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Small Bites and Small Sites: Big Gastrointestinal Pathology Diagnostic Problems

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Wei Chen, MD, PhD, FCAP
Joseph Misdraji, MD

We will use Live Audience Participation

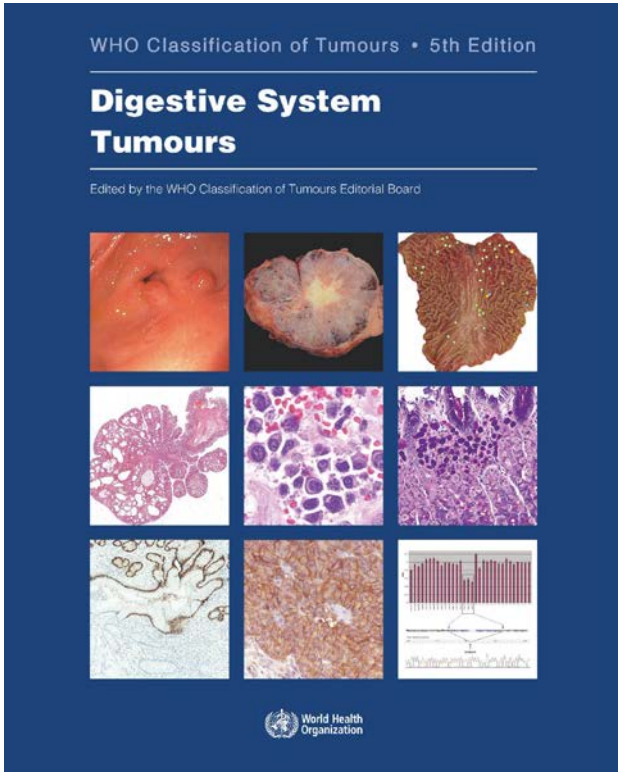
Type In Your Browser:

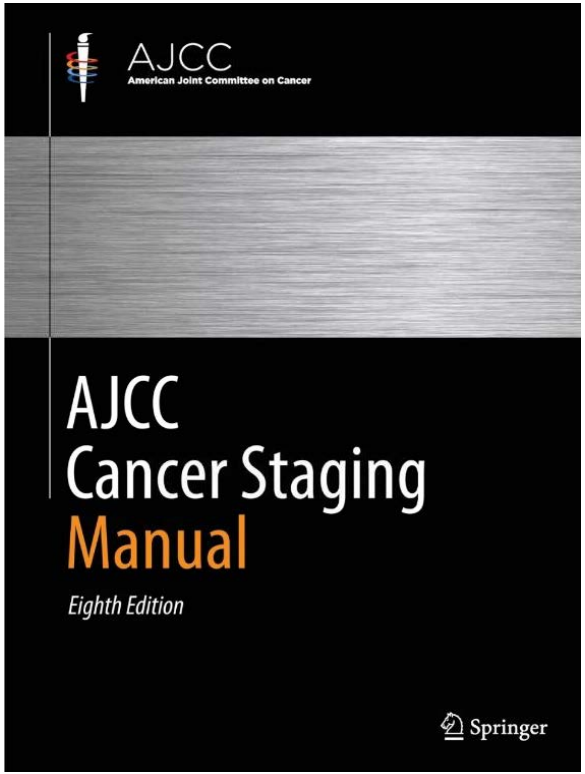
pollev.com/cap153

Objectives

- To understand the criteria for classifying squamous dysplasia in the anus.
- To effectively navigate pitfalls in evaluating ampullary specimens.
- To be aware of recent changes to the classification, nomenclature, and staging of appendiceal neoplasms.

Select Updates: *Reader's Digest Style*





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Member Resources Advocacy Labor

Home > Protocols and Guidelines > Cancer Protocol Templates

Cancer Protocol Templates

In response to user and member feedback, the CAP has moved to a Cancer Protocols. If there are updates, revisions, or new protocols to August schedule.

The CAP Cancer Reporting Protocols provide guidelines for collectin reporting of malignant tumors and optimal patient care.

The CAP Biomarker Reporting Protocols are intended to provide rep and are not currently required for accreditation purposes.

LAST But Not Least:
A Practical Approach to Anal Pathology

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Wexner Medical Center
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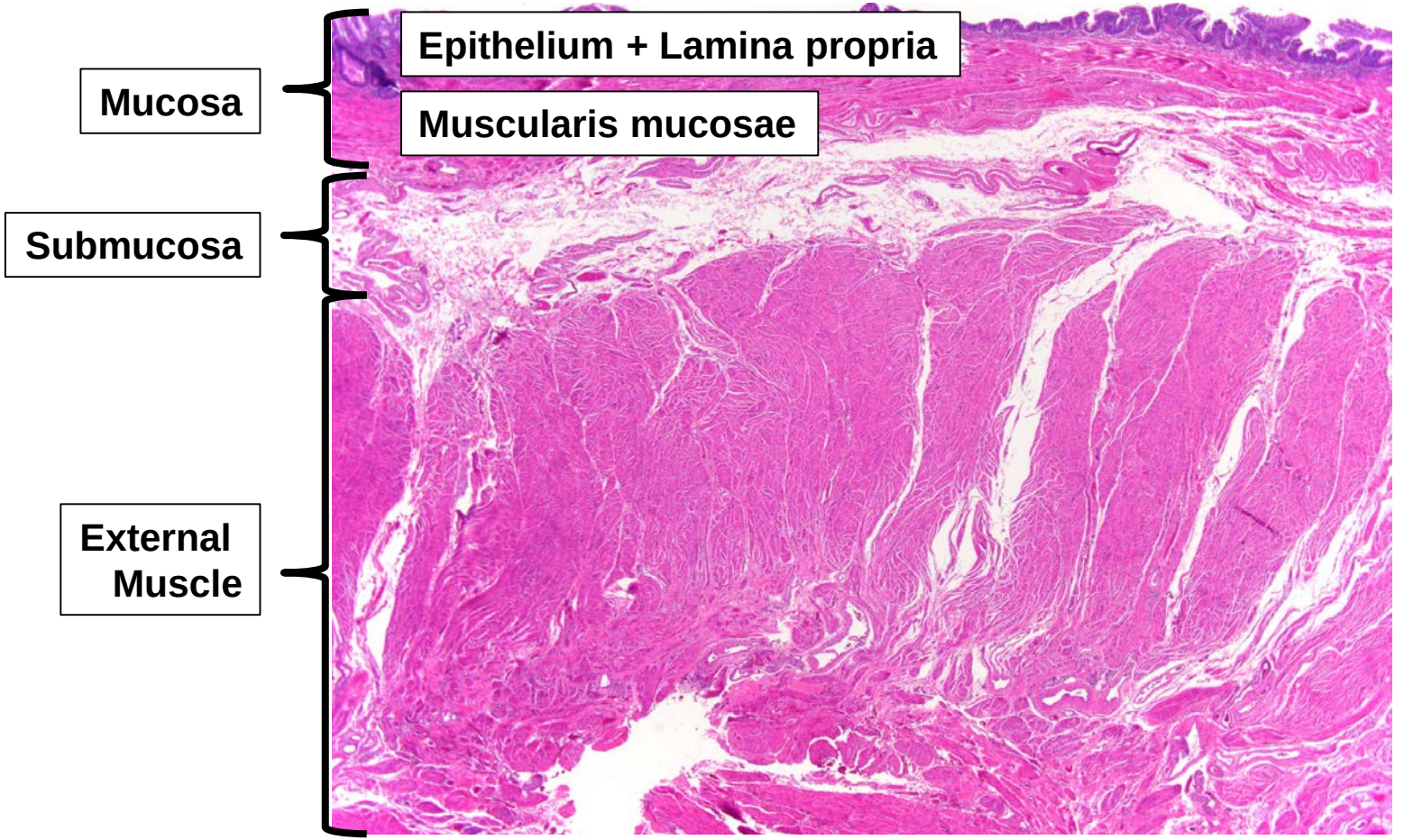
Twitter: @CArnold_GI

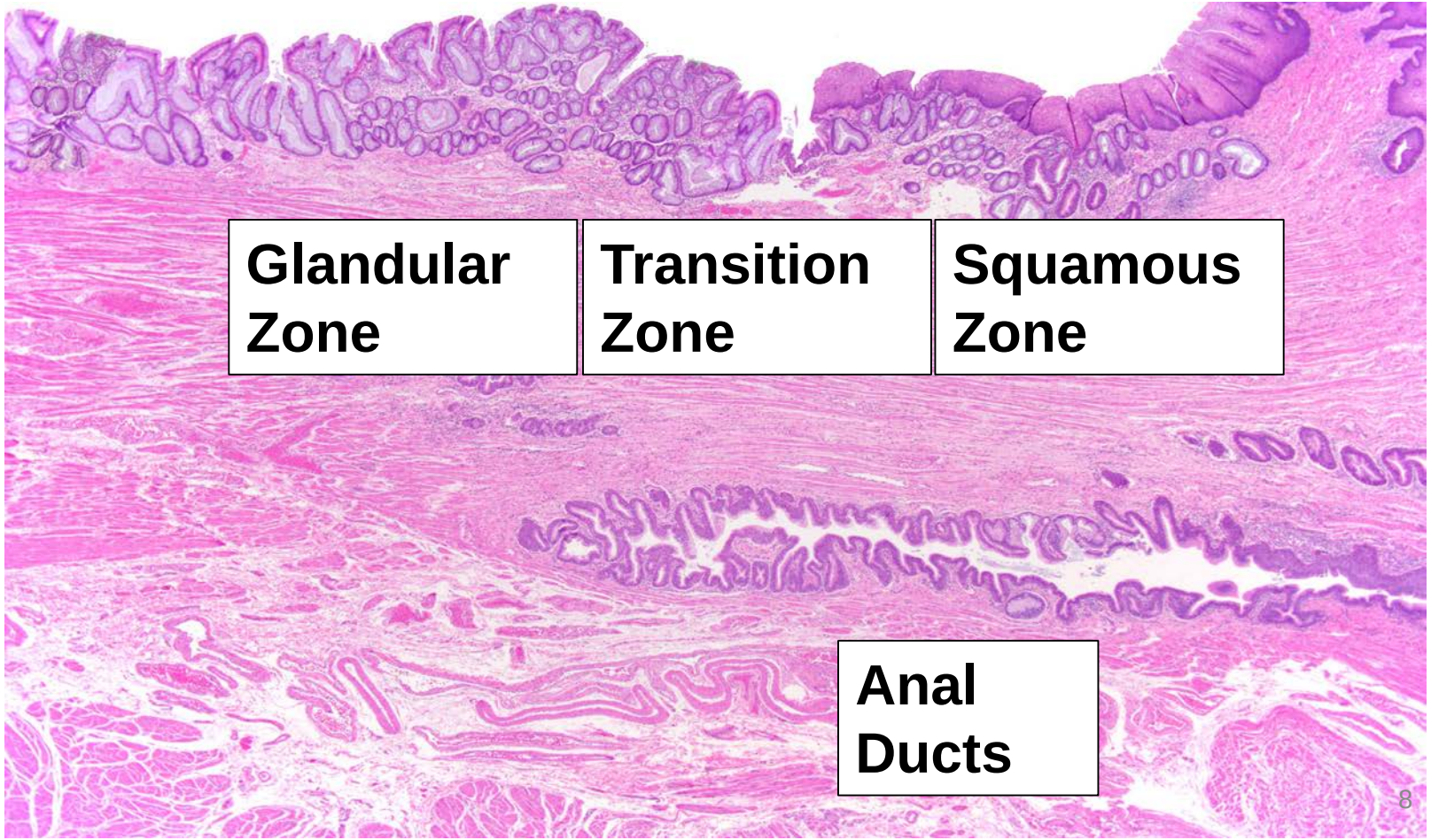
Overview

- Normal
- HPV-Related Lesions
- Extra-Mammary Paget Disease
- Melanoma
- Thrilling Cases

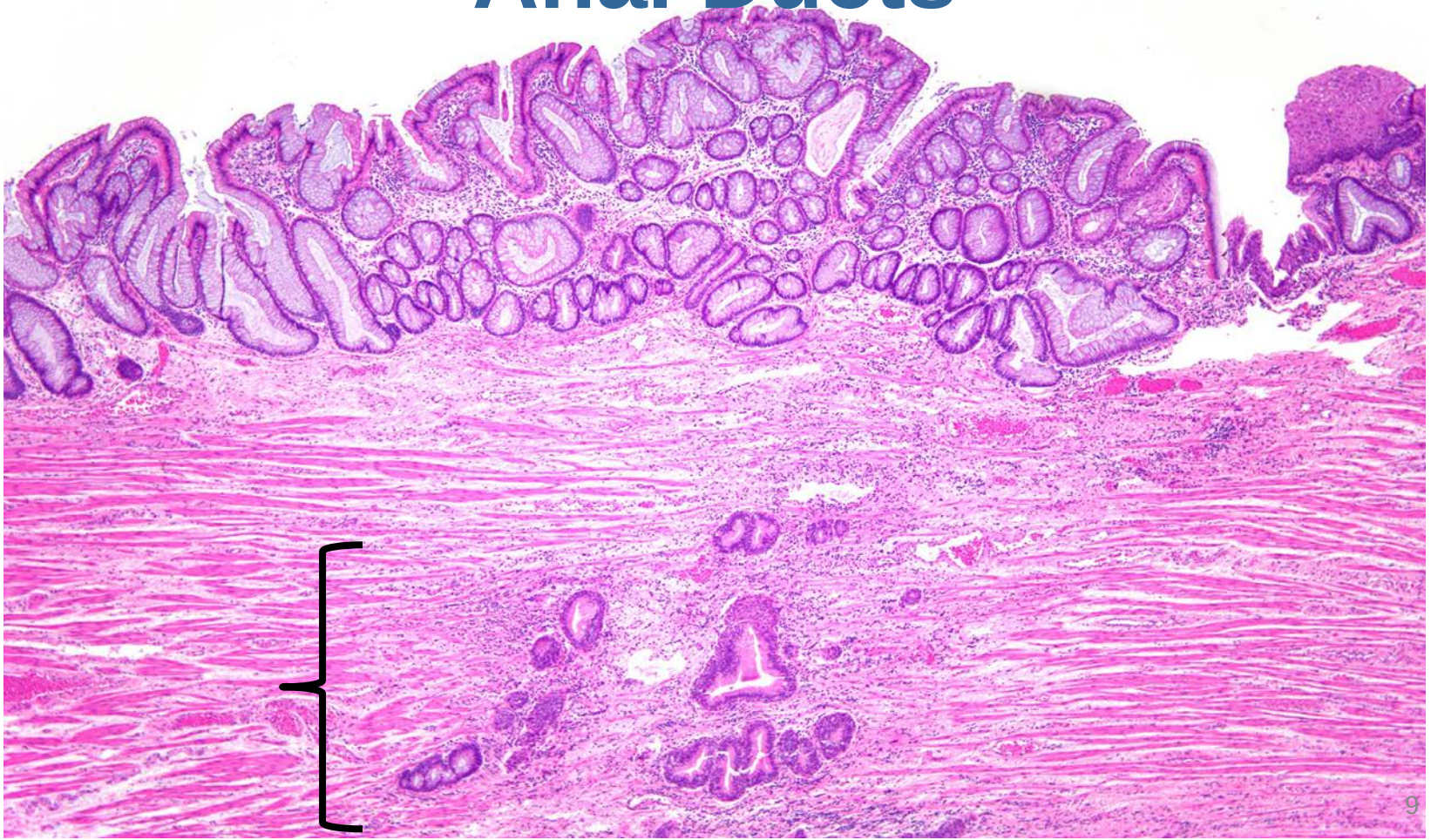
Anus Micro-Anatomy: *3 Layers*



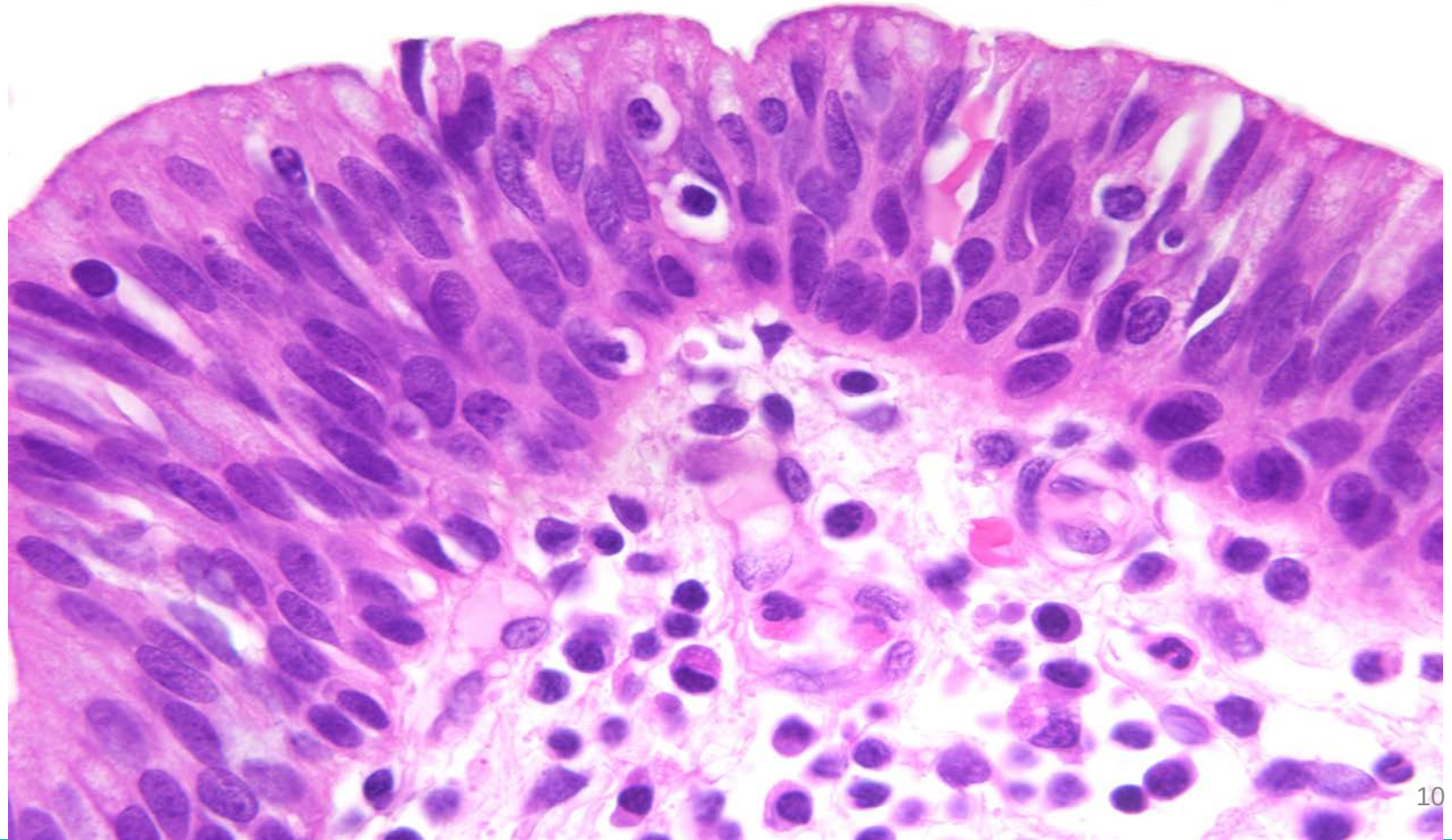
Micro-Anatomy: *3 Mucosal Zones*



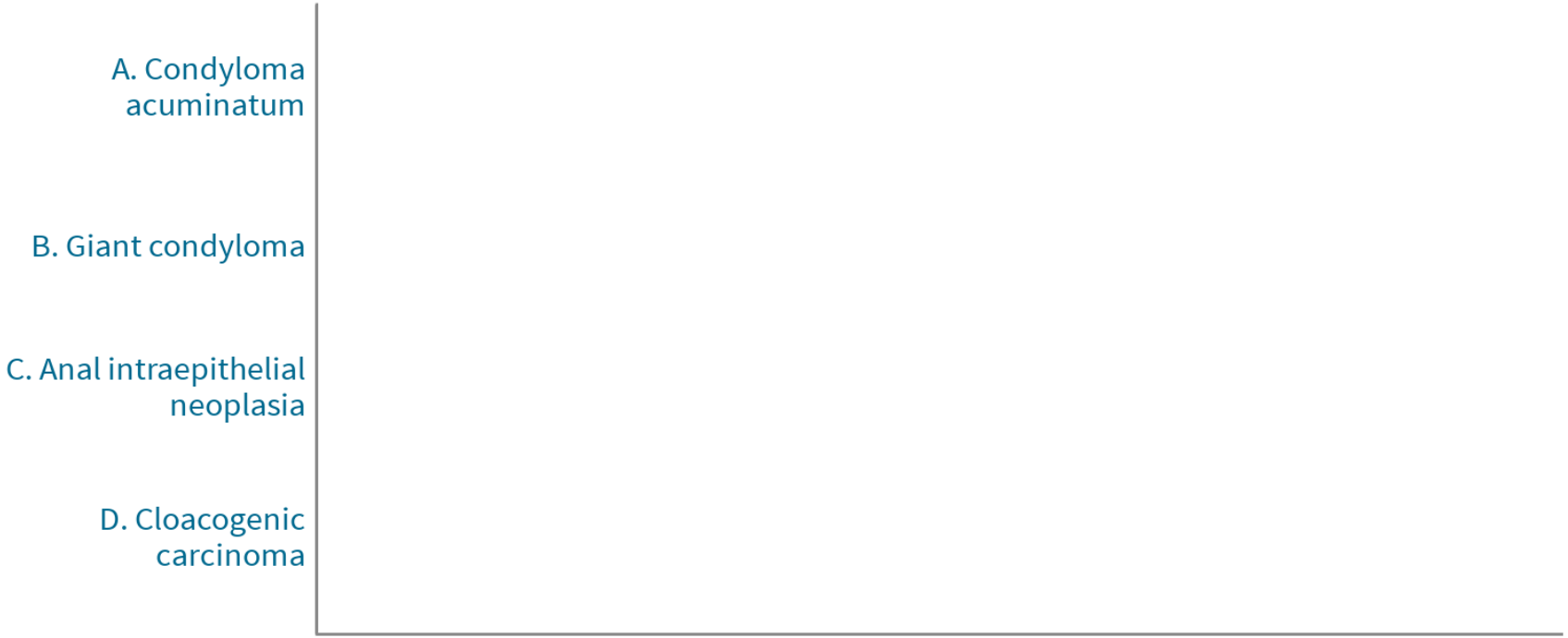
Anal Ducts



ATZ & Anal Ducts



Which of the following terms is still current in the anus?



LAST *Game-Changing* Highlights

Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions (LAST):

1. *2*-tiered system: LSIL (-IN1)v HSIL (-IN2 and –IN3)
2. Uniform grading scheme
3. Condyloma acuminatum subsumed under LSIL
4. Defines superficially invasive versus invasive
5. Biomarker Recommendations

LAST *2-tiered* system: *LSIL v HSIL*

Low-risk HPV subtypes:

- 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, and 81
- Associated with transient infections, LSIL (-IN1), low risk of squamous cancer

High-risk HPV subtypes:

- 16, 18, 31, 33, 35, 39, 45, 50, 51, 53, 56, 58, 59, and 68
- Associated with a HSIL (-IN2, -IN3), high risk of squamous cancer

LAST *Uniform Grading*

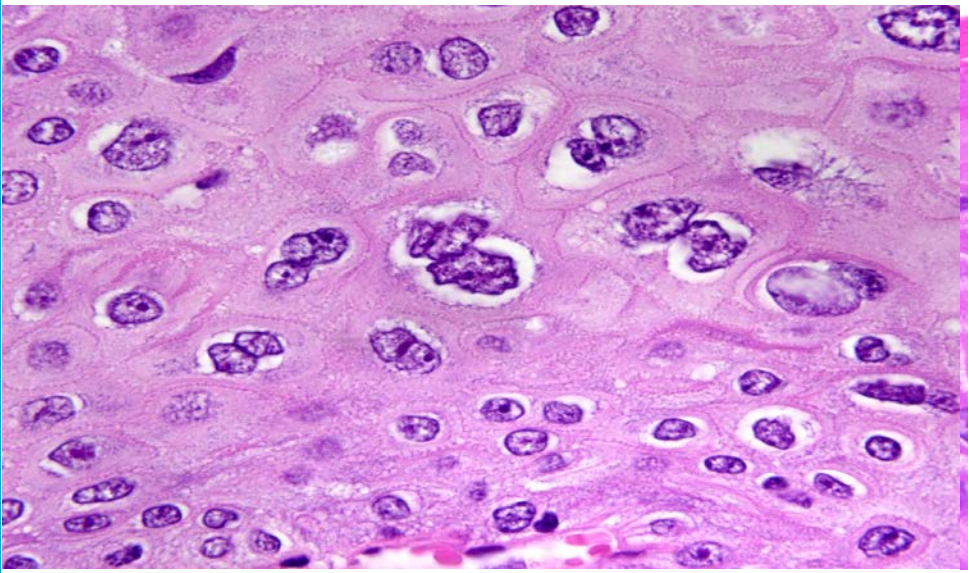
Reagan and Hamonic[2]	Dysplasia	Condyloma	Mild Dysplasia	Moderate Dysplasia	Severe Dysplasia	Carcinoma in situ
Fenger and Nielsen[3]	Anal Canal Intraepithelial Neoplasia (ACIN)	ACIN1		ACIN2	ACIN3	
Northfelt et al[4]	Anal Squamous Intraepithelial Lesion (ASIL)	Low ASIL		High ASIL		
Bowen[5]	Bowen's disease (cutaneous: anal or vulvar)					Bowen's disease
Crum et al[6]	Vulvar intraepithelial neoplasia (VIN)	VIN1		VIN2	VIN3	
WHO (Scully, et al[7])	Vulvar squamous intraepithelial lesion (SIL)	LSIL		HSIL		
ISSVD (Sideri et al[8])	VIN: usual type (HPV); differentiated type (non-HPV)	Condyloma		VIN, usual type		
LAST Project (Darragh et al[1])	Squamous intraepithelial lesion (-IN)	LSIL (condyloma)	LSIL (AIN1 or VIN1)	HSIL (AIN2 or VIN2)	HSIL (AIN3 or VIN3)	

Yang EJ, Kong CS, Longacre TA. Adv Anat Pathol. 2017 May;24(3):136-150.

