

Endometrial metaplasias

and changes

FF Nogales

Temporal changes of the endometrium

Active changes
First 2 weeks

Inactive
prepuberal

Cyclic
Fertil life

Inactive/atrophic
Postmenopause

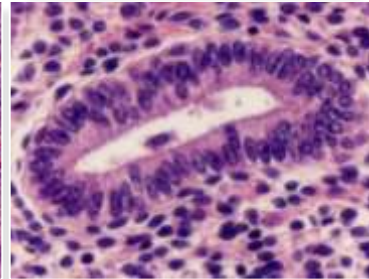
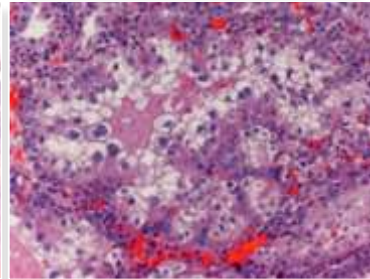
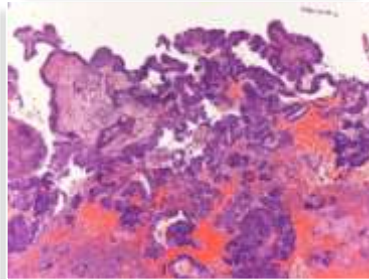
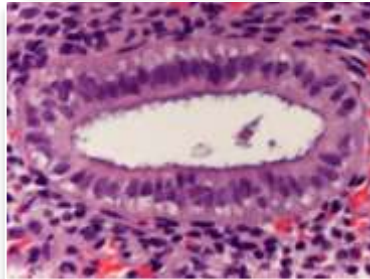
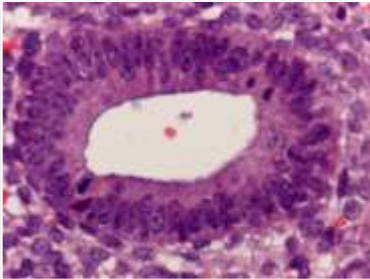
Proliferative

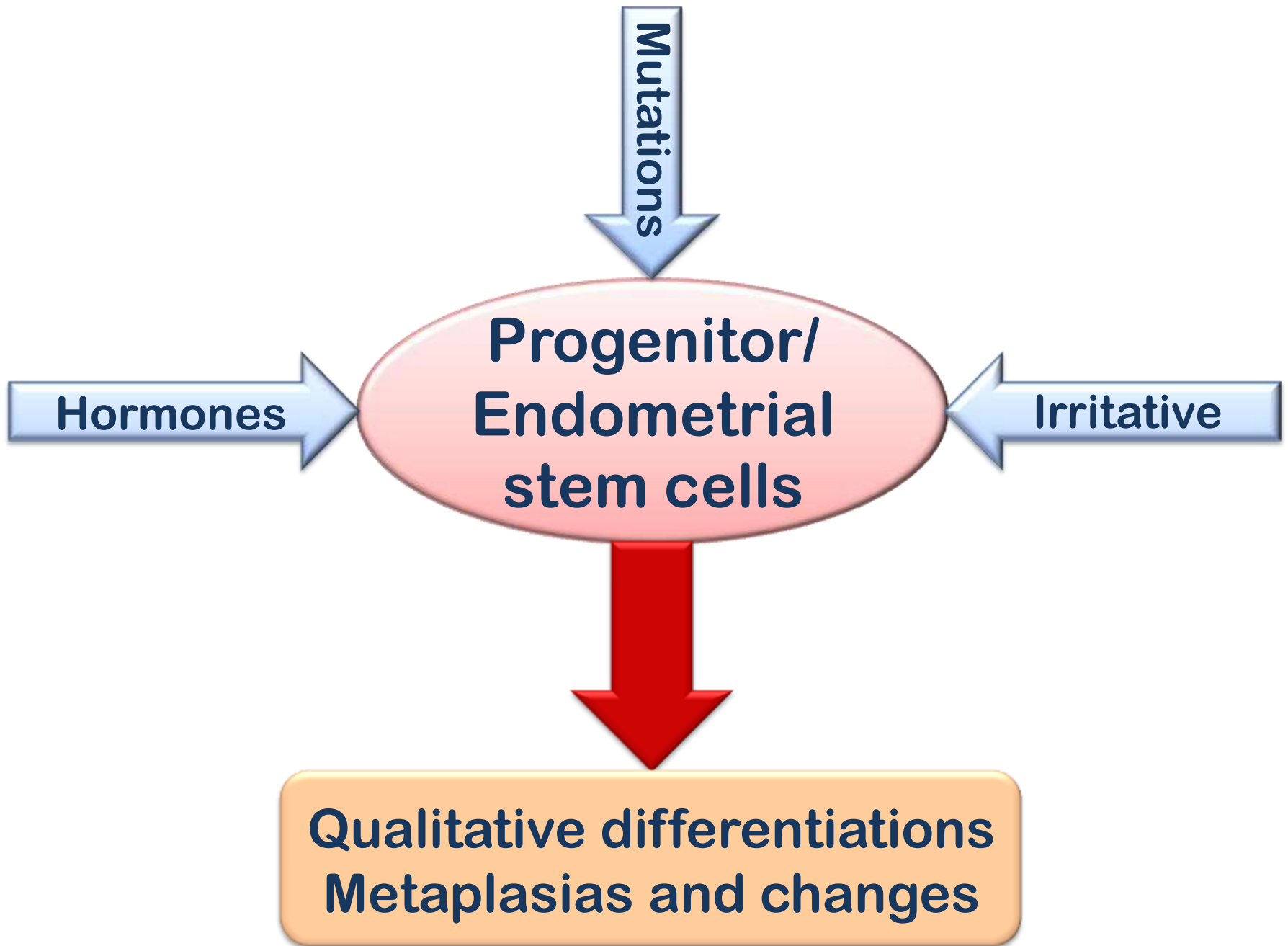
Secretory

Menstrual

Pregnancy

Atrophic





Endometrial metaplasias, origin

- **Stem cell population:**
 - clonogenic, CD146⁺PDGFR β ⁺
CD29⁺CD73⁺CD90⁺ endometrial stromal cells and (SP) side population from bone marrow, perivascular
- **Müllerian derivatives potential**



Sc

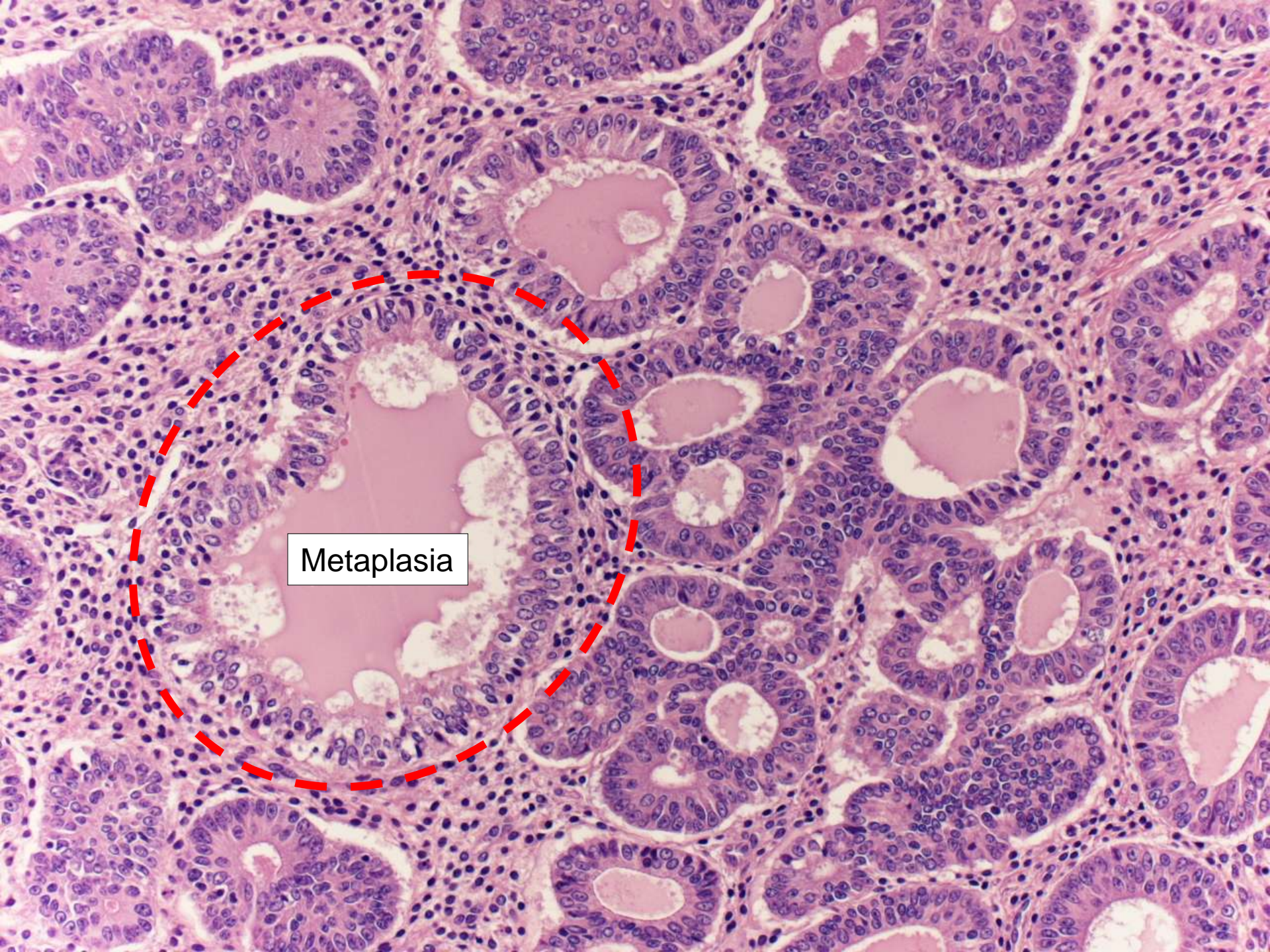
This histological section shows a tissue specimen with three labeled regions. The 'Sc' region is a large, pale, irregularly shaped area at the top, likely representing a cyst or a space. The 'TM' region is a dense, pink-stained layer on the left, composed of many small, dark-stained cells. The 'MM' region is a dense, pink-stained area at the bottom, also composed of many small, dark-stained cells. The tissue is stained with hematoxylin and eosin (H&E), showing purple nuclei and pink cytoplasm/extracellular matrix.

TM

MM

Endometrial metaplasias

- **Heterogeneous group of proliferations**
- **Involve both epithelium and stroma**
- **Often associated with hyperplasia, polyps and adenocarcinoma**
- **Usually focal and frequently overlap**
- **Diagnostic challenge**



Metaplasia

Table 1 Classification of endometrial metaplasias and changes

Endometrial metaplasias and changes

Epithelial	Ciliary, tubal (simple and complex)
	Mucinous (simple and complex)
	— Intestinal variant
	Squamous
	Morules
	Reactive changes
	— Surface, papillary syncytial change
	— Hobnail variant
	— Oncocytic, oxyphilic, eosinophilic
	— Clear cell, secretory
Stromal	Osseous
	Cartilaginous
	Adipose
	Smooth muscle
	— Myoid, sex-cord like

view

Pathology
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Stromal

Osseous

Cartilaginous

Adipose

Smooth muscle

— Myoid, sex-cord like

Ciliated and tubal metaplasias

- **Most frequent type of EM**
- **Frequent in the cervix**
- **Ciliated: ↑ of cilia. Tubal: 3 cell types**
- **Present in atrophy, hyperplasias (simple & complex) and adenocarcinoma
adenofibroma/adenosarcoma, polyps,
endometriosis**

Ciliated and tubal metaplasias

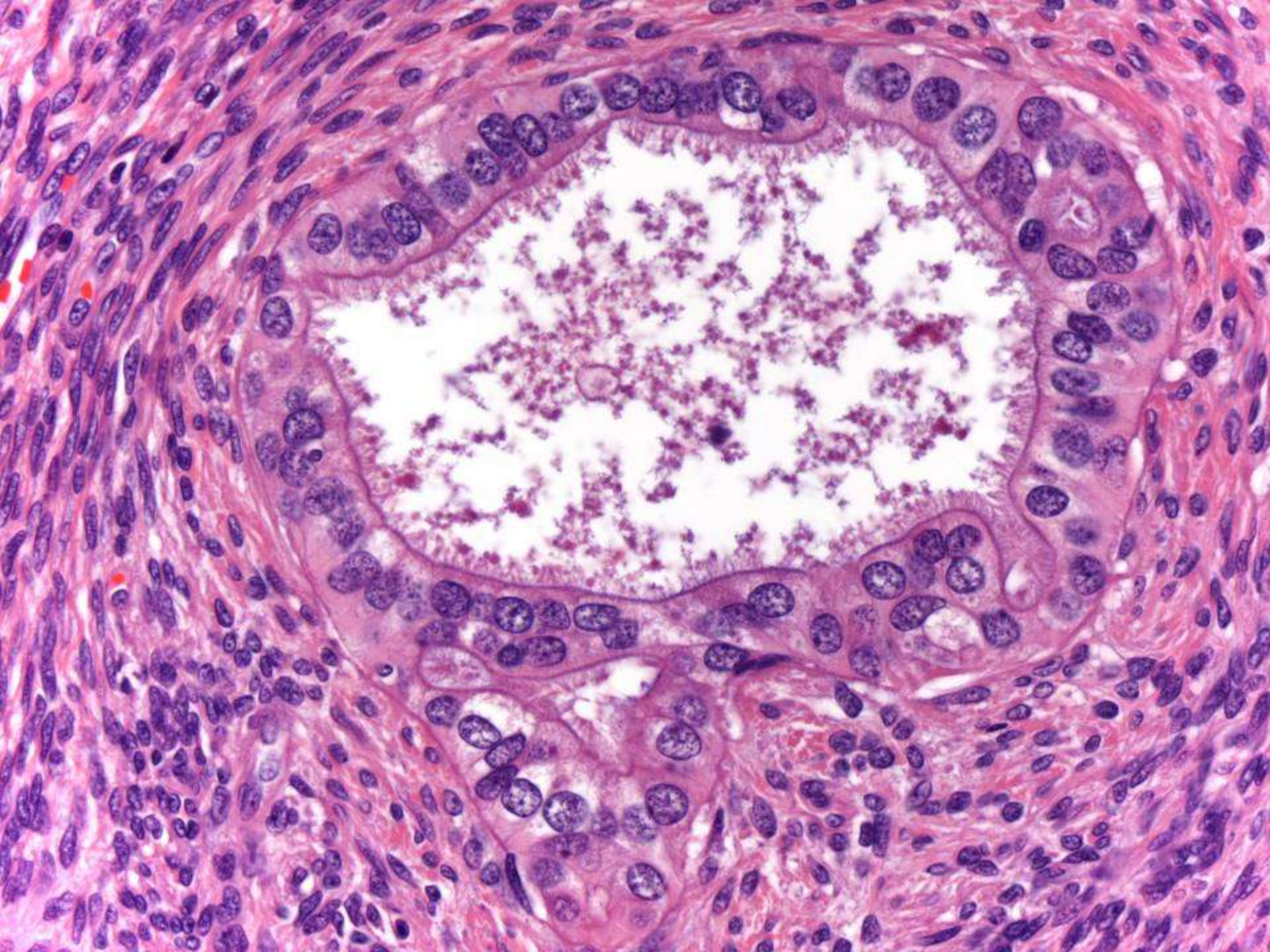
Patterns:

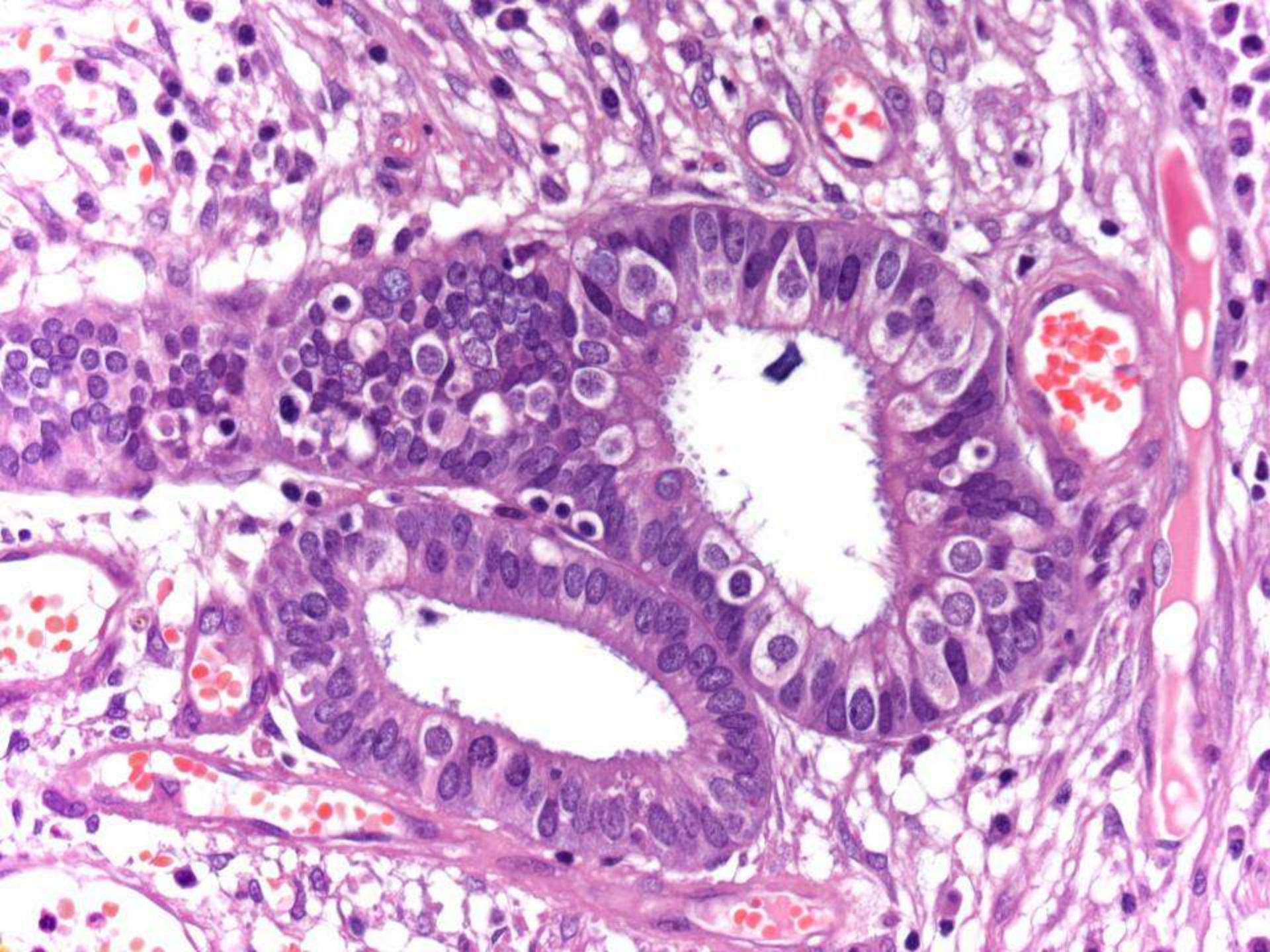
- Simple, tubular glands / surface epith.
- Complex, stellate, papillary, cribriform
and confluent glands with loss of polarity

Ciliated and tubal metaplasias

Histology:

- Simple, tubular glands / surface epith.

