



Urothelial Carcinoma Histologic Variants and Clinical Implications

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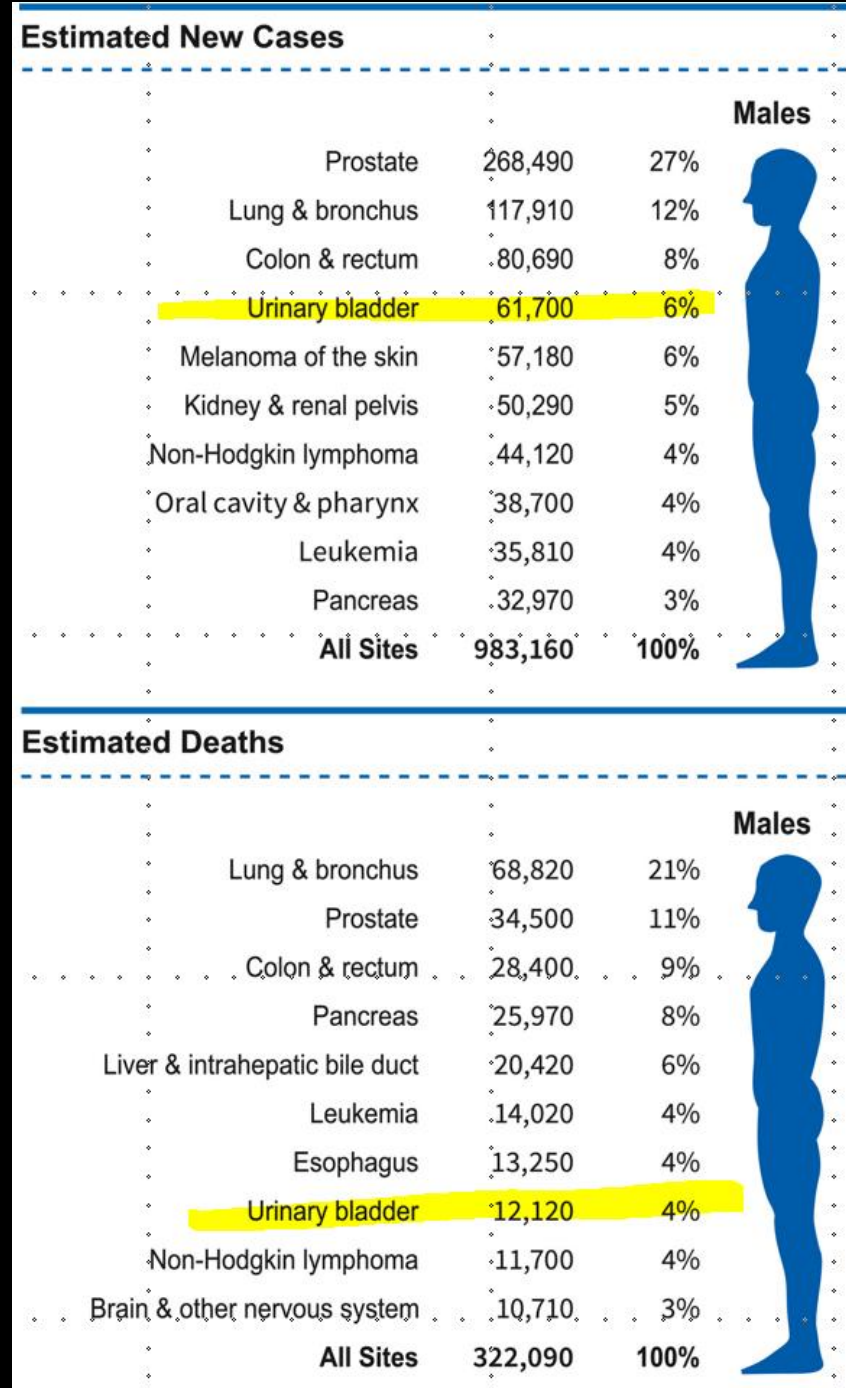
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Objectives

- Provide a brief overview of “conventional” urothelial carcinoma
- Define divergent differentiation and variant histology in urothelial carcinoma
- Review salient morphologic features of divergent differentiation/histologic subtypes
- Discuss clinical implications of select histologic variants/subtypes

Urothelial Carcinoma Facts and Figures

- Epithelial malignancy arising from the urothelial lining of the urinary tract
 - ✓ Bladder (>90%),
 - ✓ Upper tract (~5-10%),
 - ✓ Urethra (<1%)
- Clinically
 - ✓ Non-muscle invasive
 - ✓ Muscle-invasive
 - ✓ Metastatic



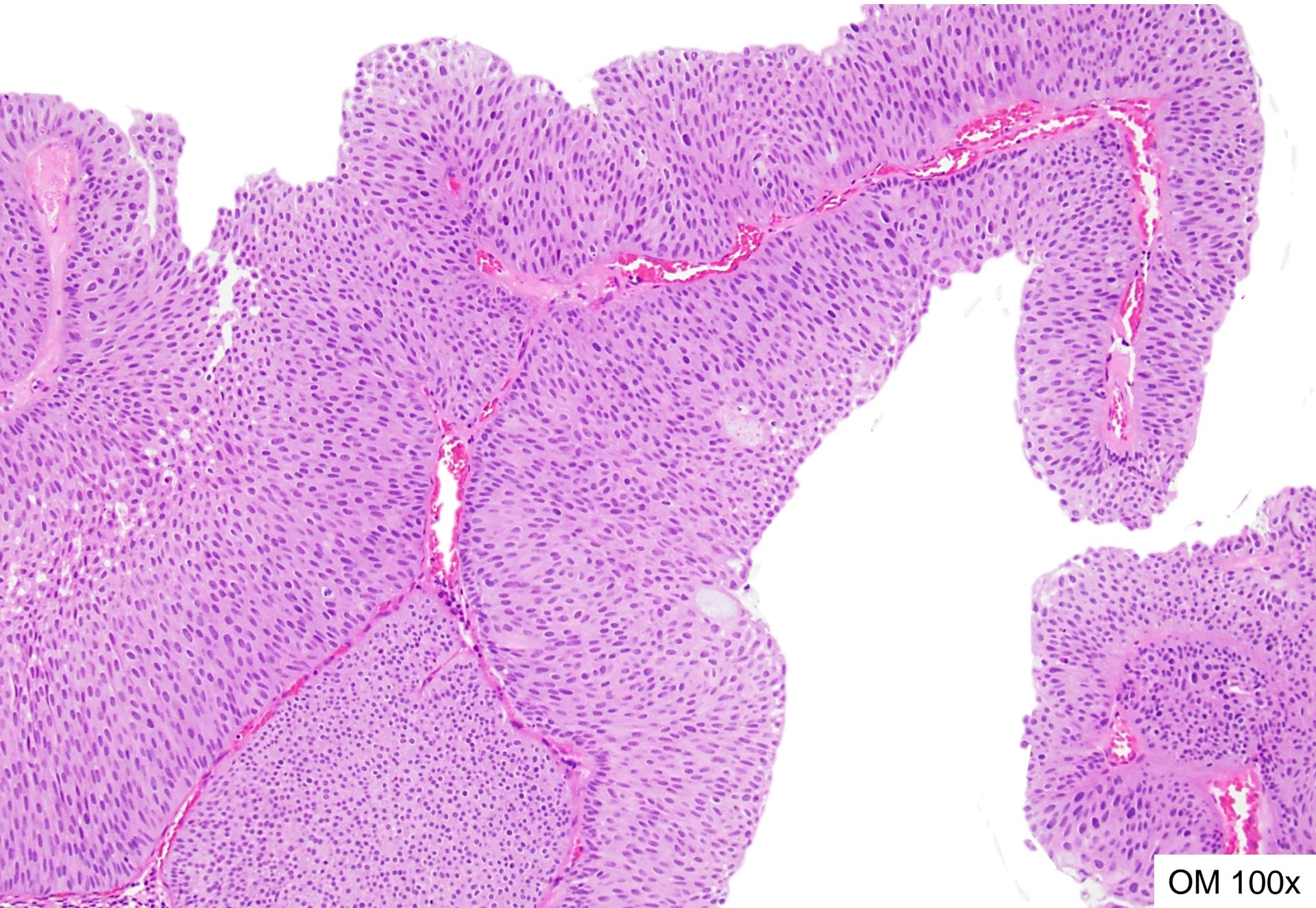
Urothelial carcinoma: morphology

- “Usual”/Conventional
 - ✓ Papillary
 - Low-grade
 - High-grade
 - ✓ Non-papillary
 - In situ (CIS)
 - Invasive
- “Unusual”
 - ✓ With divergent differentiation (“mixed”)
 - ✓ Showing variant histology = histologic subtype

Conventional Morphology

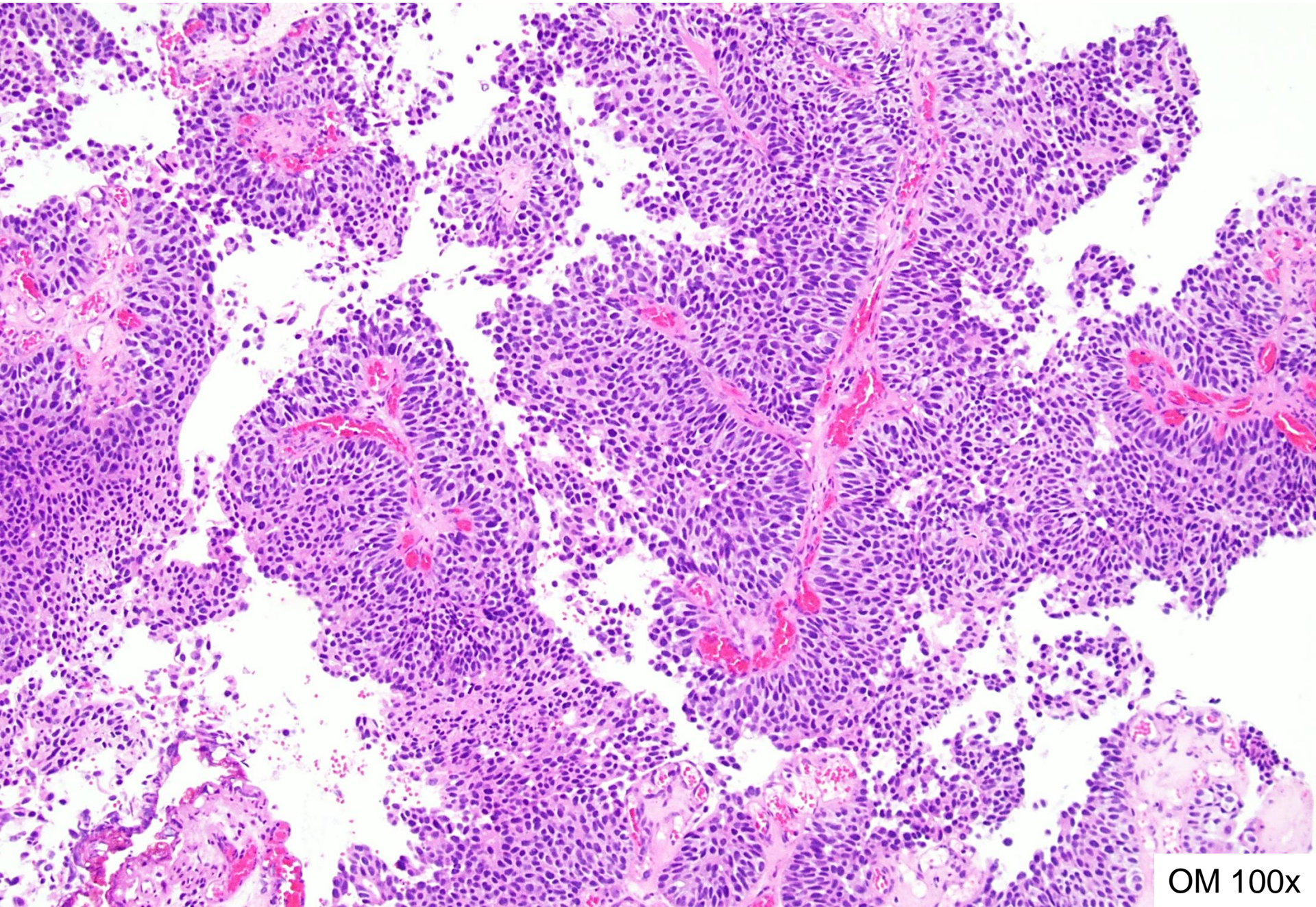


Papillary urothelial carcinoma, low-grade



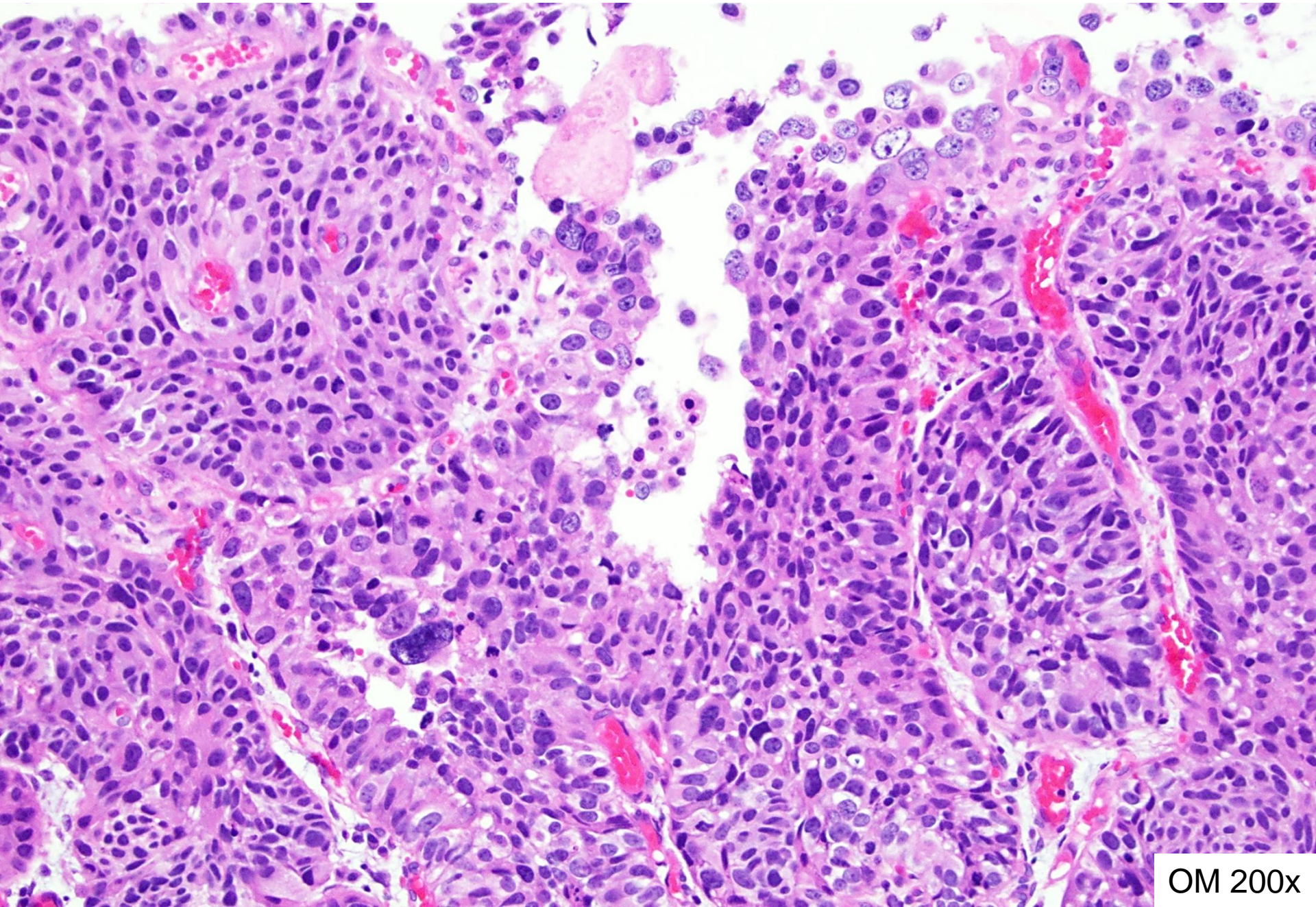
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Papillary urothelial carcinoma, high-grade



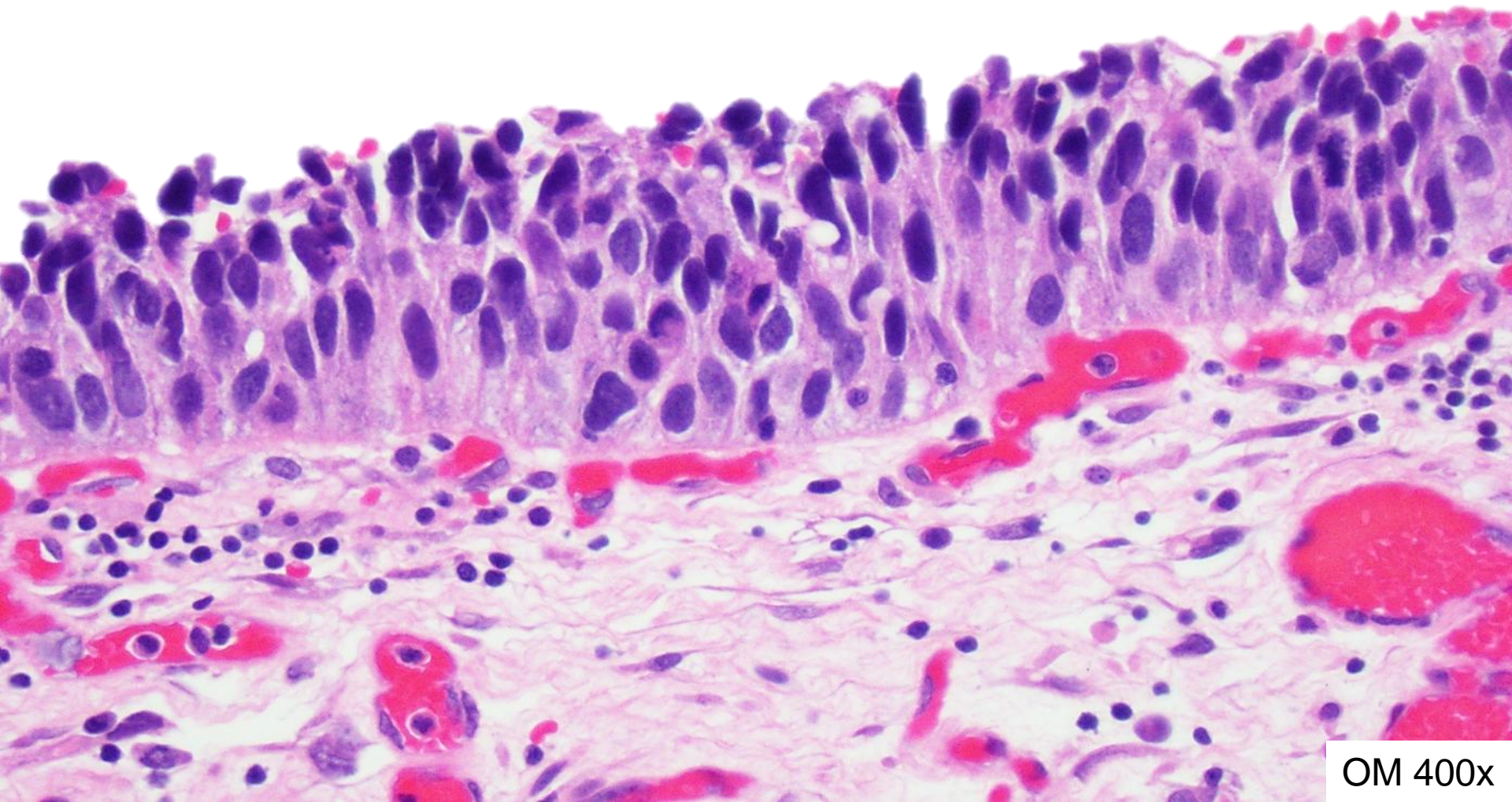
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Papillary urothelial carcinoma, high-grade



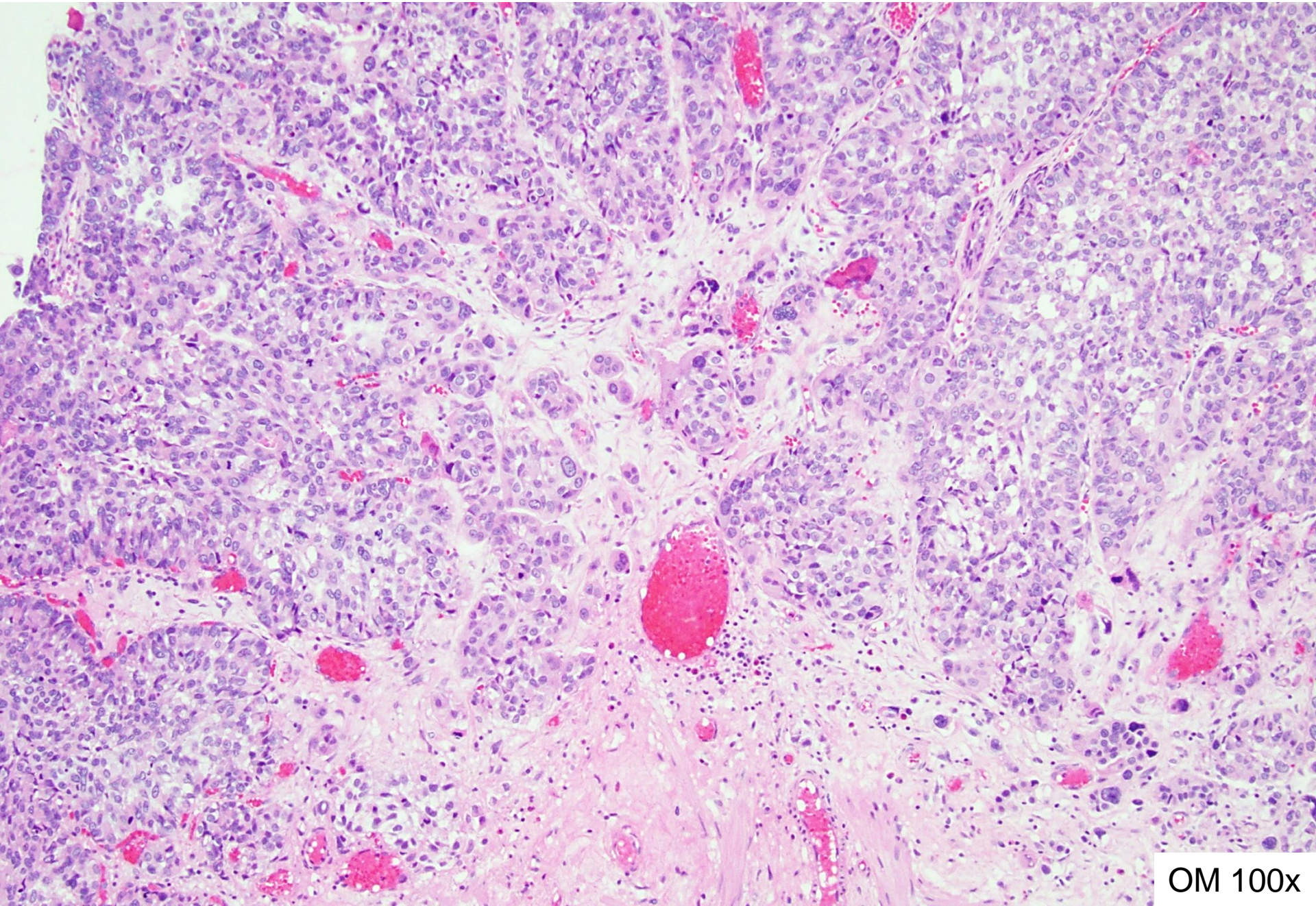
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Non-papillary (flat) noninvasive
(Urothelial carcinoma in situ - CIS)



