Intraductal Proliferative Lesions
(UDH, CCL, ADH and DCIS)
and Lobular Neoplasia

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Characteristics of a Breast Pathology Consultation Practice

Most frequent reasons for review:

Borderline atypia	33%
Papillary lesions	17%
Stromal invasion	14%
Spindle cell lesion	7.6%
Fibroepithelial lesion	7.5%
Subtyping carcinoma	5%

East EG etal: Arch Pathol Lab Med 141, 2017

Diagnostic Concordance Among Pathologists Interpreting Breast Biopsy Specimens

G Elmore et al: *JAMA.* 2015;313(11):1122-1132

Participants (N=115, 8 states) independently interpreted slides (240 total cases, 1 slide per case)

Overall agreement between the individual pathologists' interpretations and the expert consensus–derived reference diagnoses: 75.3%

Highest level of concordance for invasive carcinoma and lower levels of concordance for DCIS and atypia

Comparison of 115 Participating Pathologist's Interpretation vs the Consensus-Derived Reference Diagnosis for 6900 Total Case Interpretations

		Participating Pathologists' Interpretation				
		Benign without atypia	Atypia	DCIS	Invasive carcinoma	Total
Consensus Reference Diagnosis[b]	Benign without atypia	1803	200	46	21	2070
	Atypia	719	990	353	8	2070
	DCIS	133	146	1764	54	2097
	Invasive carcinoma	3	0	23	637	663
	Total	2658	1336	2186	720	6900

Comparison of the 3 Reference Panel Members' Independent Preconsensus Diagnoses vs the Consensus-Derived Reference Diagnosis for 240 Breast Biopsy Cases (overall 90.3%)

		Reference Panel Members' Individual Diagnoses (Preconsensus)				
		Benign without atypia	Atypia	DCIS	Invasive carcinoma	Total
Consensus Reference Diagnosis	Benign without atypia	197	15	3	1[b]	216
	Atypia	18	173	25	0	216
	DCIS	2	2	213	2[c]	219
	Invasive carcinoma	0	0	2[d]	67	69
	Total	217	190	243	70	720

Basis for Diagnosis and Diagnostic Reproducibility

Morphologic assessment of:

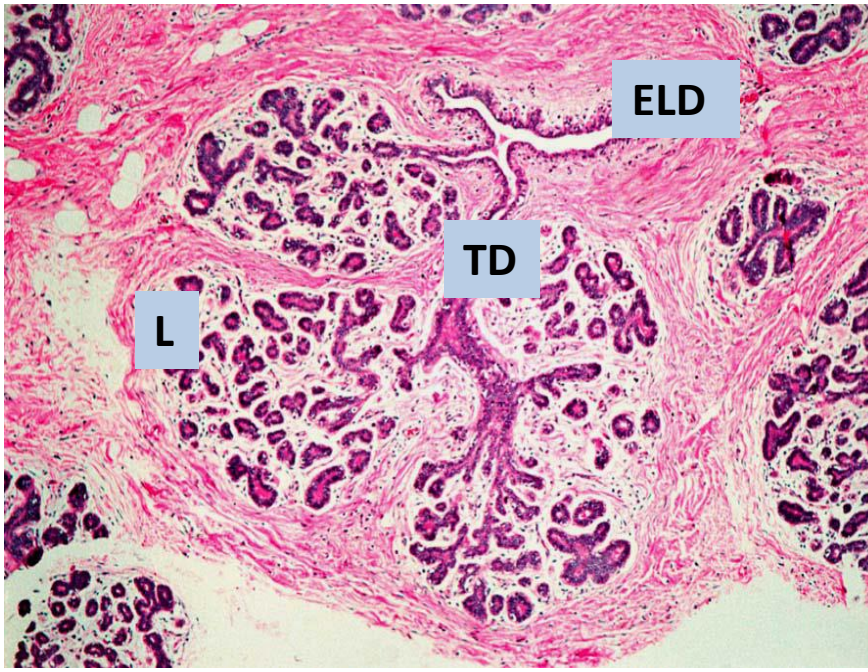
1. Architectural Features (Low mag.)
2. Cytologic Features of the Proliferation

Improved with the use of standardized criteria

Intraductal Proliferative Lesions

Cytologically and architecturally diverse proliferations, typically originating in the TDLU and confined to the mammary duct-lobular system.

Associated with an increased risk, albeit of variable magnitude, for subsequent development of invasive carcinoma.



Intraductal Proliferative Lesions

1. UDH x 1.5-2 - not a significant risk factor
2. ADH x 4-5 - moderate risk
3. DCIS x 8-10 - high risk

4. CCL with atypia (Flat epithelial atypia)
   risk is less than ADH

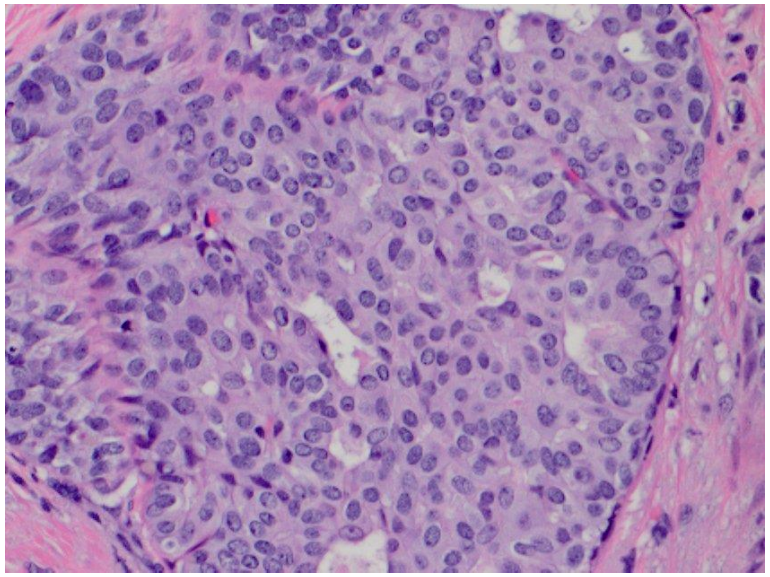
Usual Epithelial Hyperplasia (UDH)

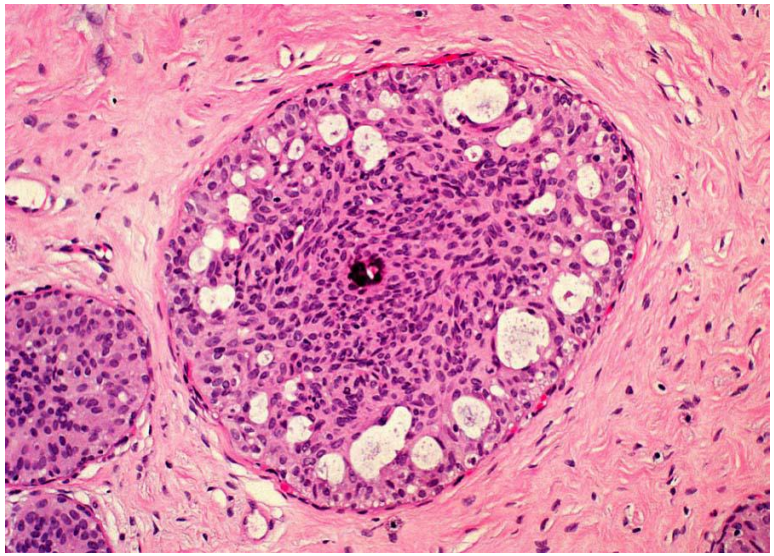
Characterized by a solid or fenestrated proliferation of epithelial cells that often show streaming growth, particularly in the center of involved spaces

3 or more cells above basement membrane (Page et al.)

Architectural features of UDH

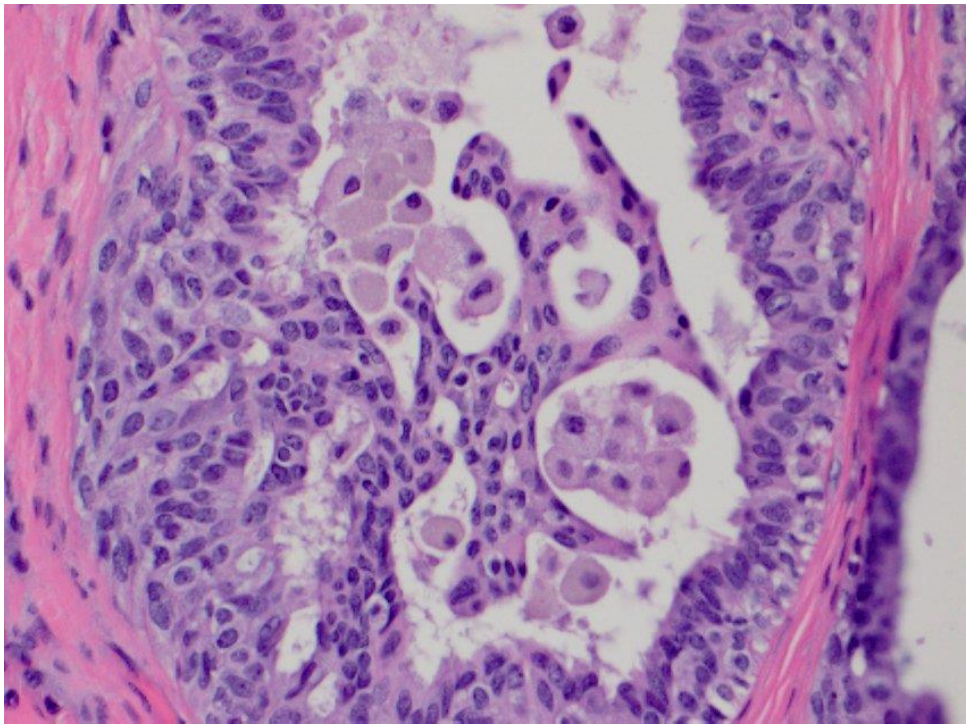
- Irregular and slit-like fenestration
- Secondary lumina often peripherally located
- Stretched epithelial bridges, nuclei parallel to the space
- Streaming/synsytial pattern
- Occasionally, solid or micropapillary (gynecomastoid)
- Uneven distribution of nuclei and overlapped nuclei

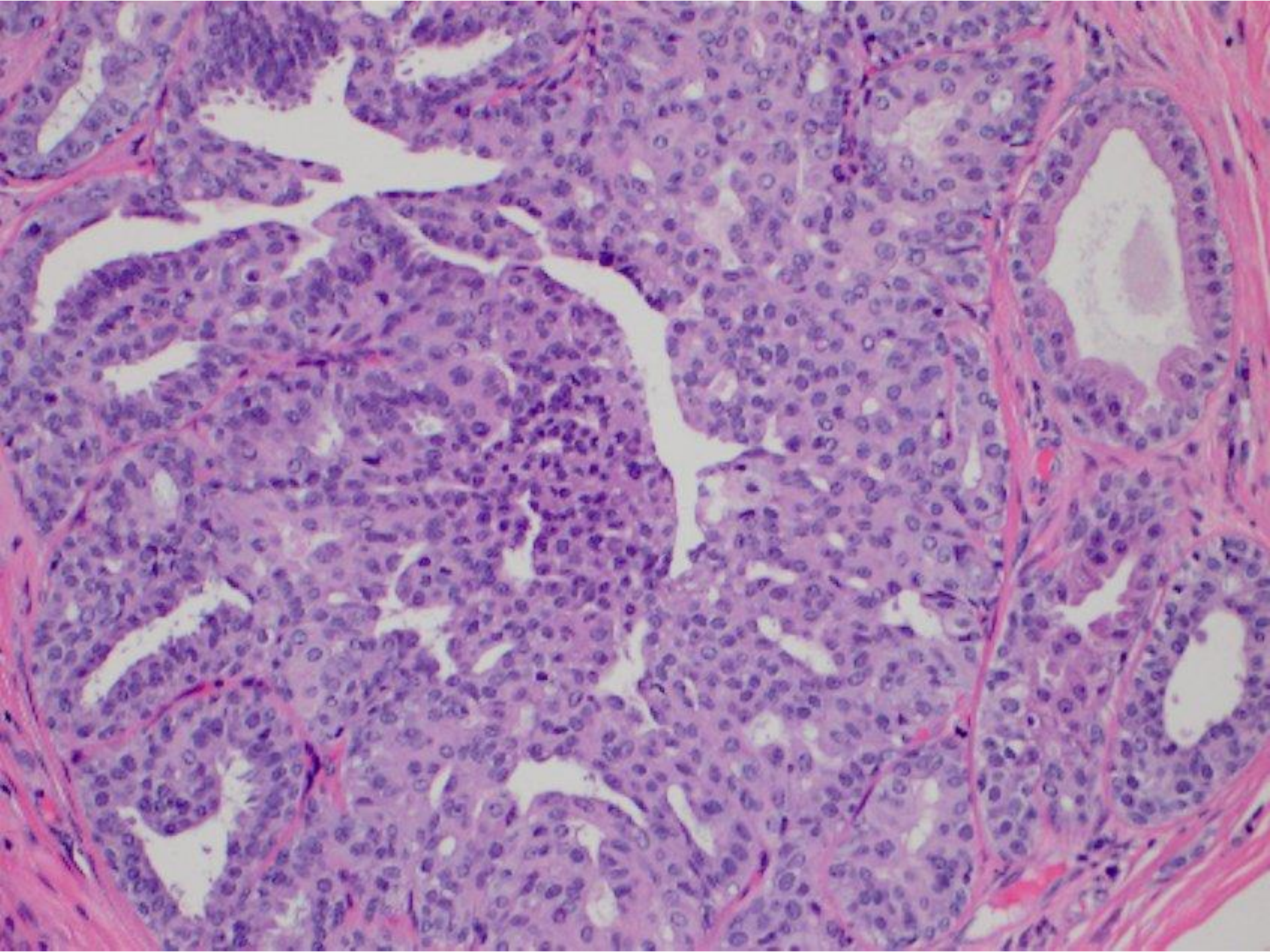


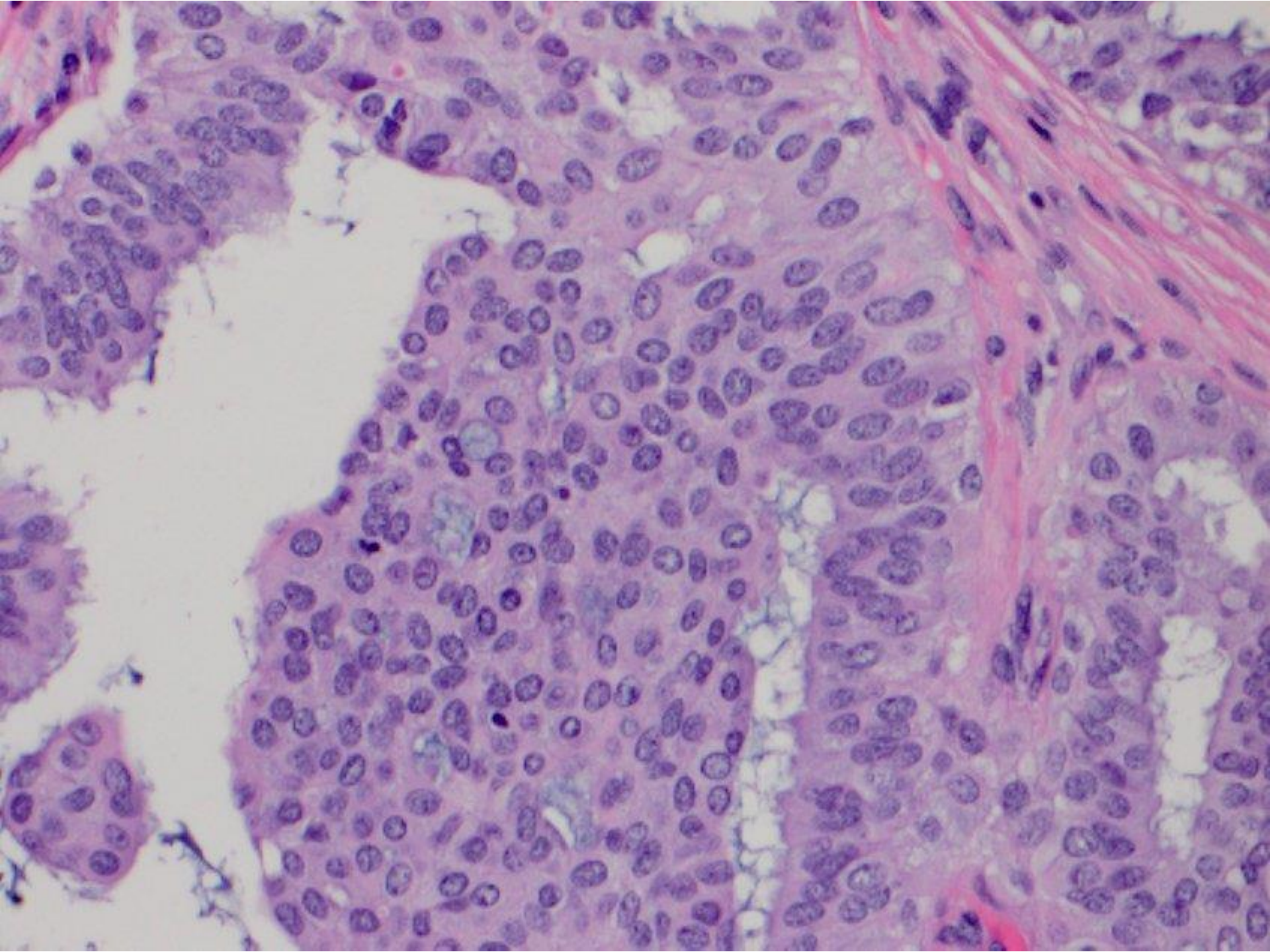


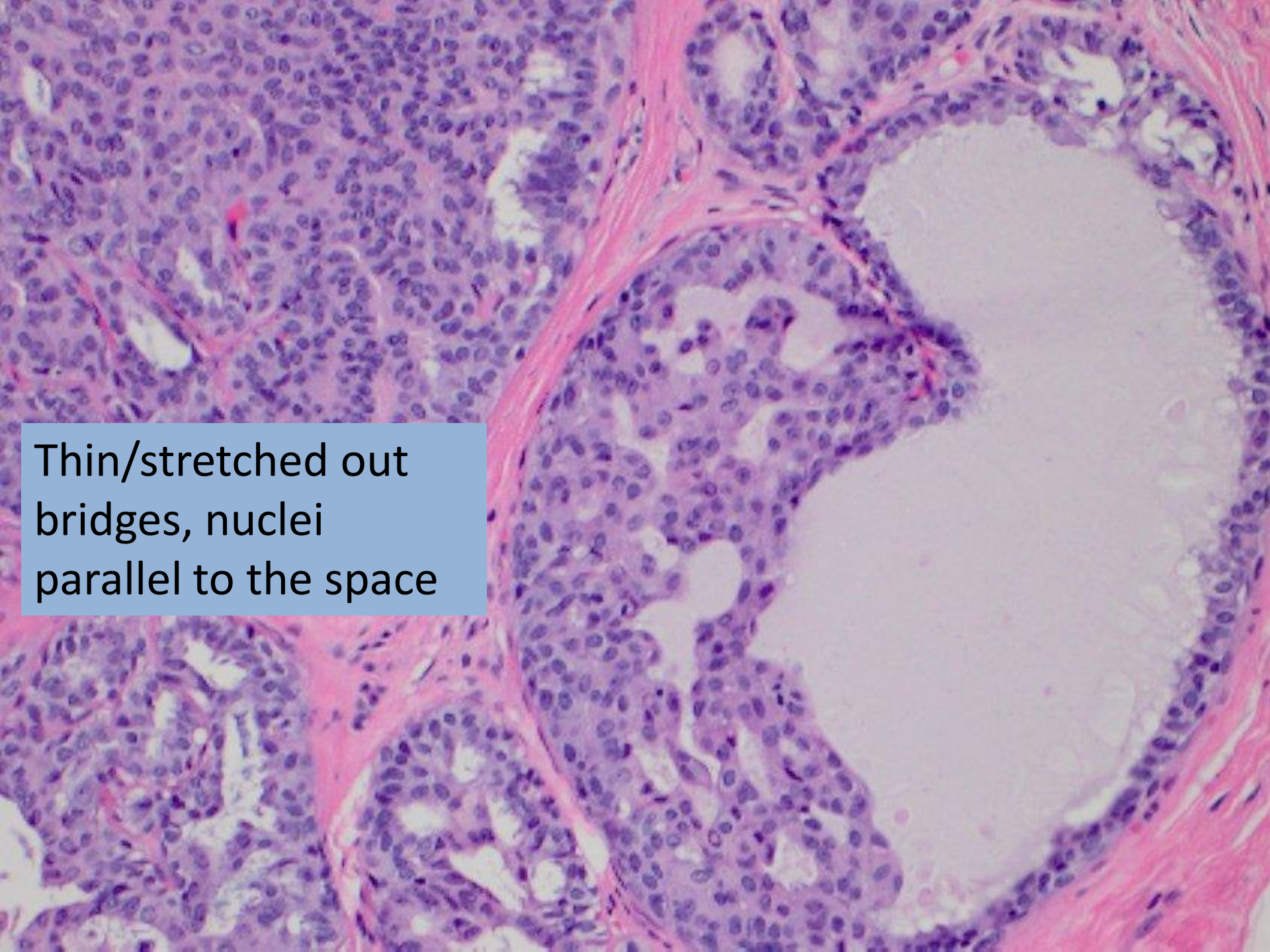
Cytologic Features of UDH

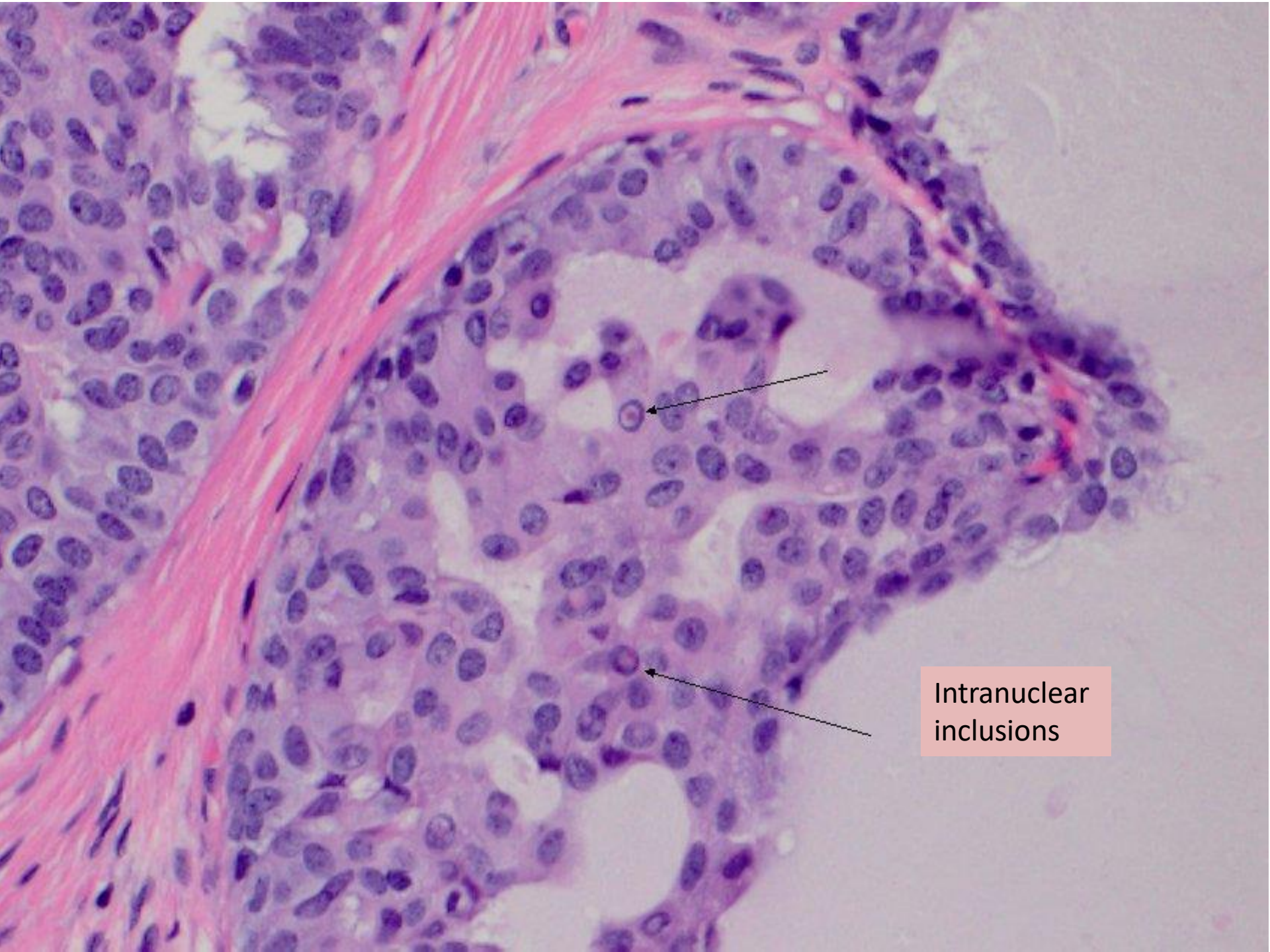
- Admixtures of cell types: epi, myo, and apocrine cells
- Variation in the appearance of the cells with indistinct borders
- Variation in the appearance of the nuclei (angulated, spindled, oval or round), often with grooves and intranuclear inclusions
- Mixed immunophenotype (HMWK, 34B E12 in mosaic pattern); ER is also hetergeneous (diffuse in ADH)

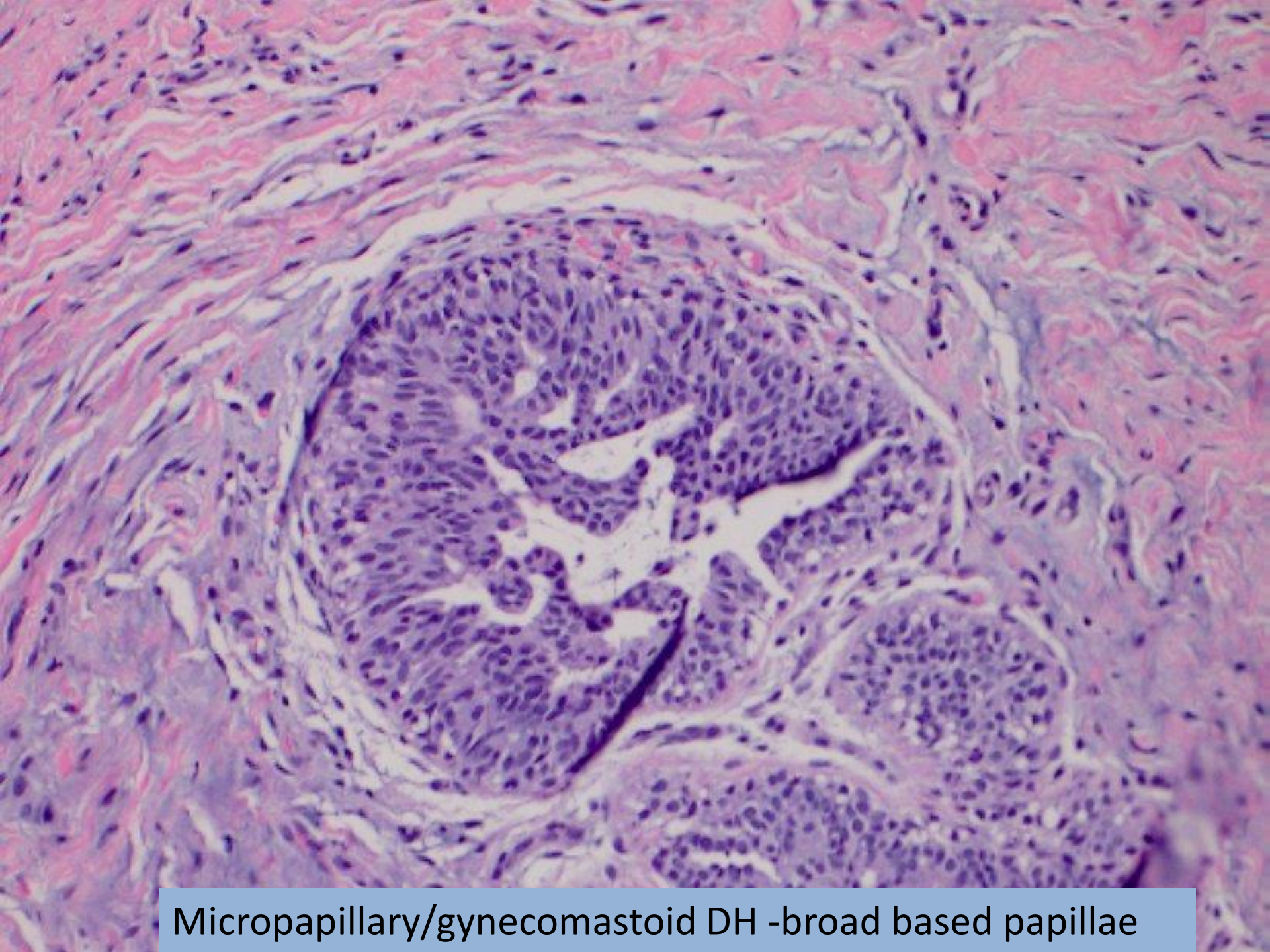




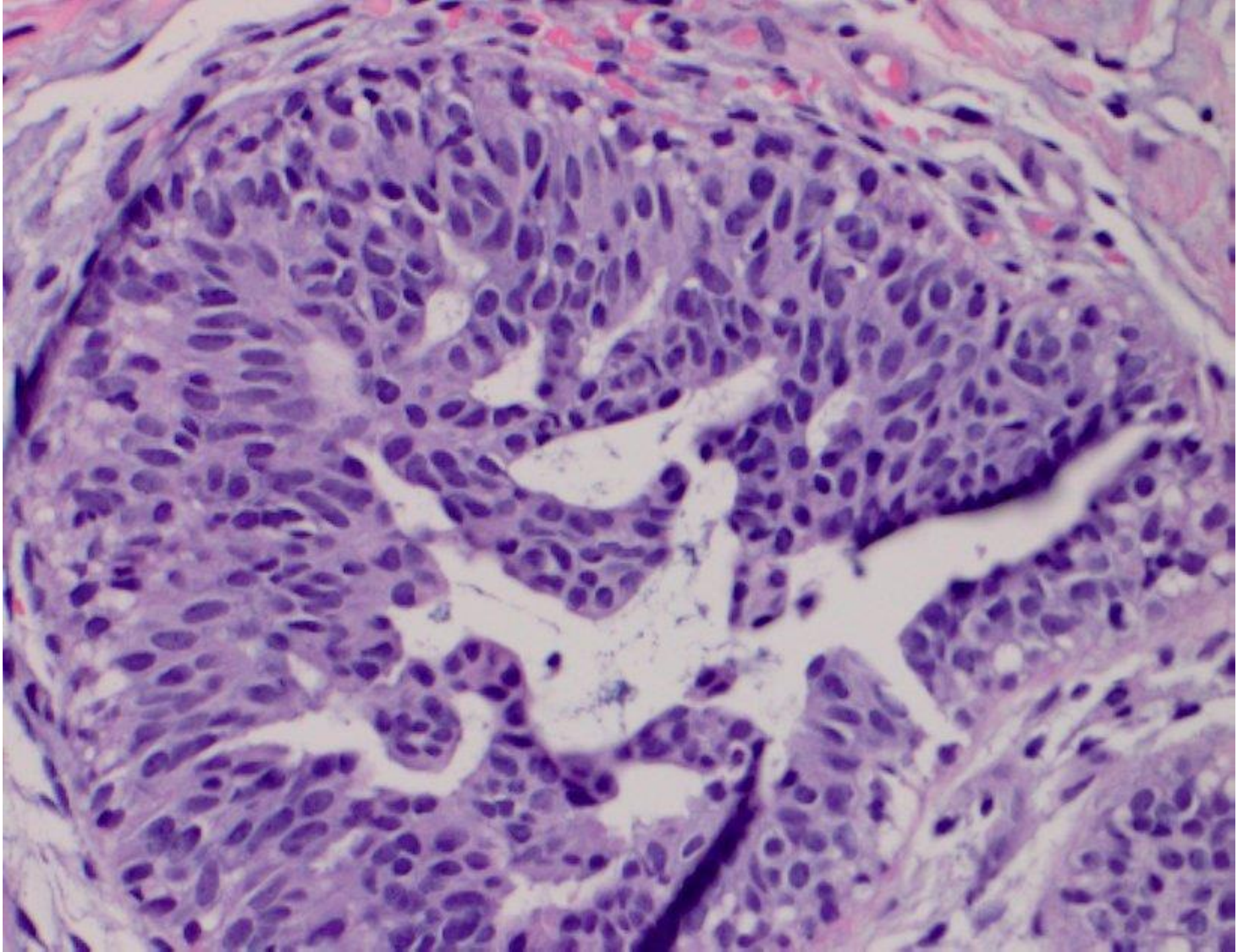


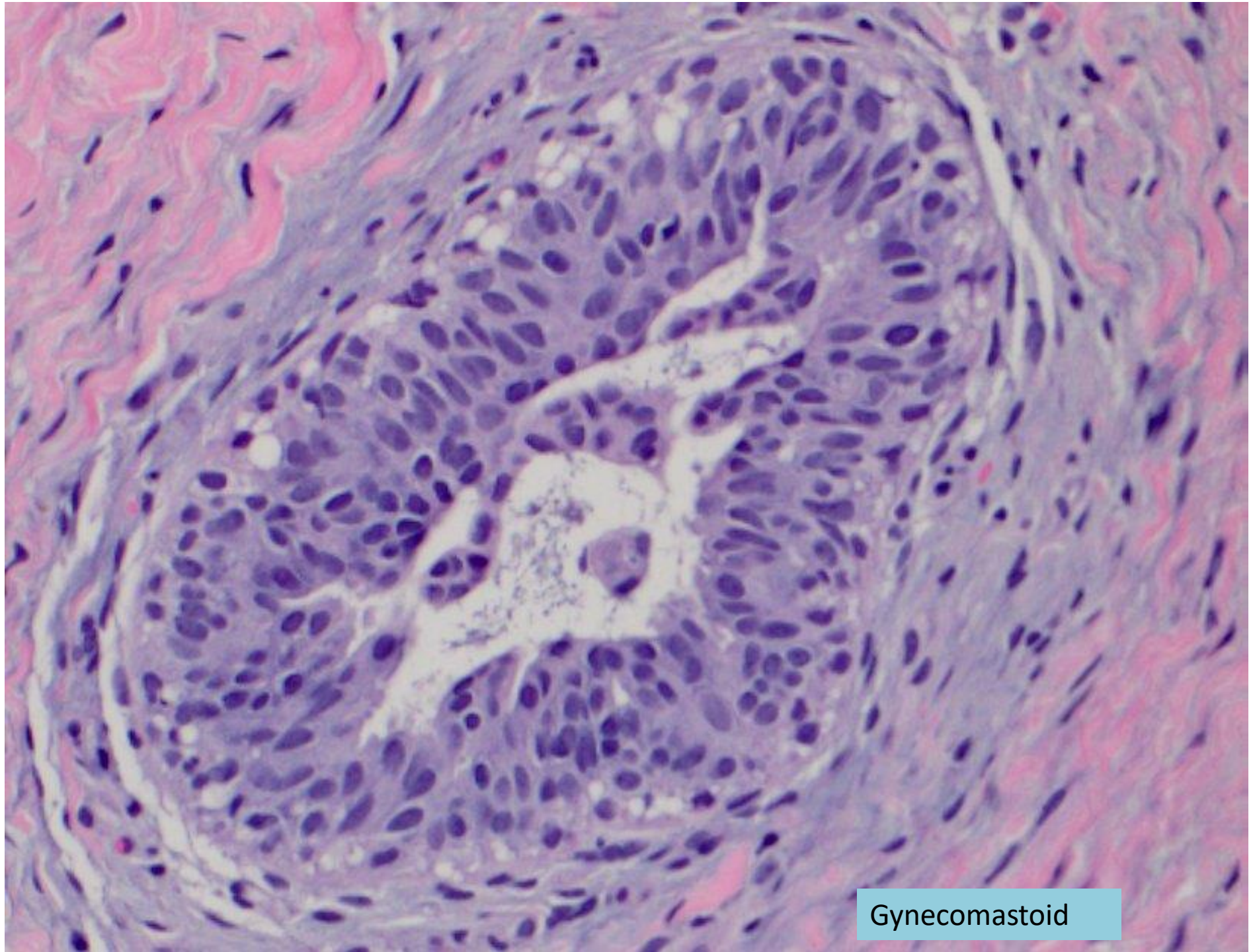

Thin/stretched out bridges, nuclei parallel to the space

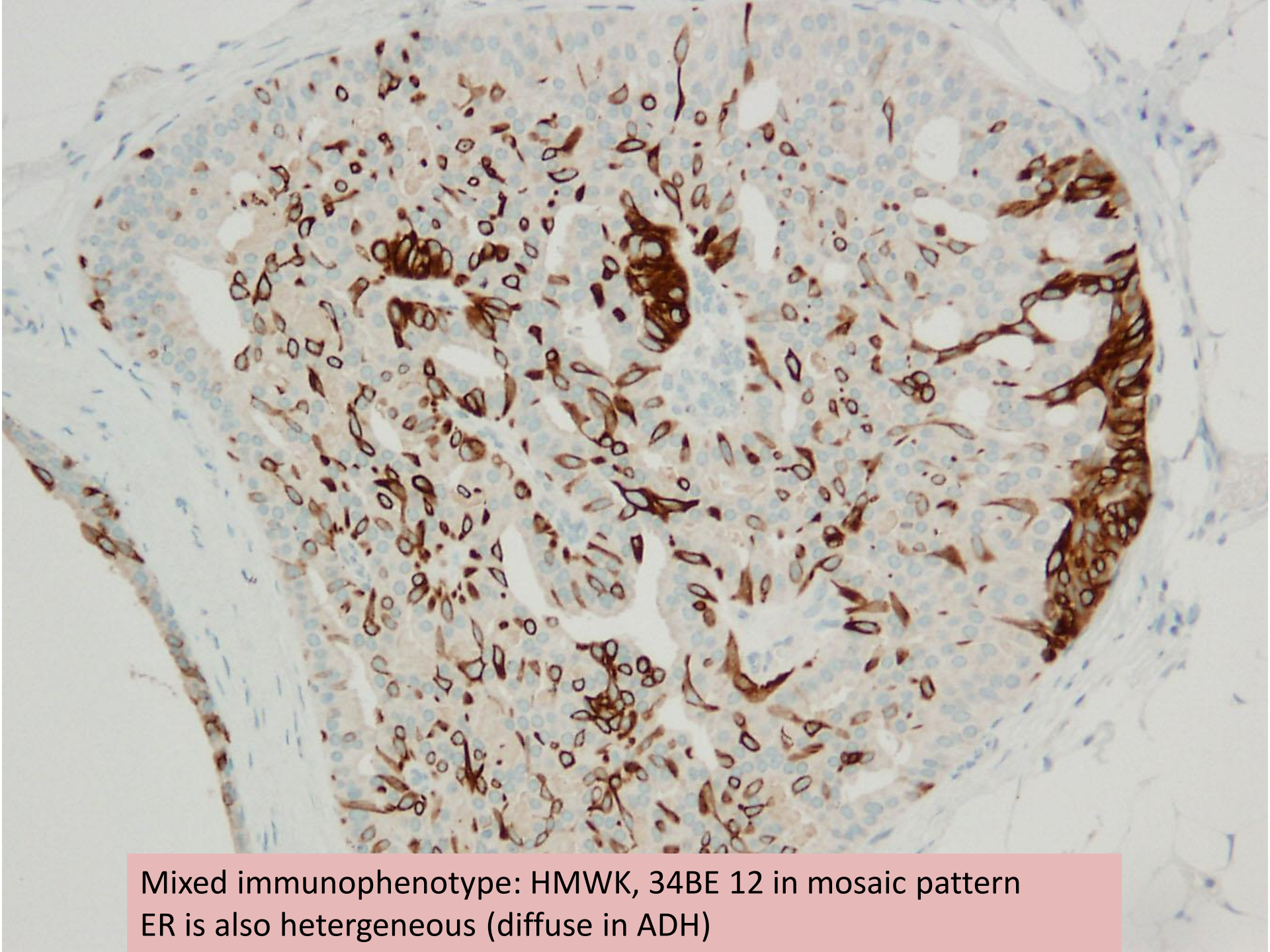

Intranuclear inclusions



Micropapillary/gynecomastoid DH -broad based papillae



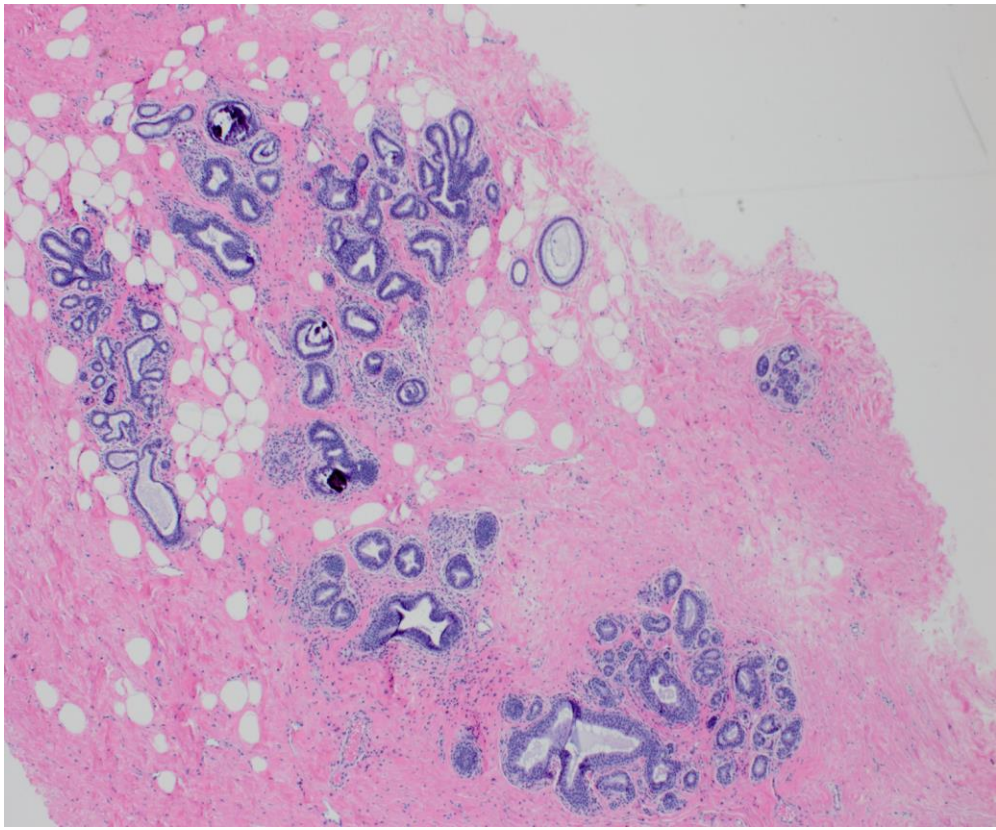

Gynecomastoid



Mixed immunophenotype: HMWK, 34BE 12 in mosaic pattern
ER is also hetergeneous (diffuse in ADH)

