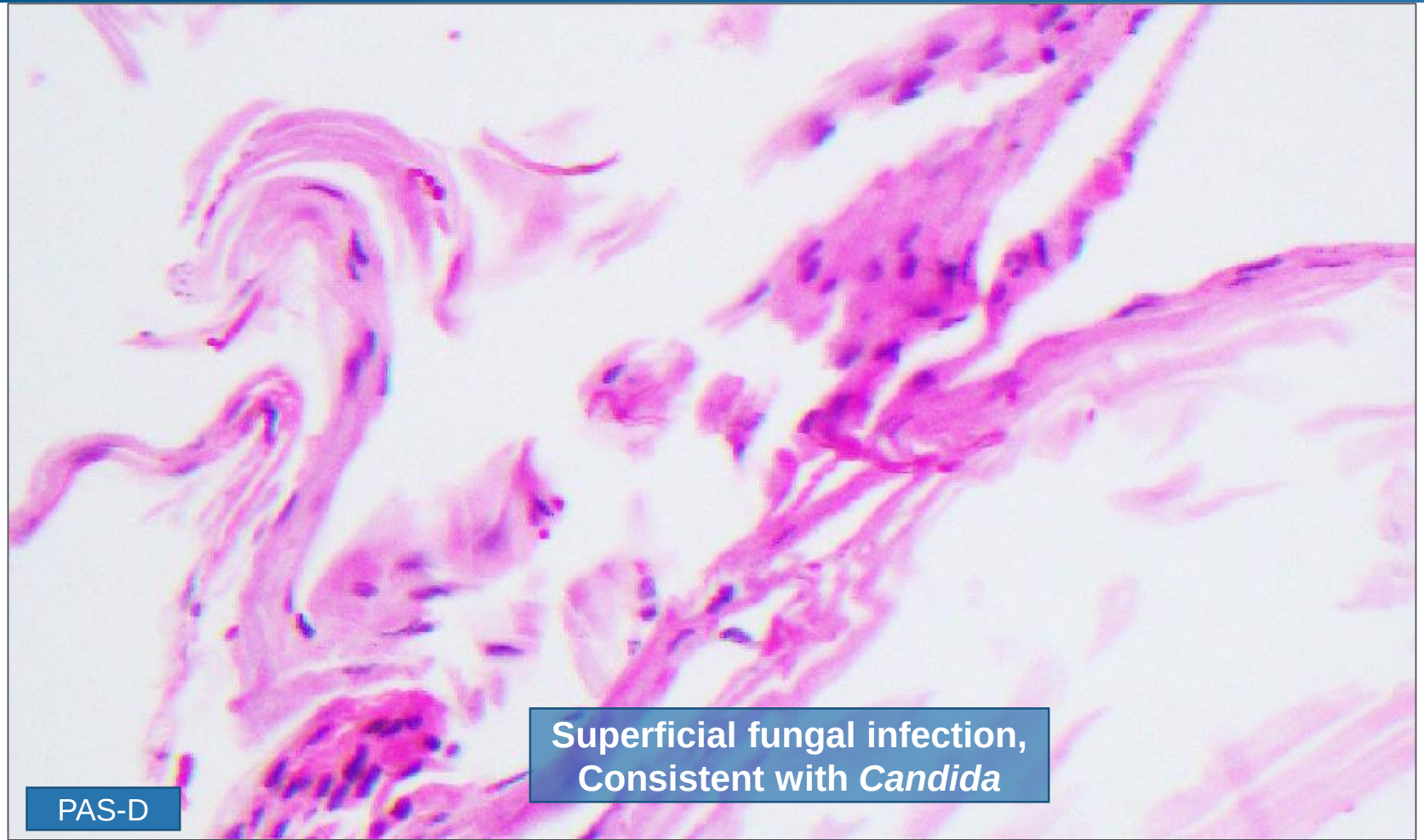
- Hyperkeratosis/hypergranulosis
- Acanthosis
- Vertical fibrosis of the papillary dermis

Subacute/chronic spongiotic dermatitis + lichen simplex chronicus

CASE 4-2



CASE 4-2


Superficial fungal infection,
Consistent with *Candida*
PAS-D

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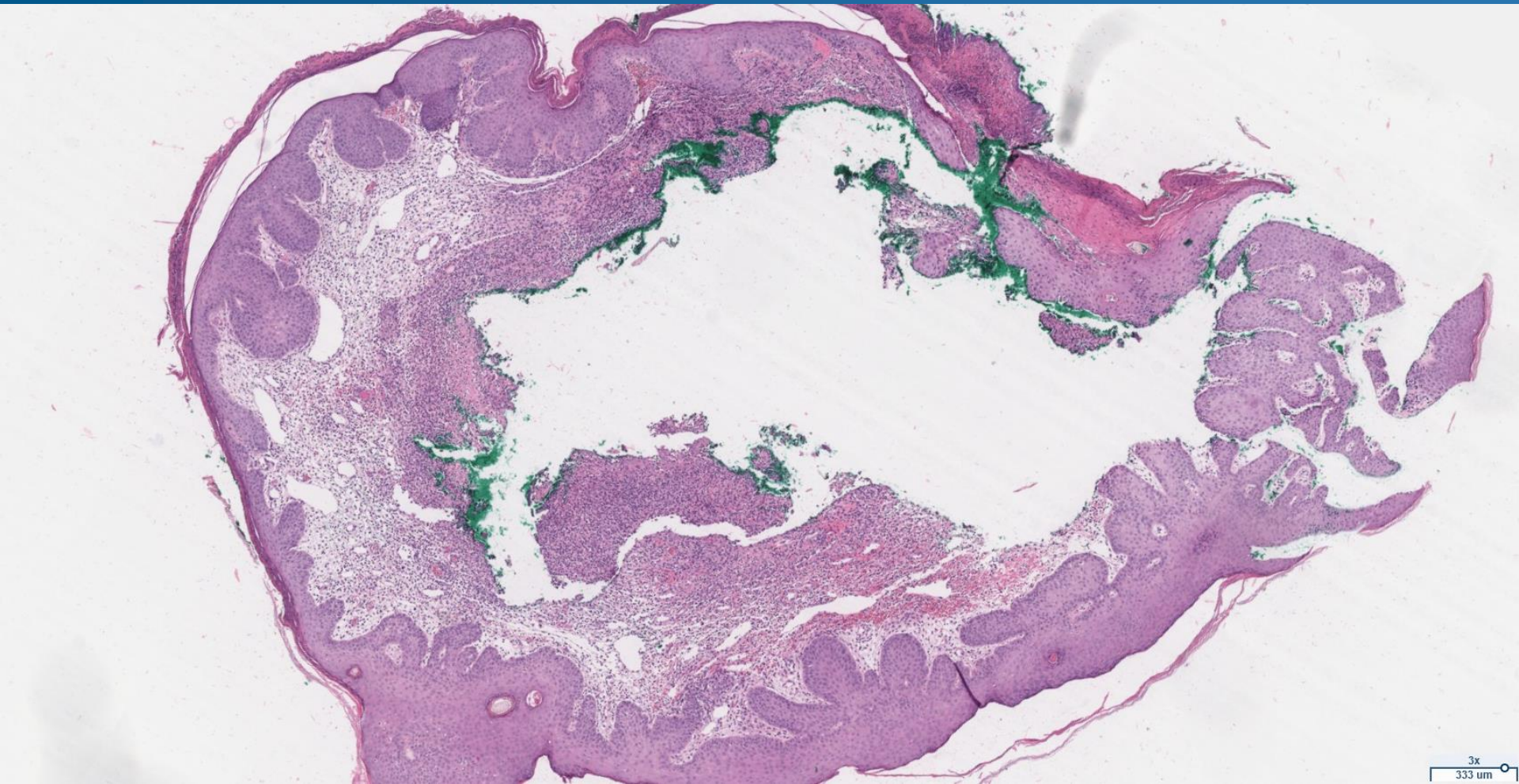
CASE 5

