

# How to Approach Select Tricky Anal Lesions

PRESENTED BY  
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# PLEASE TURN OFF YOUR CELL PHONES

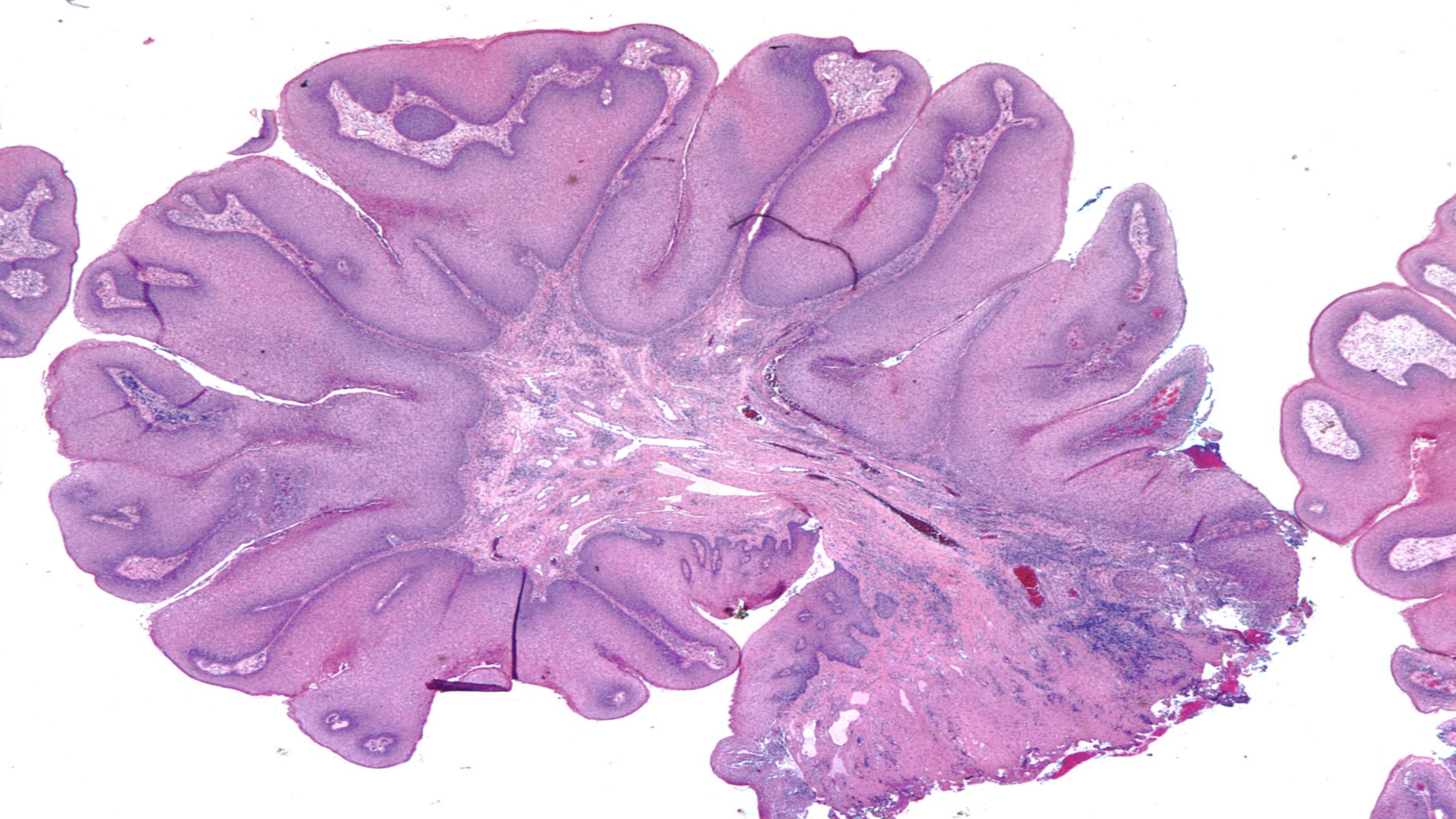
# Key Problem Areas in Evaluation of Anal & Perianal Lesions

- Condyloma (gross) mimics
- The AIN 1-2 problem
- HSIL (microscopic) mimics

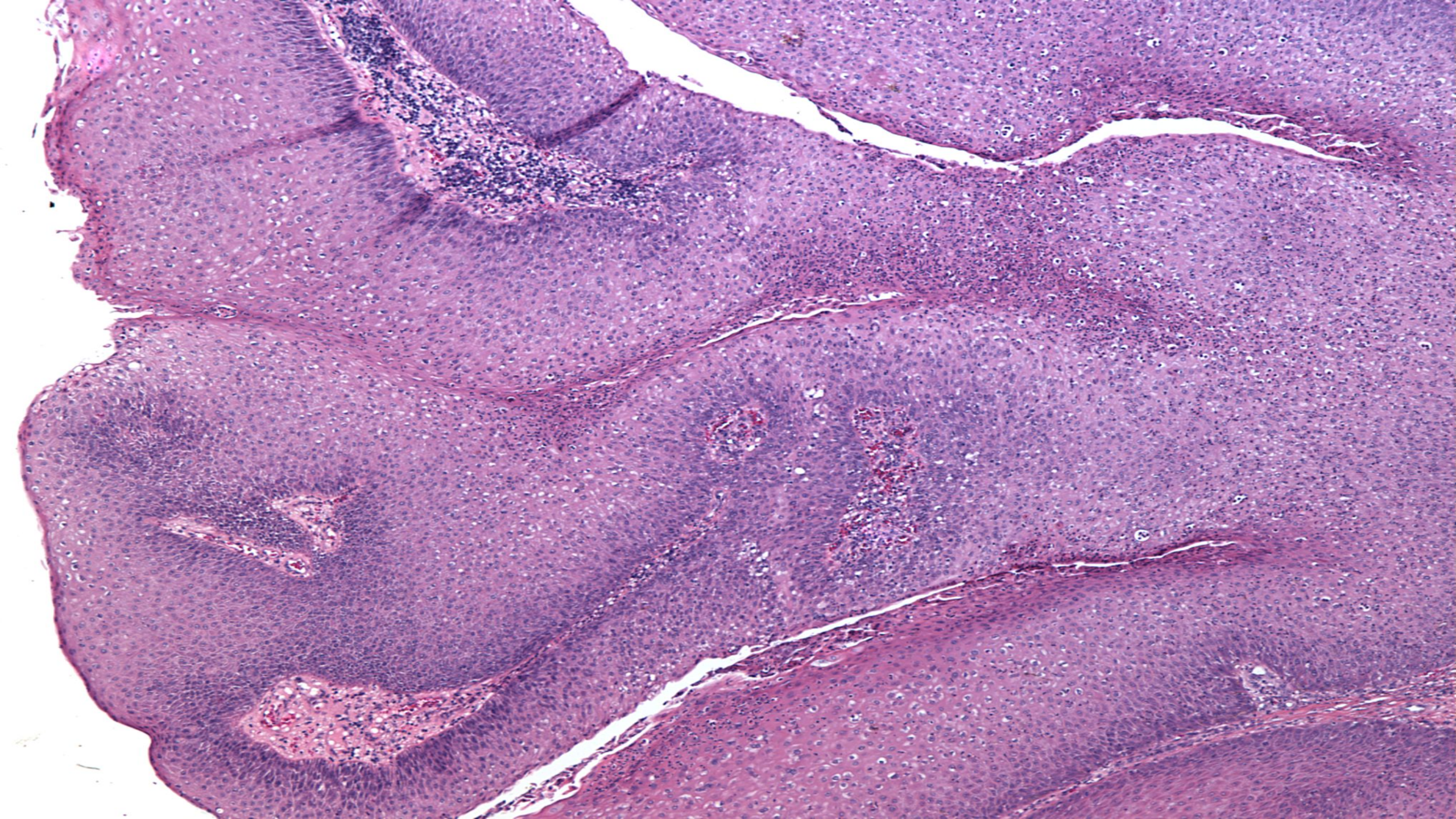
# Case 1

42-year-old female with perianal lesion

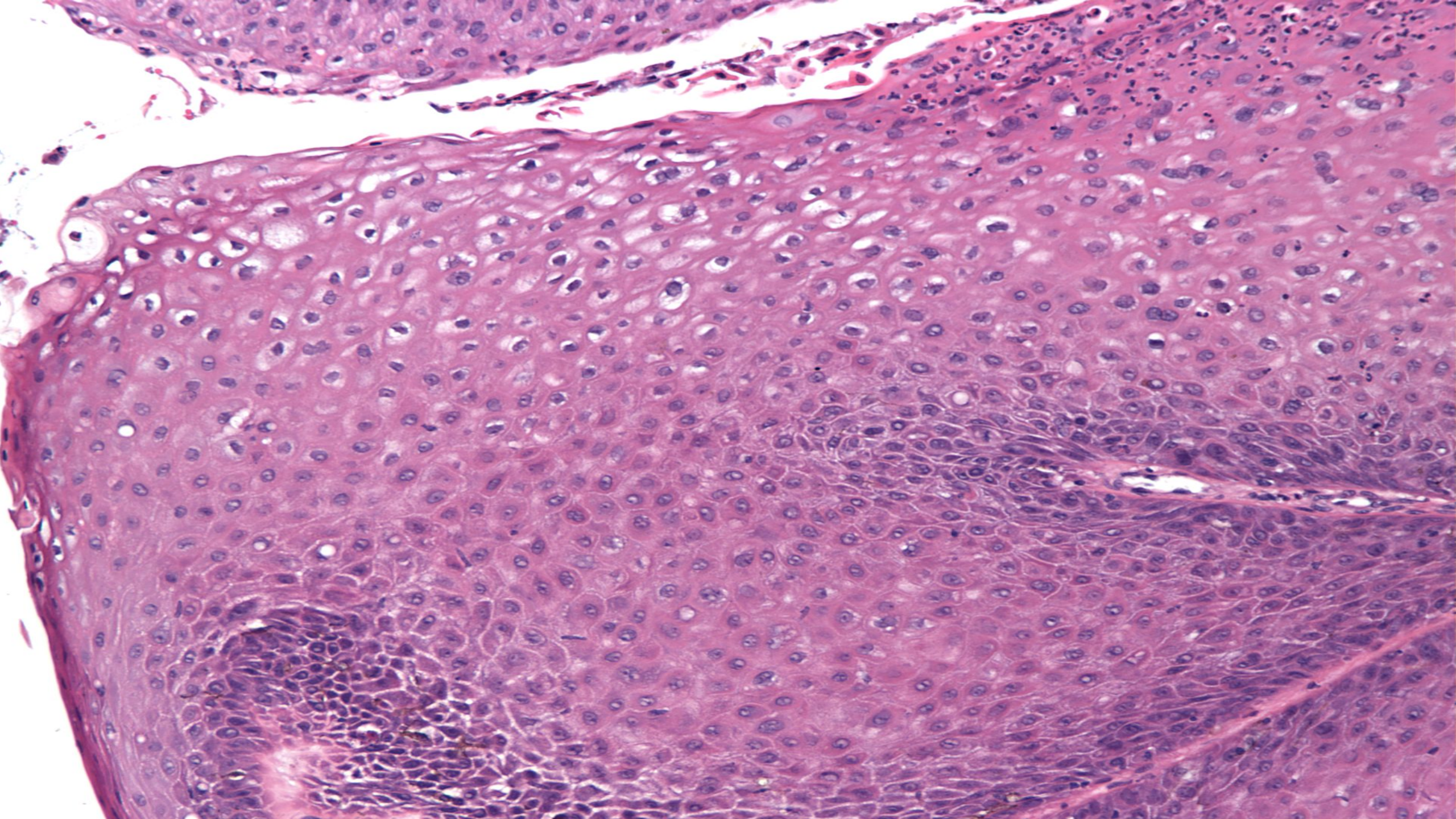






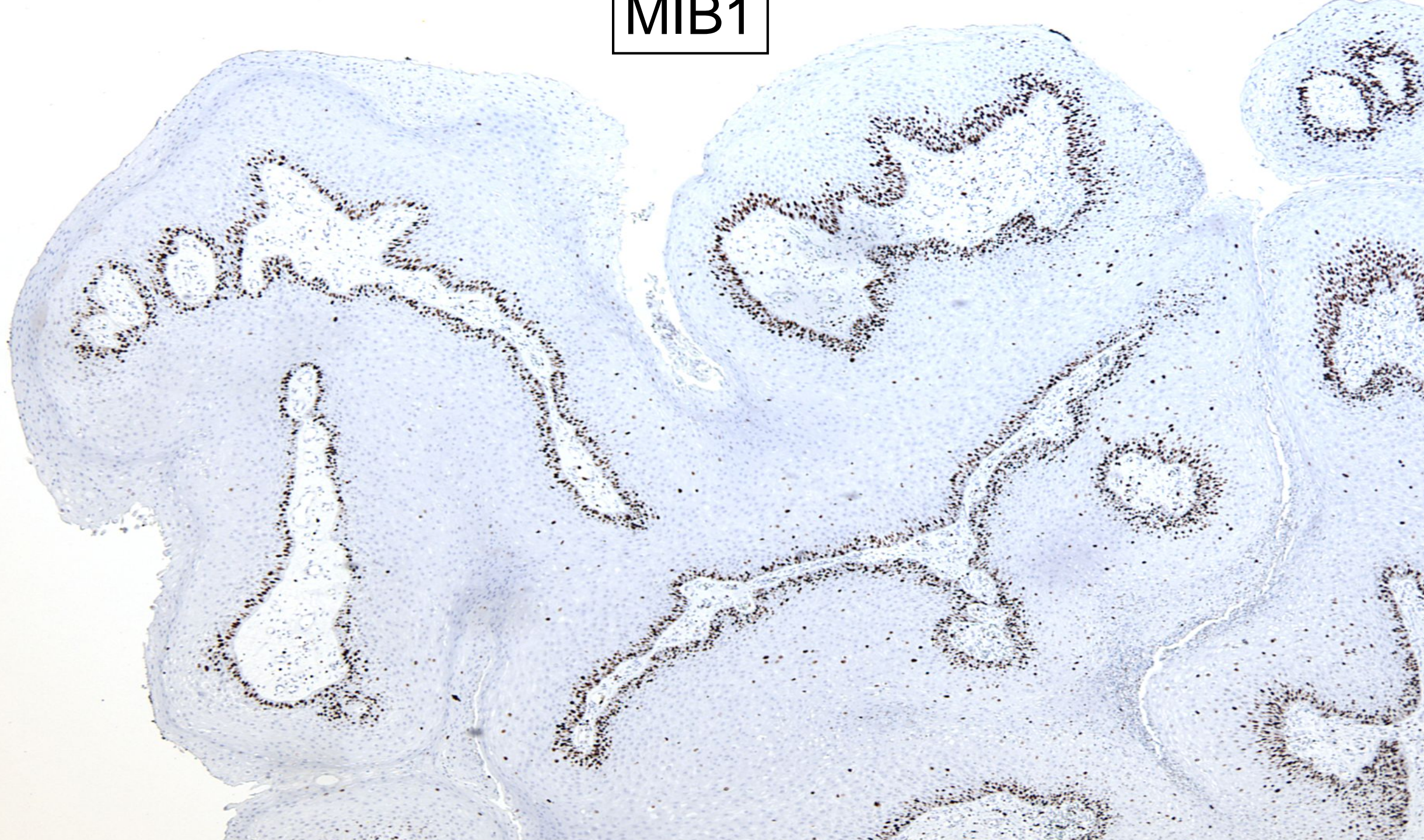








MIB1





## *Live Content Slide*

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# Poll: Diagnosis?

# Anal Condyloma: Is It A Risk Lesion?

- Anal skin condyloma largely harbor low risk HPV 6, 11 types
- Most anal skin condyloma do not progress
- Diagnostic criteria for anal skin condyloma are not particularly robust & most are histologically innocuous – LSIL at most



# Anal Condyloma: Is It A Risk Lesion?

- In contrast, anal canal condyloma often exhibit foci of HSIL (AIN 1/2)
- Anal canal condyloma often harbor high risk HPV 16, 18 types
- Anal canal condyloma can progress

McCloskey et al Int J STD AIDS 2007;18:538-542

**DEPENDS ON  
LOCATION!**

# Epidemiology of Anal Squamous Cell Carcinoma

- Anal squamous intraepithelial lesions & squamous cancer has been increasing in incidence in US since at least 1973 (predates HIV/AIDS)
- In 2006, approx 4,650 anal squamous cell carcinomas/year vs 11,150 cervical squamous cell carcinomas/year

Maggard et al Dis Colon Rectum 2003;46:1517-23  
CA Cancer J Clin 2007;57:43-46

# Epidemiology of Anal Squamous Cell Carcinoma

- Anal cancer diagnoses (2006): female to male: 1.4:1
- Anal cancer deaths (2006): female to male: 1.7:1
- Who gets screened?

CA Cancer J Clin 2007;57:43-46

# Epidemiology of Anal Squamous Cell Carcinoma

## Anal Canal (Transformation Zone)

- Women > men
- Most invasive at diagnosis

## Peri-anal

- Men > women
- Assoc with recognizable precursor lesions (screening effect?)
- Most noninvasive at diagnosis



# Cervical HSIL vs Anal HSIL

- High risk HPV types in cervix more varied & multiple: HPV 16, 18, 31, 35
- High risk HPV types in anal canal disproportionately HPV 16, with HPV 18 distant second
- Prevalence of high risk HPV in cervix high but most cleared – rates of progression/regression well defined
- Prevalence of high risk HPV in anal canal unknown – rates of progression/regression largely unknown

# Anal SIL Regression & Progression Rates

- Anal LSIL may regress in up to 30% of cases, but regression uncommon in HIV
- Anal HSIL, when associated with systemic immunosuppression, may progress to invasive carcinoma in up to 50% of cases
- Progression rate probably depends on site: skin & perianal (low) vs anal canal (high)

Br J Surg 2005;92:1133-6; Int J Cancer 2014;134:1147–1155

# Anatomic Localization: Terminology

- **Anal canal** = not visualized or incompletely visualized (intra-anal)
- **Perianal** = completely visualized & within 5 cm of anal opening (anal margin)
- **Skin** = completely visualized & > 5 cm from anal opening (cutaneous)
- **Transformation zone** = region above dentate line where squamous metaplasia is found as normal variant

Welton et al, Surg Oncol Clin N Am 2004;13:263-75

# Anatomic Localization: Benefits

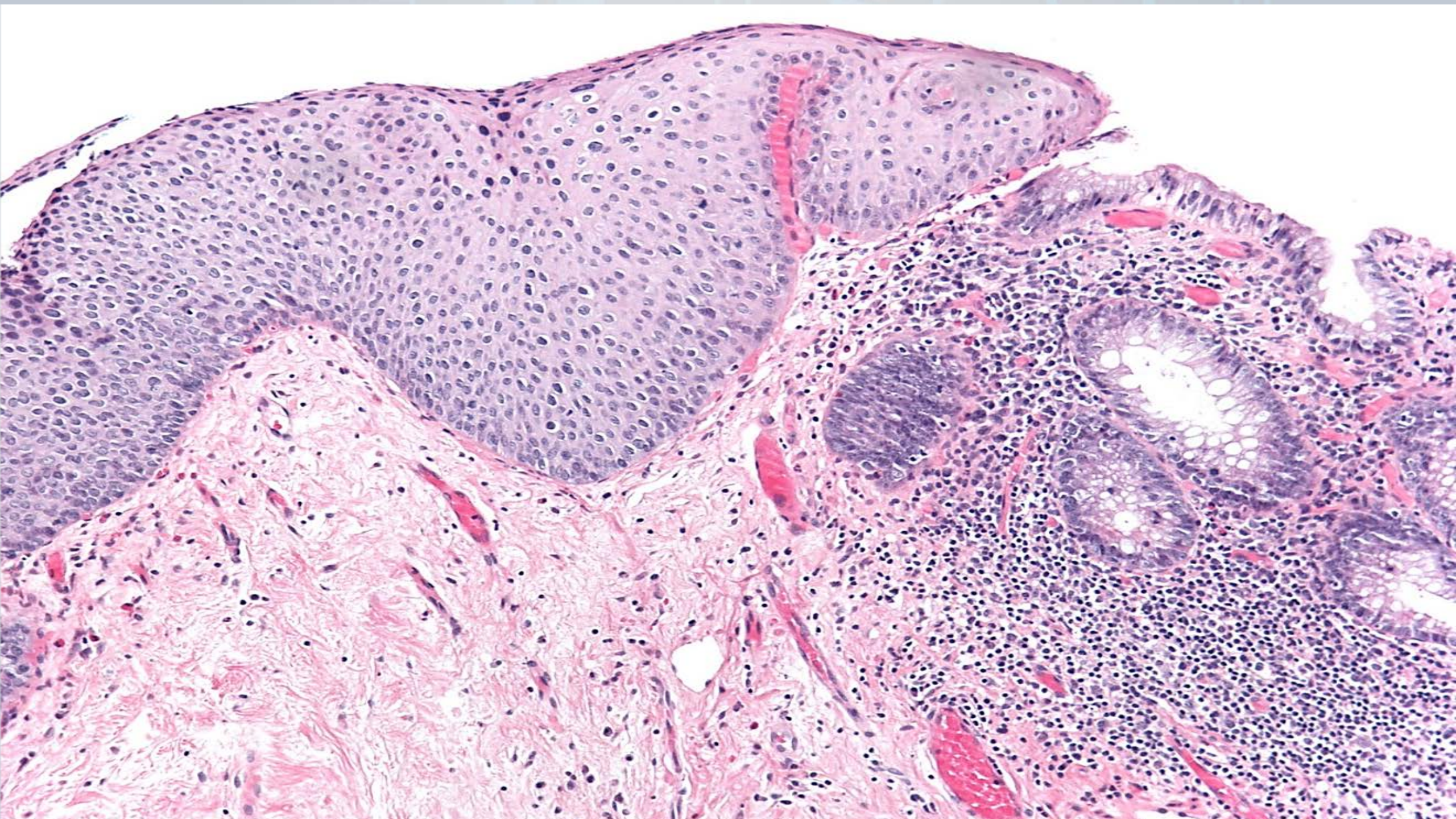
- Anatomic correlate of anal margin ill defined
- Skin condyloma differ from anal canal condyloma
- Terminology directly conveys whether lesion(s) are completely visualized – important in management
- Different set of differential diagnostic considerations

Welton et al, Surg Oncol Clin N Am 2004;13:263-75

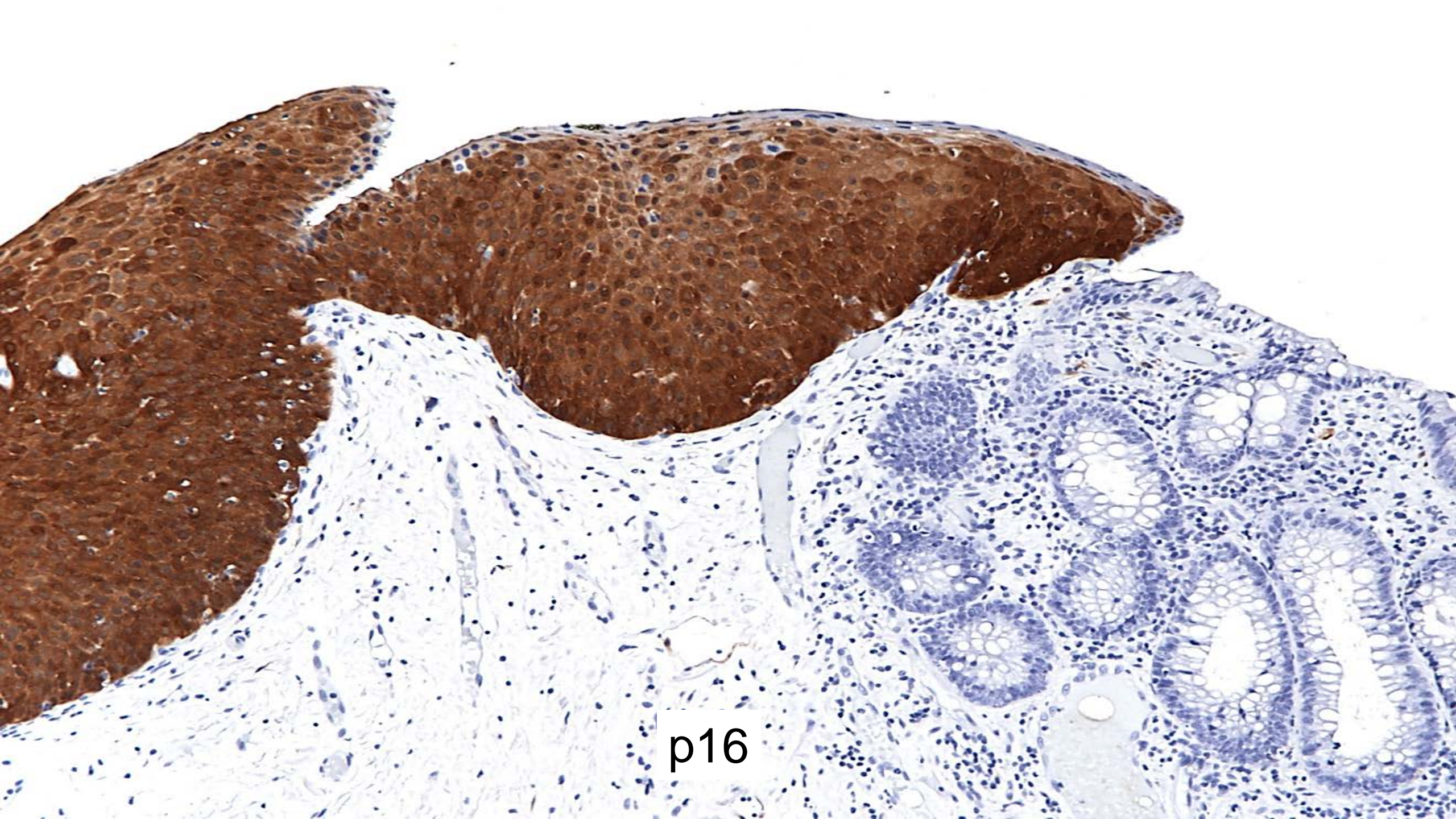
# Case 2

42-year-old male with HSIL on anal Pap smear



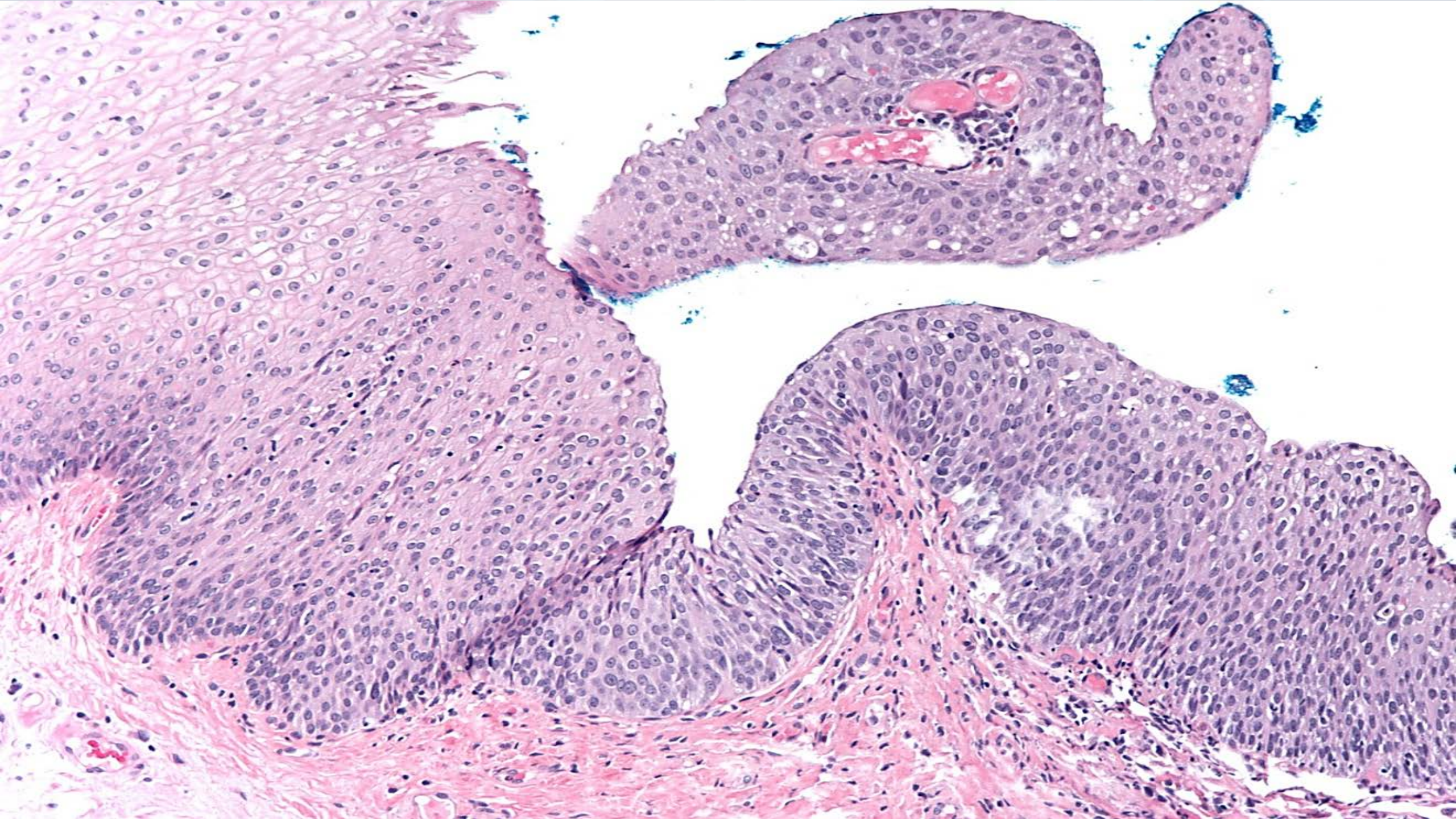




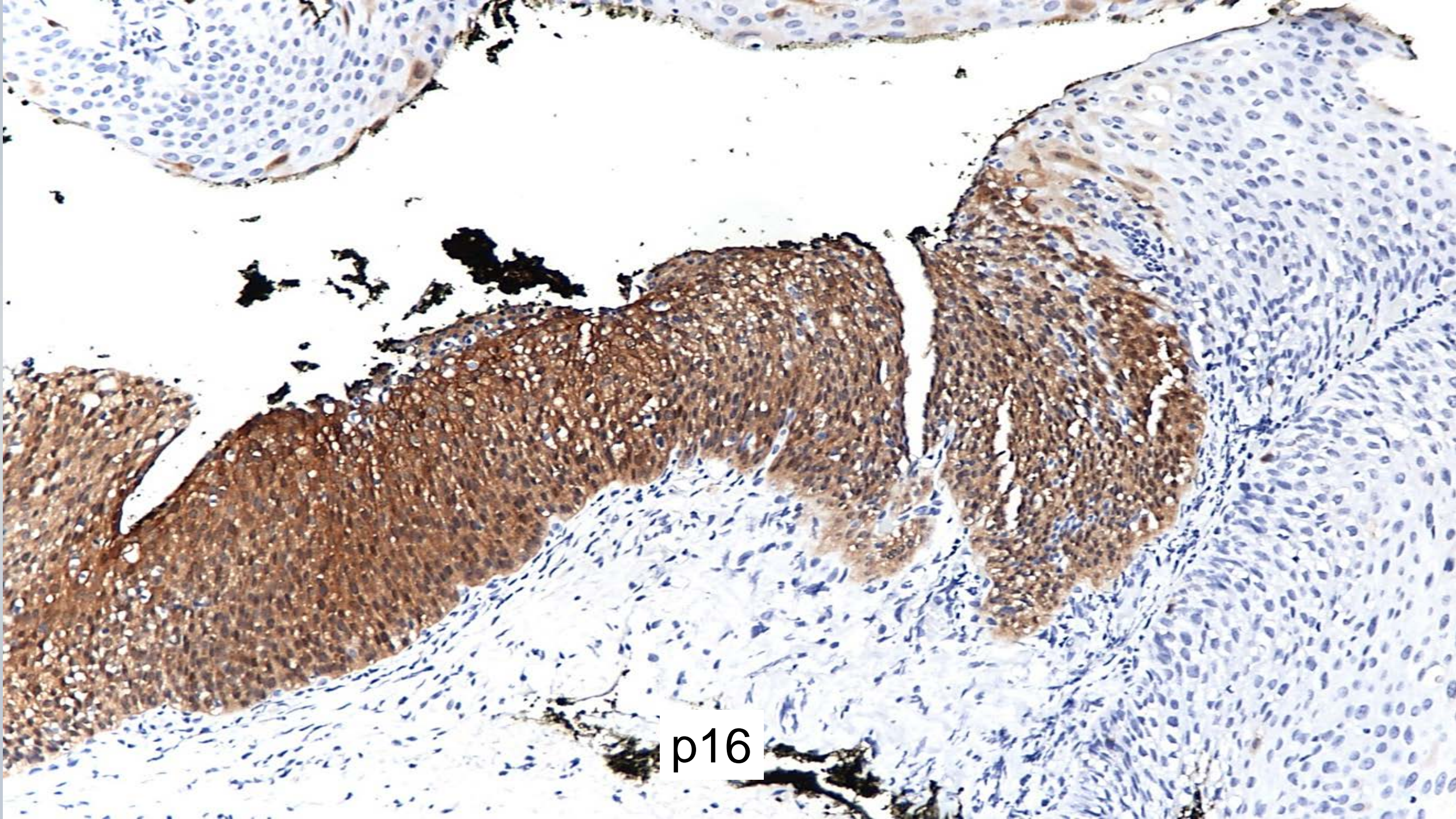


p16









p16



# Classification of Anal Lesions:

## Lower Anogenital Squamous Terminology

| Terminology                                       | Definition   |
|---|--|
| Low grade squamous intraepithelial lesion (LSIL)  | AIN 1, low grade dysplasia, condyloma                                    |
| High grade squamous intraepithelial lesion (HSIL) | AIN 2, AIN 3, CIS, Bowen's disease, moderate dysplasia, severe dysplasia |

*Arch Pathol Lab Med* 2012;136:1266-97.