Columnar Cell Lesions (with or without atypia)

Lesions of the TDLU characterized by enlarged, variably dilated acini lined by columnar cells that (frequently have apical snouts with asso. secretion and calcs



Clinical features

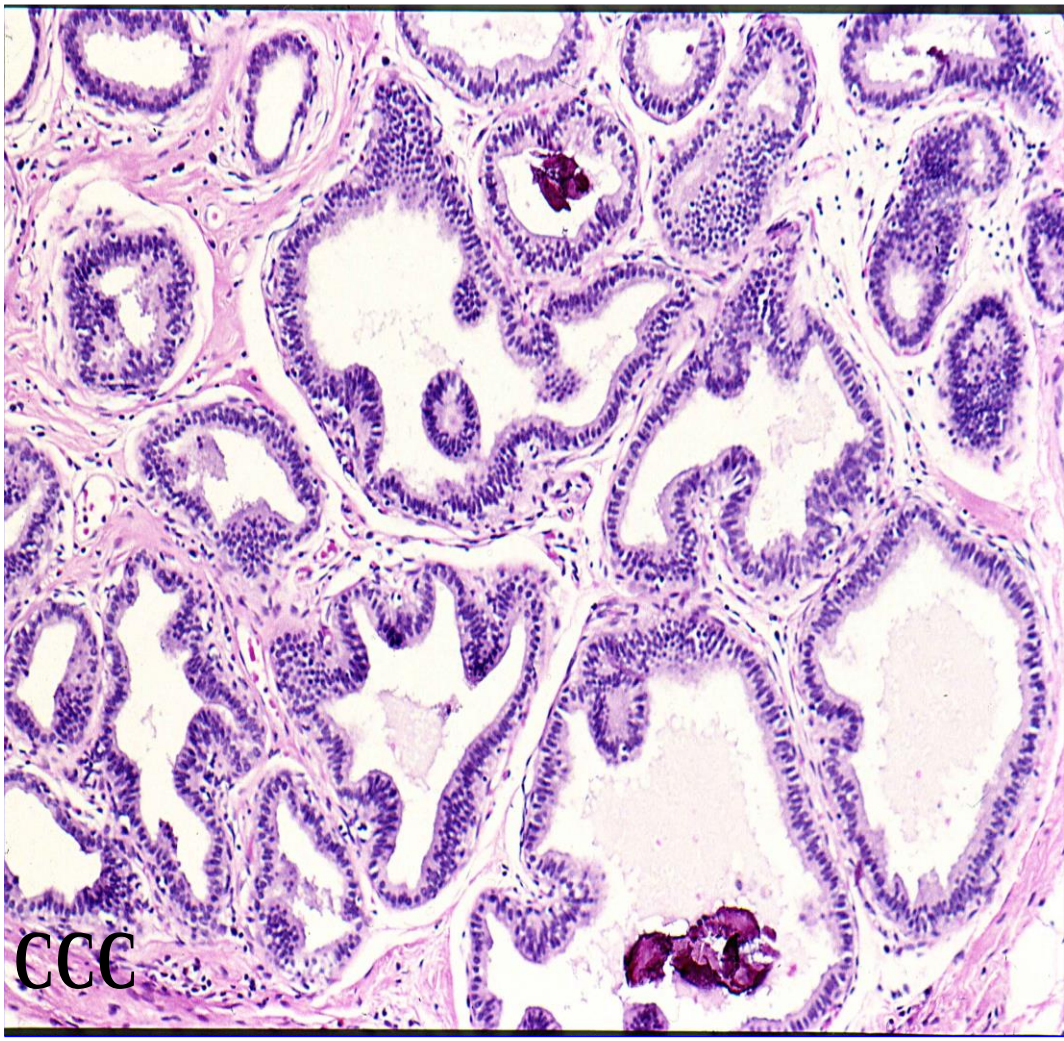
- Detected on screening mammography because of the presence of calcifications

- Incidental findings

Columnar cell change/hyperplasia --no atypia

Epithelial- cell lining is only one or two cell layers thick.

Nuclei are typically ovoid, regularly oriented perpendicular to BM, evenly dispersed chromatin, inconspicuous nucleoli



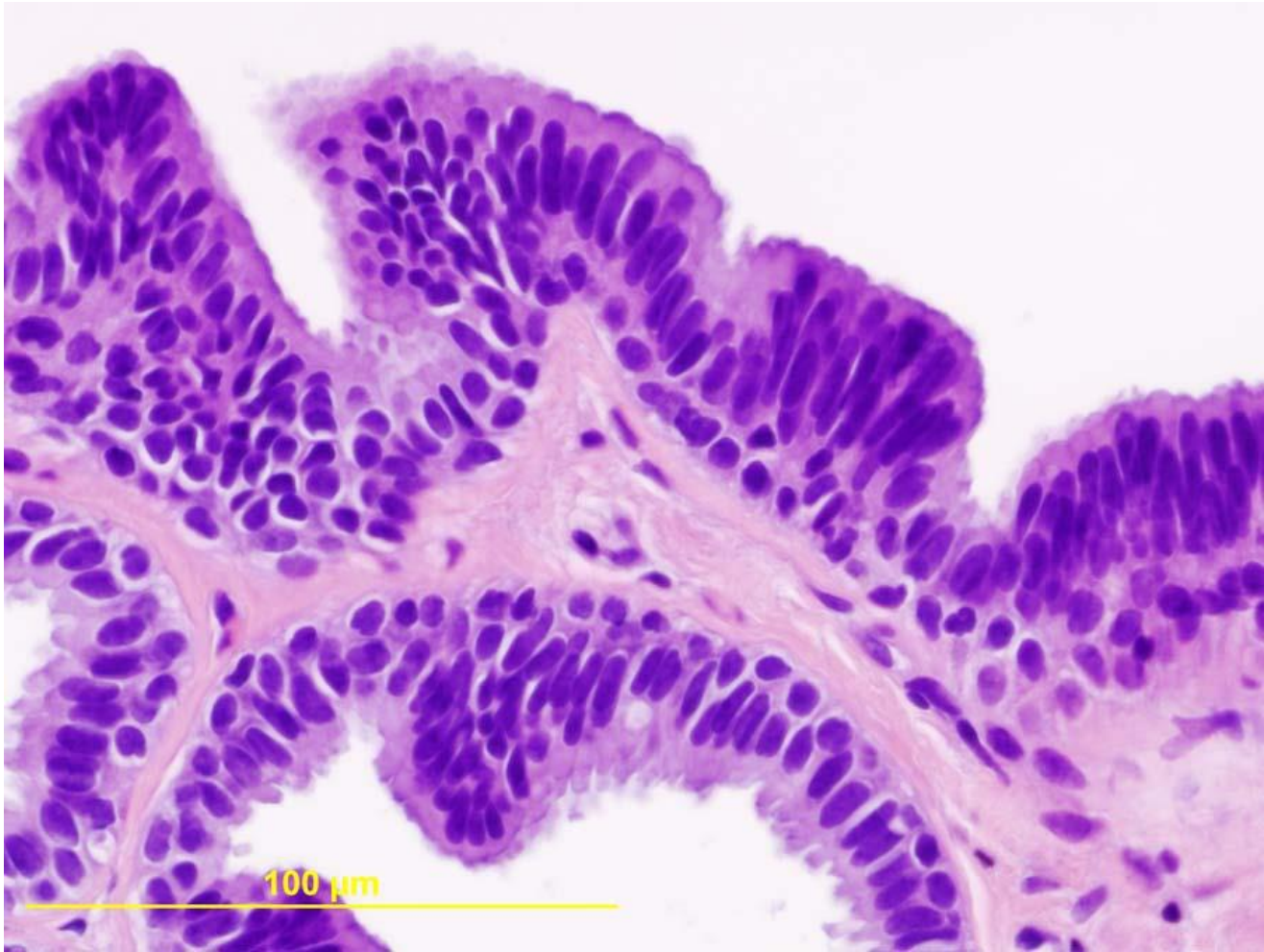
Columnar cell change/hyperplasia --no atypia

Synonyms

Blunt duct adenosis, columnar cell alteration of lobules, columnar cell metaplasia, hyperplastic unfolded lobules, hyperplastic enlarged lobular units, enlaged lobular units with columnar alteration

Columnar Cell Hyperplasia

Cellular stratification or tufting more than 2 cell layers thick



Flat Epithelial Atypia (FEA)

Definition

A neoplastic alteration of the TDLUs characterized by replacement of the native epithelial cells by one to several layers of a single epithelial cell type showing low grade (monomorphic) cytological atypia.
Frequent presence of floccular secretory material often with microcalcifications within the spaces.

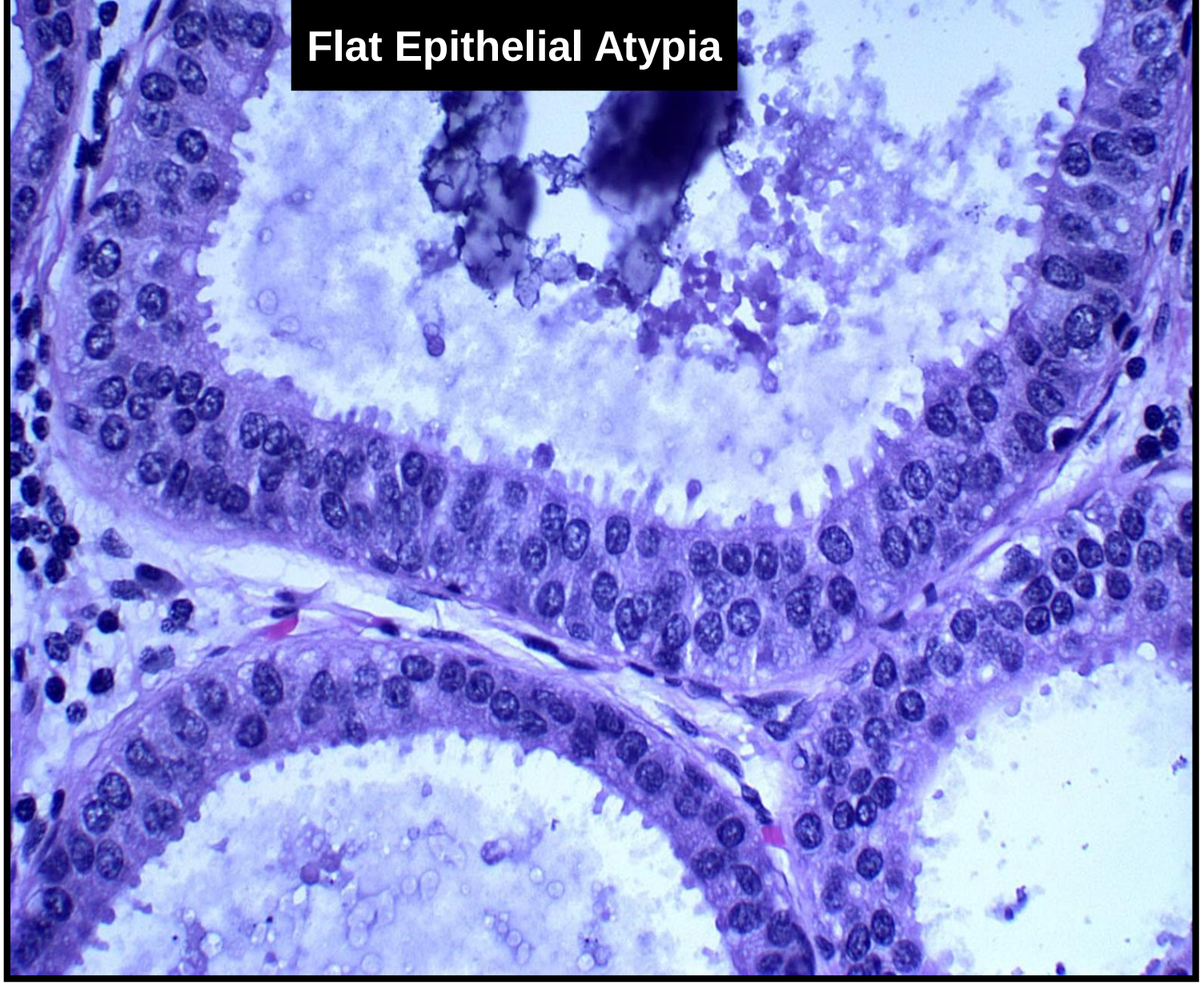
FEA

Synonyms

Columnar cell change with atypia,

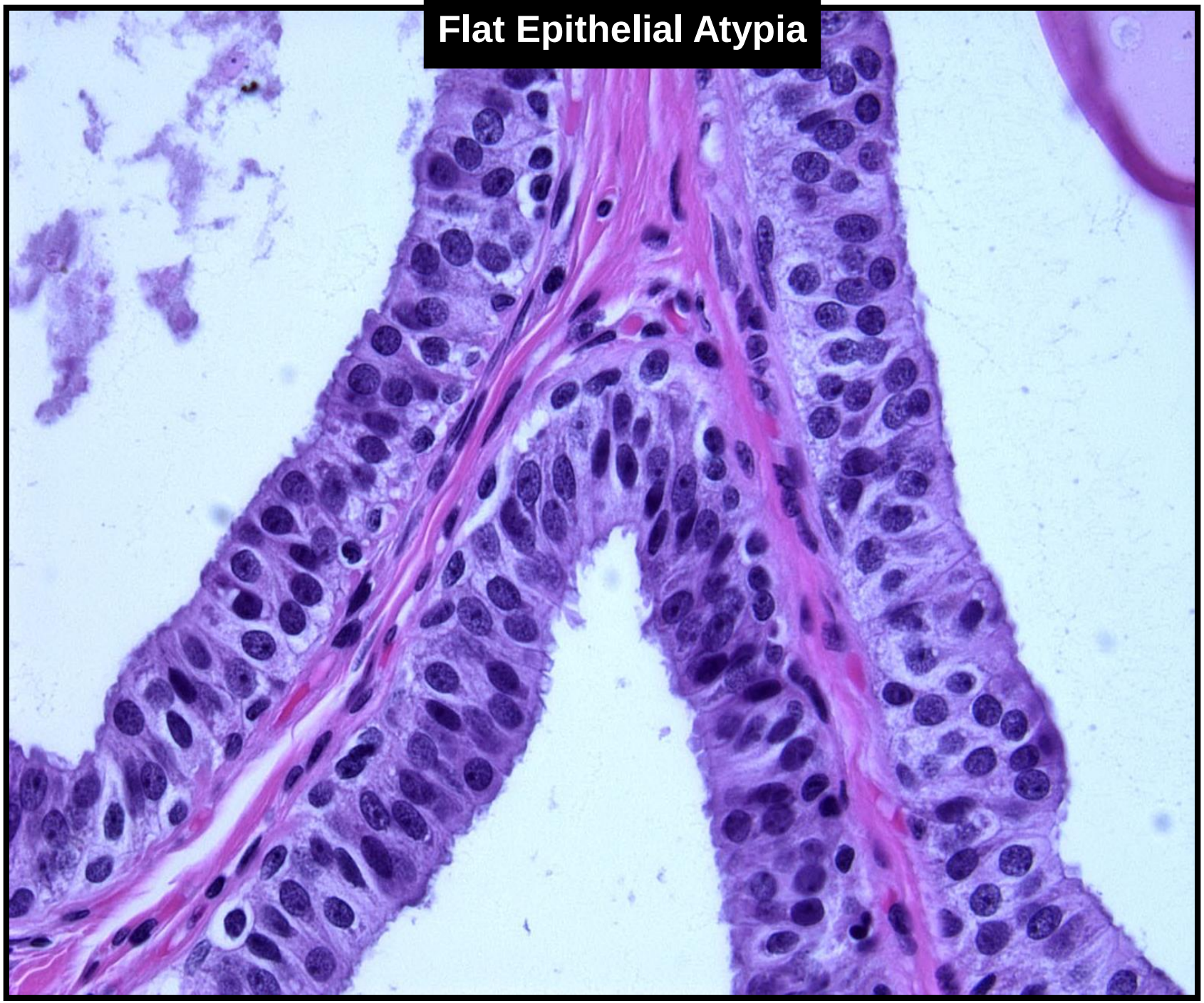
Columnar cell hyperplasia with atypia

"Clinging Ca of the monomorphic type"

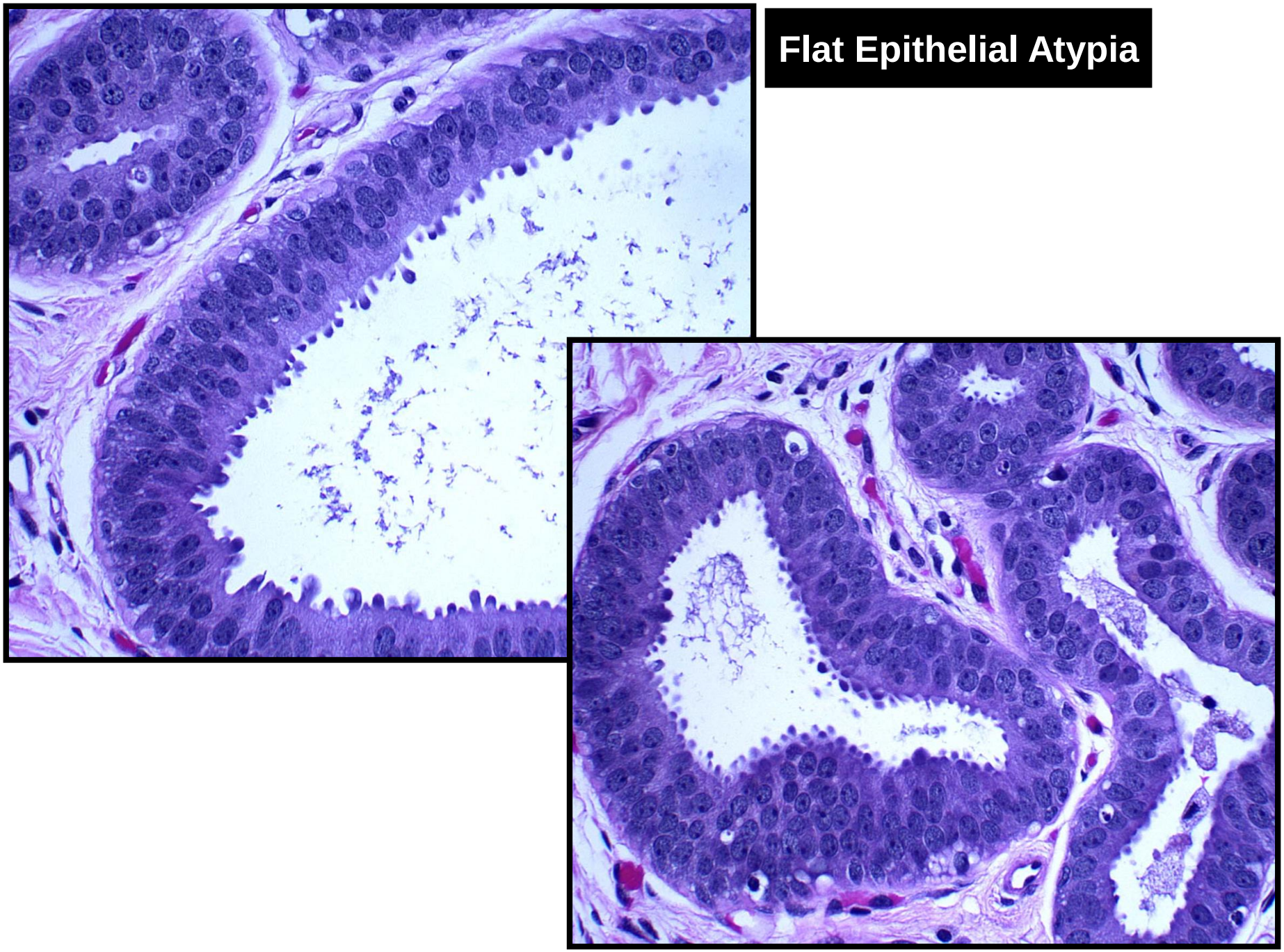


Replacement of the native epithelial cellsof TDLUs by one to several layers of cells that lack polarity

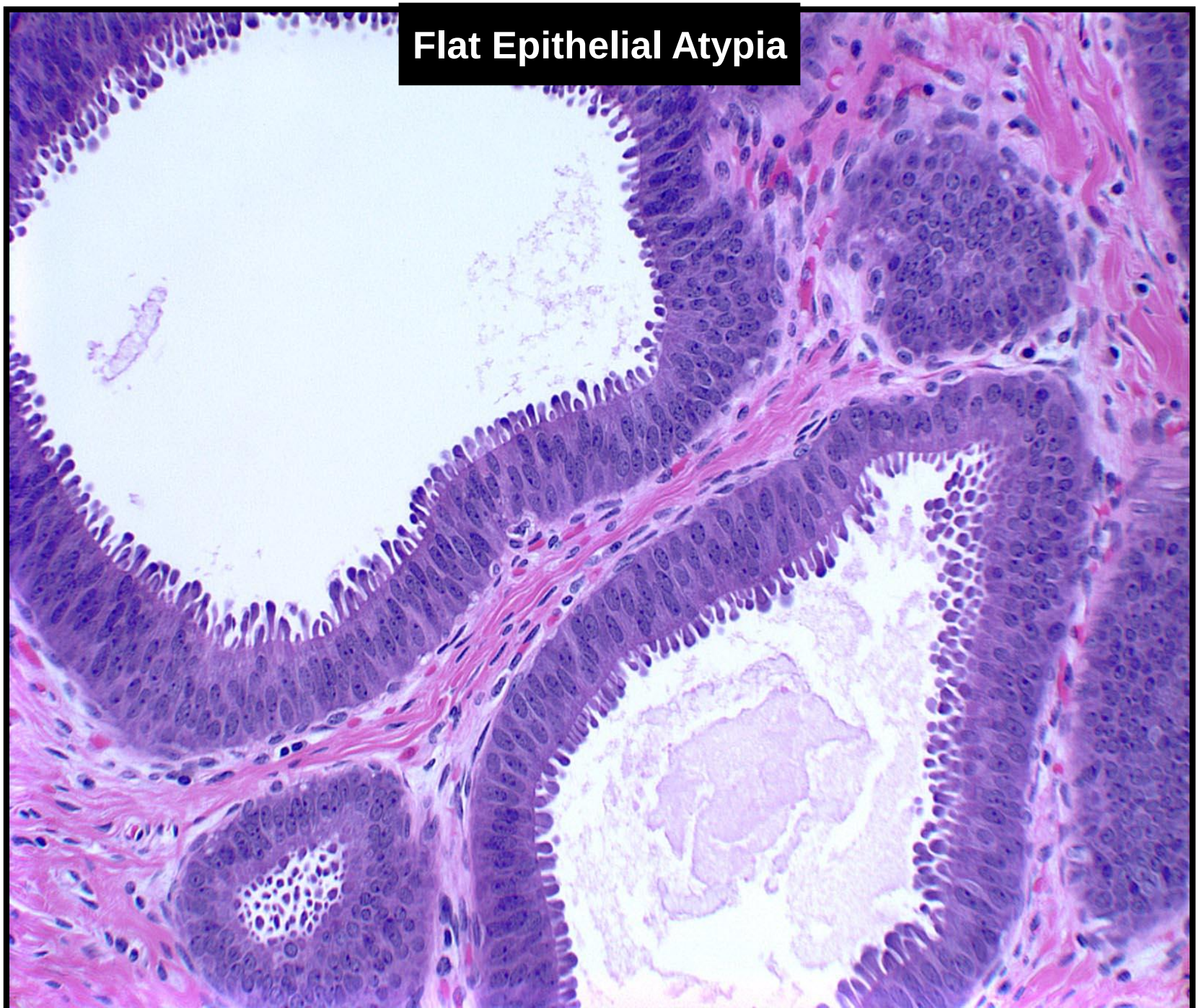
Flat Epithelial Atypia

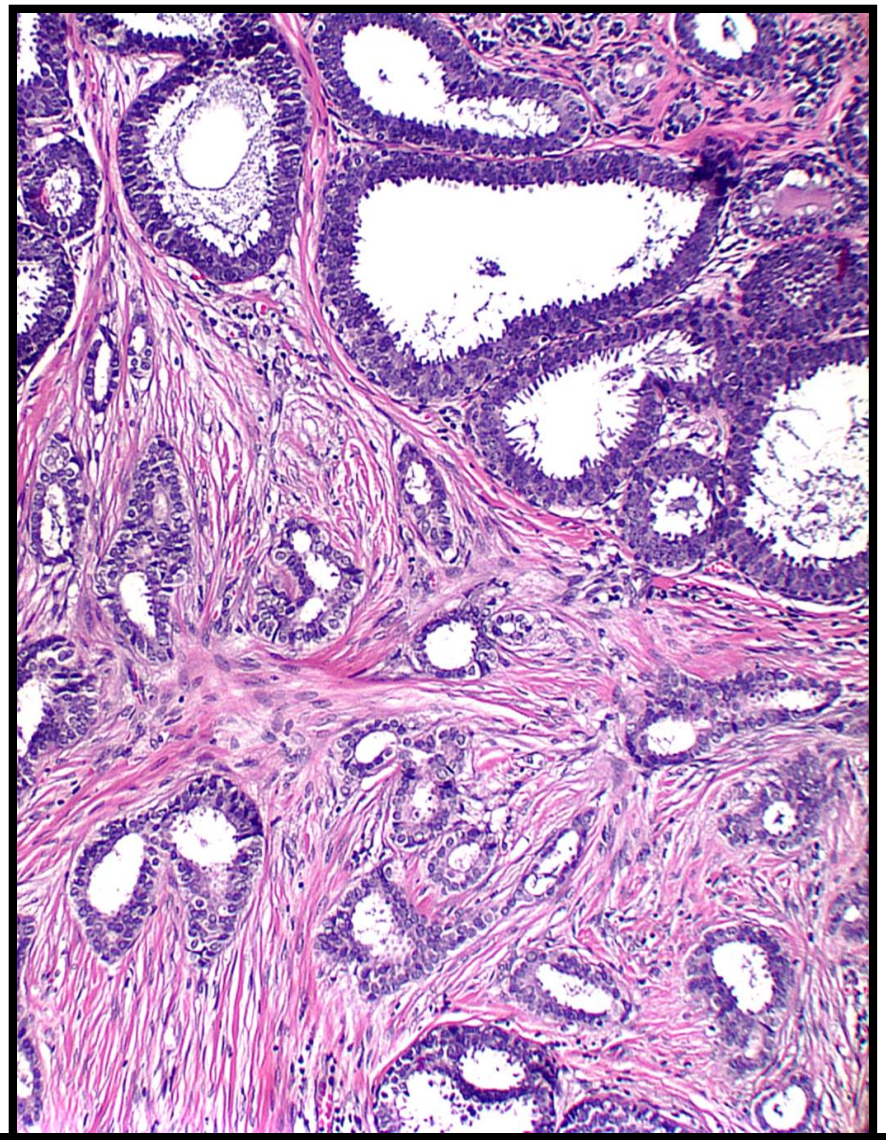


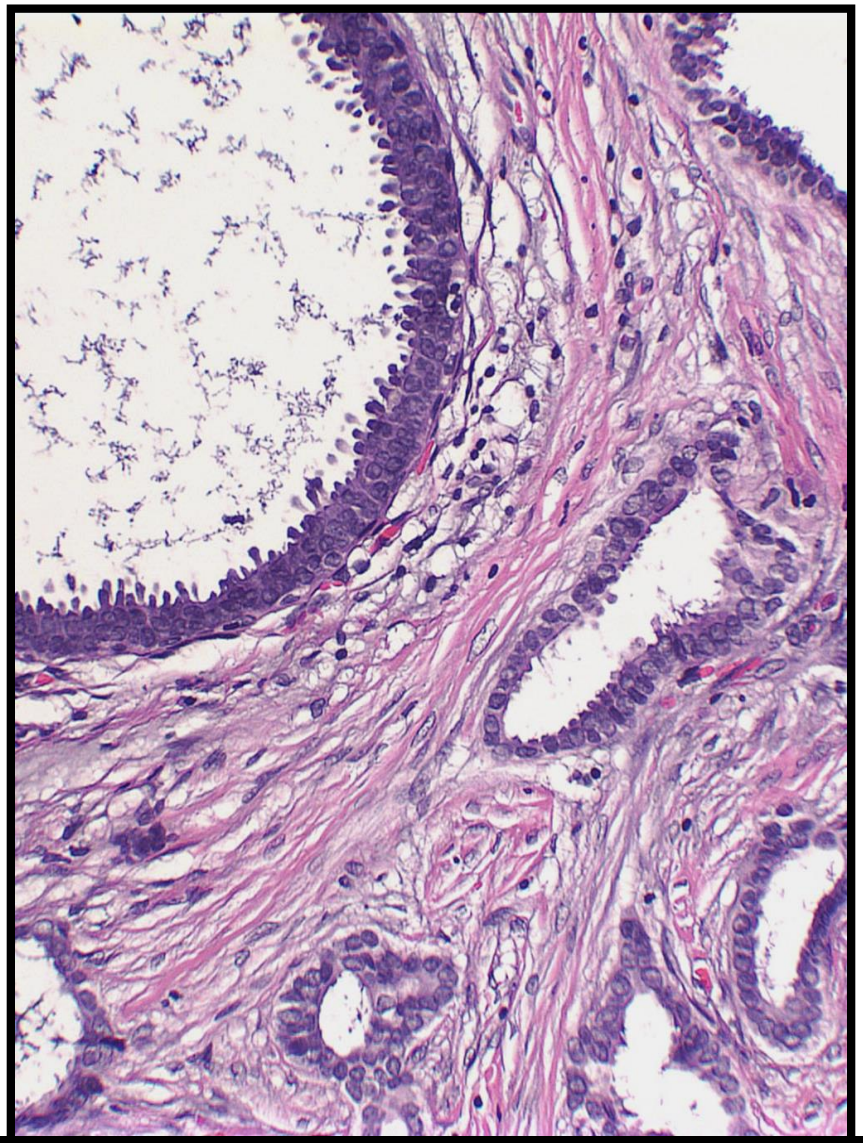
Flat Epithelial Atypia



Flat Epithelial Atypia

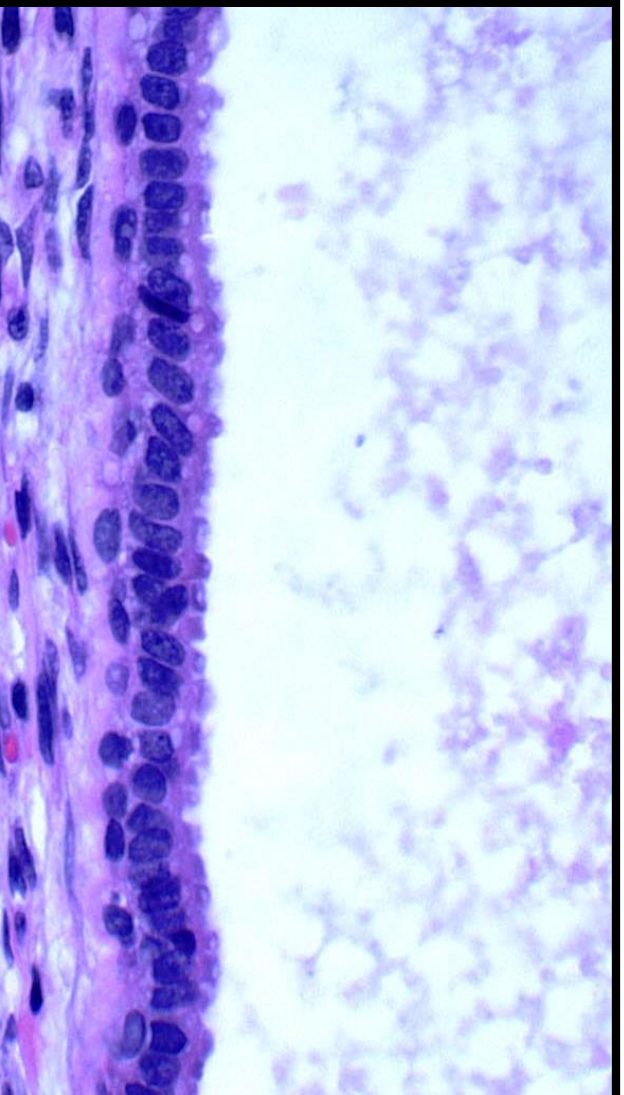




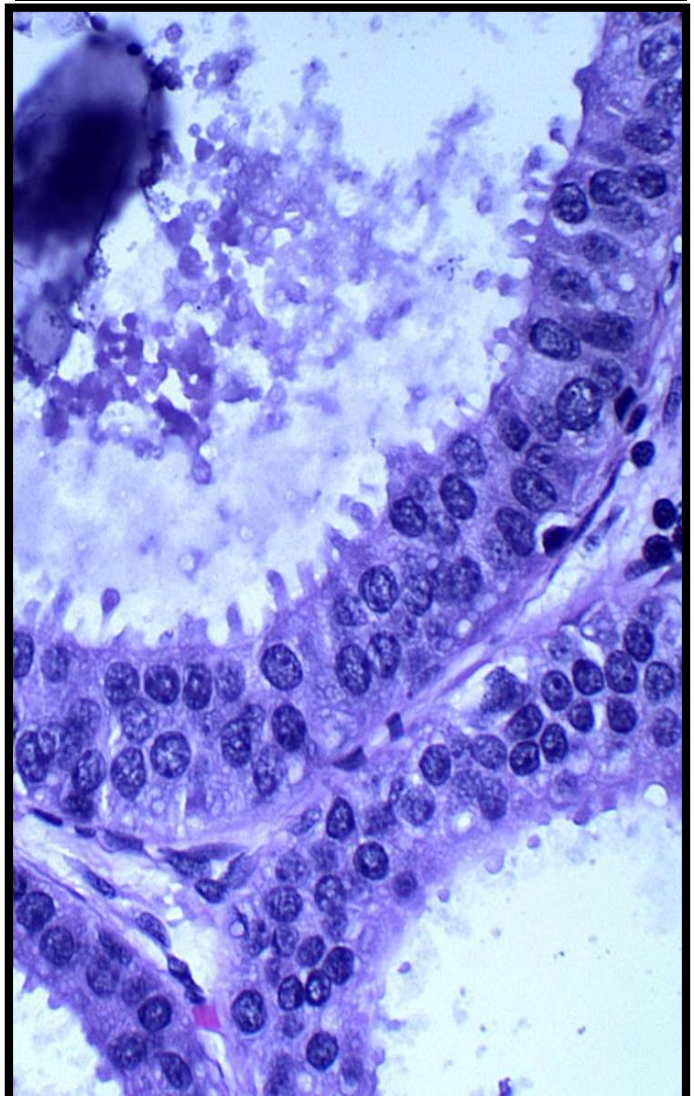


Flat Epithelial Atypia and Tubular Carcinoma

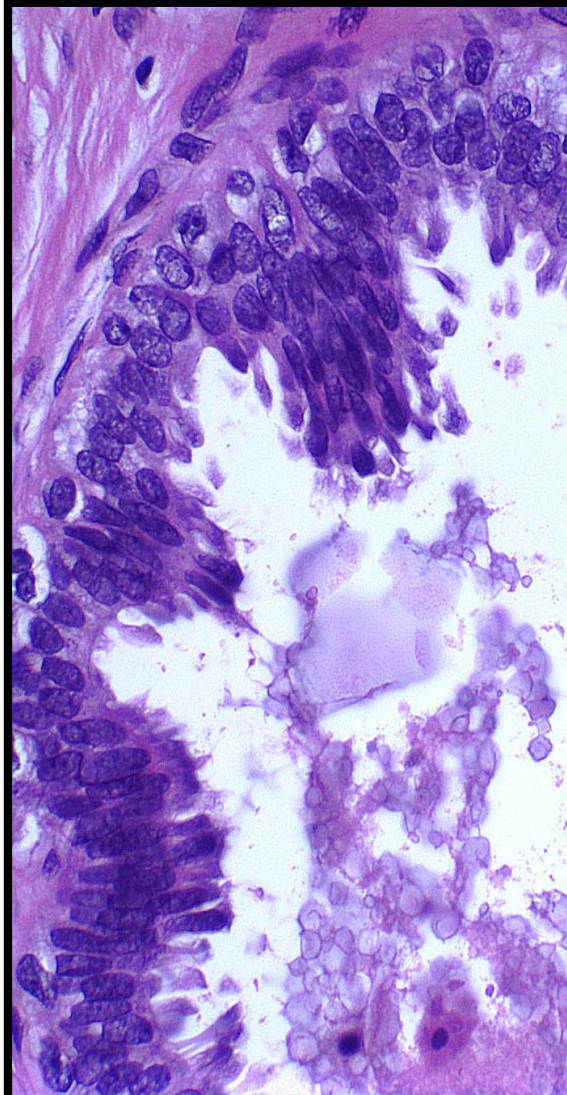
Columnar Cell Change



Flat Epithelial Atypia



Columnar Cell Hyperplasia



Molecular and Genetic Studies

FEA lesions show an immunoprofile similar to that of ADH/ low grade DCIS

(ER, PR, Bcl2, CK19) +

(CK5/6, CK14, p53, HER2neu) -

Ki67 (- or low)

Frequent loss of 16q (characteristic of" low grade lesions")

Differential diagnosis:

1. Blunt duct adenosis
2. CC with associated UDH
3. Lactational-like changes

Blunt duct adenosis vs FEA

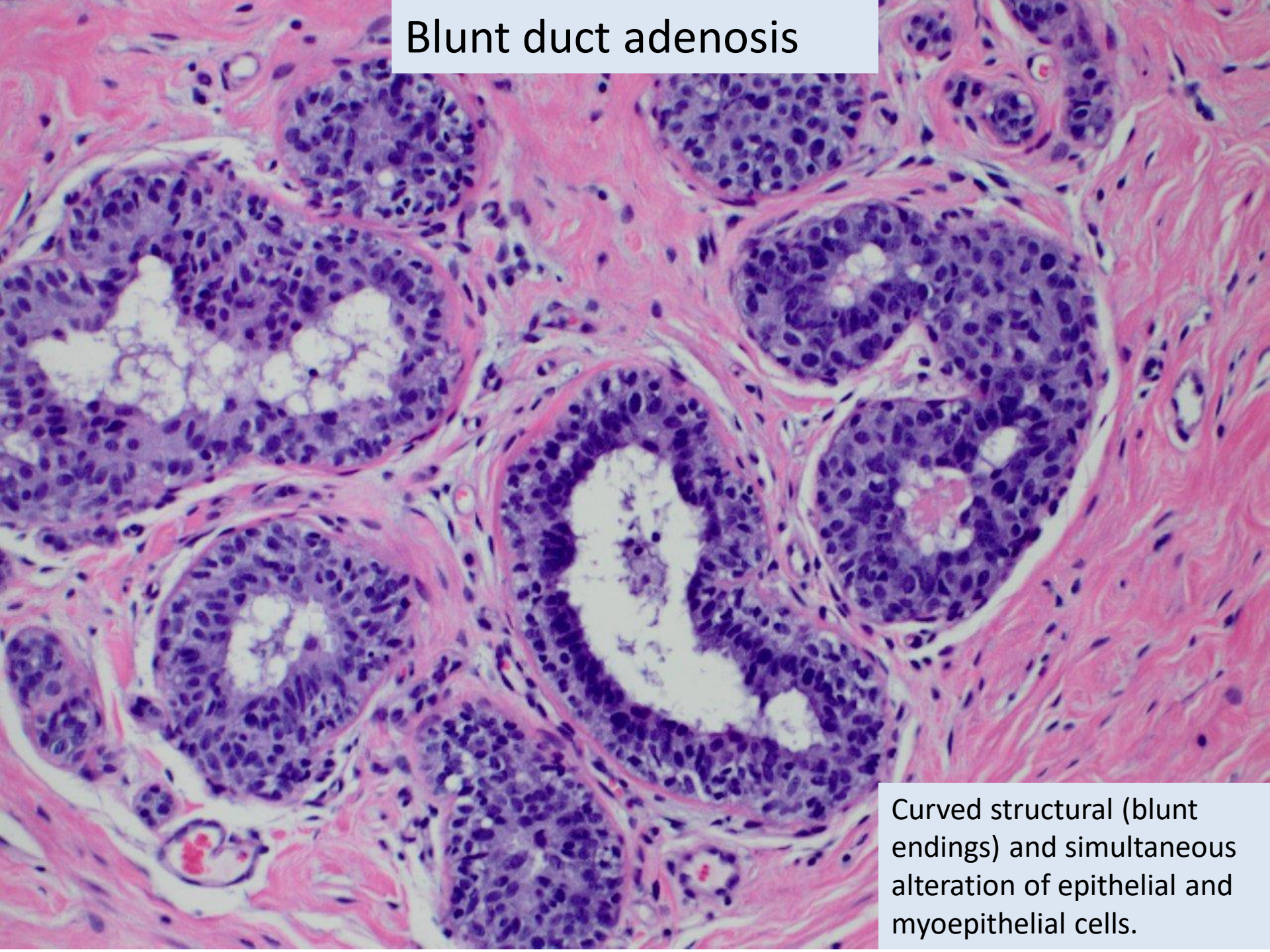
Low power: Curved structural (blunt lateral outlines, blunt endings) and simultaneous alteration of epithelial and myoepithelial cells.