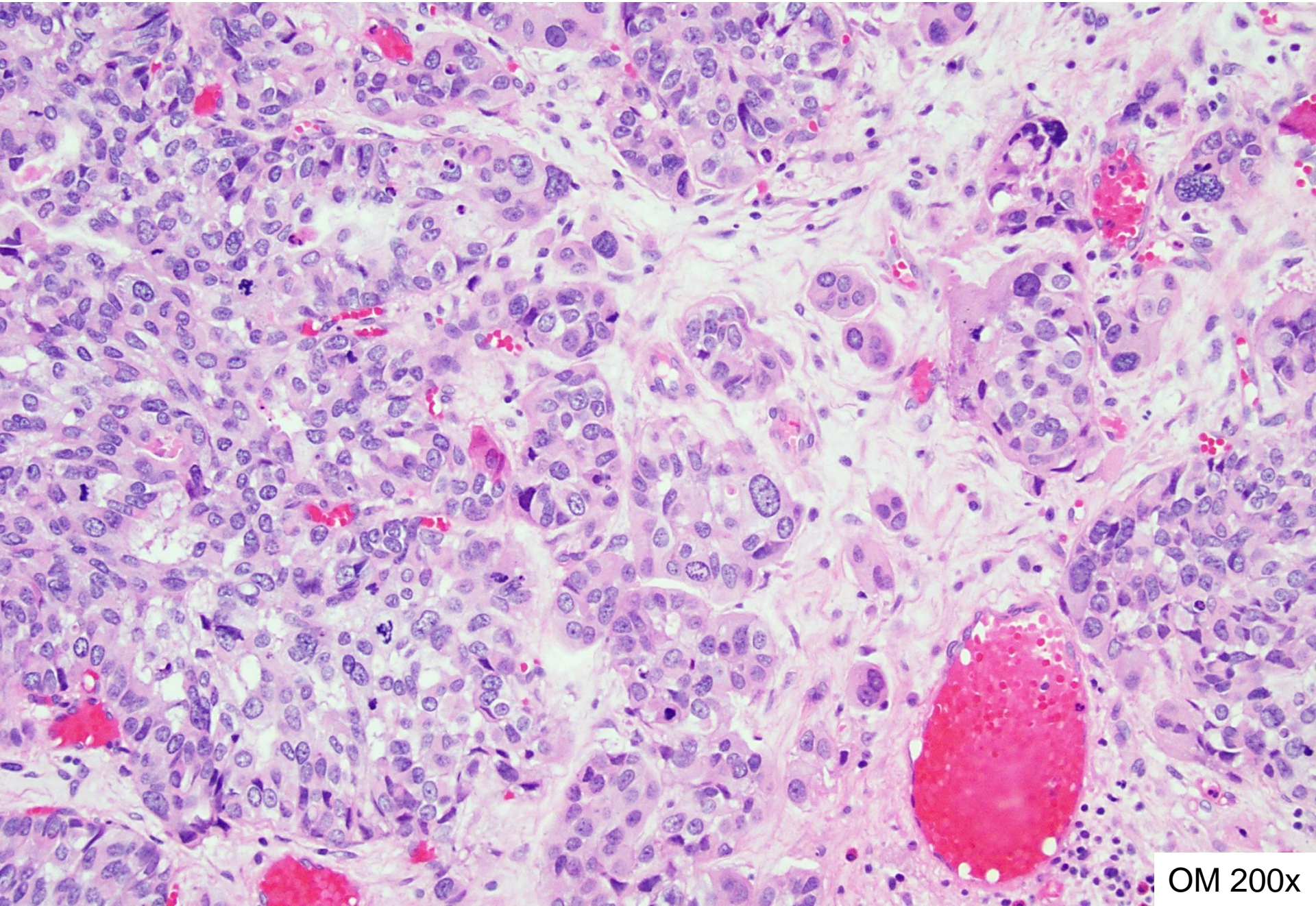
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Invasive urothelial carcinoma, "typical" pattern



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Invasive urothelial carcinoma, "typical" pattern



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Immunohistochemical Expression Profile

▪ “Luminal” markers

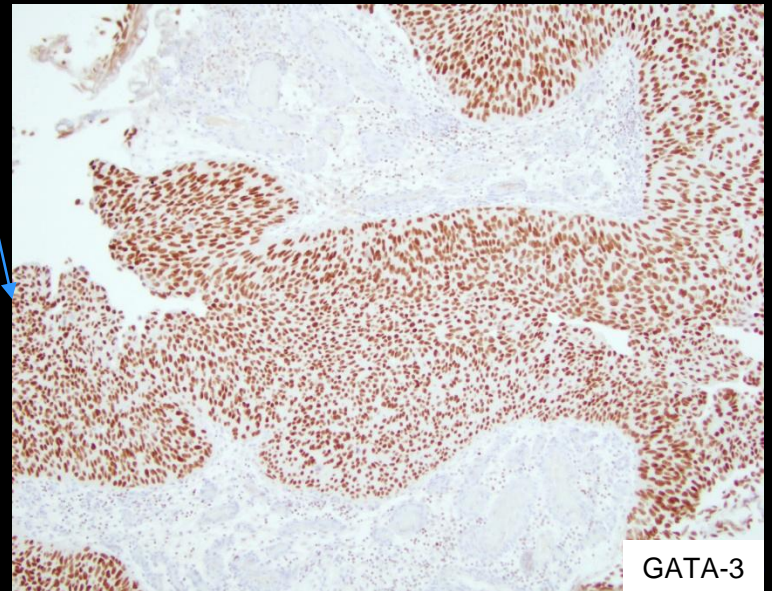
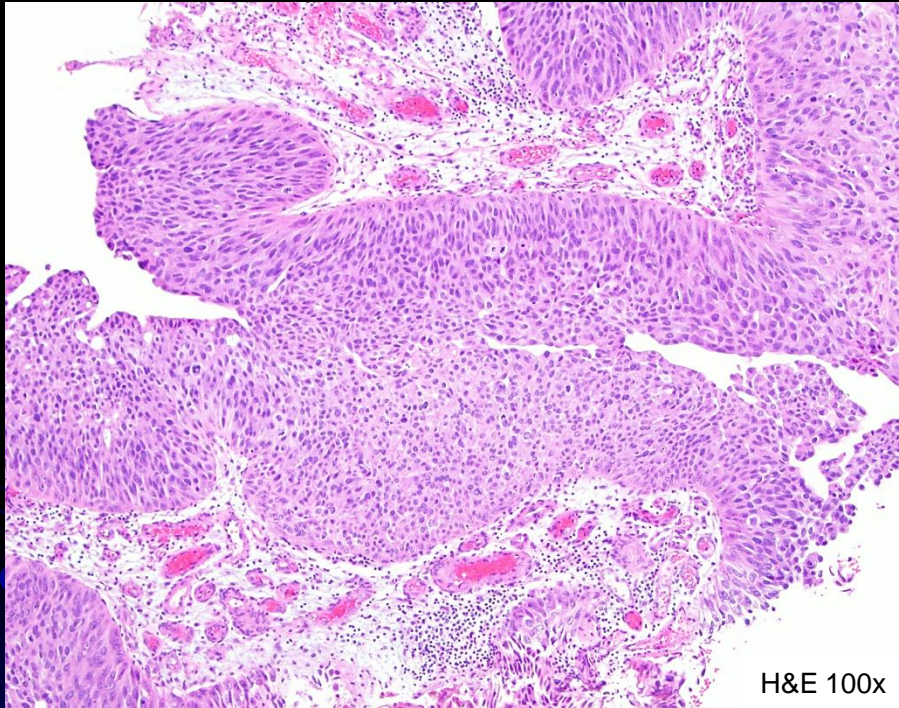
- ✓ CK20
- ✓ GATA3
- ✓ Uroplakins
- ✓ FGFR3
- ✓ FOXA1
- ✓ PPARG

▪ “Basal” markers

- ✓ CK5/6*
- ✓ CK14*
- ✓ CD44
- ✓ Desmogleins
- ✓ Desmocollins
- ✓ [p63]

*and high-molecular weight keratins cocktails (e.g., K903/34BE12)

Variable combination of “basal” and “luminal” markers in *garden-variety* urothelial carcinoma



Molecular Taxonomy

- Derived from muscle-invasive disease studies
- Six consensus subtypes
 - ✓ luminal papillary (24%)
 - ✓ luminal nonspecified (8%)
 - ✓ luminal unstable (15%)
 - ✓ stroma-rich (15%)
 - ✓ basal/squamous (35%)
 - ✓ neuroendocrine-like (3%)

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Divergent Differentiation

Differentiation along another histologic lineage



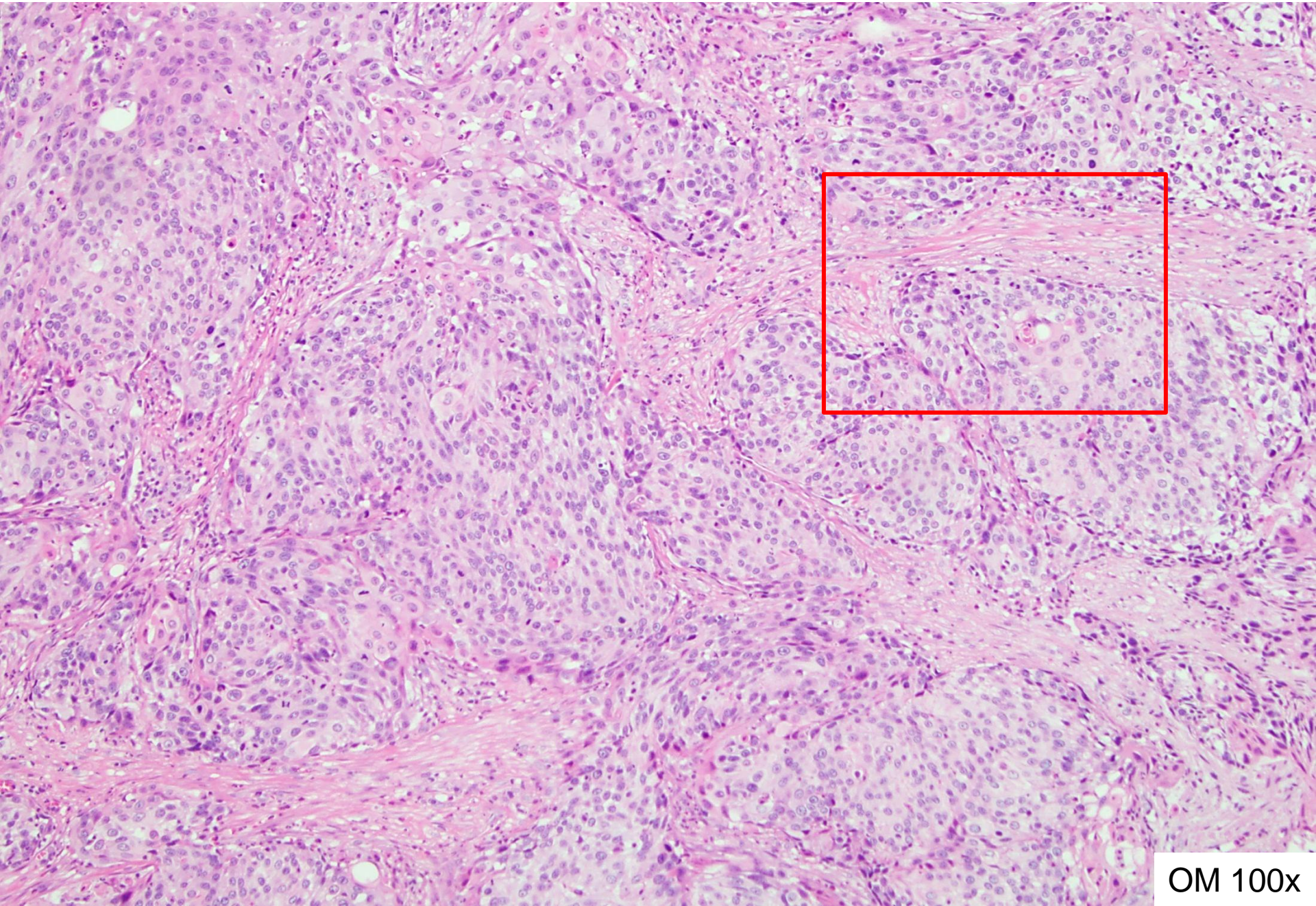
Divergent Differentiation

- Squamous
- Glandular
- Neuroendocrine (>>>small cell)
- Trophoblastic
- [Müllerian (*Clear cell adenocarcinoma of the urinary tract*)]

Divergent Differentiation Squamous

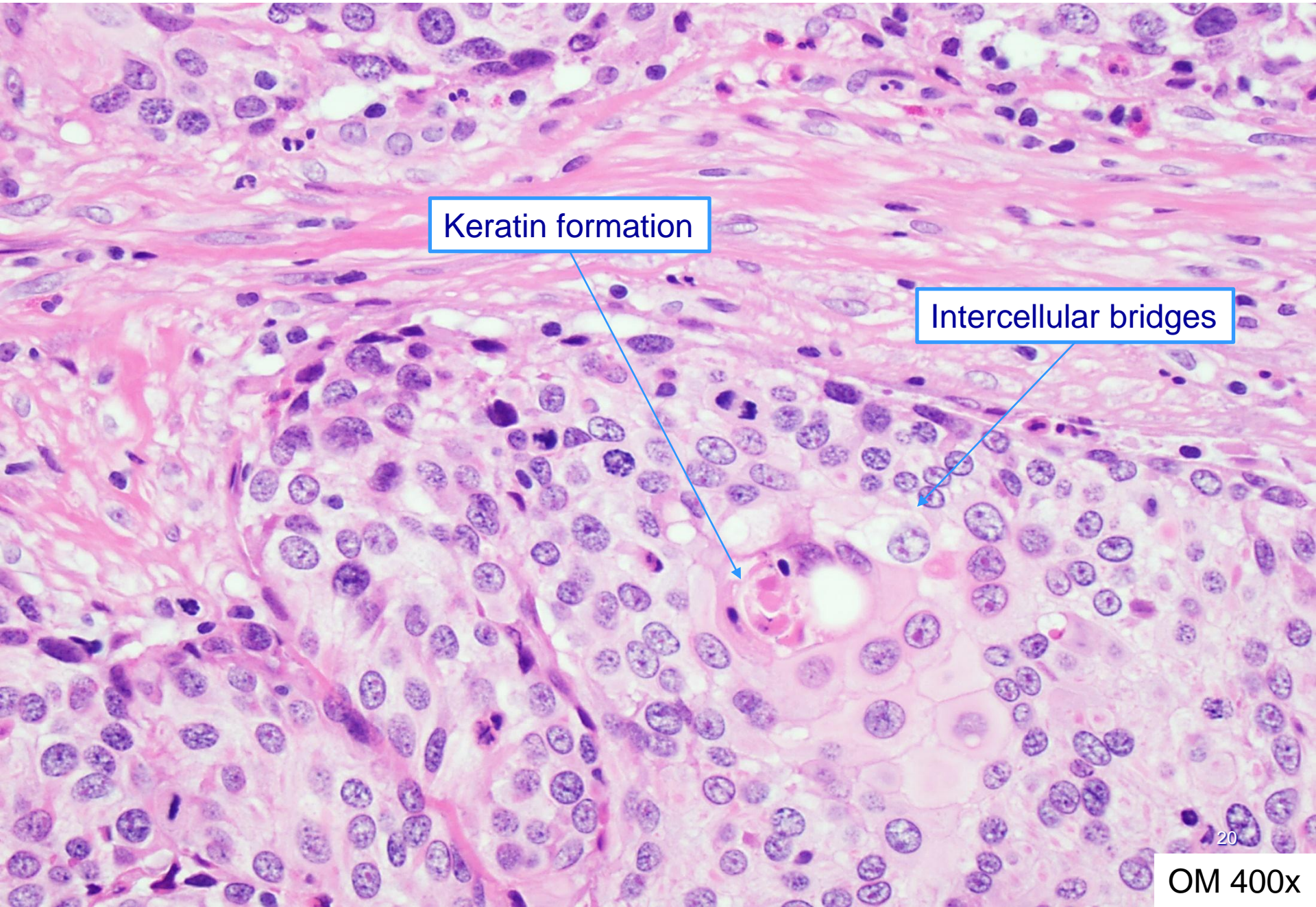
- Most frequent divergent differentiation in urothelial carcinoma (12%-31%)
- Tendency to be diagnosed at higher stage
- No significant difference in cancer-specific survival with pure urothelial of same stage
- Differential diagnosis (DDx) with squamous cell carcinoma (primary or secondary involvement)
- Basal-squamous expression profile and molecular phenotype (not helpful in DDx)

Urothelial carcinoma with squamous differentiation



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Urothelial carcinoma with squamous differentiation



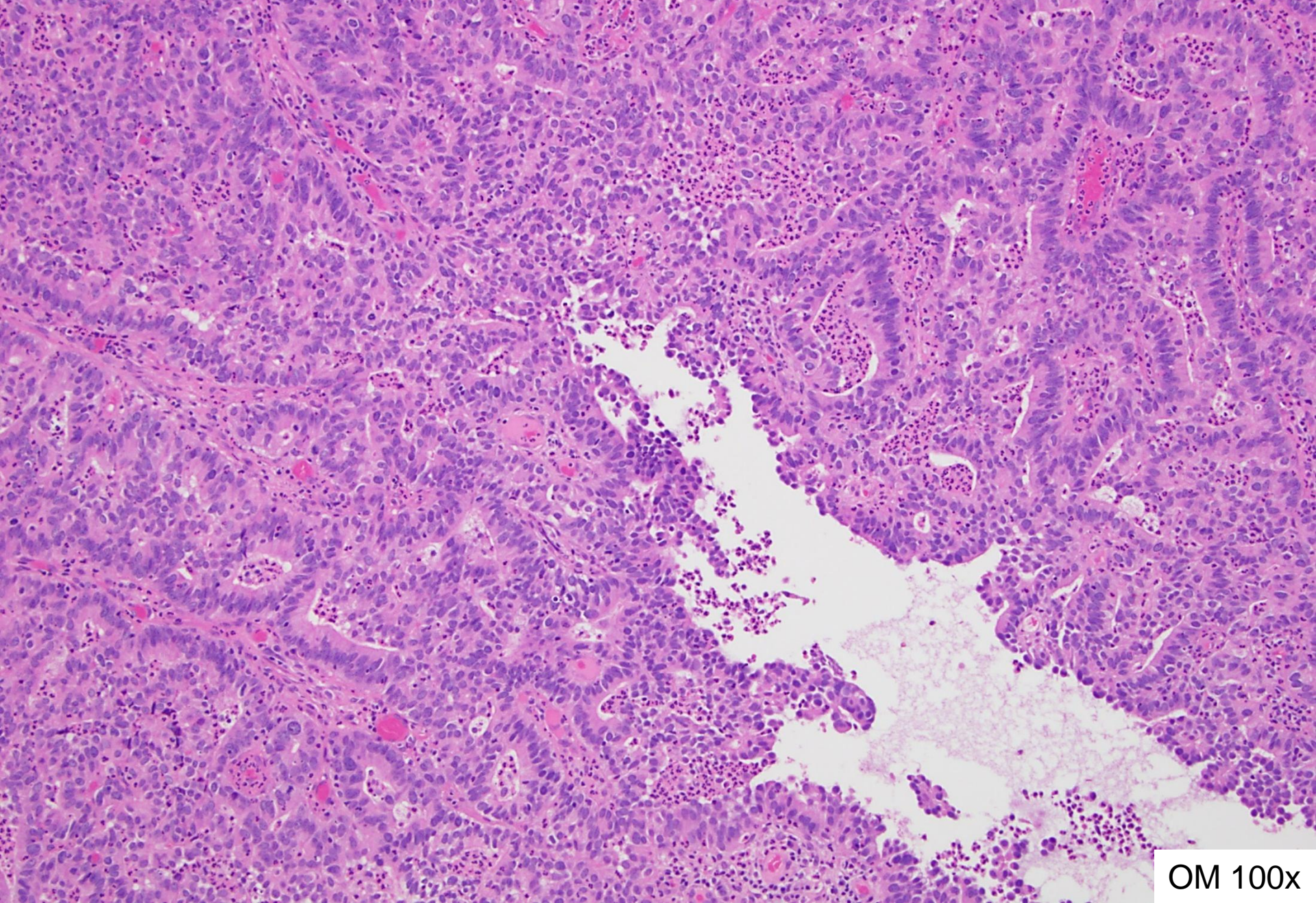
Keratin formation

Intercellular bridges

Divergent Differentiation Glandular

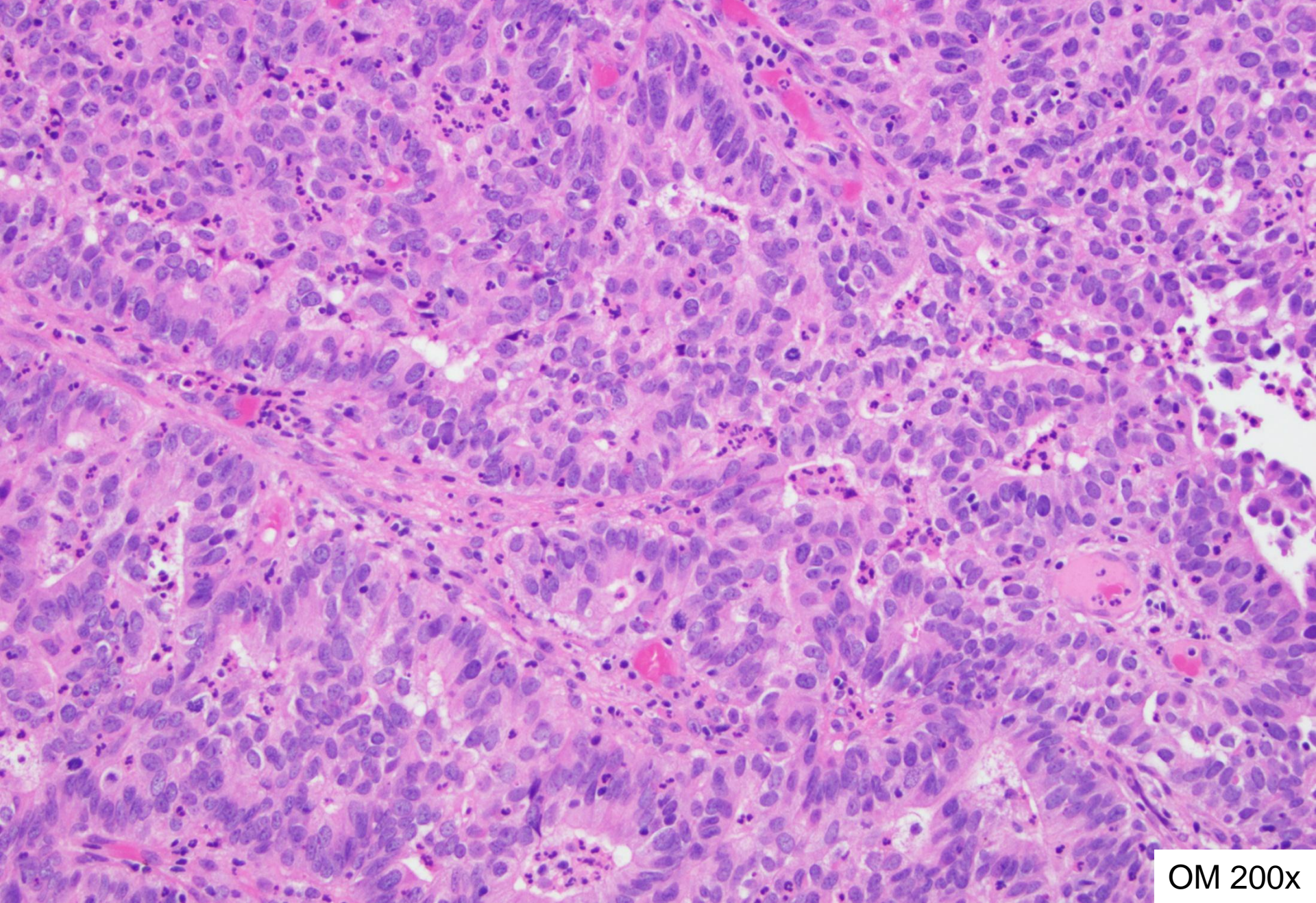
- Second most common divergent differentiation in urothelial carcinoma (UC) (10%-18%)
- Often presenting at high stage
- No significant difference in cancer-specific survival with pure UC of same stage
- DDX with adenocarcinoma (primary or secondary involvement)
 - ✓ Luminal (pseudo-glandular) spaces formation in UC
- >> Enteric-type expression profile (e.g., CK20, CDX-2) +/- UC lineage markers (GATA3, p63, HMWCK)