# LSIL vs HSIL (The AIN 1-2 Problem)

## LSIL

- Mitotic activity in lower 2/3 mucosa
- Koilocytosis – often involves upper 1/3 mucosa
- No atypical mitotic figures

## HSIL

- Mitotic activity in upper 1/3 mucosa
- High N:C ratio
- Loss of surface maturation
- Atypical mitotic figures

# Surrogate Markers for High Risk Lesions

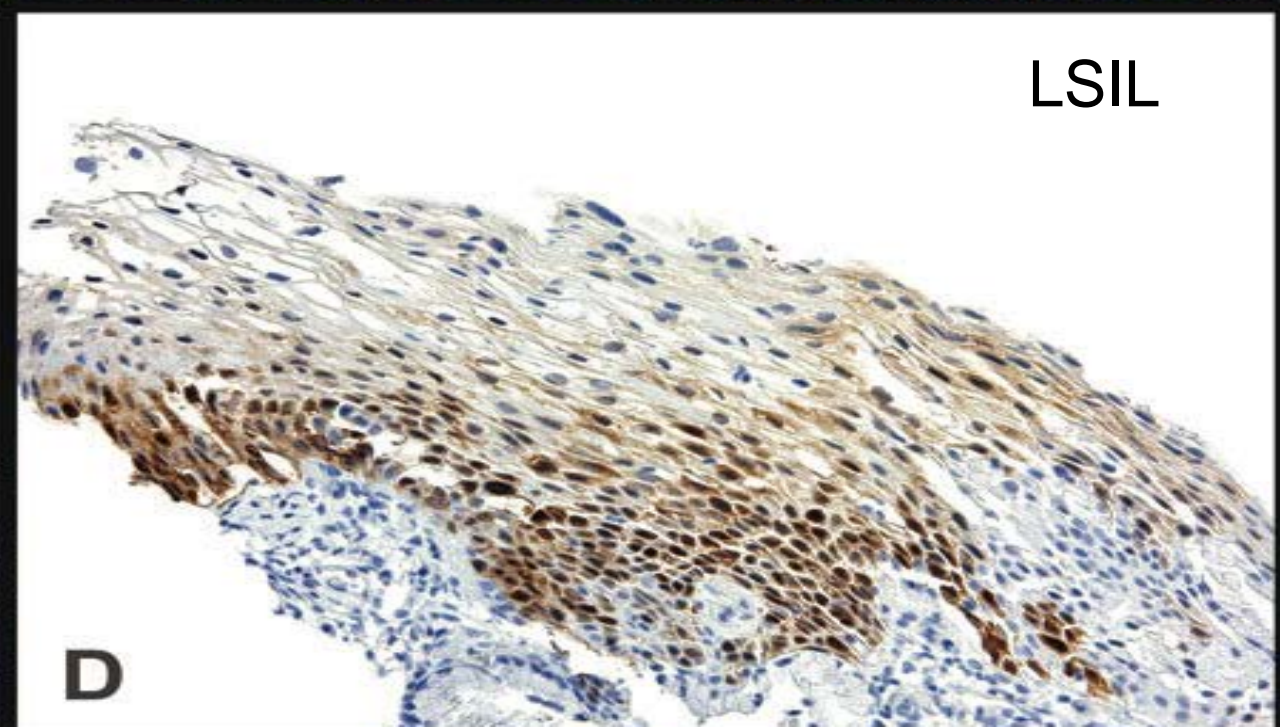
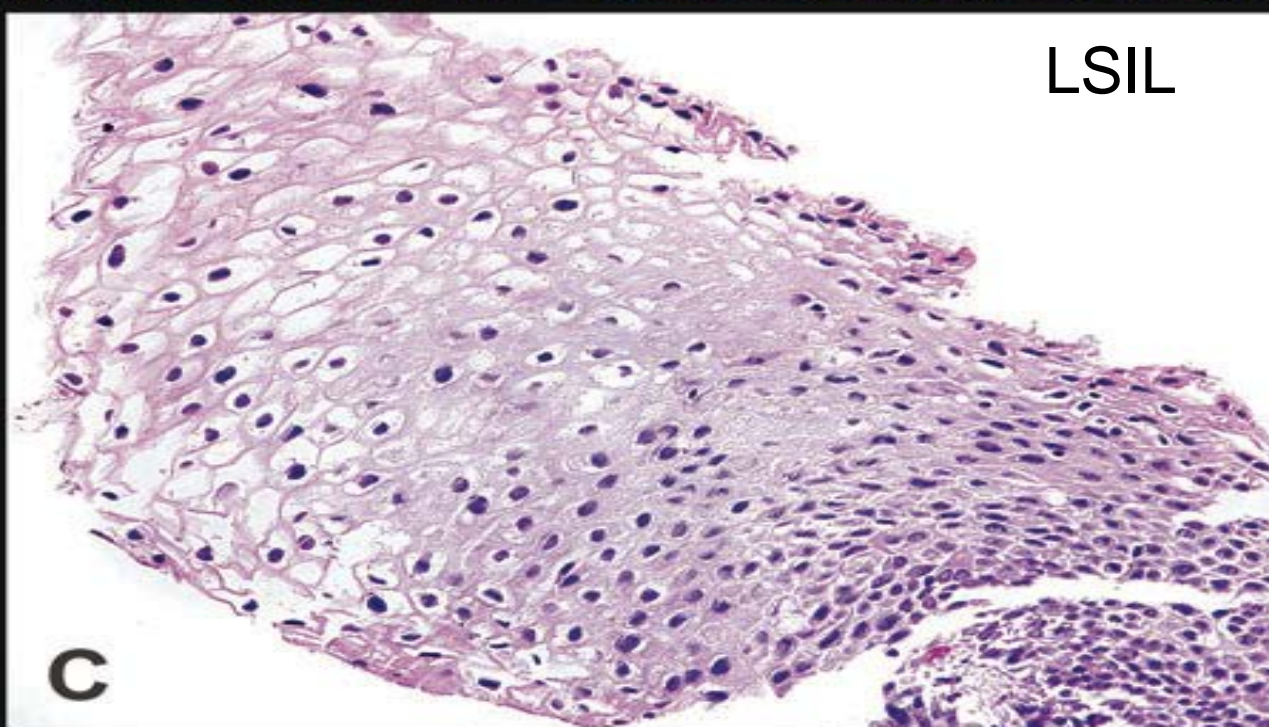
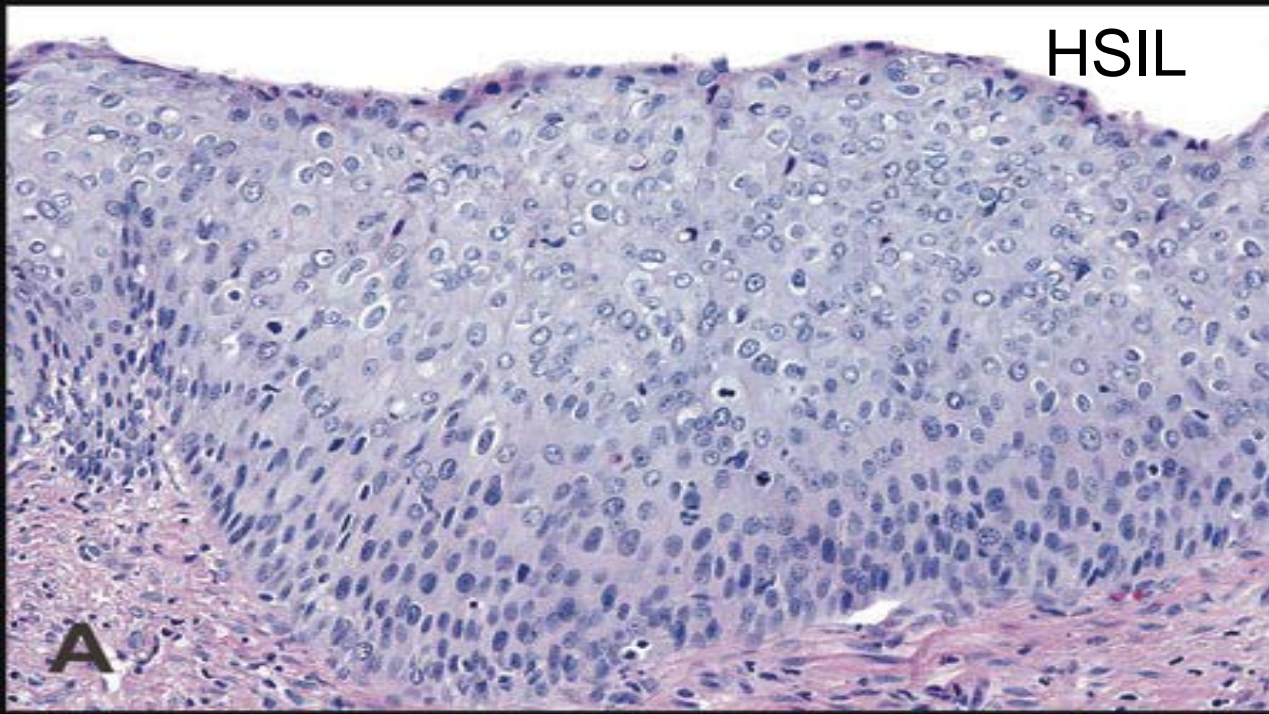
- p16
- Ki-67 (mib-1)
- ProEx C

# p16 Immunohistochemistry

- Diffuse (>80%) strong nuclear *or* nuclear and cytoplasmic reactivity block positive involving at least 1/3 basal layer:
  - Correlates with presence of HR-HPV and diagnosis of dysplasia
  - Grading of dysplasia must be based on histology
- Focal strong (5-80%) reactivity
  - Equivocal: Atypical

J Low Genit Tract Dis. 2012;16:205-42







# p16 Immunohistochemistry: Indications

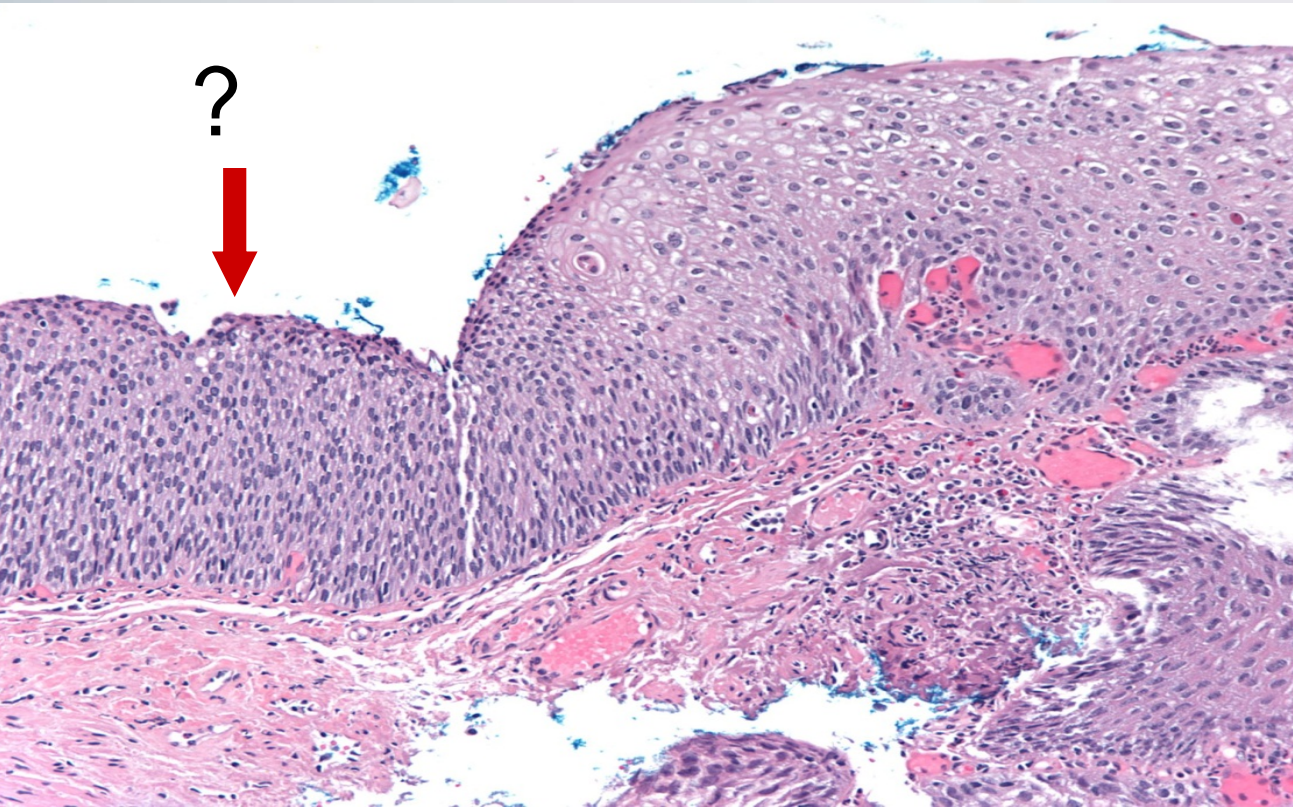
- LSIL versus HSIL (AIN 2)
- HSIL versus benign mimic
- Interobserver disagreement
- Persistent abnormal Pap but no noticeable abnormality

J Low Genit Tract Dis. 2012;16:205-42

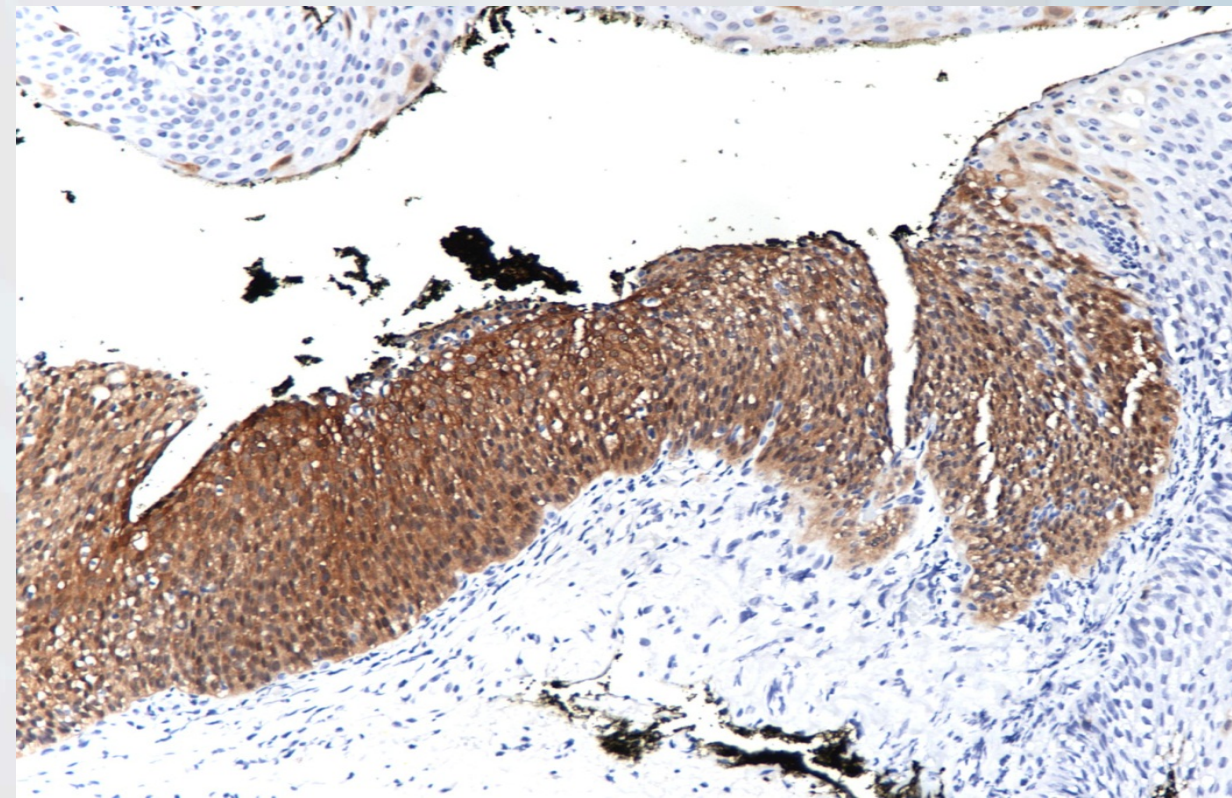
# When Is p16 Useful in Anal Canal?

- Condyloma with possible HSIL
- Tangential sectioning or suboptimal orientation – interpret with caution
- Transitional zone
- Inflammation with atypia

# Transitional Mucosa vs HSIL



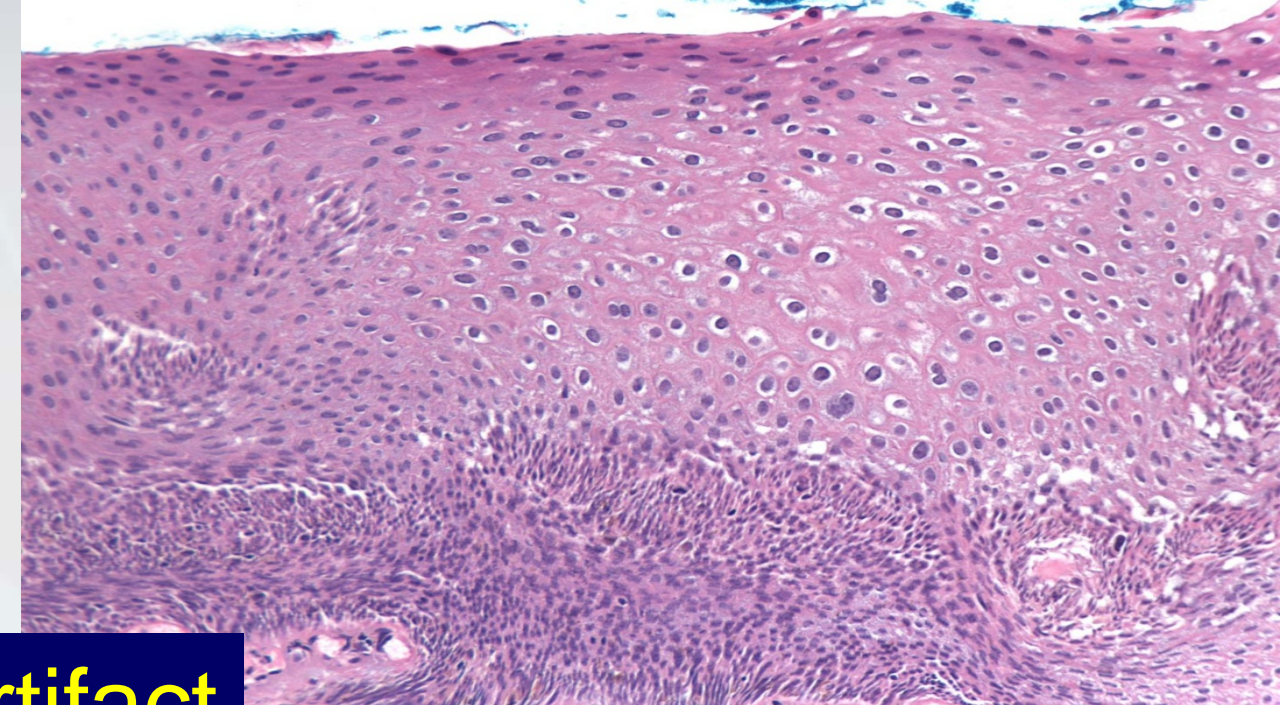
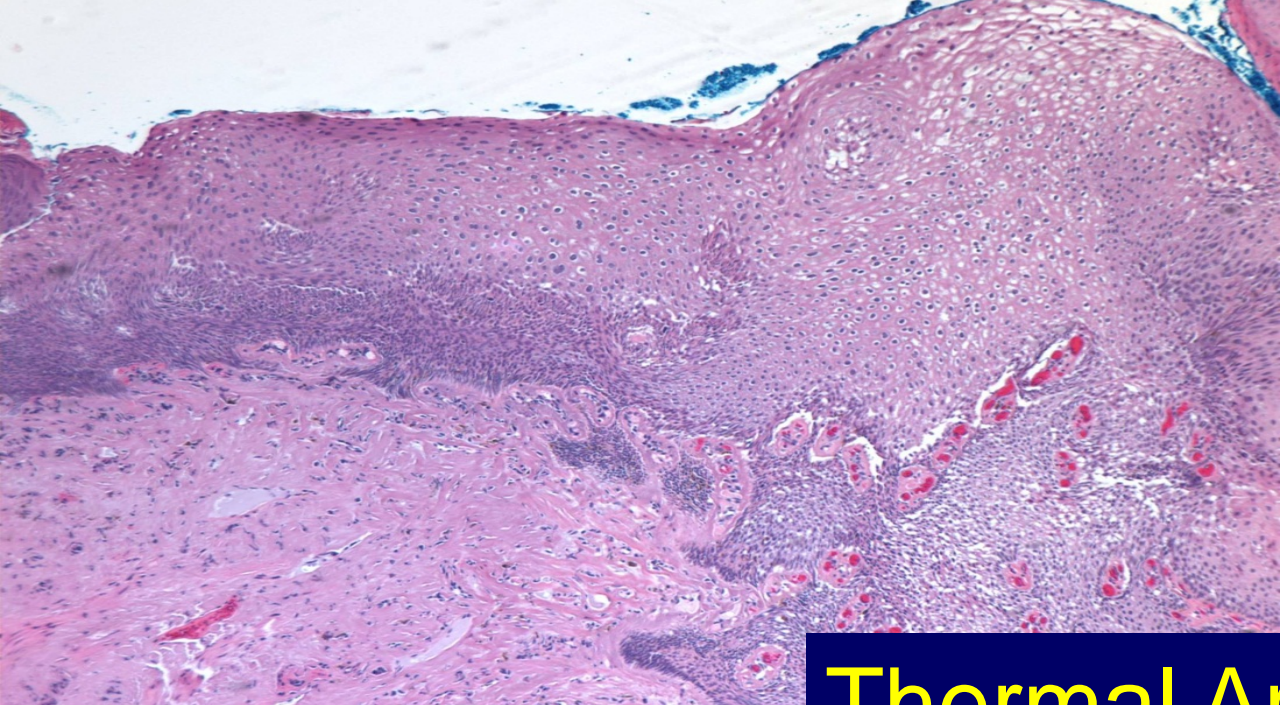
H&E



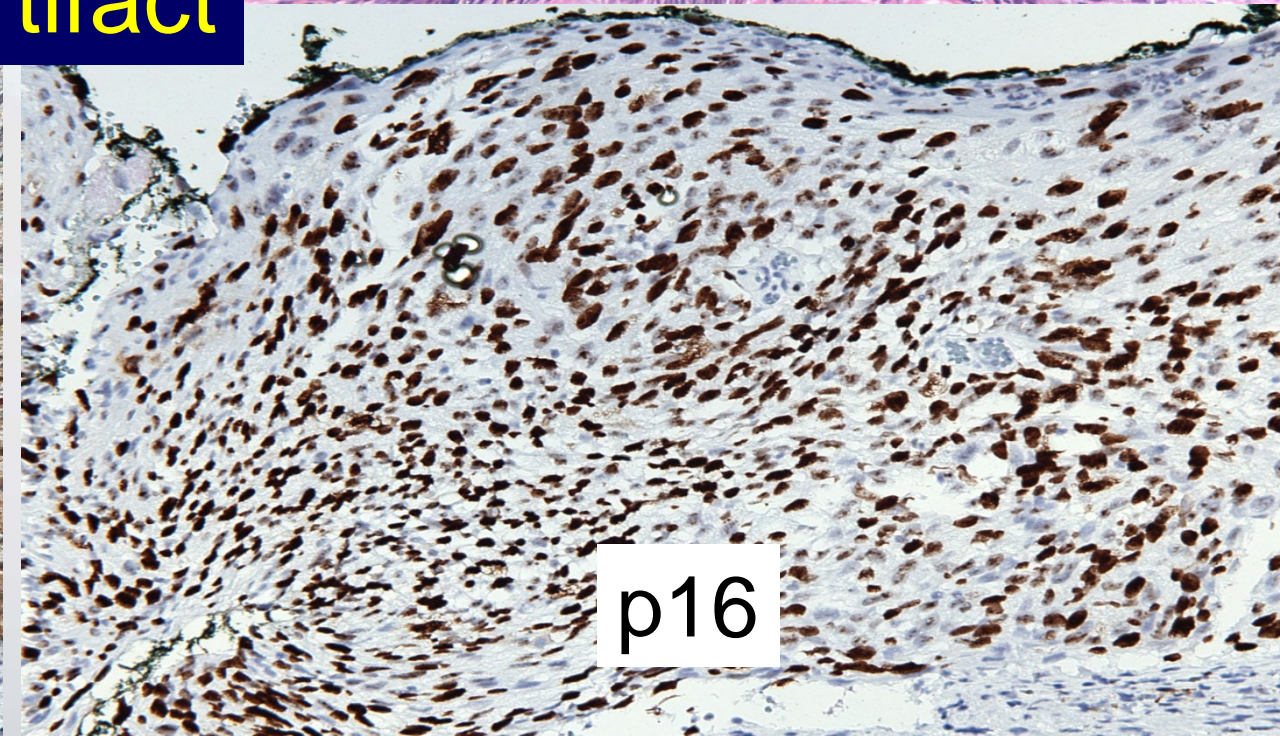
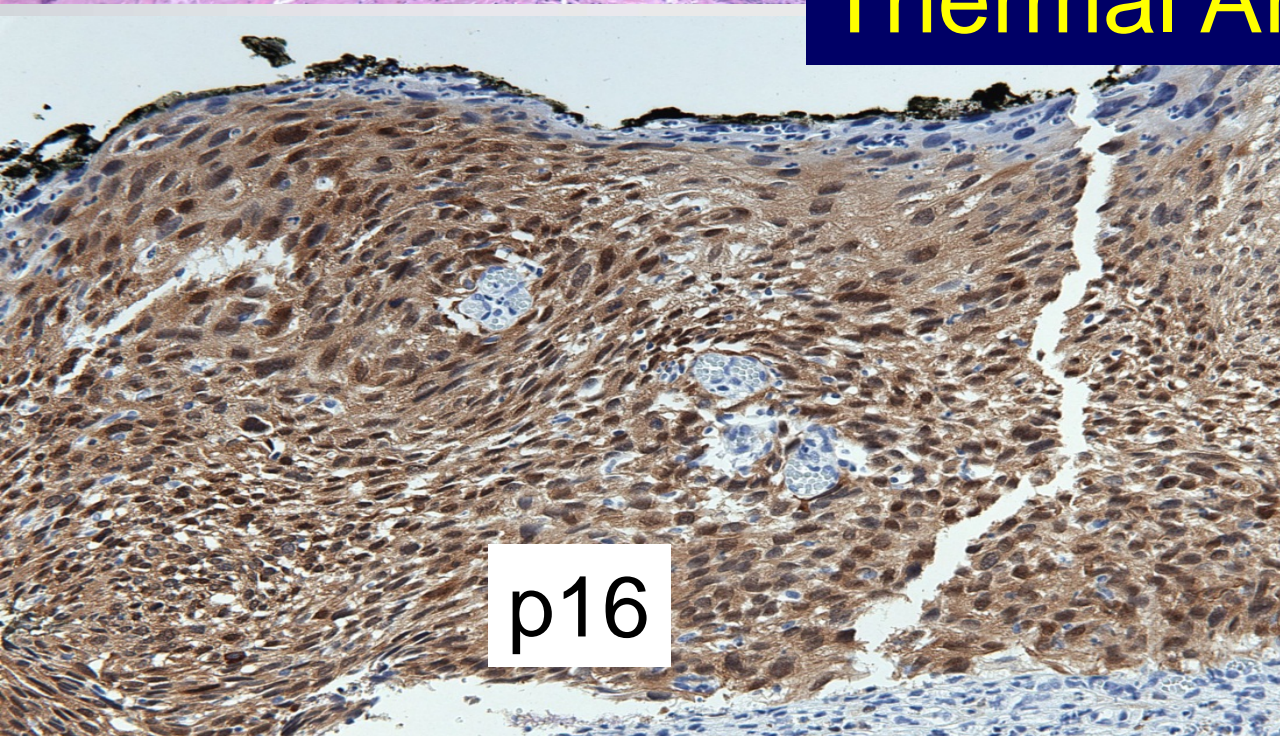
p16

Condyloma (at right)





Thermal Artifact

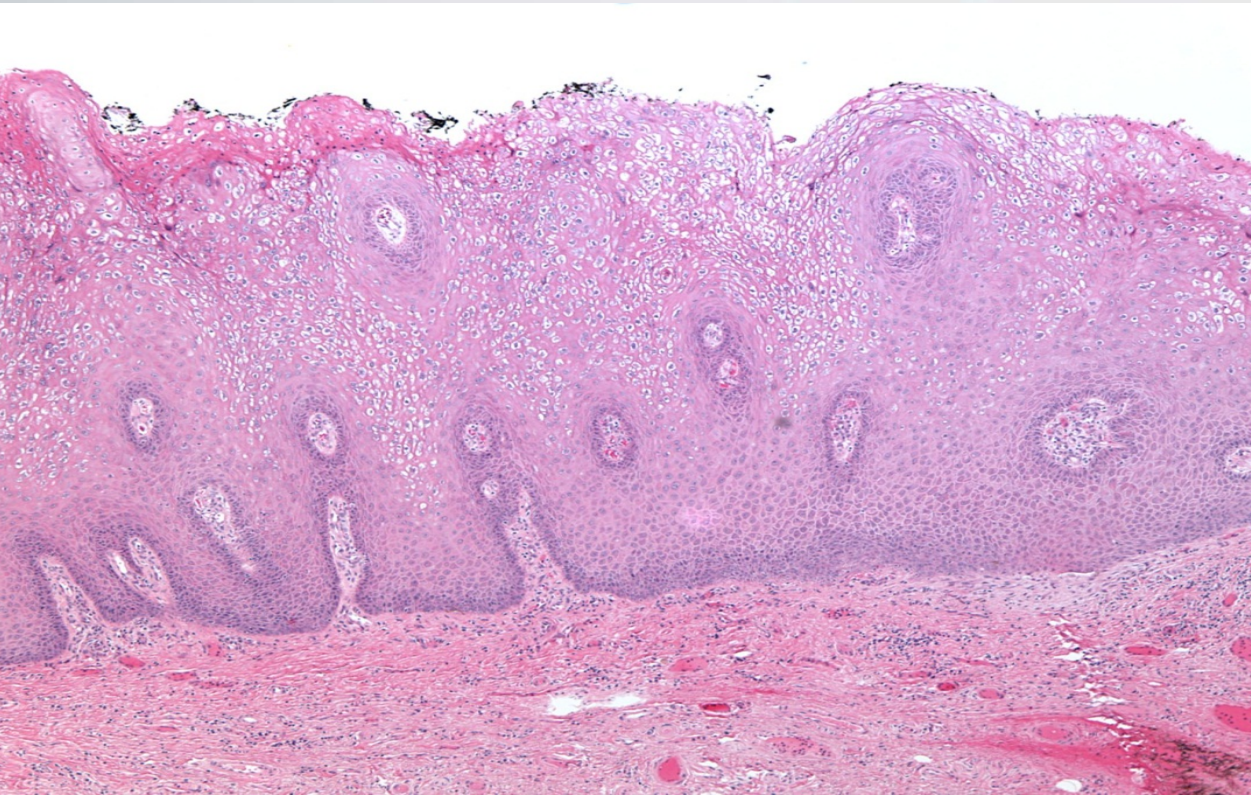




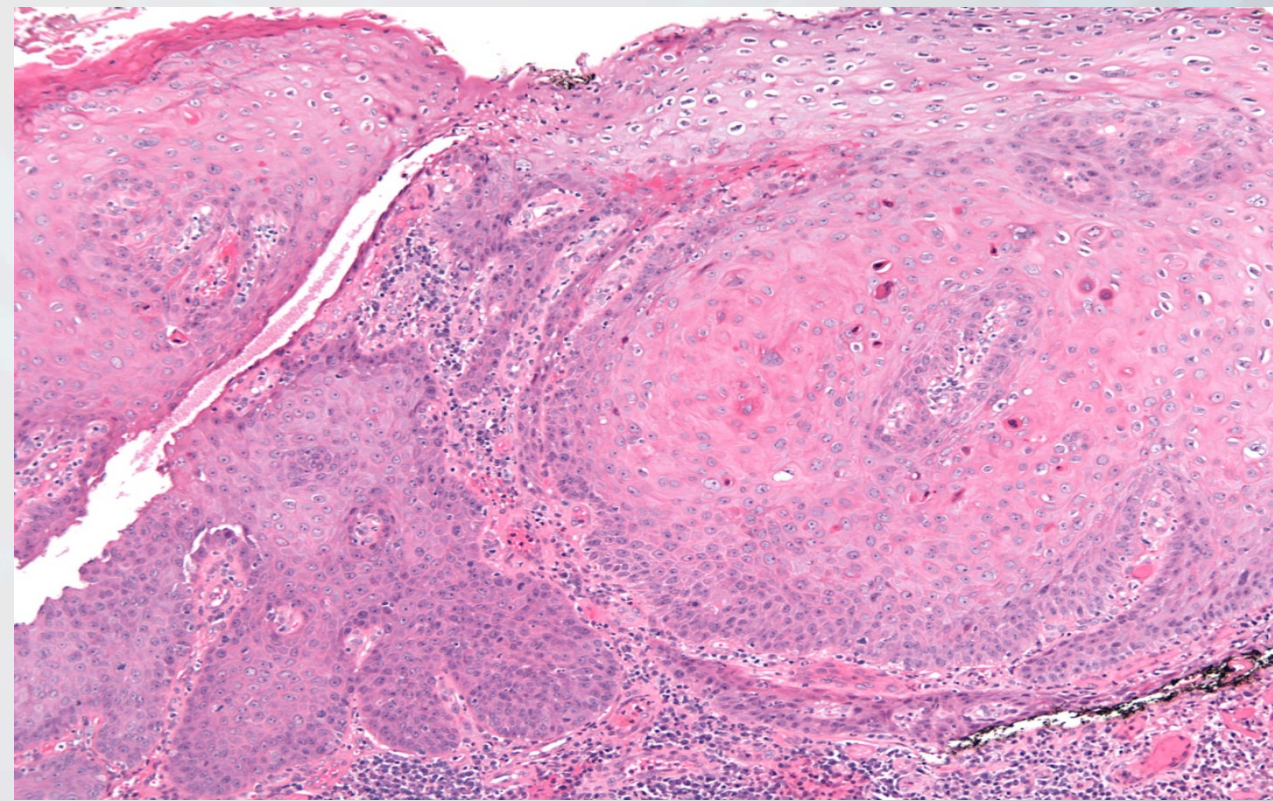
# Ki-67

- Localized to basal layer in normal mucosa
- Present throughout mucosa layer in high grade SIL
- Increased % and upper (2/3) mucosal distribution considered abnormal
- Increased in inflammation, hyperplasia, some condyloma; dependent on orientation

# Condyloma (LSIL) vs HSIL: “The AIN 1-2 Problem”



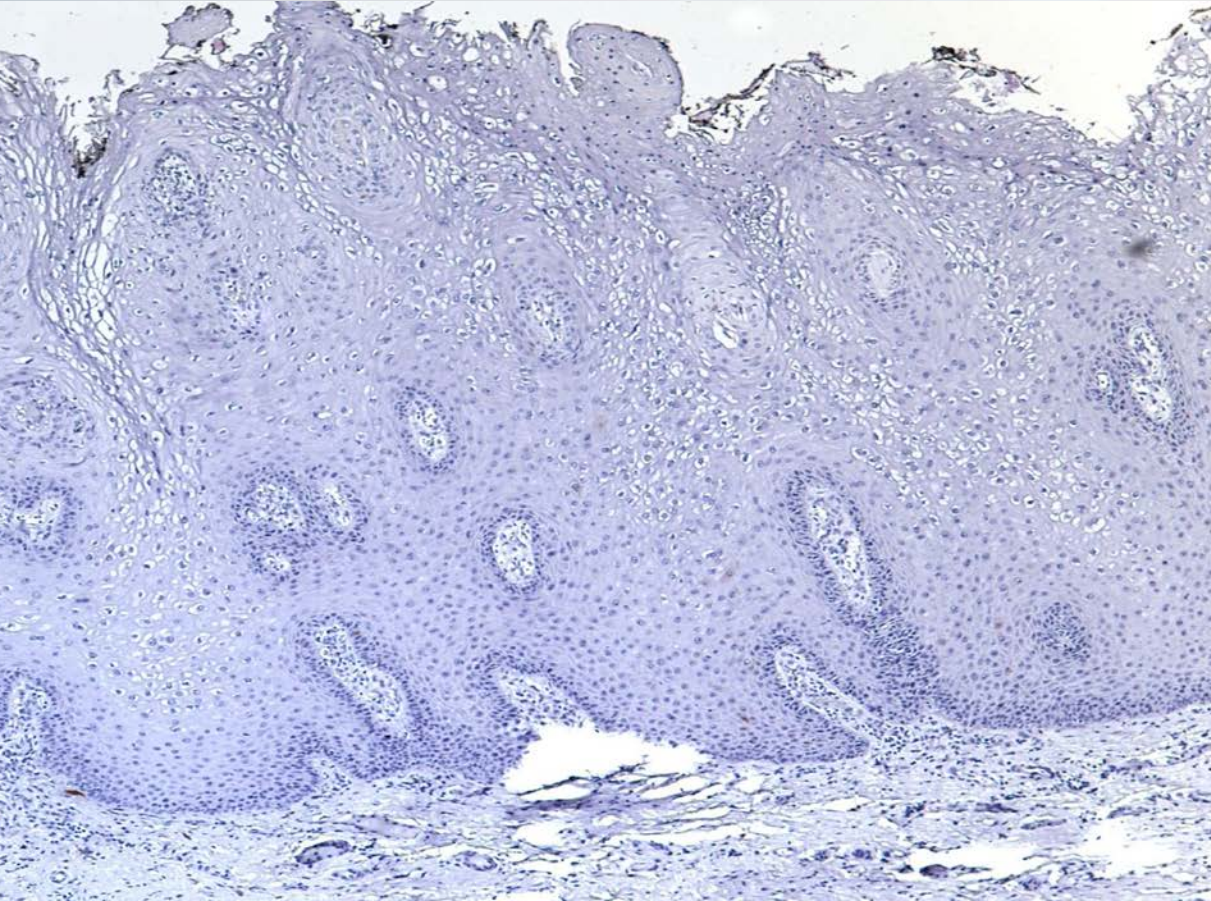
Condyloma (LSIL)



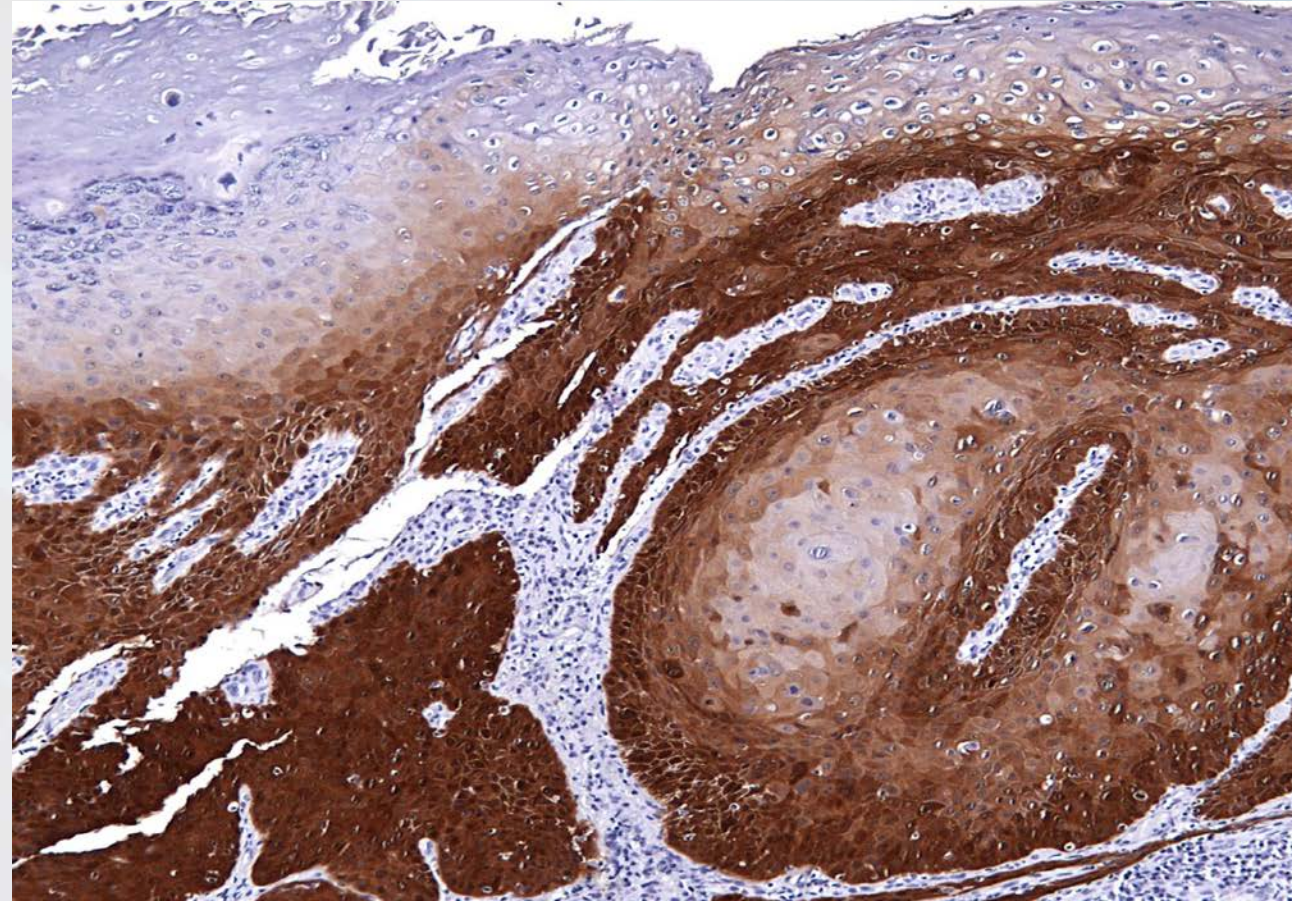
? Focal HSIL (AIN 2)