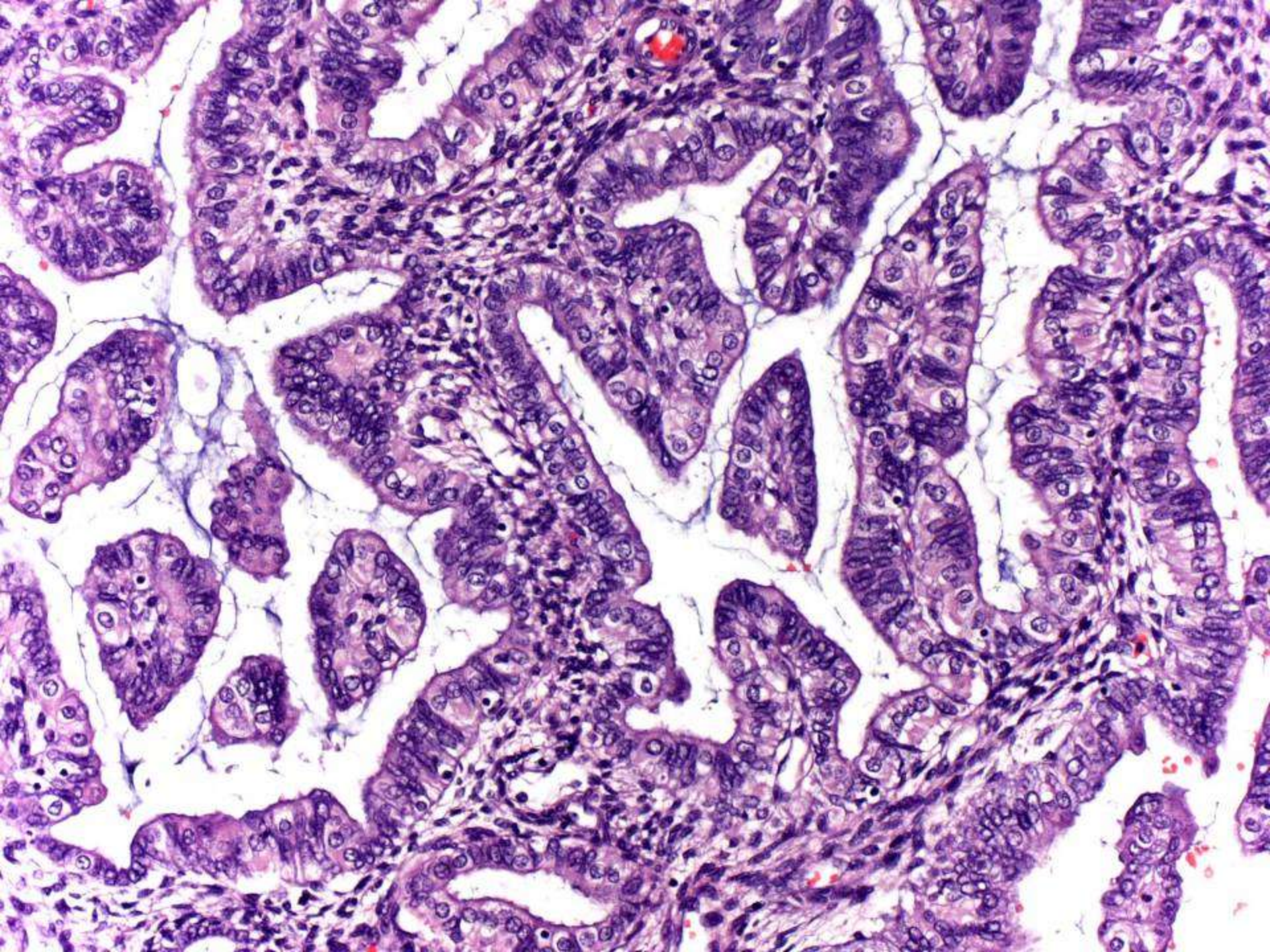


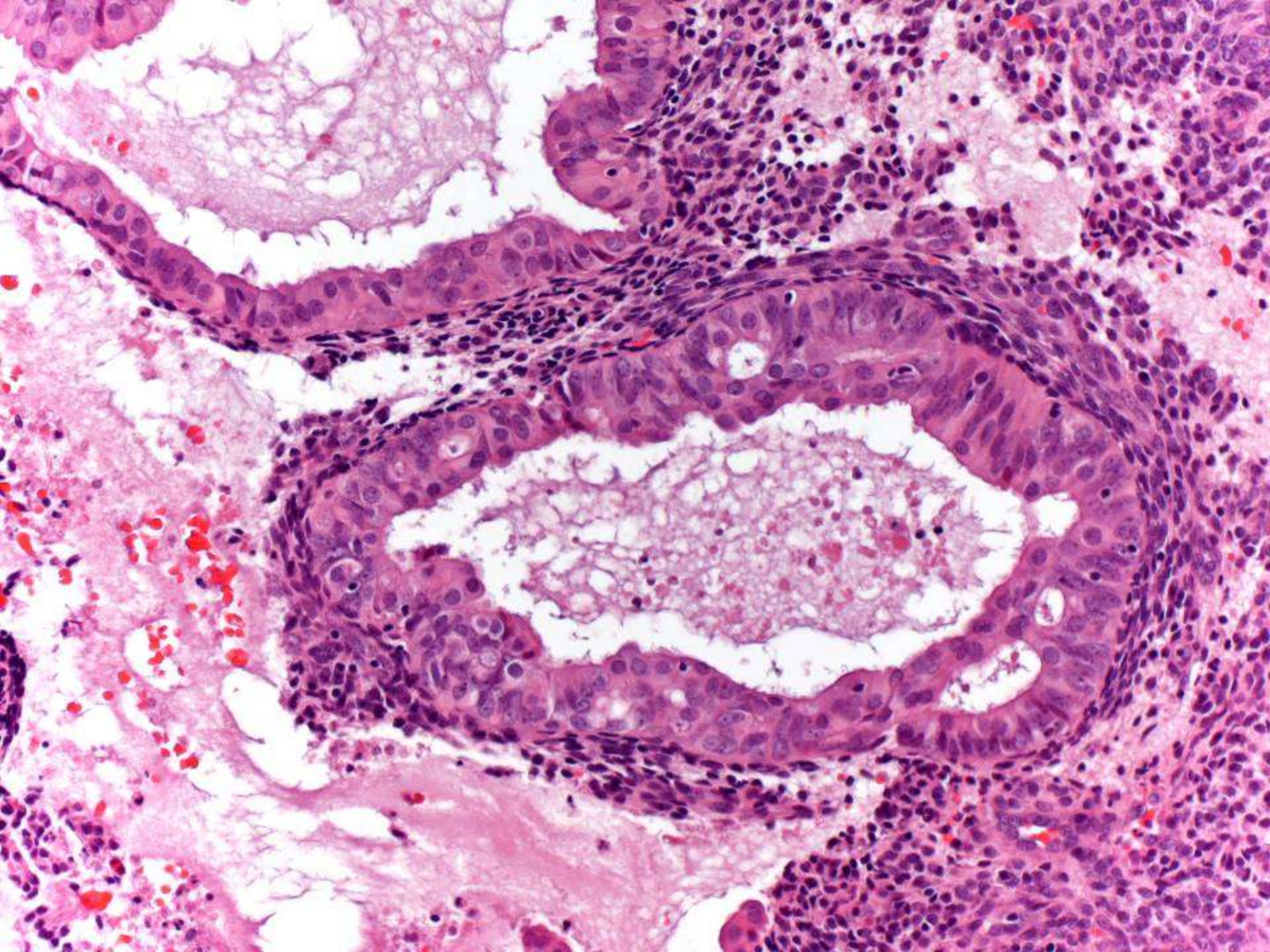


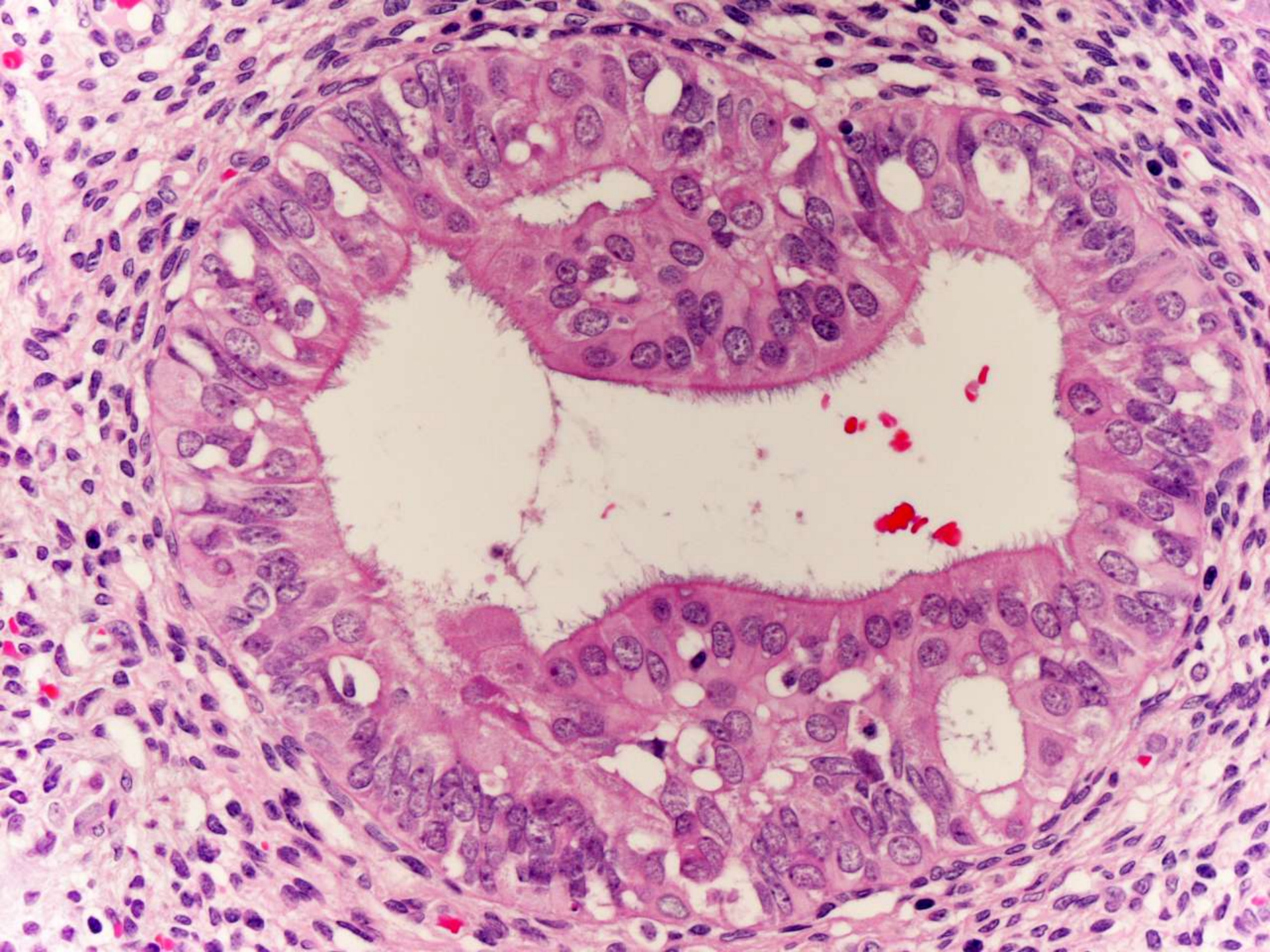
Ciliated and tubal metaplasias

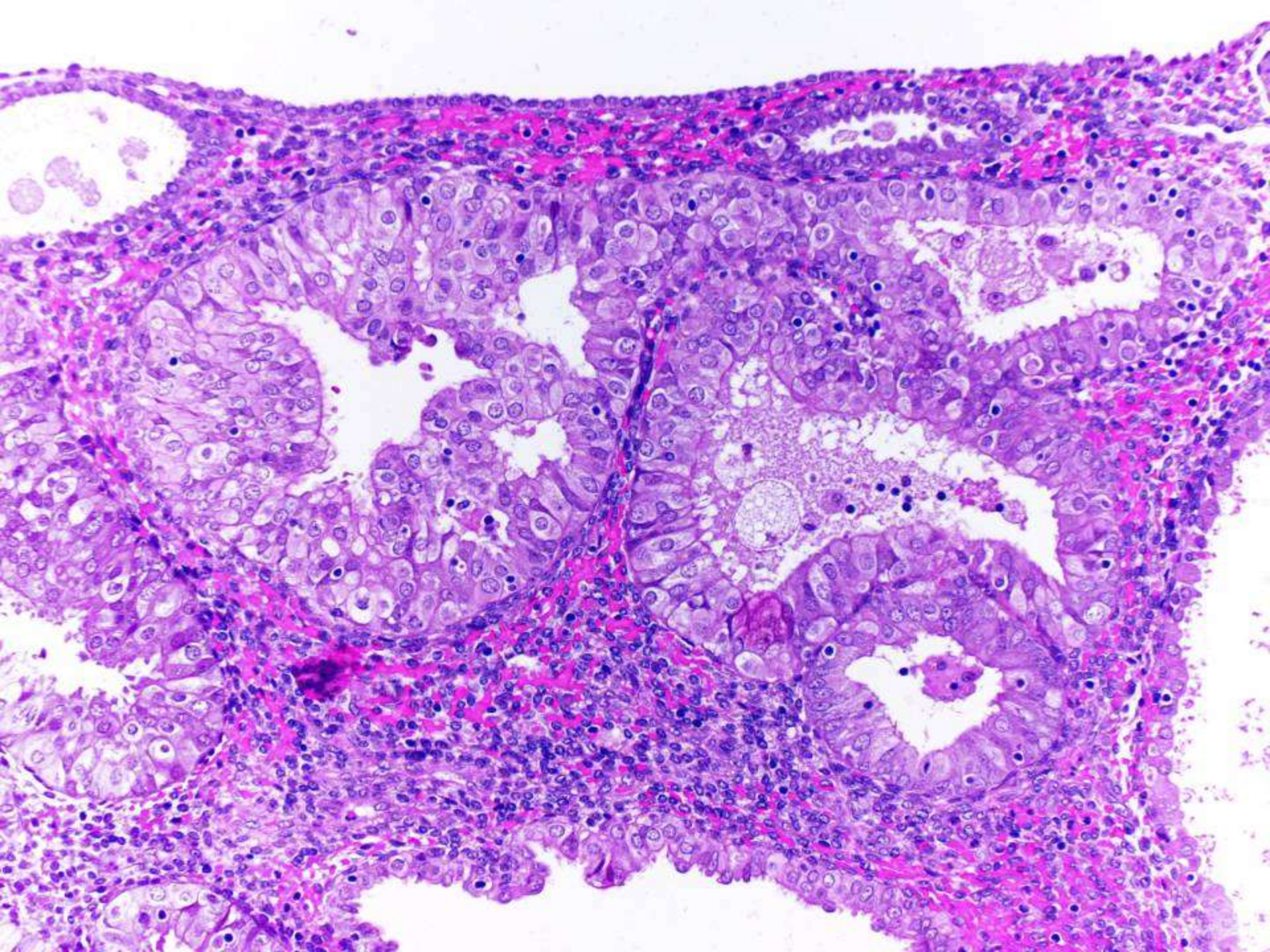
Histology:

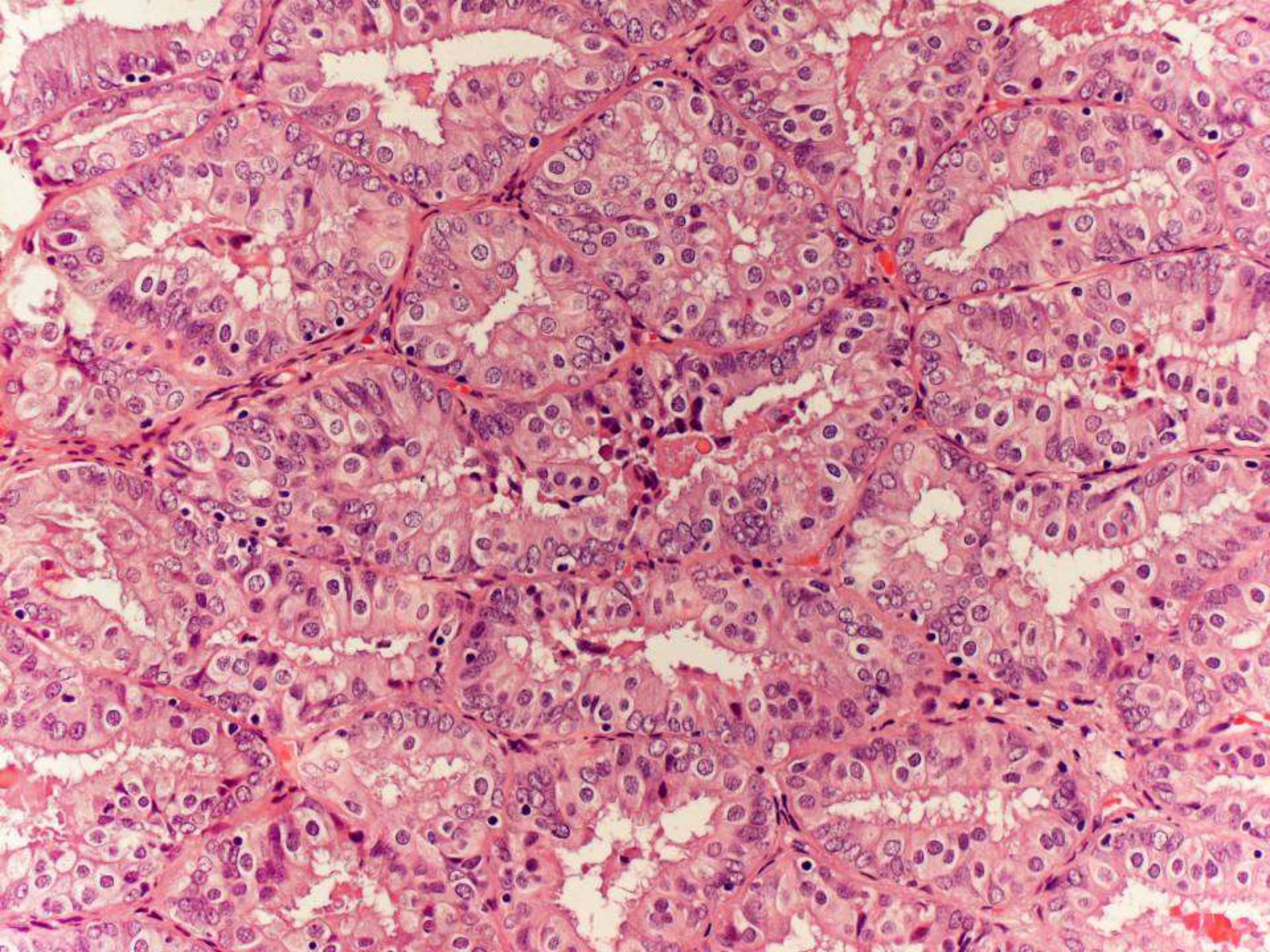
- Simple, tubular glands / surface epith.
- Complex, micropapillary, cribriform
and confluent glands with loss of polarity







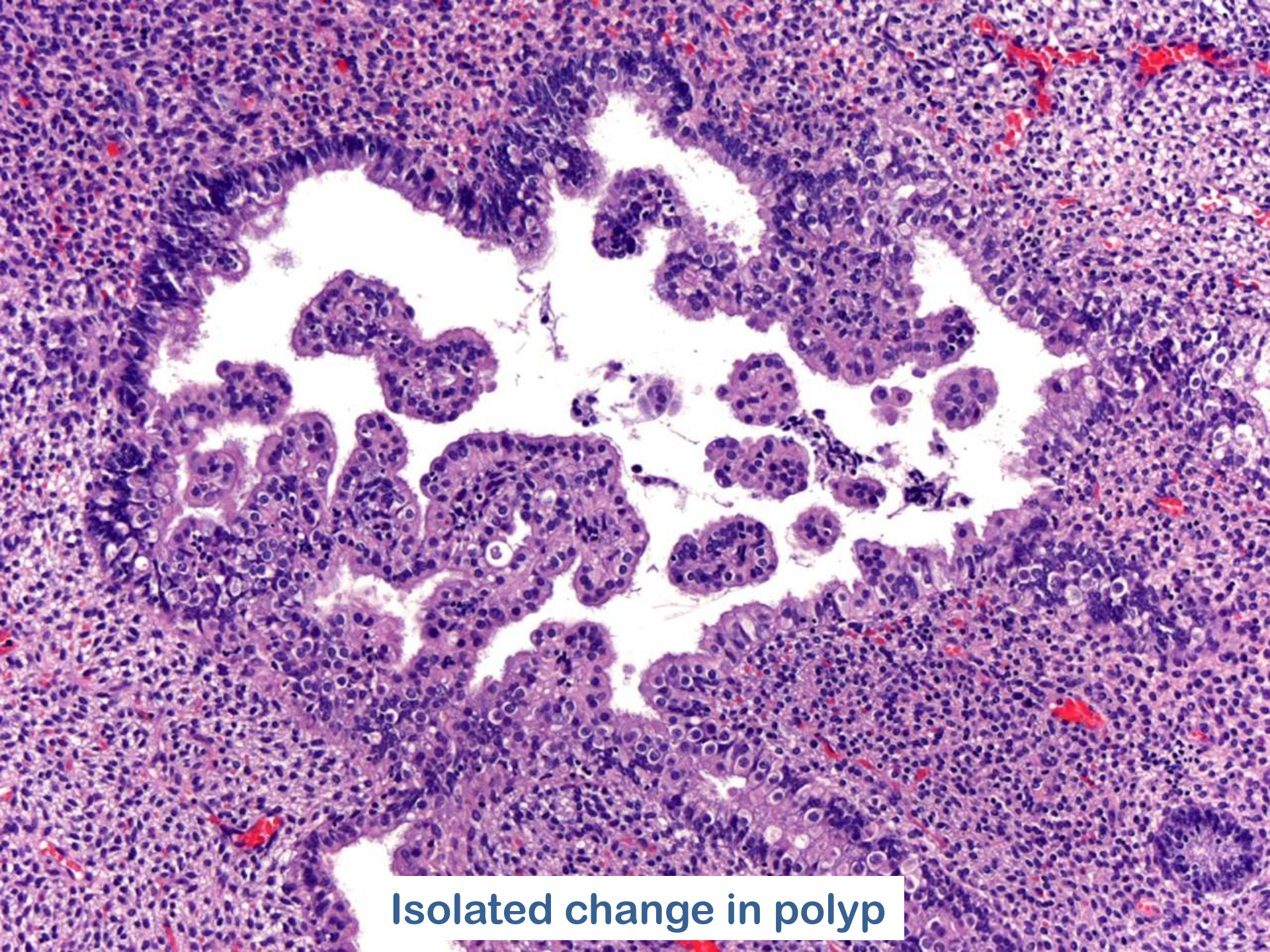




Ciliated and tubal metaplasias

Significance:

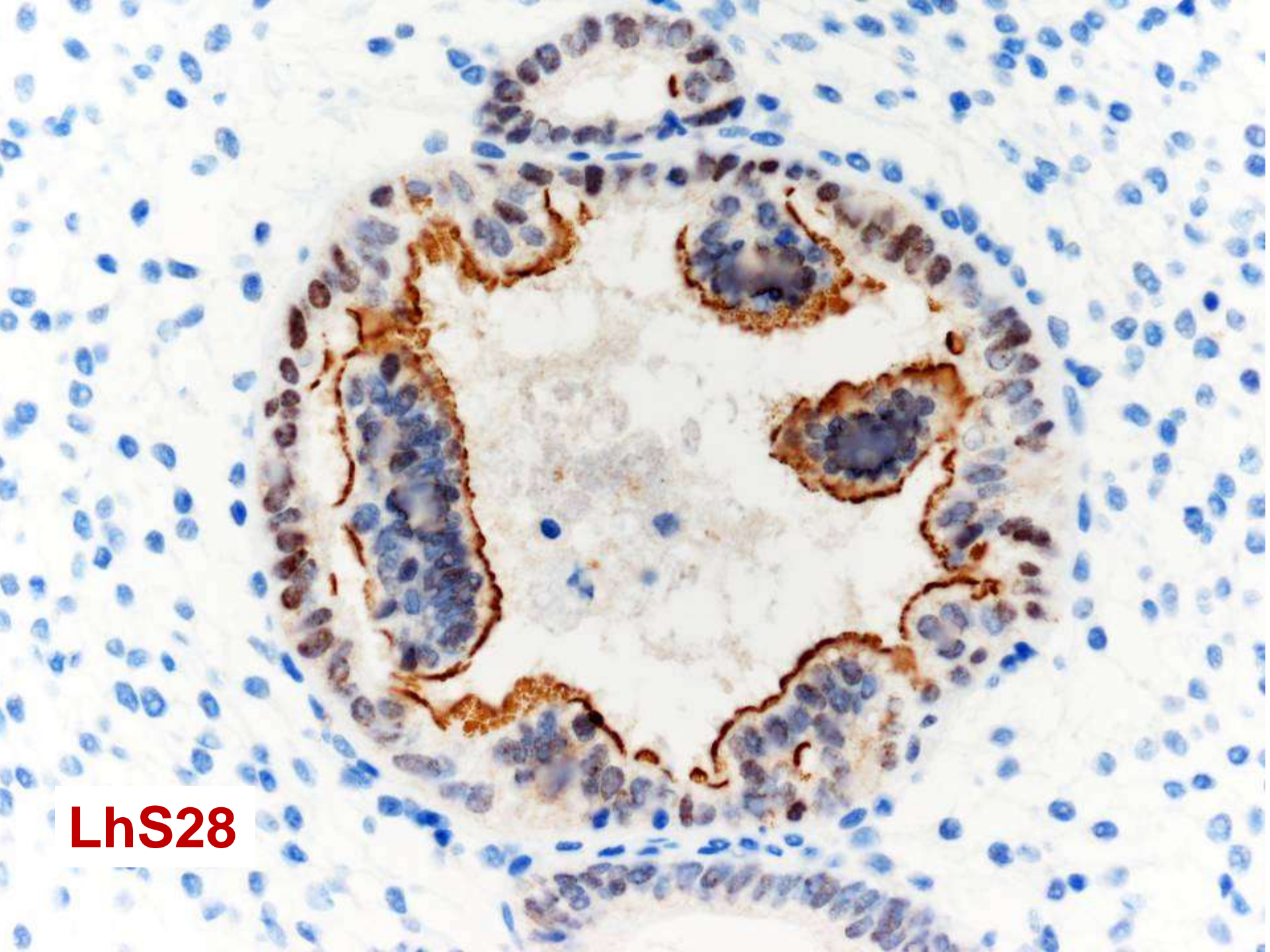
- Simple: **benign**
- Complex: **preneoplastic, neoplastic?**
 - Atypia always mild to moderate
 - Isolated, complex changes in polyps have little significance



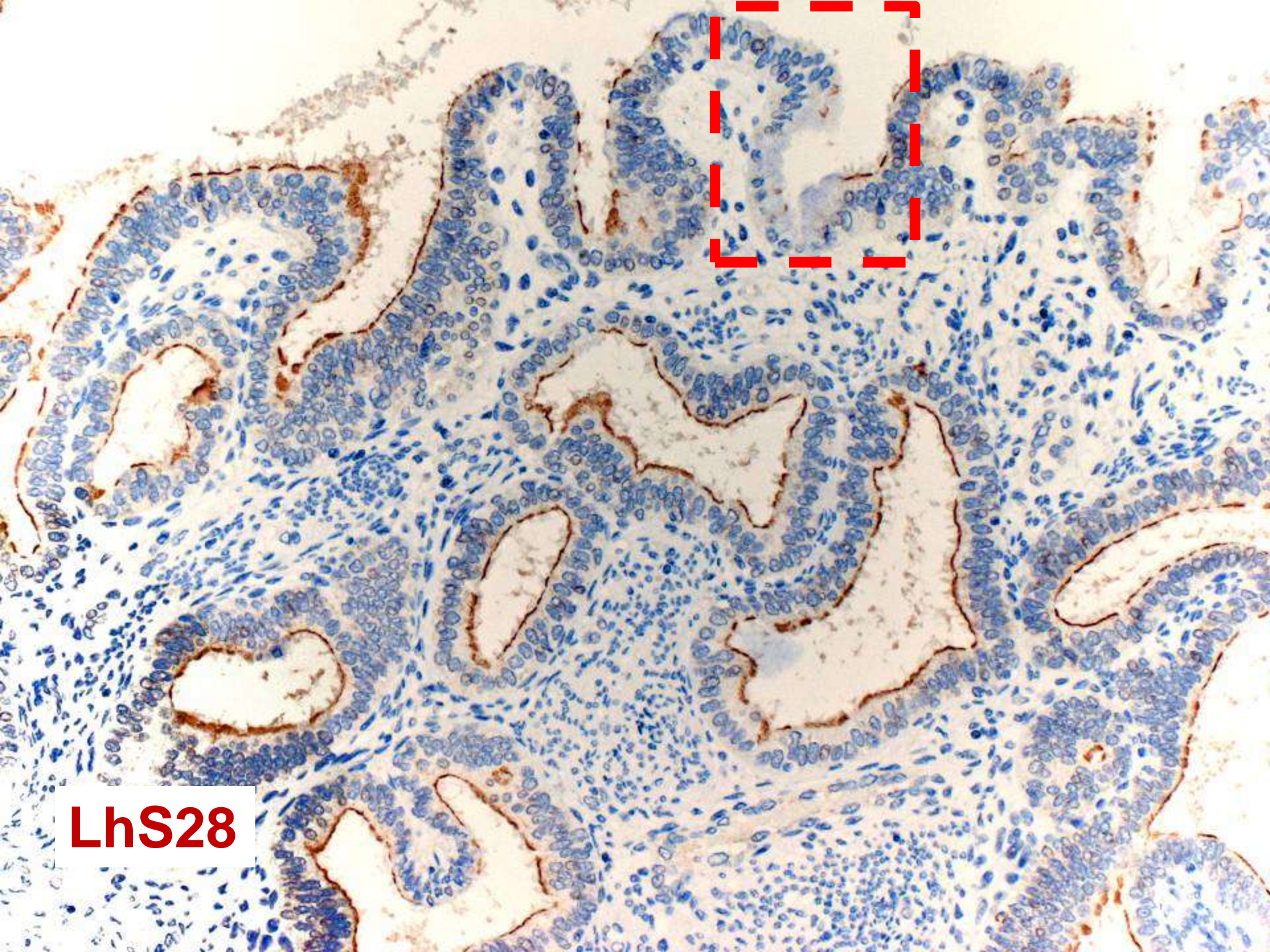
Isolated change in polyp

Ciliated and Tubal metaplasias

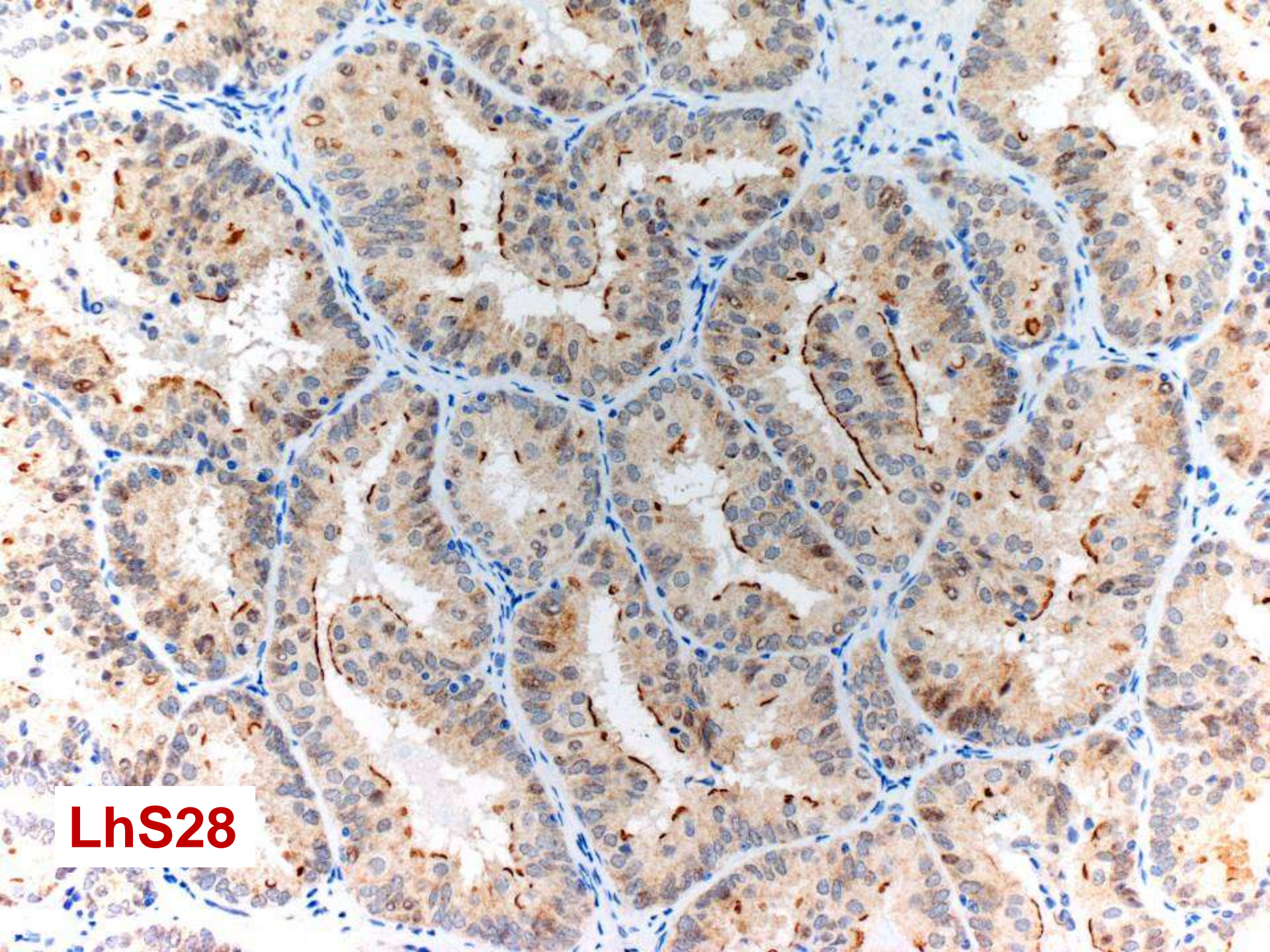
- **Immunophenotype**
 - LhS28 ++, p16^{INK4A} ++ , p53 weak, **PAX2 & bcl2 ++**