Urothelial carcinoma with glandular differentiation



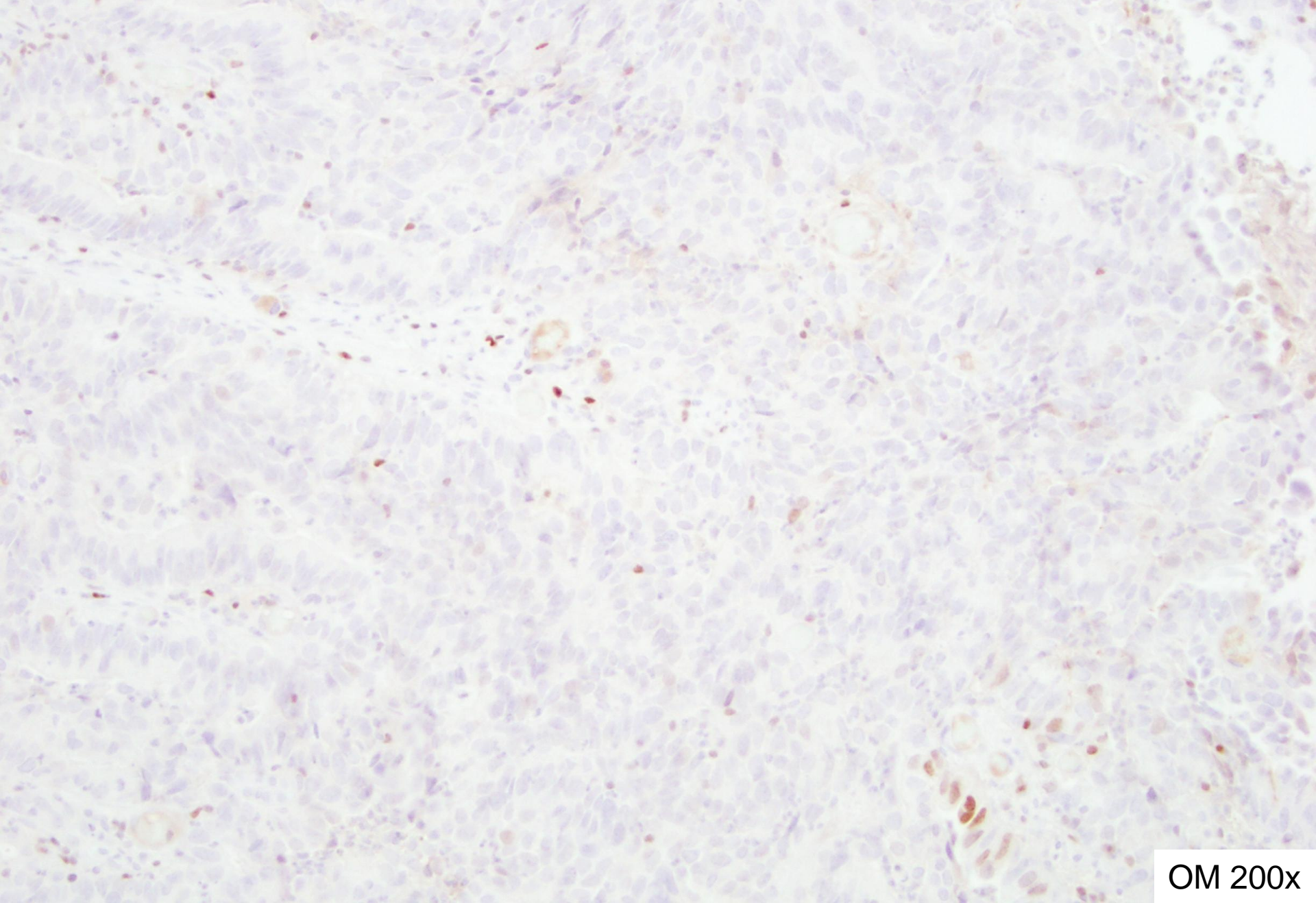
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Urothelial carcinoma with glandular differentiation



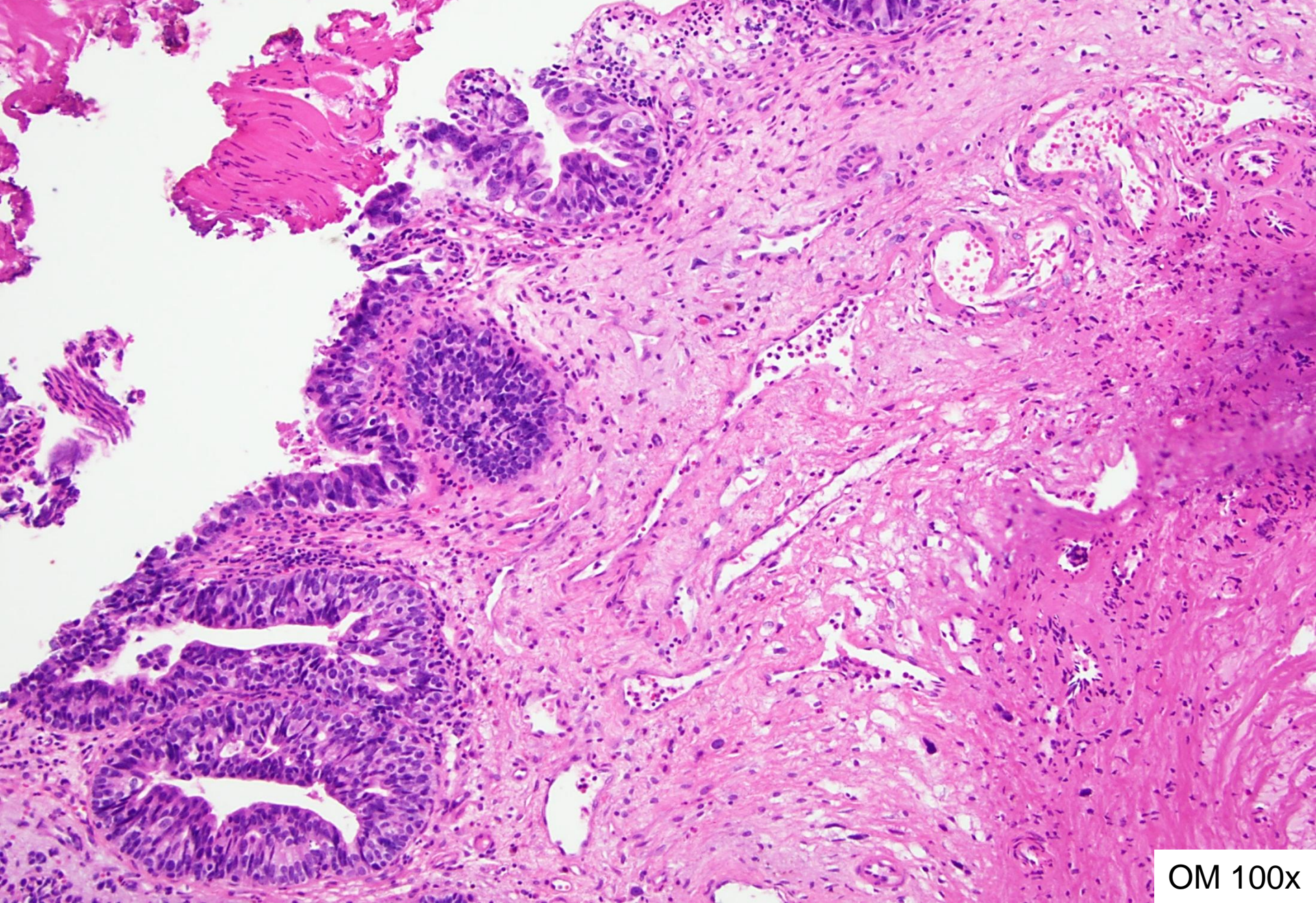
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Glandular differentiation: GATA-3



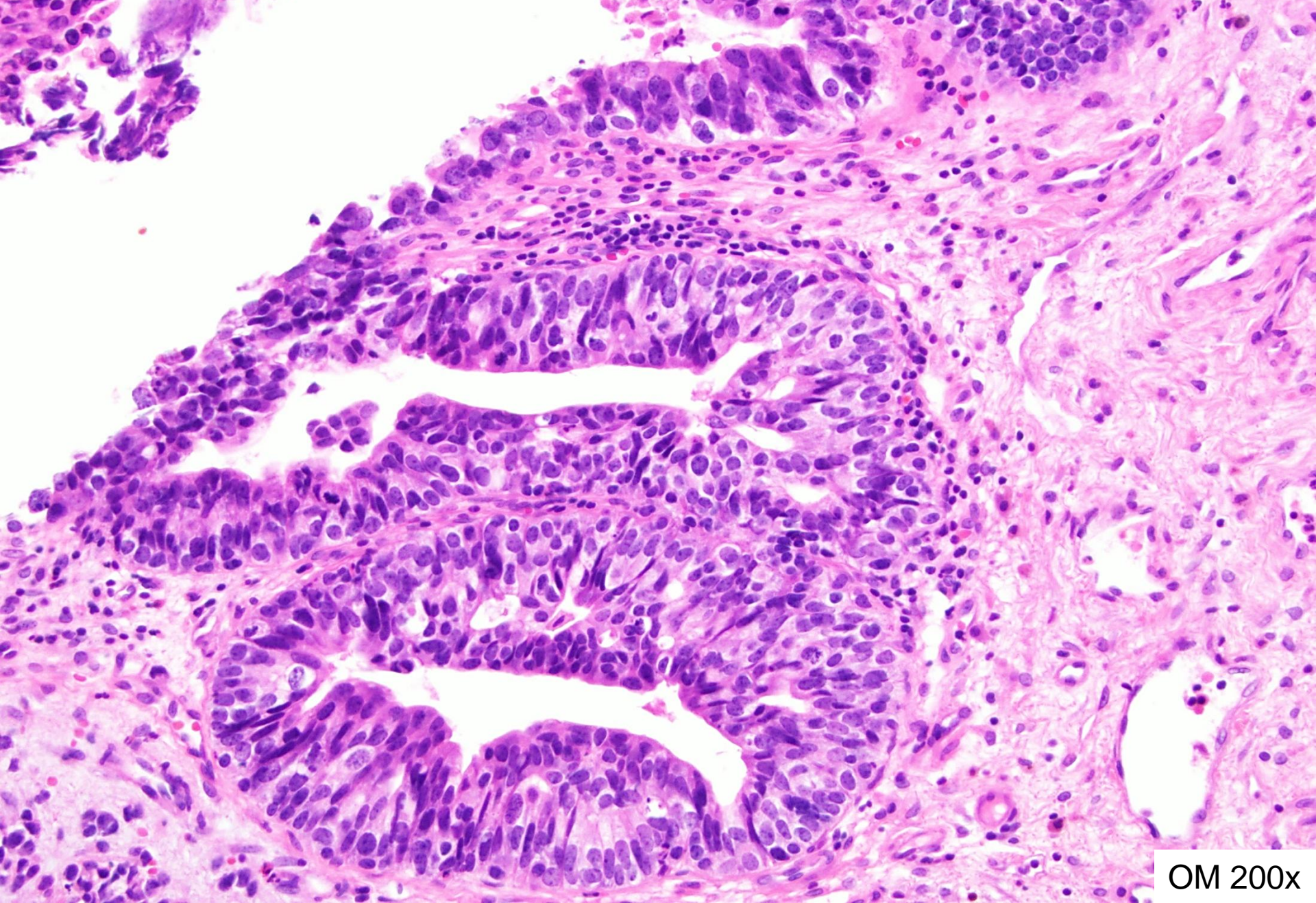
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Urothelial carcinoma with glandular differentiation



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Urothelial carcinoma with glandular differentiation

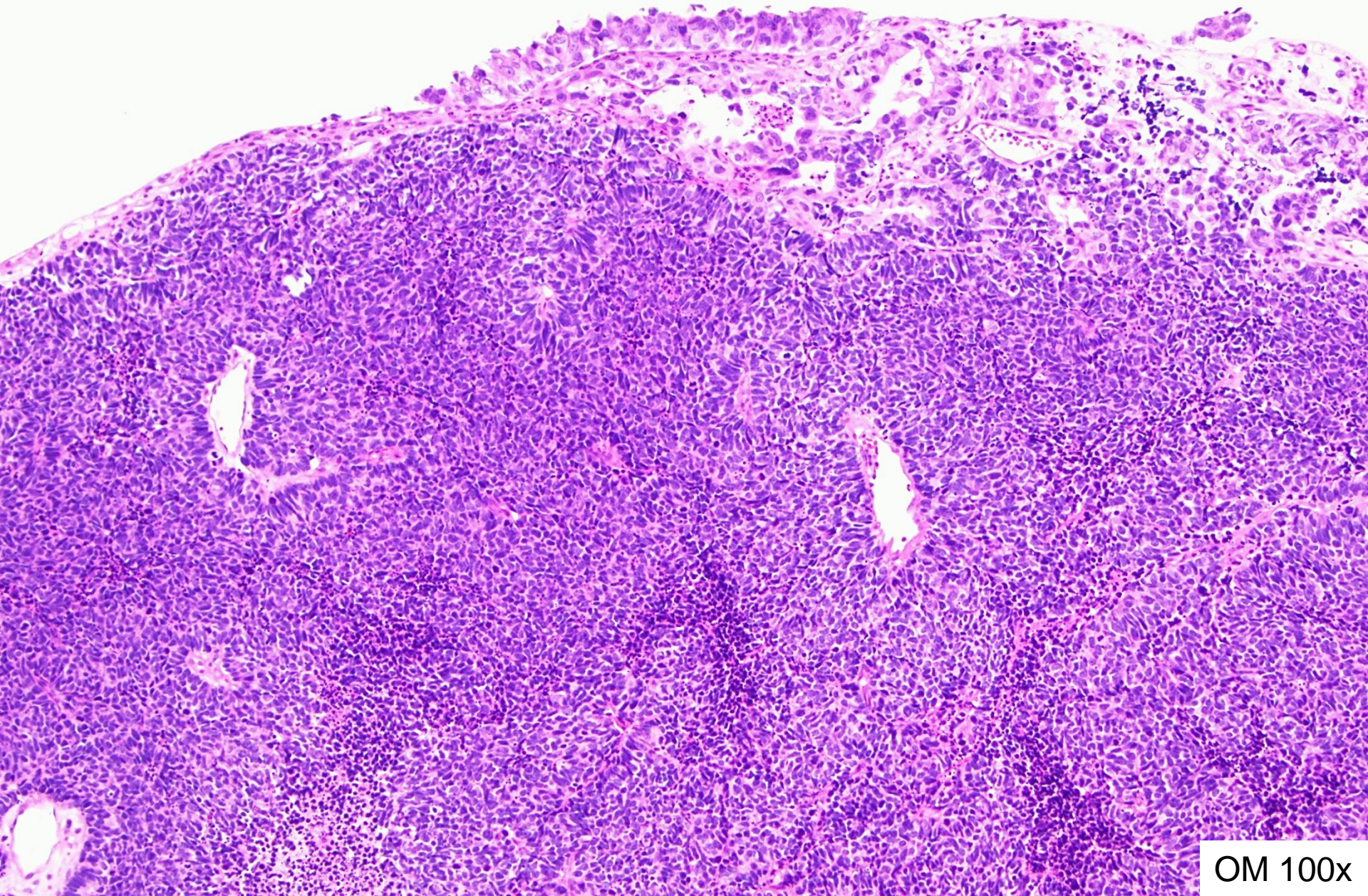


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Divergent Differentiation [Small Cell] Neuroendocrine

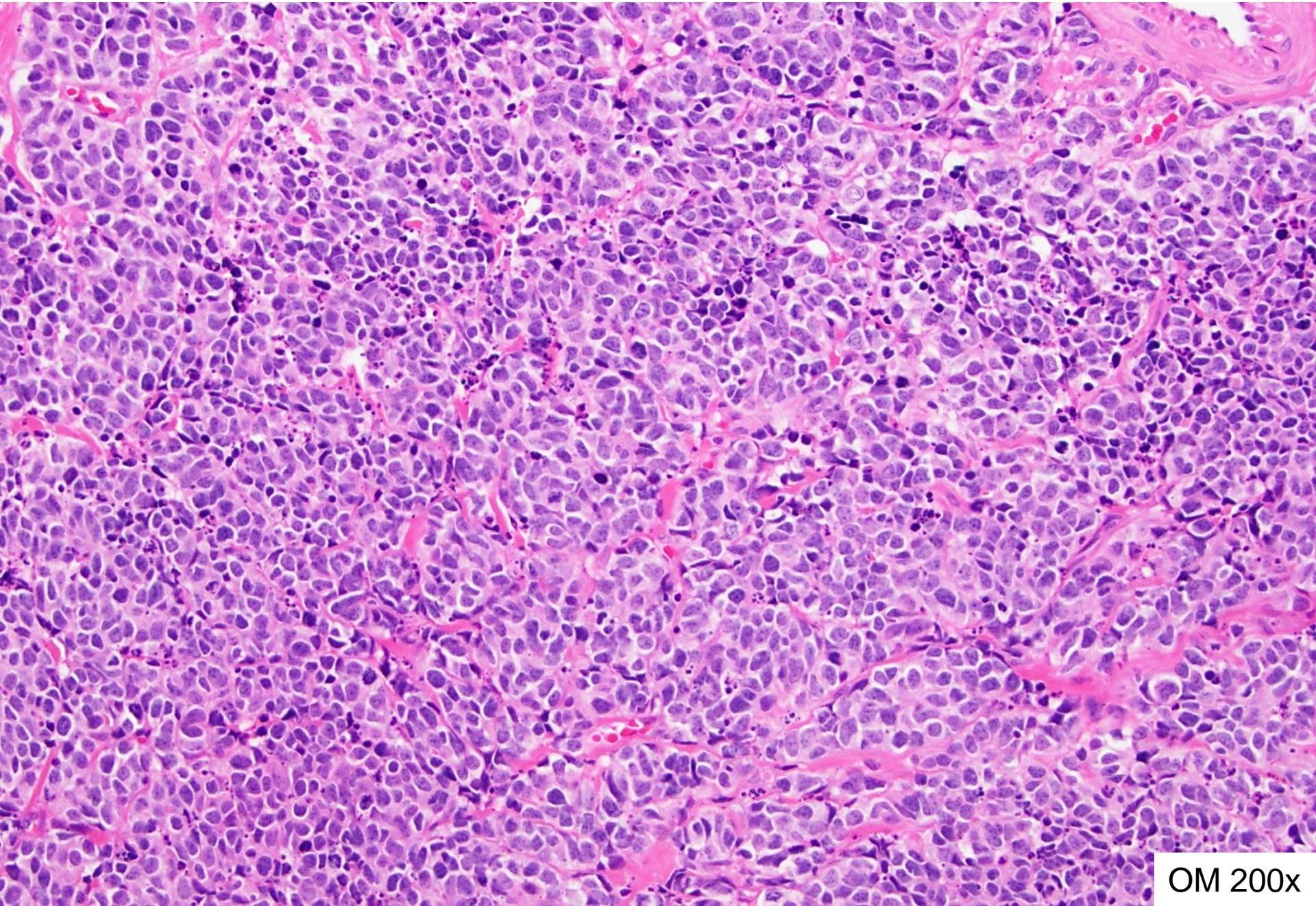
- Less than 1% of bladder cancers
- Rapid growth with a predilection for early metastases to sites including brain and bone (>>brain imaging)
- Chemosensitive
- **Metastatic disease worse than pure urothelial**
- Main DDX with lymphoma, poorly differentiated urothelial and small cells from other sites (less critical for management)

Small cell carcinoma with overlying CIS



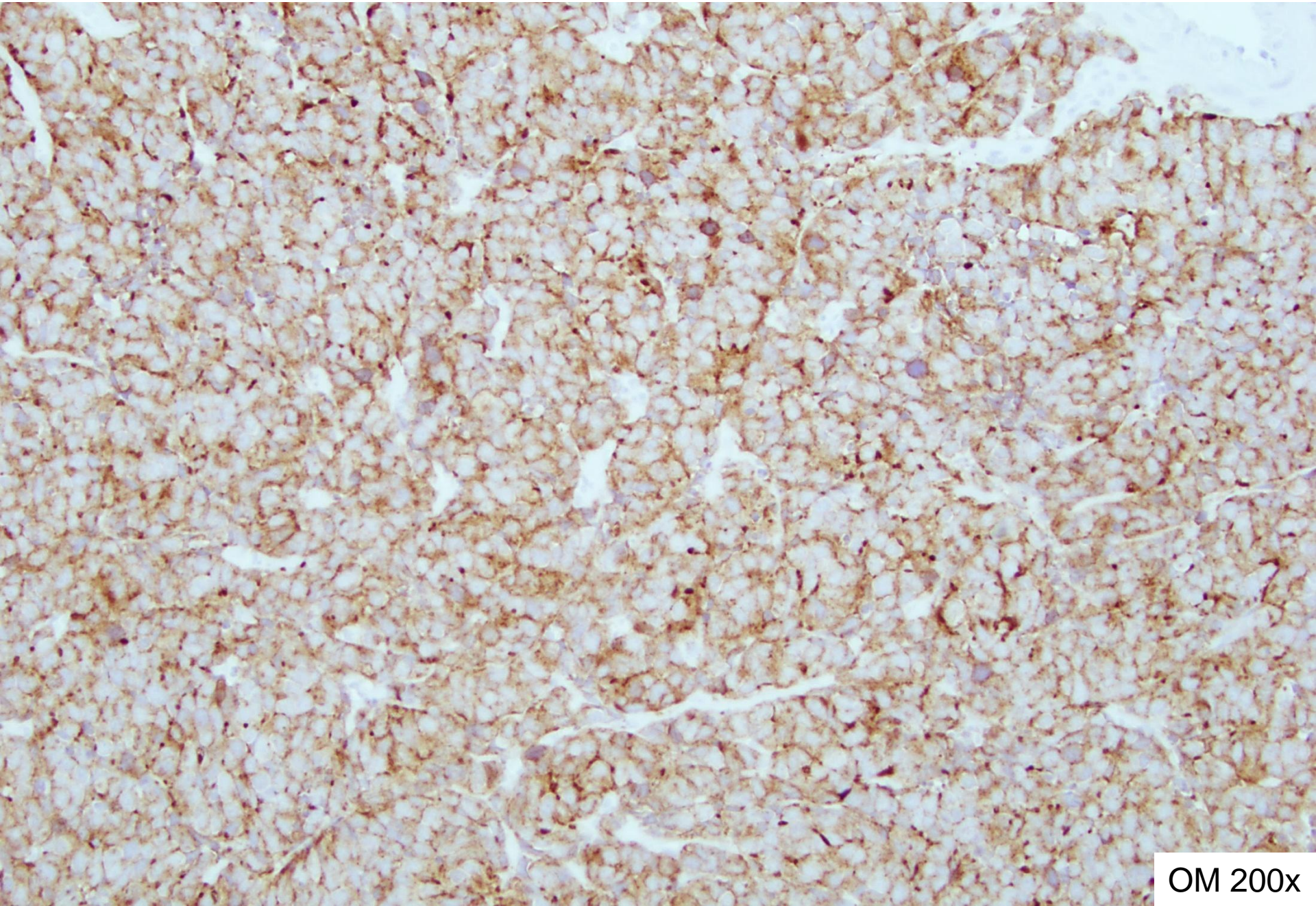
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Small cell carcinoma of bladder