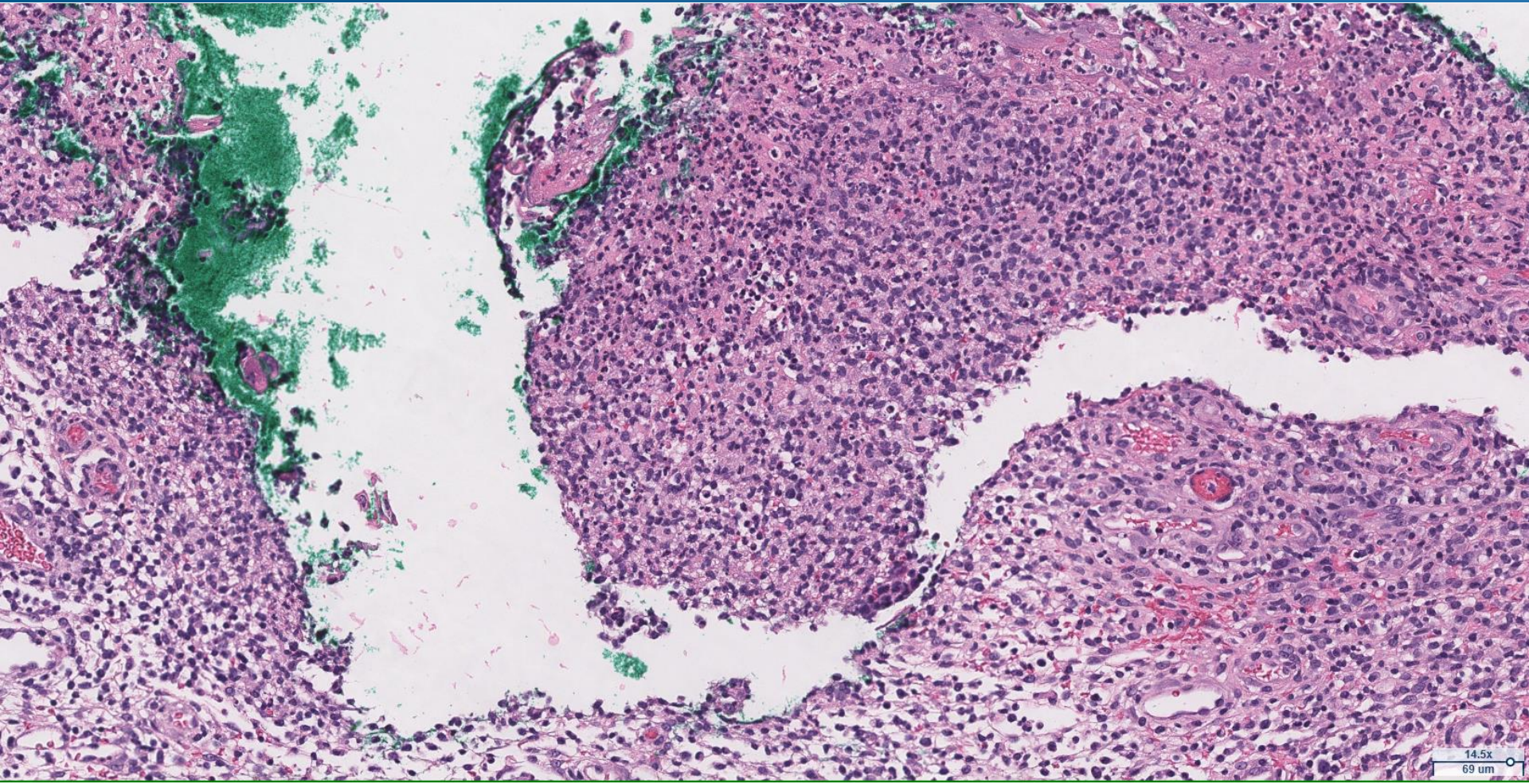
48F, newly found raised area in vulva, rule out wart

(Mimics of condylomas)