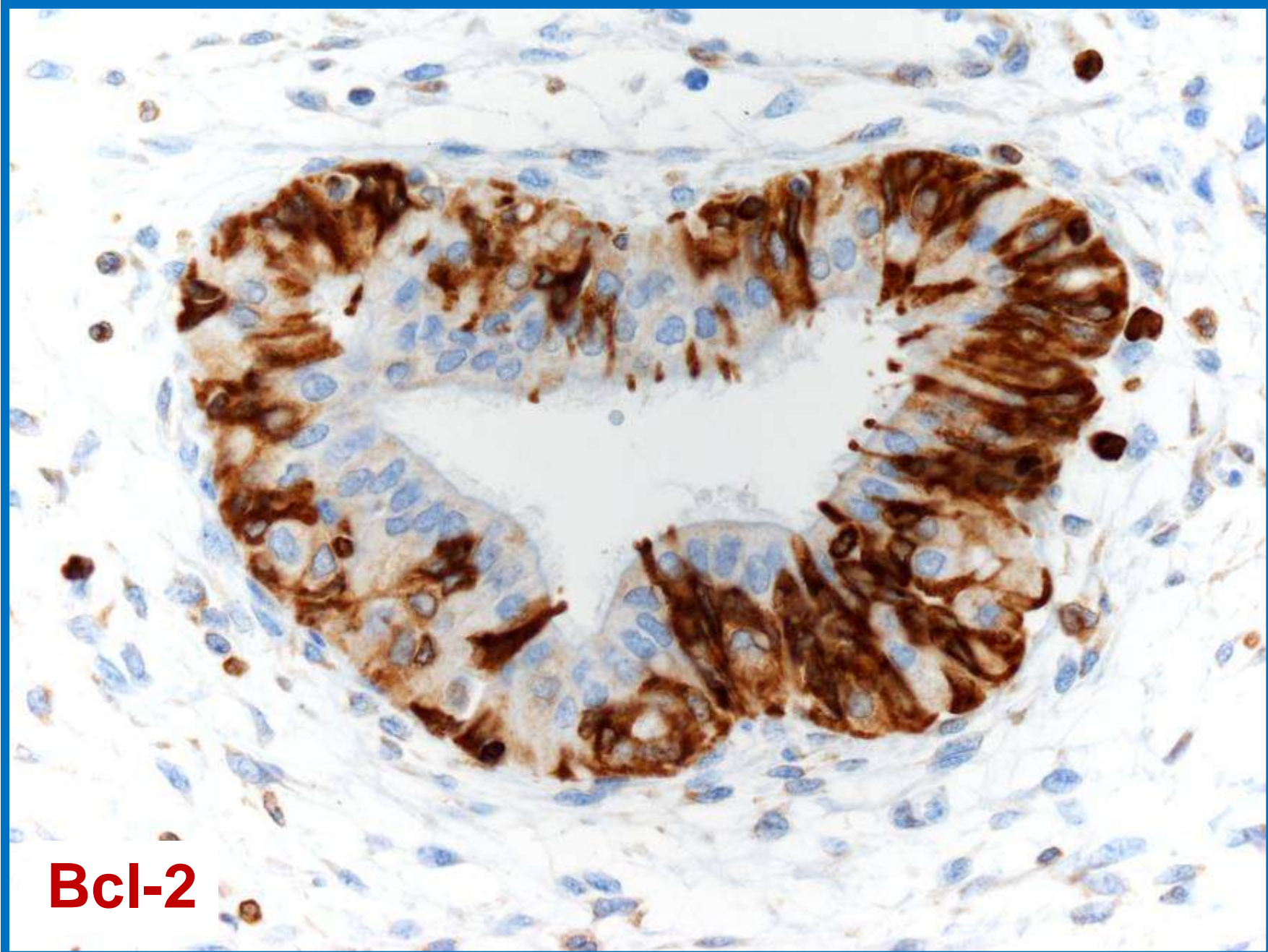
LhS28



LhS28



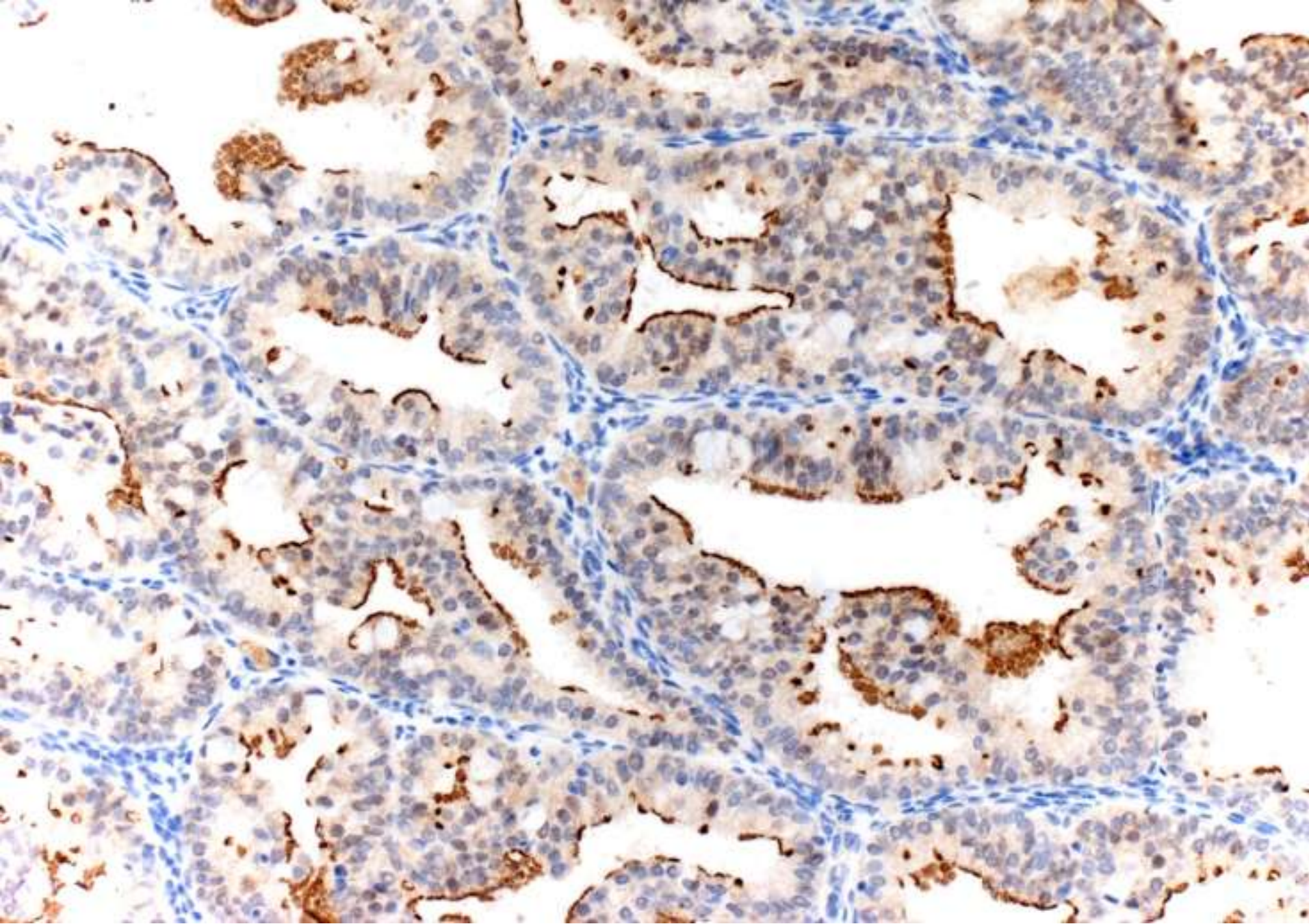
LhS28



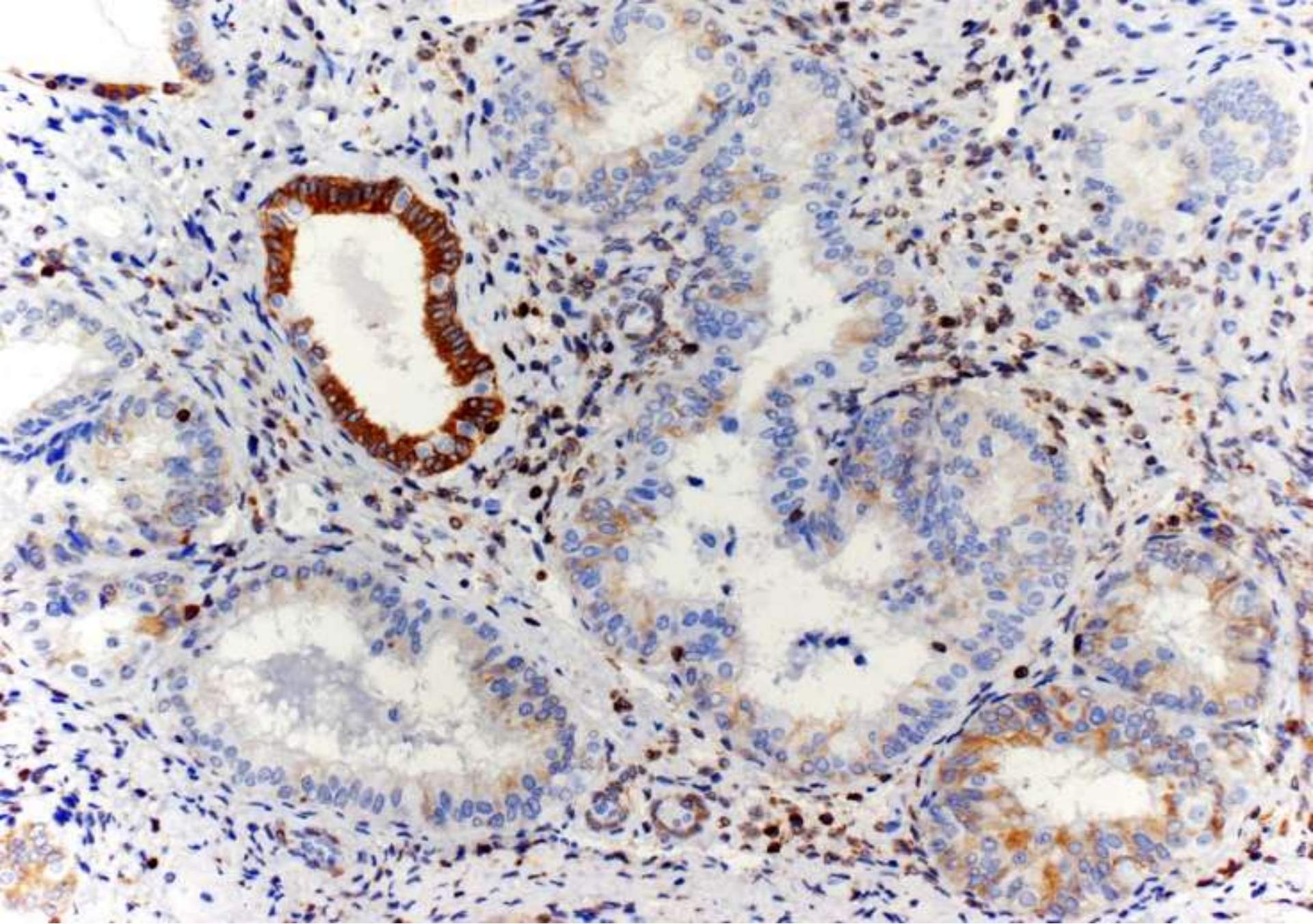
Bcl-2

Ciliated and Tubal metaplasias

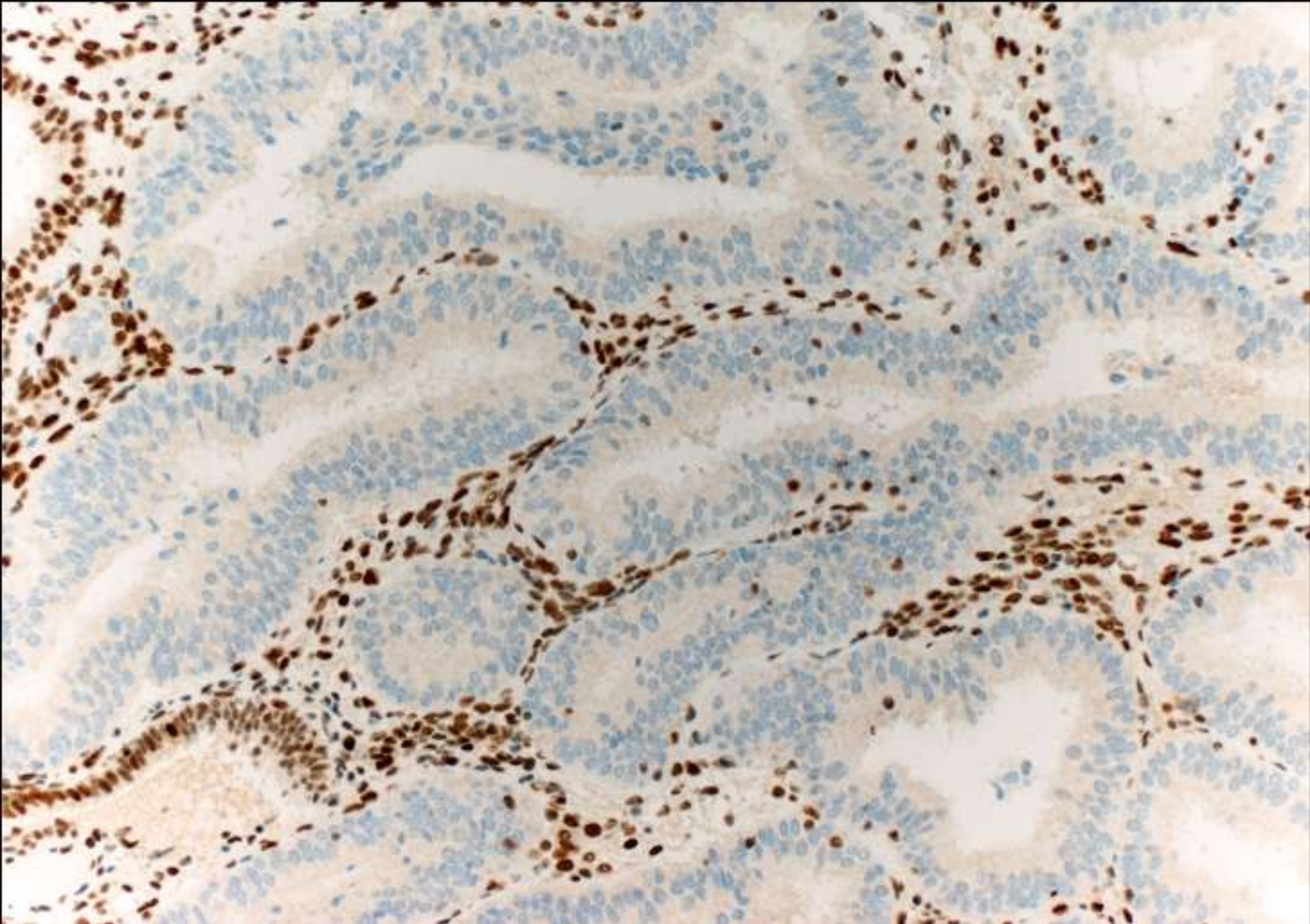
- Immunohistochemistry of *complex* ciliated metaplasias



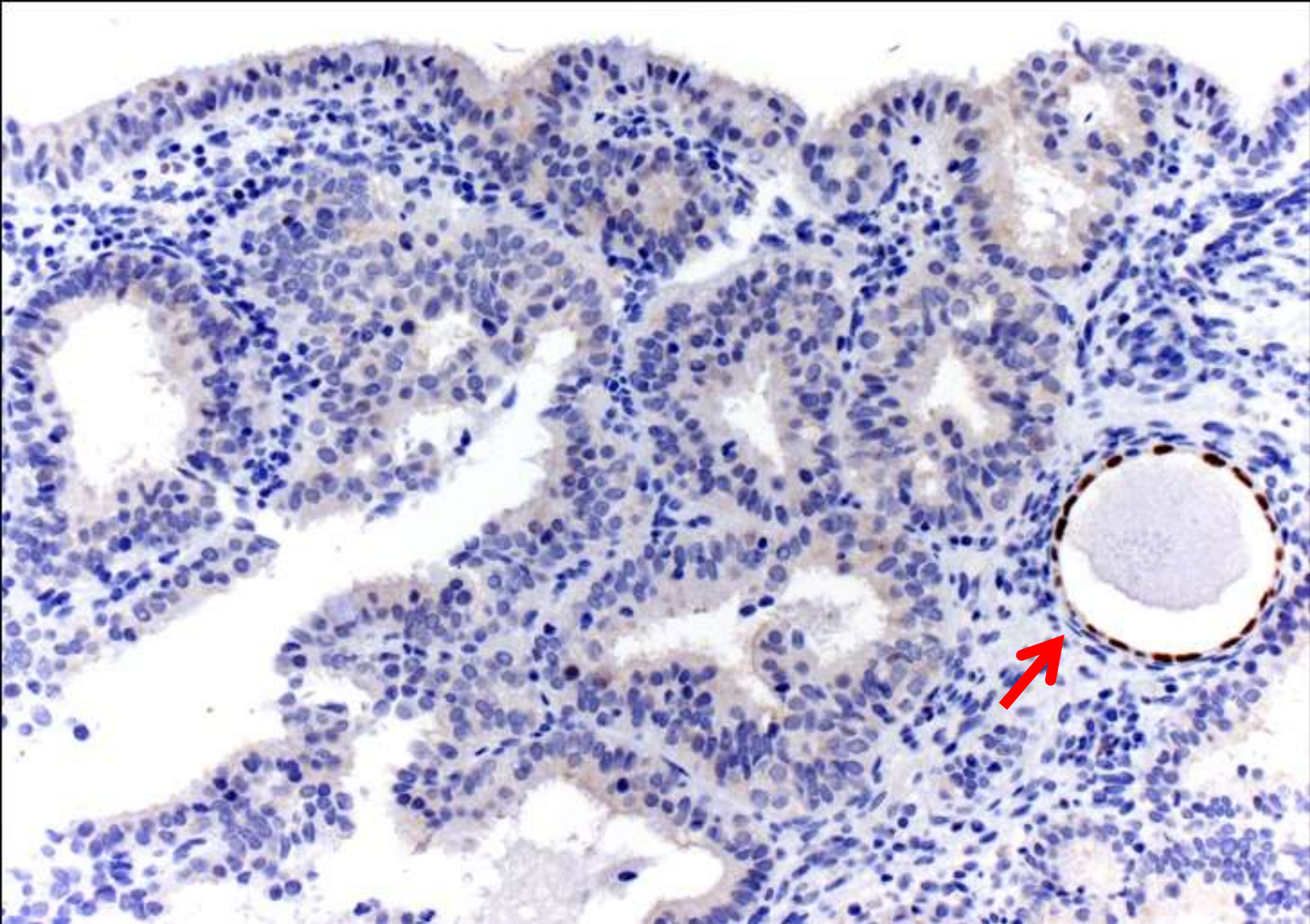
LhS28



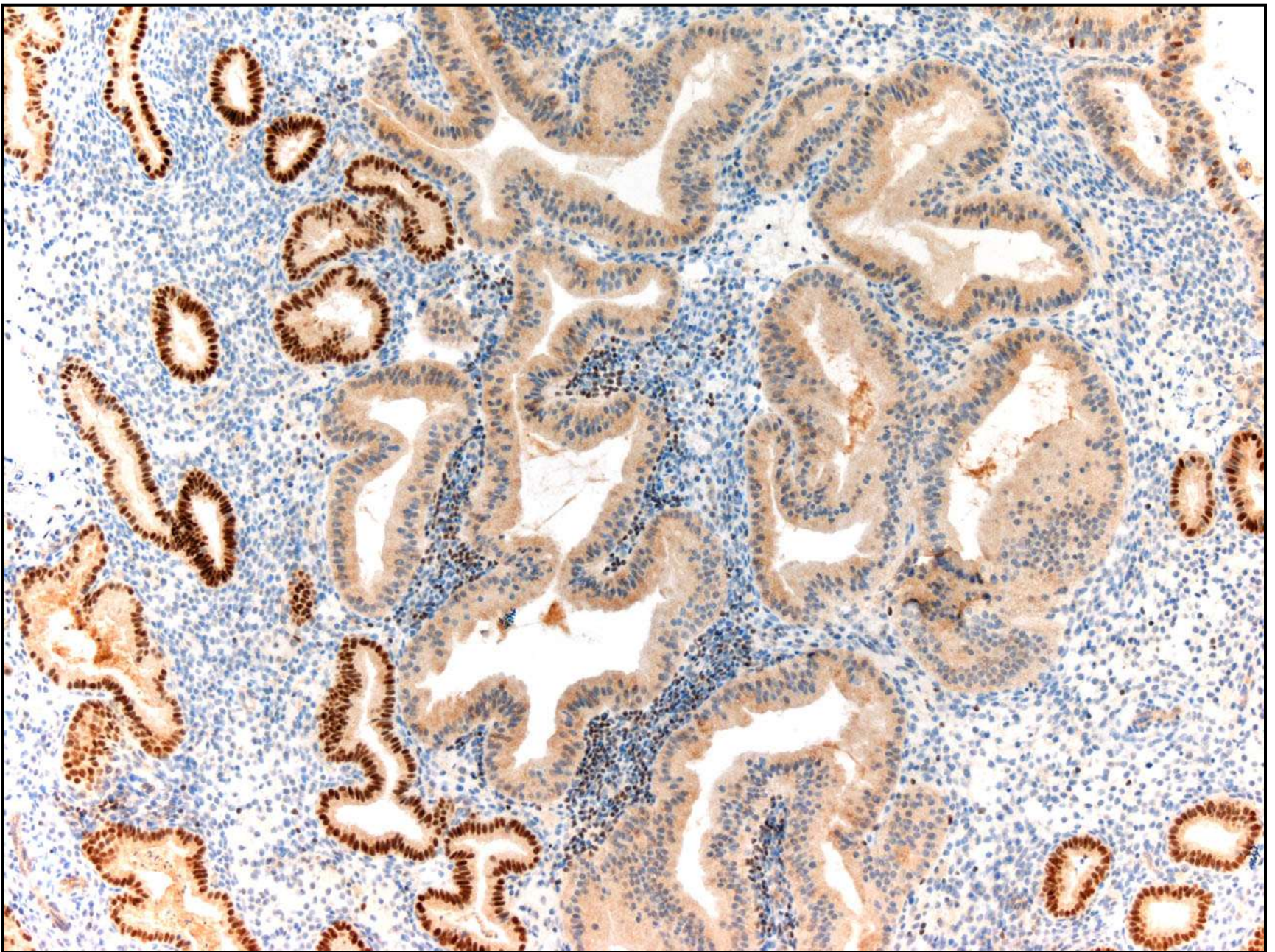
BCL-2 and cyclin D1



MLH1-PMS2



PAX2



PAX2 relevance Monte *et al.* Cancer Res. 2010;70:6225-32

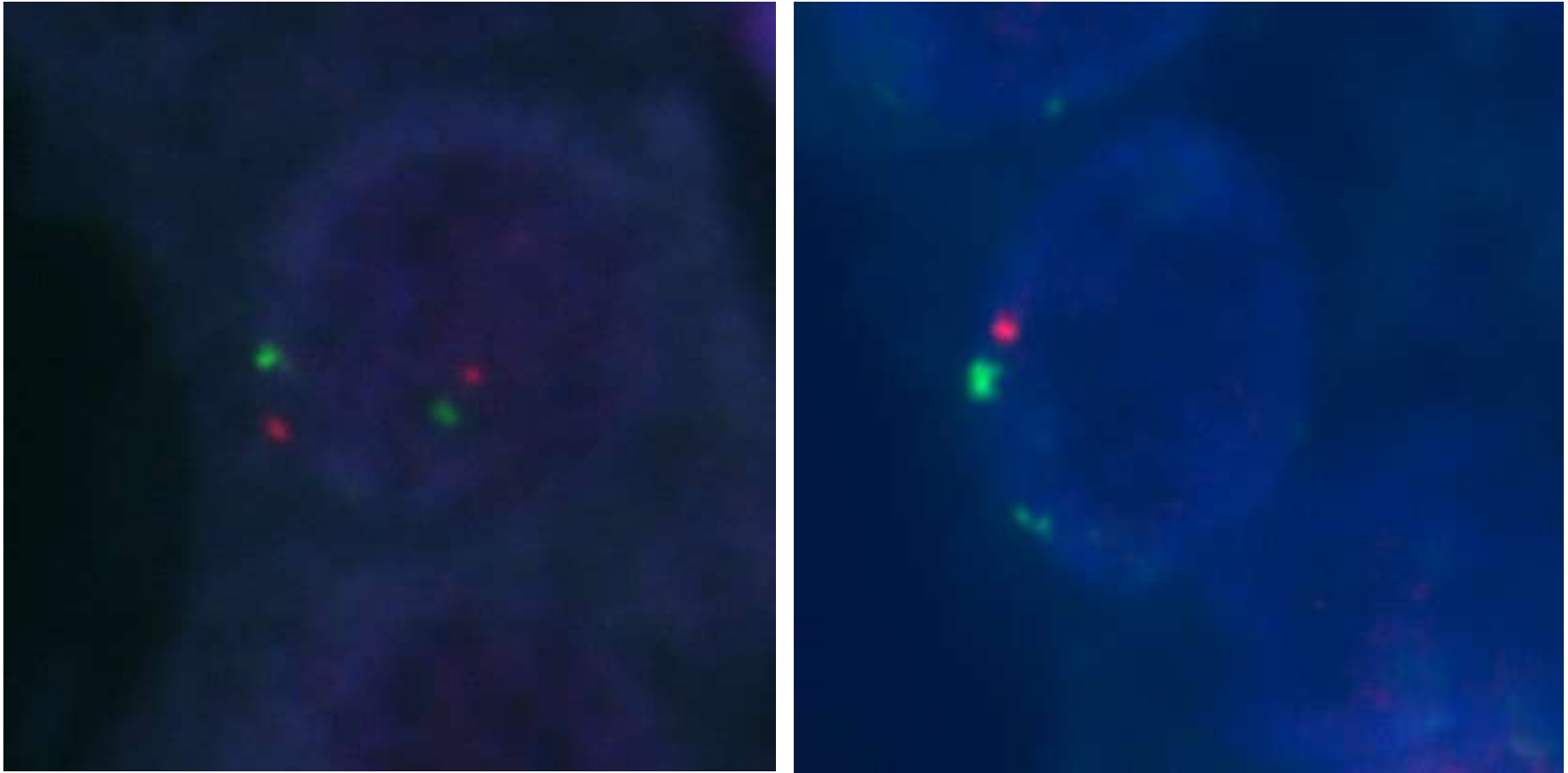
Ciliated and tubal metaplasias

Genetics of Complex tubal lesions

- PTEN deletion
- K-ras point mutations

(codons 12, 12&13)

1/8 case PTEN hemizygous deletion



Right image - normal pattern of PTEN gene. Left - loss of one of the signal for PTEN, indicating hemizygous deletion of 10q23/PTEN locus

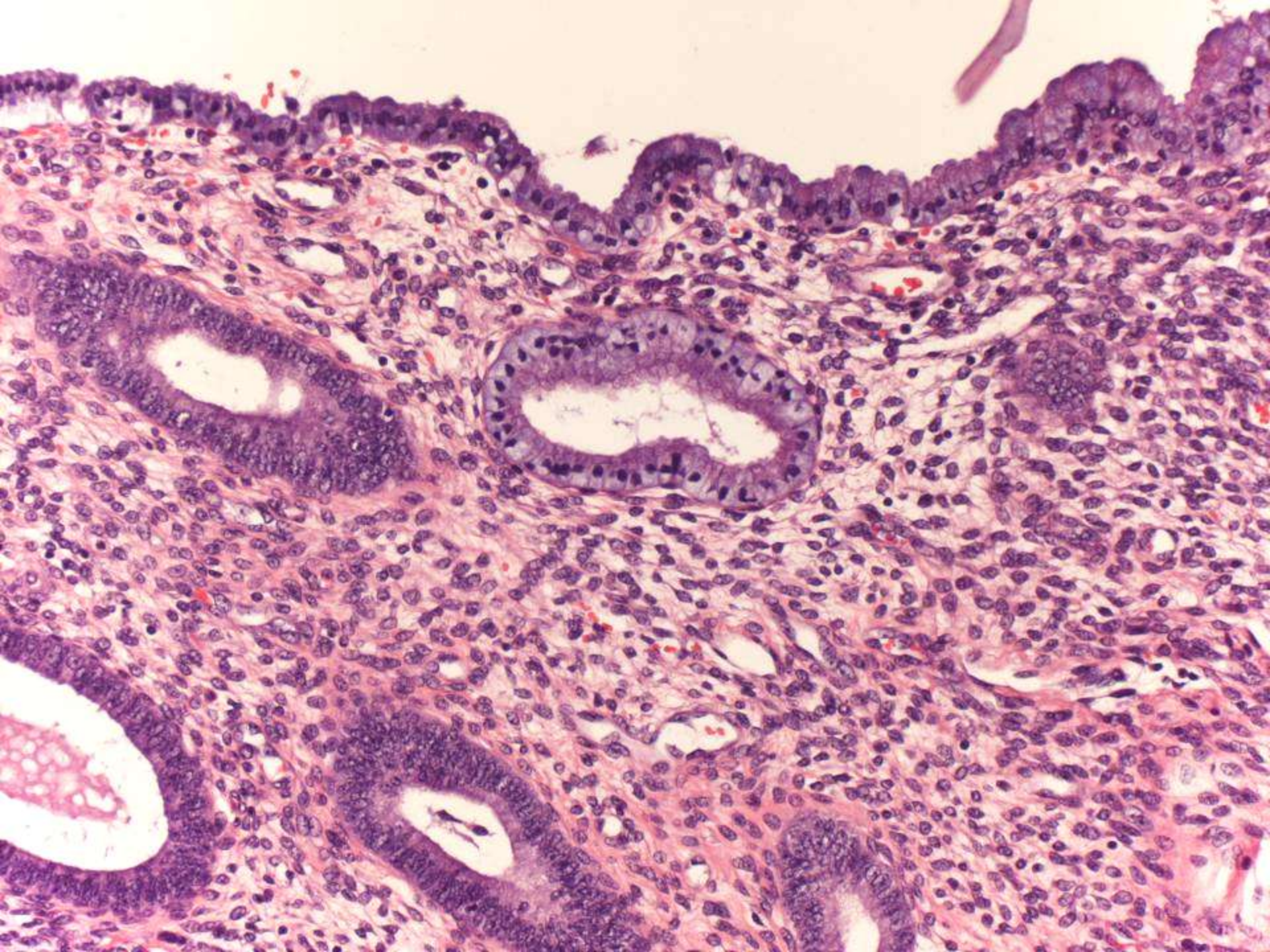
Table 1 Classification of endometrial metaplasias and changes