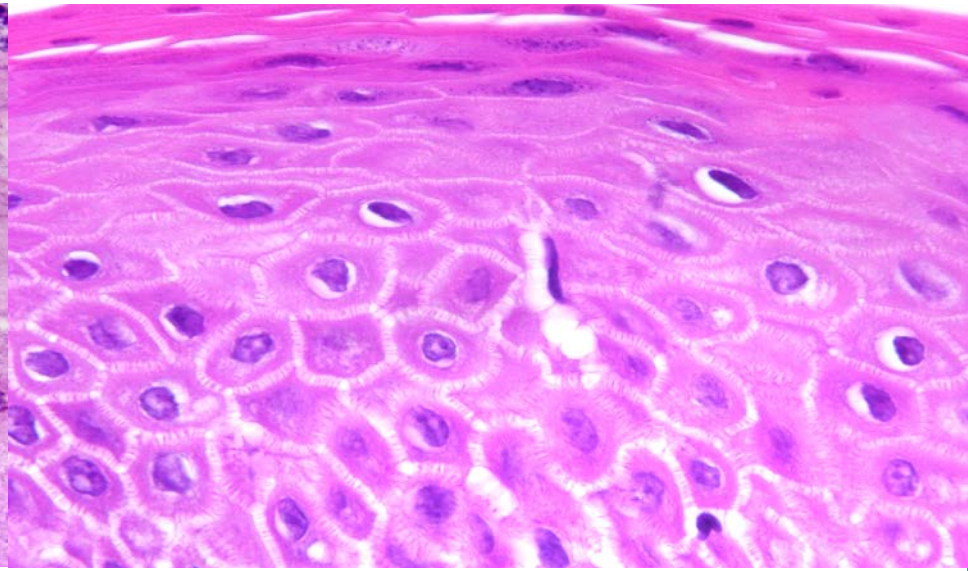
LAST Dysplasia Grading: *LSIL*

- Formerly -IN 1, Condyloma acuminatum
- “Koilocytic” / rasinoid change
  - Increased N:C, peri-nuclear halos, hyperchromasia, irregular nuclear contours
- Per WHO, 5th edition,
  - Mitoses and atypia confined to lower 1/3, OR
  - Papillomatous growth with koilocytic atypia

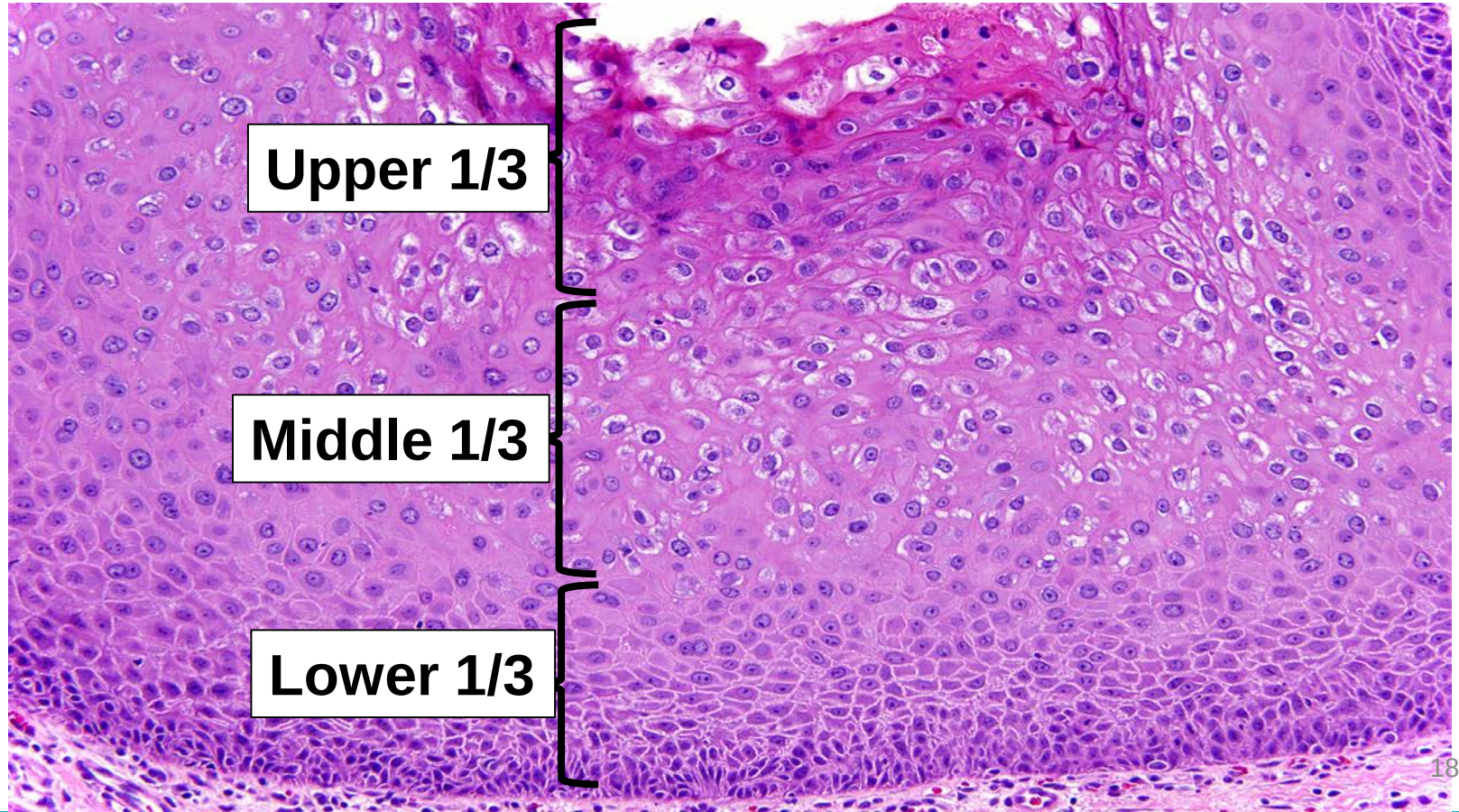
LSIL: *Real Halos*



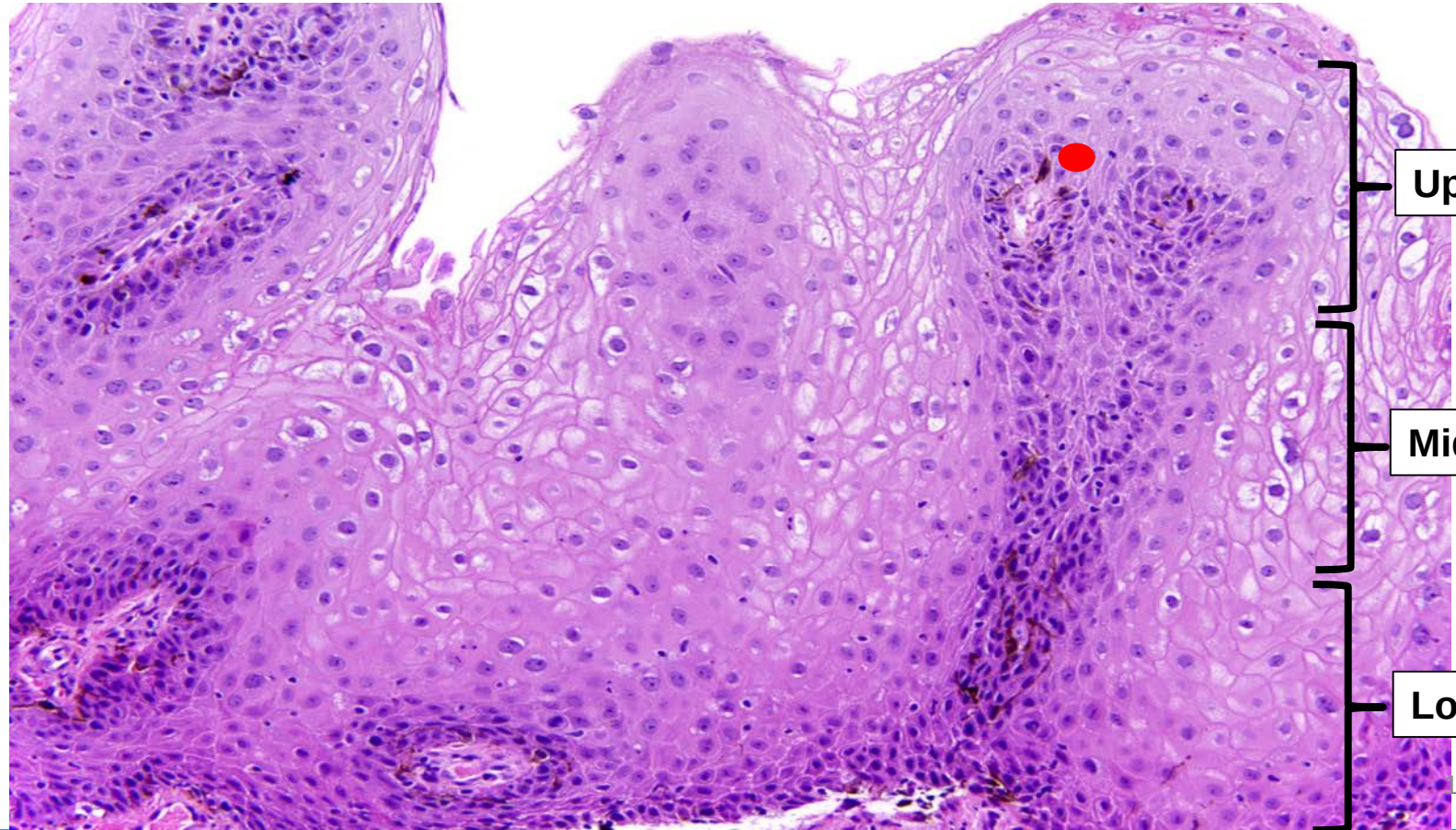
Beware Fake Halos



LSIL: *Mits/atypia in lower 1/3 + Koilocytes*



FAQ: *Where is the “bottom”?*



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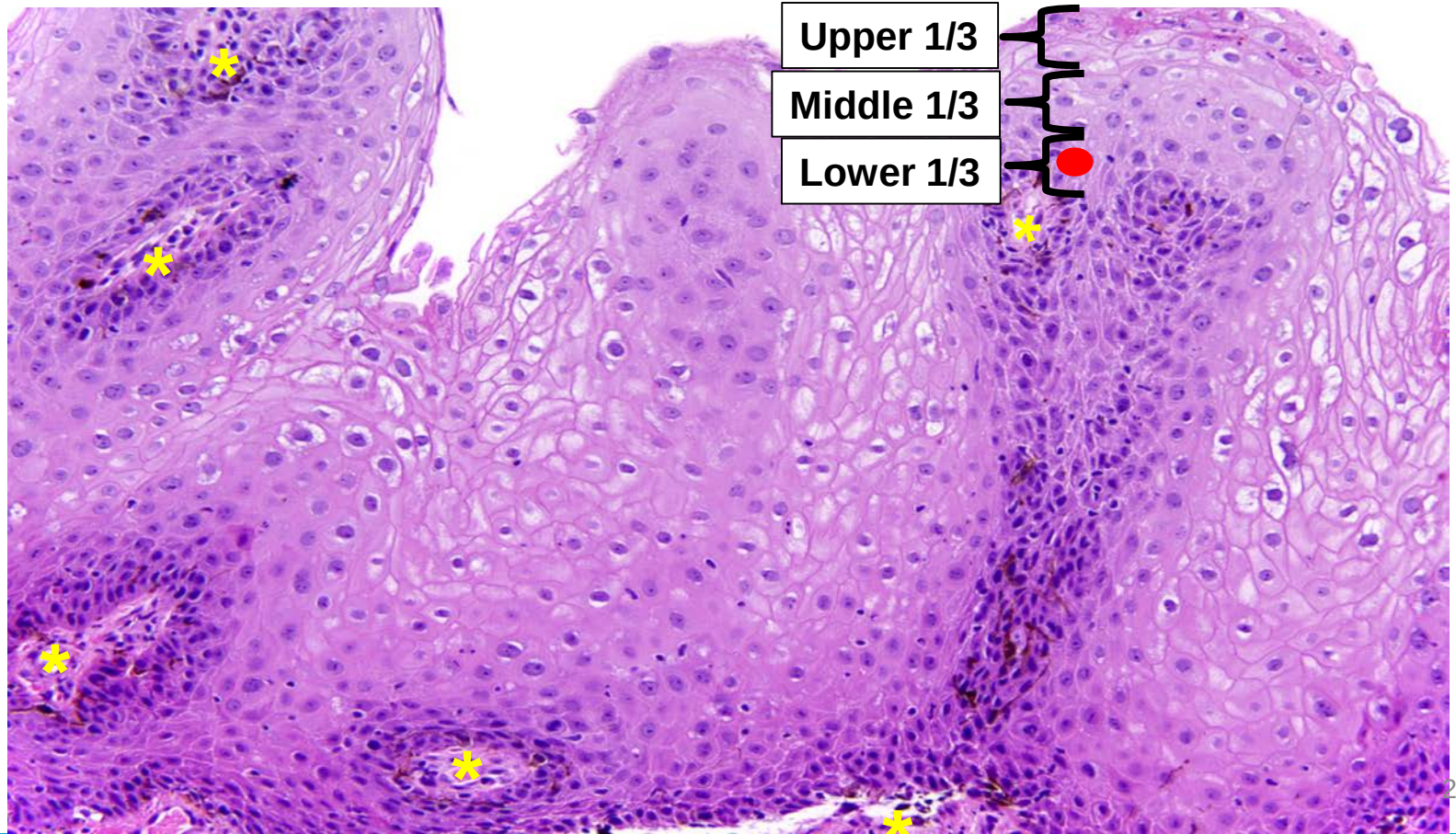


Sample Note: *LSIL*

Anus, biopsy:

-Low-grade squamous intraepithelial neoplasia (LSIL)(formerly “AIN 1”)

Sample Note:

LAST Discourages "Condyloma acuminatum"; Term OK per WHO, 5th edition

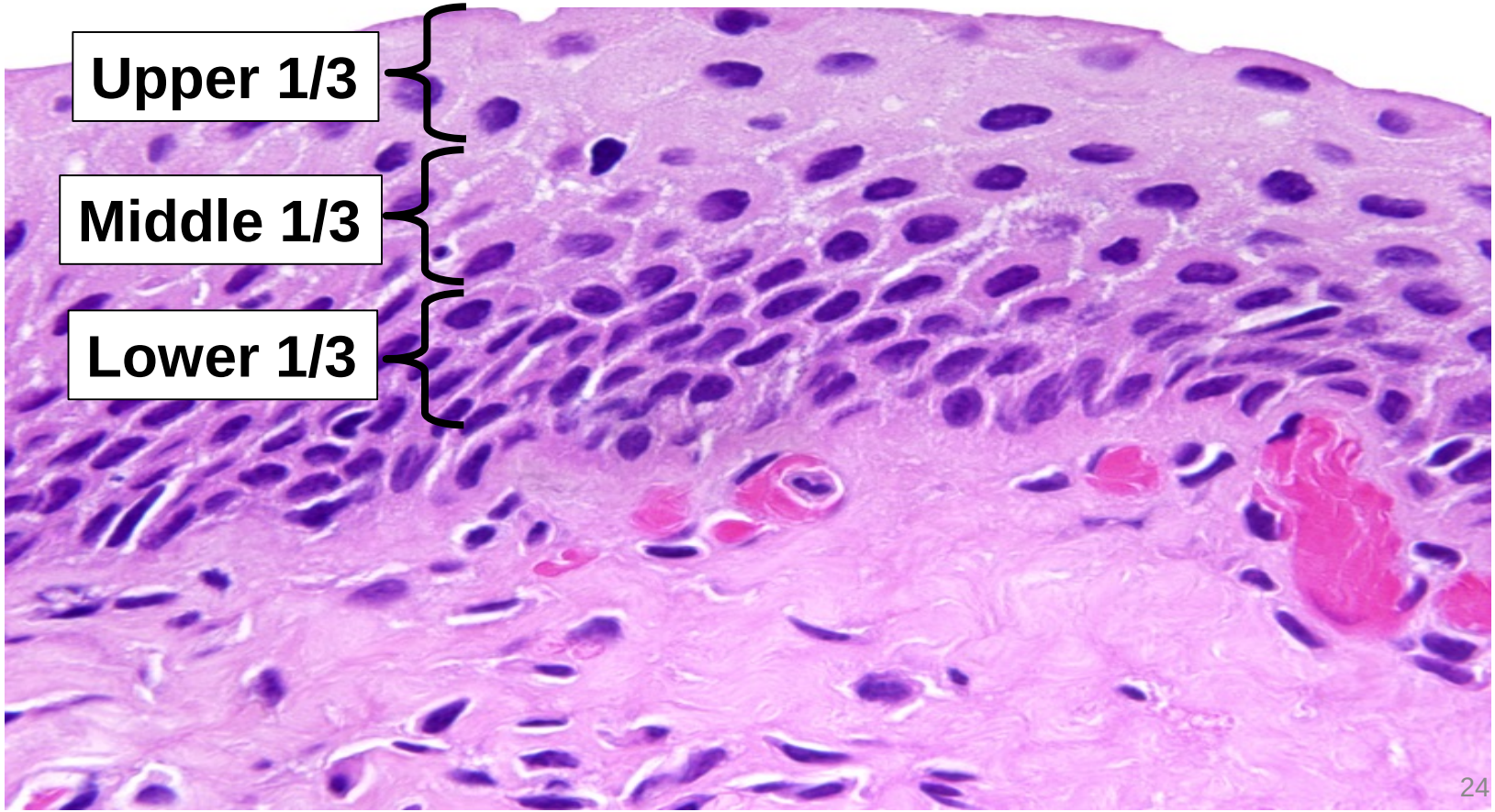
Anus, Polyp, biopsy:

-Low-grade squamous intraepithelial neoplasia (LSIL)(formerly "condyloma acuminatum")

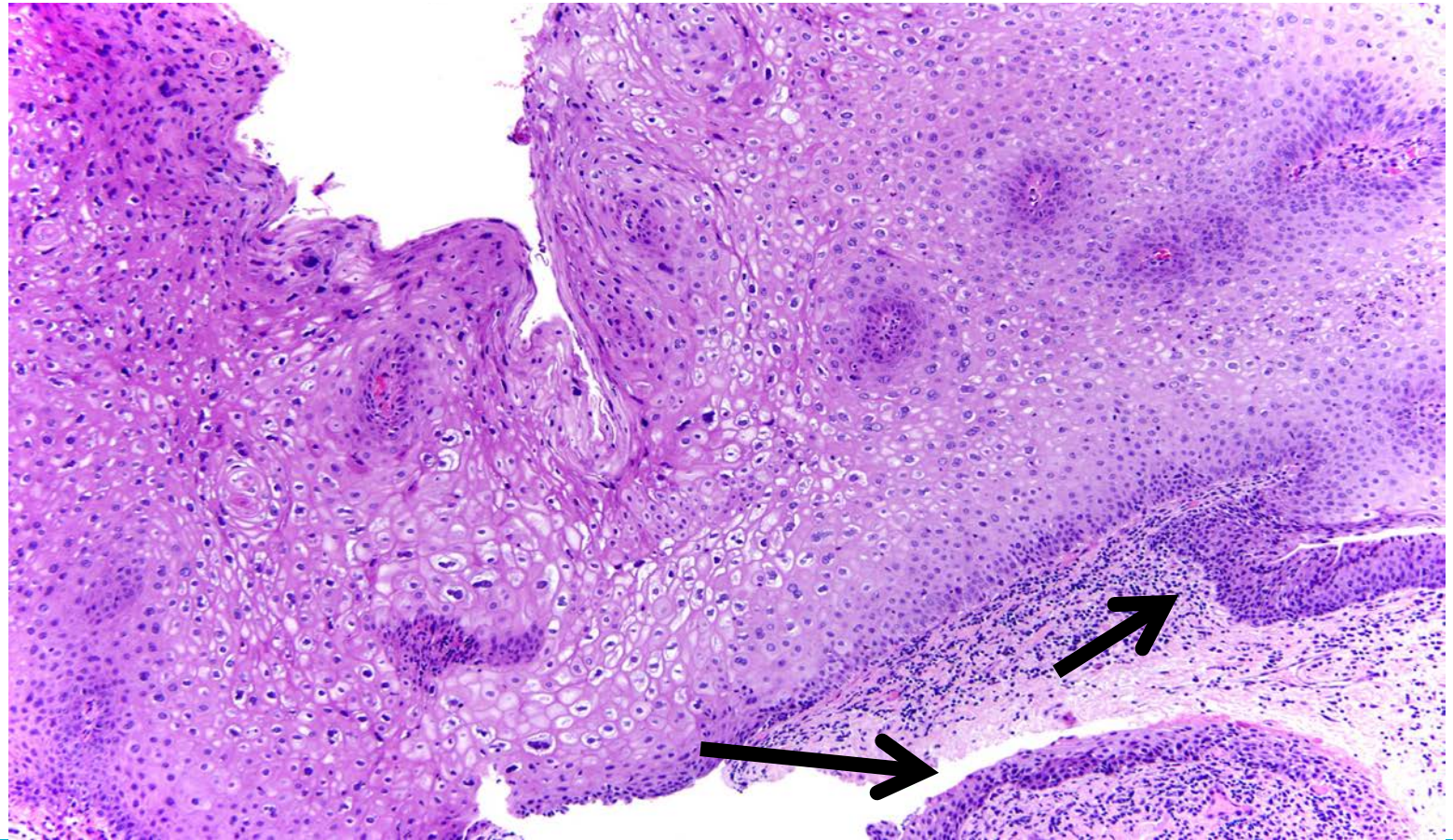
LAST Dysplasia Grading: *HSIL*

- Formerly -IN 2,-IN 3
- More atypical than LSIL:
  - N:C, hyperchromasia, anisonucleosis
- Per WHO, 5th edition,
  - Mitoses and atypia into ≥ top 2/3
    - Middle 1/3 = -IN2
    - Upper 1/3 = -IN3
  - p16 reactivity desirable

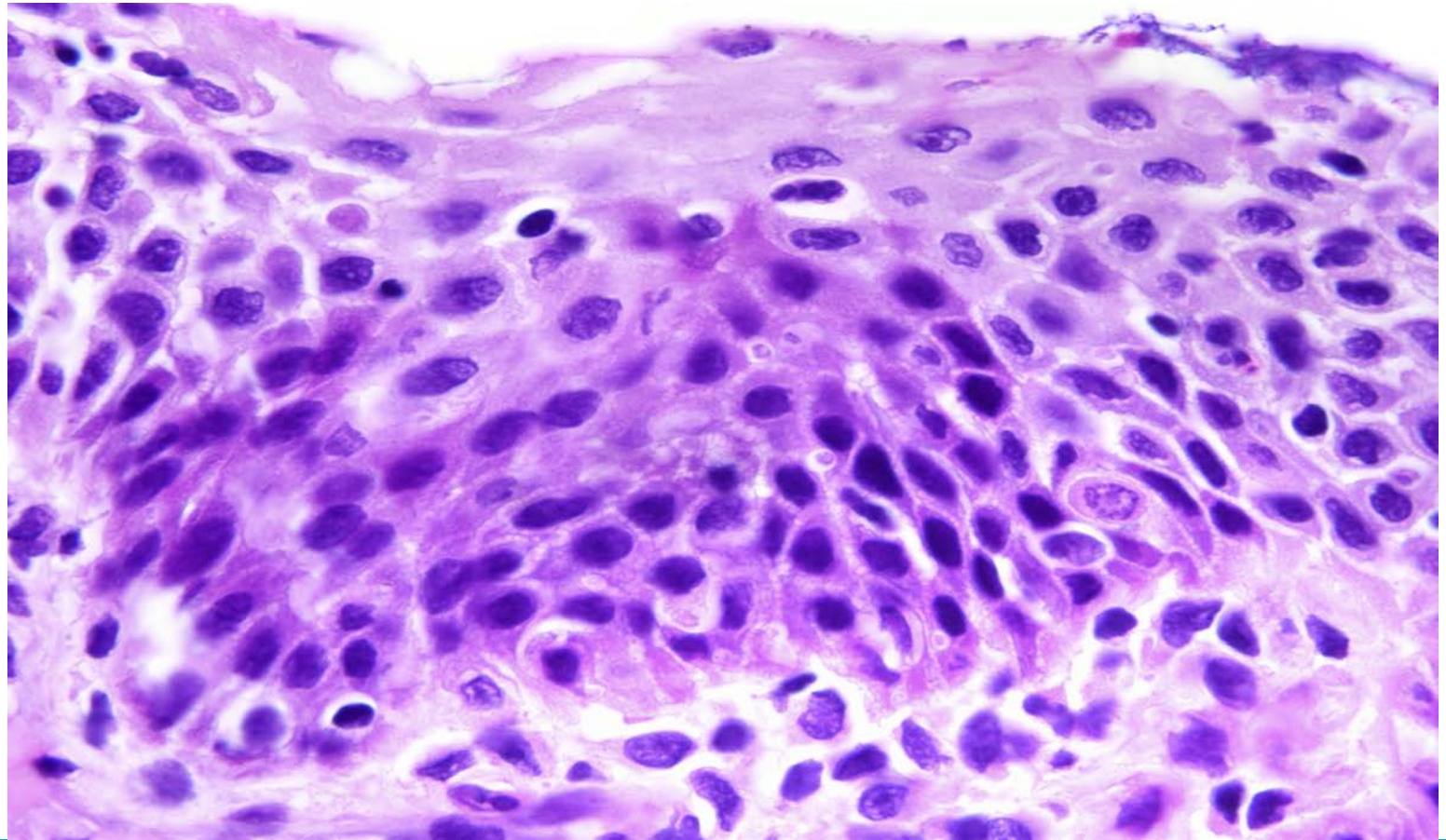
HSIL (AIN2): *Top 1/3 Mature, Mid Mitoses*