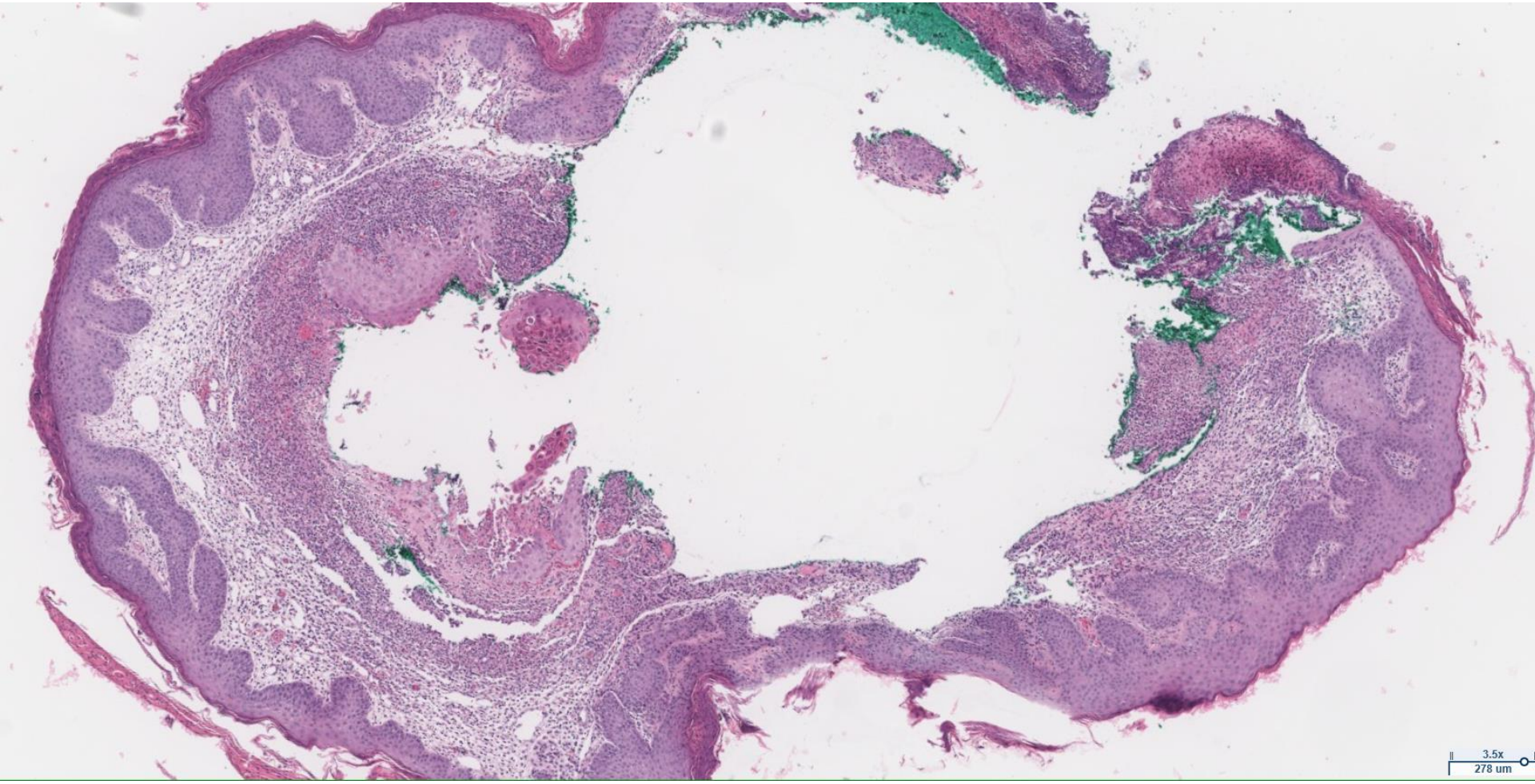
CASE 5-1



CASE 5-1

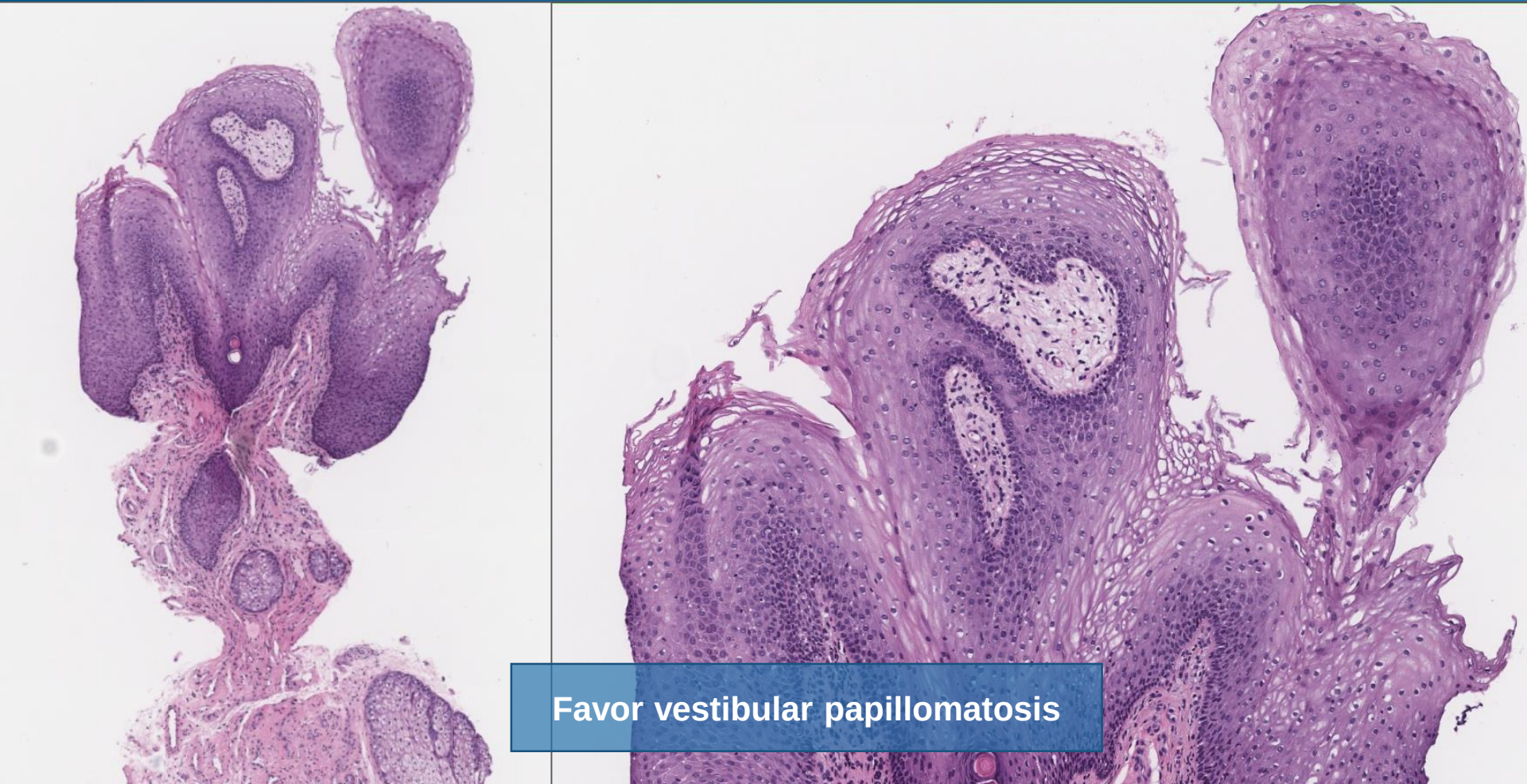


CASE 5-1



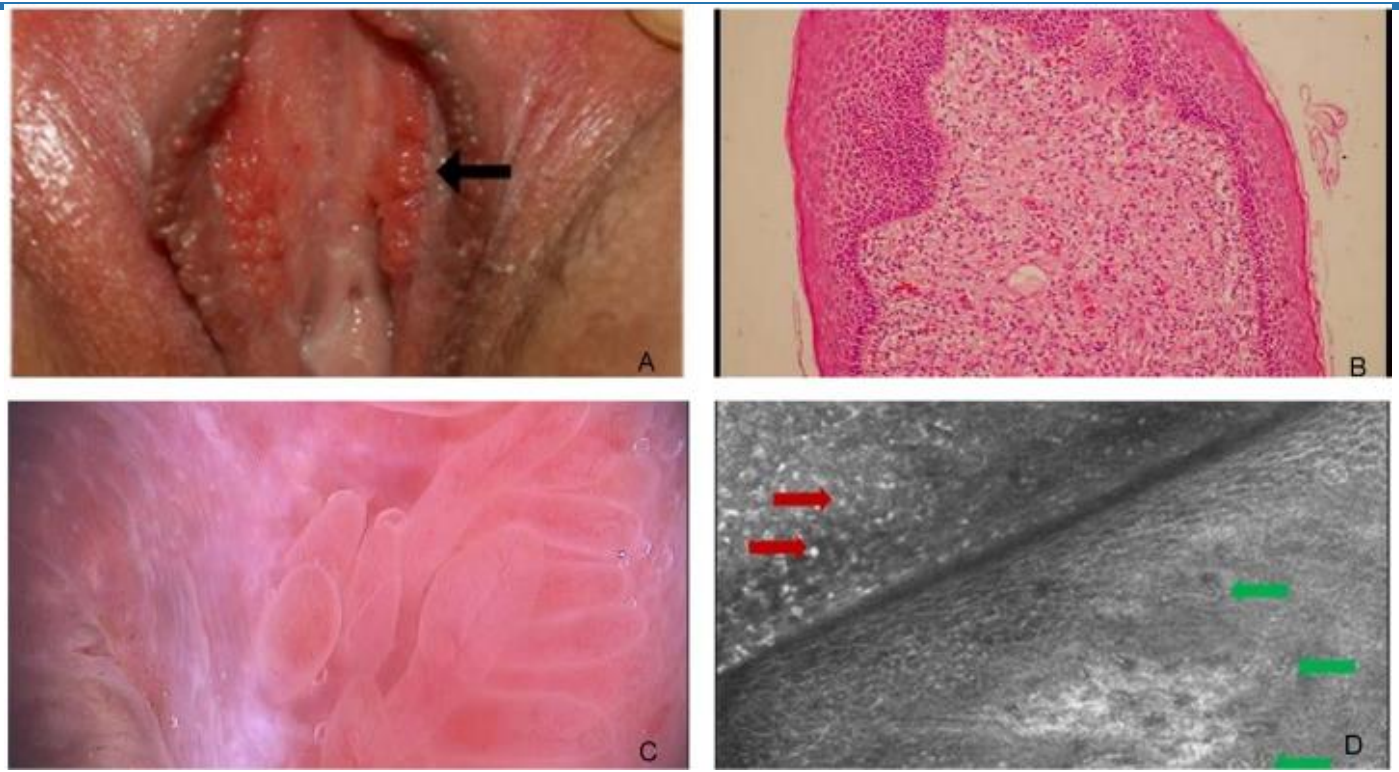

Molluscum contagiosum
12.5x
79 um

