香港中文大學
The Chinese University of Hong Kong

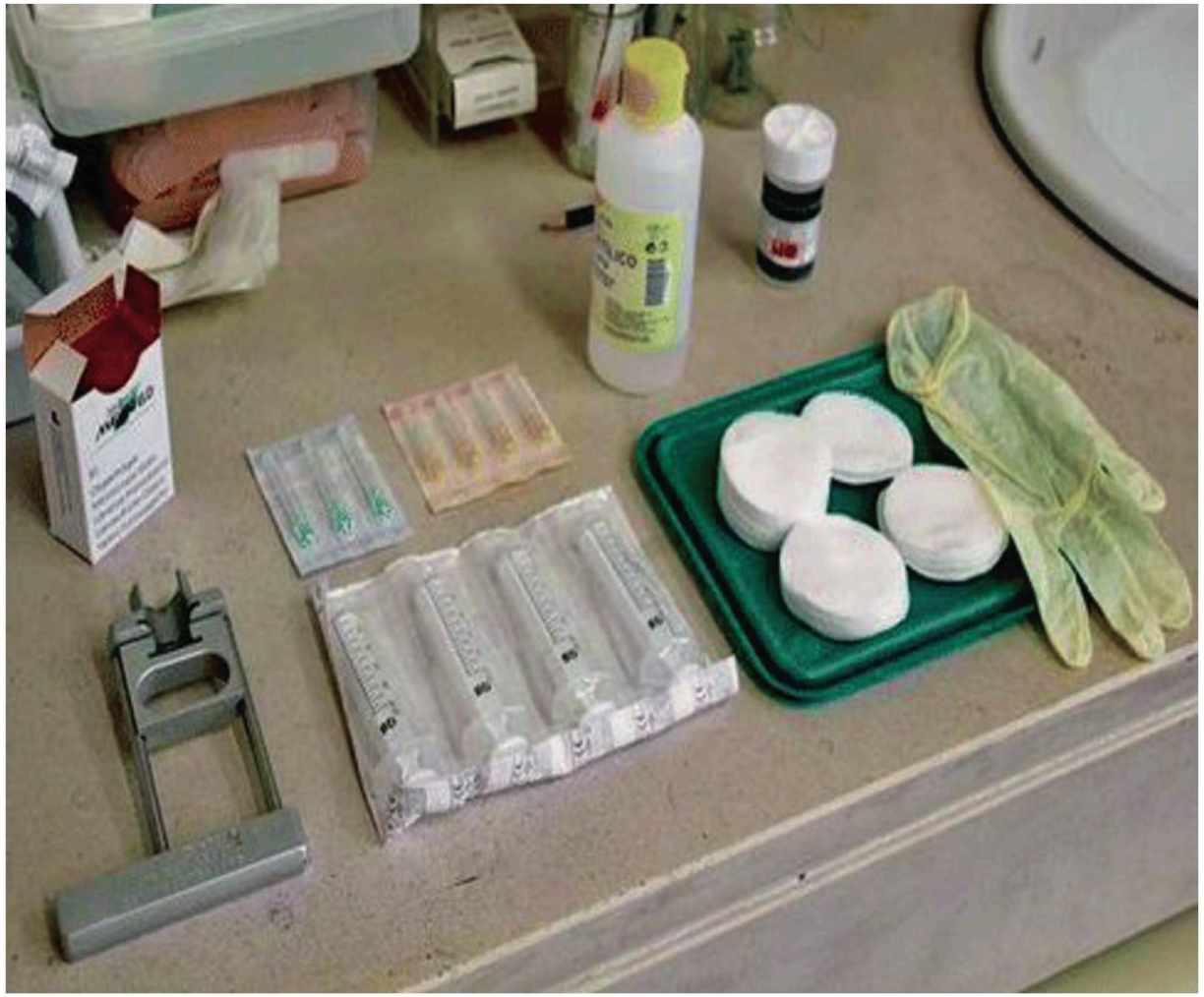
香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

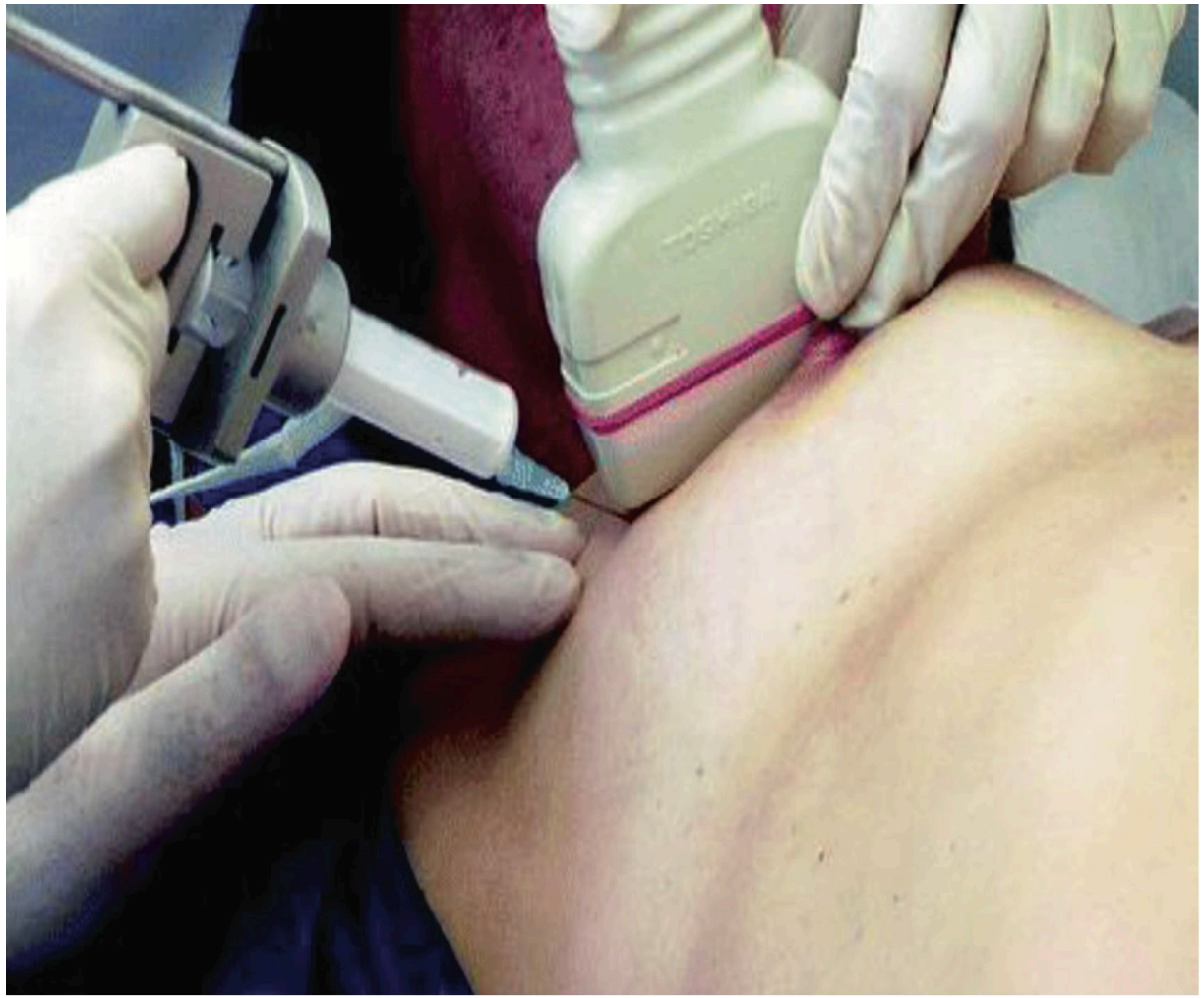
Essentials in breast cytology

Gary Tse
Anatomical and Cellular Pathology
The Chinese University of Hong Kong

Role of Cytopathology: Breast FNA

- Breast is highly accessible to biopsy sampling
  - palpable masses: imaging guided/ blindly
  - non-palpable: imaging guided
- No need for anaesthesia or hospitalization, with low rate of complications
- Breast FNA: Sensitivity of 90-99%; PPV approaching 100%
- Facilitates the performance of rapid onsite evaluation (ROSE) for immediate diagnosis and appropriate triage of material





Role of Cytopathology: Breast FNA

- Indications for breast FNA:
  - diagnosis and drainage of simple cysts
  - diagnosis of palpable/impalpable mass lesion and rendering a final diagnosis in conjunction with the triple test
  - diagnosis of inflammatory conditions with the ability to obtain material for microbiologic evaluation, in pregnant or lactating patients to avoid sinus formation and in patients with bleeding disorders
  - nipple discharge
  - axillary lymph node sampling
  - concurrent lesions, recurrences

Role of Cytopathology: Triple Test

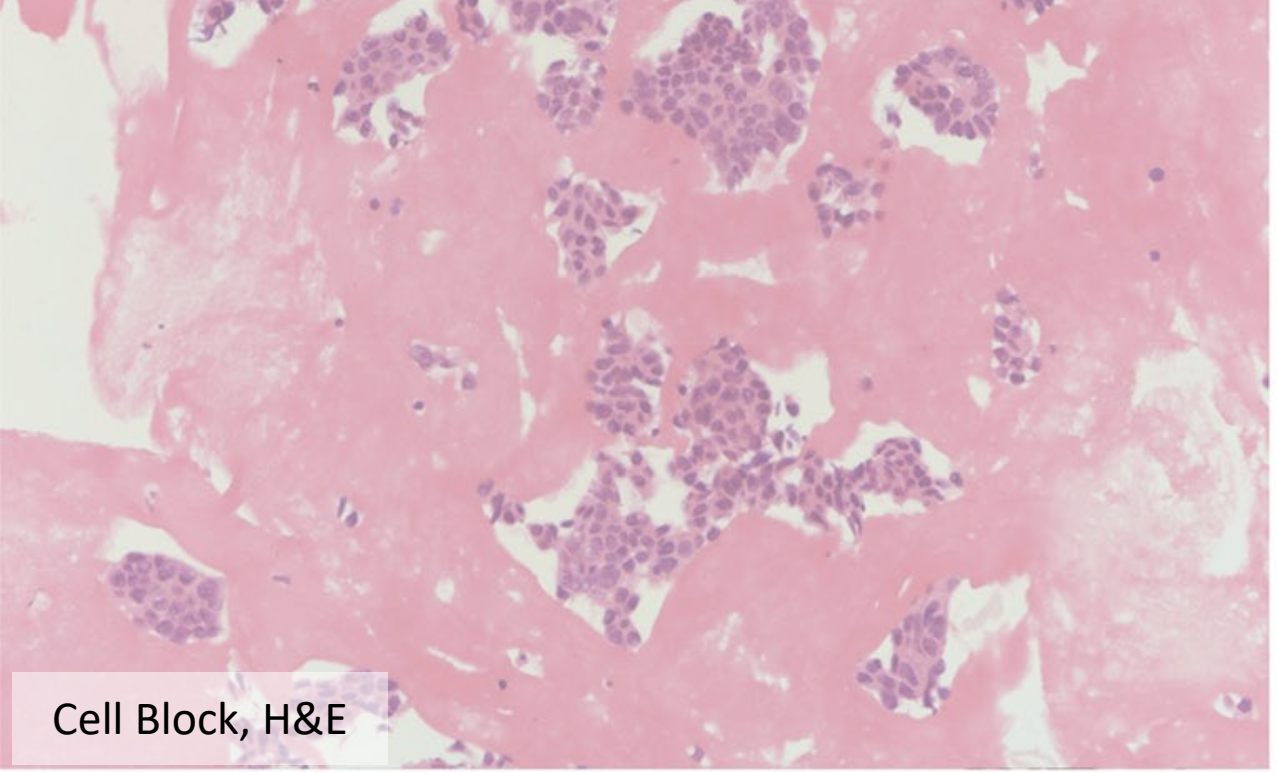
- The cytologic findings should always be correlated with the clinical and radiologic features wherever possible
- Triple test
- ROSE performed at the time of FNA will reduce the rate of inadequate diagnoses and facilitate triage of additional material and selection of ancillary procedures

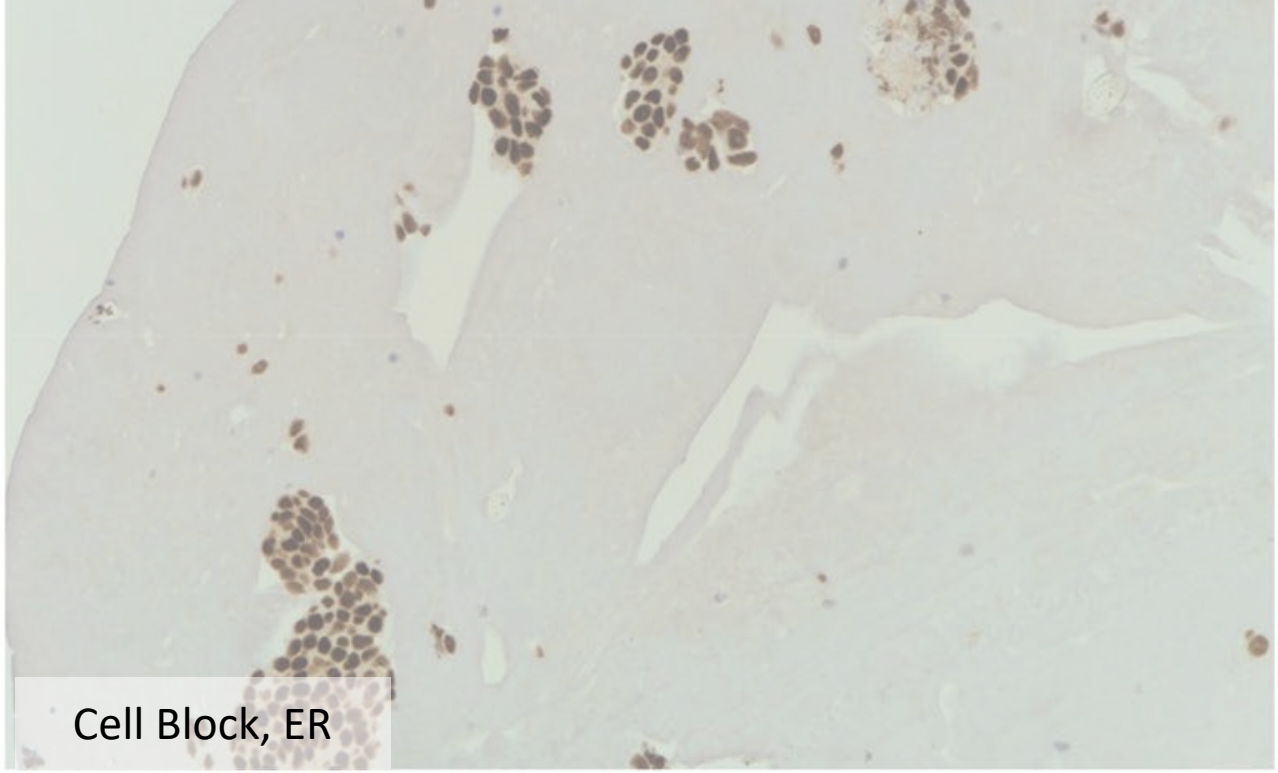
Triple Test: ROSE

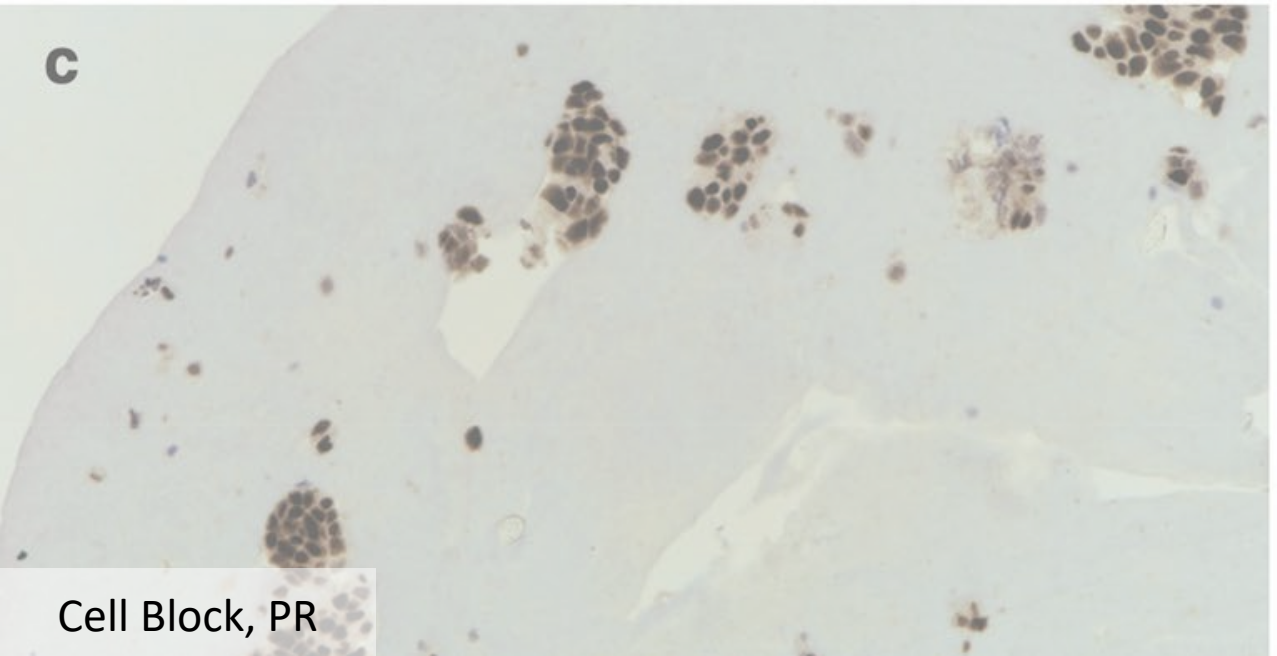
Clinical impression	Imaging	ROSE	Recommendations
Benign	Benign	Sufficient quantity and quality of well-preserved benign ductal cells and stroma or cyst fluid	Adequate
Benign	Benign	Insufficient quantity or quality of ductal cells	An additional FNAB biopsy pass should be considered, possibly targeting a different area of the lesion.
Malignant	Malignant	Malignant or atypical ductal cells	Adequate; additional passes for cell block, IHC or other ancillary testing as indicated
Benign	Benign	Malignant	Additional FNAB passes should be considered to provide a cell block, IHC or other ancillary tests that may help confirm the diagnosis at final review.
Malignant	Malignant	Benign	Additional evaluation such as CNB or excision as clinically indicated

Triple Test: Ancillary Testing

- The most common ancillary study is the Cell Block (histogel/agarose system or colloidal bag system)
- Cell blocks can provide suitable material for :
  - IHC to confirm cell type such as ductal, lobular, mesenchymal, or lymphoid
  - Breast biomarker studies including ER, PR and HER2
  - Cell blocks - follow CNB handling procedures with immediate formalin fixation Identification of primary site for metastatic disease using NGS or other molecular diagnostics
    - the most common metastatic tumors to the breast include melanoma, lymphoma, lung and ovarian carcinoma. These primary sites can be confirmed with IHC or NGS on cell block


Cell Block, H&E


Cell Block, ER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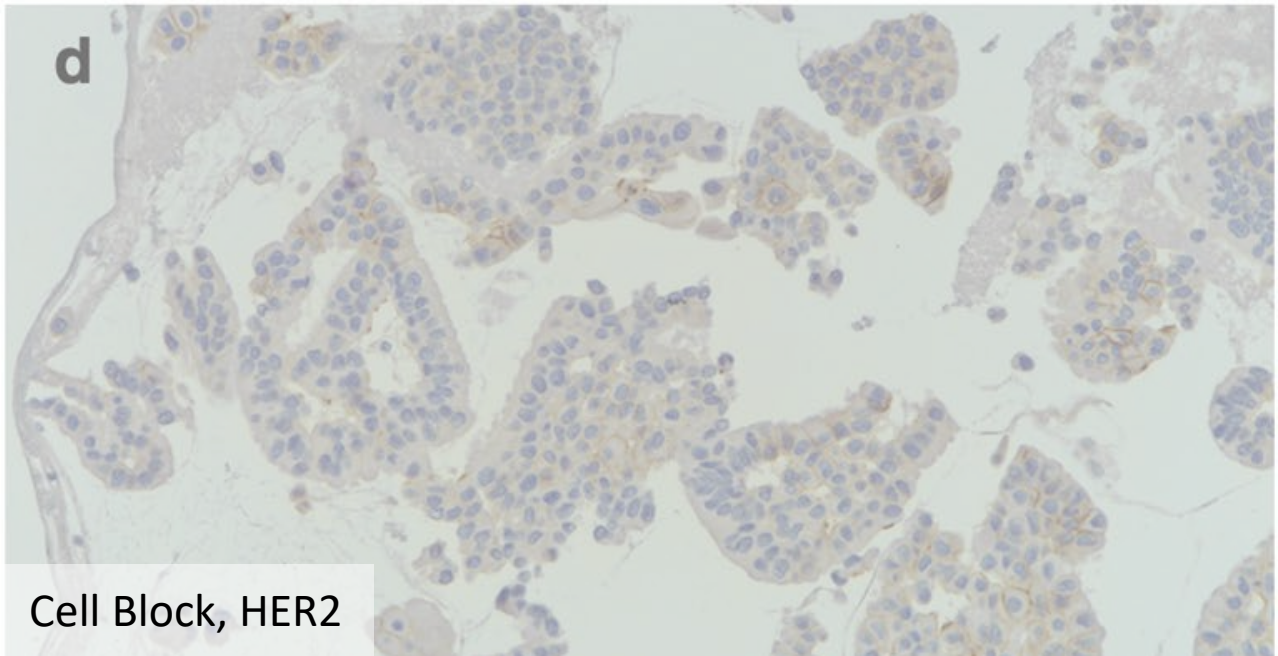
Cell Block, PR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Cell Block, HER2

System categories and structured reporting

- The WHO System has five categories for breast fine needle aspiration (FNAB) cytopathology but these can be applied to touch preparations of core needle biopsies (CNB), liquid based cytopathology (LBC) and to nipple discharge cases

- These categories are:
  - Insufficient/Inadequate/Non-diagnostic
  - Benign
  - Atypical
  - Suspicious for malignancy
  - Malignant

Category	ROM[a, b]	Management[c]	LMICMX[d]	Comment
Insufficient	2.6–4.8%	Review clinical & imaging findings: If imaging indeterminate or suspicious, repeat FNAB or proceed to CNB; if imaging benign consider repeat FNAB	Review clinical; if indeterminate or suspicious repeat FNAB	At ROSE, if inadequate due to a technical issue or the material does not explain the clinical or imaging findings, repeat FNAB up to a total of 3 times, ideally using ultrasound guidance. If FNAB still insufficient, proceed to CNB
Benign	1.4–2.3%	Review clinical & imaging; if 'triple test' benign, no further biopsy required and review depends on the nature of the lesion; if clinical &/or imaging indeterminate or suspicious, repeat FNAB or proceed to CNB	Review clinical: if benign nil further; if suspicious repeat FNAB	At ROSE, if the cellular material does not explain the clinical or imaging findings, repeat FNAB, up to a total of 3 times, using ultrasound guidance. Follow-up depends on the nature of the lesion, e.g. abscess, 2 weeks after antibiotics; fibroadenoma, 12 months. Some centres review in line with screening programme policy
Atypical	13–15.7%	Review clinical & imaging: repeat FNAB if atypia considered likely to be due to a technical issue. If good material available and atypical, repeat FNAB or preferably proceed to CNB.[e]	Review clinical and repeat FNAB; manage based on FNAB category. If further FNAB atypical, consider excisional biopsy	At ROSE, if atypia is considered due to a technical issue, repeat FNAB; if cellular material adequate and atypical, proceed to CNB
Suspicious	84.6–97.1%	Review clinical & imaging: CNB is mandatory. [f]	If no CNB available, excision biopsy	At ROSE proceed to CNB
Malignant	99.0–100%	Review clinical & imaging: proceed to CNB if any discrepant findings. If 'triple test' is concordant and malignant, proceed to definitive management. [g, h]	If no CNB available, excision biopsy	At ROSE may proceed to CNB

ROM risk of malignancy, *FNAB* fine needle aspiration biopsy, *CNB* core needle biopsy, *ROSE* rapid on-site evaluation

[a]Montezuma et al. [15]

[b]Wong et al. [14]

C1

- The assessment of adequacy may not require epithelial material to be present if the cytologic findings correlate with the clinical and imaging findings in the triple test and are sufficient to make a precise diagnosis

- Examples:
  - Pus consistent with abscess
  - Proteinaceous background ± histiocytes consistent with cyst content
  - Fat tissue fragments consistent with lipoma or fatty nodule
  - Spindle cells lesion
  - Fat necrosis
  - Reactive lymphoid material consistent with an intramammary lymph node

C1

- *Abscess* – acute inflammatory cells and debris (pus) are present
- *Cyst contents or fluid* – there is a proteinaceous background with or without histiocytes. The report should state there is no apocrine or other epithelium. The palpable cyst disappears following the FNAB with no residual mass, or the cyst seen on ultrasound is completely drained by the FNAB with no residual lesion
- *Lipoma/fatty nodule* – usually diagnosed by ultrasound, the FNAB yields a considerable number of fibrofatty tissue fragments. The report should state there is no epithelium
- *Spindle cell lesions* – fibroblasts, other spindle cells or stromal tissue fragments are obtained by the FNAB, but no epithelial cells are seen
- *Scar* – stromal cells or sclerotic tissue fragments are seen in the FNAB without epithelium and may be associated with fat necrosis
- *Fat necrosis* – degenerate cellular material, histiocytes, multinucleated histiocytes and fragments of necrotic fat tissue are seen in a background of granular debris. The report should state that there is no epithelium
- *Hyalinized/sclerotic fibroadenomas* – these may yield no material or minimal stromal fragments or only bare bipolar nuclei. If the imaging is characteristic, this may be regarded as adequate