# Condyloma (LSIL) vs HSIL: “The AIN 1-2 Problem”



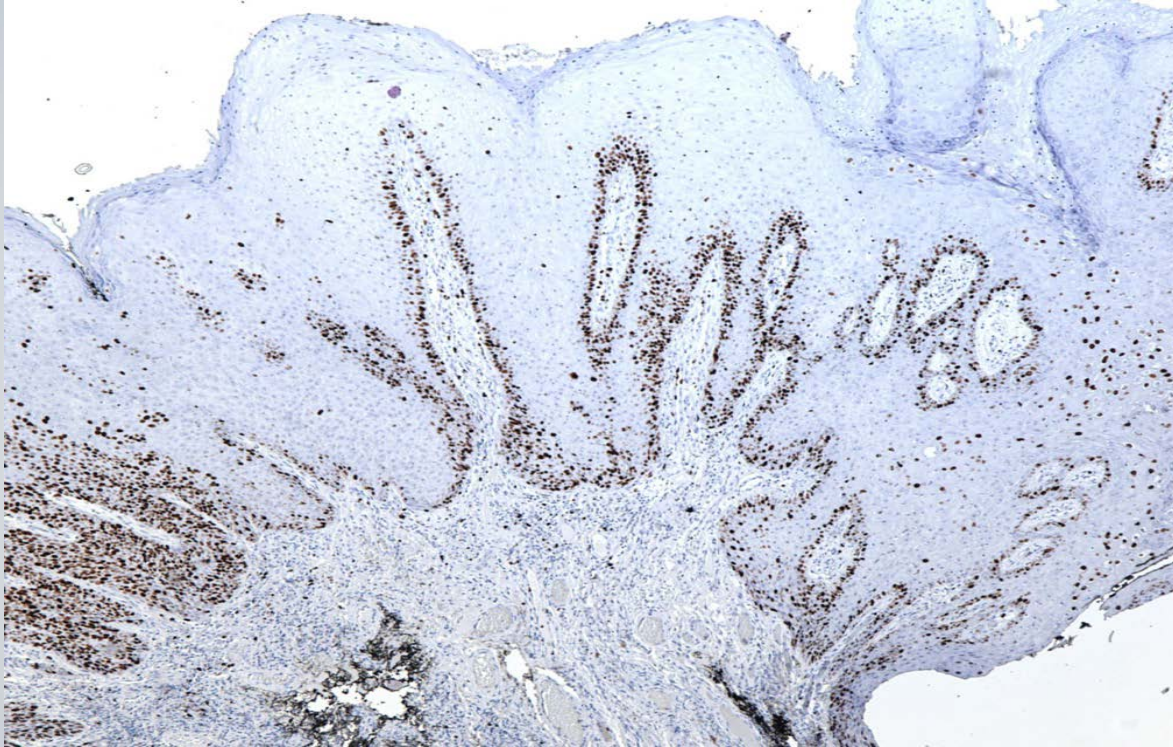
Condyloma (LSIL)



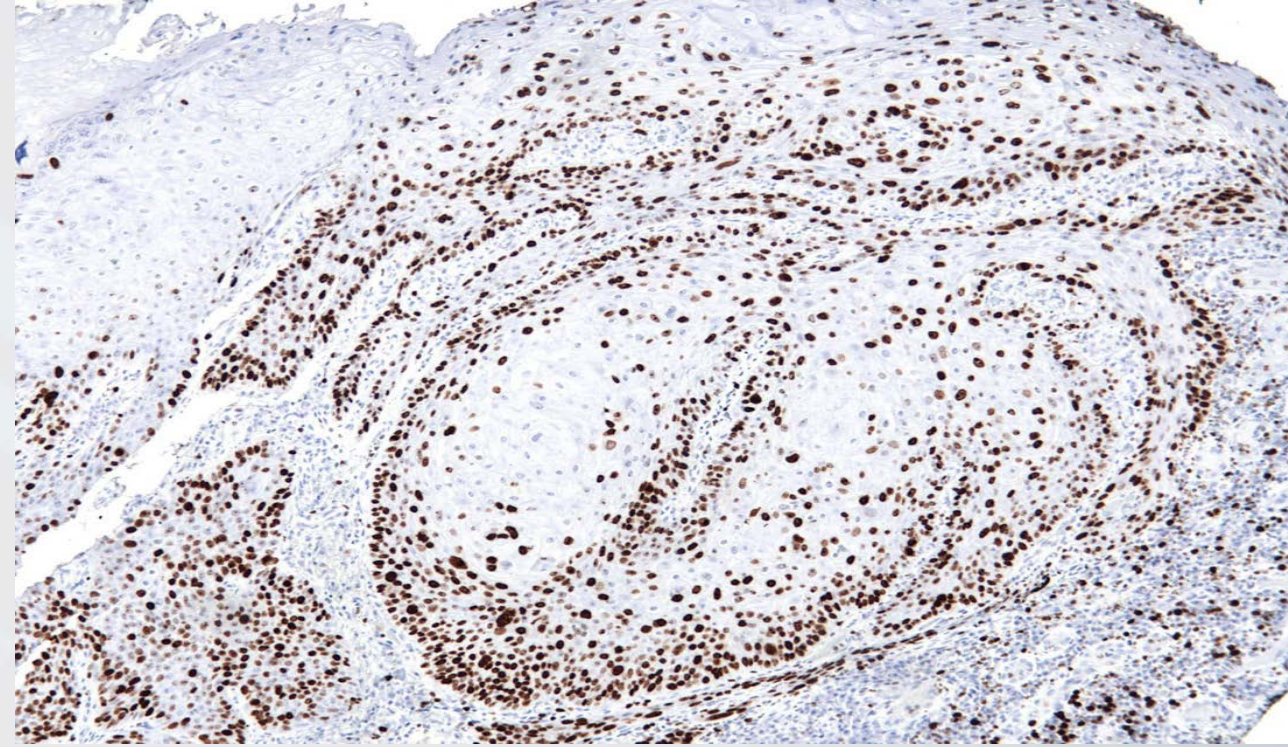
? Focal HSIL (AIN 2)



# Condyloma (LSIL) vs HSIL: “The AIN 1-2 Problem”



Condyloma (LSIL)



? Focal HSIL (AIN 2)

Ki-67 (mib-1)

# Screening For Anal Dysplasia

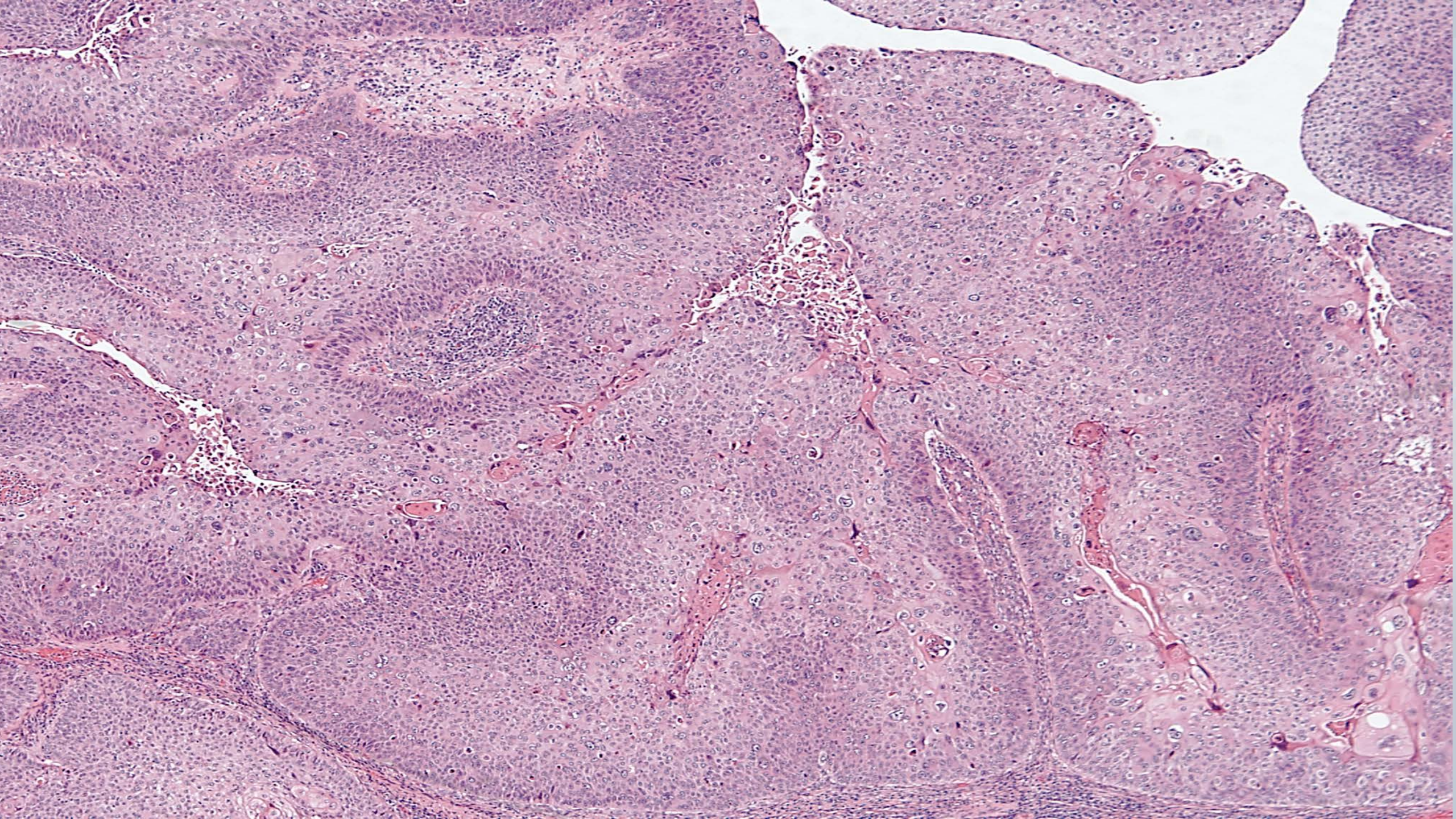
- Digital anal rectal exam – detects mass lesions
- High resolution anoscopy with biopsy & mapping – may not detect all flat lesions
- Anal Papanicolaou smear – doesn't detect extent or distribution of disease
- Hybrid capture – indicates presence of high risk HPV types (high risk probe)



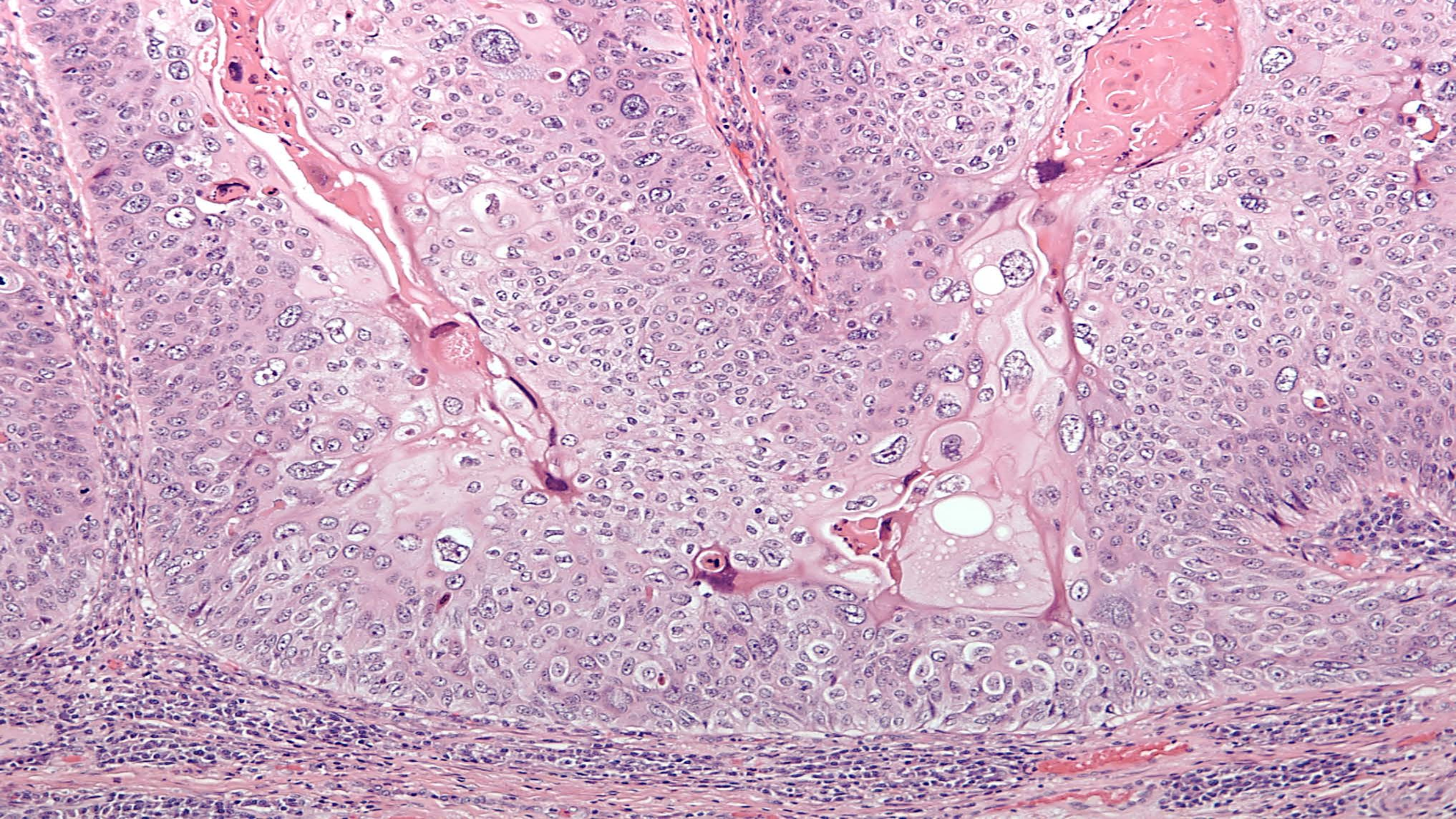
# Case 3

36-year-old male with large condyloma

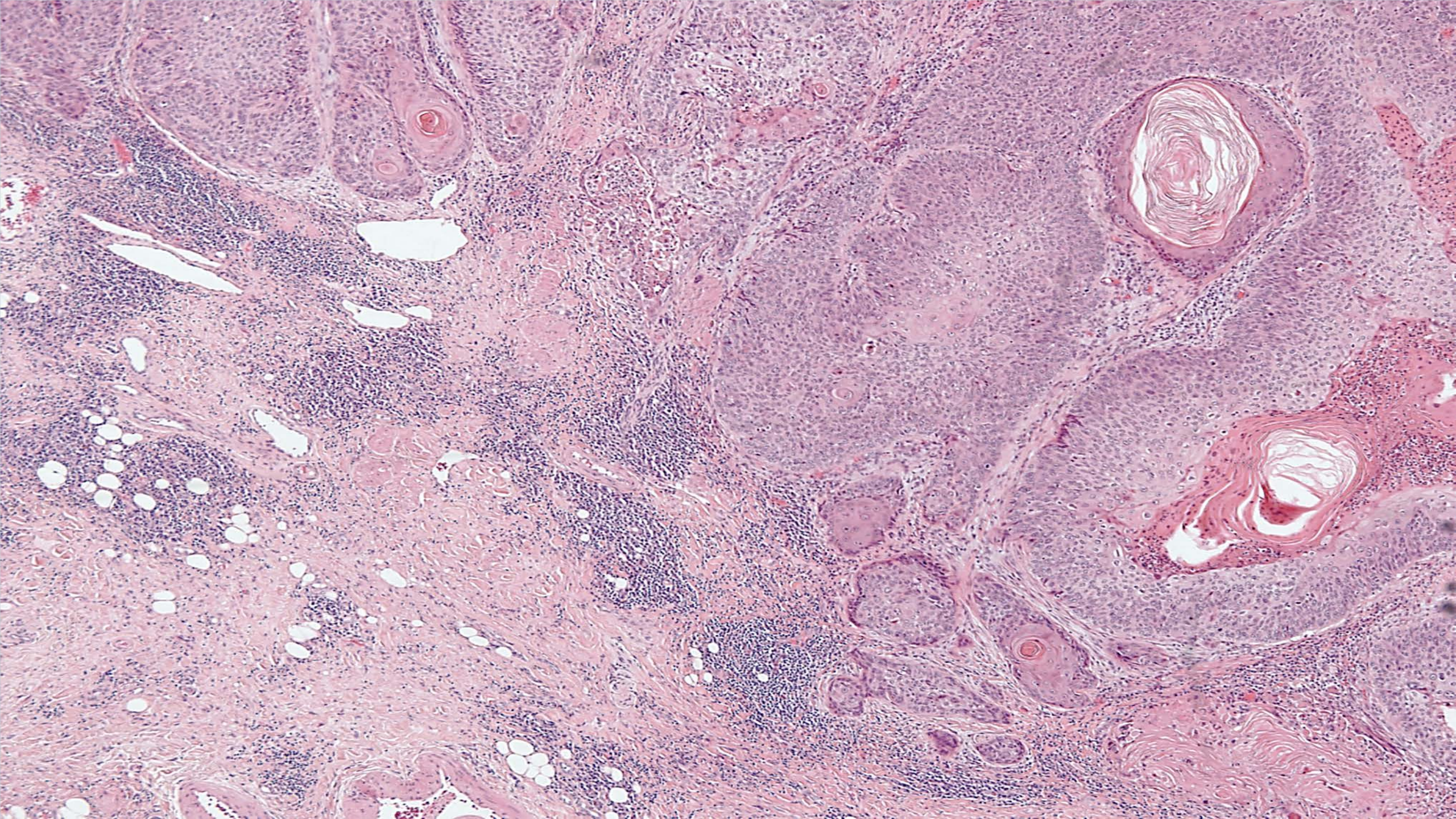




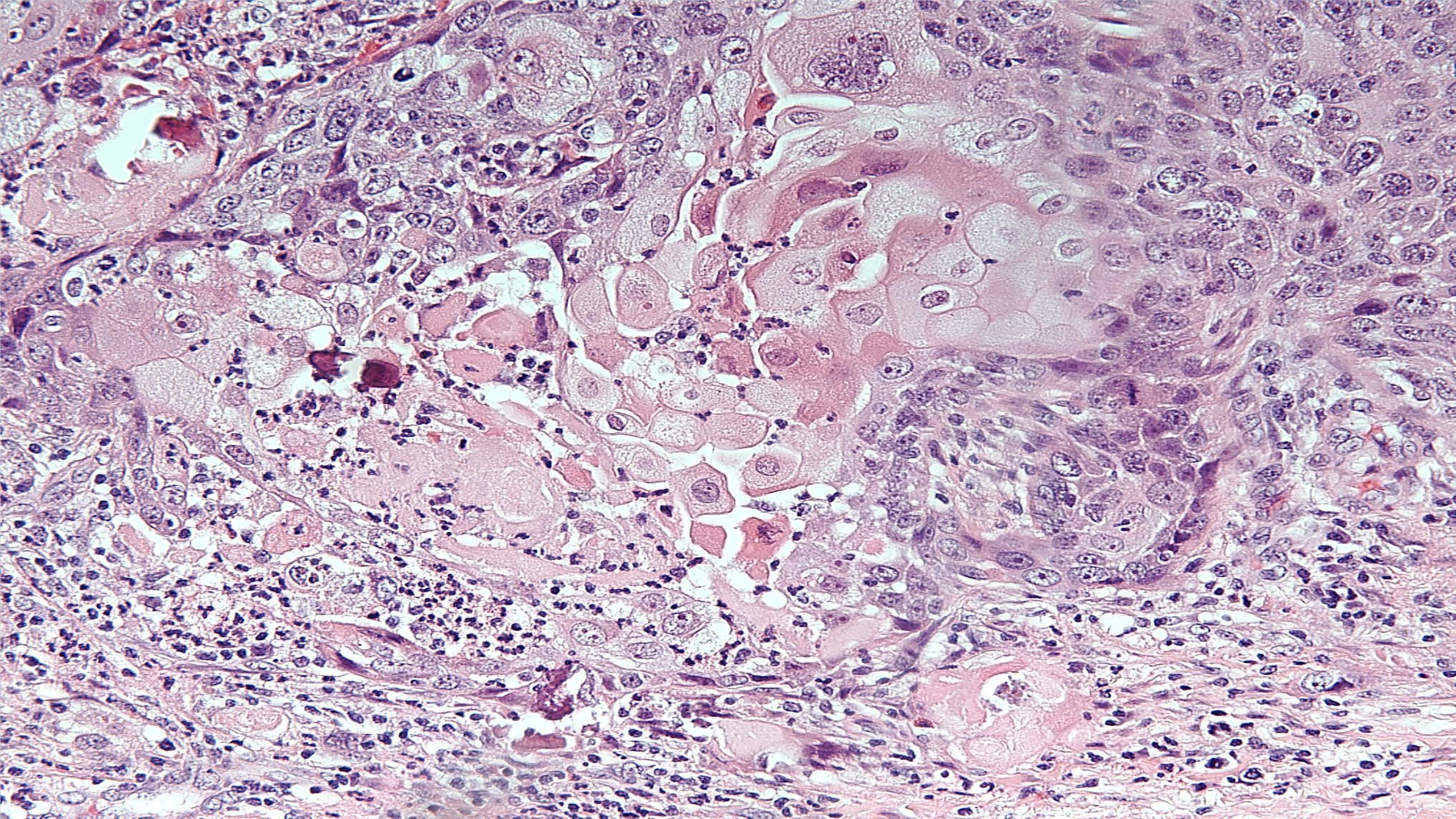














# Superficially Invasive Squamous Cell Carcinoma

- Jagged nests of tumor cells
- Stromal response with inflammation and desmoplasia

J Low Genit Tract Dis. 2012;16:205-42

# Anal Superficially Invasive Squamous Cell Carcinoma

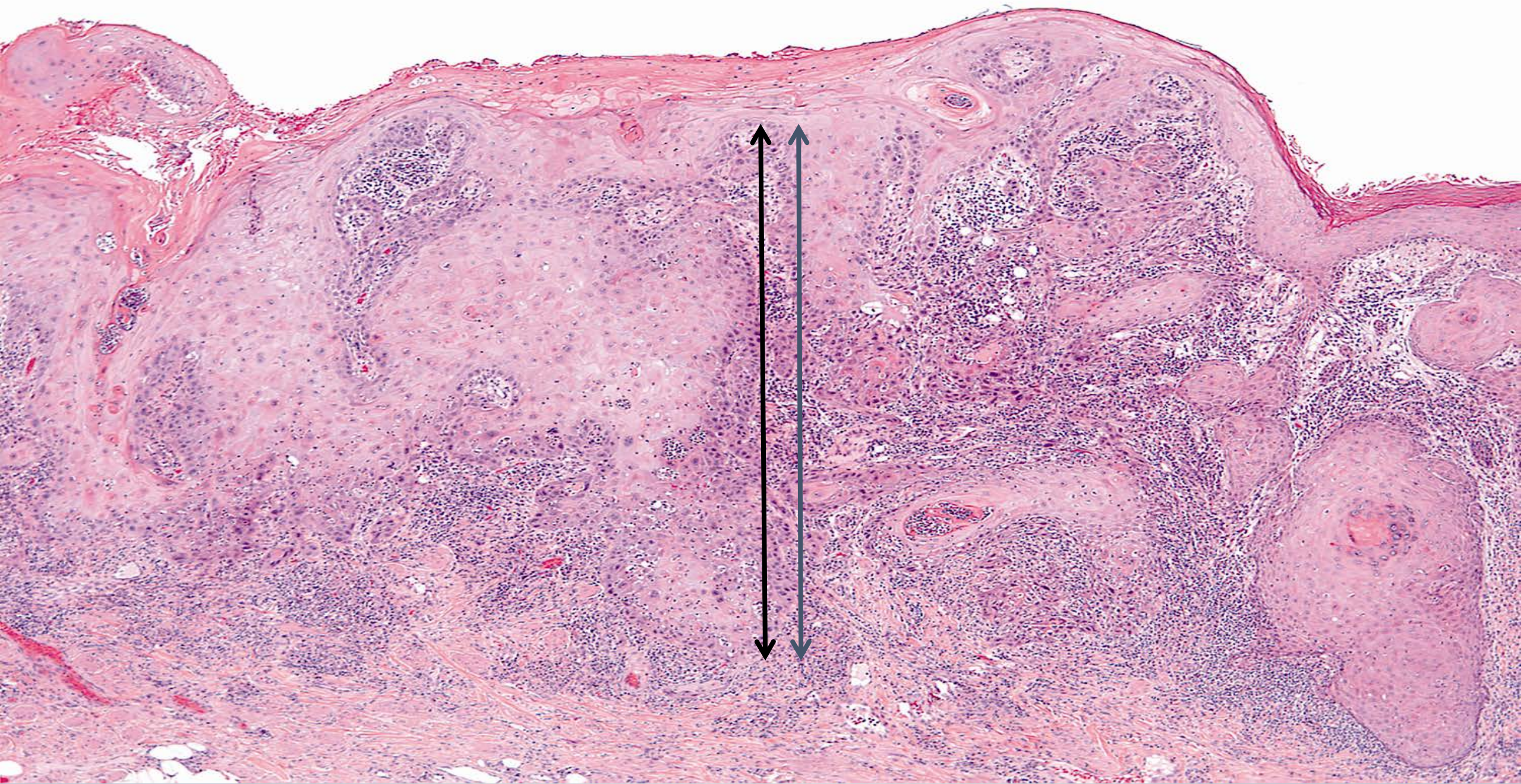
- Definition T1a:
  - $\leq 7$  cm size and  $\leq 3$  mm stromal invasion
- Measuring depth (AJCC):
  - Basement membrane of point of origin to deepest point of invasion
  - Include measurement of tumor thickness

*Note that the presence or absence of lymphatic invasion does not impact the assessment of invasion per se, although it should always be noted in the pathology report*

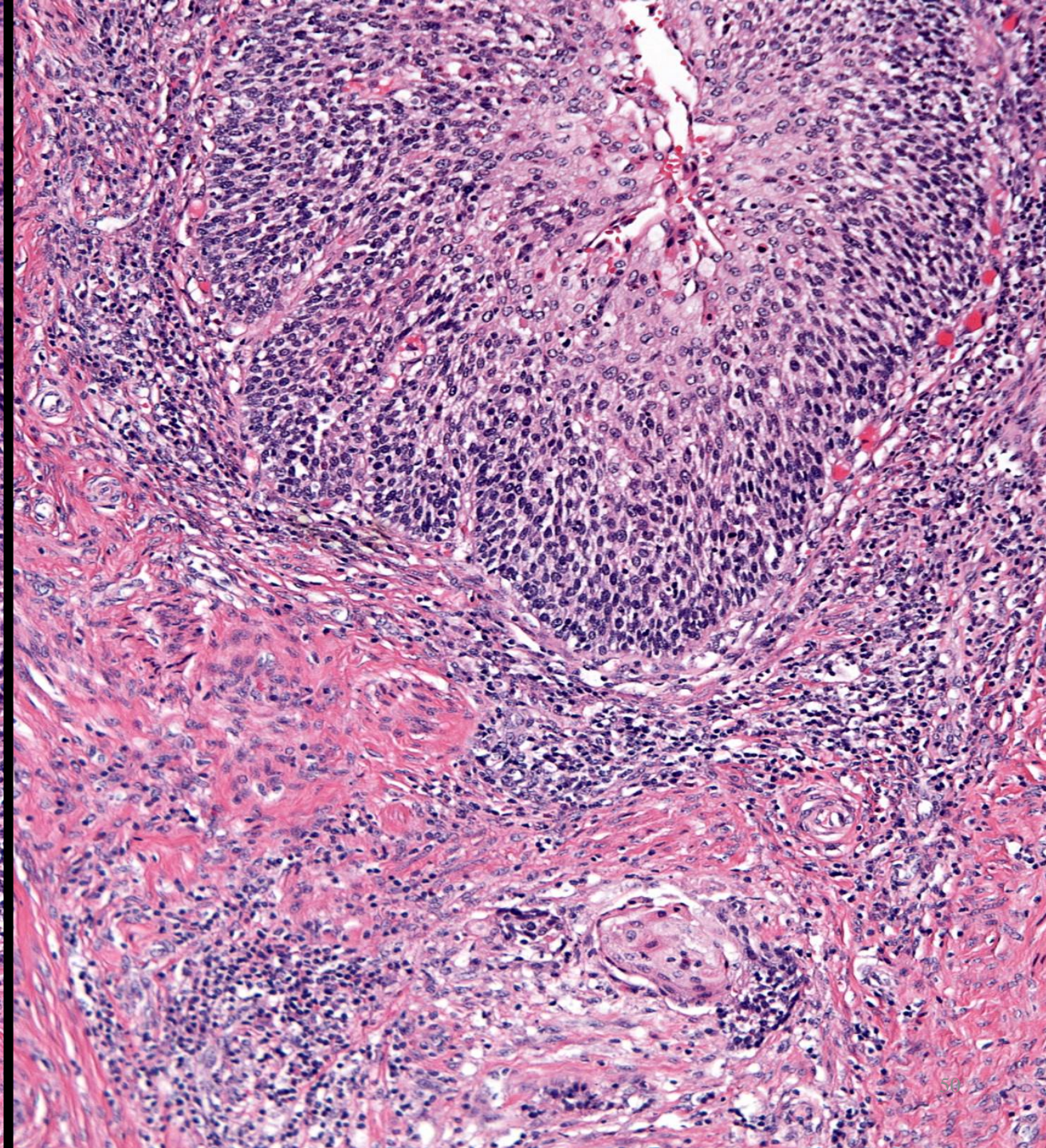
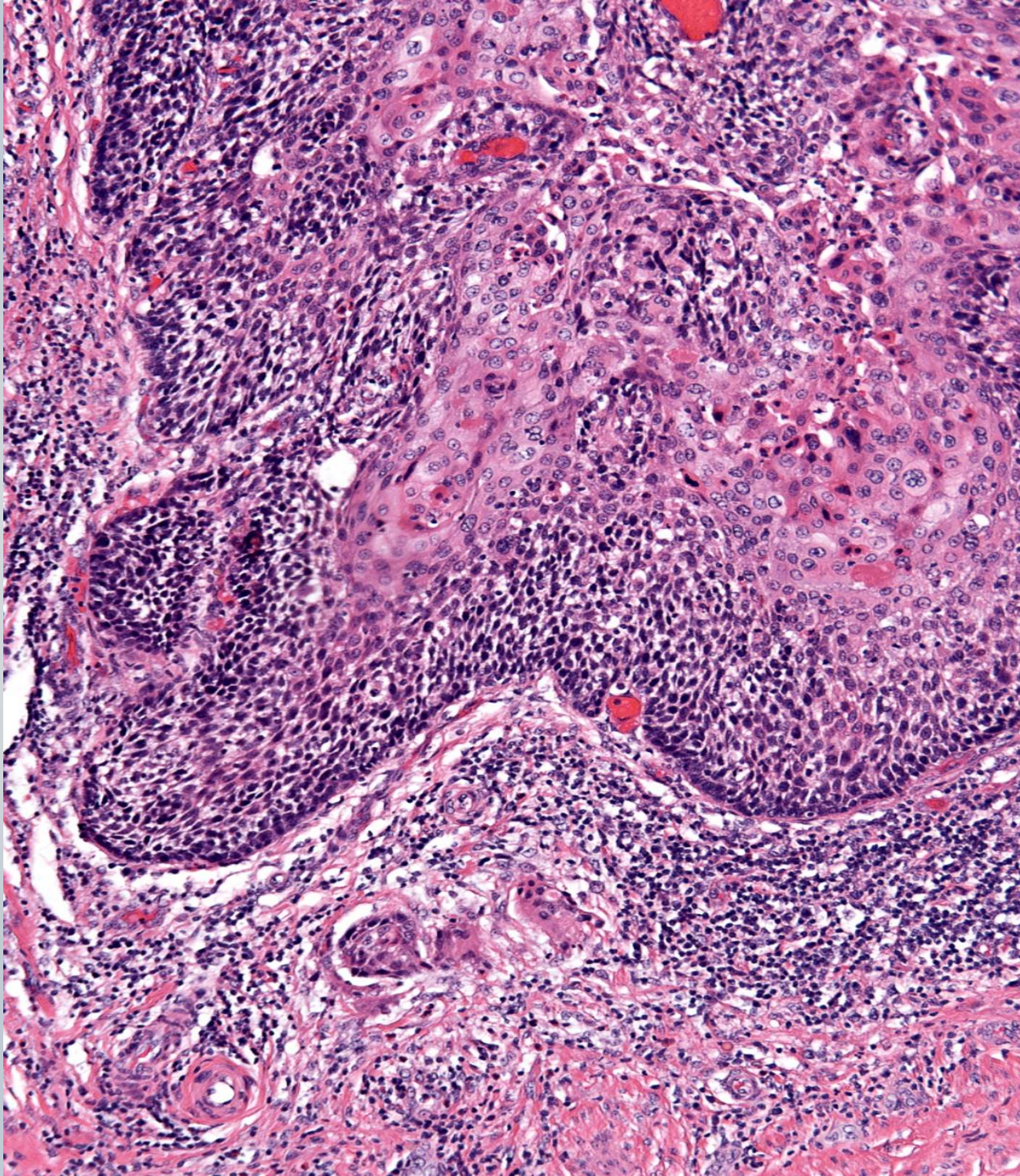














# Superficially Invasive Squamous Cell Carcinoma

- If incompletely excised and meets size criteria, diagnose as “At least superficially invasive squamous carcinoma”
- If exceeds dimensions for superficial invasion, state “The examined invasive tumor exceeds the dimensions for a superficially invasive SCC.”

