

Endometrial Biopsy Interpretation

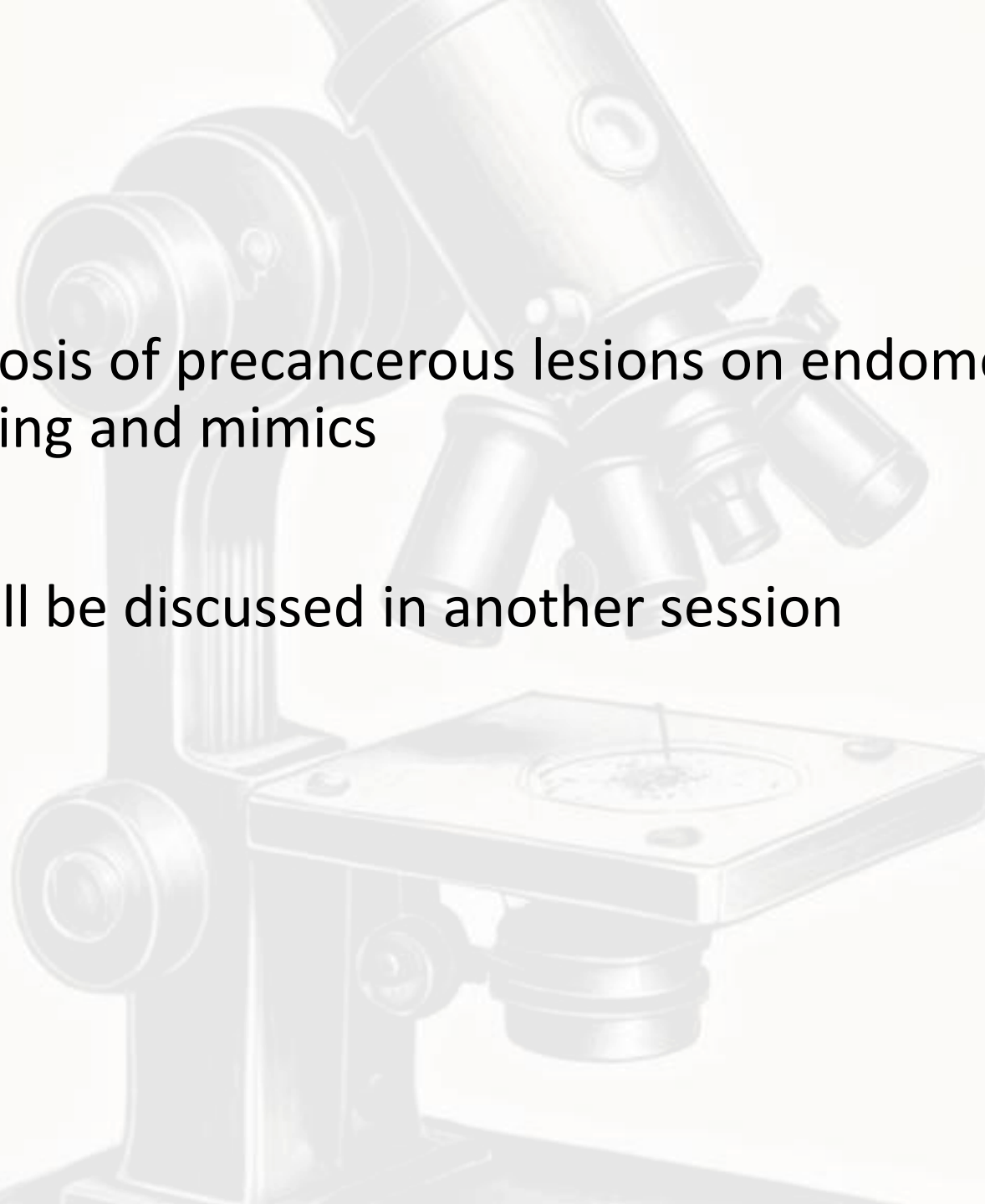
Kyle Devins, MD

Massachusetts General Hospital

Harvard Medical School

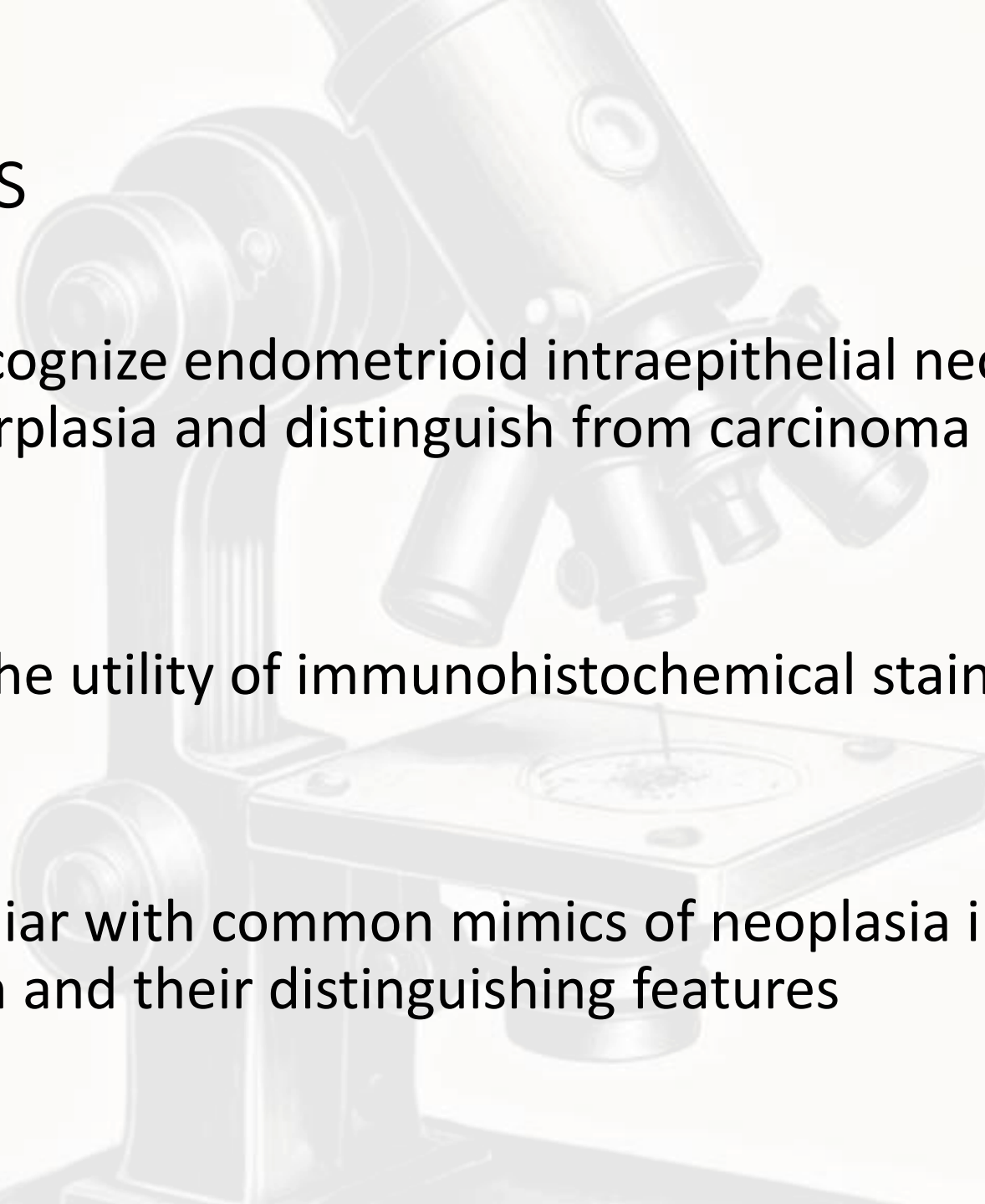
Agenda

- Discuss diagnosis of precancerous lesions on endometrial biopsy/curetting and mimics
- Carcinoma will be discussed in another session



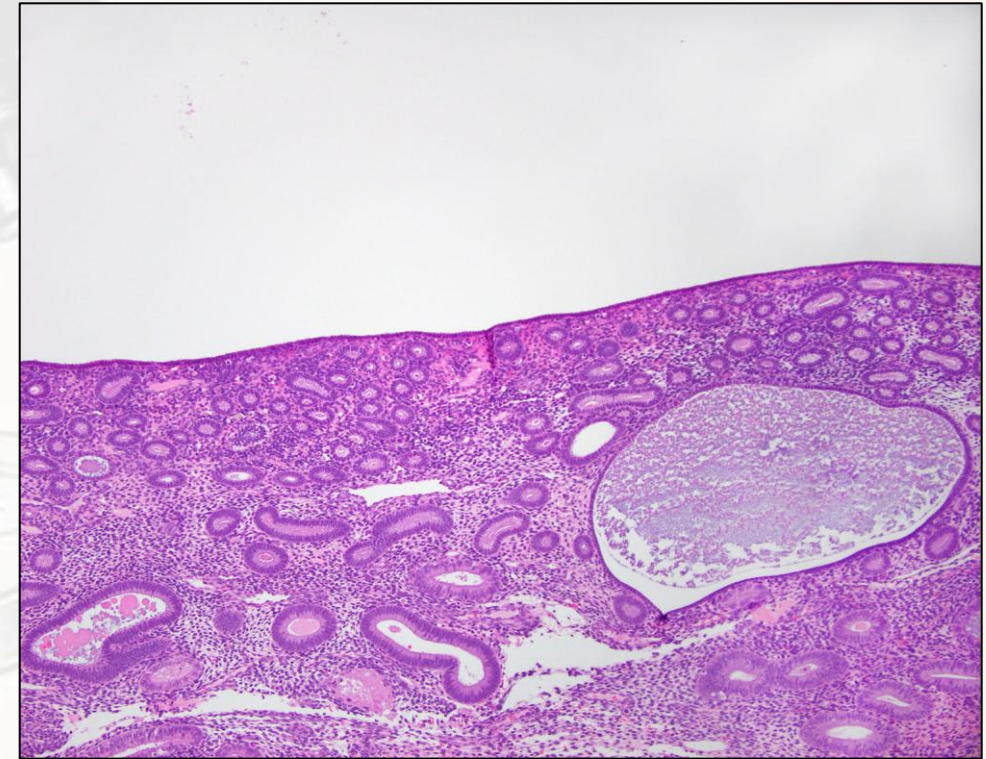
Objectives

- Be able to recognize endometrioid intraepithelial neoplasia (EIN)/ atypical hyperplasia and distinguish from carcinoma and benign mimics
- Understand the utility of immunohistochemical stains in the diagnosis of EIN
- Become familiar with common mimics of neoplasia in the endometrium and their distinguishing features



Endometrial Hyperplasia Without Atypia

- Most common in perimenopause or younger women with hyperestrogenism (e.g. polycystic ovary syndrome, obesity)
- Glandular crowding without cytologic/architectural atypia or cytologic shift from background glandular morphology
- Often diffusely involving endometrium
- Disorganized, irregular gland size/shape
- Slightly increase risk of progression to cancer due to hyperestrogenism (20-year risk <5%)

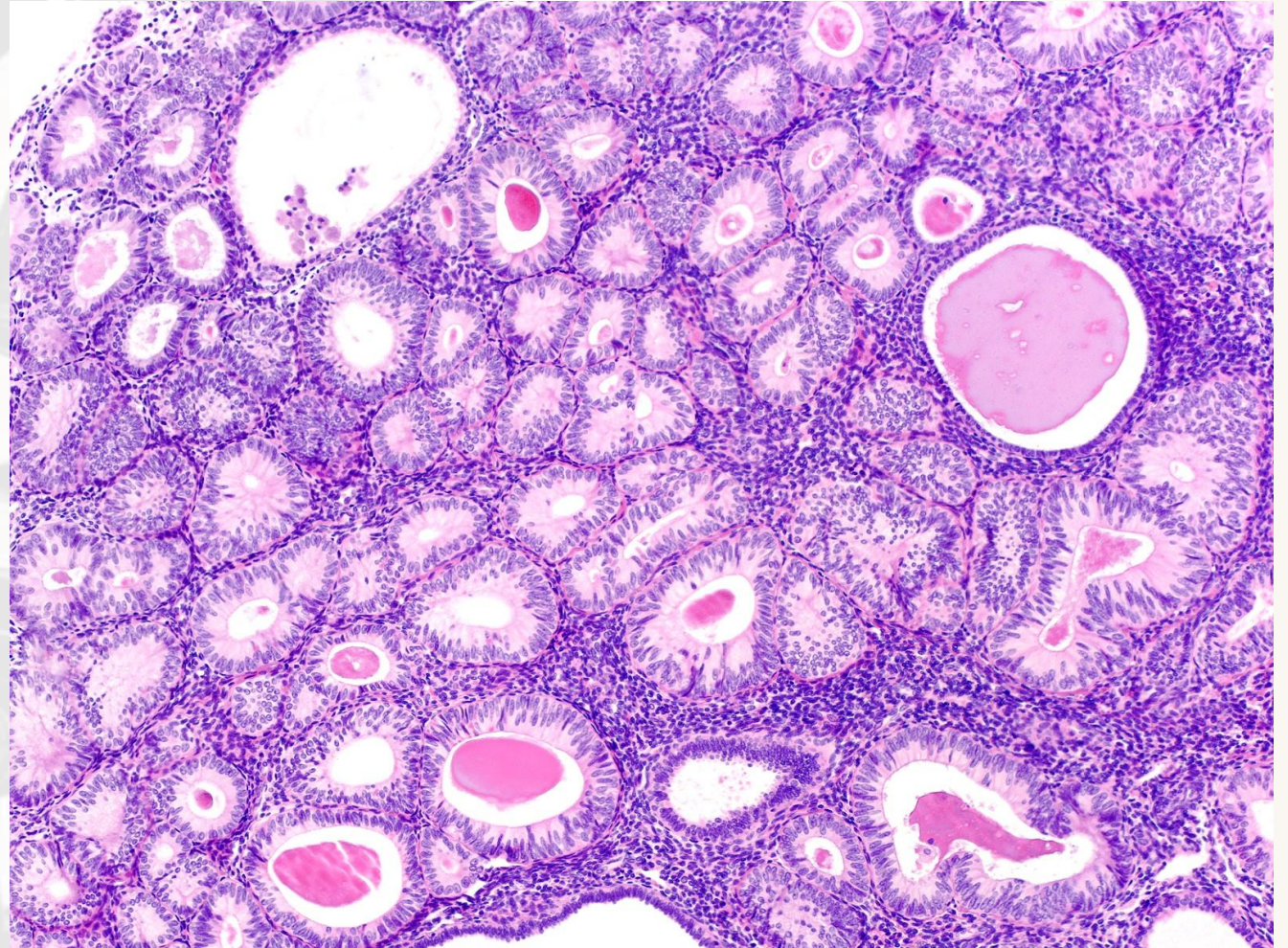


Endometrioid intraepithelial neoplasia (EIN) / Atypical hyperplasia (AH)

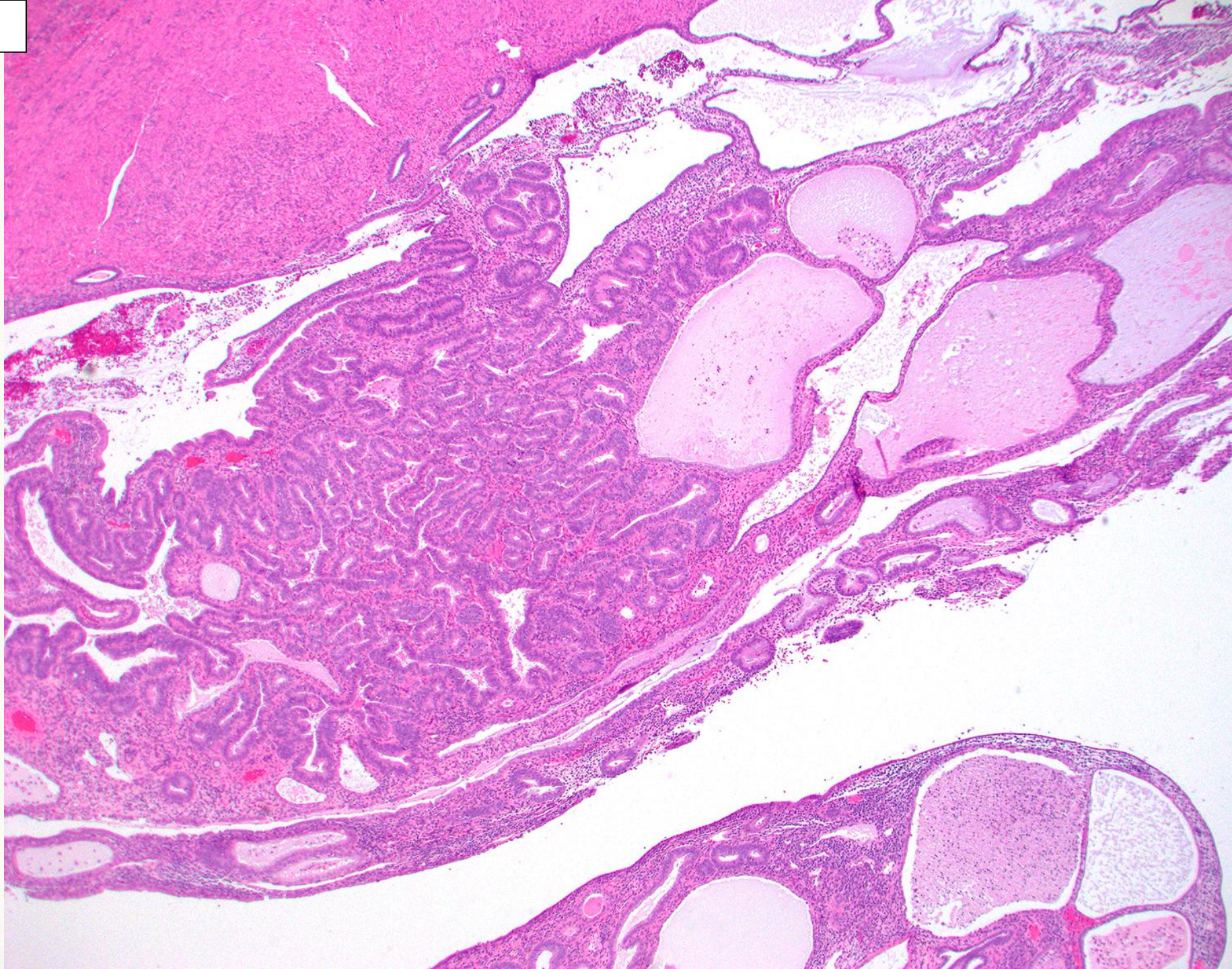
- Considered synonymous despite historically differing criteria
- Incidence ~ 56/100,000 women
 - Increased risk with genomic predisposition syndromes such as Cowden and Lynch
 - Other risk factors: hyperestrogenism, obesity, polycystic ovary syndrome
- Avg age 50-60 years
- Risk of progression to endometrioid adenocarcinoma
 - ~1/3 of women with EIN/AH on biopsy are diagnosed with carcinoma on subsequent hysterectomy
- Treated with hysterectomy or conservatively with hormone therapy

Endometrioid intraepithelial neoplasia (EIN) / Atypical hyperplasia (AH)

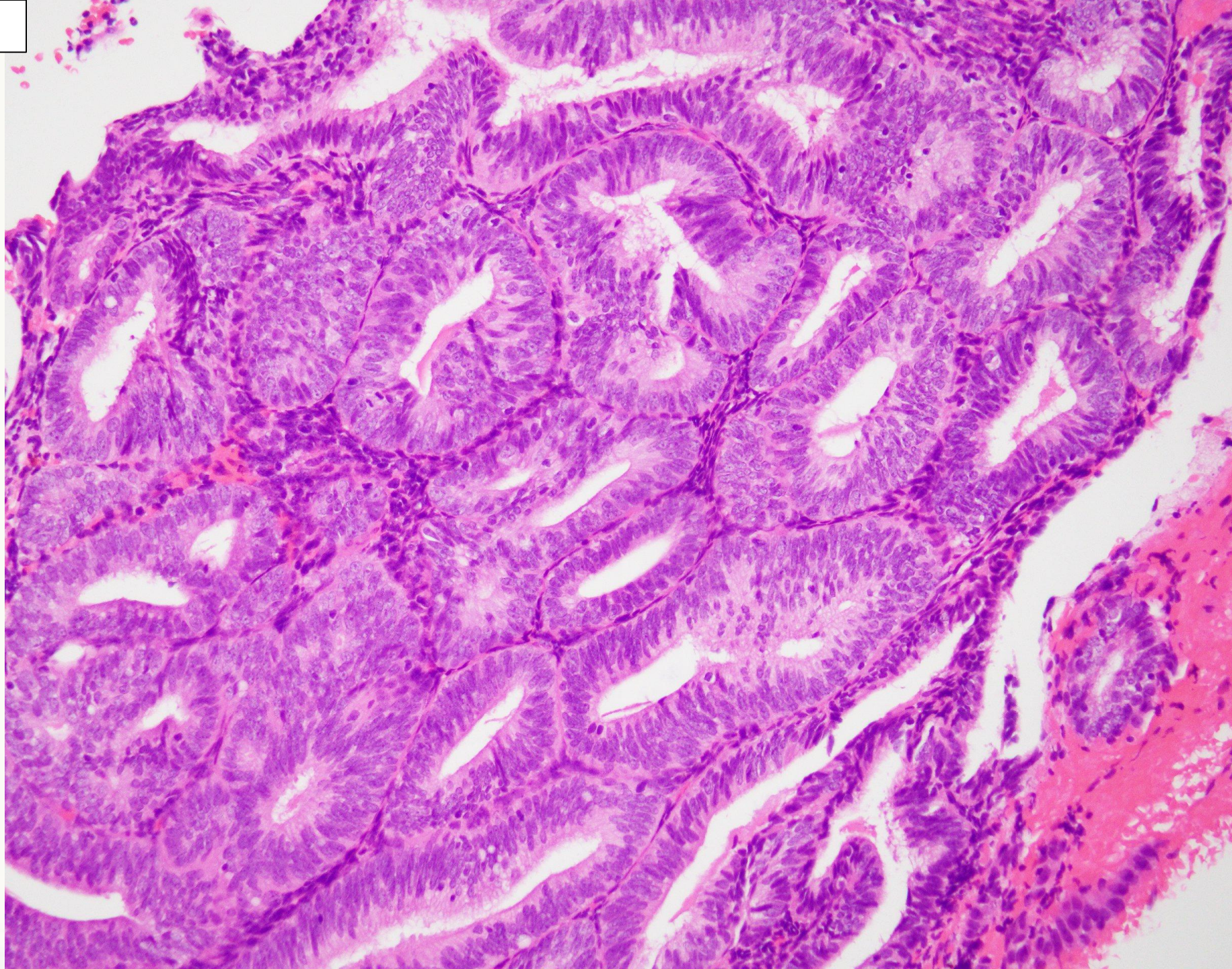
- Diagnosis:
 - Glandular crowding ($>2:1$ gland to stromal ratio)
 - Cytological distinction from background endometrium
 - Exclusion of mimics