C2

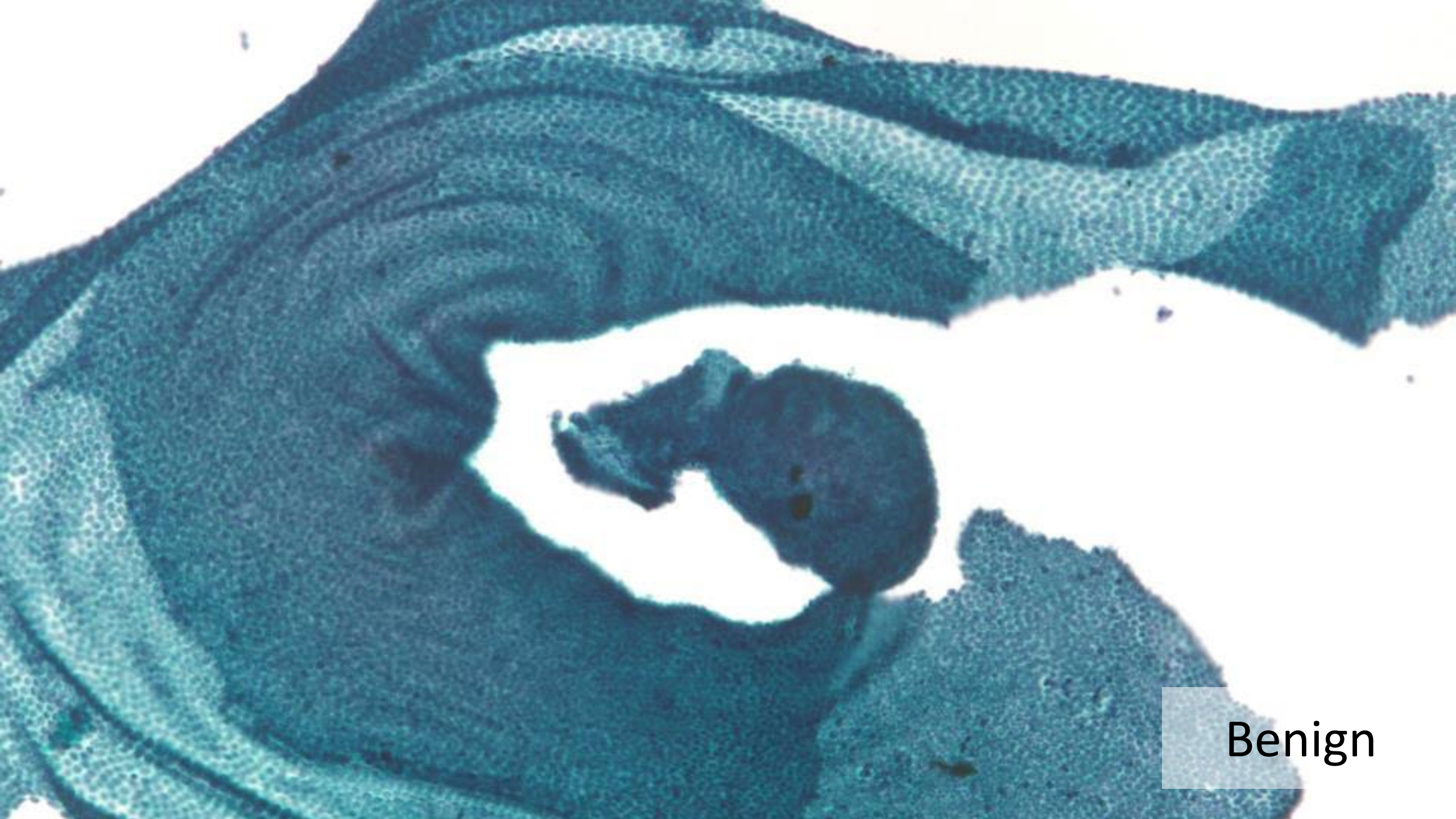
- NPV 97.1% to 98.97%
- Key cytologic features of benign lesions include:
  - A pattern of predominantly large, *cohesive monolayered sheets of uniform ductal epithelial cells or cohesive 3-dimensional epithelial tissue fragments* showing streaming of epithelial cells around irregular slit-like holes (‘secondary lumina’); there may be a mix of smaller tissue fragments and sheets, but dispersal is usually not prominent
  - *Myoepithelial cells* represented by perfectly ovoid nuclei with fine even chromatin and no nucleoli or definable cytoplasm are seen on the cohesive sheets and tissue fragments, in a slightly different focal plane, imparting a ‘bimodal’ pattern to these tissue fragments
  - Stripped myoepithelial nuclei or ‘*bare bipolar nuclei*’ in the background, which may occur as ‘benign pairs’ when the oval nuclei gently touch each other on one extremity; these nuclei are oval with fine chromatin and no nucleoli

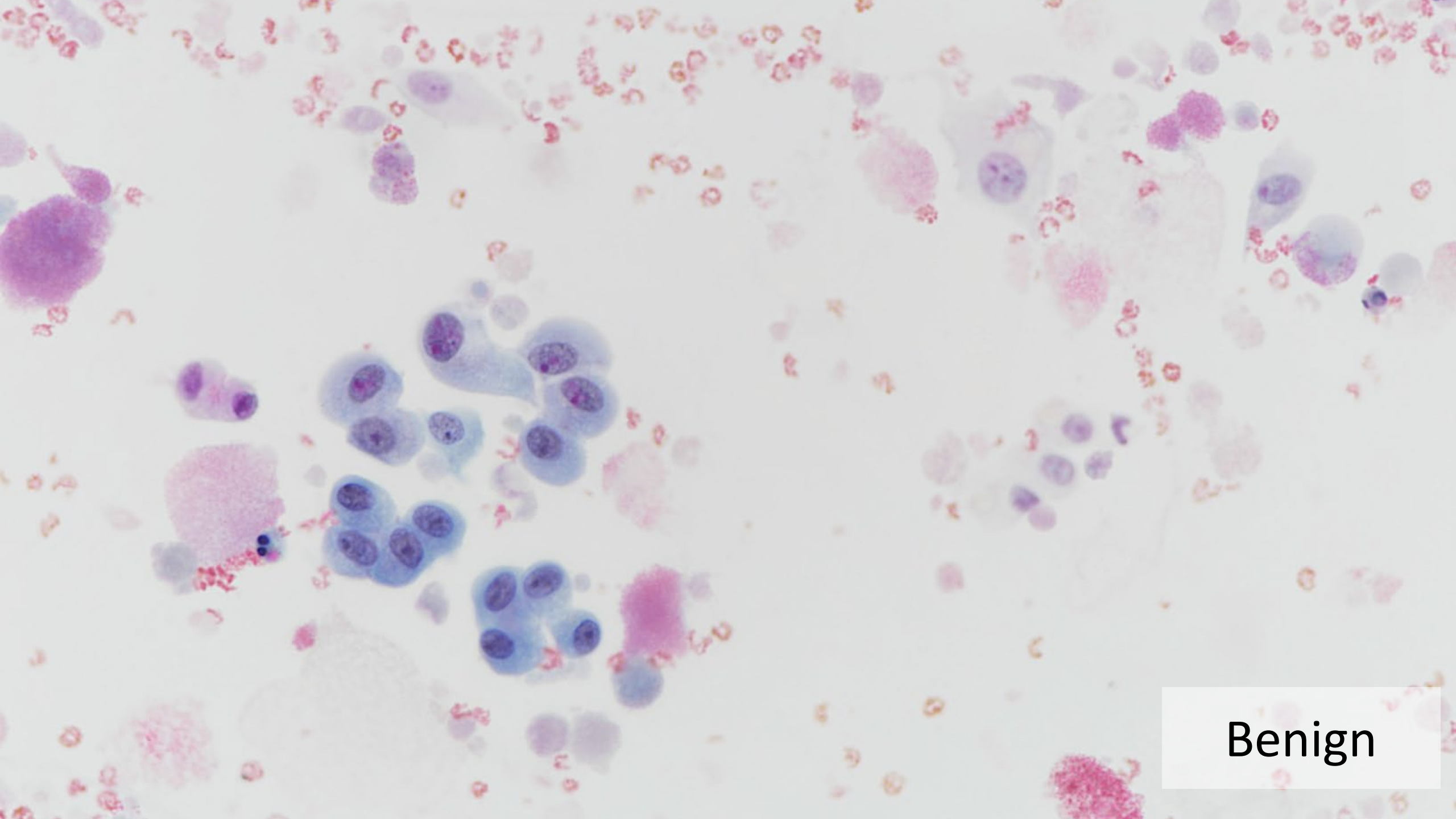
C2

- *Epithelial nuclei* from terminal ductules and smaller ducts are small, uniform and round, with fine to mildly clumped coarse chromatin, with or without small nucleoli. Nuclear size gradually increases to moderate with mildly coarse chromatin and small- to medium-sized round nucleoli in benign proliferative lesions
- *Normal breast* may show a pattern of small terminal ductular tissue fragments with myoepithelial cell nuclei, intact or fragments of lobules and bare bipolar nuclei in the background
- *Apocrine sheets, foamy histiocytes and a granular proteinaceous background* are commonly seen and are evidence of fibrocystic change

C2：The most common benign lesions

- Acute mastitis and breast abscess
- Granulomatous mastitis
- Foreign body reaction
- Fat necrosis
- Consistent with cyst content/ fibrocystic changes
- Lactational changes
- Normal breast
- Usual epithelial hyperplasia
- Fibroadenoma
- Intraductal papilloma
- Intramammary lymph nodes


Benign


Benign

C3

- The specific cytologic features that are considered atypical:
  - High cellularity
  - Increased dispersal of single intact cells
  - Enlargement and pleomorphism of nuclei
  - Presence of necrosis or mucin
  - Complex micropapillary or cribriform architecture of epithelial tissue fragments

C3

- Concerning features for a higher grade or malignant process includes:
  - prominent dispersal of single intact epithelial cells (cellular dyscohesion)
  - small epithelial cell fragments (of 3-4 cells only)
  - moderate nuclear enlargement or pleomorphism in the absence of an explanation (i.e. inflammation)
  - very high cellularity
  - reduced or absent bare bipolar nuclei
  - background of mucin or necrosis
  - complex micropapillary or cribriform architecture with bland nuclear features
  - spindle cell proliferation
- Other features: papillary fragments, lobular-type cells, marked nuclear crowding, atypical apocrine cells, low grade spindle cells or vascular proliferations

C3 : differential diagnoses

- Fibroadenomas
- Papillomas
- Sclerosing adenosis
- Usual ductal hyperplasia
- Radial scars/ complex sclerosing lesion
- Lesions associated with columnar cell change

- Spindle cell lesions: fibromatosis, adenomyoepithelioma, myofibroblastoma, PT, myxoma, schwannoma, fibroma
- Low grade malignancy: tubular carcinoma, mixed tubular-lobular carcinoma, low grade DCIS

Factors contribute to atypia

- Nature of the lesions
- Many technical difficulties
- Interpretation

al-Kaisi N. *Acta Cytol.* 1994;38(6):898-908.

C3: Factors contributing to atypia

- *Inherent nature of some breast lesions or processes*
  - The diagnostic features of certain benign and atypical proliferative lesions and of LG DCIS show overlap
  - Fibroepithelial lesion, intraductal papilloma, UDH, sclerosing adenosis, low grade carcinoma, LN, spindle cell lesions

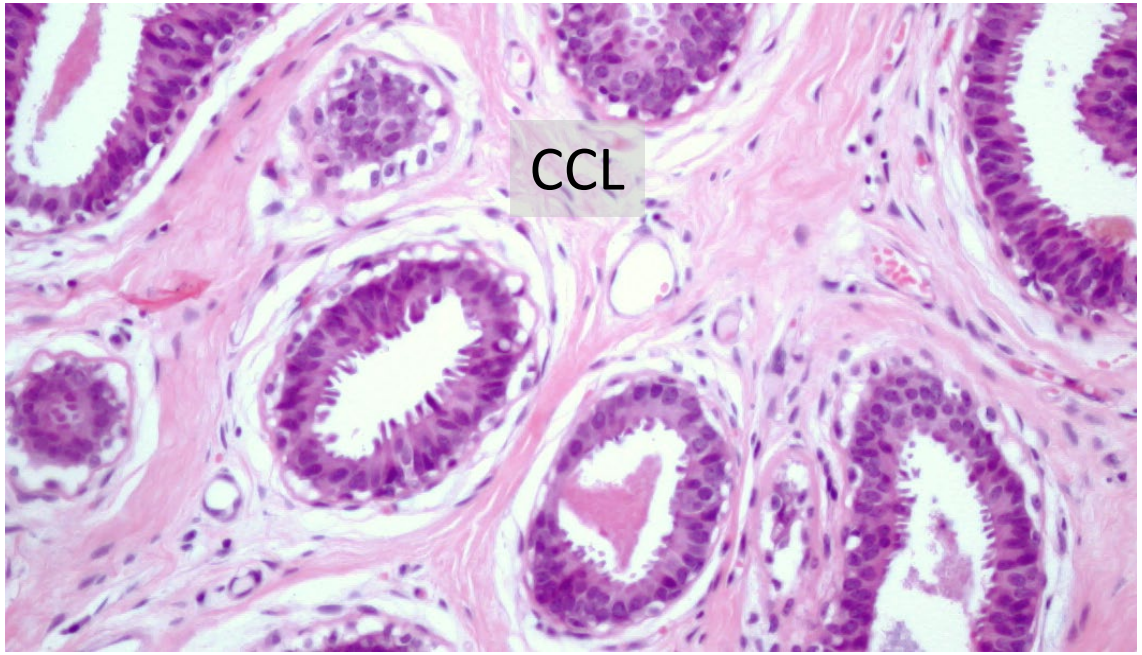
Nature of the lesions in atypia

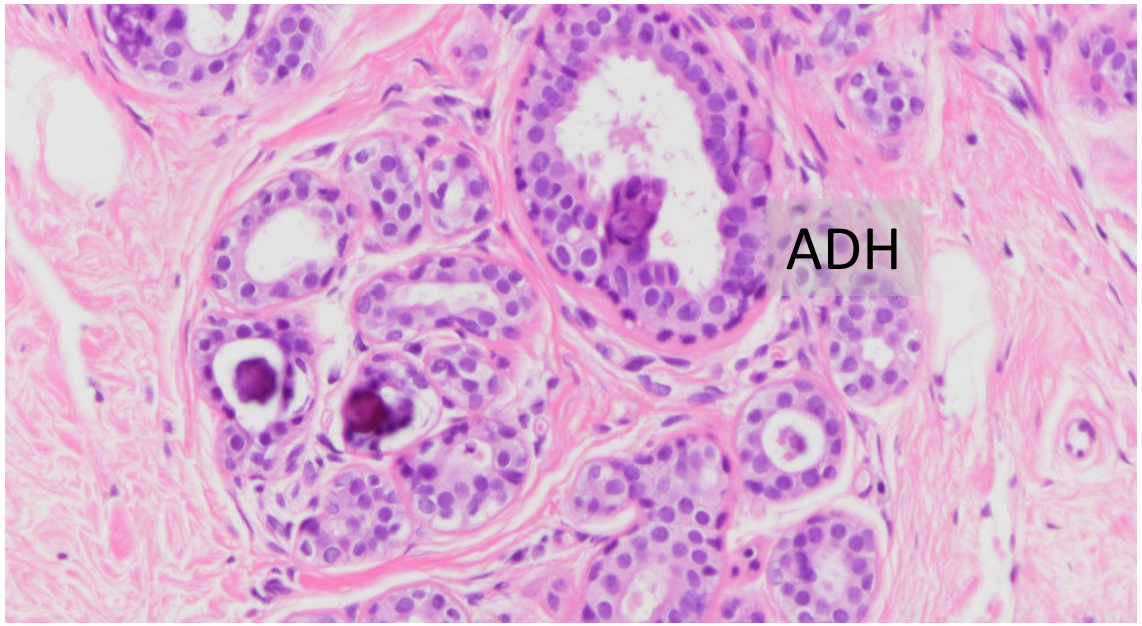
- Histologic overlap between atypical and low grade malignant lesions
- Physiological states – hyperplastic changes
- Accounted for 21% of all atypical cases

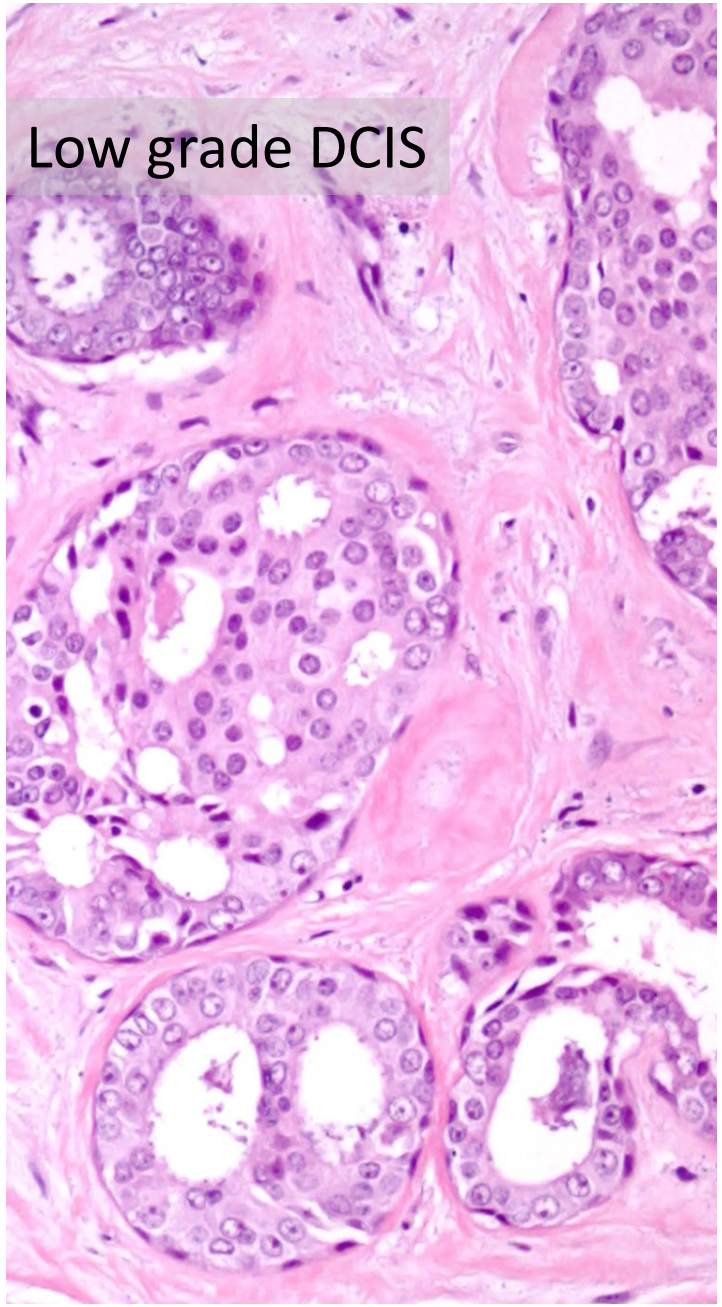
- Nuclear atypia, particularly of mild extent, can be seen in FNACs of some fibroadenomas
- Aspiration of some low-grade malignant cases could yield bland nuclei with minimal pleomorphism
- High cellularity, a cytologic feature that is usually associated with malignancy in other organs, may actually be observed in aspirates of common breast lesions e.g. epithelial hyperplasia complicating fibroadenomas, papillomas and radial scars

al-Kaisi N. *Acta Cytol.* 1994;38(6):898-908.

Non atypical nuclear change	Atypical cytologic changes	Non atypical architecture	Atypical architecture	Size	Diagnosis
✓					FH
✓		✓			CCC
	✓	✓			FEA
	✓		✓	<2mm	ADH
	✓		✓	>=2mm	DCIS low grade

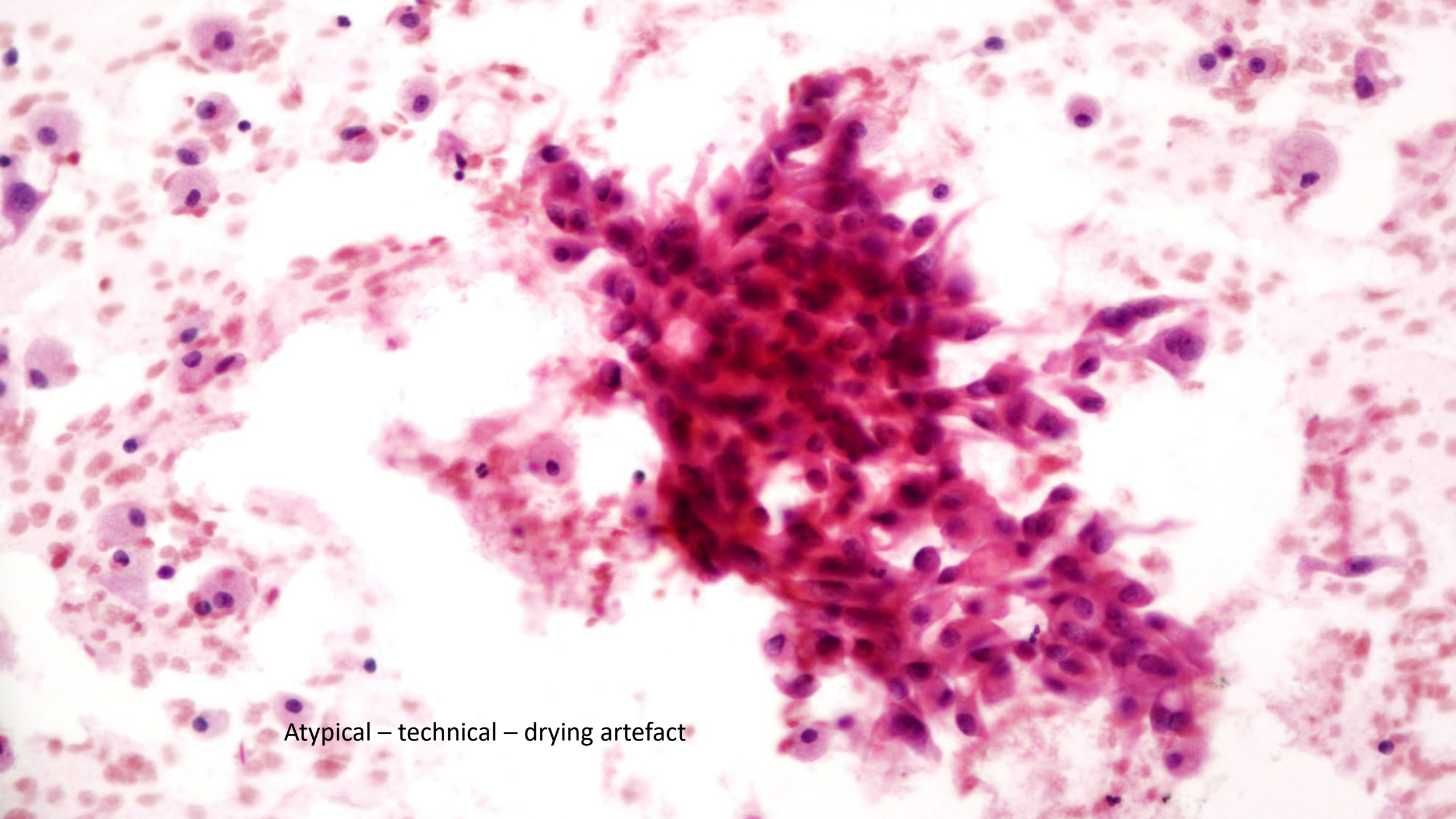

CCL


ADH


Low grade DCIS

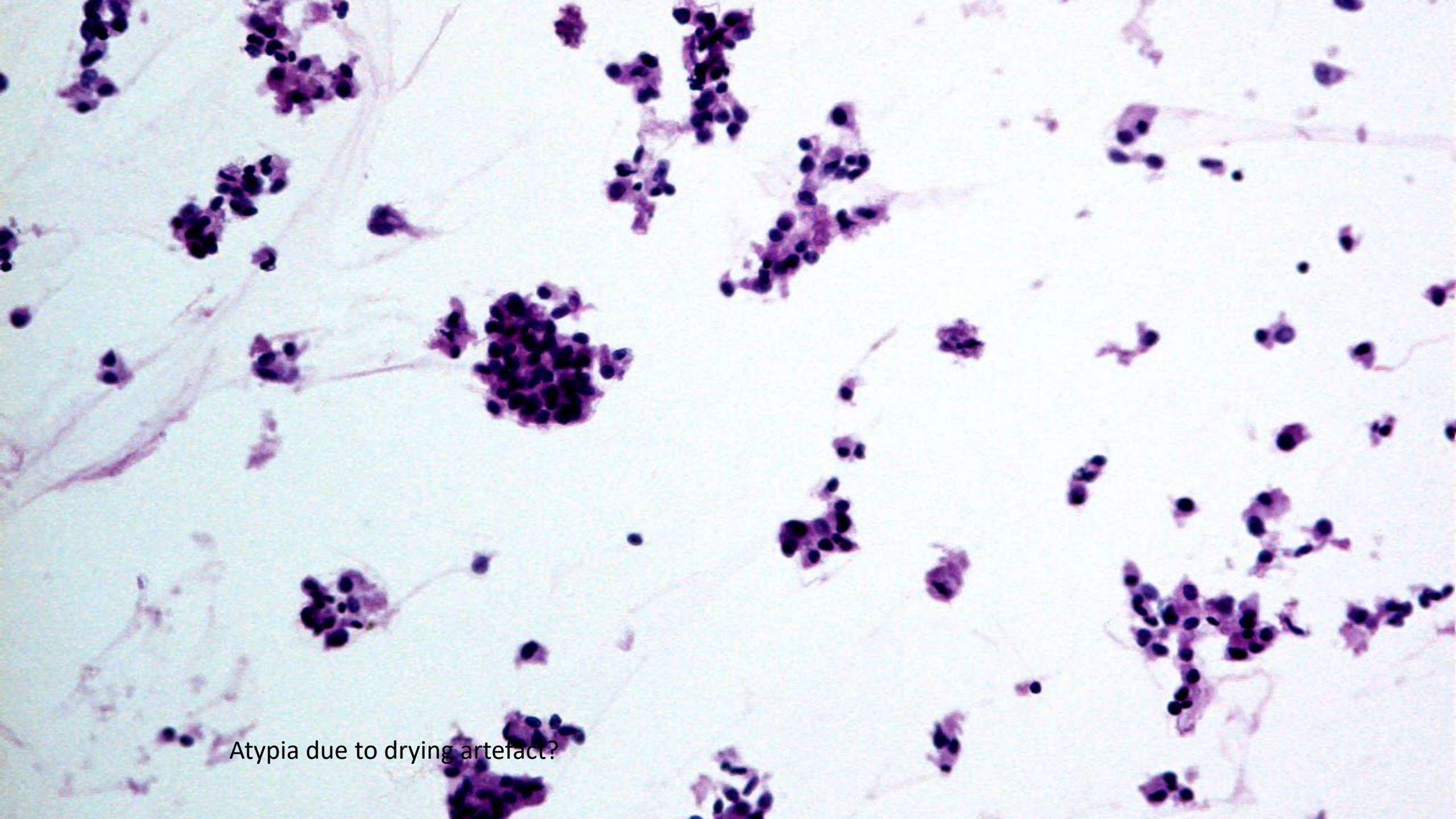
C3: Factors contributing to atypia

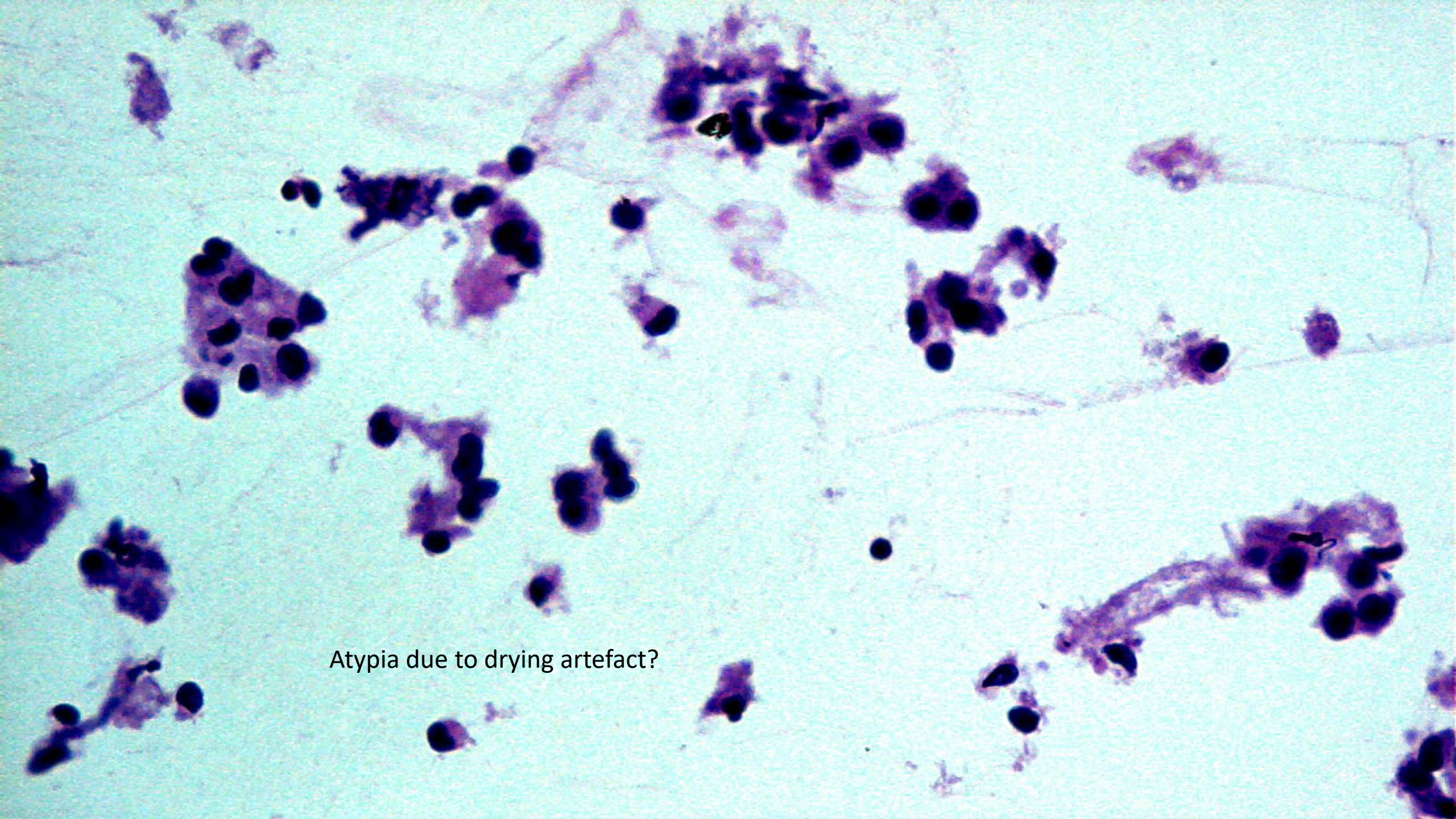
- *Limitations in specimen technical quality*
  - Cases with low cellularity or scanty interpretable material
  - Cases with smearing and fixation artefacts
  - In Papanicolaou staining, air-drying artefact occurs when smeared slides are not immediately immersed in alcohol, resulting in apparent nuclear enlargement and lack of chromatin structure.
  - In Giemsa staining, slow air-drying of directly smeared material containing considerable watery fluid can also lead to severe artefact due to rupture of cells and nuclear distortion
  - Forceful smearing leads to either crush artefact or dispersal of otherwise benign cohesive material, particularly towards the tail of the smear, mimicking the loss of cell adhesion seen in carcinoma
  - Blood or ultrasound gel and clotting of material in the needle can obscure cells