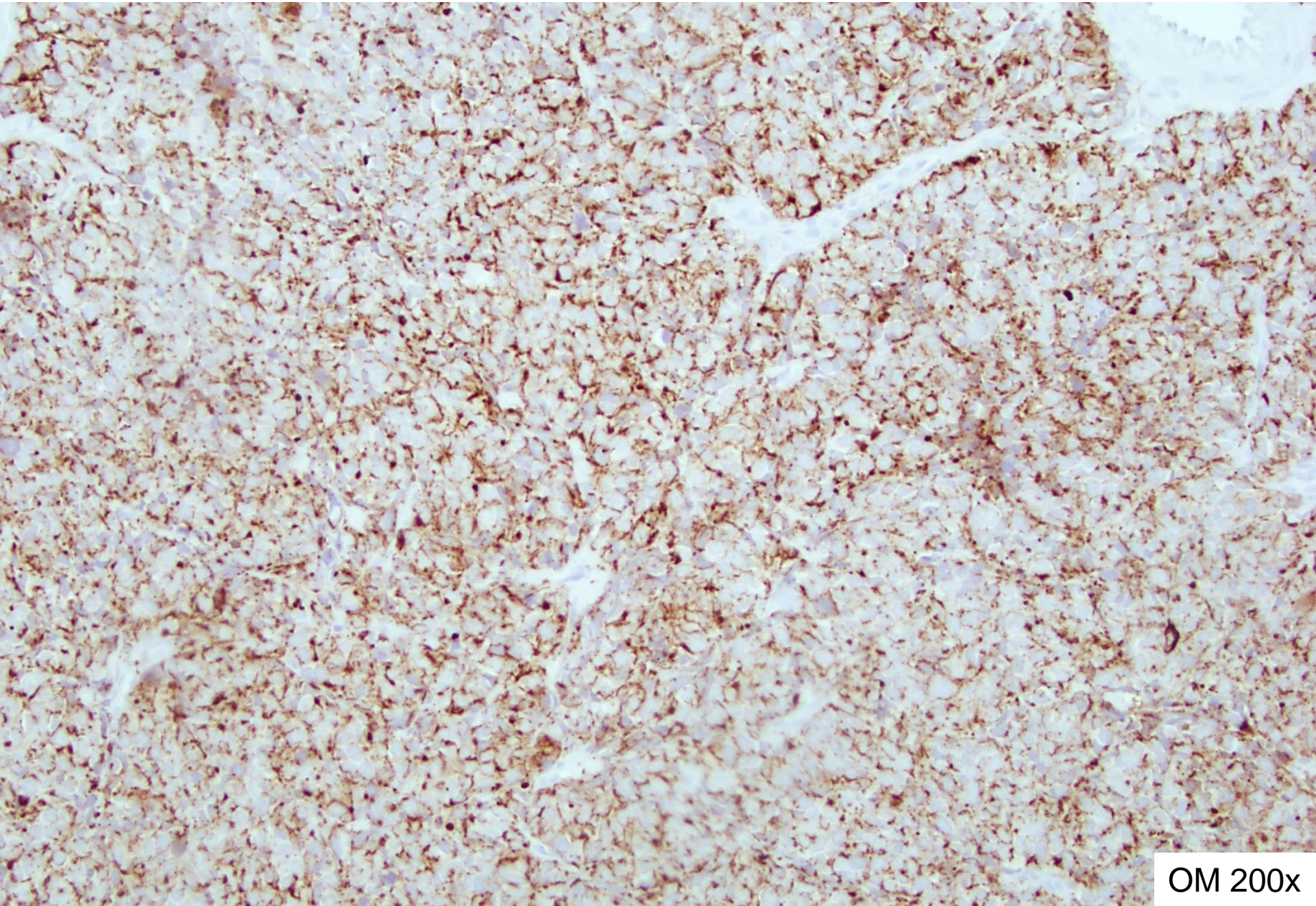
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Synaptophysin

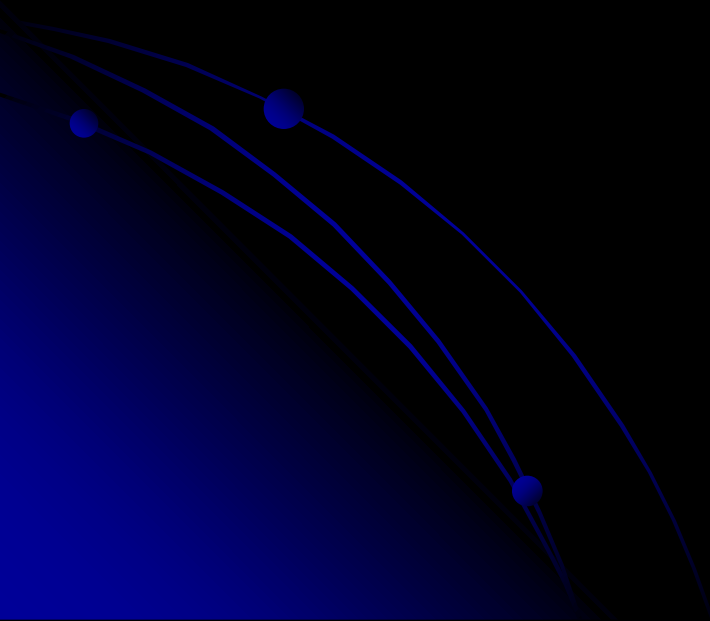
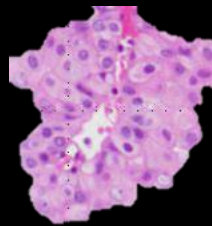
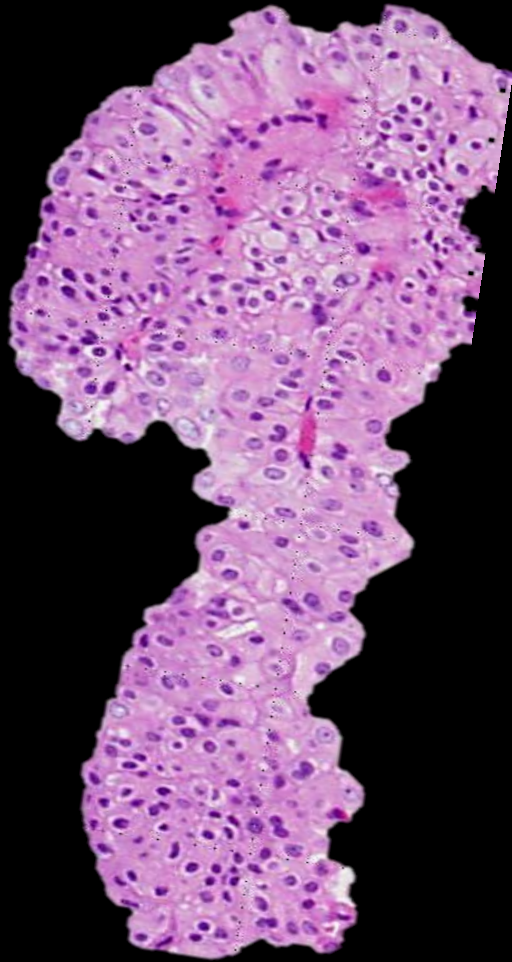


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AE1/AE3



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Histologic Variant (Subtype)

Urothelial lineage with diverse morphology



Histologic Variant (Subtype)

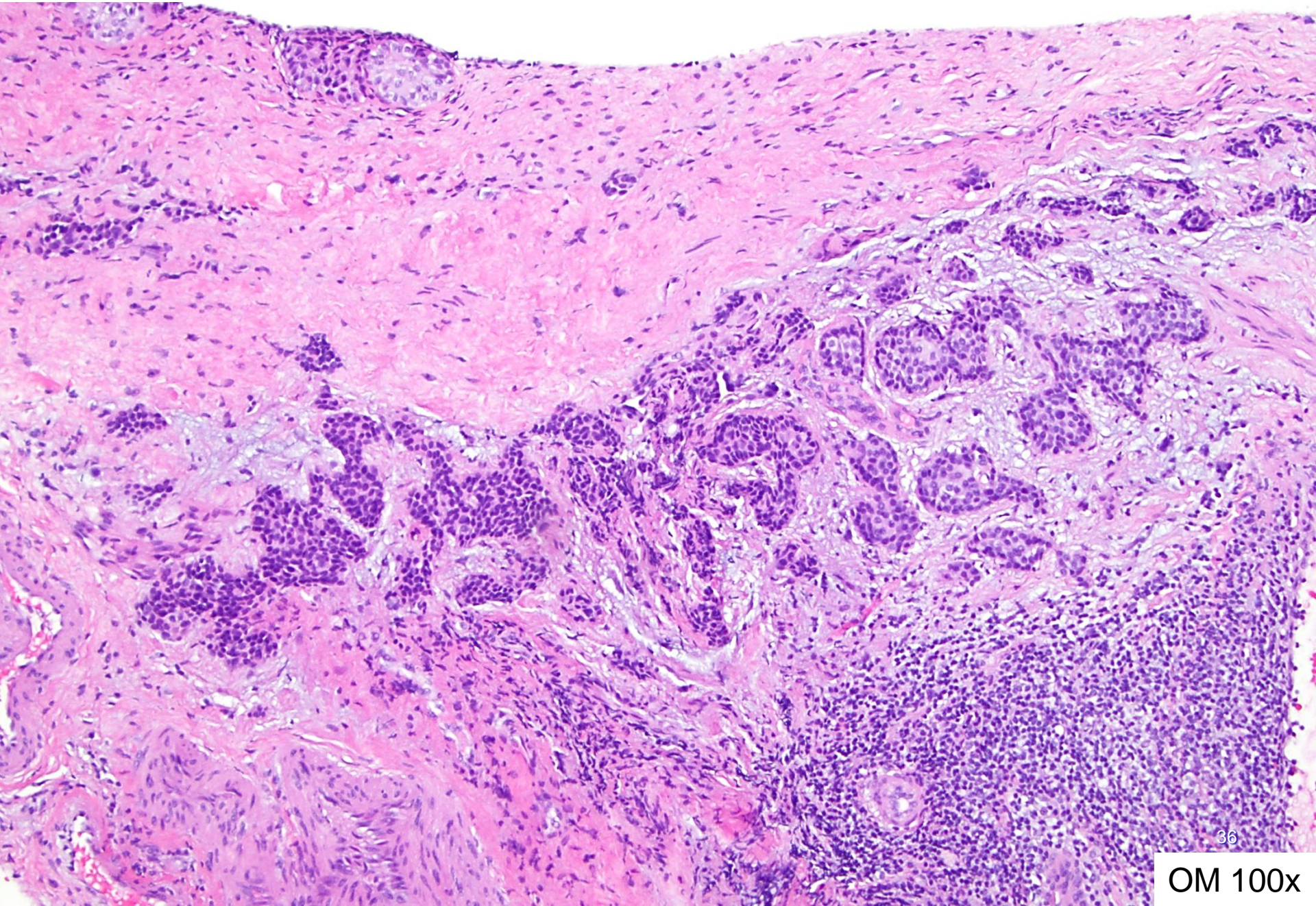
- Nested/large nested/microcystic
- Micropapillary
- Plasmacytoid (signet ring/diffuse)
- Sarcomatoid
- Lipid-rich
- Lymphoepithelioma-like
- Clear cell (glycogen-rich)
- Giant cell
- Poorly differentiated

Histologic Variant

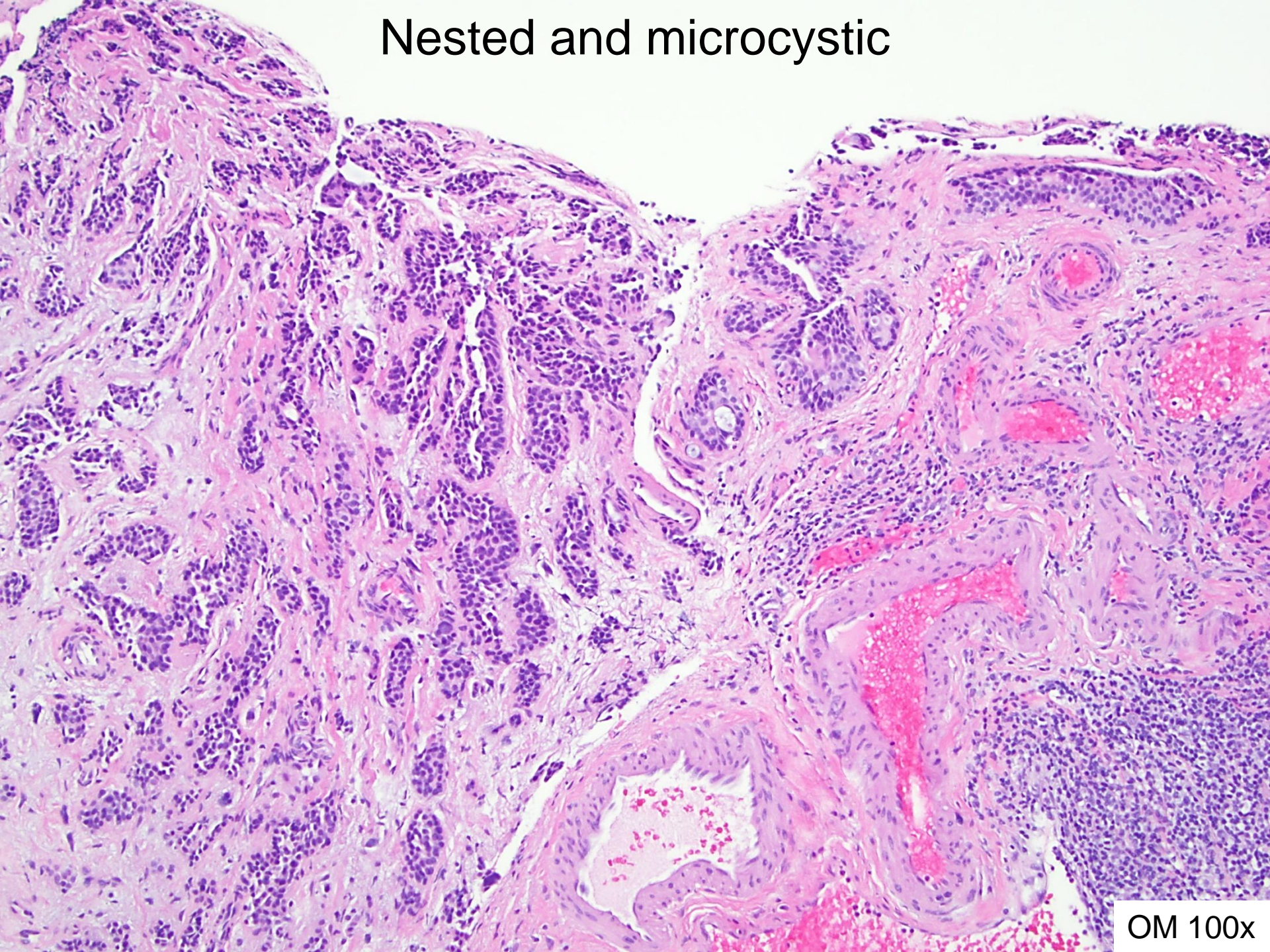
Nested/Large nested/Microcystic

- <5% of invasive bladder tumors (each <1%)
- Often presenting at high stage
- Prognosis similar to UC of same stage
- DDX with benign proliferations (von Brunn nests, cystitis cystica, nephrogenic adenoma), pseudocarcinomatous hyperplasia, paraganglioma, noninvasive inverted growth
- Luminal-type expression and molecular profile (low FGFR3 mutation)
 - ✓ *TERT* promoter mutation absent in benign mimickers
 - ✓ Expresses PAX-8!!!

Nested variant UC

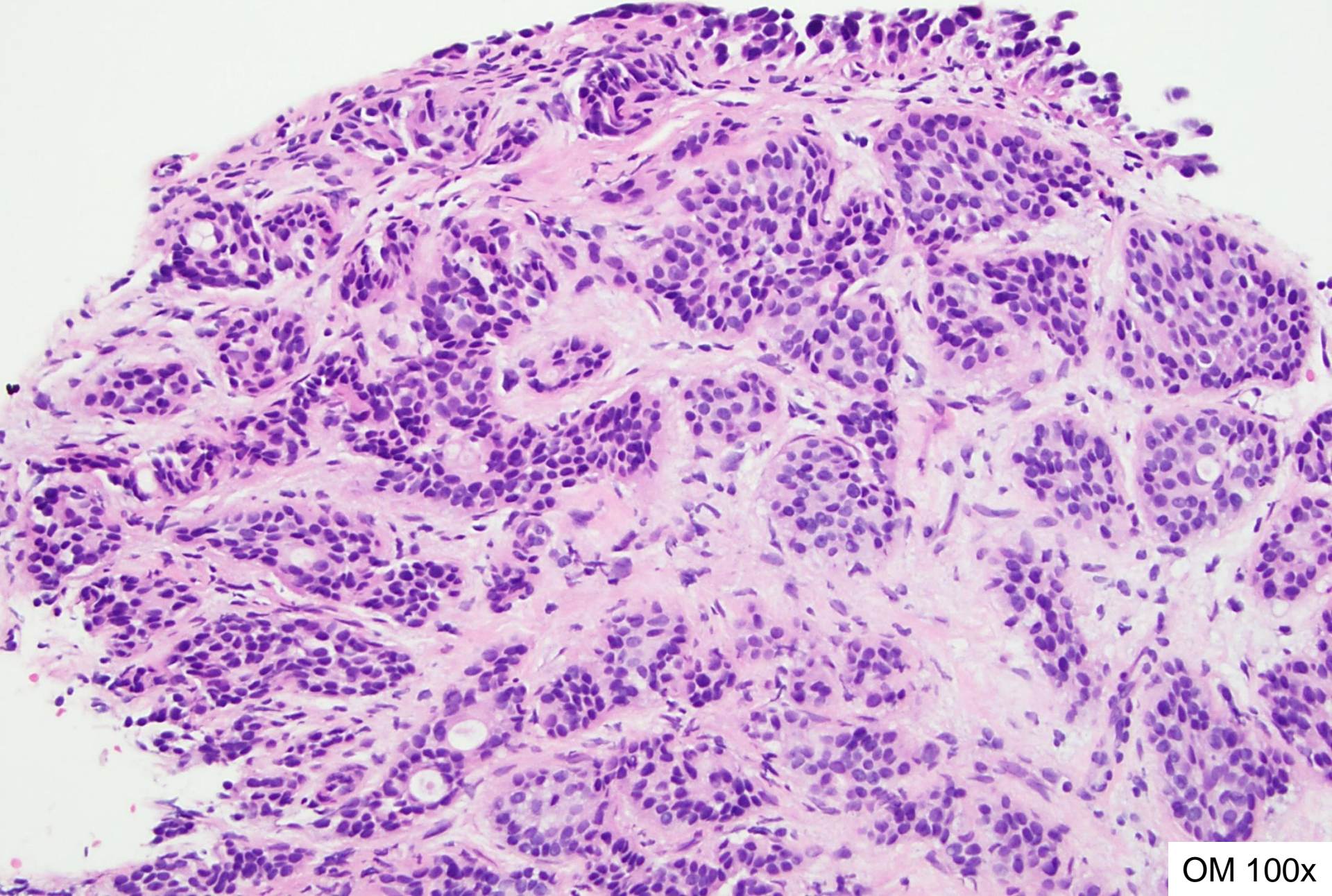


Nested and microcystic



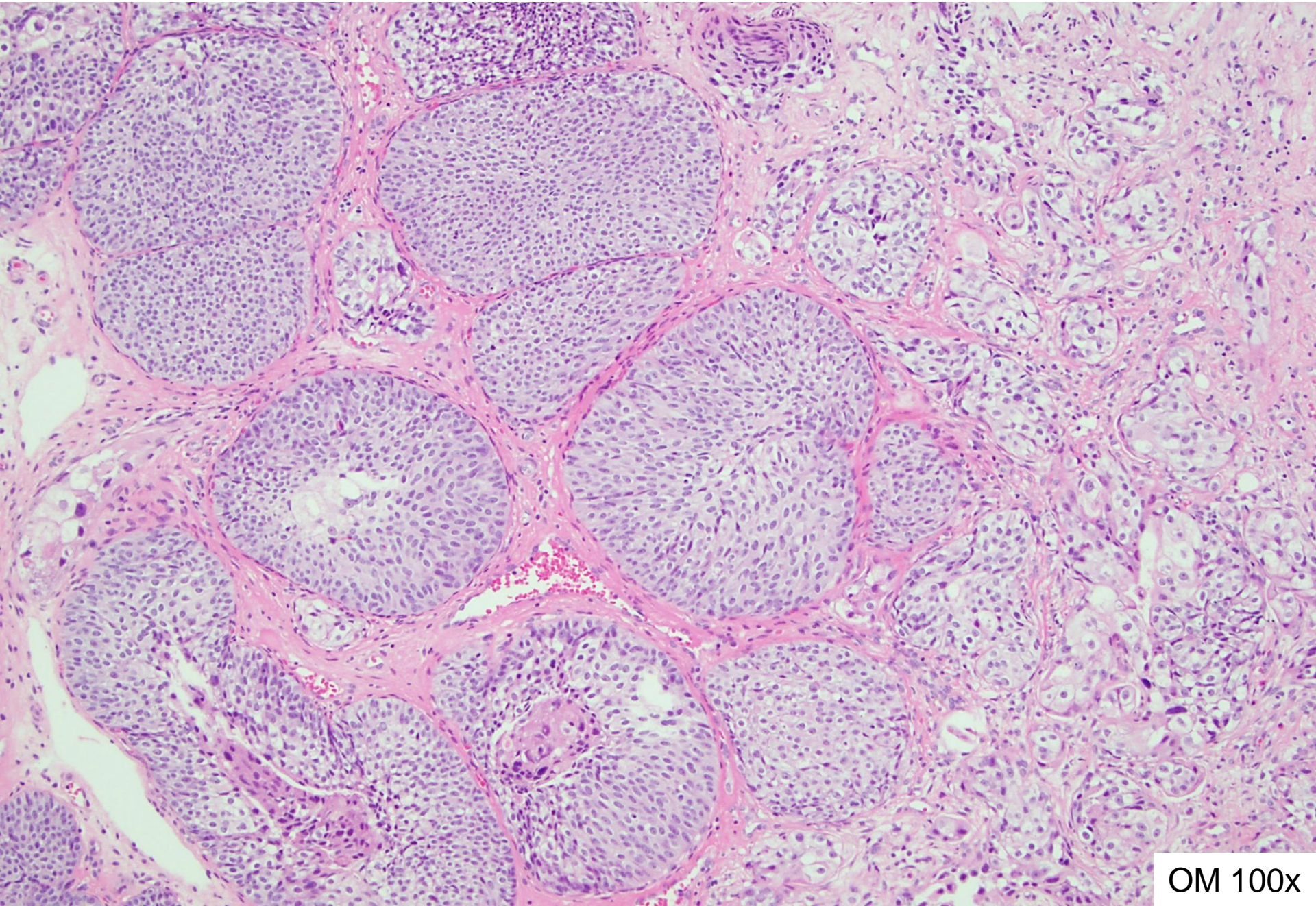
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Nested and microcystic