J Low Genit Tract Dis. 2012;16:205-42



# Multifocal Invasion

- Measure each focus separately
- Do not add measurements for each focus
- If each focus meets size criteria, diagnose as superficially invasive SCC

J Low Genit Tract Dis. 2012;16:205-42



# Superficially Invasive Squamous Cell Carcinoma

Report should comment on:

- Lymphatic-vascular invasion
- Presence, number and size of independent multifocal carcinomas

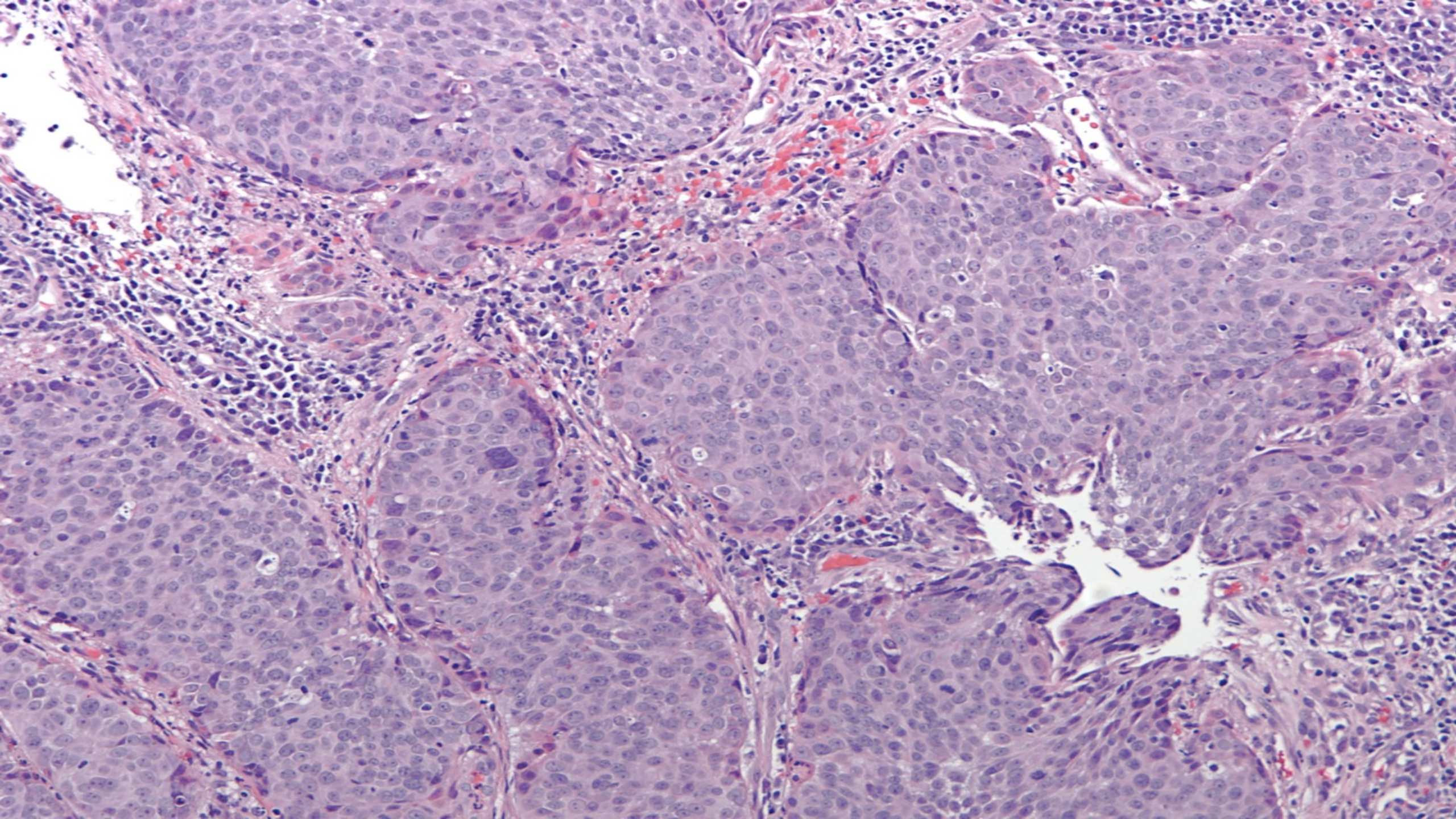
J Low Genit Tract Dis. 2012;16:205-42



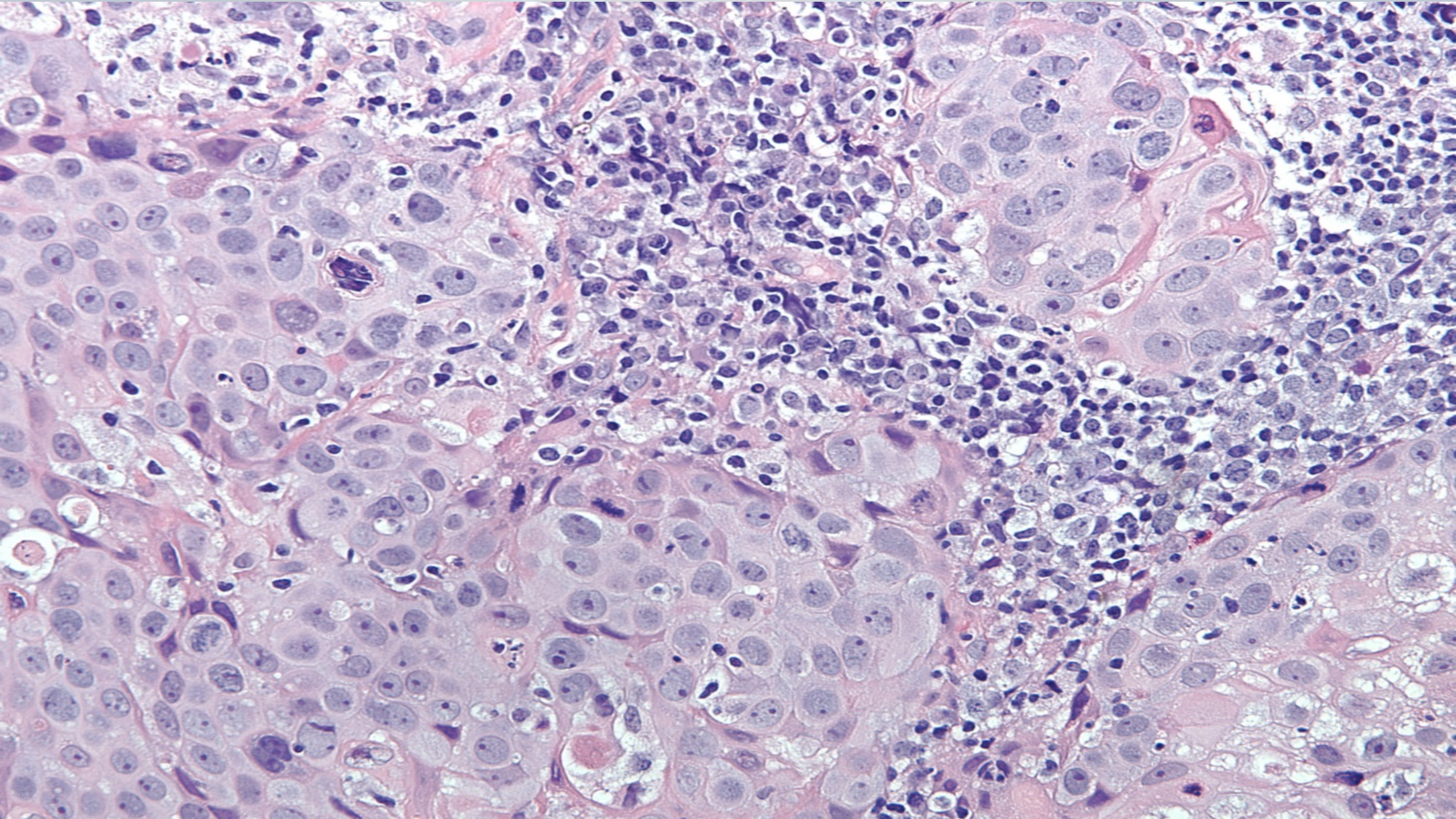
# Case 4

46-year-old female with rectal bleeding











# Anal Canal Squamous Cell Carcinoma

- Keratinizing
- Nonkeratinizing
- Cloacogenic
- Transitional
- Basaloid
- Adenoid cystic
- Mucoepidermoid or mucinous microcystic

No clear difference in prognosis or response to therapy



(ALMOST)  
ALL  
HARBOR  
HIGH RISK HPV



# Risk Factors for Anal Squamous Cell Carcinoma

- History of HPV-mediated genital tract disease – esp. multifocal (esp. HSIL, cancer)
- HIV seropositivity
- Low CD4 count
- Other immunosuppression: solid organ transplant, ulcerative colitis
- Heavy cigarette smoking



# Risk Factors for Anal Squamous Cell Carcinoma

- Frequent anoreceptive intercourse – *not required*
- Multiple HPV genotypes
- Persistent high risk HPV genotype infection
- Radiation
- Chronic irritation: persistent hemorrhoids



# HPV Status in Anal SCC

- Up to 15% are HPV negative – often p53+
- HPV+ status appears to predict better prognosis & response to therapy
- Role for HPV and/or p16 testing in all anal SCC?!?

Cancer Chemother Pharmacol 2014;74:1033-8; BMC Gastroenterol 2018;18:30; Br J Cancer 2015;112:1358-66; J Clin Oncol 2014;32:1812-7.



# Is There a DSIN?

- Some authors have described similar precursor lesion to DVIN in non-HPV-associated anal SCC
- p53 overexpressed
- No usual SIL lesion
- Reproducibility of diagnosis is unknown

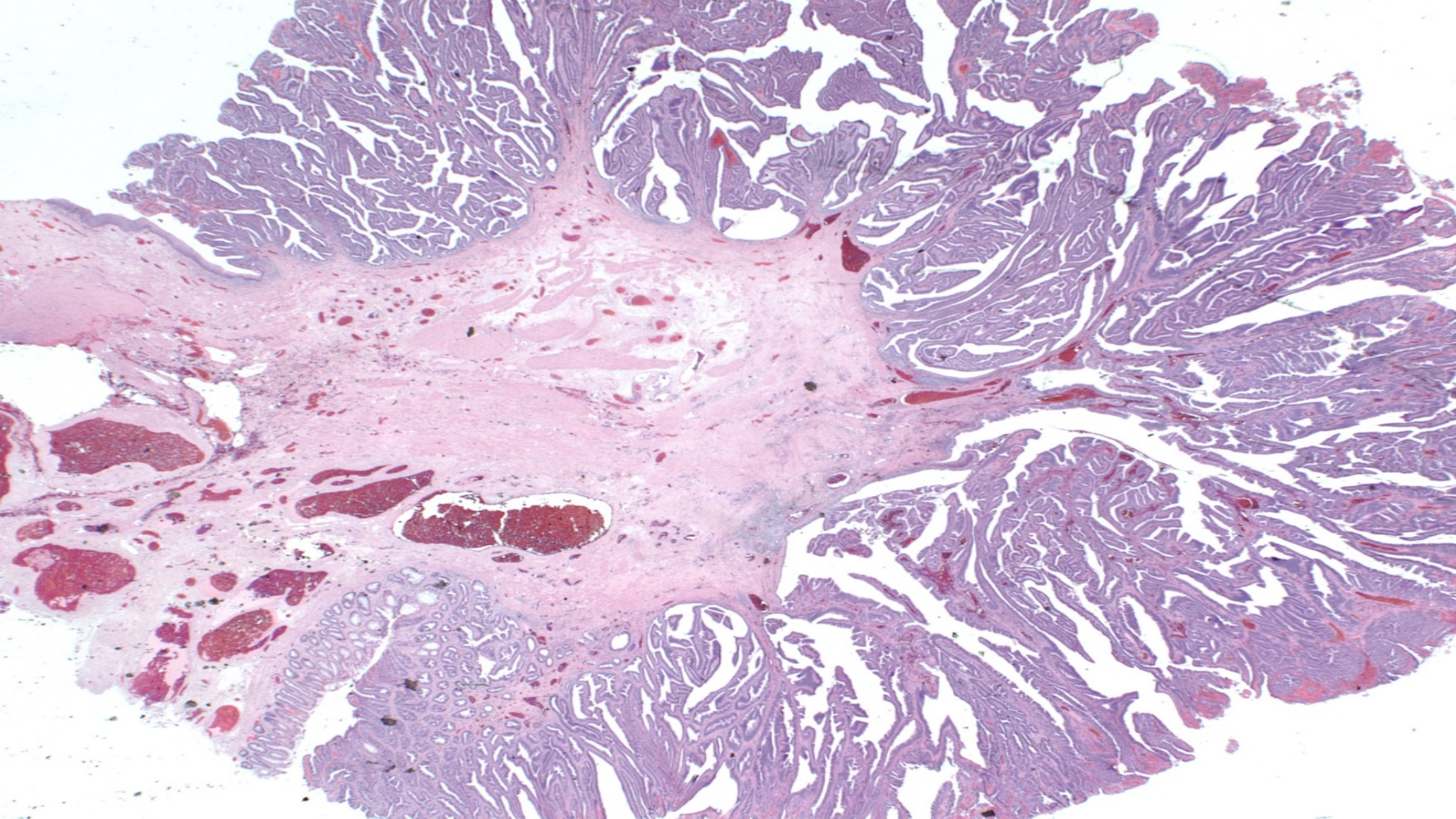
Histopathology 2016;68:834-42.



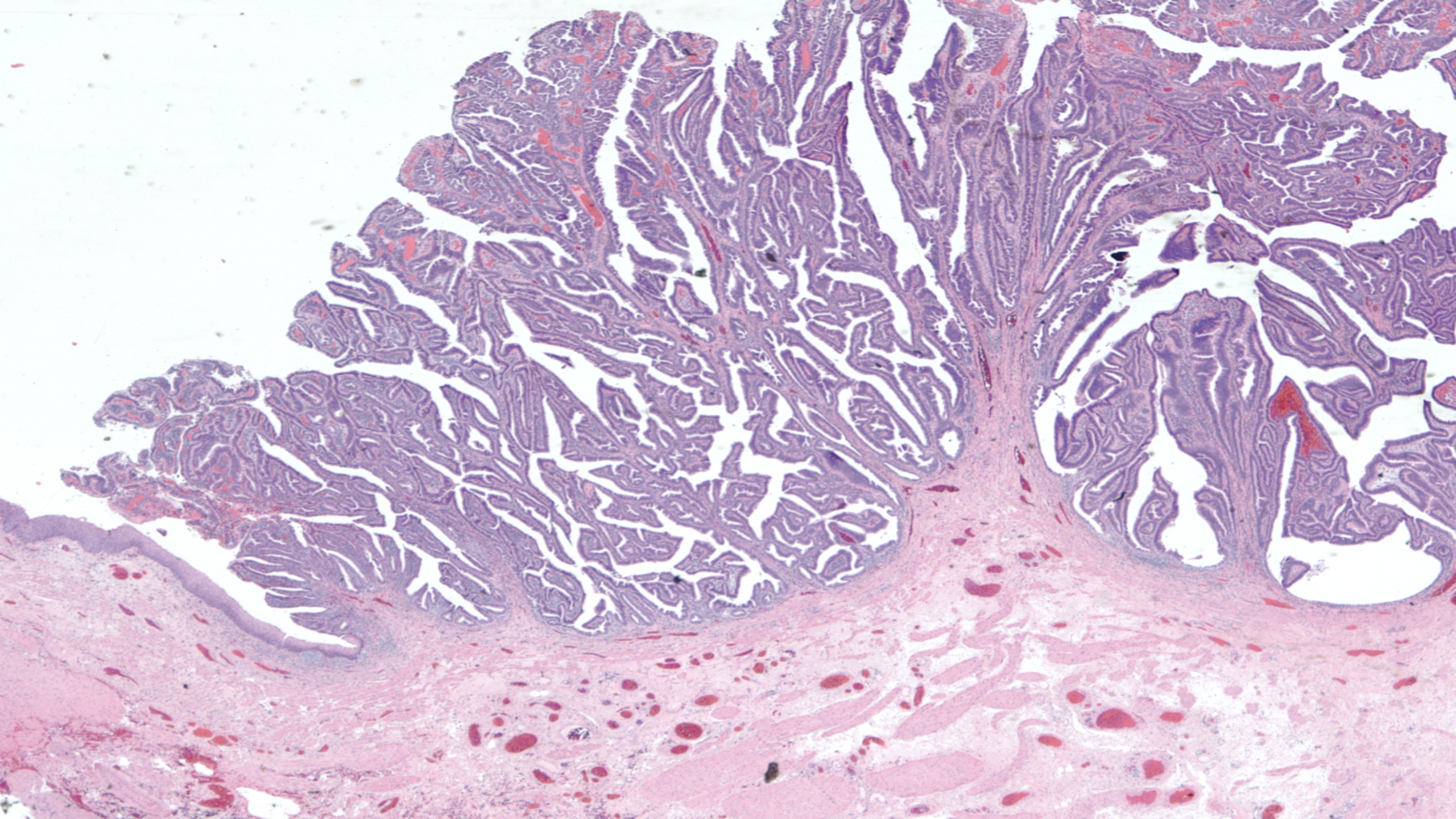
# Case 5

32-year-old male with “rectal carcinoma”

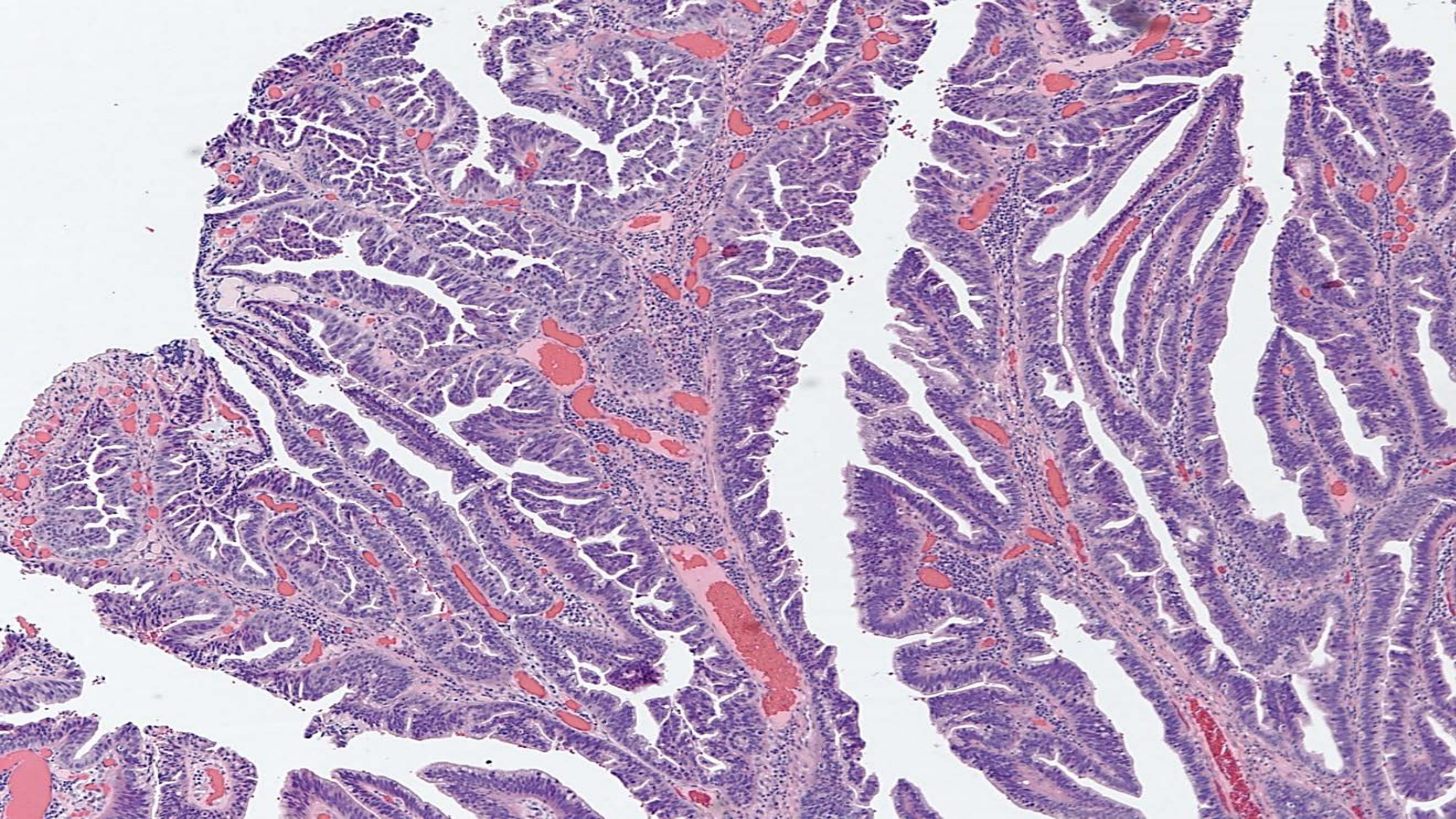




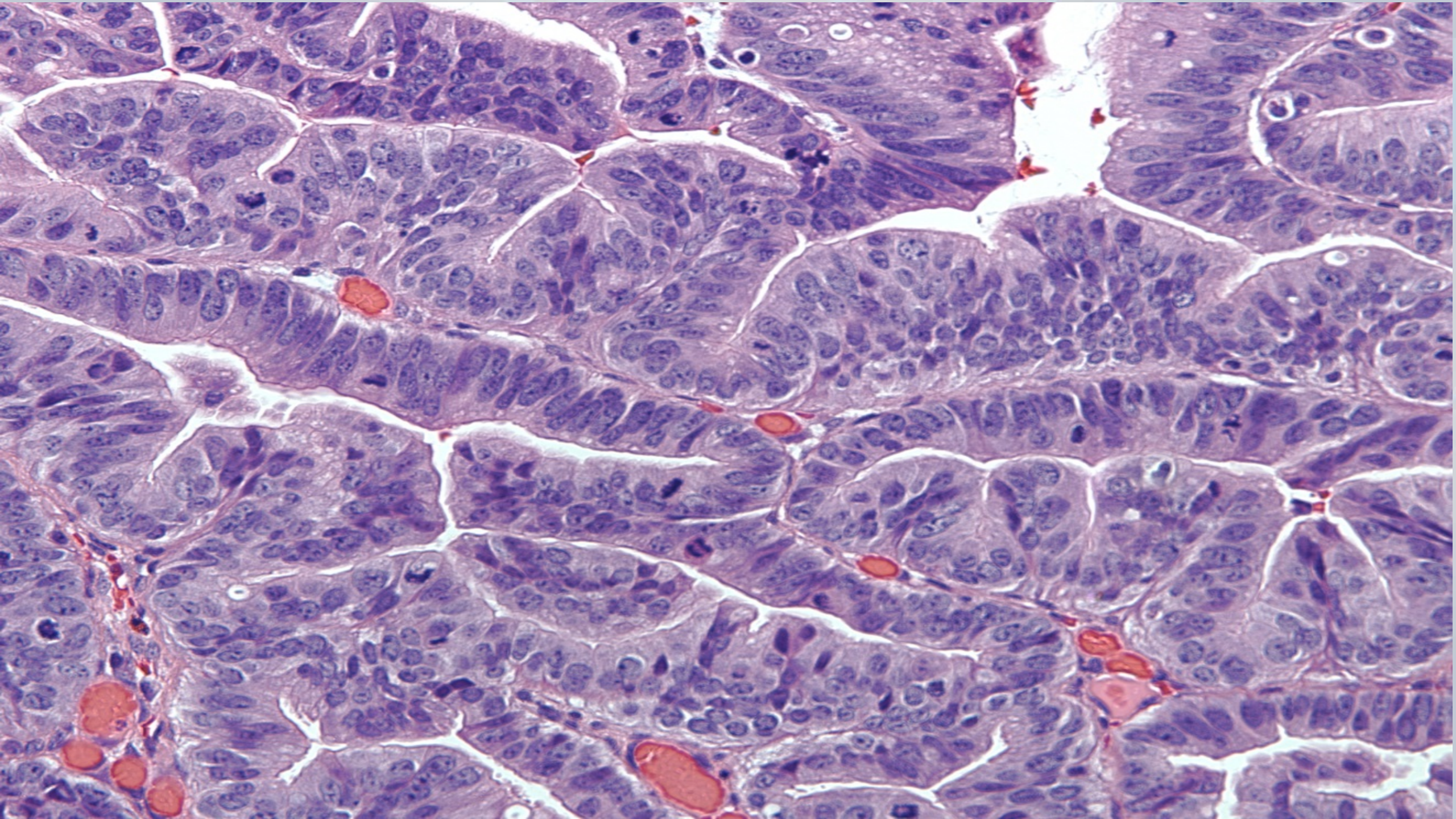




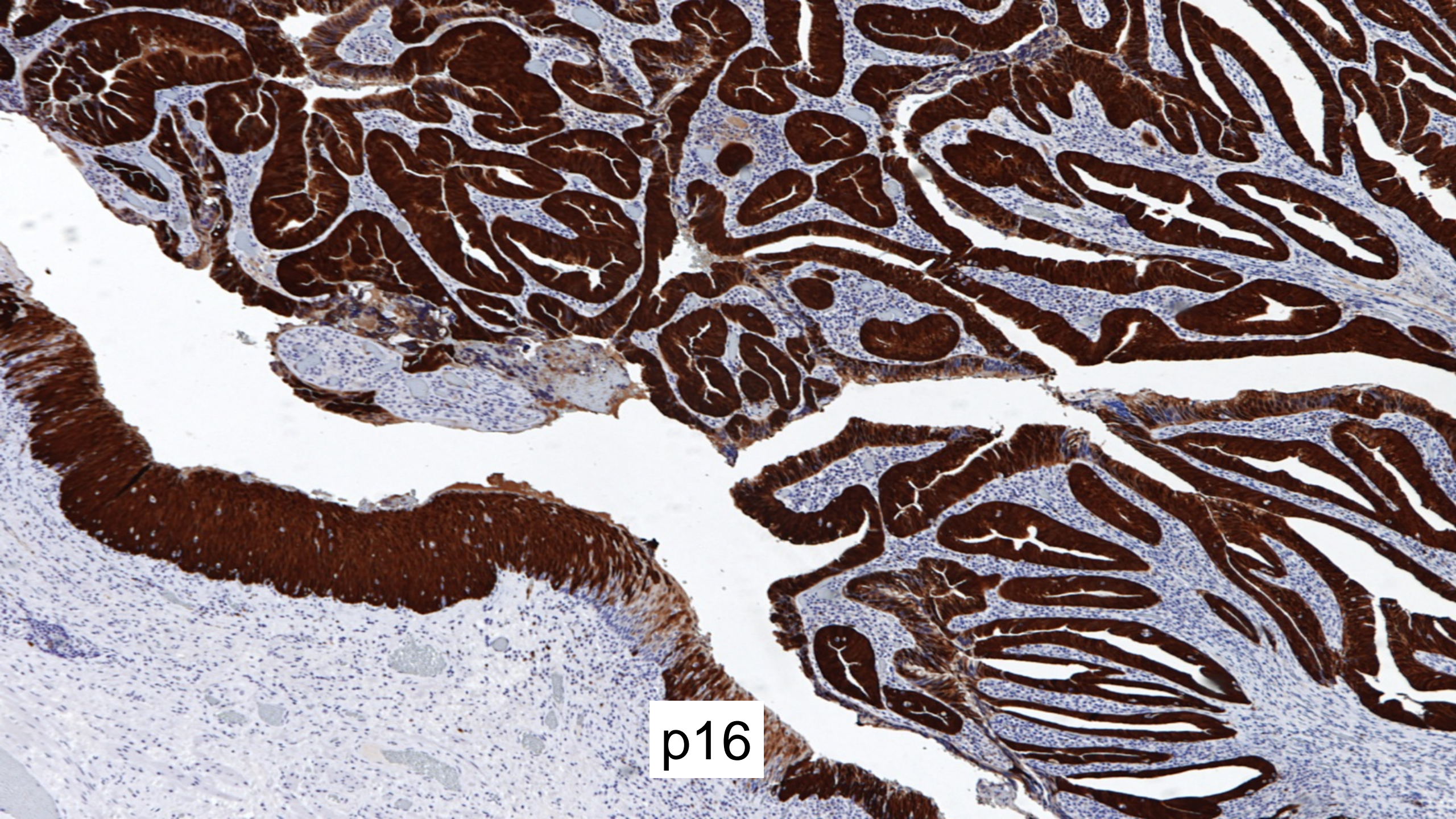












p16



# HPV-Associated Anorectal Adenocarcinoma

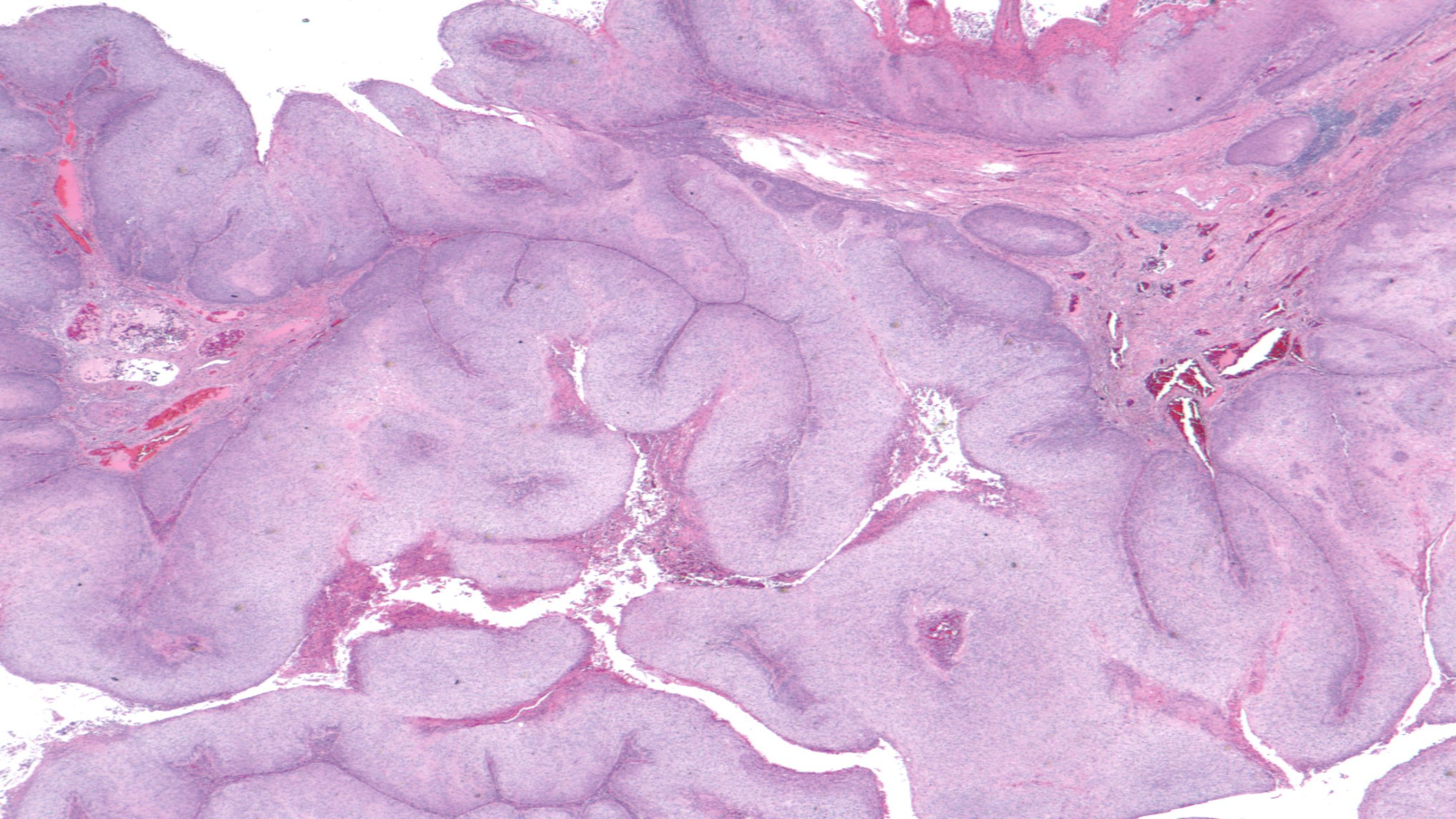
- Papillary or villiform/villoglandular morphology & cytologic features similar to those of usual type, high-risk HPV-related endocervical adenocarcinoma
- Associated with HSIL
- HPV 18
- Prevalence ???



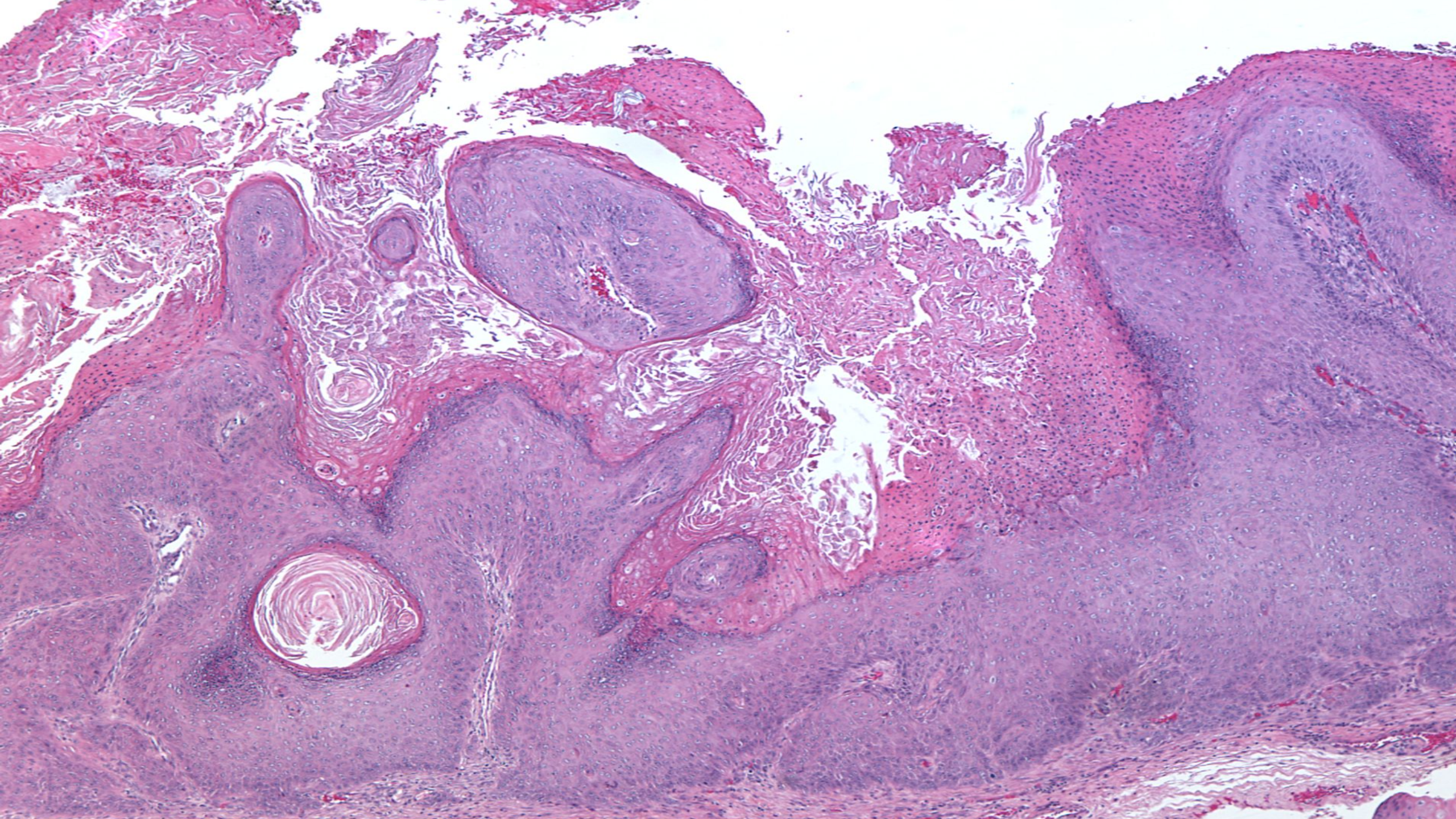
# Case 6

34-year-old male with recurrent anal lesion involving perianal skin and anal canal