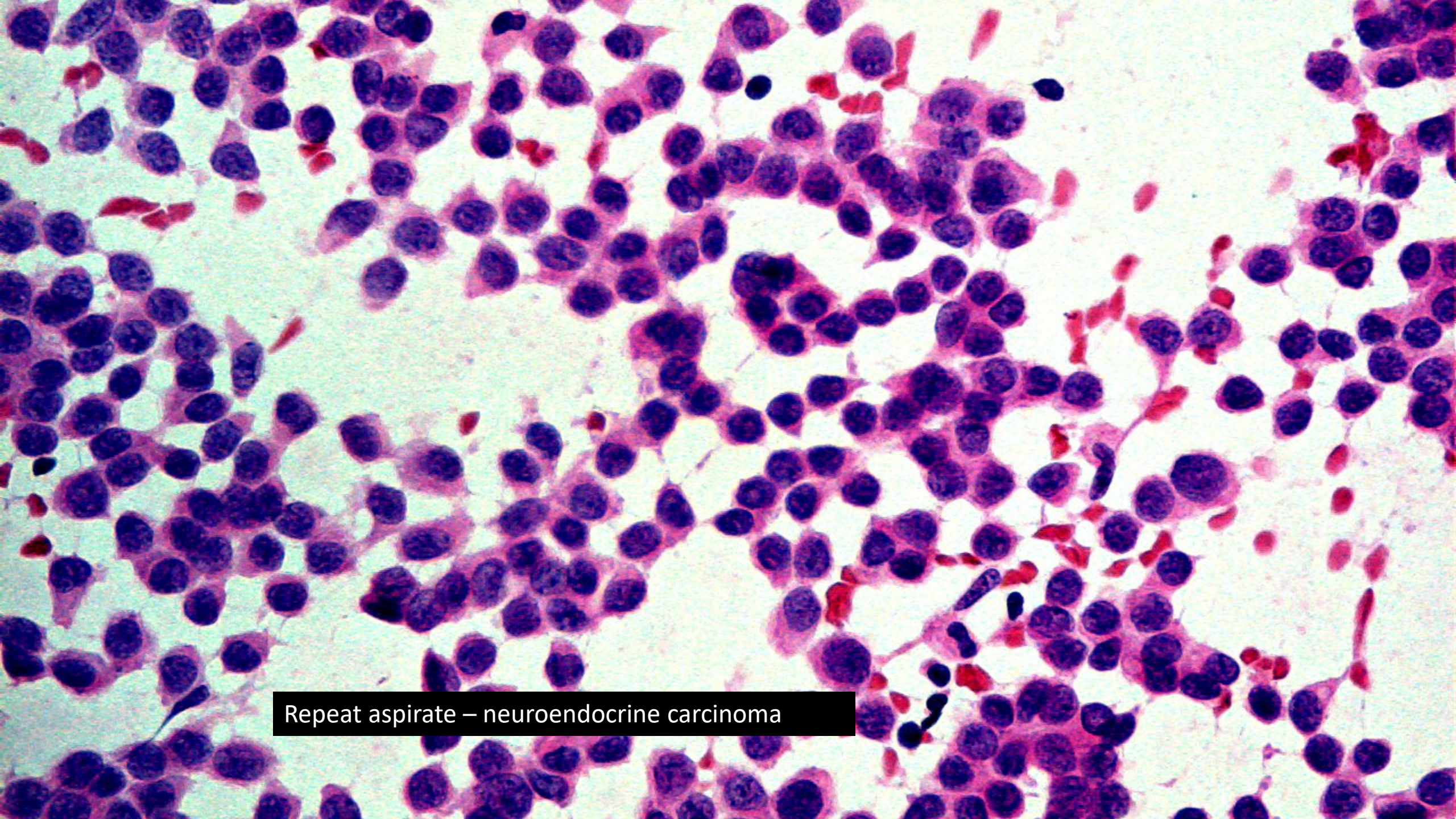


Atypical – technical – drying artefact

- Another case


Atypia due to drying artefact?

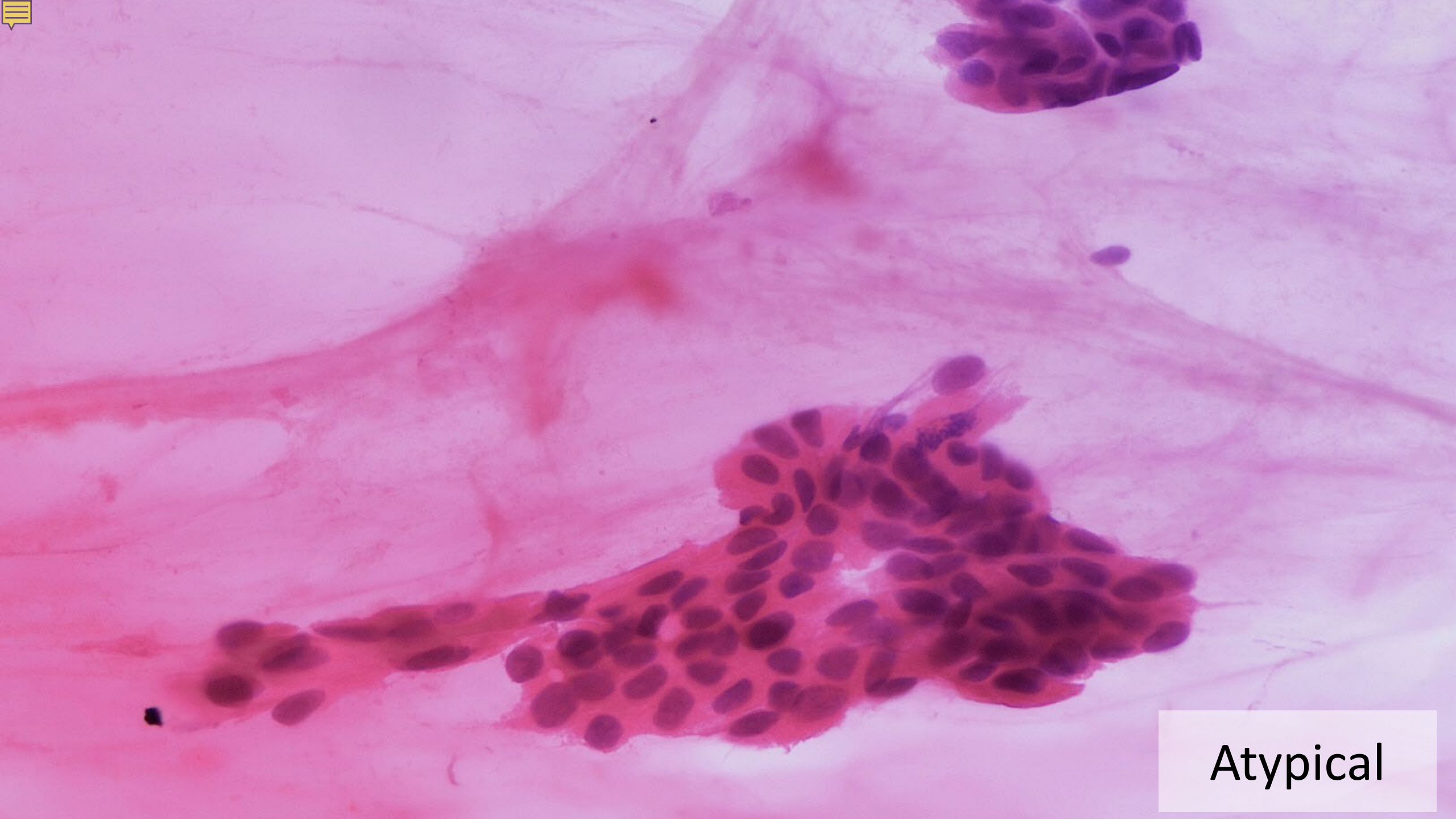

Atypia due to drying artefact?

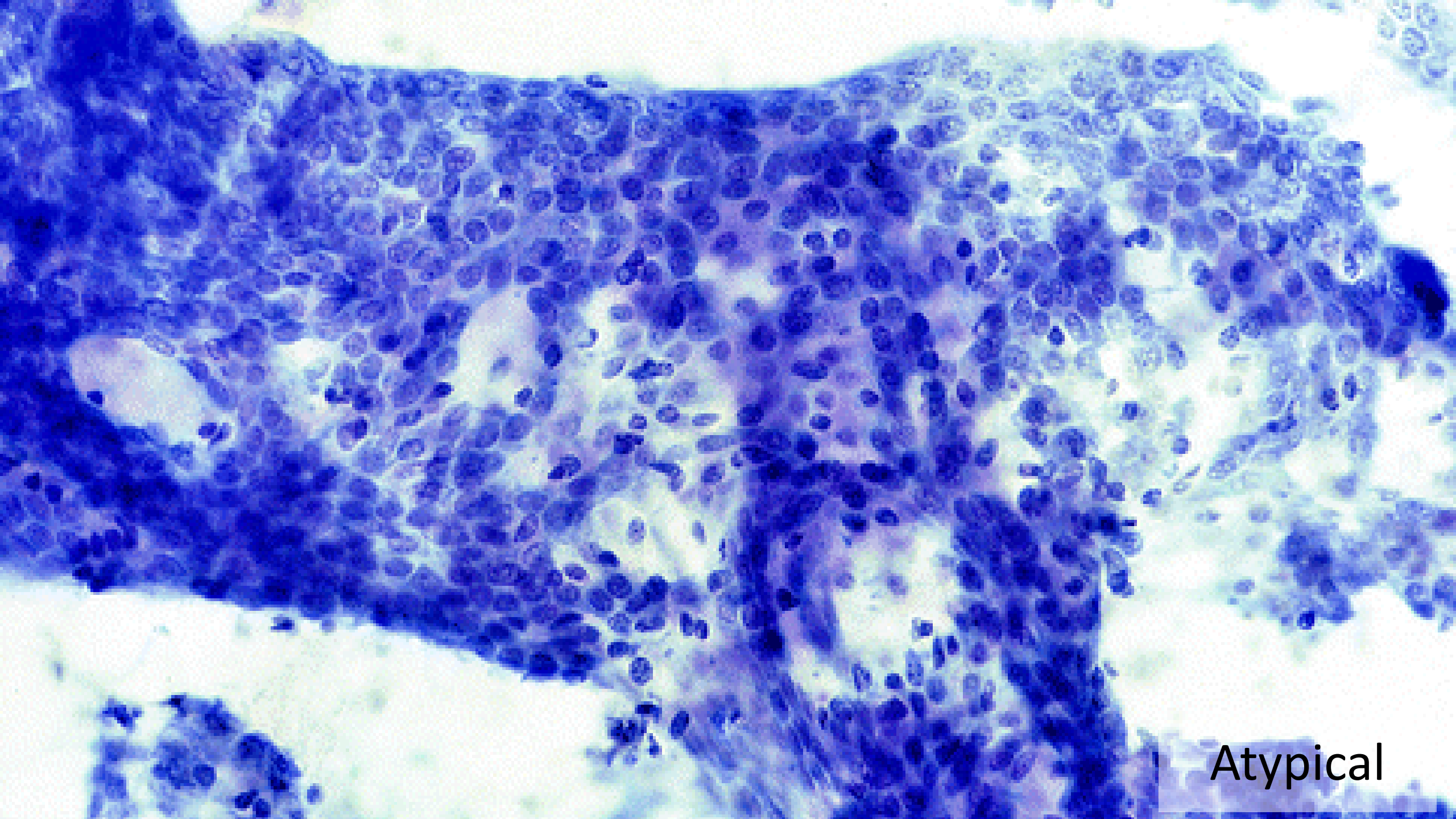

Repeat aspirate – neuroendocrine carcinoma

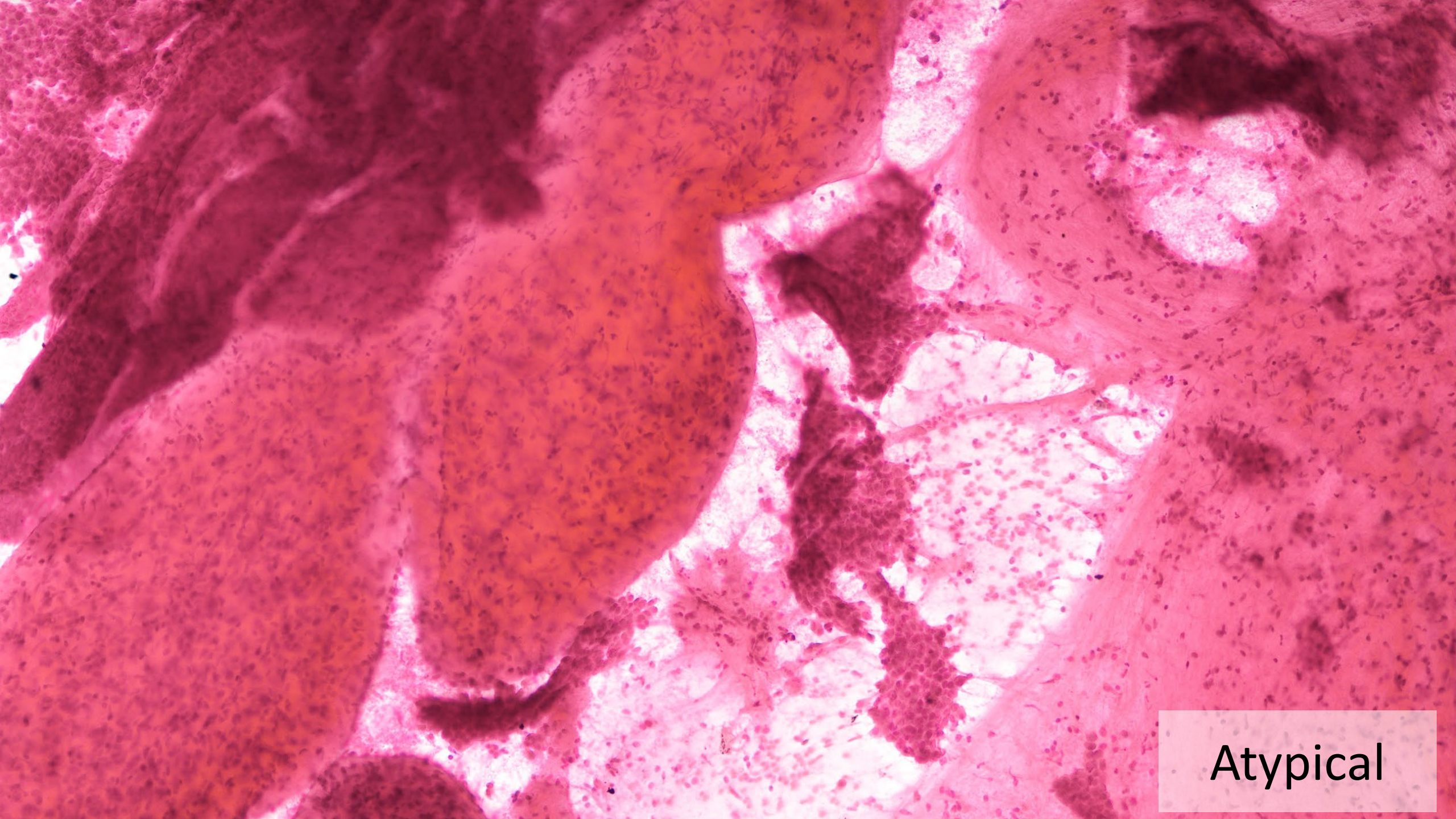
Interpretation for atypia

- Inexperience or unfamiliarity of the interpreting cytopathologist accounted for 24% of C3 FNACs
- When dealing with limited material it can be difficult to determine if the interpretation was at fault or if the quality of the specimen is the main issue
- Inexperienced cytopathologist may more likely give an inappropriate amount of weight to an ‘atypical’ feature while failing to recognize the overall diagnostic pattern and features, leading to a higher ‘atypical’ rate

al-Kaisi N. *Acta Cytol.* 1994;38(6):898-908.


Atypical


Atypical

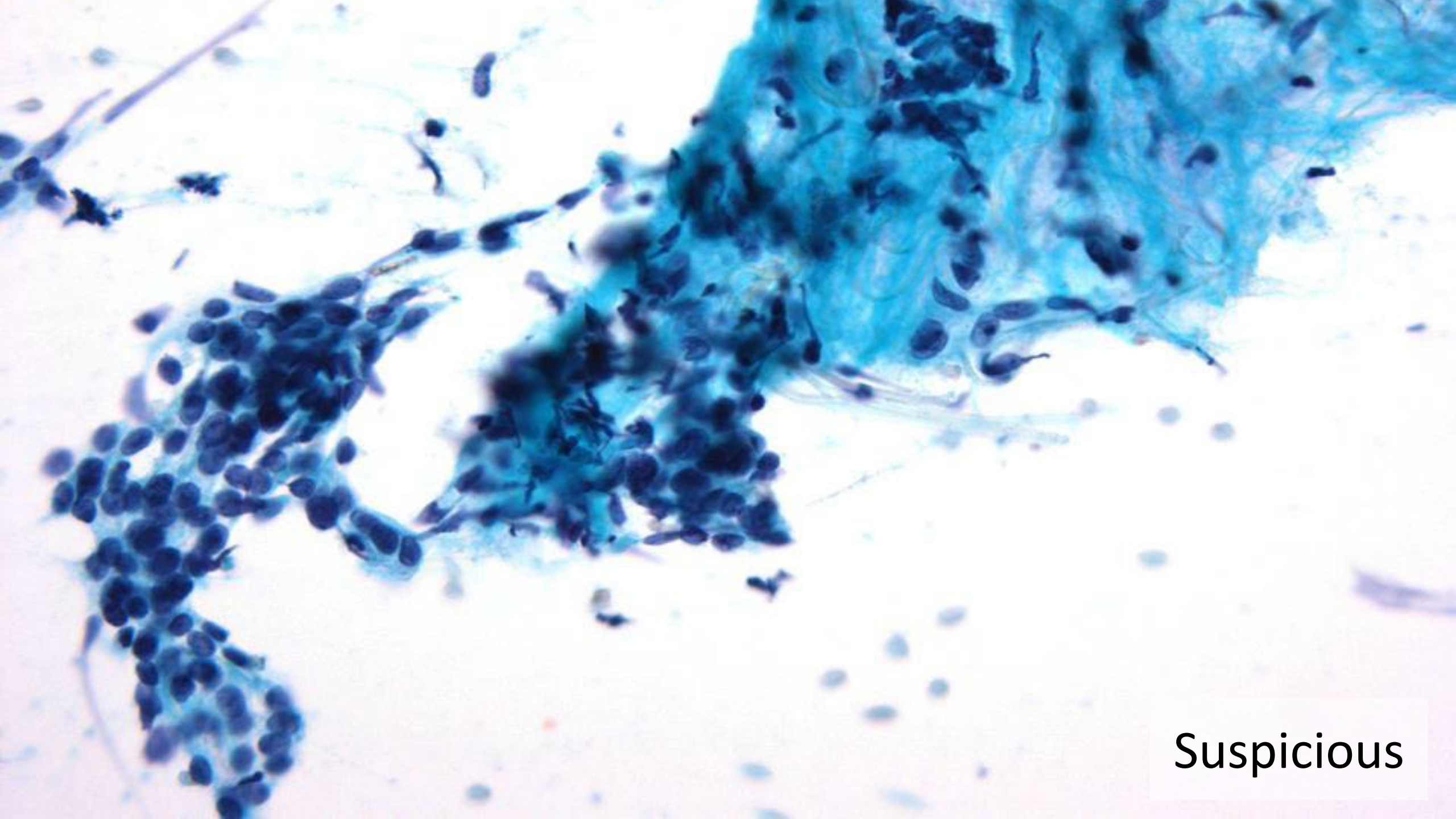

Atypical

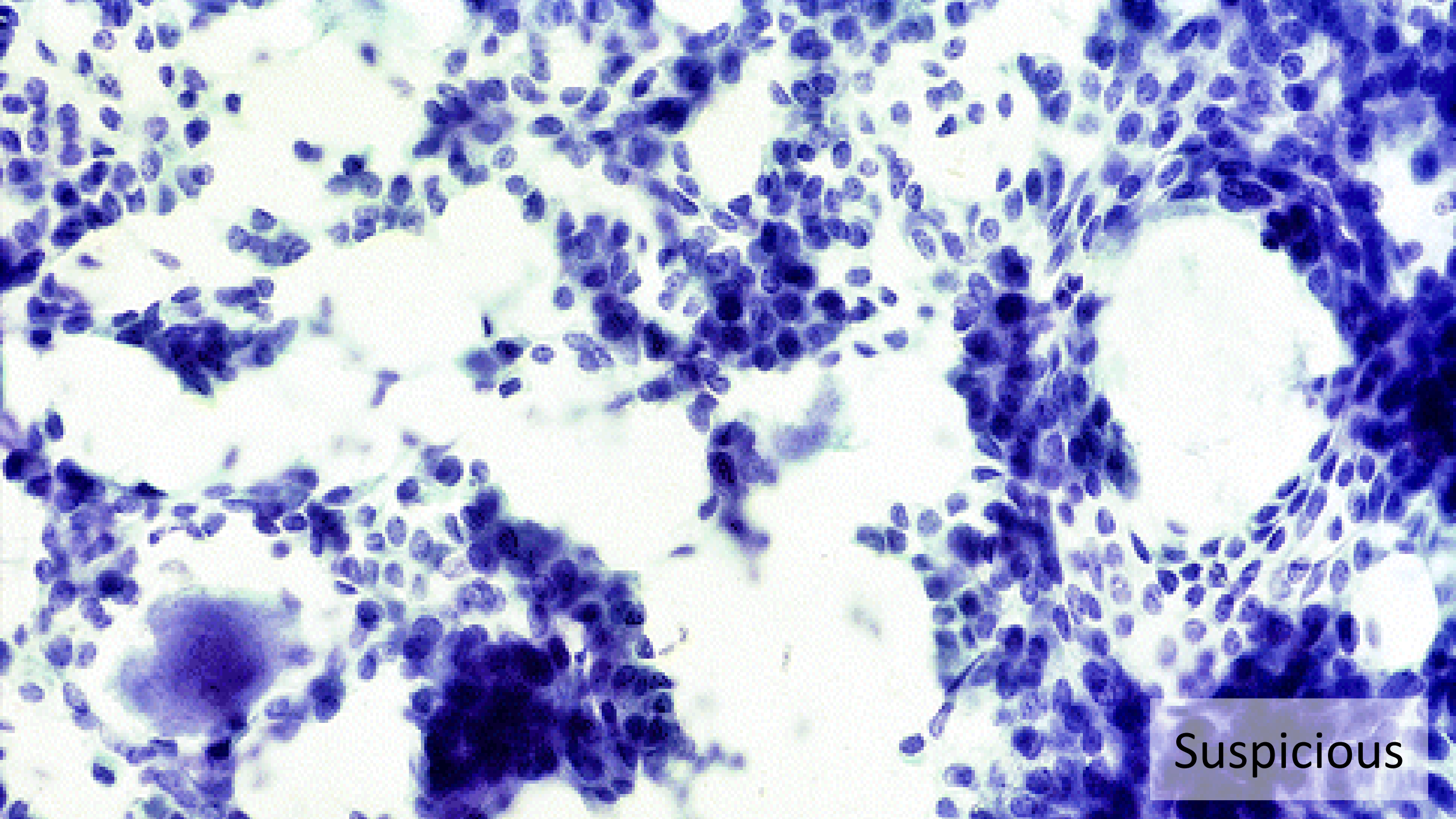
C4

- The presence of some cytomorphological features that are usually found in malignant lesions but with insufficient malignant features, either in number or quality, to make a definitive malignant diagnosis
- Limitation in specimen quality