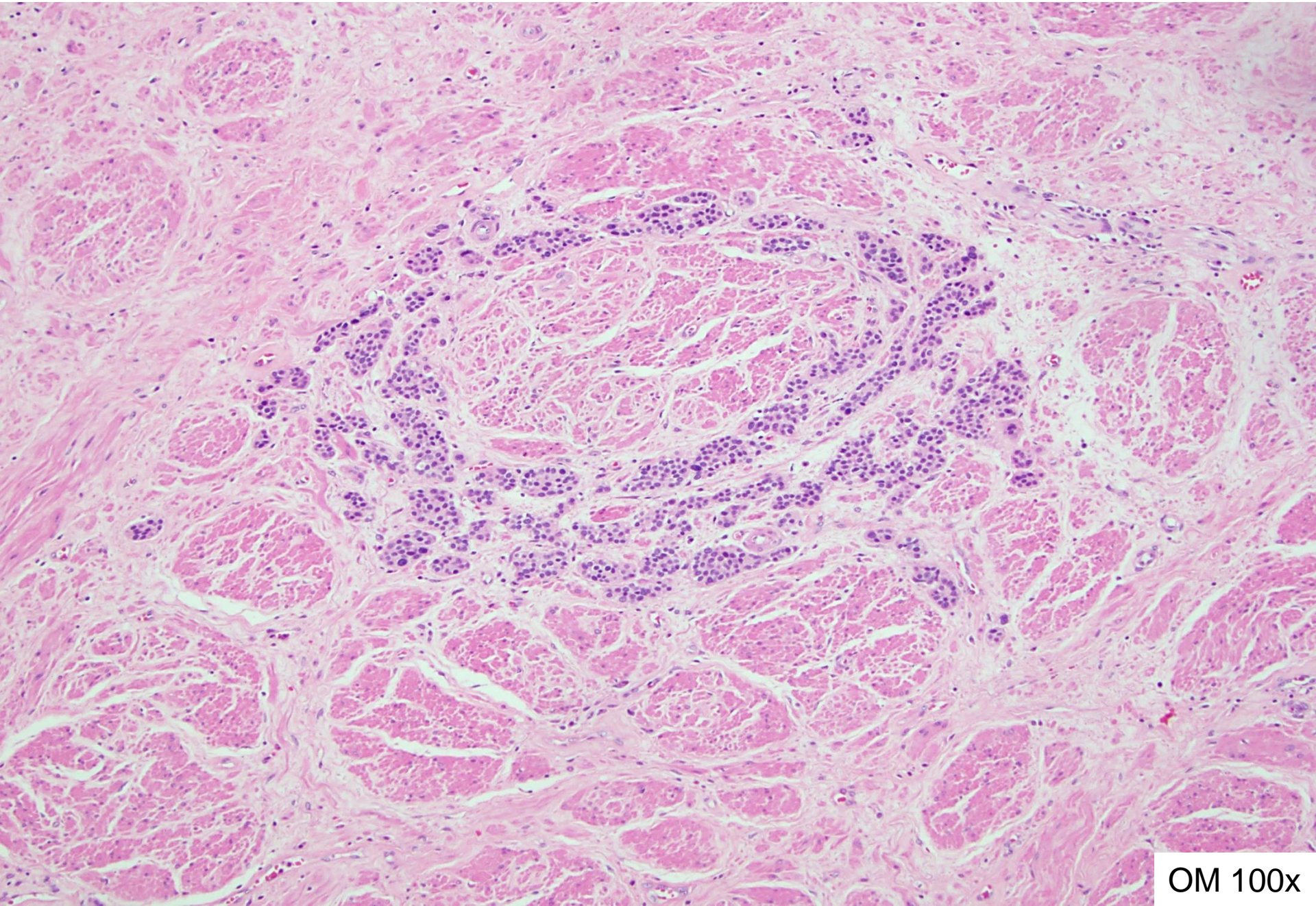
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Large nested UC



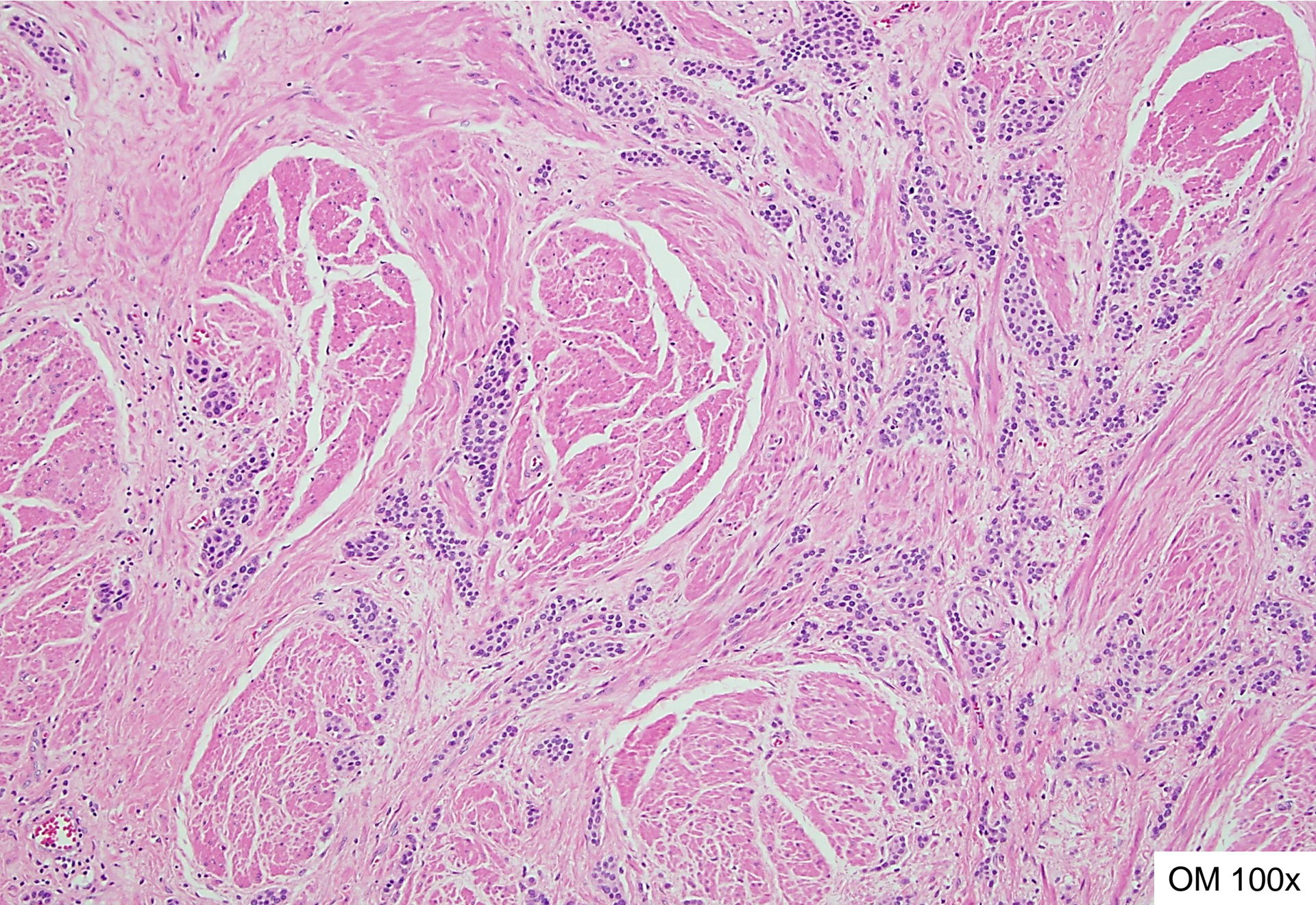
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Nested variant UC: detrusor muscle invasion



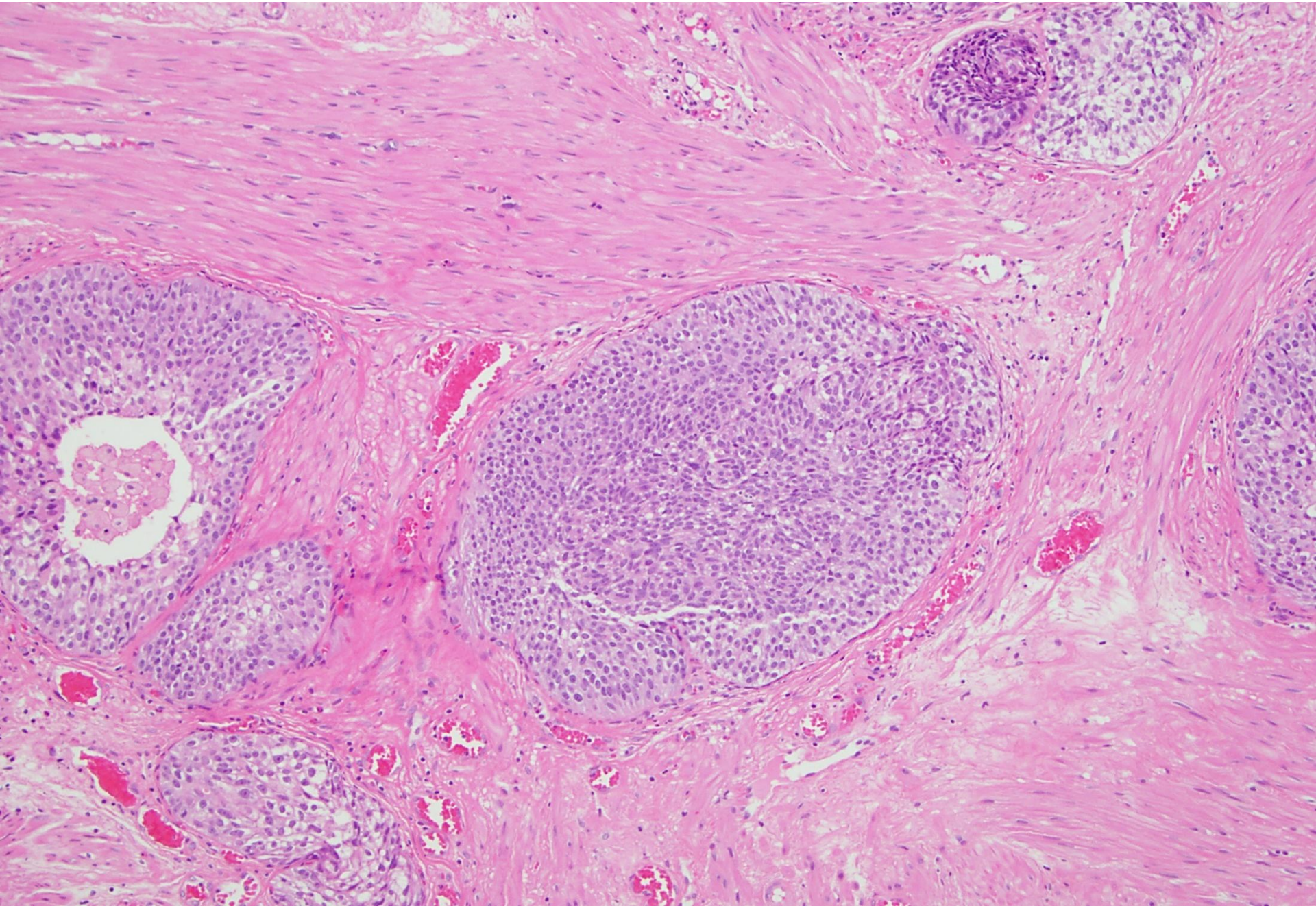
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Nested variant UC: detrusor muscle invasion

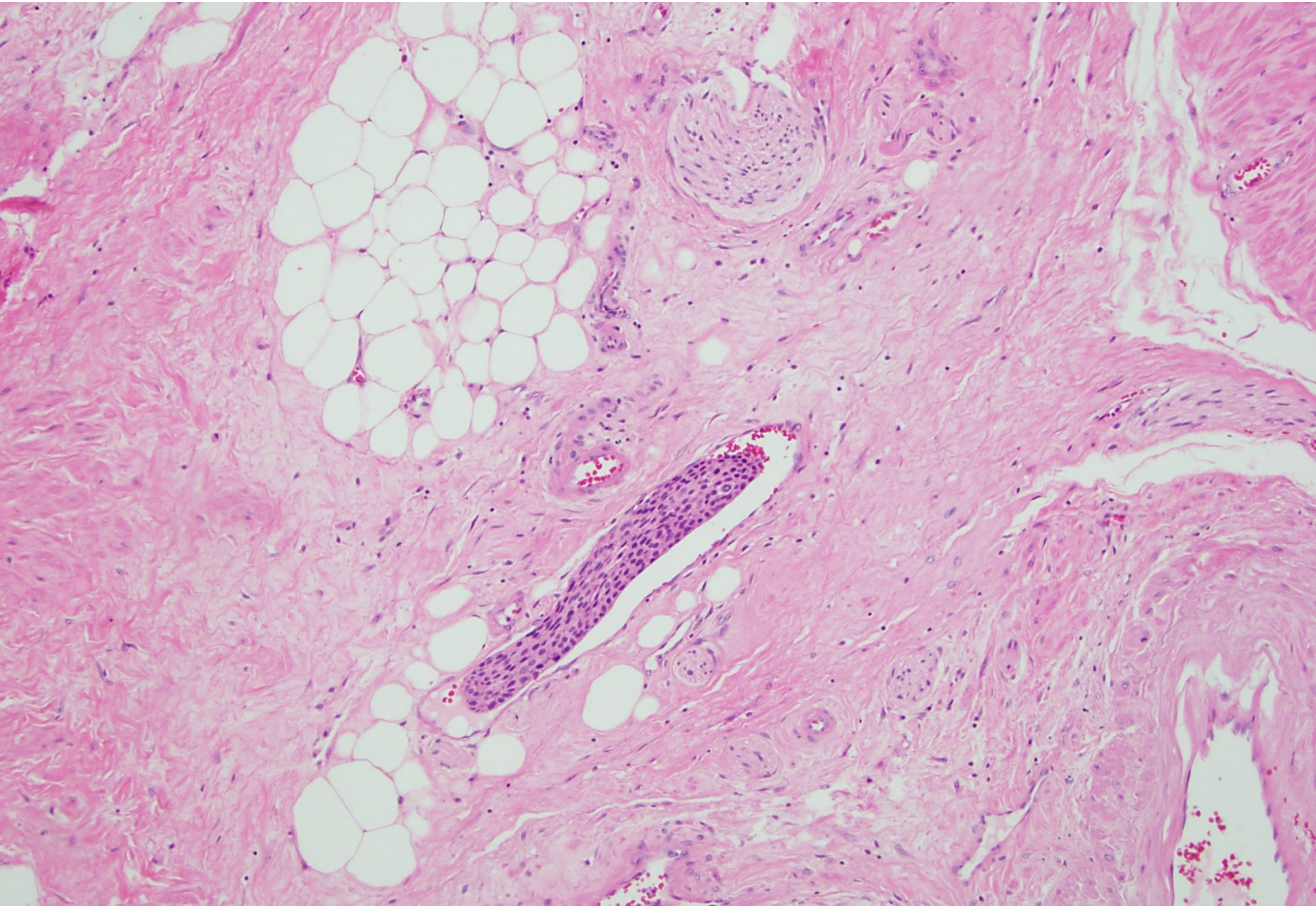


OM 100x

Large nested UC in detrusor muscle



Nested variant UC: LVI



Histologic Variant Micropapillary

- 0.6% to 2.2%
- **Aggressive variant**
- Extent of variant morphology may impact management and prognosis
 - ✓ Cutoff not well established (<10% and >50% most used to define “focal” and “extensive”, respectively)
 - ✓ Early cystectomy (T1 disease!) often undertaken
 - ✓ Bladder sparing trimodal therapy contraindicated if $\geq 30\%$
- DDX with metastases (>>breast/GI)
- Overexpression and/or amplification of *ERBB2/HER2* (15%-74%)

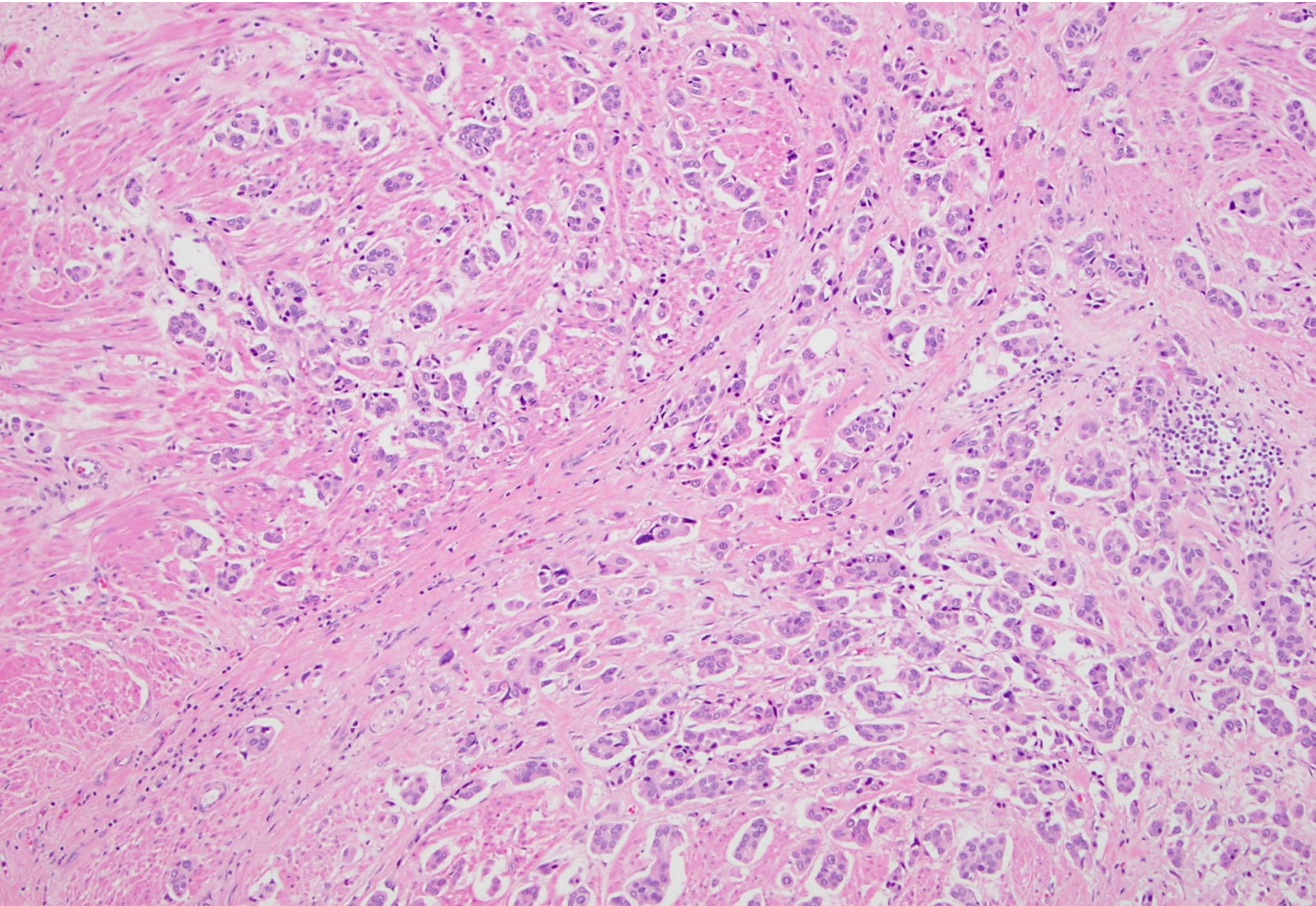
Sanguedolce F. et al. Mol Clin Oncol. 2019 Feb;10(2):205-213

Bertz S et al. Virchows Arch. 2016 Sep;469(3):339-44

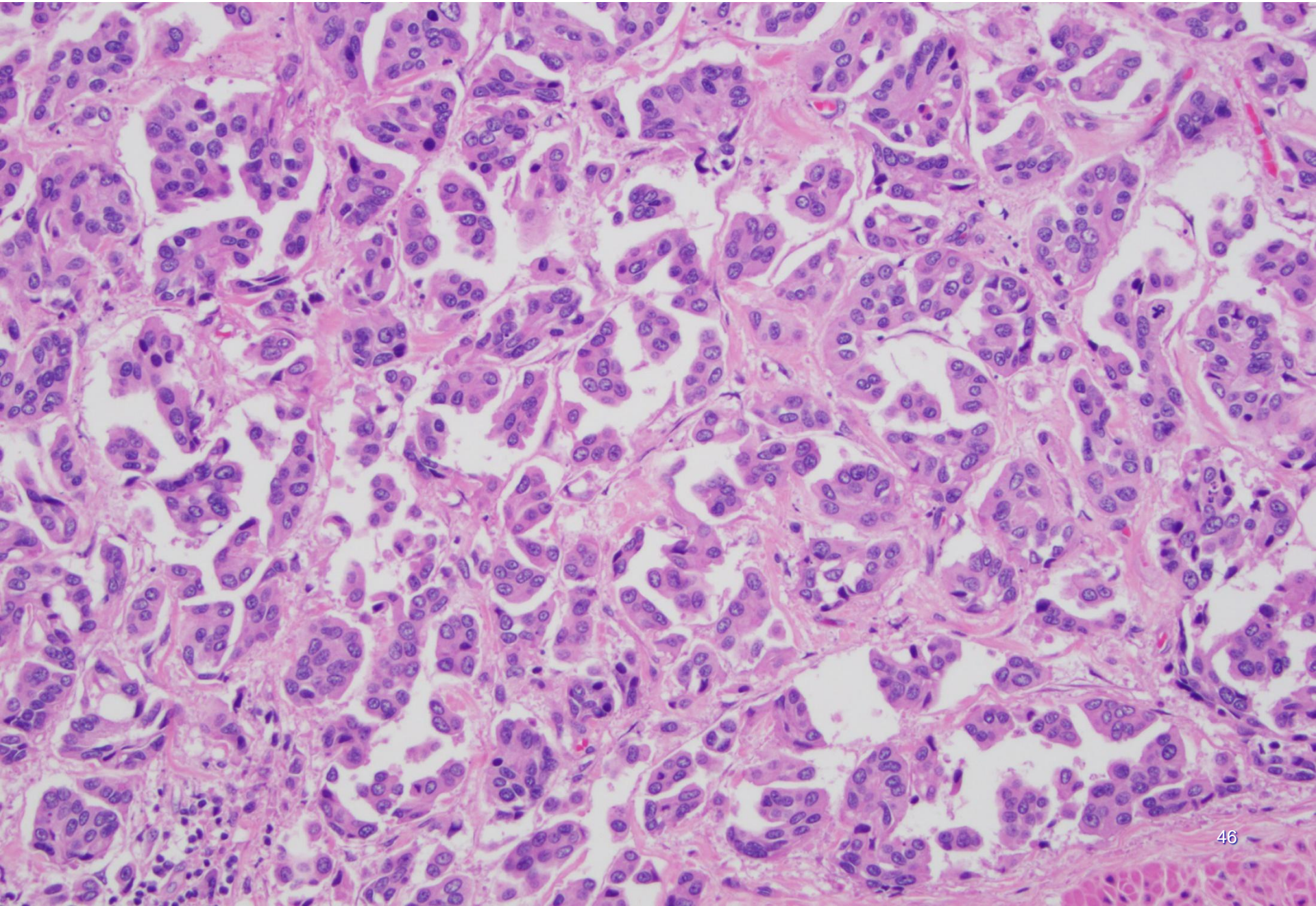
Willis DL et al. Urol Oncol. 2014 Aug;32(6):826-32