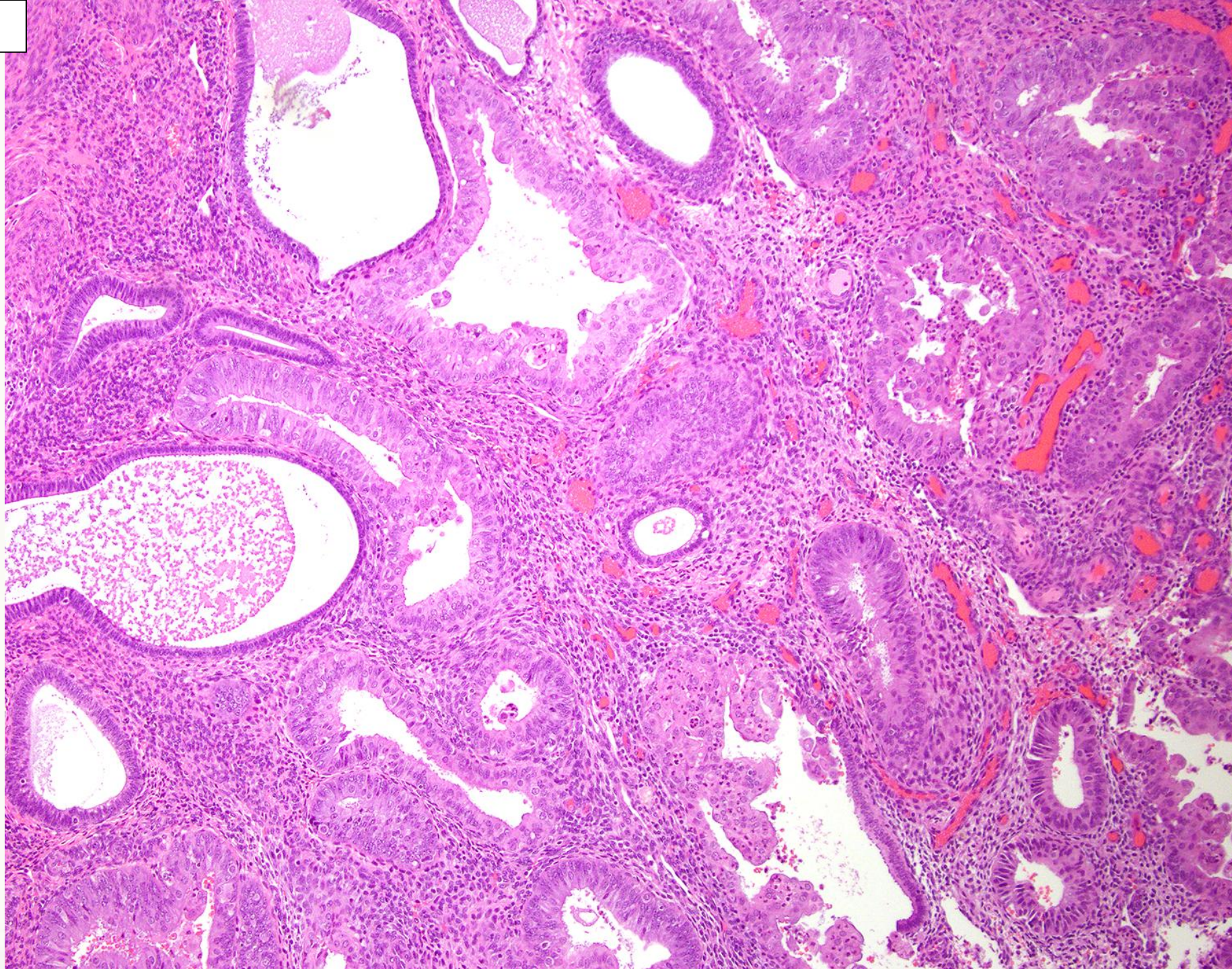
EIN



EIN

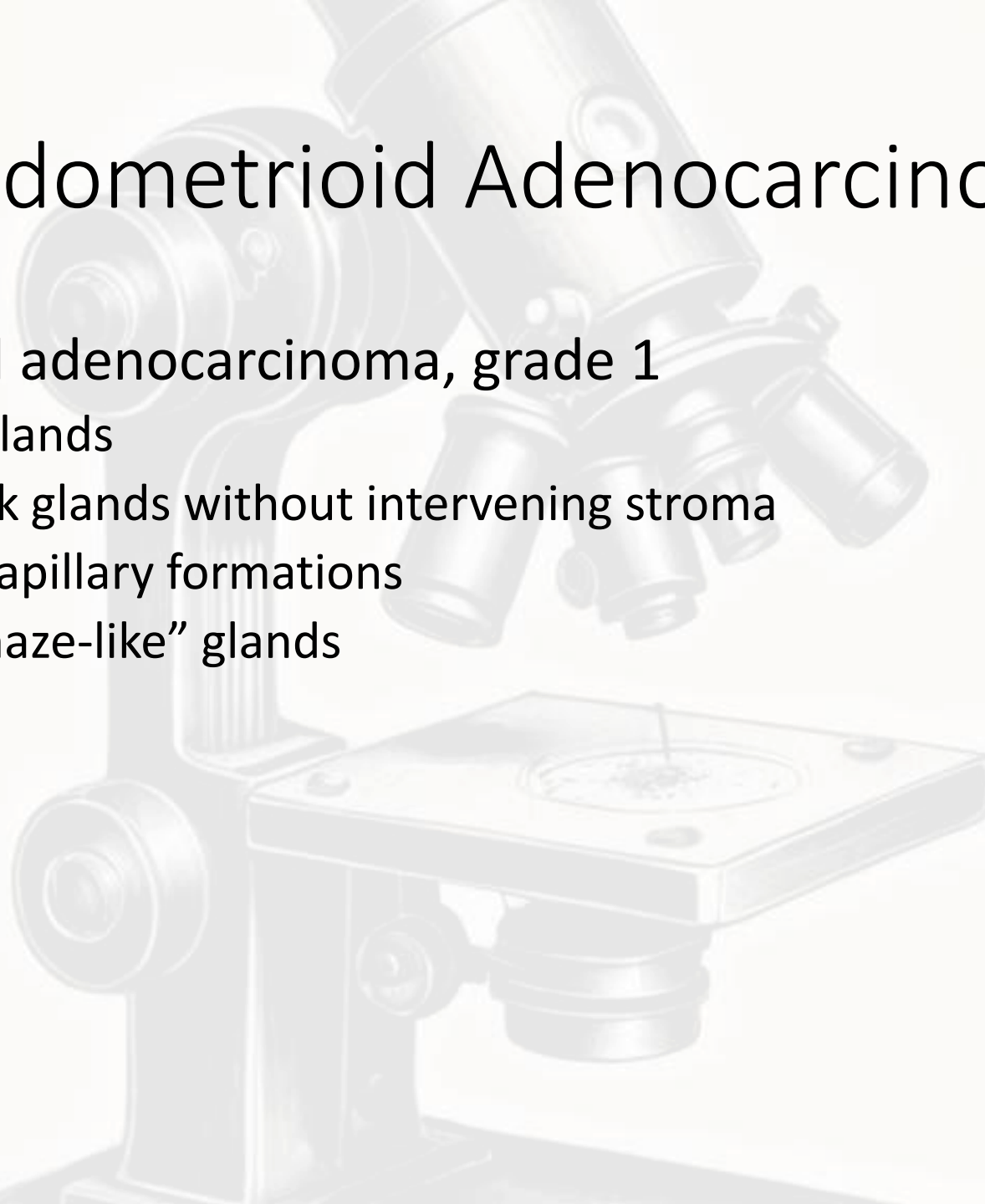


EIN



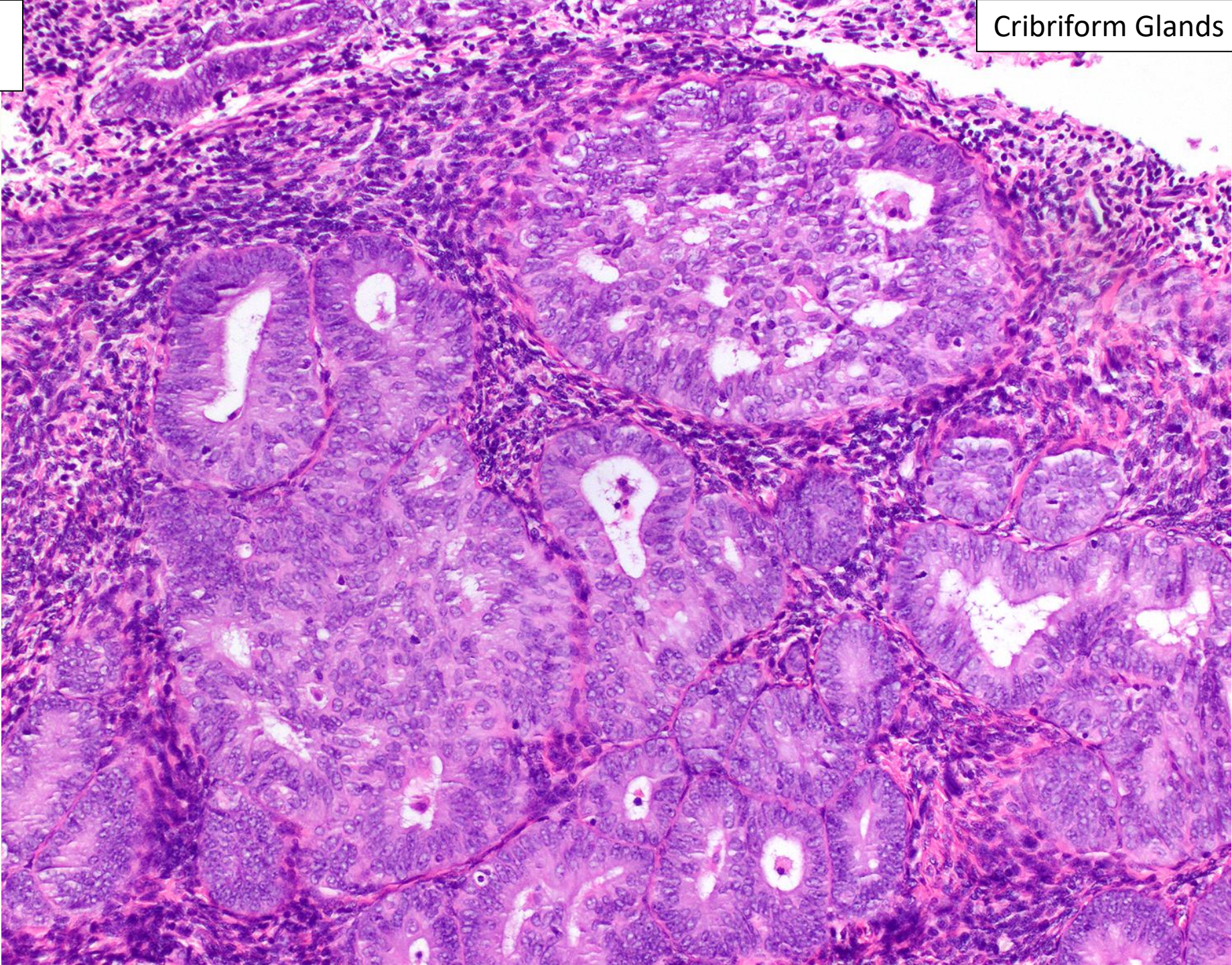
EIN vs. Endometrioid Adenocarcinoma

- Endometrioid adenocarcinoma, grade 1
 - Cribriform glands
 - Back-to-back glands without intervening stroma
 - Elongated papillary formations
 - Complex “maze-like” glands



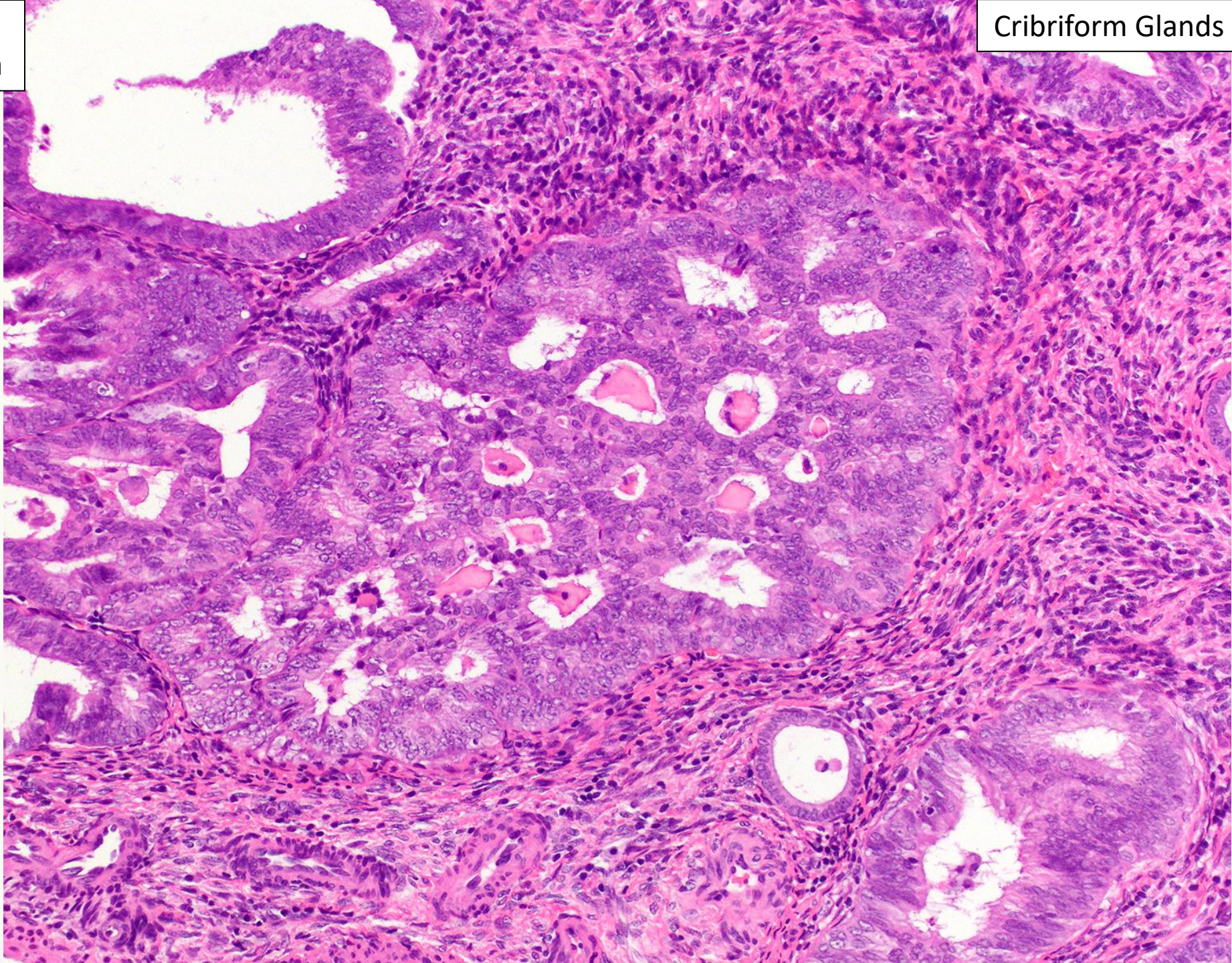
Endometrioid
Adenocarcinoma

Cribriform Glands



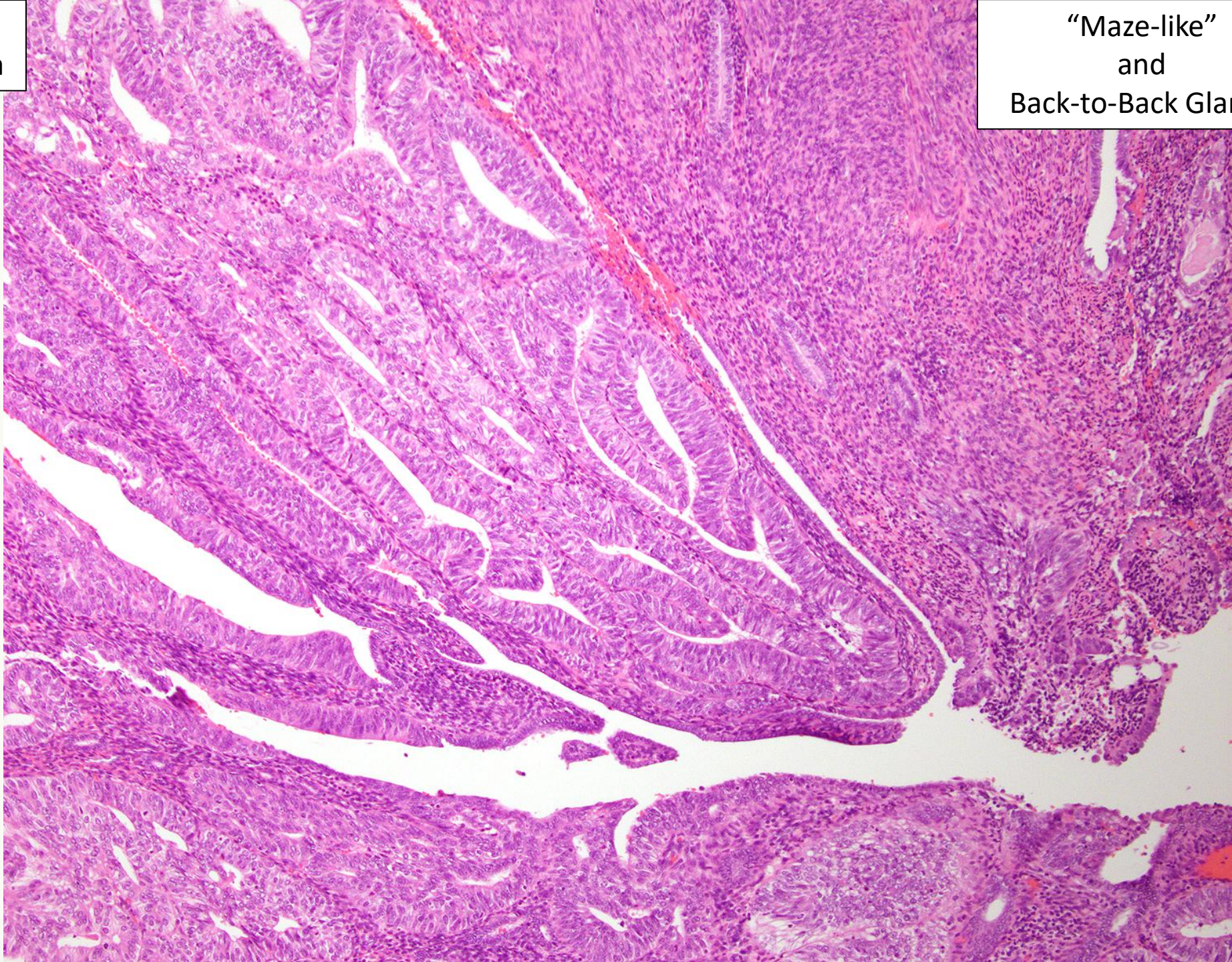
Endometrioid
Adenocarcinoma

Cribriform Glands



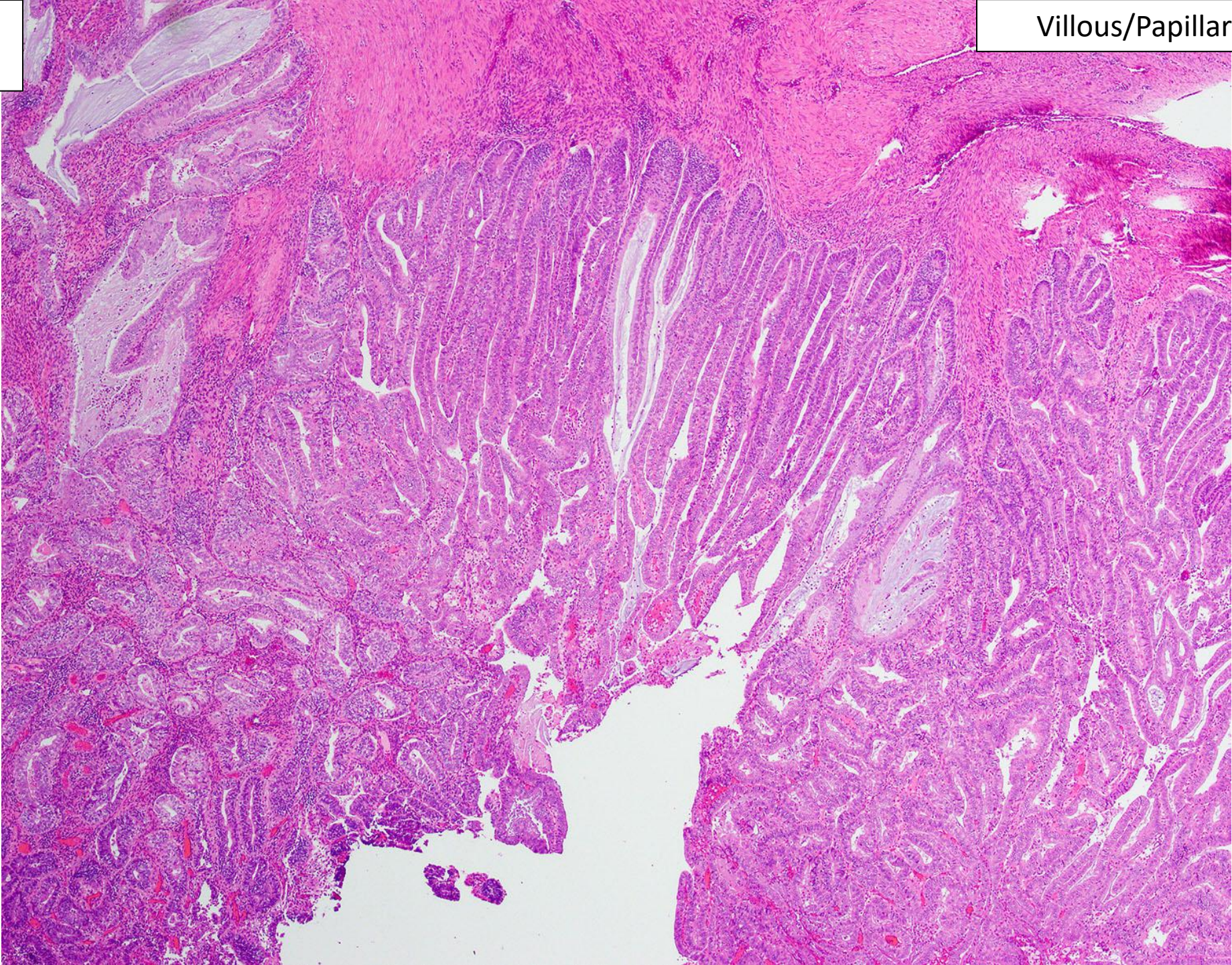
Endometrioid
Adenocarcinoma

“Maze-like”
and
Back-to-Back Glands



Endometrioid
Adenocarcinoma

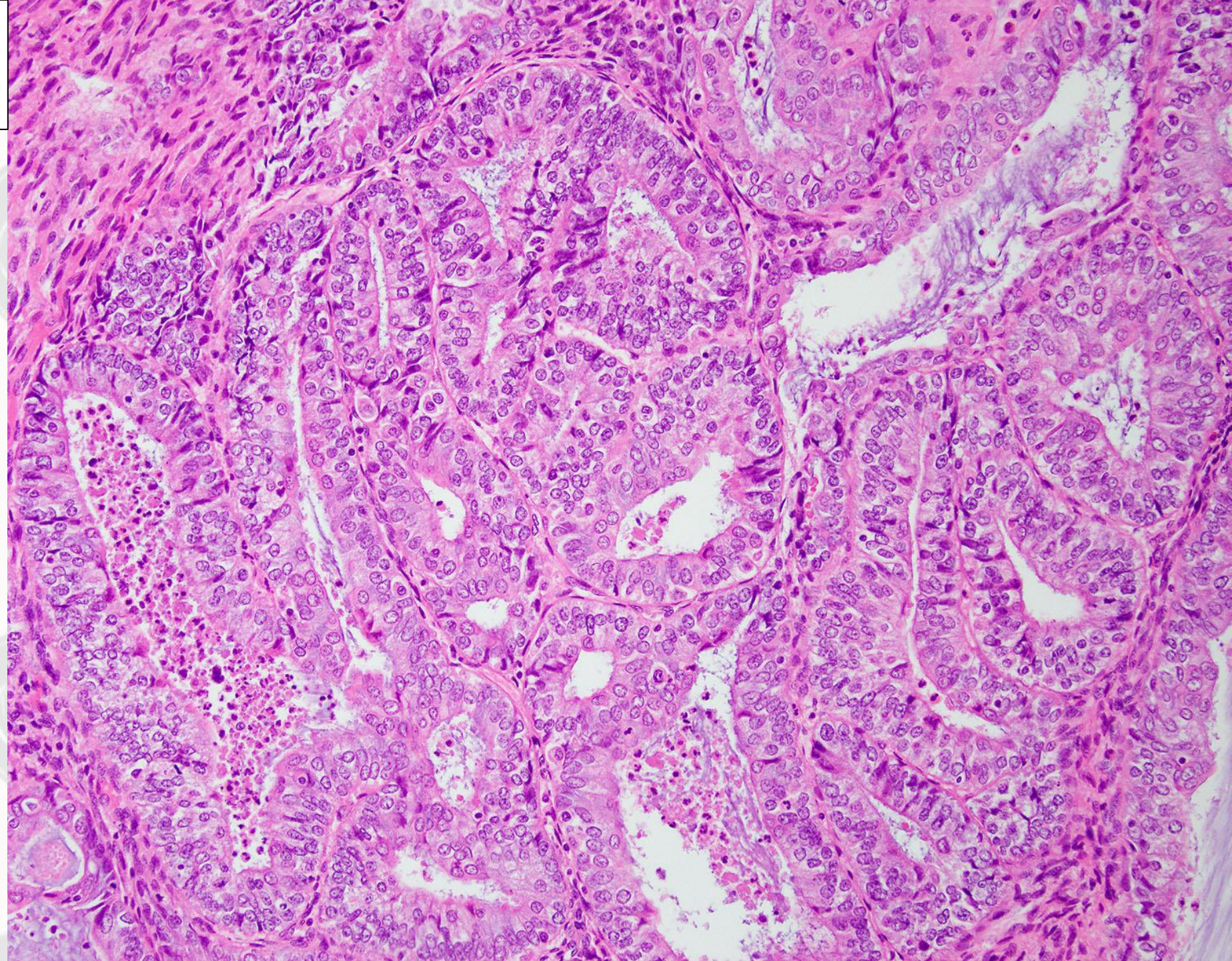
Villous/Papillary



Equivocal areas between EIN and grade 1 adenocarcinoma on limited sampling

Ask “If the subsequent hysterectomy is negative, do I have sufficient evidence to diagnose carcinoma on this slide(s)”

Consider a descriptive diagnosis such as: “EIN with areas bordering on grade 1 endometrioid adenocarcinoma”



IHC in the Assessment of EIN/AH

- UT Southwestern system

- PAX2
- PTEN
- Beta-catenin

At least 1 aberrant marker
in 92.8% of EIN/AH

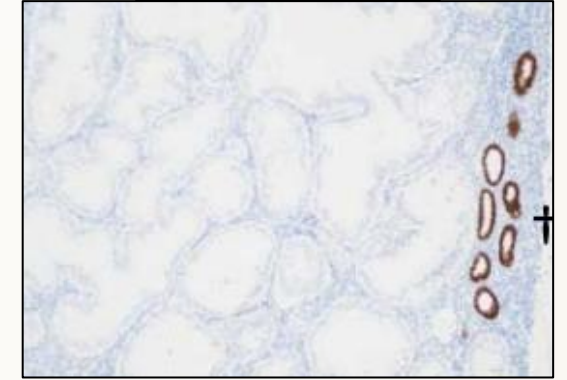
- p53
- ARID1A
- MLH1

No significant
improvement in detection

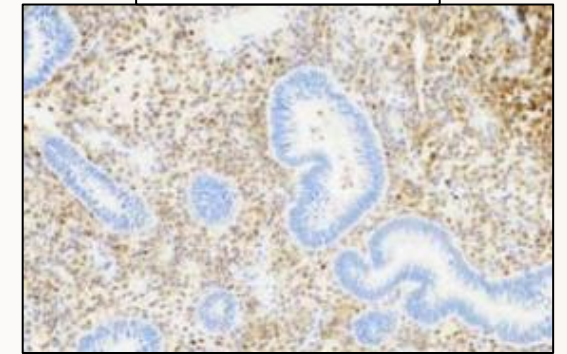
*Only useful as diagnostic adjunct in areas of morphologic concern

- Outcomes data for morphologic EIN/AH
- Occasional transient, morphologically unremarkable clones in endometrium