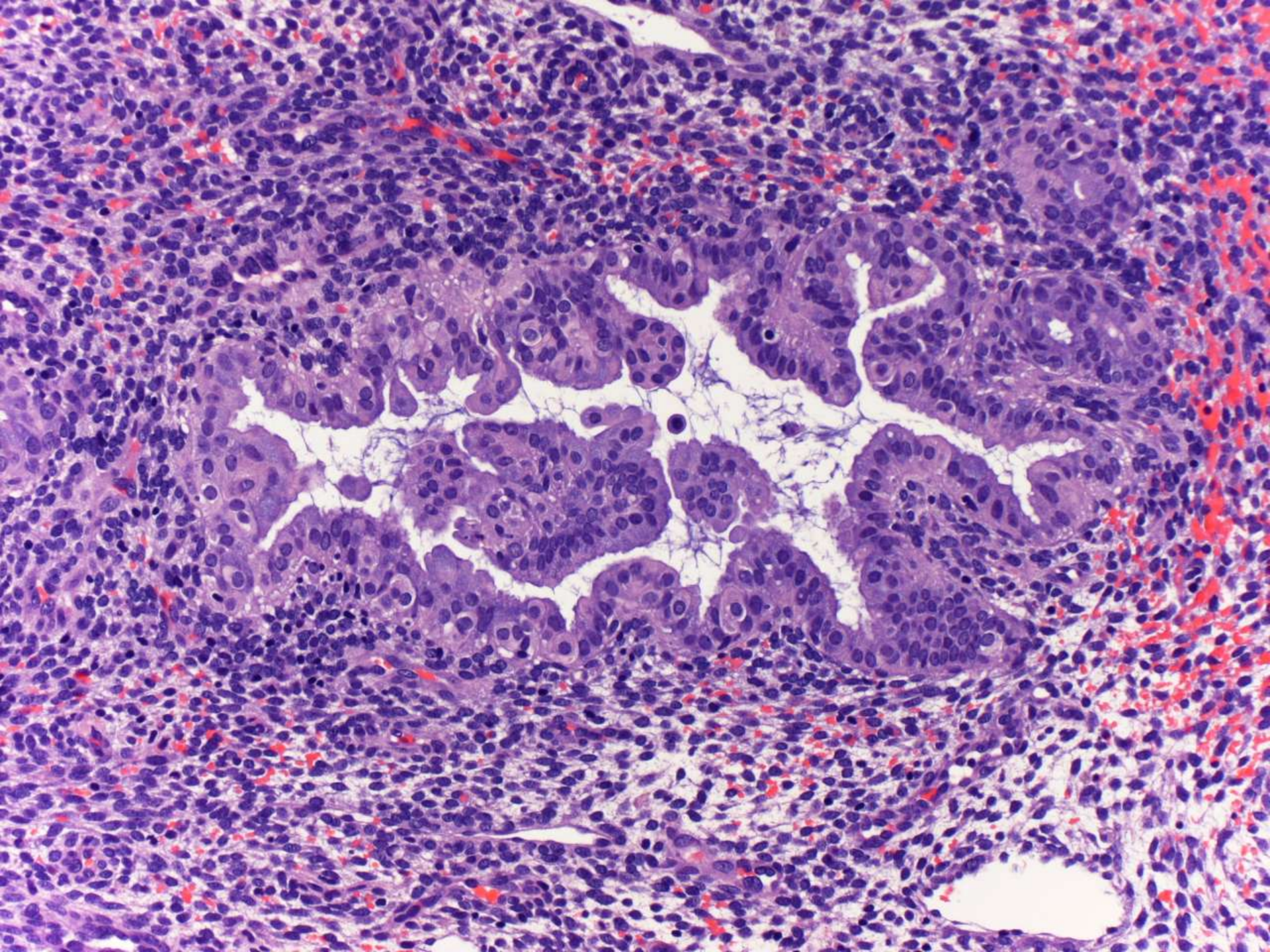
Endometrial metaplasias and changes

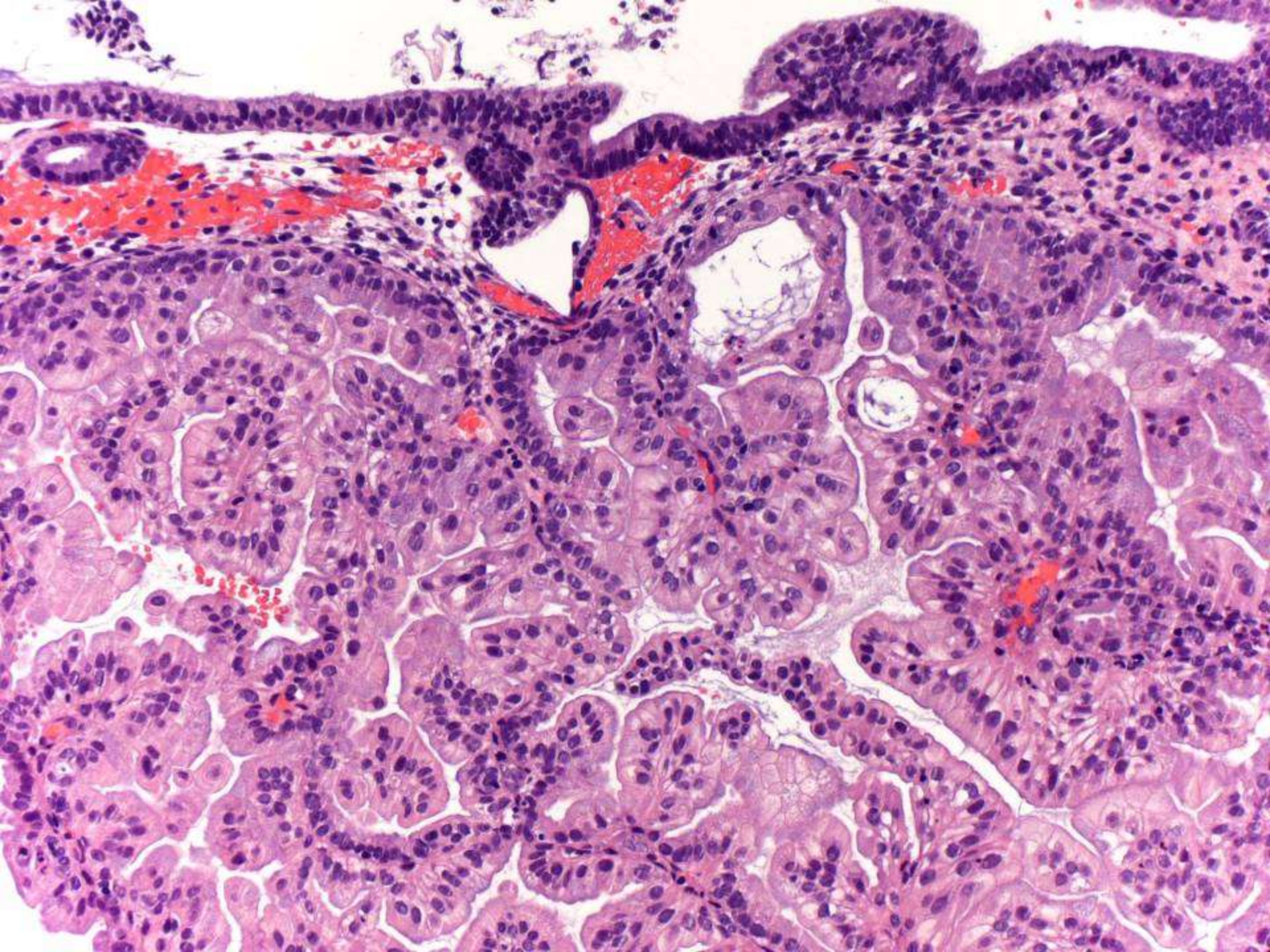
Epithelial	Ciliary, tubal (simple and complex)
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	Cartilaginous
	Adipose
	Smooth muscle
	— Myoid, sex-cord like

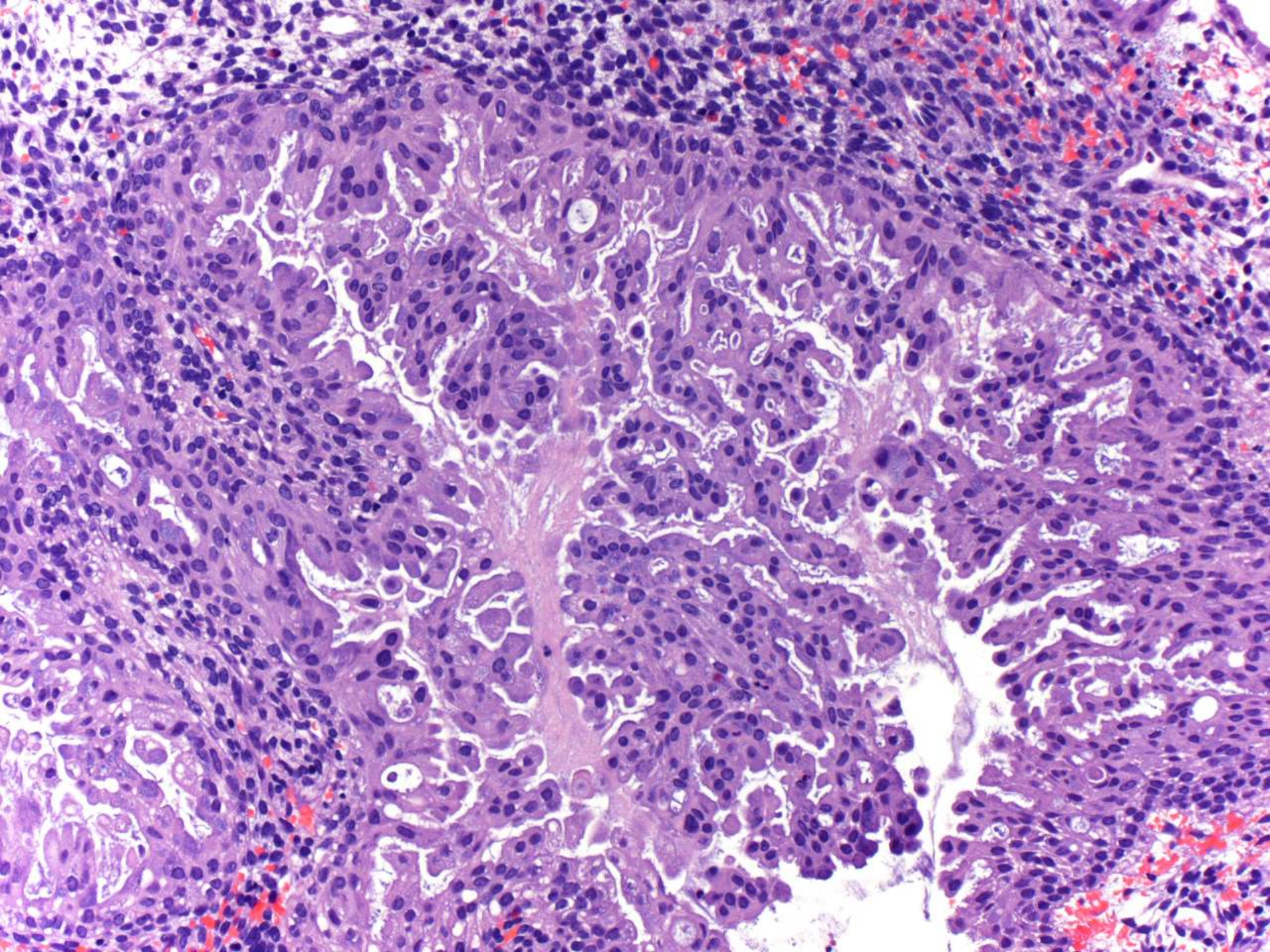
Mucinous metaplasias

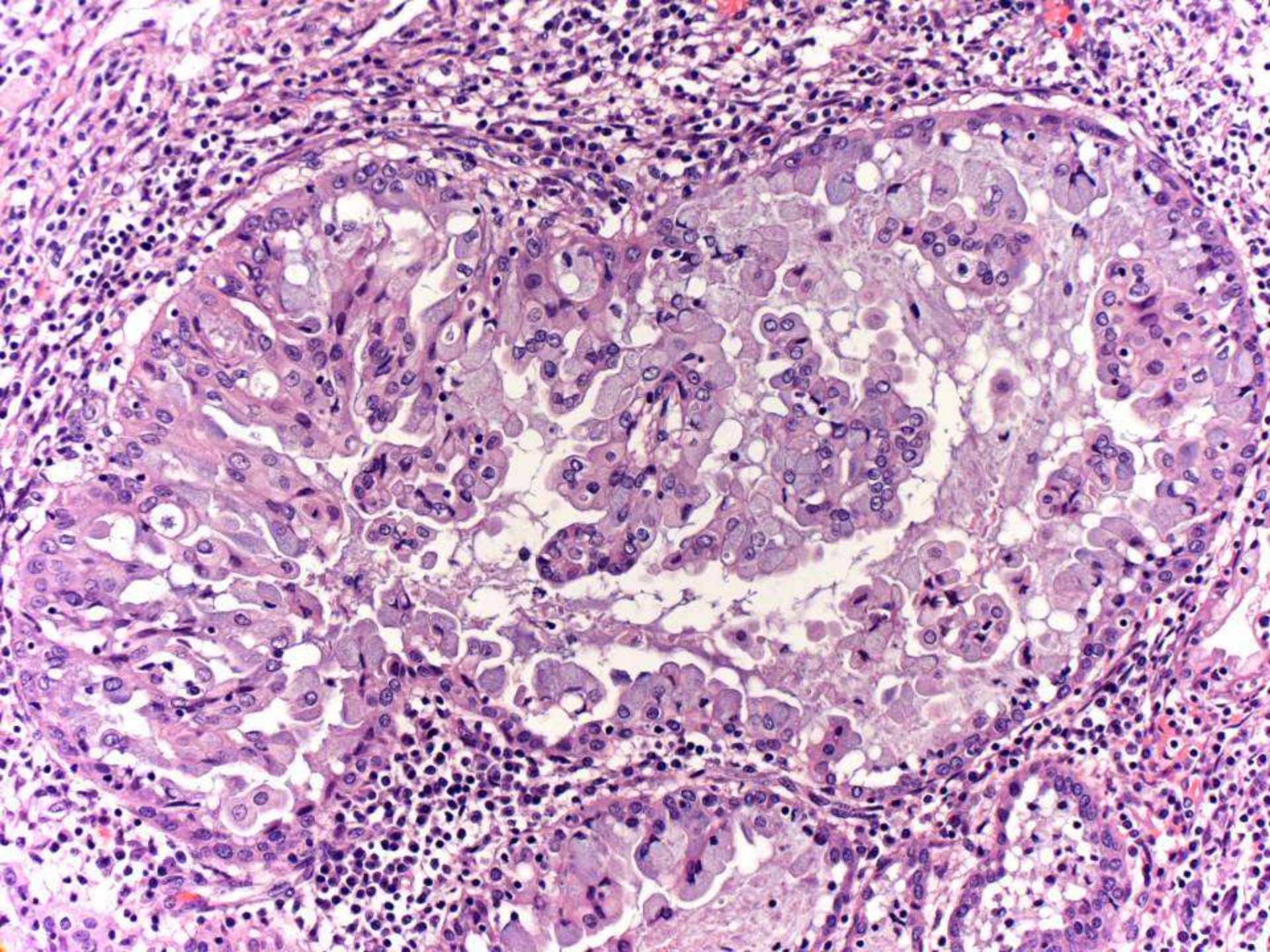
- **Present in:**
 - **Same context as in CTM**
 - **Polyps (tamoxifen)**
 - **Multifocality in myxometra and STK11 gene mutations, Peutz-Jeghers**

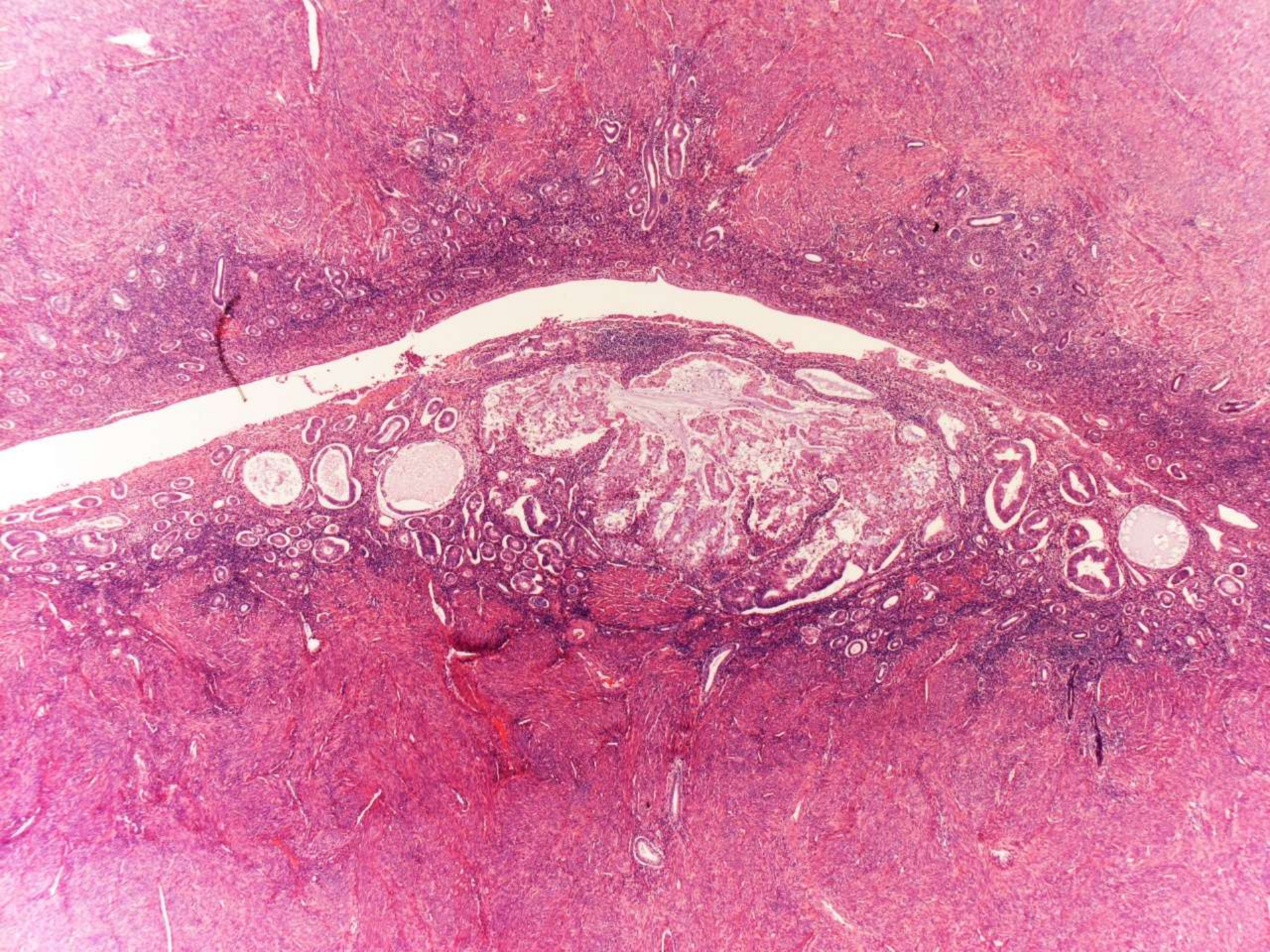












Mucinous metaplasias

- Frequently overlapping with CTM
- Evaluation:
 - Three tier system (A, B, C)
 - » Nucci MR et al. Mod Pathol. 1999;12:1137-42.
 - Reproducibility: poor
 - » Vang R et al. Int J Surg Pathol. 2003 ;11:261-70.
- A two tier system preferable

Mucinous metaplasias: interpretation

Analogous to CTM

- Simple, tubular glands or surface epithelium: **benign**
- Complex, stellate, papillary, cribriform and confluent glands with loss of polarity: **preneoplastic / neoplastic?**
- Atypia always mild to moderate

Mucinous metaplasias

- **Differential diagnosis:**
 - Due to its low grade atypicality, malignancy threshold should be lower than in endometrioid lesions
 - Microglandular cervical hyperplasia is a frequent pitfall in aspiration biopsy
 - Microglandular variant of endometrioid ca.

**Mucinous change in
polyps: simple and
papillary**

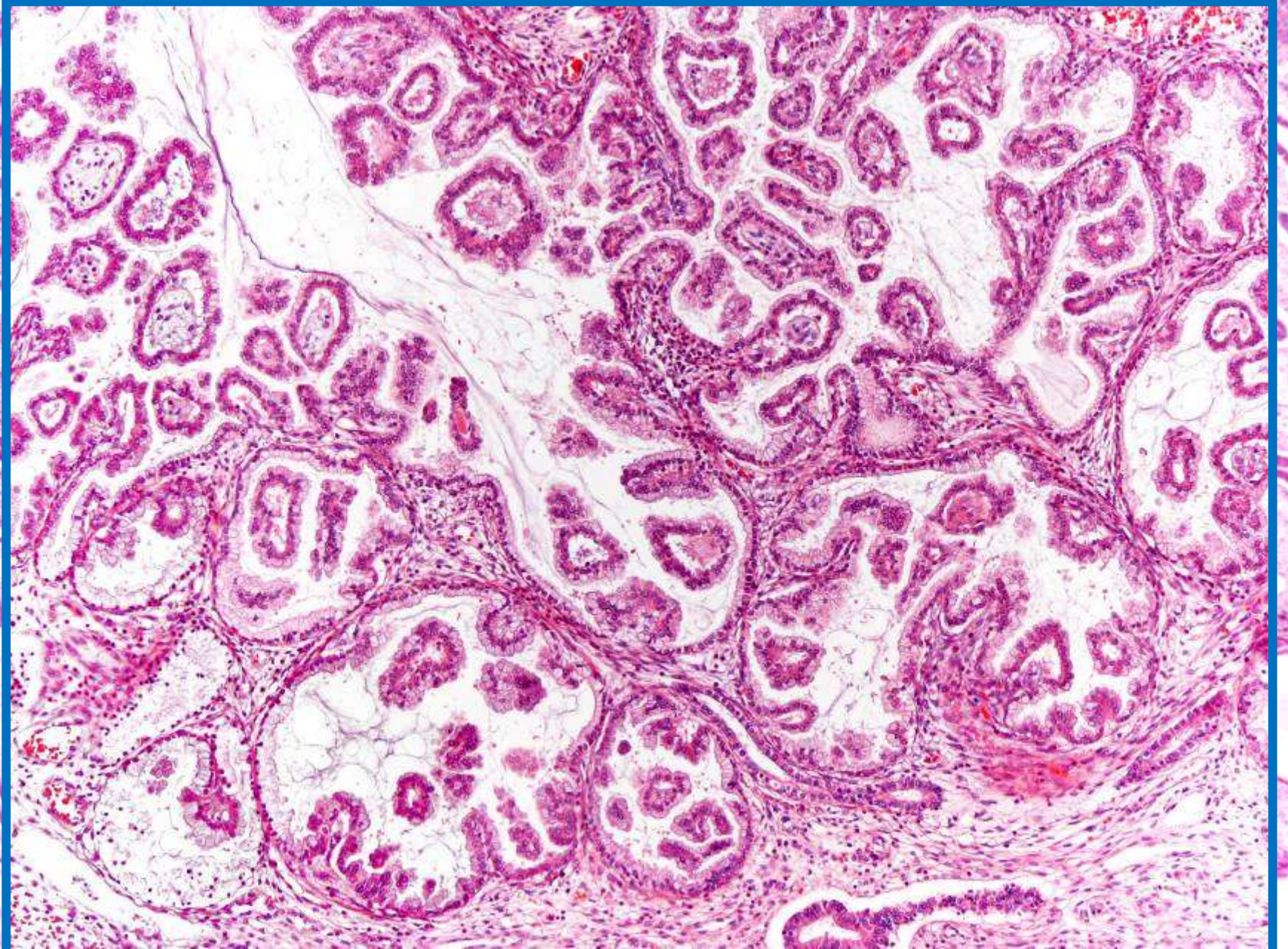


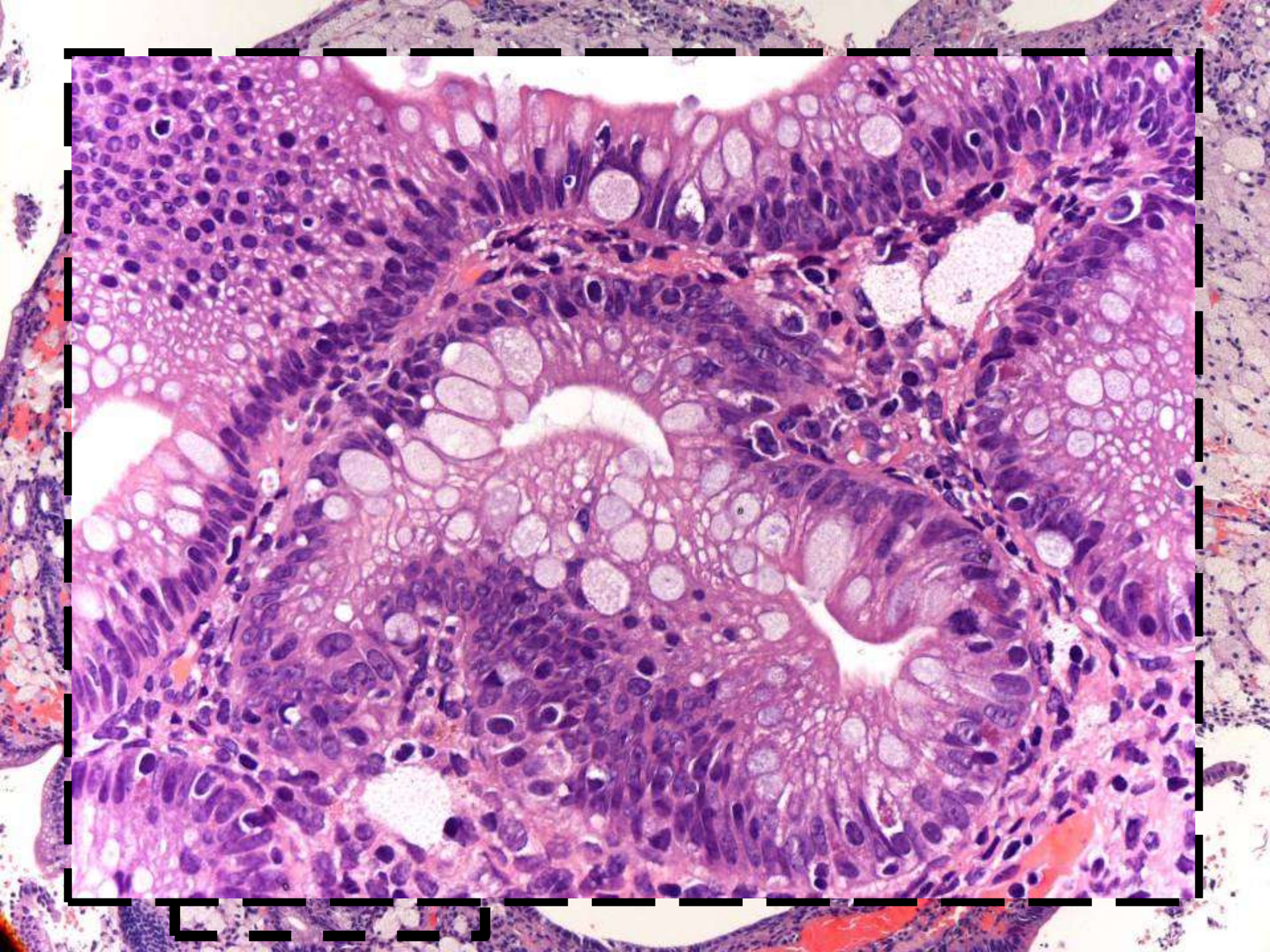
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Endometrial metaplasias and changes

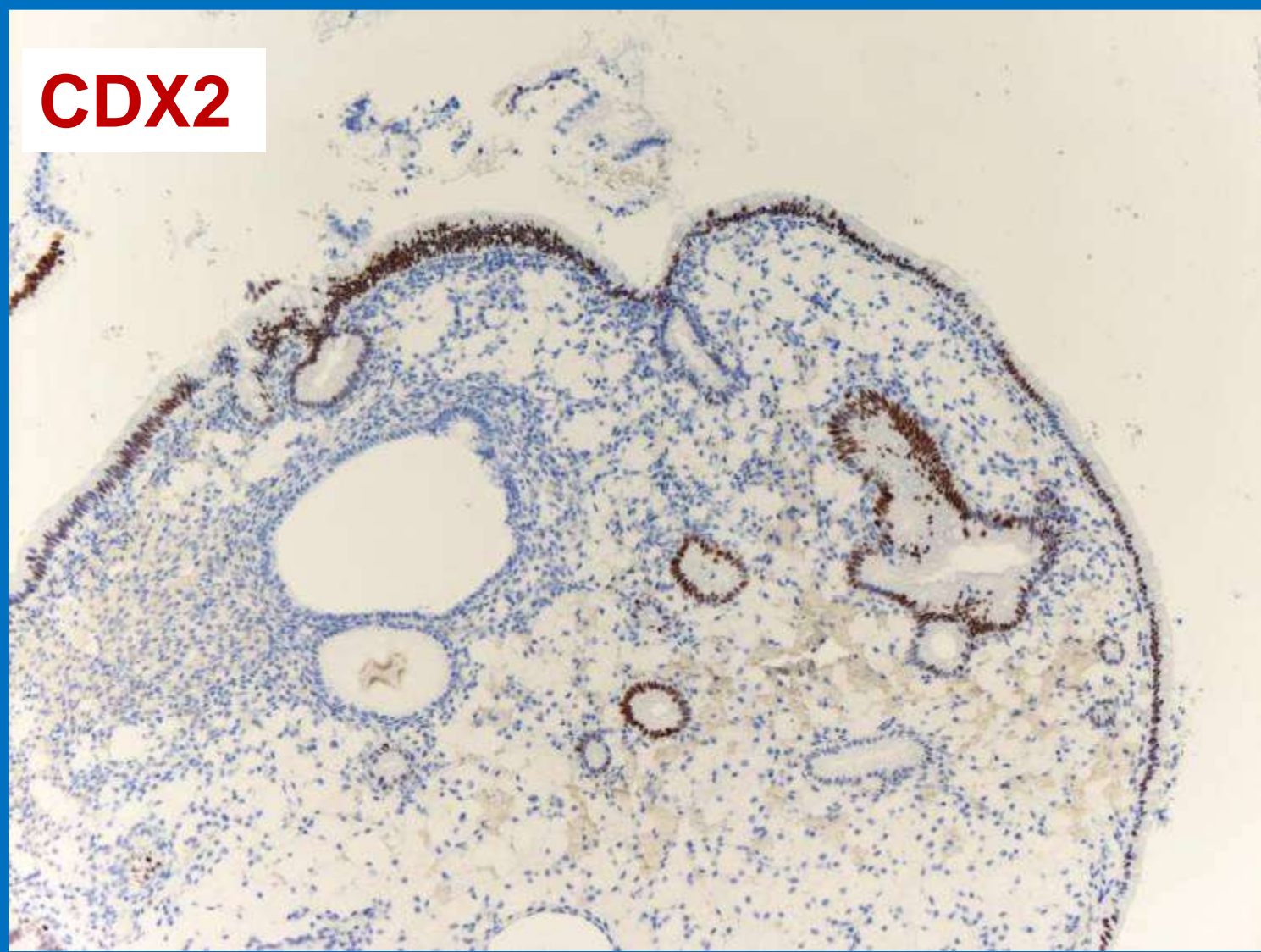
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Stromal	Osseous
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	Adipose
	Smooth muscle
	— Myoid, sex-cord like

E. Intestinal mucinous metaplasias

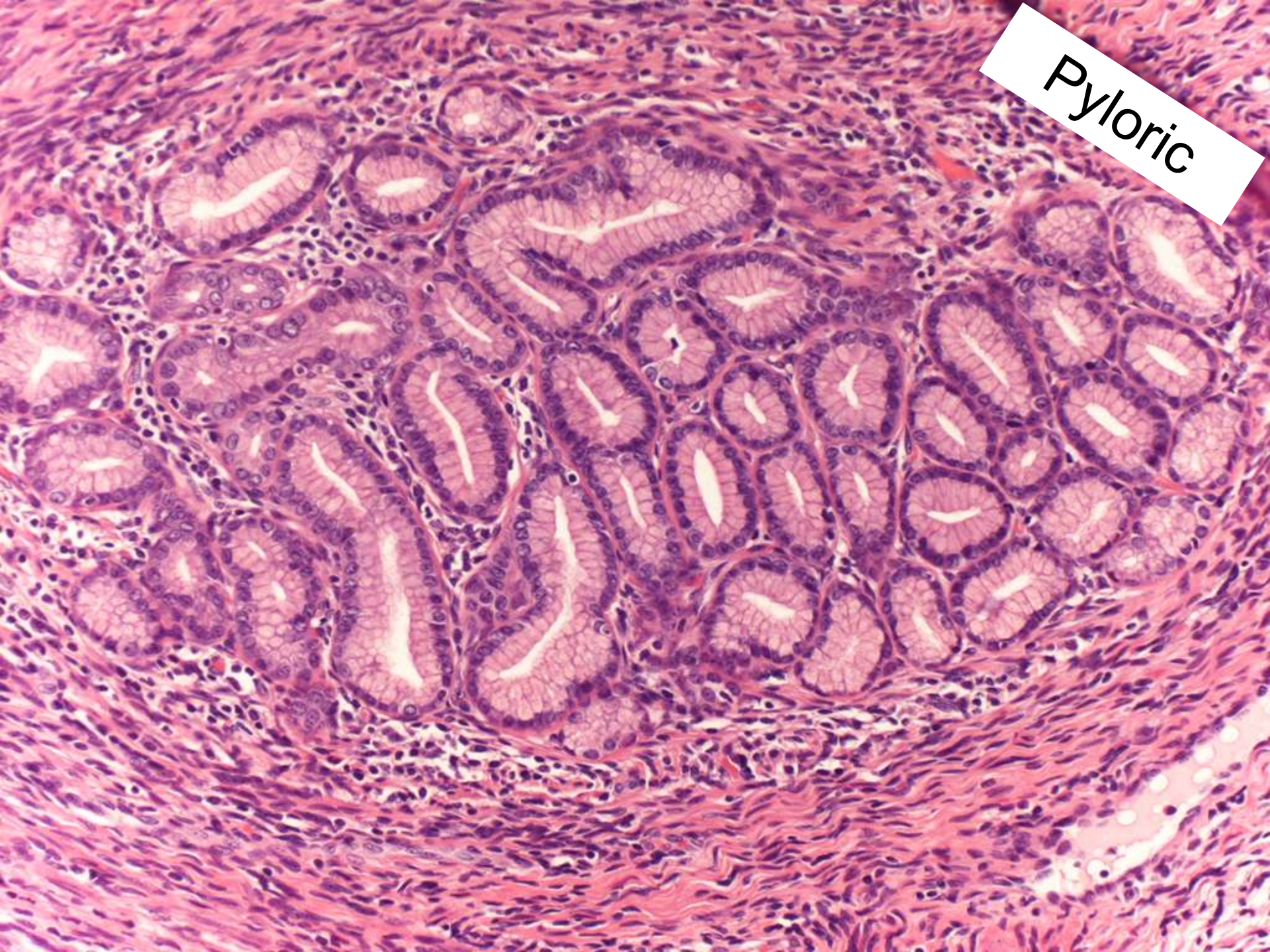
- **Extremely rare**
- **Full intestinal phenotype**
- **EIMM can be found in the cervix where it is nearly always associated with adenocarcinoma**
- **IEMM should be managed cautiously to exclude any endocervical lesions**



CDX2



Pyloric



Case Report

Endometrial Intestinal Metaplasia: A Report of Two Cases, Including One Associated With Cervical Intestinal and Pyloric Metaplasia

Alina Nicolae, M.D., Pablo Goyenaga, M.D., W. Glenn McCluggage, M.D., Ph.D.,
Ovidiu Preda, M.D., and Francisco F. Nogales, M.D., Ph.D.