CASE 5-2: Labia minora/vestibular polypoid lesion concerning for wart



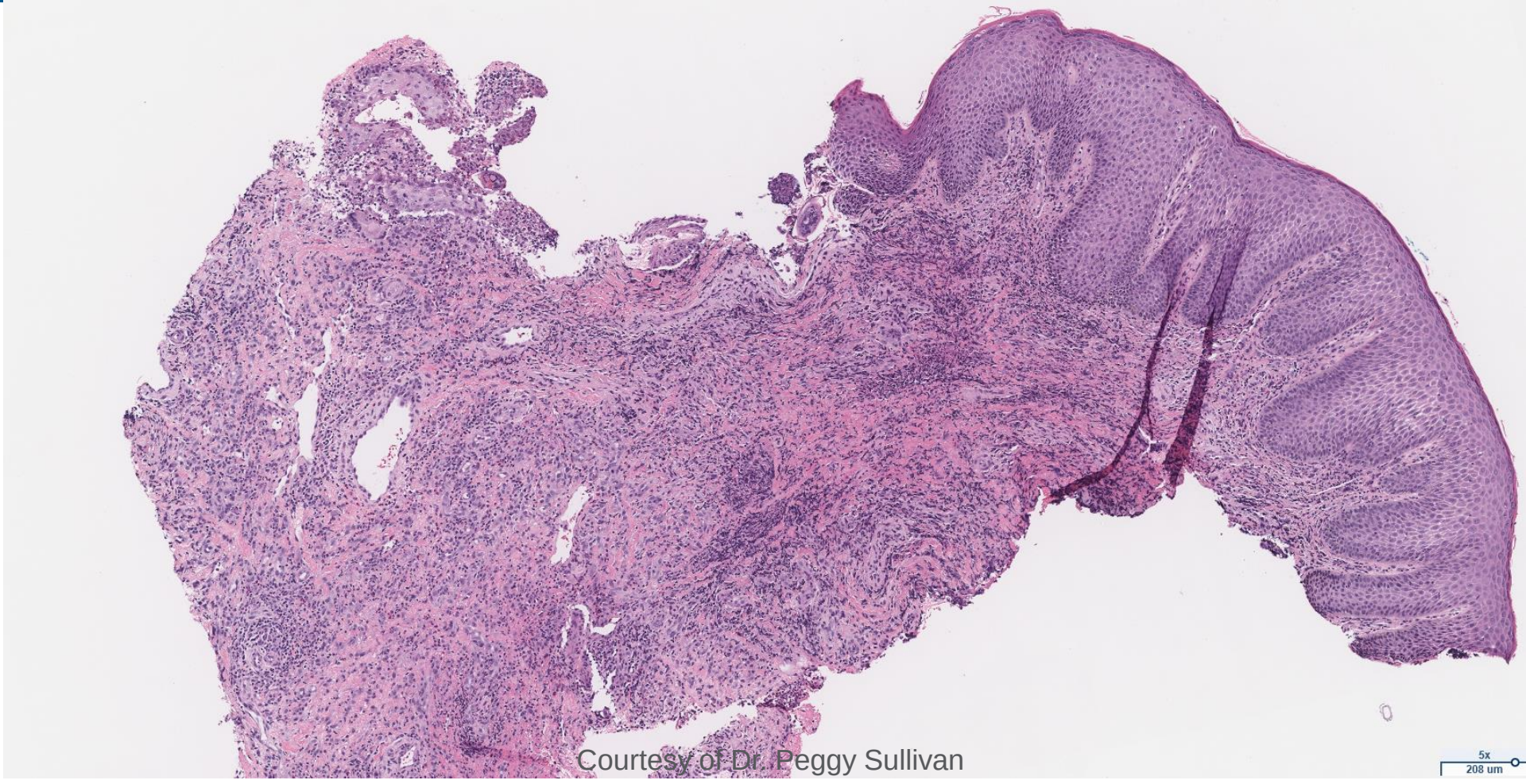
Favor vestibular papillomatosis

Vestibular papillomatosis



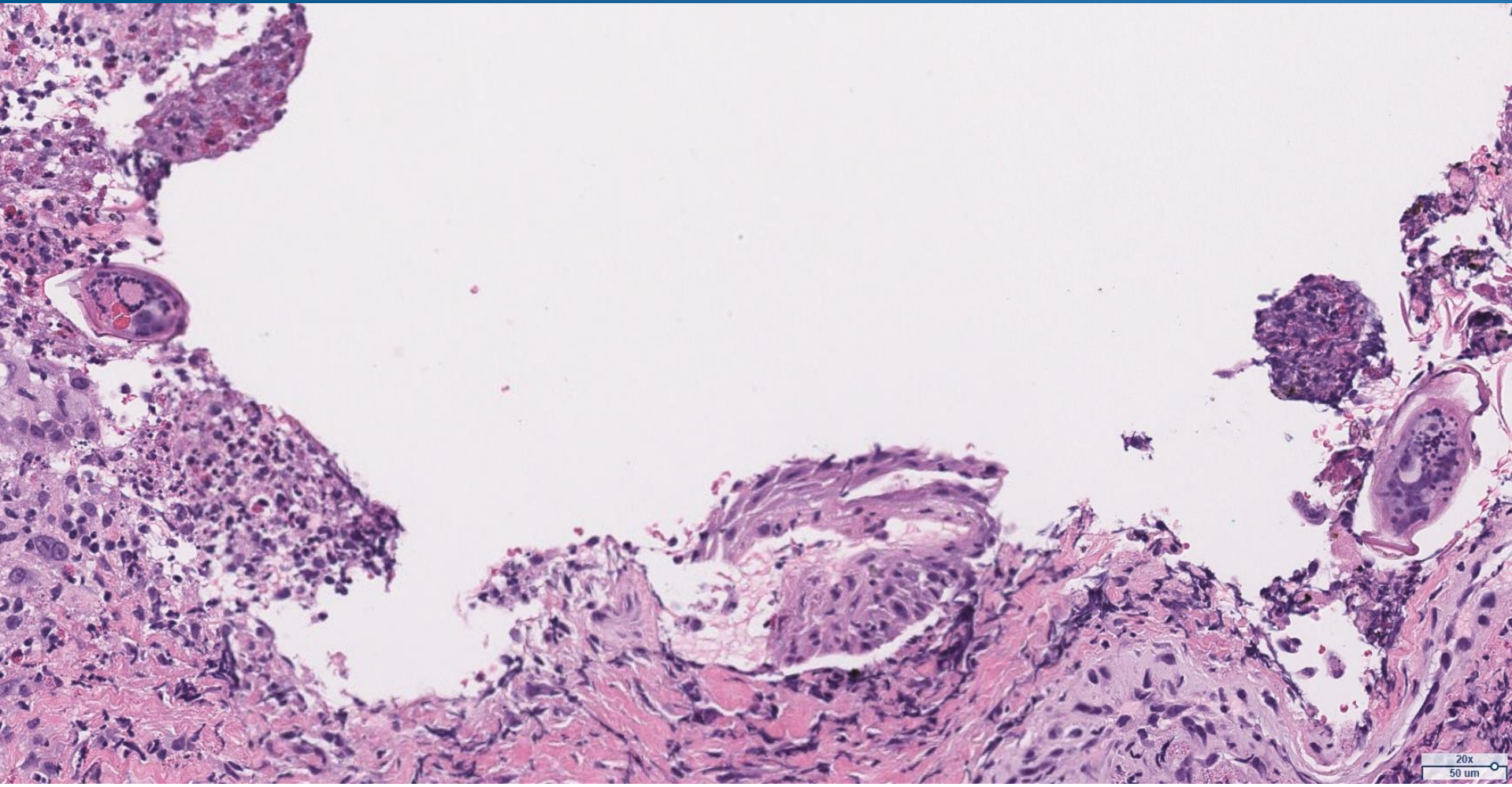
Ozkur, E., Falay, T., Turgut Erdemir, A. V., Gurel, M. S., & Leblebici, C. (2016). Vestibular papillomatosis: An important differential diagnosis of vulvar papillomas. Dermatology online journal, 22(3) November 17, 2020

CASE 5-3: 2 cm wart?