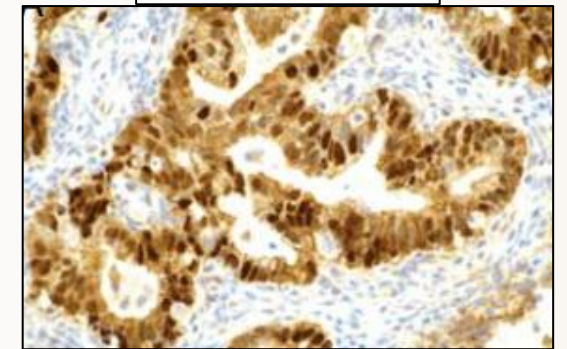
PAX2



PTEN

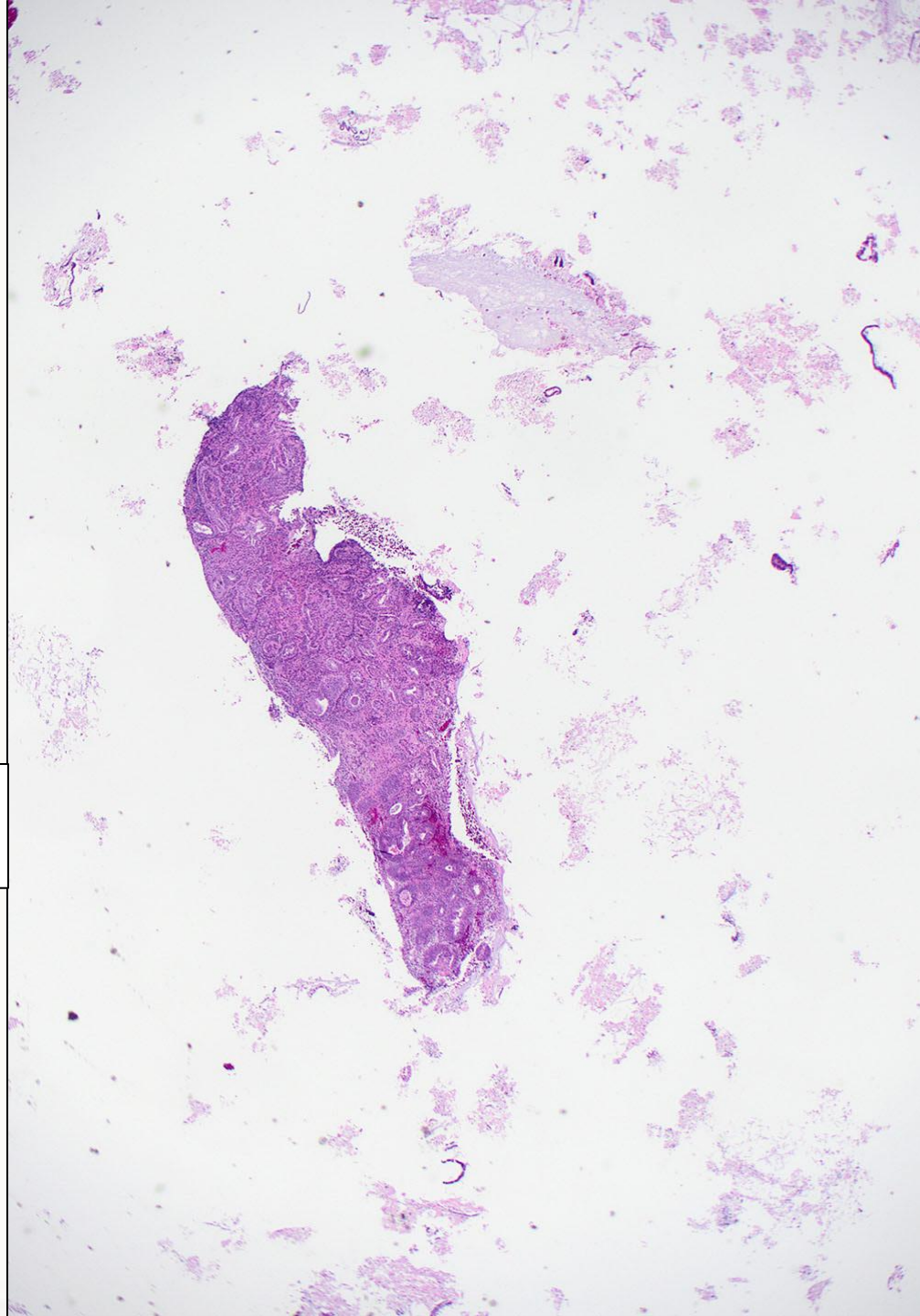


B-catenin

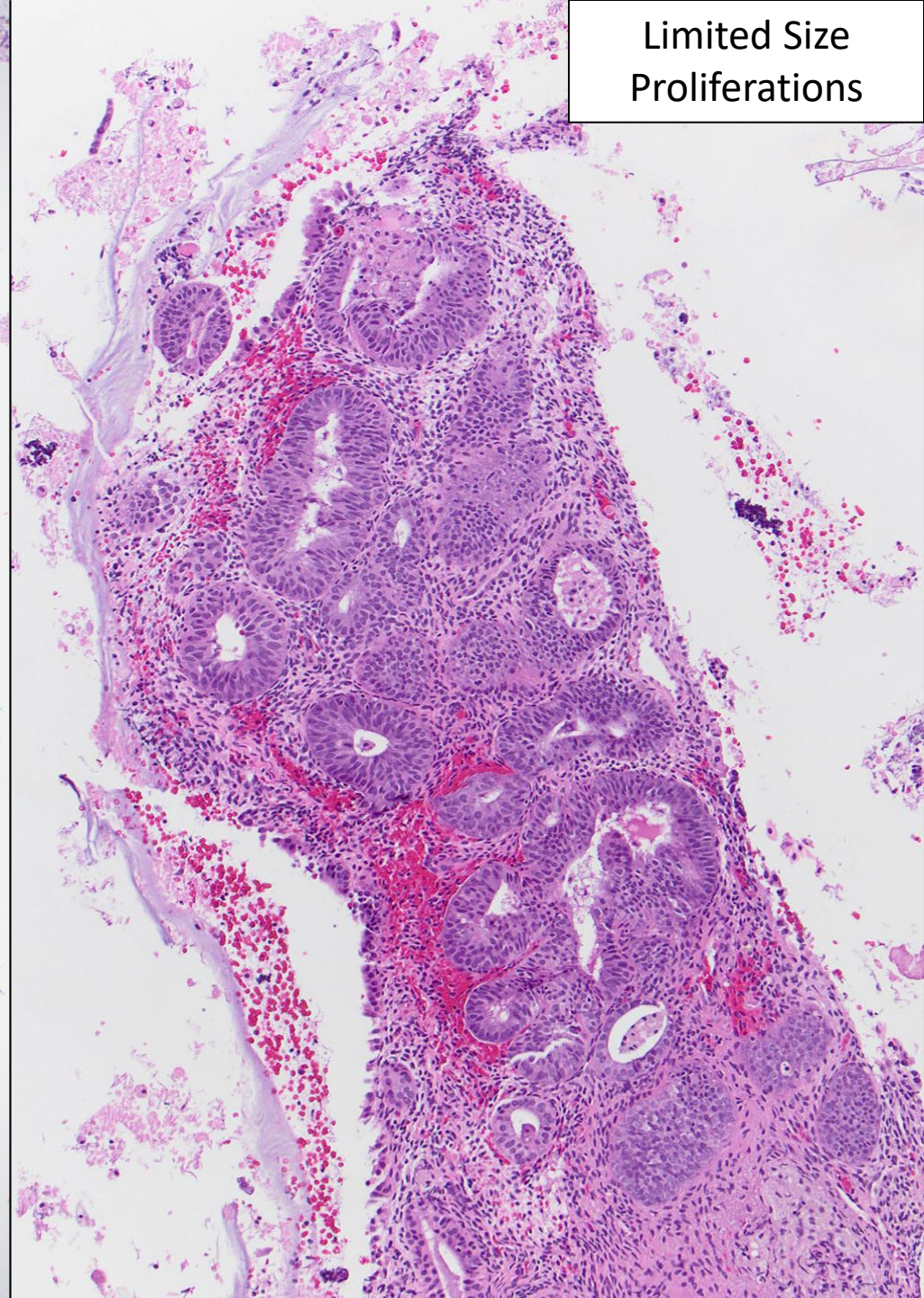


IHC Use Cases

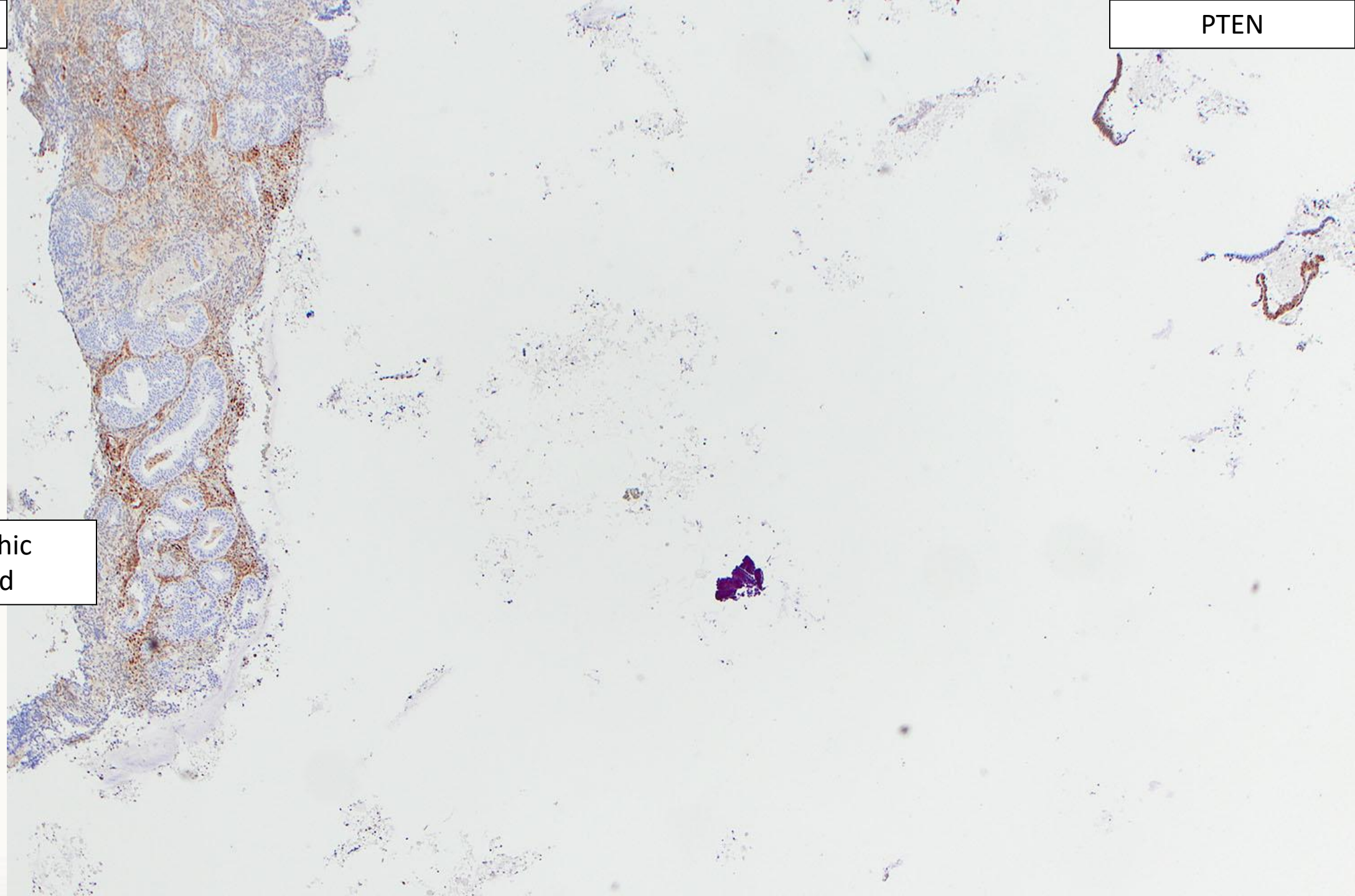
EIN in atrophic
background



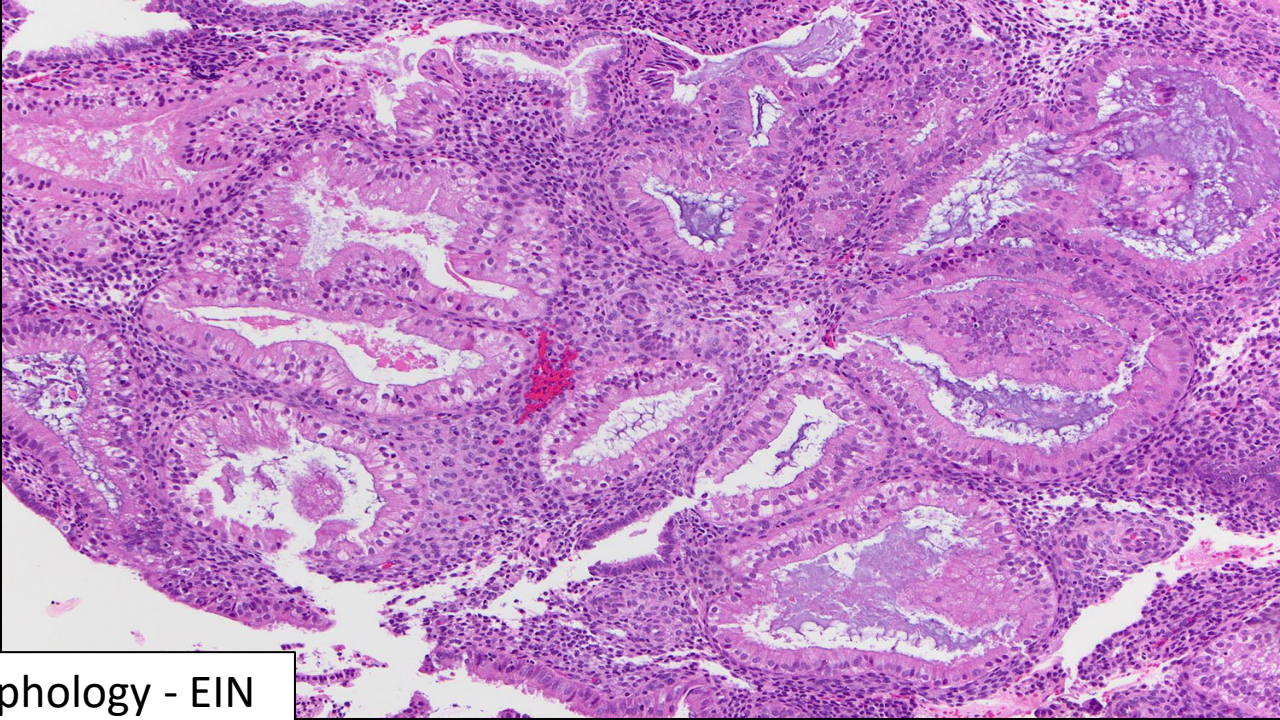
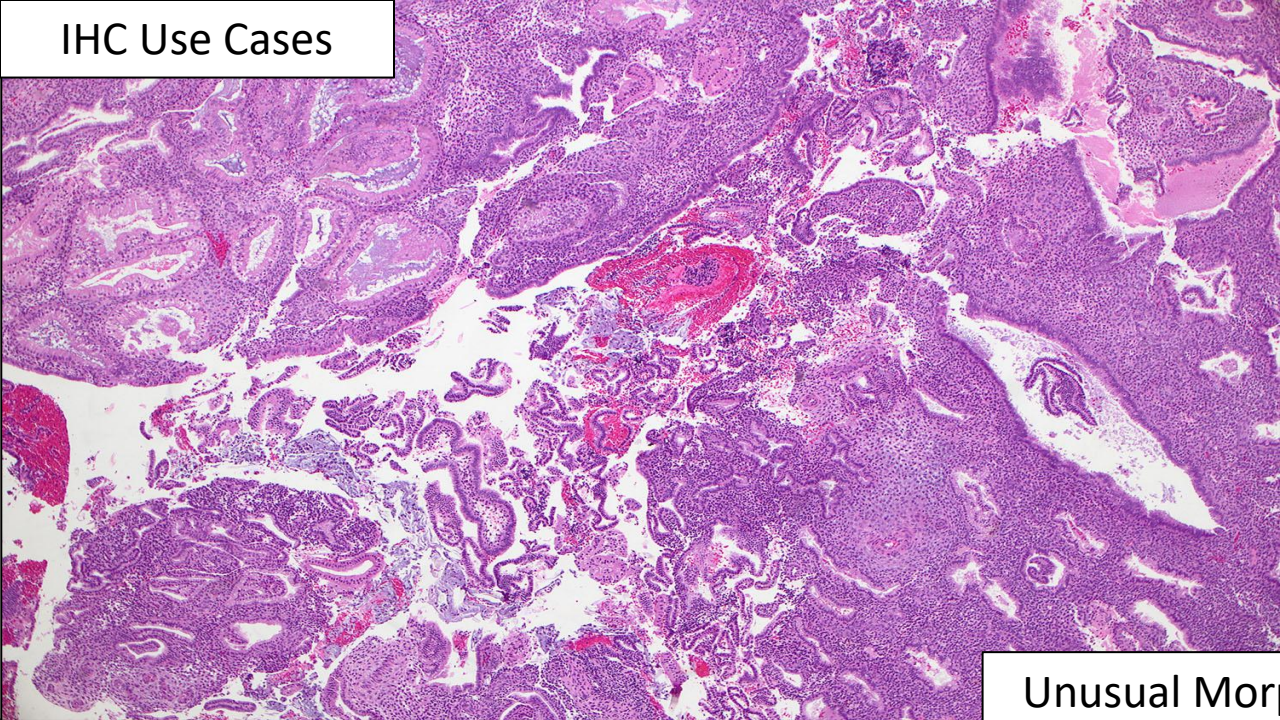
Limited Size
Proliferations



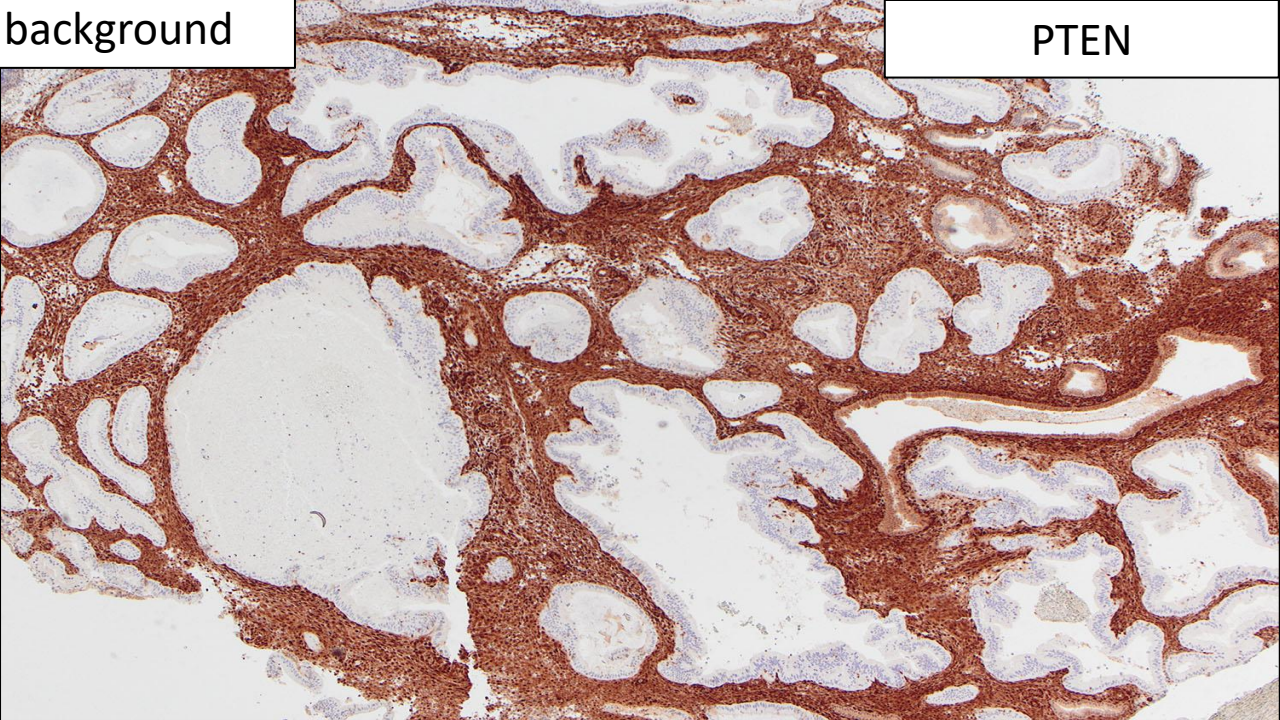
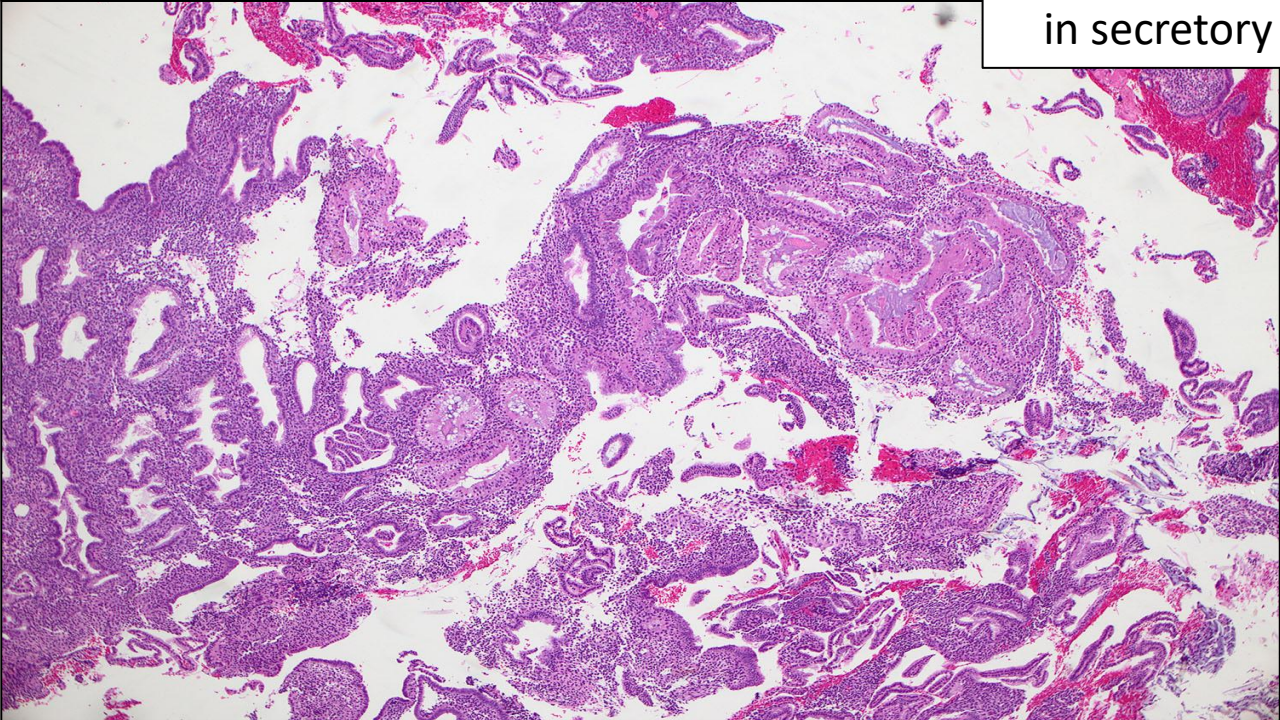
EIN in atrophic
background



IHC Use Cases



Unusual Morphology - EIN
in secretory background



PTEN

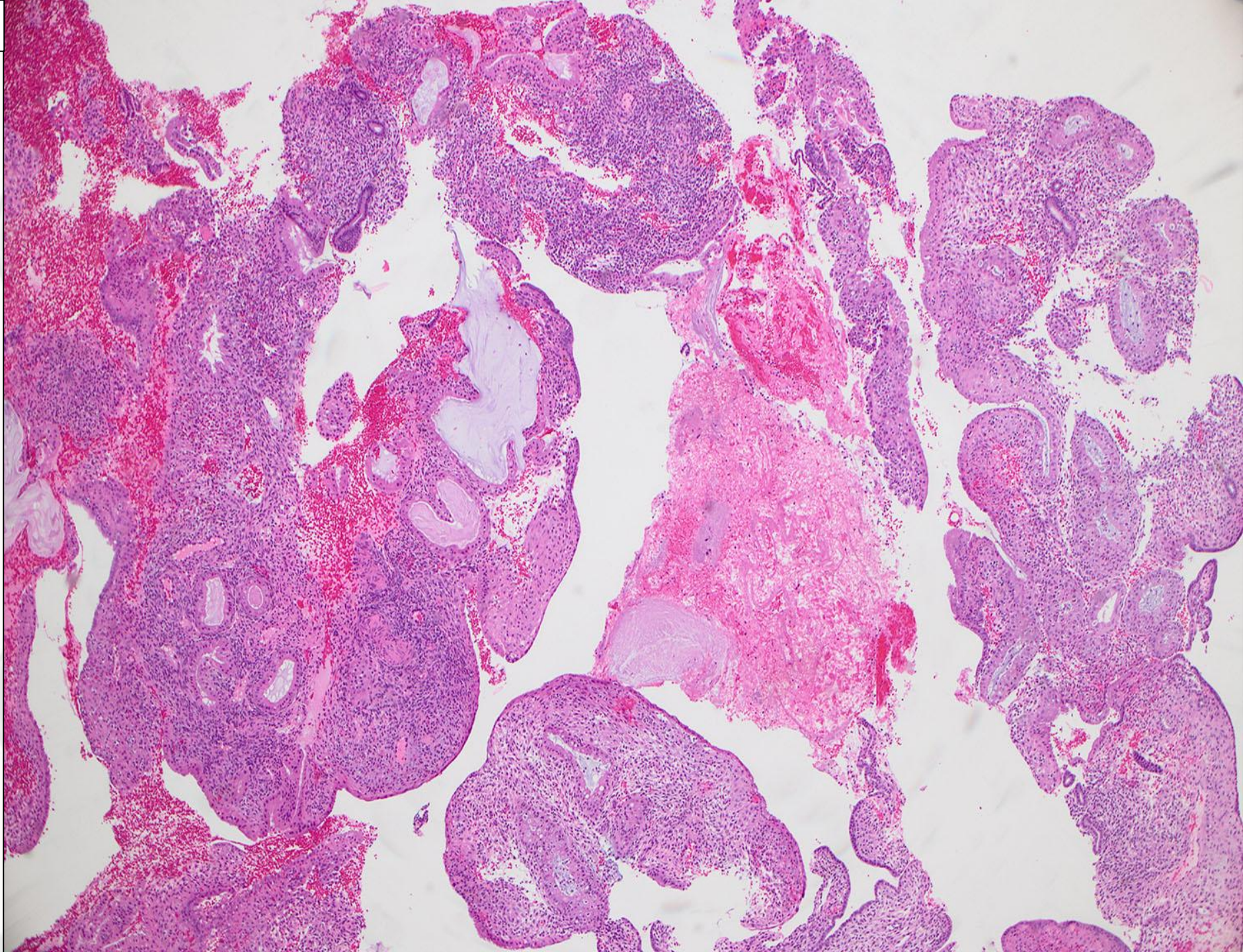
Progestin Therapy for EIN

Progestin-treated EIN may have relatively bland cytology and less complex architecture

Low threshold for considering residual neoplasia with any architectural atypia / cytologic shift in this setting

Should be diagnosed as “residual endometrioid neoplasia with treatment effect”