Alvarado-Cabrero I et al. Ann Diagn Pathol. 2005 Feb;9(1):1-5

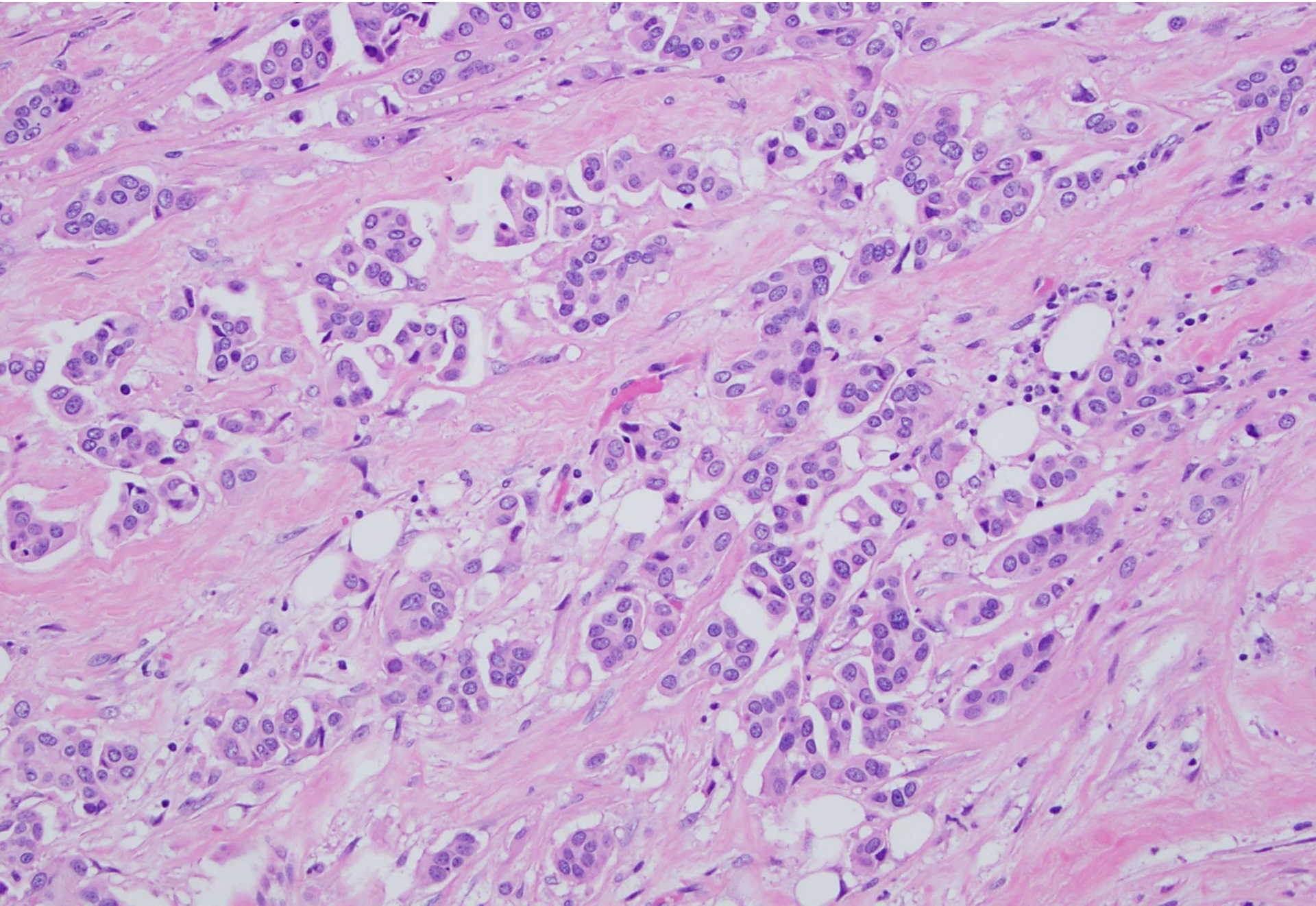
Micropapillary UC: detrusor muscle invasion



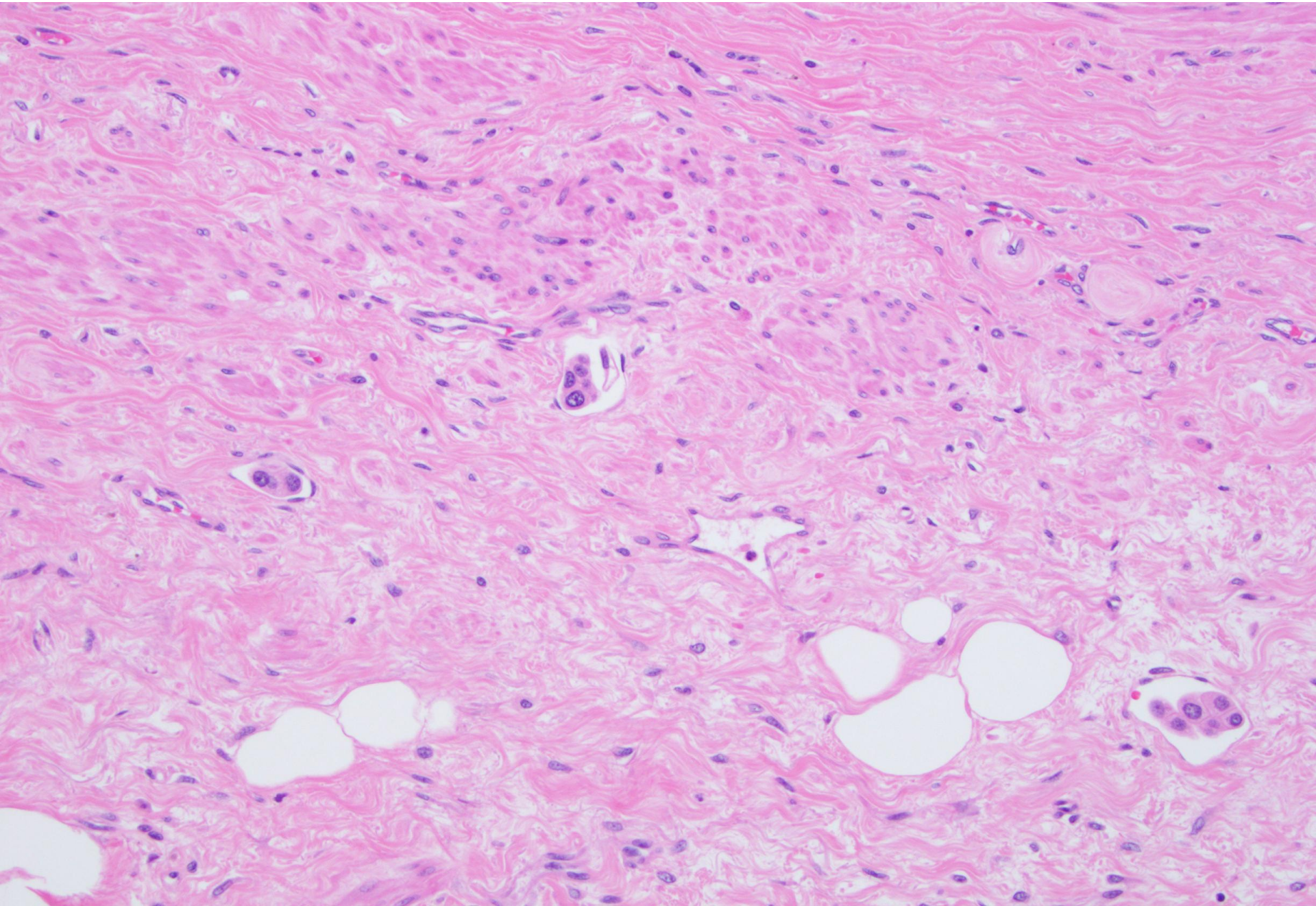
Micropapillary UC: multiple clusters in the same lacuna



Micropapillary UC: clusters in lacunae and ring forms



Micropapillary UC: LVI

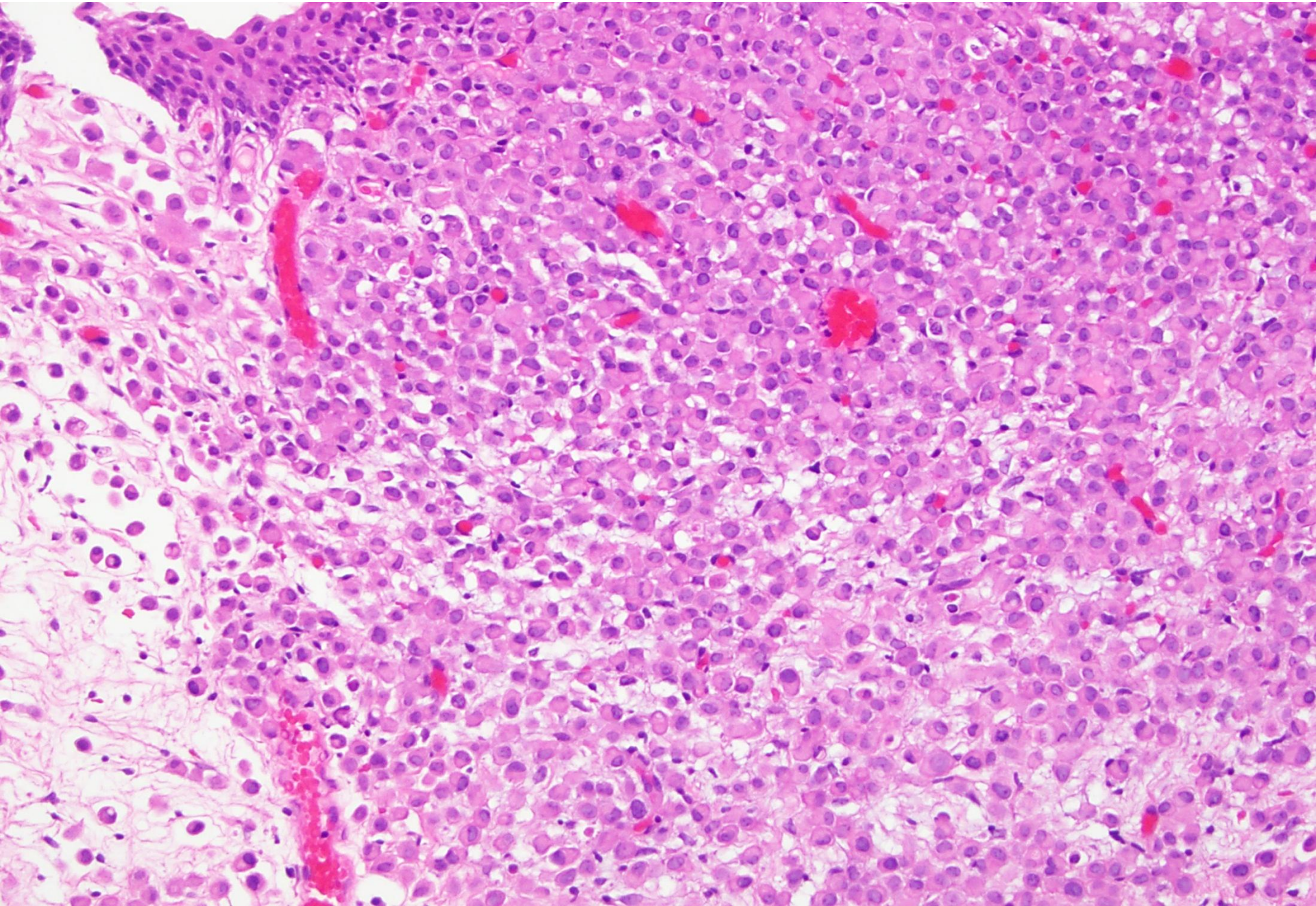


Histologic Variant

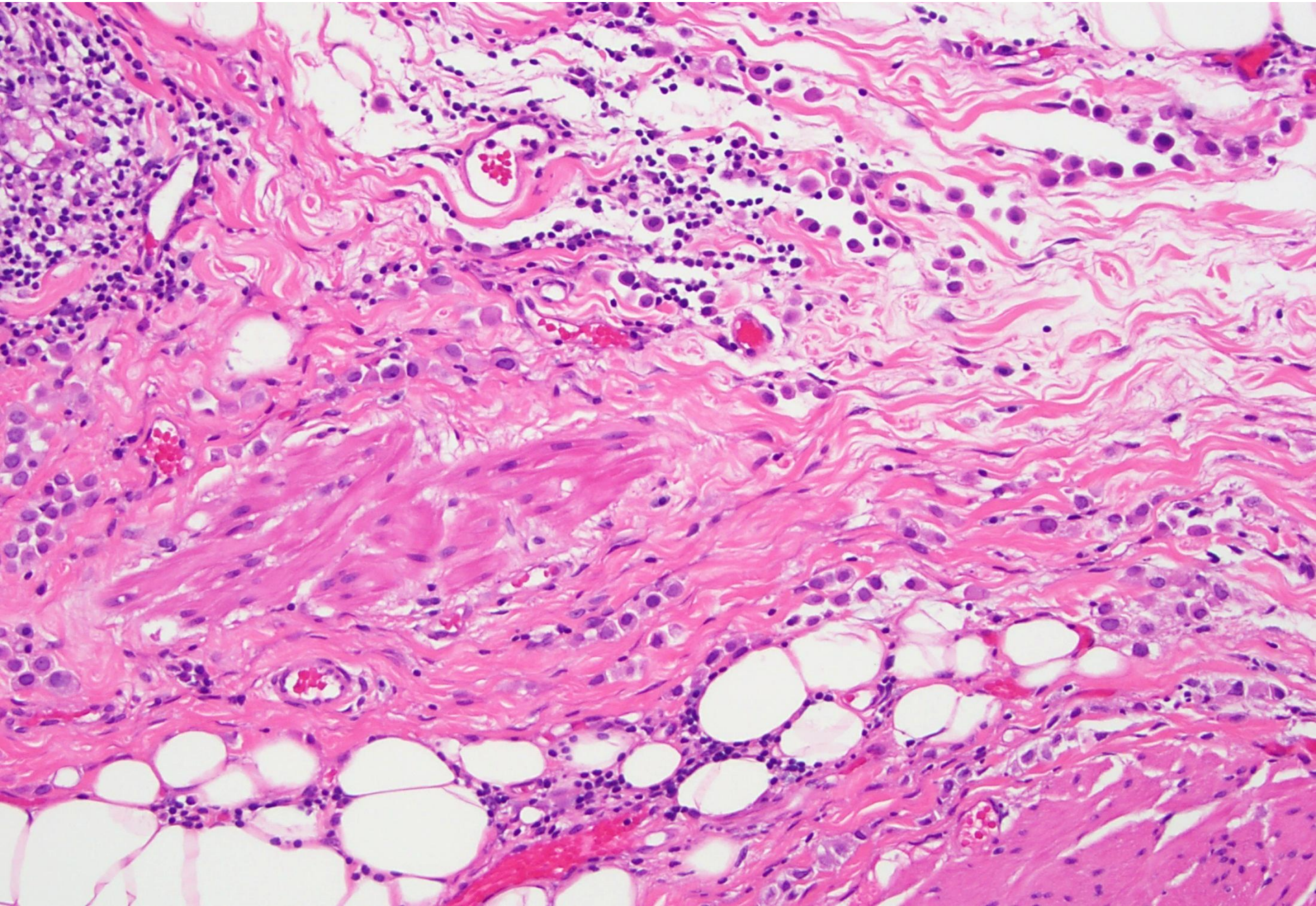
Plasmacytoid/Signet ring/Diffuse

- Rare (<1%)
- **Aggressive variant**
 - ✓ Higher stage at presentation than conventional UC
 - ✓ Early cystectomy advocated
- DDX with melanoma, plasmacytoma, lymphoma, secondary involvement from other cancers (>>>breast, GI)
- Positive UC lineage markers (both GATA-3 and p63)
- Loss of E-cadherin membranous expression (>70%)
 - ✓ >>>due to *CDH1* nonsense mutation (84%)

Plasmacytoid UC



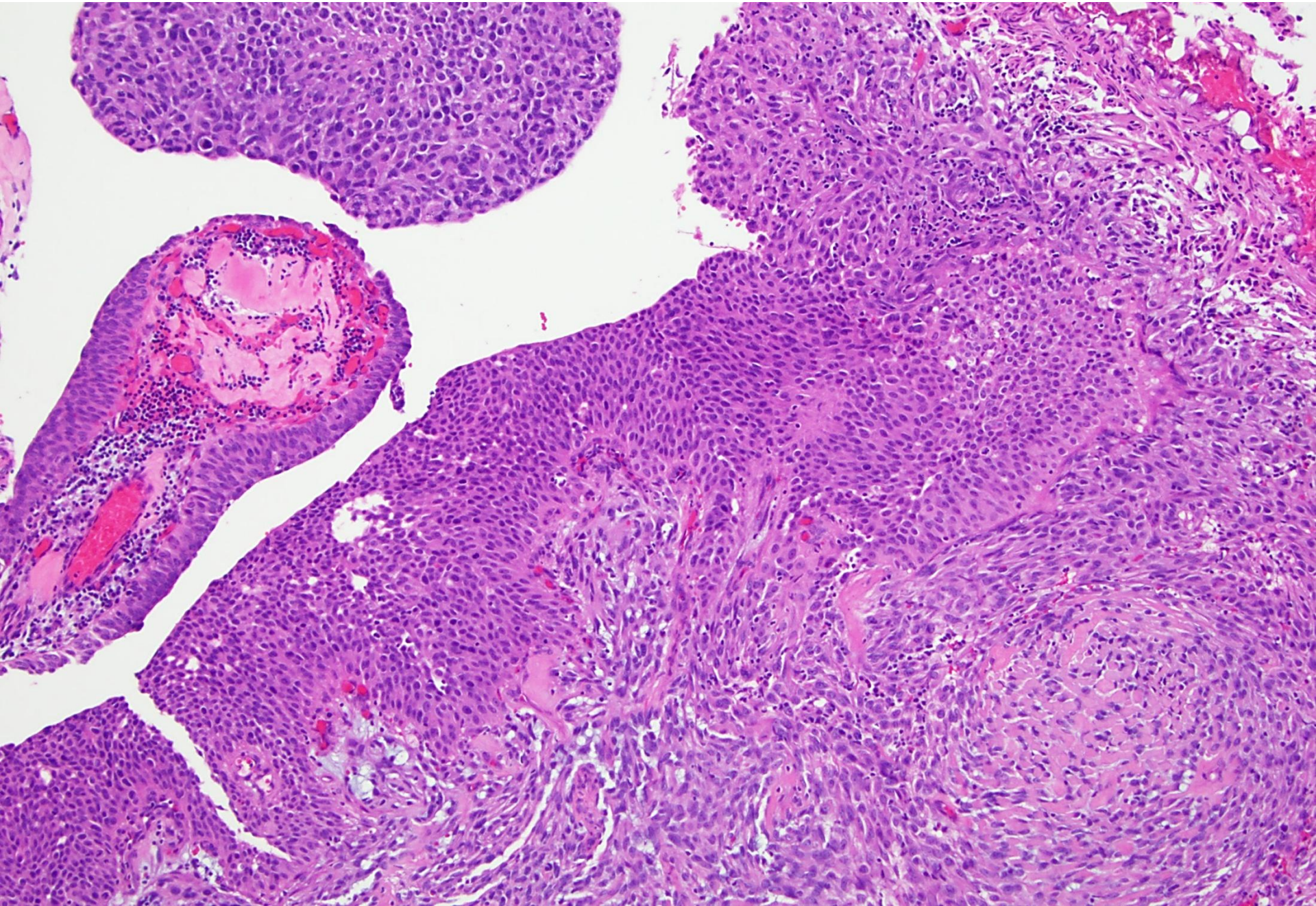
Plasmacytoid UC: sneaky!



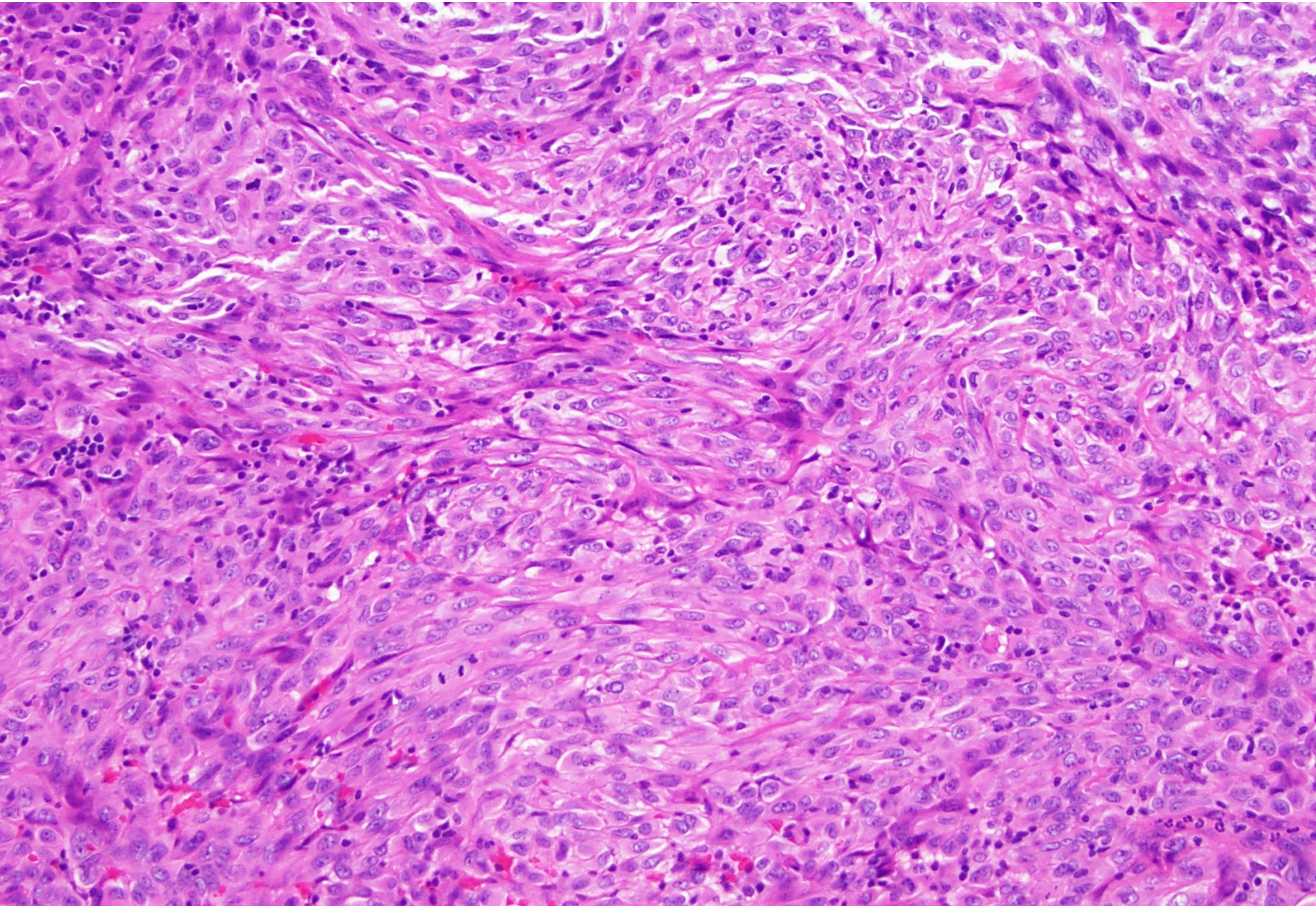
Histologic Variant Sarcomatoid

- Extremely rare (0.1%-0.3%)
- **Aggressive variant**
 - ✓ Presenting at advanced stage
 - ✓ Worse disease specific survival
 - ✓ Upfront radical cystectomy
- Report presence of heterologous component
- Must contain:
 - ✓ Associated recognizable UC
 - ✓ High-molecular weight keratin or GATA-3 expression