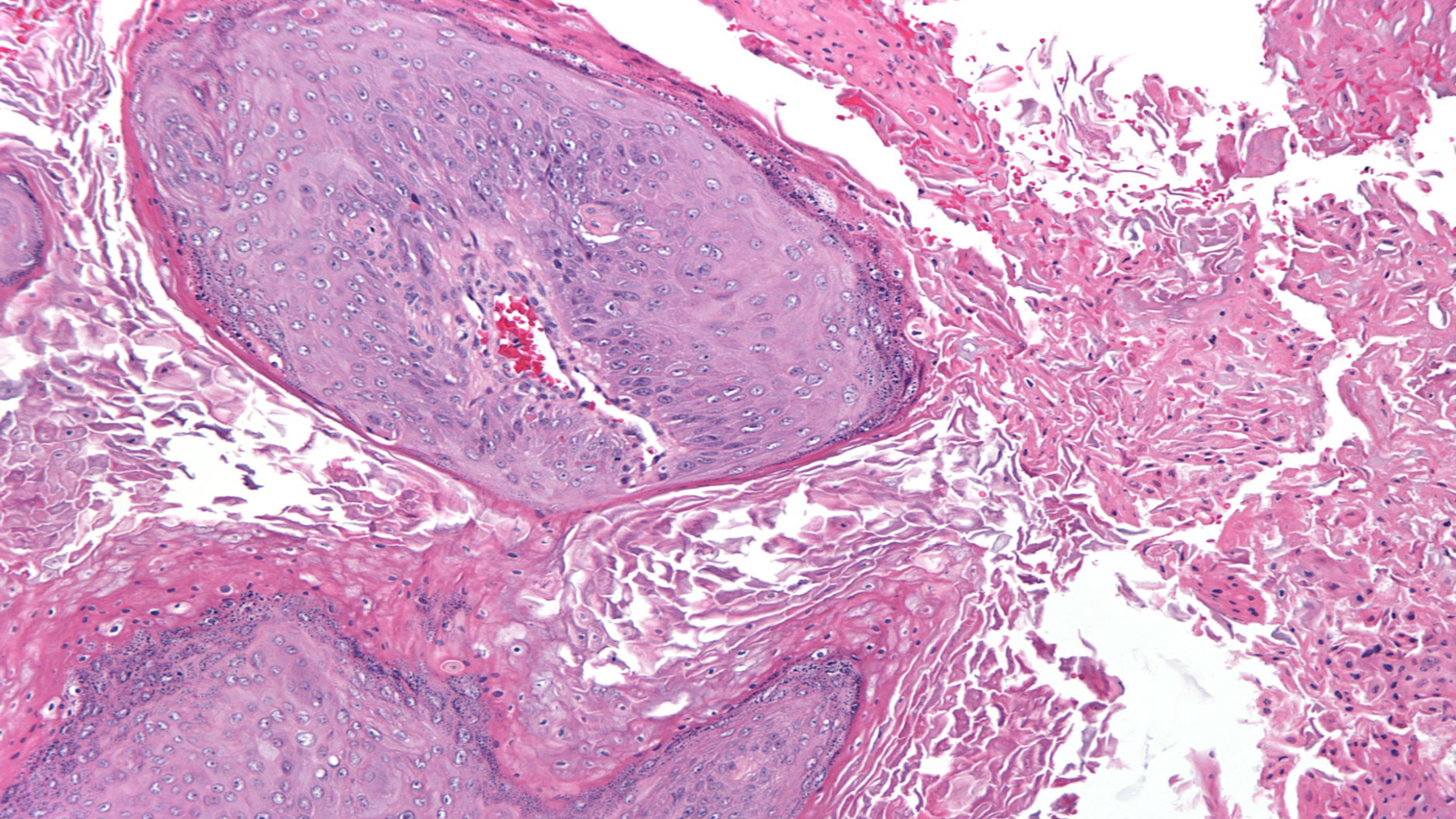




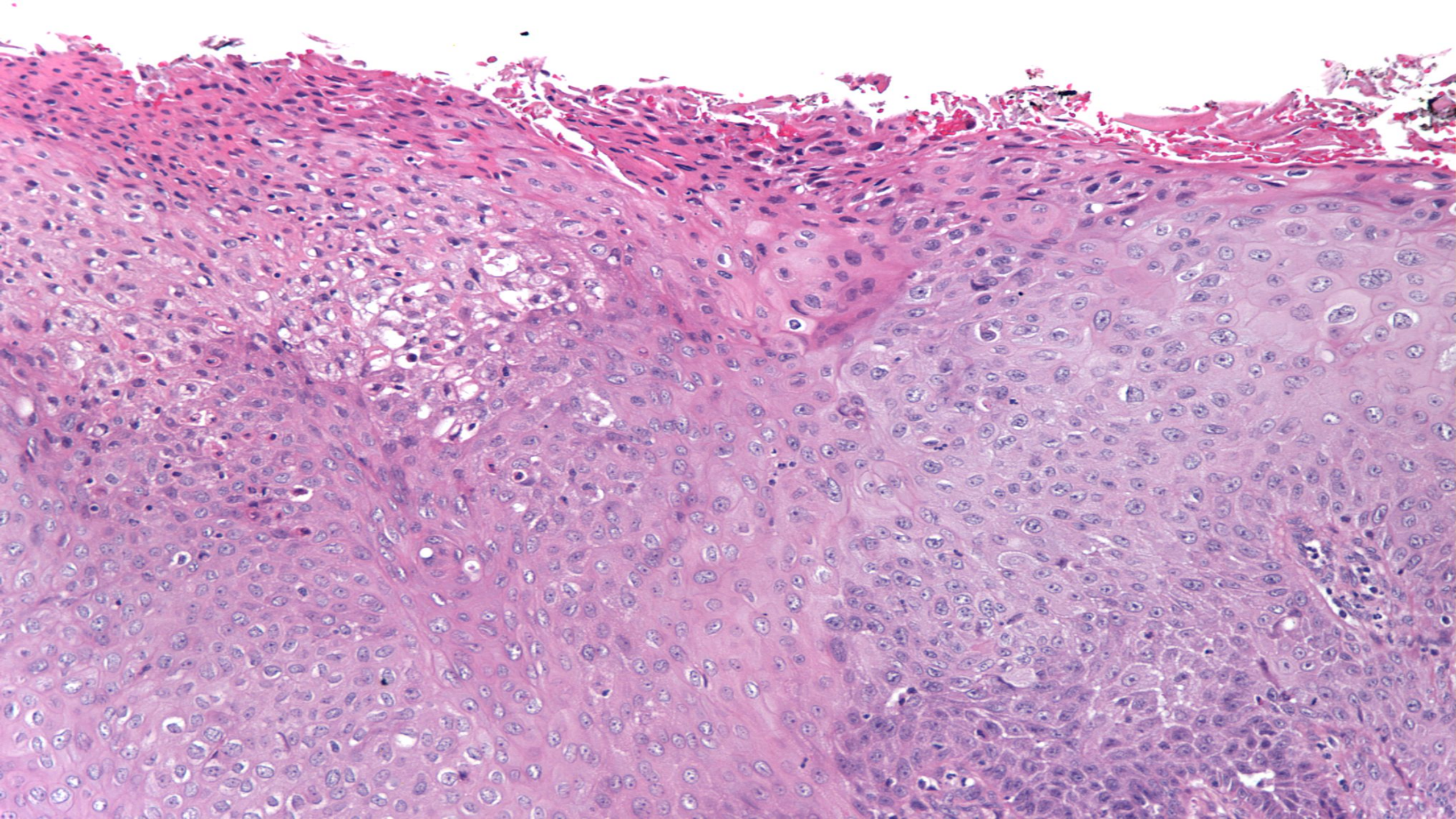




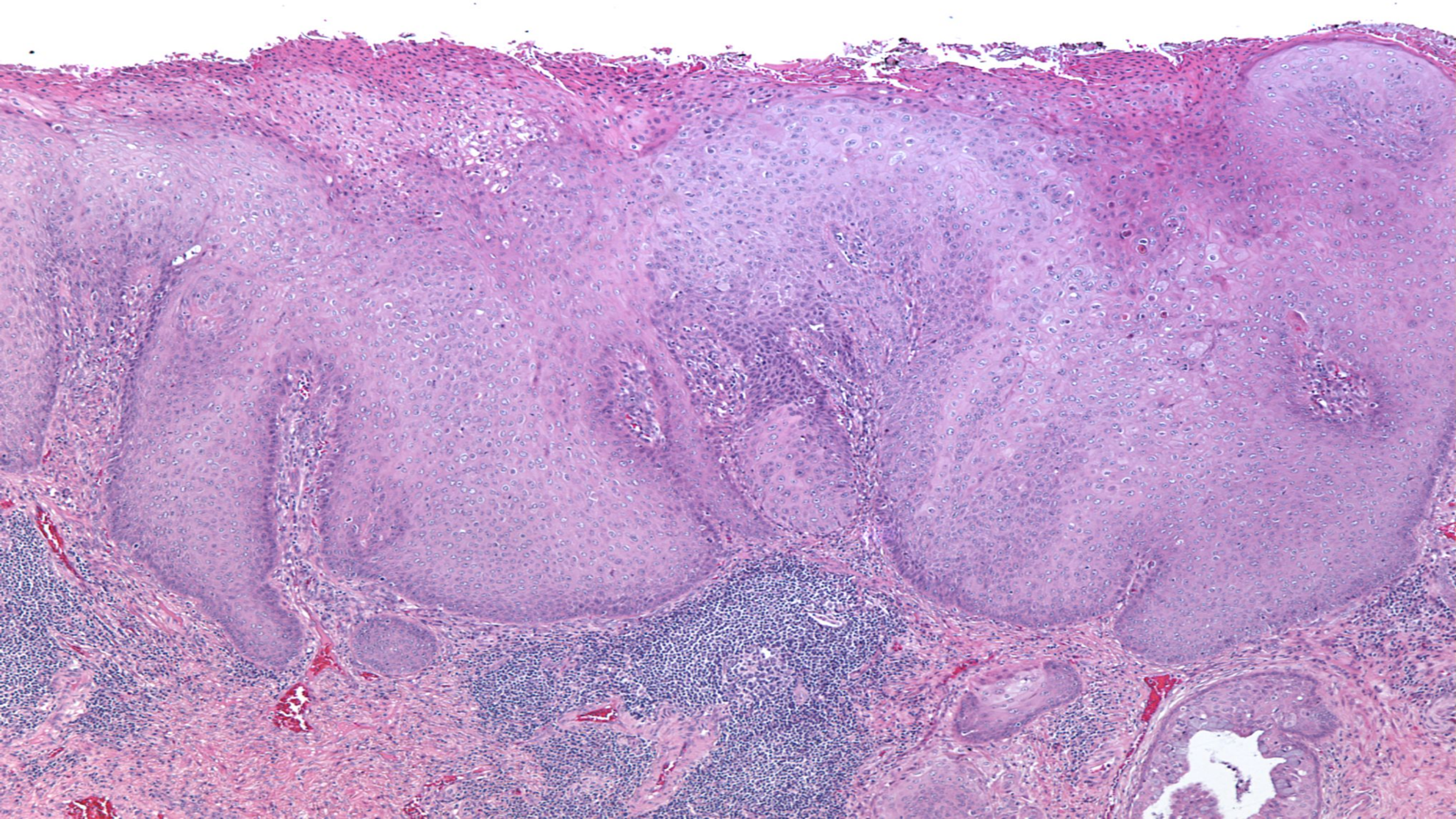




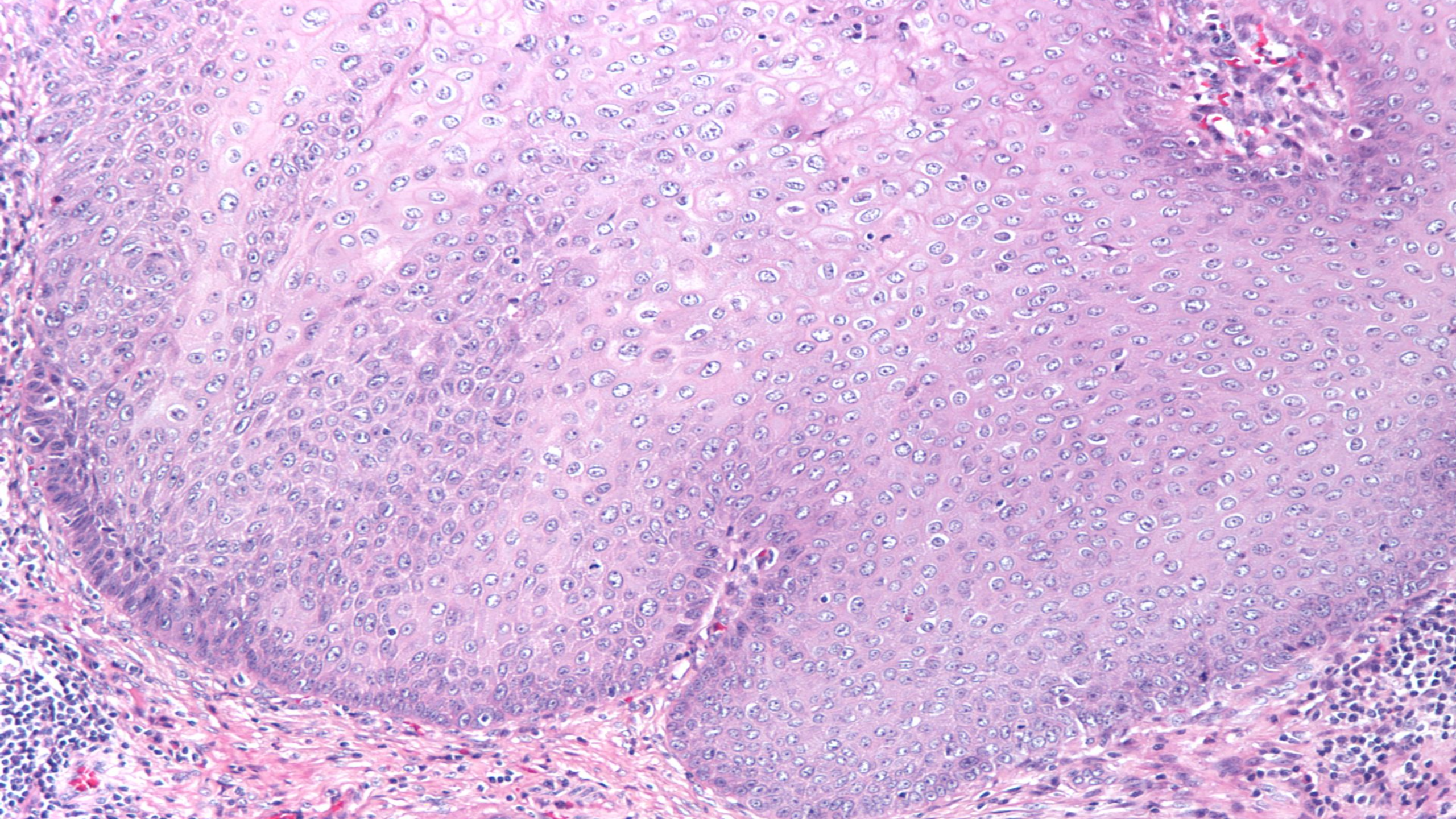














# Verrucous Carcinoma (Giant Condyloma of Buschke-Lowenstein)

- Often large size (>10 cm)
- Thick stratum corneum
- Marked papillary architecture
- Displacement of deep tissue
- Non-metastasizing
- Role of high risk HPV uncertain



# Verrucous Carcinoma (Giant Condyloma of Buschke-Lowenstein)

- HPV 6, 11 often reported in these lesions
- A second, high risk HPV type may be present in a portion of the lesion
- Alternatively, alteration in control genes for low risk HPV type may occur



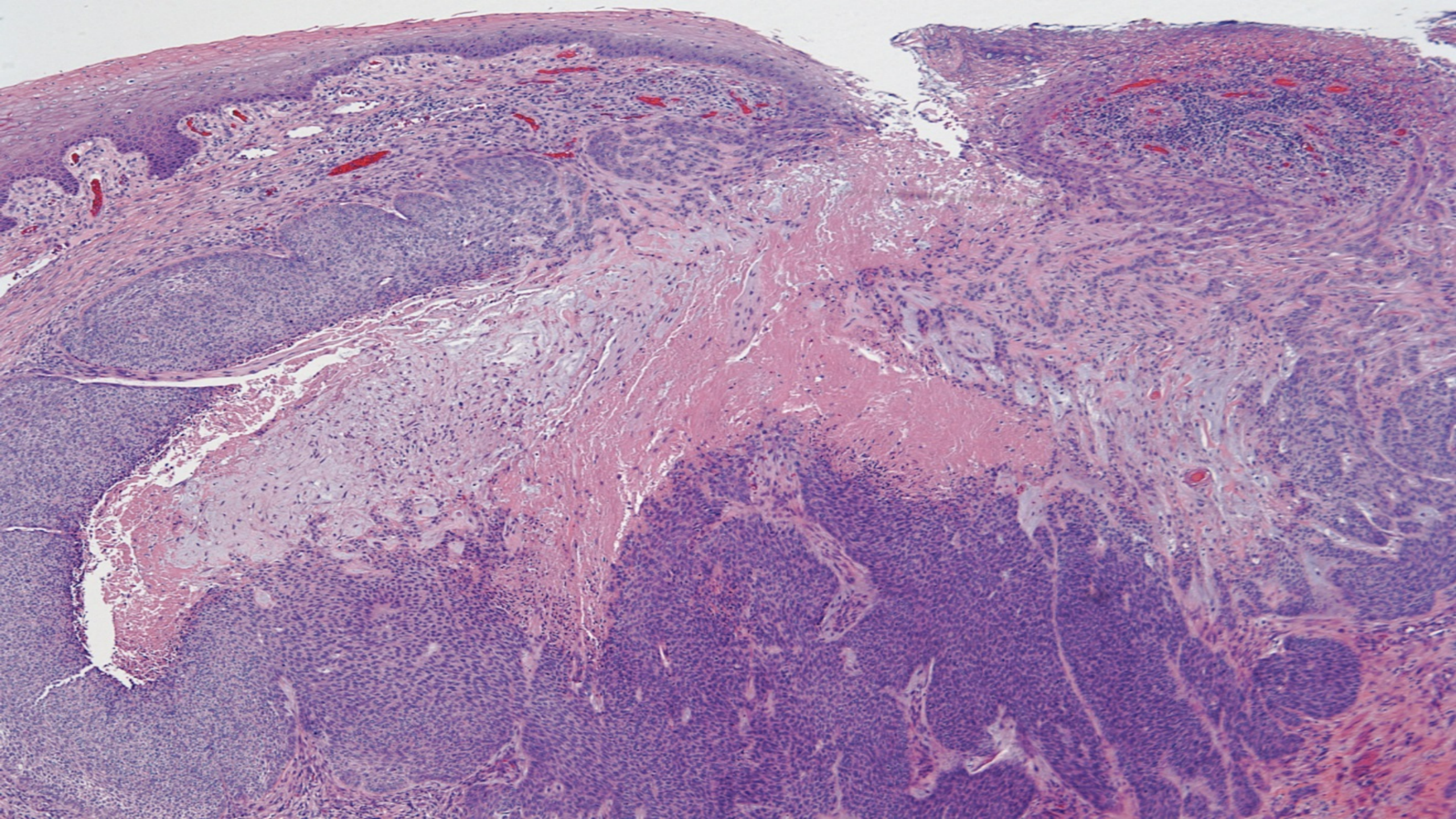
**NOT ALL ANAL  
CONDYLOMAS ARE  
INNOCUOUS!**



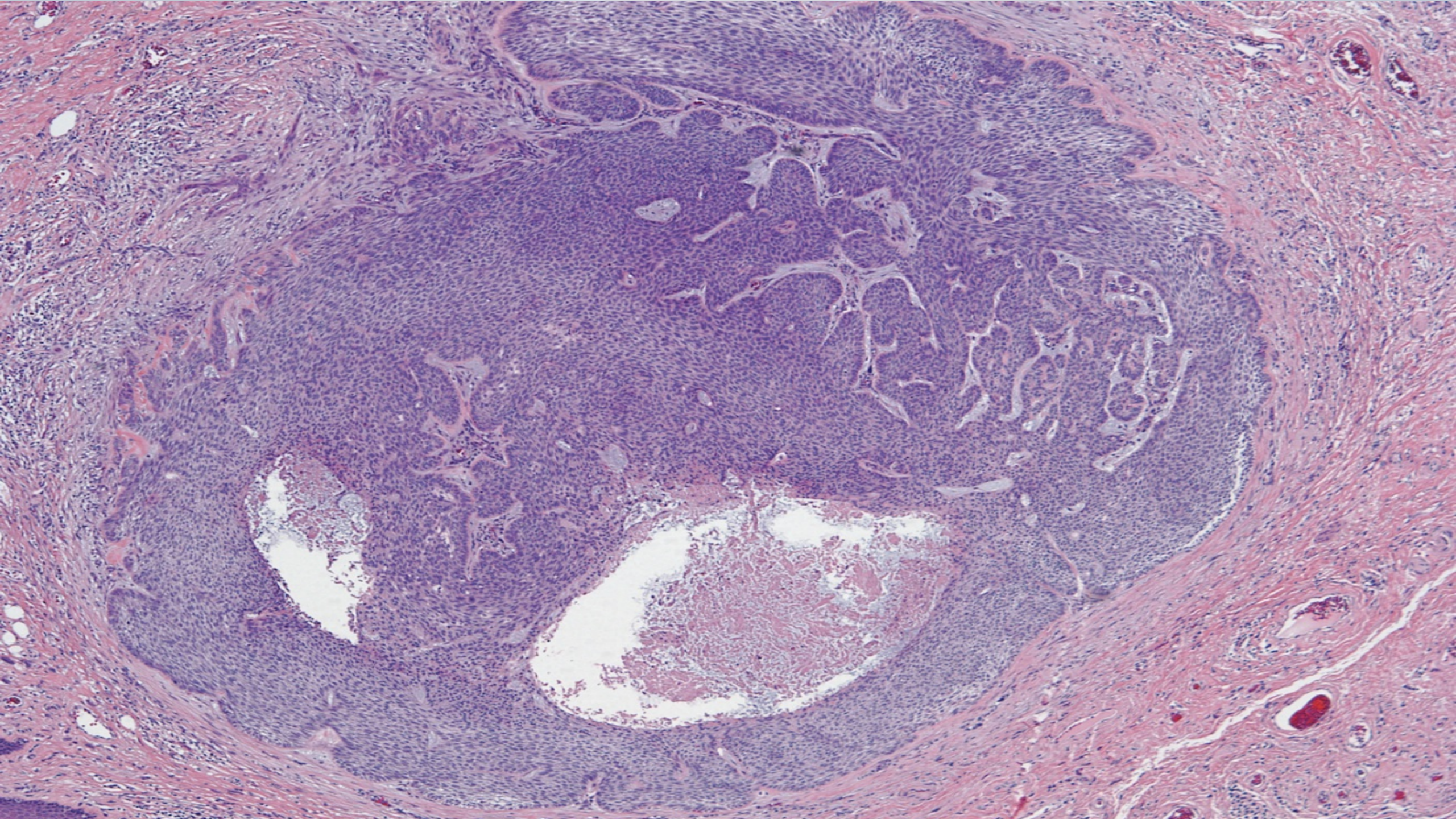
# Case 7

55-year-old with large ulcerated perianal lesion

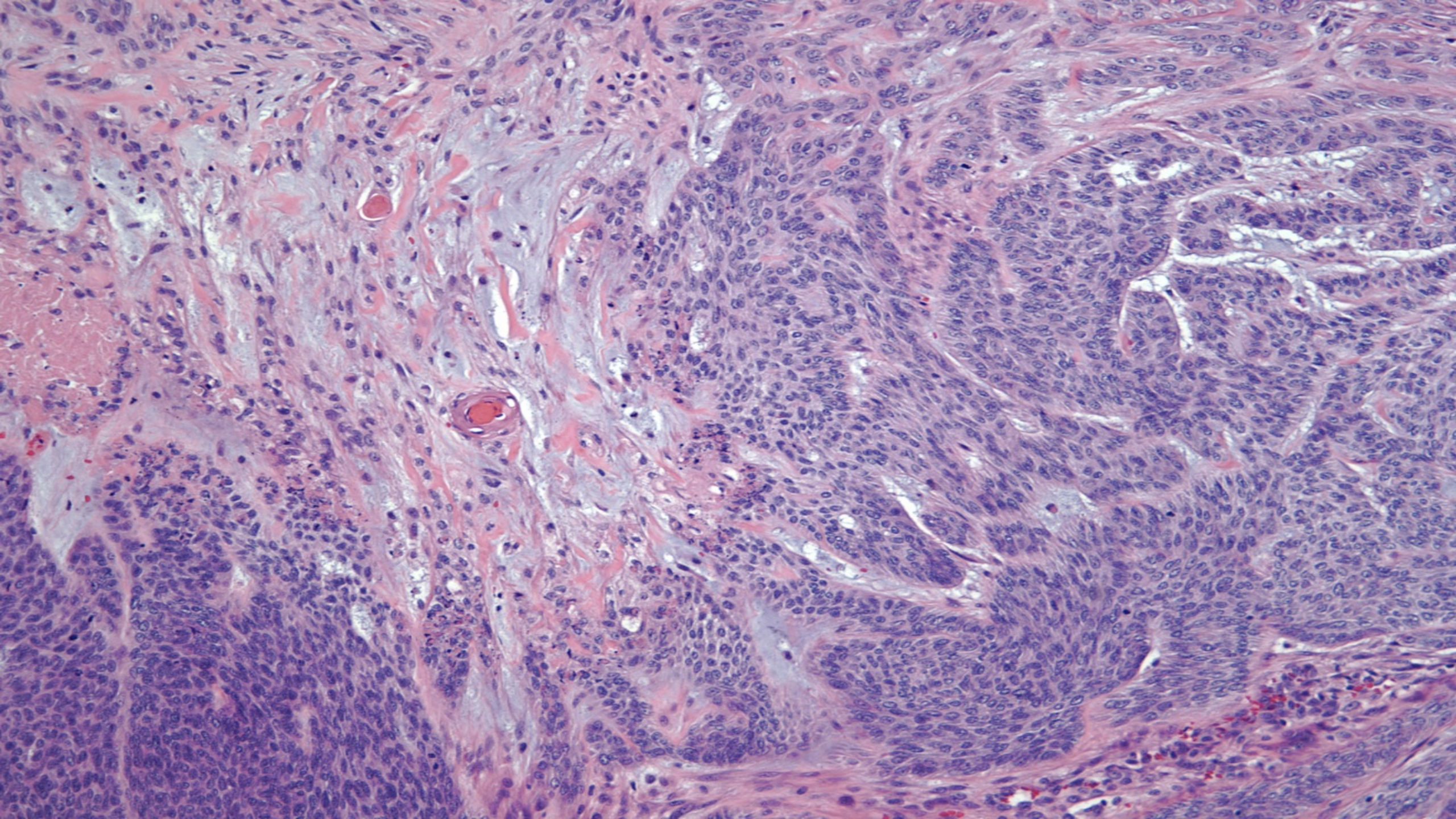












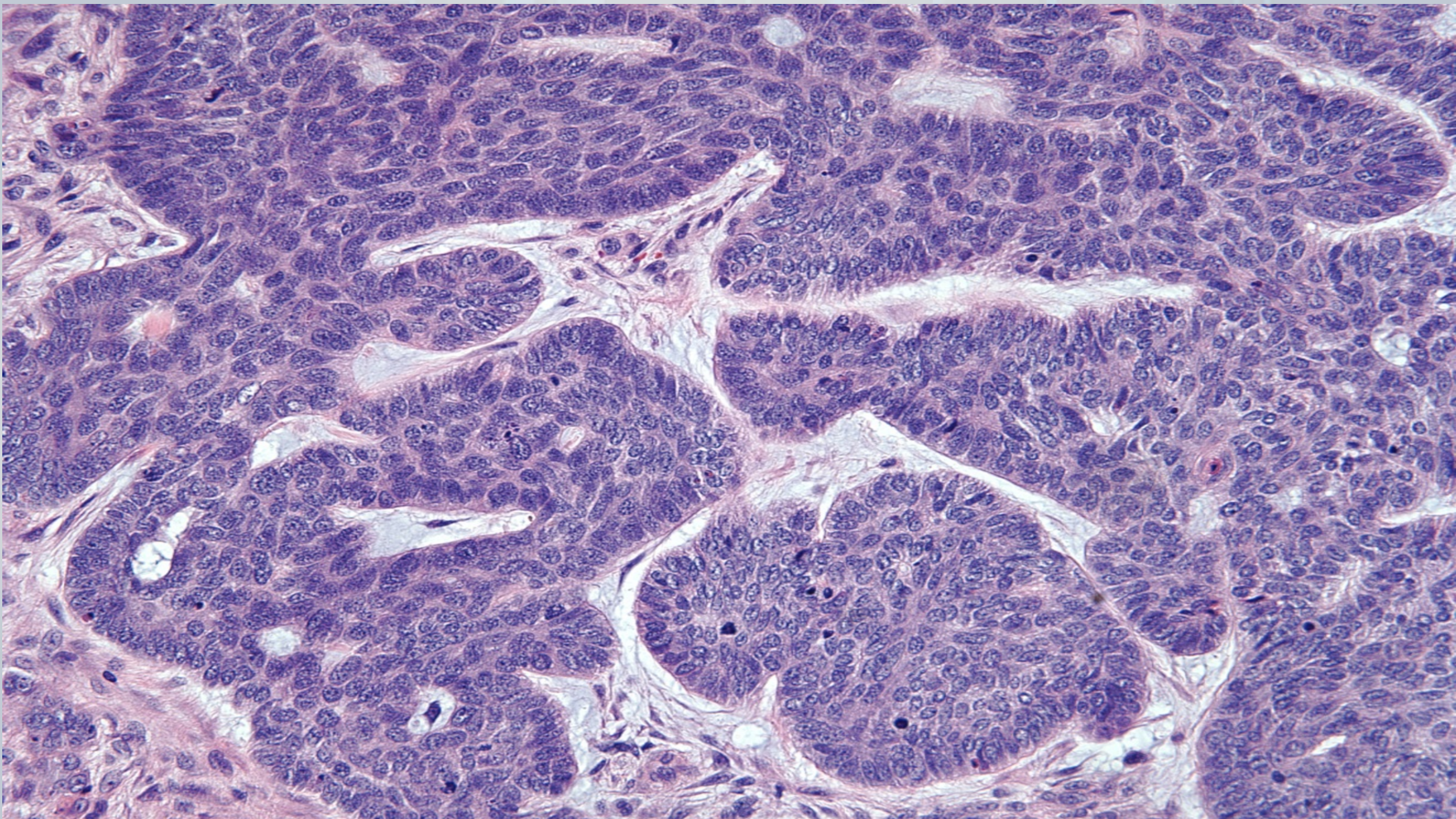


## *Live Content Slide*

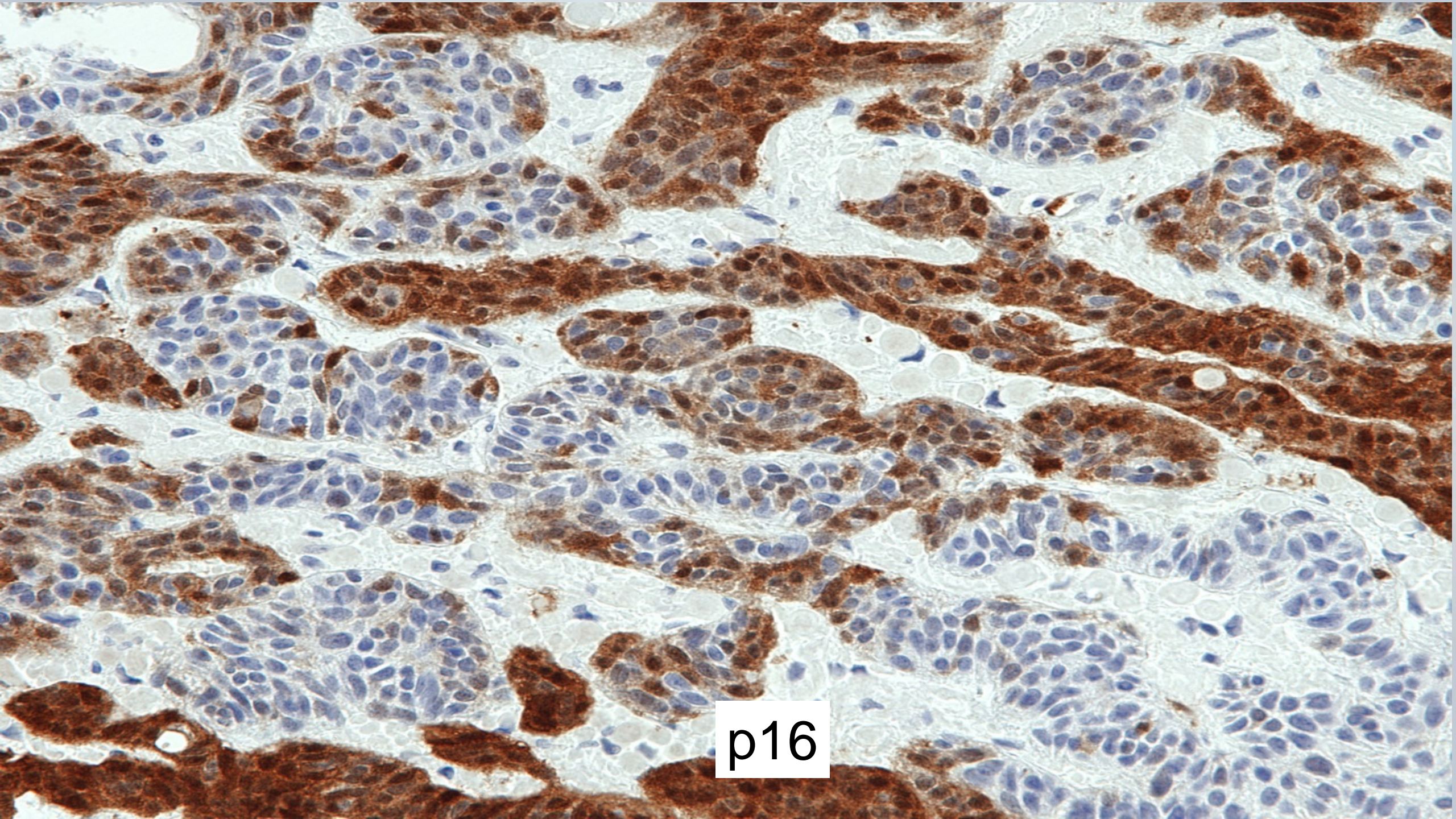
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**Poll: Diagnosis?**



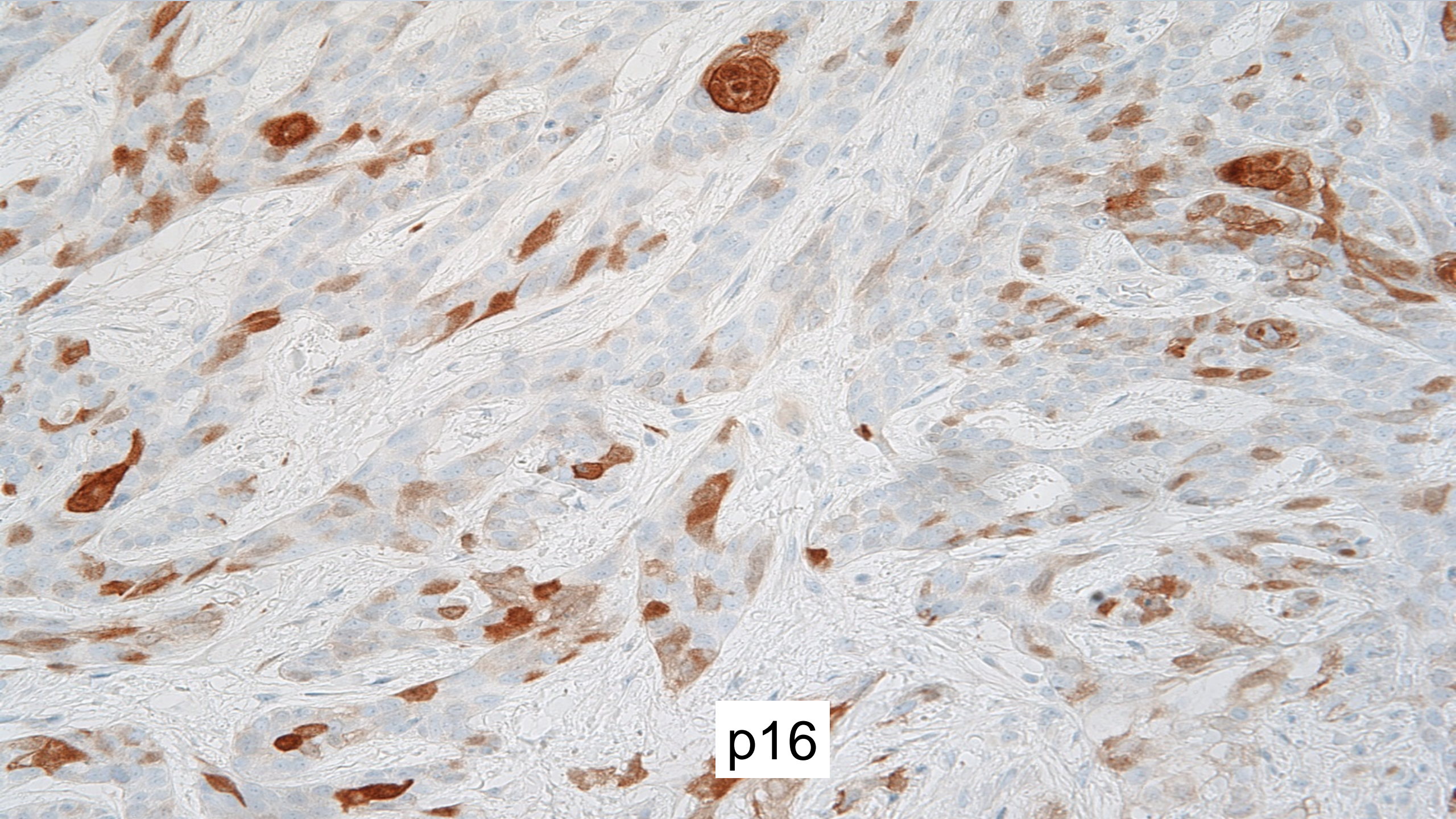






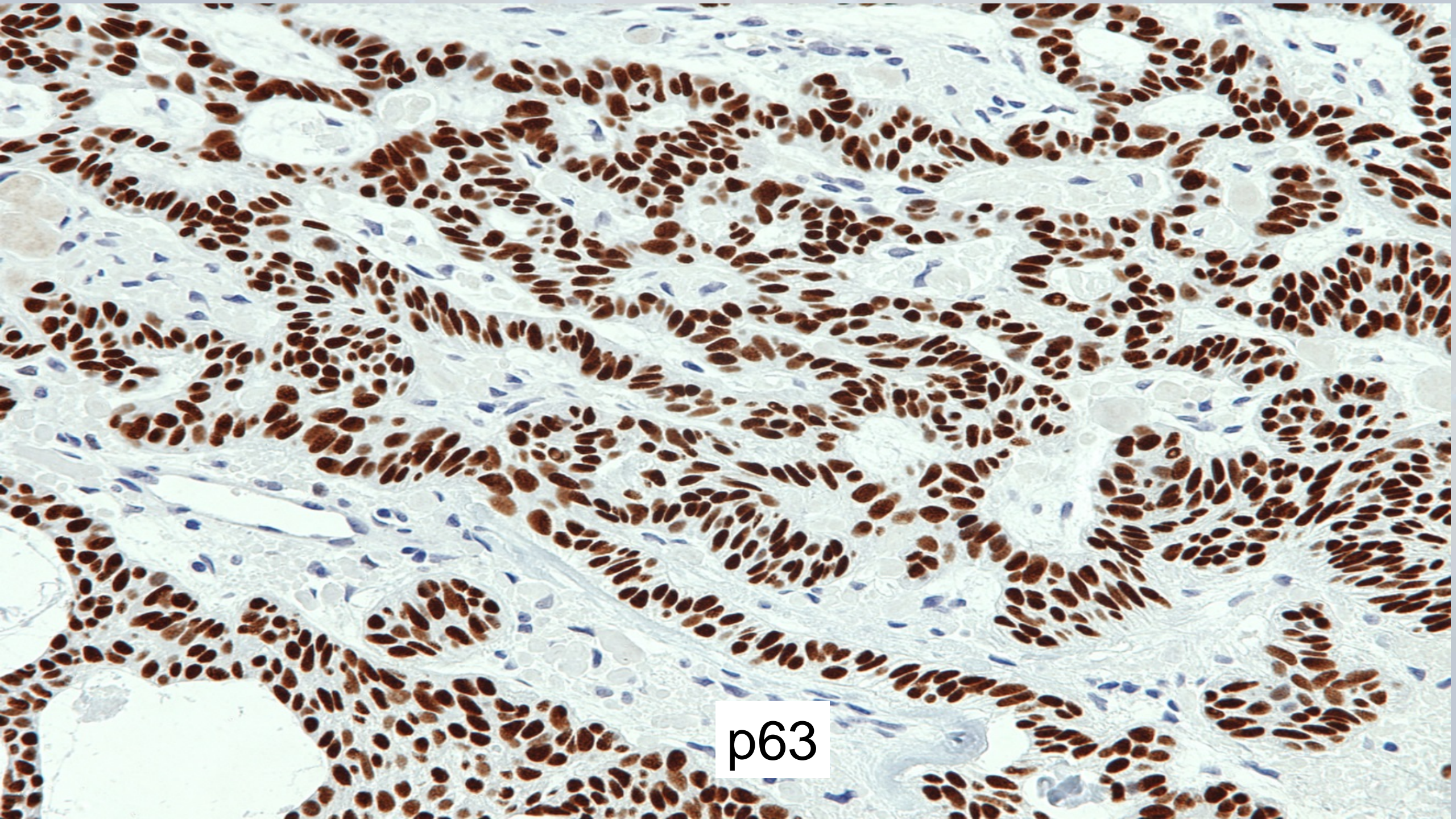
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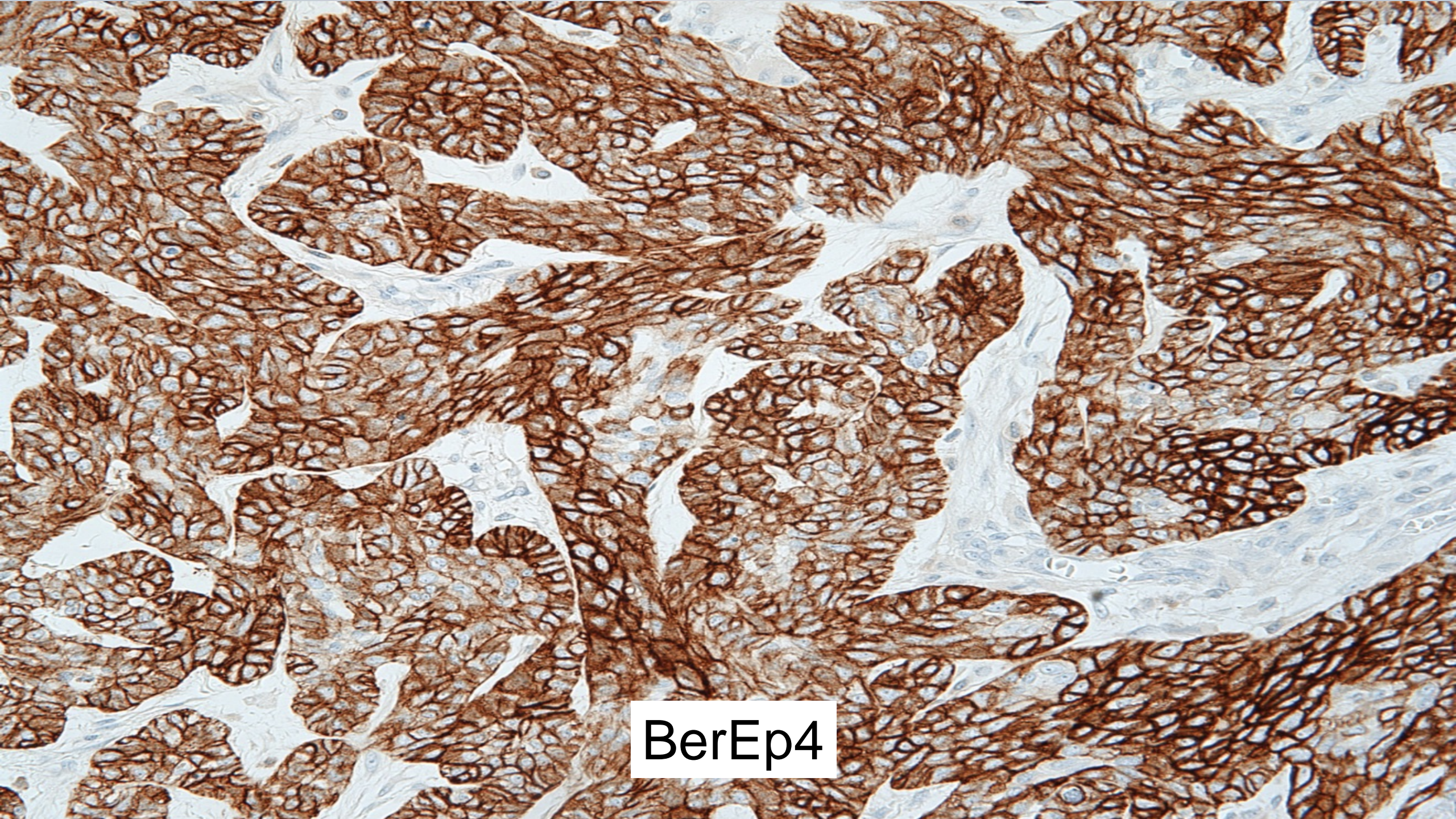
p16





p63





BerEp4



# Anal Basal Cell Carcinoma

- Anal skin and perianal location
- Ulcer or mass with central ulceration and raised edges
- May mimic external hemorrhoids