If no appreciable treatment effect is seen, this should be noted



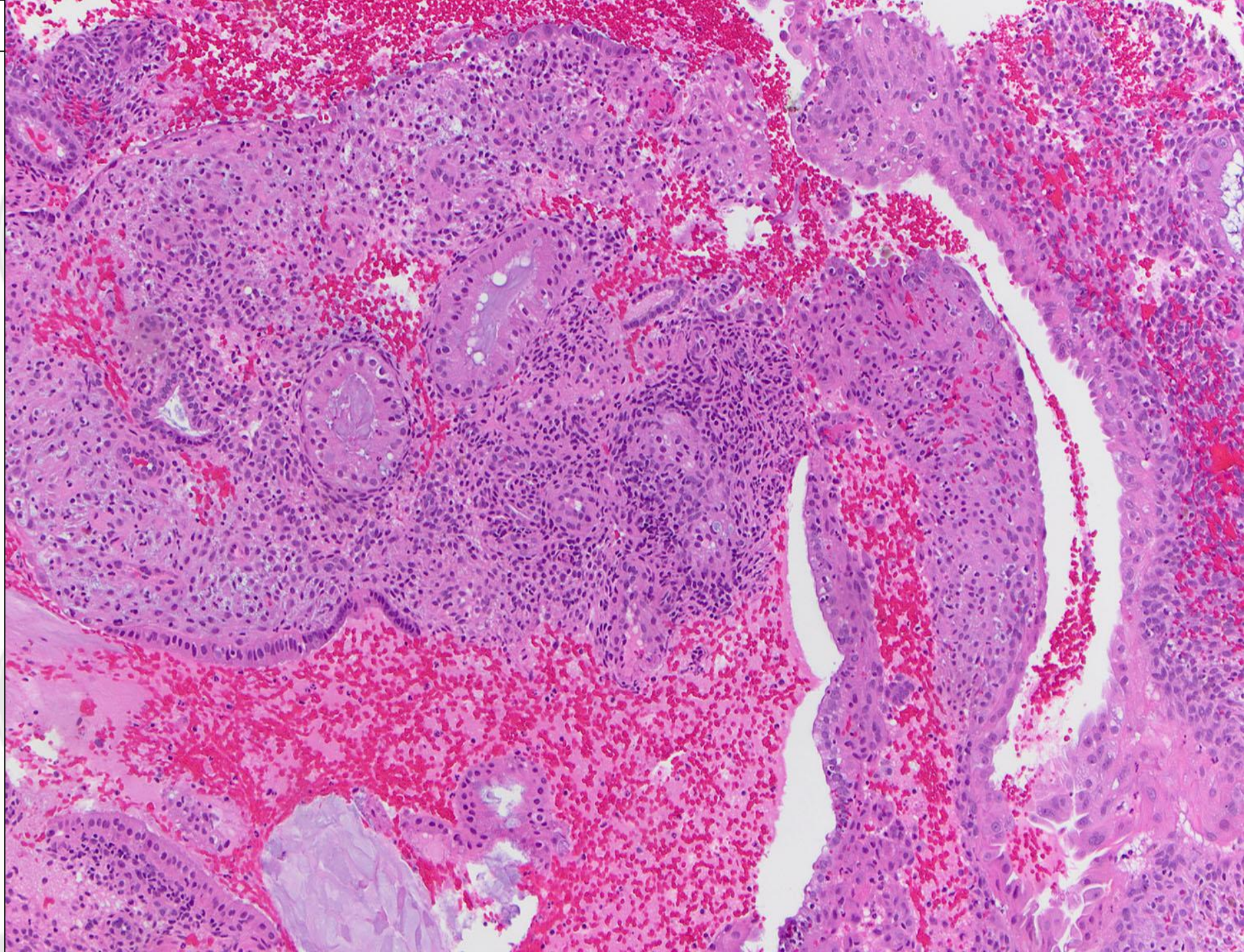
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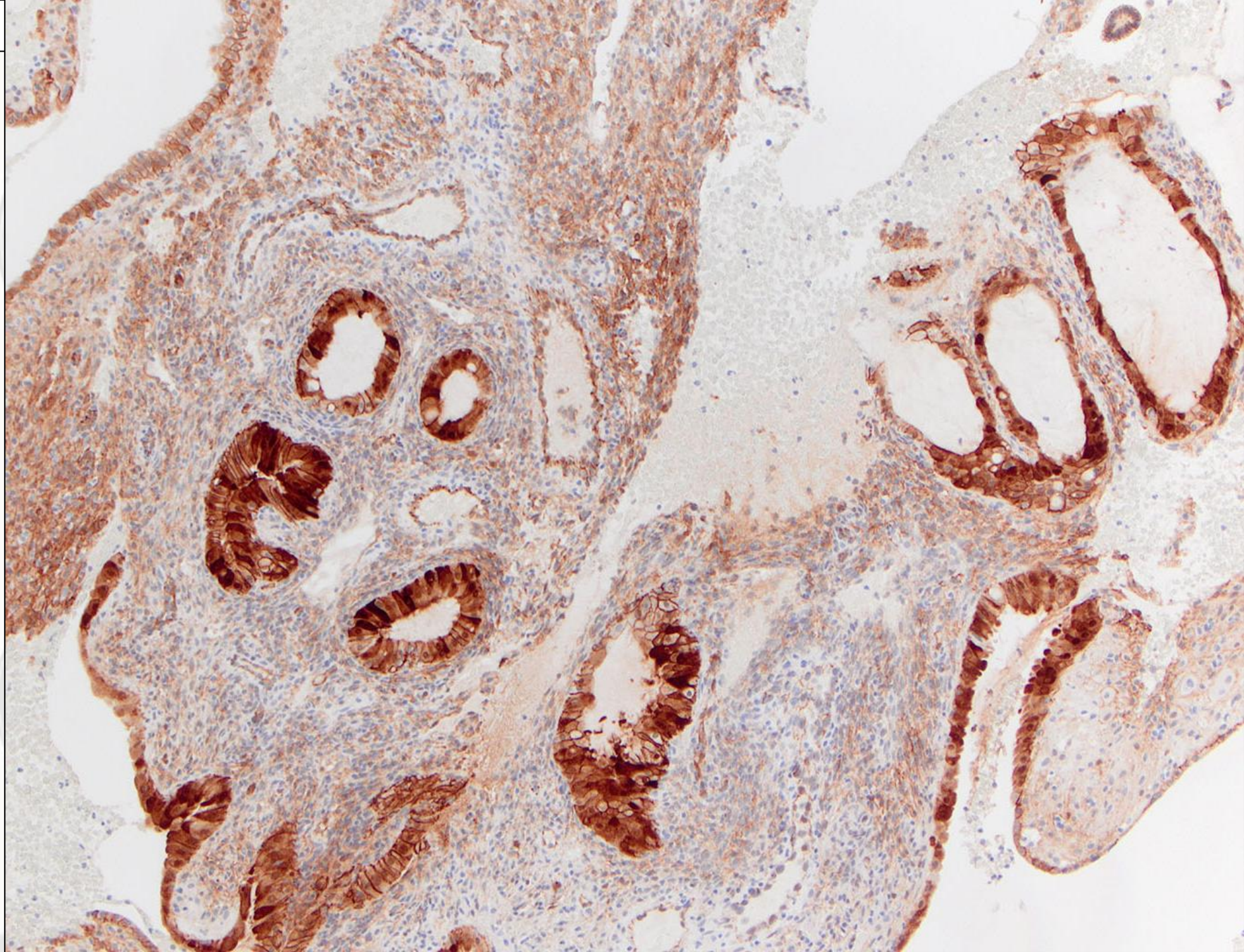
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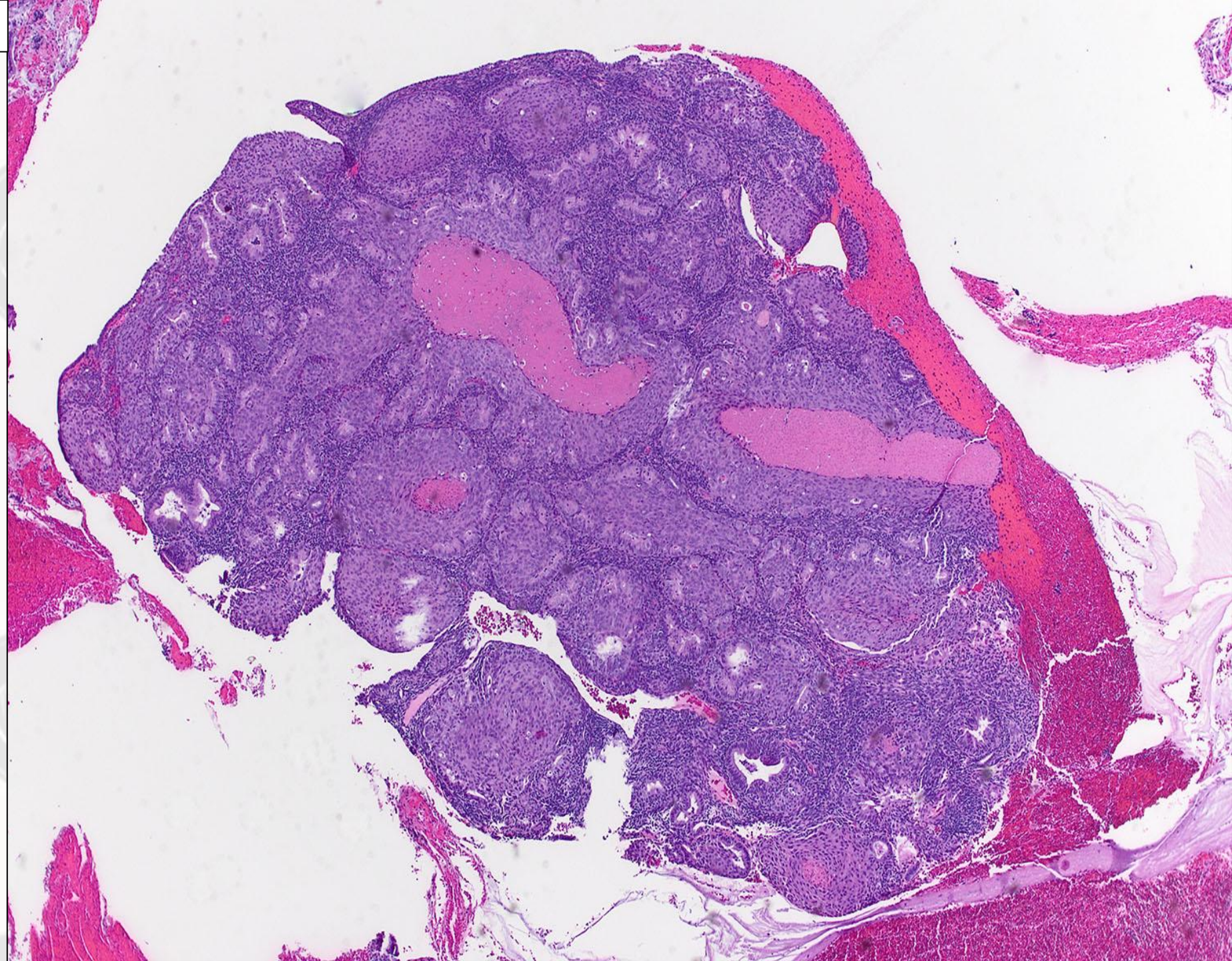
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Squamous Morules in EIN/AH

Subtract squamous differentiation
from assessment of glandular
complexity

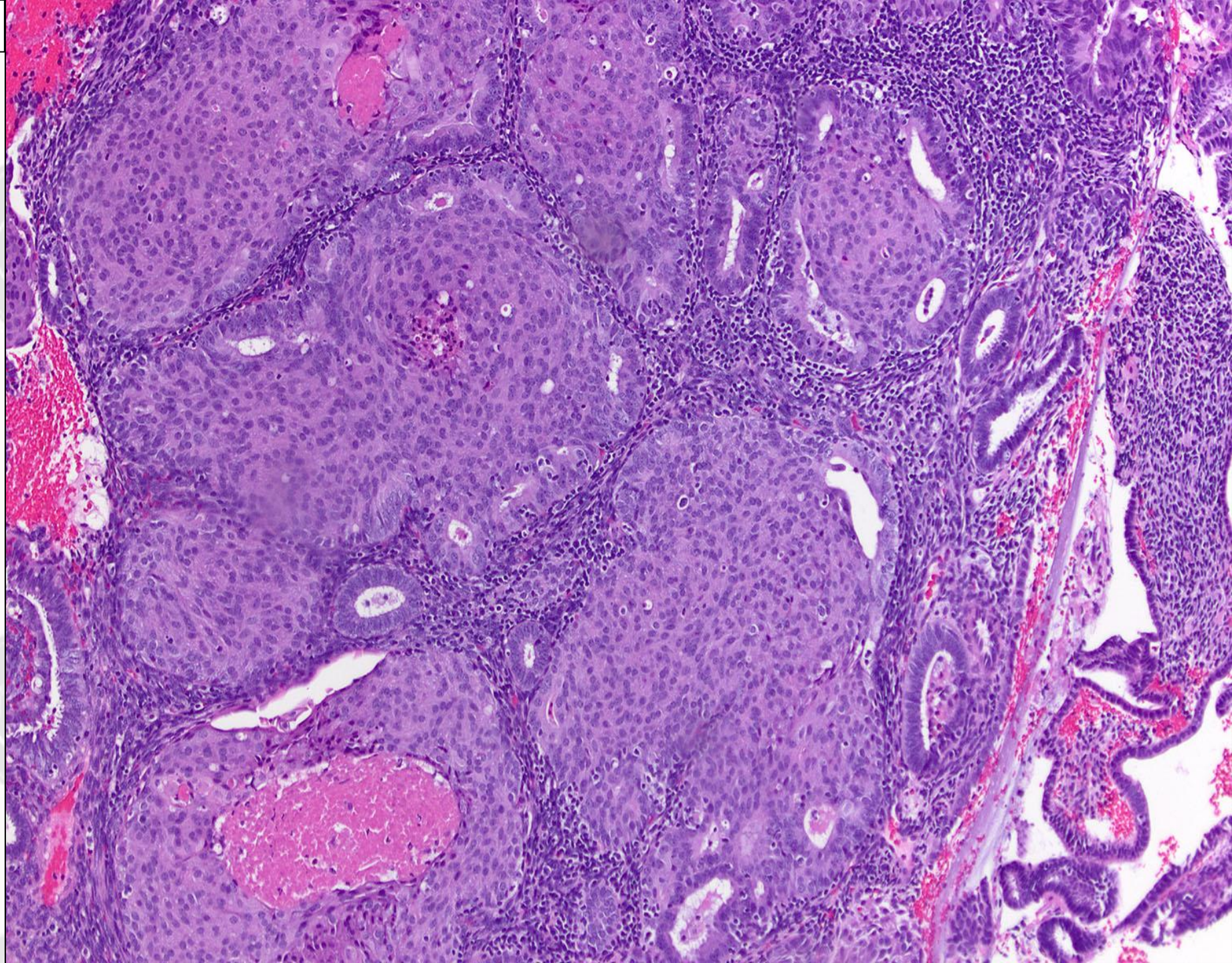
If glands are complex enough for a
carcinoma diagnosis independent
of squamous morules, diagnose
carcinoma



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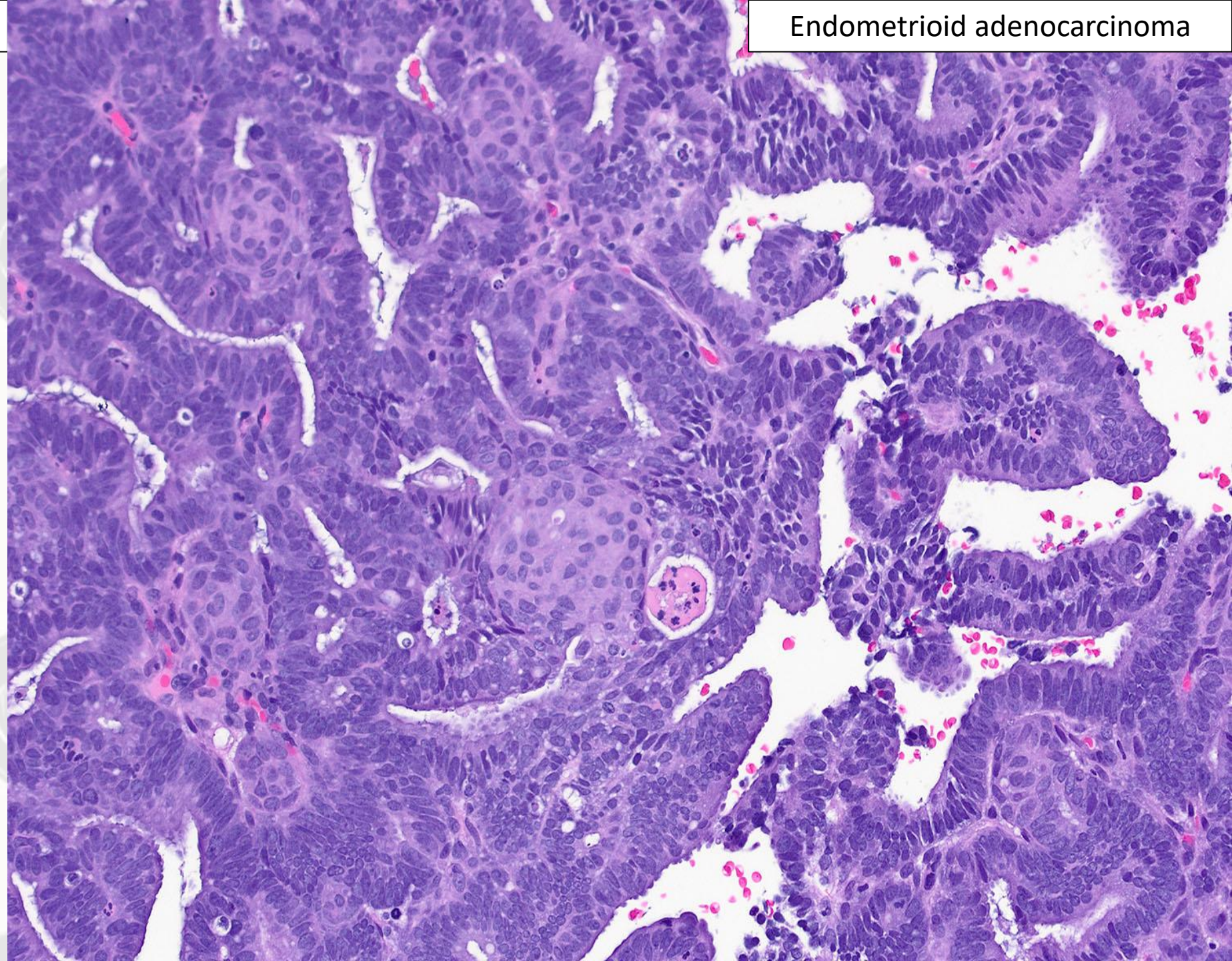


Squamous Morules

Endometrioid adenocarcinoma

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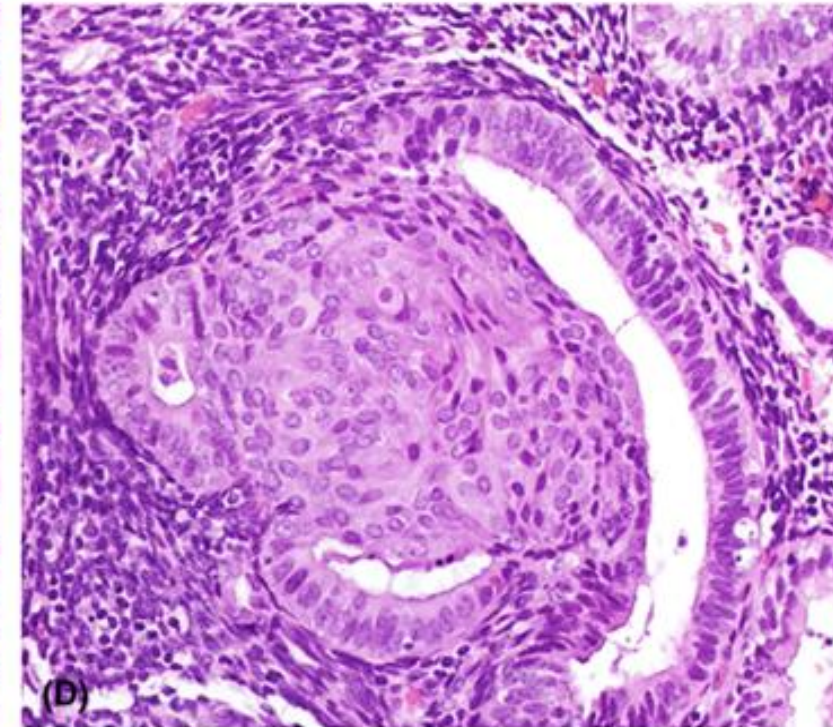
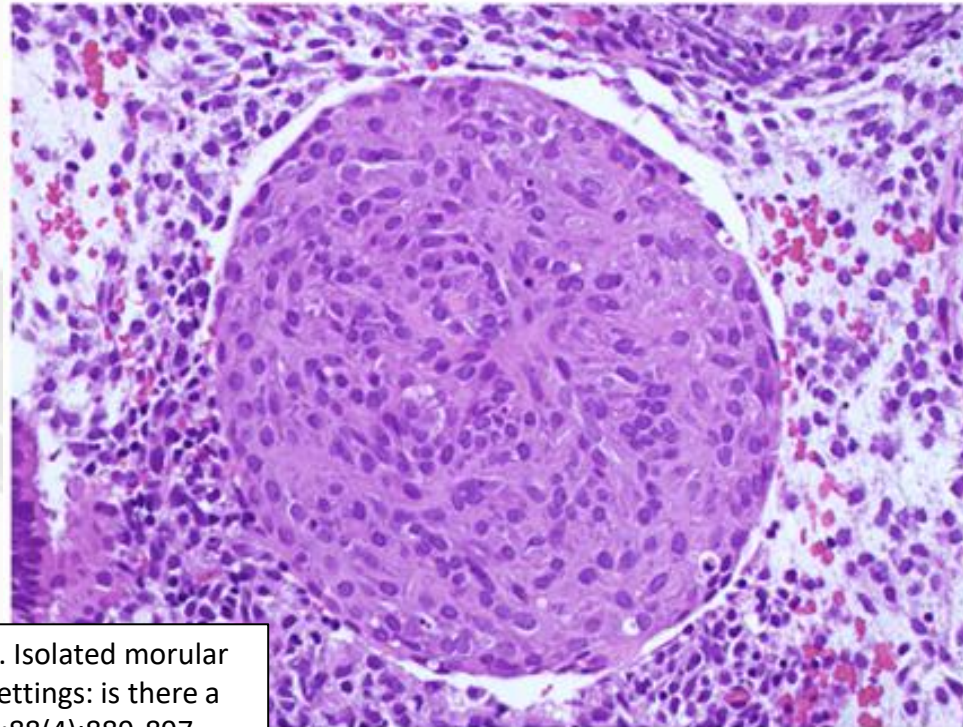
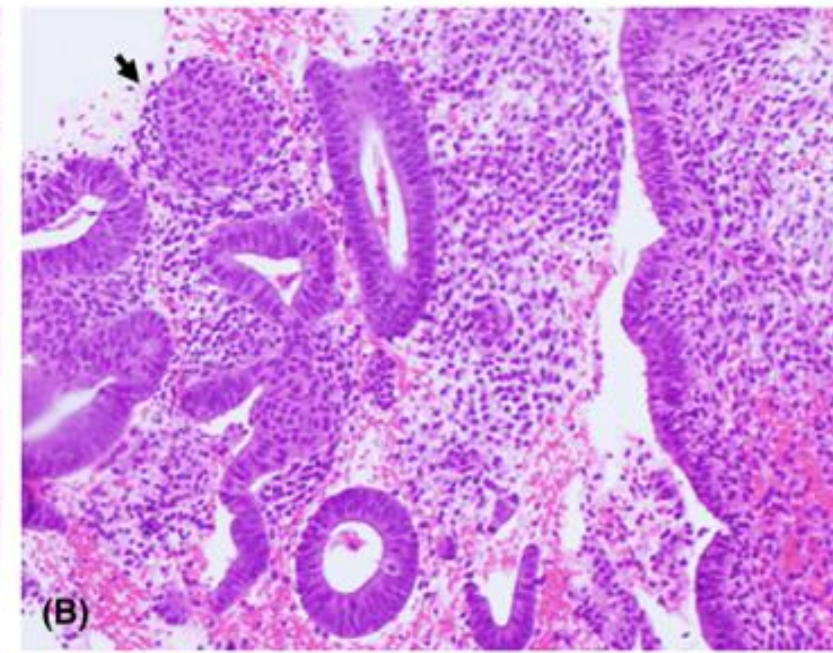
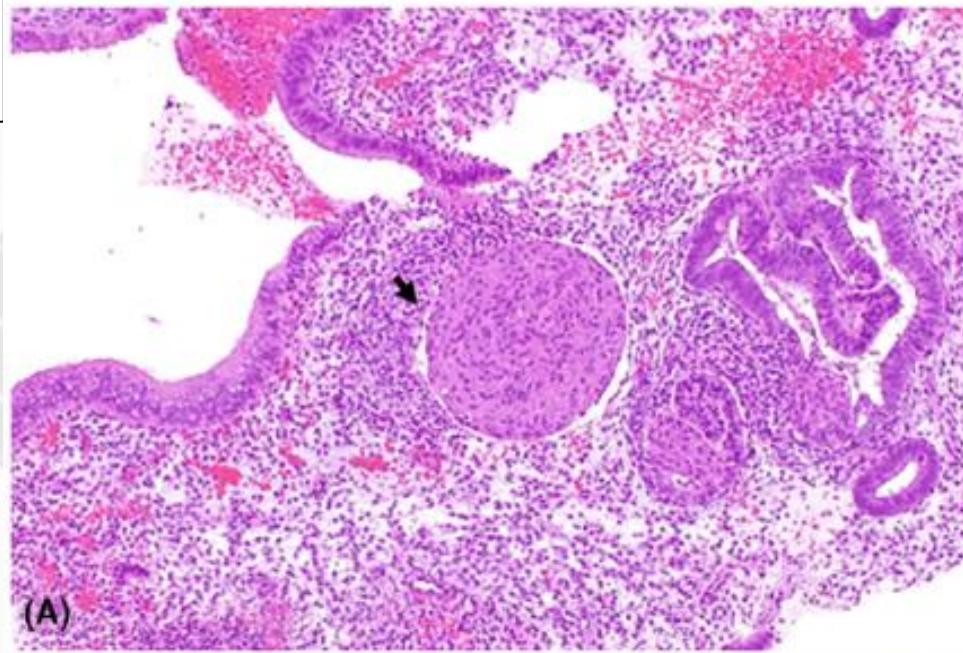
Isolated Squamous Morular Metaplasia

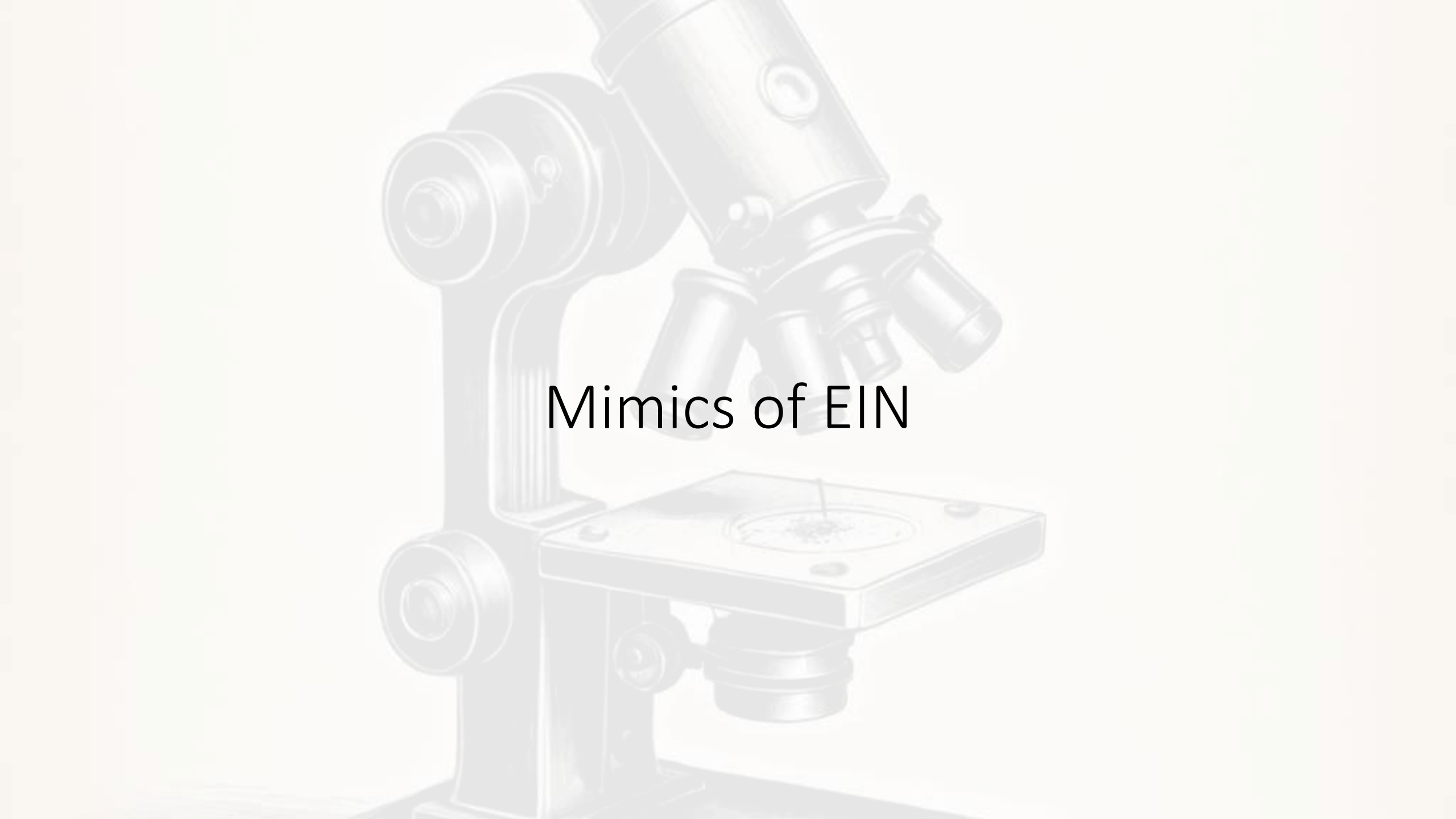
Squamous morules without morphologic EIN or carcinoma is rare (0.17% of samples)