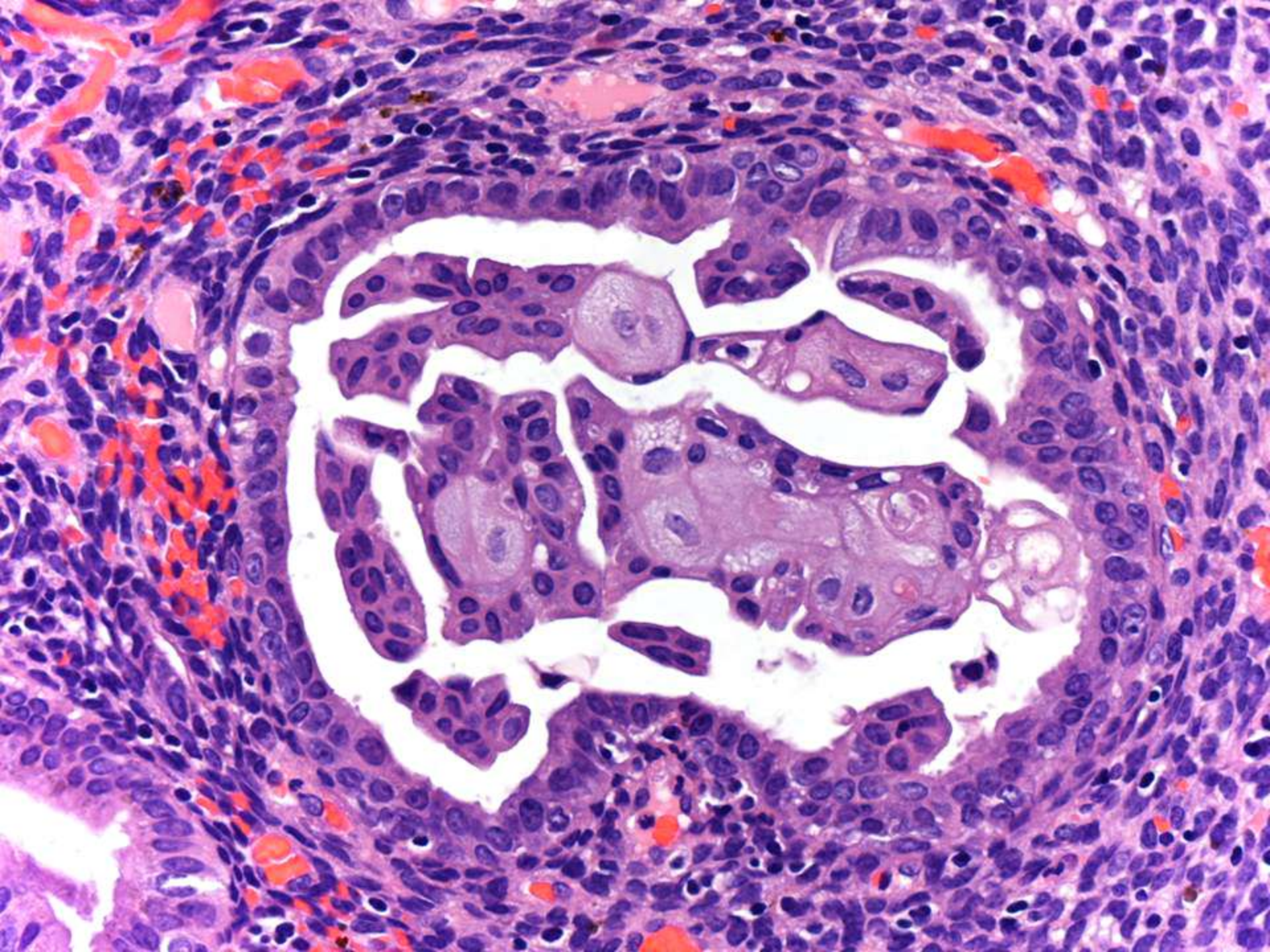
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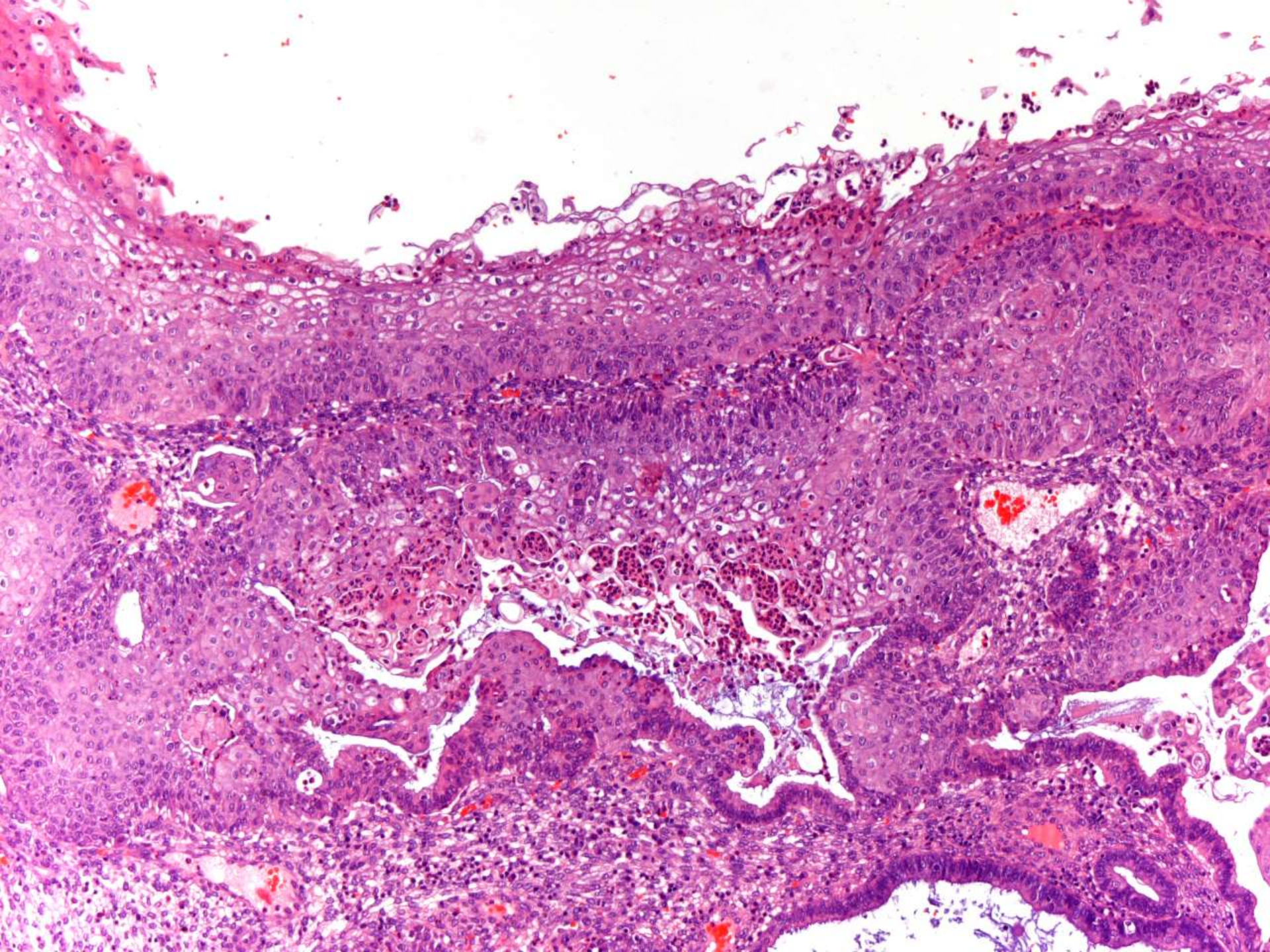
Endometrial metaplasias and changes

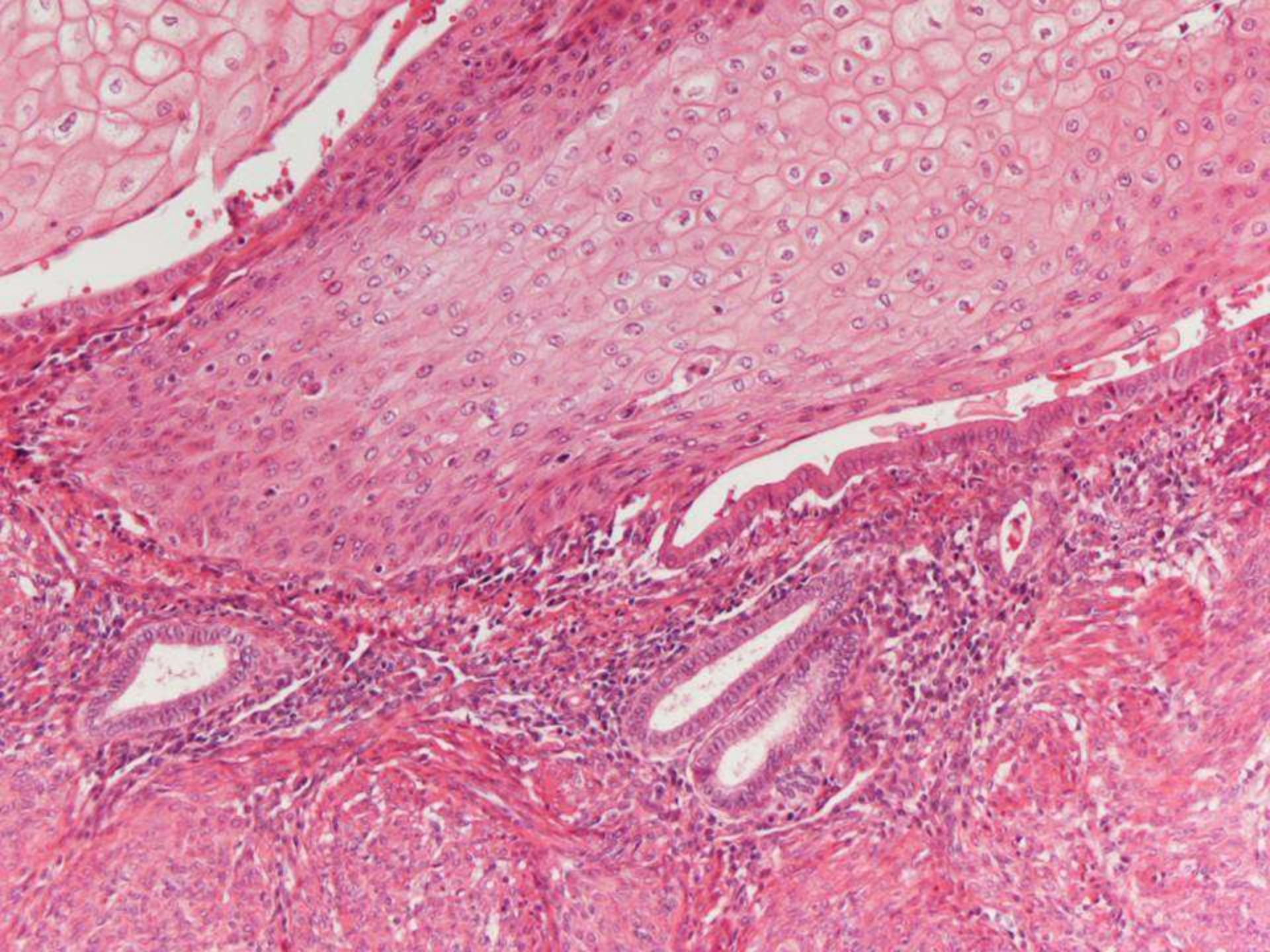
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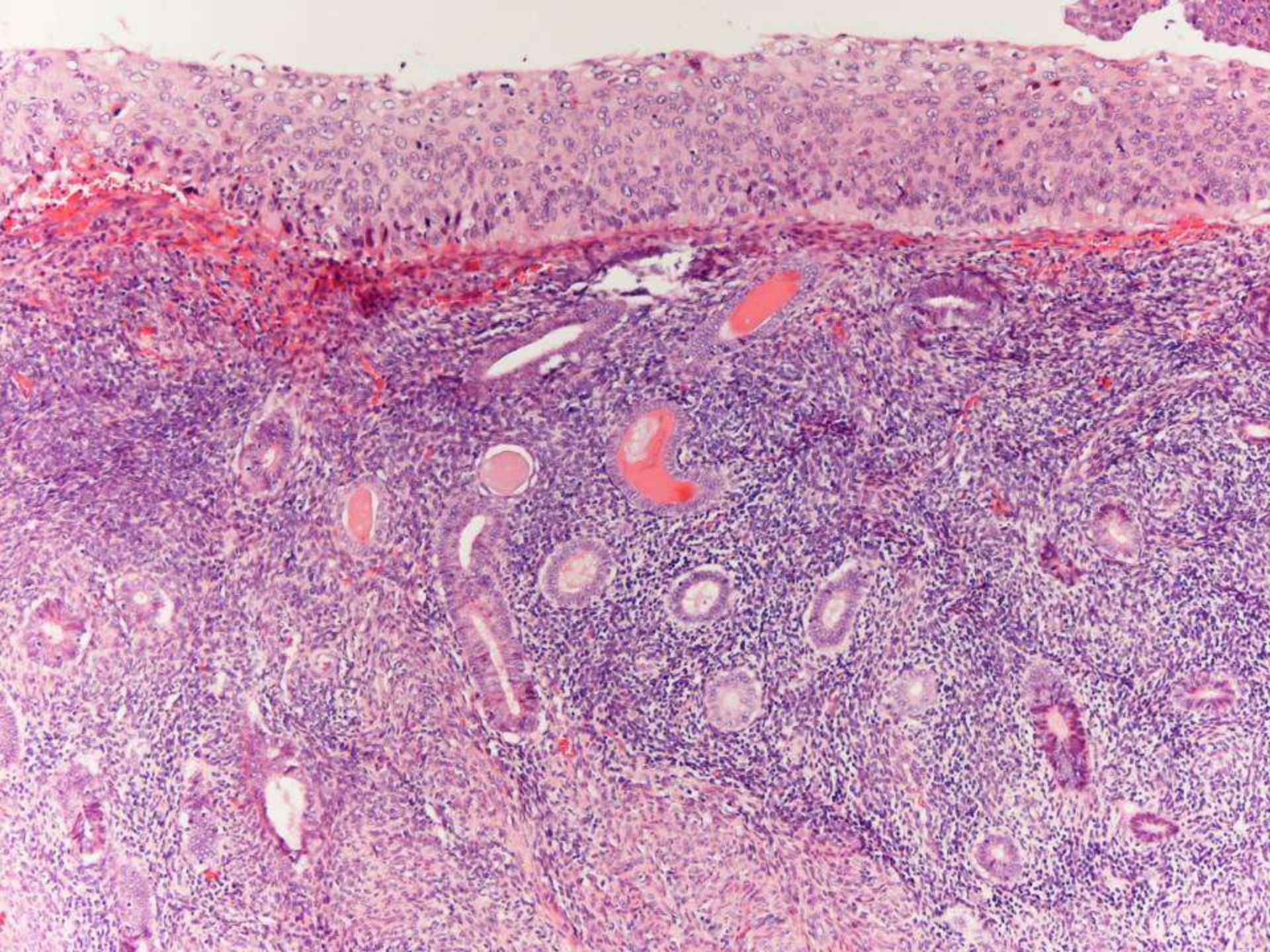
E. Squamous metaplasia

- Term reserved for benign conditions
- Focal but may occur as diffuse (ichthyosis uteri)
- Response to cervical obstruction-
pyometra-tuberculosis-foreign body
- Low malignant potential
- Exclude invasion from cervical Ca and
endometrioid with extensive sq. diff.









E. Squamous metaplasia

Relationship with morules:

- **20% ESM originates from morules**
- **Not all ESM are neoplastic**

Table 1 Classification of endometrial metaplasias and changes

Endometrial metaplasias and changes

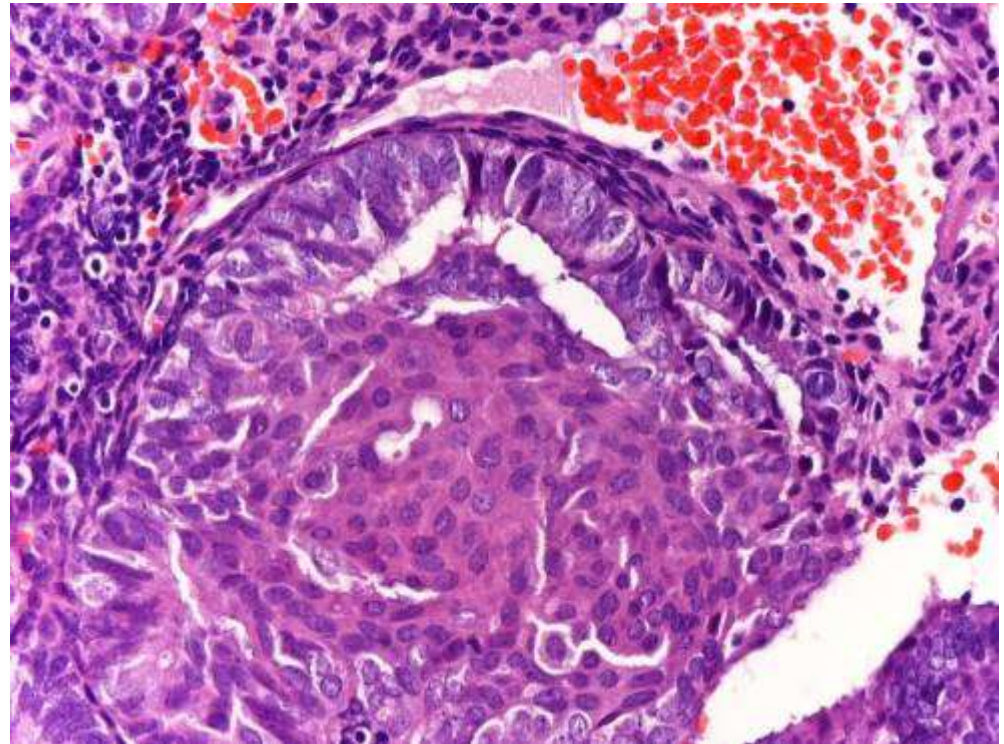
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INTRAGLANDULAR MORULES OF THE ENDOMETRIUM

FRANK R. DUTRA, M.D.

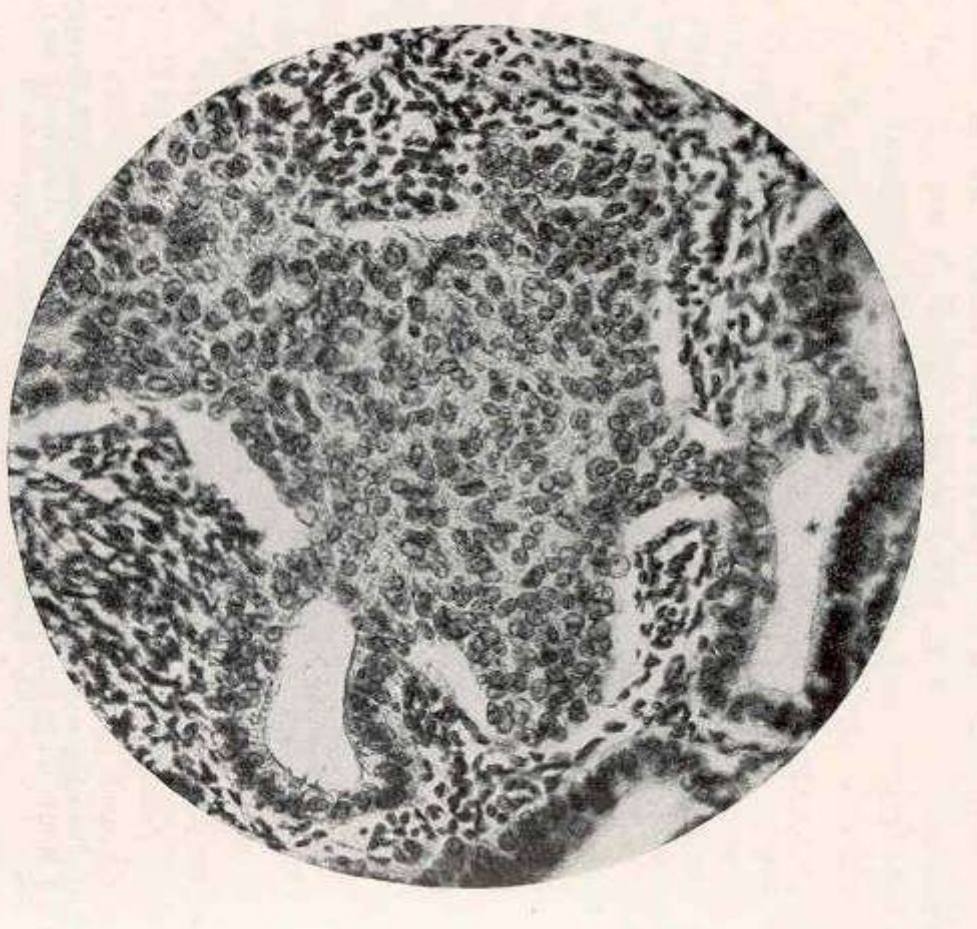
Eden Hospital, Castro Valley, California

- Dutra's description defined morules as a characteristic type of metaplasia



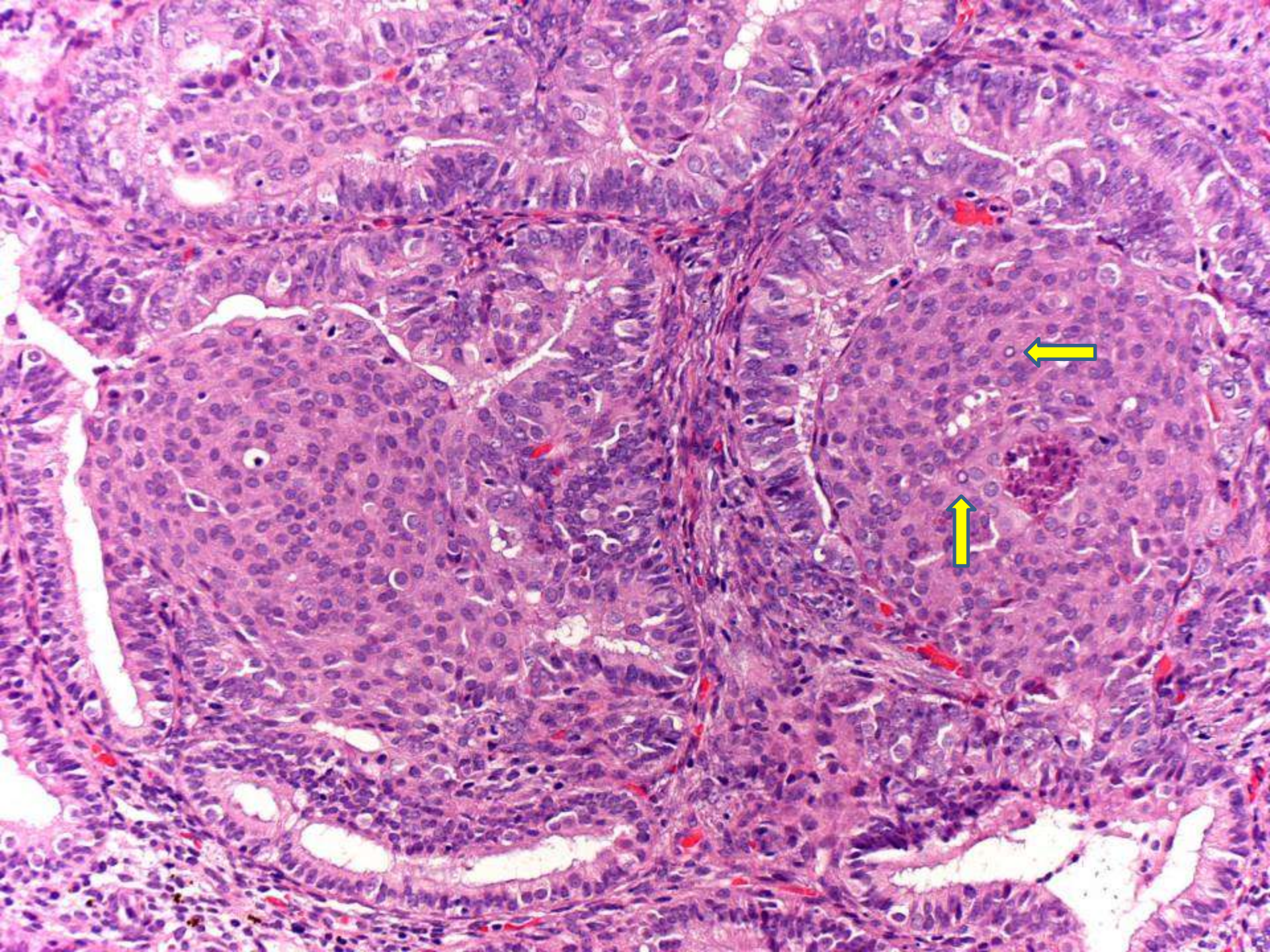
Sogenannte Plattenepithelknötchen in der hyperplastischen Korpusschleimhaut und in Korpuspolypen. Karzinoide.