Mod Pathol 2013;26:1382–1389



# Anal Basal Cell Carcinoma

- No squamous intraepithelial component
- Stromal retraction – but may not be present
- CK5/6-pos, p63-pos
- BerEp4-pos, BCL2-pos
- P16-neg or patchy peripheral

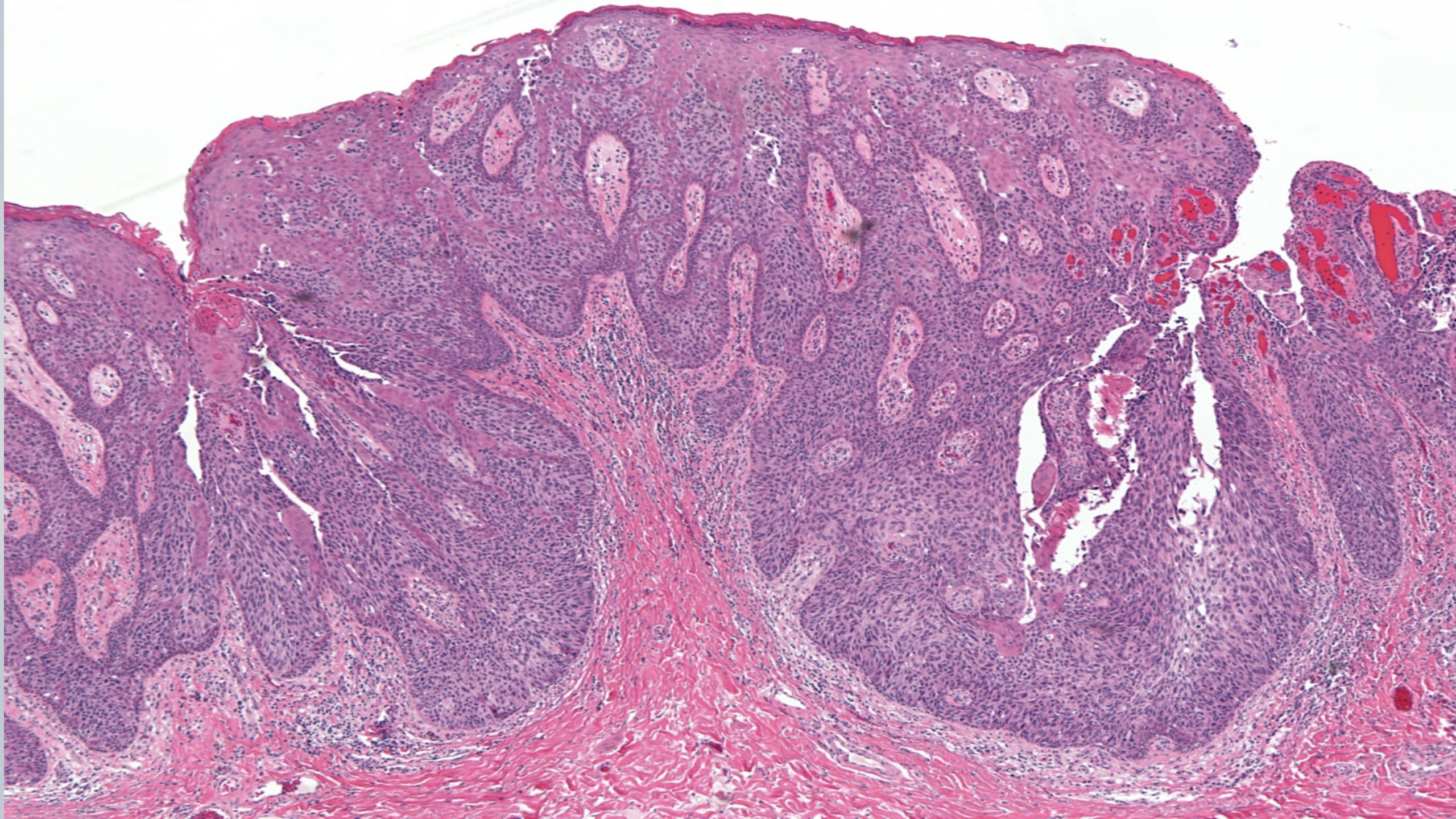
Mod Pathol 2013;26:1382–1389



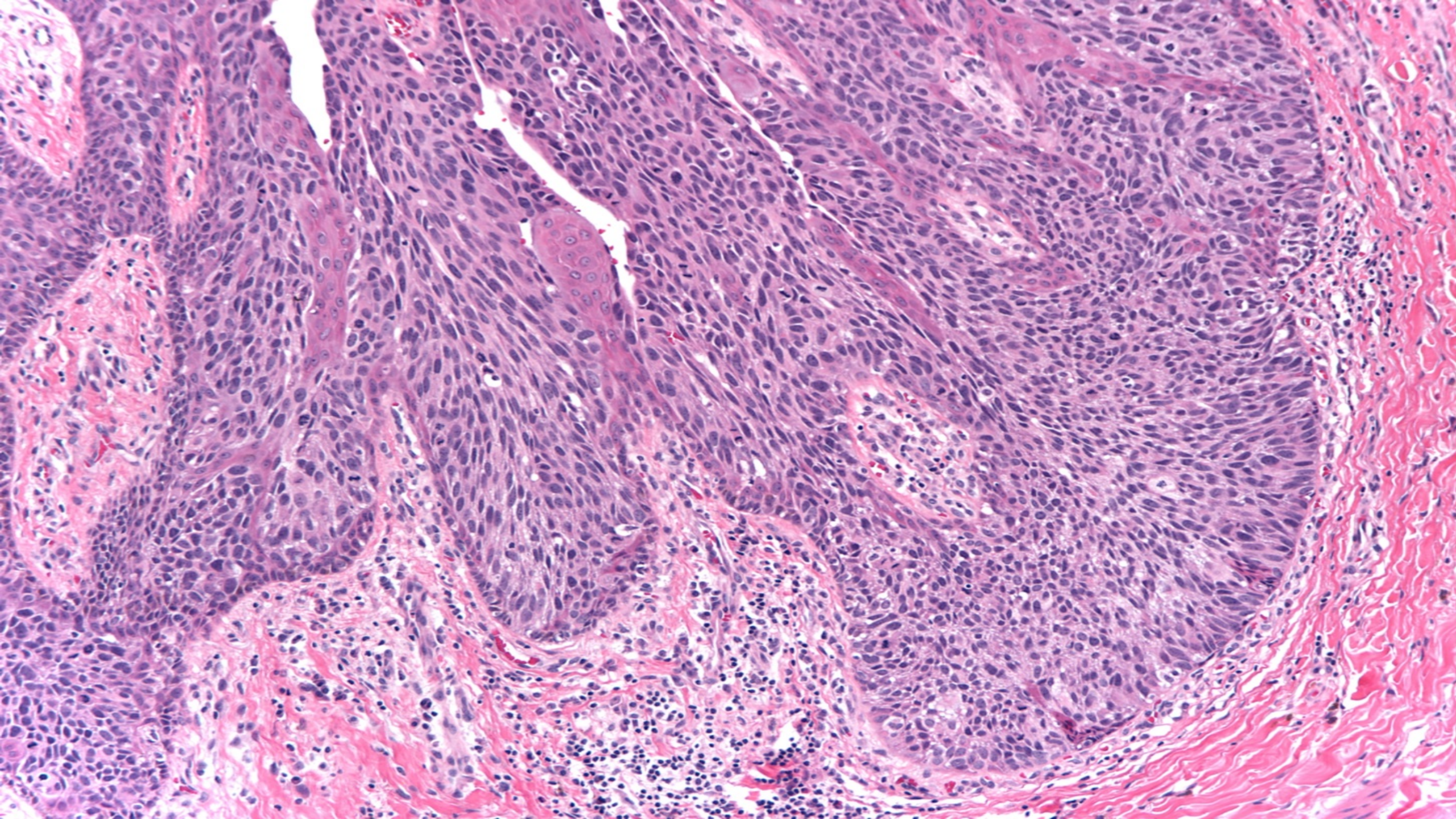
## Case 8

- 38 year old with anal lesion

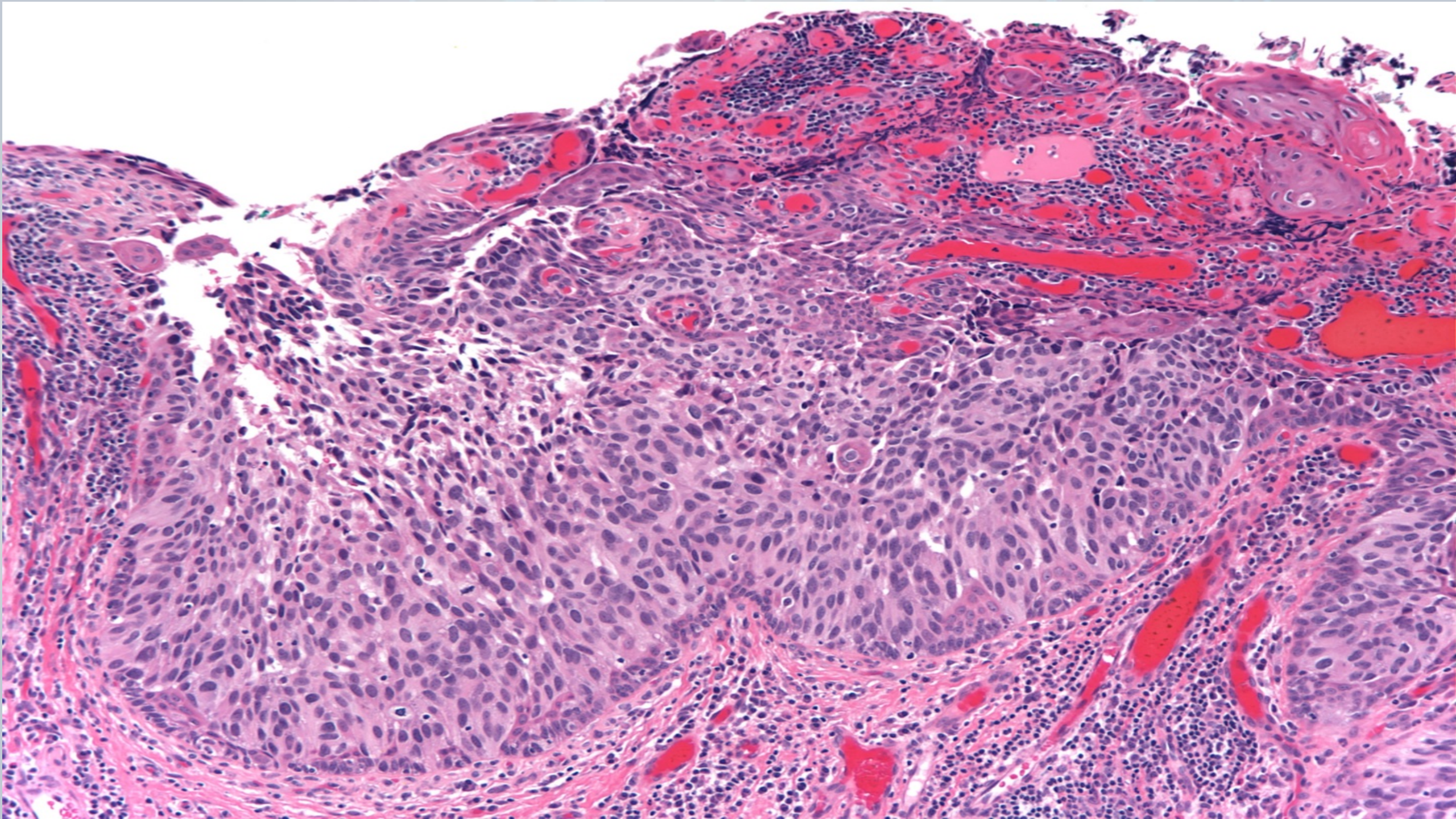




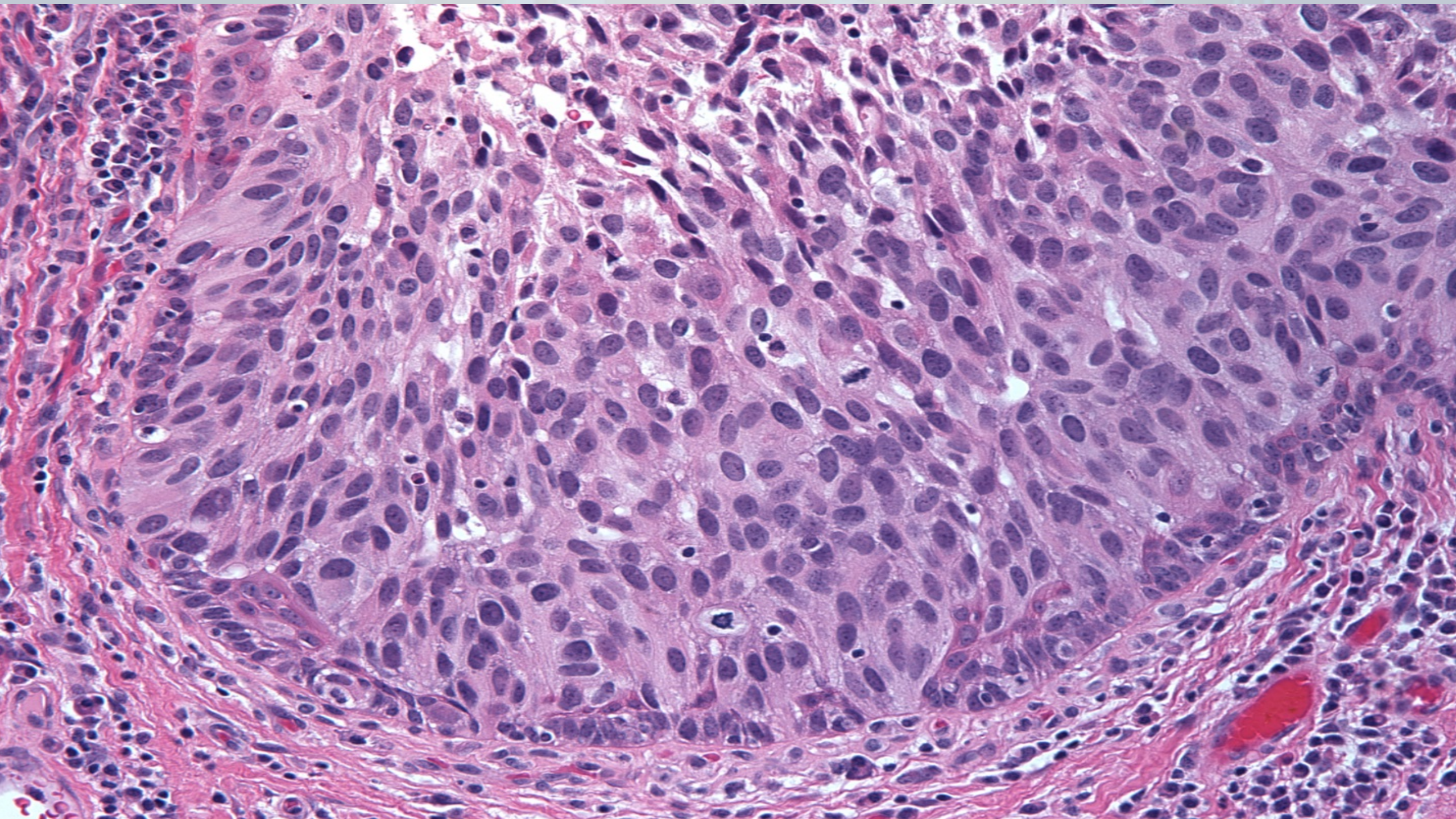














## *Live Content Slide*

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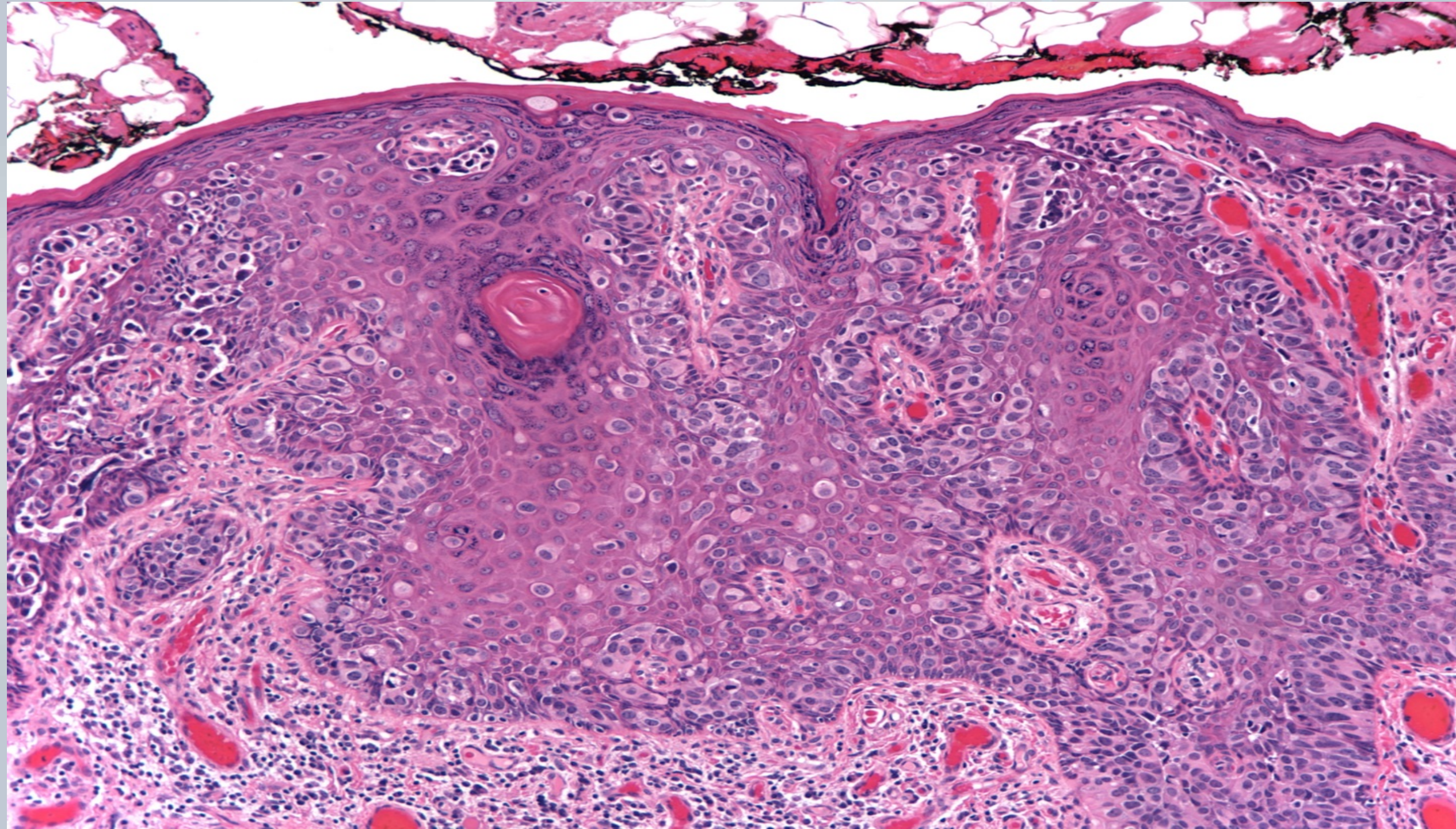
**Poll: Diagnosis?**



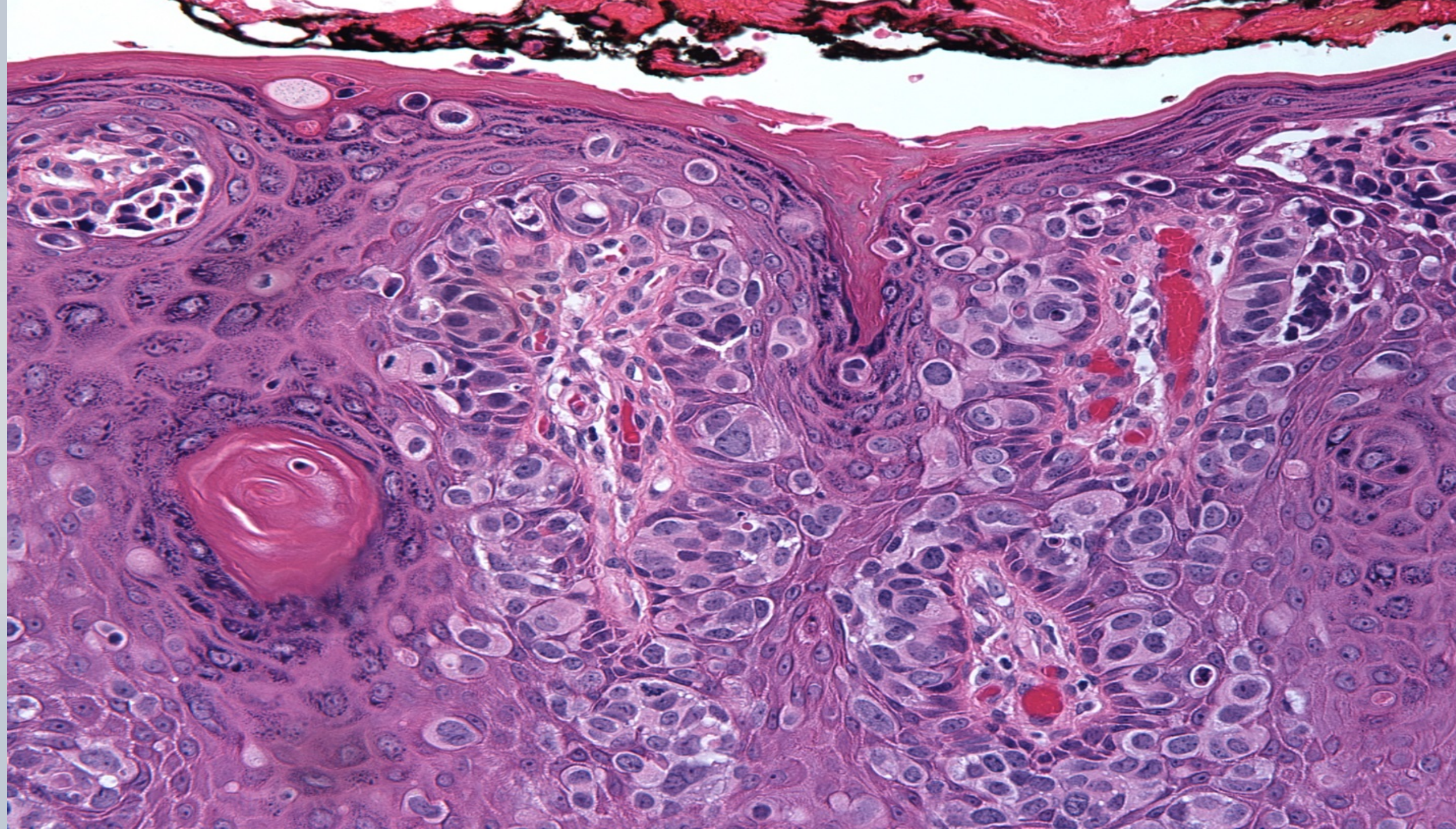
# Anogenital Paget's Disease

- Squamous hyperplasia with hyperkeratosis and parakeratosis in 90% of anal extra-mammary Paget's
  - Pseudoepitheliomatous hyperplasia
  - Fibroepithelioma-like
  - Papillomatous (mimics HPV)
- Paget cells may be inapparent







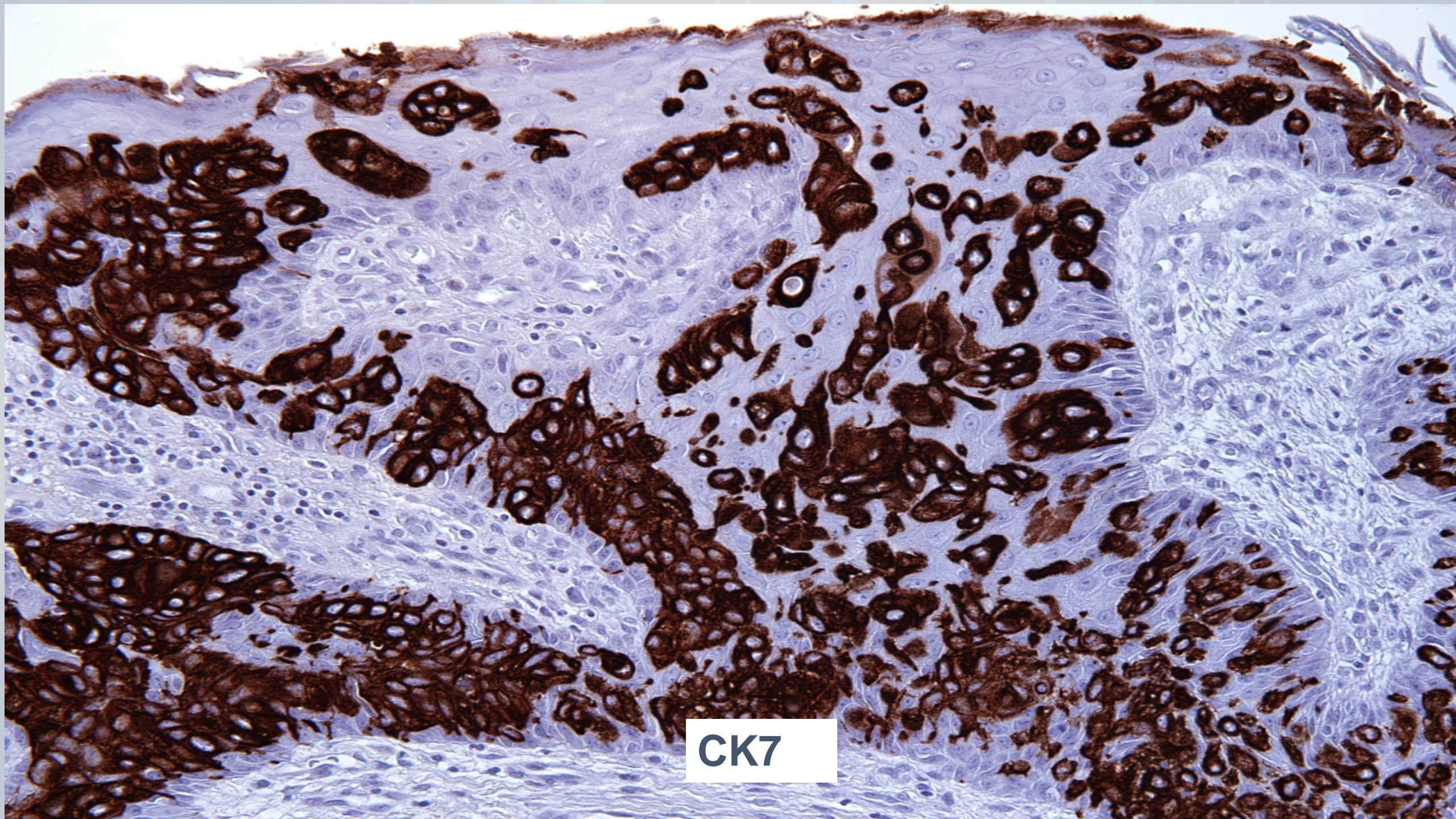




# Anogenital Paget's Disease

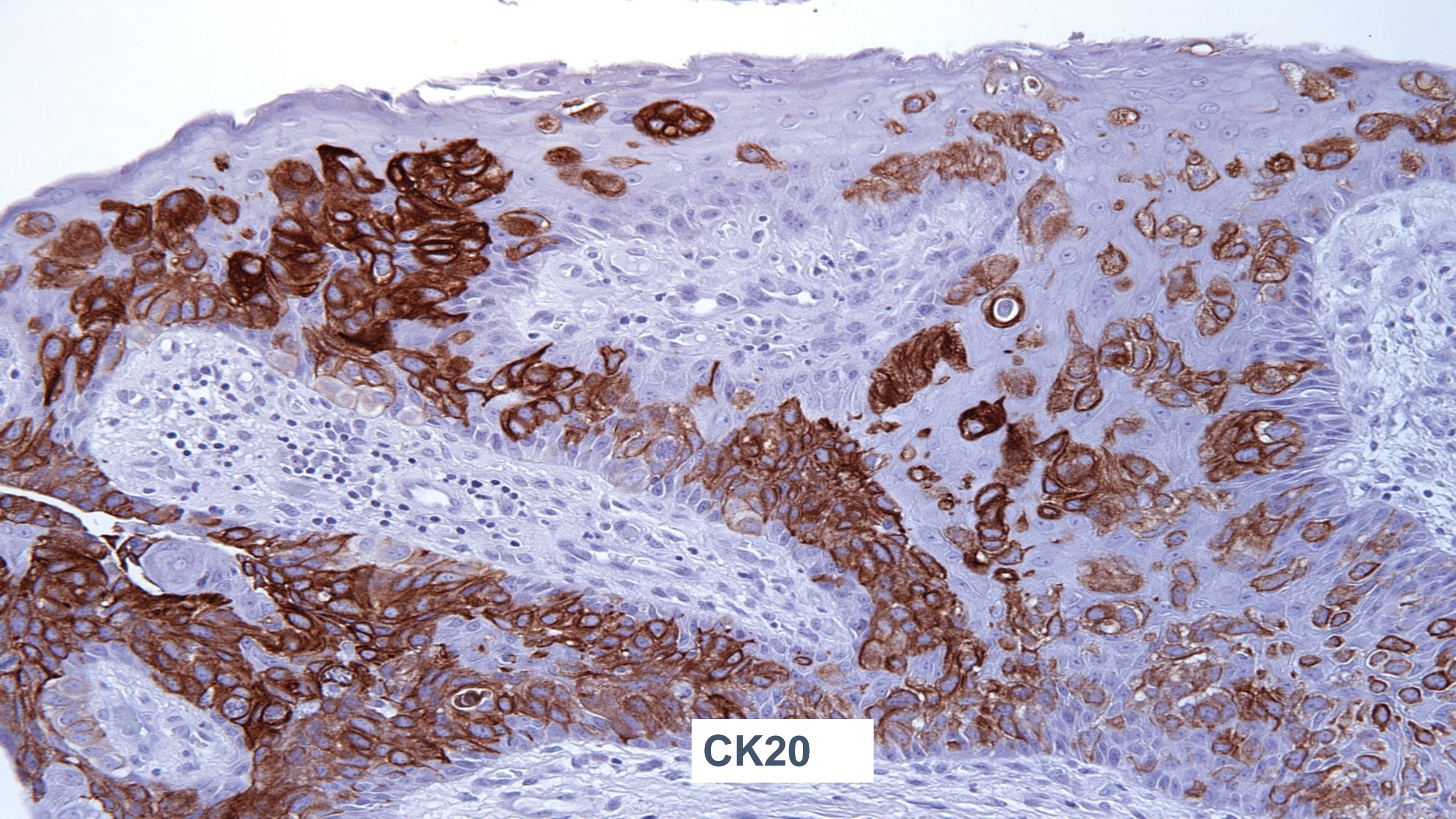
- Primary (may rarely invade)
  - CK7+/CK20-/HER2neu+
- Secondary to anorectal or bladder cancer
  - CK7+/CK20+/GATA3+
  - CK7+/-/CK20+/-/CDX2+