C4

- High cellularity: a feature of carcinoma, but also be associated proliferative changes, such as epithelial hyperplasia, fibroadenoma, papillomas and radial scars
- The pattern of large epithelial tissue fragment with some showing a cribriform or micropapillary architecture, in association with smaller tissue fragments and plentiful dispersed cells showing low to intermediate grade nuclear atypia : features overlapped with low grade DCIS and IDC
- Necrosis: seen in high grade IDC and DCIS
    - High grade DCIS is usually associated with small numbers of dispersed markedly atypical cells and epithelial fragments and calcificaiton admixed with the granular necrotic debris


Suspicious


Suspicious

C5

- An unequivocal statement that the material is malignant and the type of malignancy identified should be stated whenever possible
- PPV 92% to 100%
- The key cytologic findings include:
  - High cellularity
  - Prominent dispersal of single cells
  - Crowded tissue fragments with overlapping nuclei
  - Nuclear enlargement
  - Anisonucleosis
  - Pleomorphism of the nuclear margin and size
  - Chromatin hyperchromasia
  - Prominent nucleoli

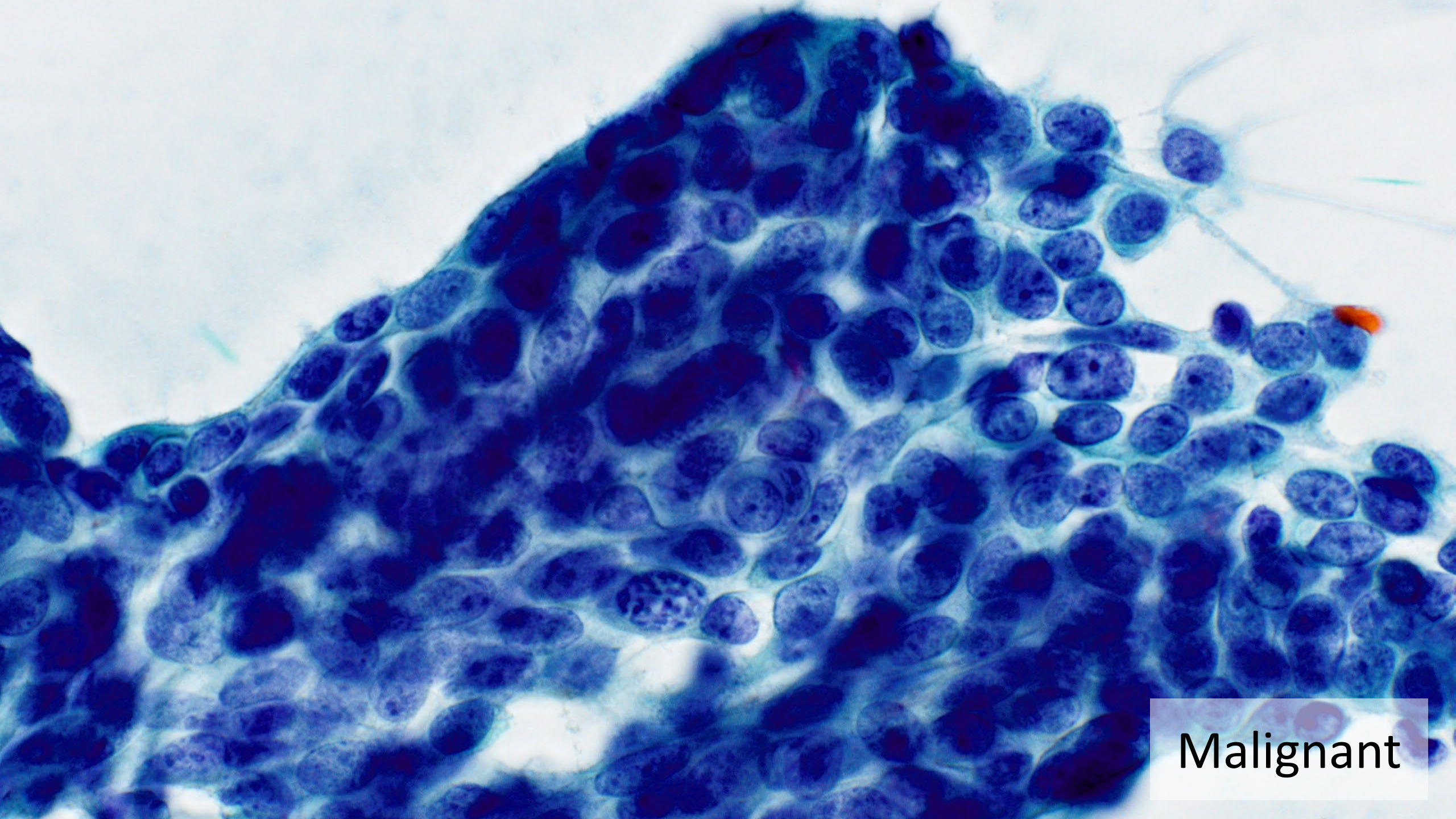
C5

The most common types of carcinoma diagnosed at FNAC

- No special type (ductal)
- Lobular
- Mucinous
- Tubular
- Metaplastic

Less common carcinomas diagnosed at FNAC

- Carcinoma with medullary features
- Adenoid cystic carcinoma
- Carcinoma with apocrine differentiation
- Carcinoma with neuroendocrine features
- Carcinoma with osteoclastic giant cells
- Malignant lymphomas
- Angiosarcomas
- Some metastatic carcinomas and metastatic melanoma


Malignant

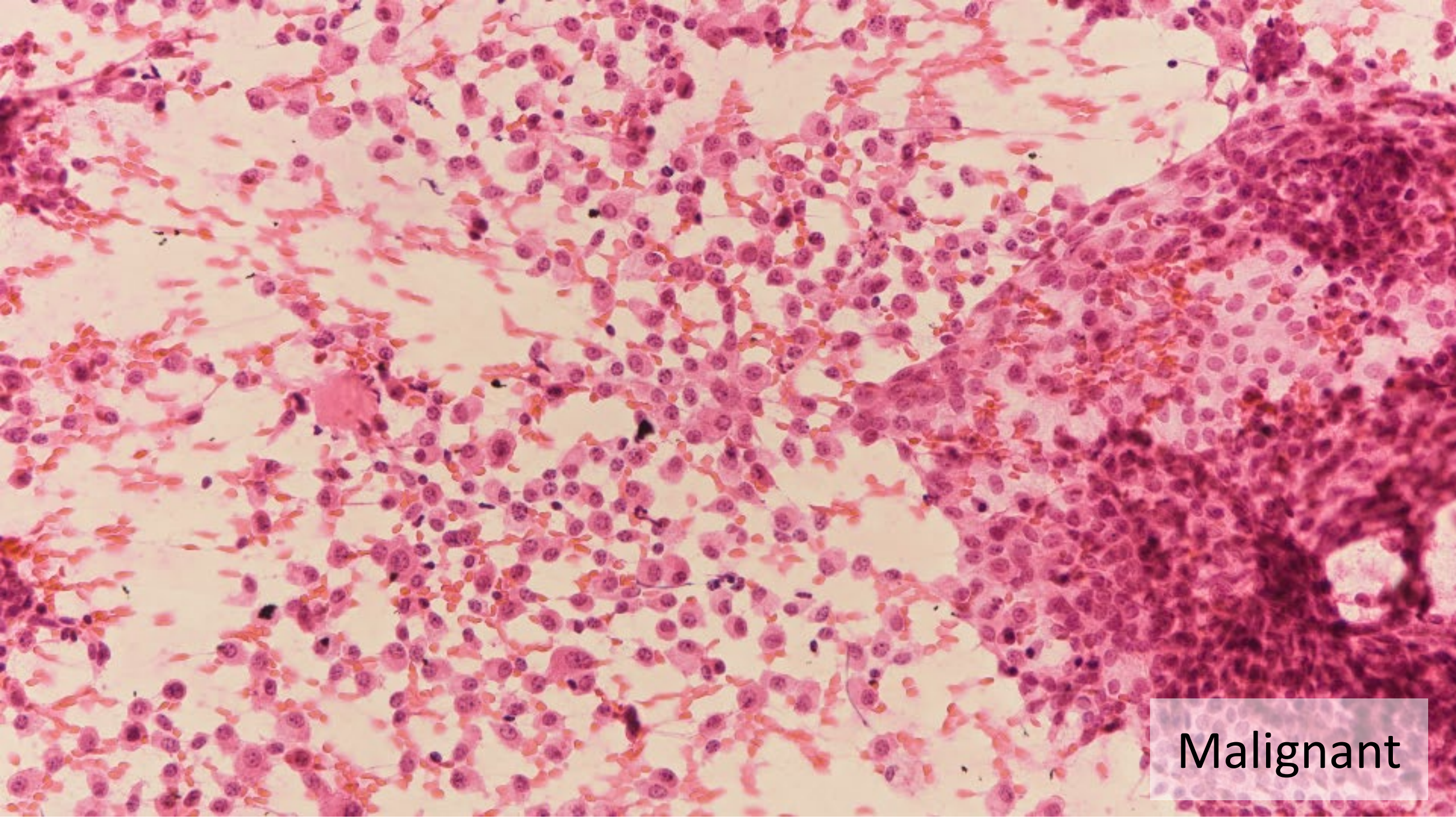

Malignant

Table 1. The WHO Reporting System : implied ROM and clinical management options by diagnostic category

Diagnostic category	**Estimated ROM[a]**	**Clinical management options[b]**
Insufficient/ Inadequate/ Non-diagnostic	0-60.9%	Repeat FNAB or consider CNB. If low clinical suspicion, consider repeat clinical and radiologic examination in 3-6 months
Benign	0-11.7%	Correlate clinically
Atypical	13.0-40.0%	Repeat FNAB or consider CNB. If low clinical suspicion, consider repeat clinical and radiologic examination in 3-6 months
Suspicious	45.8-100%	CNB or surgical management
Malignant	91.1-100%	If clinical or imaging discordant, CNB; if clinical and imaging concordant, treat per clinical stage

Abbreviations: CNB, core needle biopsy; FNAB, fine needle aspiration biopsy; ROM, risk of malignancy.

[a] Estimated ROMs are based on retrospective and prospective studies on International Academy of Cytology Yokohama System for reporting breast fine needle aspiration biopsy cytology {30783035; 31524134; 33017520; 30929288; 32749785; 31108486; 33755356; 34133084; 34029453; 33629823; 34321772; 34866246; 34876918; 34515039; 34535580; 34703093; 36516743; 36988122}.

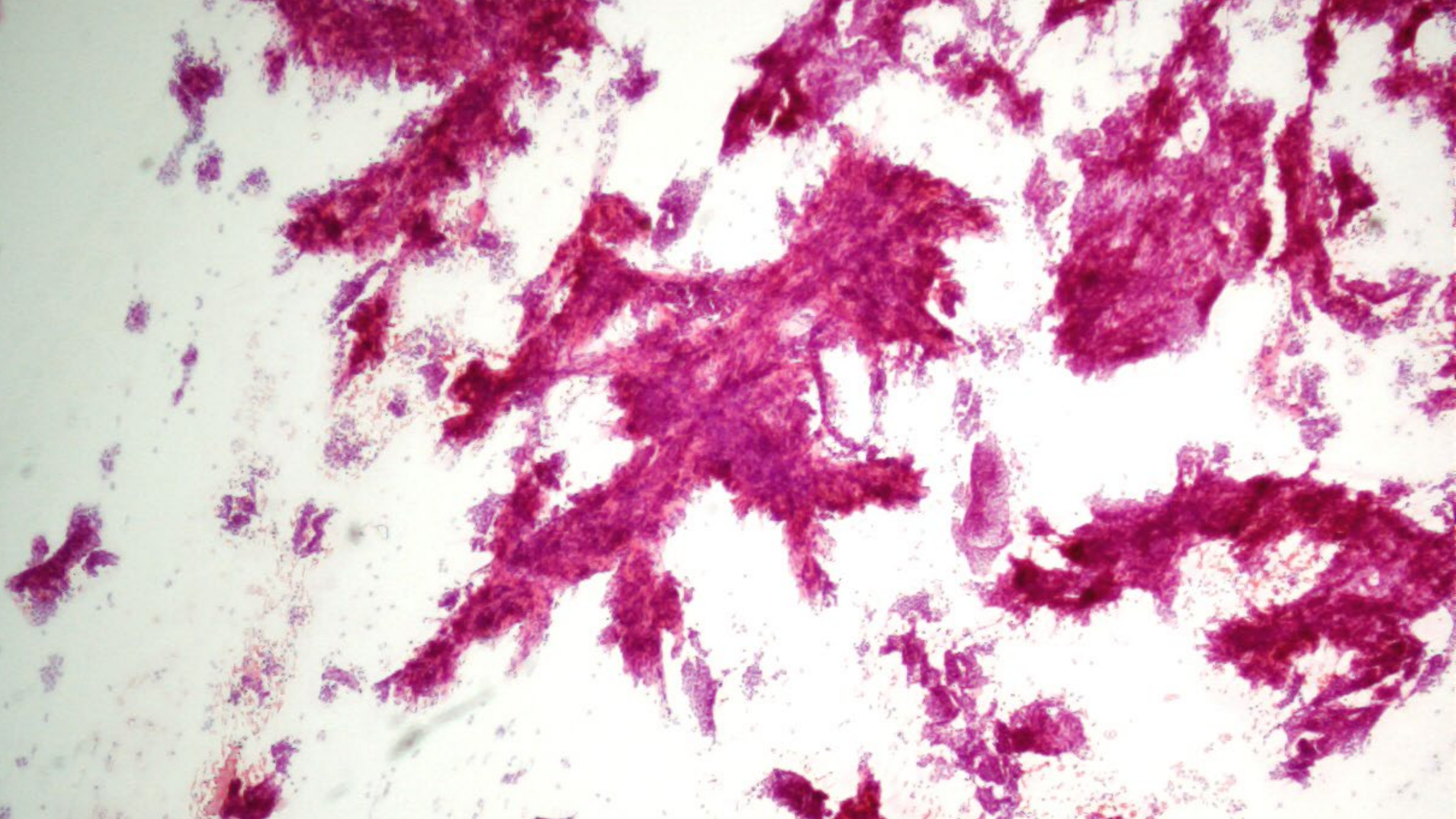
[b] While clinical management options are outlined above, individualized treatment approaches depend on a variety of factors, including clinical and imaging characteristics, overall functional status of the patient, and equipment availability of treating facility.

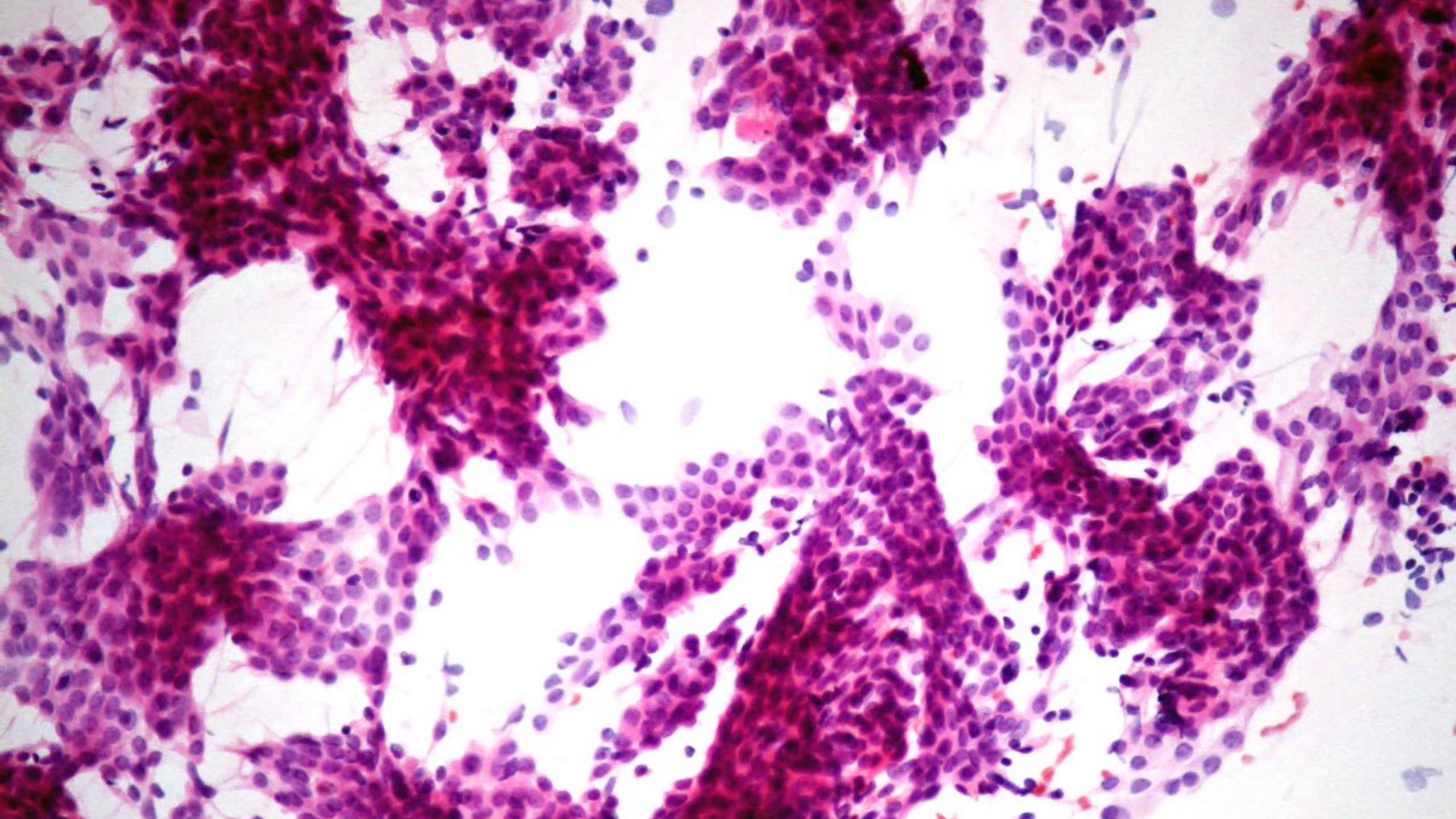
Cytology of common breast lesions

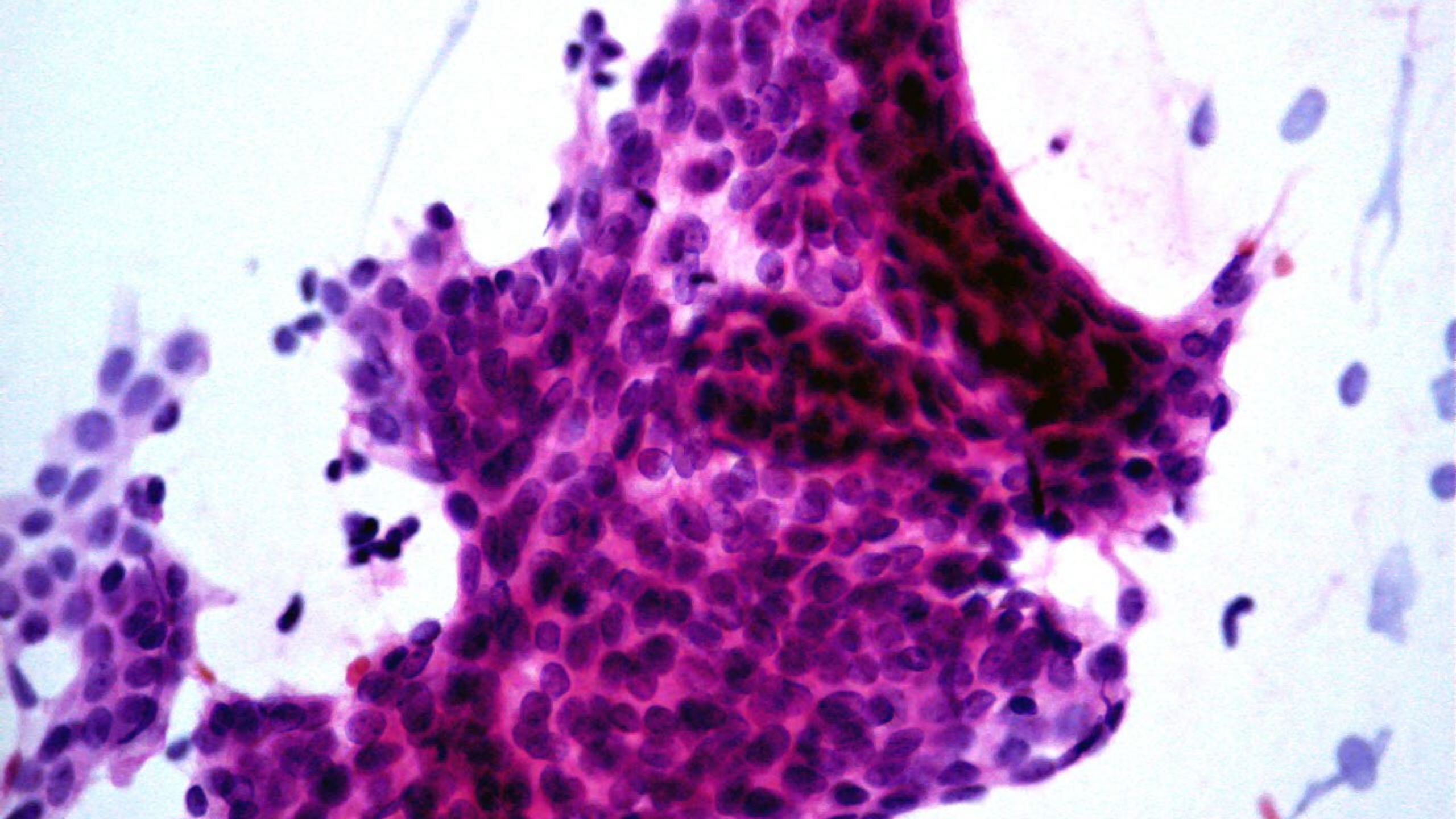
- Fibrocystic changes and hyperplasia
- Atypical hyperplasia and low grade malignancy
- Lobular neoplasia
- Fibroadenoma
- Phyllodes tumors
- Papillary lesions

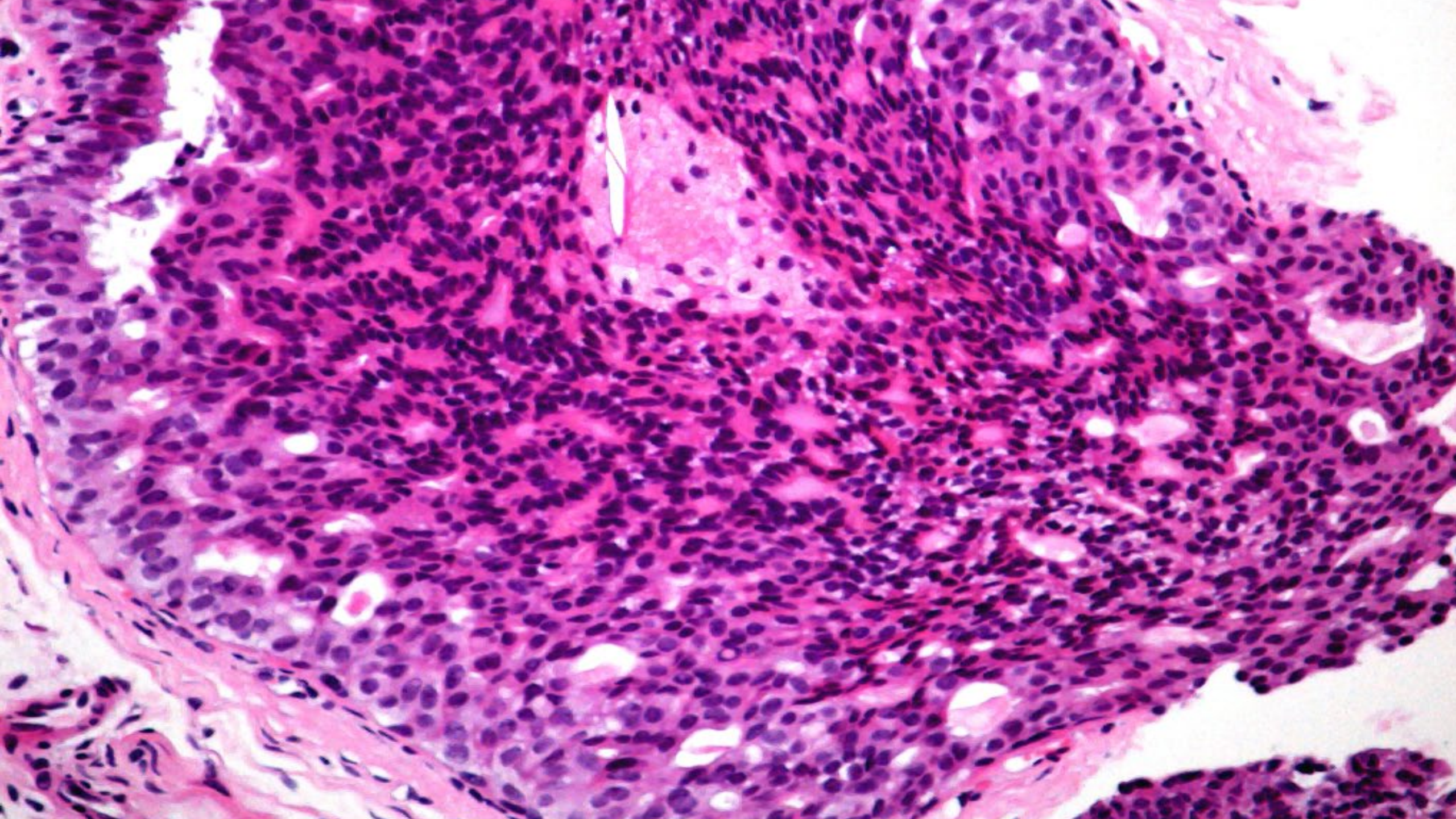
Fibrocystic changes

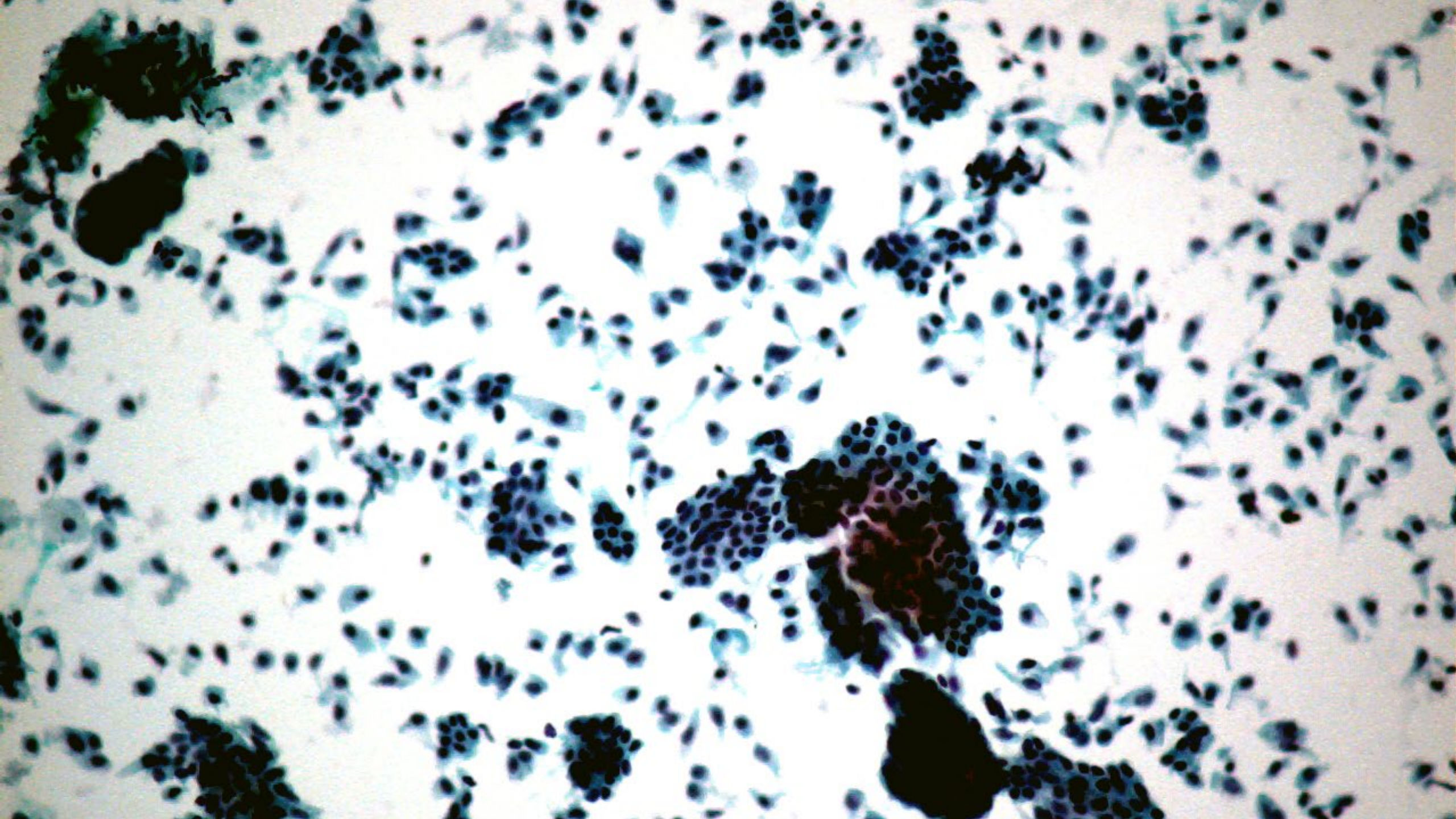
- Smears with variable cellularity; areas of proliferation are highly cellular, areas of fibrosis are rubbery and yield few cells and cysts yield fluid
- Predominantly solid lesions show a variable moderate to high cellularity
- Smear shows cohesive epithelial groups without or with mild nuclear overlapping and presence of myoepithelial cells
- Bipolar naked nuclei, foam cells, apocrine metaplasia and stromal fragments can be observed
- The cytologic diagnosis of FCC associated with proliferative lesions can be very difficult because there is a significant overlap of cytological features among the different lesions, notably ductal hyperplasia, sclerosing and tubular adenosis, radical scar, atypical hyperplasia and even tumors such as papilloma and low grade DCIS and invasive carcinomas.