Von der einfachen Oberflächenbekleidung der Korpushöhle mit Plattenepithel ist zu unterscheiden ein scheinbar recht seltener Befund, den ich in 11 Fällen erhoben habe und mit dem andere Befunde von HUNZIKER, ENGELHORN, POLANO, SITZENFREY, ASCHHEIM, AHLSTRÖM, SCHILLER in Übereinstimmung stehen. Es handelt sich (s. Abb. 73—76) um Epithelaufschichtung



R Mayer 1930, in Henke Lubarsch

Nihil sub sole novum
nec valet quisquam
dicere ecce hoc
recens est iam enim
præcessit in
saeculis quæ fuerunt
ante nos



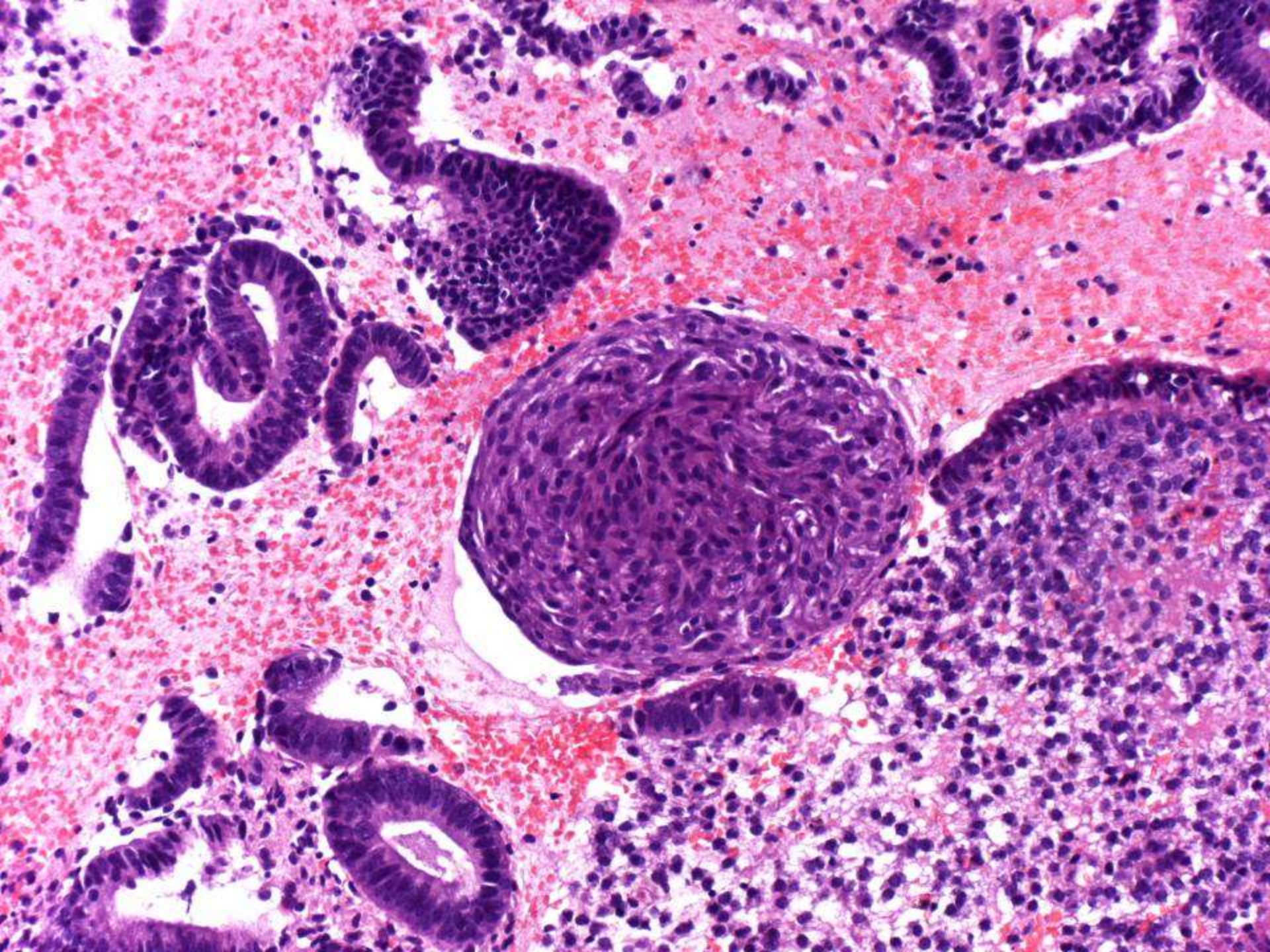
An Immunohistochemical Study of Morules in Endometrioid Lesions of the Female Genital Tract: CD10 Is a Characteristic Marker of Morular Metaplasia

Clin Cancer Res 2006;12(14) July 15, 2006

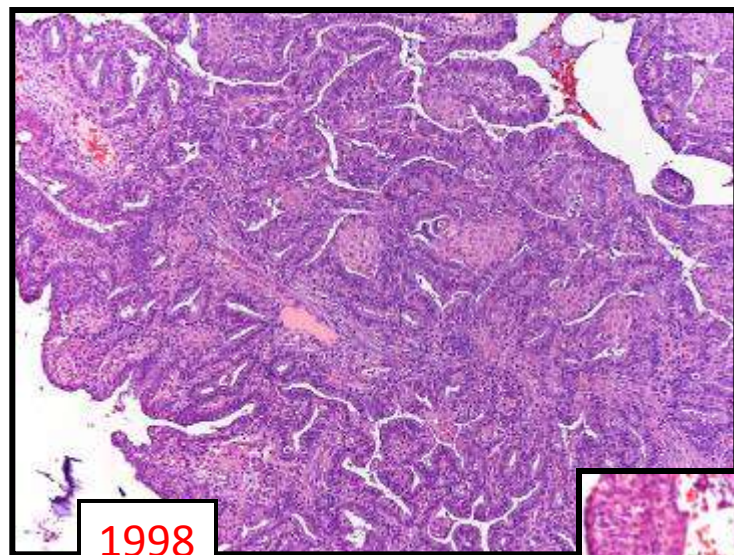
- **46 patients corresponding to 53 specimens**
- **Age: 21 to 86 years (m 52.6)**
- **Follow-up in 26 patients, range 4-62 month**
- **Simultaneous and with repeated biopsies**

Clinicopathological features of morules

- Association with low grade lesions
- A persistent lesion unchanged by progesterone treatment
- Morules are identical in simultaneous ovarian / endometrial *endometrioid* lesions
- Associated with glandular complexity and consequently a marker (Exception 2%)

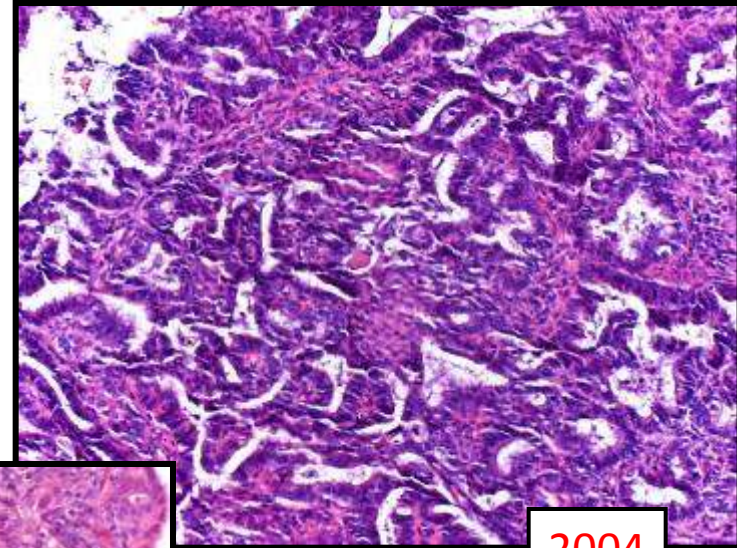


No hormonal response (mutational)

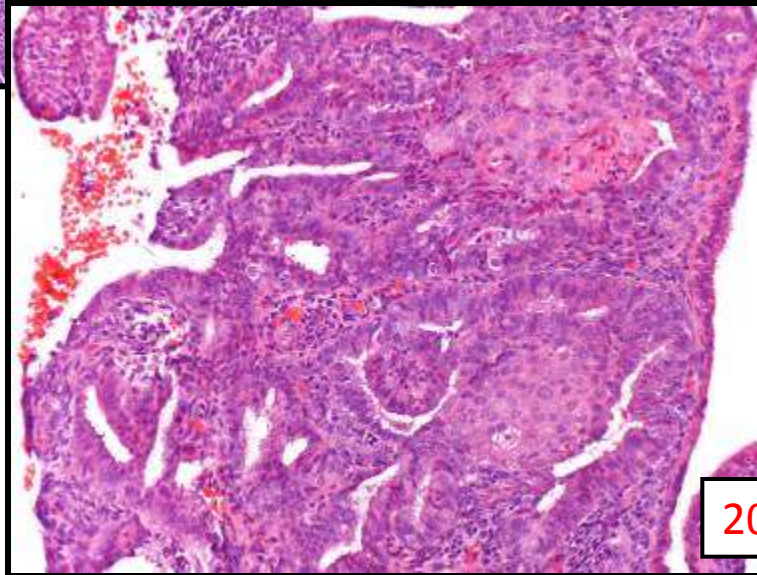


1998

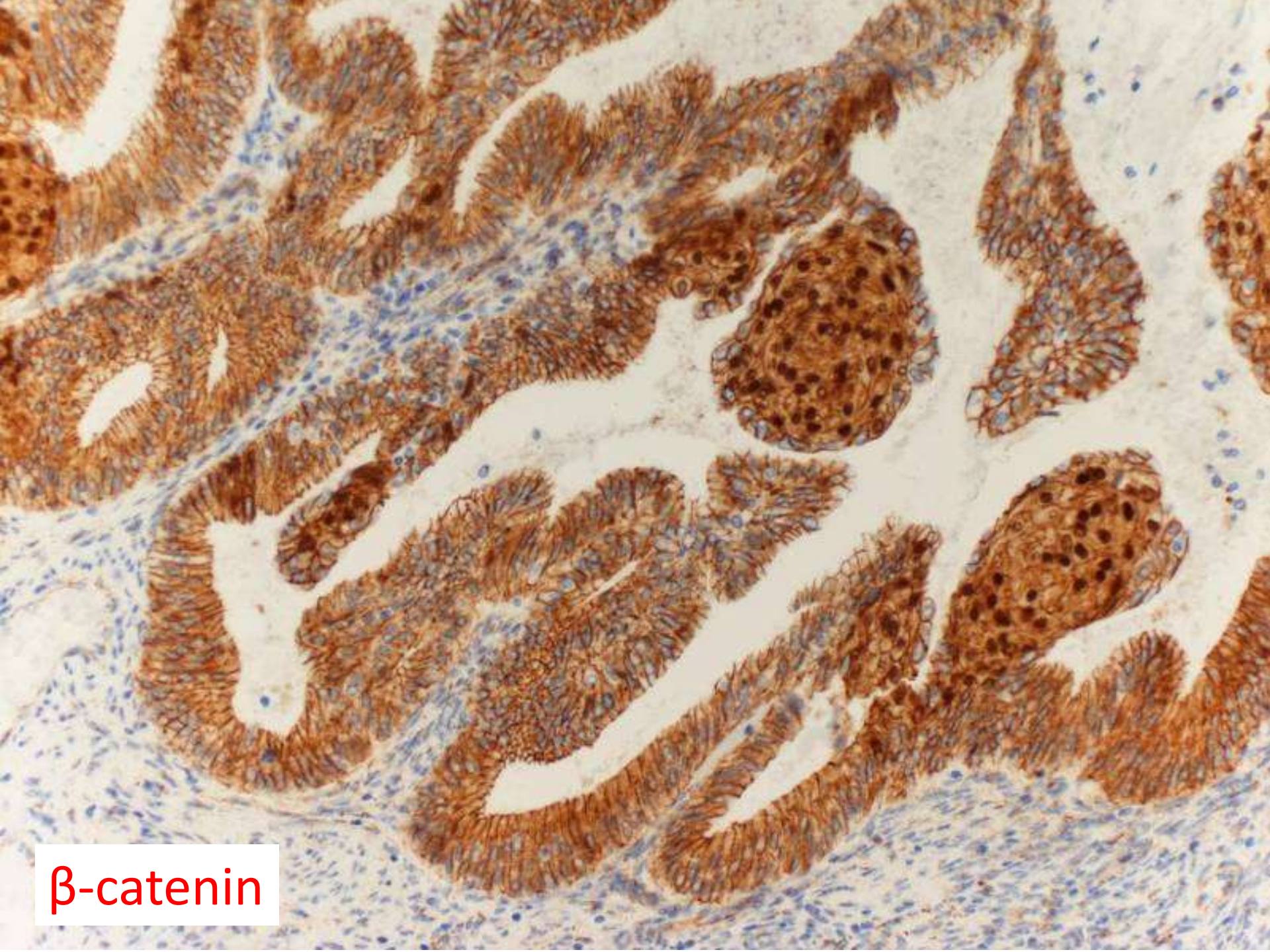
35 yr infertile pt
MPA treatment



2004



2000



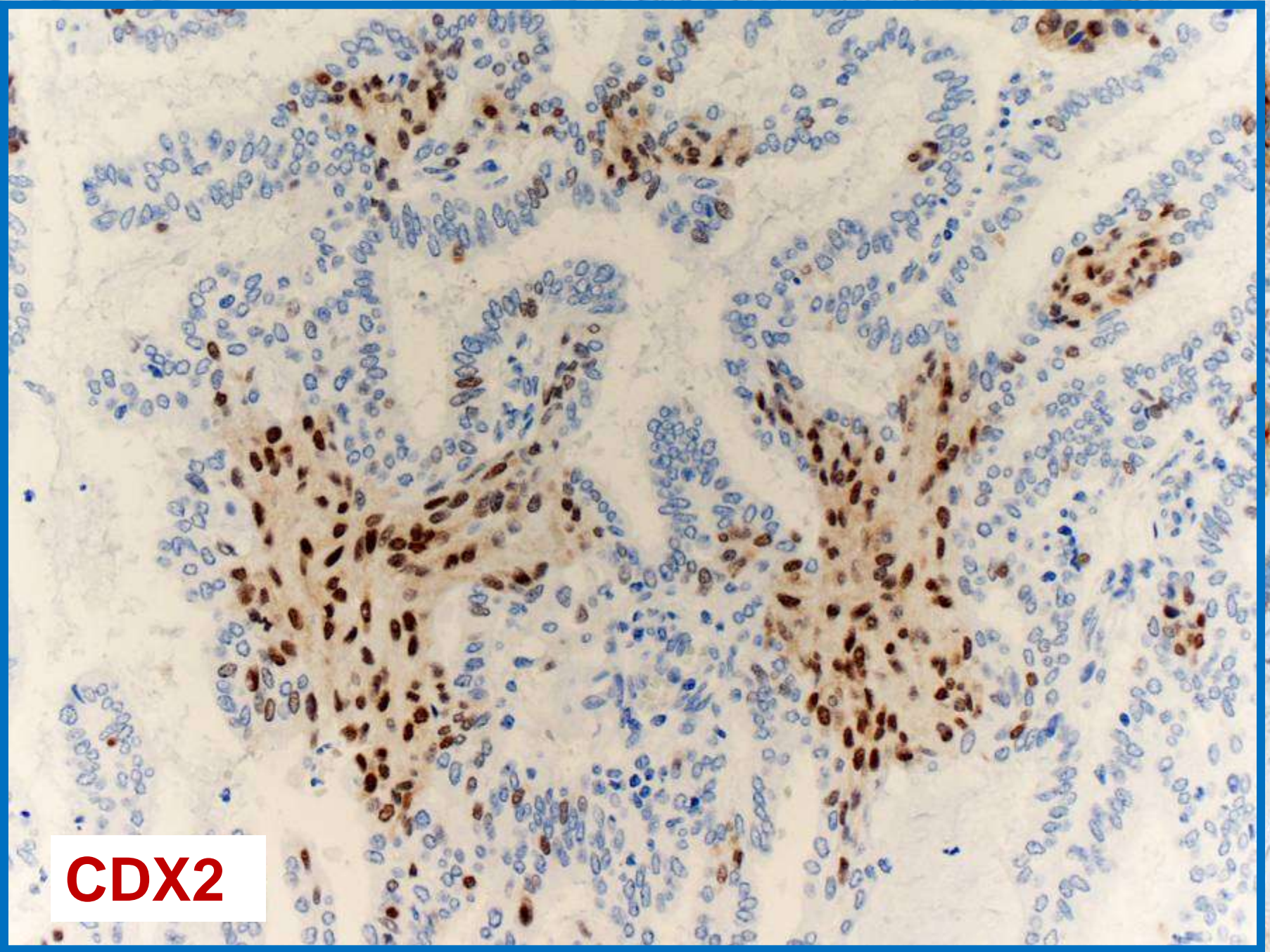
β -catenin

Distinct Molecular Alterations in Complex Endometrial Hyperplasia (CEH) With and Without Immature Squamous Metaplasia (Squamous Morules)

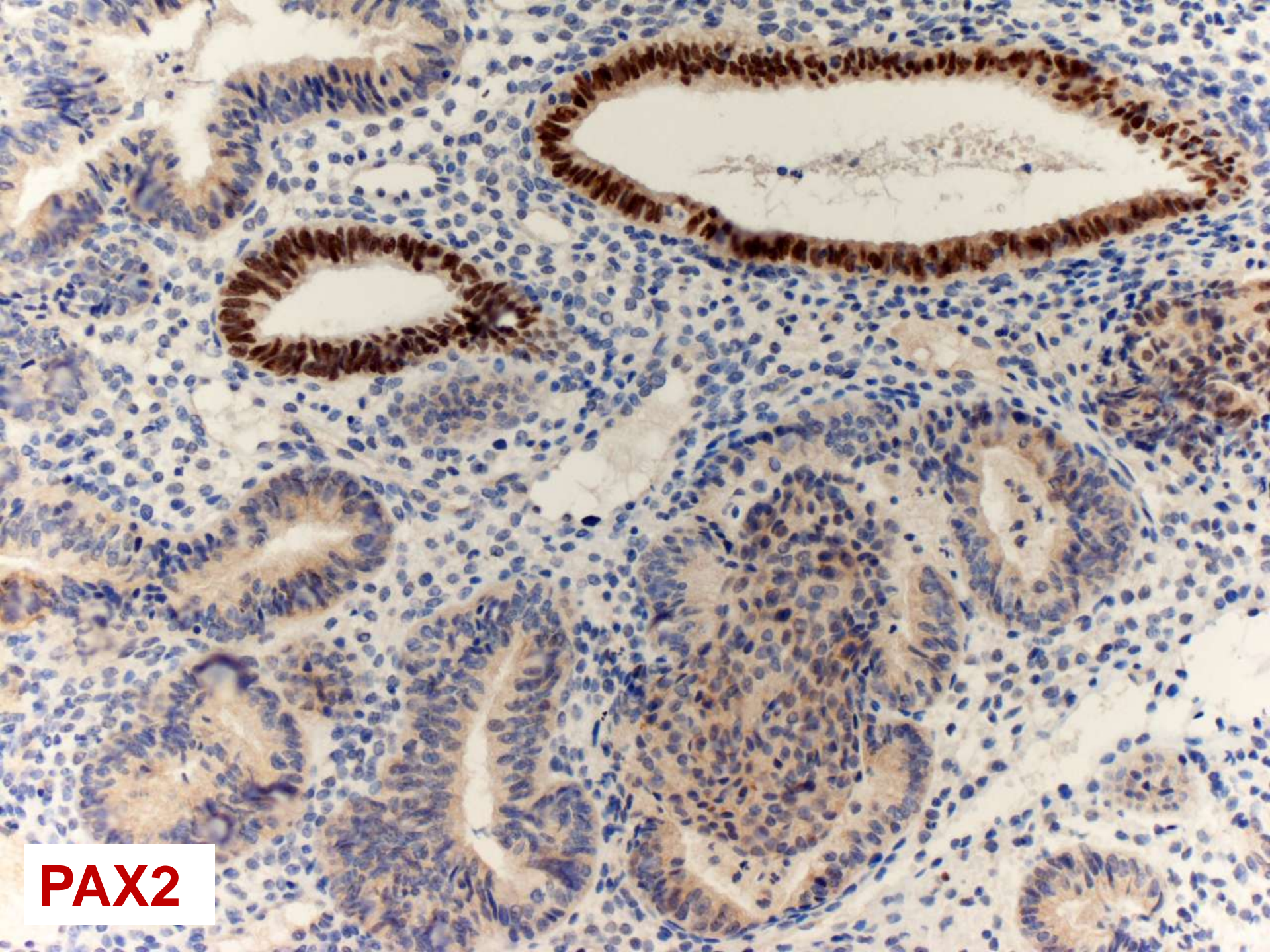
Brachtel et al

TABLE 1. Immunohistochemical and Mutational Analysis

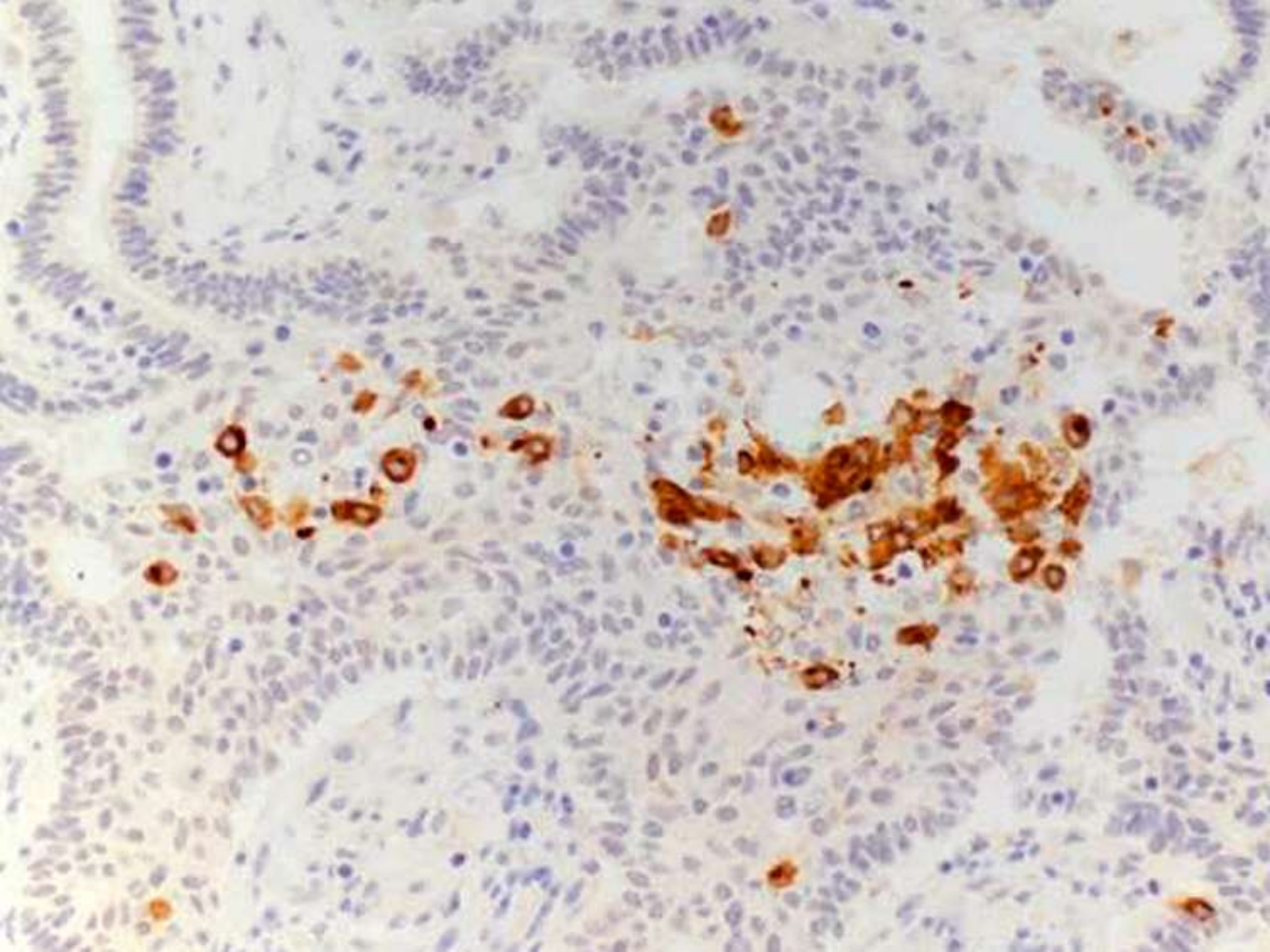
Case No.	Immunohistochemical Nuclear Beta-Catenin Expression		Mutational Analysis			Microsatellite Instability
	Glands	Morules	Beta-Catenin	PTEN	K-ras	
Complex Endometrial Hyperplasia With Squamous Morules						
1	n +	n +++	N	N	N	N
2	n +	n +++	G(GGA)34(GAA)E	N	N	N
3	n +	n +++	N	N	N	N
4	n +	n +++	G(GGA)34(GTA)V	N	N	N
5	n +	n ++	N	N	N	N
6	n +	n +	N	N	N	N
7	n +	n ++	S(TCT)33(TGT)C	N	N	N
8	n (+)	n ++	N	N	N	N
9	n ++	n ++	N	N	N	N
10	n +	n ++	D(GAC)32(TAC)Y	N	N	N
11	n +	n ++	D(GAC)32(TAC)Y	N	N	N
12	n +	n ++	S(TCT)33(TTT)F	N	N	N
13	n +	n ++	D(GAC)32(GCC)A	N	N	N
Complex Endometrial Hyperplasia Without Squamous Morules						
14	n neg		N	C(TGT)296(TGA)Stop(Ex.8)	G(GGT)12(GTT)V	MI +
15	n neg		N	244 del C (Ex.7)	G(GGT)12(GAT)D	N
16	n ++		N	N	N	N
17	n neg		N	N	N	N
18	n neg		N	N	N	N
19	n ++		N	G(GGA)230(GAA)E (Ex.7)	N	N
20	n neg		N	N	N	N
21	n neg		N	251 ins TGAT (Ex.7)	G(GGC)13(GAC)D	N
22	n neg		S(TCT)45(GCT)A	N	G(GGT)12(GAT)D	N
23	n + (rare)		N	N	N	N
24	n neg		N	N	N	N



CDX2



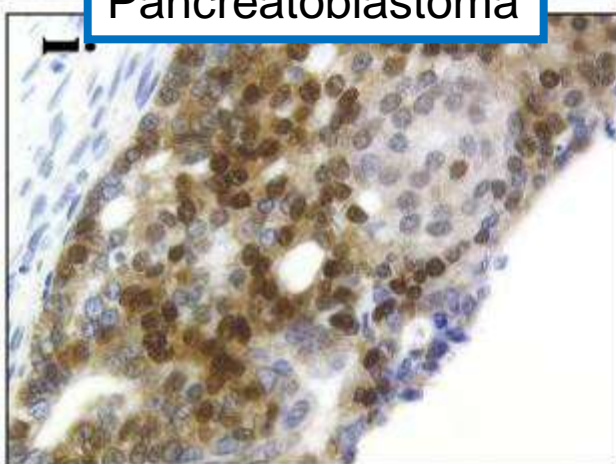
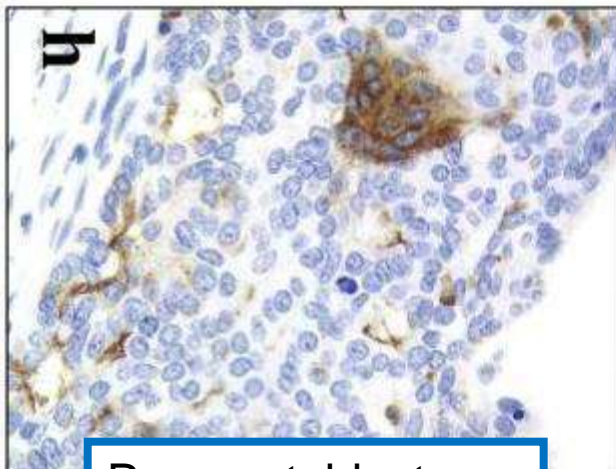
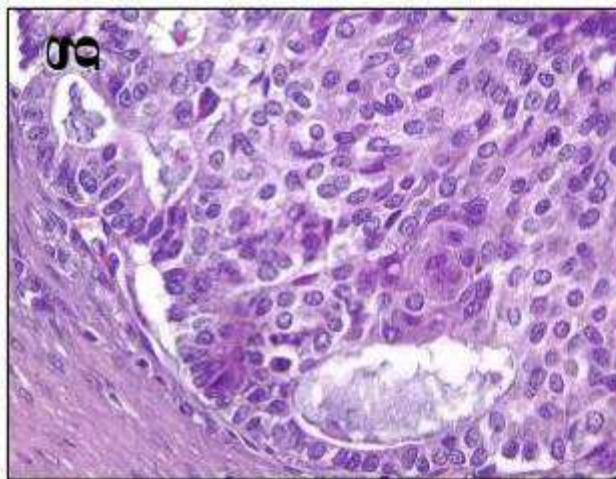
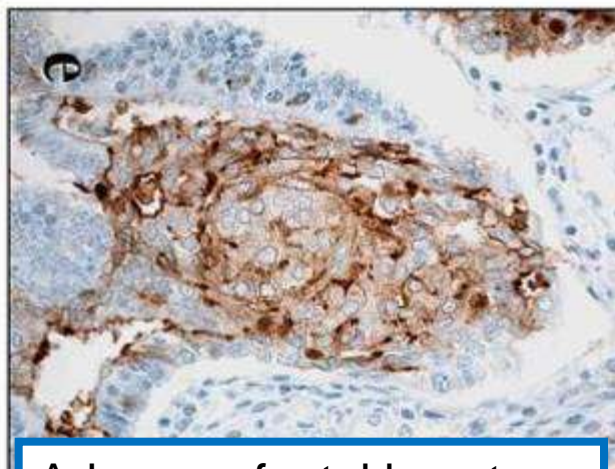
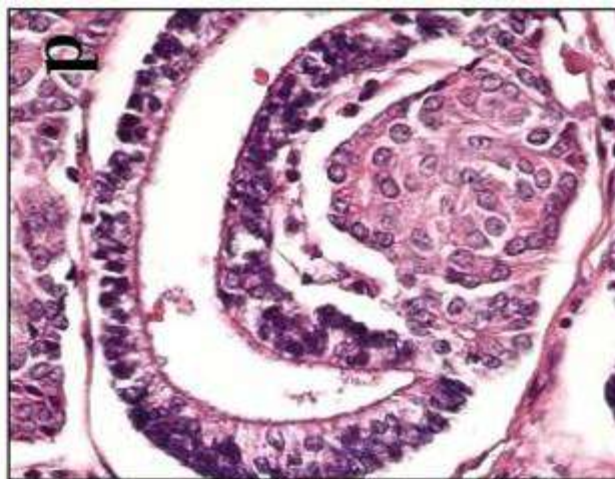
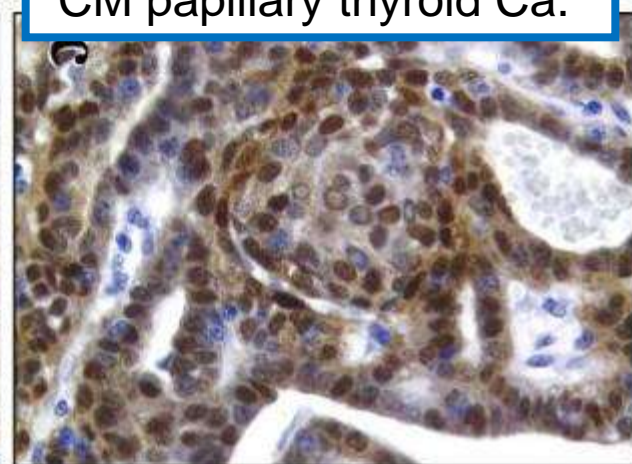
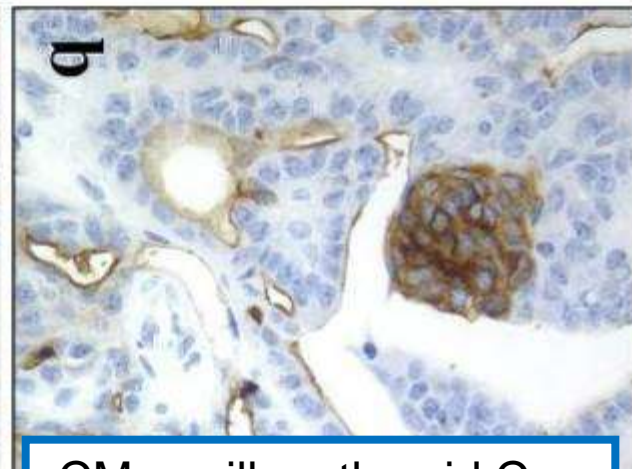
PAX2





A high-magnification microscopic image of a tissue section. The image shows numerous cells with prominent, dark blue nuclei, likely stained with hematoxylin. The cytoplasm and extracellular matrix are stained with a brownish-orange dye, possibly eosin or a specific immunohistochemical stain. The overall appearance is that of a histological slide, possibly showing a glandular or epithelial structure. The image is framed by a blue border.