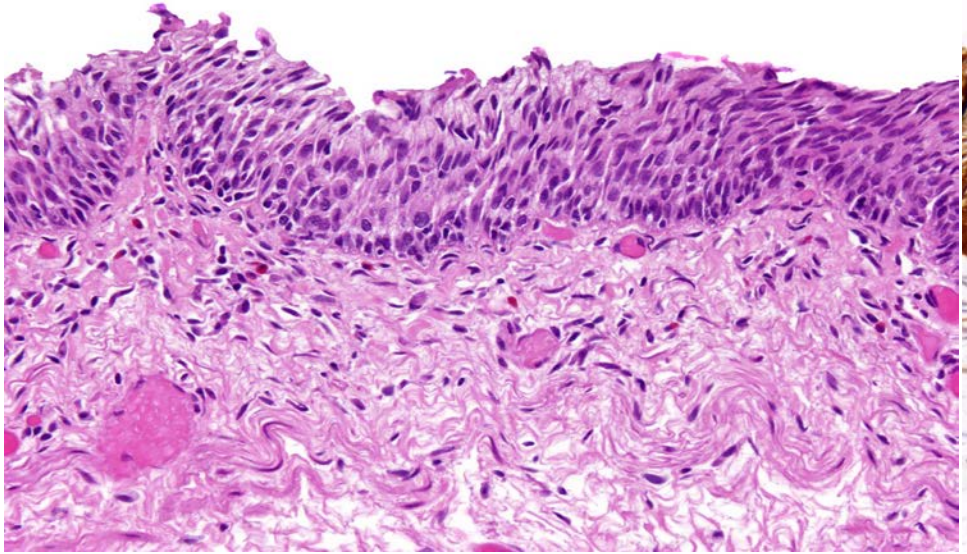
Beware: *HSIL can be Hard to find in a Pile of LSIL*

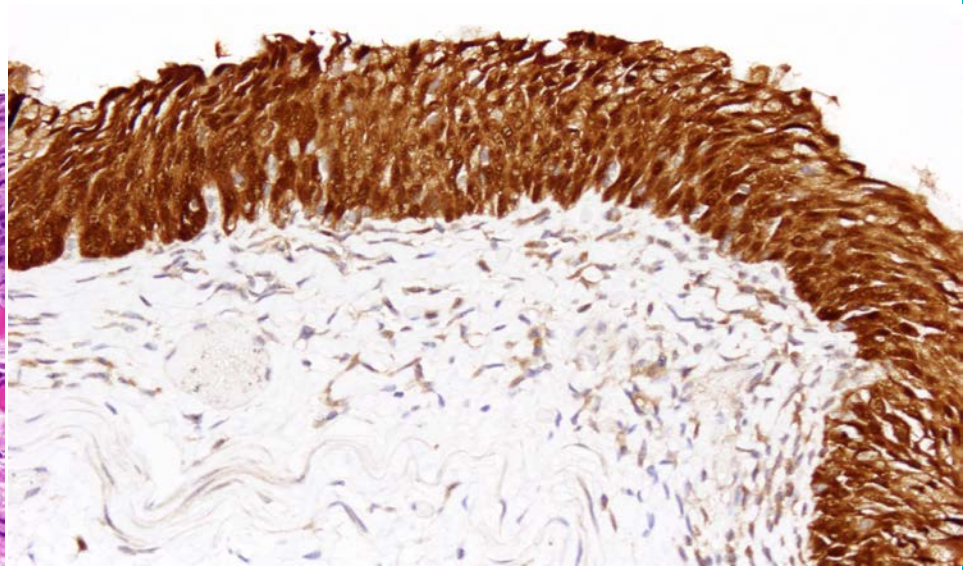


Beware: *HSIL can be Hard to find in a Pile of LSIL*

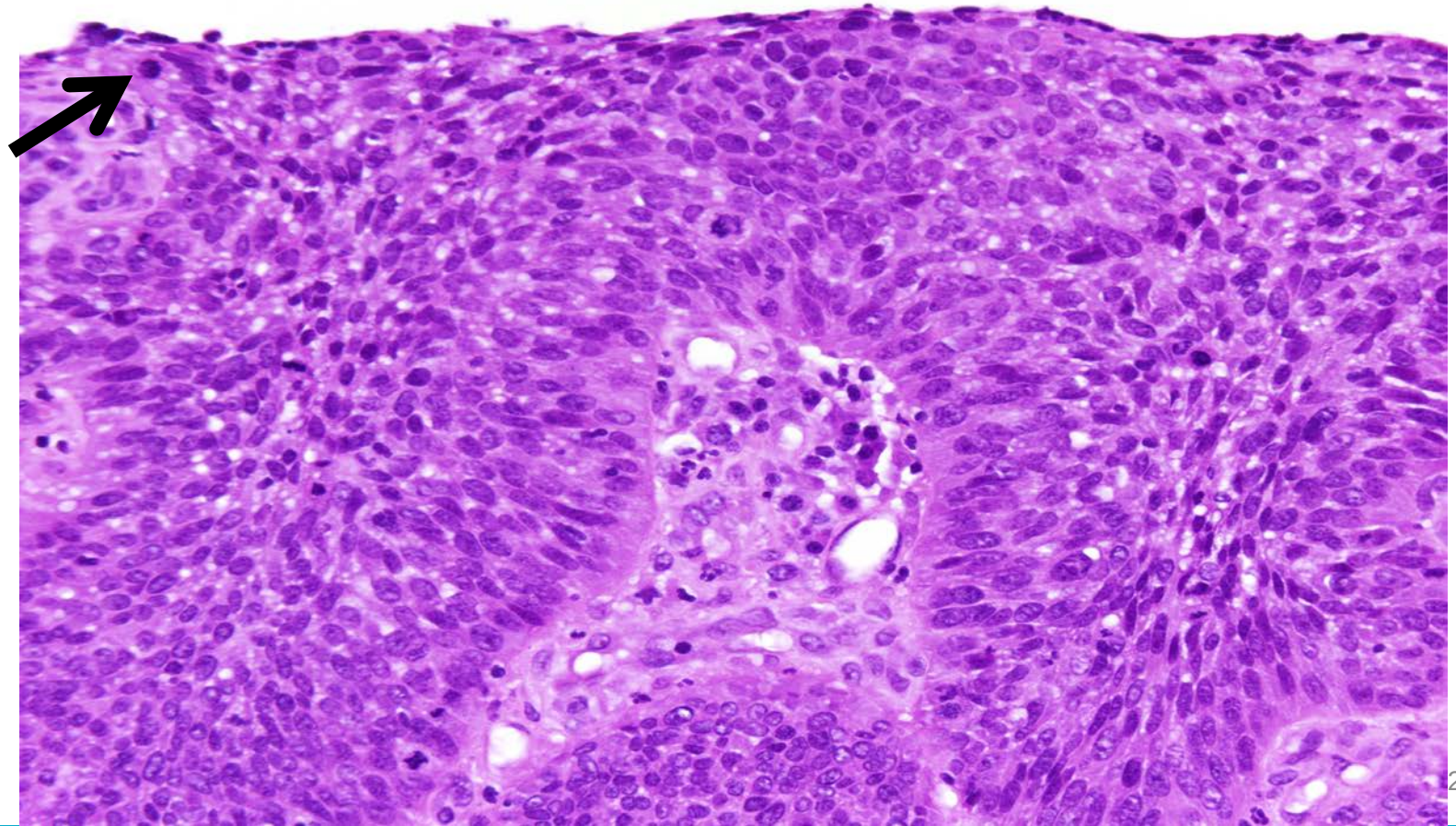


Beware: *HSIL can be Hard to find in Cauterized, Crushed Tissue (p16)*

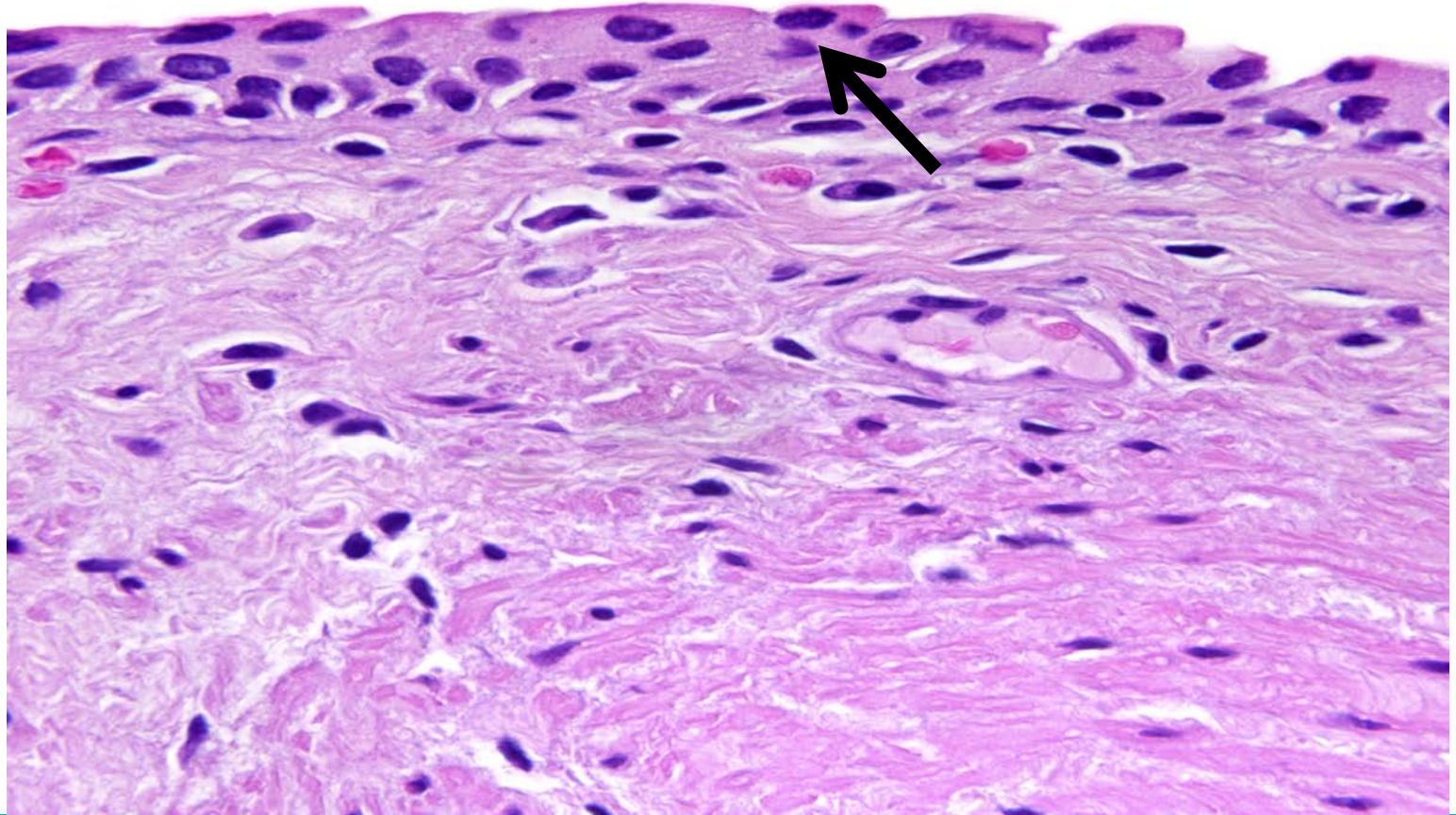




HSIL (AIN3): *Full-Thickness Immaturity, Upper Mitoses*



HSIL (AIN3): *Full-Thickness Immaturity, Upper Mitoses*



Sample Note: *HSIL*

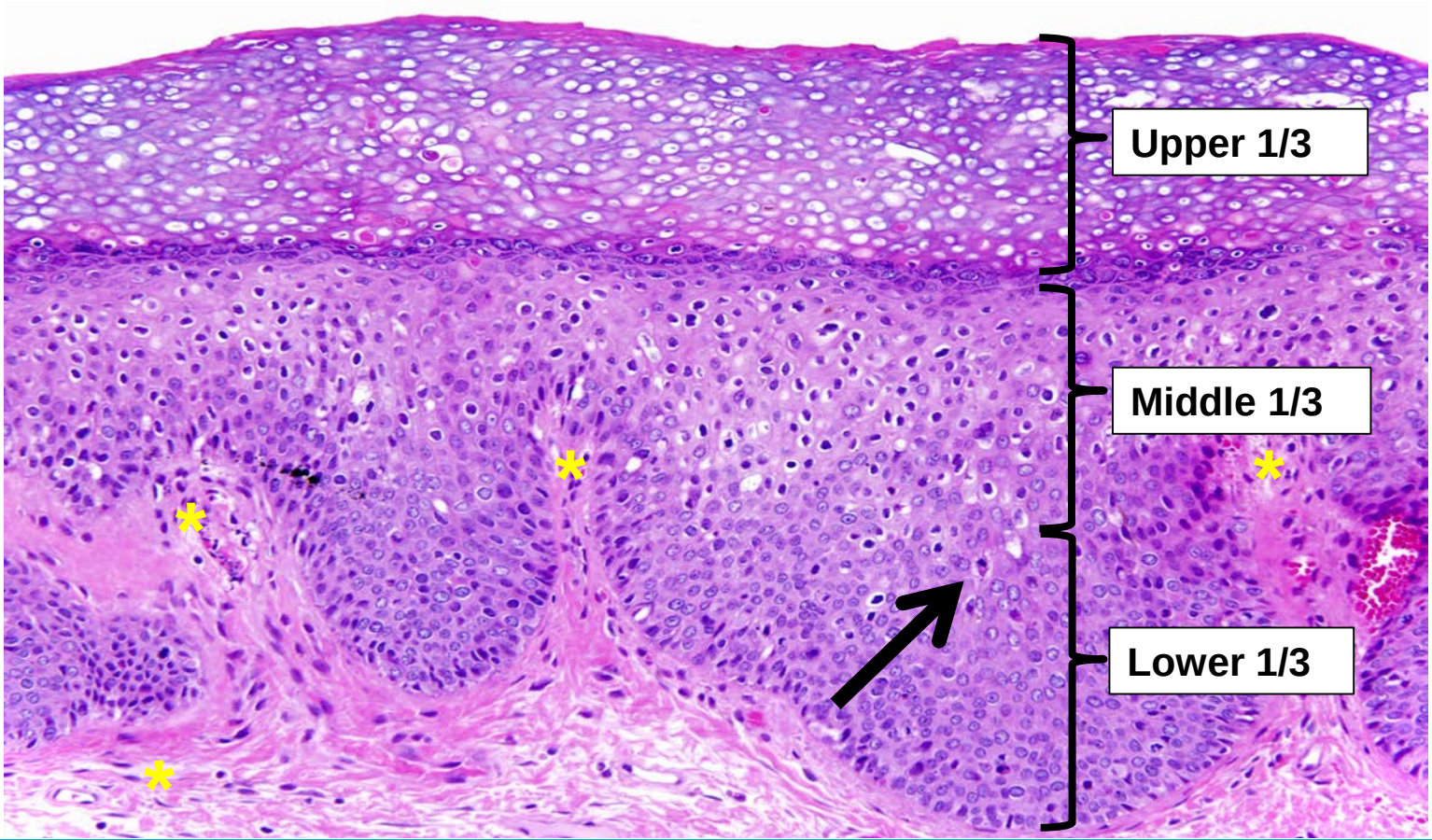
Anus, biopsy:

-High-grade squamous intraepithelial neoplasia (HSIL)(formerly “AIN 3”)

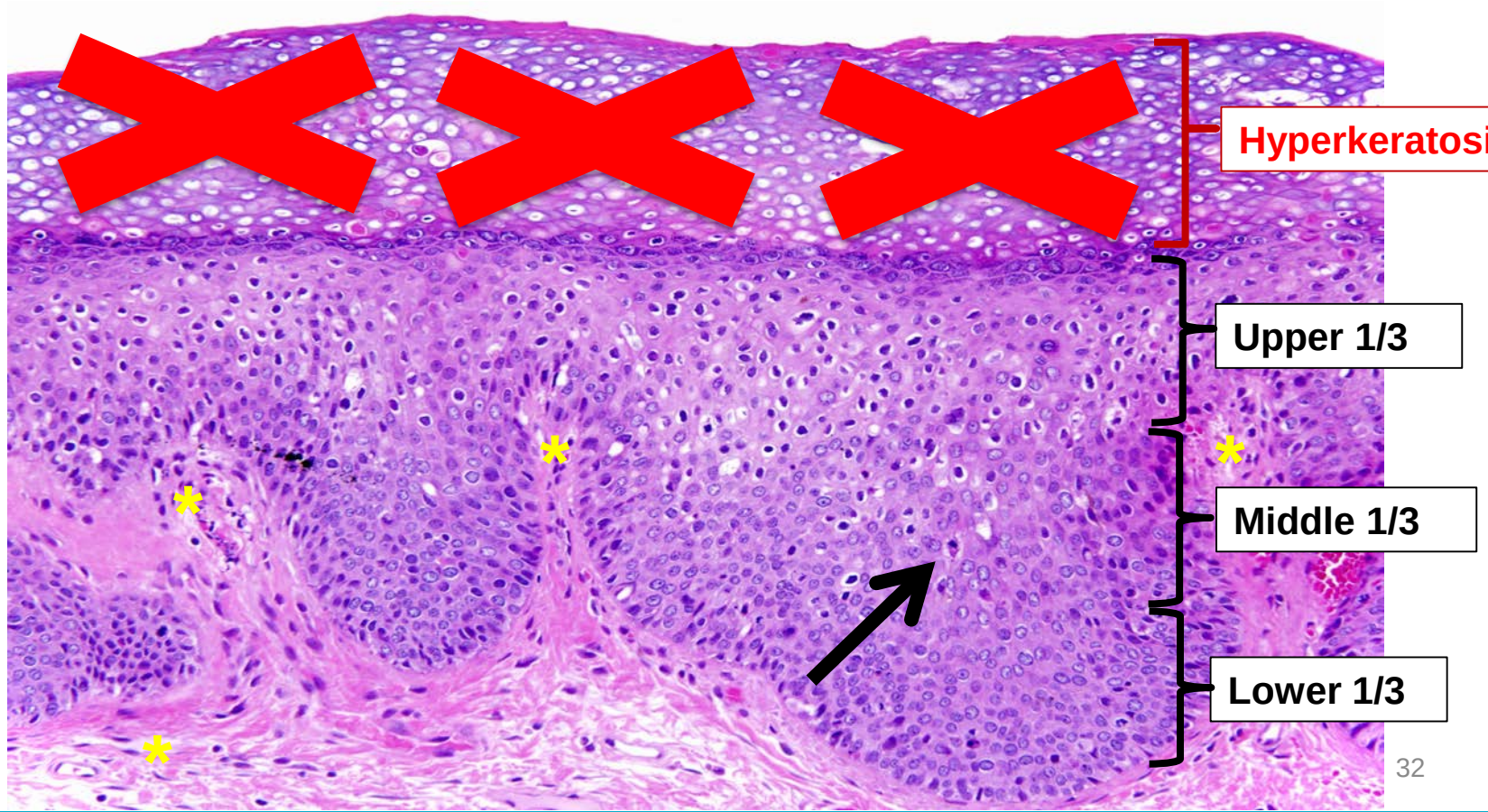
-Negative for invasion

-Margins uninvolved

FAQ: *Where is the “top”?*



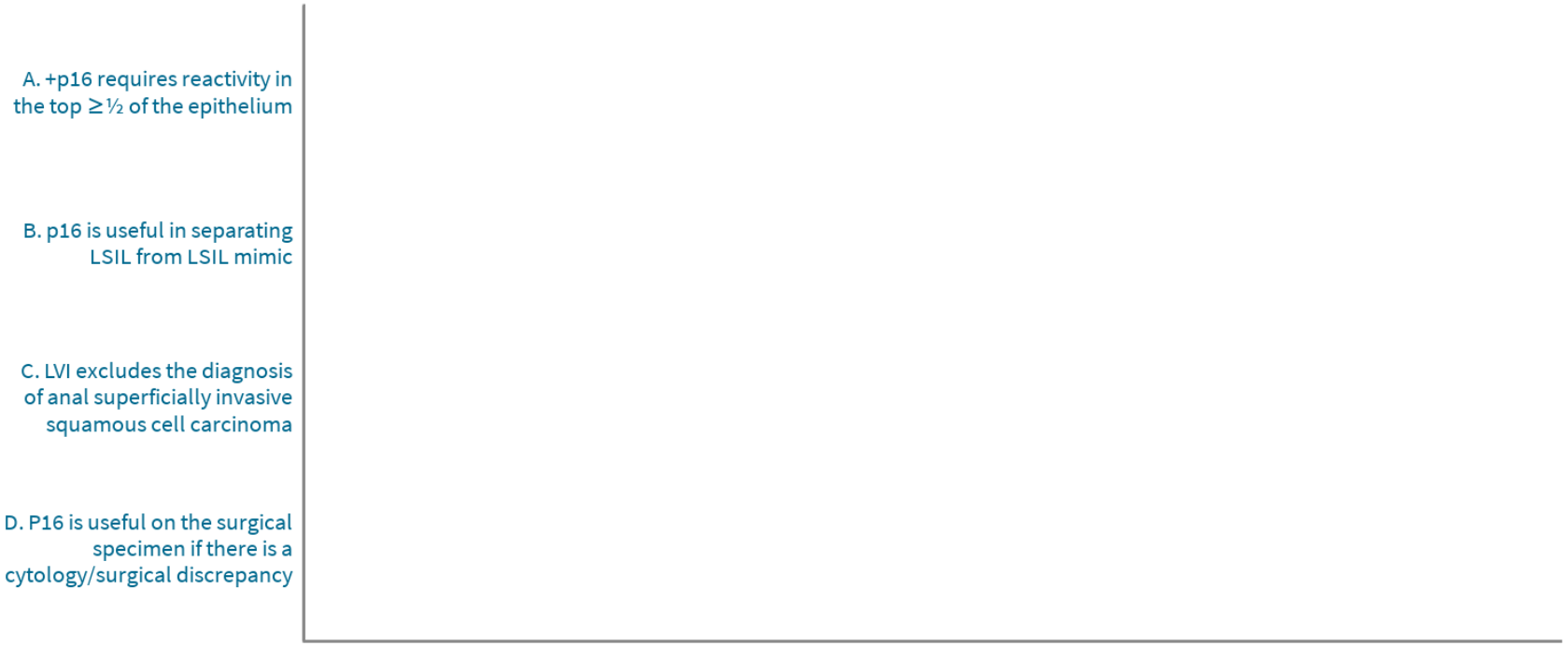
FAQ: *Where is the "top"?*



FAQ: *How to classify dysplastic lesions with discordant morphology & mitotic figures?*

- Keep swimming
- p16 helpful
- Prioritize morphology
  - LSIL morphology and high mitosis=LSIL
  - HSIL morphology and only low mitosis=HSIL

According to LAST, select the correct statement:



Pearls & Pitfalls:
p16 IHC is Not a Magic Bullet

Avoid ordering p16 upfront on all cases

- HSIL versus an HSIL mimic, *or*
- Discrepancy between cytology & surgical biopsy

The H&E morphology is the priority

- A positive p16 supports HSIL only if morphologic criteria for HSIL seen on H&E
- Avoid p16 in non-HSIL ddx to avoid mismanagement
  - p16 is unreliable in LSIL and sometimes can be strong
  - A subset of HSIL is p16 non-reactive

Pearls & Pitfalls:
p16 IHC is Not a Magic Bullet

Reactive p16

- Diffuse, block reactivity of nucleus and cytoplasm of basal layer and ≥ contiguous 1/3 of the epithelial thickness in the atypical focus on H&E
- Full-thickness reactivity not required

Nonreactive p16

- Entirely negative, focal, patchy, or only cytoplasmic

New LAST Definitions

Superficially invasive squamous cell carcinoma (SISCCA)

- Eligible conservative, local excision
- Depth ≤ 3 mm AND Horizontal ≤ 7 mm, AND
- Completely excised
- +/- LVI