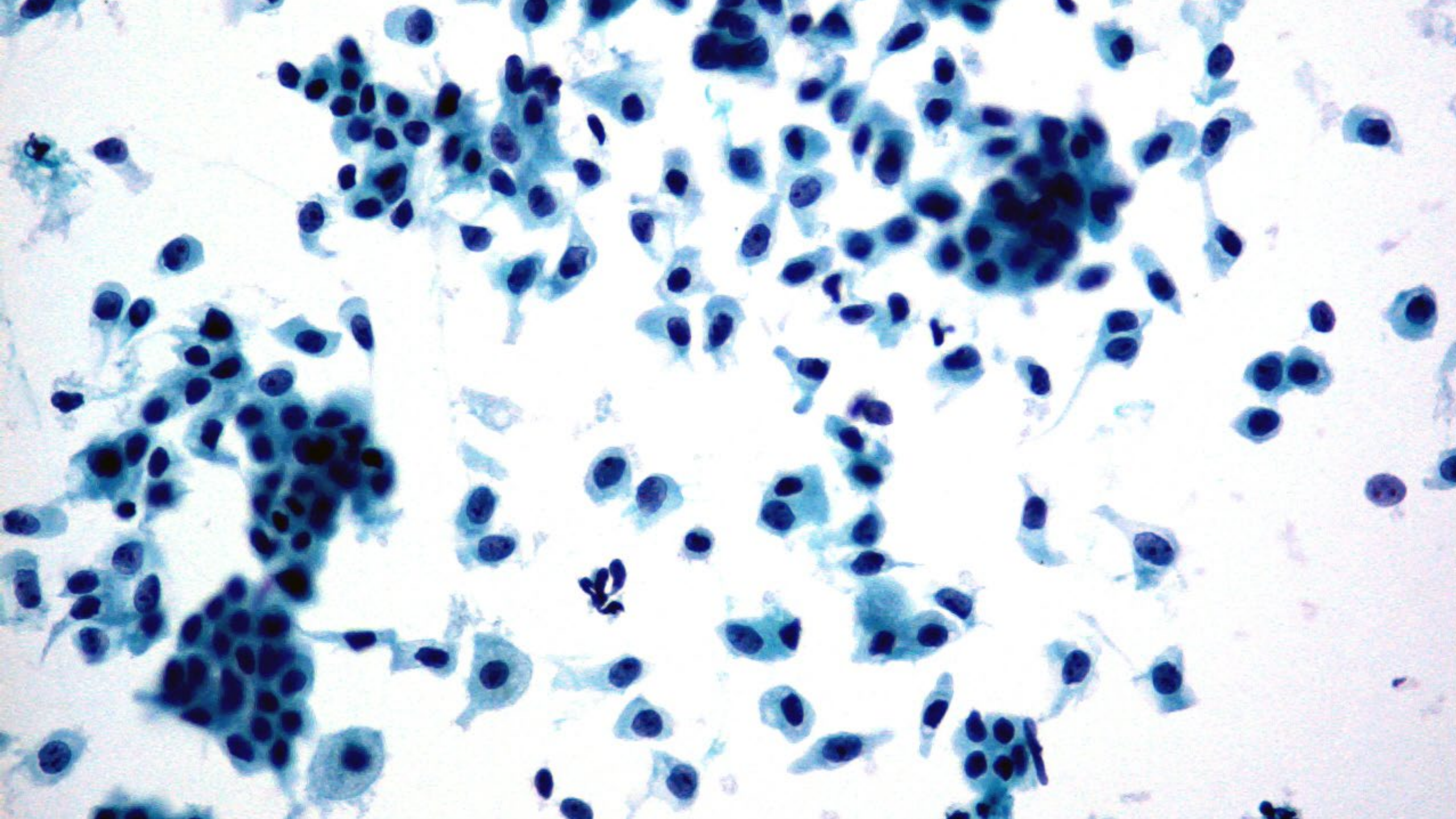


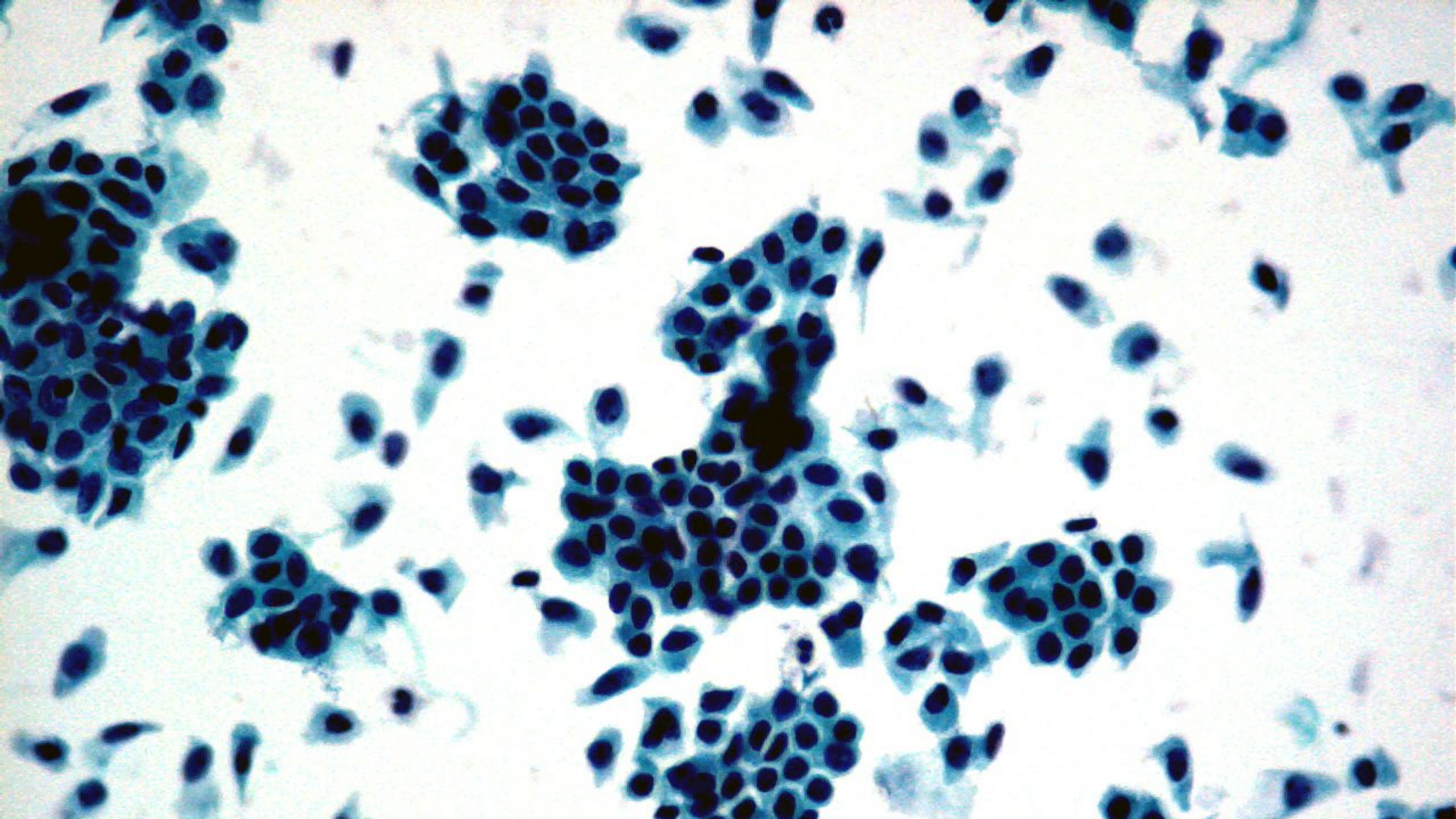












ADH / low grade DCIS

ADH

- Variable cytology
- Monotonous, evenly spaced epithelial cells
- Round nuclei, fine chromatin, inconspicuous nucleoli
- Cellular cohesion may be reduced

DCIS

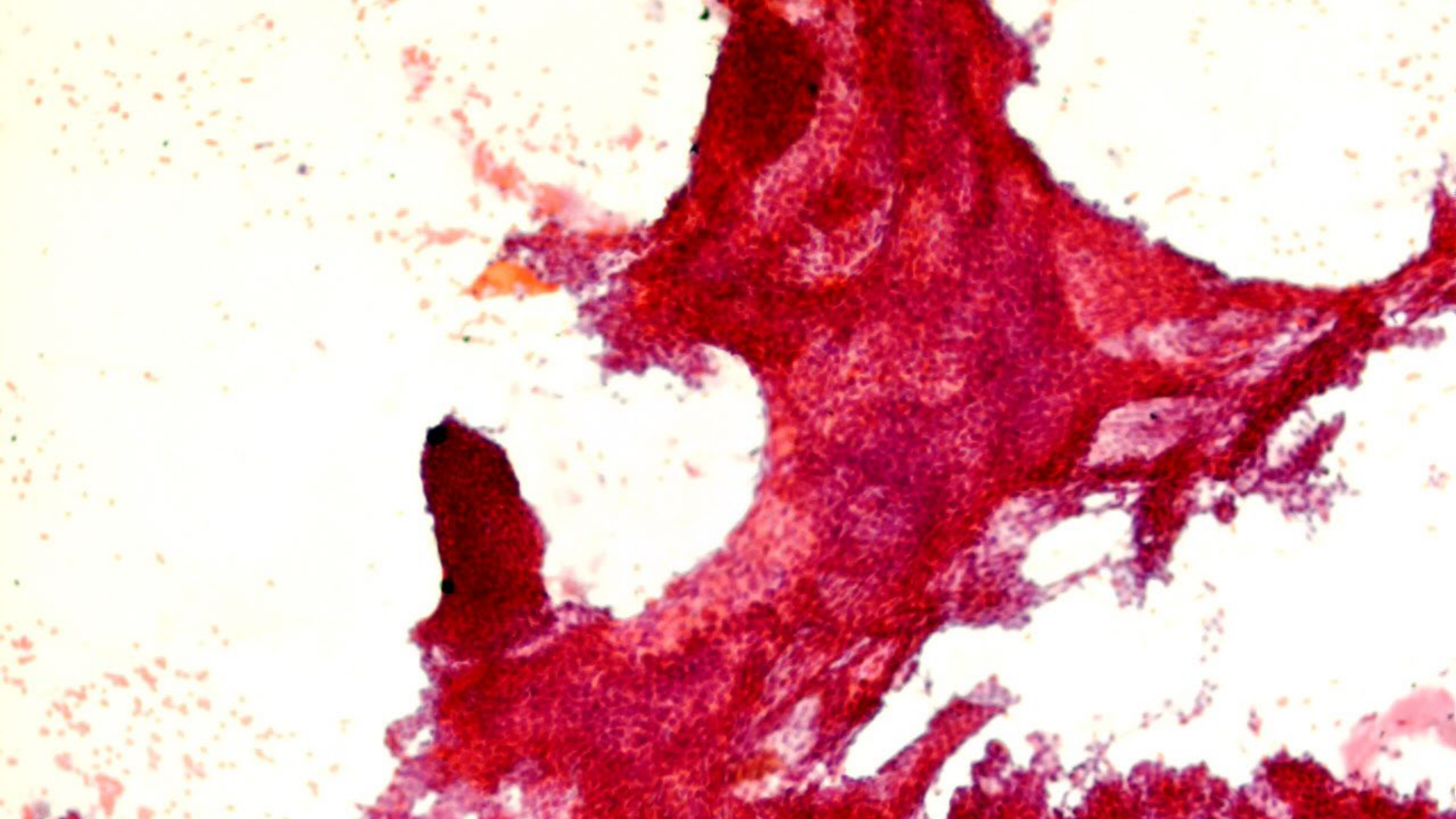
- Tend to have more sheets or tubules than single cells
- Nuclei are usually rather small, with single nucleoli, twice that of lymphocytes
- Tell tale sign : monomorphic population, devoid of myoepithelial cells
- No necrosis

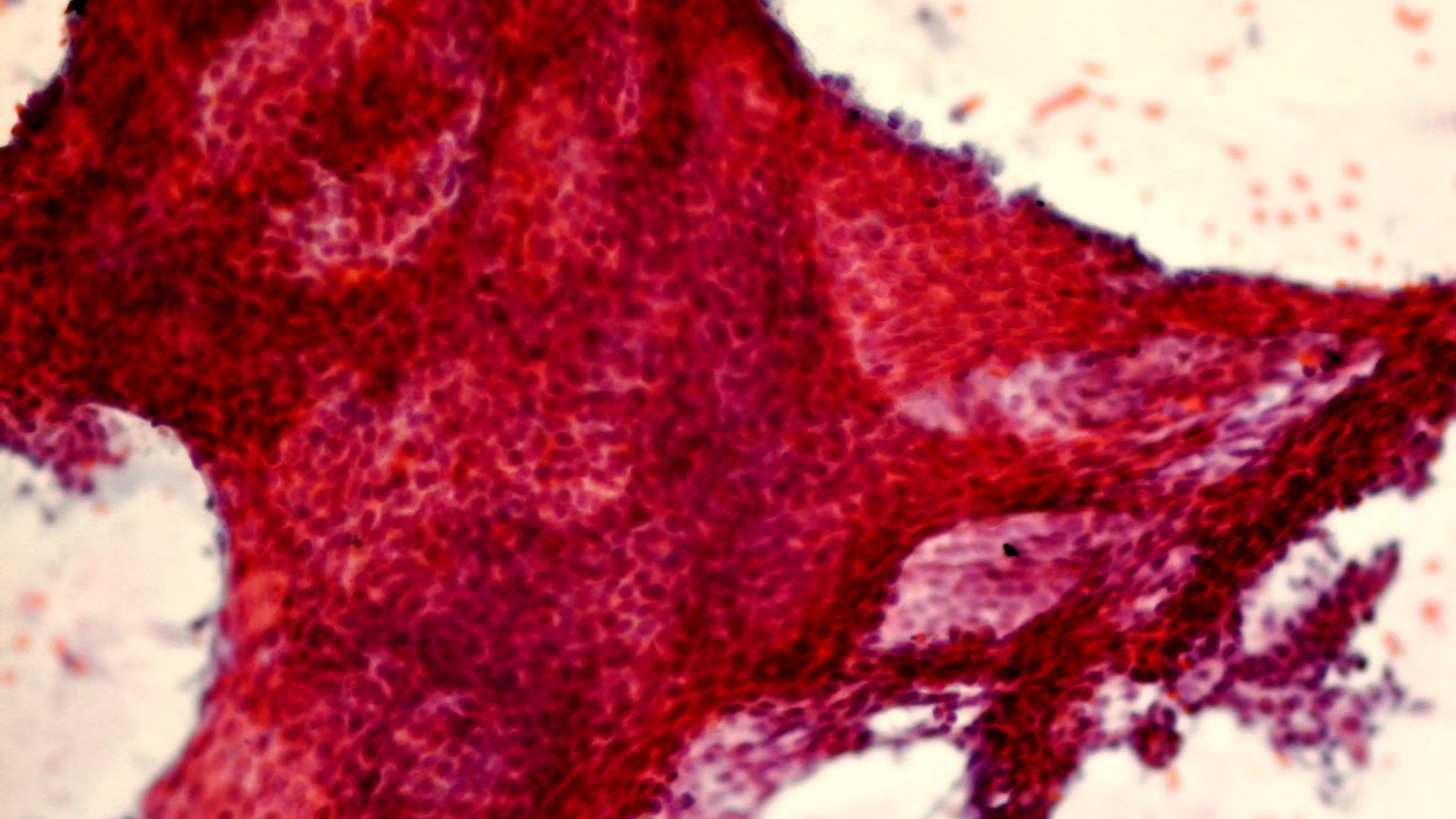
ADH / low grade DCIS

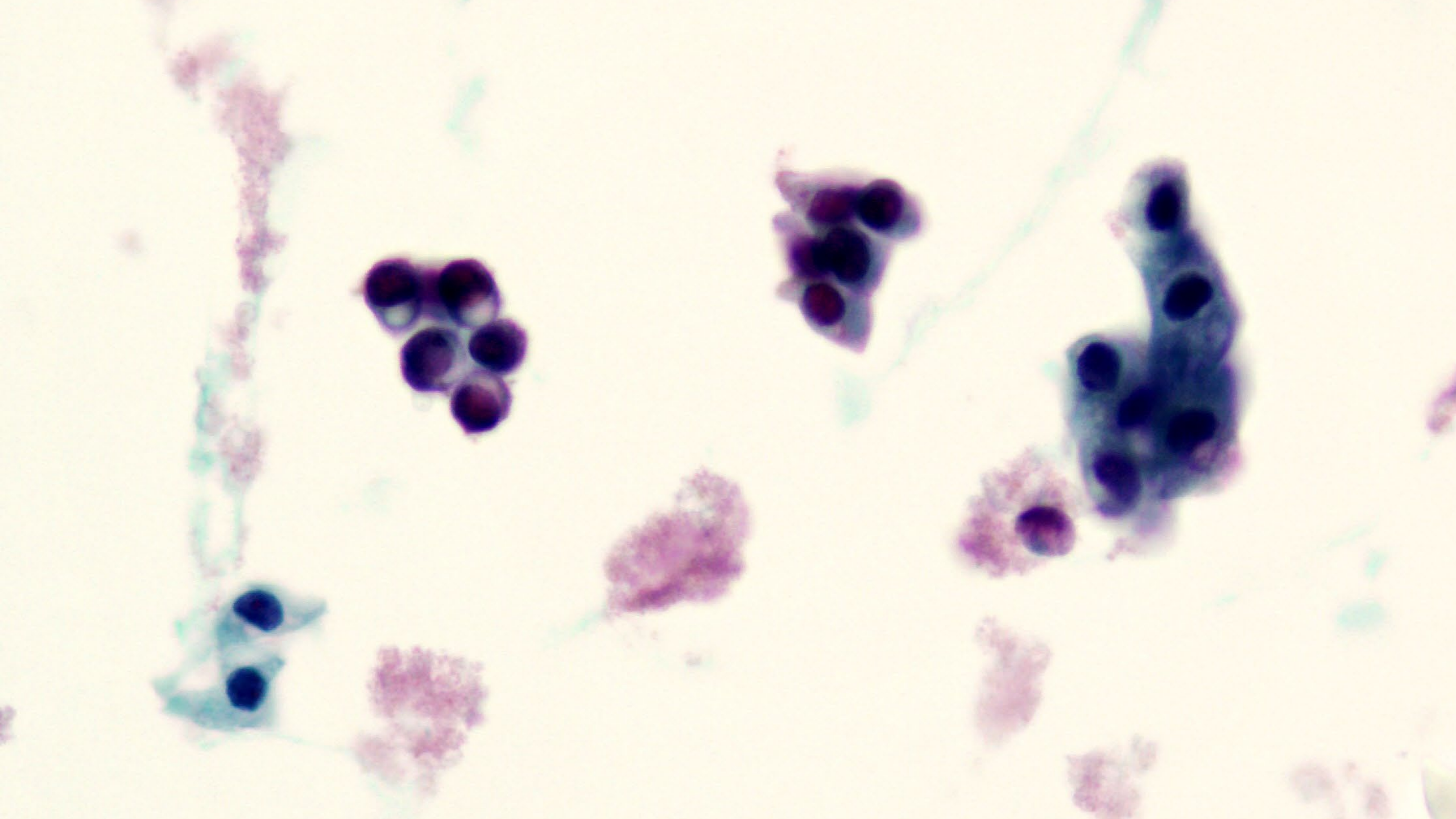
- ADH and low grade DCIS are grouped together as a low nuclear grade malignant breast lesions
- The aspirates exhibit low grade cytomorphology - uniform, rounded, monotonous nuclei with small nucleoli, and moderate amount of cytoplasm with rather distinct cell borders.
- Mitotic activity is not markedly increased and there is usually no significant necrosis.
- The main differentiating features : architecture and size, NOT cytomorphology

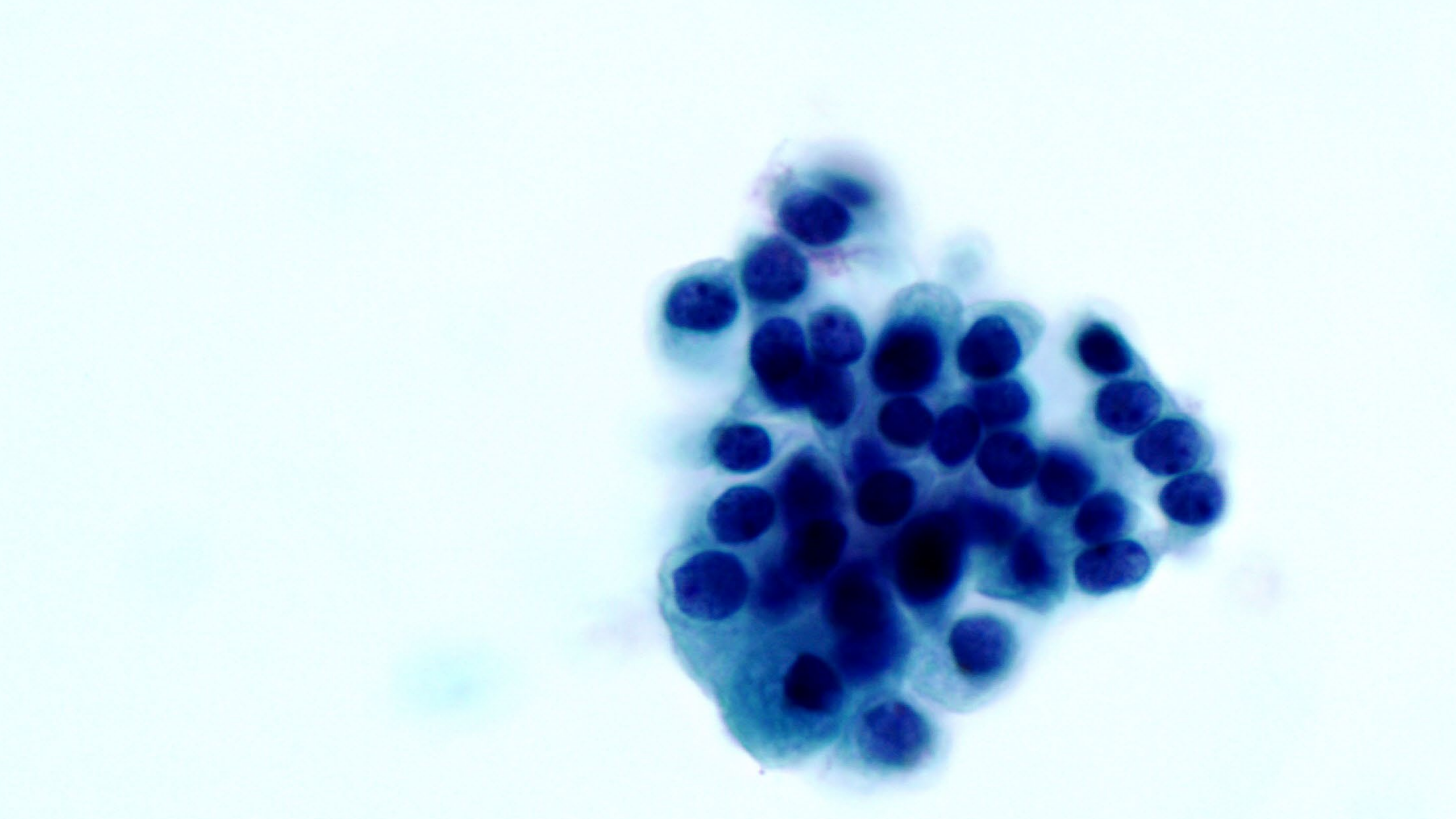
- Differentiation from benign hyperplasia : cellular monotomy, even nuclear placement and slight nuclear enlargement and hyperchromasia (vs nuclear variability, cell streaming and prominent myoepothelial cells or presence of apocrine metaplasia)