Risk of subsequent endometrioid neoplasia is low (5.4%), but unsampled EIN/carcinoma cannot be entirely excluded

Descriptive diagnosis recommending repeat sampling in 3-6 months may be warranted

Persistent morular metaplasia on repeated samples is uncommon (4.5%) and typically does not progress to carcinoma



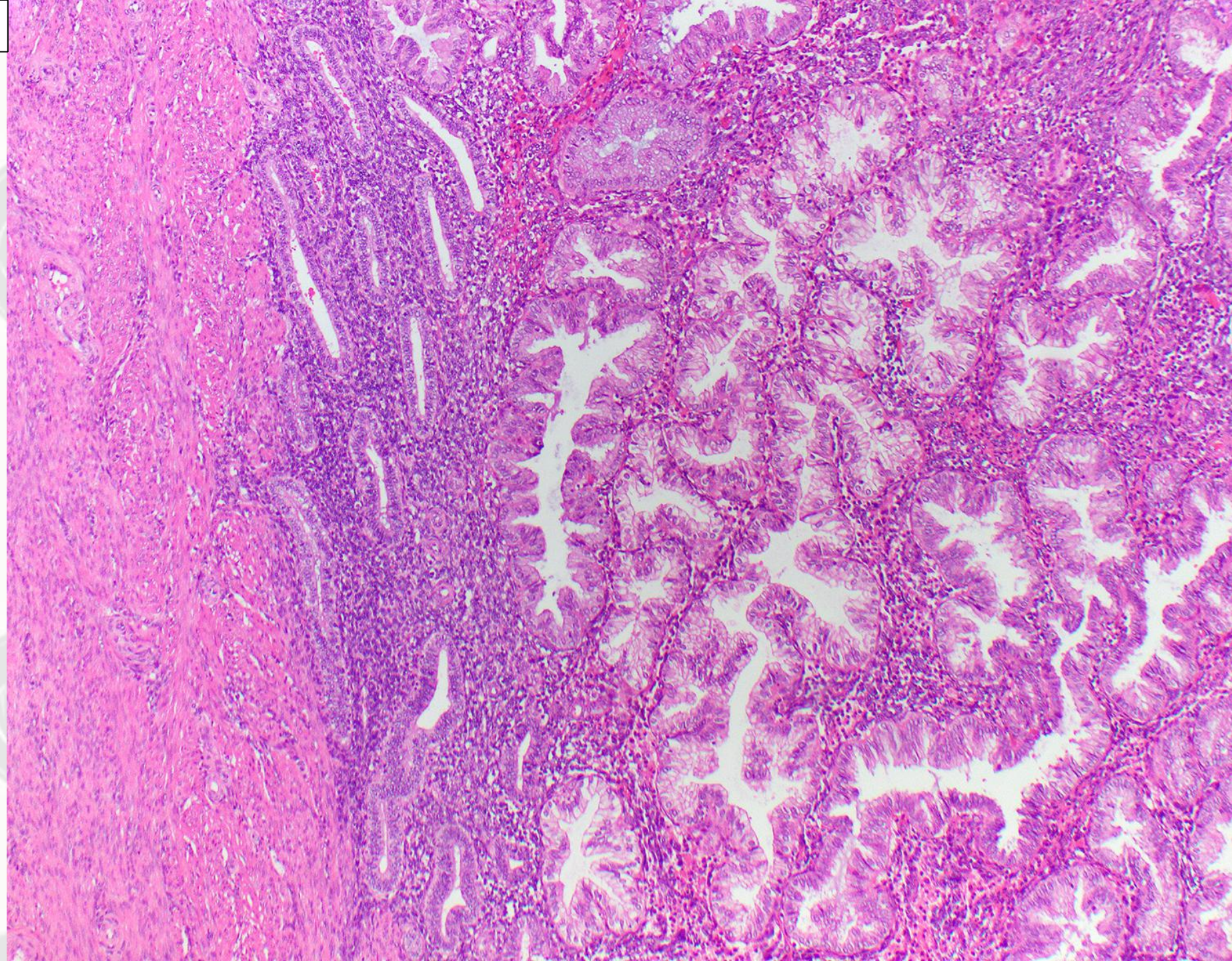


Mimics of EIN

Stratum basalis glands

Functionally inert

May generate false
appearance of
morphologic shift in
normal glands



Disordered Proliferative Endometrium

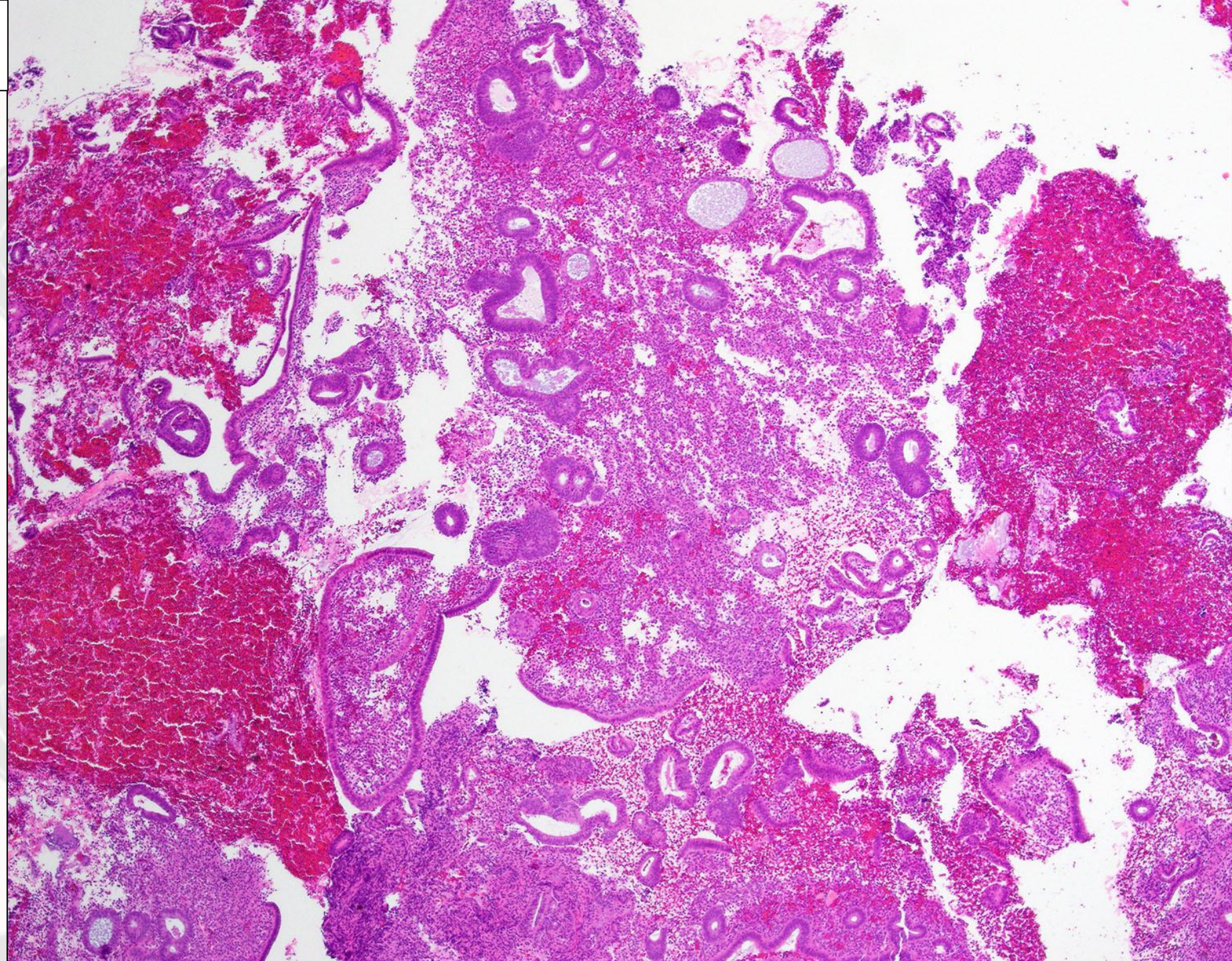
Often related to anovulatory cycles, most commonly in perimenopause

Irregular, often cystically dilated glands

Variable crowding falling short of hyperplasia diagnosis

No evidence of EIN

Tubal and eosinophilic metaplasias are common



Disordered Proliferative Endometrium

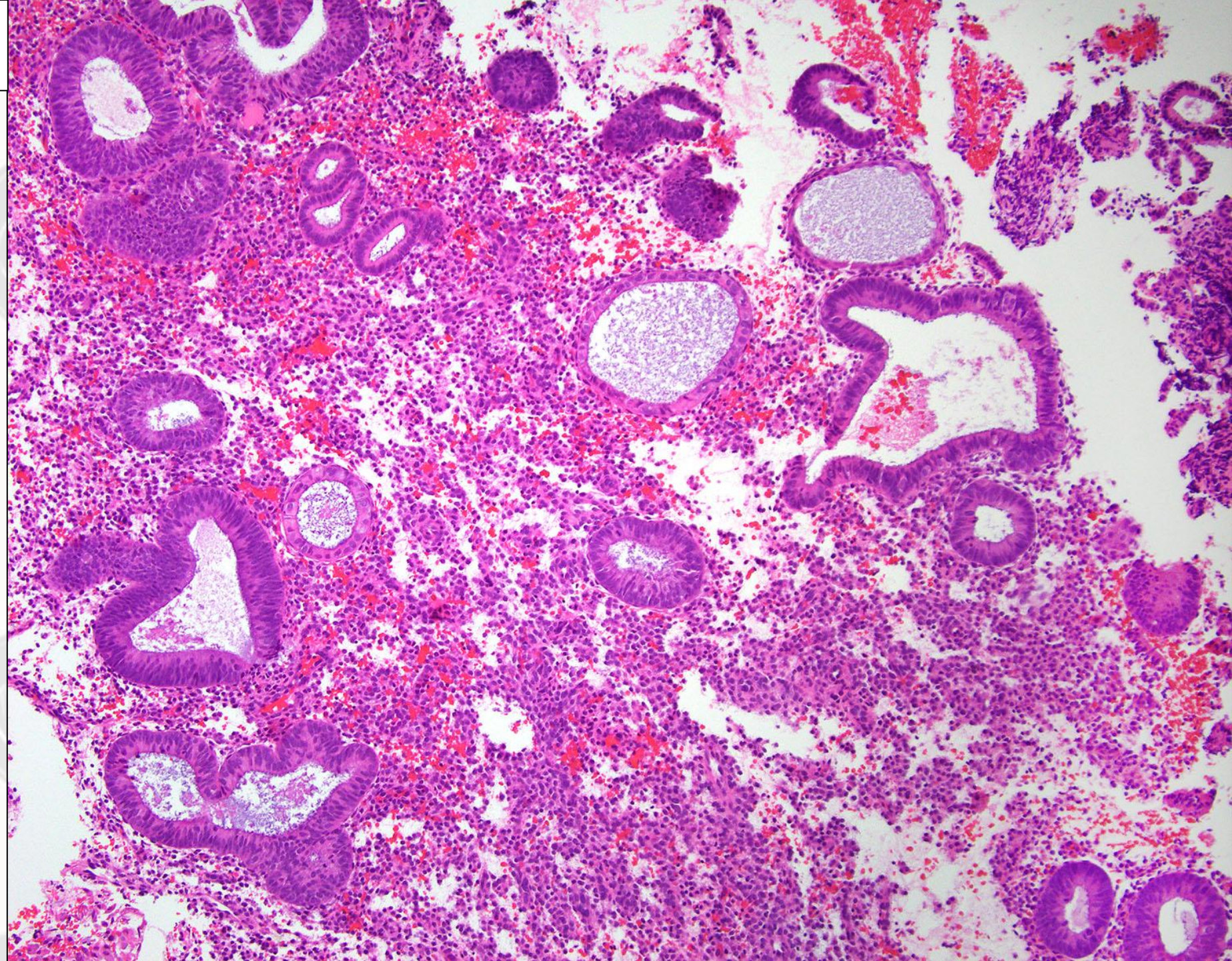
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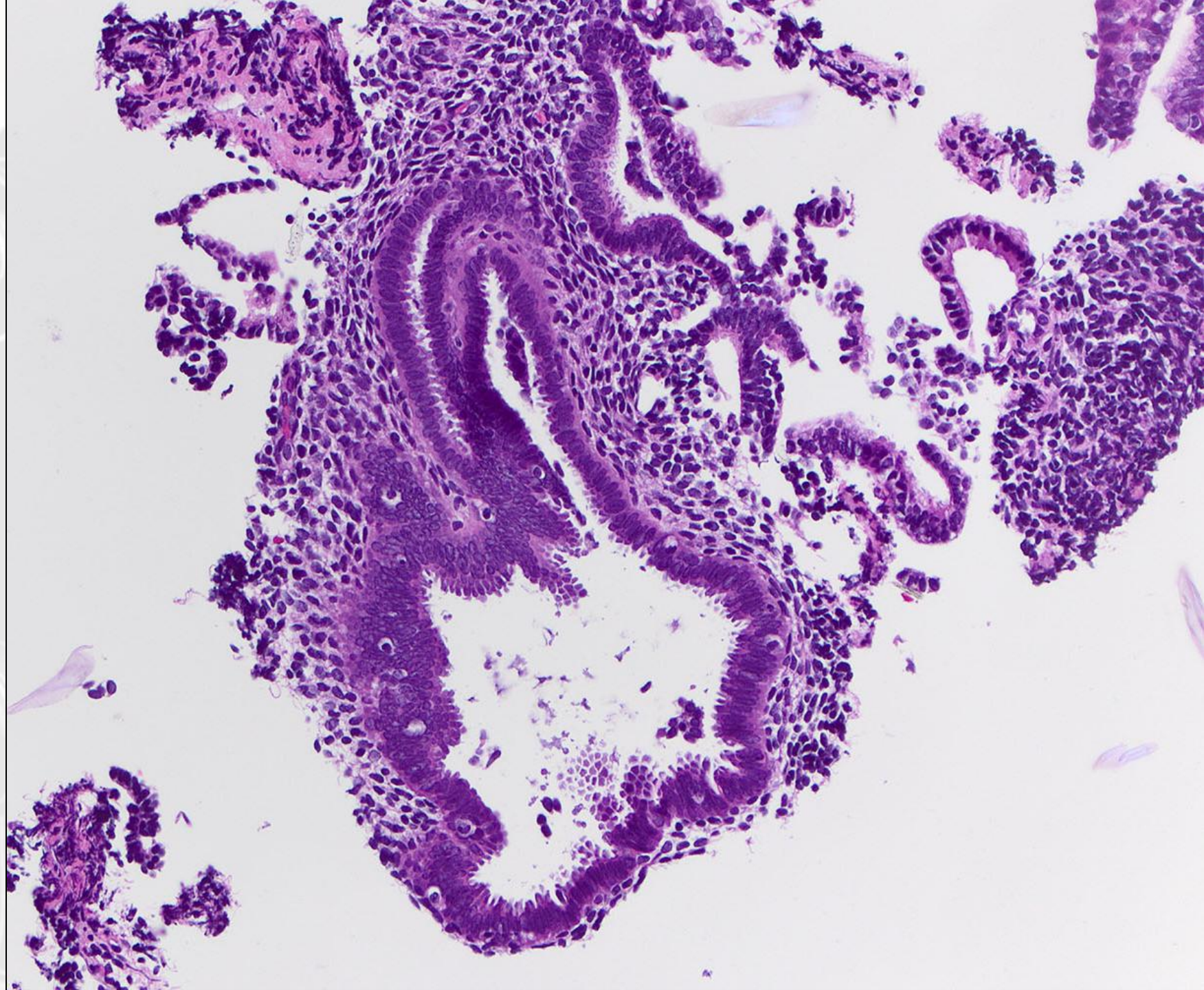
Tubal Metaplasia

Ciliated columnar cells reminiscent of fallopian tube

May be associated with mild architectural abnormalities such as intraluminal tufting

May generate appearance of cytologic shift

EIN and carcinomas may also undergo tubal metaplasia, so the presence of cilia alone is not synonymous with a benign diagnosis



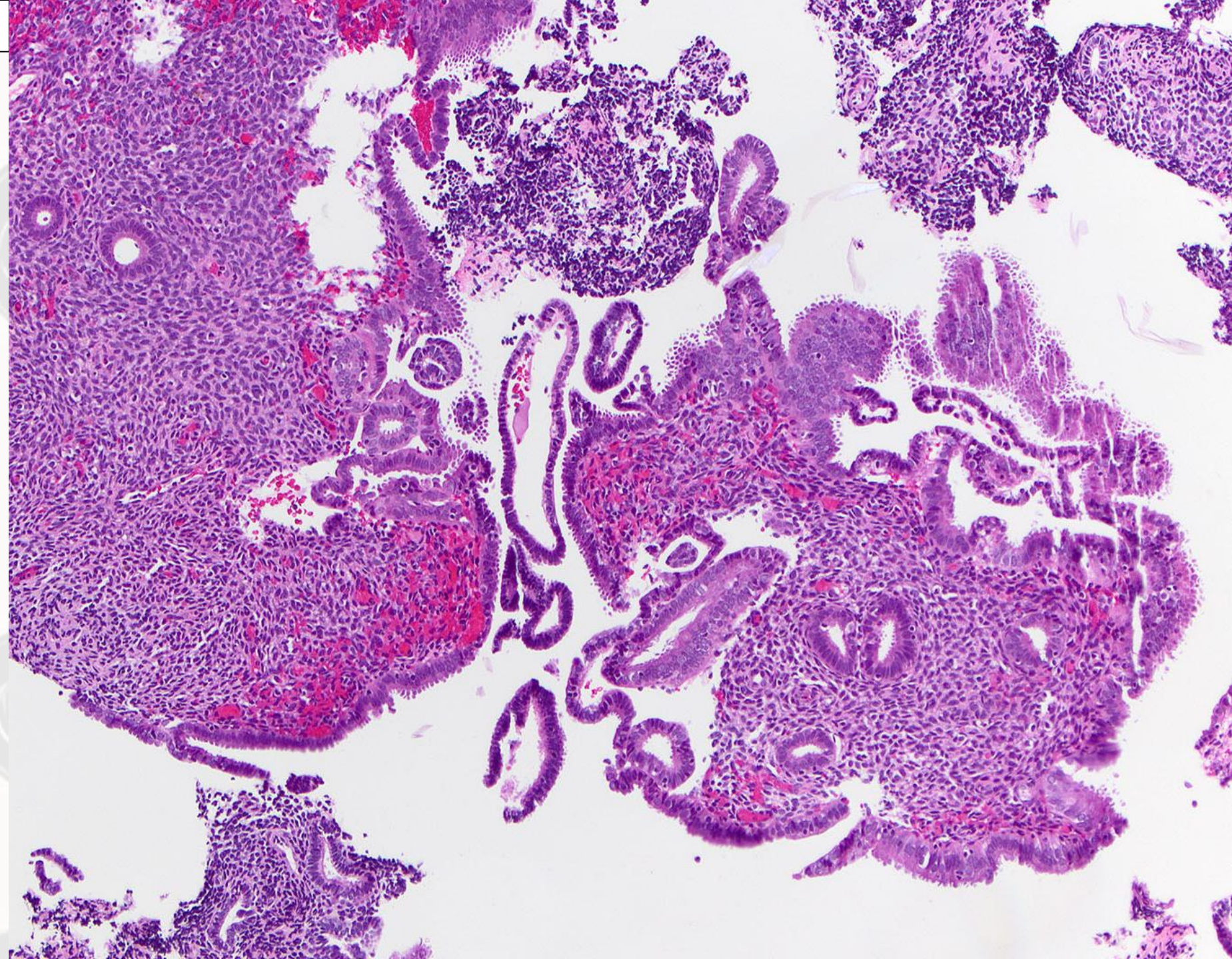
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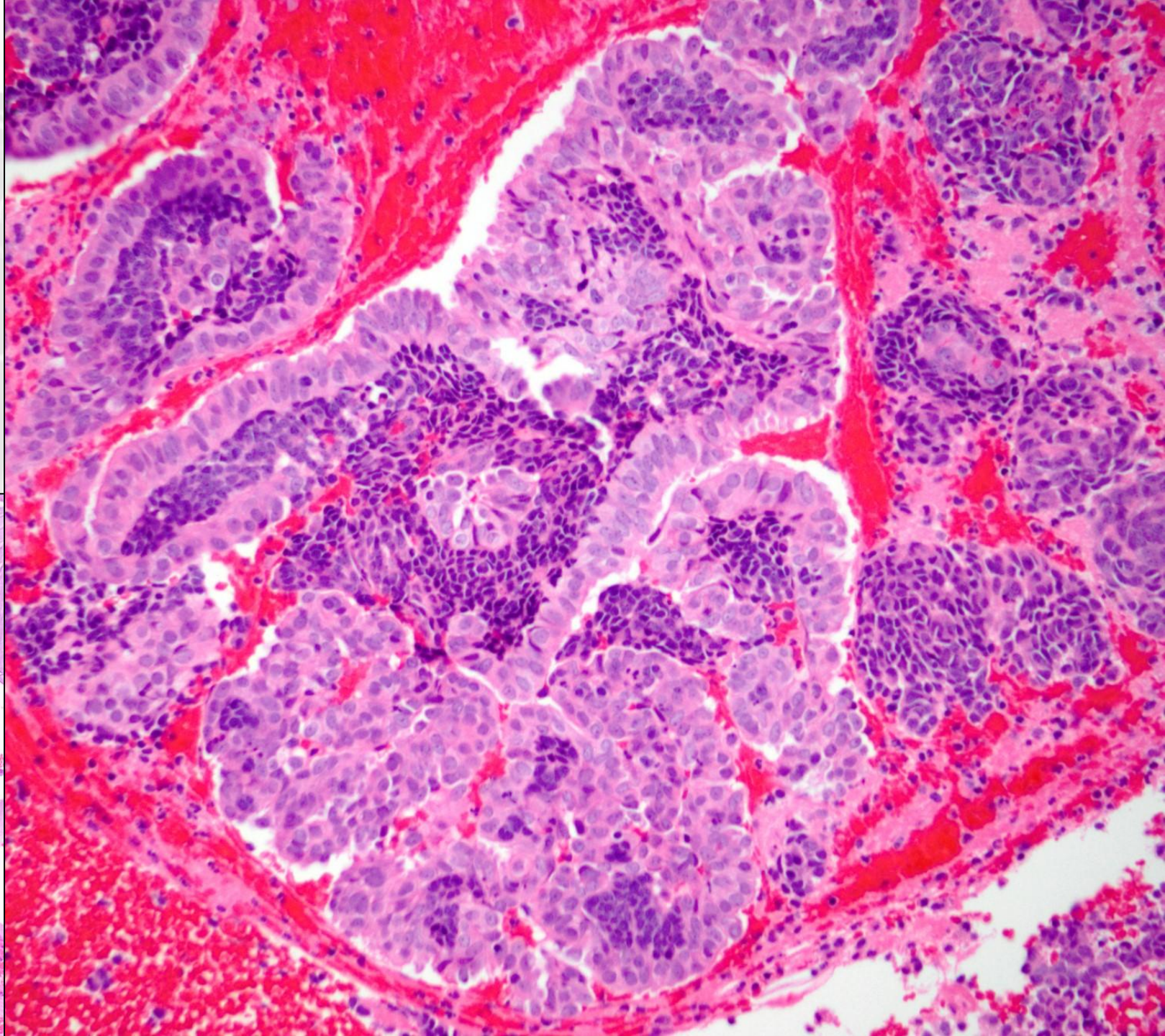
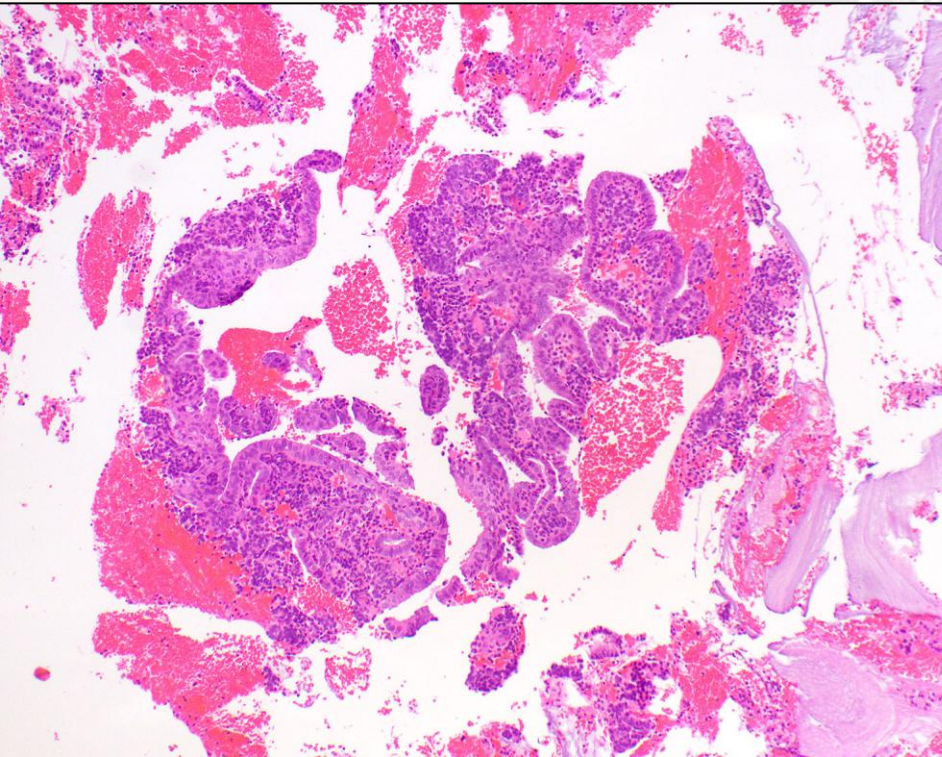
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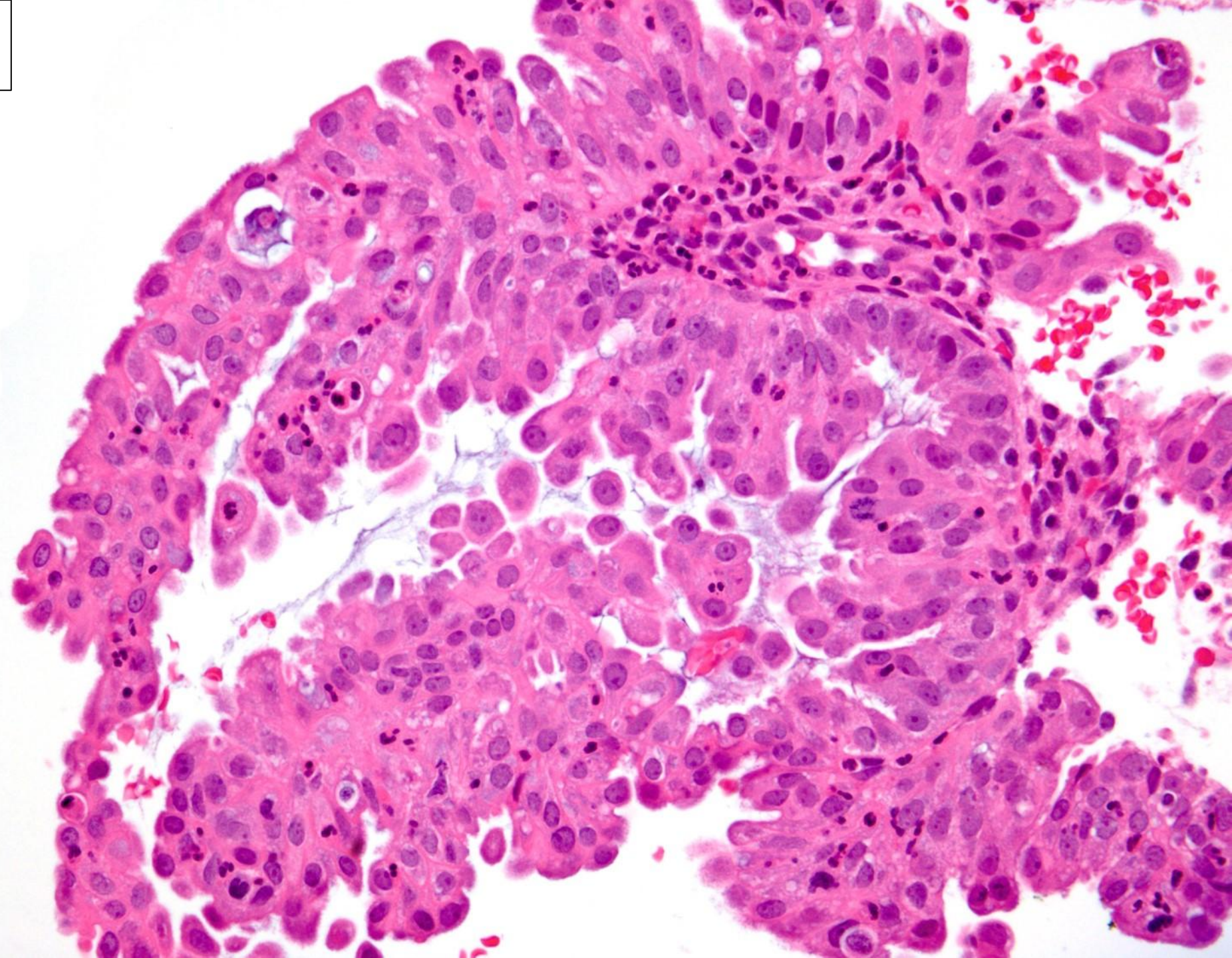
Changes Associated with Stromal Breakdown