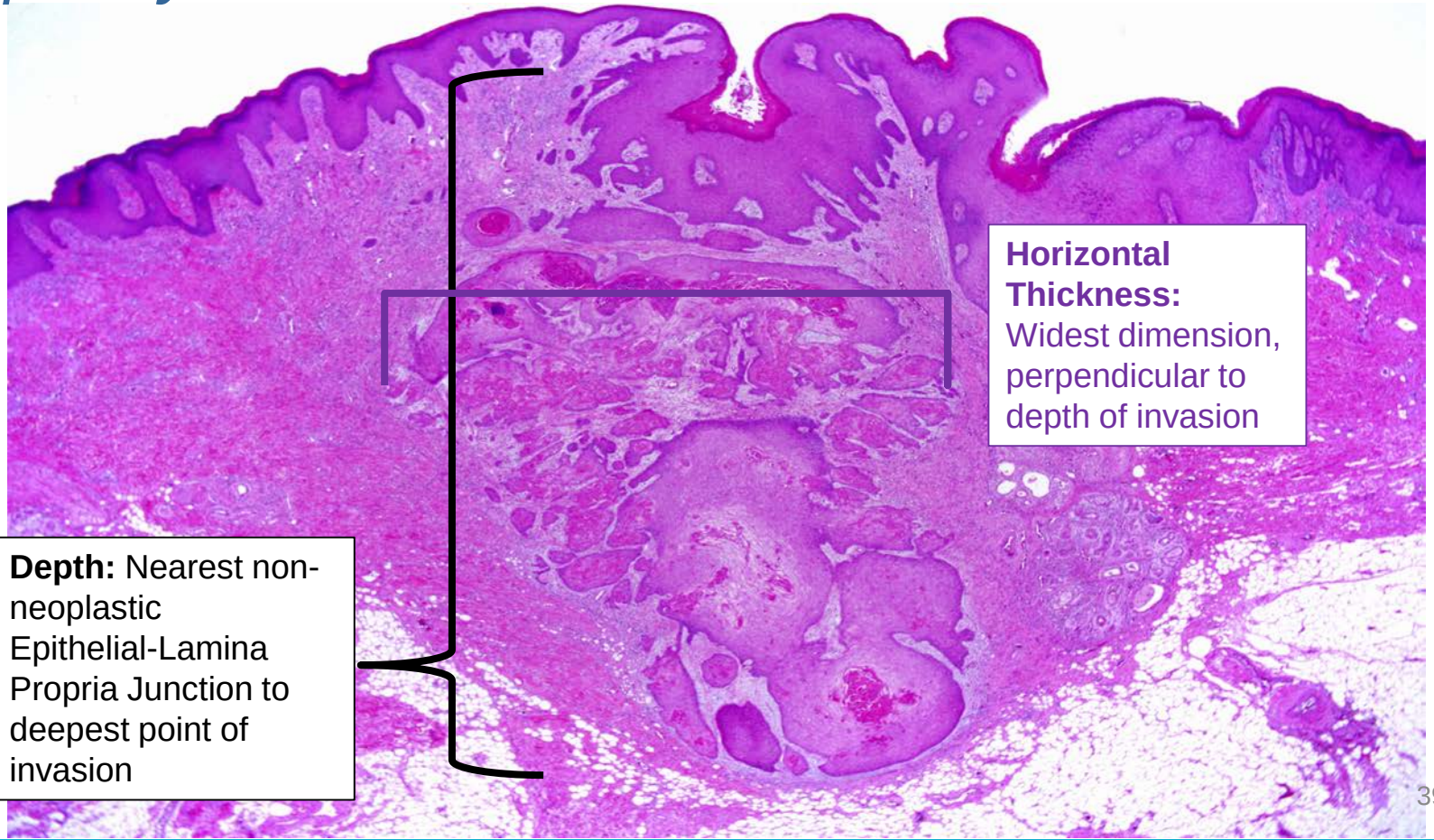
At least SISCCA

- Depth ≤ 3 mm, Horizontal ≤ 7 mm, AND
- Incompletely excised

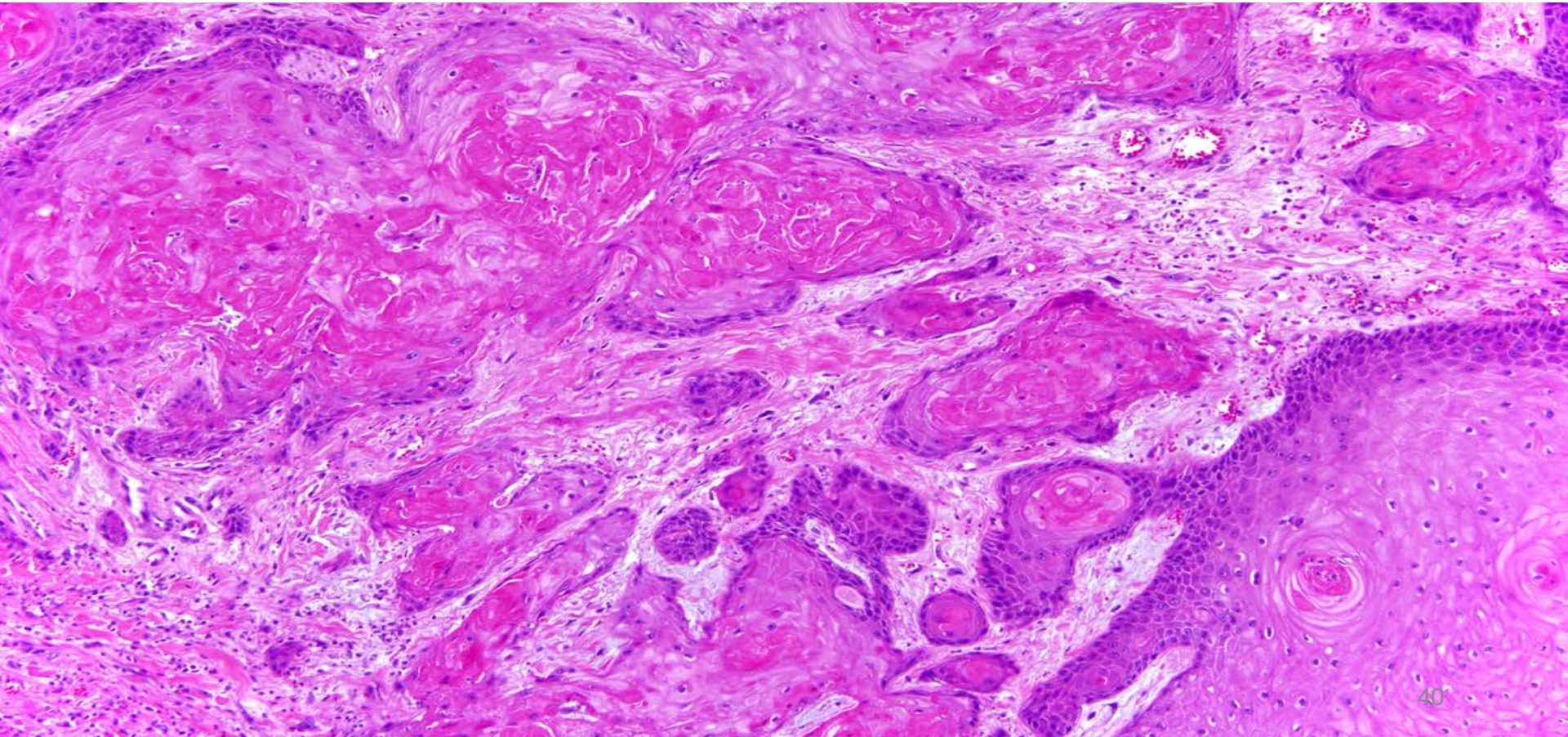
Invasive squamous cell carcinoma

- Depth > 3 mm, Horizontal > 7 mm

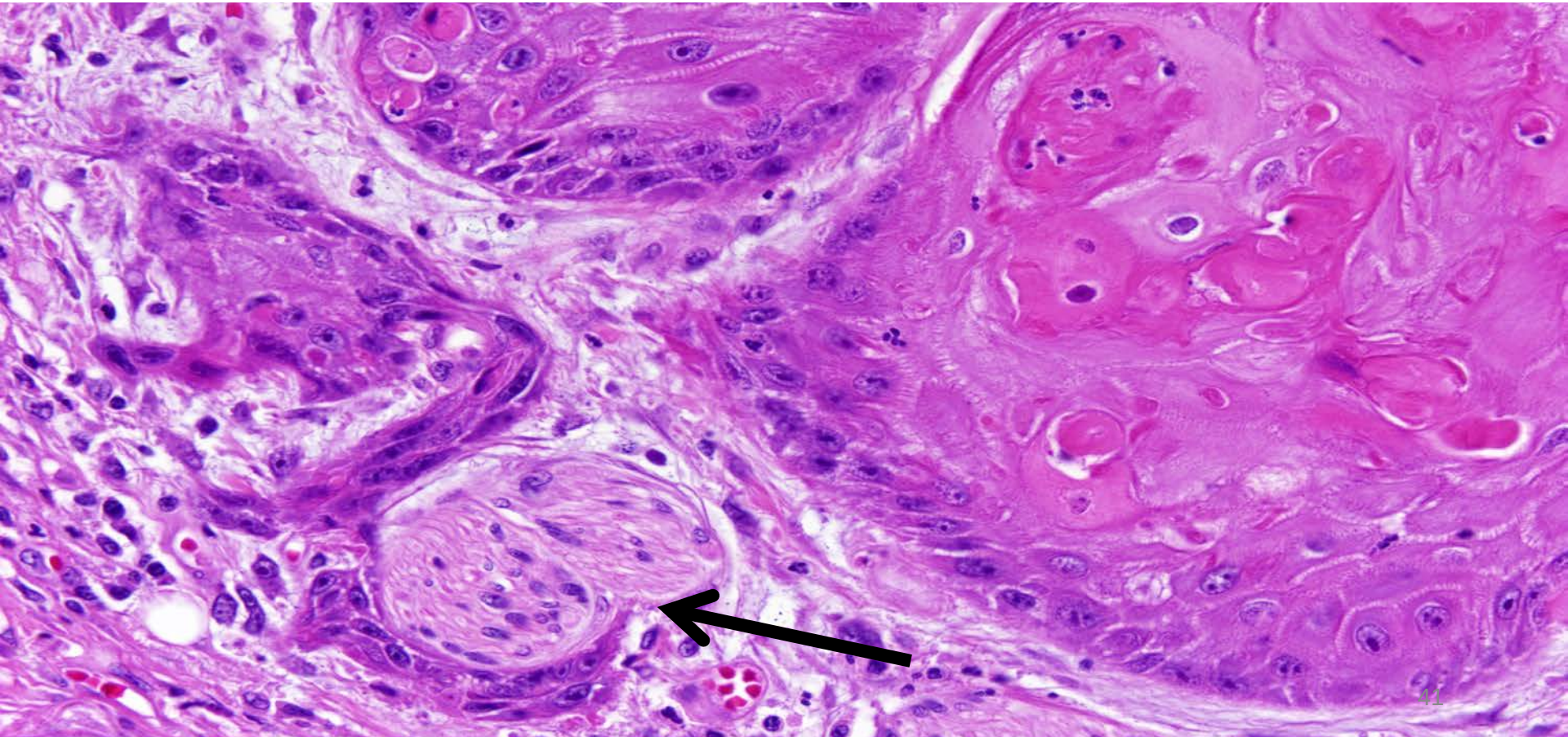
SISCCA: *Depth ≤ 3 mm, Horizontal spread ≤ 7 mm, Completely excised*



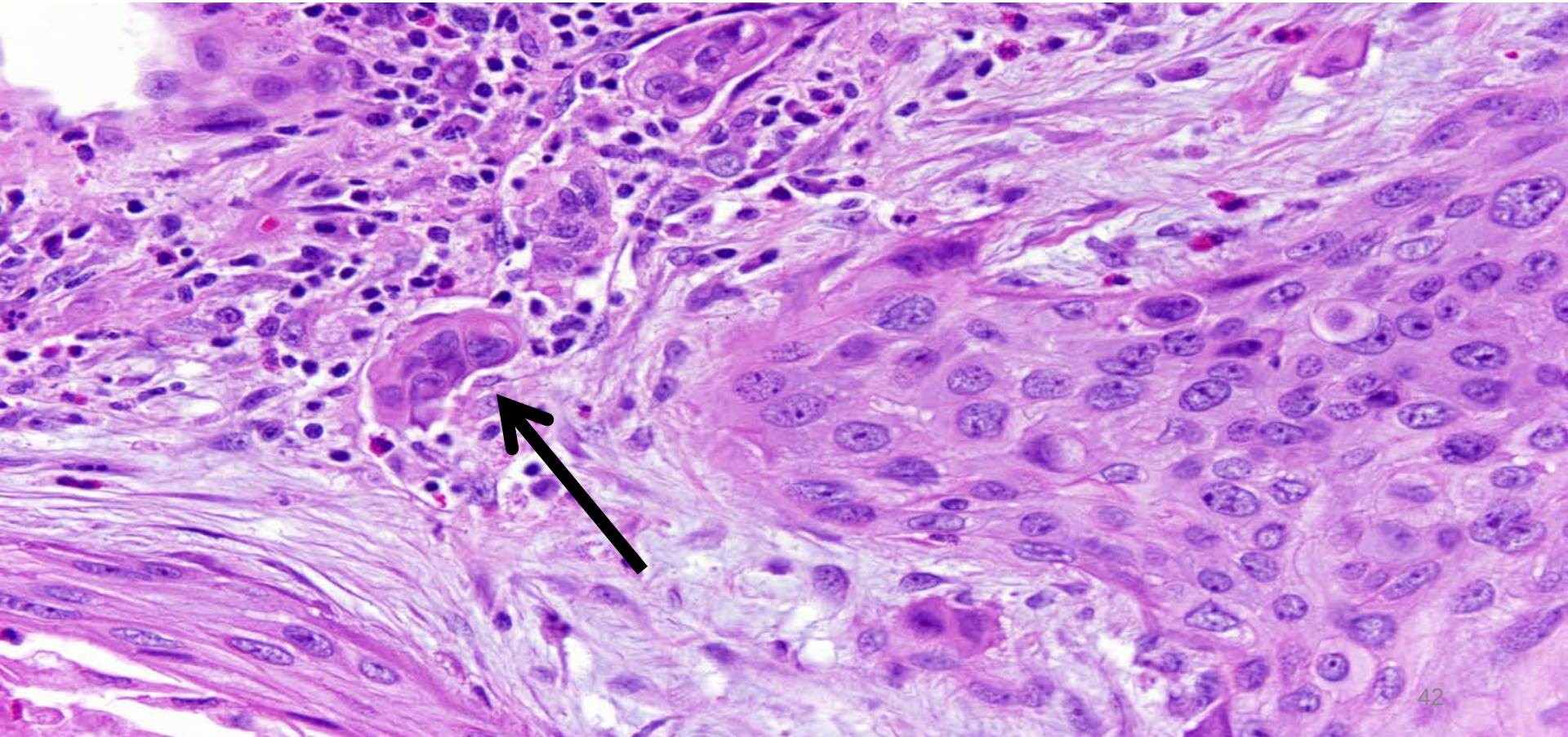
SCCA: *Angulated Glands, Desmoplastic Background*



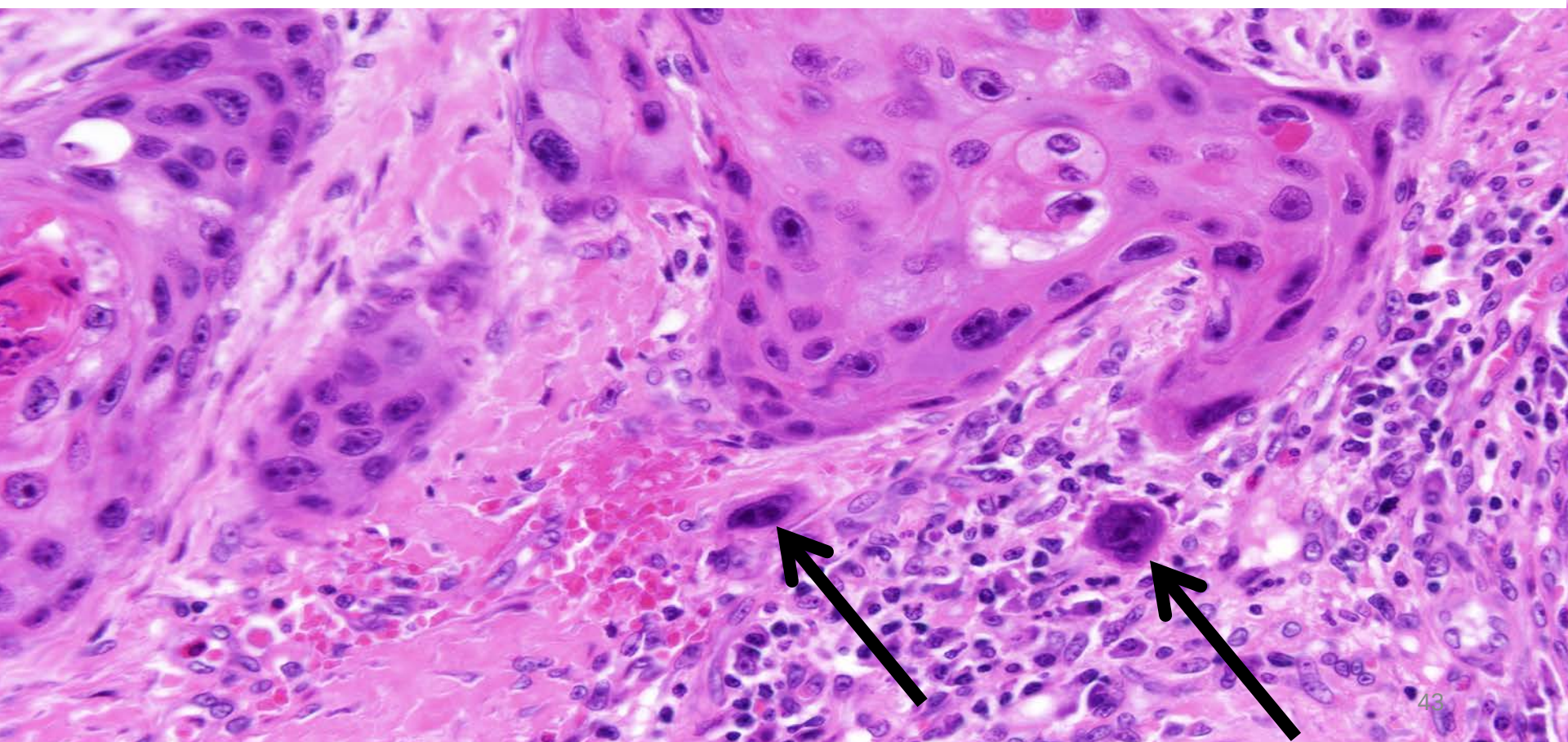
SCCA: *Perineural Invasion*

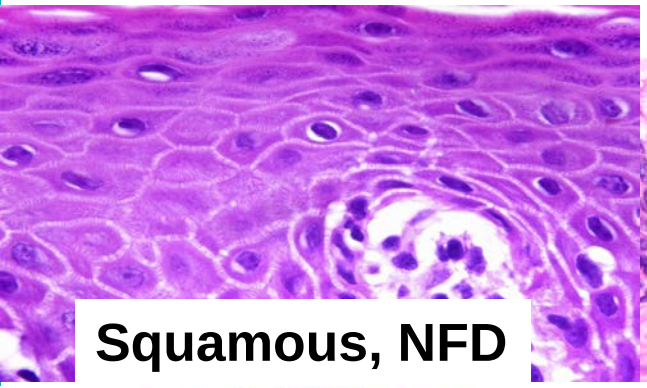


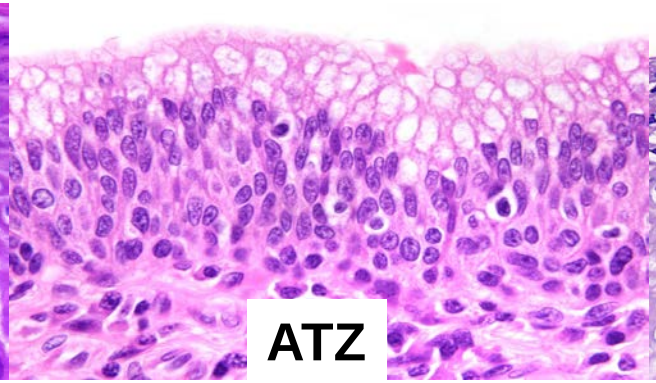
SCCA: *Lymphovascular Invasion*

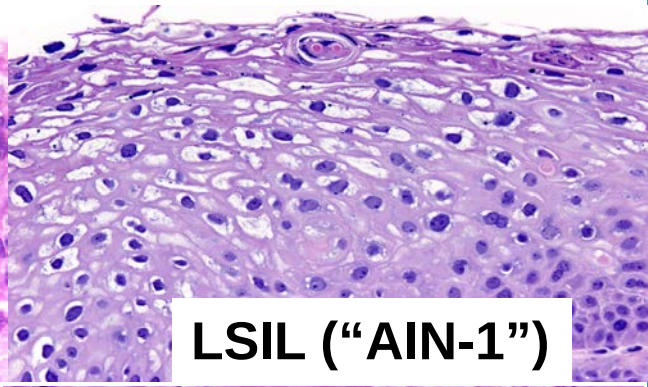


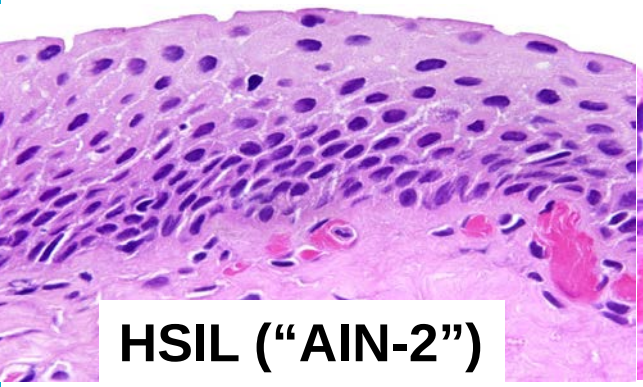
SCCA: *Individual Infiltrating Cells*

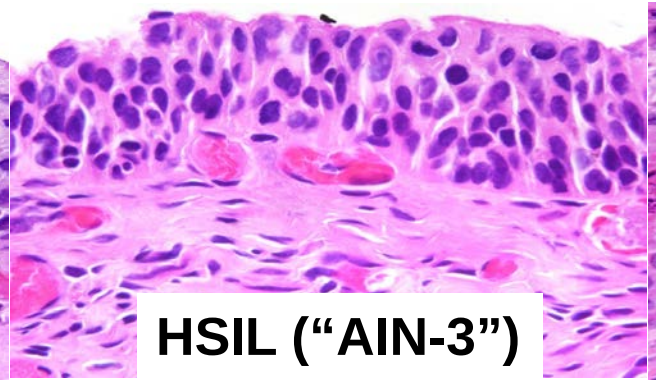


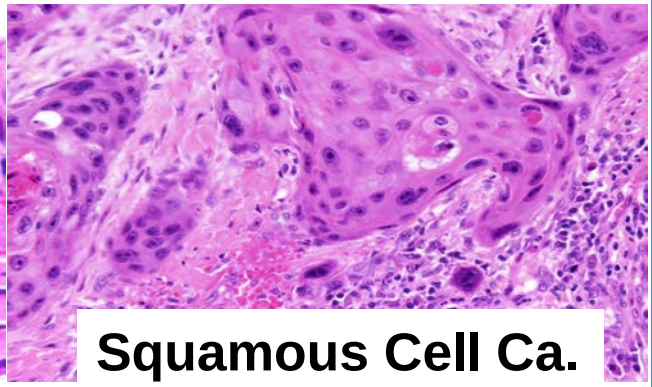

Squamous, NFD


ATZ

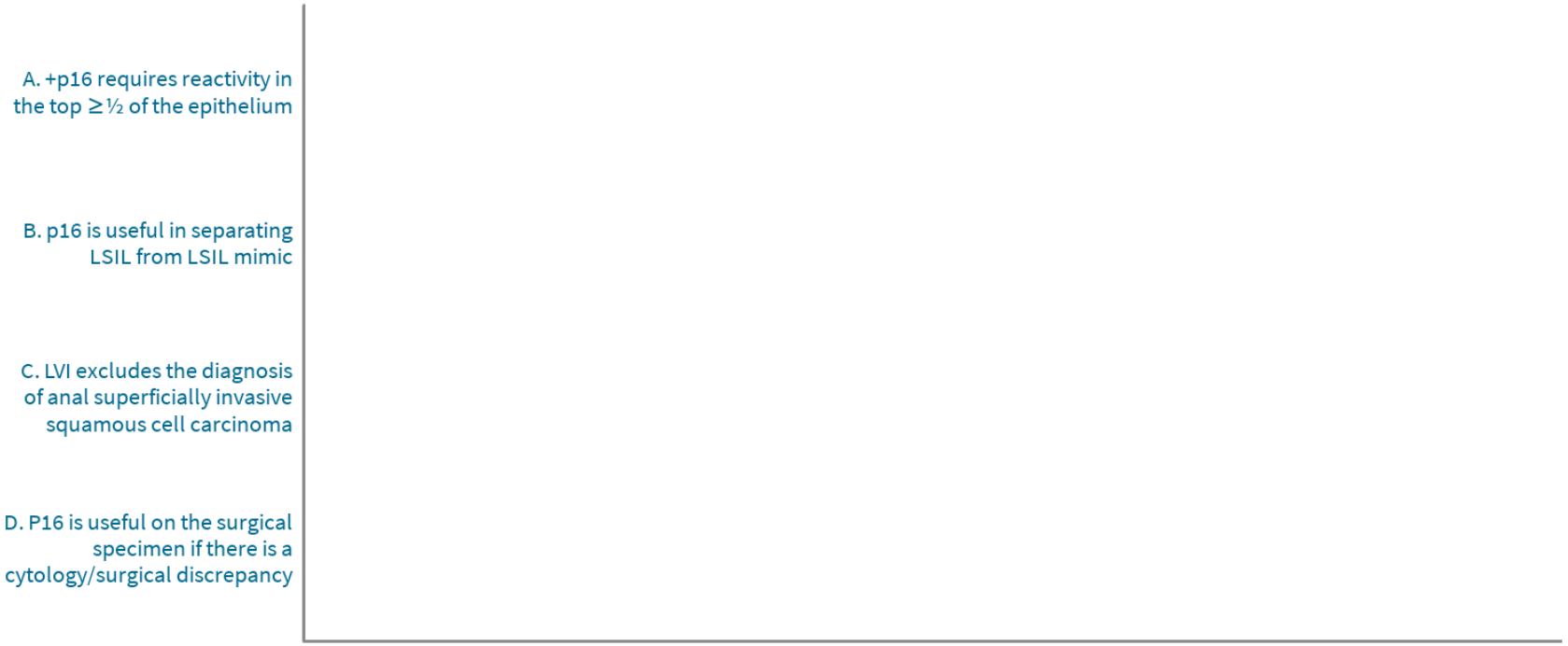

LSIL (“AIN-1”)


HSIL (“AIN-2”)


HSIL (“AIN-3”)


Squamous Cell Ca.