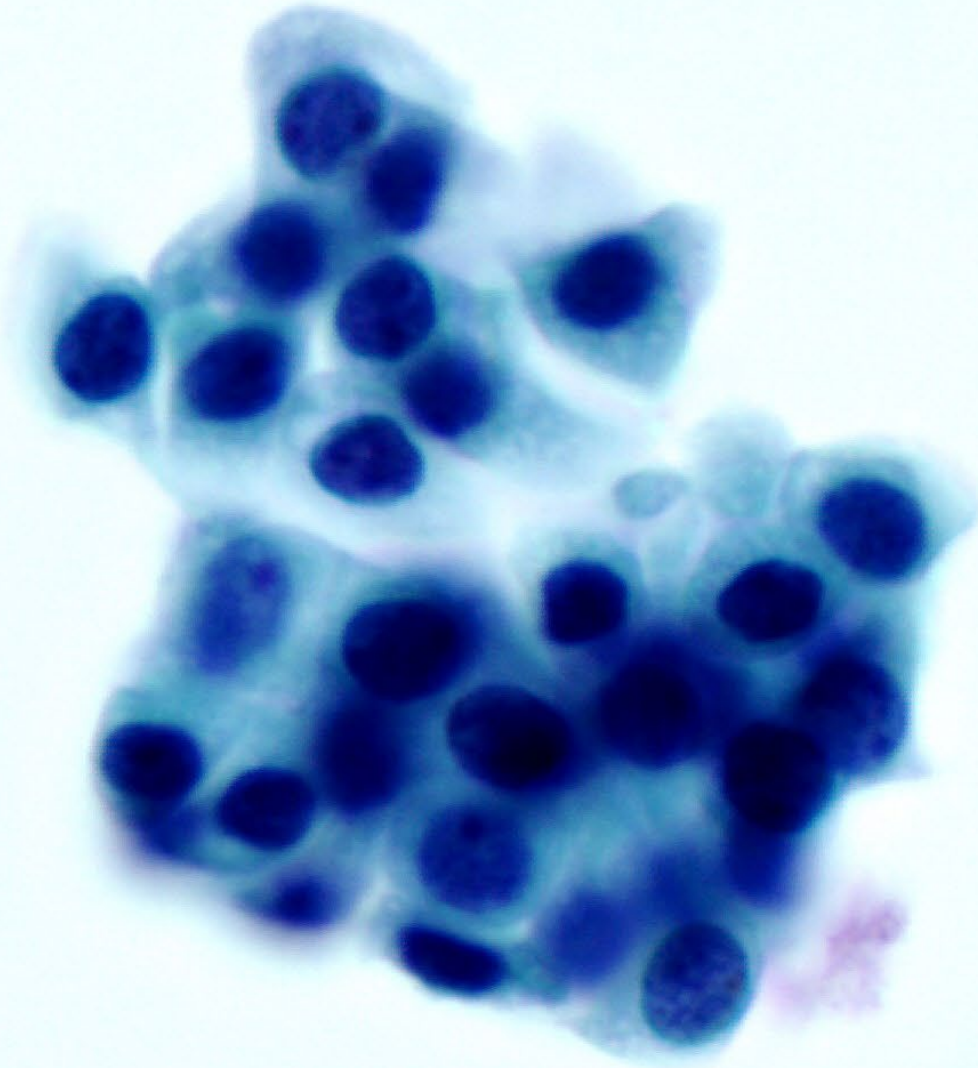
- Differentiation between ADH and DCIS, the cytologic differentiation is only based on lesional size and almost not possible in cytology.
- Aspirates that are more cellular with a monotonous cell population and the presence of numerous single cells, particularly in at least two separate smears, favor low grade DCIS over ADH