Rigid dilatation but may be curved

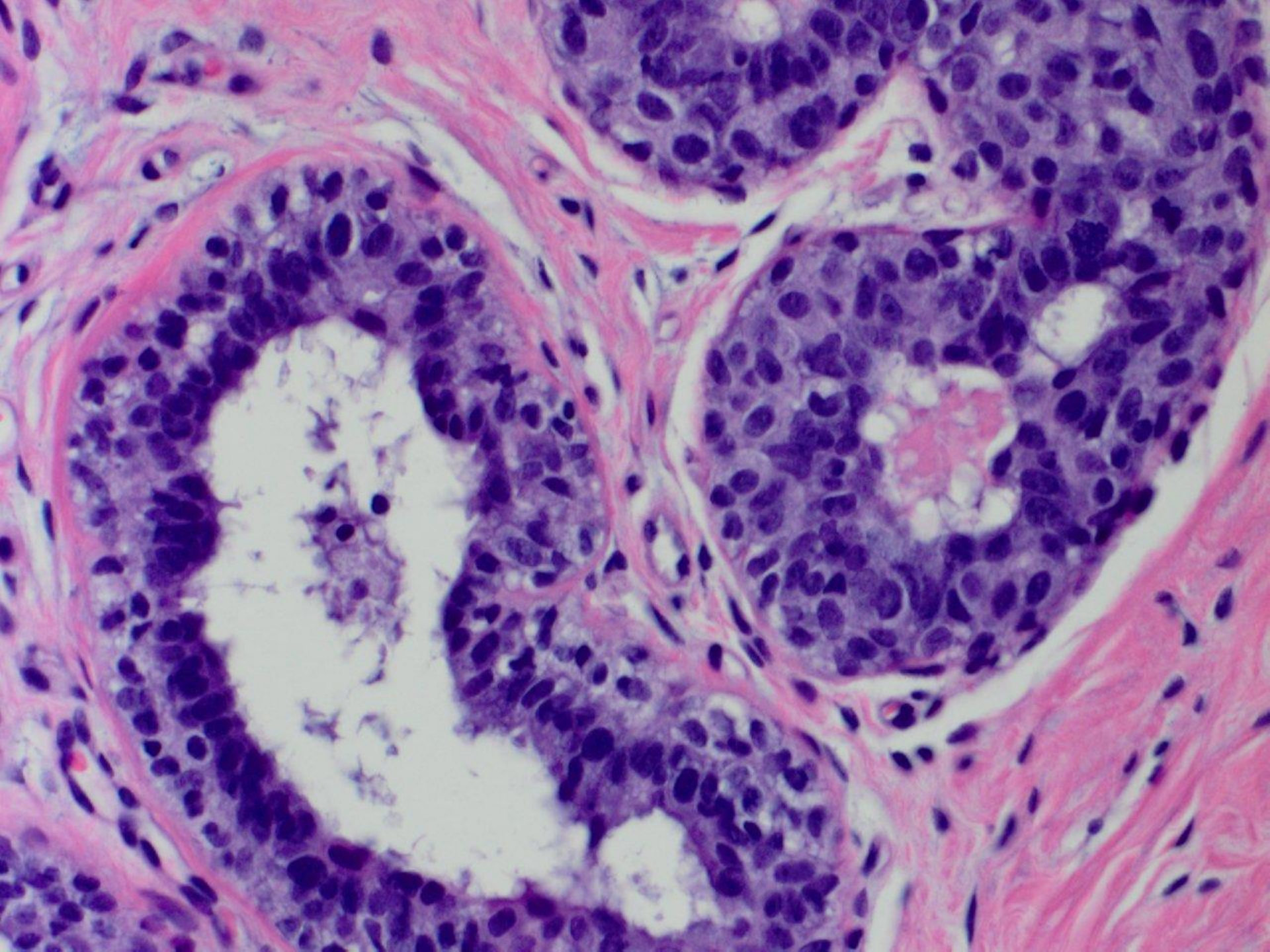
Immunohistochemistry:

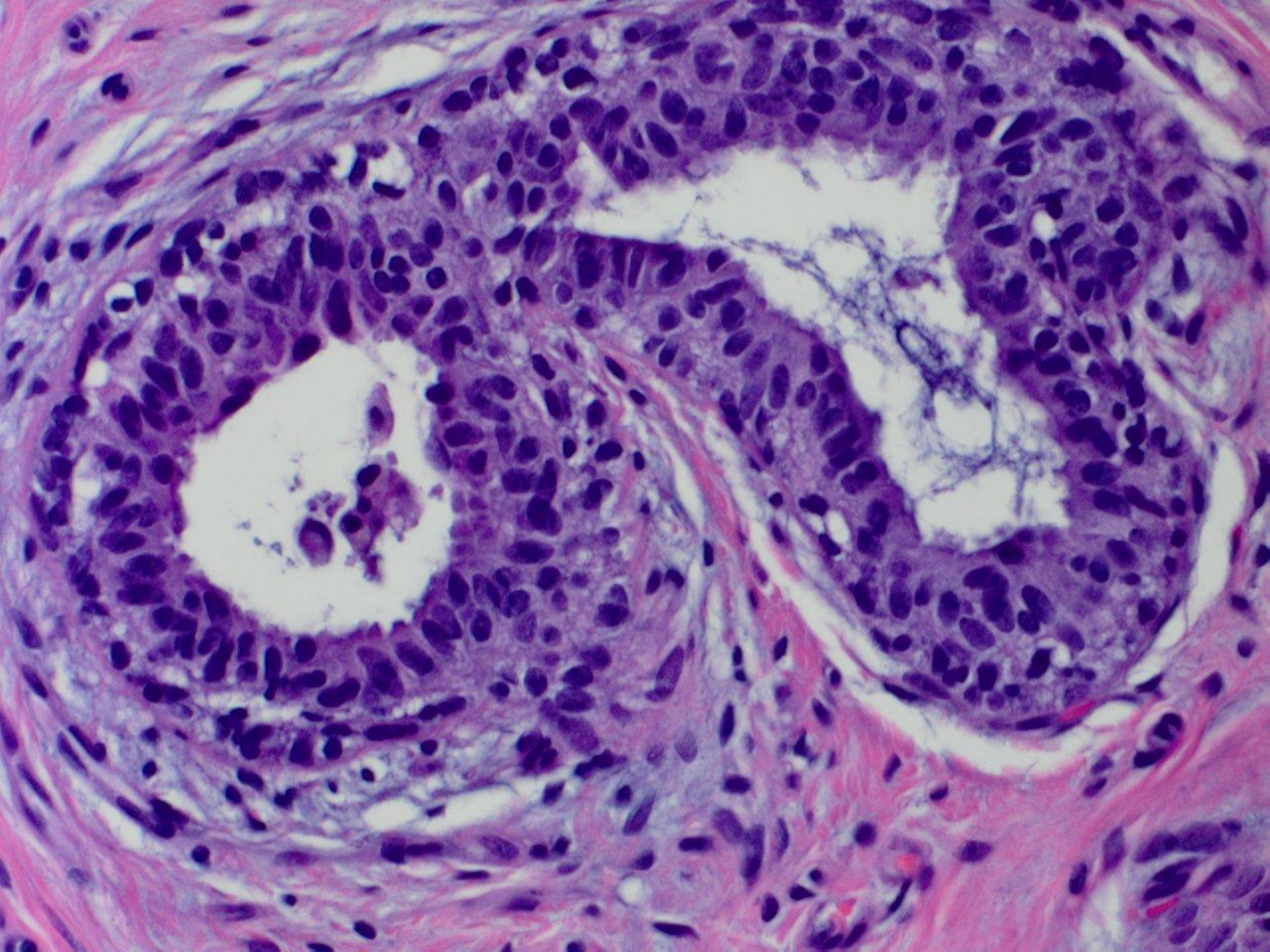
CK5/6 and 34ßE12 expressed in UDH (heterogeneously positive) but not in FEA

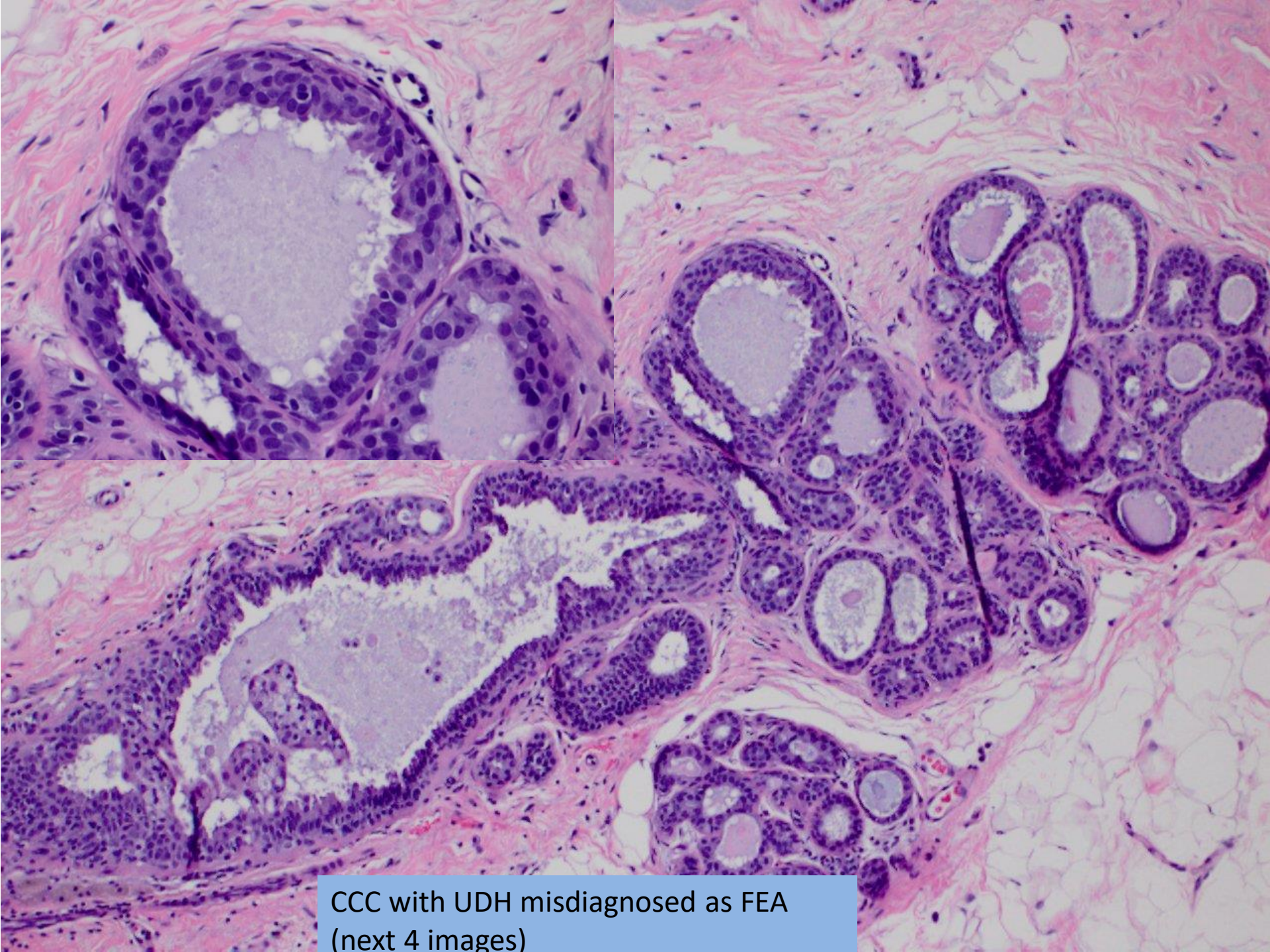
Blunt duct adenosis



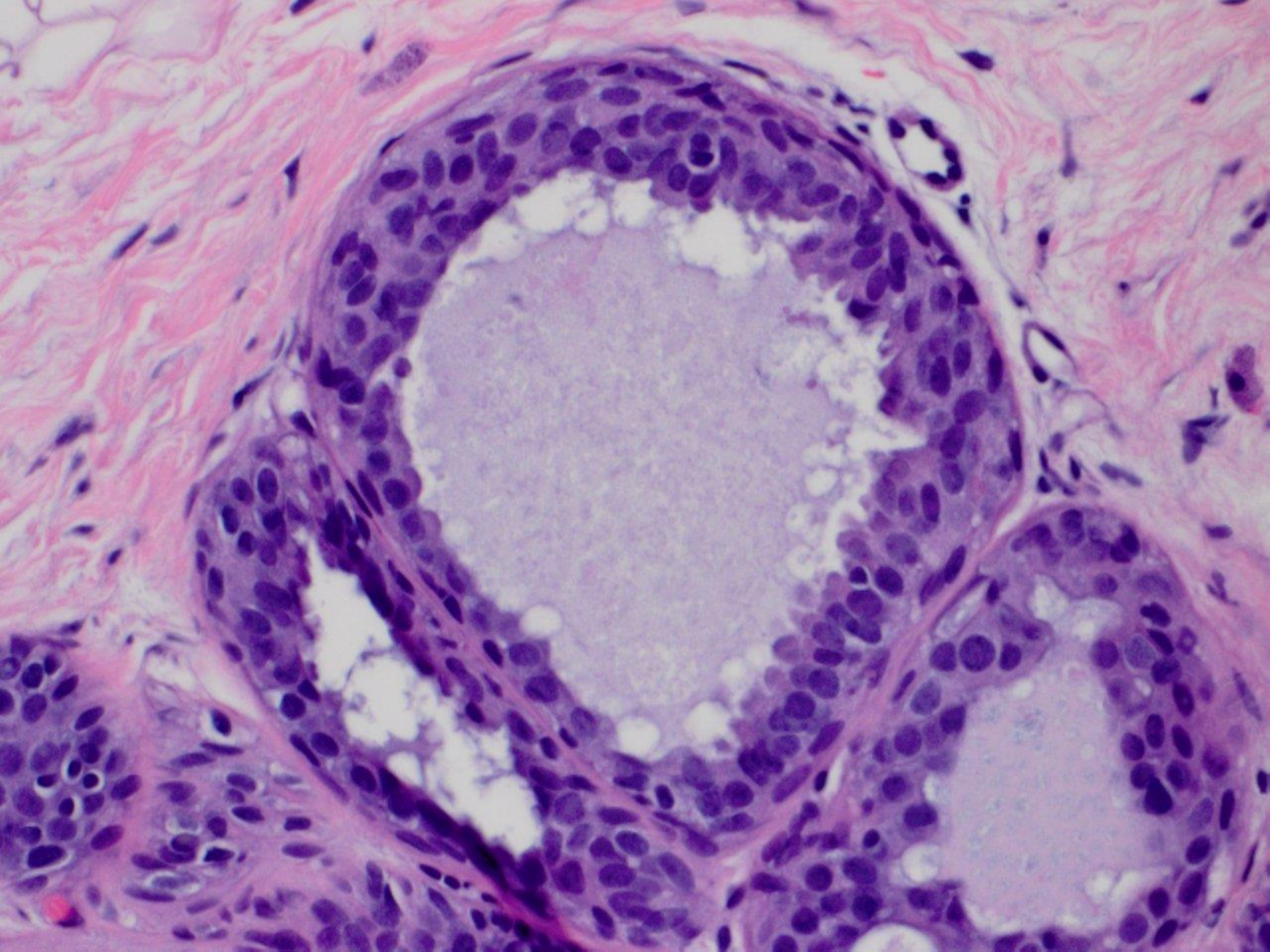
Curved structural (blunt endings) and simultaneous alteration of epithelial and myoepithelial cells.

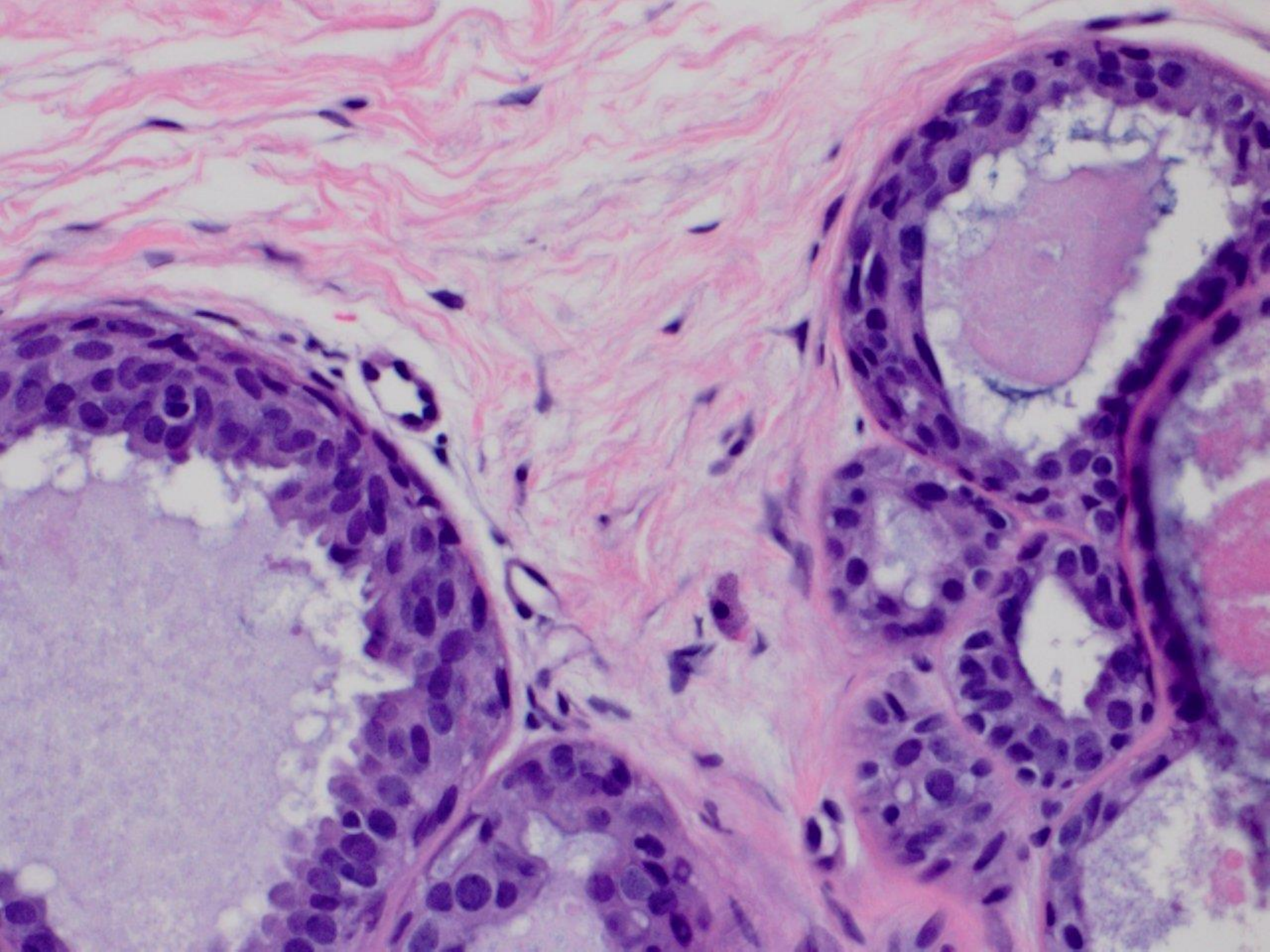


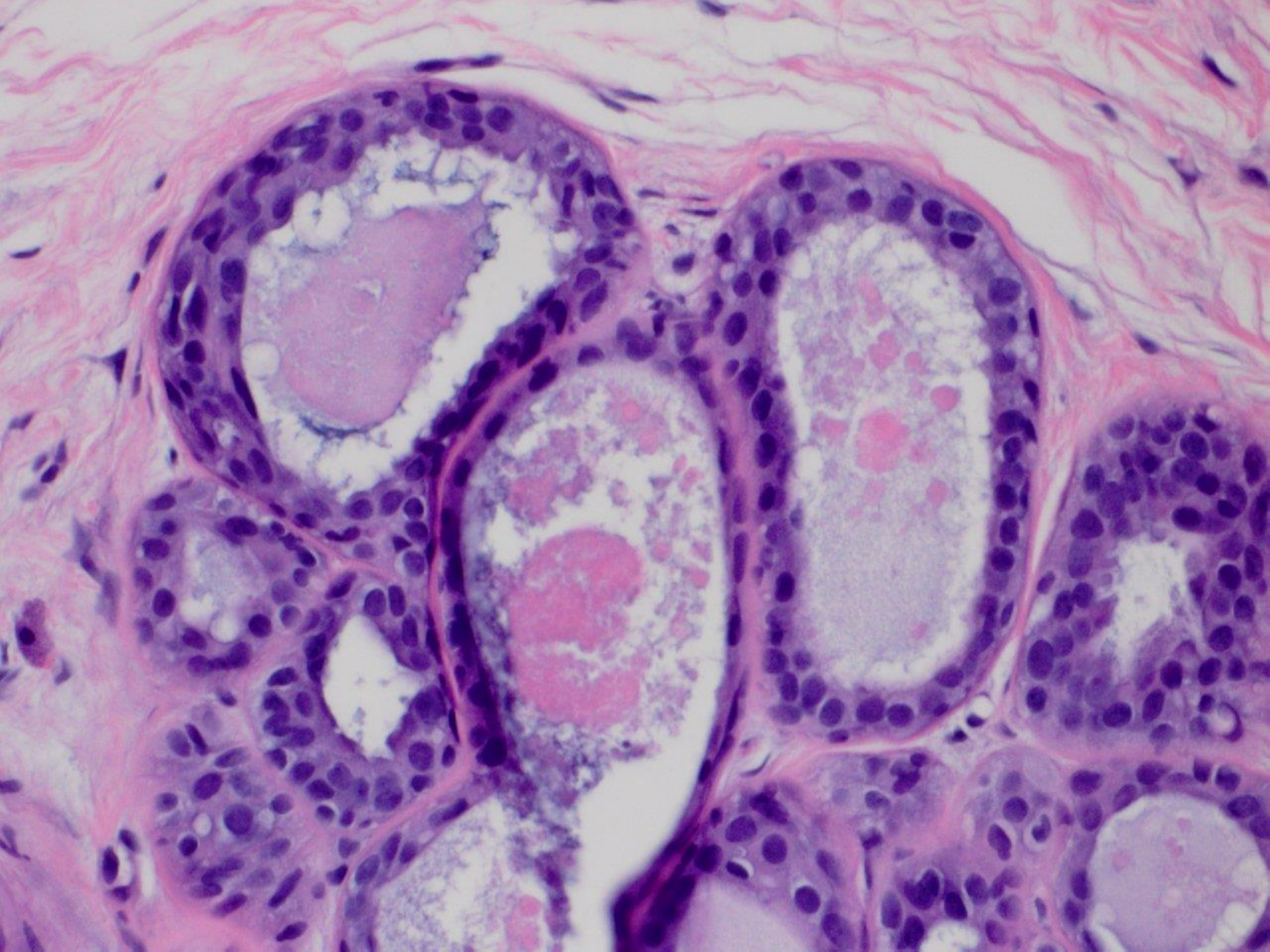




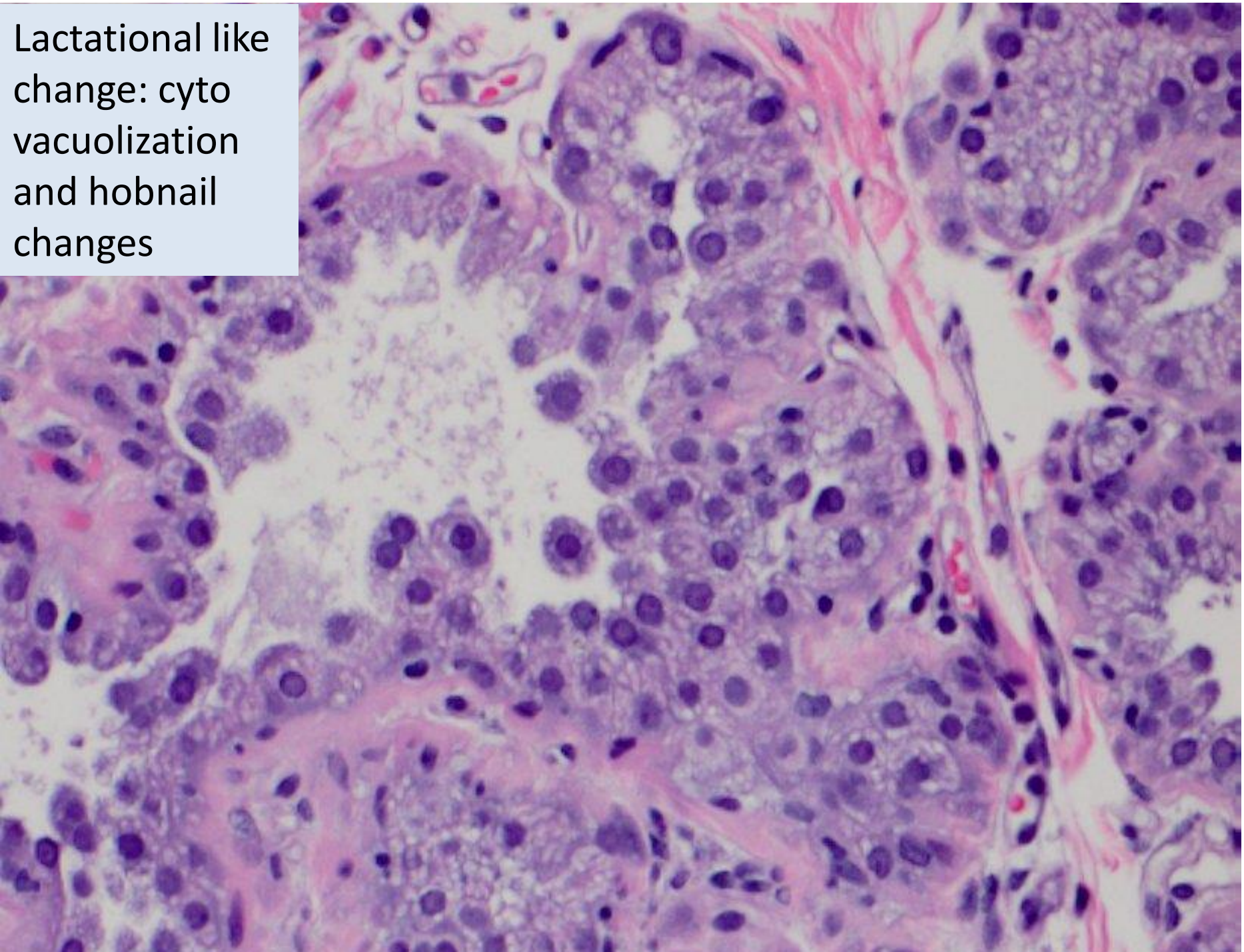
CCC with UDH misdiagnosed as FEA
(next 4 images)

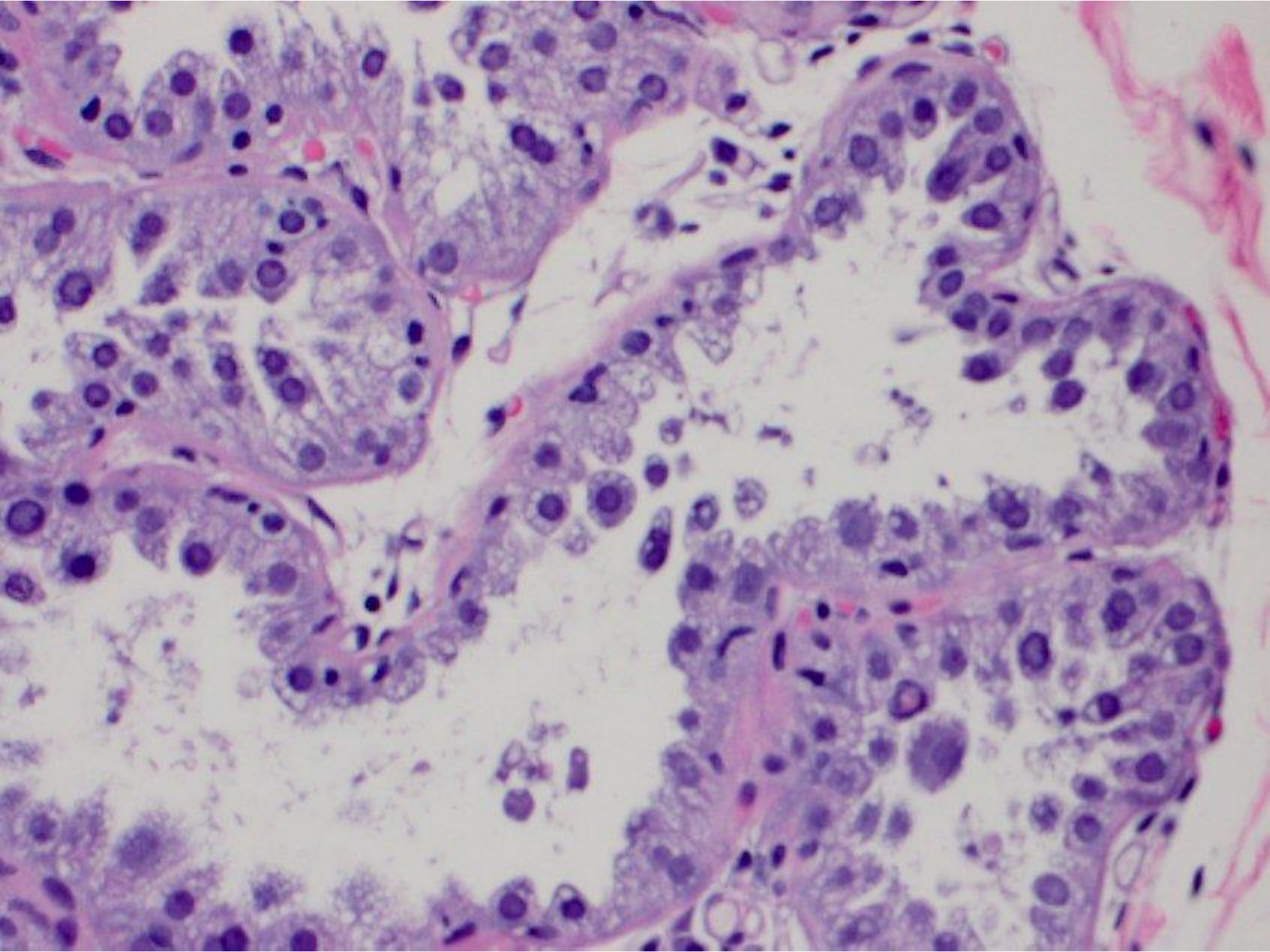






Lactational like change: cyto vacuolization and hobnail changes





Flat Epithelial Atypia Often Seen in Association with:

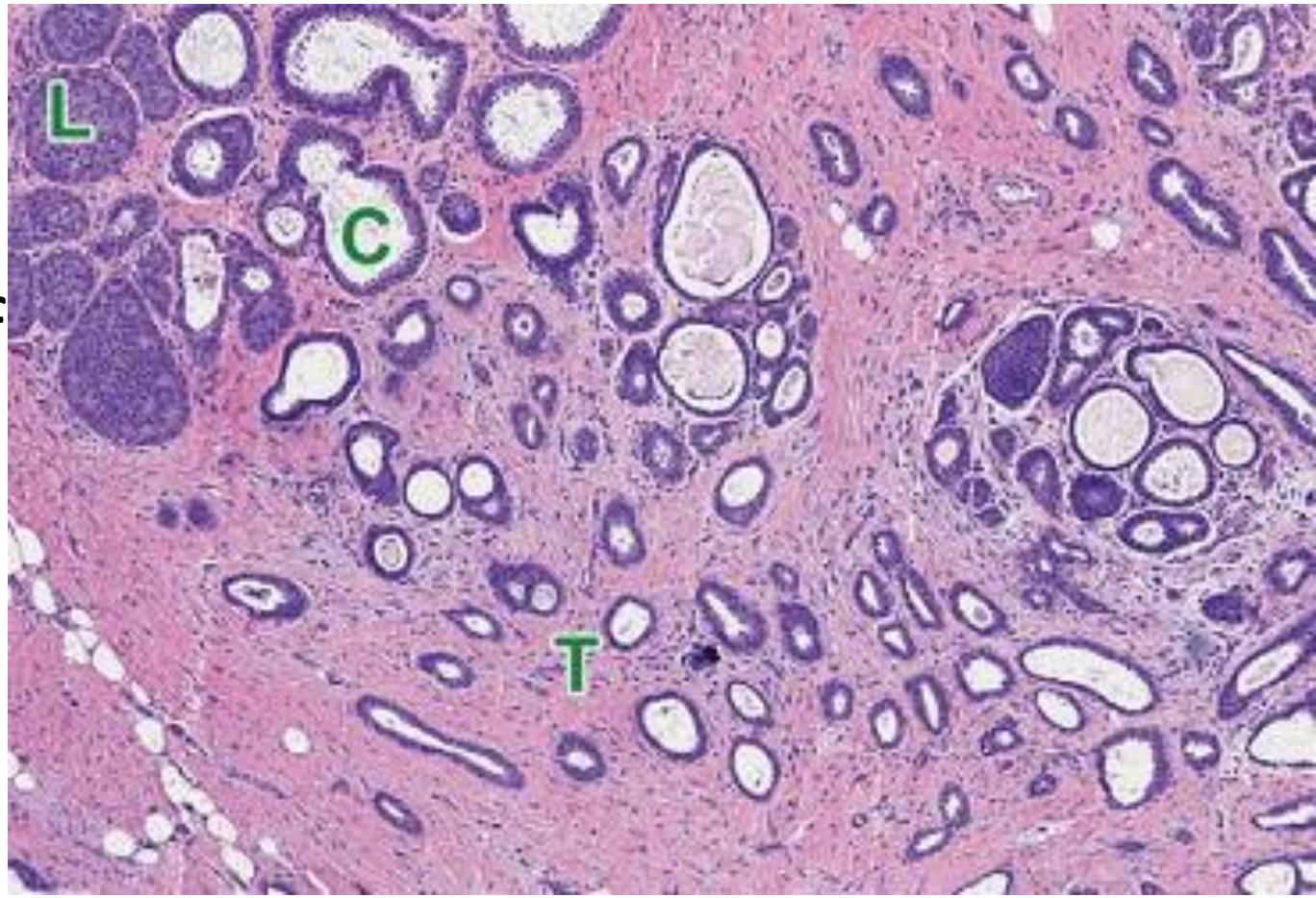
- Tubular carcinoma
- ADH
- DCIS
- Lobular neoplasia (ALH/LCIS)