According to LAST, select the correct statement:



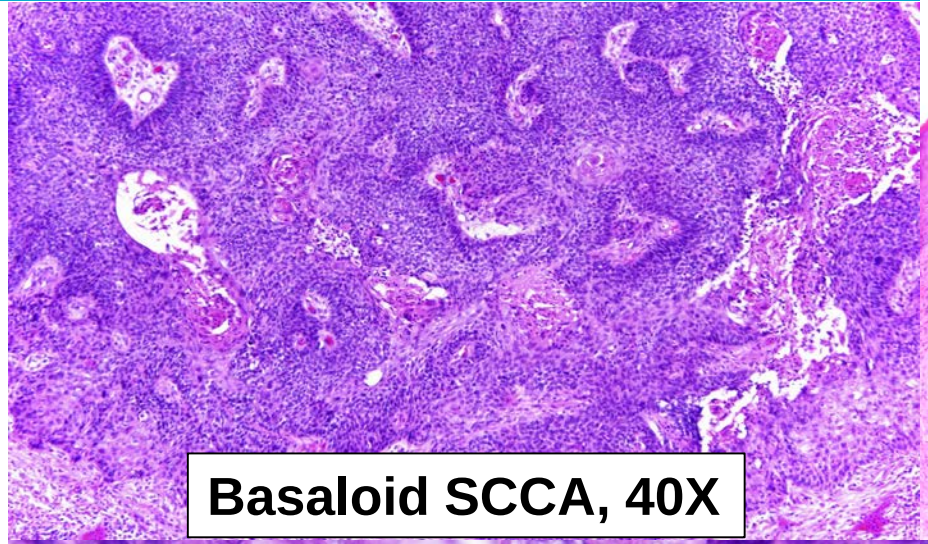
Pearls & Pitfalls:

Term "Cloacogenic Carcinoma" Obsolete

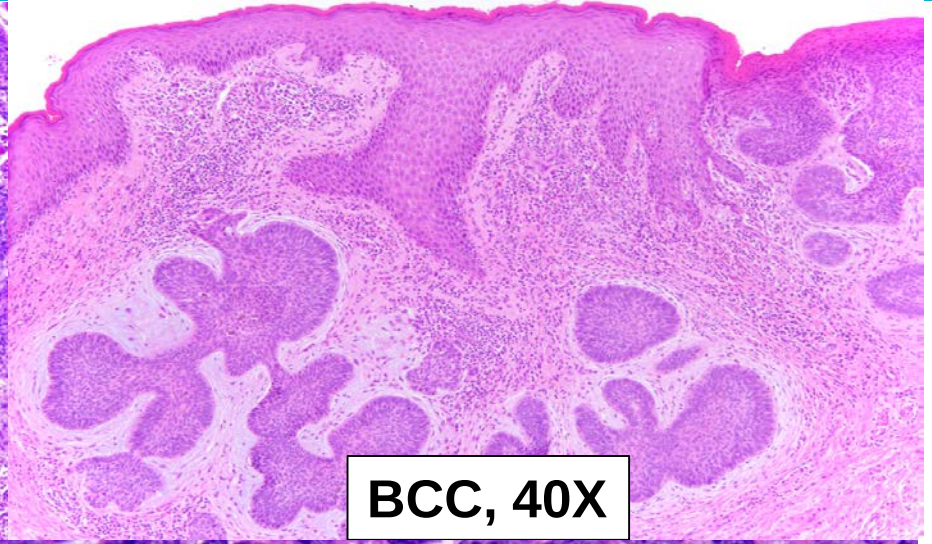
- A type of squamous cell carcinoma with basaloid or transitional type differentiation
- Dark lesion, no inter-cellular bridges, high-grade cytology, necrosis, mitotic figures
- WHO, 5th edition advises against subclassification beyond "squamous cell carcinoma"

FAQ: *How to Distinguish Basaloid SCCA & Basal Cell Carcinoma?*

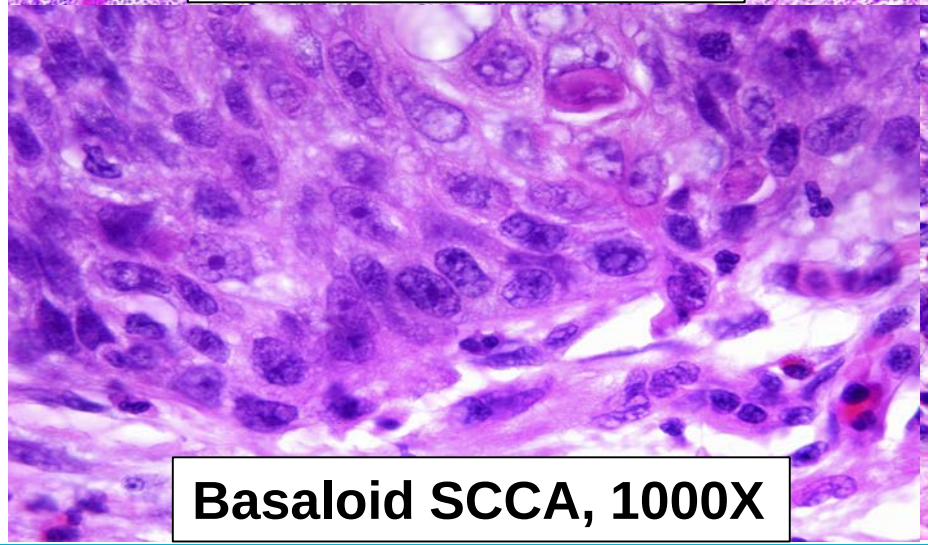
	Basaloid SCCA	BCC
Treatment	Aggressive	Conservative
Origin	Anal Canal	Perianal skin
HPV related	Yes	No
Background LSIL/HSIL	Common	No
Prominent mitoses, necrosis	Yes	No
Retraction artifact	No	Yes
Peripheral nuclear palisading	Vague	Crisp
Cytologic atypia	High-grade	Low-grade
IHC reactivity	CDKN2A, SOX2	Ber-EP4, BCL2



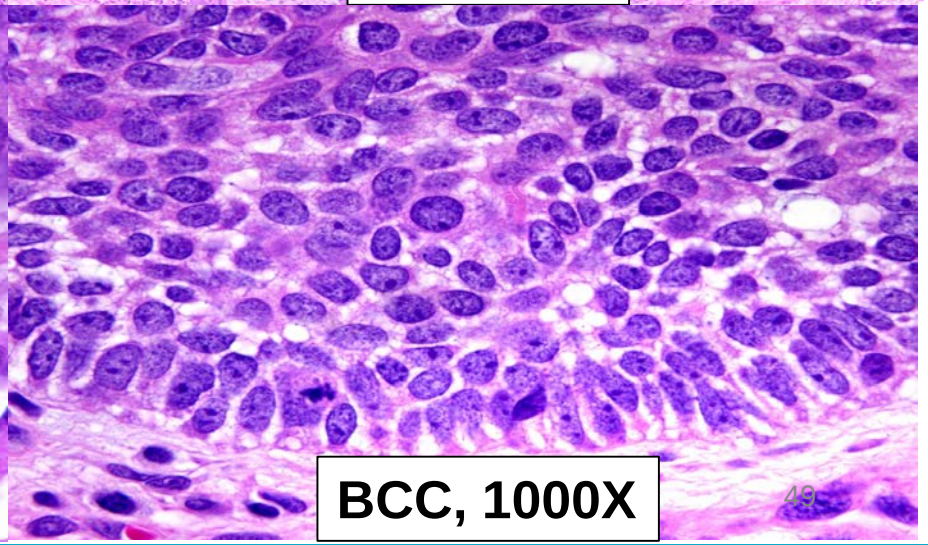
Basaloid SCCA, 40X



BCC, 40X



Basaloid SCCA, 1000X



BCC, 1000X

Nomenclature Mess Alert: Verrucous Ca ≠ Giant Condyloma

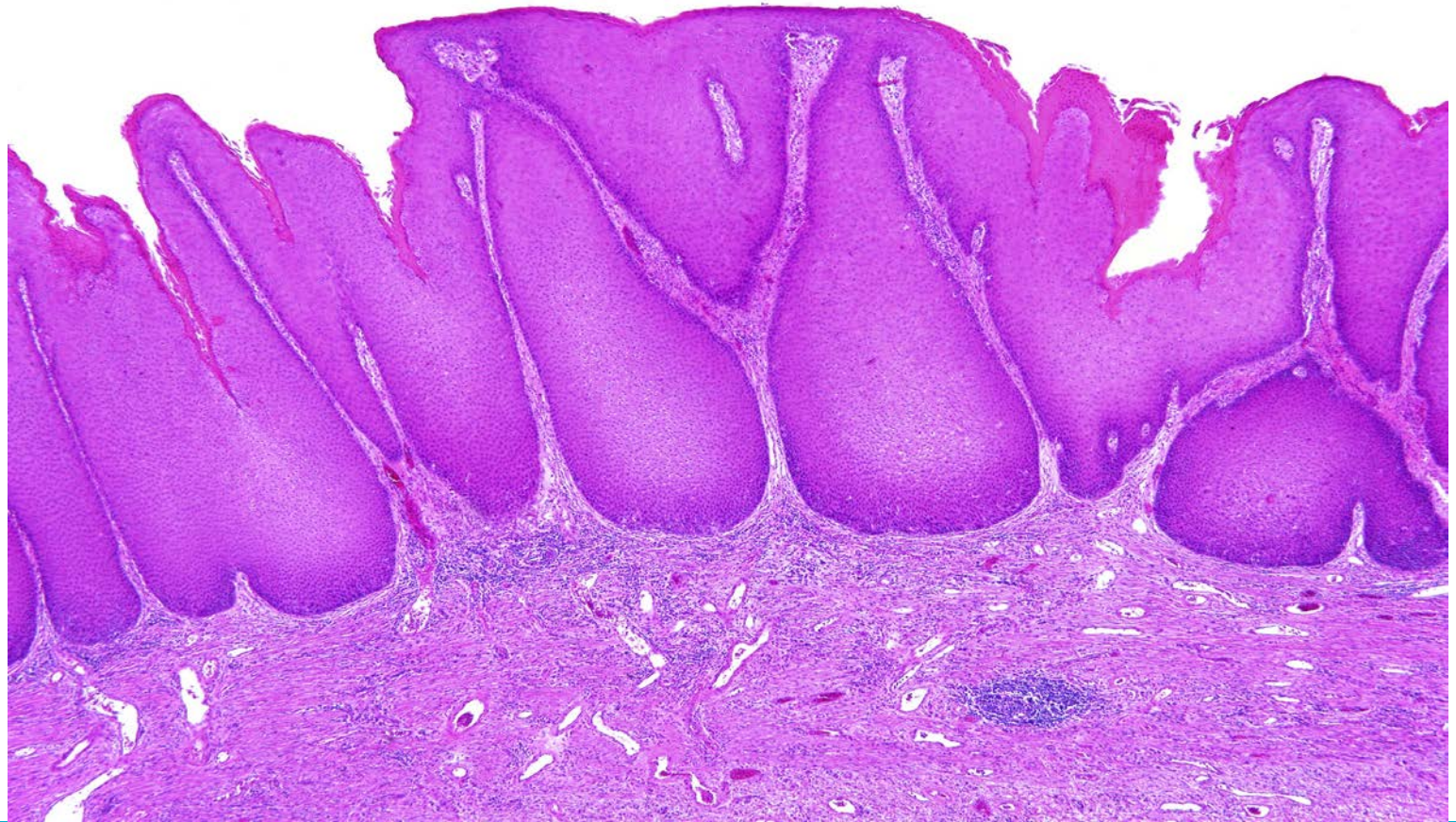
- Older literature equated verrucous carcinoma & giant condyloma (Buschke-Lowenstein tumor)
- More recent studies suggest VC is not HPV associated
- **Per WHO, 5th edition, VC is distinct from giant condyloma based on disparate etiology, HPV associations, histology**

Verrucous Carcinoma

- Slow-growing, destructive, negligible risk of metastasis
- Broad, pushing borders, “church-spire” parakeratosis, micro-abscesses, lymphoplasmacytic inflammation
- **Atypia and koilocytes are absent**
- Rare mitoses confined to basal layer
- Diagnosis best reserved for the thoroughly sampled resection specimen

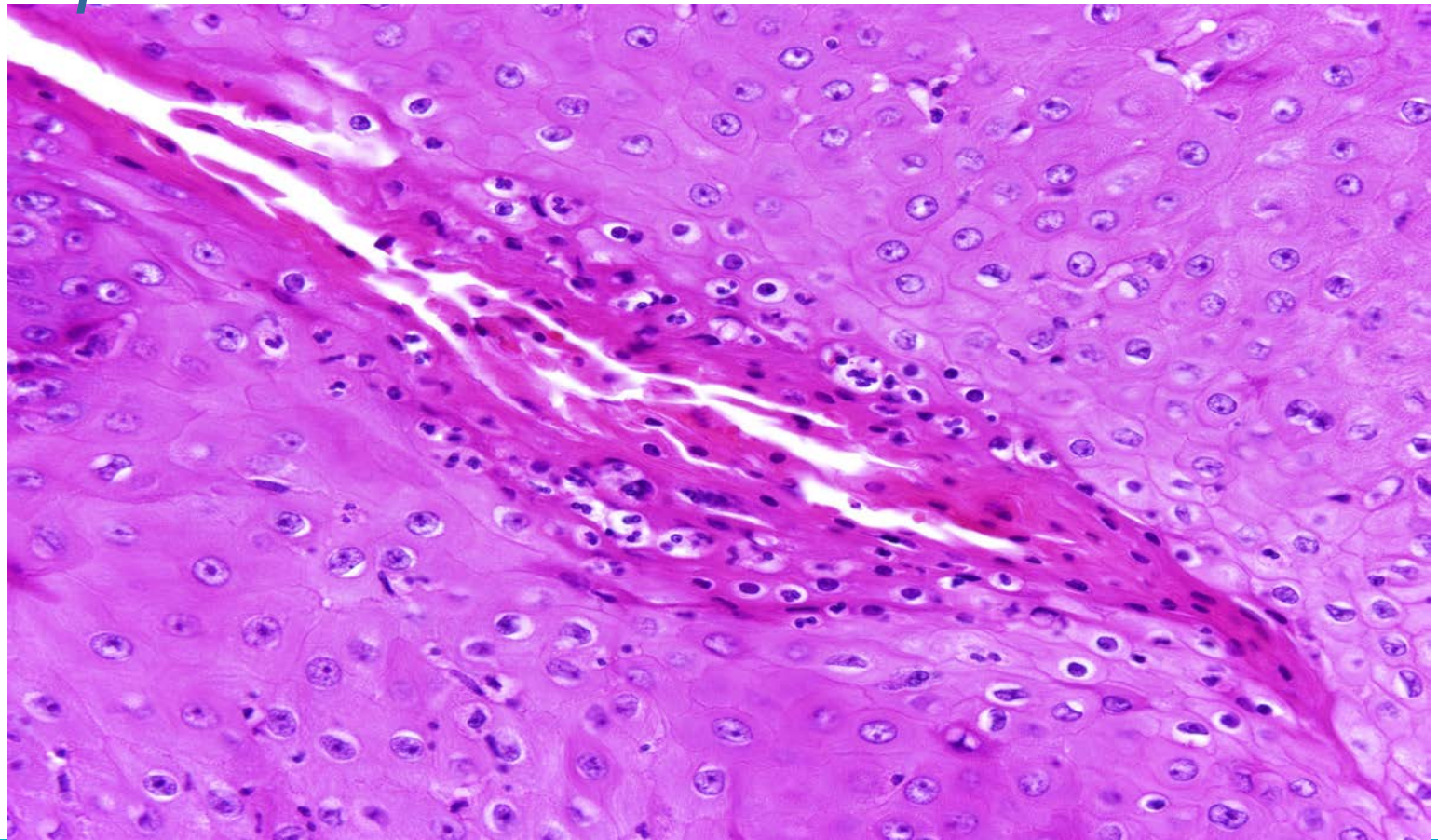
Verrucous Carcinoma:

Broad, Pushing Borders and Parakeratosis



Verrucous Carcinoma:

Intra-Epithelial Micro-Abscesses



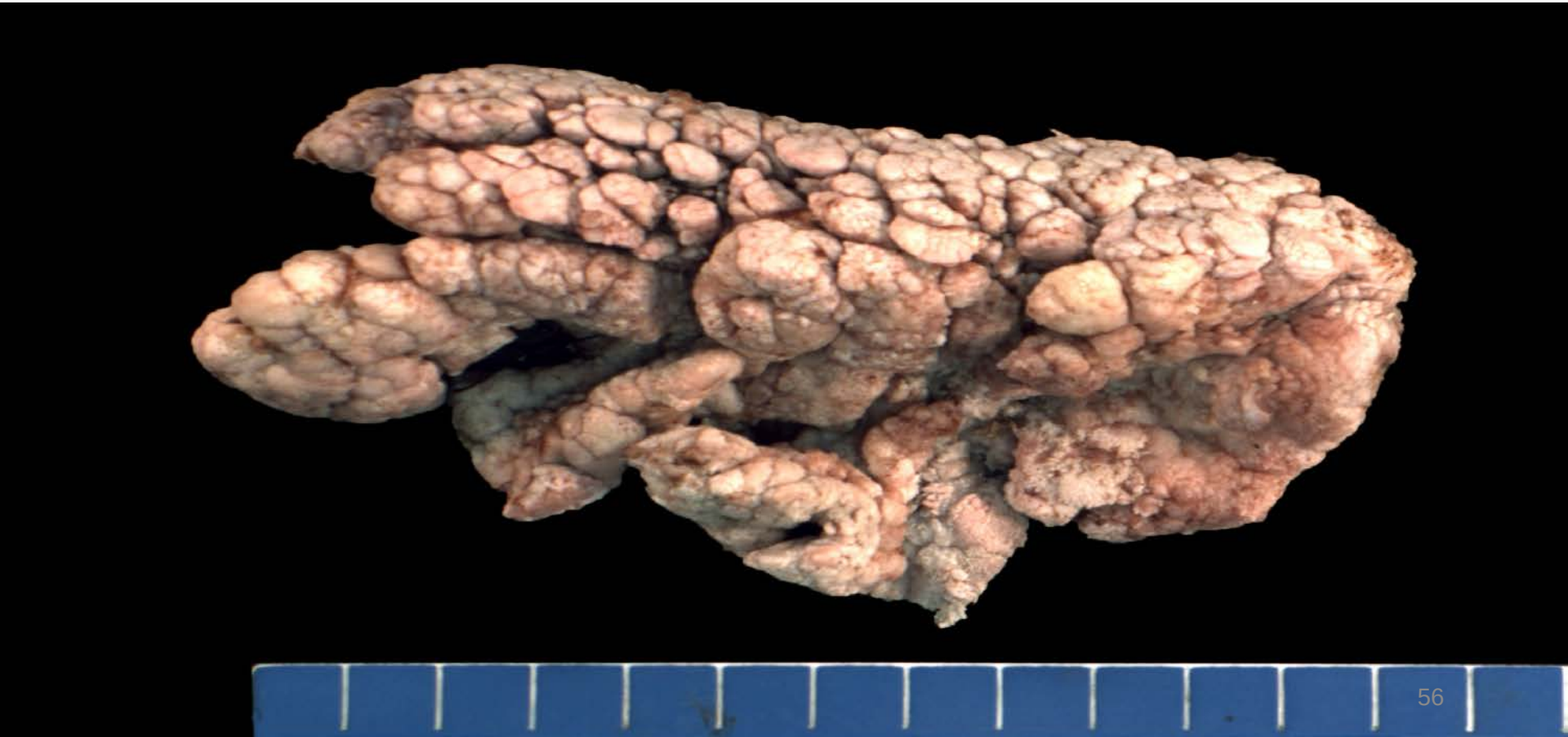
Verrucous Carcinoma:

Lymphoplasmacytic Inflammation Common

Giant Condyloma (Buschke-Lowenstein)

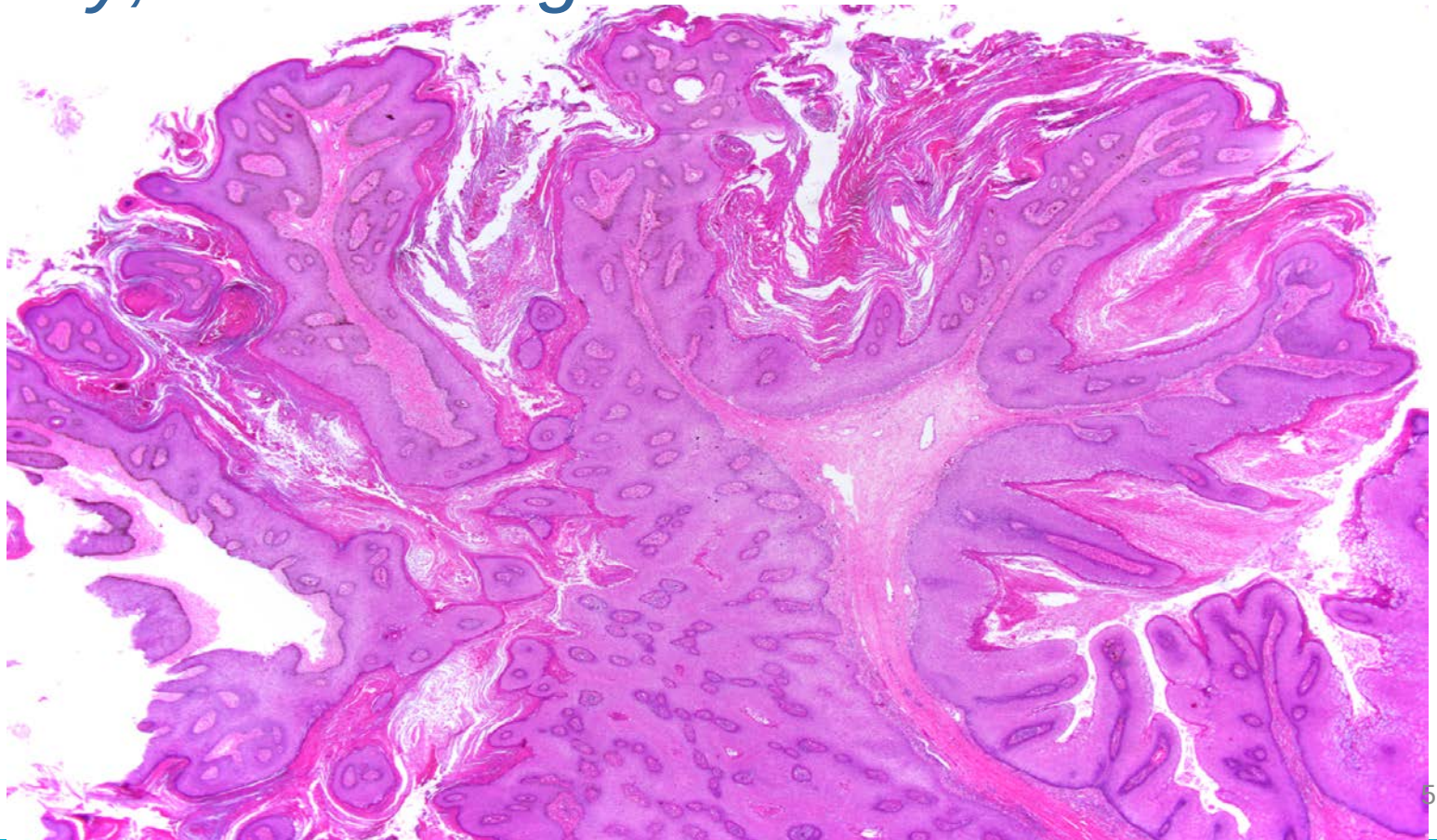
- Benign, associated with low-risk HPV 6 and 11
- Usually large resection specimen
- Papillary architecture, **prominent koilocytes**, an absence of endophytic pushing borders, and mitotic figures easy to identify in lower 1/3
- Absence of atypia