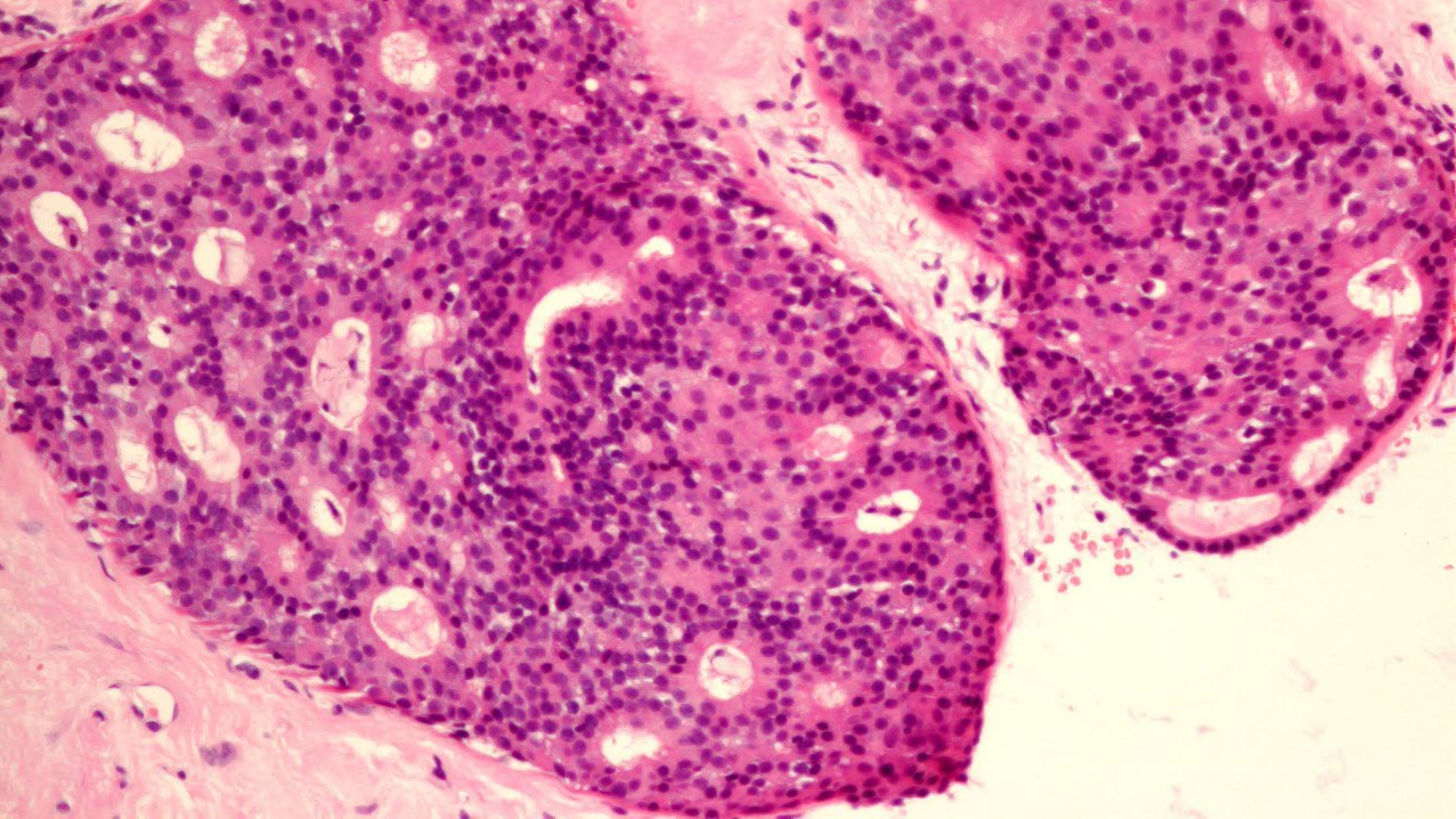




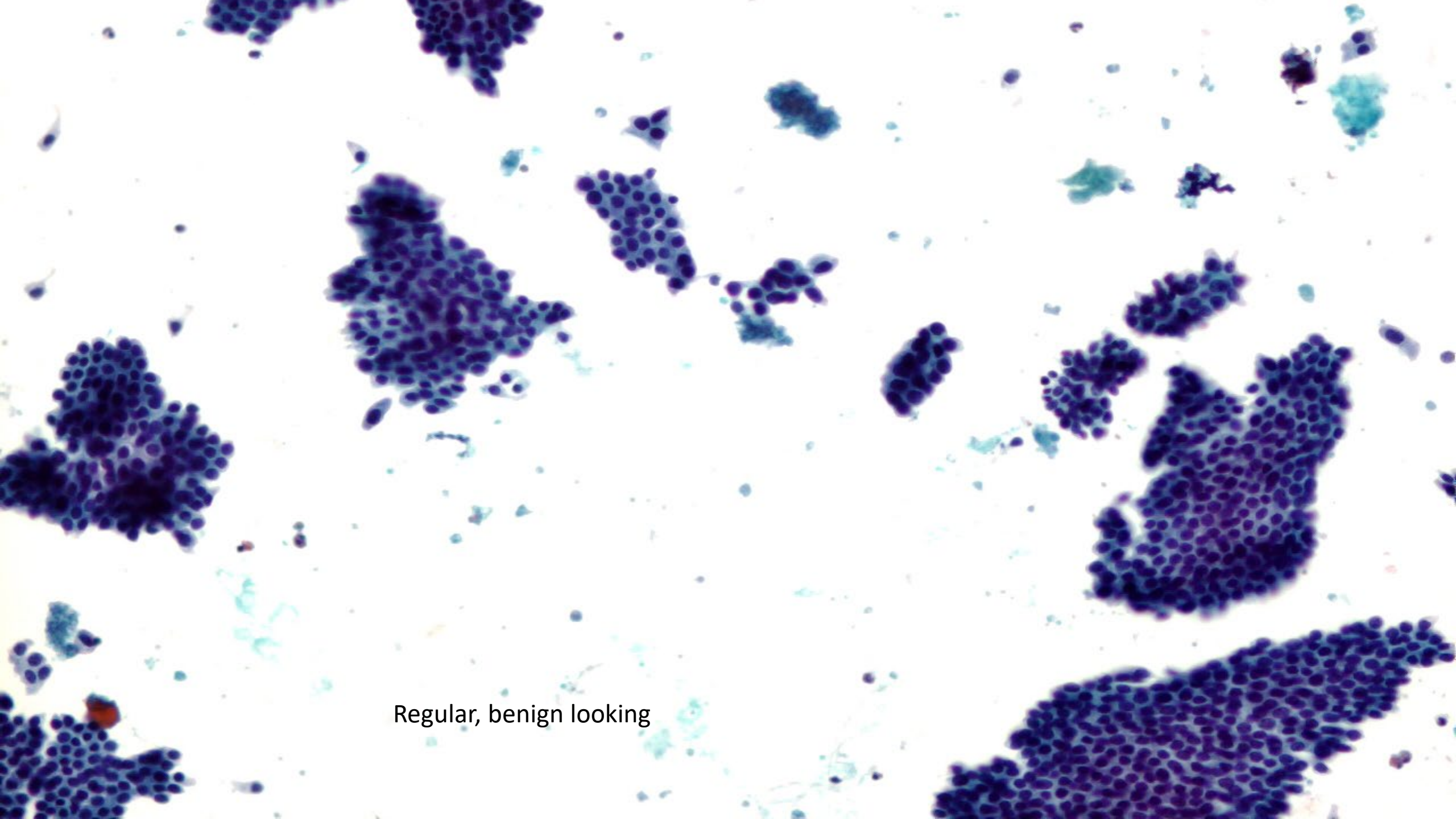


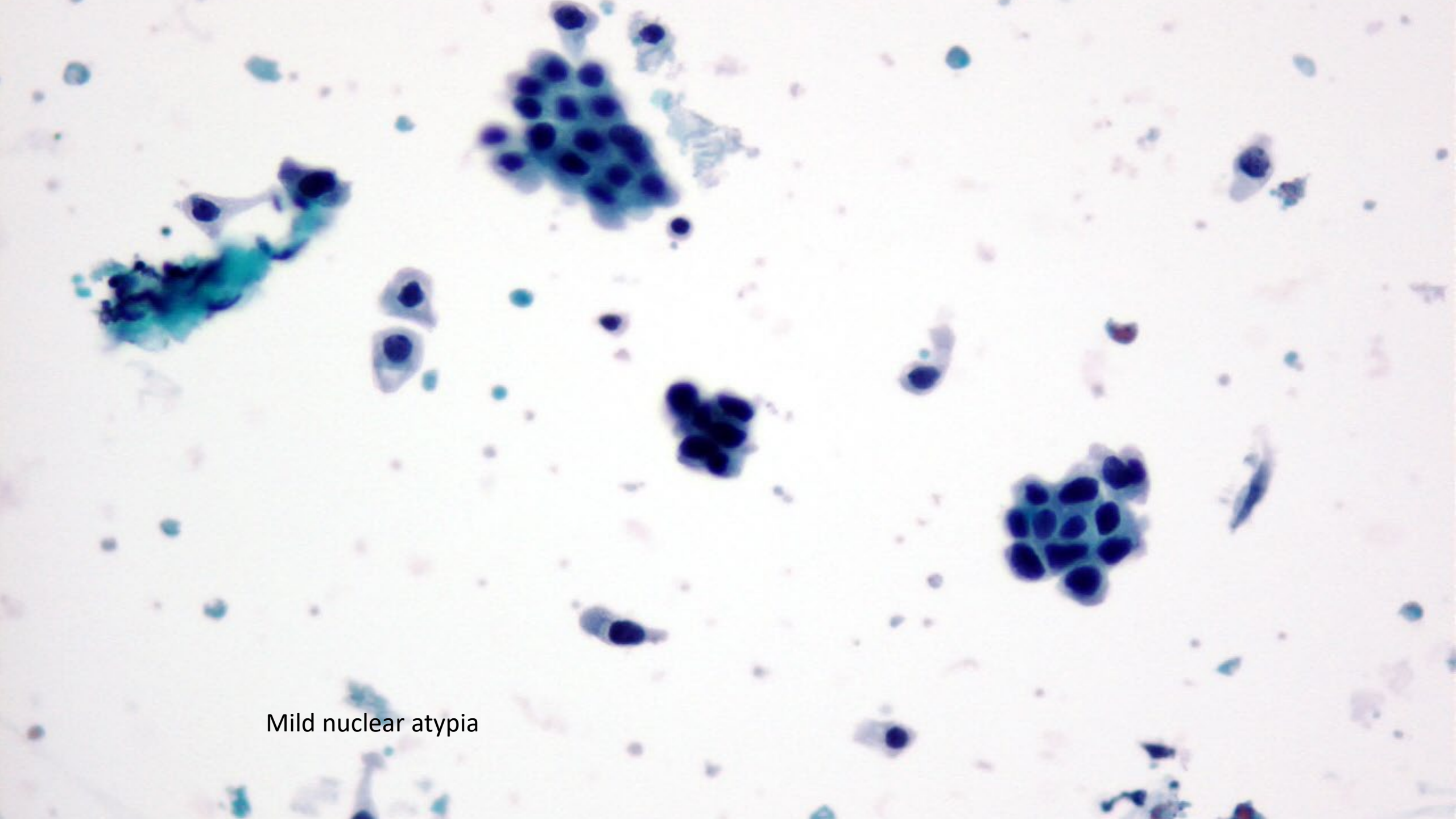




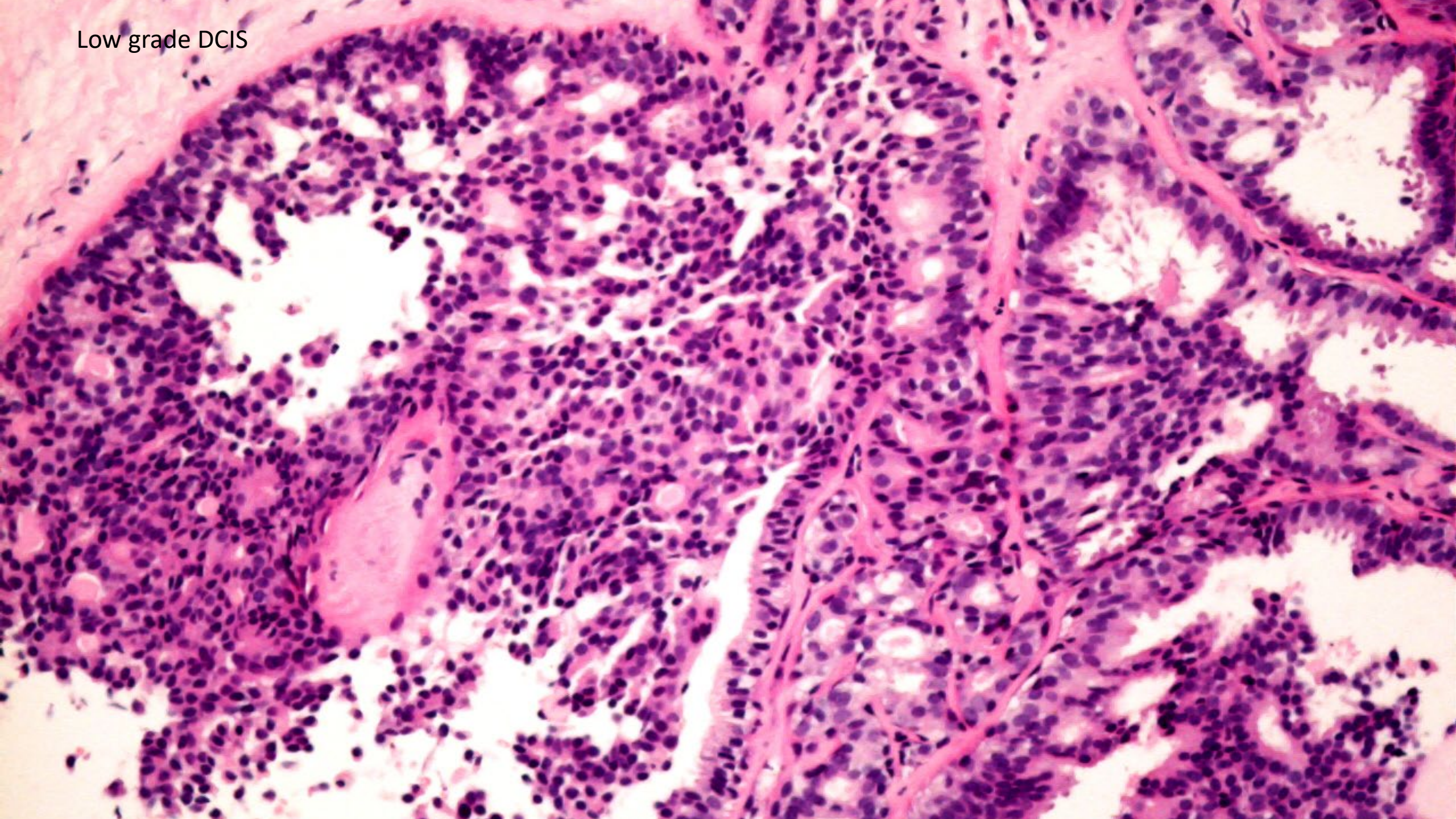


- 45 years old, vague breast mass for 3 months


Regular, benign looking

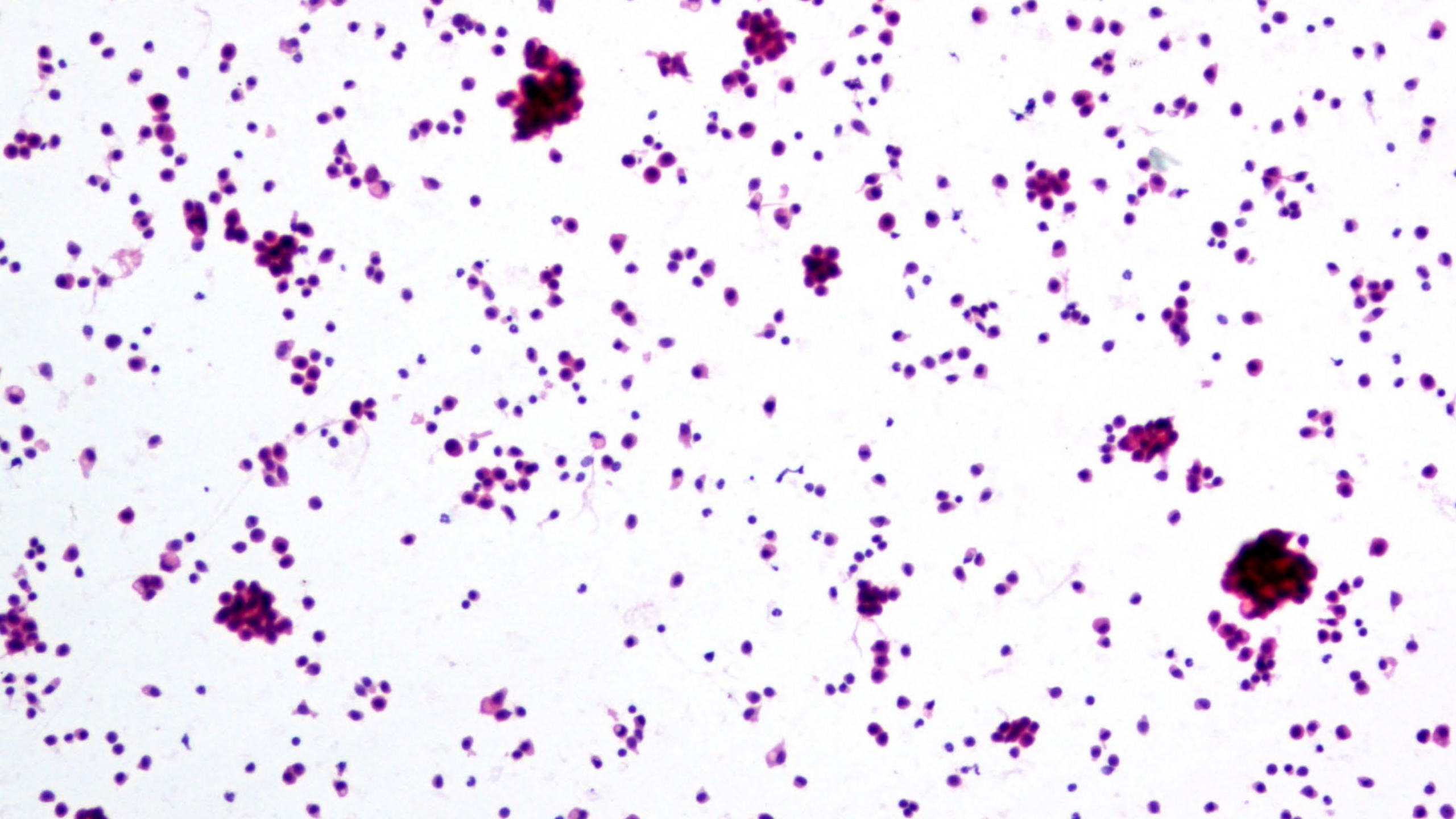

Mild nuclear atypia

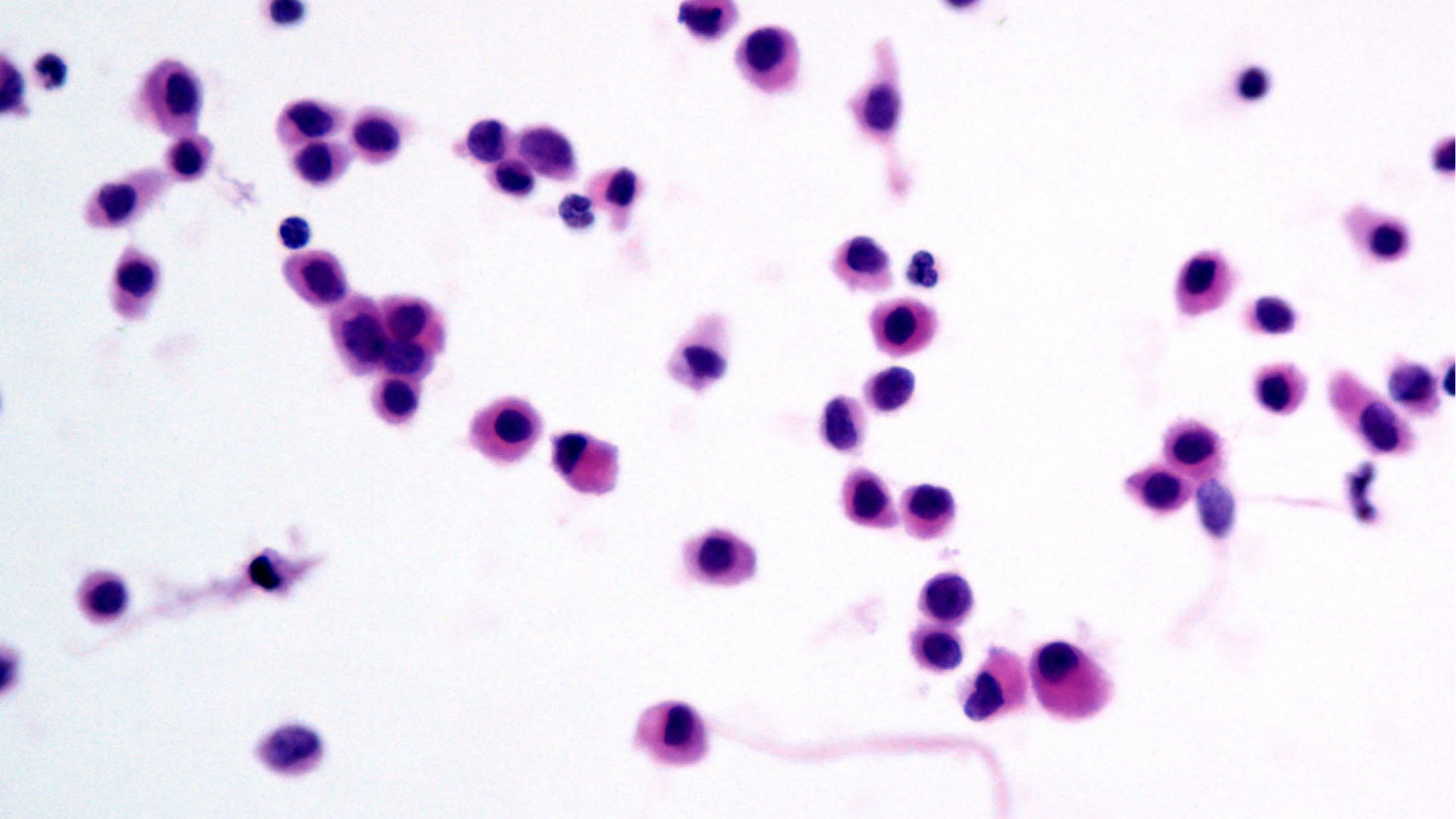
Low grade DCIS

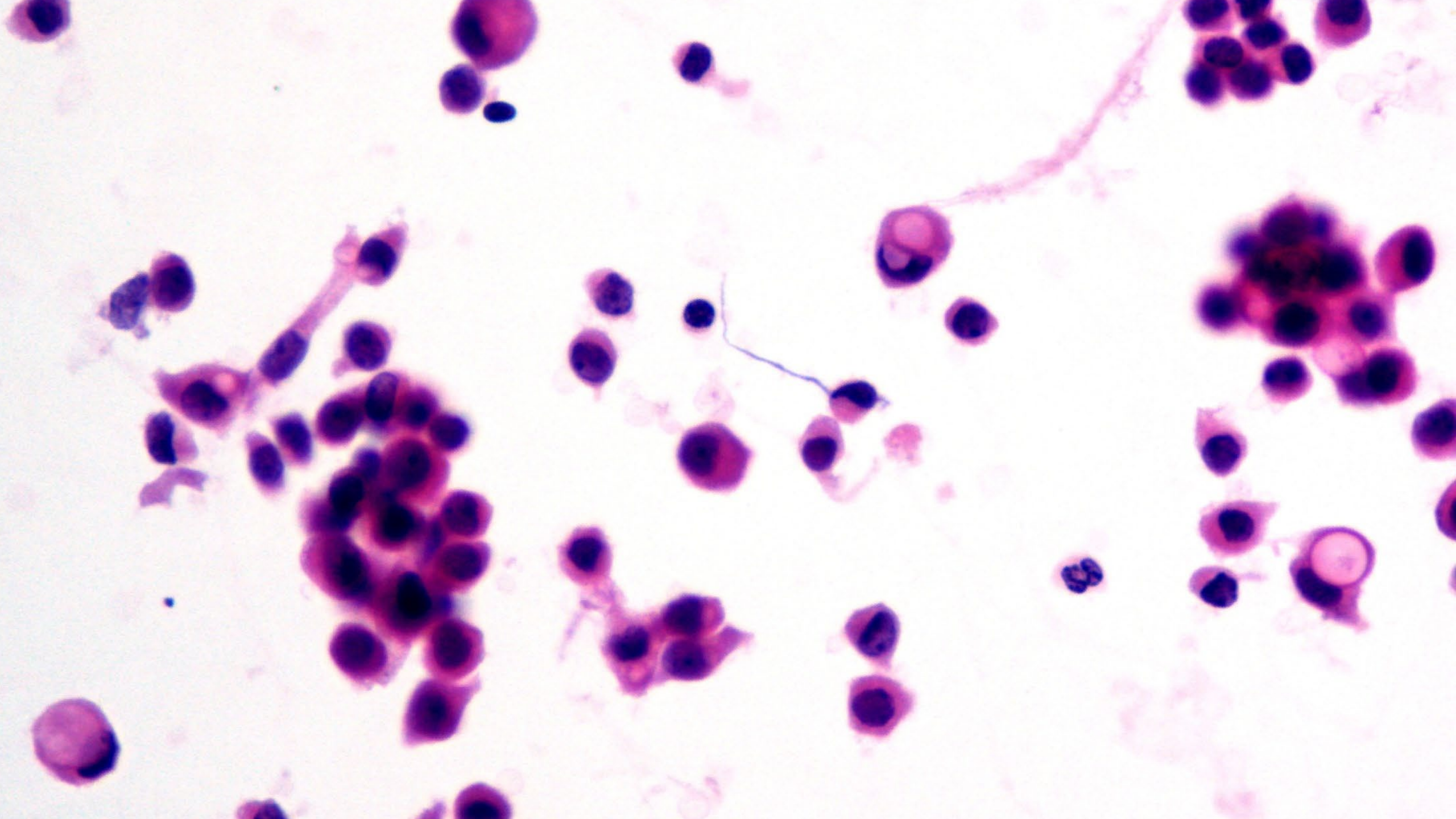


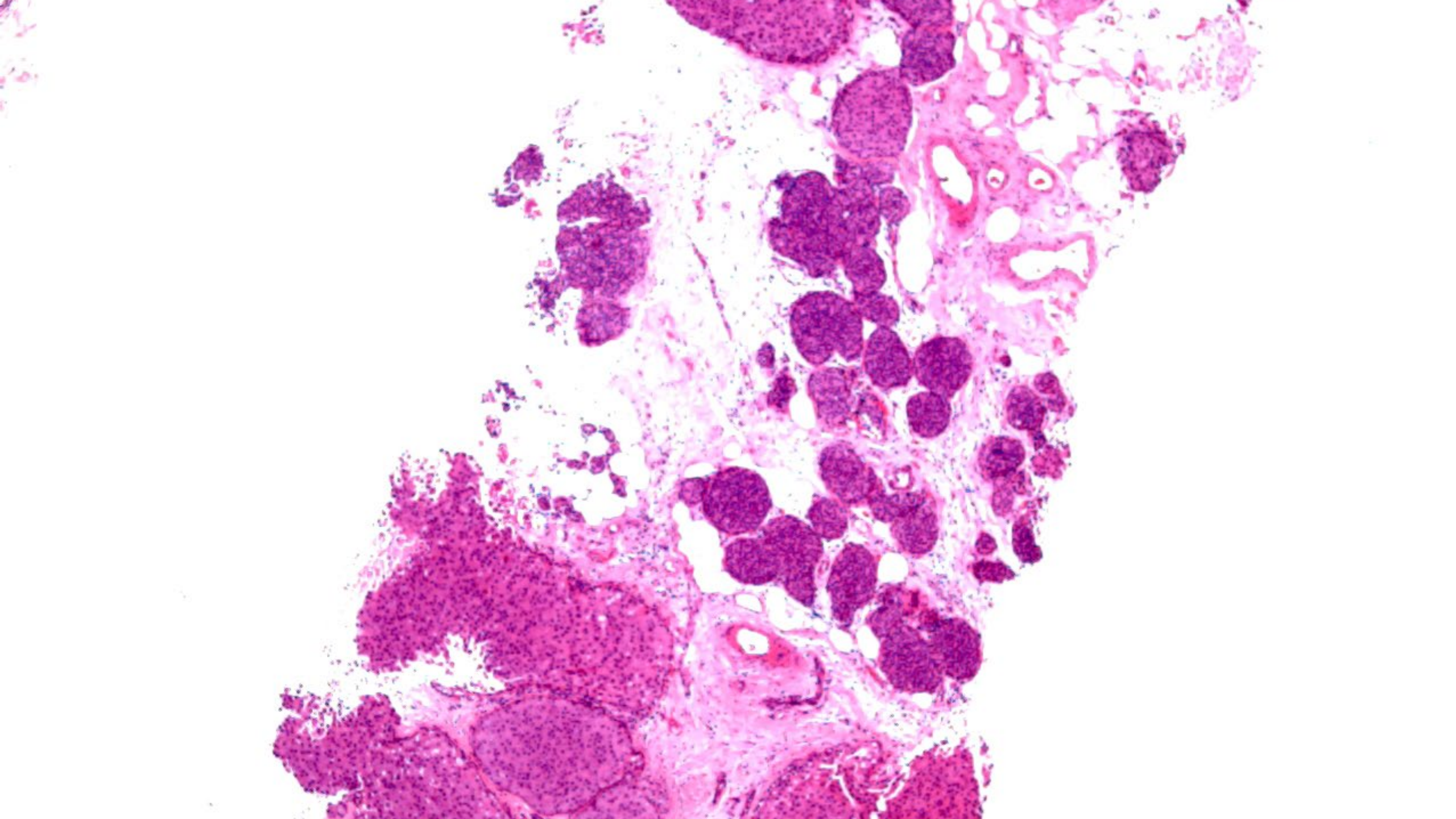
Lobular neoplasia

- LN = ALH and LCIS (size difference)
- The characteristic cytologic features reflect the typical histology
- Cells are small, uniform with eccentric nuclei and may also show intracytoplasmic vacuoles.
- Arranged in tight clusters, single cell files or singly
- Highest false negative rate among breast malignancies
- For the diagnosis of LN, cytologic atypia is insignificant; rather the diagnosis is more based on the paucicellularity, monomorphic pattern and absence of myoepithelial cells.
- Difficult scenarios include scant material showing a dispersed cell pattern with few minute tissue fragments and few bare bipolar nuclei
    - DD : under-sampled benign breast tissue VS lobular neoplasia









Fibroadenoma

- The most common benign breast lesion yielding C3 and C4 in FNAC
- Aspirates of FA are hypercellular with antler- or staghorn shaped epithelial clusters and honeycomb monolayered sheets, set within a clean background with many naked biopolar nuclei, giving an appearance of sesame seeds strewn among epithelial fragments

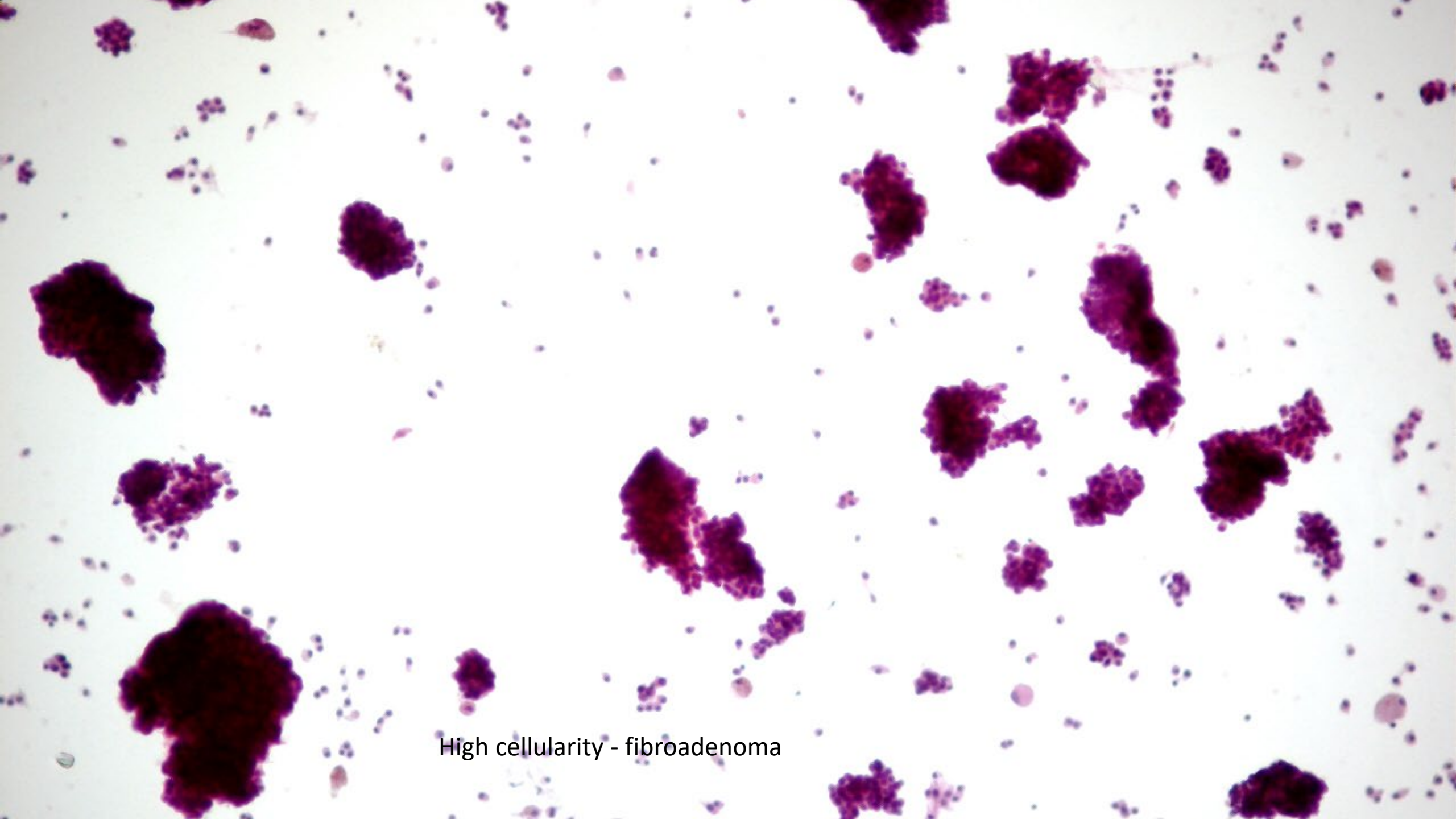
Fibroadenoma

- The smears maybe atypical, with isolated intact epithelial cells with nuclear atypia
  - DD: fibroadenoma VS low grade carcinoma including tubular carcinoma

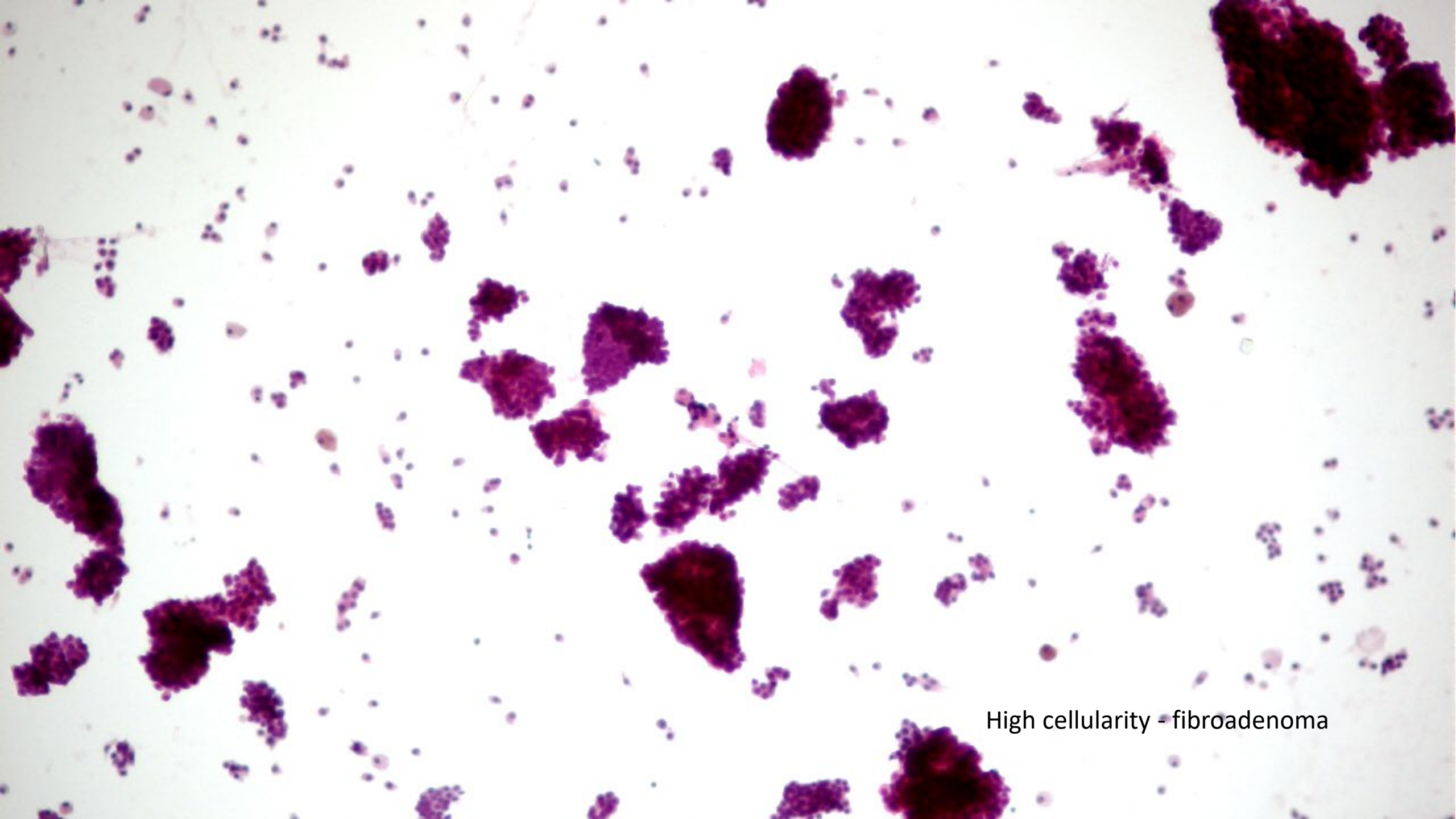
- A large epithelial tissue fragment pattern with rounded, scalloped or more fibrillary stromal fragments suggesting a fibroadenoma but with focal or more diffuse epithelial nuclear enlargement, pleomorphism, granular hyperchromatic chromatin and larger nucleoli, and increased dispersal
  - DD: fibroadenoma with epithelial hyperplasia VS fibroadenoma with carcinoma (in situ/inv)

- High cellularity, apocrine metaplasia especially with degeneration, and multinucleation may be confused with carcinoma with osteoclastic giant cells

- Smears of FA with myxoid changes may be confused with mucinous carcinoma



High cellularity - fibroadenoma

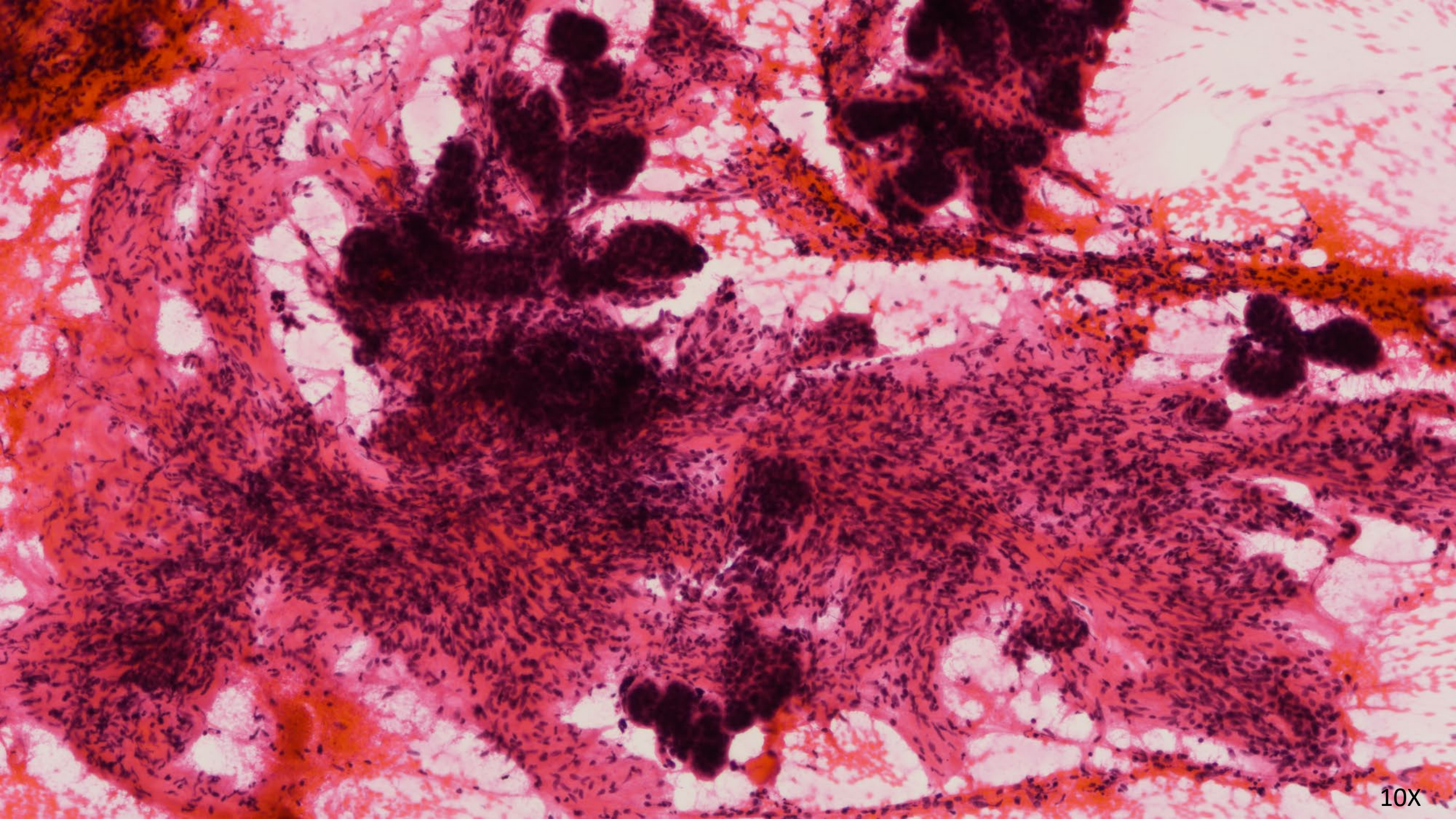


High cellularity - fibroadenoma

Phyllodes tumor

- PT is less common, but can also be encountered in a C3 aspirate
- Cytologic distinction between PT and FA can be problematic - overlapping characteristics
- PT : fibromyxoid and cellular stromal clumps containing spindled nuclei, fibroblastic pavements, reduced epithelial stromal ratio, larger epithelial clusters with wavy or folded shapes and stromal cytologic atypia