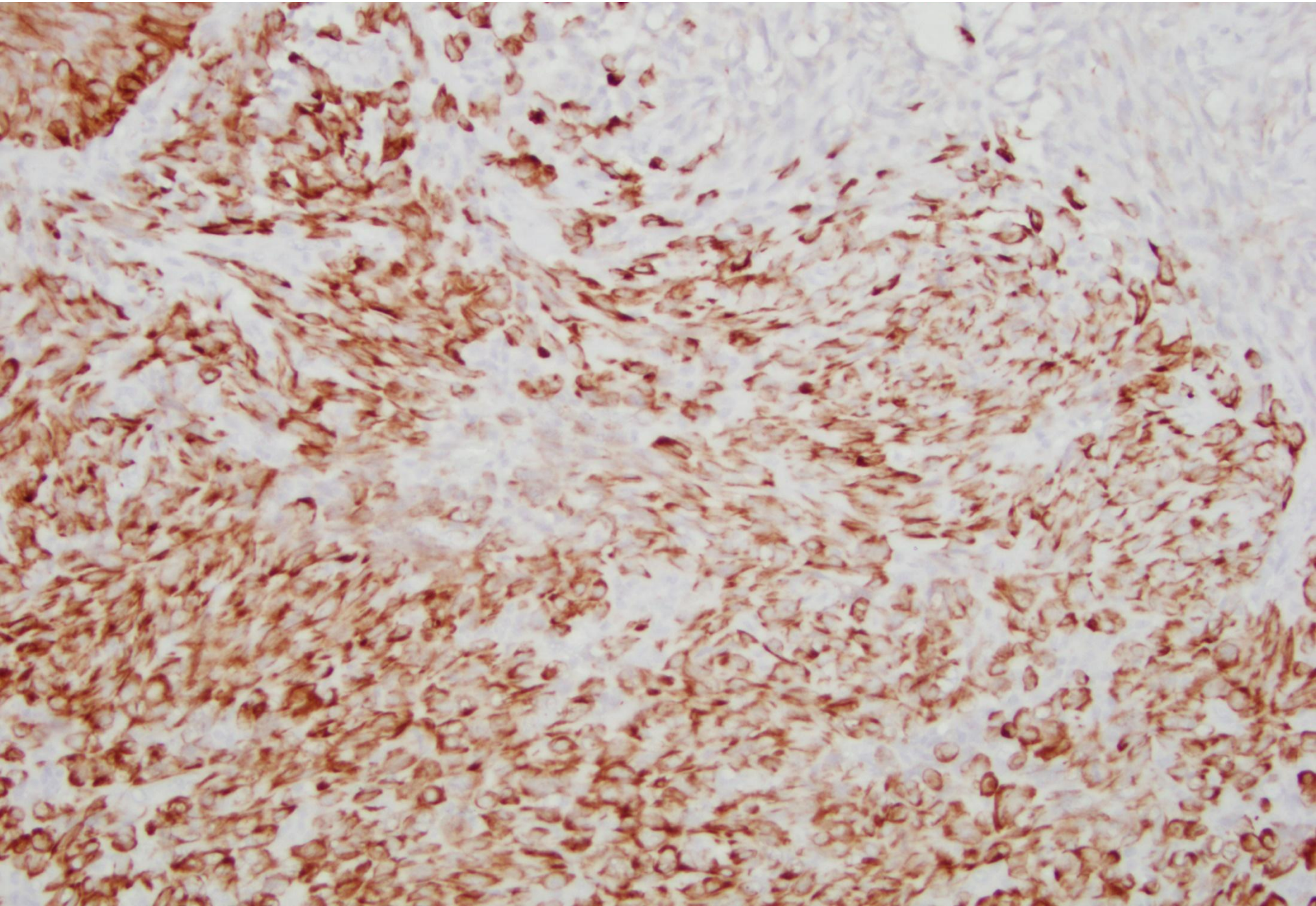
Sarcomatoid UC: undescrpt spindled cell morphology



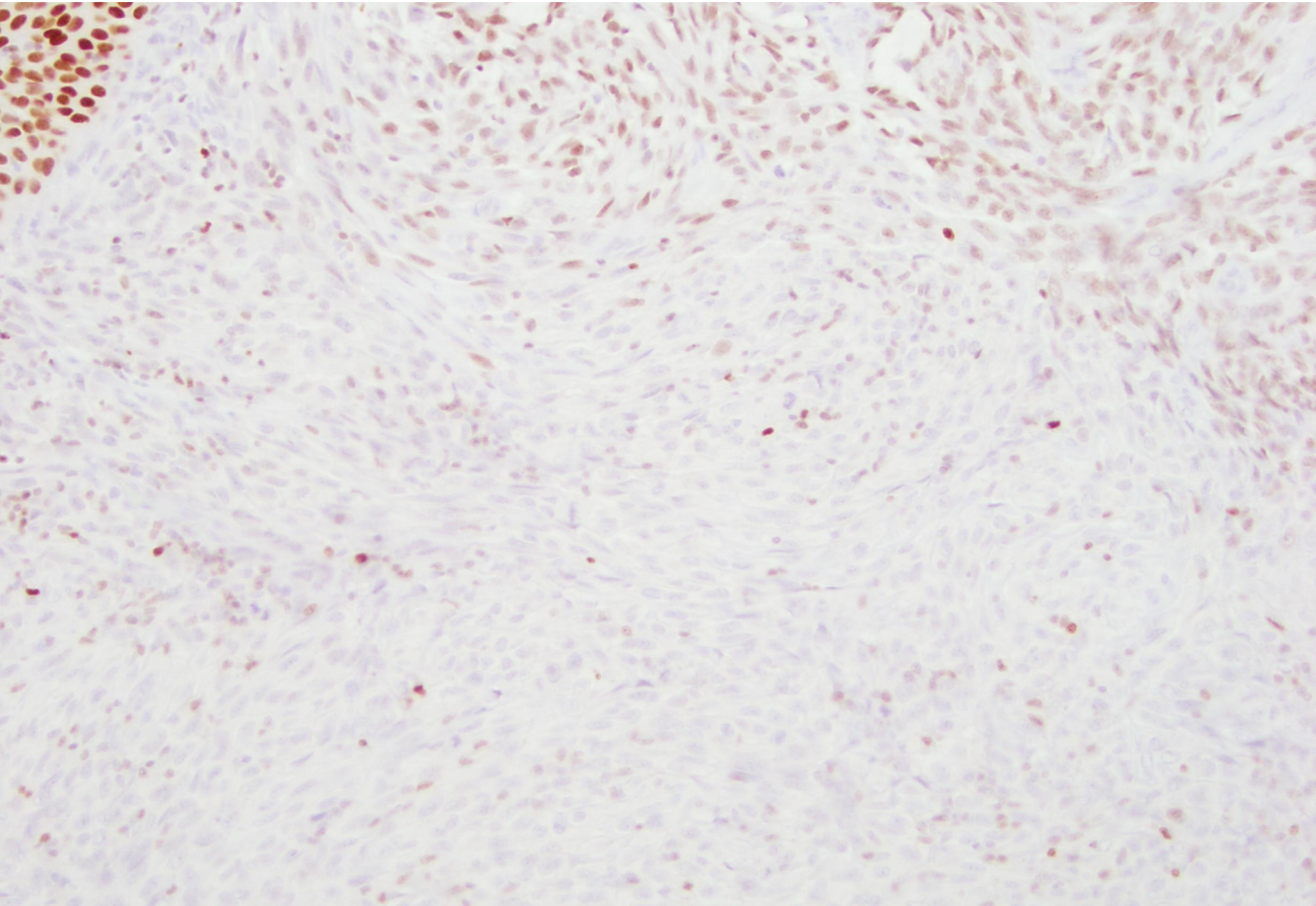
Sarcomatoid UC: undescrpt spindled cell morphology



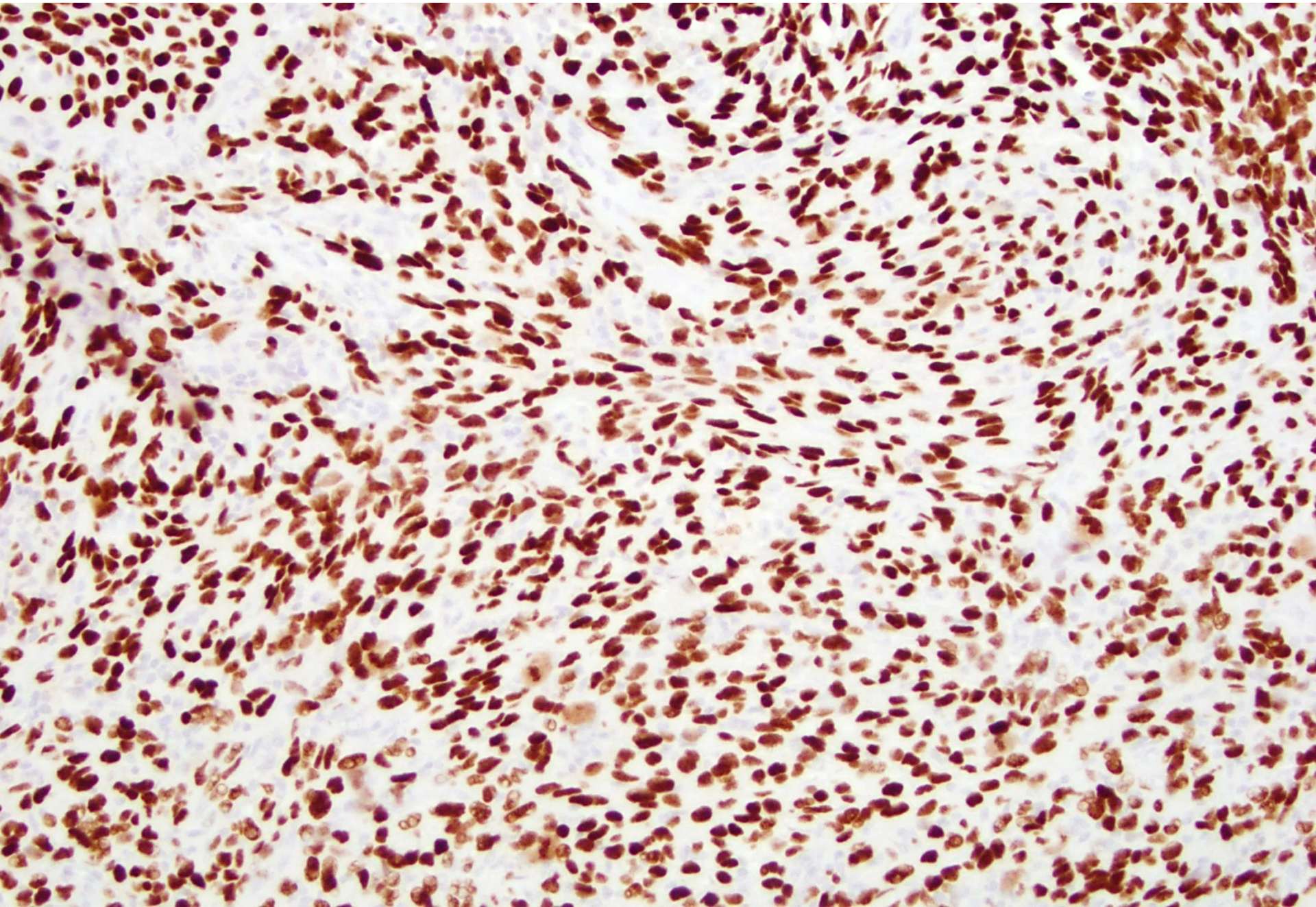
Sarcomatoid UC: 34BetaE12



Sarcomatoid UC: GATA-3



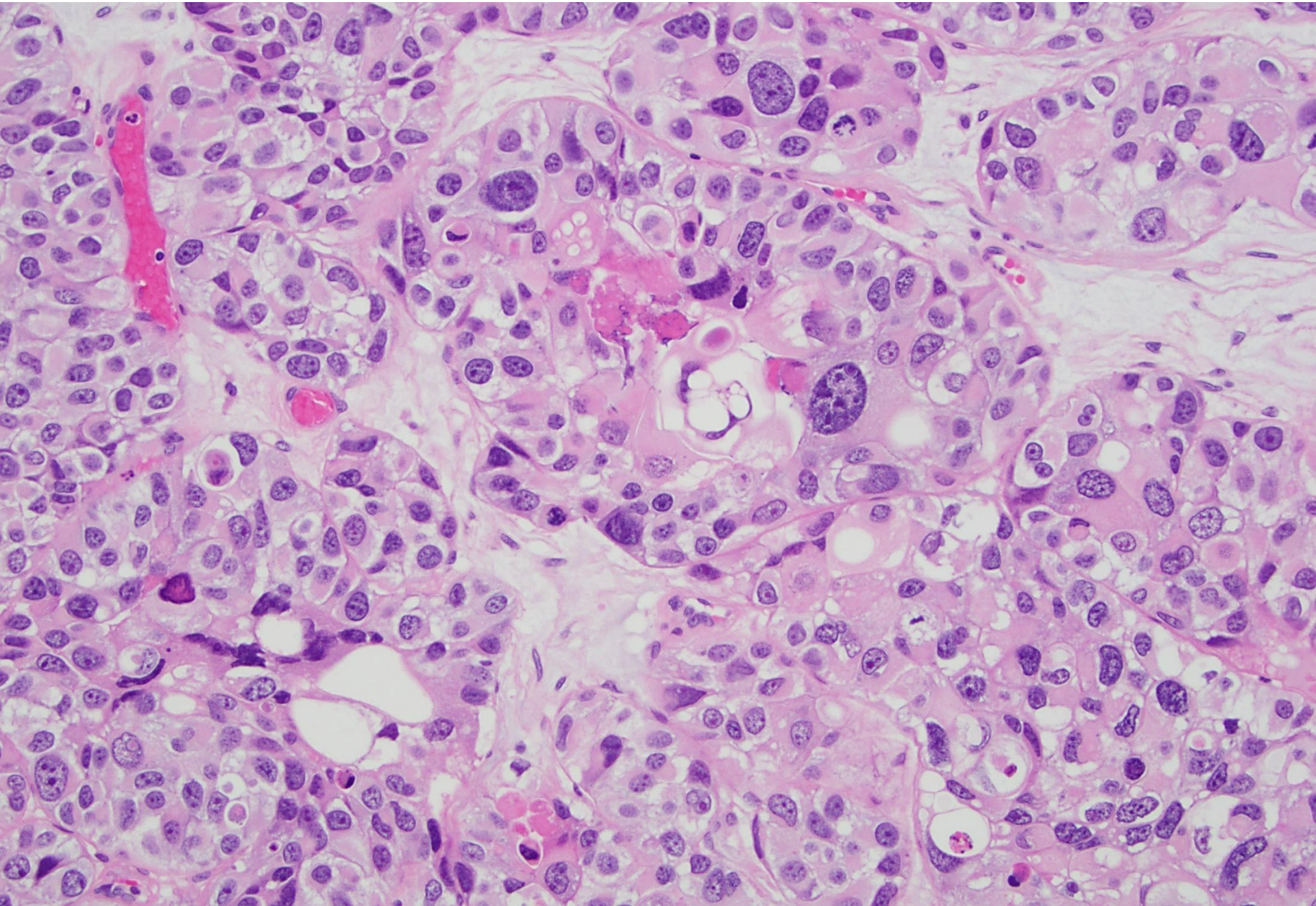
Sarcomatoid UC: p63



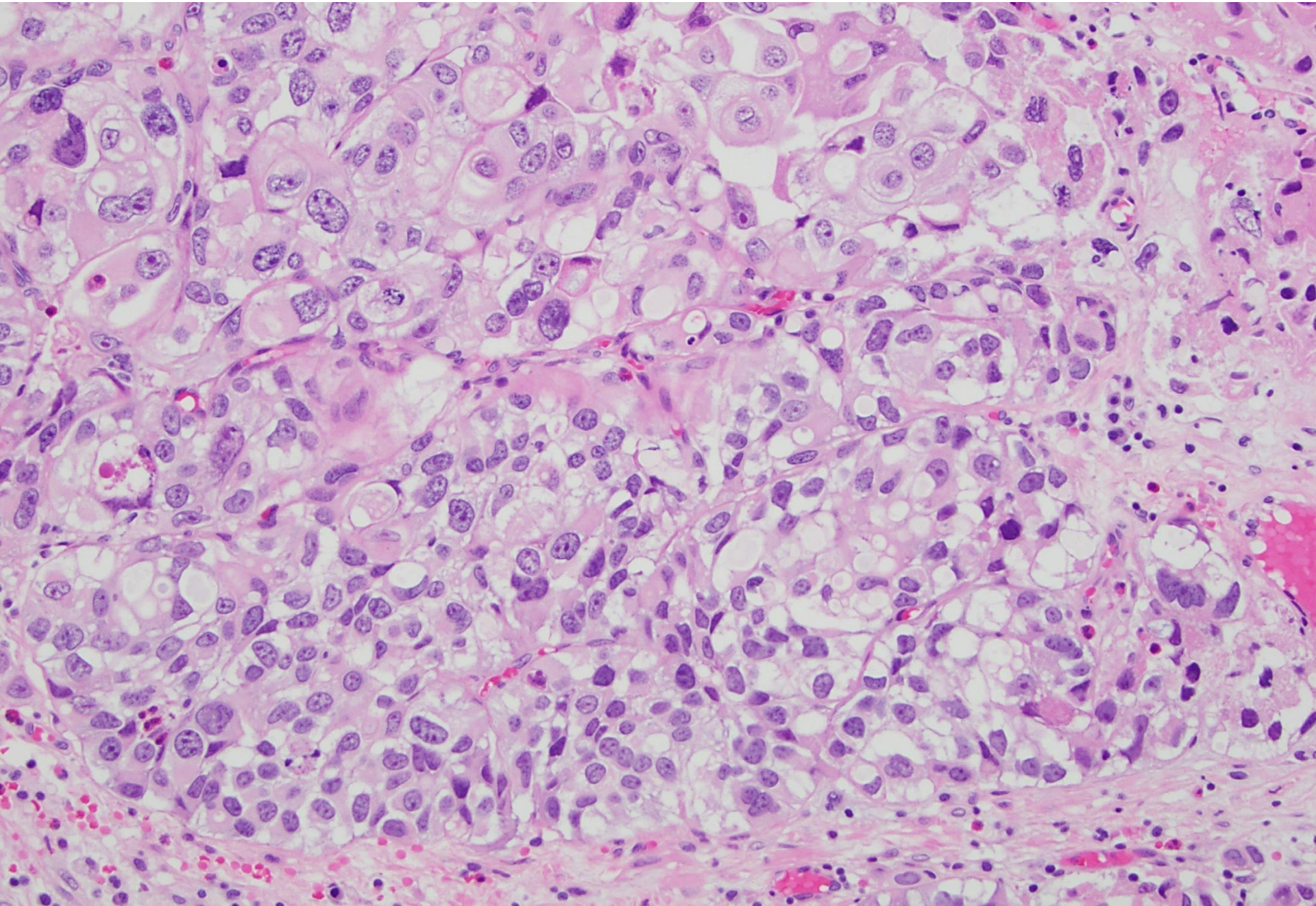
Histologic Variant Lipid-Rich

- Extremely rare
- **Aggressive variant**
 - ✓ Presenting at advanced stage
 - ✓ Poor 5-year survival outcome
- DDX liposarcoma, sarcomatoid carcinoma

Lipid-rich features



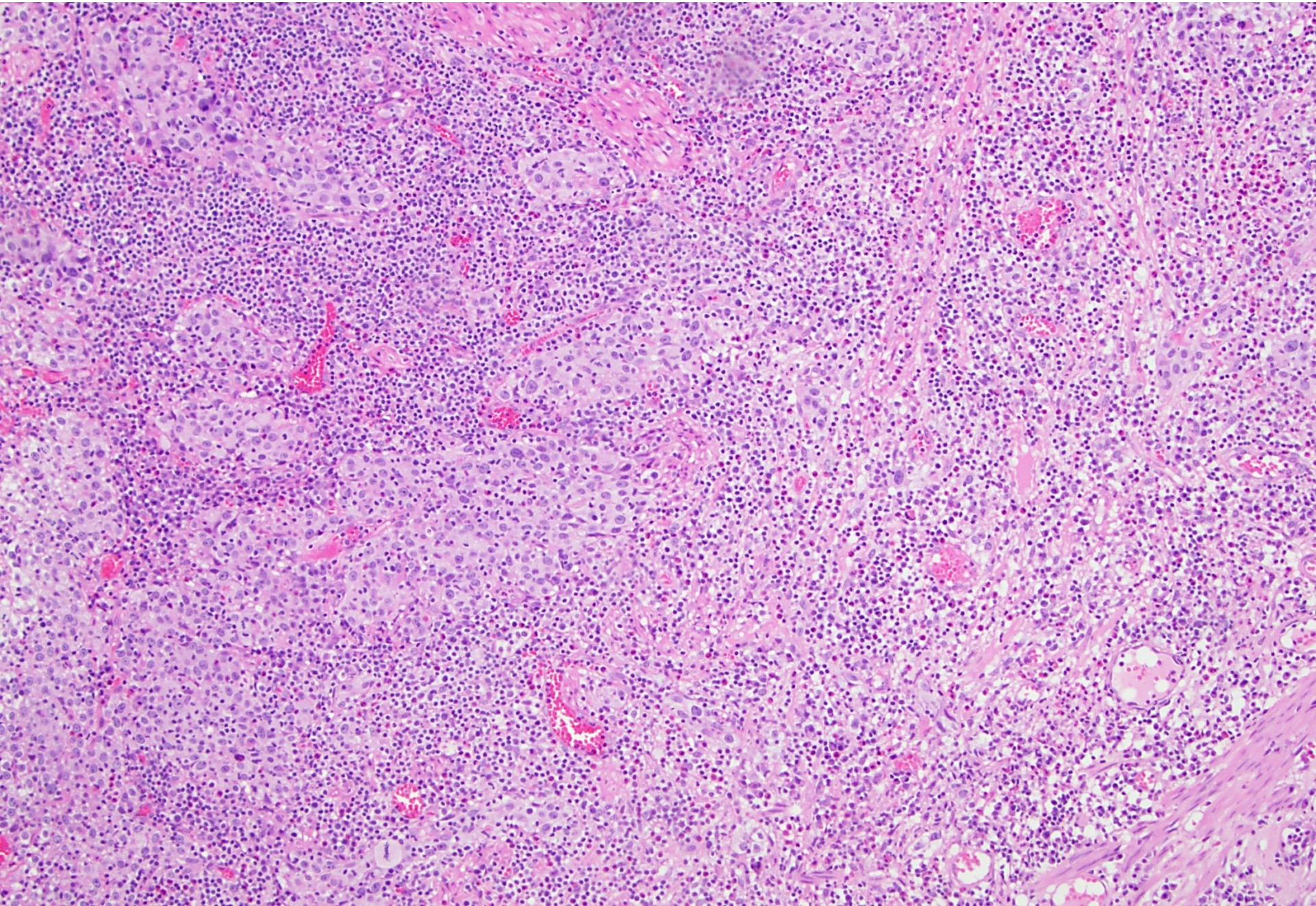
Lipid-rich features



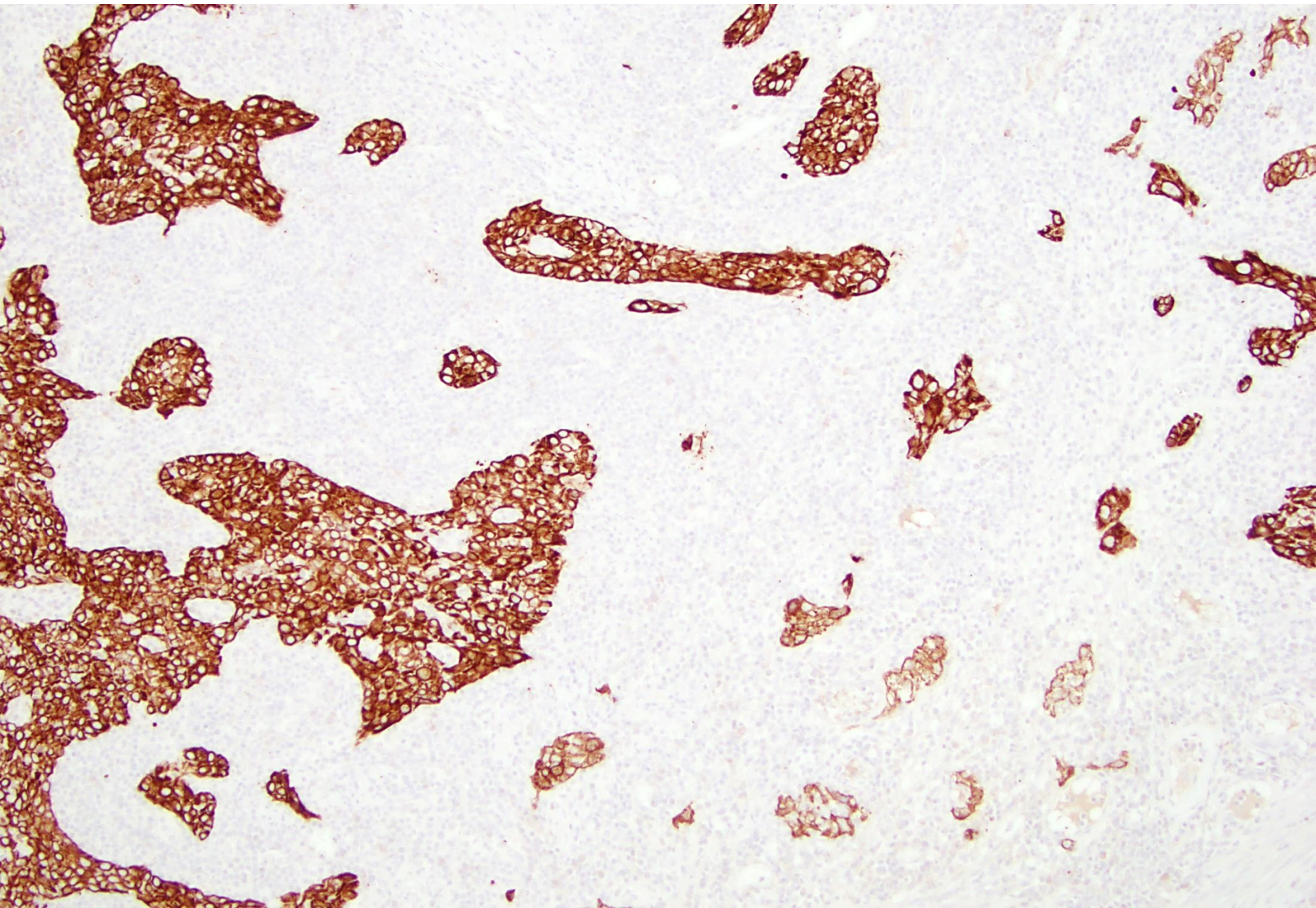
Histologic Variant Lymphoepithelioma-like (LELC)