Giant Condyloma (B-L): *Large Resections*



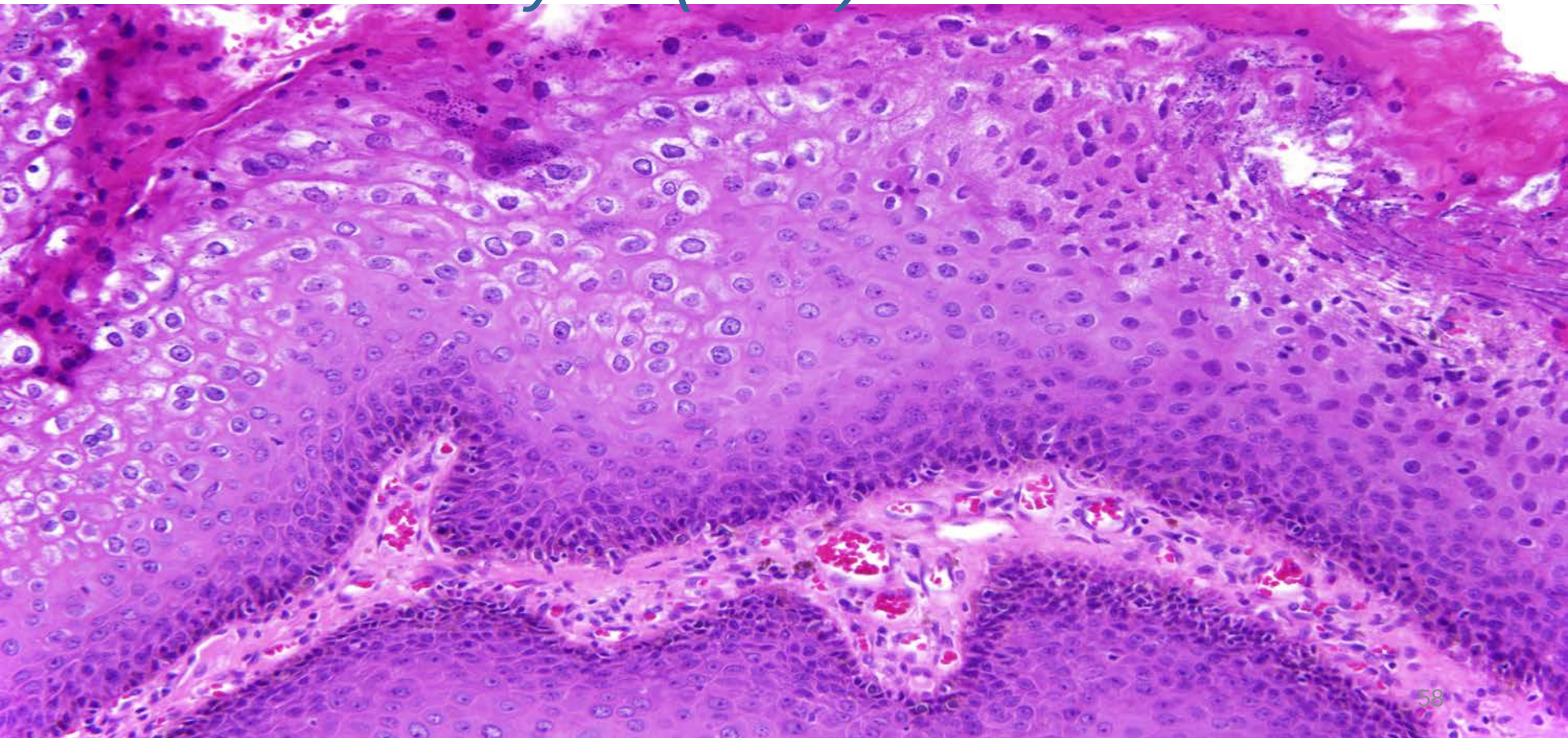
Giant Condyloma (B-L):

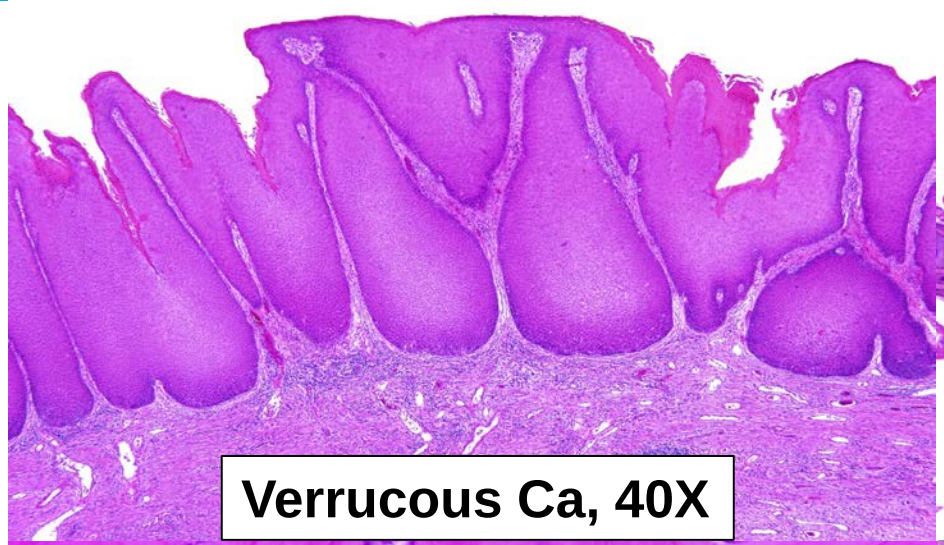
Papillary; No Pushing Borders



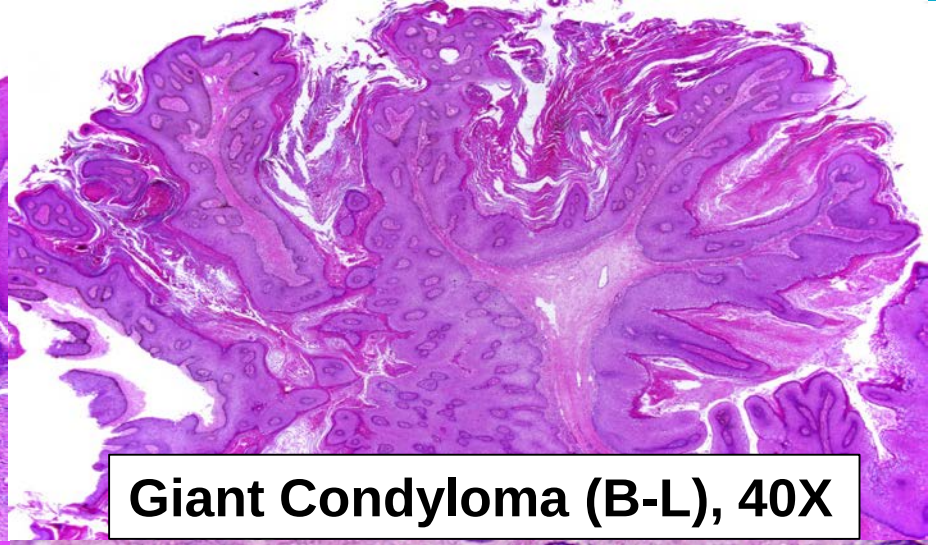
Giant Condyloma (B-L):

Extensive Koilocytes (LSIL)

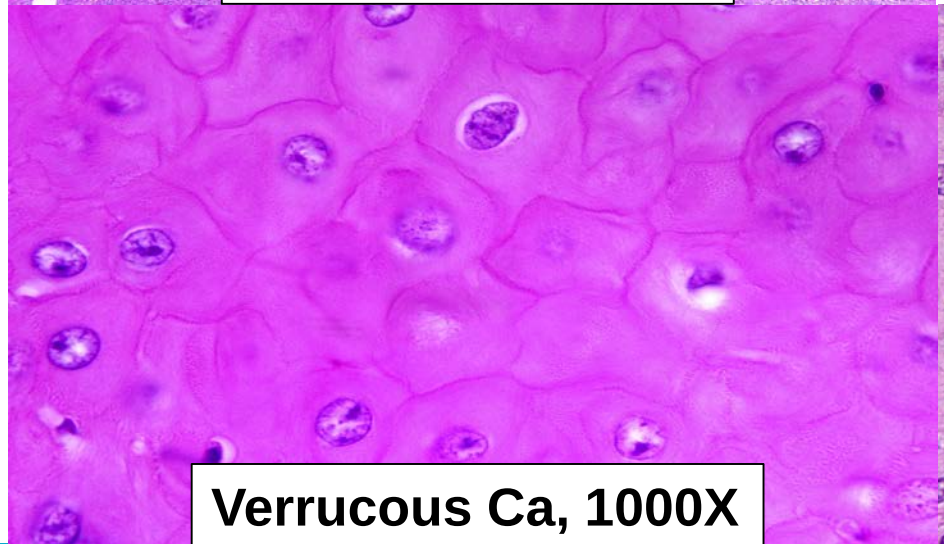




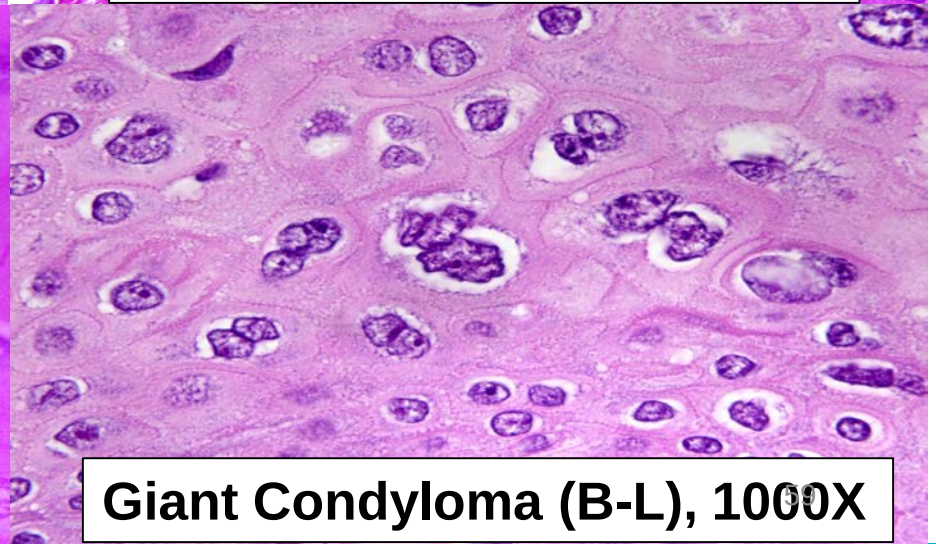
Verrucous Ca, 40X



Giant Condyloma (B-L), 40X



Verrucous Ca, 1000X

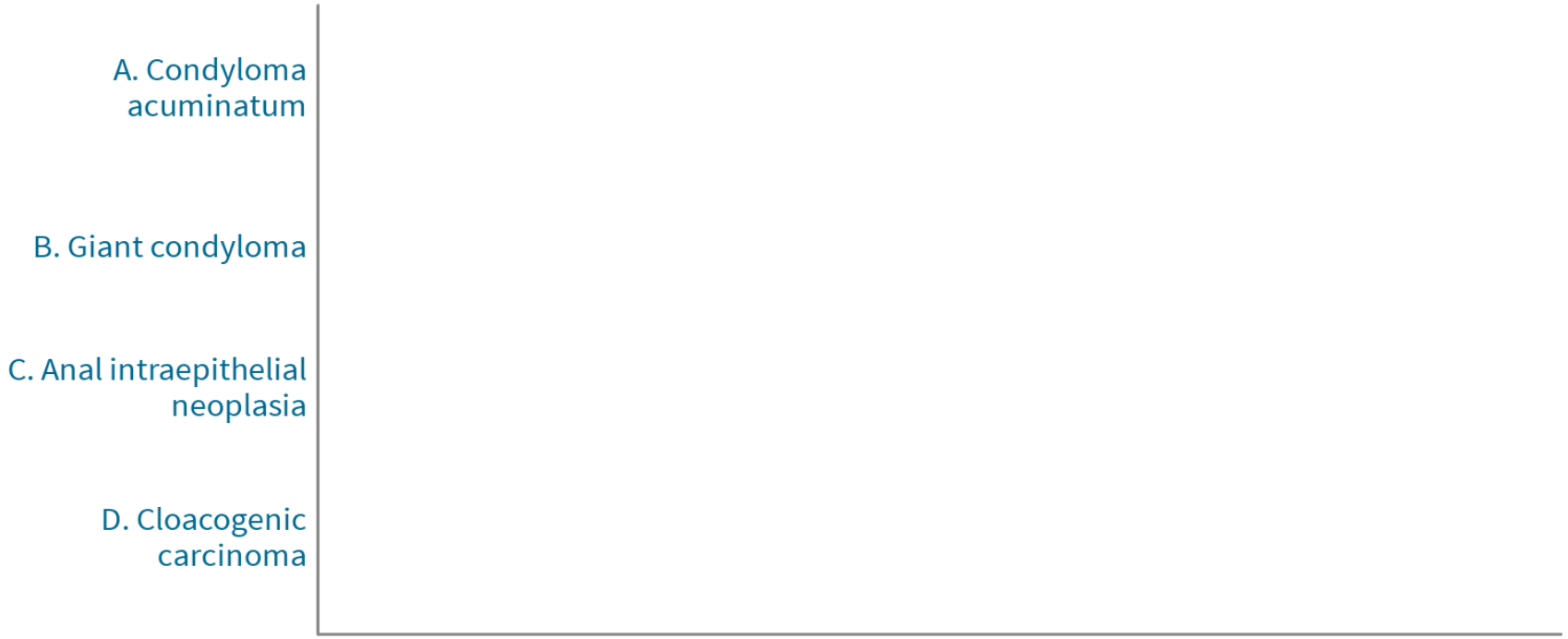


Giant Condyloma (B-L), 1000X

Pearls & Pitfalls

- Both verrucous carcinoma and giant condyloma lack marked atypia
- If identified, thorough sampling, if not complete submission, should be pursued to evaluate for invasion
- Lesions with invasion or metastasis are best classified as invasive squamous cell carcinoma, which may result in chemoradiation

Which of the following terms is still current in the anus?



Extra-Mammary Paget Disease

- Precursor to adenocarcinoma
- Anal Paget disease is **staged in AJCC and CAP**
- Presents as a slow-growing plaque
- Squamous epithelium infiltrated by large neoplastic cells with abundant pale cytoplasm, vesicular chromatin, and prominent nucleoli
- ***Not* an H&E diagnosis**
  - Must exclude melanoma and determine type

Extra-Mammary Paget Disease

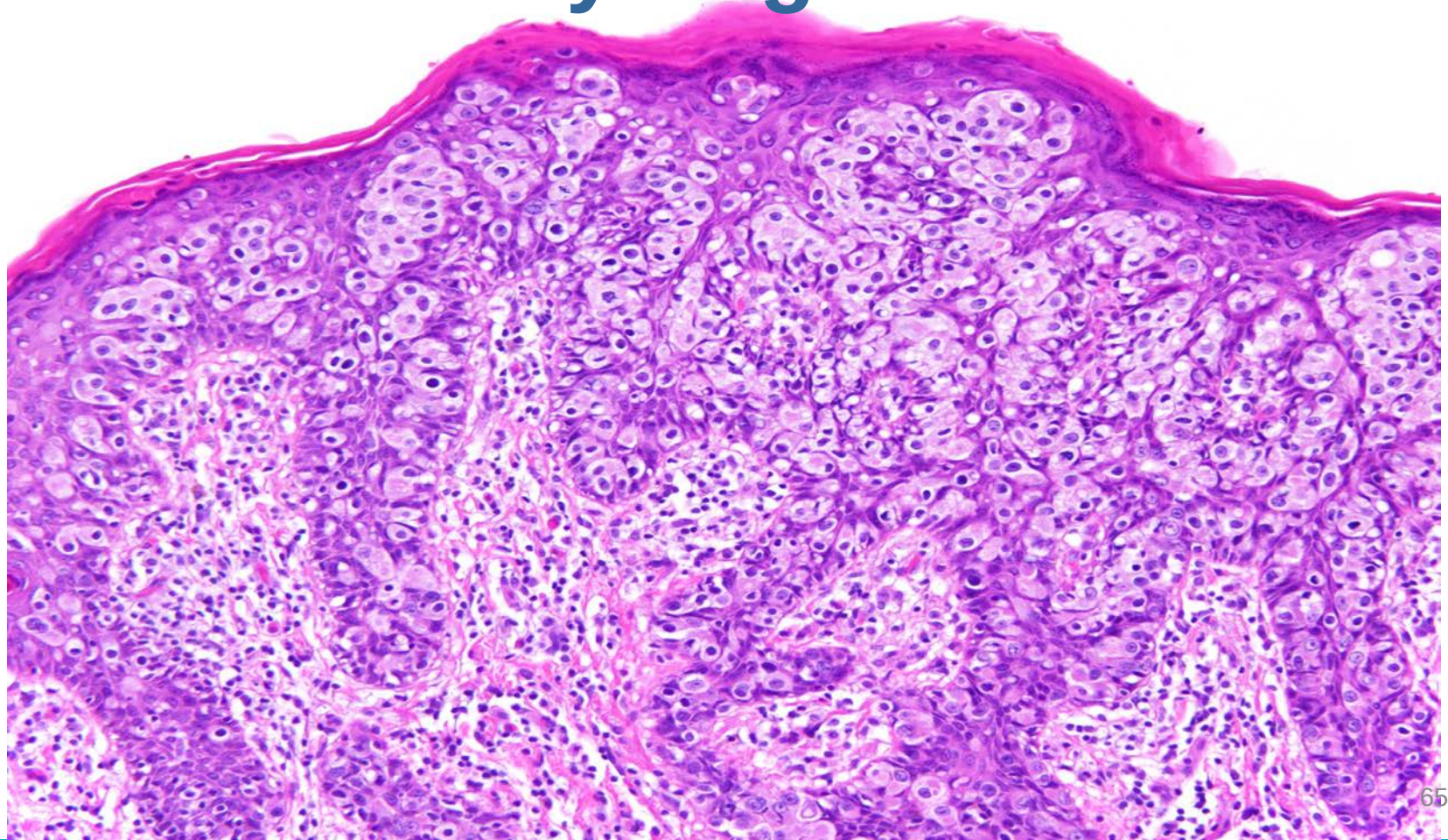
1.) <u>Primary</u>

- Invasion uncommon
- Identical immunoprofile as breast Paget
- CK7+, CK20-, GCDFP+

2.) <u>Secondary</u>

- Immunoprofile reflects immunoprofile of underlying malignancy
- Usually CRC, but also GYN, GU primaries
- GCDFP-

Extra-Mammary Paget Disease



Sample Note: *Anal Paget Disease*

Anus, plaque, biopsy:

-Extramammary Paget Disease

-Negative for an invasive component

Note: There are two forms of extramammary Paget disease: a primary apocrine type, and a secondary form that is associated with an underlying synchronous or metachronous malignancy. The immunoprofile (GCDFP-, CK7-, CK20+, CDX2+) suggests the latter. Careful correlation with imaging studies to assess for the site of potential primary suggested (colorectal favored).

Anal Melanoma

- Site important
  - Cutaneous melanomas = surgery alone; staged with skin; UV light exposure a risk, *BRAF* mutations
  - Mucosal melanomas = surgery and radiation; NOT staged in AJCC; *Kit* mutations
- Histology similar to melanoma at any site
  - Solid, nested, or fascicular architecture of epithelioid, plasmacytoid, or spindled neoplastic cells
  - Up to 30% of anal melanoma are amelanotic
  - Can histologically mimic extra-mammary Paget disease

Anal Melanoma IHC Panel Approach

- Two melanoma markers: S100 protein, MiTF

  -S100 also evaluates for neural processes

- AE1/3 to evaluate for sarcomatoid carcinoma*
- CD117* and DOG1 to evaluate for a GIST
- SMA and Desmin to evaluate for a smooth muscle tumor

*Anal melanomas commonly display CD117 and often show focal cytokeratin reactivity

Anal Melanoma

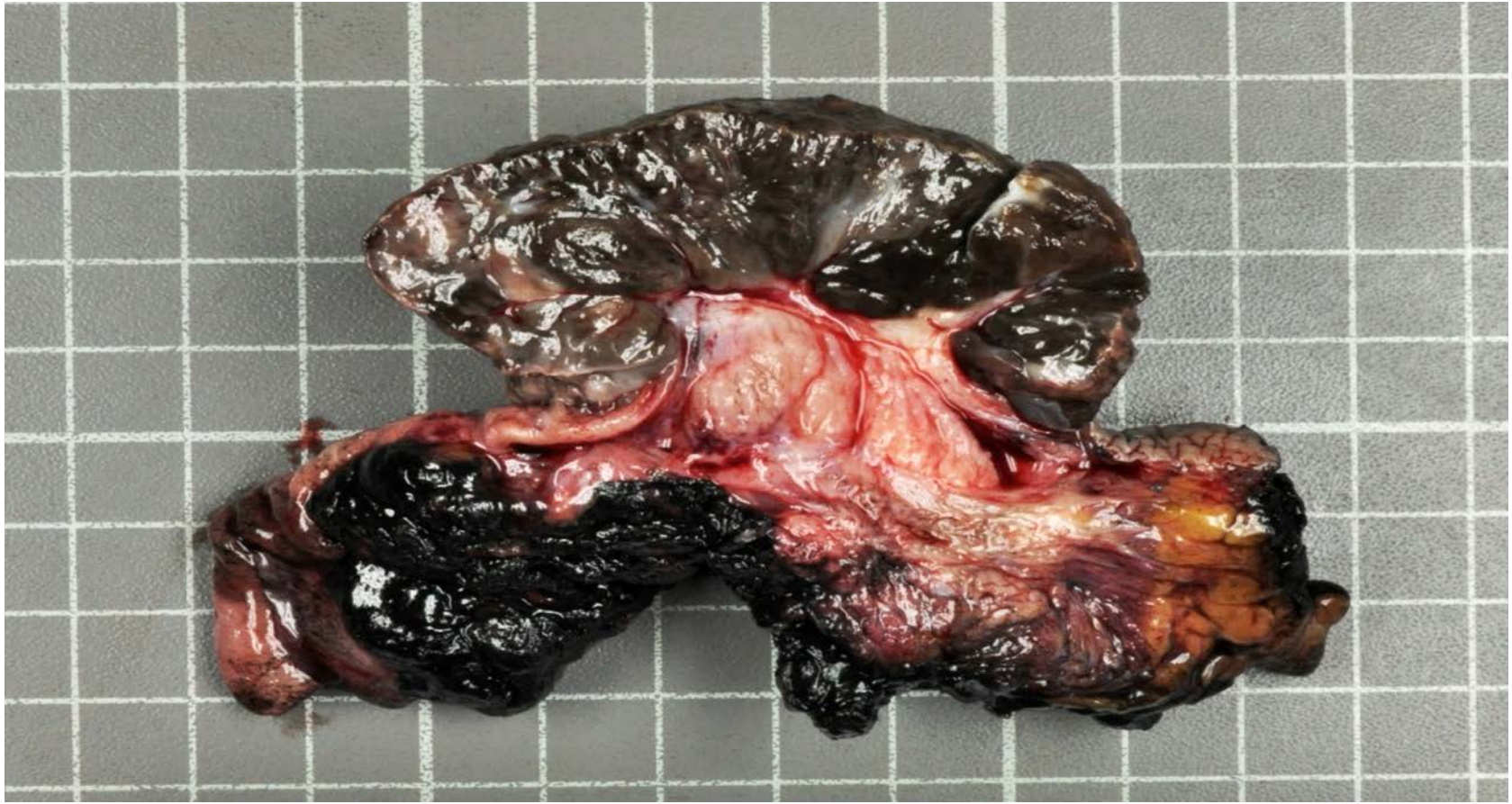
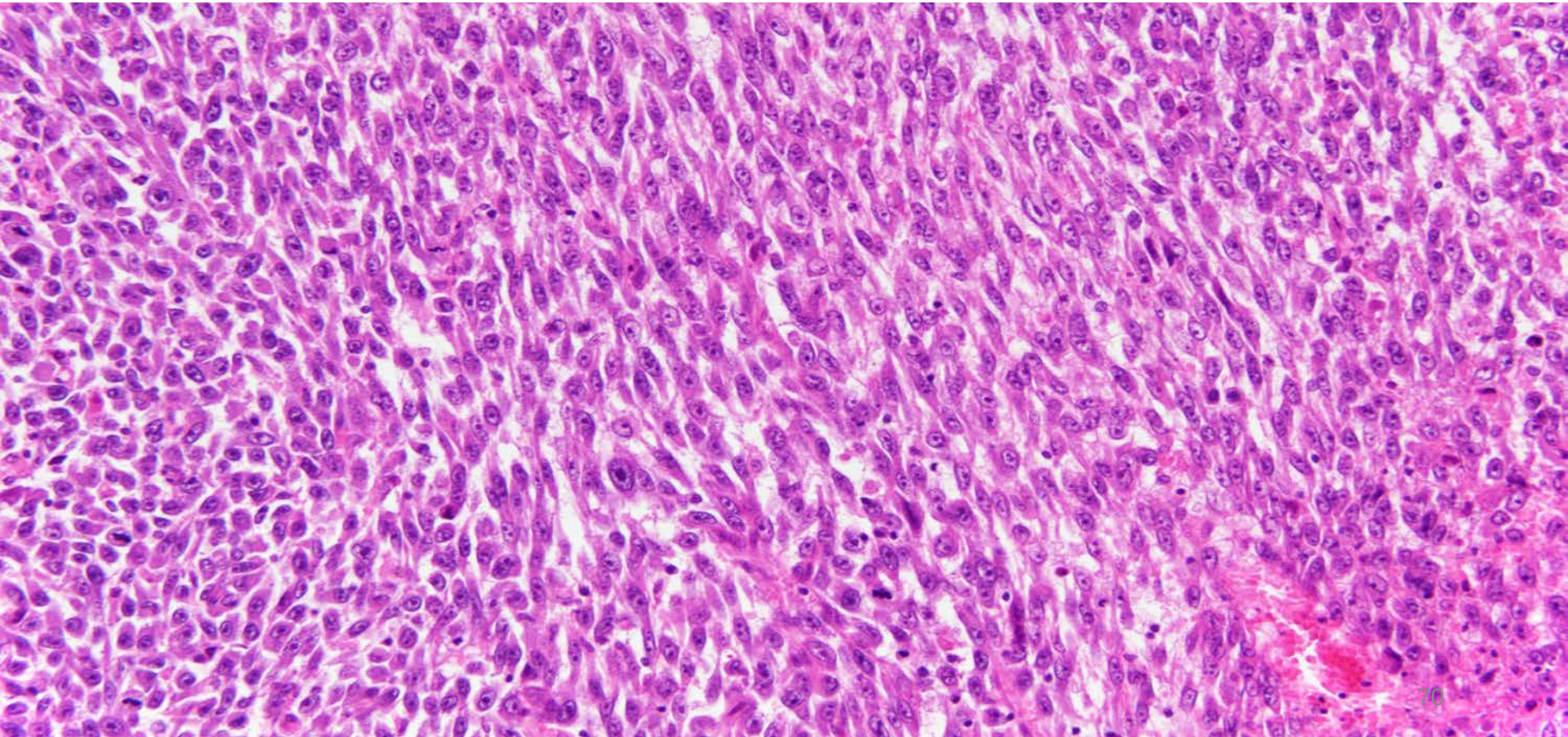
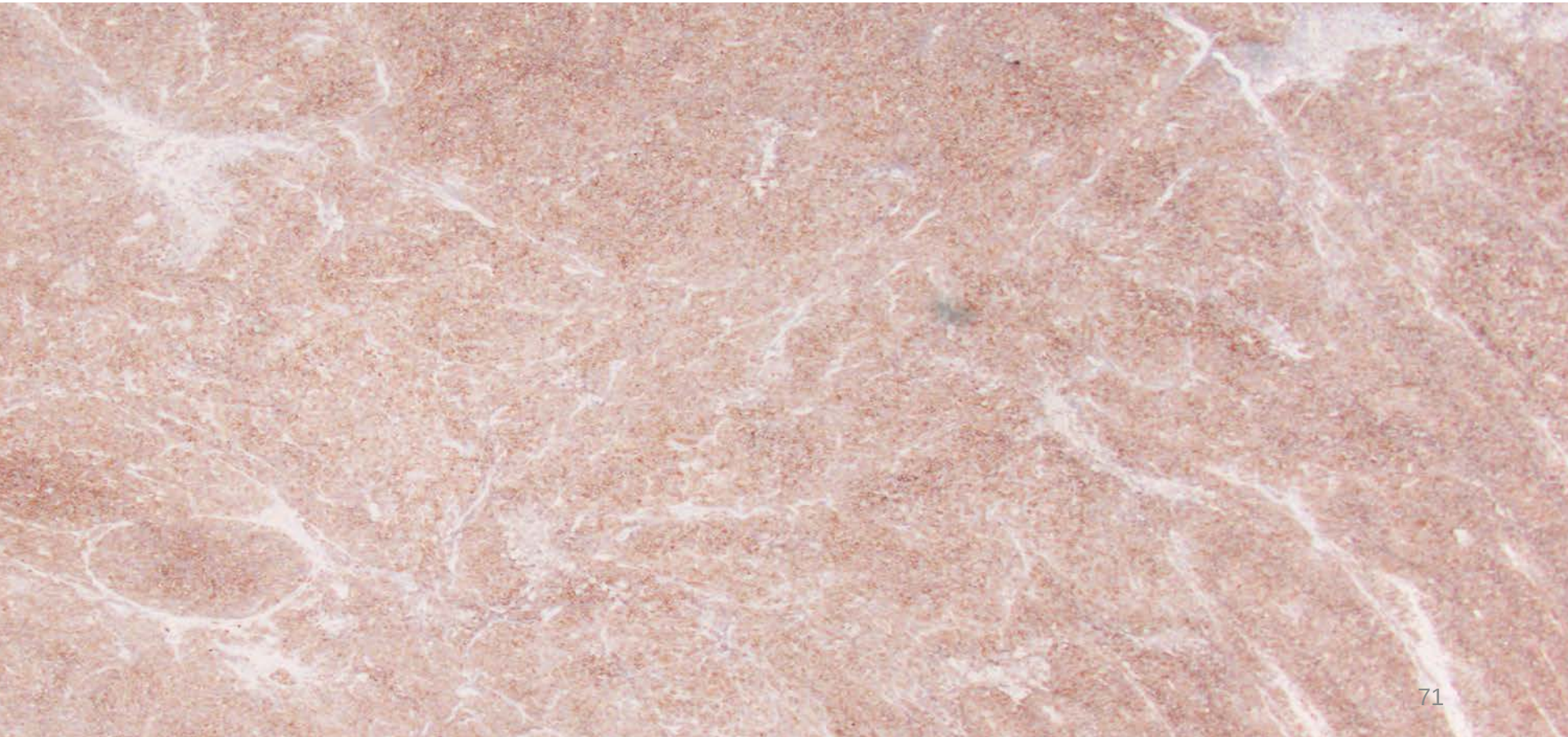