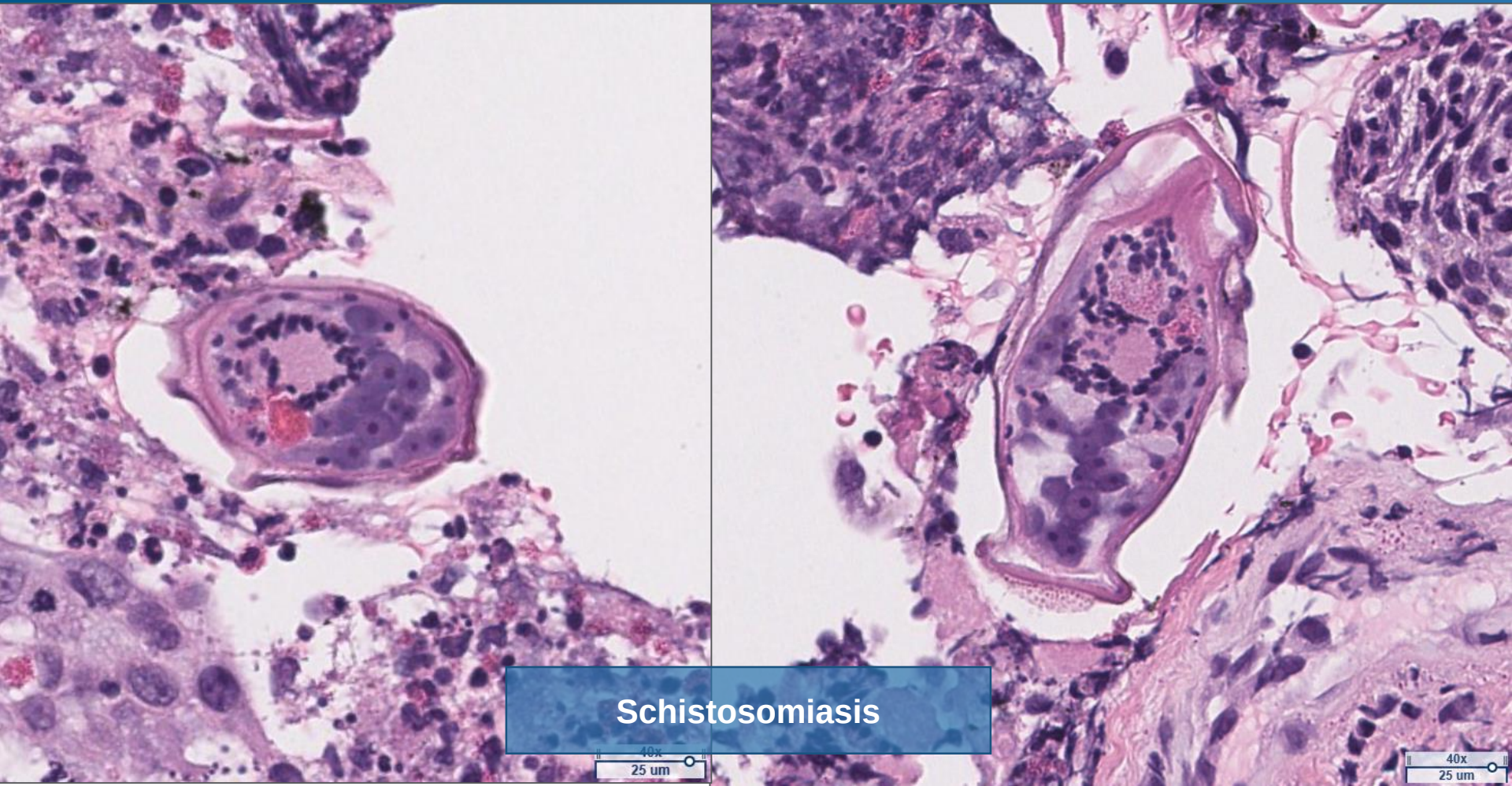


Courtesy of Dr. Peggy Sullivan

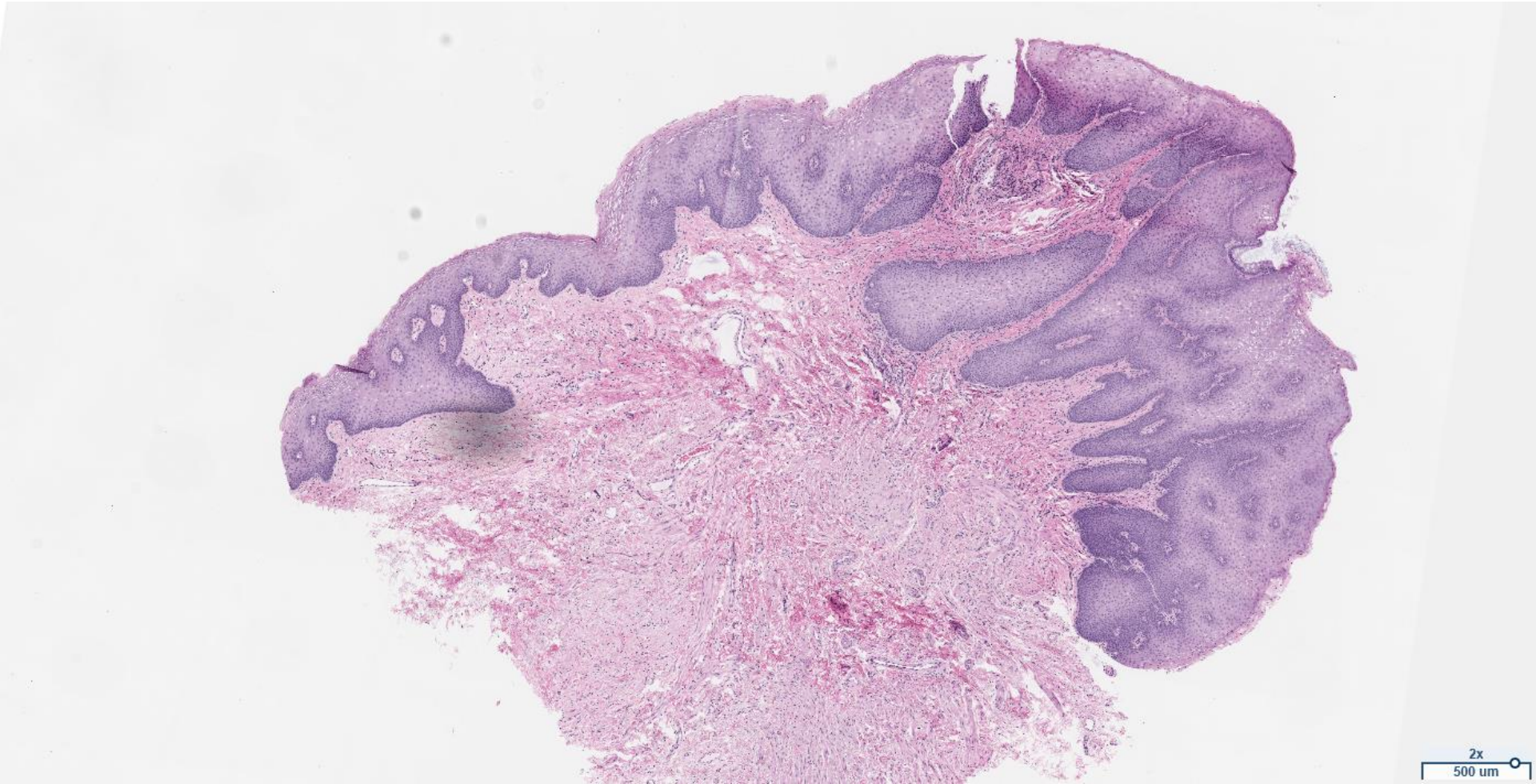
CASE 5-3



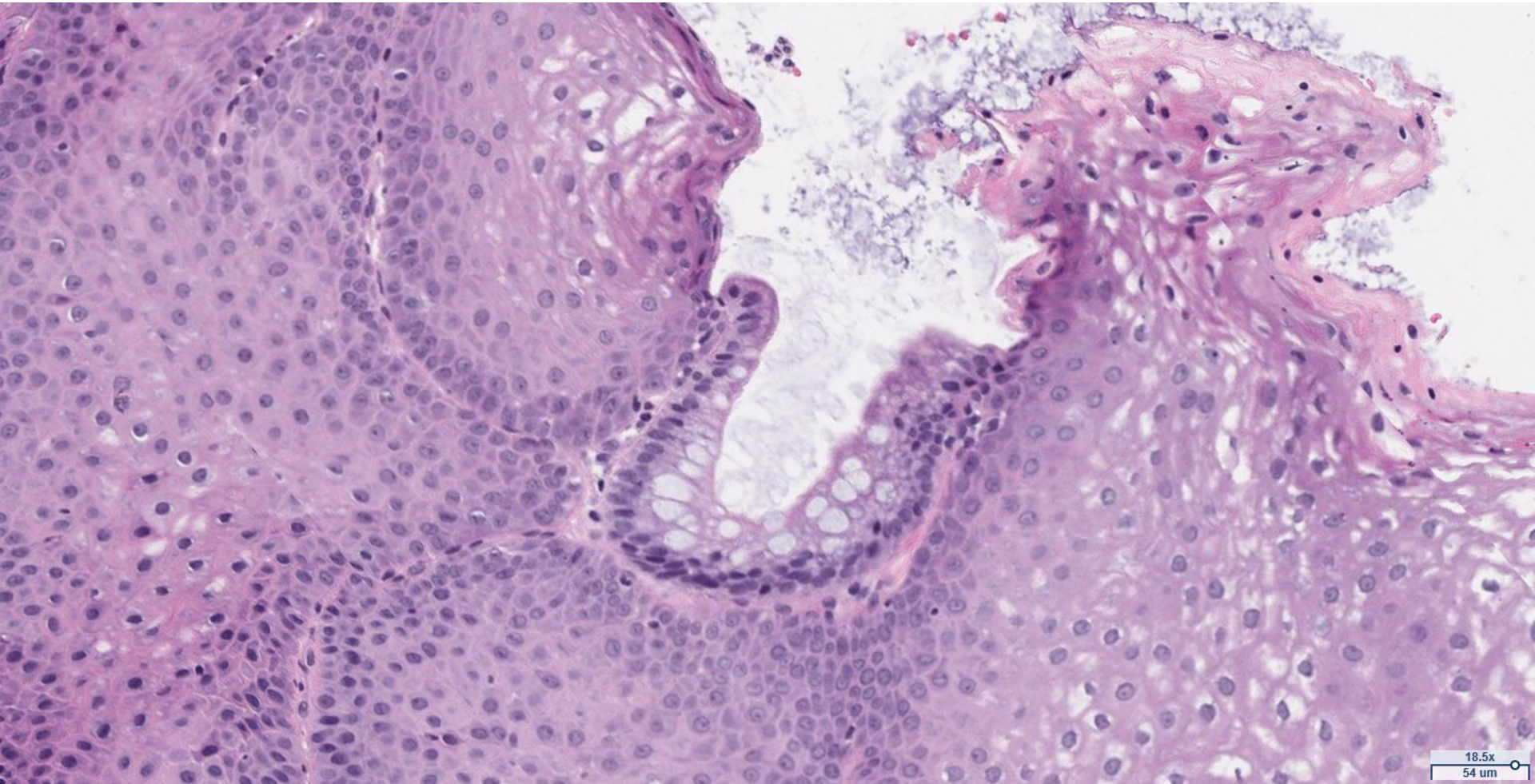
CASE 5-3



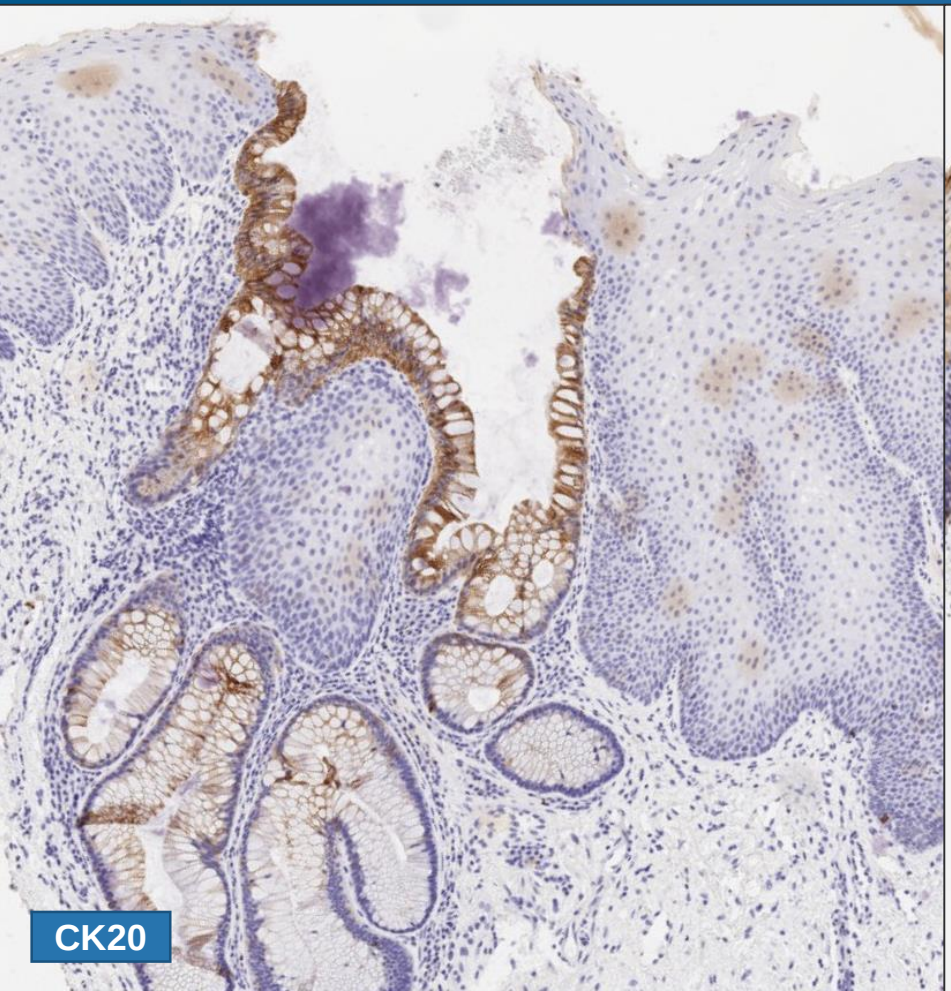
CASE 5-4

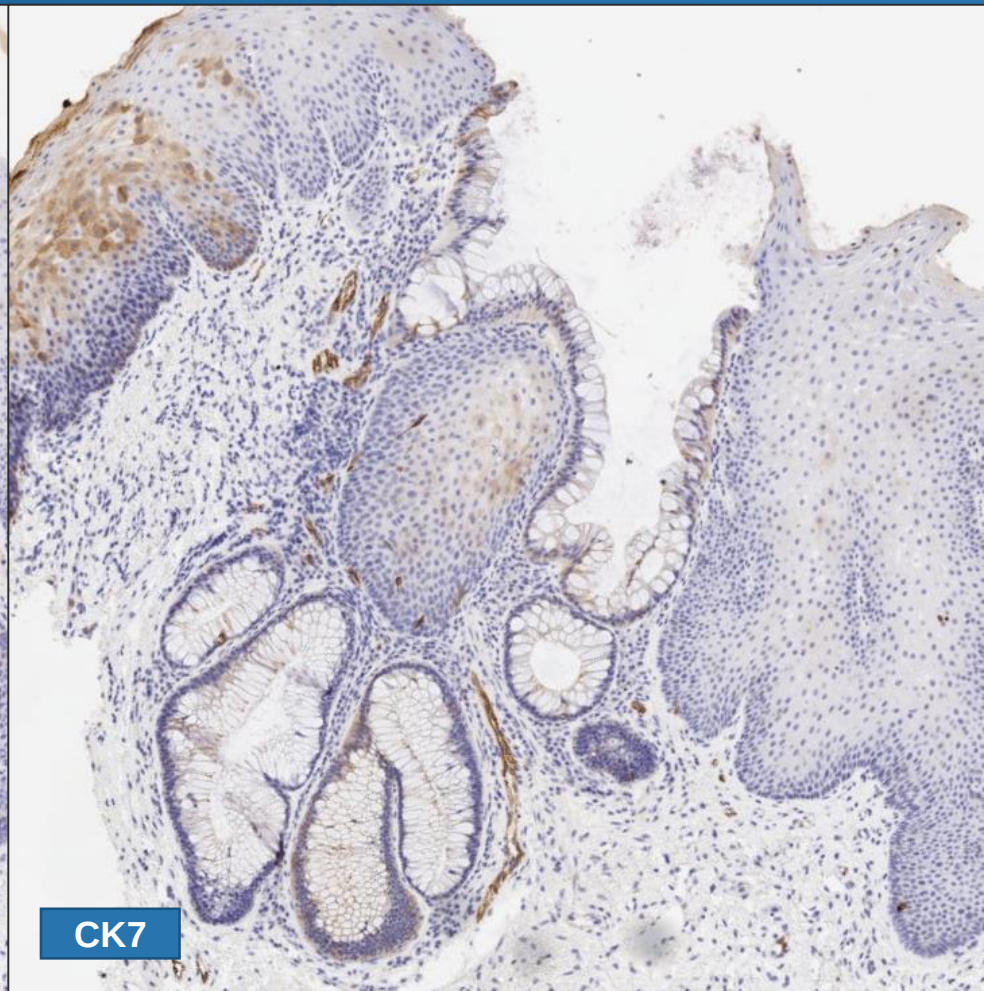


CASE 5-4

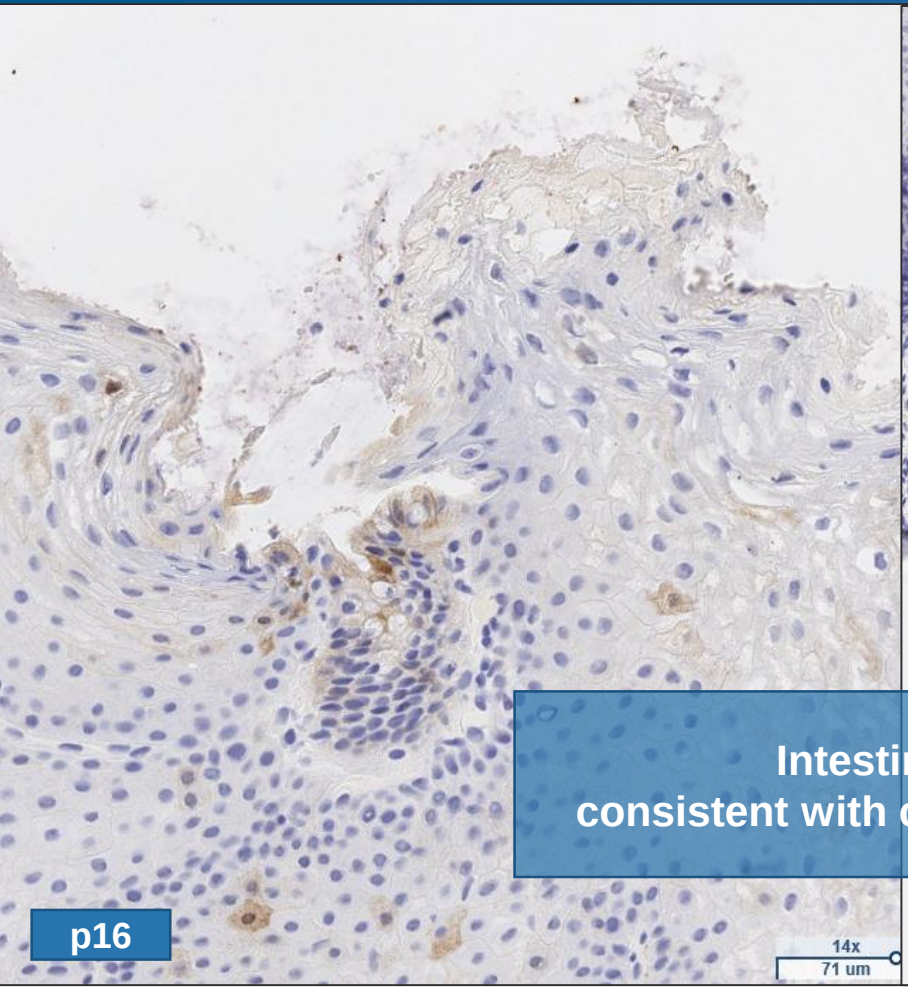


CASE 5-4

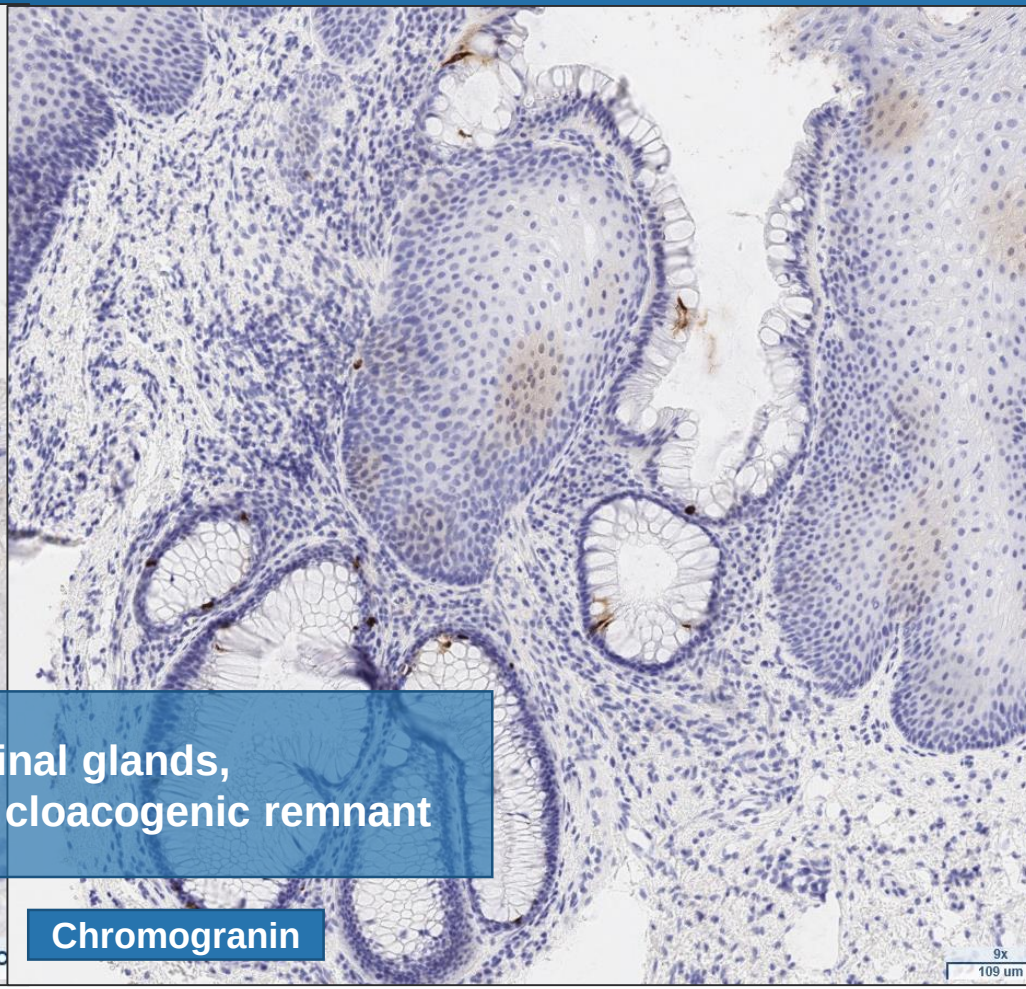




CASE 5-4



p16



Chromogranin

Intestinal glands,
consistent with cloacogenic remnant

Take home points

1) Clinical correlation is important—dig into the chart and lab values.
2) Run through the questions of all of the possibilities before signing out the case (Neoplastic? Infection/infestation? Can it be LS, if not, then what?).
3) If you can't get to a specific diagnosis, it's okay to have a differential and have the clinician follow the patient.
4) Early LS can have nonspecific findings—look for thickened basement membrane, follicular changes.
5) When things are equivocal, get level sections, as the answer may be deeper in the block.

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Thank You

for your time and attention

& to the faculty and trainees at UCLA Pathology


Questions?
Please email me with any questions/comments:
[yunakang@mednet.ucla.edu]