- Extremely rare
- Pure or predominant (> 50%) LELC features suggested to be associated with better overall survival than mixed LELC-conventional UC
- DDX lymphoma
- Not EBV or HPV related
- Enriched for basal-squamous molecular subtype markers and for PDL1 expression

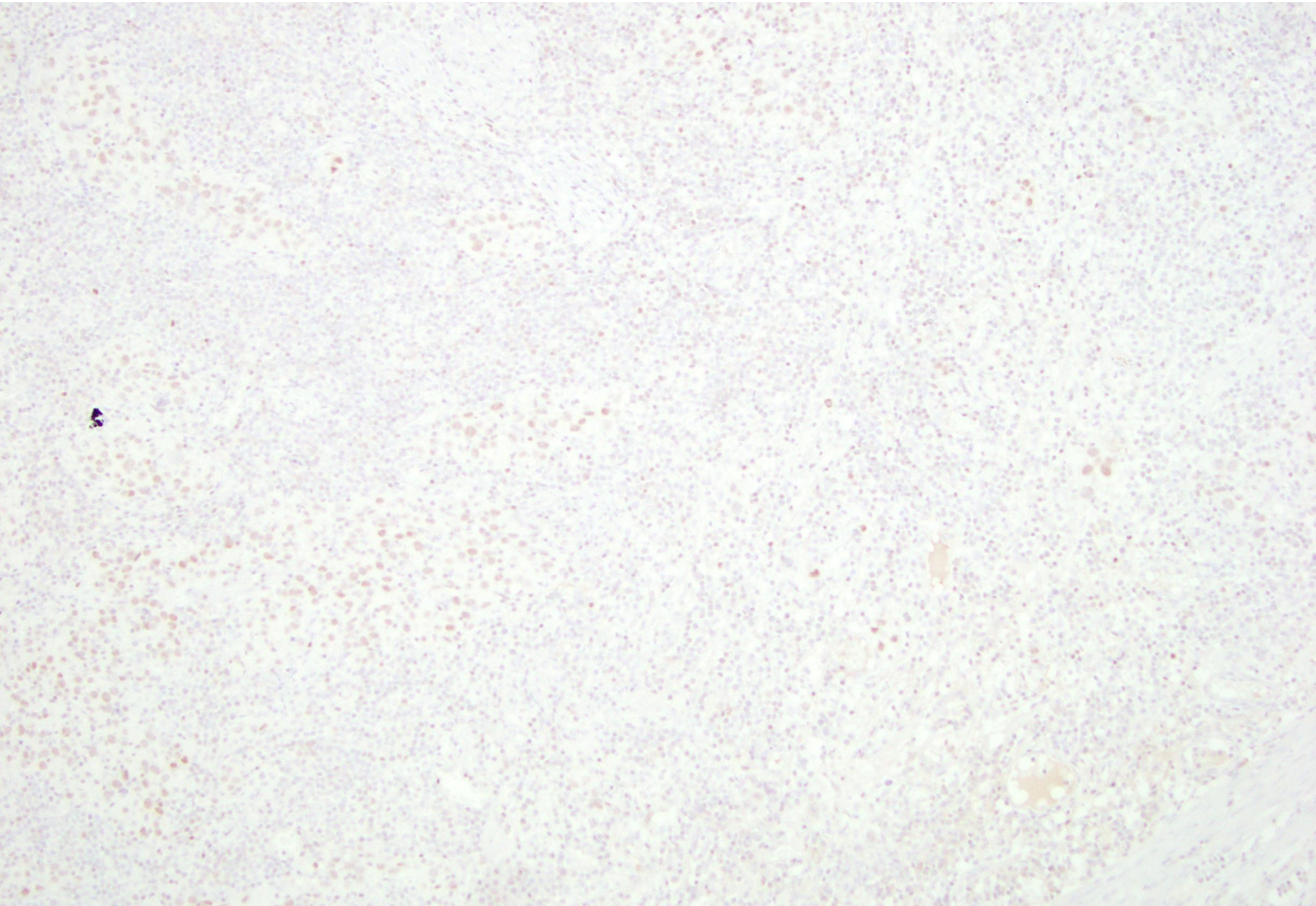
LELC features



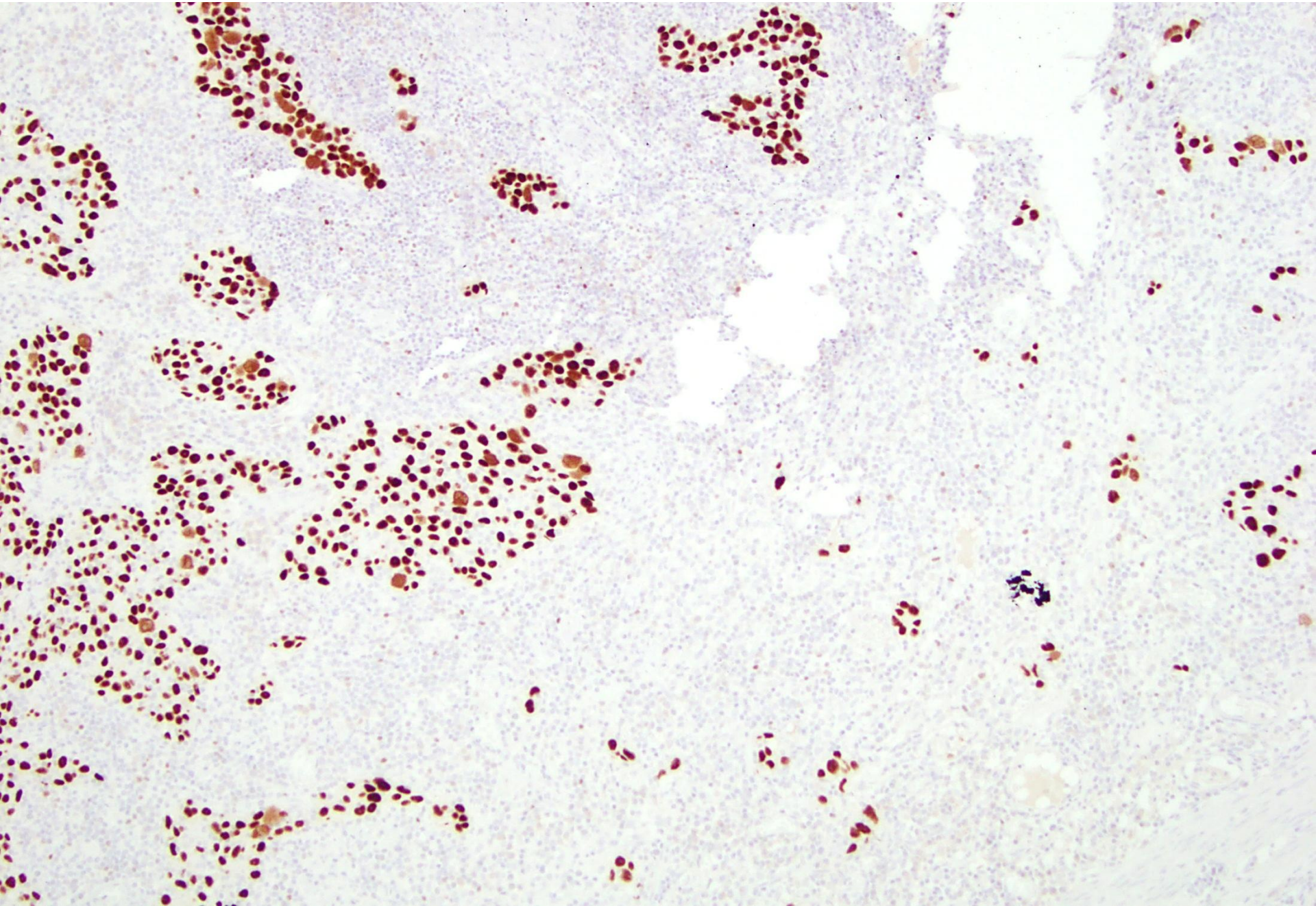
LELC features: AE1/AE3



LELC features: GATA-3



LELC features: p63

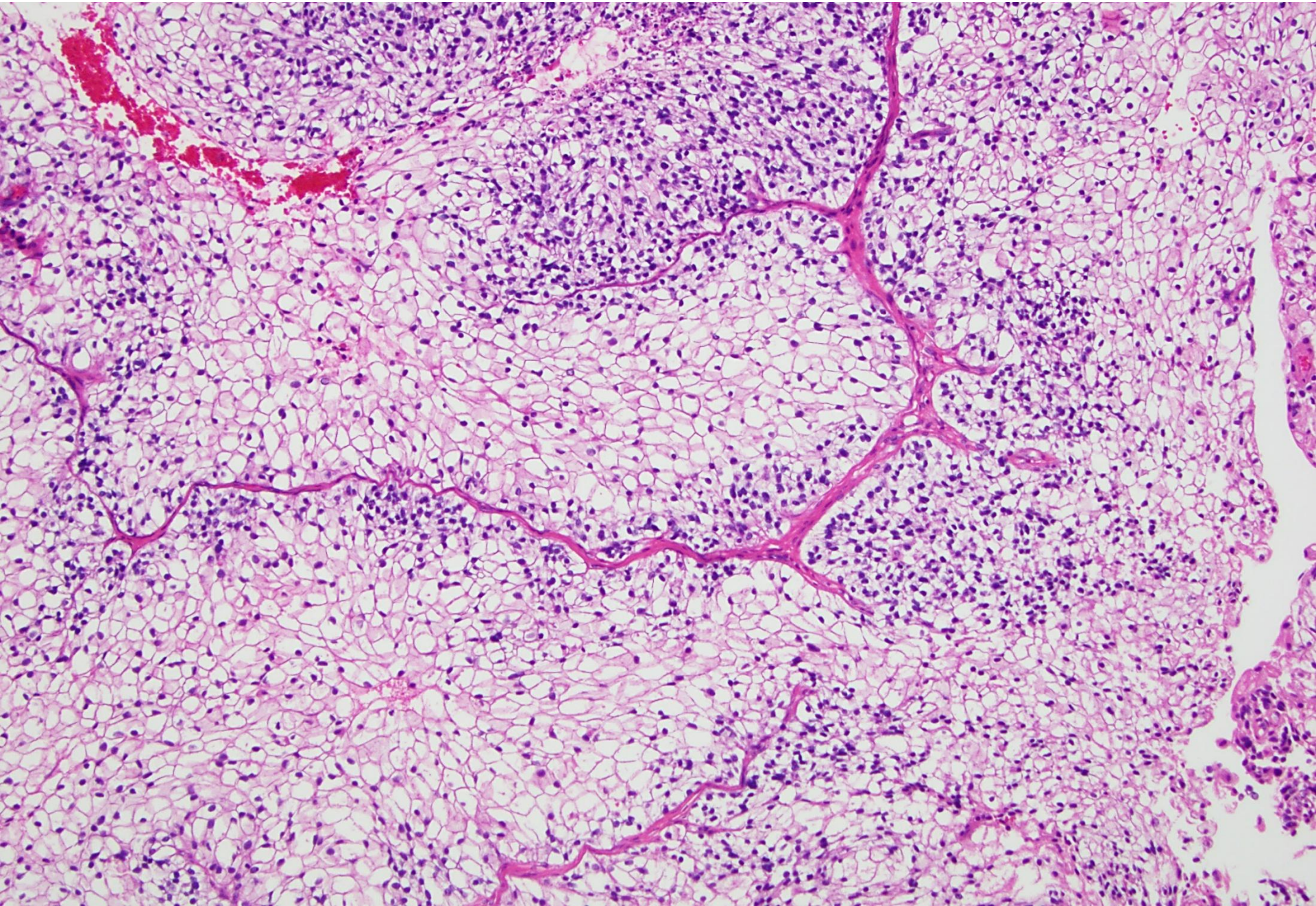


Histologic Variant

Clear cell (glycogen-rich)

- Rare
- DDx Clear cell carcinoma and clear cell adenocarcinoma (Mullerian-type)
- Expression profile of garden-variety UC

LELC features: p63

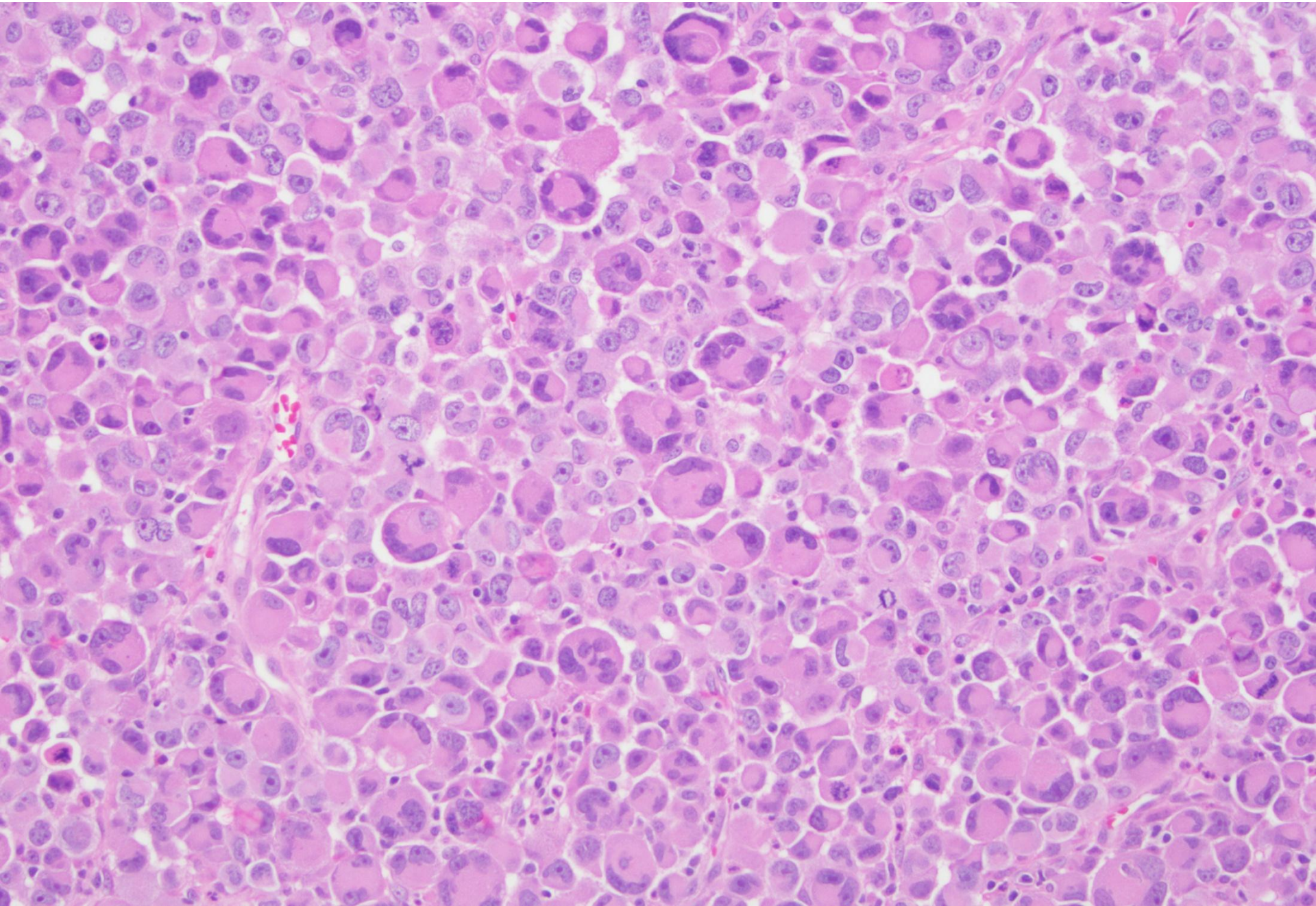


Histologic Variant

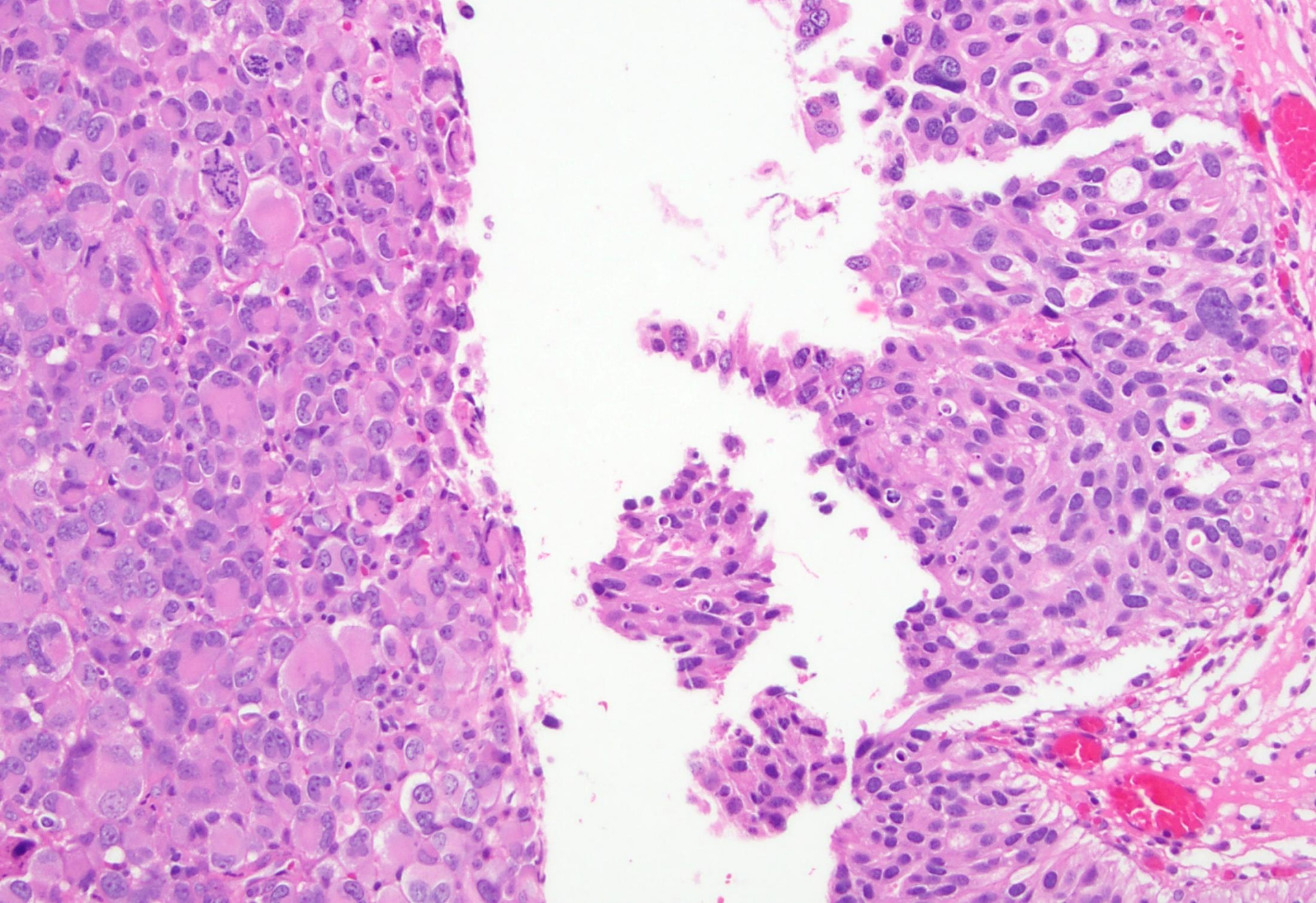
Giant cell/Poorly differentiated

- Rare
- Highly aggressive
- Conventional UC or in situ needed for diagnosis

Giant cell/Poorly differentiated UC



Giant cell/Poorly differentiated UC with CIS



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Why heightening awareness and reporting?



https://commons.wikimedia.org/wiki/File:Apocalypse_vasnetsov.jpg

Appropriate management: Non-UC tumors potential misidentification

- Squamous differentiation
 - ✓ Primary squamous cell carcinoma of bladder
 - Neoadjuvant chemotherapy inefficient
 - ✓ Spread of anogenital tract squamous cell carcinoma
 - Radiation therapy in advanced gynecological malignancy
- Glandular differentiation
 - ✓ Primary adenocarcinoma of bladder/urachus
 - Maybe amenable of partial cystectomy
 - Colon cancer-like chemotherapy regimens
 - ✓ Spread from other sites

Appropriate management: Benign entities potential misidentification

- Nested/large nested/microcystic
 - ✓ High risk of progression in underrecognized
 - ✓ [Potential harm if overcalled]

Appropriate management: Prognostic significance

- High (AUA/SUO)/Very high (EAU) risk category in non-muscle invasive disease classifications
- >>Micropapillary, sarcomatoid, plasmacytoid
 - ✓ At higher risk of progression
 - ✓ Early cystectomy advocated
- [Small cell] neuroendocrine differentiation
 - ✓ Poorer outcome if metastatic
 - ✓ Brain imaging

Appropriate management: Trial enrollment

- Any amount of neuroendocrine differentiation and predominant/ $\geq 50\%$ variant histology or divergent differentiation included in “rare genitourinary tumors” phase II interventional trial (carbozantinib versus checkpoint inhibitors)

Take Home Message

- Urothelial carcinoma is a heterogeneous disease with a variety of morphologic patterns which may impact biologic behavior
- Correct identification of divergent differentiation and histologic subtypes matters for appropriate clinical management and prognosis
- Reporting divergent differentiation and histologic variants with corresponding percentage has become a must

A photograph of a light brown horse with a long, flowing mane, standing in a grassy field. The horse's mouth is wide open, revealing its teeth and tongue. In the background, there is a body of water and mountains under a clear sky. A white speech bubble is positioned above the horse's head.

Aneigh queeestion???