Photo Courtesy of Laura G. Pastrián MD, "La Paz" University Hospital, Madrid, Spain, @DraEosina

Anal Melanoma



Anal Melanoma: *Can Display CD117, Focal Cytokeratin Reactivity*



Thrilling Cases

Take Home Messages

- LAST consensus statement:
  - LSIL v HSIL
  - p16 for HSIL v HSIL mimic, *or* cyto-bx discrepancy
- Subclassify anal Paget
- Site important for melanomas

COLLEGE of AMERICAN PATHOLOGISTS
Education

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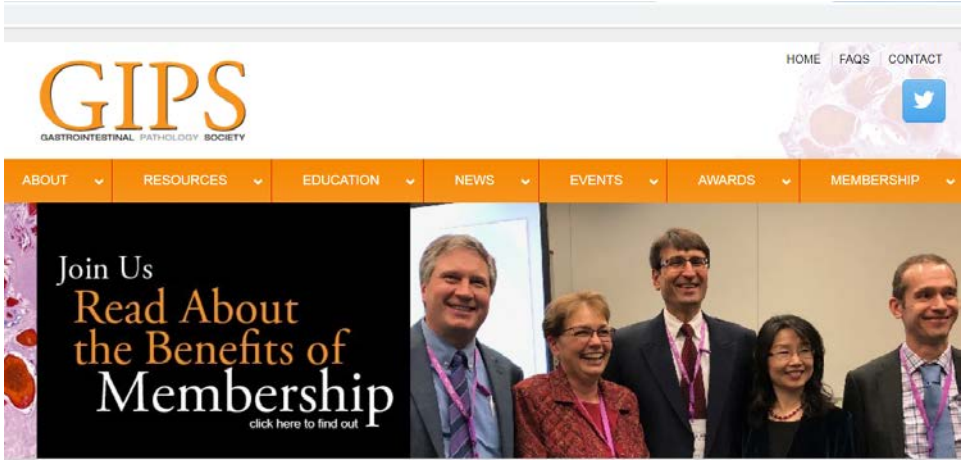
Knowledge
Relationships
Expertise

S1921C

Small Bites and Small Sites: Big Gastrointestinal Pathology Diagnostic Problems

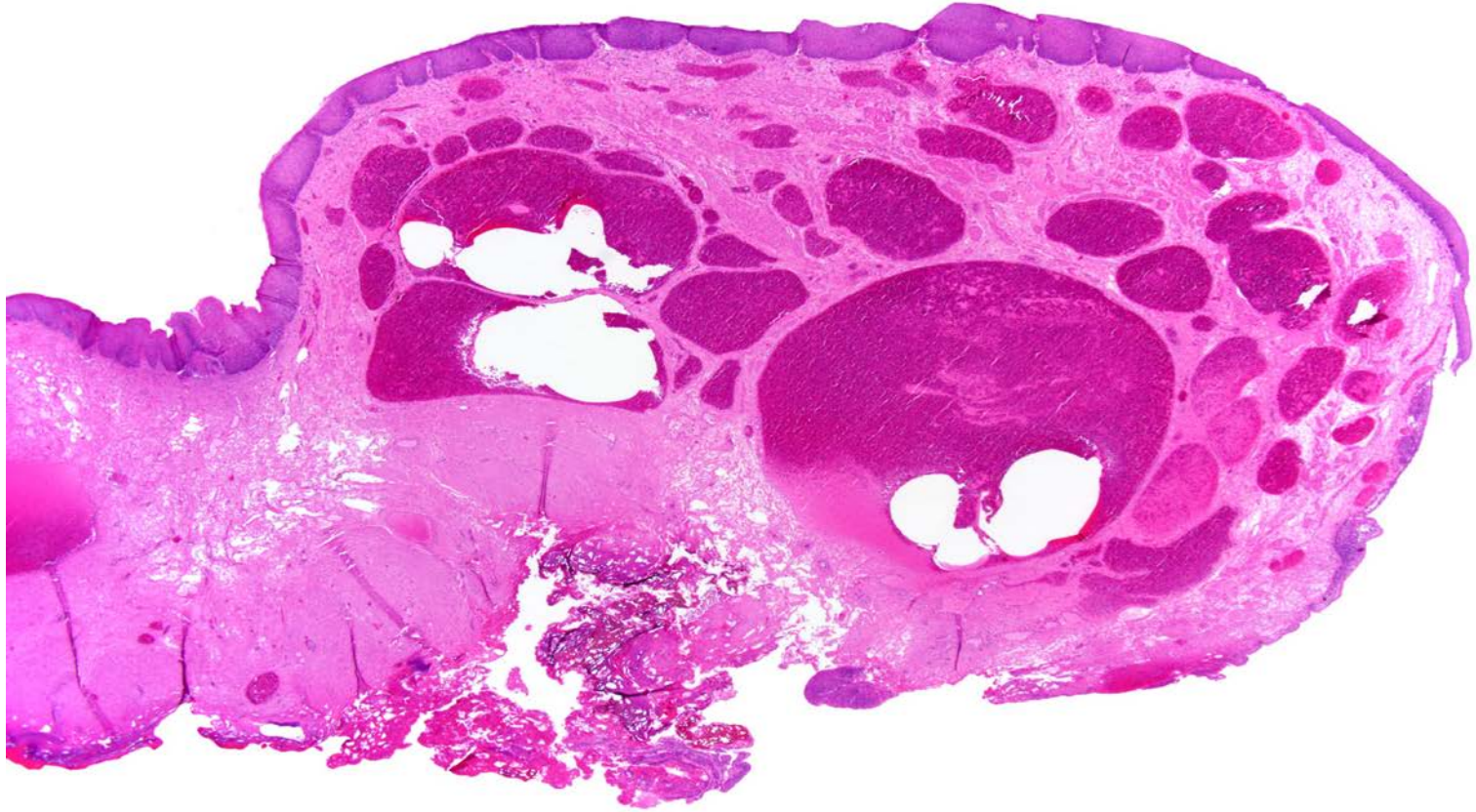
Christina A. Arnold, MD
Wei Chen, MD, PhD, FCAP
Joseph Misdraji, MD

GIPS Membership!

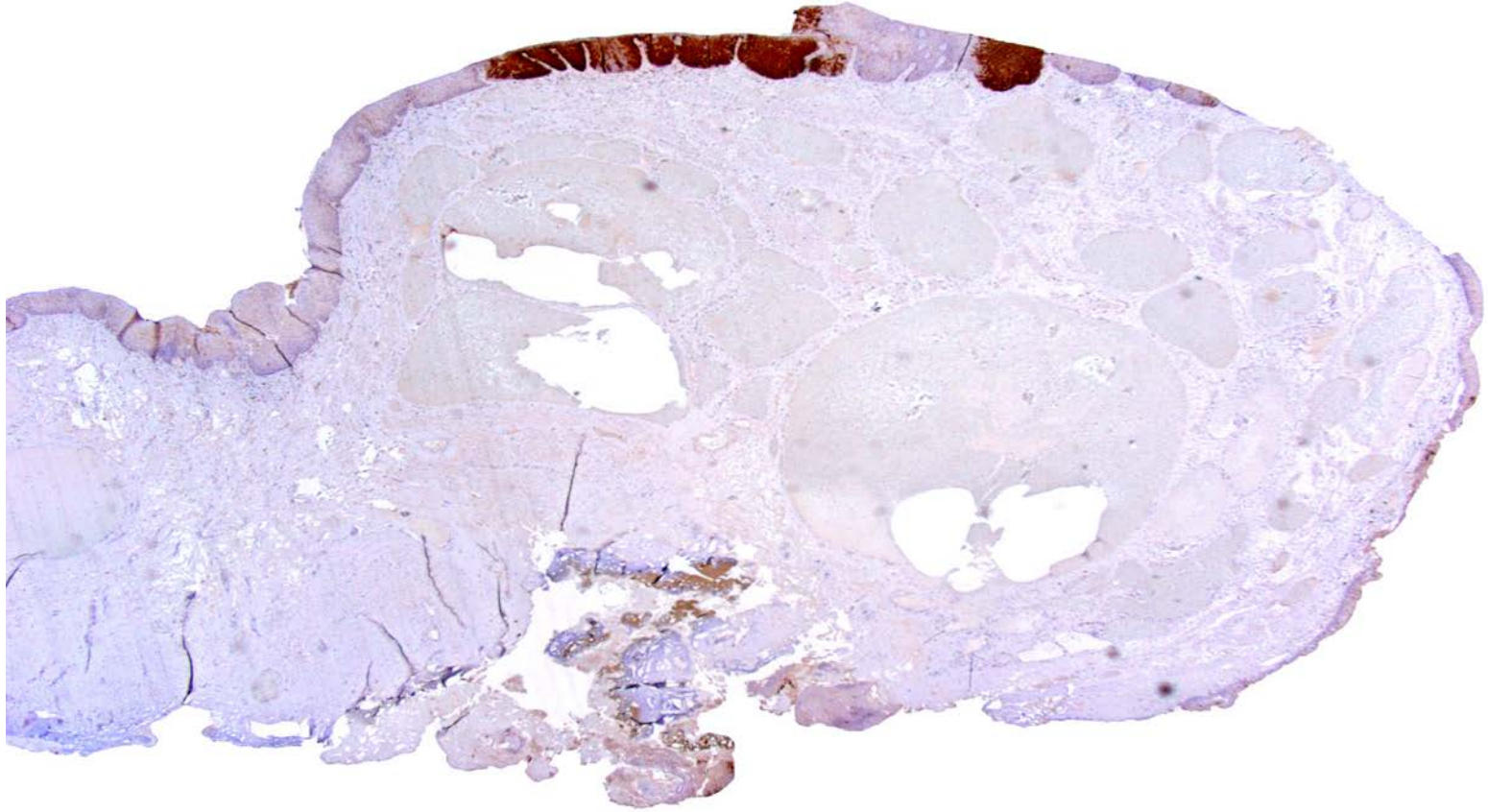


- Meetings
- Archived lectures
- Journal Watch
- Case of the Month
- Job/fellowship postings
- Receptions

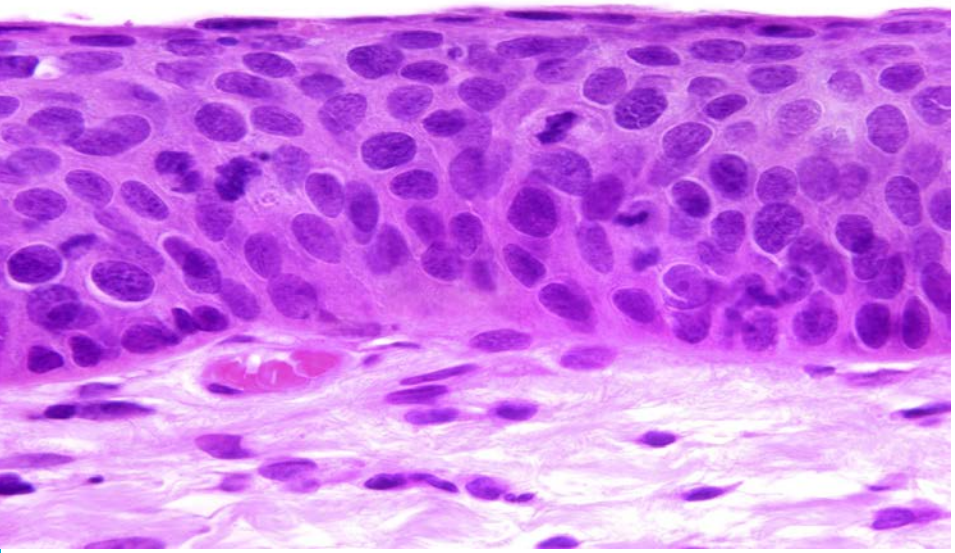
Near Miss: *Don’t fall asleep on a hemorrhoid*

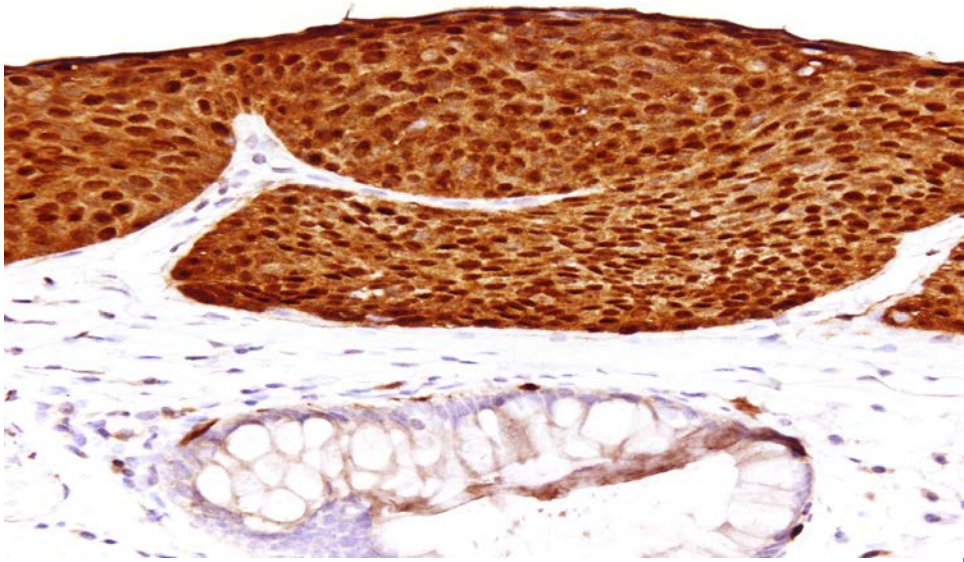


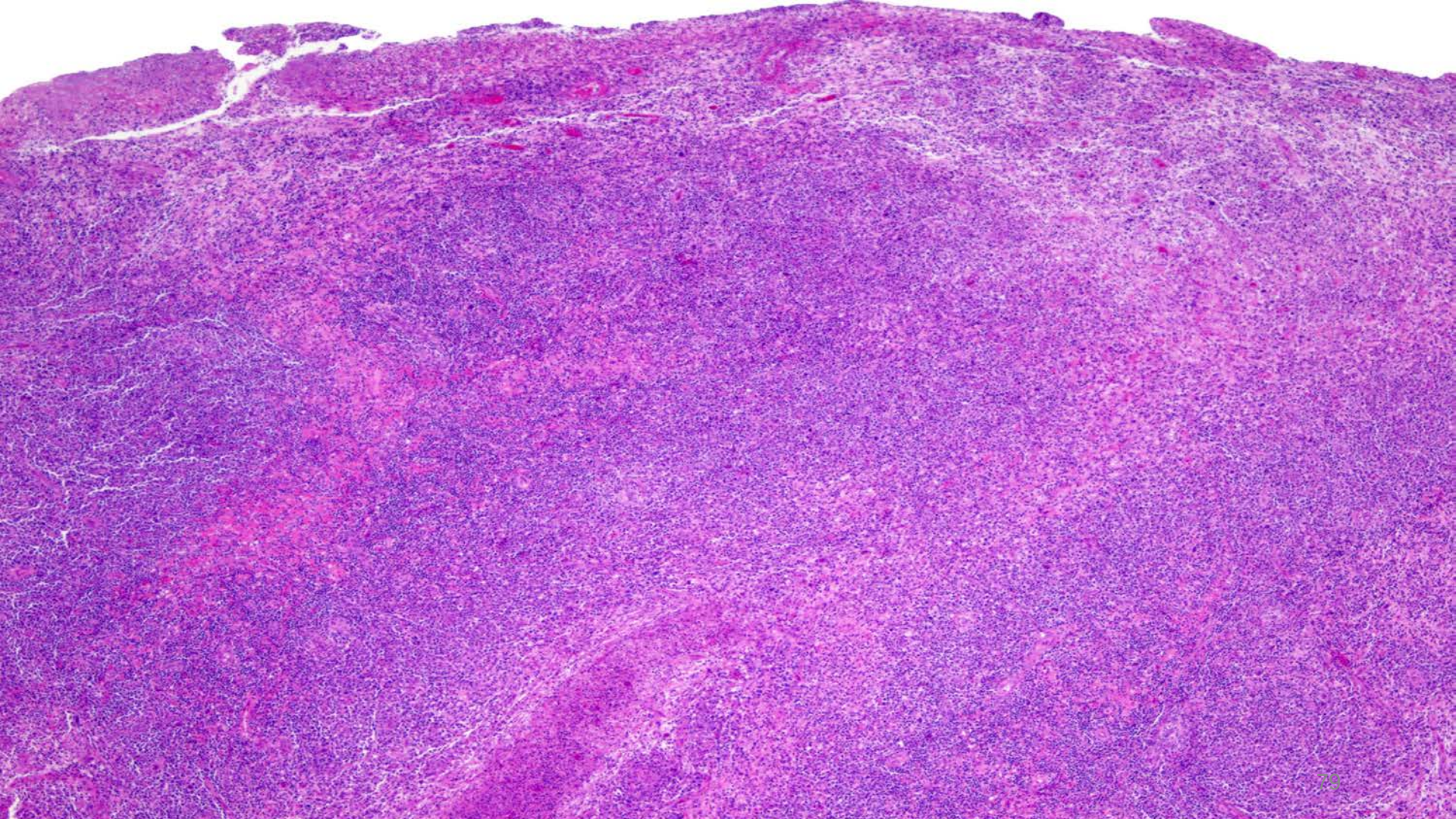
Near Miss: *Hemorrhoid + Unexpected HSIL (AIN2)*