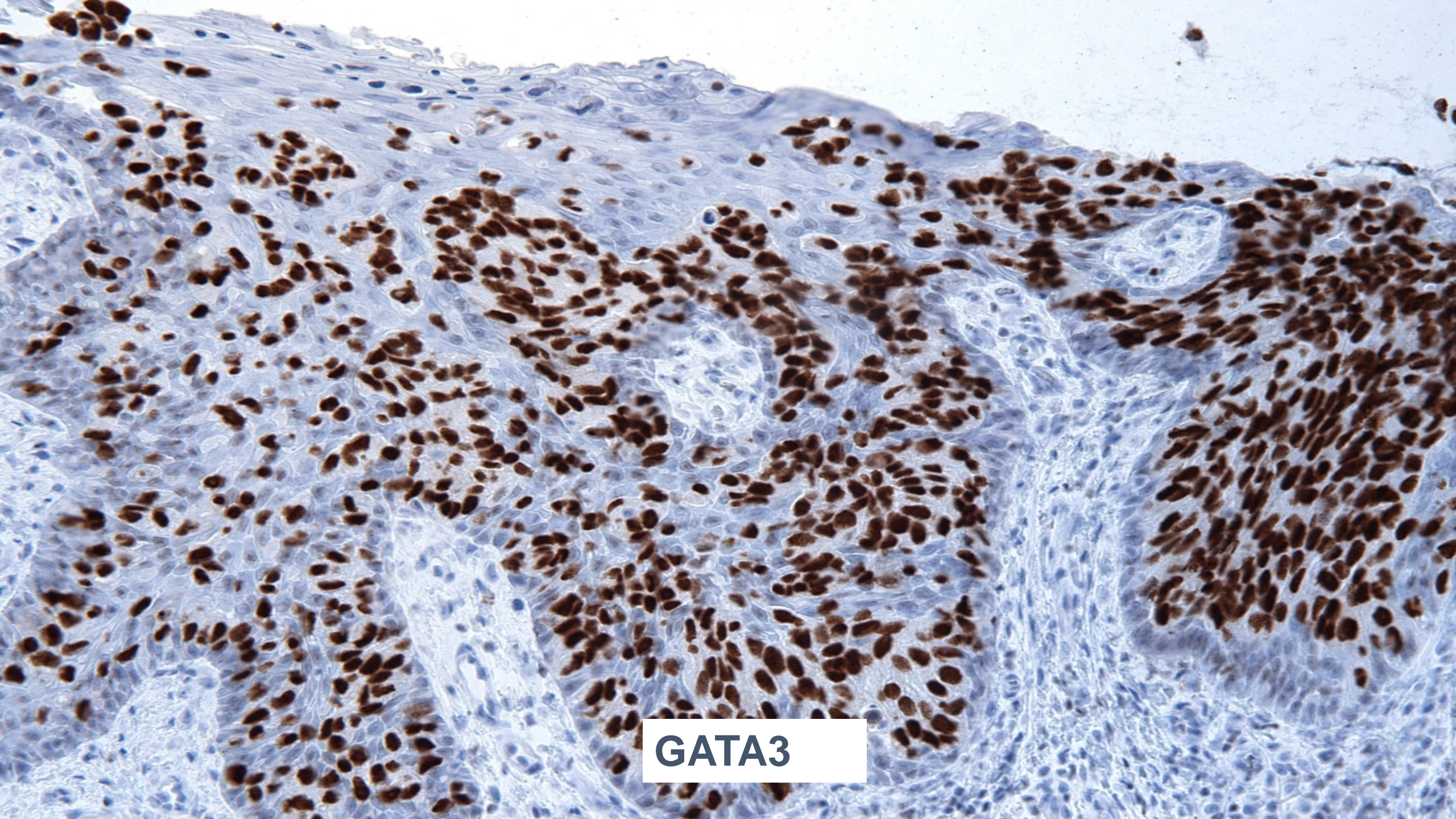
CK7





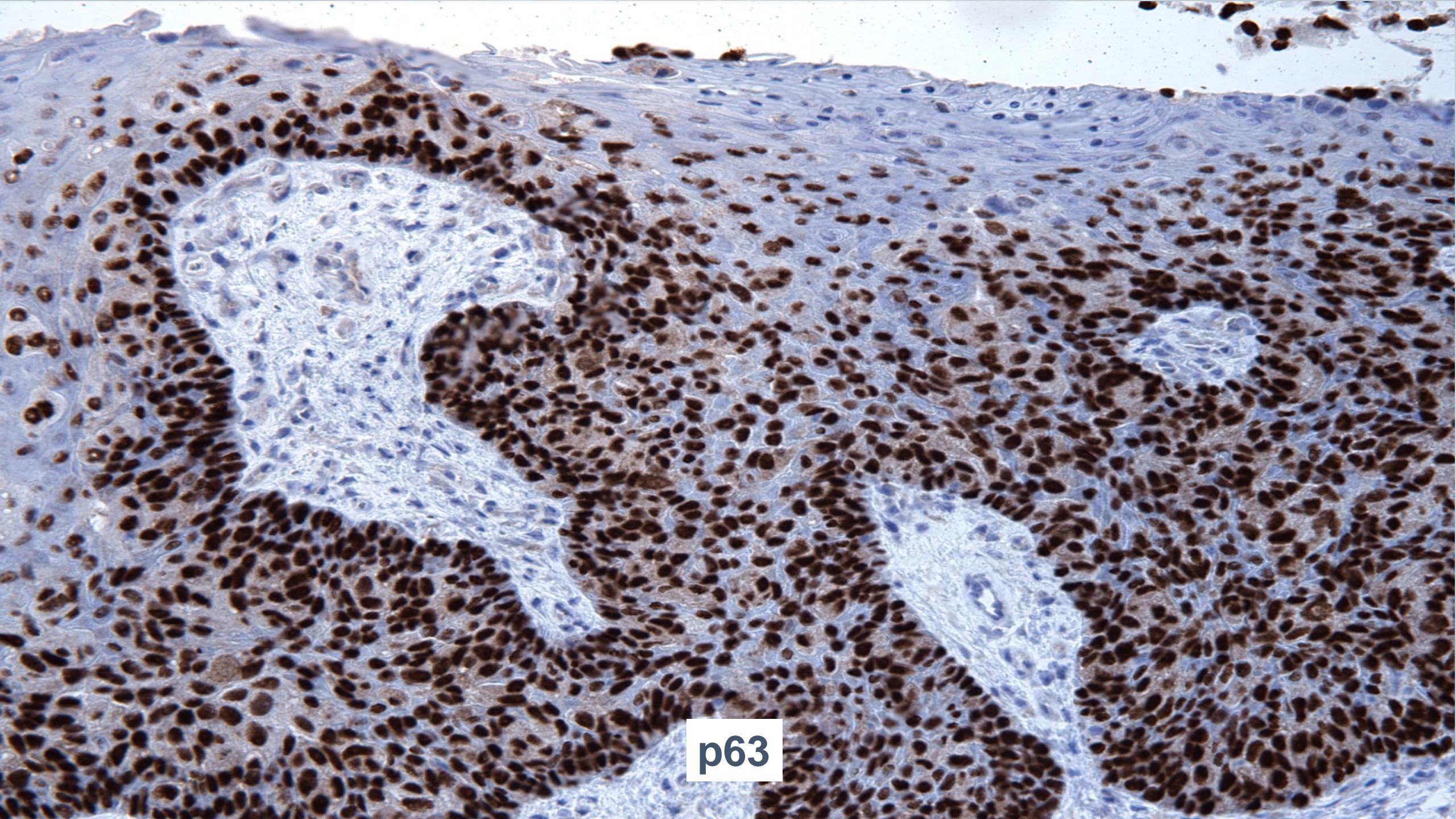
CK20





**GATA3**





p63



# Anogenital Paget's Disease

- Primary (may rarely invade)
  - CK7+/CK20-/HER2neu+
- Secondary to anorectal or bladder cancer
  - CK7+/CK20+/GATA3+
  - CK7+/-/CK20+/-/CDX2+

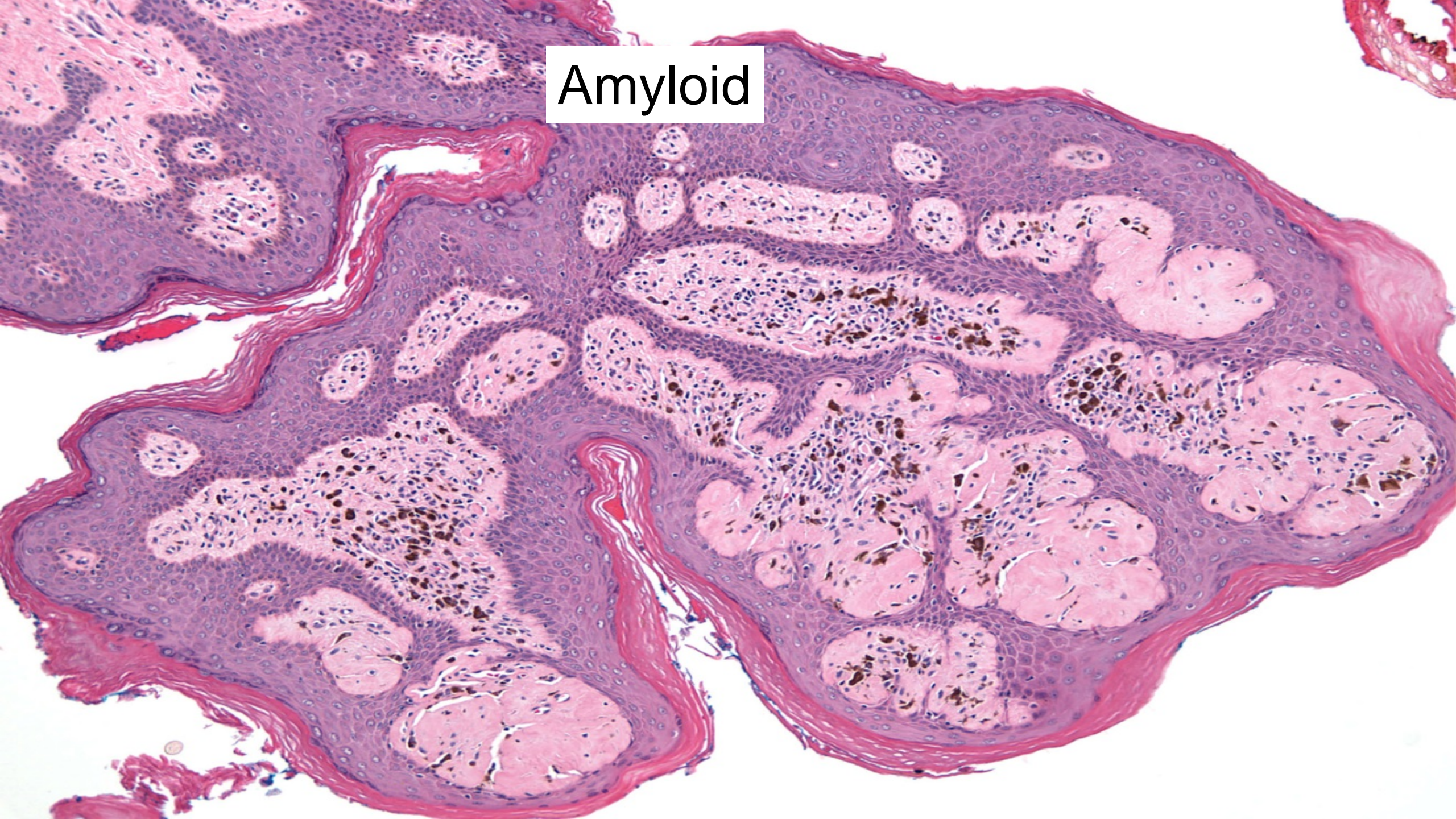


# Differential Diagnosis: Anal Skin Lesions

- Fibroepithelial polyp (skin tag)
- Basal cell carcinoma
- Anogenital Paget's disease
- Other stuff: amyloid, lymphangioma, etc

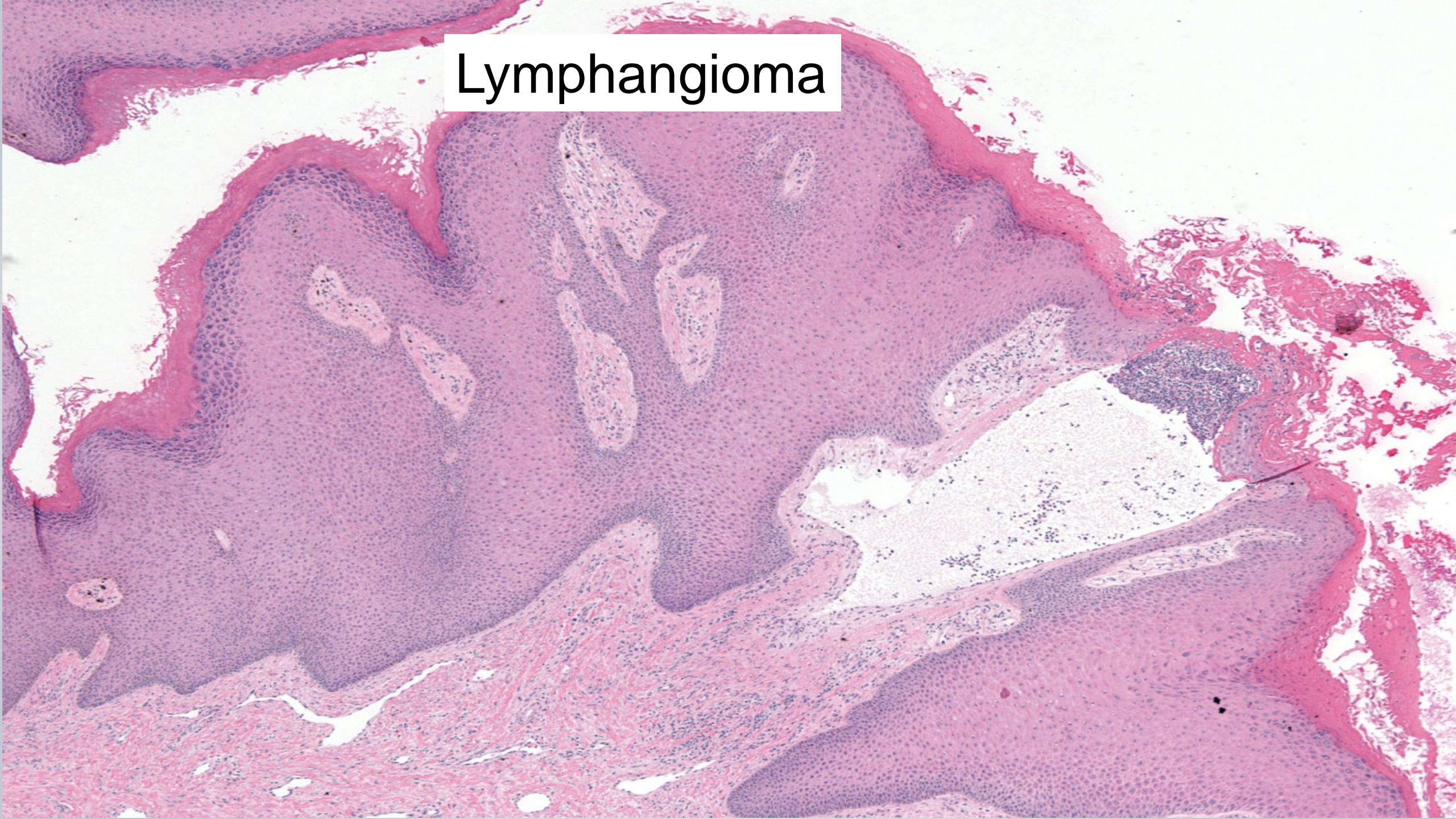


Amyloid



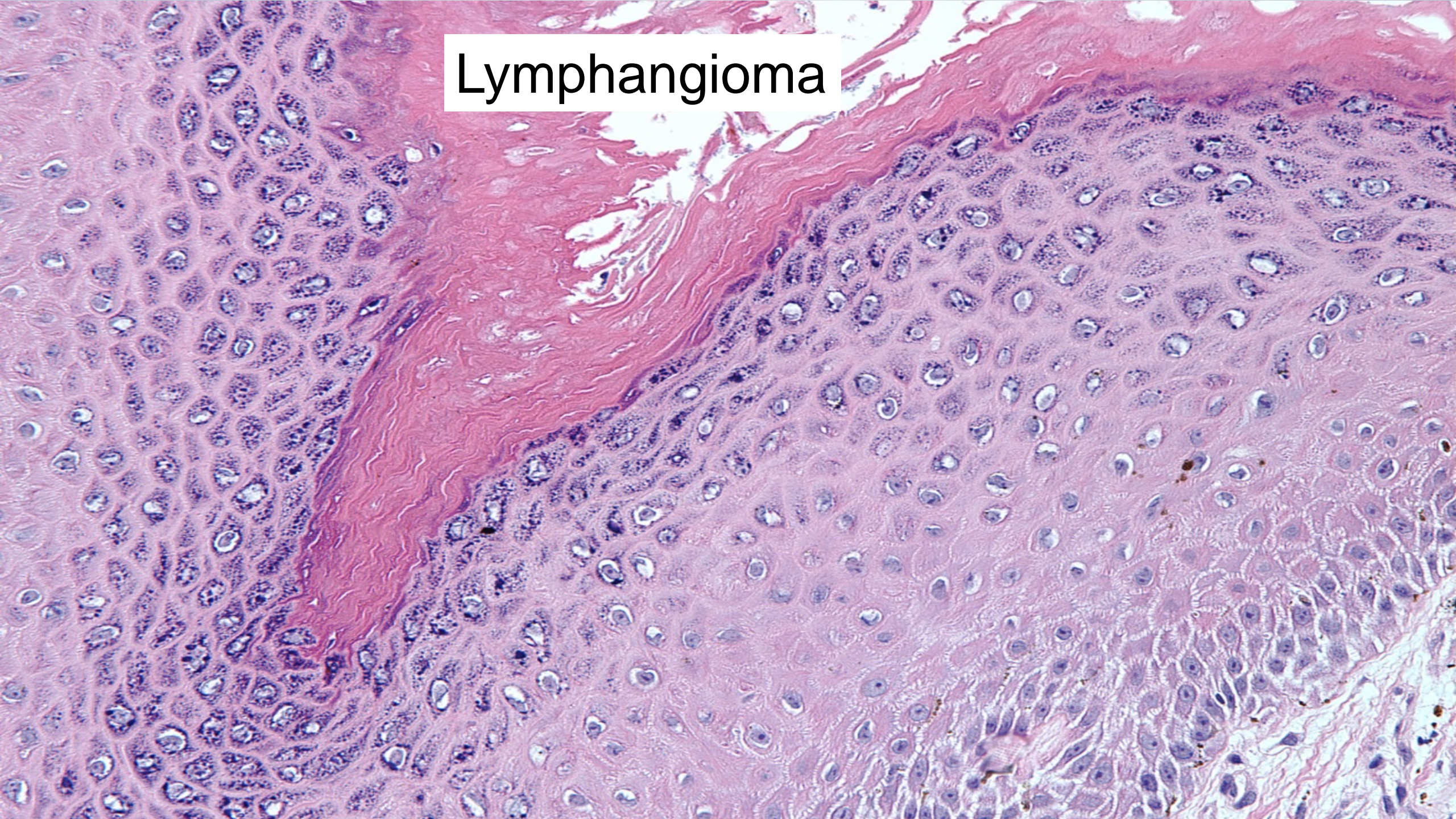


# Lymphangioma





Lymphangioma

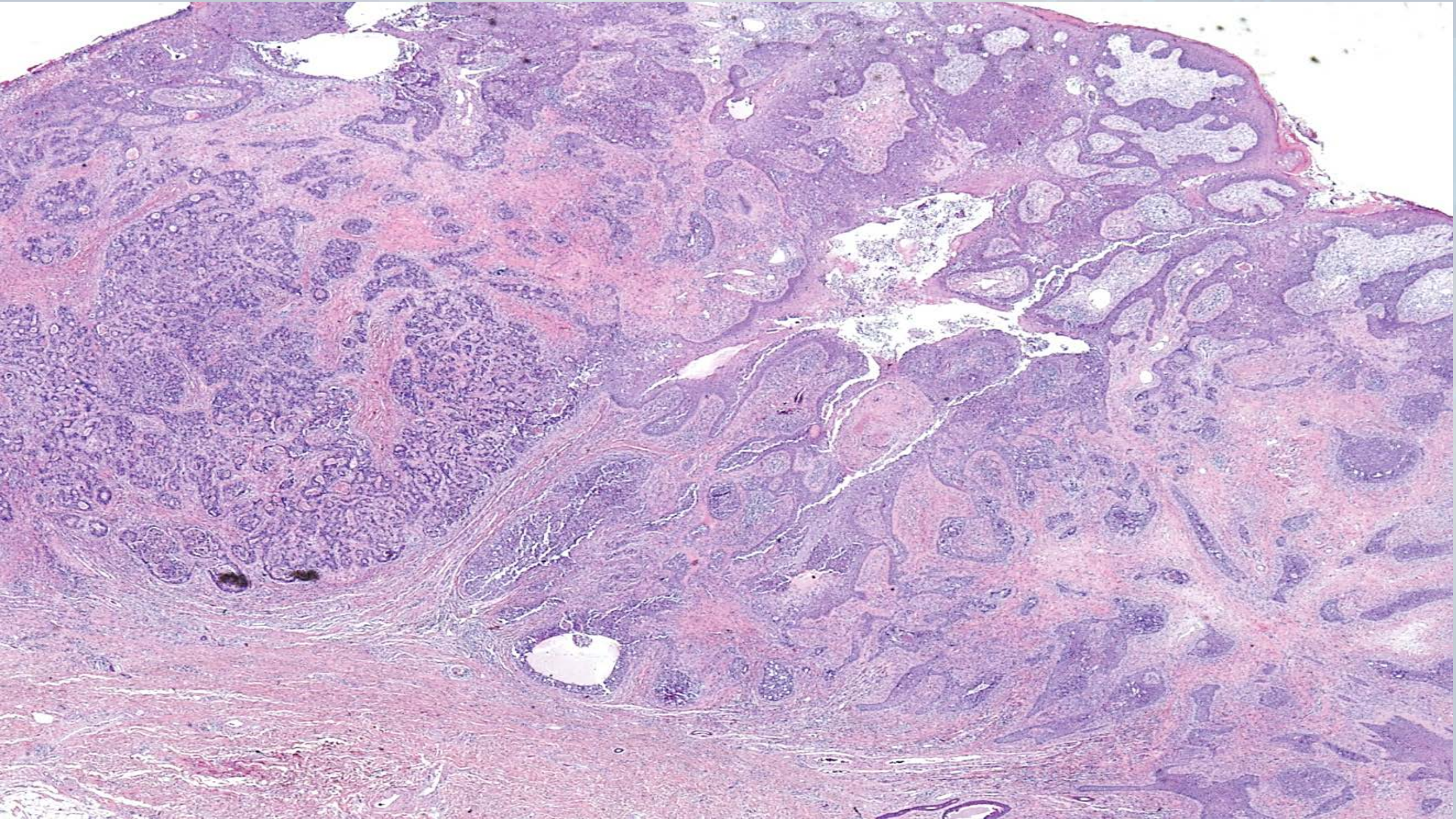




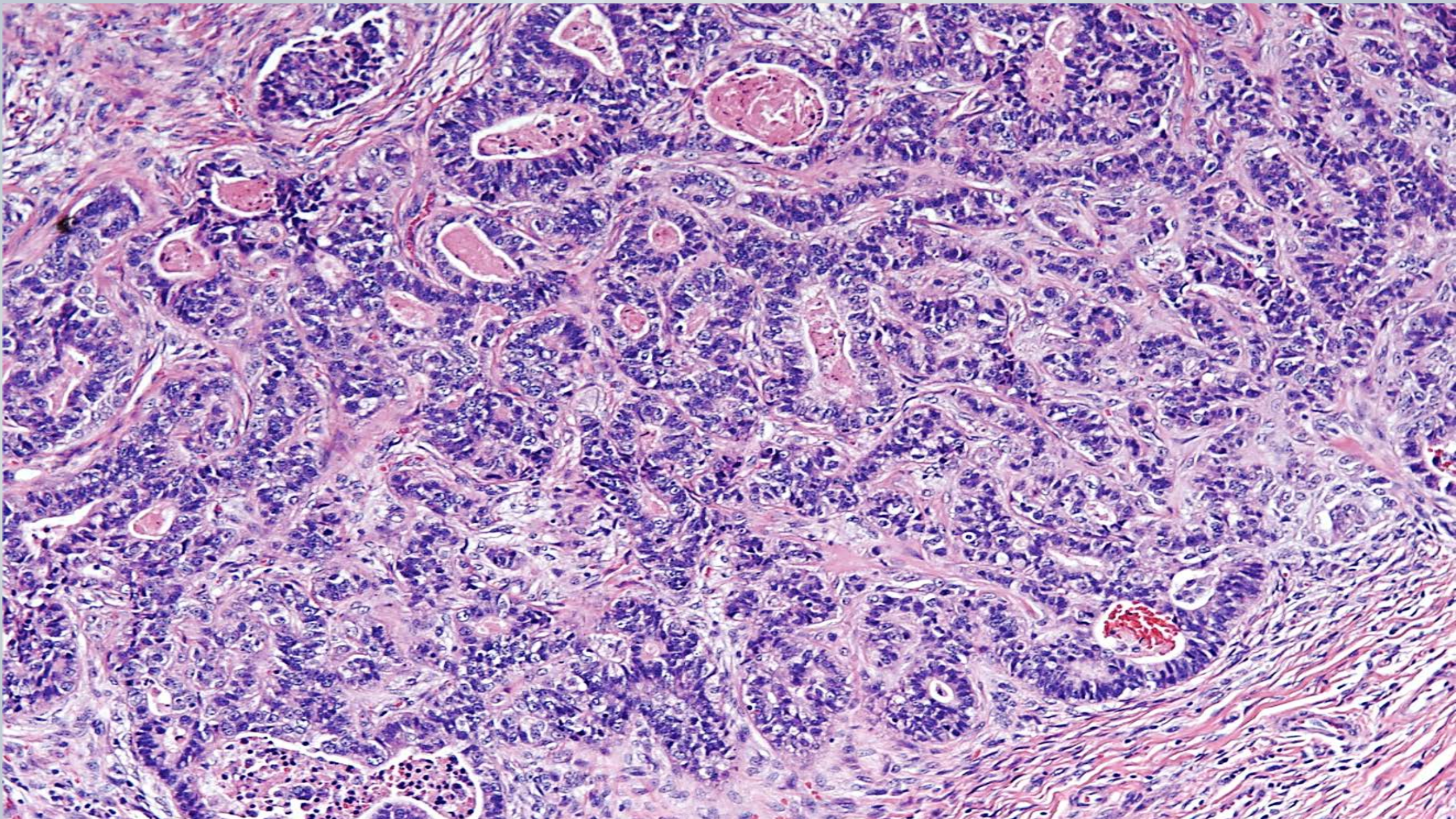
# Case 9

64-year-old with rectal adenocarcinoma and anal  
“lesion”

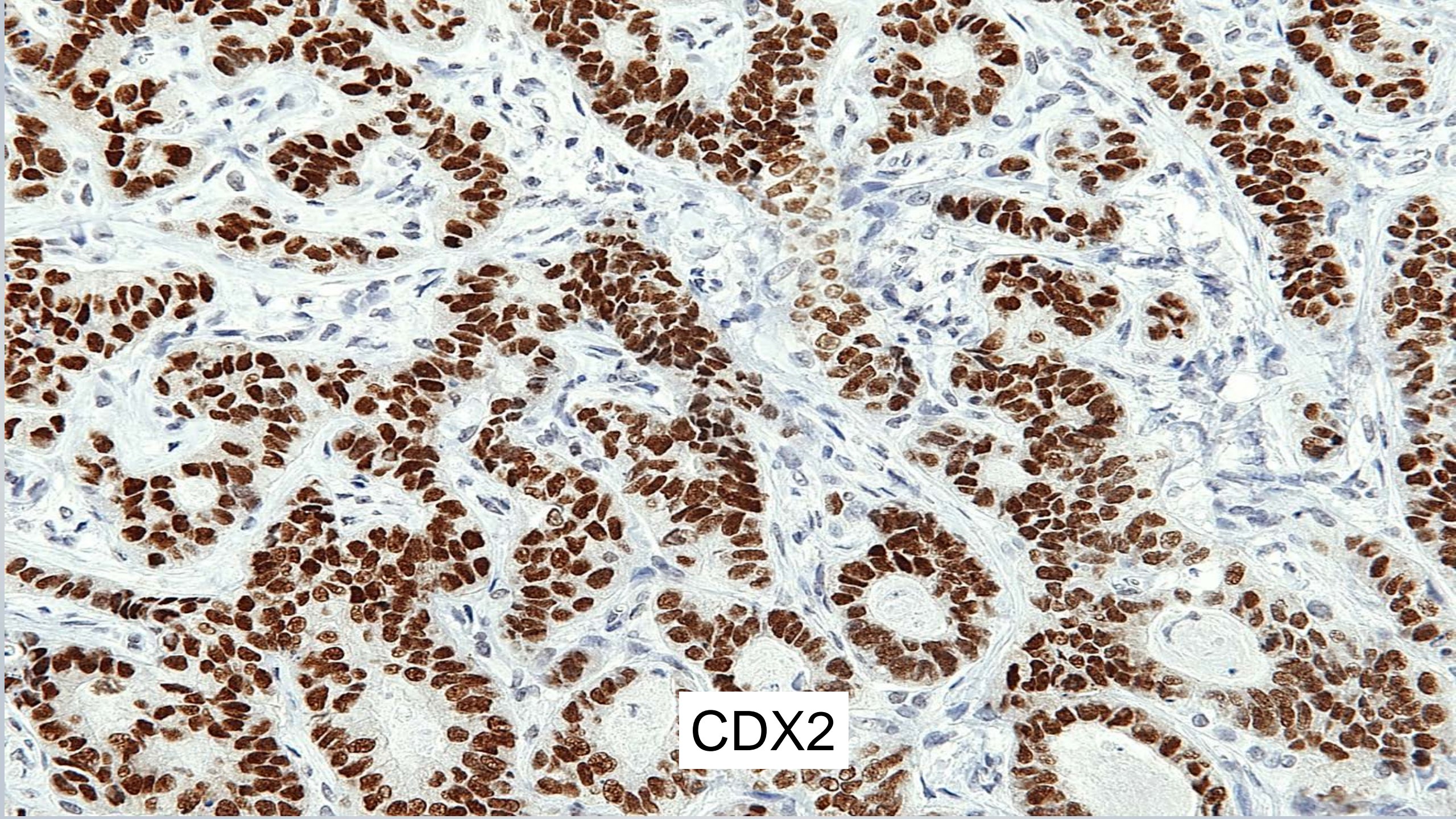












CDX2



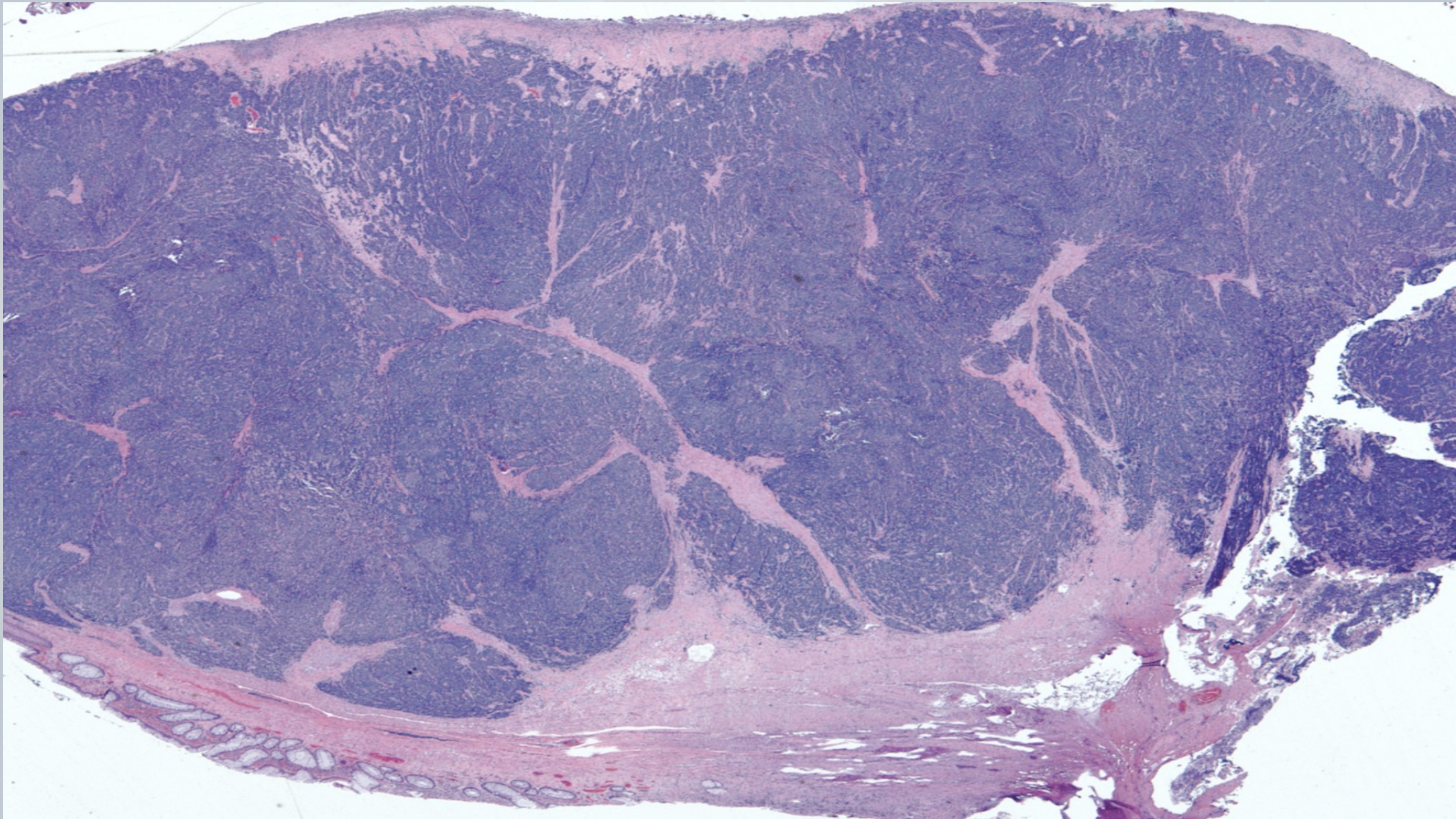
# **Rectal Adenocarcinoma with Pagetoid Spread**