Frequency of FEA Association with other Lesions

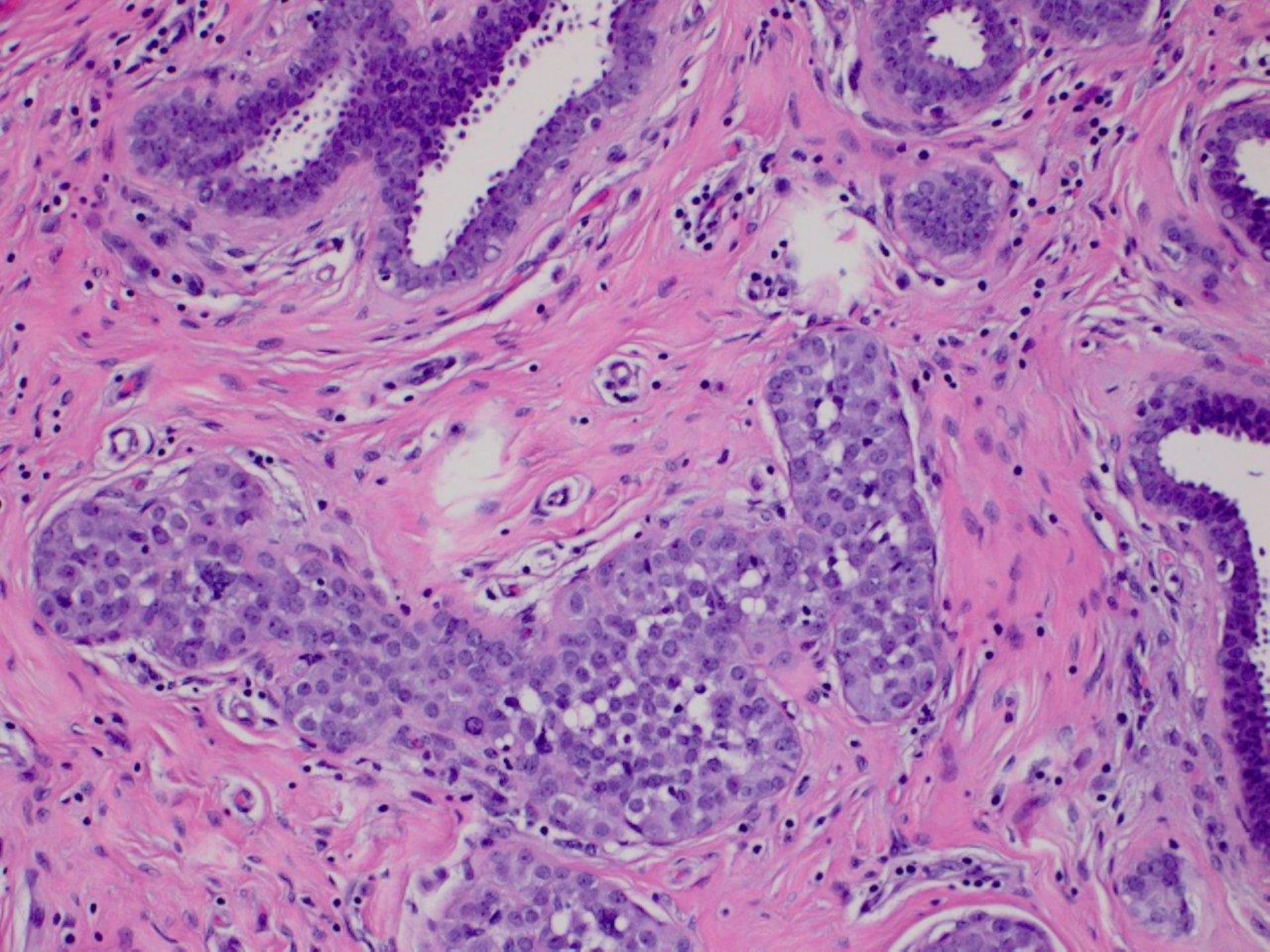
- LCIS (30-80%)
- ADH (>50%)
- DCIS, Low grade (50%)
- Tubular Carcinoma including well diff IDC (50%)

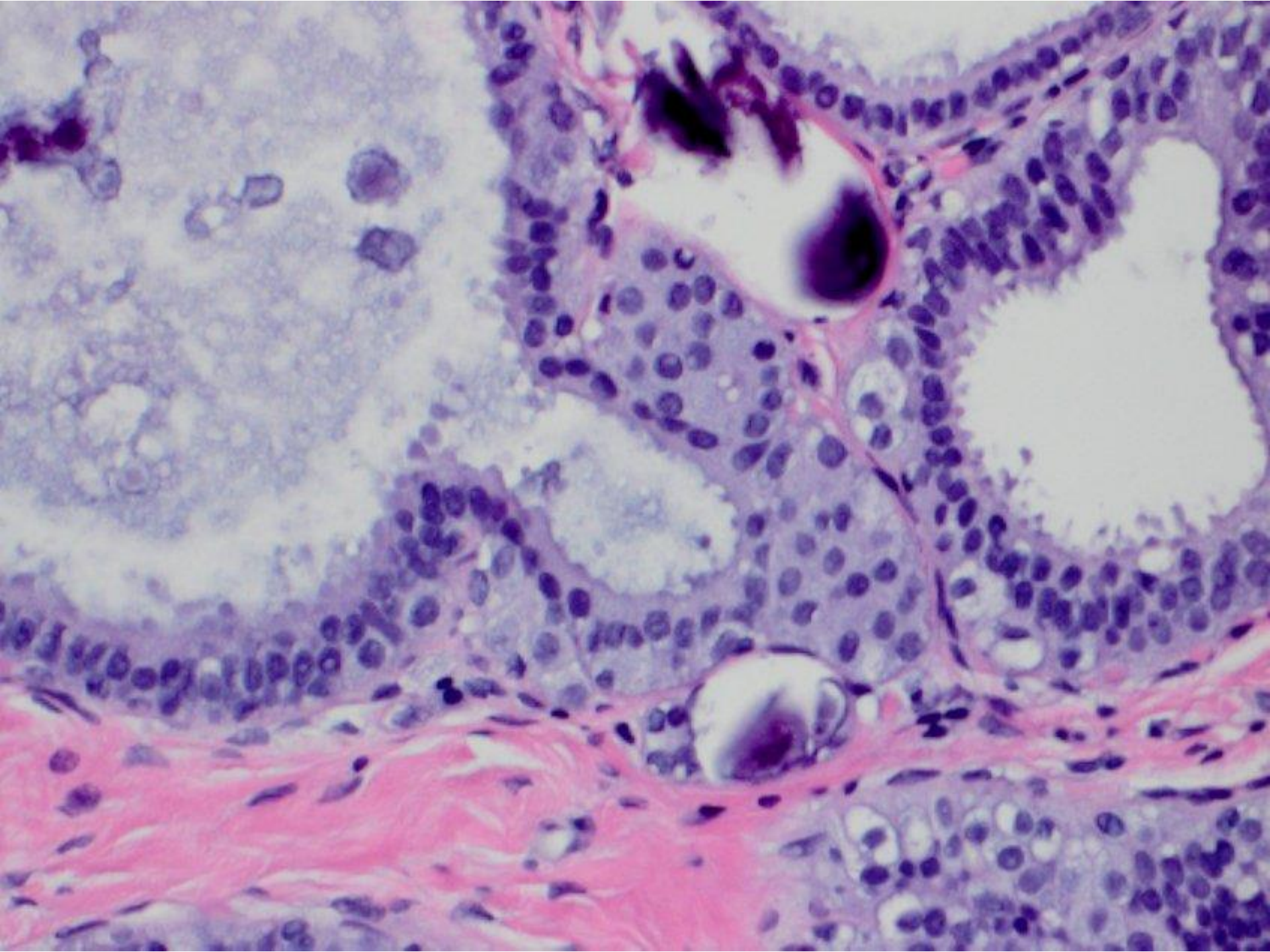
“Rosen triad”

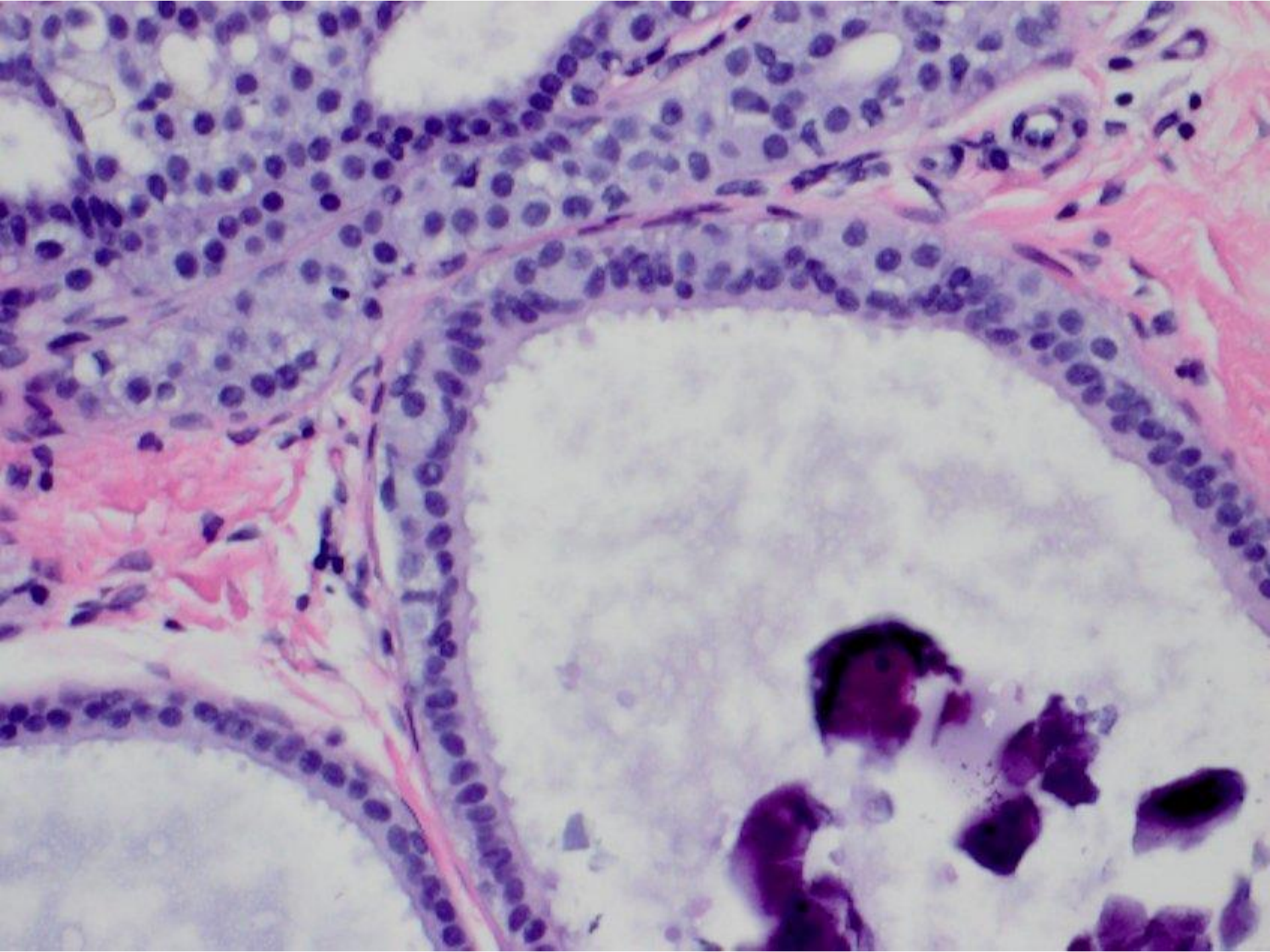
Breast lesions consisting of CCL + LCIS + tubular carcinoma

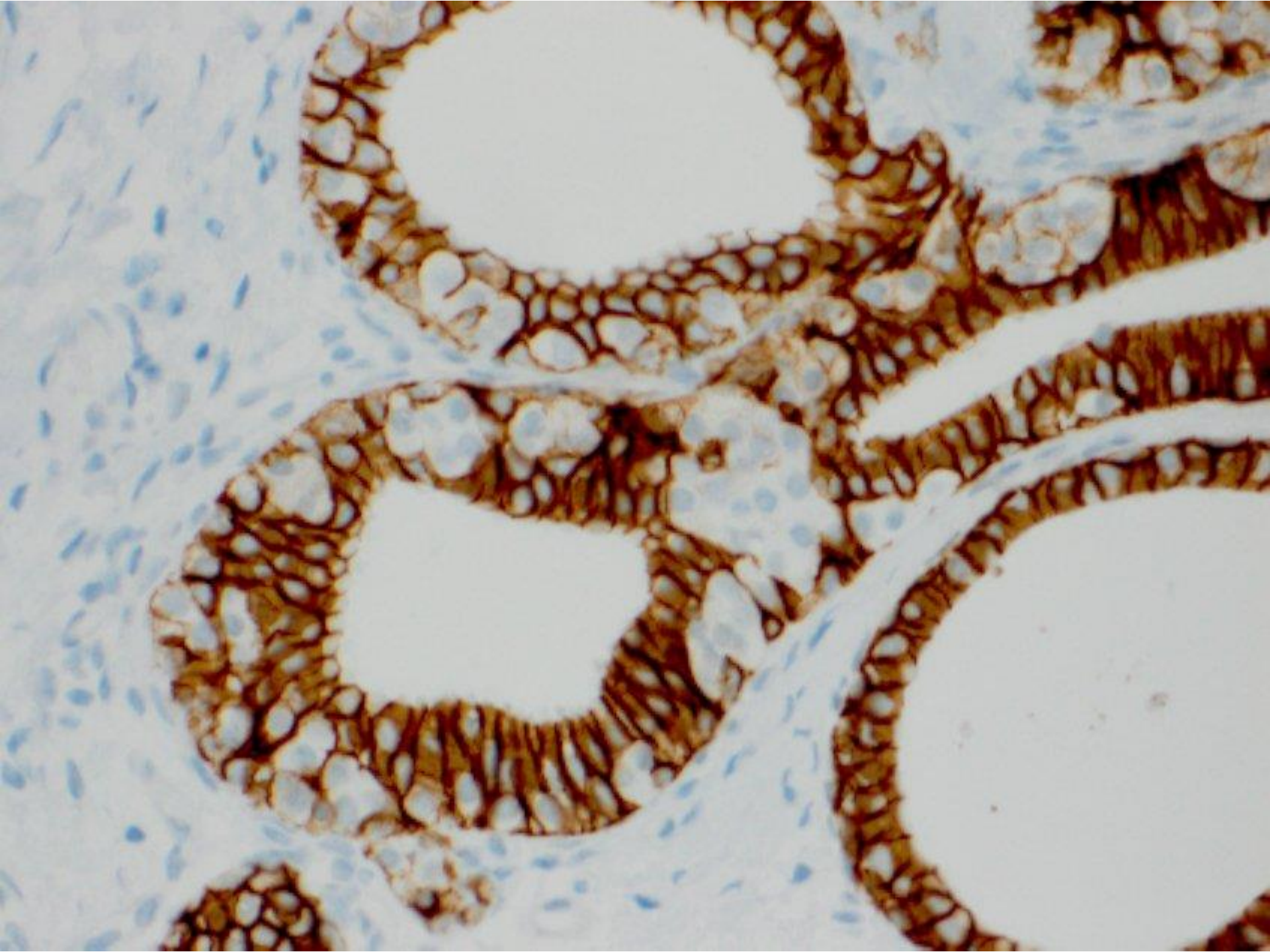


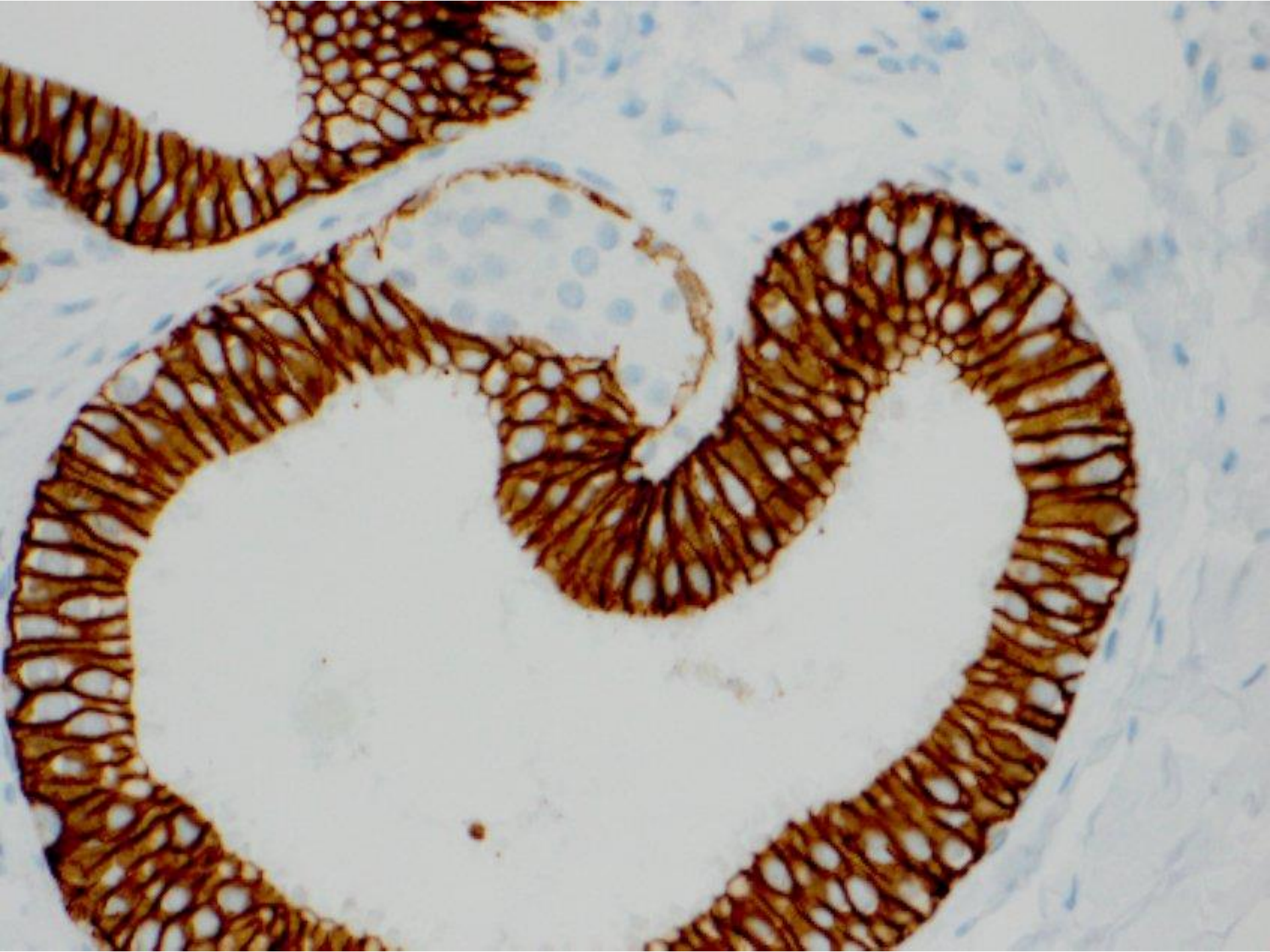
Brandt S et al, Adv Anat Pathol, 2008

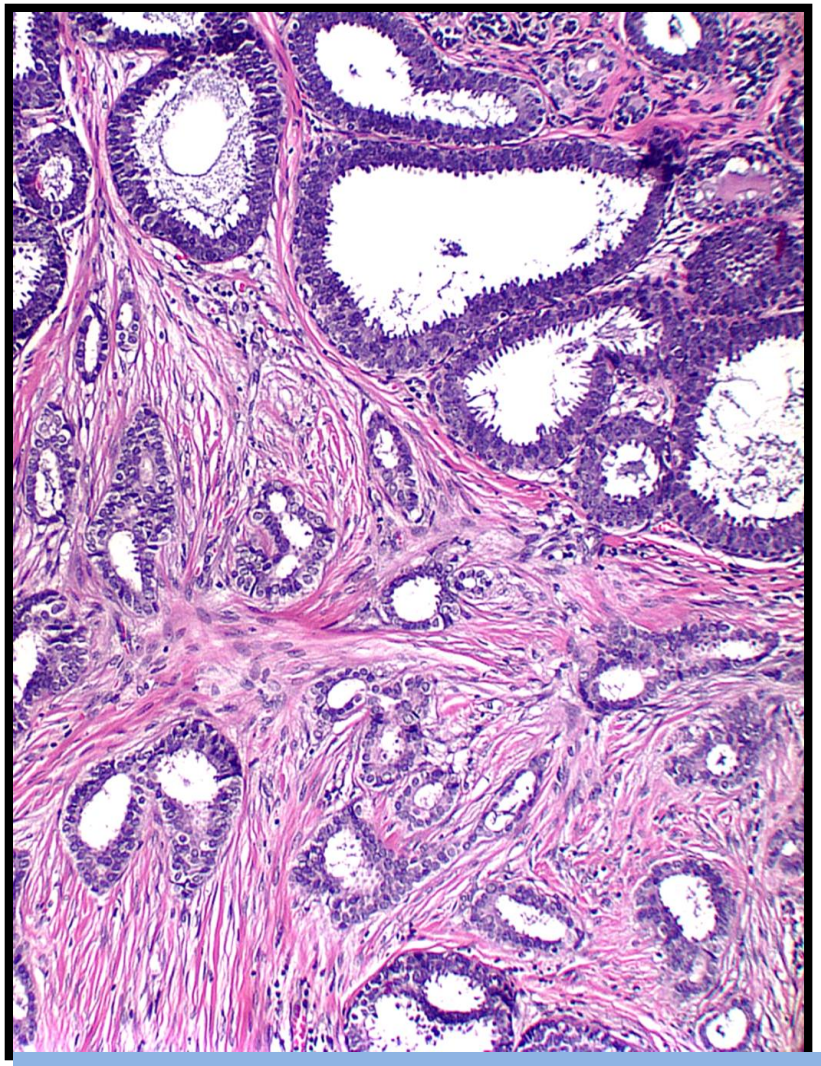


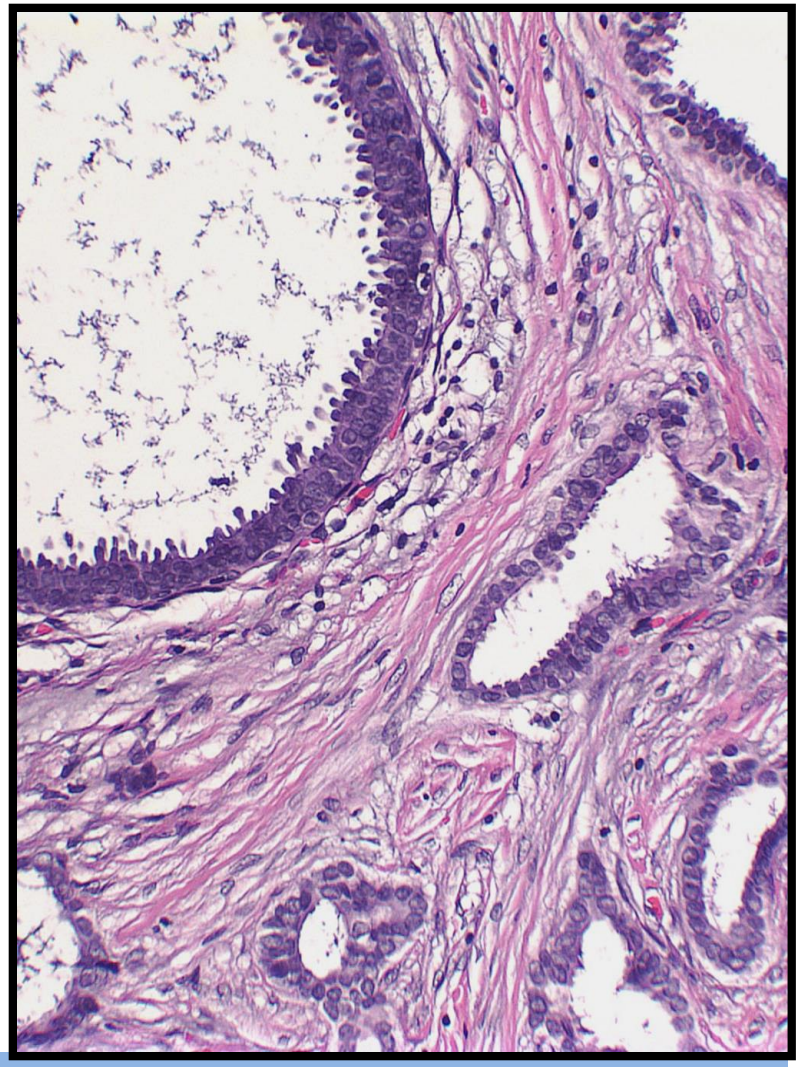












Flat epithelial atypia and Tubular carcinoma

Relative risk of breast cancer in FEA ?

Outcome data failed to detect a significant risk for subsequent cancer on long term follow-up

Flat Epithelial Atypia and Risk of Breast Cancer: A Mayo Cohort Study

Said, Visscher, --and Degnim

Cancer, 2015

11,591 women

FEA in 282 (2.4%); 130 (46%) had associated AH.

Median F/U 16.8 yrs

Standardized incidence ratio (SIR) for:

AH plus FEA: 4.74 vs

AH without FEA: 4.23

Conclusion: FEA does not appear to convey an independent risk of breast cancer beyond that of the associated PDWA or AH

Long Term Cancer Risk in CCL of the Breast

Boulos et al. Cancer 2008;113:2415-21

Evaluated overall cancer risk in 1262 CCLs (also classified 229 bx into 3 categories CCL, CCL with hyperplasia and CCL with atypia)

- Mild increase in overall cancer risk (RR=1.47 at 17 years)
- No difference among CCLs with and without atypia with regard to future breast cancer risk
- 2- to3- fold increase for AH in presence of CCLs
- A finding of CCL may indicate the presence of AH, a more worrisome lesion.

Practical Consideration in the Diagnosis of Biopsy Specimens with FEA- Tavassoli

1. If FEA is the only lesion, perform additional 3-4 levels beyond the 3 initial level to exclude a more advanced lesion. If rigid bridges or micropapillary structures become apparent—dx: ADH
2. Carefully search for accompanied lesions such as ALH, TC and low grade ductal ca.
3. Similar to ALH, assessment of resection margins containing FEA is meaningless.
4. High grade atypia –is not a feature of FEA.

Atypical Ductal Hyperplasia (ADH)

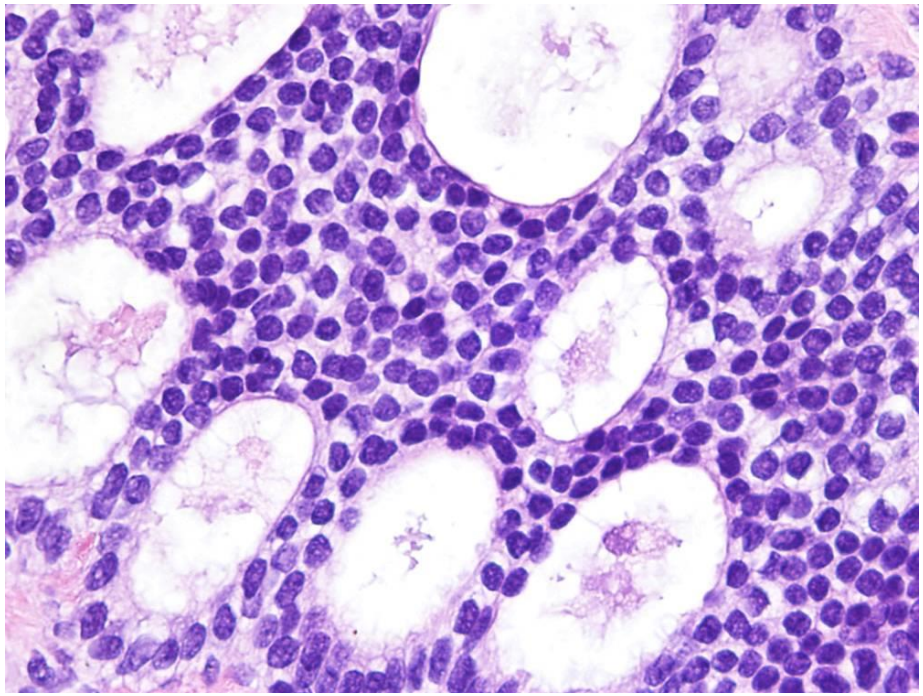
Definition

ADH is a proliferation of monomorphic, evenly placed epithelial cells involving TDLUs

ADH is associated with a moderately increased risk for subsequent development of invasive ca (RR 3-5)

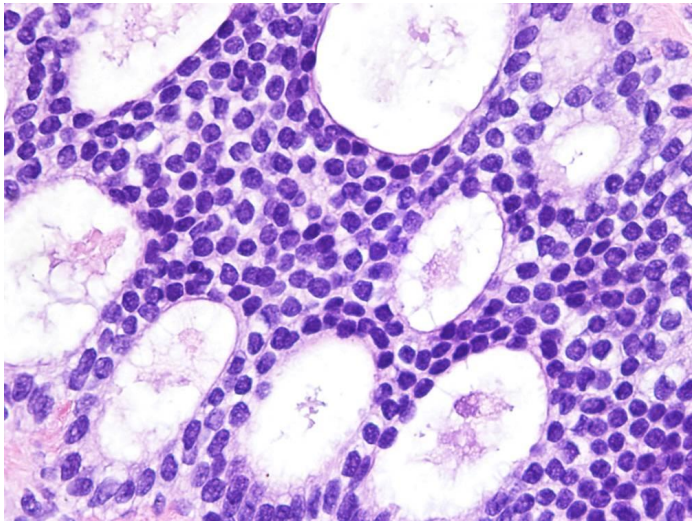
Cytologic Features of ADH

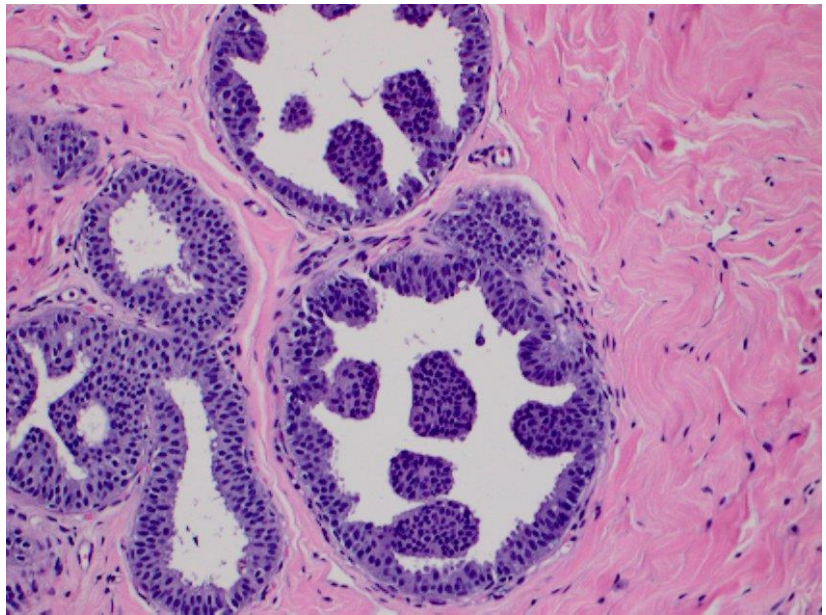
- Monotonous, uniform, rounded cells
- Equidistant, highly organized or rosette-like nuclear distribution
- Hyperchromasia may or may not be present
- Subtle increase in nuclear to cytoplasmic ratio



Architectural Features of ADH

- Cribriform with “punched out spaces” surrounded by polarized cells or
- Micropapillary with epithelial projections that are typically narrower at the base than the apex
- Solid with or without subtle micracini



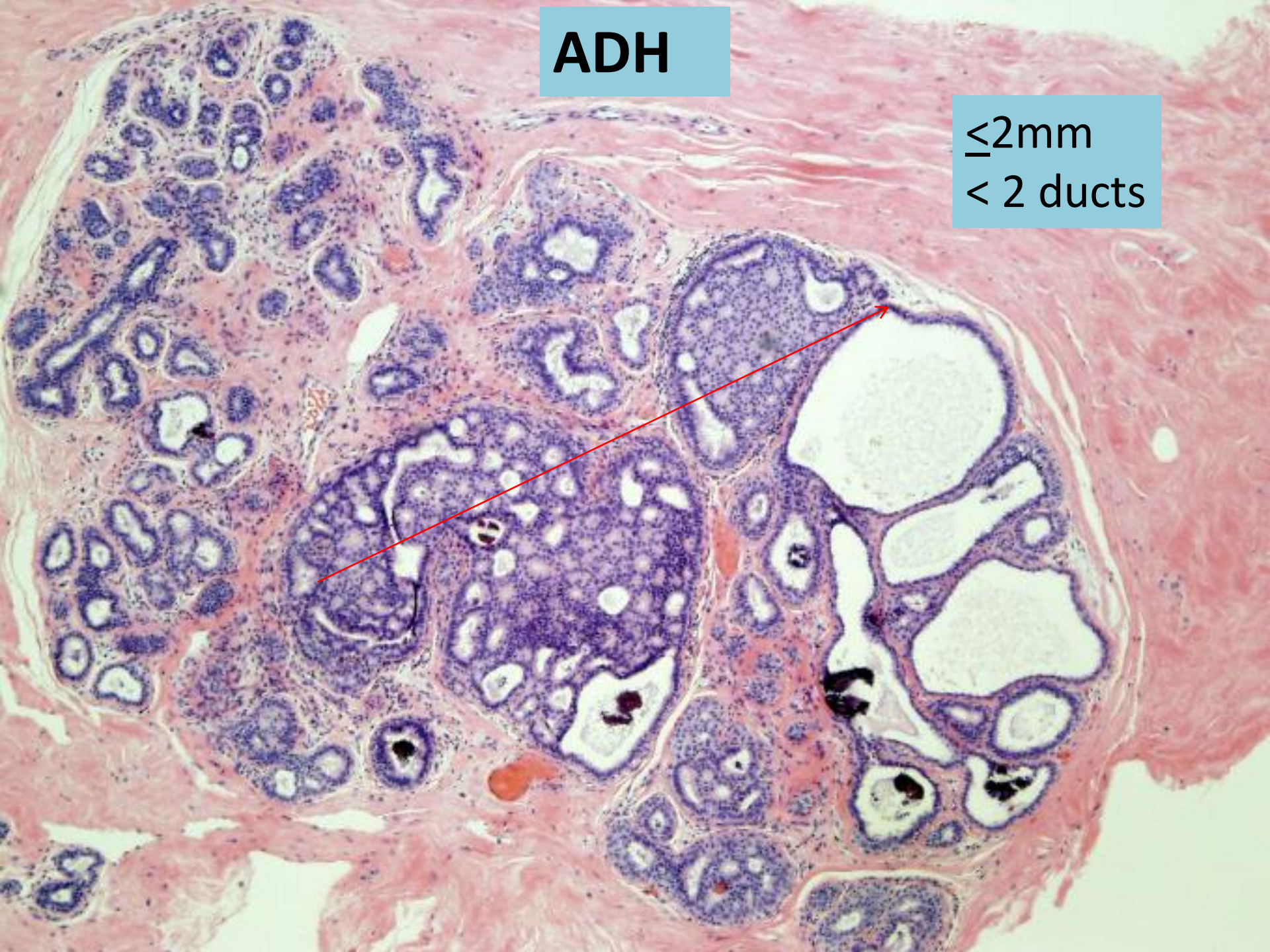


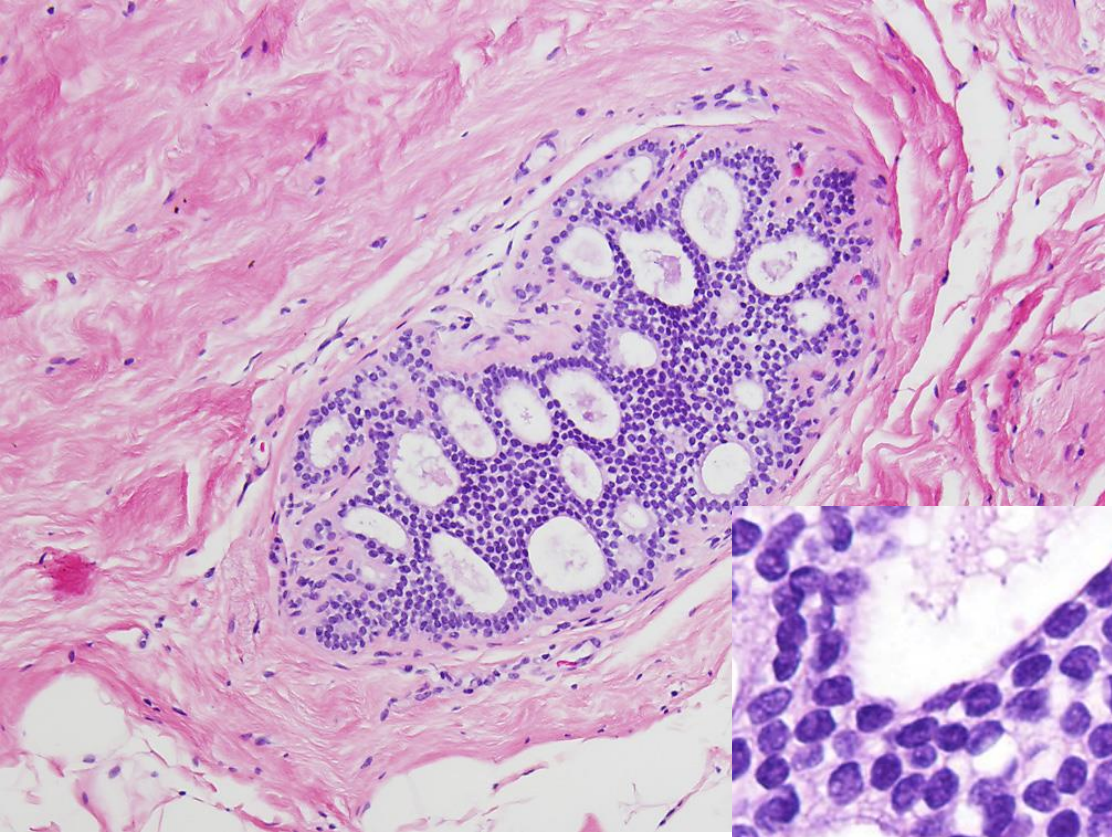
ADH vs DCIS, Gr 1
Quantitative :