Papillary syncytial metaplasia may mimic neoplasia

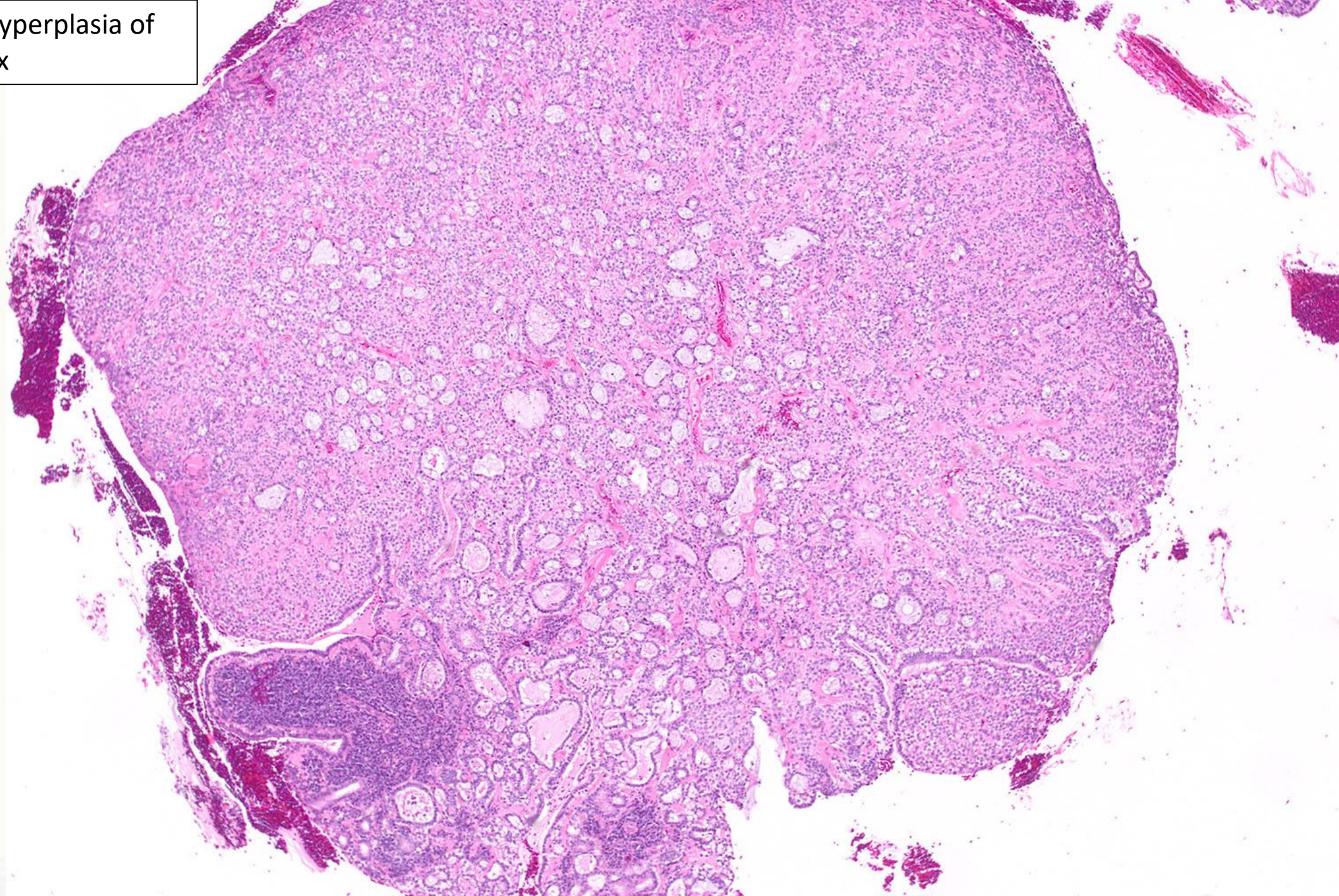
Cannot assess gland crowding without intact stroma



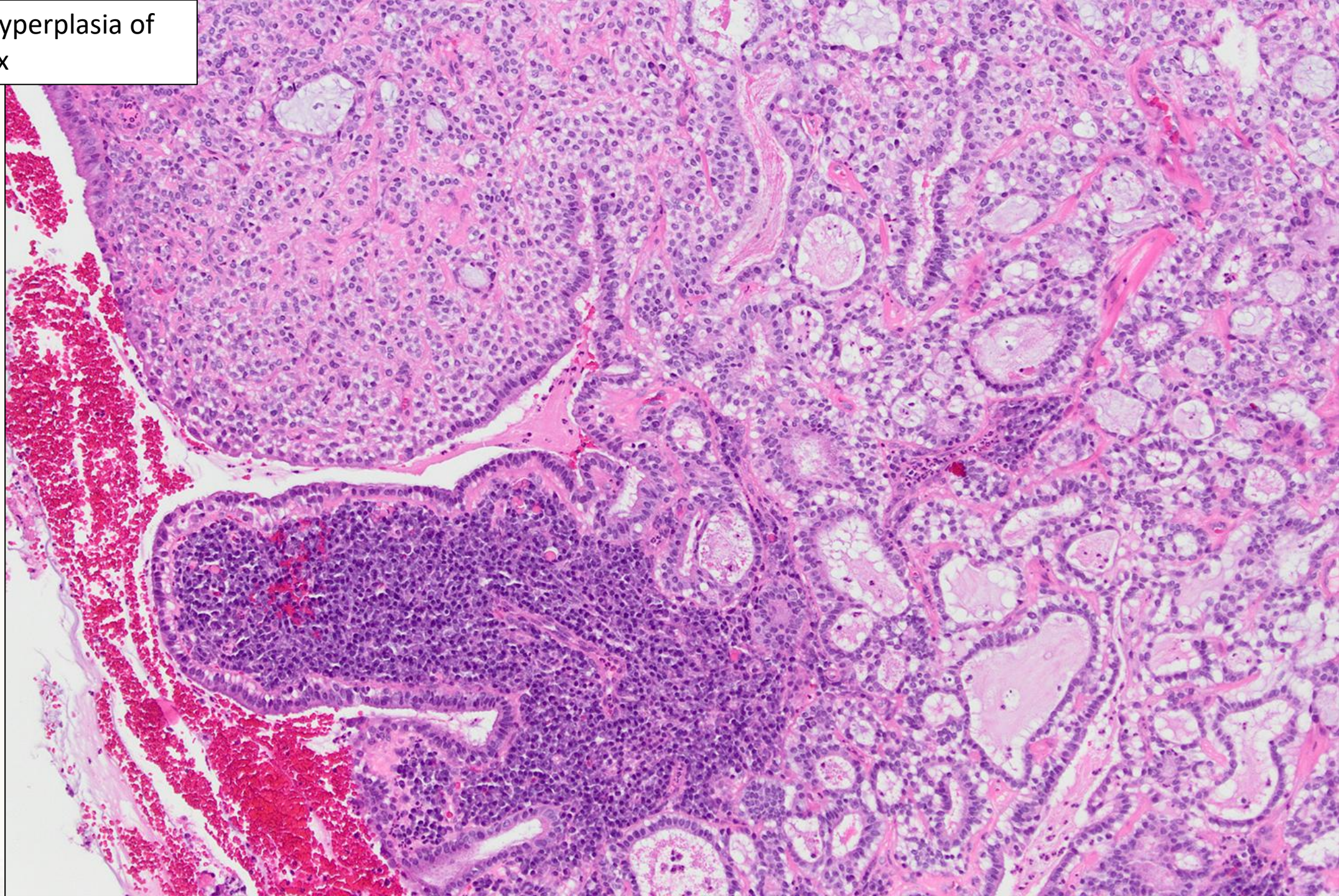
Carcinoma Mimicking Syncytial
Metaplasia



Microglandular Hyperplasia of
Cervix



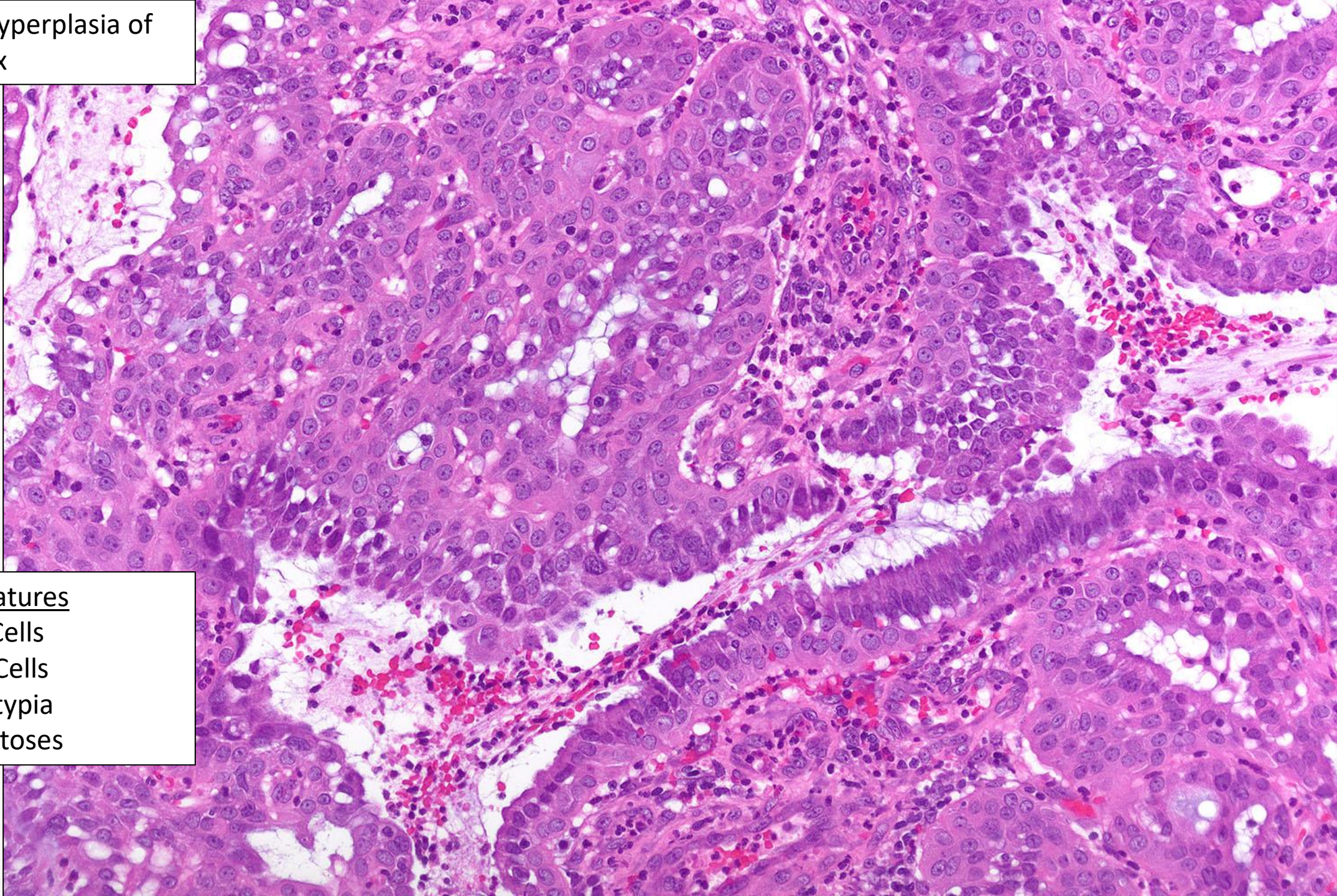
Microglandular Hyperplasia of
Cervix



Microglandular Hyperplasia of Cervix

Helpful Features

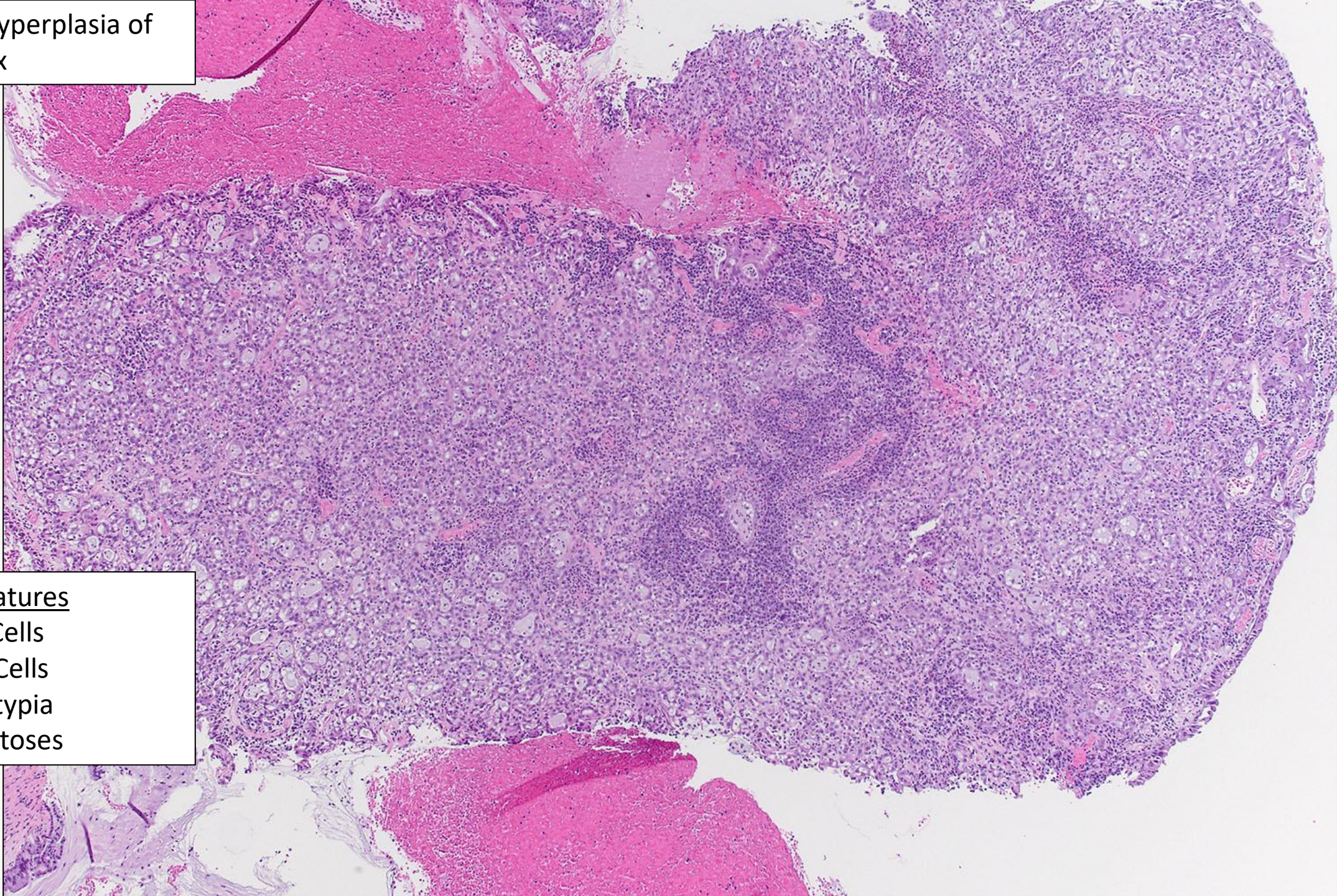
- Plasma Cells
- Reserve Cells
- Lack of Atypia
- Lack of Mitoses



Microglandular Hyperplasia of Cervix

Helpful Features

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- Reserve Cells
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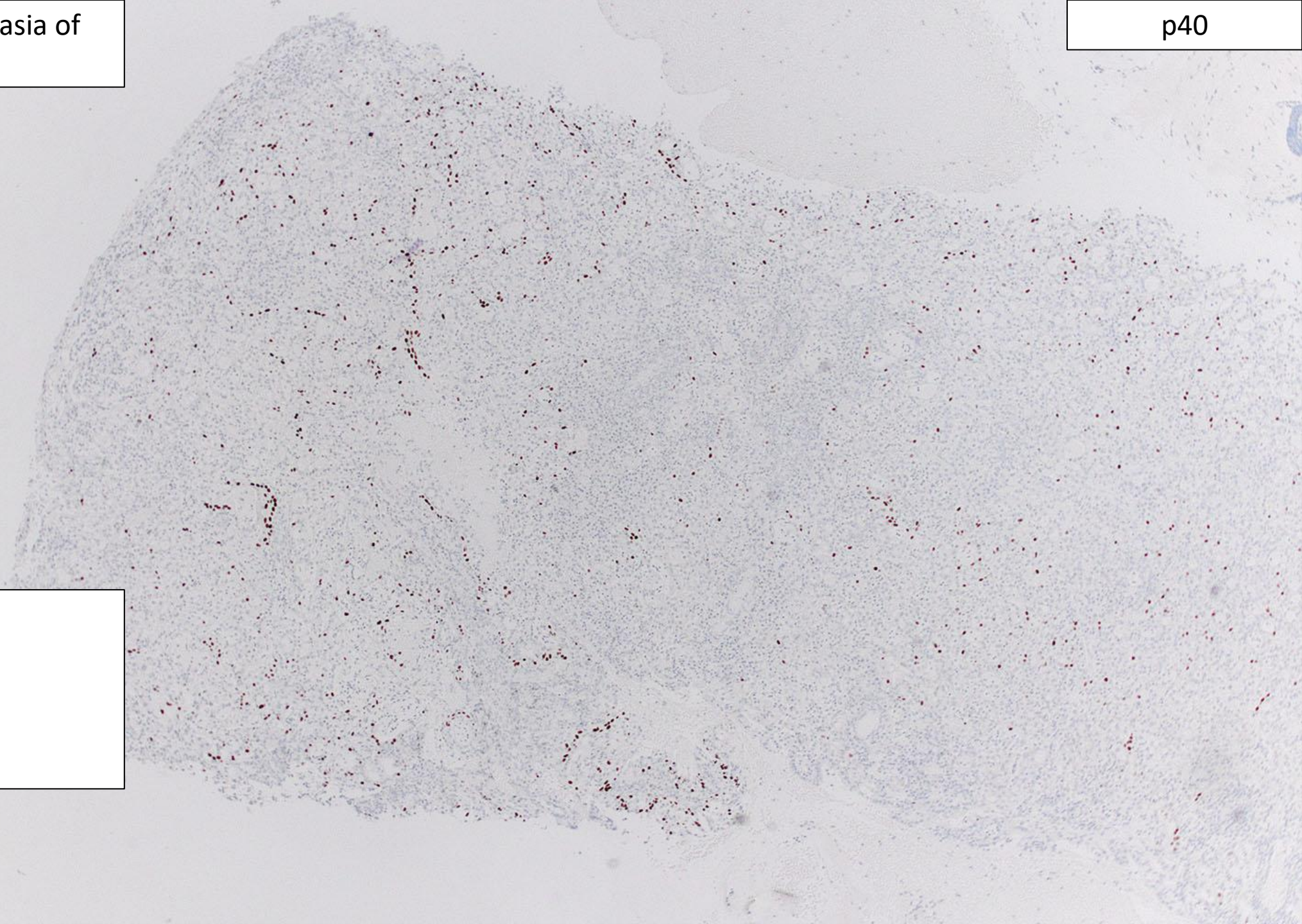