CRG



Pancreatoblastoma

Adenoca. foetal lung type

CM papillary thyroid Ca.

Table 1 Classification of endometrial metaplasias and changes

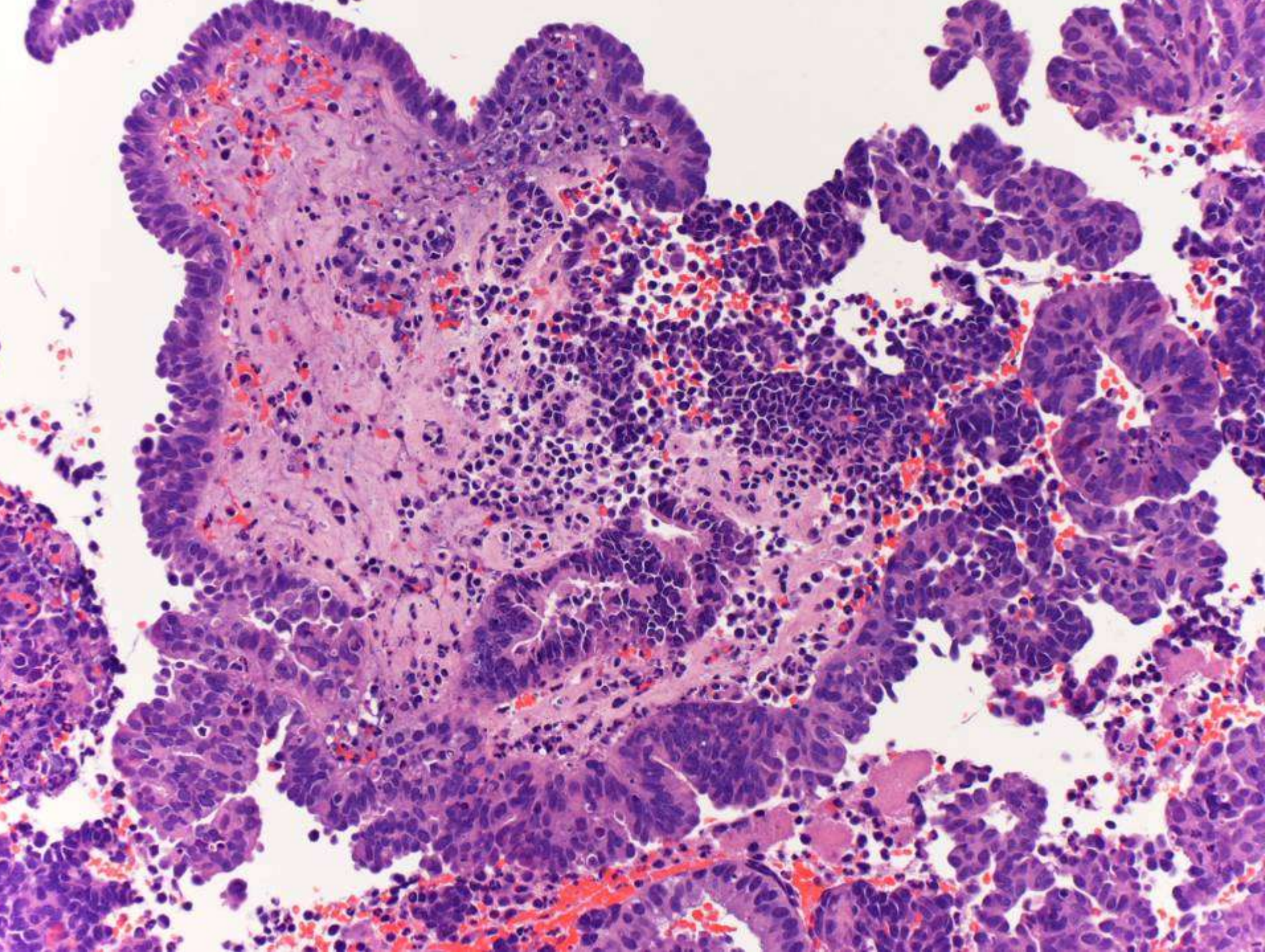
Endometrial metaplasias and changes

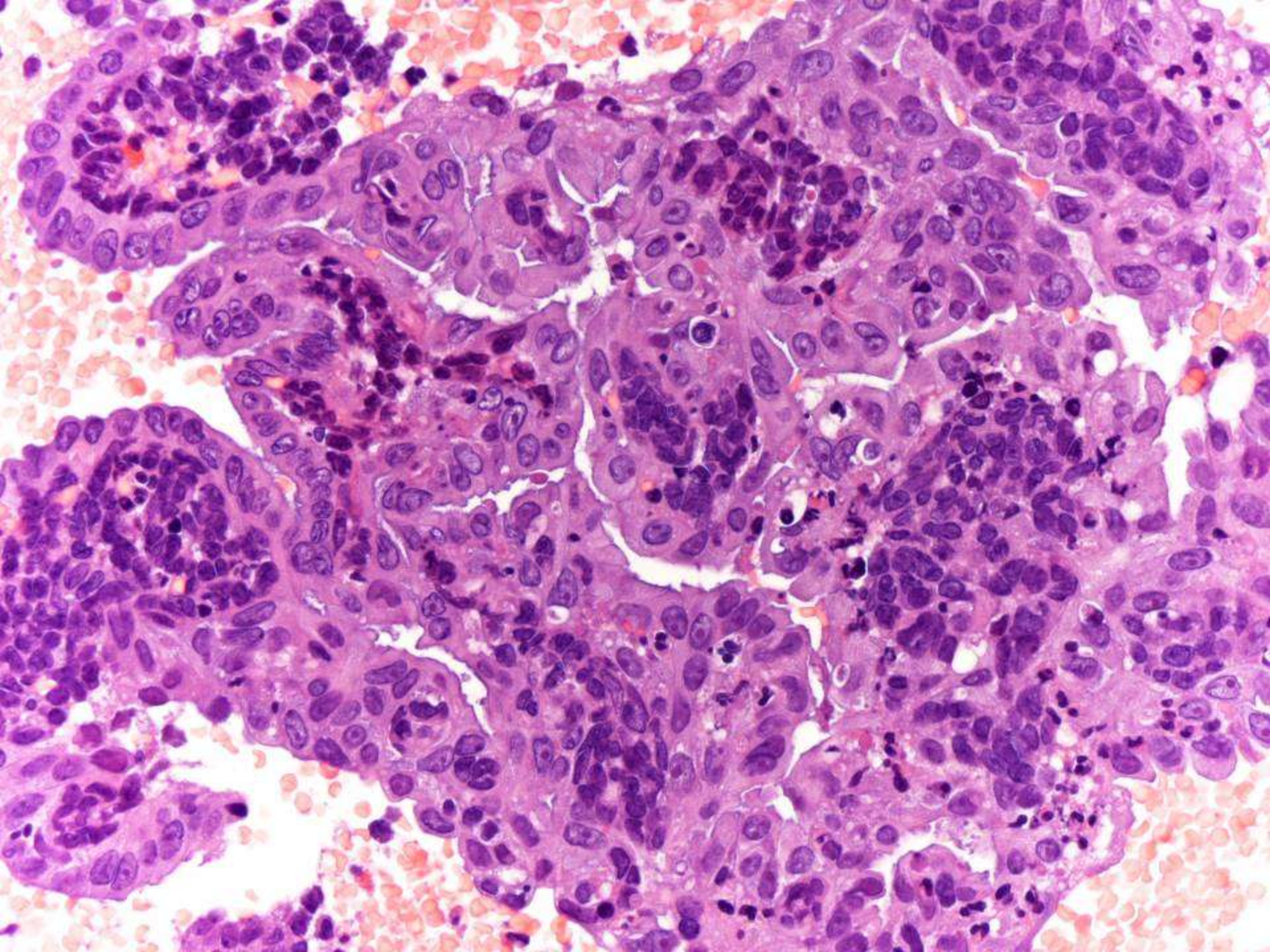
Epithelial	Ciliary, tubal (simple and complex)
	Mucinous (simple and complex)
	— Intestinal variant
	Squamous
	Morules
	Reactive changes
	— Surface, papillary syncytial change
	— Hobnail variant
	— Oncocytic, oxyphilic, eosinophilic
	— Clear cell, secretory
Stromal	Osseous
	Cartilaginous
	Adipose
	Smooth muscle
	— Myoid, sex-cord like

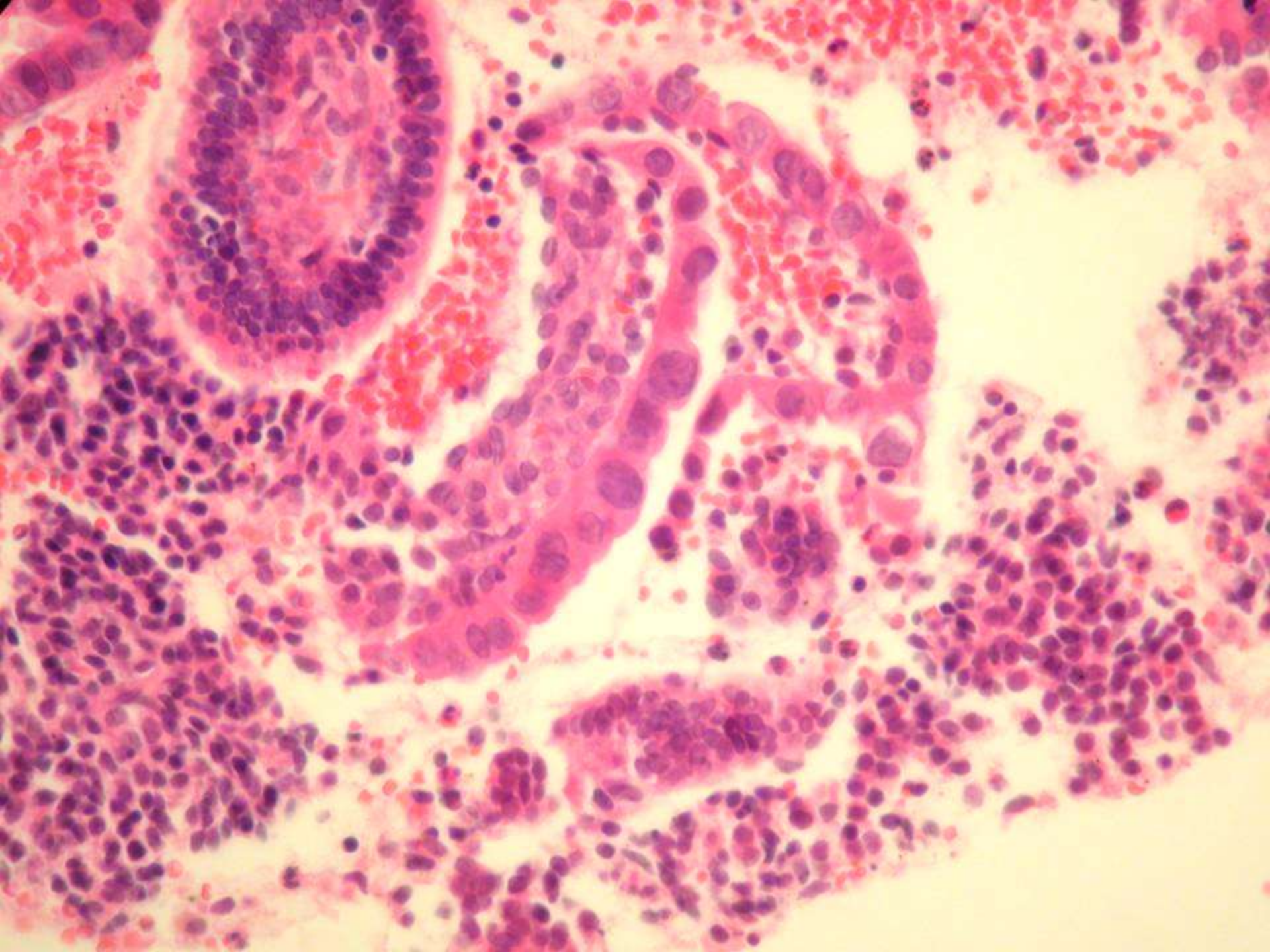
Endometrial surface papillary syncitial change (SPSC)

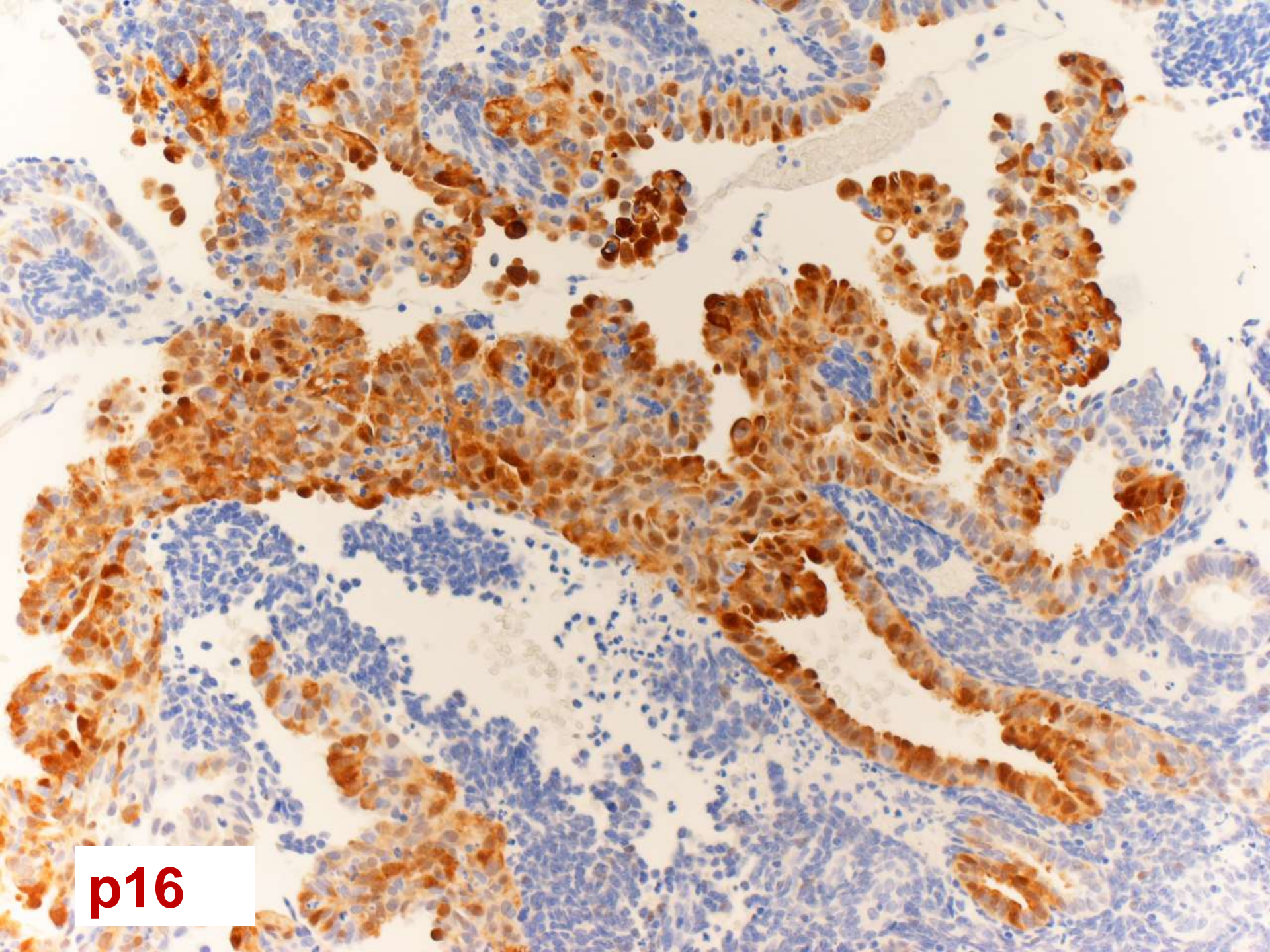
Associated with endometrial breakdown:

- (cyclic desquamation, uterine bleeding episodes of any type incl. carcinoma)
- **Significance unknown**
 - Related to endometrial regeneration ?
 - A degenerative phenomenon secondary to ischaemia ?





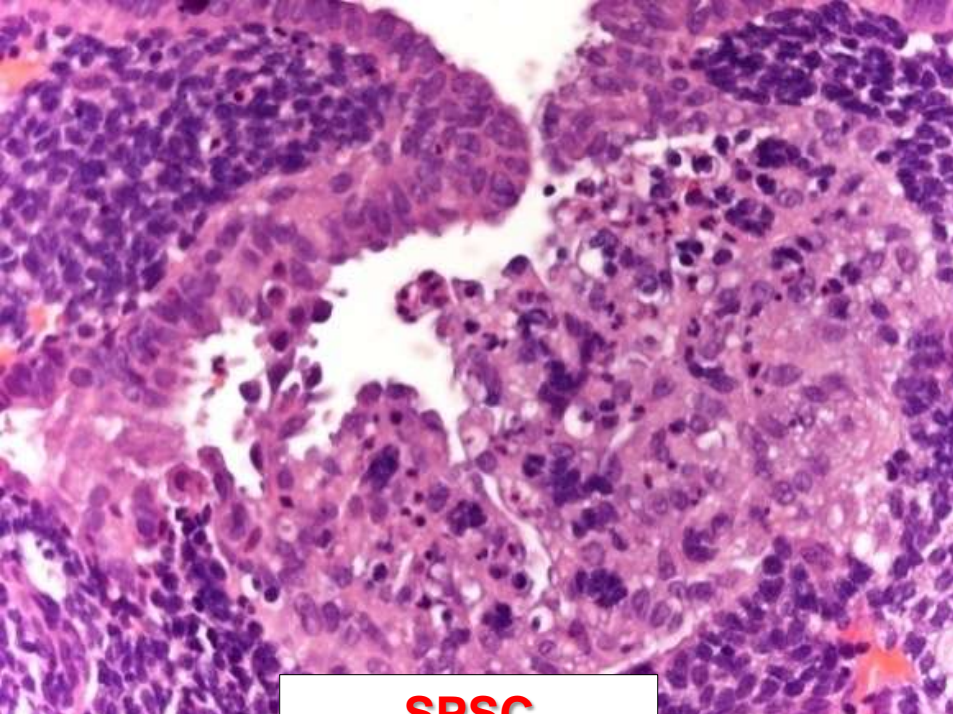




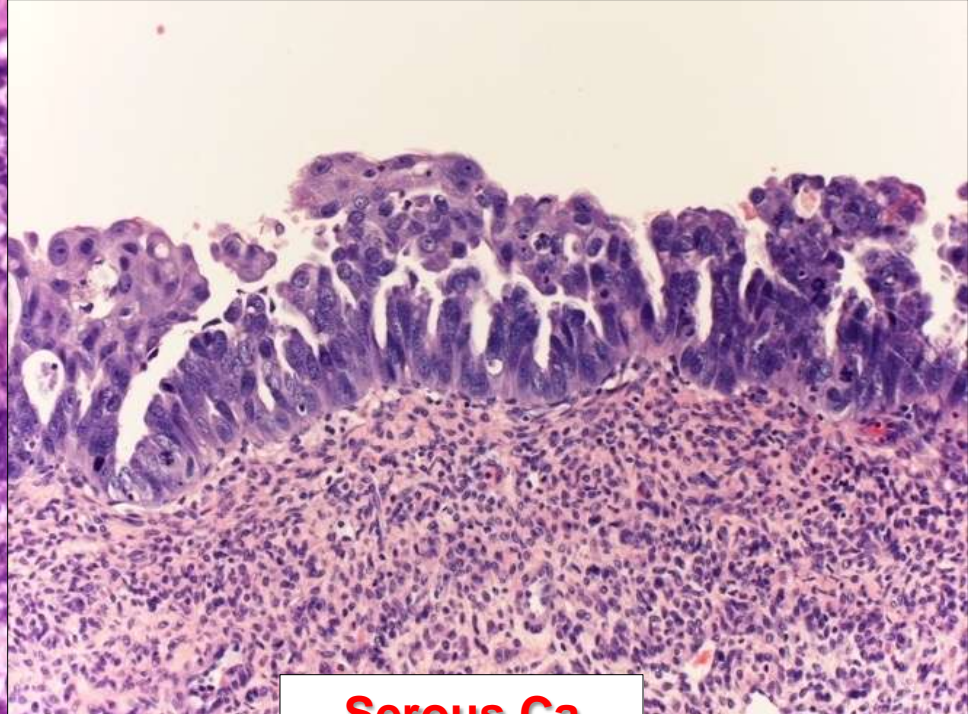
p16

Endometrial surface papillary syncytial change (SPSC)

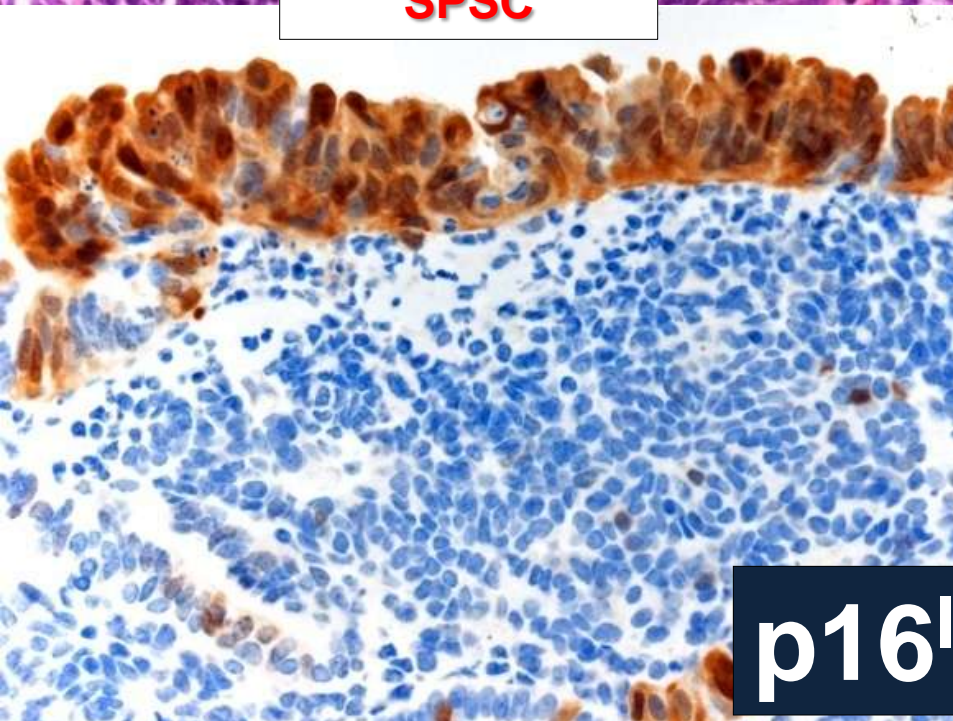
- **Relevant to differential diagnosis with incipient, surface serous papillary carcinoma**
 - **Associated with breakdown changes**
 - **Immunophenotype:**
 - **Weak p53**
 - **Low or absent Ki67 index**
 - **Strong p16^{INK4A} positivity**



SPSC



Serous Ca



p16^{INK4A}



This figure displays four immunohistochemistry (IHC) images comparing two types of ovarian cancer: Serous Papillary Cystic Carcinoma (SPSC) and Serous Cystic Carcinoma (Serous Ca). The images are arranged in a 2x2 grid. The top row shows Ki67 staining, and the bottom row shows p53 staining. In the SPSC images (left column), there is a lower density of brown-stained cells compared to the Serous Ca images (right column). The Serous Ca images show a high density of brown-stained cells, indicating a higher proliferation rate and more frequent p53 expression. The labels 'Ki67' and 'p53' are in dark blue boxes at the top and bottom center, respectively. The labels 'SPSC' and 'Serous Ca' are in red text boxes at the bottom left and right, respectively.