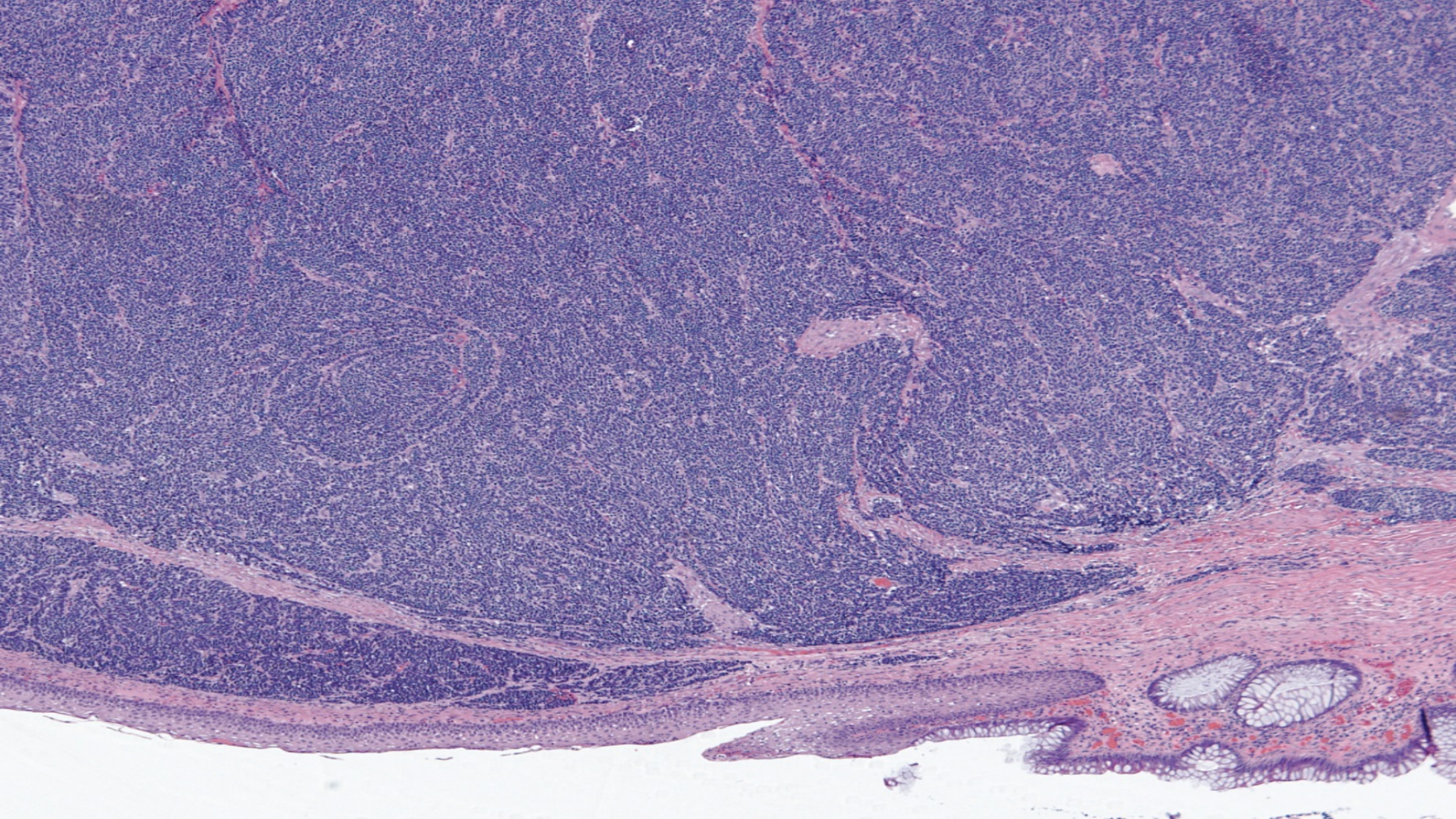
# Case 10

Another routine hemorrhoidectomy

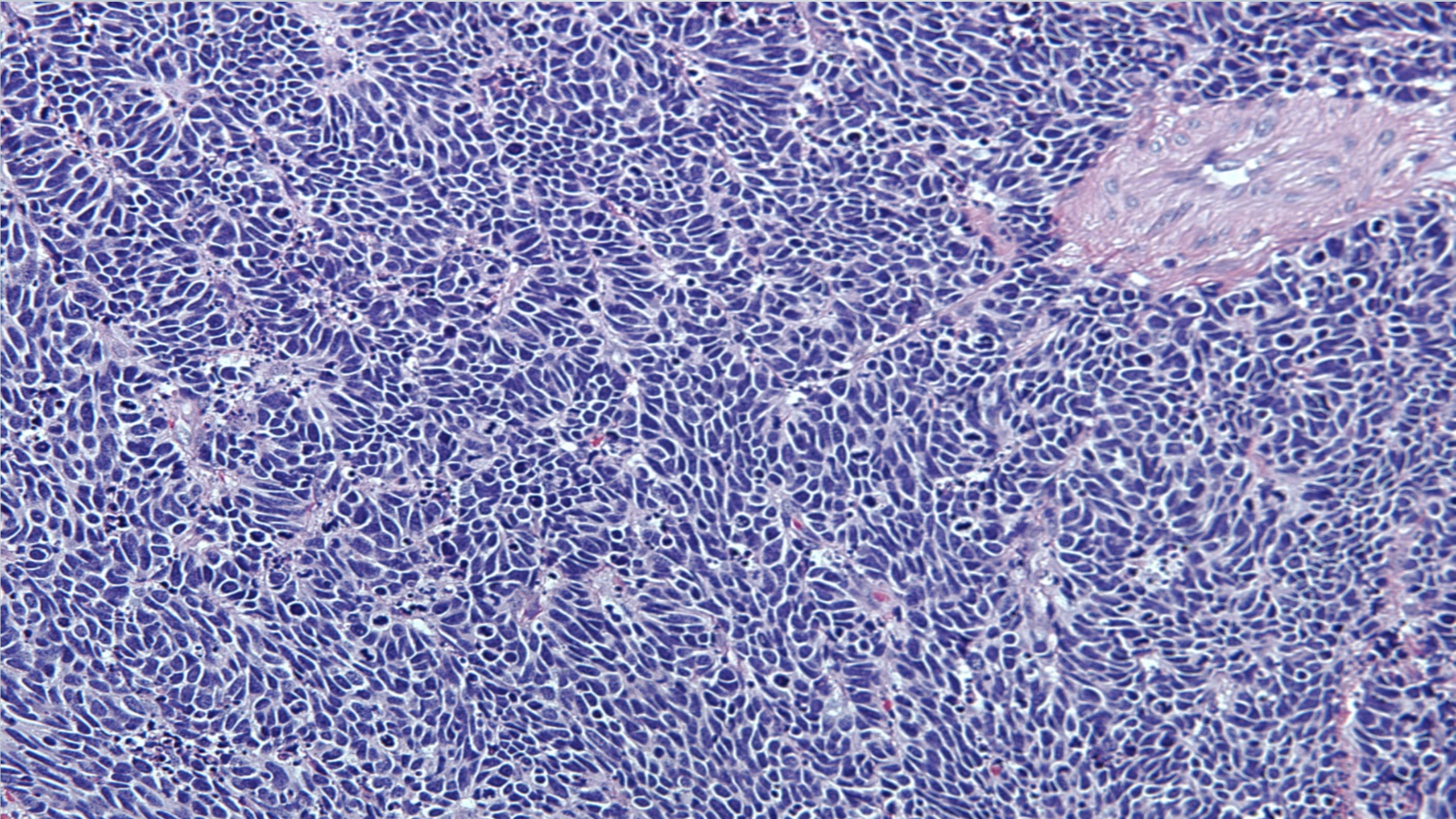




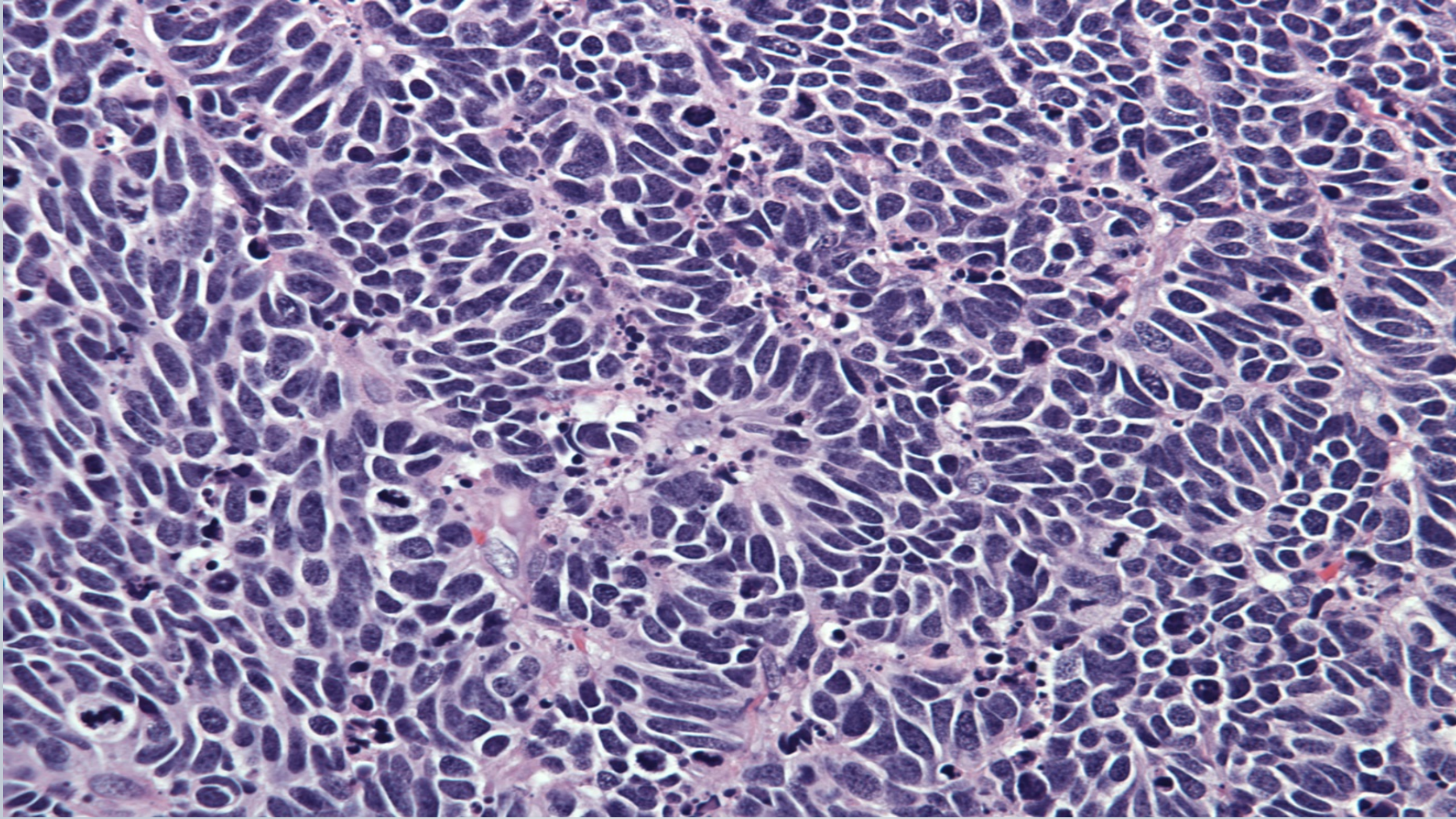




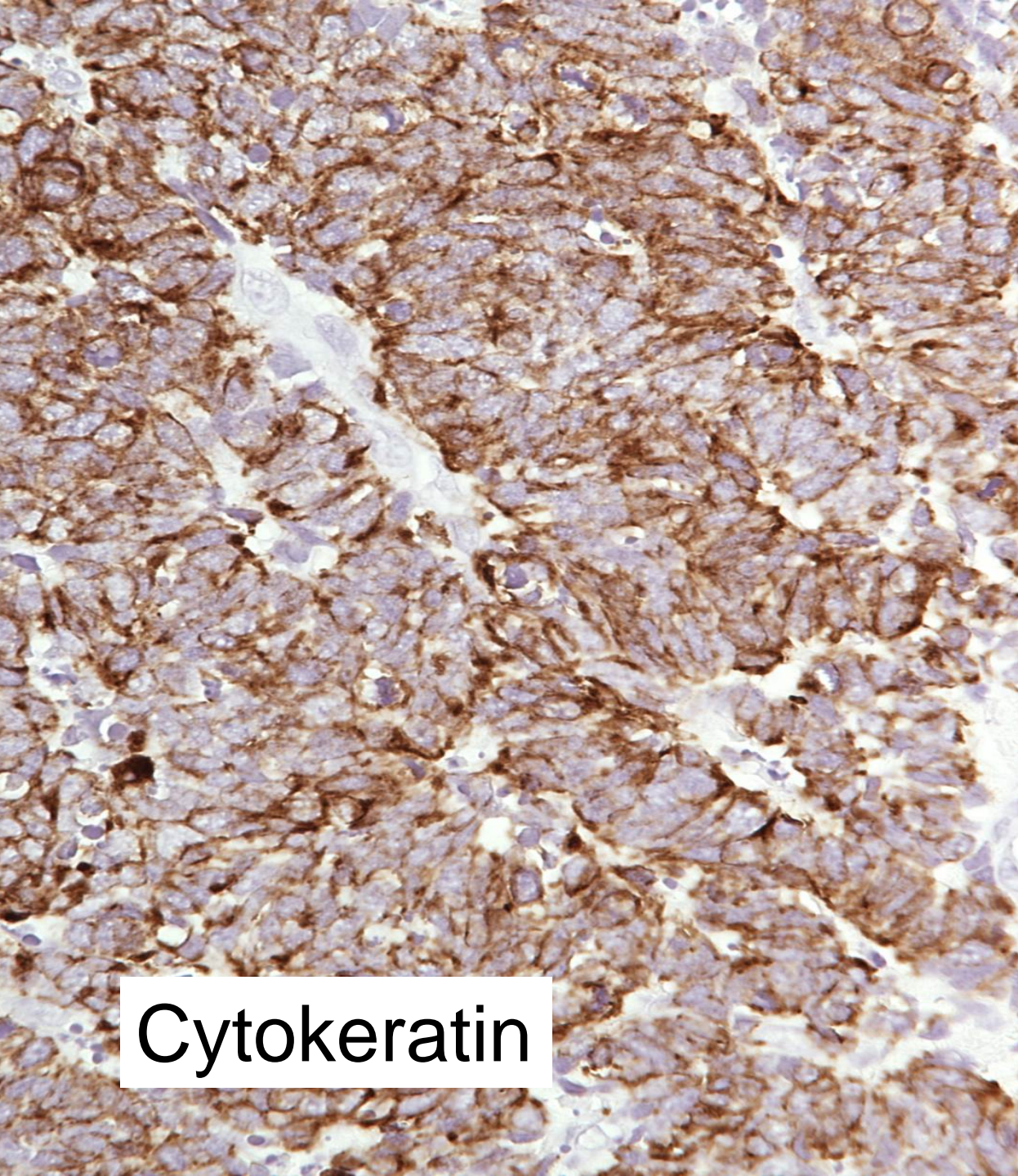




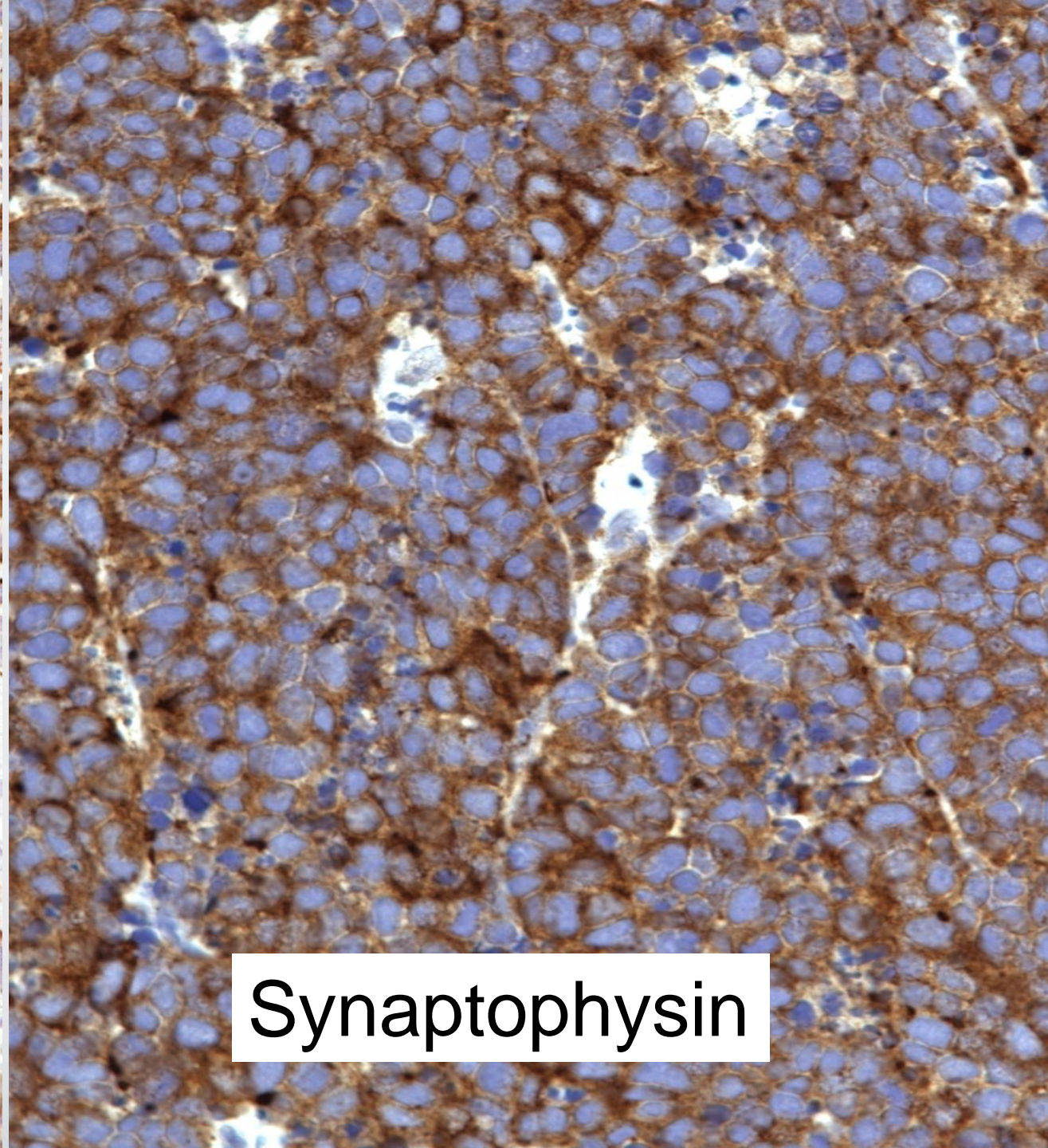






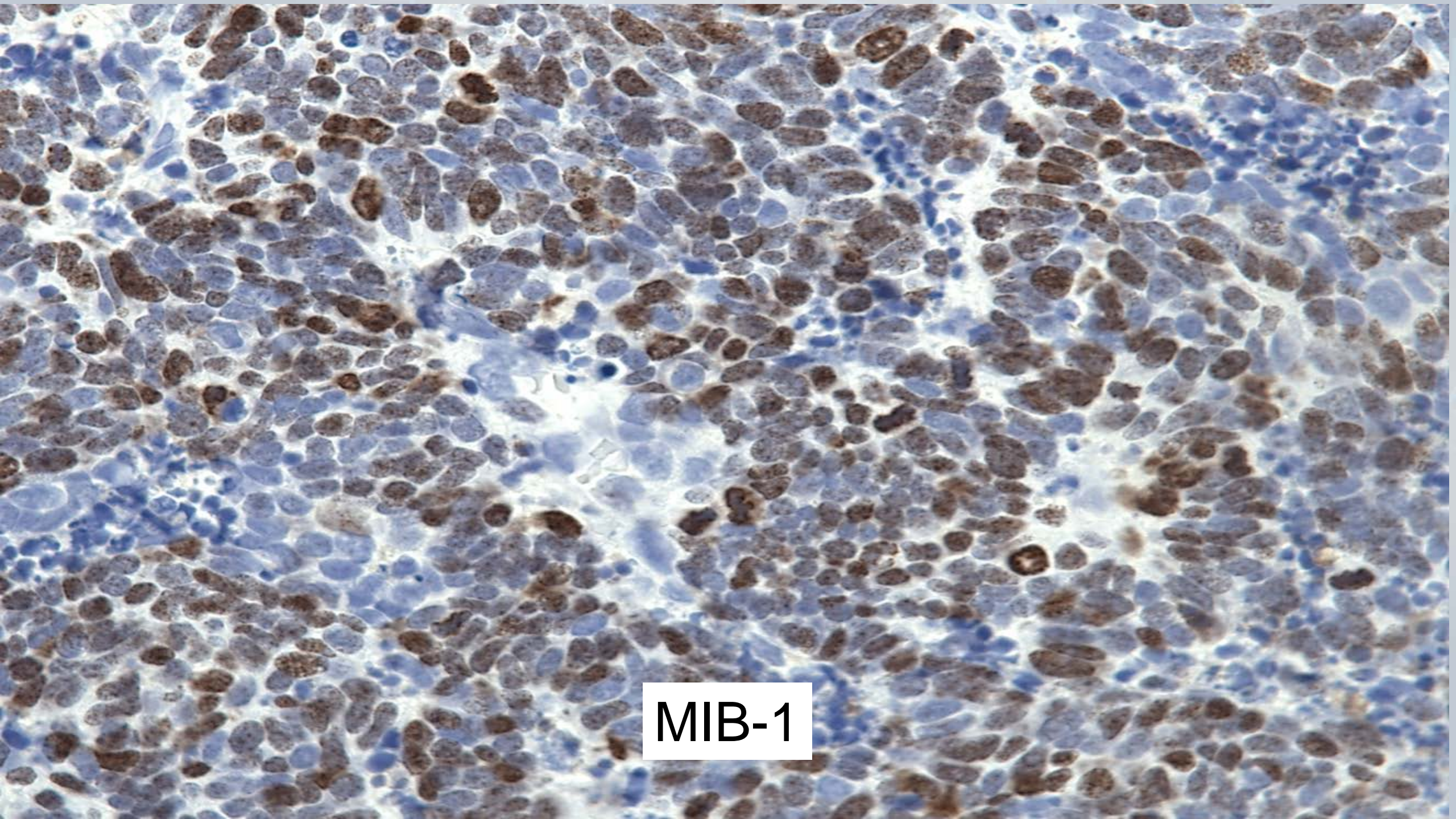


Cytokeratin



Synaptophysin





MIB-1



# Neuroendocrine Carcinoma: Anal & Colorectal

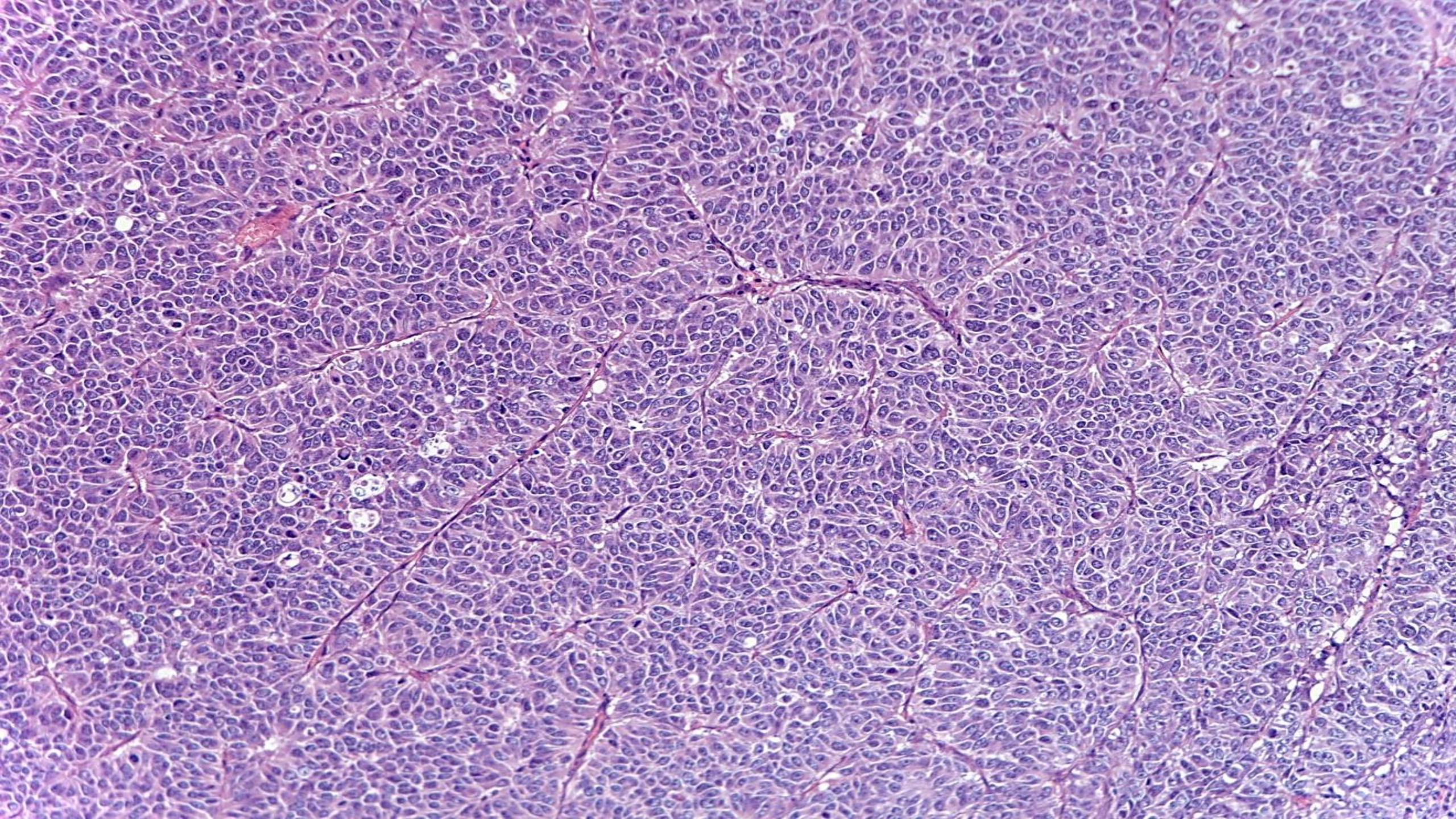
- Rectal bleeding or pain – but may be asymptomatic (15%)
- At least 1/3 have metastatic disease at time of diagnosis
- Role of HPV18 in anal lesions has been proposed
- Poor prognosis



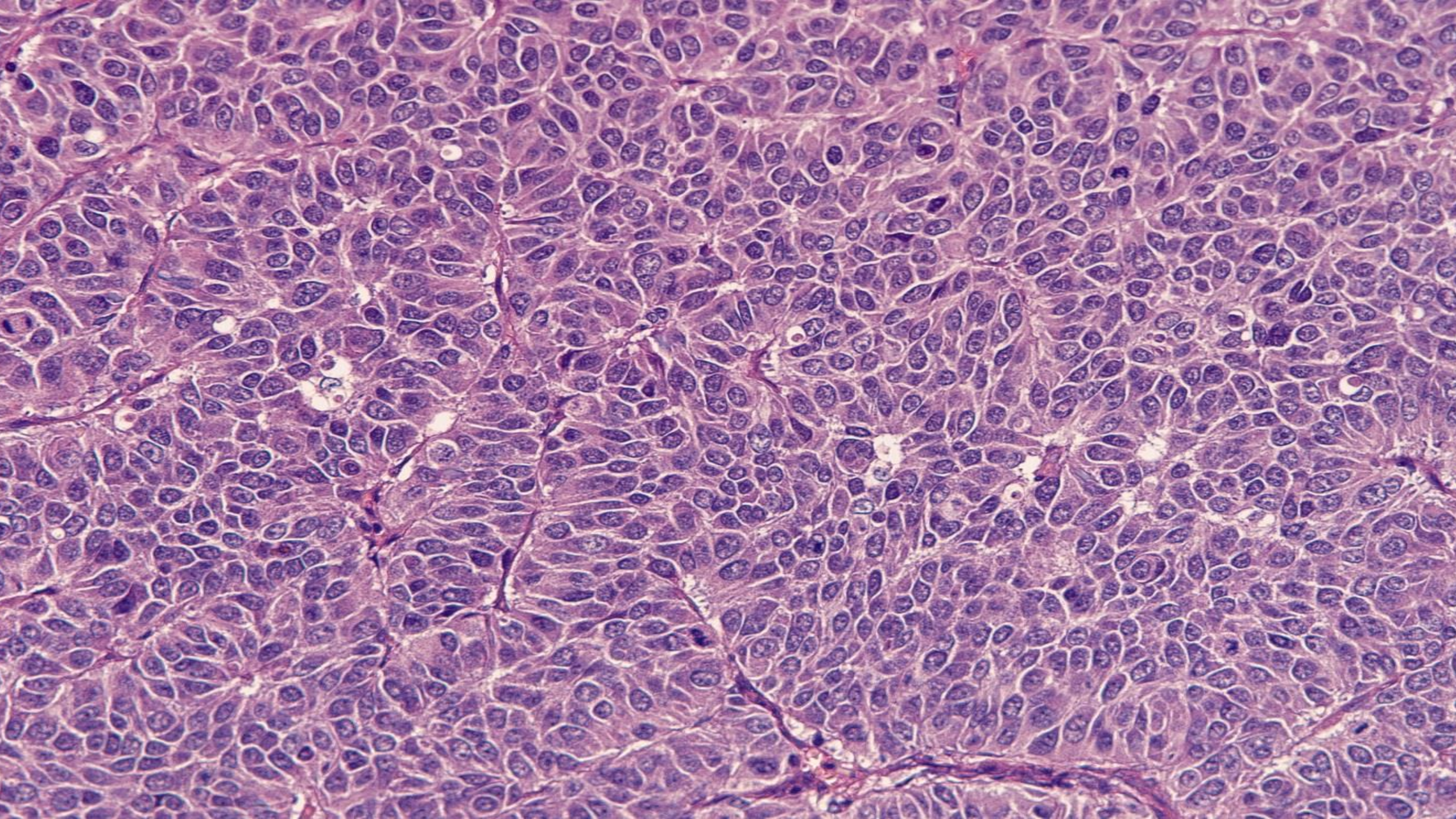
# Differential Diagnosis: Anal Canal

- Neuroendocrine carcinoma – may be p16 positive
- Adenocarcinoma – may be p16 positive, but not p63 positive
- Melanoma – may be p16 positive
- Reactive atypia or immature squamous metaplasia at transformation zone
- Metastasis

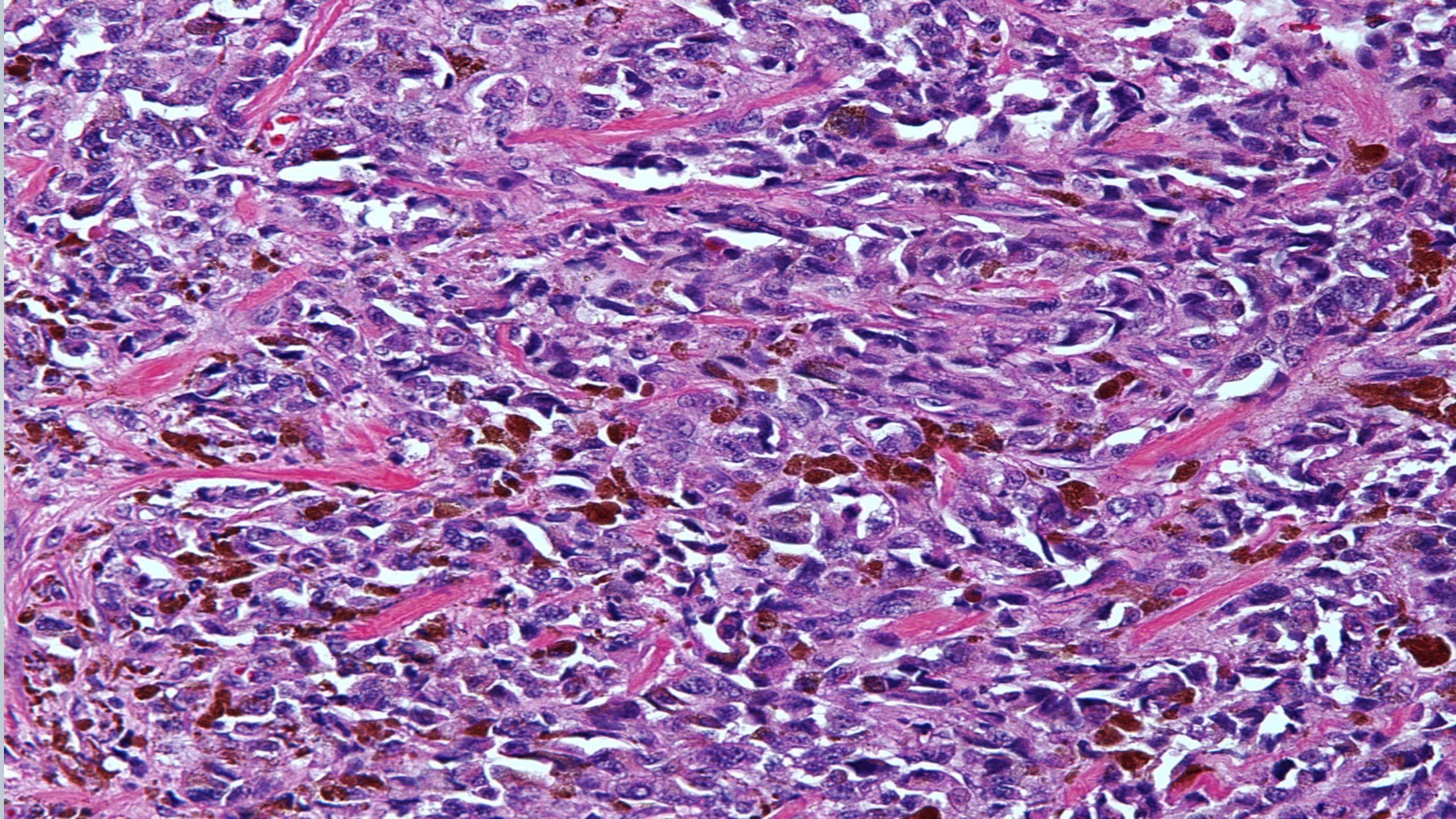




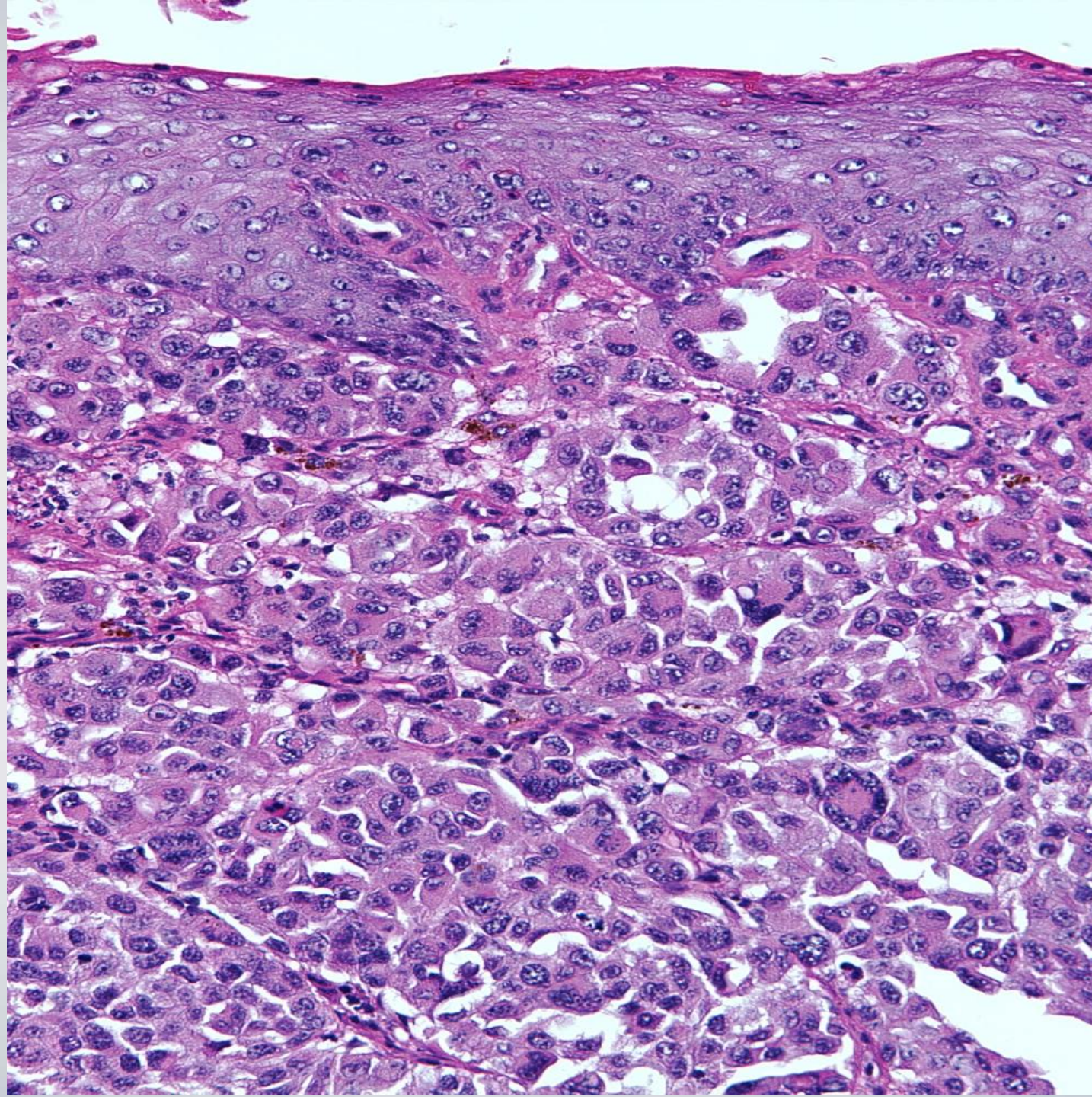




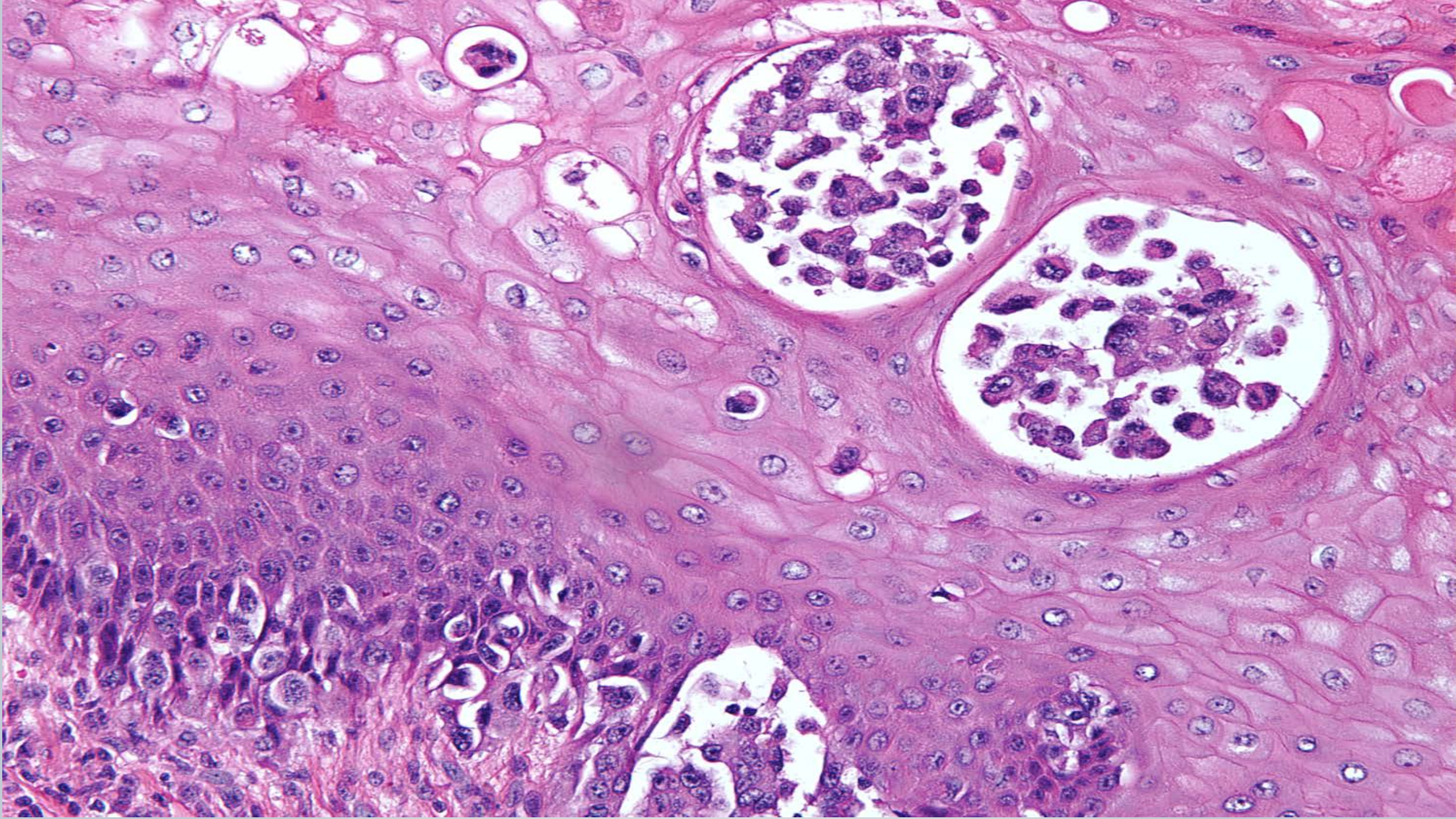














# Summary

- Like real estate, location matters
- LAST terminology
- High index of suspicion
- Use immunohistochemistry wisely (& sparingly)
- Be wary the “routine” condyloma excision & hemorrhoidectomy



# THANK YOU!