Microglandular Hyperplasia of Cervix

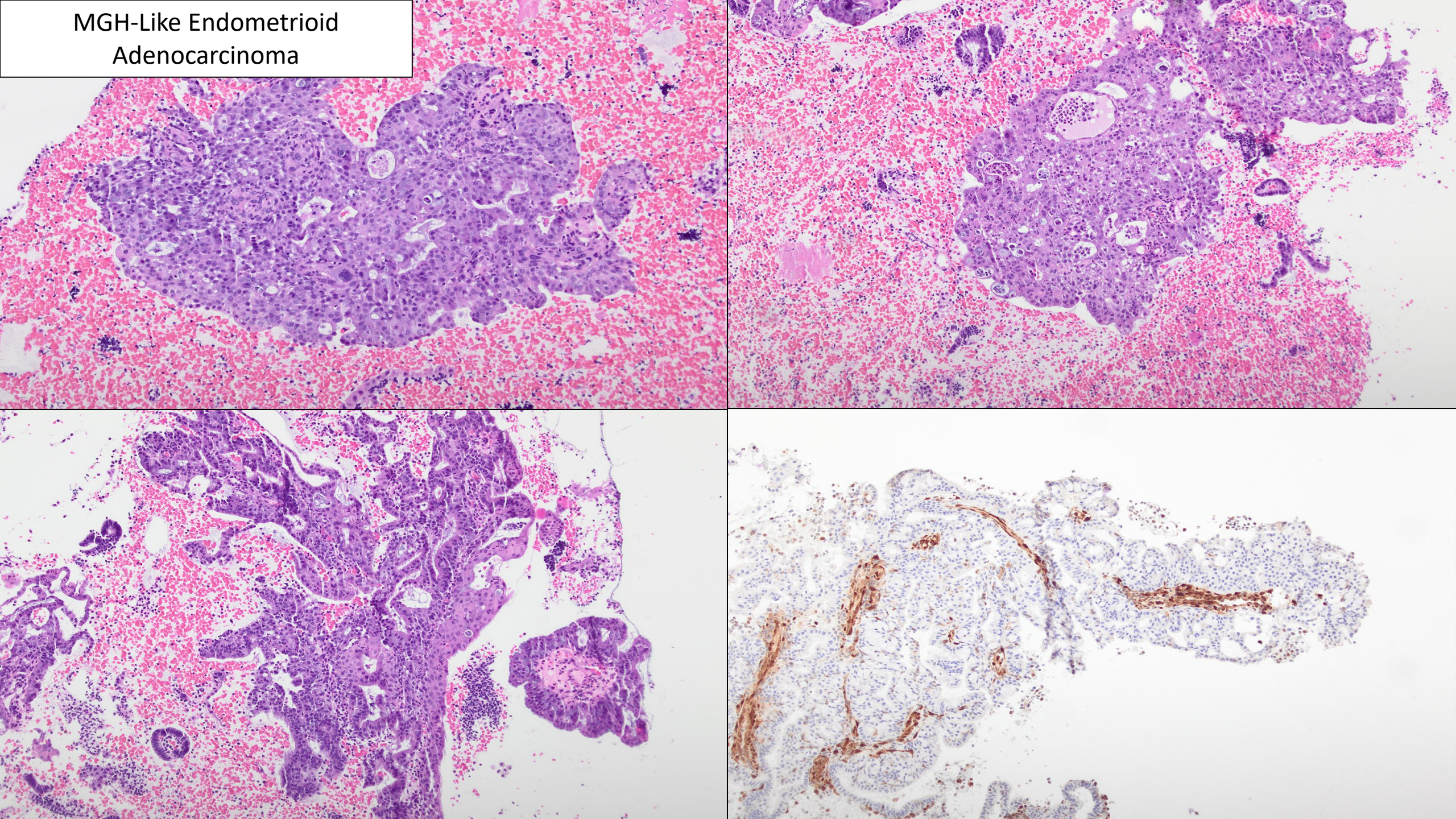
p40

Helpful Features

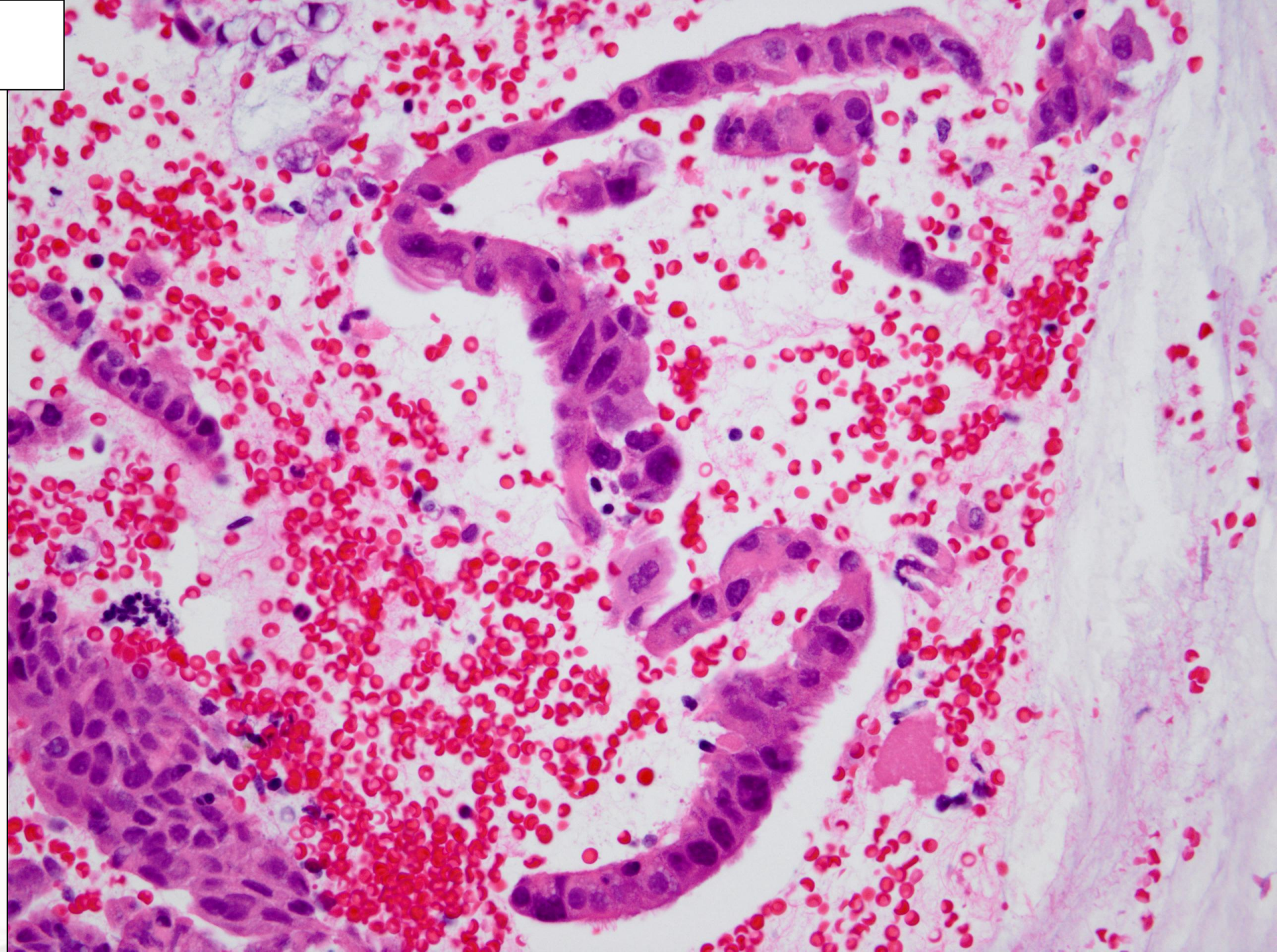
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- Reserve Cells
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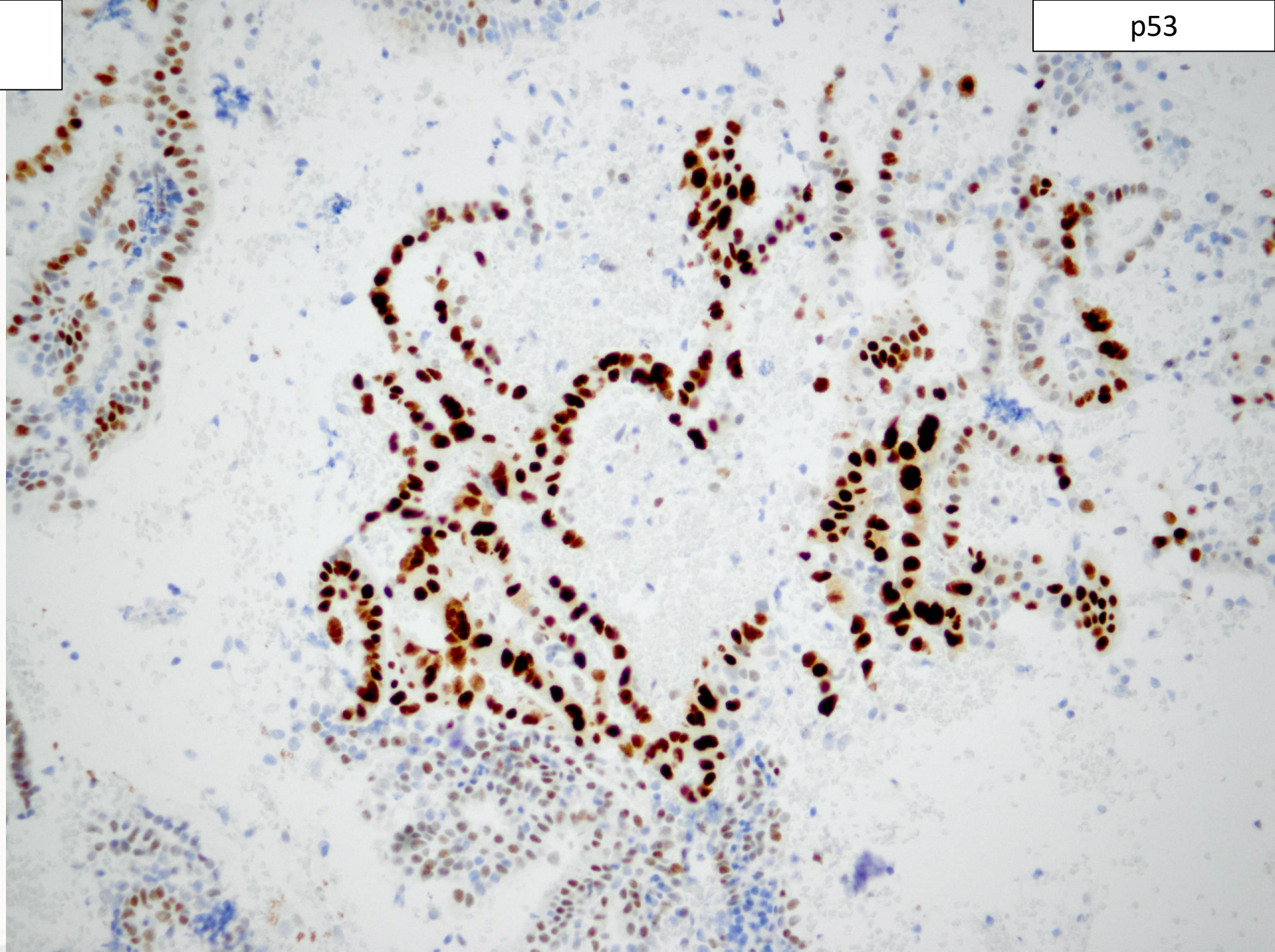


MGH-Like Endometrioid
Adenocarcinoma



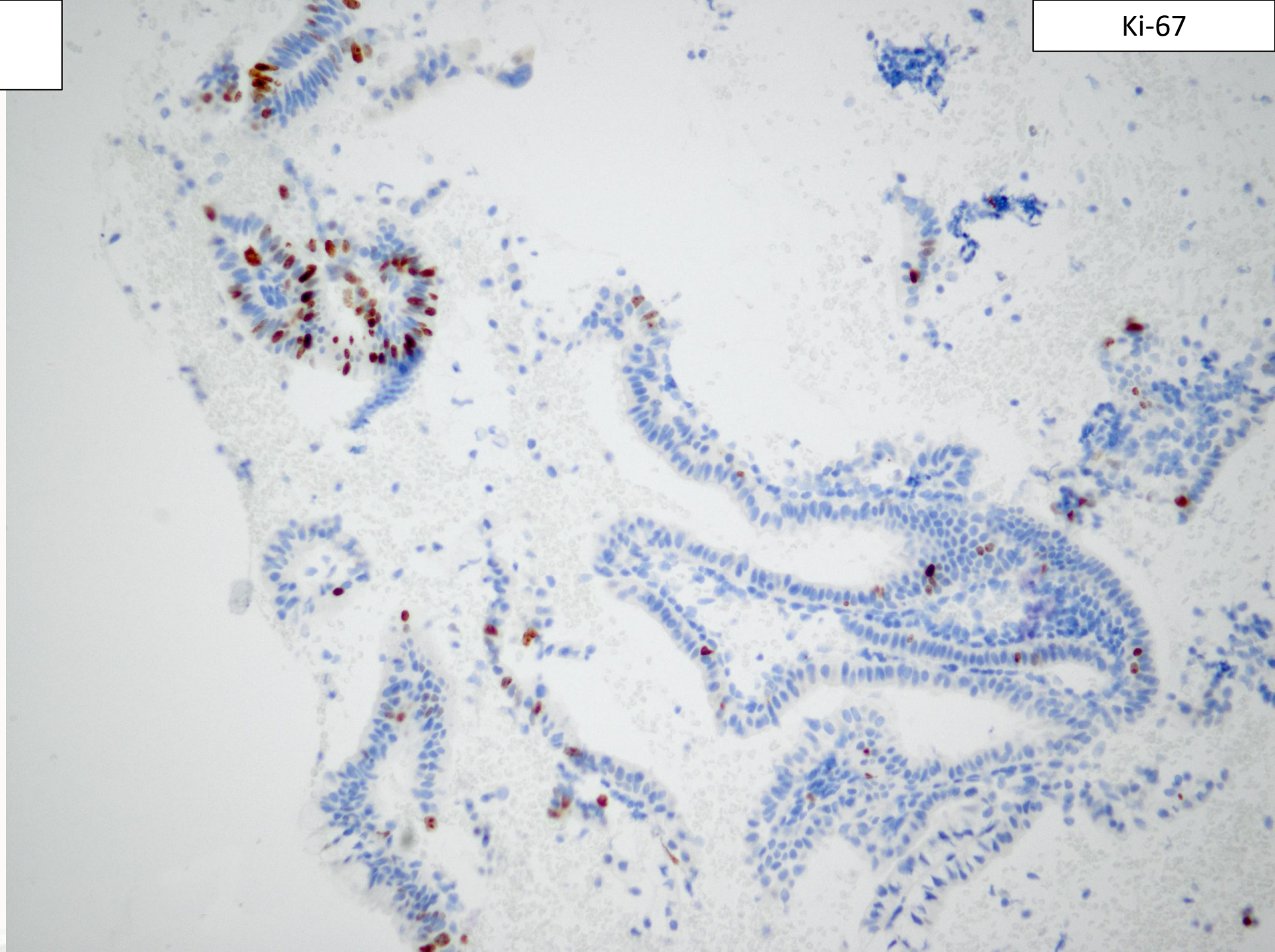
Epithelial Atypia – Atrophic
Endometrium



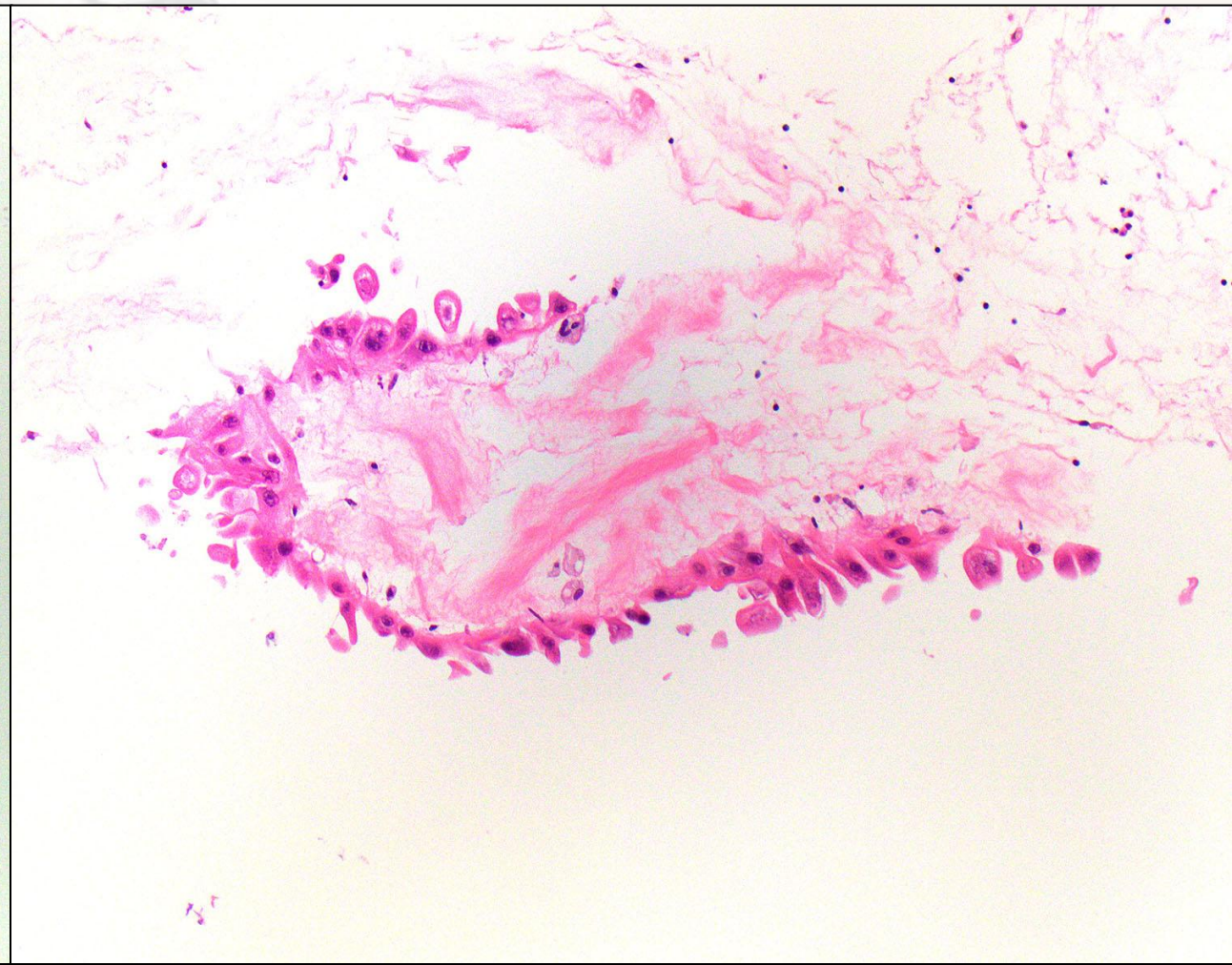
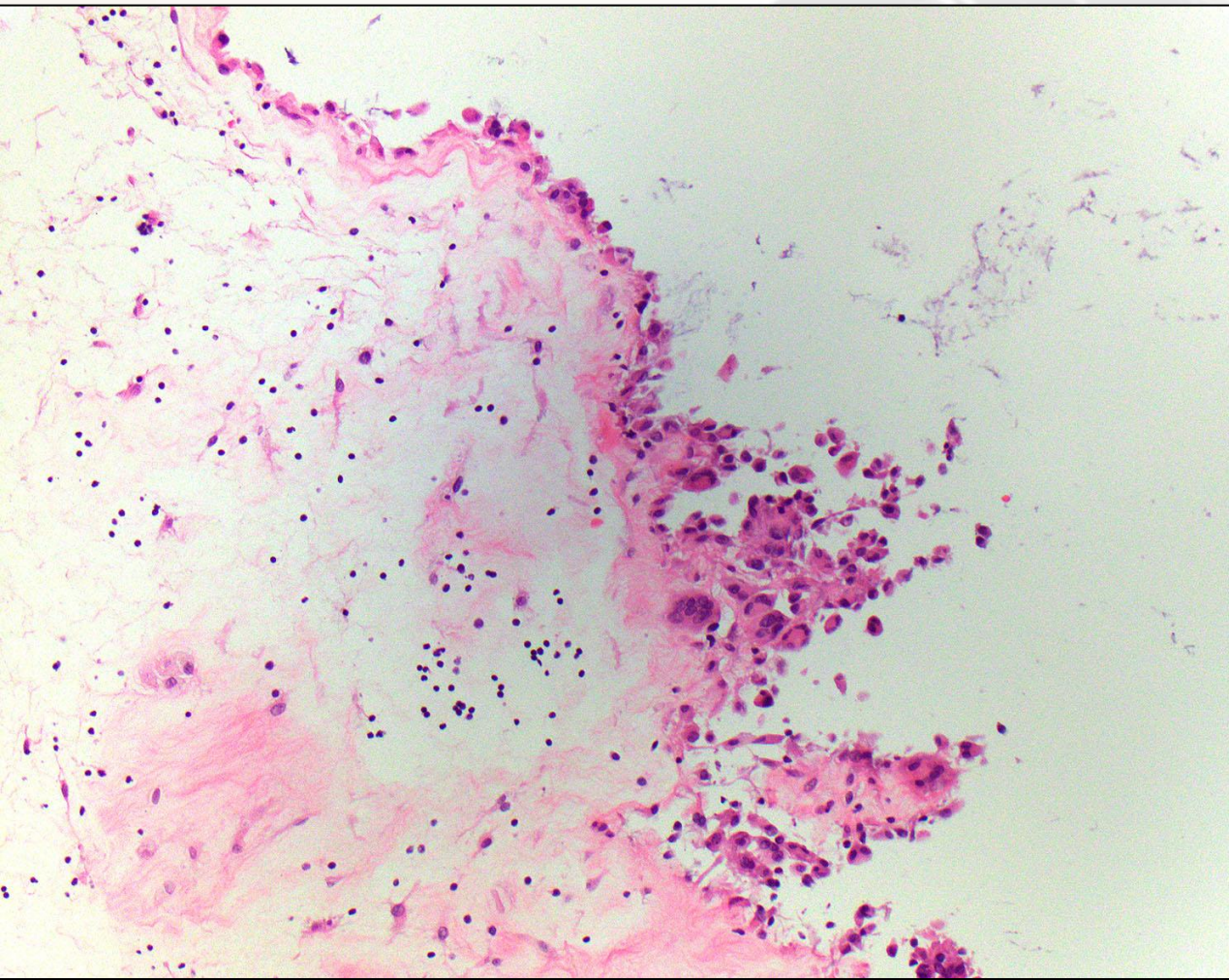


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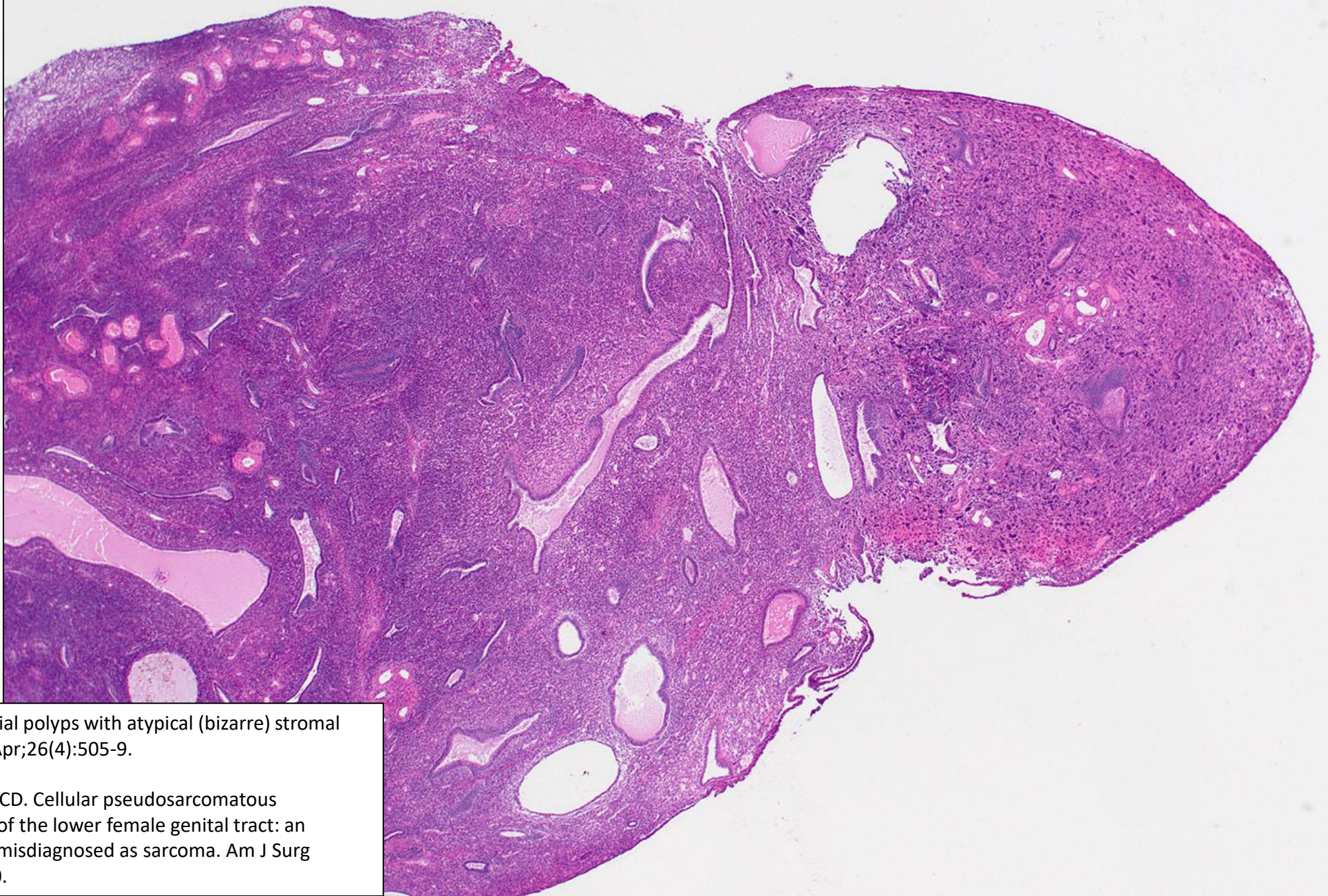
Ki-67



Epithelial Atypia - Infarcted Polyp



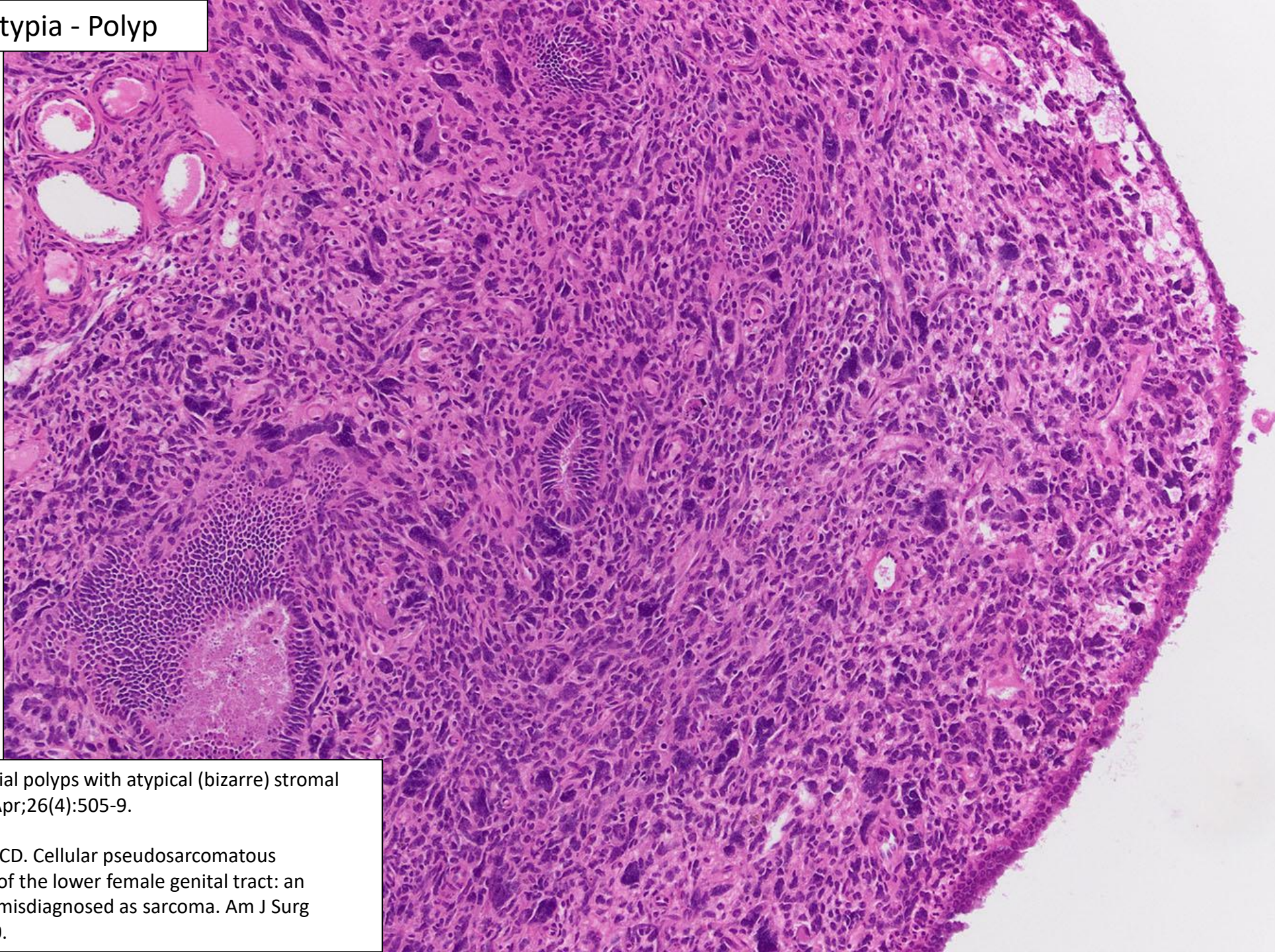
Bizarre Stromal Atypia - Polyp



Tai LH, Tavassoli FA. Endometrial polyps with atypical (bizarre) stromal cells. *Am J Surg Pathol*. 2002 Apr;26(4):505-9.

Nucci MR, Young RH, Fletcher CD. Cellular pseudosarcomatous fibroepithelial stromal polyps of the lower female genital tract: an underrecognized lesion often misdiagnosed as sarcoma. *Am J Surg Pathol*. 2000 Feb;24(2):231-40.