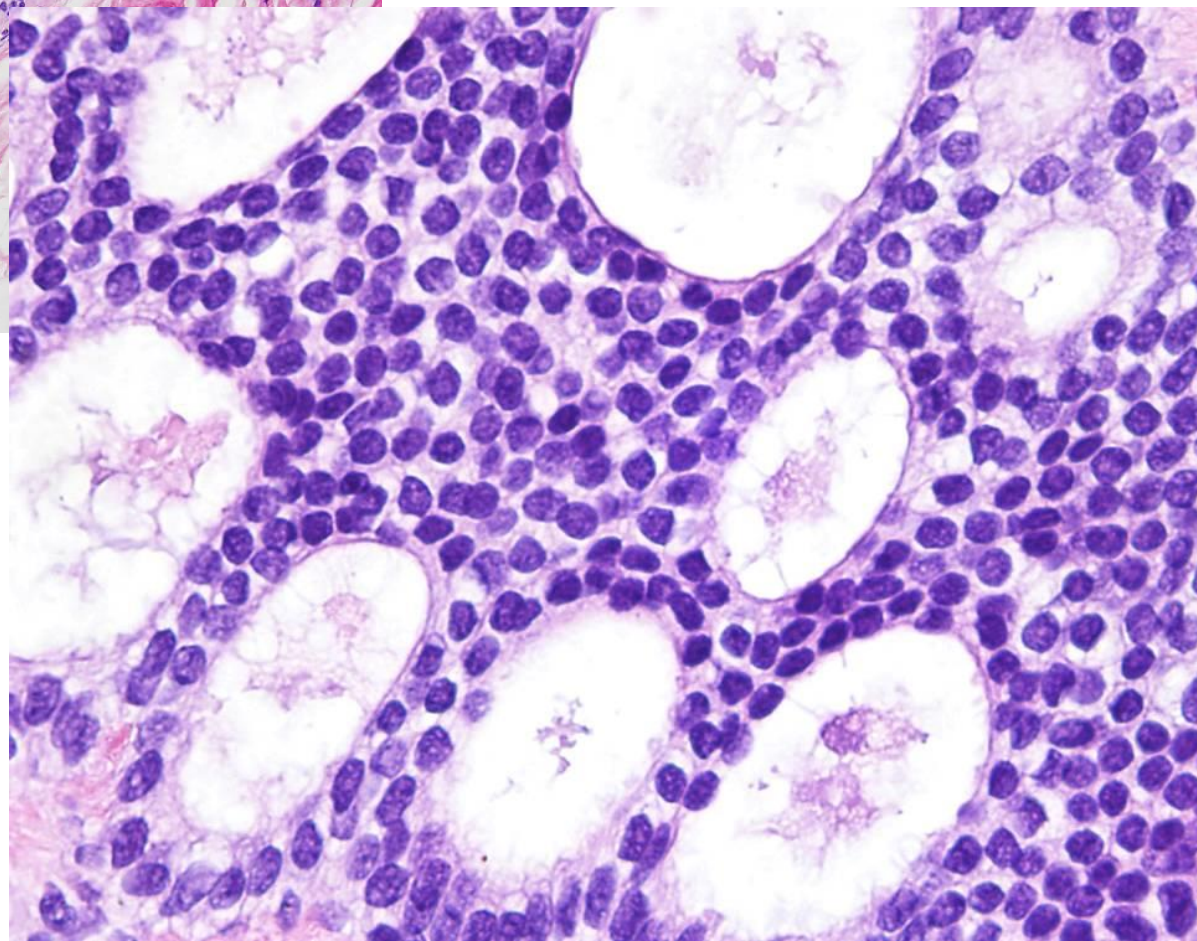
DCIS=complete involvement of at least 2 ductal spaces

or the aggregate cross- sectional diameter more than 2 mm

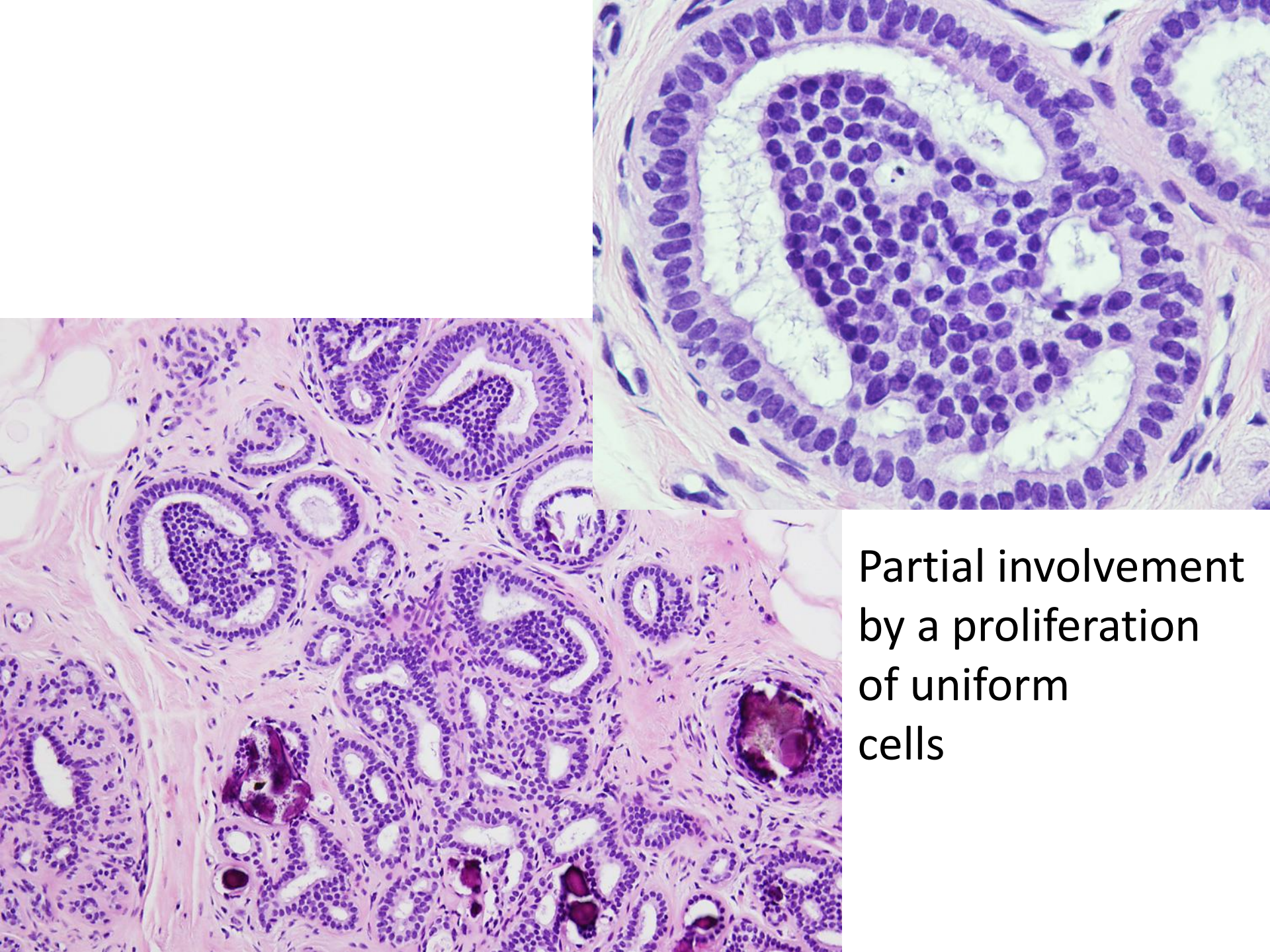
WHO 2012 “did not consider that it was possible to recommend one approach rather than another, and many experts use combinations of both in their clinical practice”


ADH
≤2mm
< 2 ducts





ADH, one duct, <2 mm



Partial involvement by a proliferation of uniform cells

Ductal Carcinoma In Situ (DCIS)

Infrequent prior to screening programs, accounting for 2-3% of palpable breast cancers, but now accounts for 20-30% of newly diagnosed breast cancer

Calcs most common mammographic presentation of DCIS

Ductal Carcinoma In Situ (DCIS)-
Classification and grading

1. Nuclear grade (low, intermediate, and high)
2. Necrosis (punctate vs comedo)
3. Architectural pattern(s), cell polarization
4. Size and extent of the lesion
5. Location of calcifications (DCIS alone, in benign tissue, or both)
6. Surgical margins

Nuclear grading:

Black's nuclear grading or Modified SBR

Low grade: monomorphic nuclei

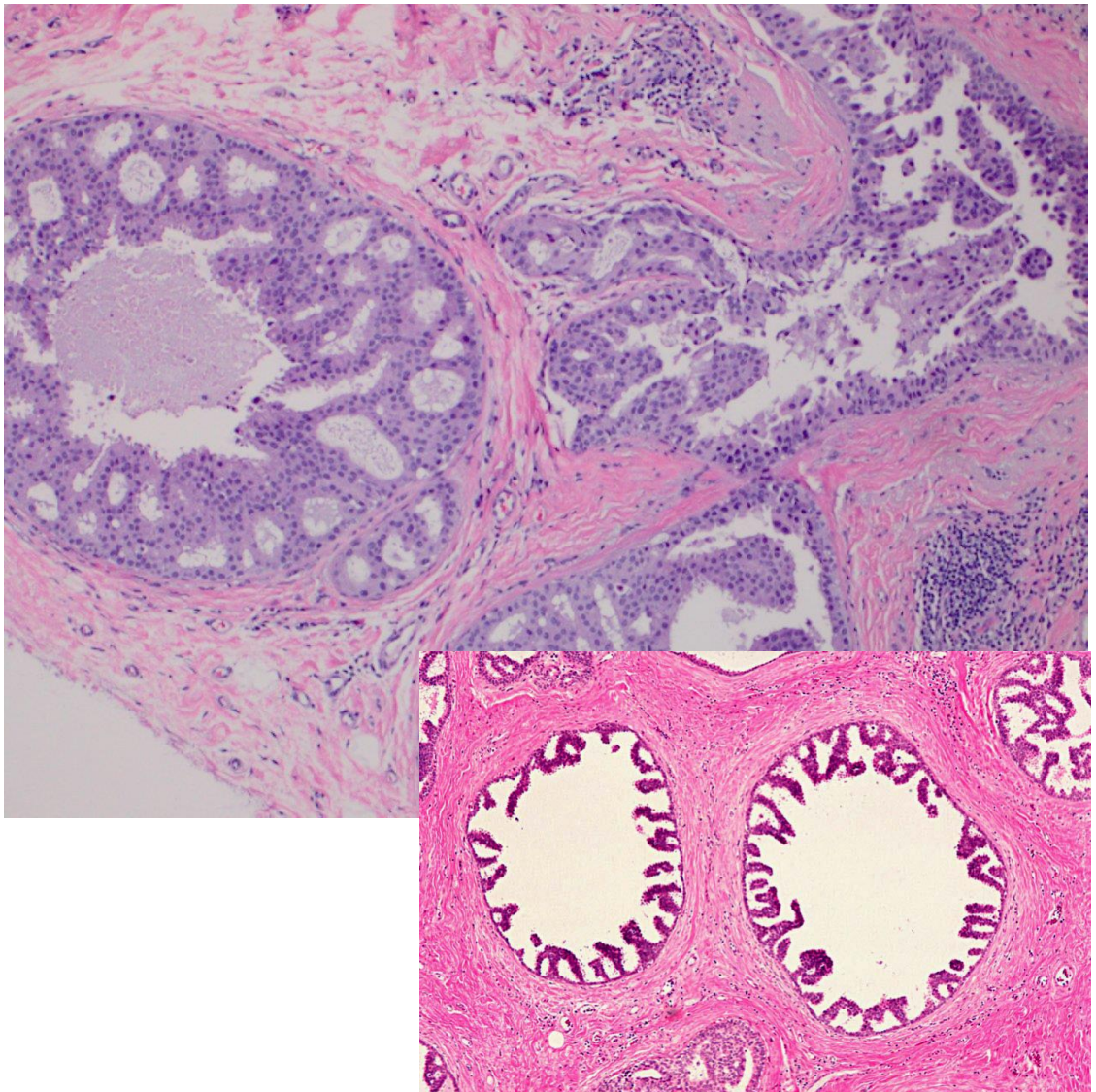
Intermediate grade: mild to moderate variability in size, shape and placement, Variably coarse chromatin and variability prominent nucleoli, mitosis may be present.

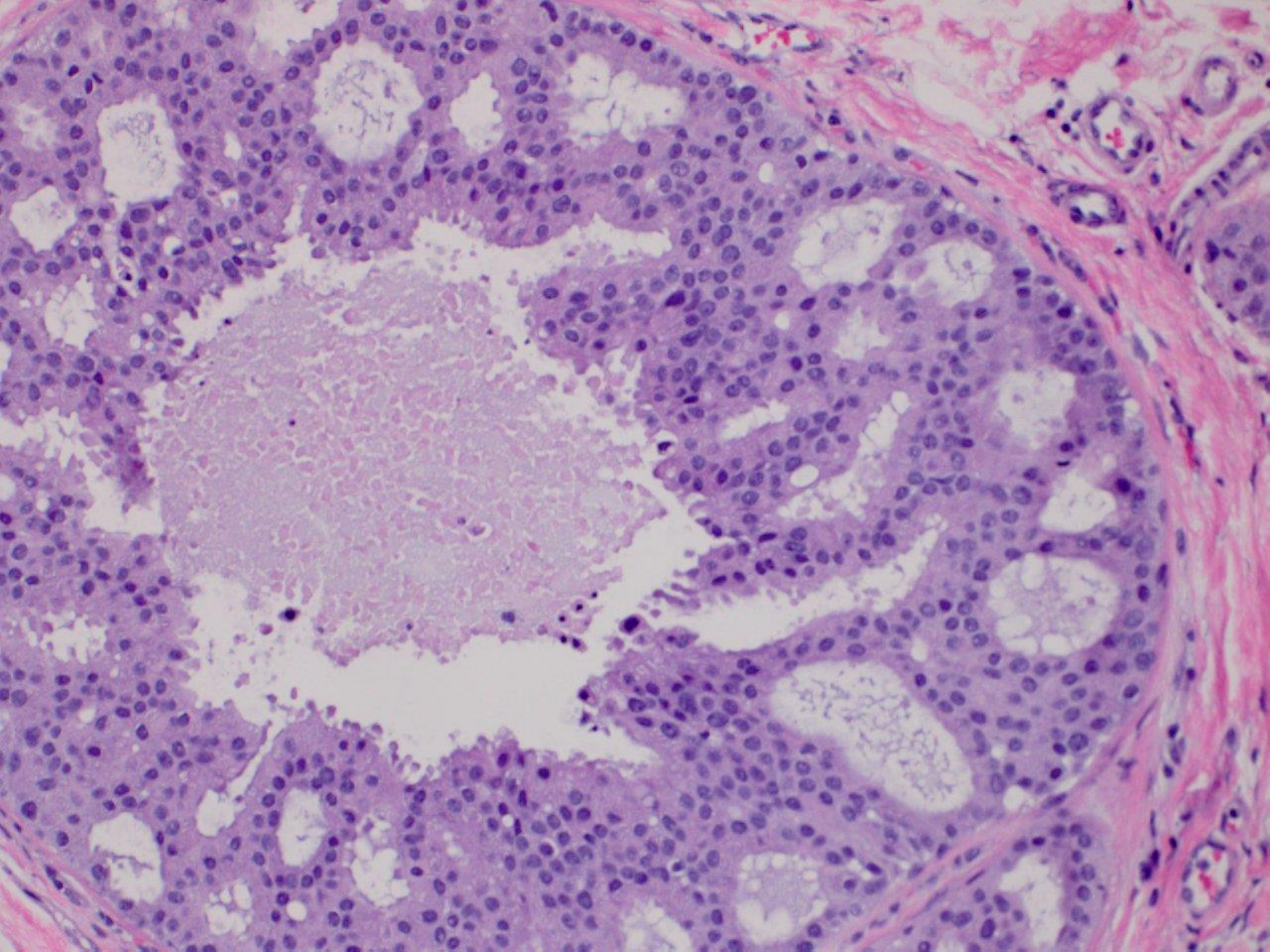
High grade: Highly atypical cells. Nulcei are pleomorphic, poorly polarized with irregular countour, coarse clumped chromatin and prominent nucleoli. Mitoses are common

DCIS, low nuclear grade

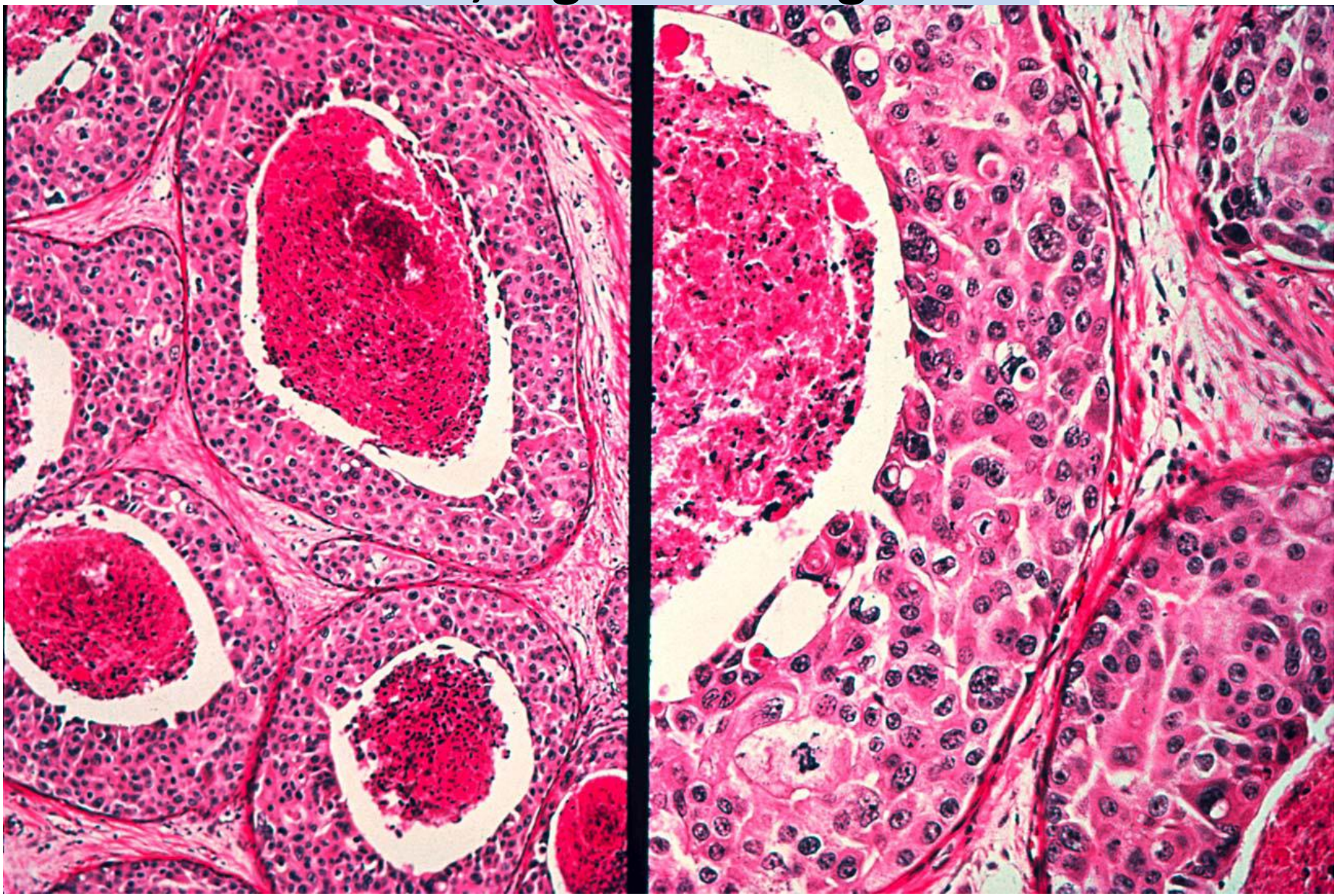
Monomorphic cells growing in cribriform, micropapillae or solid pattern.

Punctate or comedo type necrosis do not preclude the diagnosis of LG.

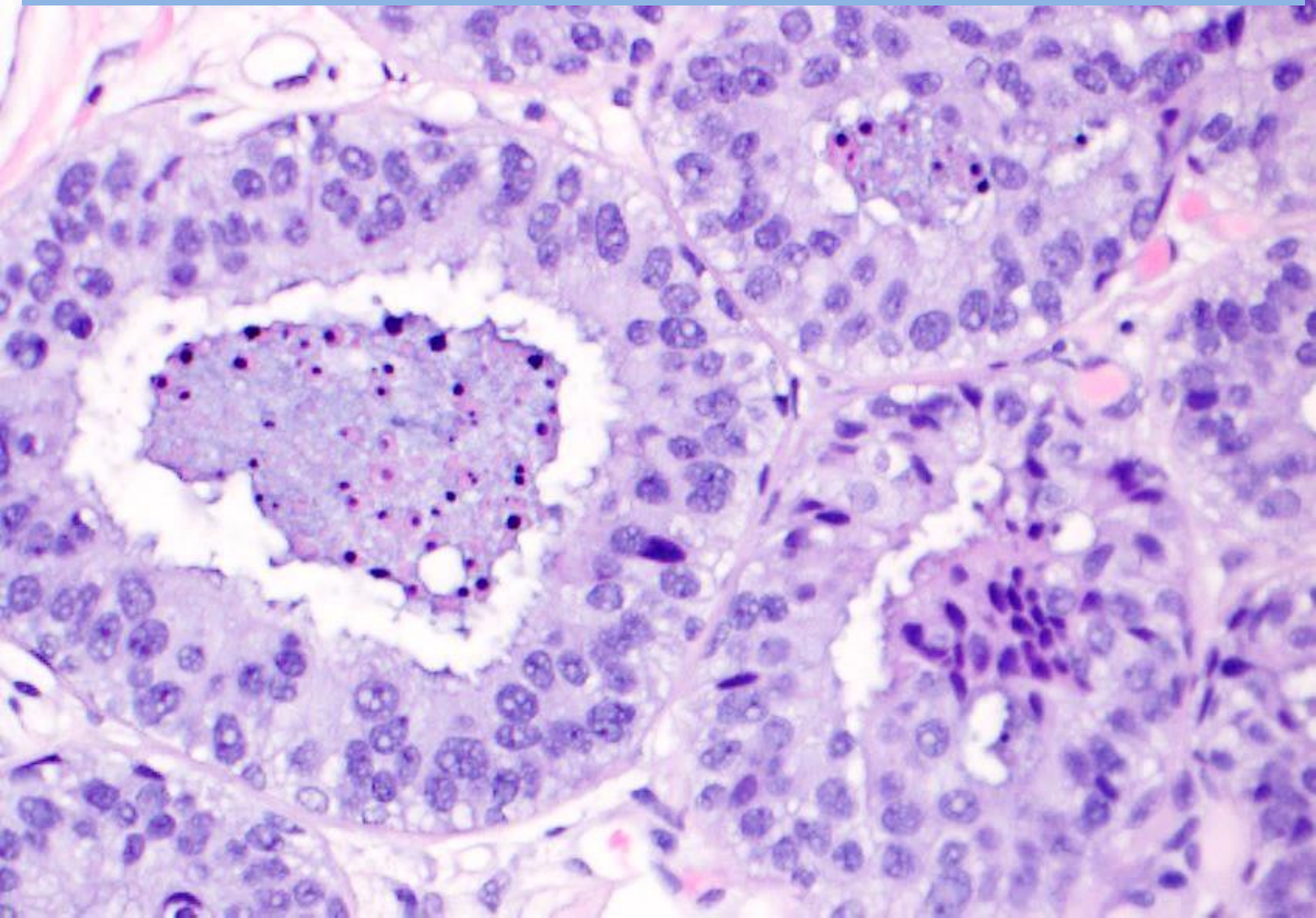


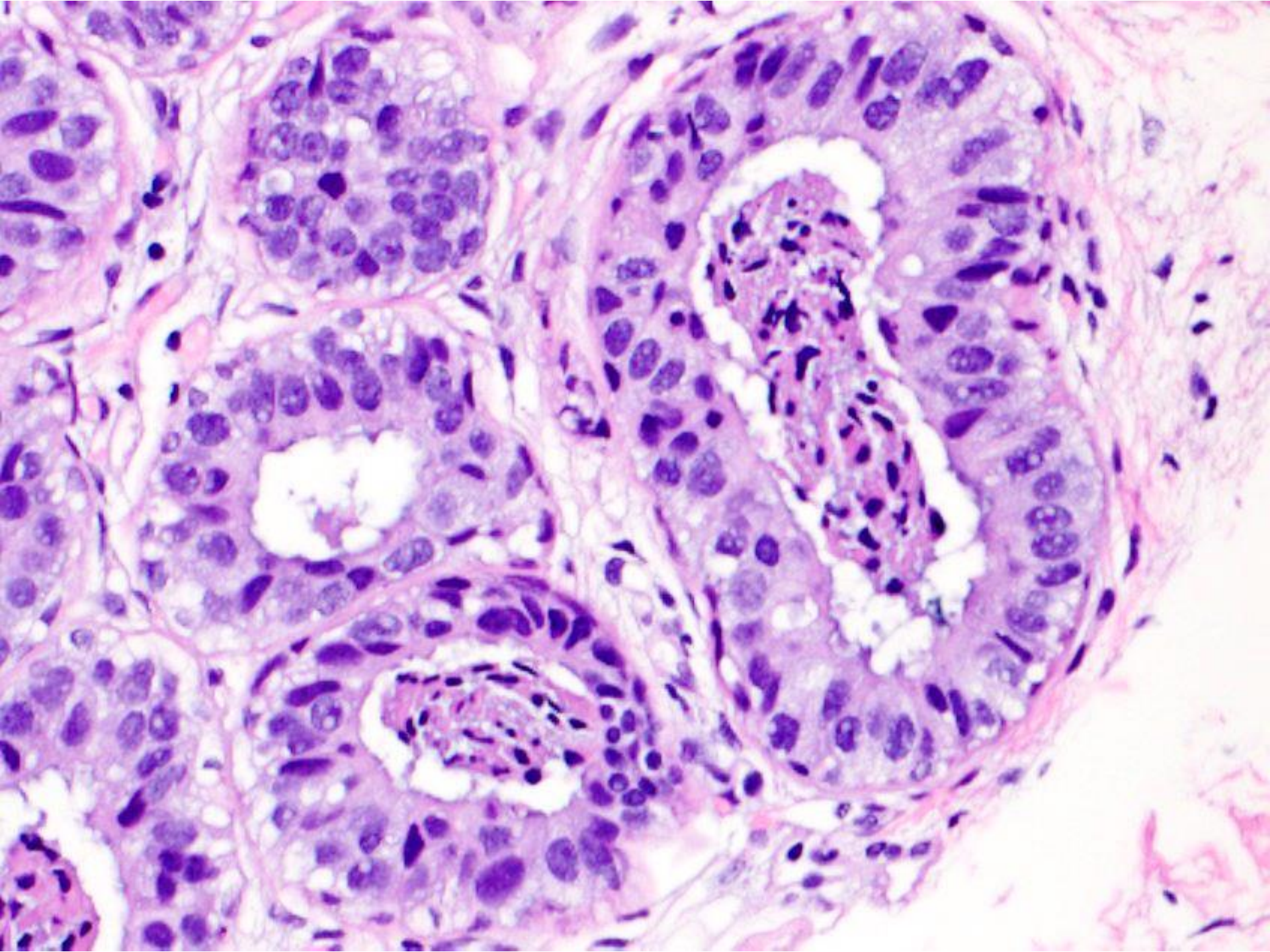


DCIS, high nuclear grade



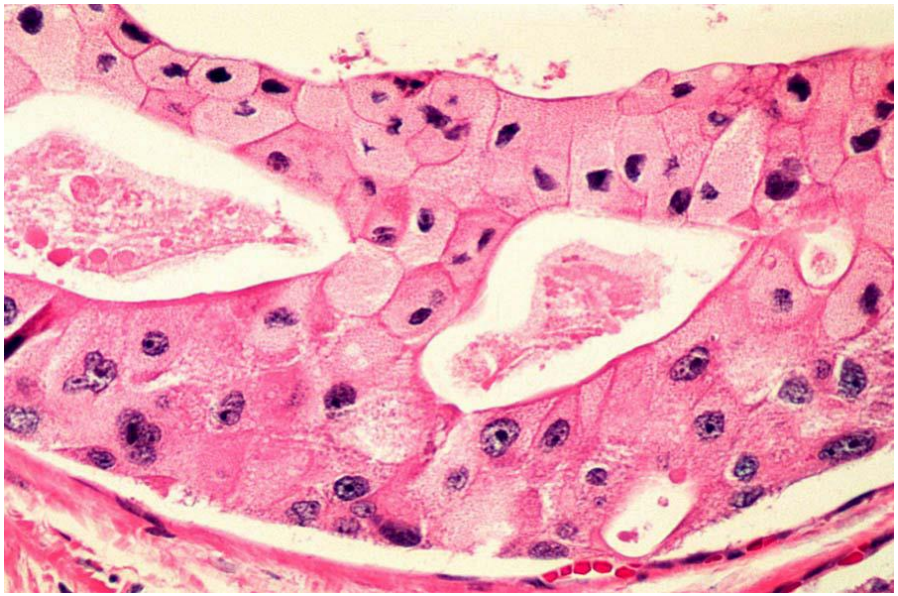
DCIS, intermediate to high nuclear grade Clinging pattern

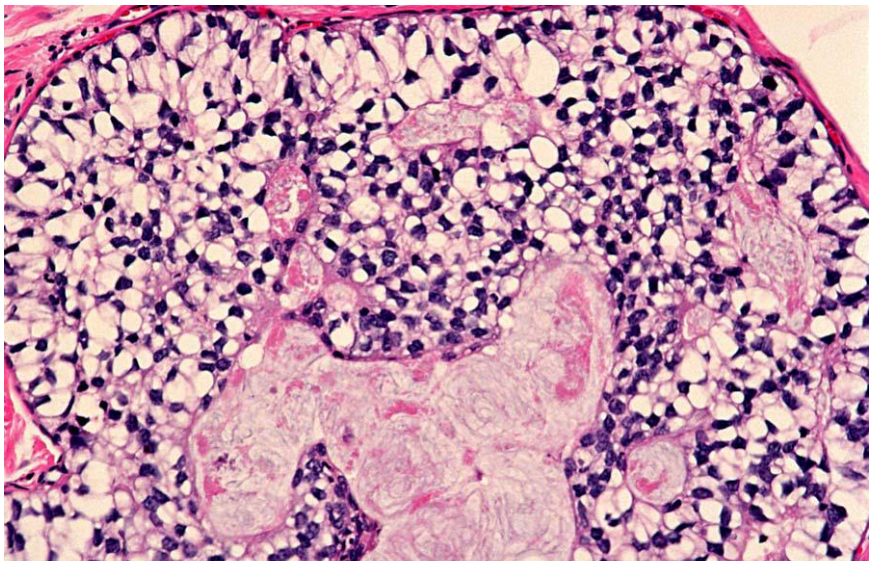




Unusual variants of DCIS

- Apocrine
- Signet ring
- Neuroendocrine
- Spindled, squamous or clear cells





Biomarkers in DCIS (ER/PR)

- ER is the only validated biomarker for routine clinical practice in DCIS
- Distribution of receptor expression is similar to that of invasive cancer (75-80% pos nuclear staining <1-100% cells)
- Tamoxifen reduces ipsilateral risk of DCIS recurrence and or progression to invasive carcinoma in 50% of cases treated with lumpectomy and XRT (benefit restricted to pts with ER positive DCIS)

Lobular Neoplasia (LN)

Definition

Lobular neoplasia (LN) refers to the entire spectrum of atypical epithelial lesions originating in the TDLU and characterized by a proliferation of generally small, loosely cohesive cells

Designation of ALH and LCIS is widely used to describe the variable extent of proliferation/ involvement of individual TDLU

LN

- 0.5-4% of benign breast biopsies
- Predominantely in premenopausal women (average age 49 yrs)
- Multicentric, 85%
- Bilateral in up to 60%
- No specific clinical features for LN

LN: Relative risk for subsequent development of invasive carcinoma

4-12 X that of woman without LN

Variations due to differences in length of F/U, which LN lesions were included (ALH alone, LCIS alone or both) and lack of complete path review

Approximately 2/3 of subsequent carcinomas occur in the ipsilateral breast

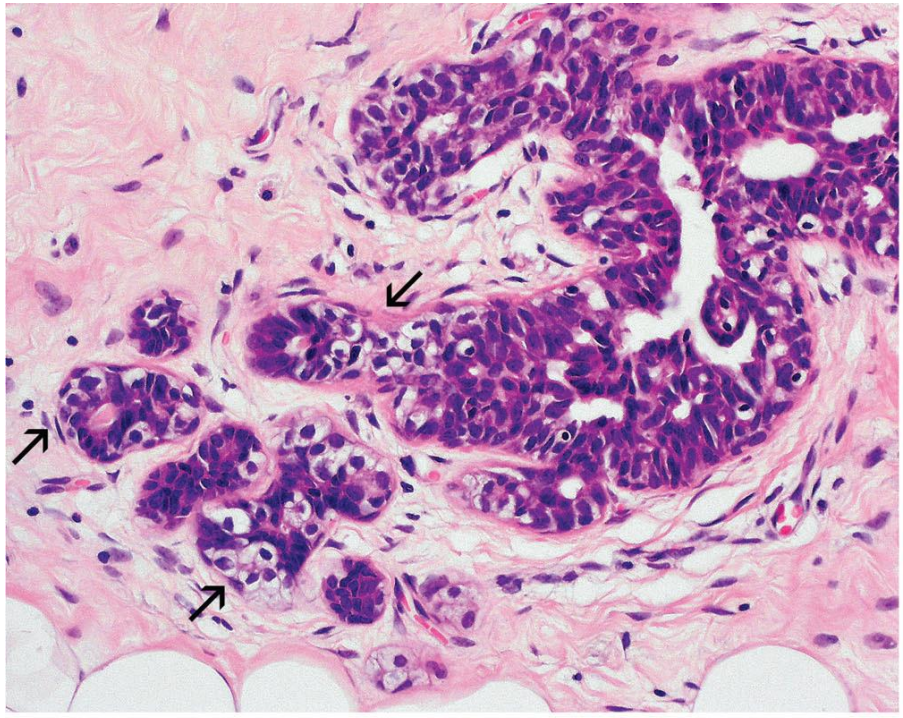
LN-Histopathology

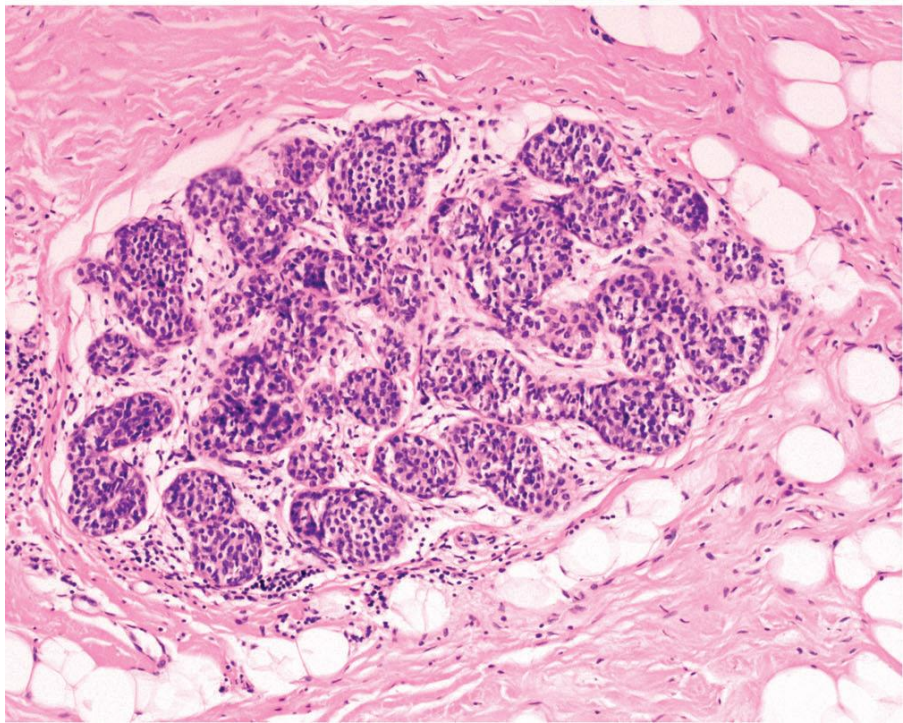
- Monomorphic proliferation of dyshesive cells, with uniform round nuclei, indistinct nucleoli, uniform chromatin and scant cytoplasm.
- Intracytoplasmic lumina often present.
- May have a pagetoid involvement of terminal ducts
- LN may involve a variety of lesions: SA, RS, PL, FA and may be associated with collagenous spherulosis

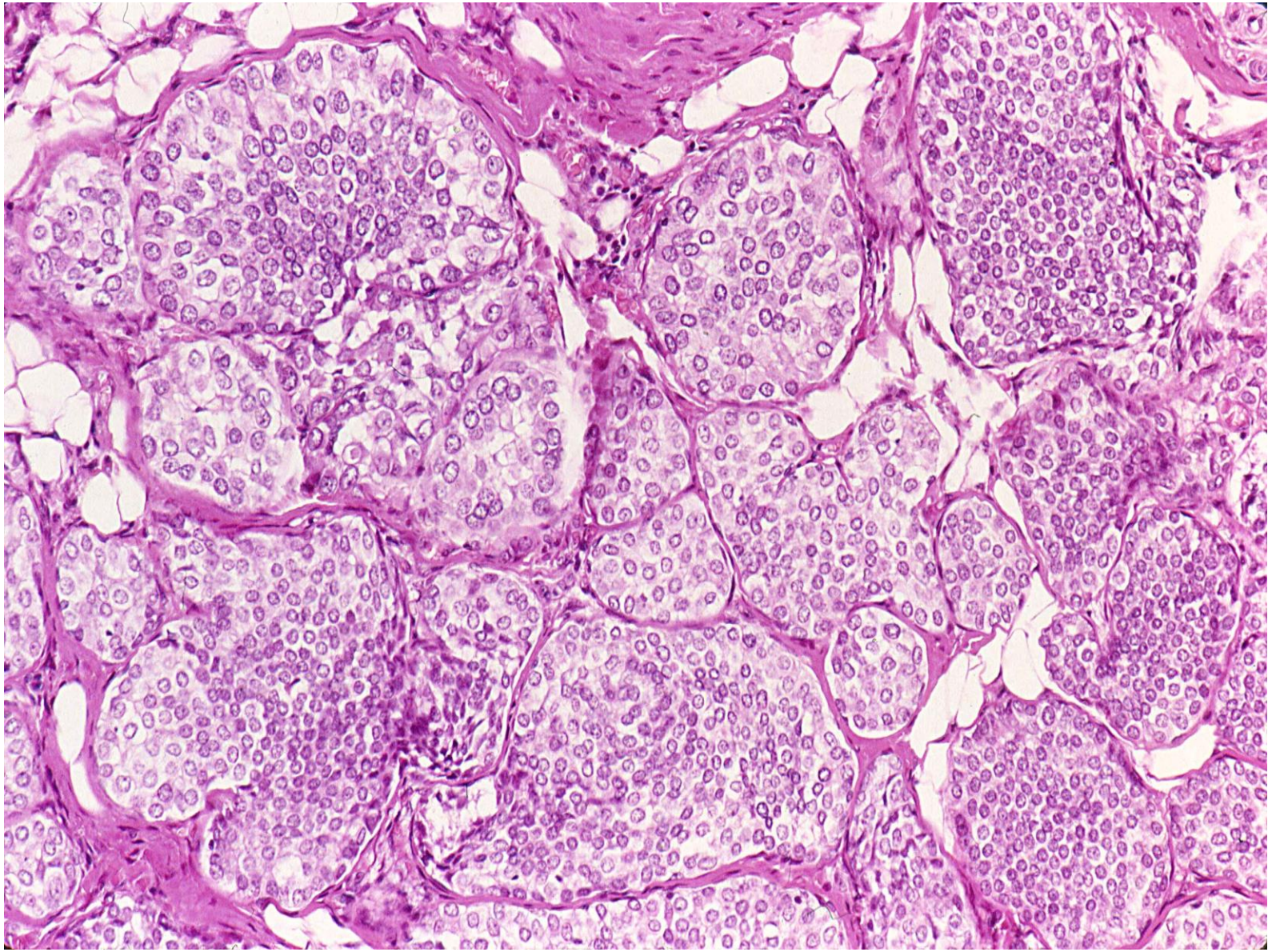
ALH vs LCIS (WHO)

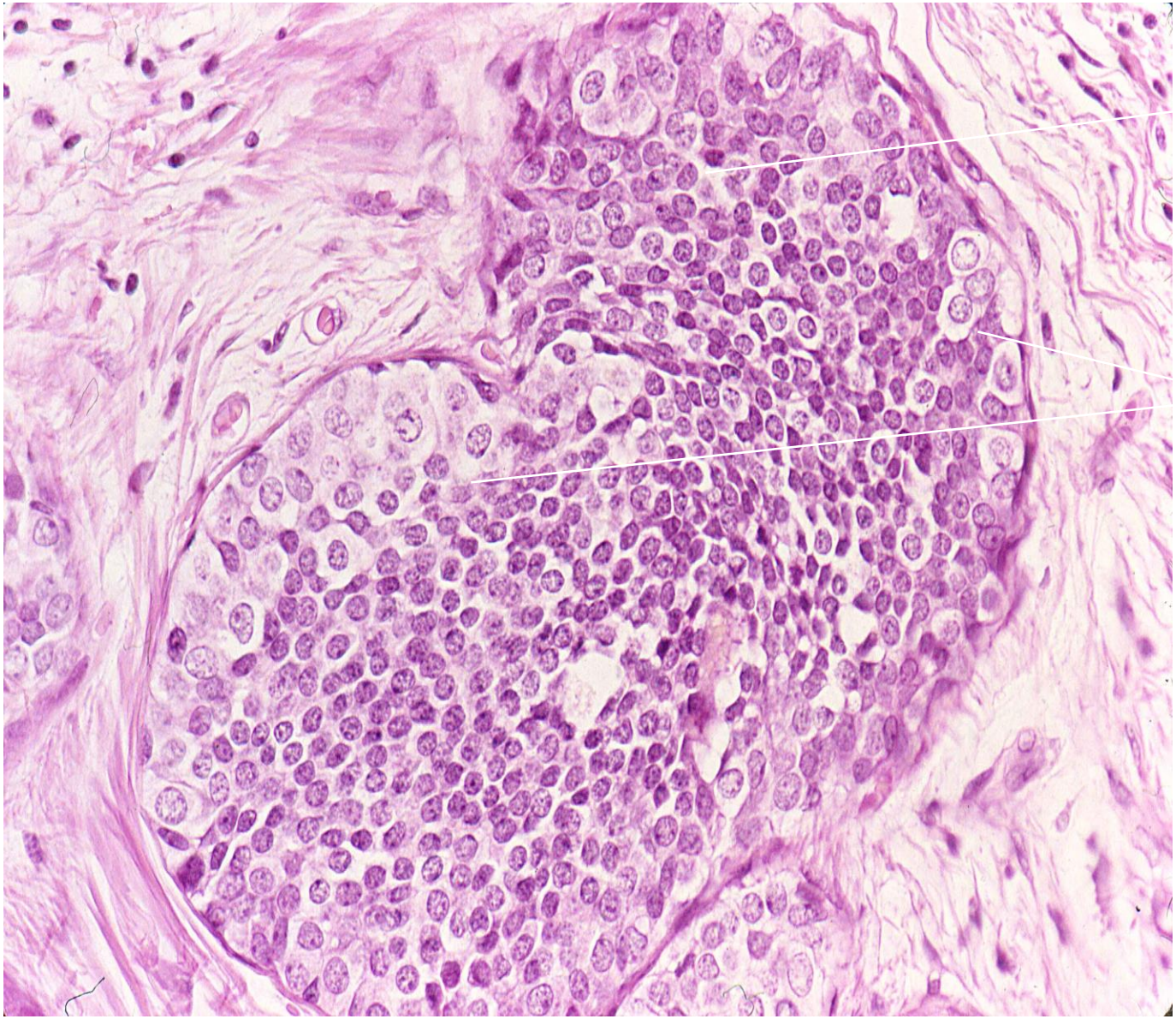
LCIS: requires more than one half of the spaces in a given lobule be filled with and distended by the characteristic cells.