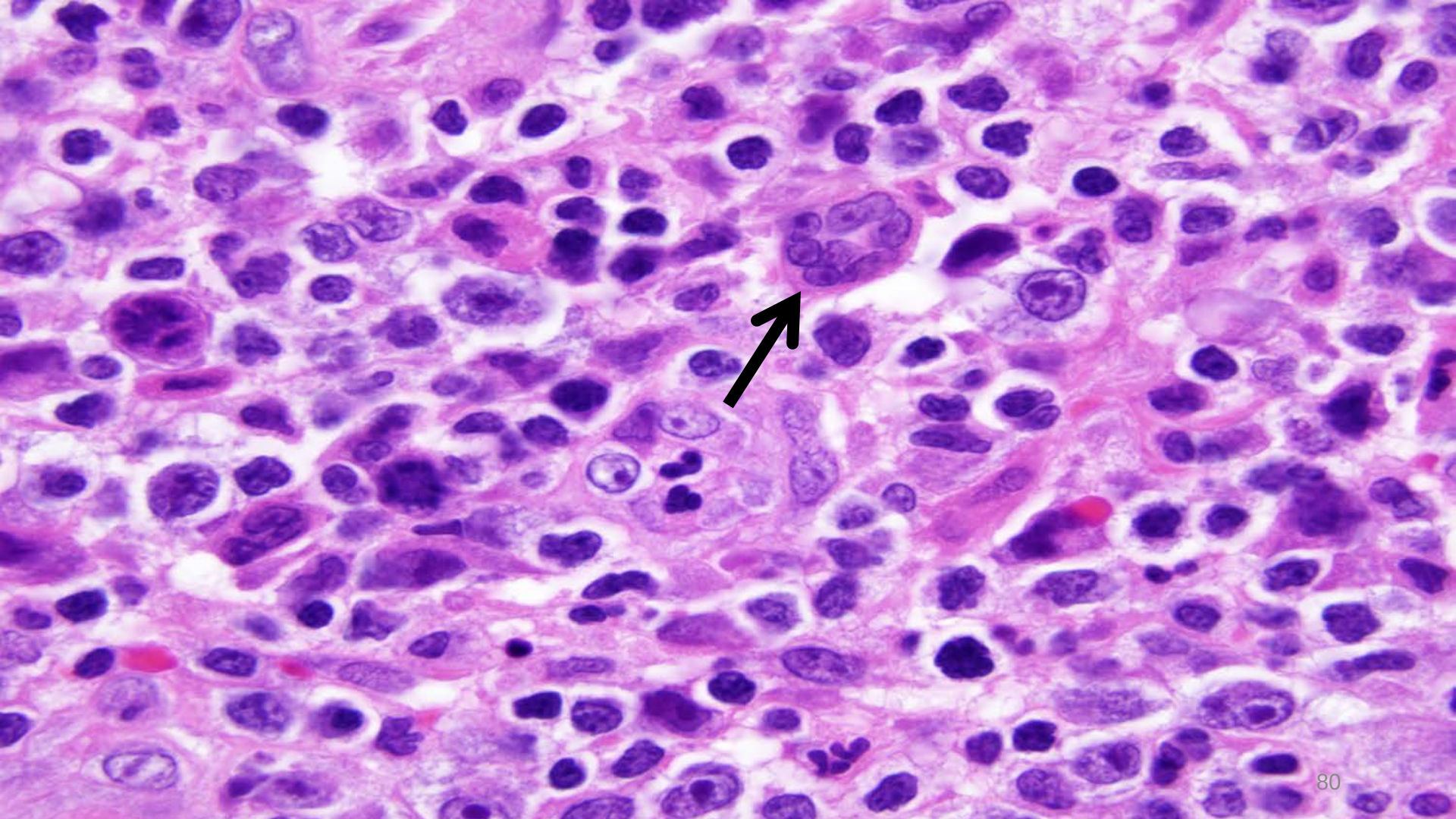


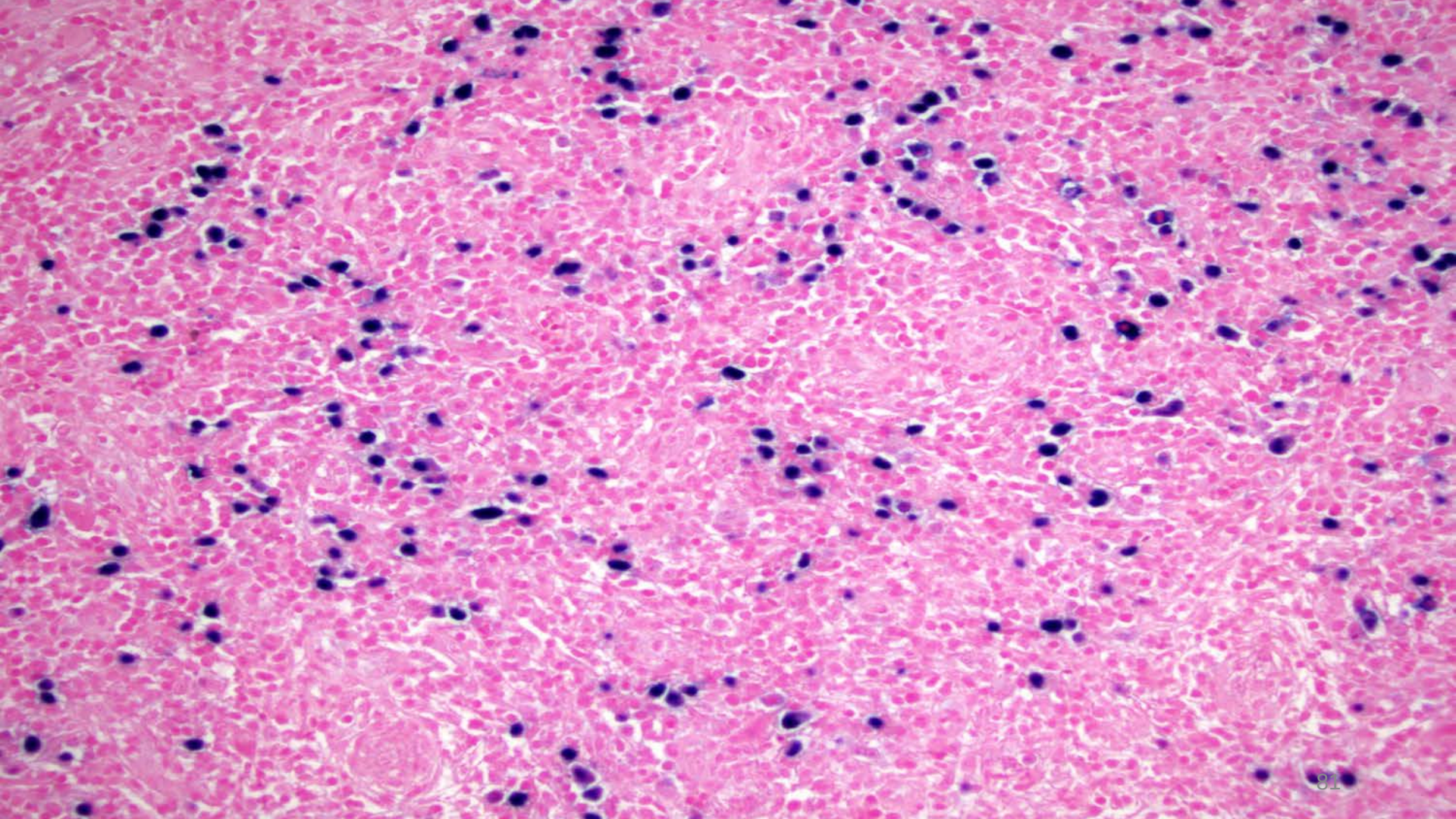
Near Miss: *Hemorrhoid + Unexpected HSIL (AIN2)*





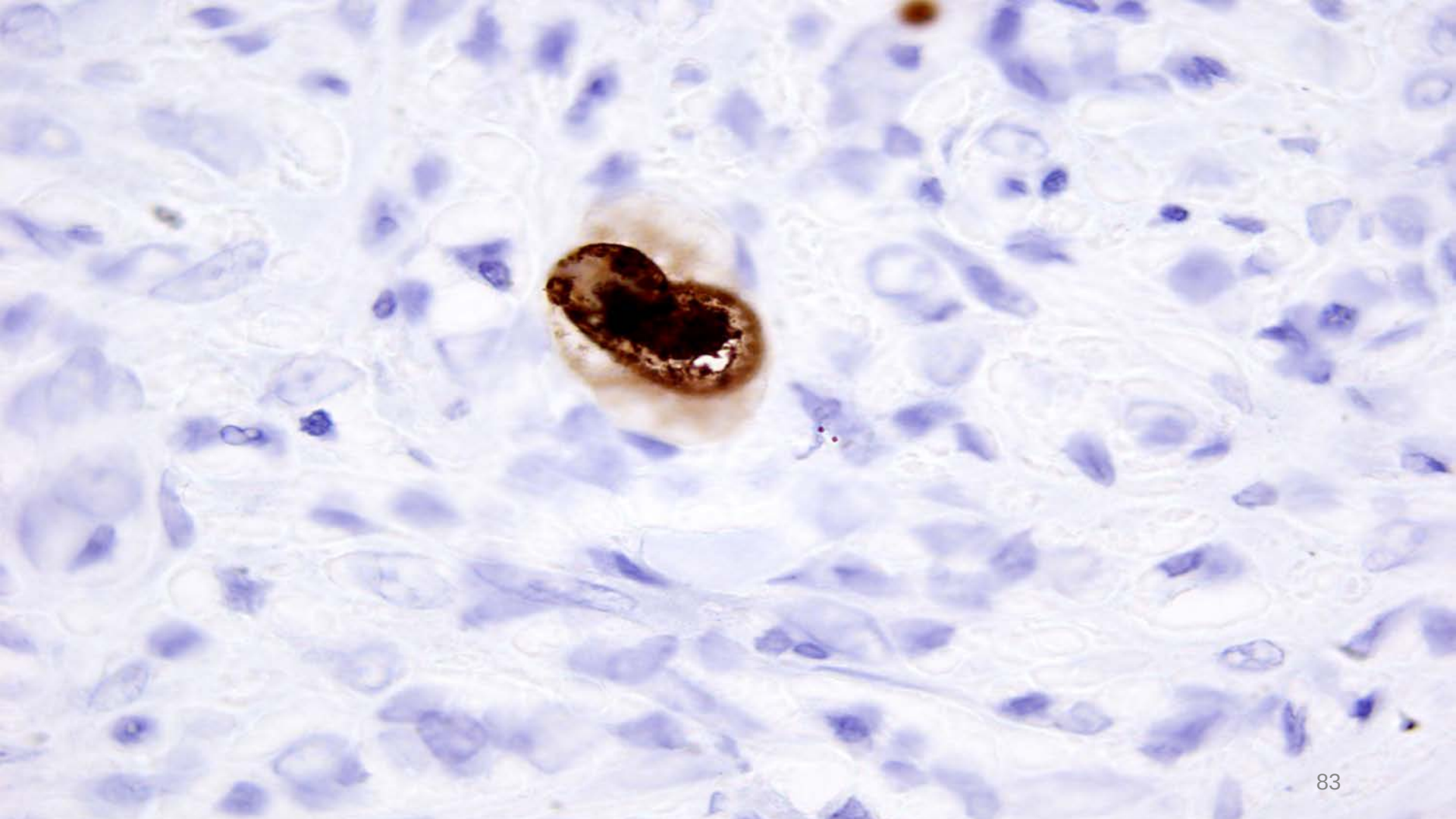


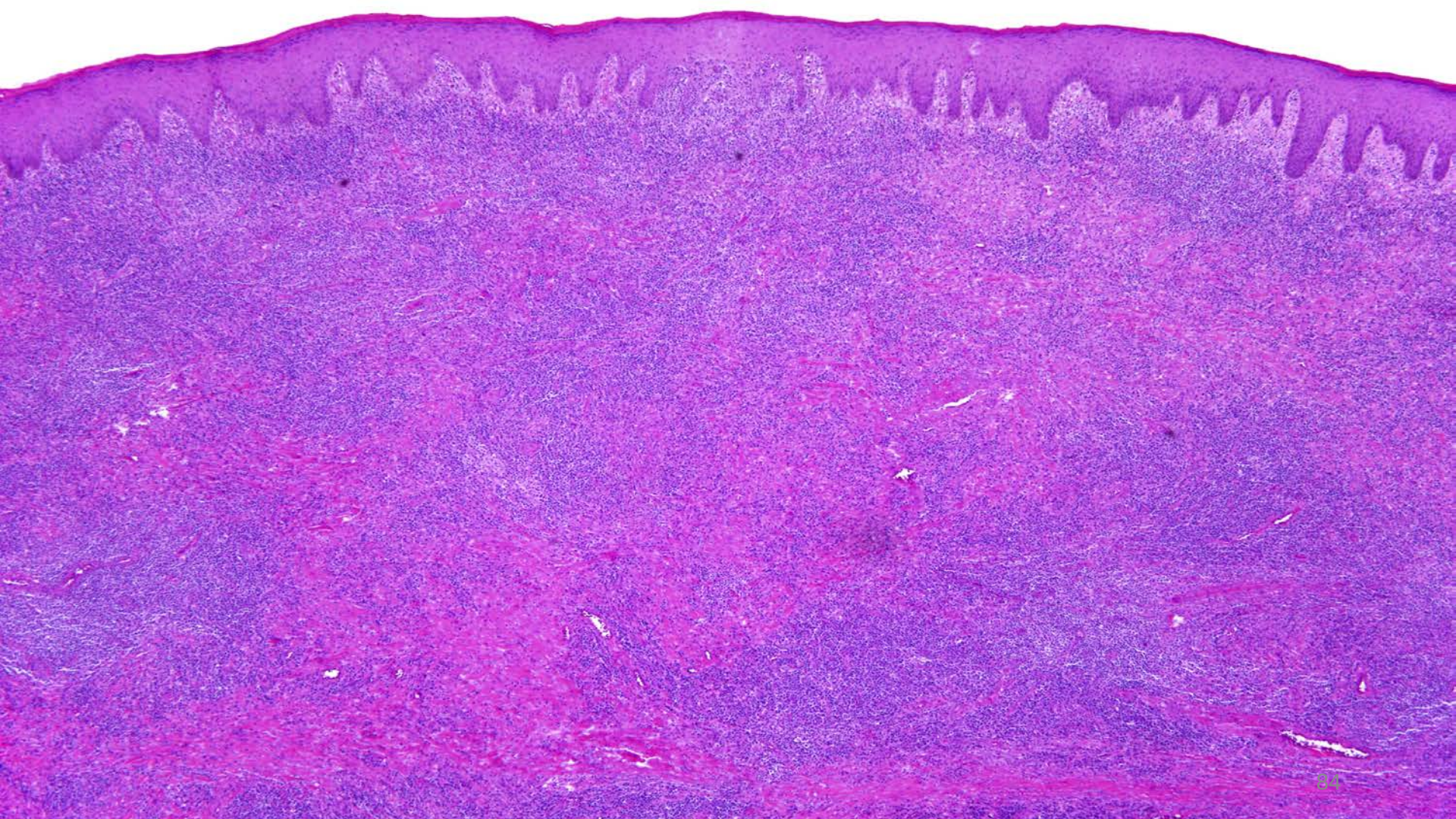


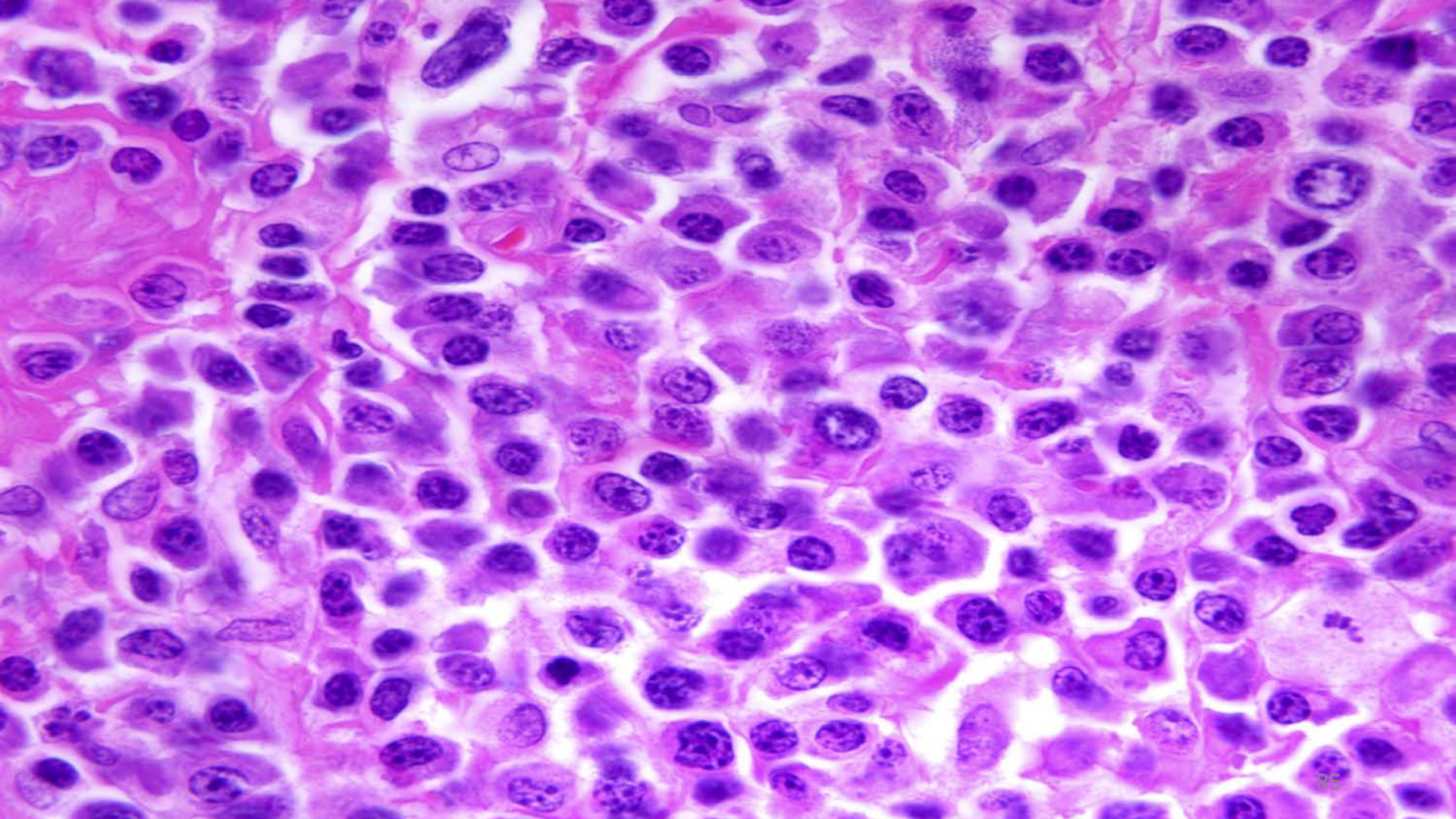


Near Miss: *EBV Mucocutaneous Ulcer*

- Associated with immunosuppression
- Self-limited lesion with an indolent course
- Heavy polymorphous infiltrate and Reed-Sternberg-like cells
- B-cells label with CD30 and EBER
- Clonal immunoglobulin heavy chain gene rearrangements and T-cell patterns
- Circulating EBV DNA NEGATIVE in peripheral blood
- A hematopathology evaluation is worthwhile
- A CMV IHC is suggested in all cases







Near Miss: *Sexually Transmitted Infectious (STI) Proctitis*

- Syphilis and or LGV
- HIV+, Men who have Sex with Men
  - Most cases prospectively lack these clues
- Presents as ulcerations, nodules, polyps, masses
- Intense band-like plasma cells infiltrate at the squamous epithelium-lamina propria interface with variable granulomata and fibrosis
- Clinical tests are gold standard to establish dx
- Also consider HPV associated neoplasia, CMV, and a hematolymphoid evaluation

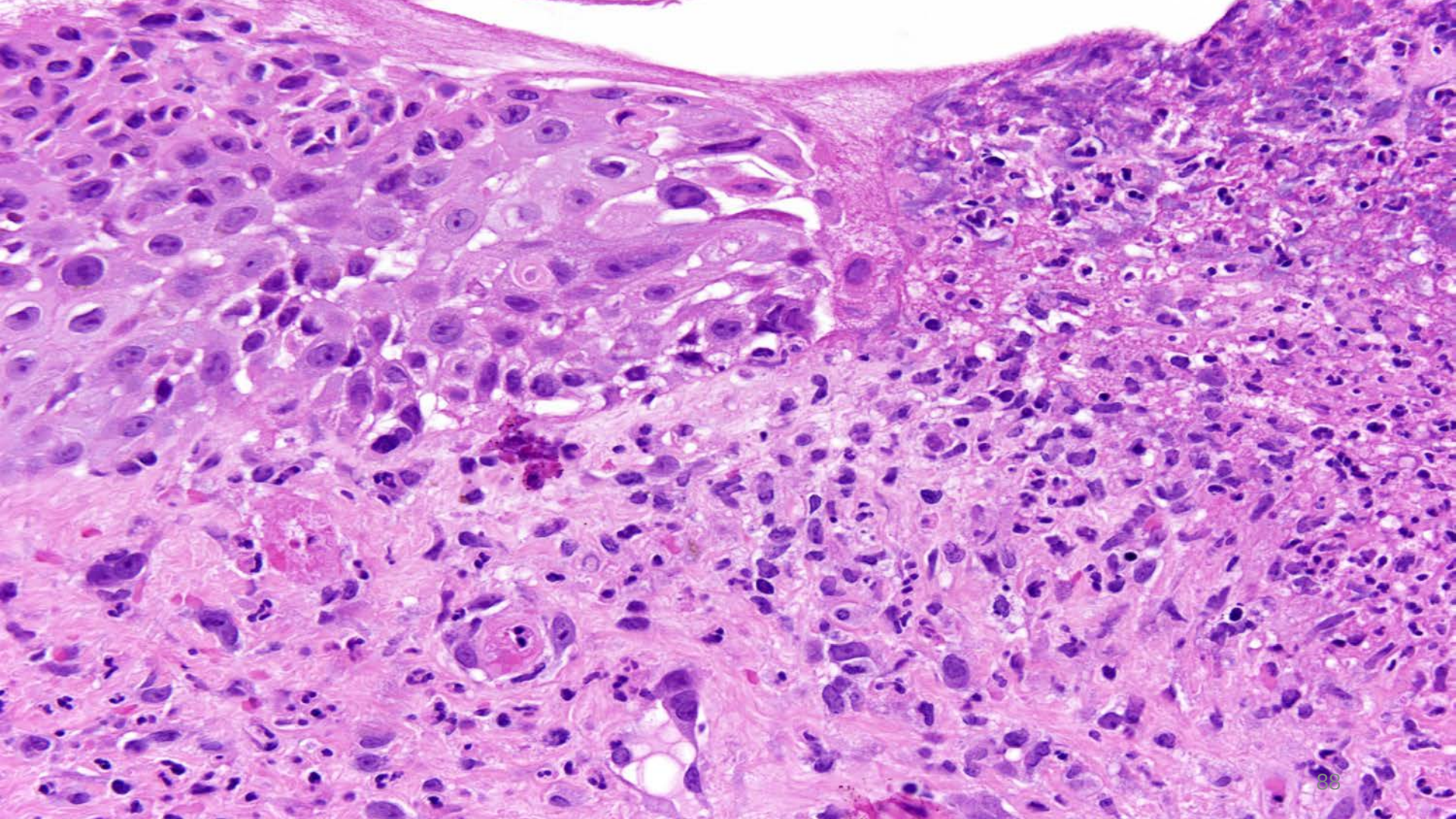
Sample Note: *STI Proctitis*

Anus, mass, biopsy:

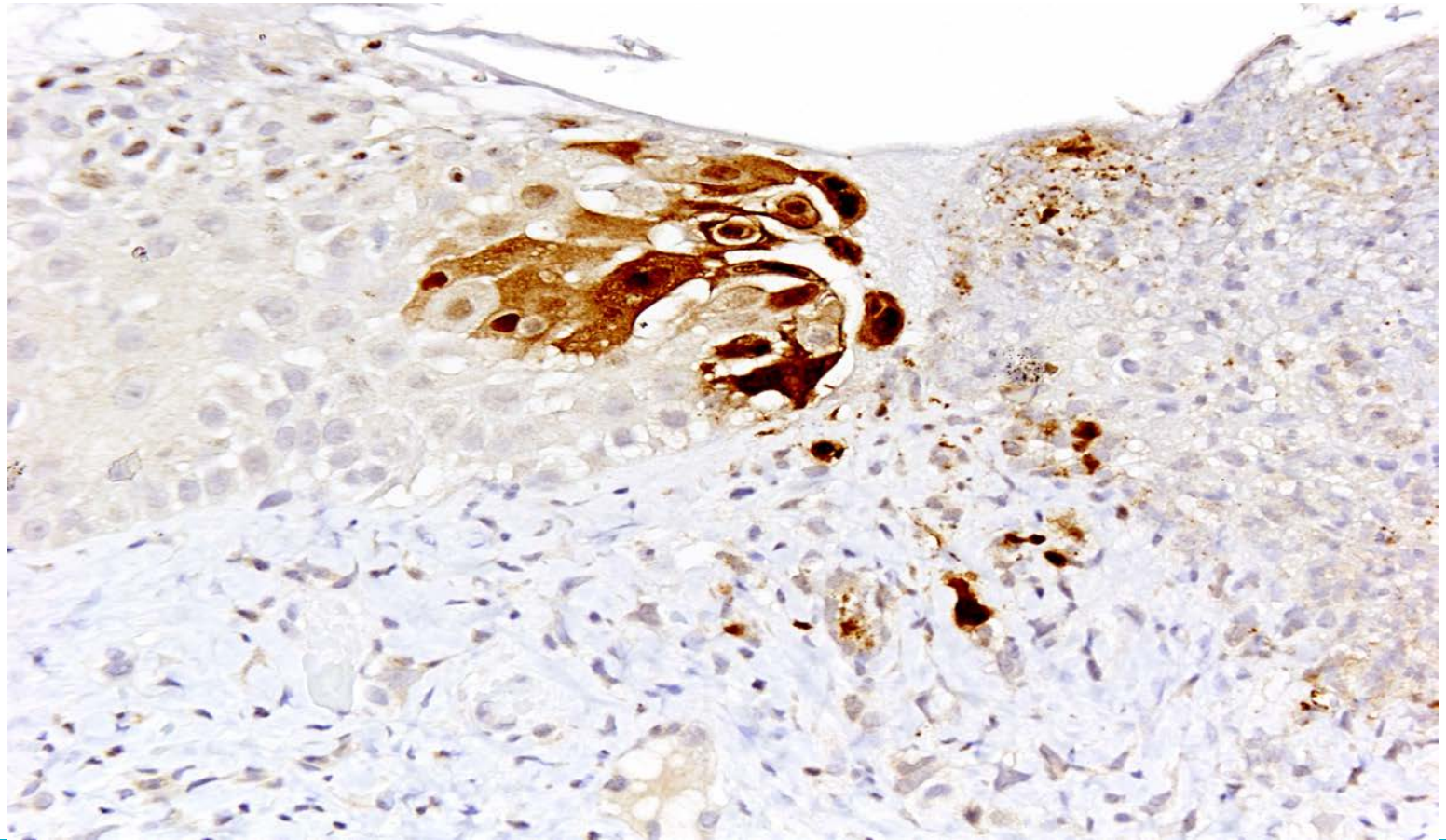
-Squamous mucosa with intense plasma cell-rich inflammation, See note

Note: The history of a mass is noted. The biopsy findings have been associated with syphilitic and/or LGV infections. In such cases, clinical studies provide the best means of evaluation. It would be important to evaluate for *both*since identical histologic features can be seen with either agent in either isolation or in combination. A CMV immunostain is negative. Deeper sections examined. A hematopathology workup was non-contributory. If the lesion remains concerning, repeat sampling is a consideration.

Syphilis: Serum RPR, RPR titer, and a treponemal specific serology
LGV: Rectal swab collected in the absence of lubricant for C. trachomatis nucleic acid probe test, indirect immunofluorescence, culture, or LGV PCR
Reference: Arnold CA et al. Am J Surg Pathol. 2013 Jan;37(1):38-46.



Near Miss: *CMV and HSV Worthwhile*



Take Home Messages

- LAST consensus statement:
  - LSIL v HSIL
  - p16 for HSIL v HSIL mimic, *or* cyto-bx discrepancy
  - Following terms retired:
    - Condyloma acuminatum (OK per WHO), AIN, Cloacogenic carcinoma
- Subclassify anal Paget
- Mucosal melanomas = surgery and radiation; NOT staged in AJCC; CD117+ & focal cytokeratin common

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