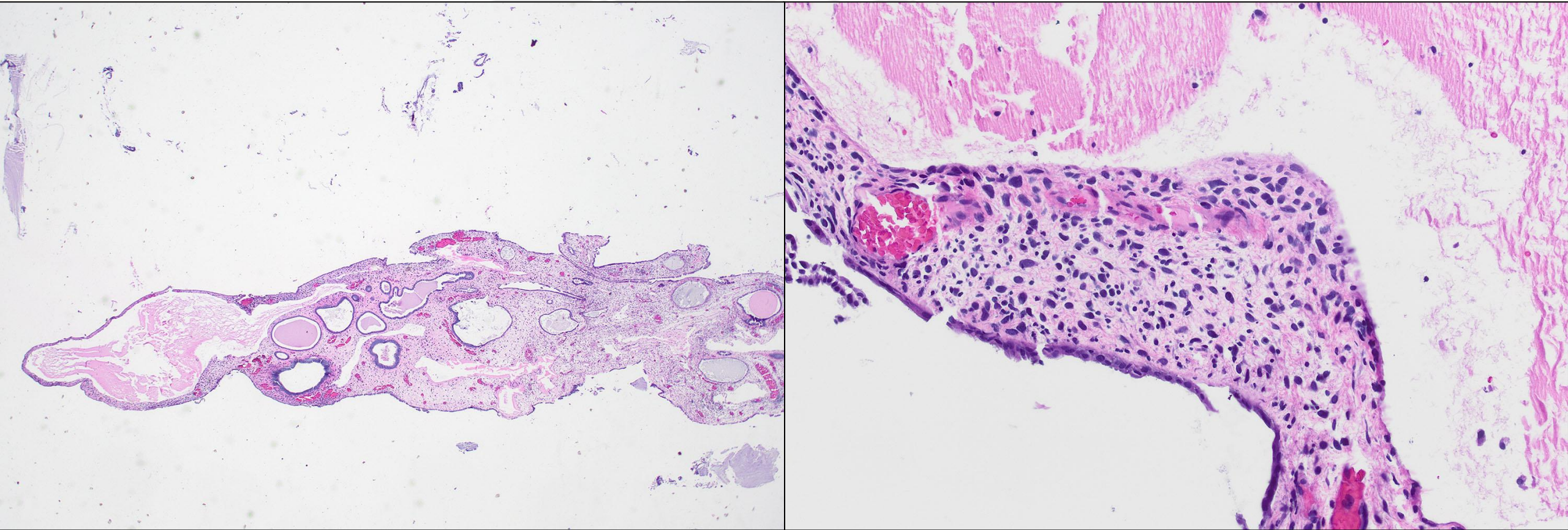
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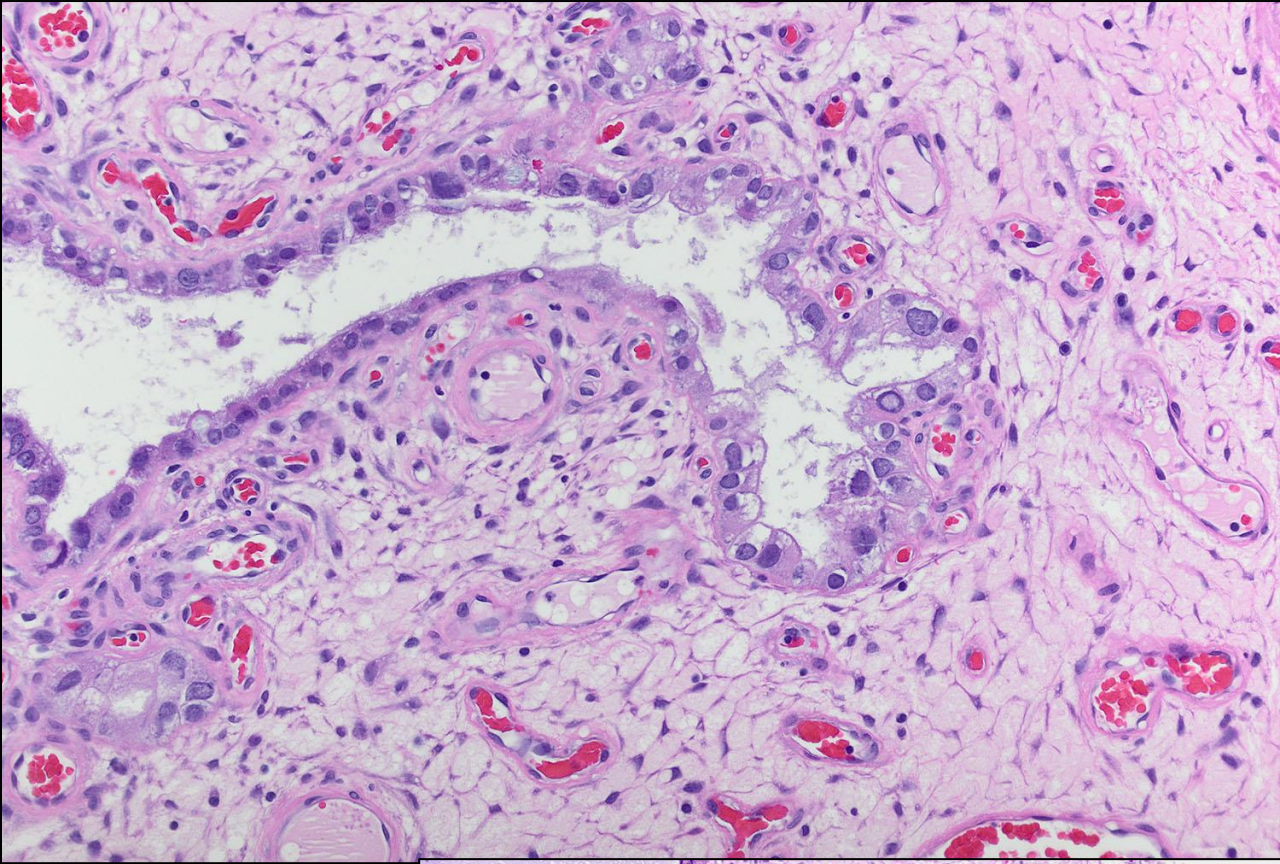
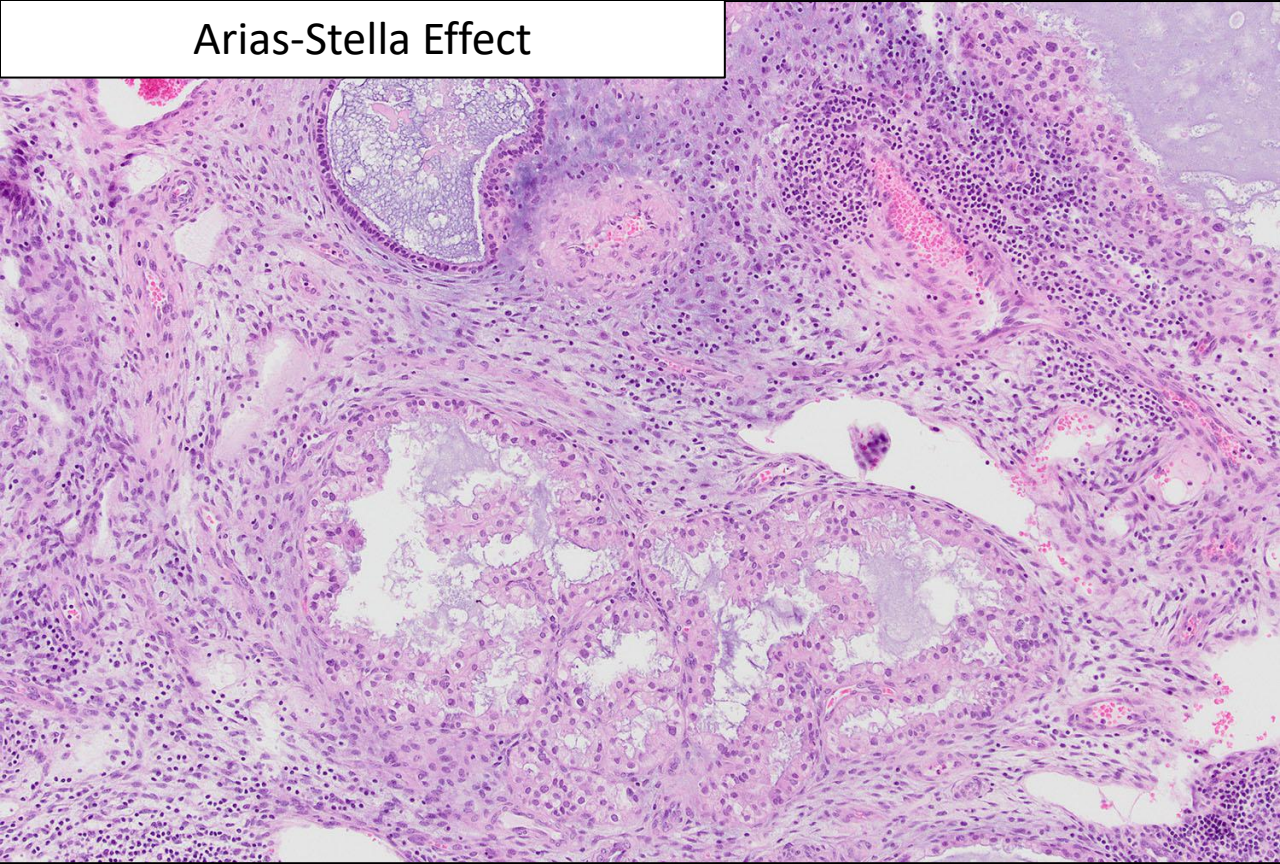
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Arias-Stella Effect



Clear to eosinophilic cytoplasm

Hobnail appearance

Bizarre nuclear atypia

Usually lack mitoses

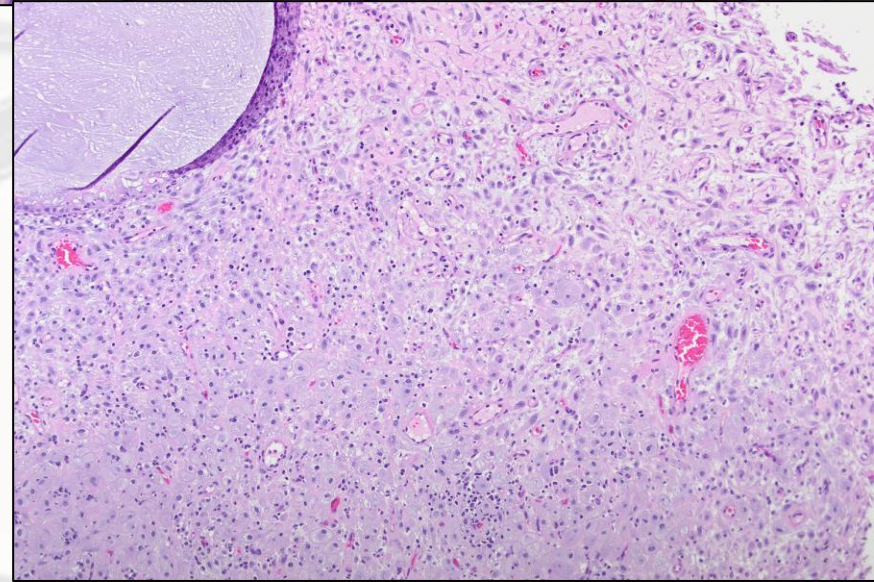
N:C ratio not elevated

Classically occurs in GYN tract of pregnant patients

May occur in patients on hormonal therapy
– even post menopause

Partial gland involvement helpful if present

Lack of infiltrative pattern

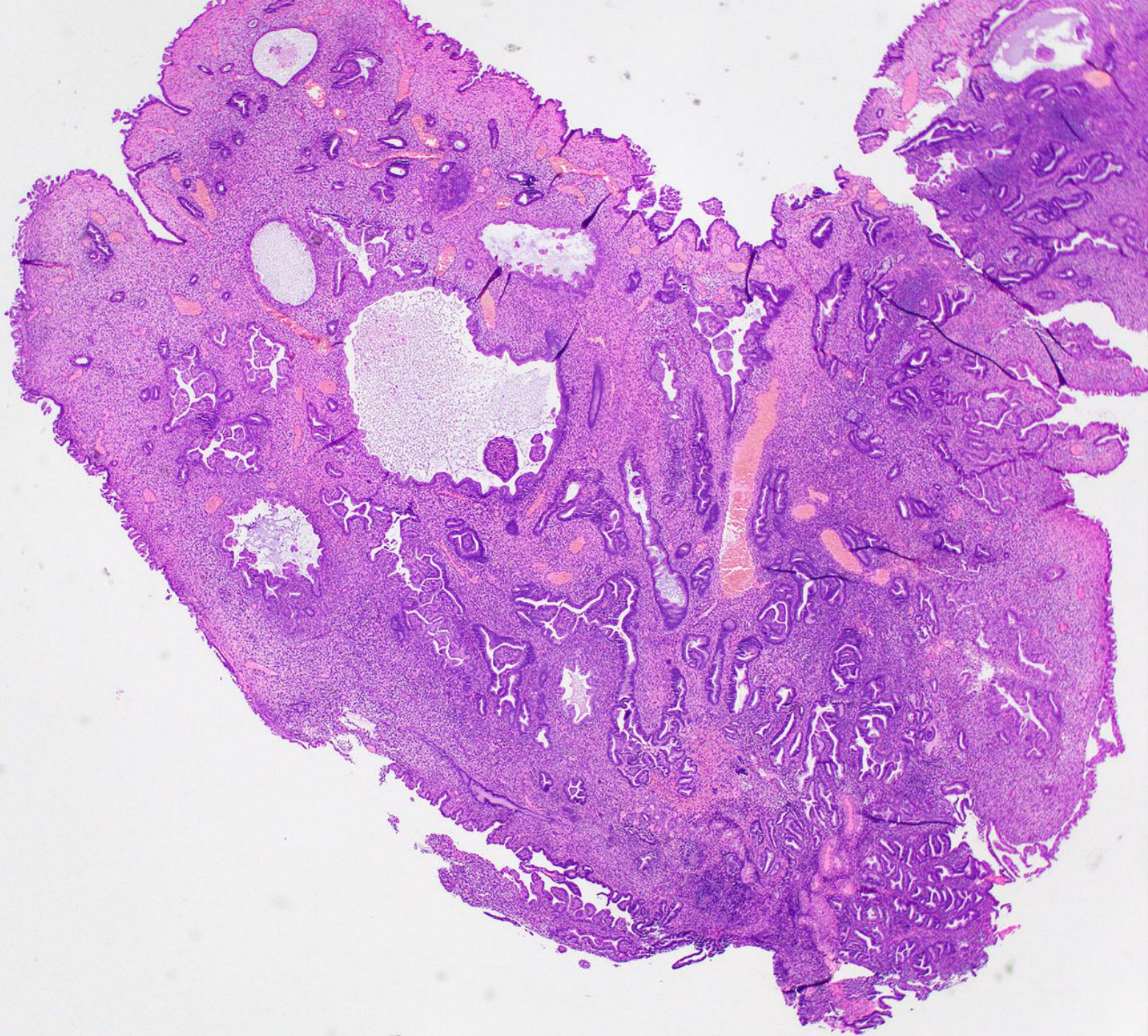


Papillary Proliferation of the Endometrium

Bland limited intraglandular
papillary projections

Frequent mucinous metaplasia

Often involve endometrial polyp



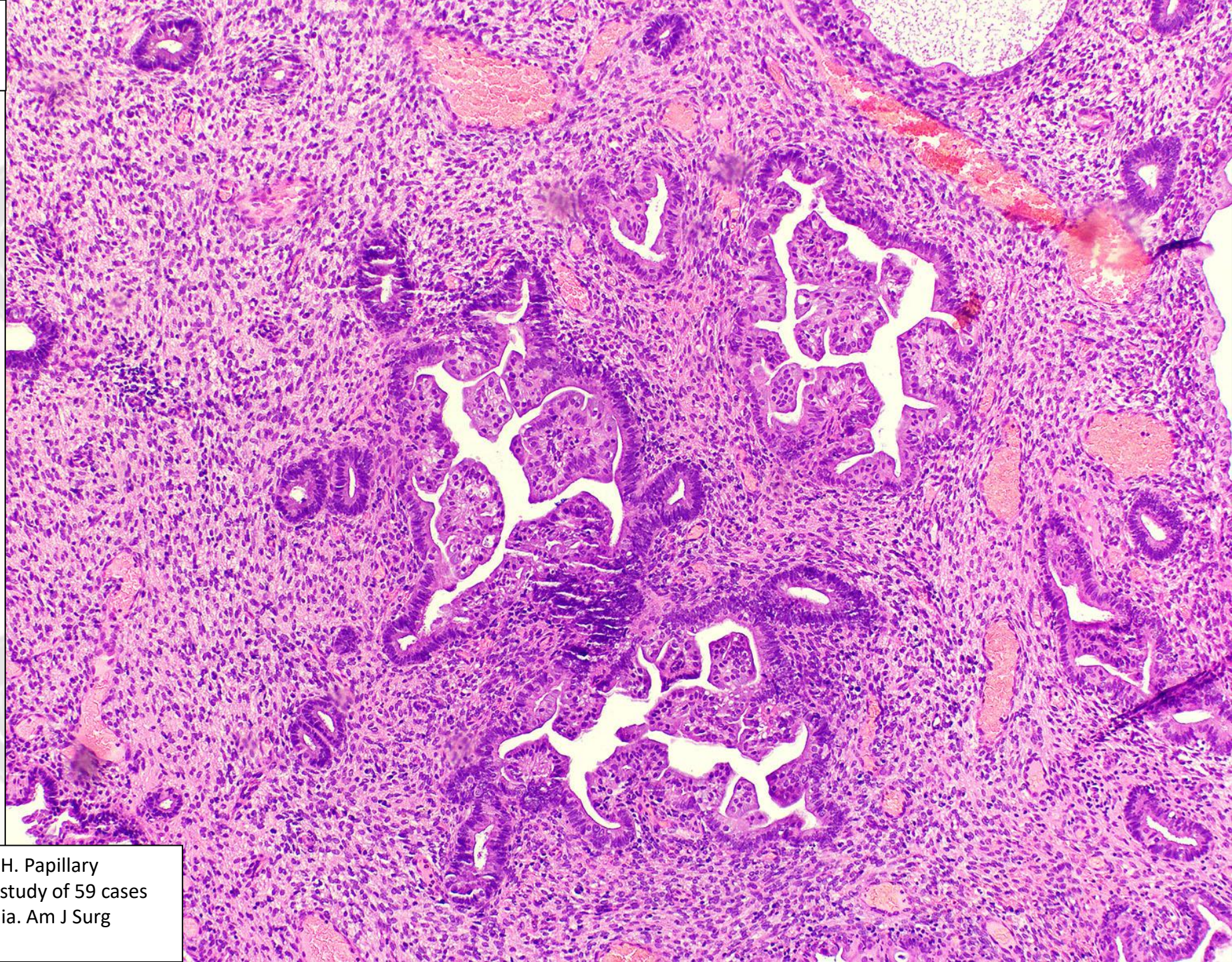
Ip PP, Irving JA, McCluggage WG, Clement PB, Young RH. Papillary proliferation of the endometrium: a clinicopathologic study of 59 cases of simple and complex papillae without cytologic atypia. Am J Surg Pathol. 2013 Feb;37(2):167-77.

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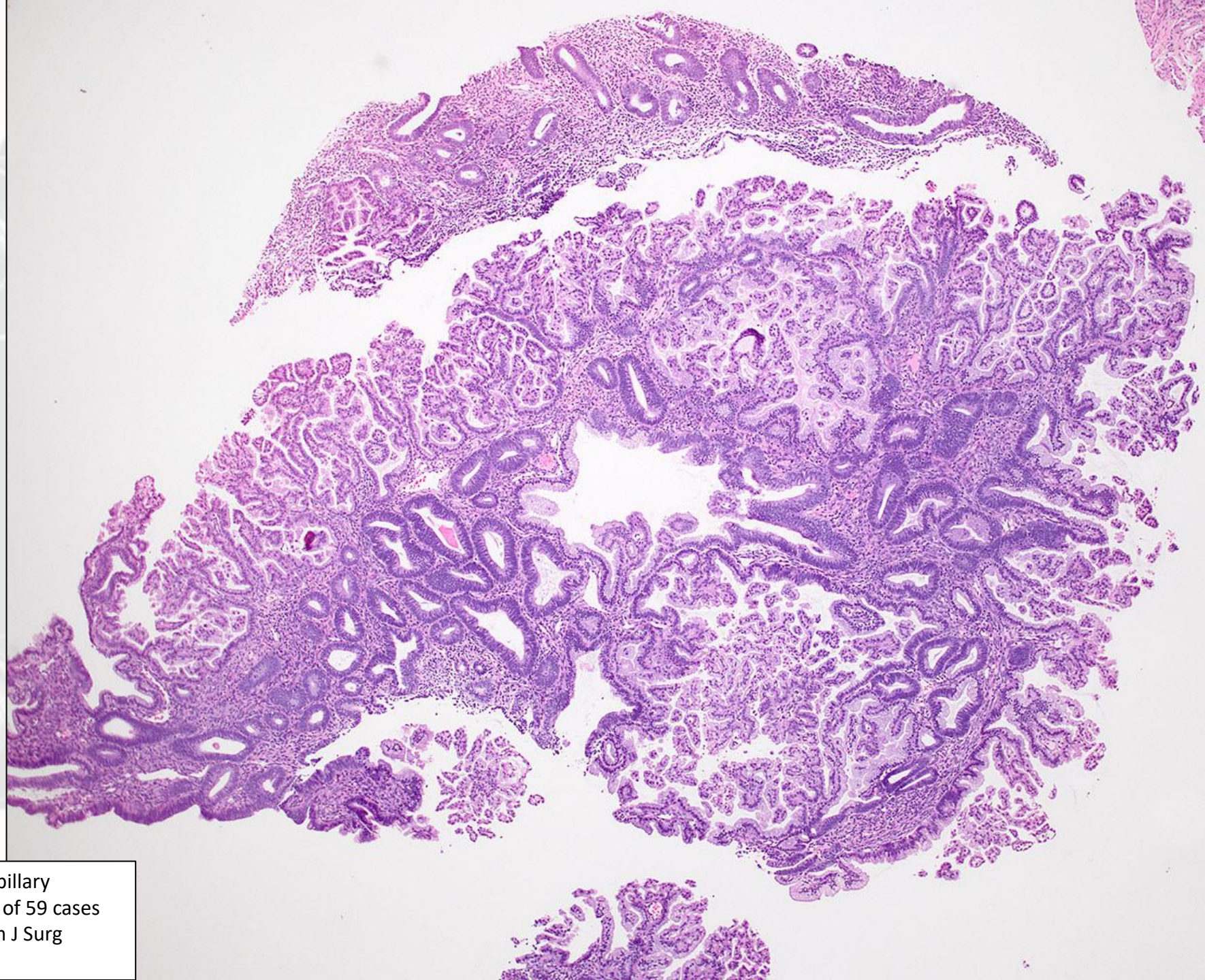
If limited and confined to polyp –
often no recurrence/progression

More complex/extensive
proliferations may be associated with
conventional EIN or carcinoma

Concurrent or subsequent
EIN/carcinoma in ~25% overall

Frequent *KRAS* alterations

Should be treated as an endometrioid
precursor similar to EIN



Papillary Proliferation of the Endometrium

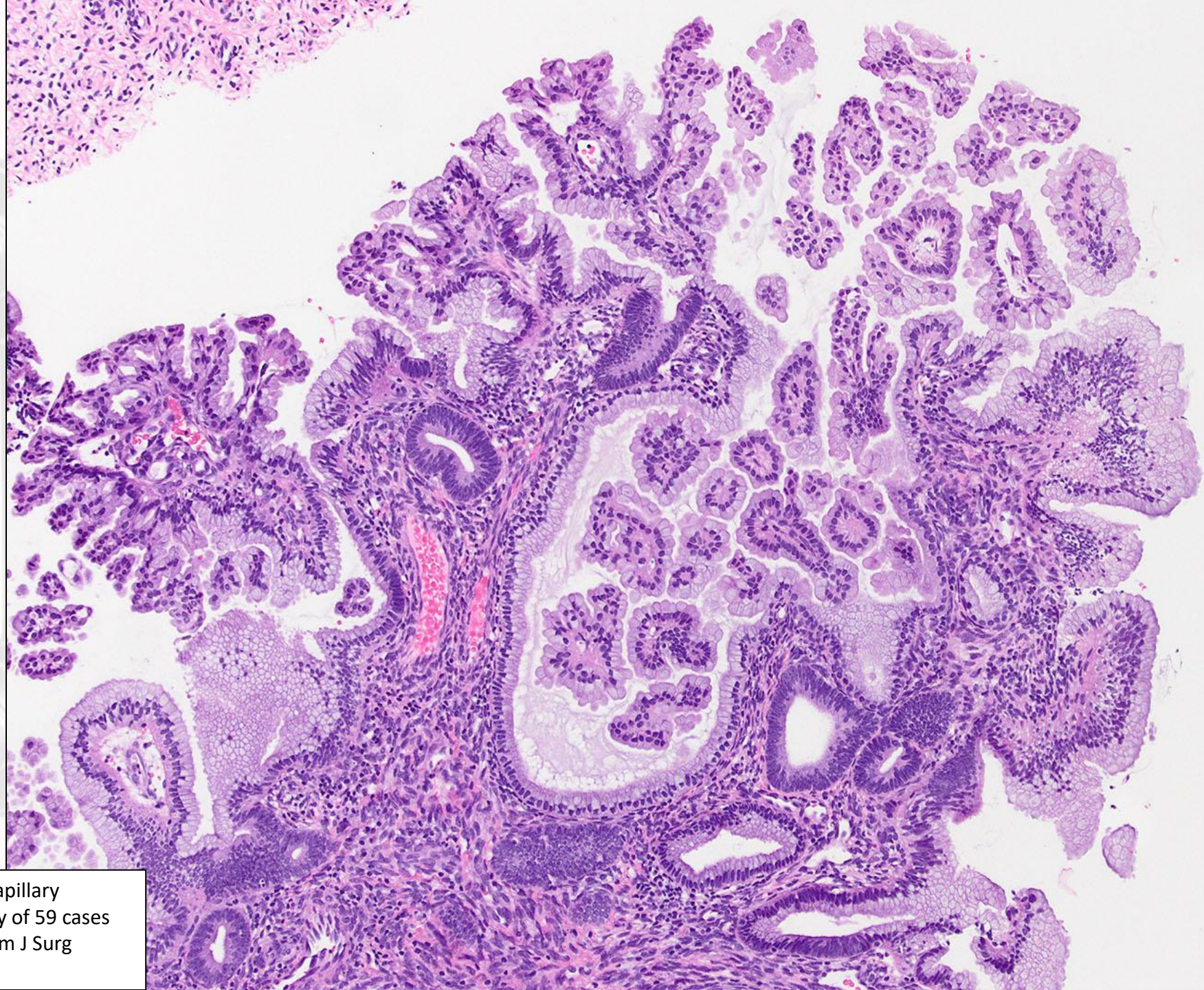
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Summary

- EIN/AH should be diagnosed based on morphologic features
 - Outcomes studies based on morphology
 - IHC may be useful in select settings
- Numerous morphologic mimics of EIN/AH
- Consider deeper levels, request repeat sampling if definitive diagnosis cannot be reached