Cases with lesser degree of involvement are given the diagnosis of ALH









LCIS classic type

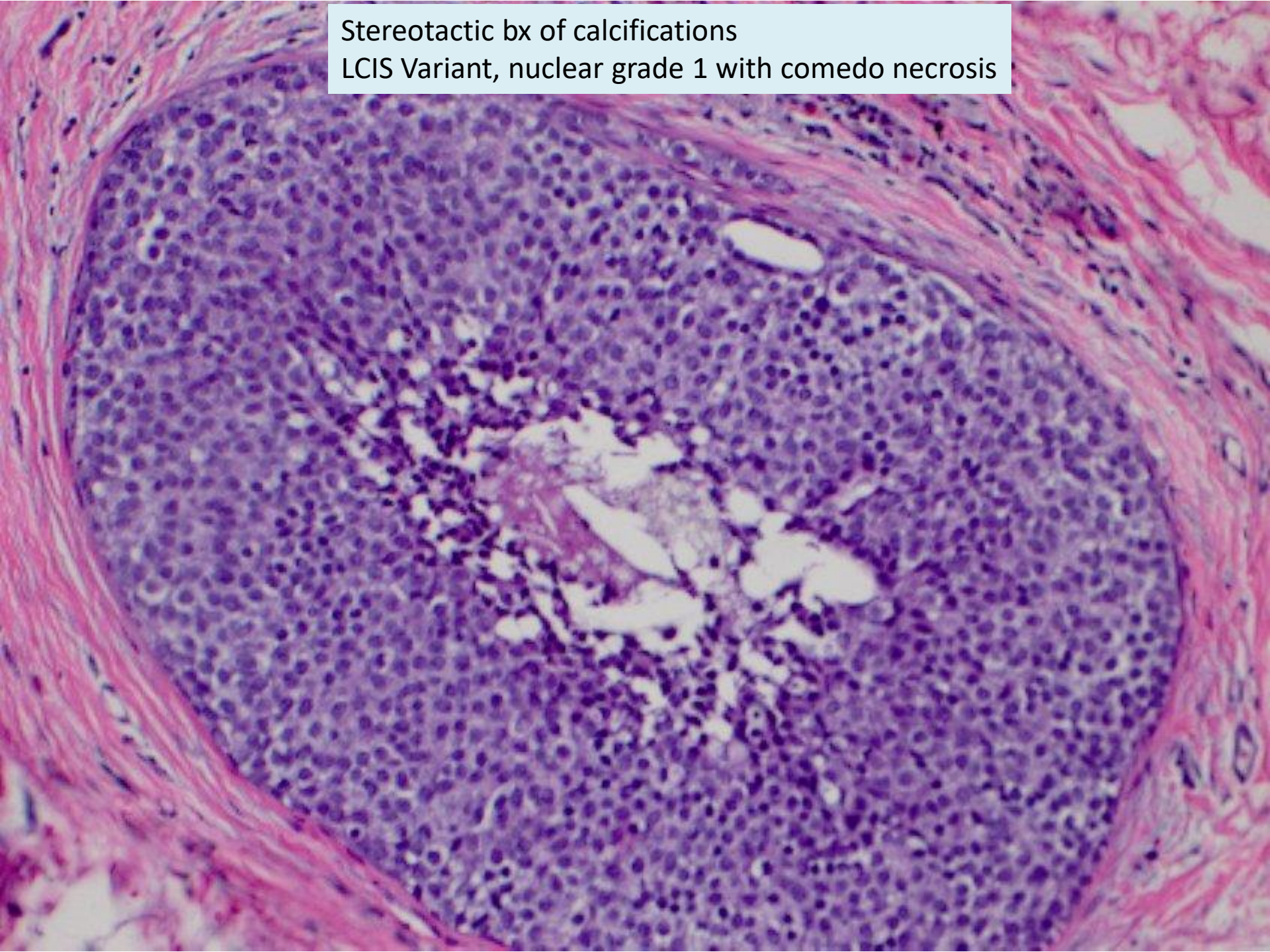
LCIS Variants

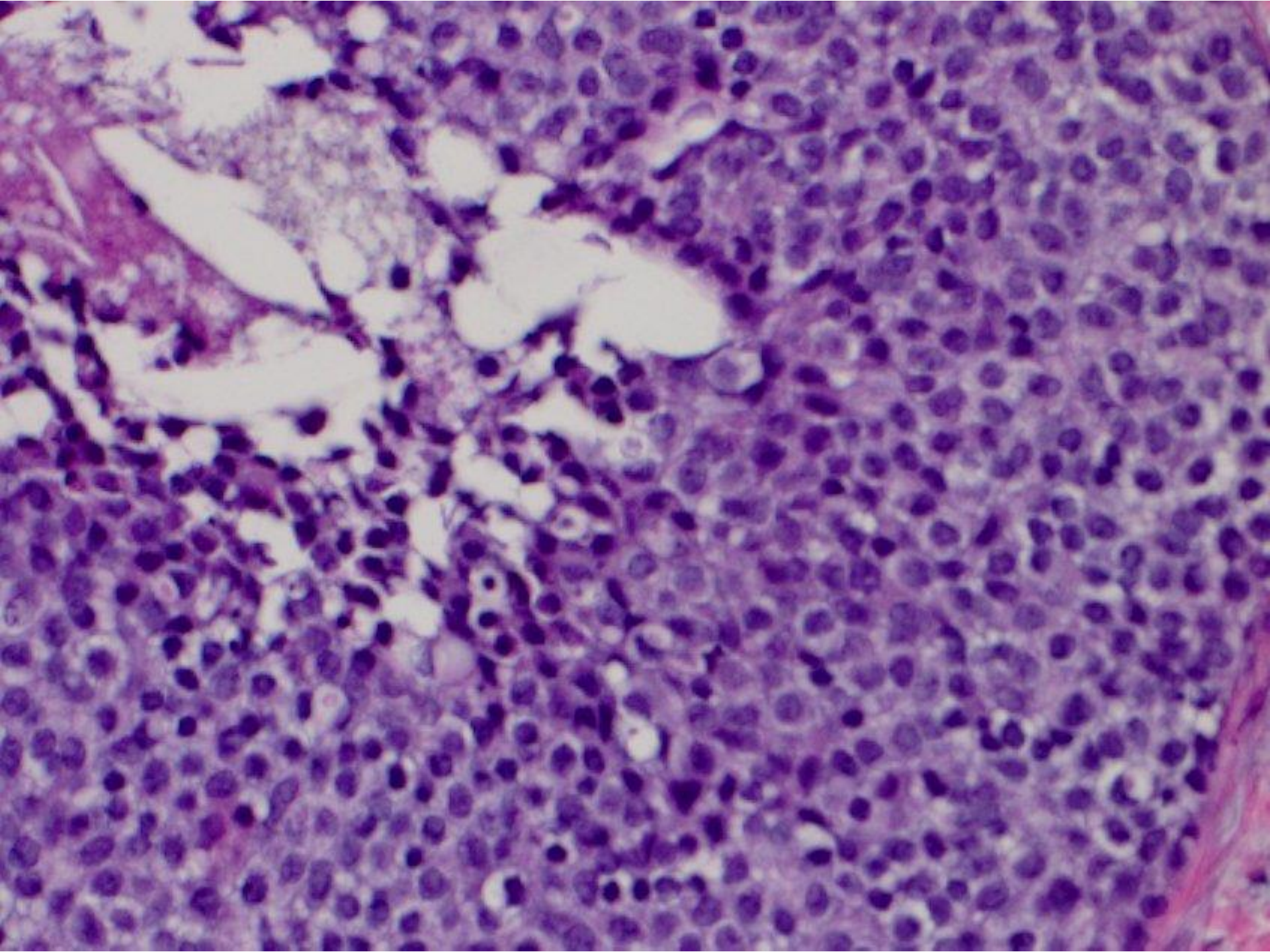
Mammographically detected lesions:

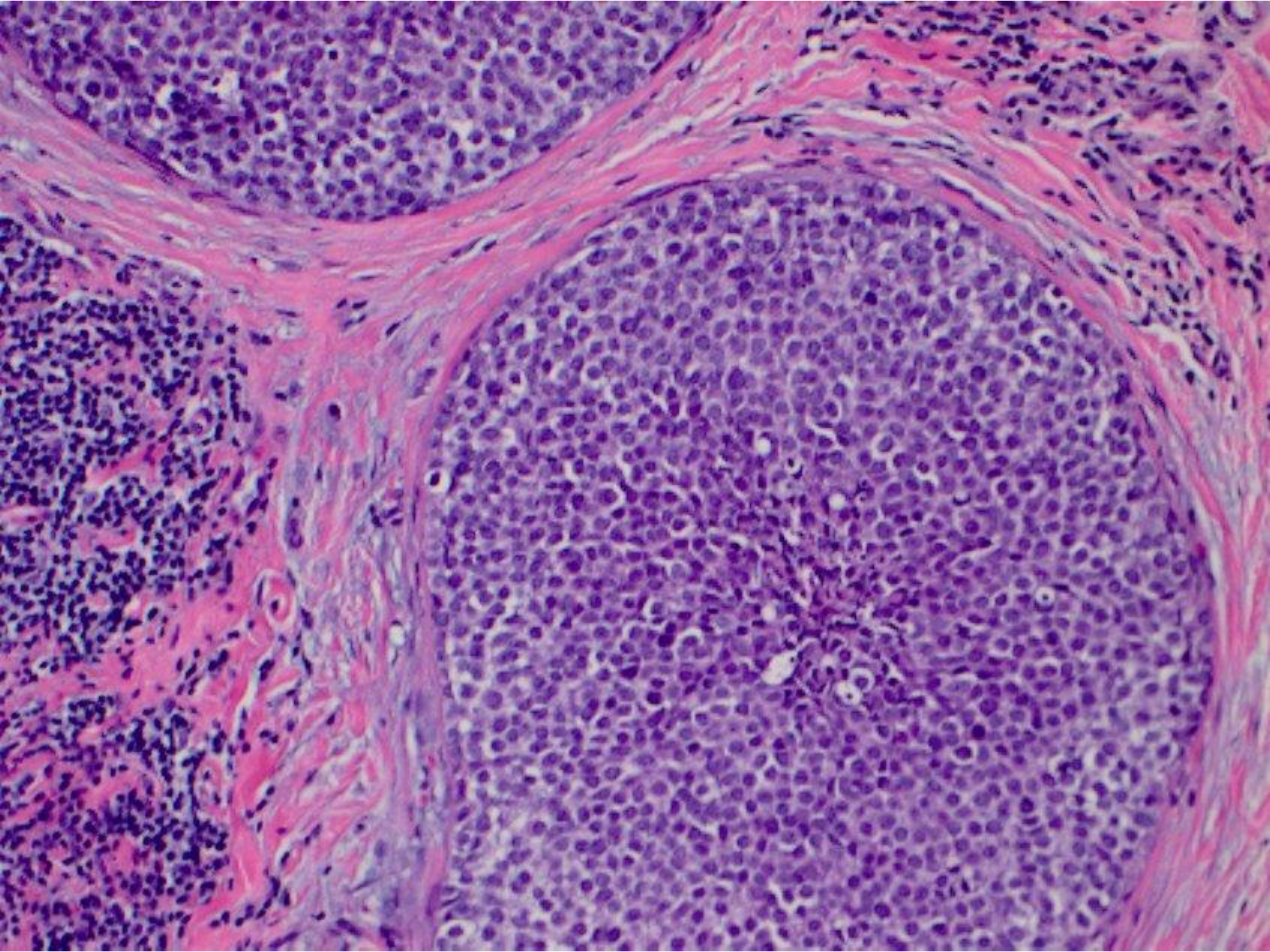
1. Classic LCIS (type A or B) cells with marked distention of involved spaces with areas of comedo necrosis and calcifications

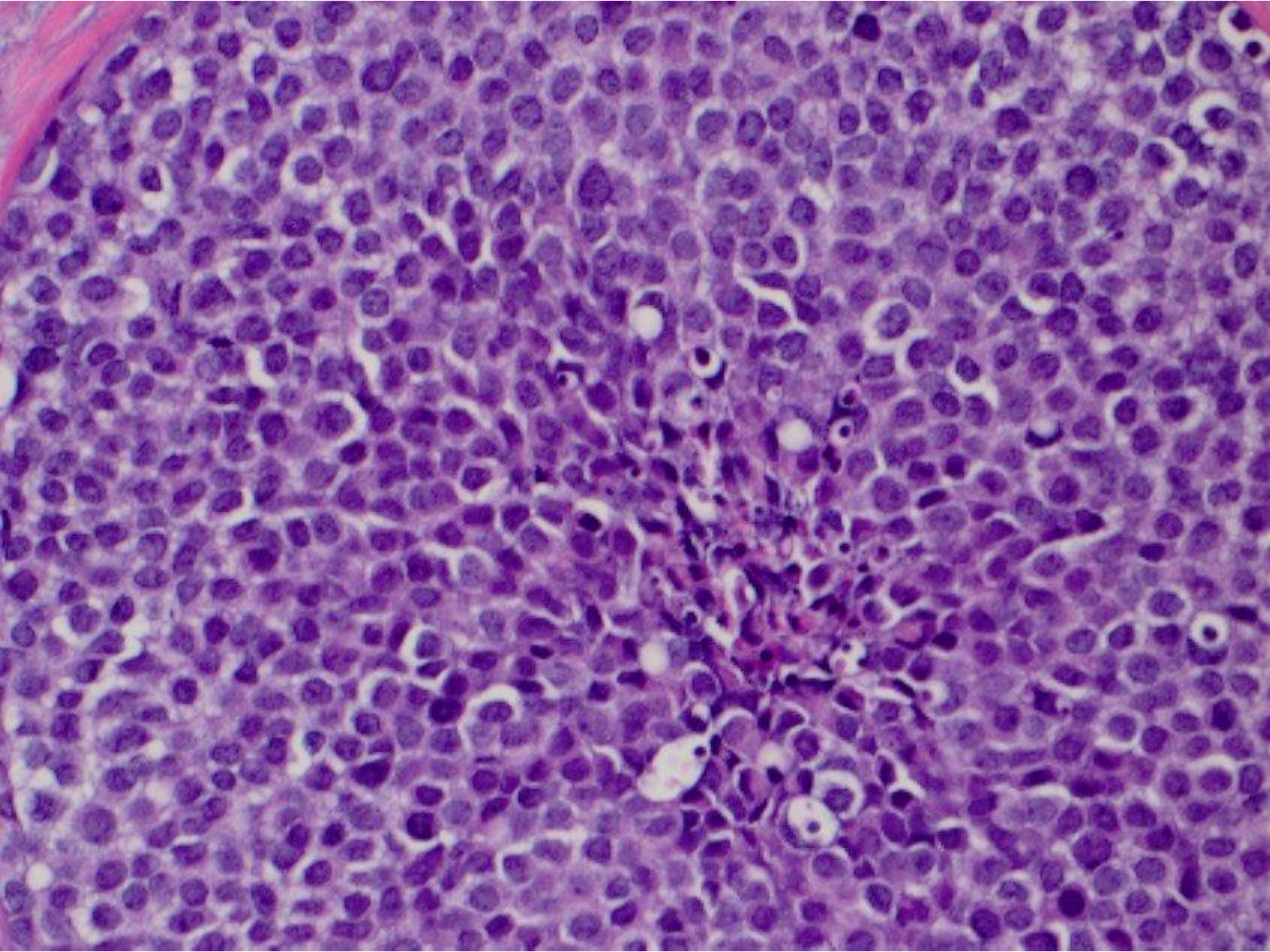
2. Pleomorphic cells with or without apocrine features and comedo necrosis

All lesions in this group lack E-cadherin expression and display genomic alterations by CGH typical of lobular lesions (16q loss and 1q gains)

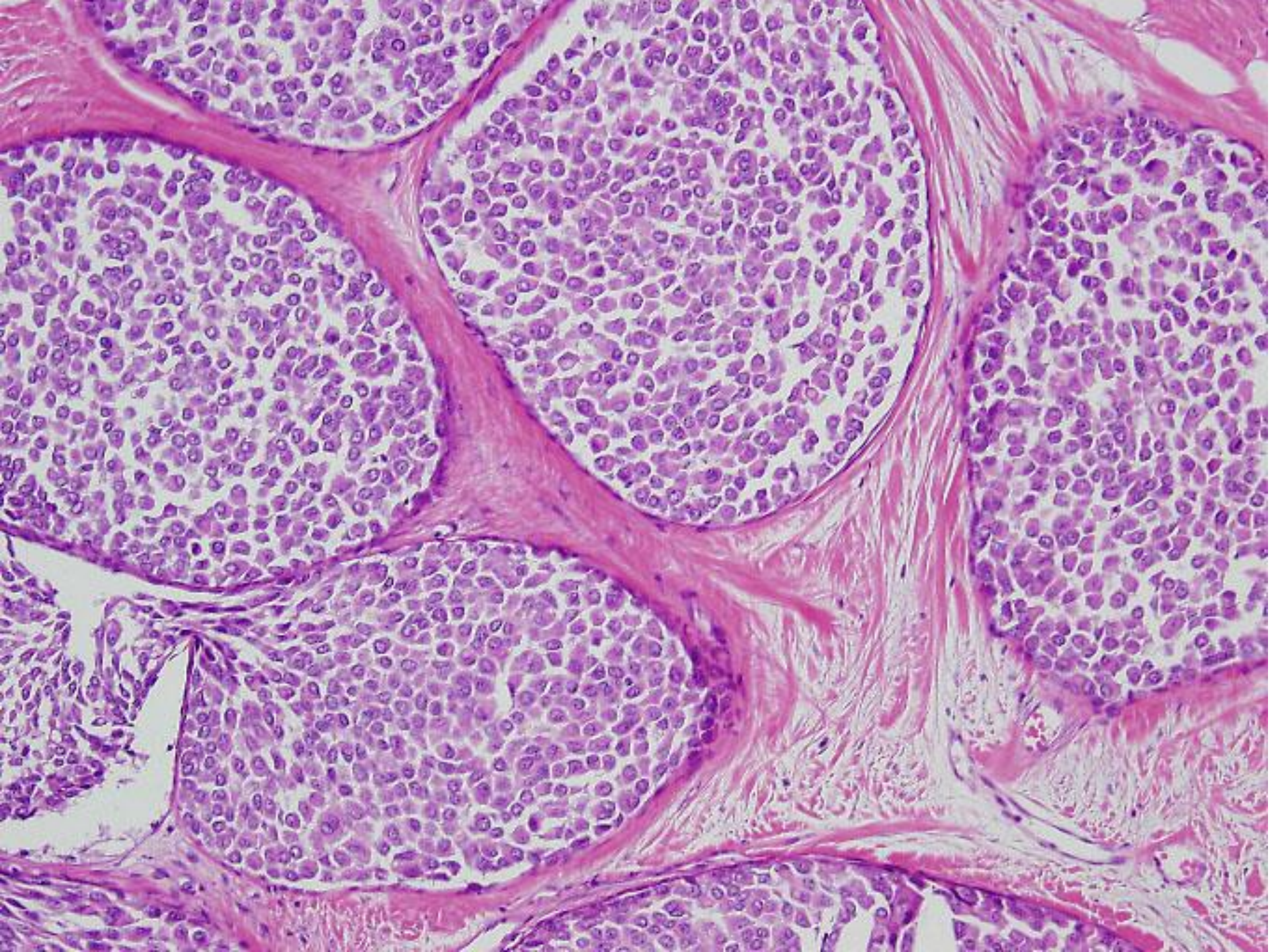

Stereotactic bx of calcifications
LCIS Variant, nuclear grade 1 with comedo necrosis

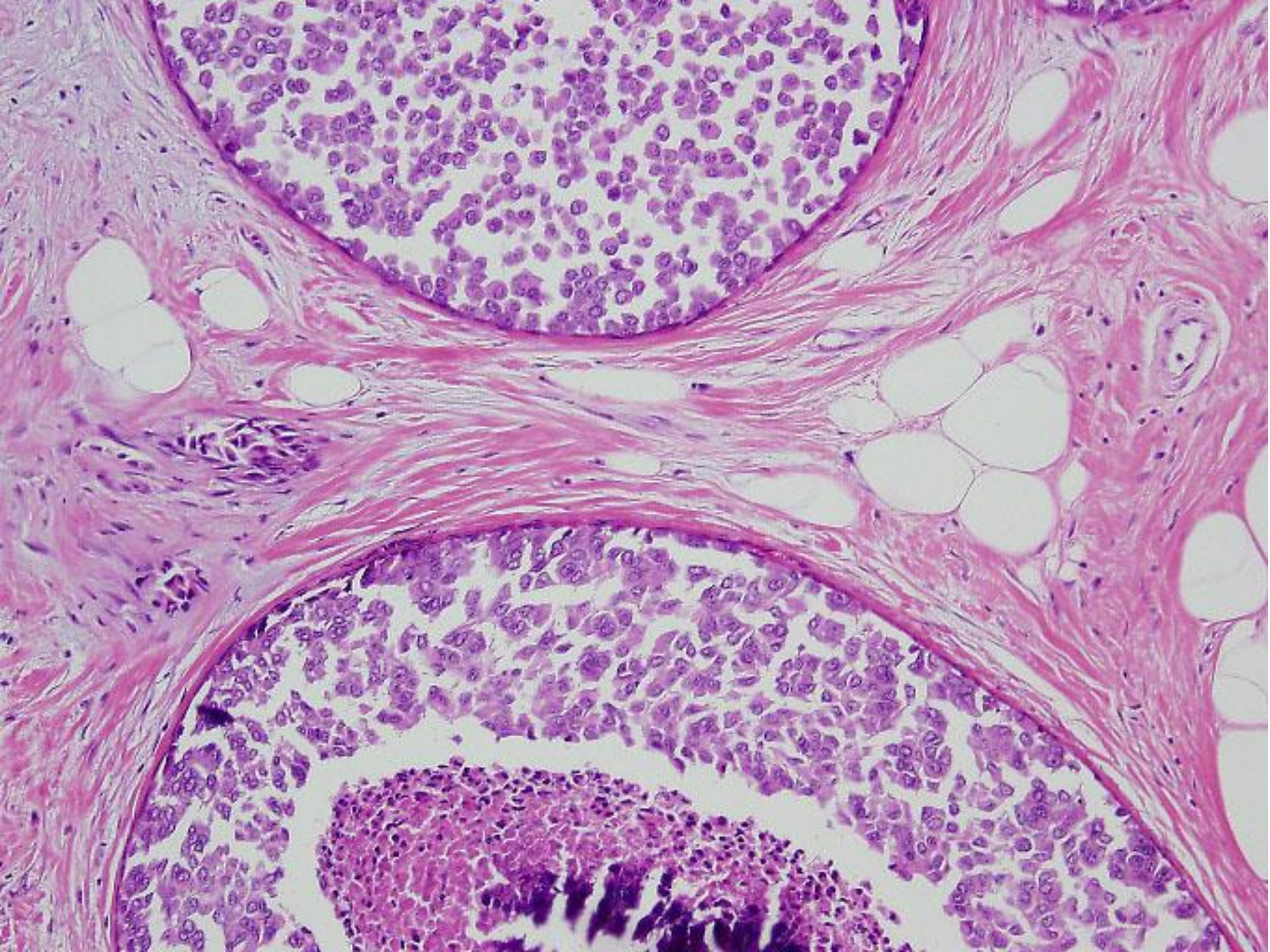


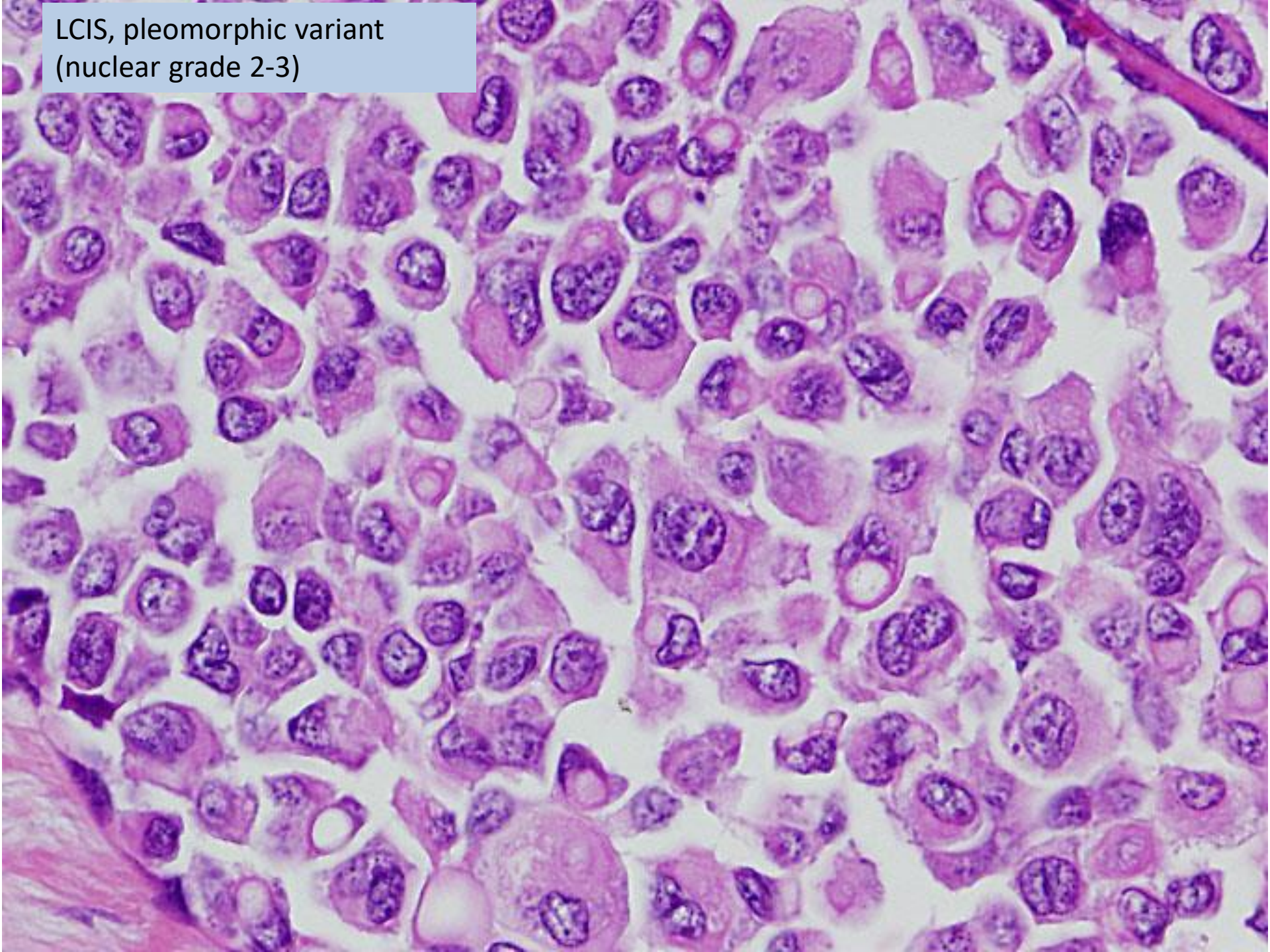


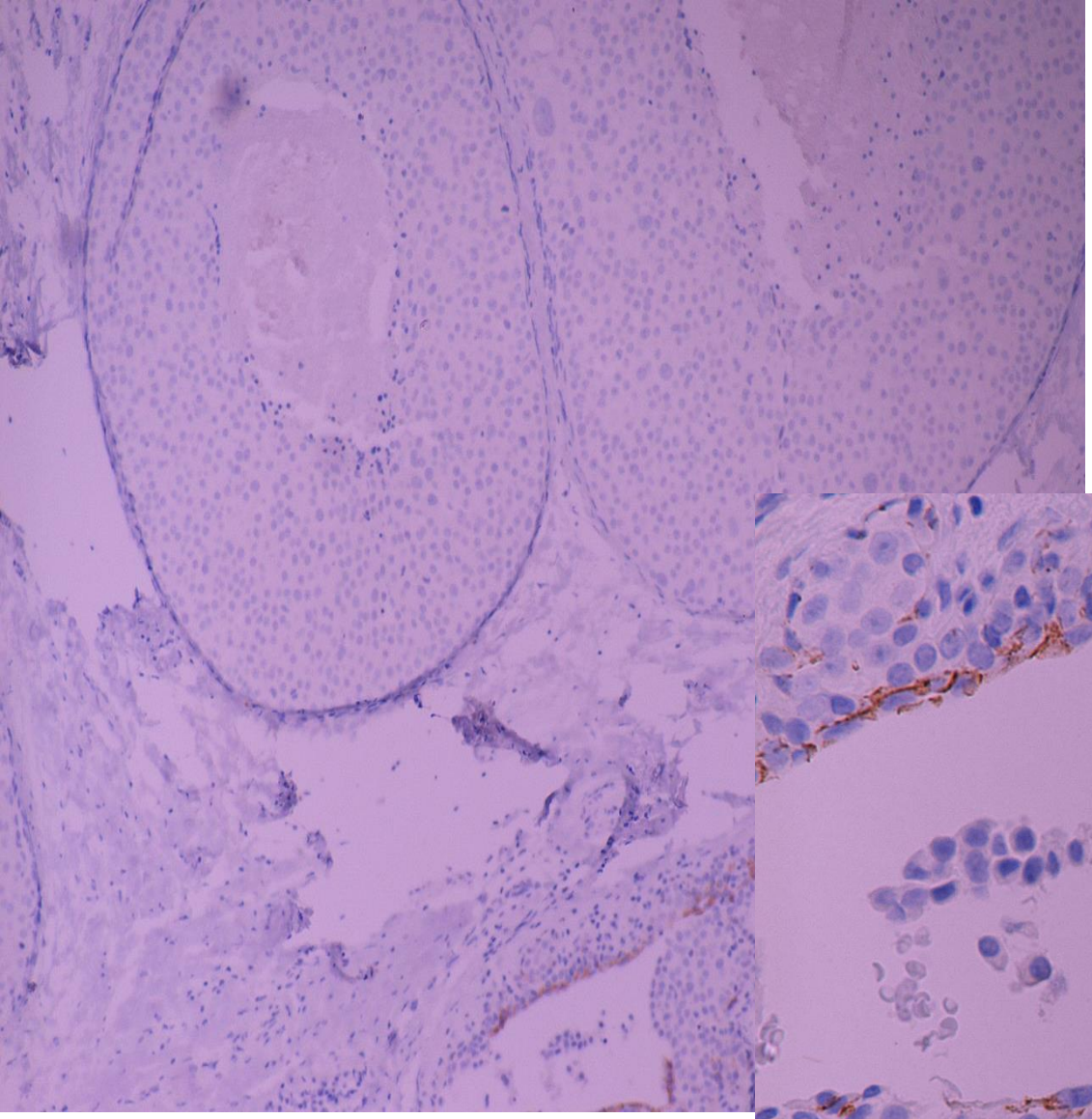


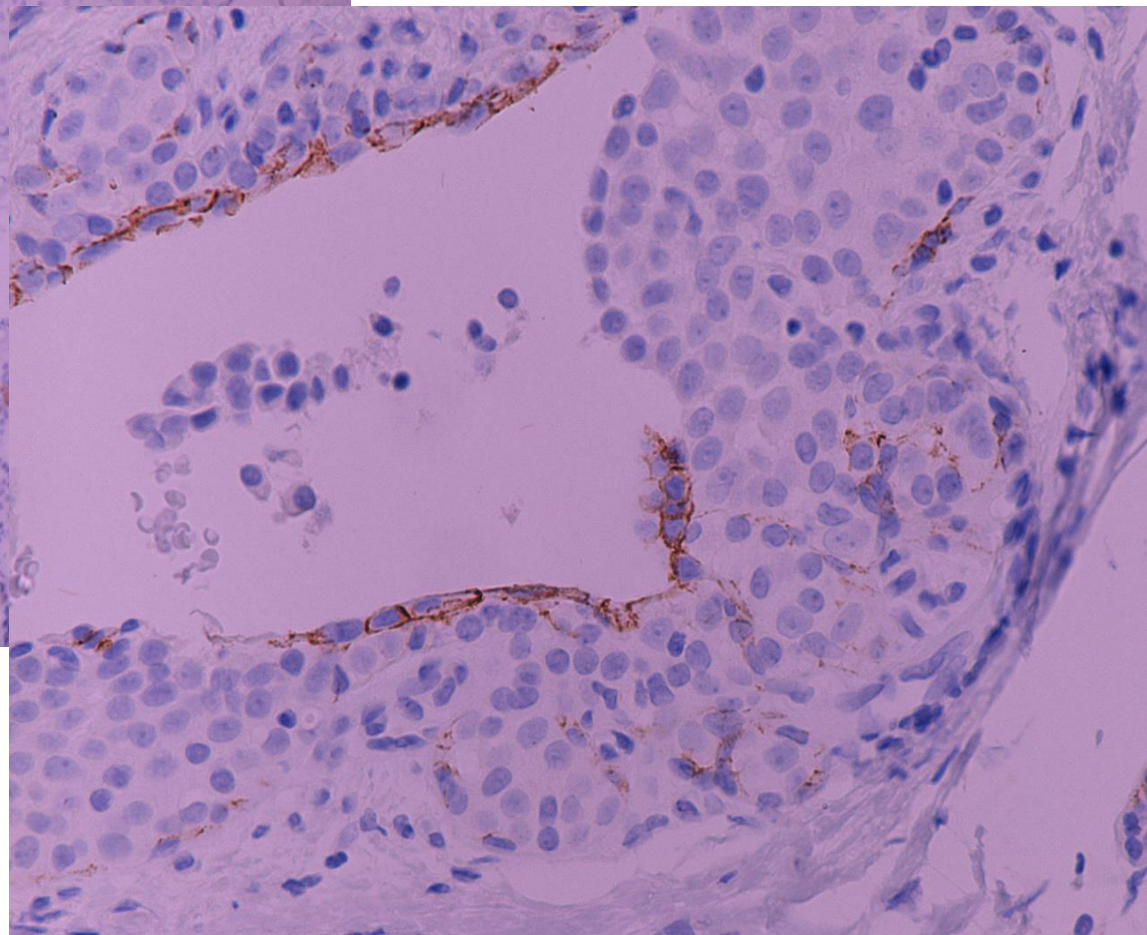
Stereo guided biopsy for microcalcs
Misdiagnosed as DCIS