Ki67

SPSC

Serous Ca

p53

Endometrial surface papillary syncytial change (SPSC)

- **Relevant to differential diagnosis with micropapillary carcinoma**
 - **SPSC may occur in adenocarcinoma during abnormal uterine bleeding**
 - **Classic breakdown features absent**
 - **Patient's age**

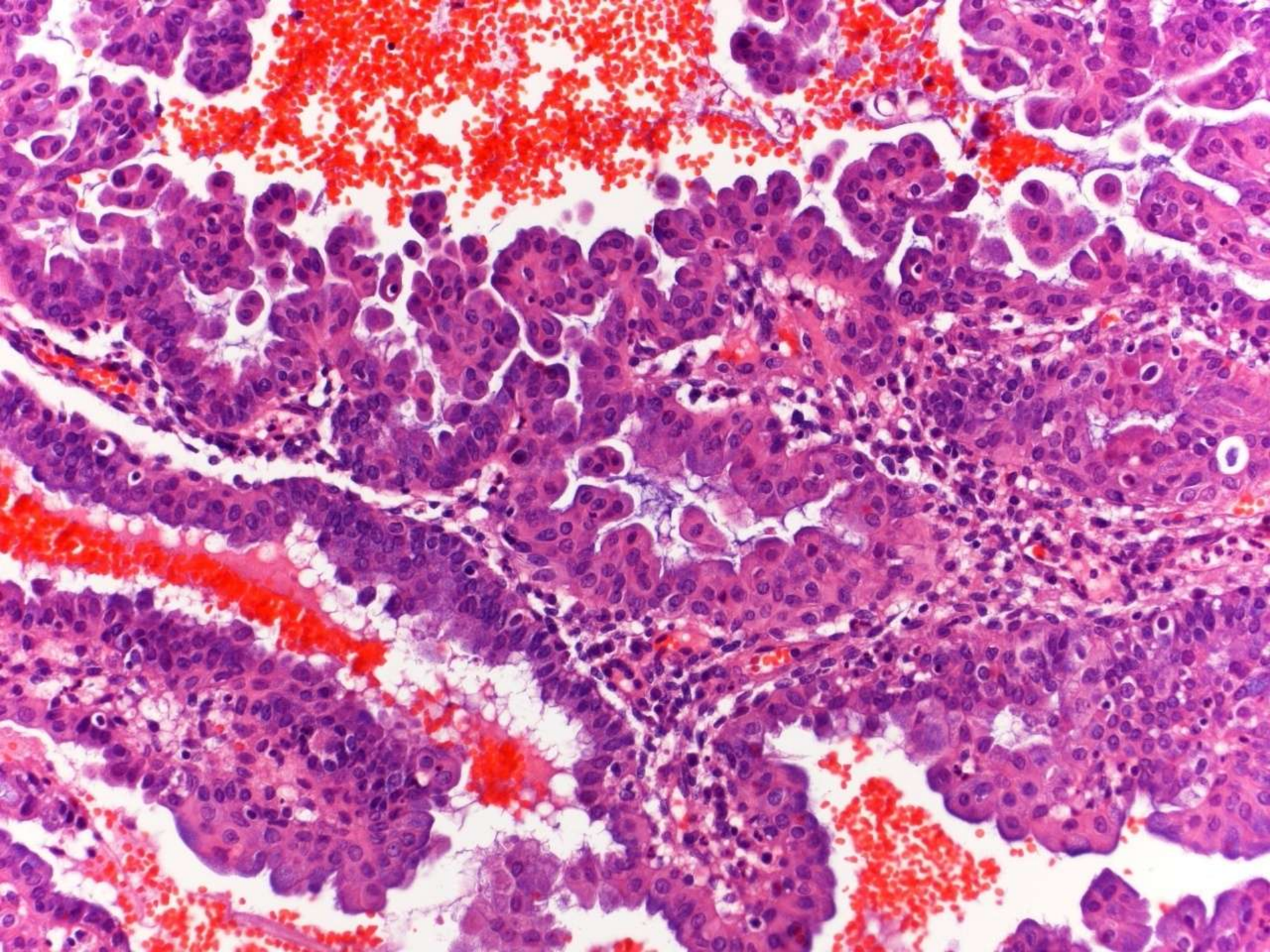


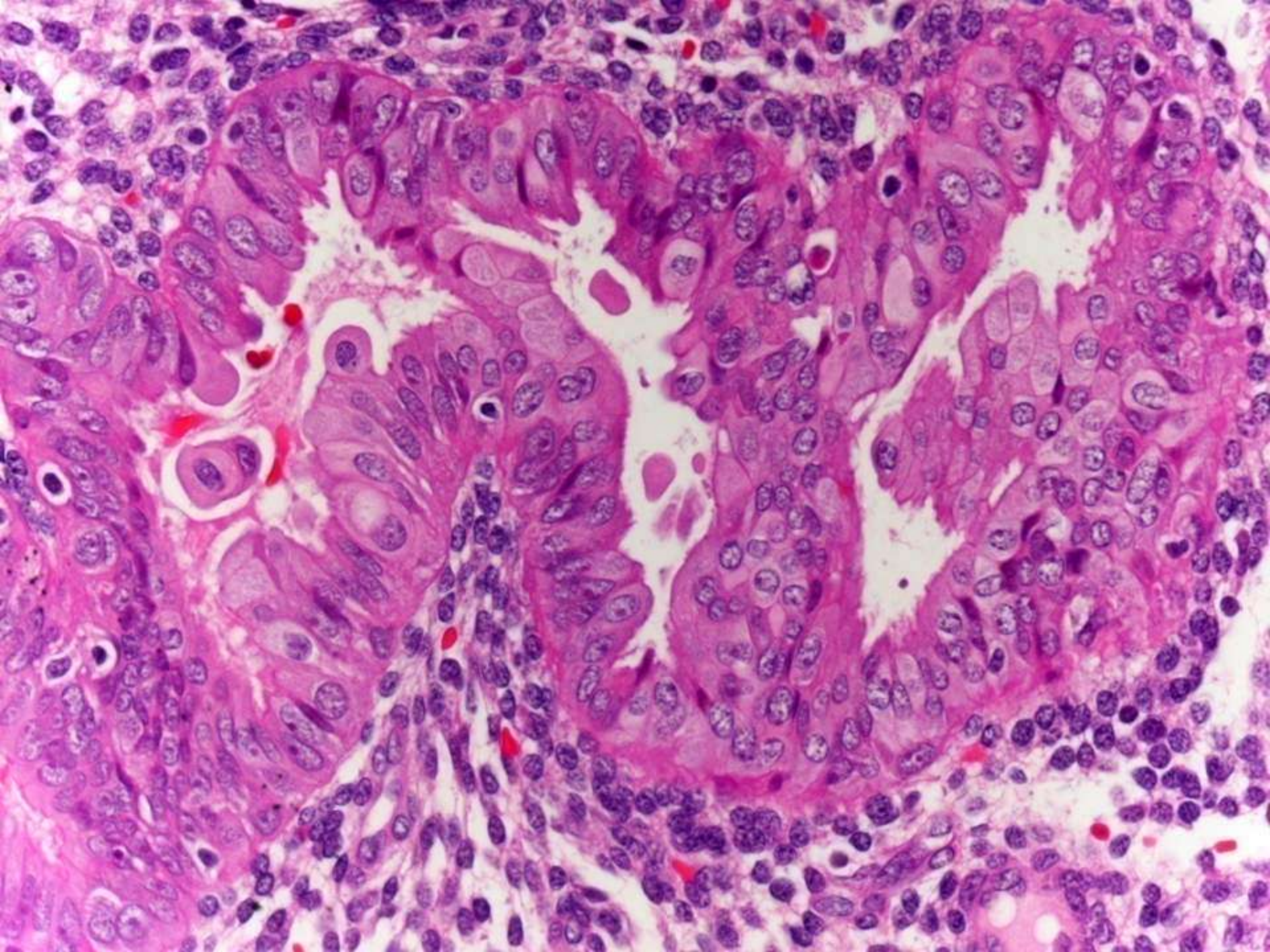
Table 1 Classification of endometrial metaplasias and changes

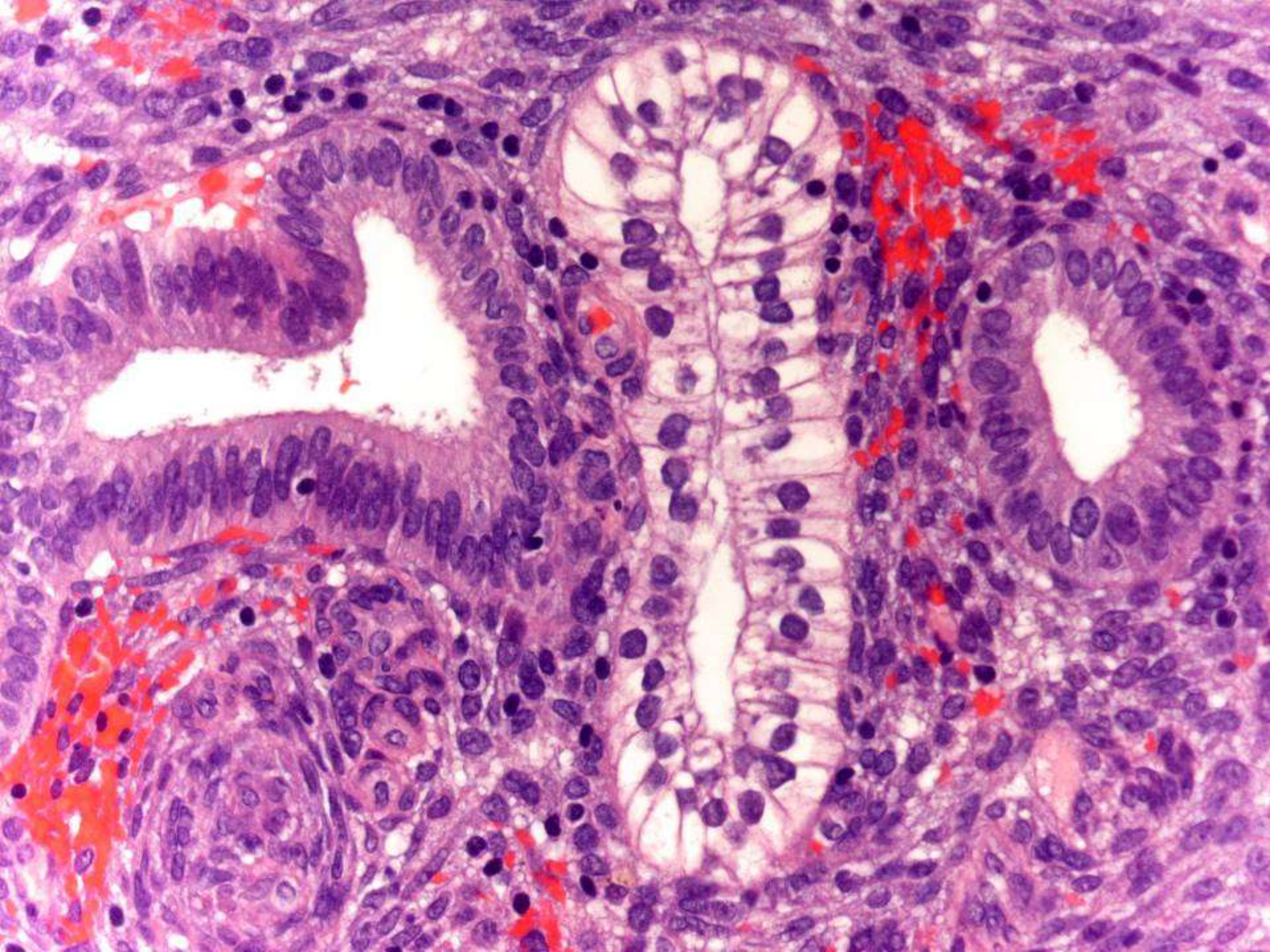
Endometrial metaplasias and changes

Epithelial	Ciliary, tubal (simple and complex)
	Mucinous (simple and complex)
	— Intestinal variant
	Squamous
	Morules
	Reactive changes
	— Surface, papillary syncytial change
	— Hobnail variant
	— Oncocytic, oxyphilic, eosinophilic
	— Clear cell, secretory
Stromal	Osseous
	Cartilaginous
	Adipose
	Smooth muscle
	— Myoid, sex-cord like

Miscellaneous, non-specific reactive changes

- **Oxyphilic, oncocytic, eosinophilic**
 - **Common for many types of metaplasia**
 - (CTM, mucinous etc)
 - **Reactive, may occur in any type of lesion**
 - **Significance: degenerative**
- **Clear cell, secretory**





Possible malignant potential

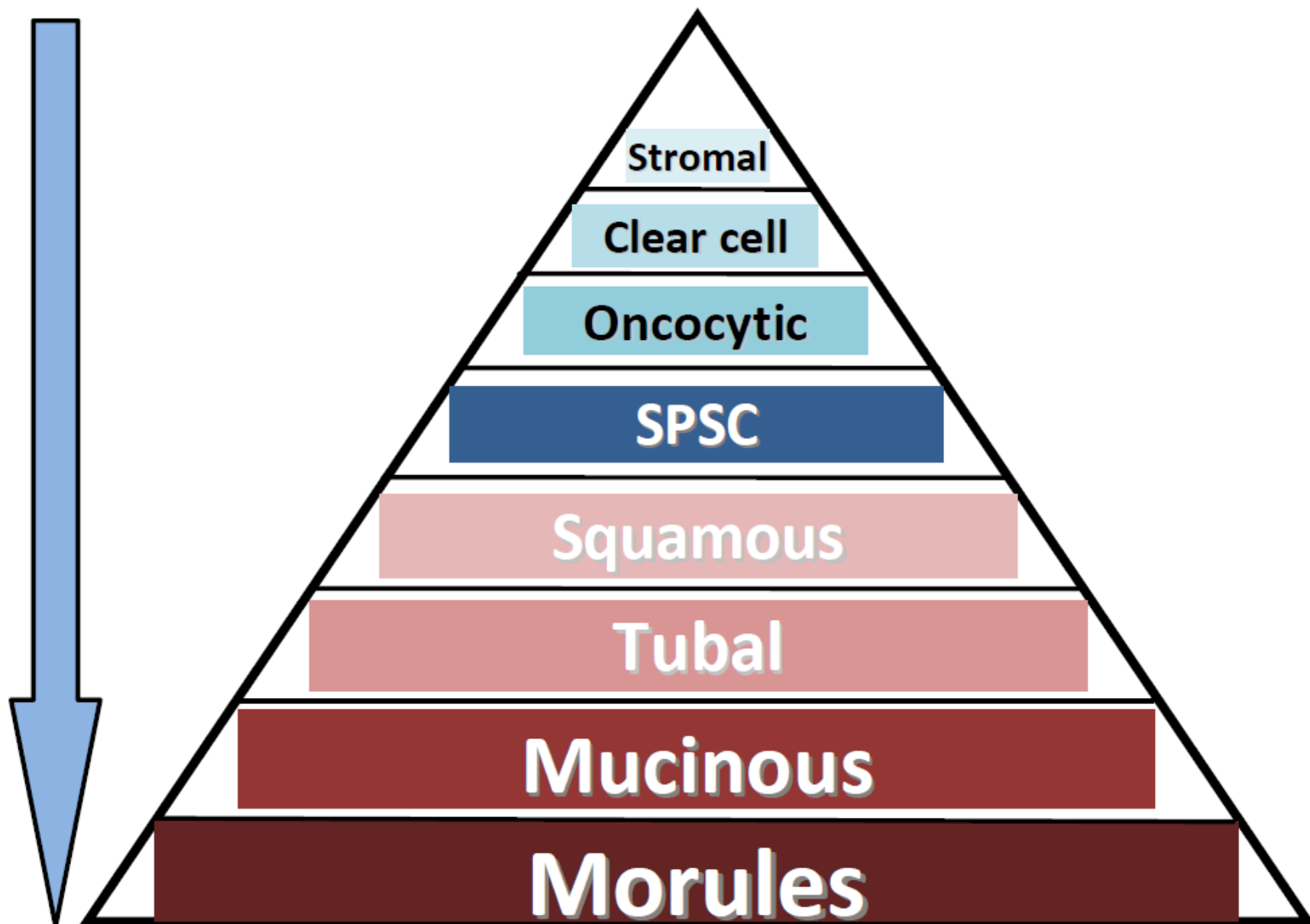


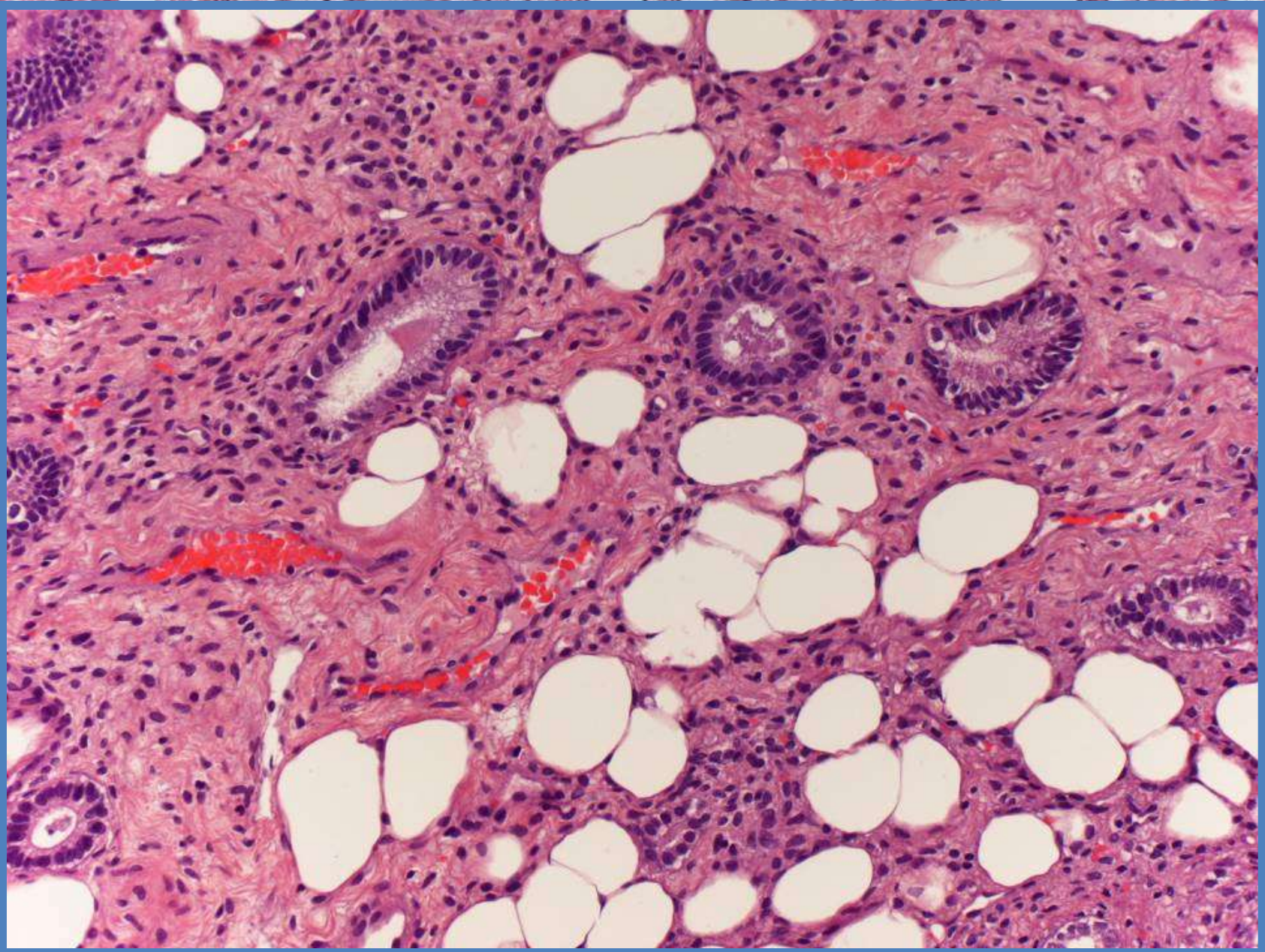
Table 1 Classification of endometrial metaplasias and changes

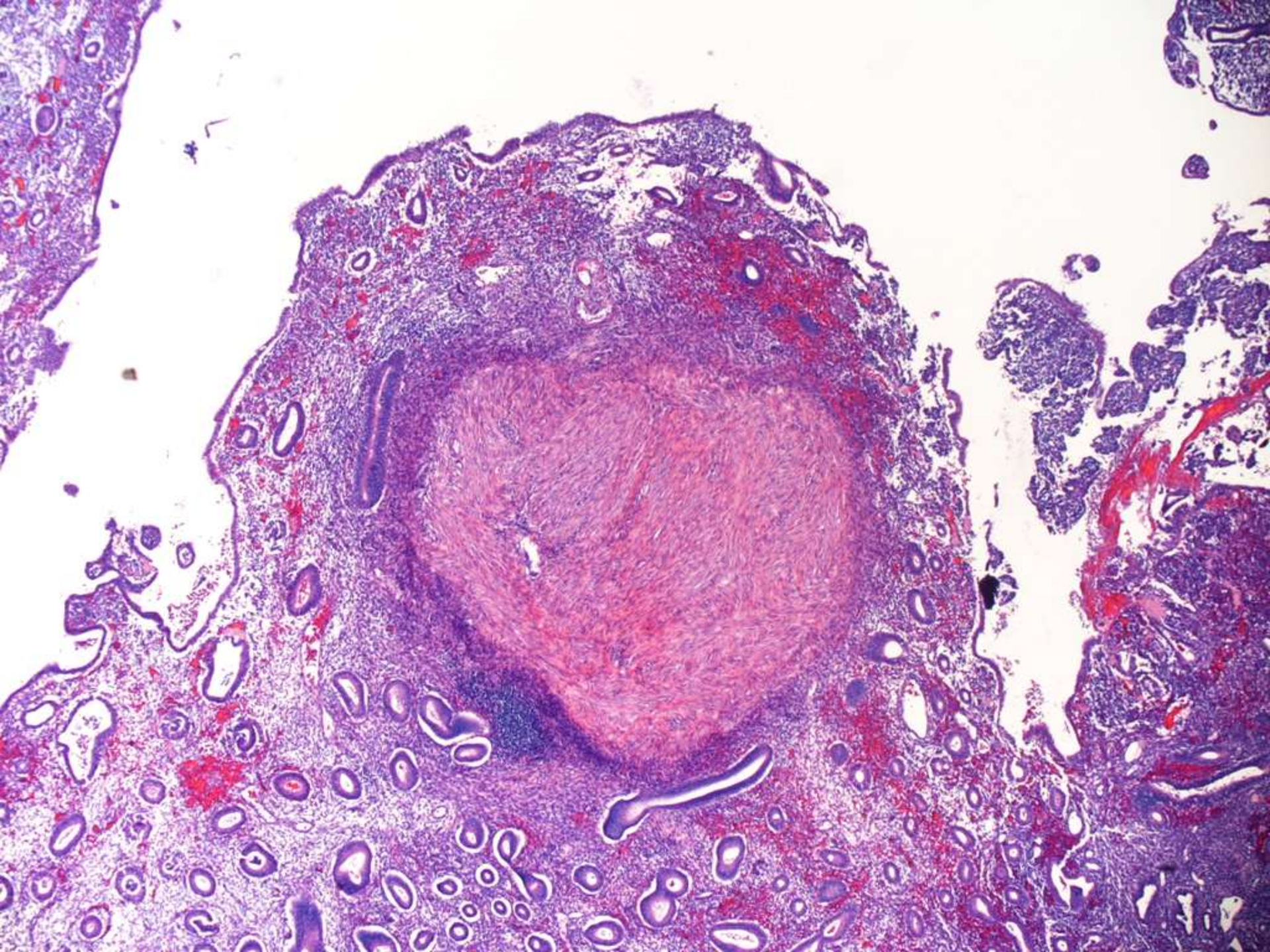
Endometrial metaplasias and changes

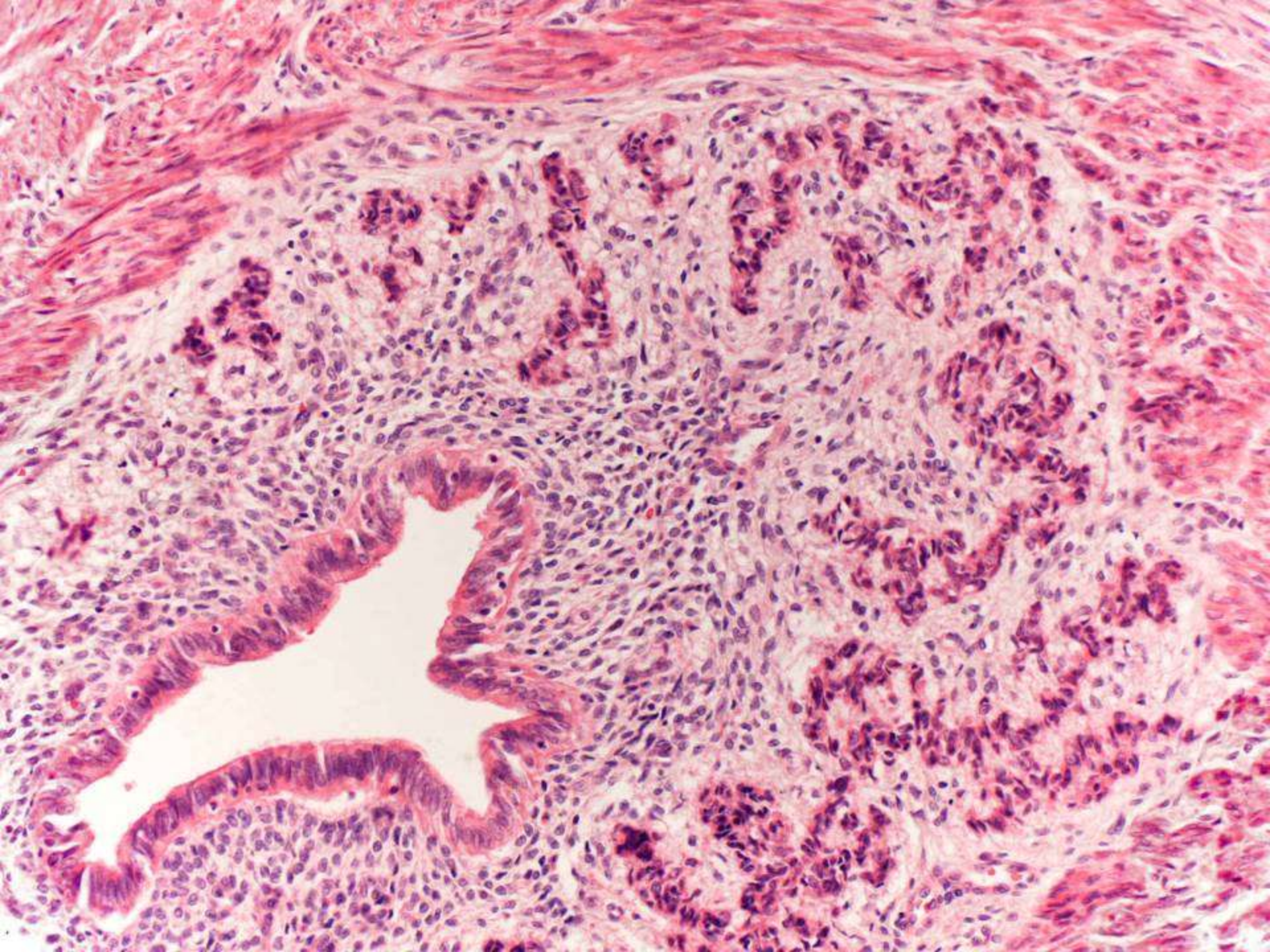
Epithelial	<ul style="list-style-type: none">Ciliary, tubal (simple and complex)Mucinous (simple and complex)<ul style="list-style-type: none">— Intestinal variantSquamousMorulesReactive changes<ul style="list-style-type: none">— Surface, papillary syncytial change<ul style="list-style-type: none">— Hobnail variant— Oncocytic, oxyphilic, eosinophilic— Clear cell, secretory
Stromal	<ul style="list-style-type: none">OsseousCartilaginousAdiposeSmooth muscle<ul style="list-style-type: none">— Myoid, sex-cord like

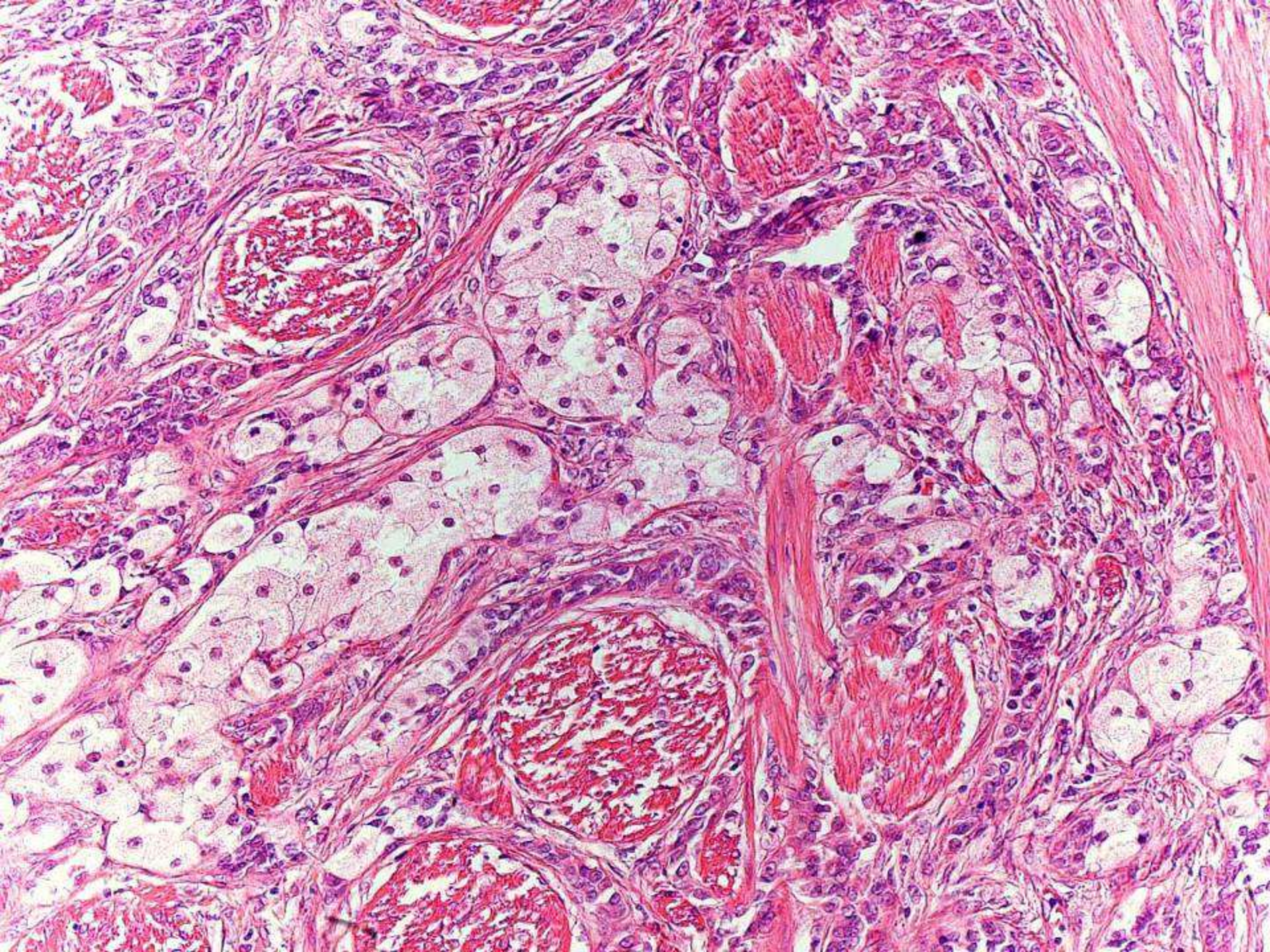
End. Stromal metaplasias: origin

- **Discard foetal or embryonal origin for rare heterotopic tissues**
- **Mesenchymal or stromal stem cell-like precursors can induce any type of mesenchymal differentiation**









A histopathological micrograph showing a dense cellular structure. The tissue is stained with hematoxylin and eosin (H&E). The background is a pale pinkish-white, representing the extracellular matrix or stroma. Numerous small, dark blue nuclei are scattered throughout. Interspersed among these nuclei are clusters and cords of cells that are more densely packed and stained a darker brownish-purple. These structures resemble the architecture of sex-cord-like tumours. Some areas show more organized, swirling patterns, which are characteristic of myoid features.

Uterine and extrauterine plexiform
tumourlets are sex-cord-like tumours with
myoid features *Histopathology*, 54, 494–512

DES