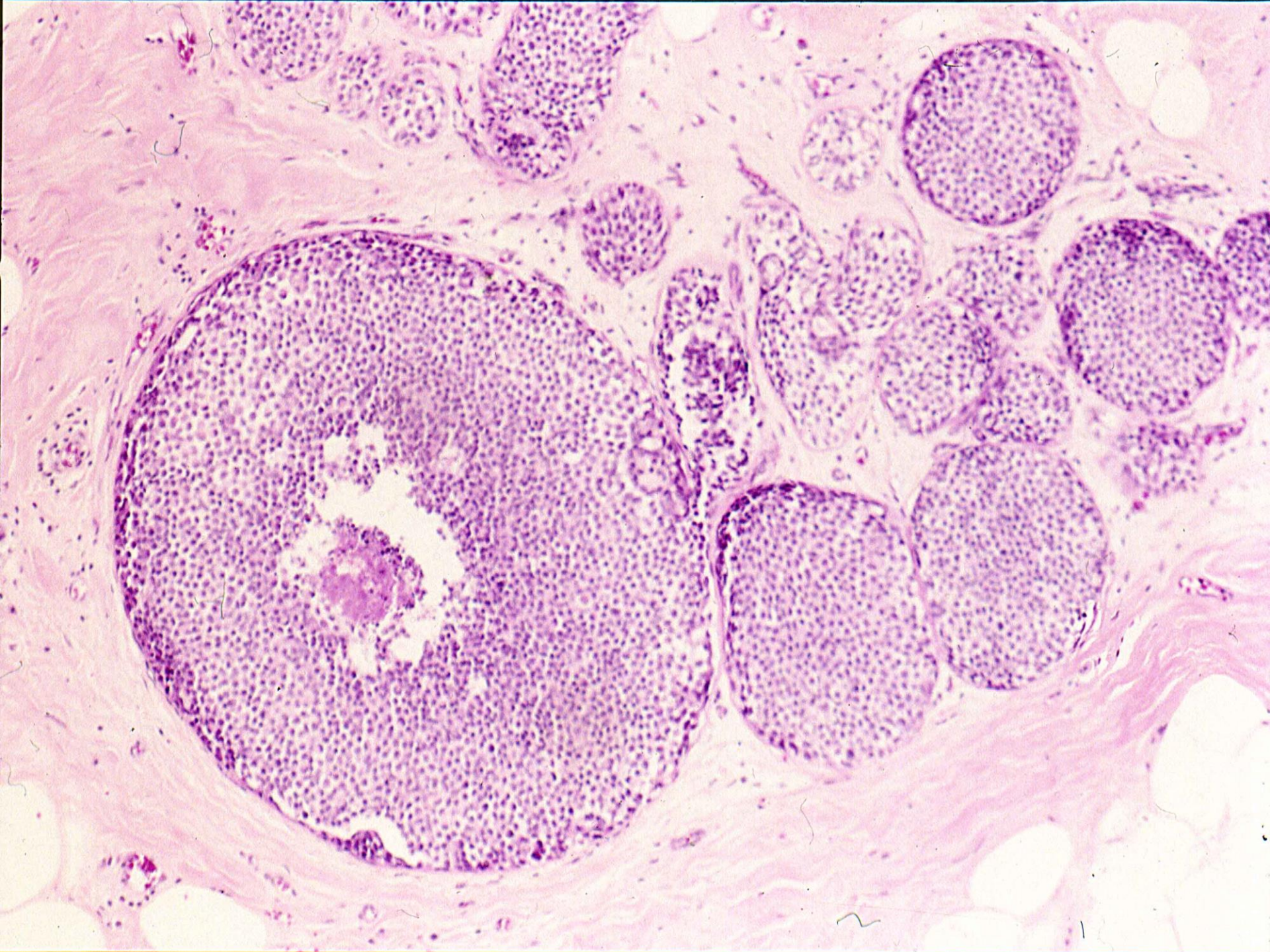


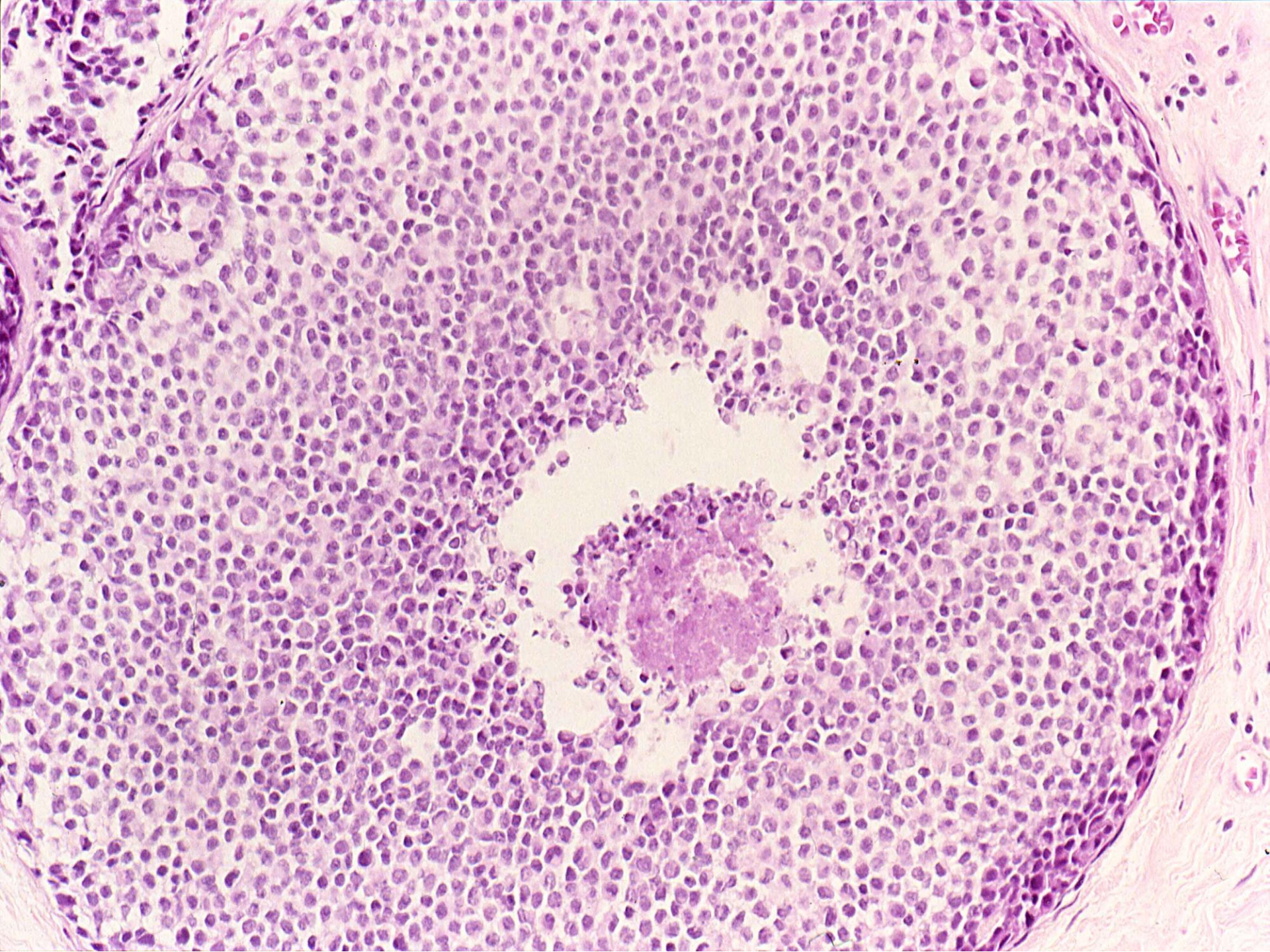

LCIS, pleomorphic variant
(nuclear grade 2-3)

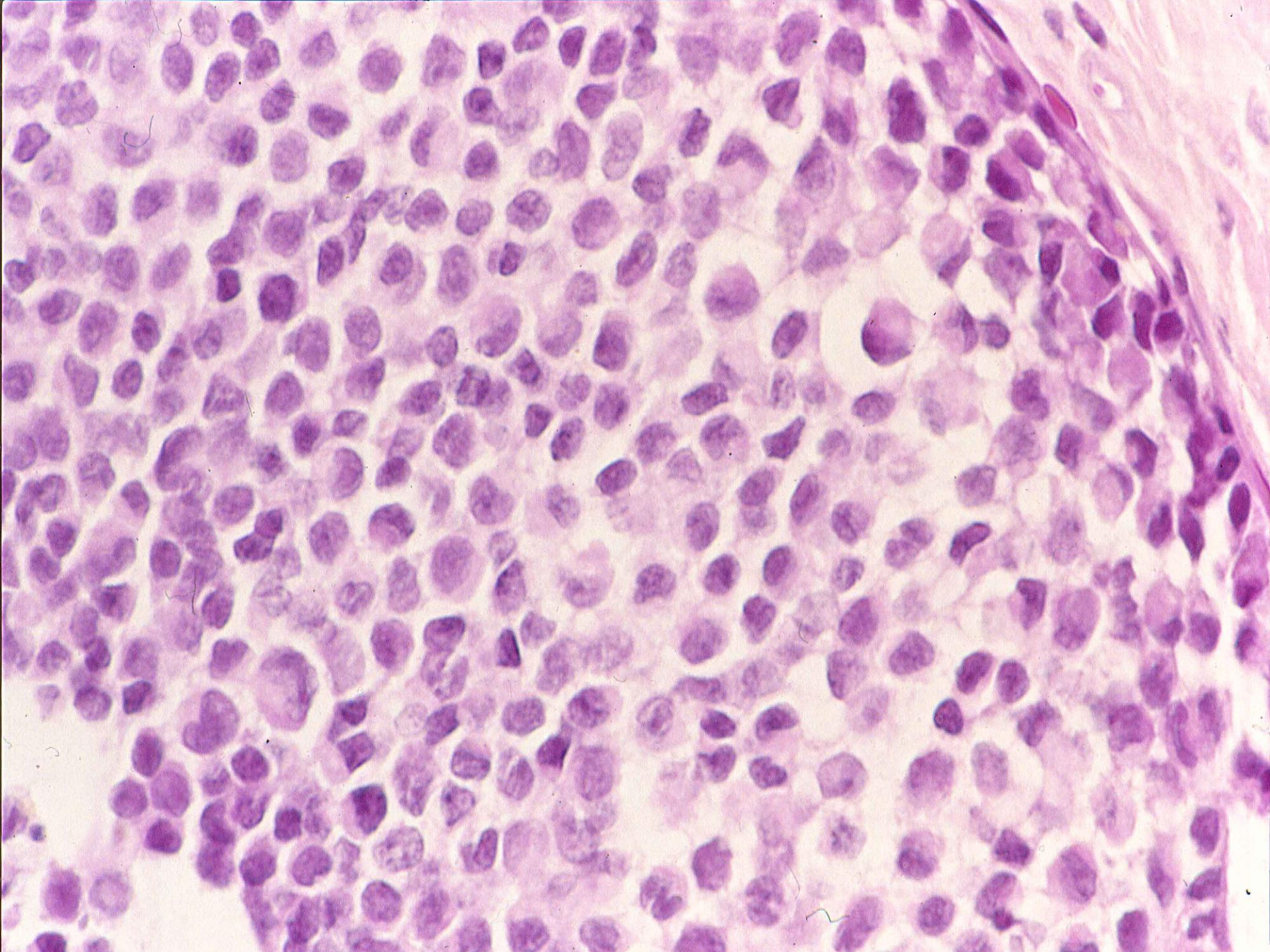


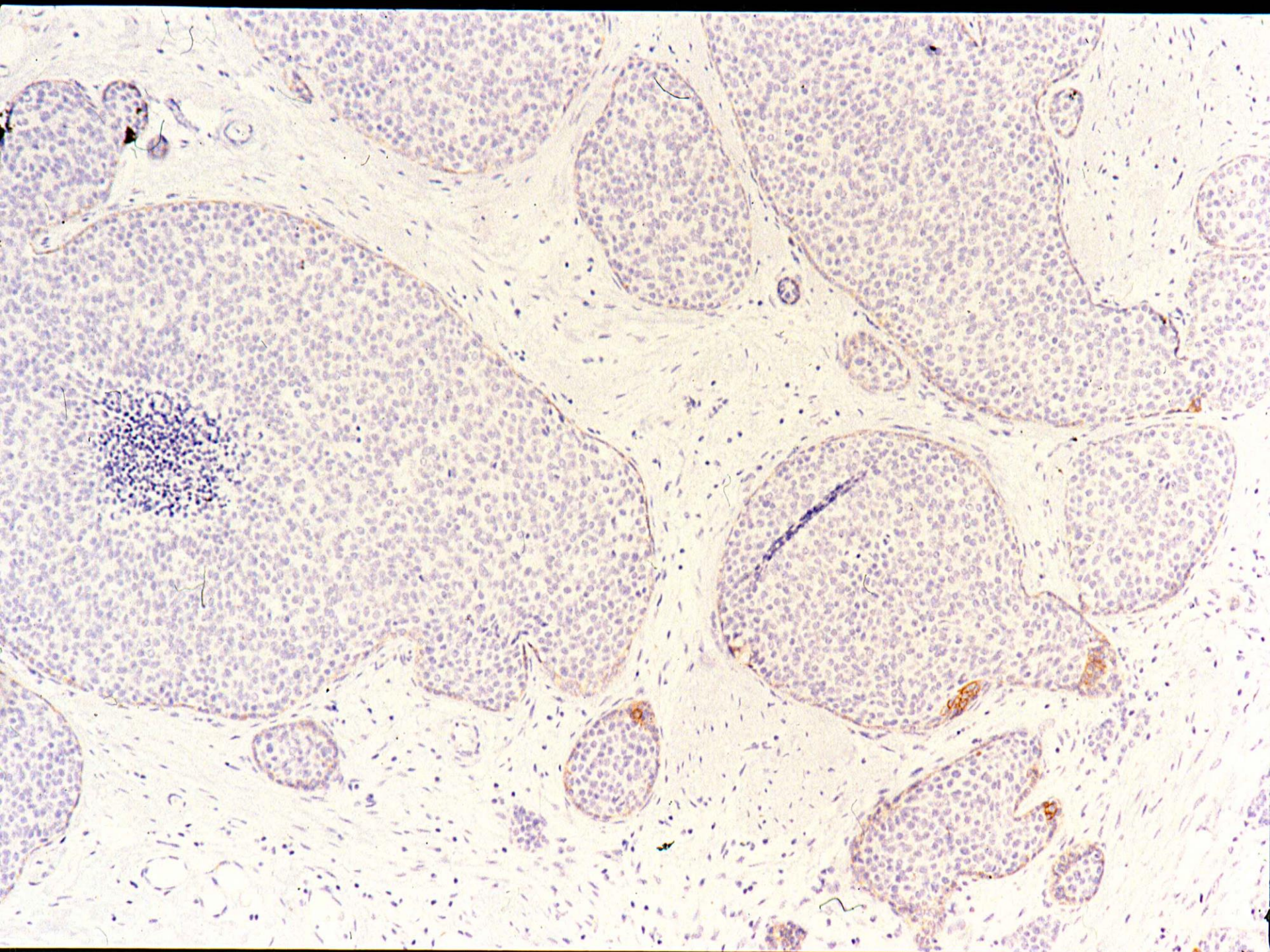


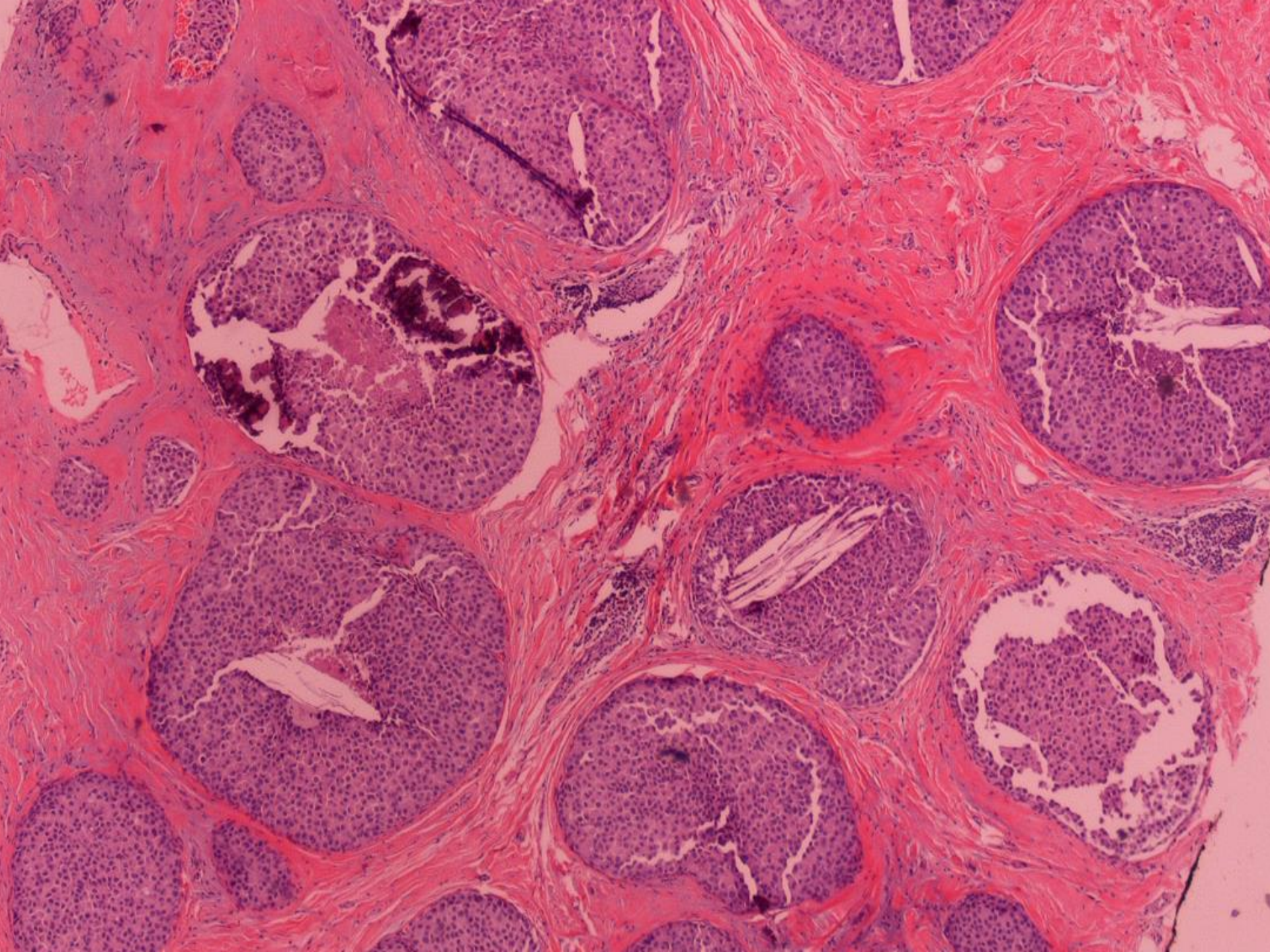
E-cadherin
negative

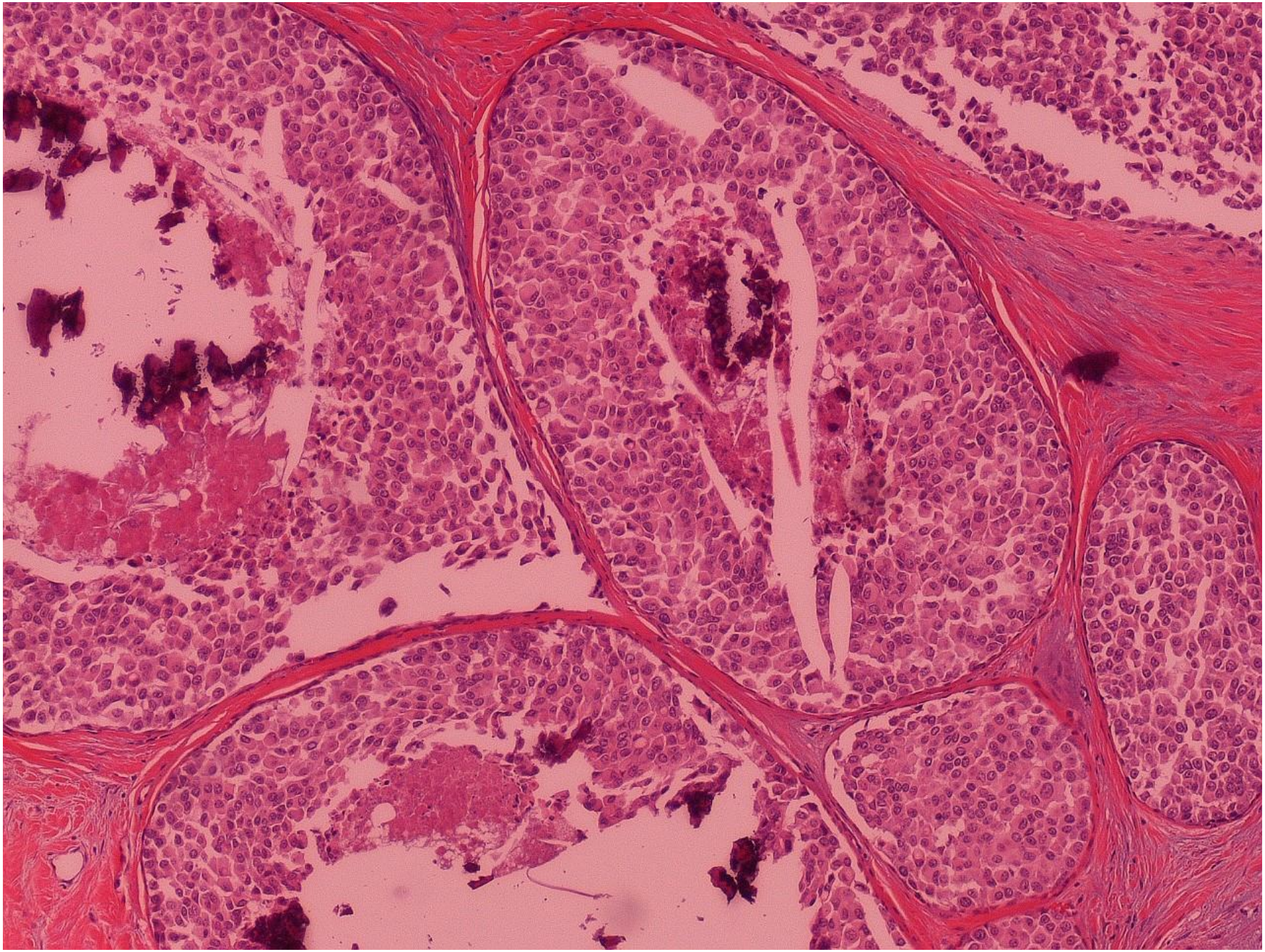


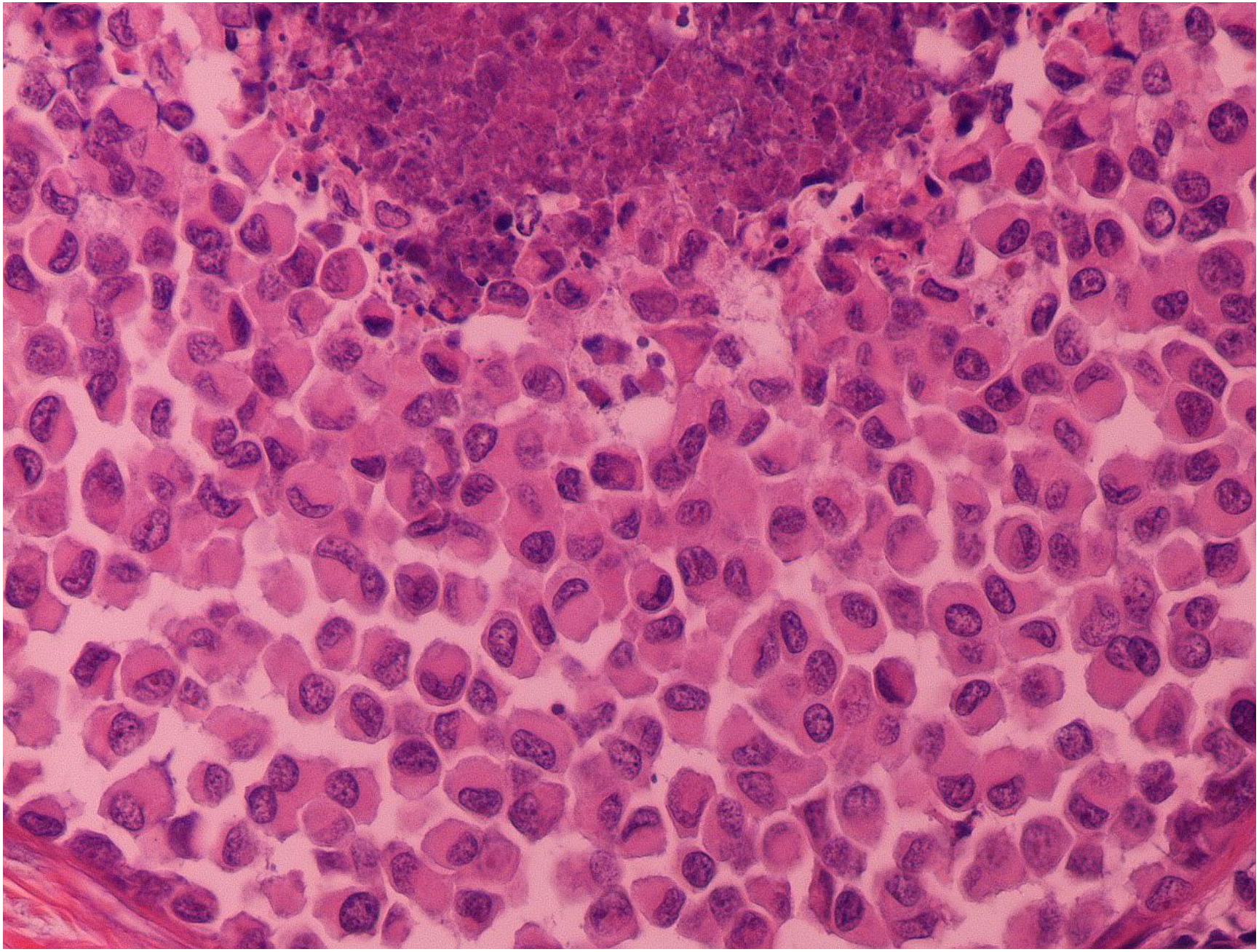


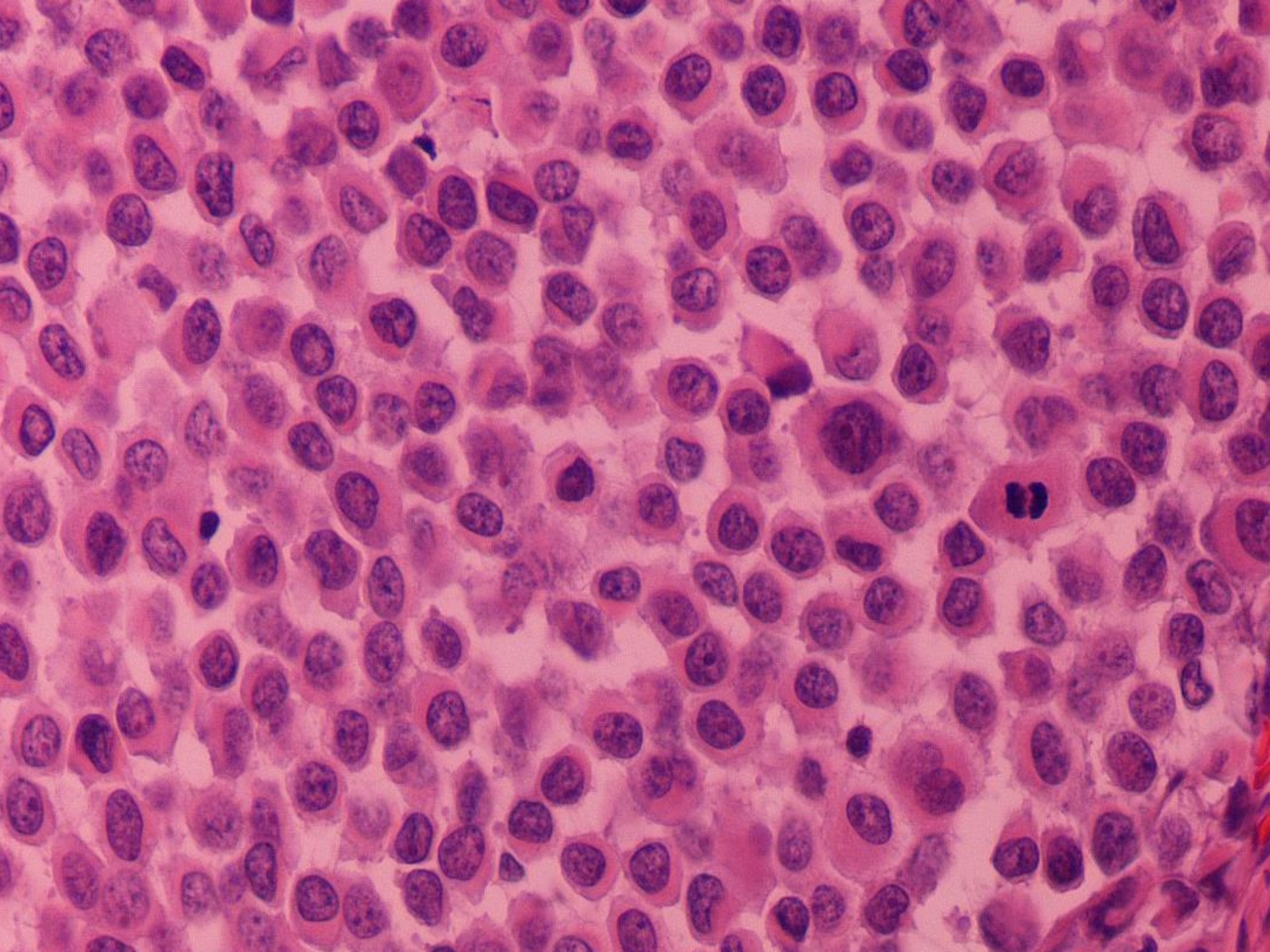


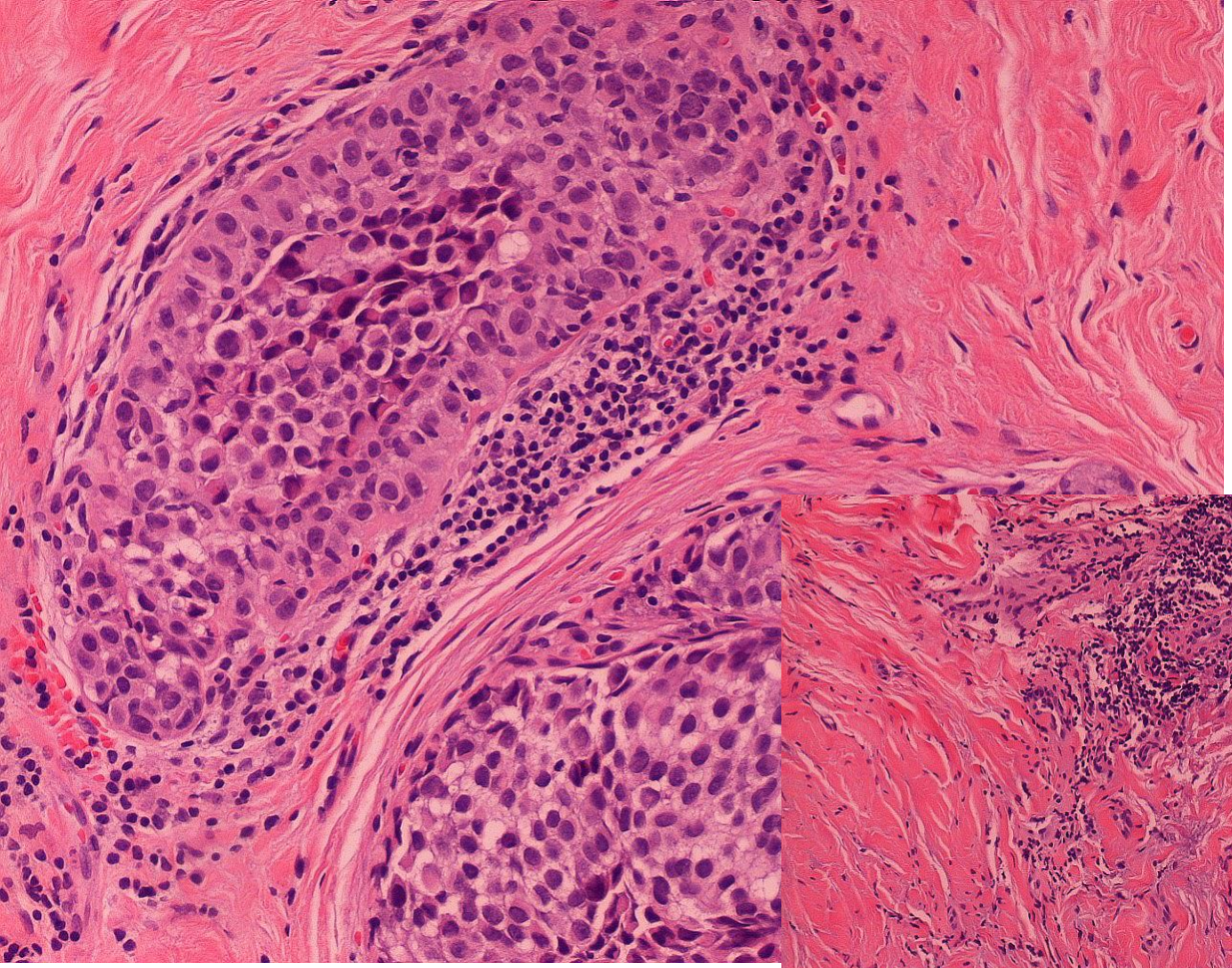


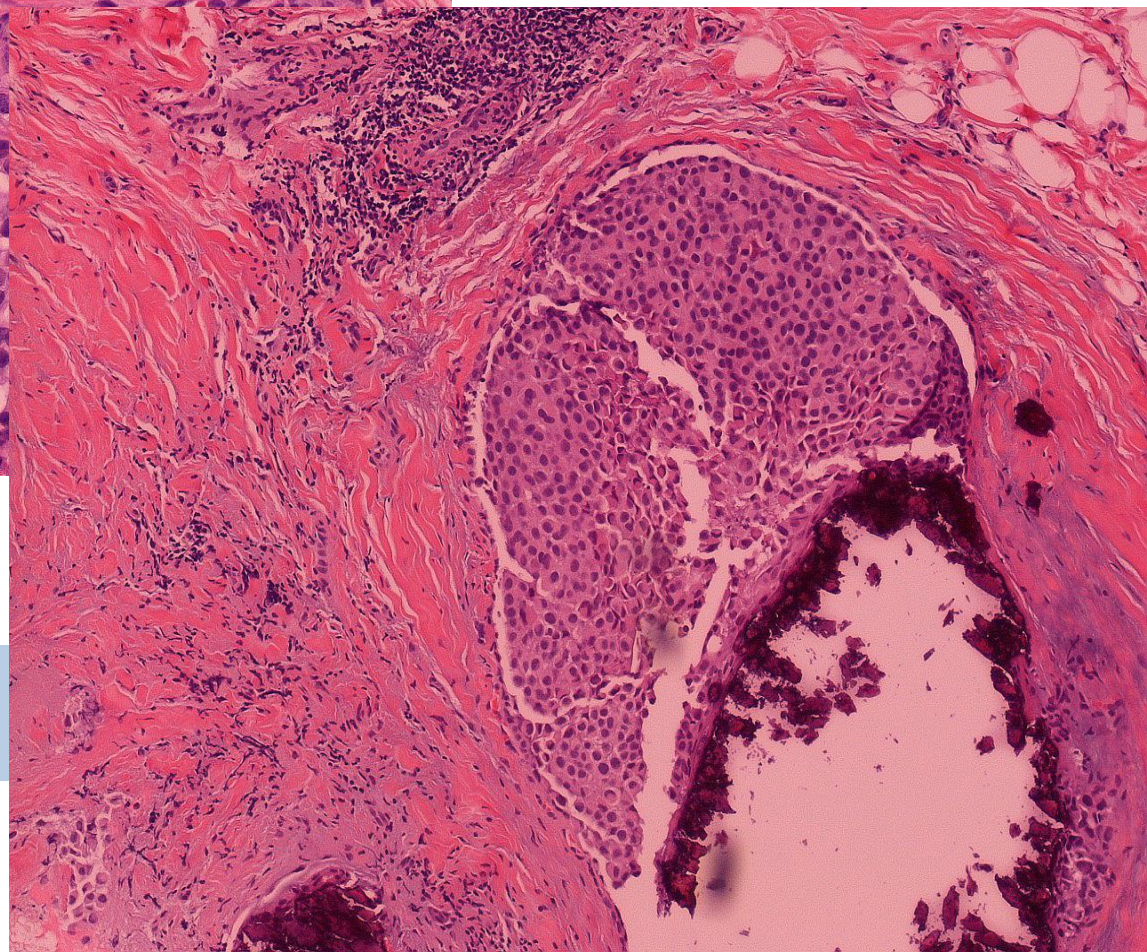




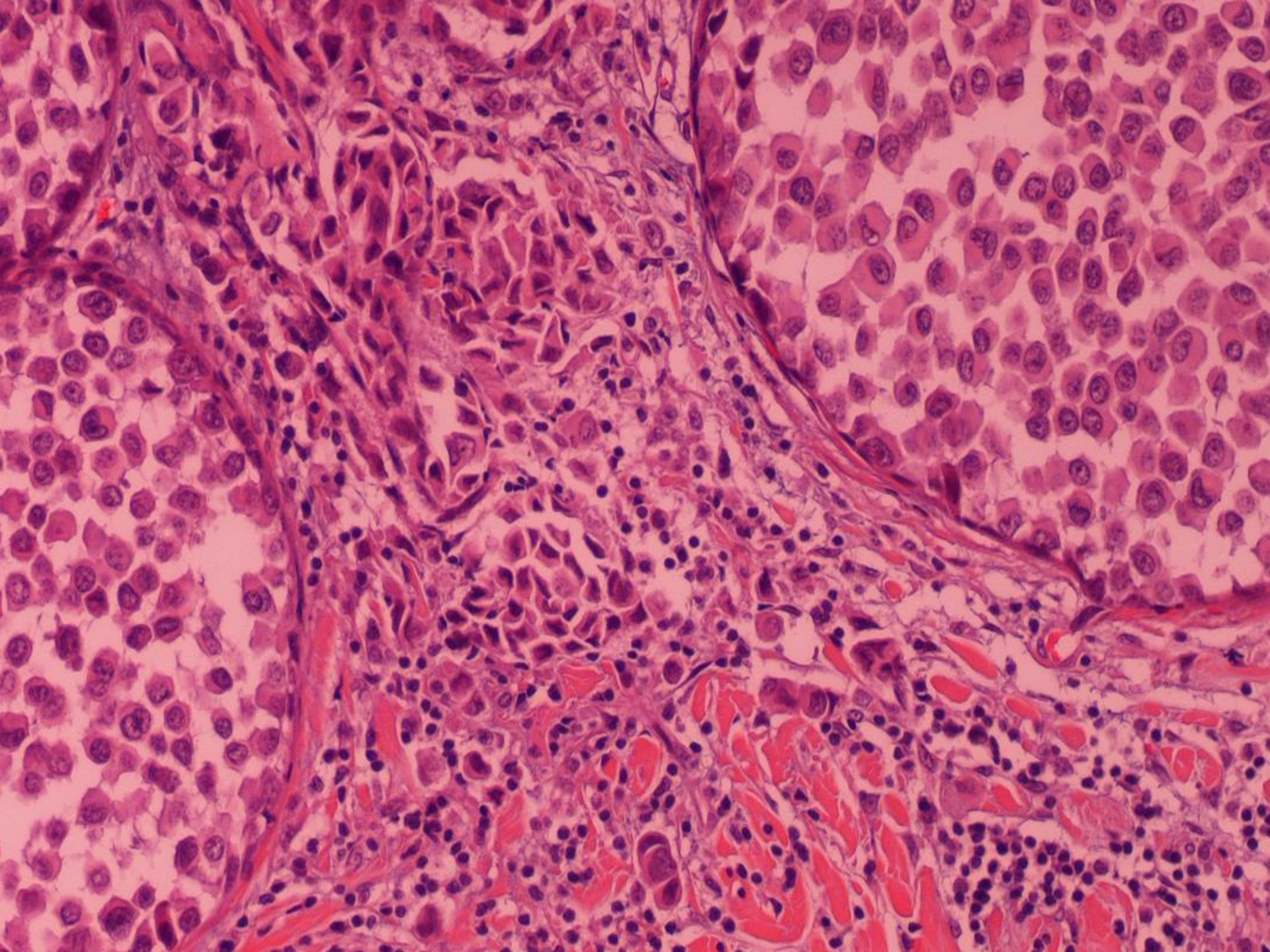


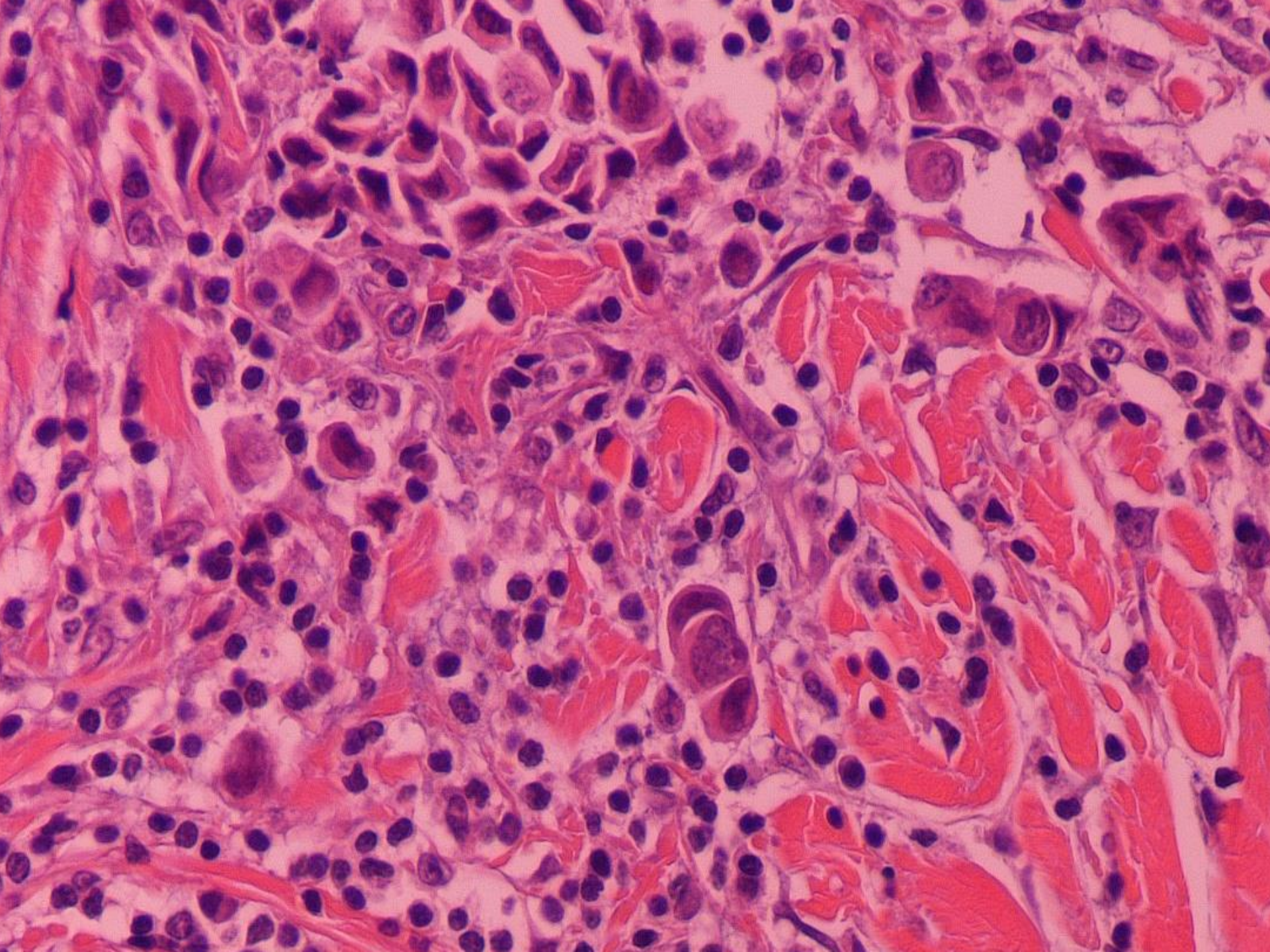






Excisional biopsy with fibrosis and--





LCIS Variants in Breast CNB
Potential for Misdiagnosis and Upgrade at Surgical excision

- Among 75 cases of solid DCIS, 10 (13.3%) were reclassified as LCIS (5 PLCIS, 4 LCIS with necrosis, 1 classic). One-tenth of "solid DCIS" dx on CNB in the past may represent LCIS variants
- 7 (25%) upgraded to invasive in surgical excision

Sullivan et al. Arch Pathol Lab Med 1024, 2010

E-cadherin Expression in LCIS

- Complete loss common
- Reduced expression
- Fragmented, patchy or incomplete pattern of membrane staining (some E-cad +)

  other markers (HMW-CK, B-catenin, p120-cytoplasmic but membranous in DCIS)

  Uncertain: In situ ca with mixed DL/indet.

PLCIS- Molecular genetics:

Overlapping genetic changes with both classic lobular and HG ductal ca..

gain of 1q and loss of 16q (features typical of LCs, but not HG ductal lesions. In addition, genetic changes more analogous to HG ductal, gains of c-myc, Her-2, gains on 8p+q and 13q and losses on 1p, 8p,12p, 14q, 18q and 19+q.

PLCIS

Natural History

??

Fisher: Ductulolobular carcinoma in situ (NSABP B-17)

Page and Anderson: In situ carcinoma of both lobular and ductal type

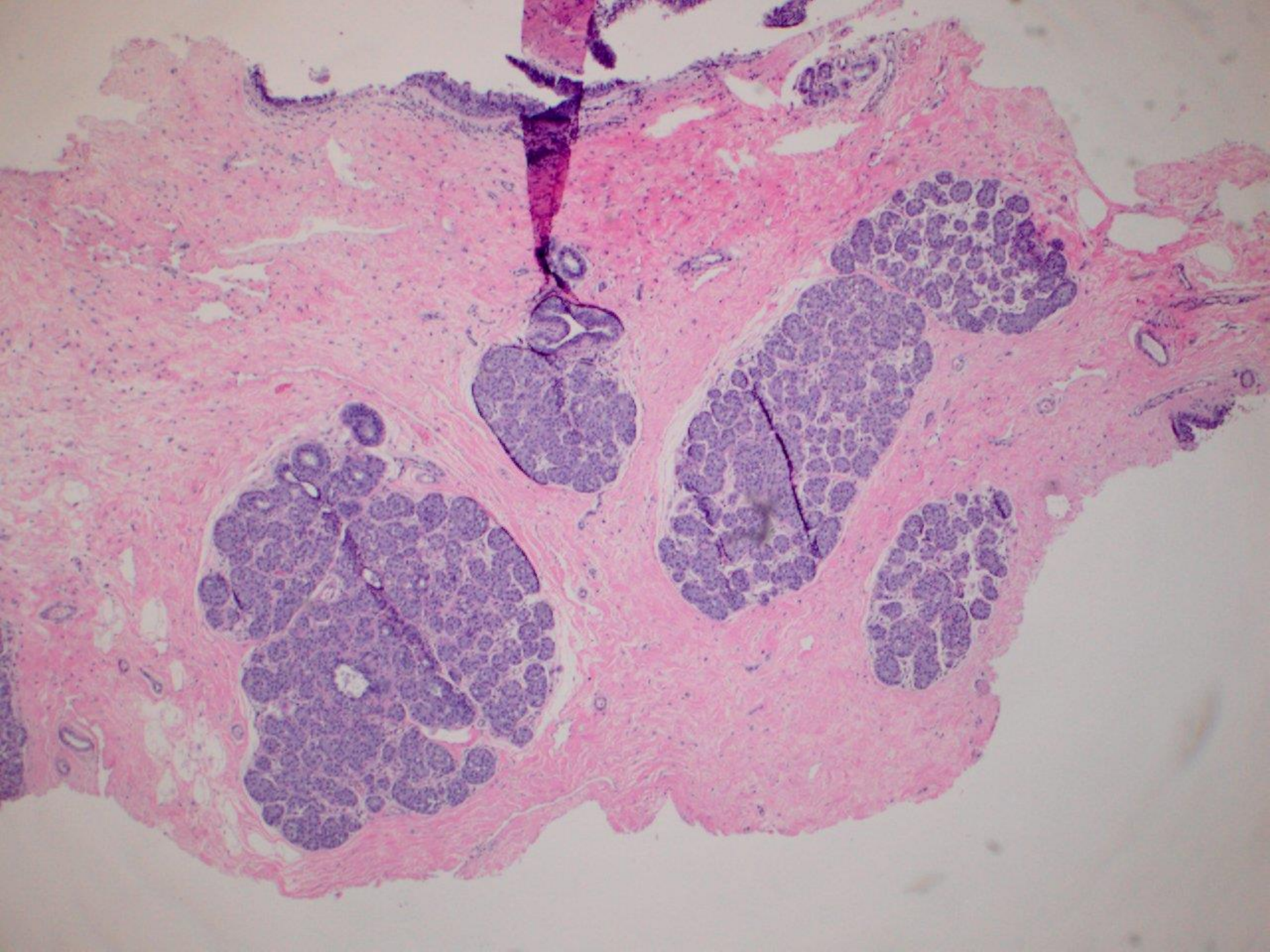
WHO “Although nuclear pleomorphic and necrosis suggest a more aggressive lesion, it remains unproven that the lesion is associated with a higher risk of subsequent breast cancer than that associated with classic LCIS”

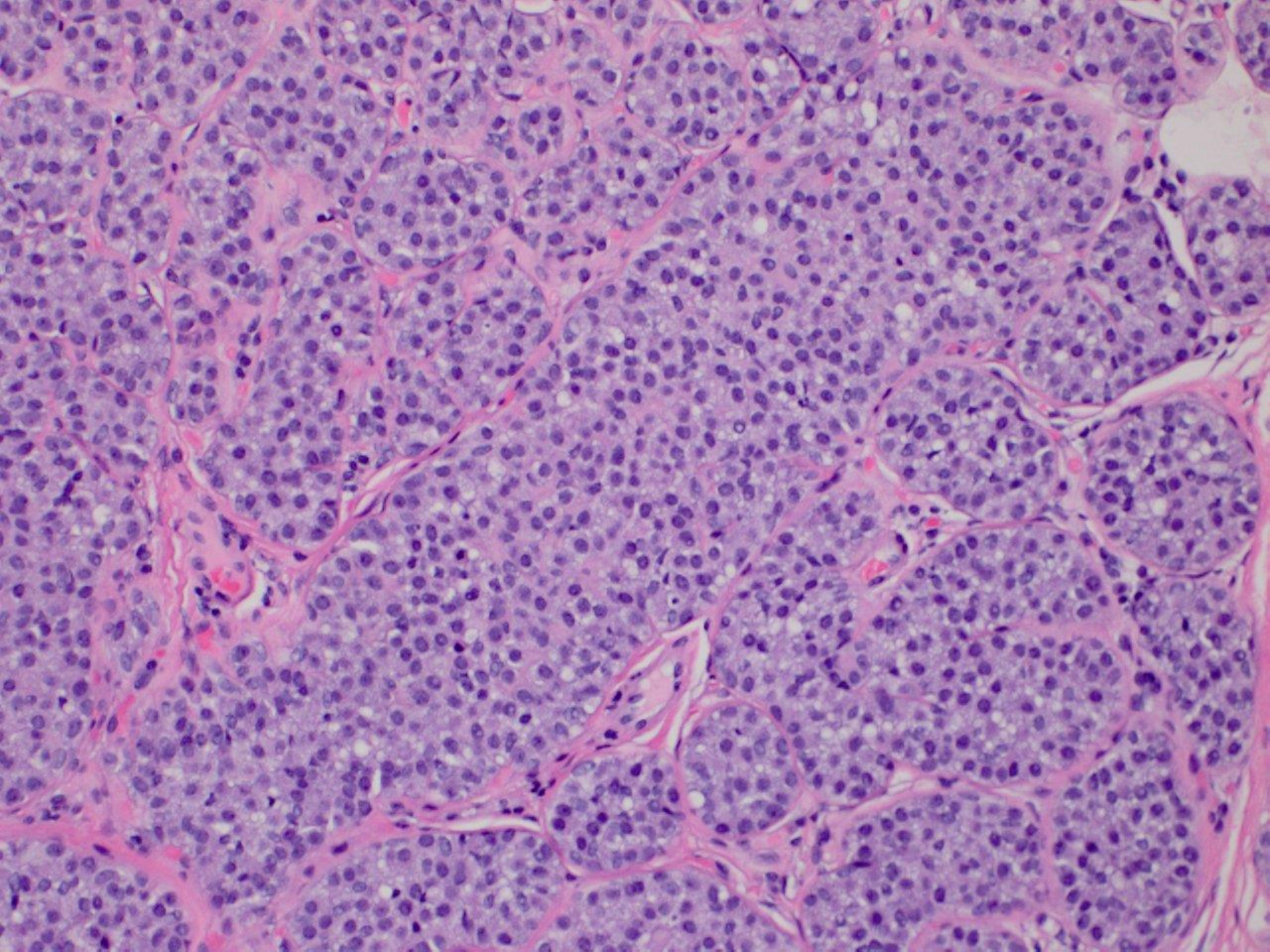
Management of LCIS variants:

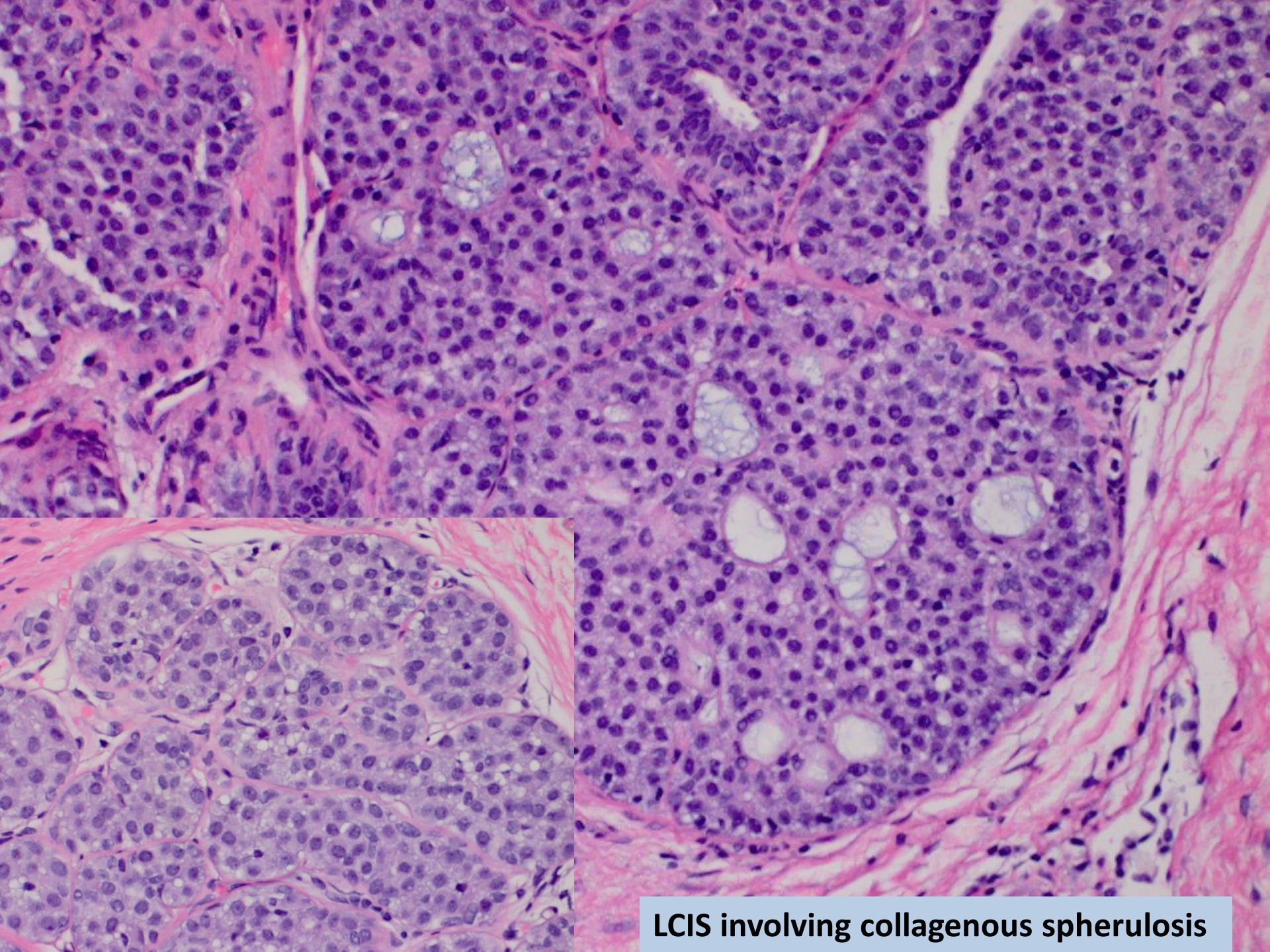
as low/intermediate DCIS
with free resection margins

LCIS in association with other lesions (diagnostic errors)

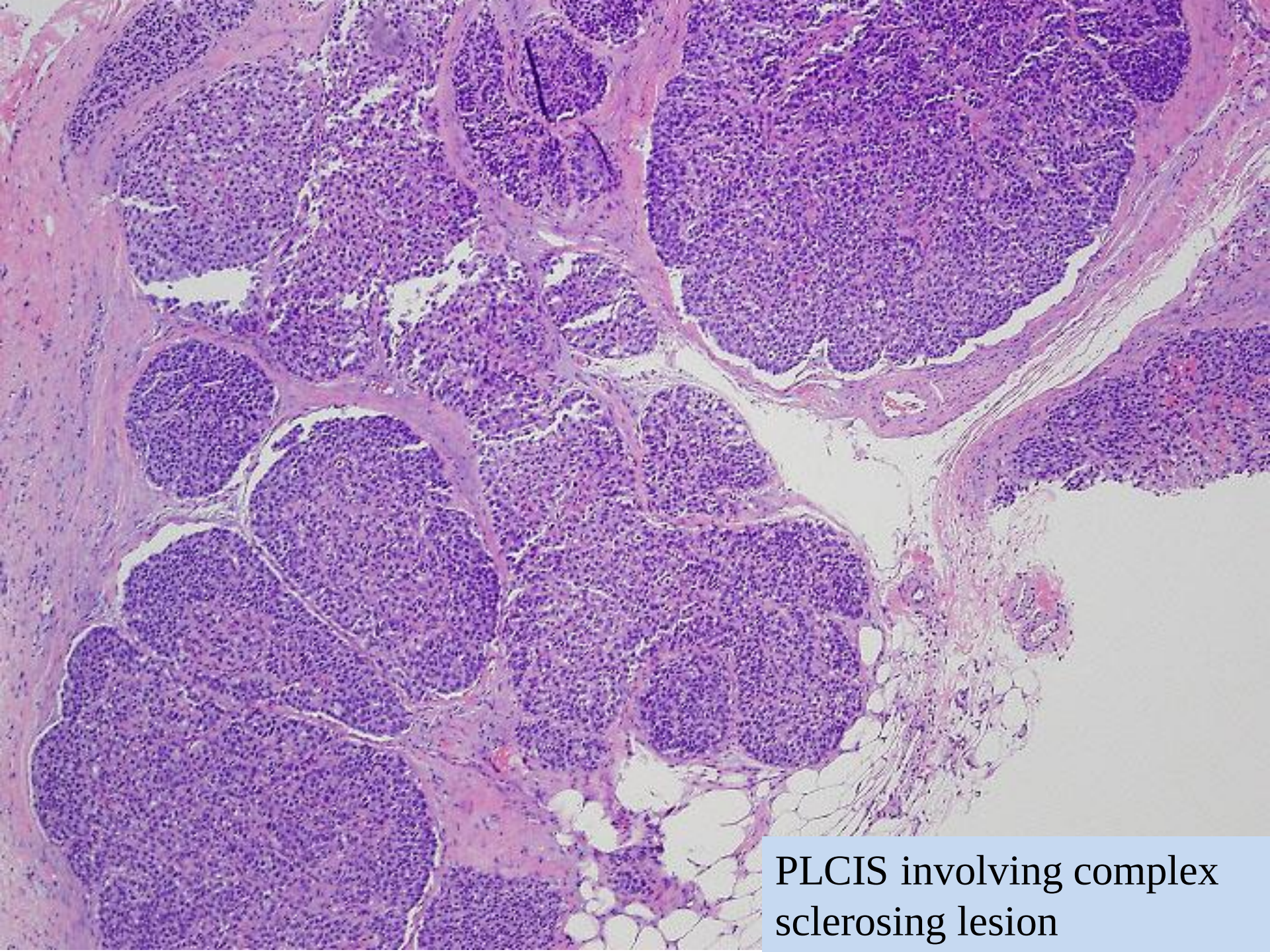
1. with collagenous spherulosis (may be mistaken for DCIS)
2. Complex sclerosing lesion (may be mistaken for invasive ca)



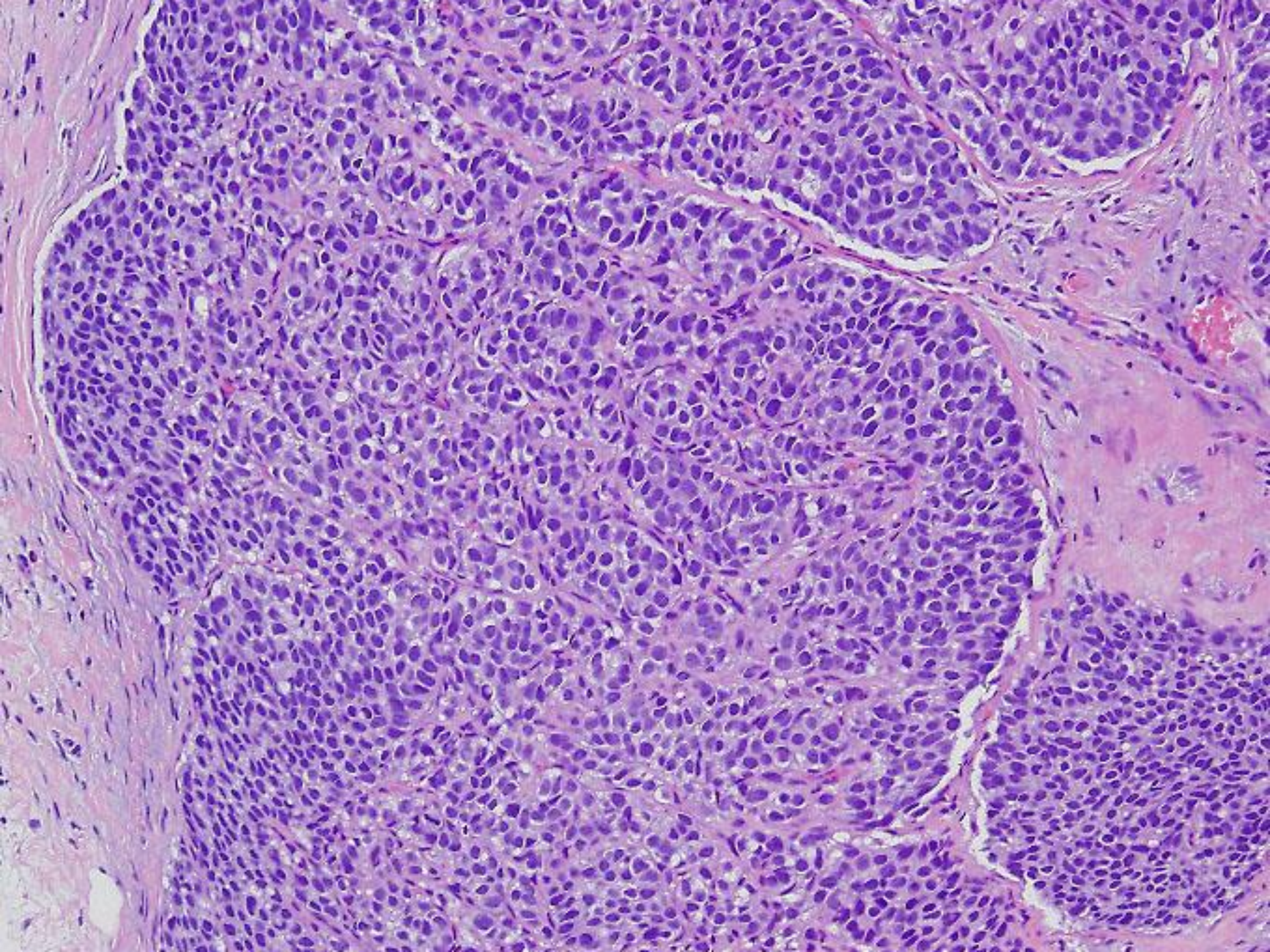


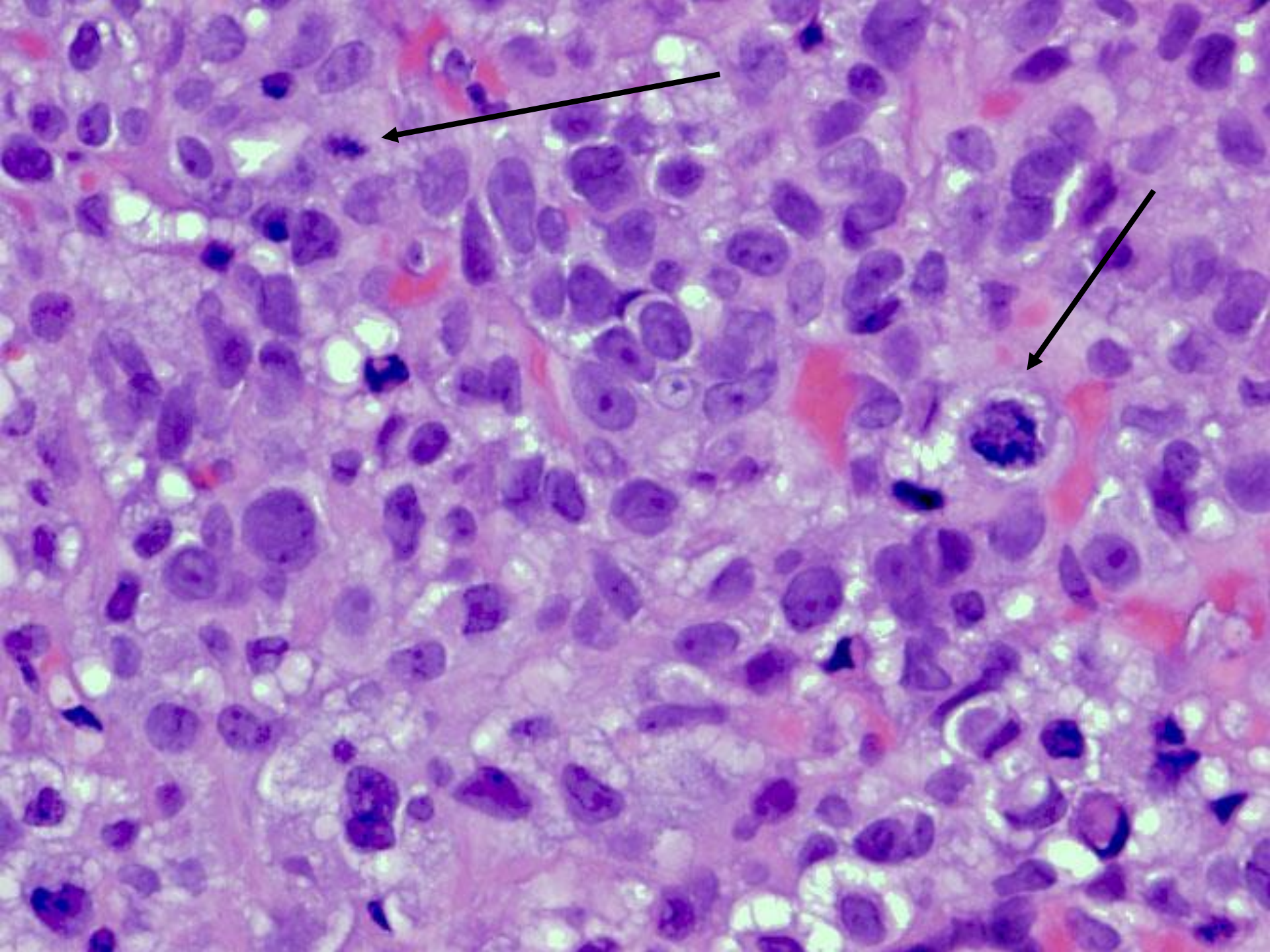


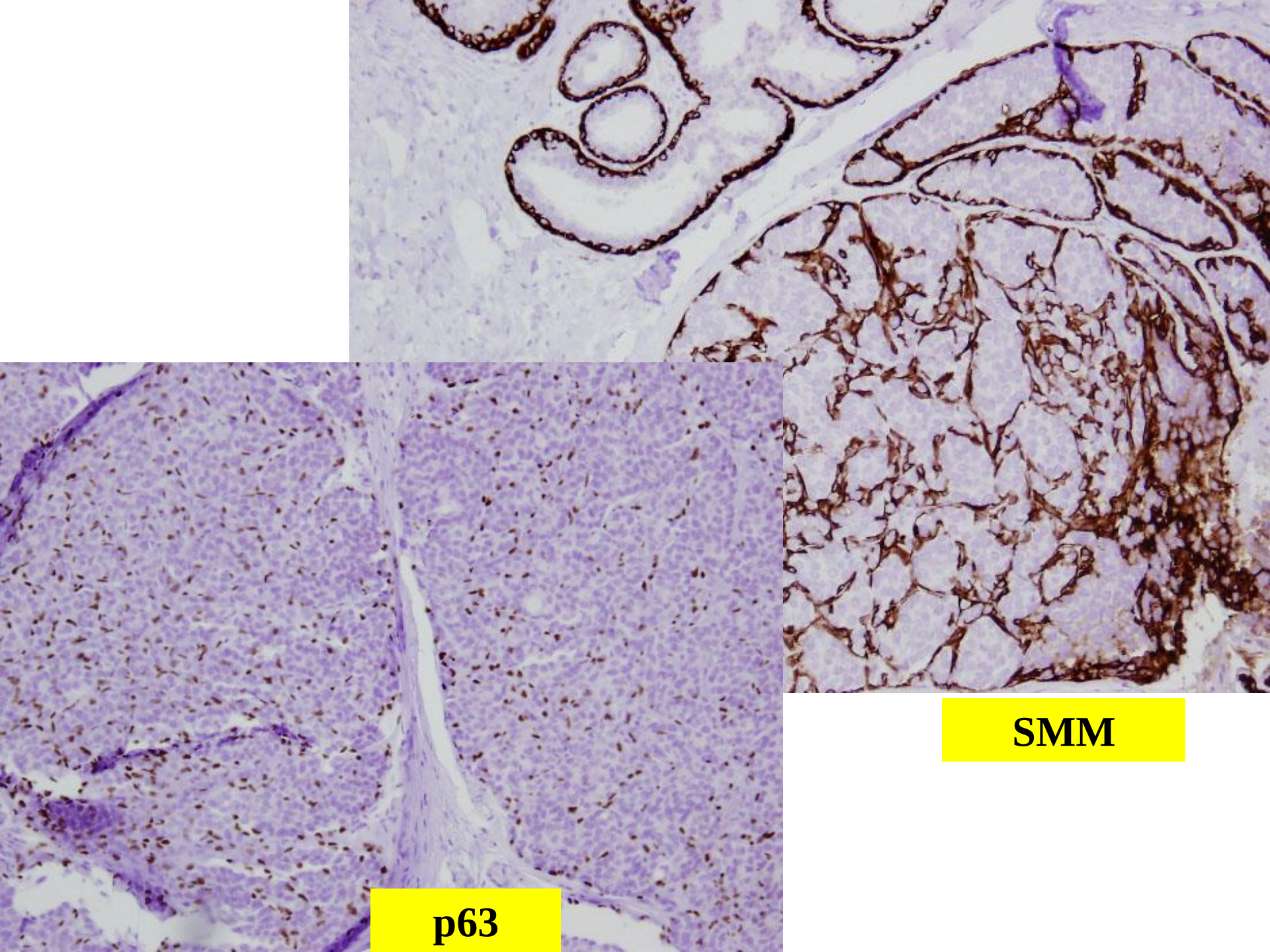
LCIS involving collagenous spherulosis

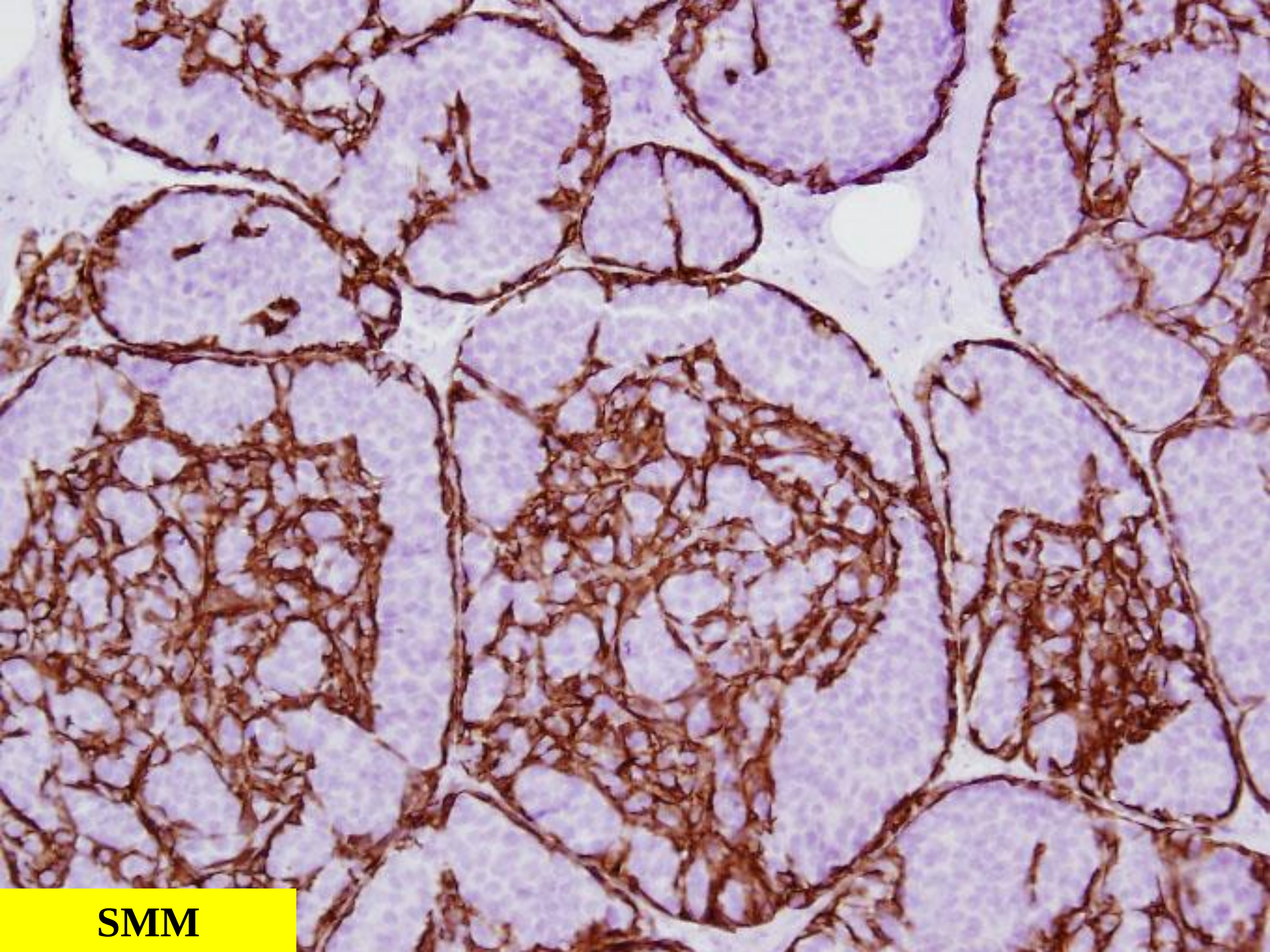


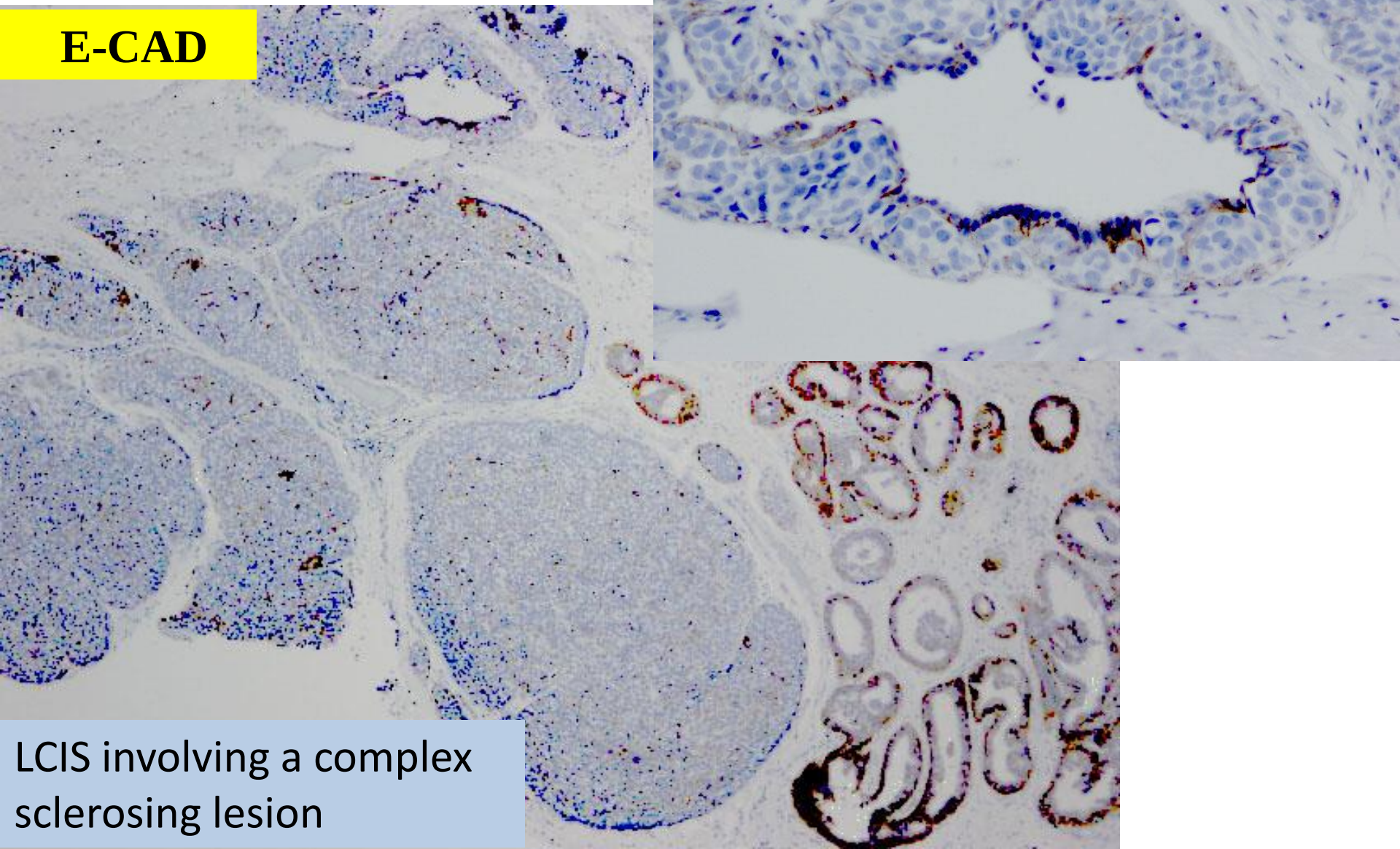
PLCIS involving complex sclerosing lesion






SMM
p63


SMM



LCIS involving a complex sclerosing lesion