- The cytologic grading of PT is very difficult : overlap between benign, borderline and malignant PT
- Some reported the presence of hypercellular smears, mitotic figures, phyllodes fragments, and atypia of stromal cells in malignant cases, but mitoses can be difficult to assess in FNAC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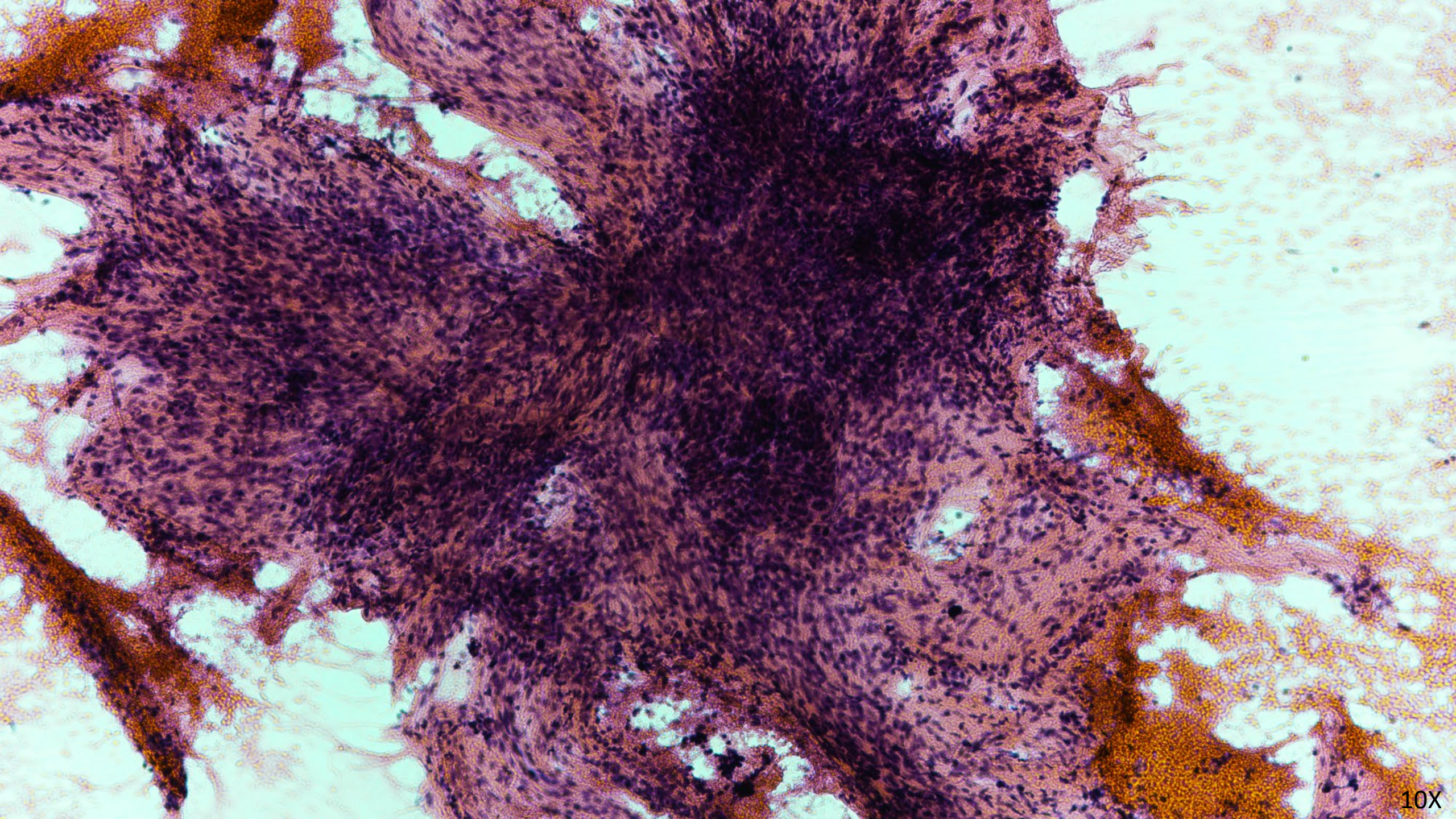
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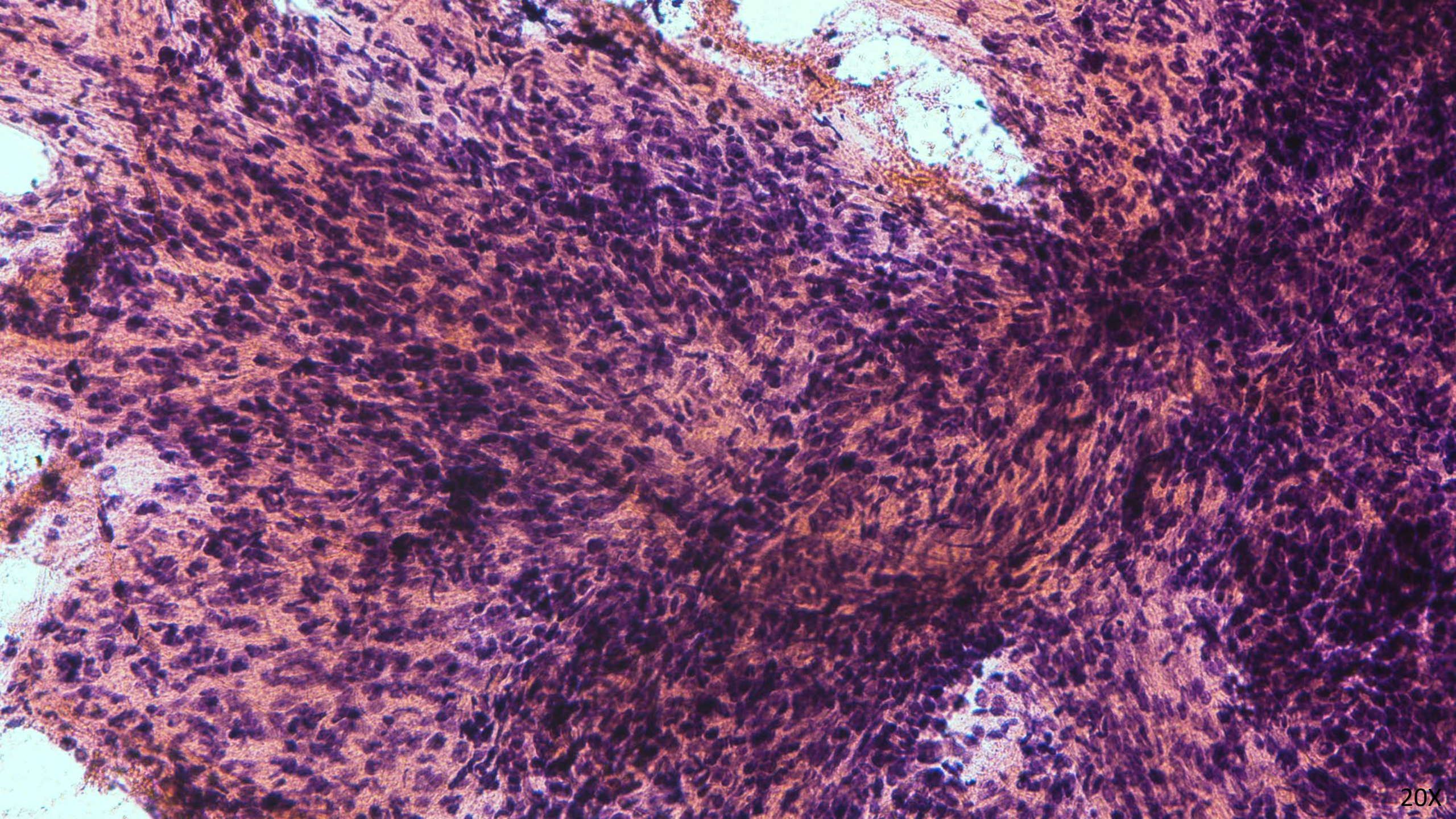
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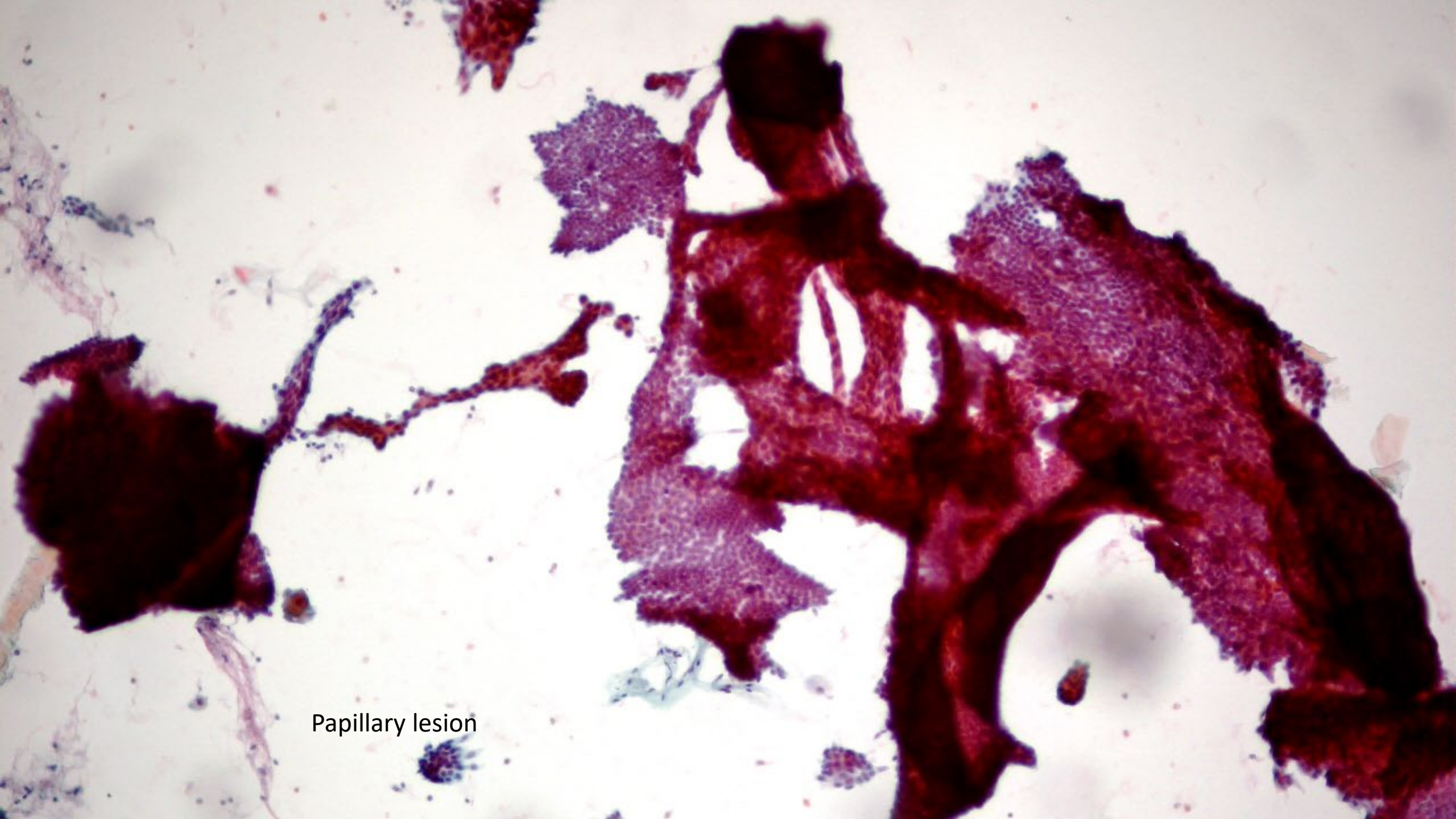
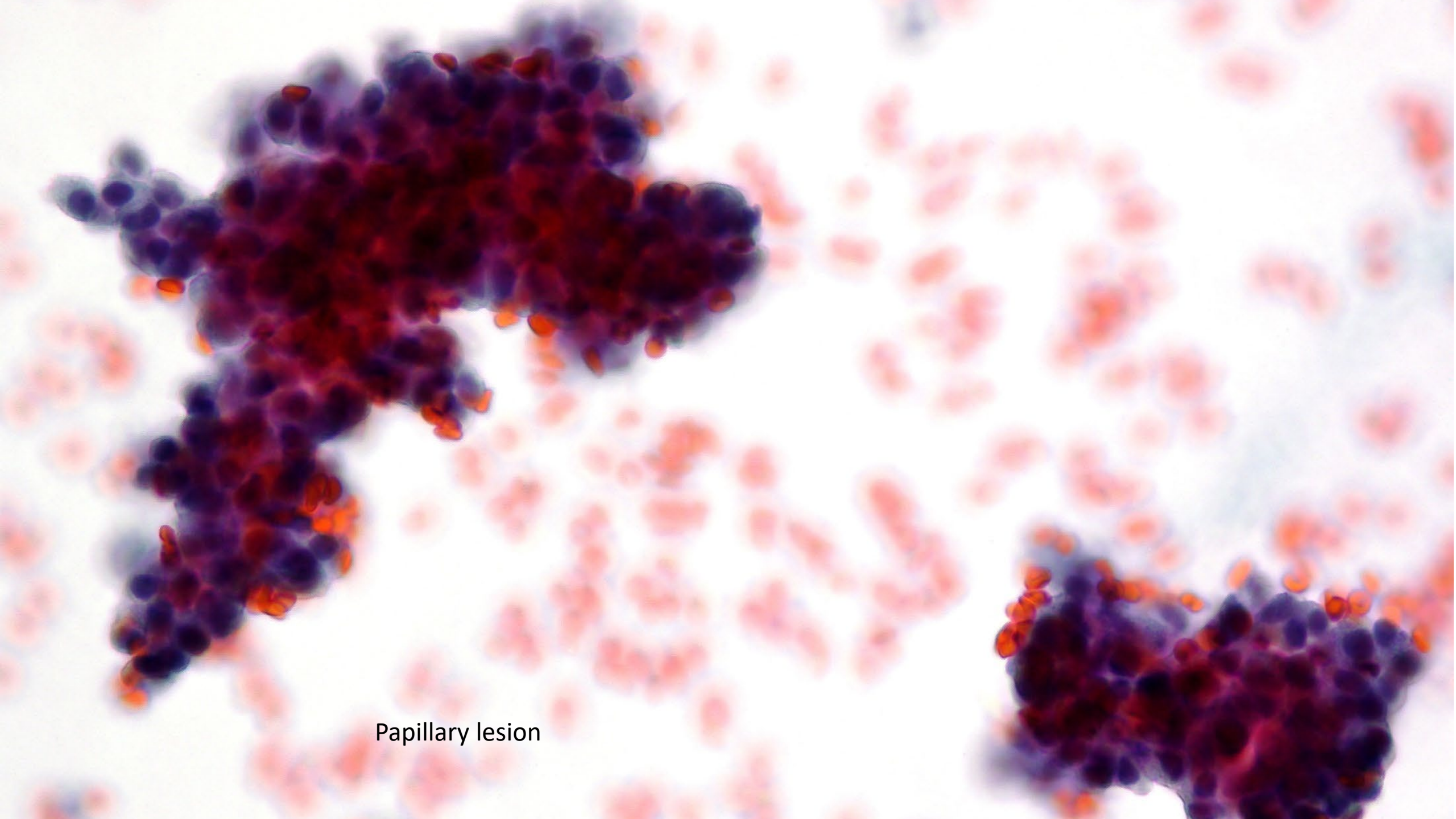
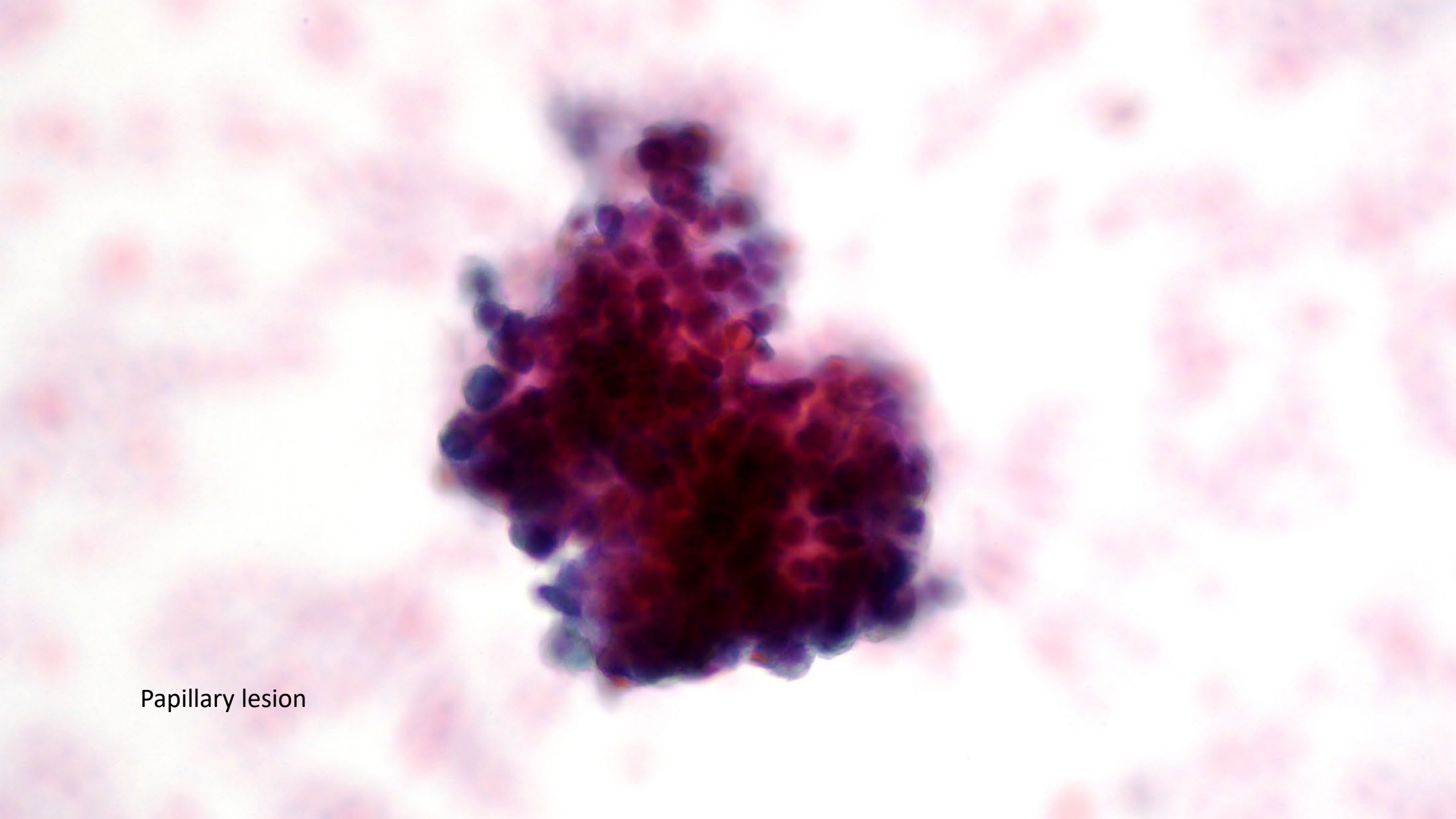
Papillary lesions

- Papillary lesions include benign duct papilloma and papillary carcinoma, with many atypical forms
- FNAC diagnosis of papillary lesions is difficult; NCI guideline has placed this into an intermediate category
- Intraductal papilloma : telltale papillary fronds with fibrovascular cores (only present in as few as 56% of all cases)
- Other cytologic parameters include high overall cellularity, epithelial cell balls without fibrovascular cores, and single cells with or without atypia in the background
- In general most of the papillary lesions are benign, diagnosable on FNAB and CNB

- The overall ability of FNAC to differentiate between benign and malignant papillary lesions remains poor
- Papillary carcinomas tend to have more elaborate and slender fibrovascular cores, higher overall cellularity, more epithelial cell balls, and atypical cells in the background
- Other additional useful features to identify malignancy include the presence of plasmacytoid cells, lack of bare bipolar nuclei, loss of cohesion and a non-cystic background


Papillary lesion


Papillary lesion



Papillary lesion

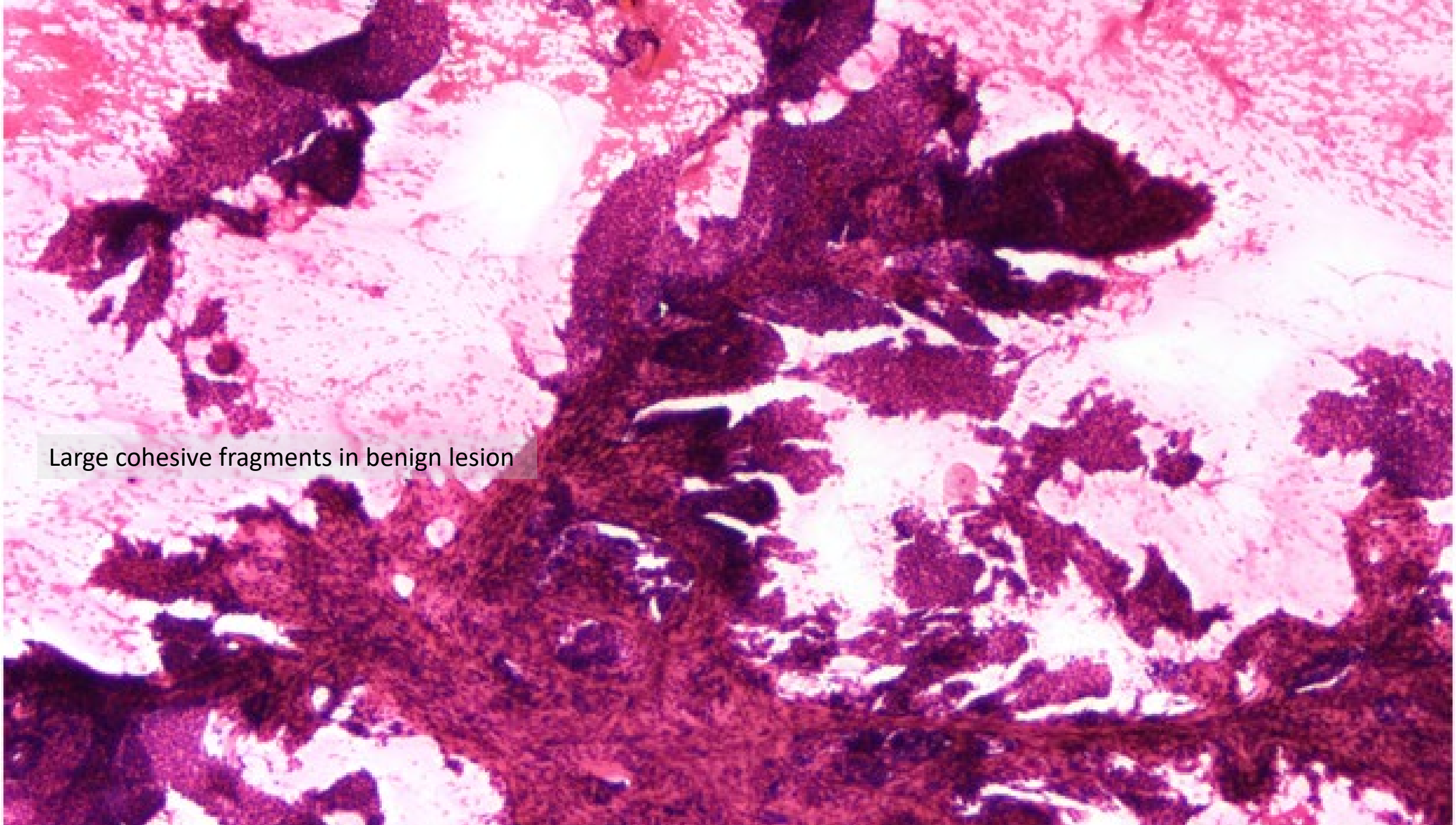
Papillary FNAC : review of 153 cases

Jamidi SK et al 2021 Cancer Cytopathol

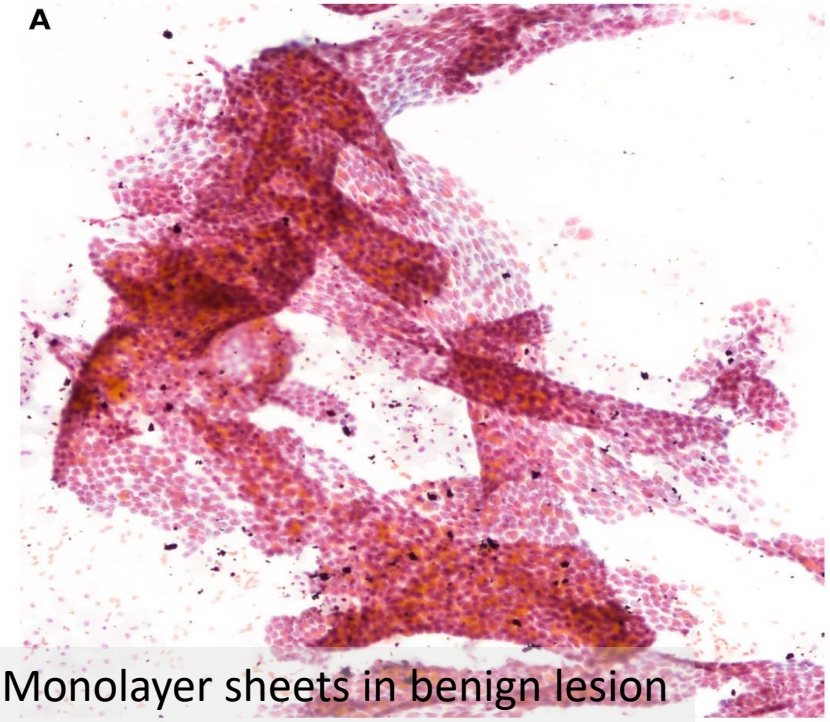
Feature	Benign	Malignant	Total	*P*
Age, y				
Mean	49.4	68.1	54.4	<.001
SD	11.5	14.2	14.8	
Range	19-85	32-94		
Cellularity				
Low	32	12	44	.462
Moderate	28	15	43	
High	44	12	56	
Cohesiveness				
% epithelial cell clusters				<.001
Mean	95.6	64.2	87.8	
SD	10.3	26.2	21.7	
Range	0-100	0-100		
% single epithelial cells				<.001
Mean	3.4	35.8	12.2	
SD	10.3	26.2	21.7	
Range	0-100	0-100		
Fragment size				<.001
Small	19	26	45	
Medium	38	12	50	
Large	47	1	48	
Growth pattern				
Papillary				.021
Absent	34	21	55	
Present	70	18	88	
Monolayer sheet				<.001
Absent	1	25	26	
Present	103	14	117	

Feature	Benign	Malignant	Total	*P*
Solid aggregate				<.001
Absent	49	1	50	
Present	55	38	93	
Cribriform				<.001
Absent	104	28	132	
Present	0	11	11	
Micropapillary				.073
Absent	104	37	141	
Present	0	2	2	
Cell balls				.004
Absent	29	21	50	
Few	47	14	61	
Moderate	21	3	24	
Many	7	1	8	
Myoepithelial cells within cluster				<.001
Absent	3	38	41	
Present	101	1	102	
Neutrophils within cluster				.025
Absent	91	28	119	
Present	13	11	24	

- Patients from the malignant group were significantly older
- Benign papillary lesions showed higher epithelial cell cohesiveness with larger tissue size fragments, more epithelial structures with papillary architecture and monolayer sheets
- Solid and cribriform structures were found in malignant cases
- Cell balls, the presence of myoepithelial cells within epithelial clusters and the paucity of neutrophils were more in benign cases


Large cohesive fragments in benign lesion

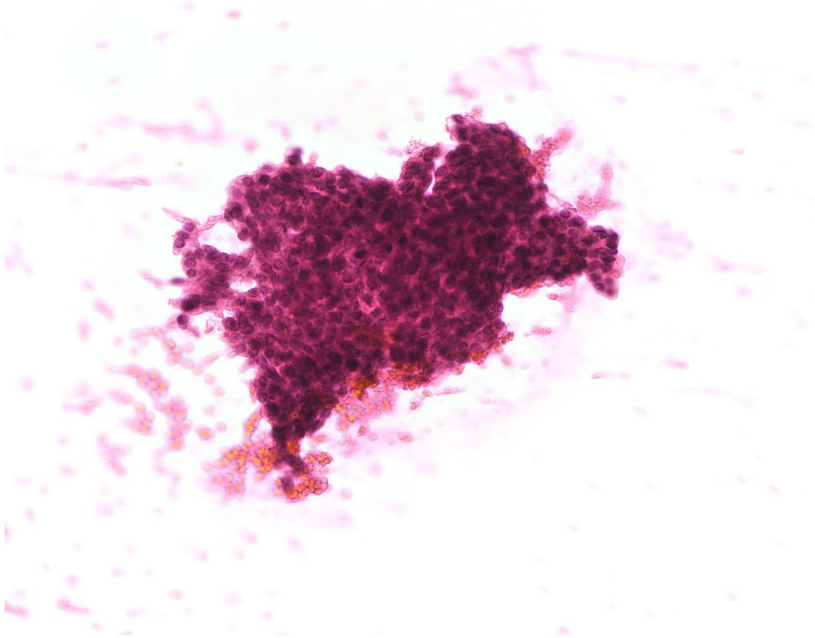
A



Monolayer sheets in benign lesion

B

Solid aggregates in malignant lesion



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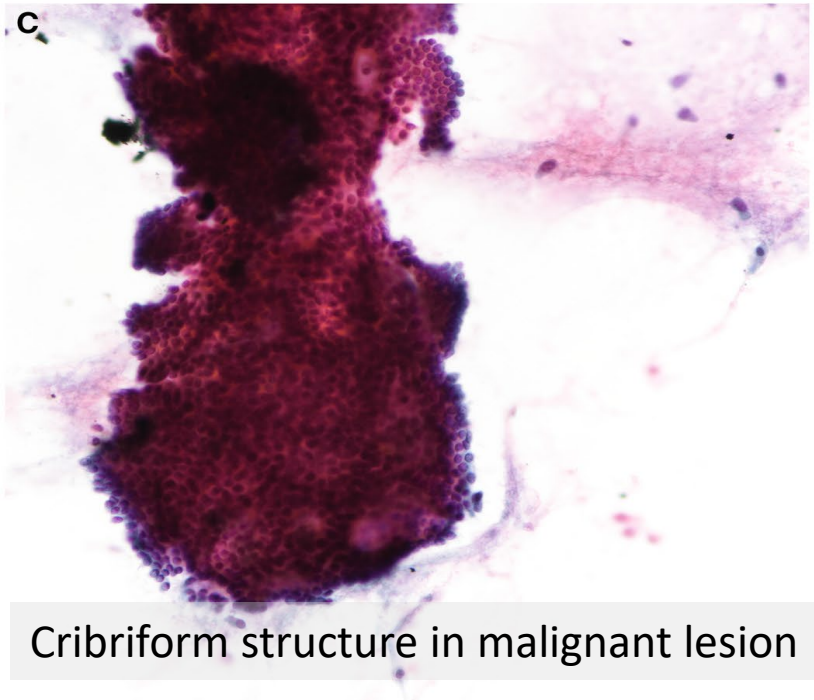
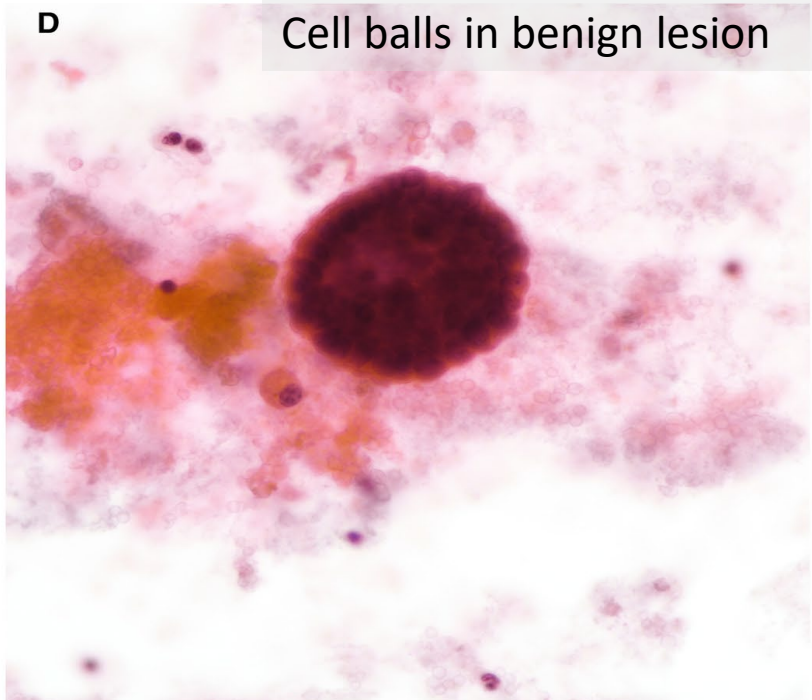


Cribriform structure in malignant lesion

D

Cell balls in benign lesion



Background composition in papillary FNAC

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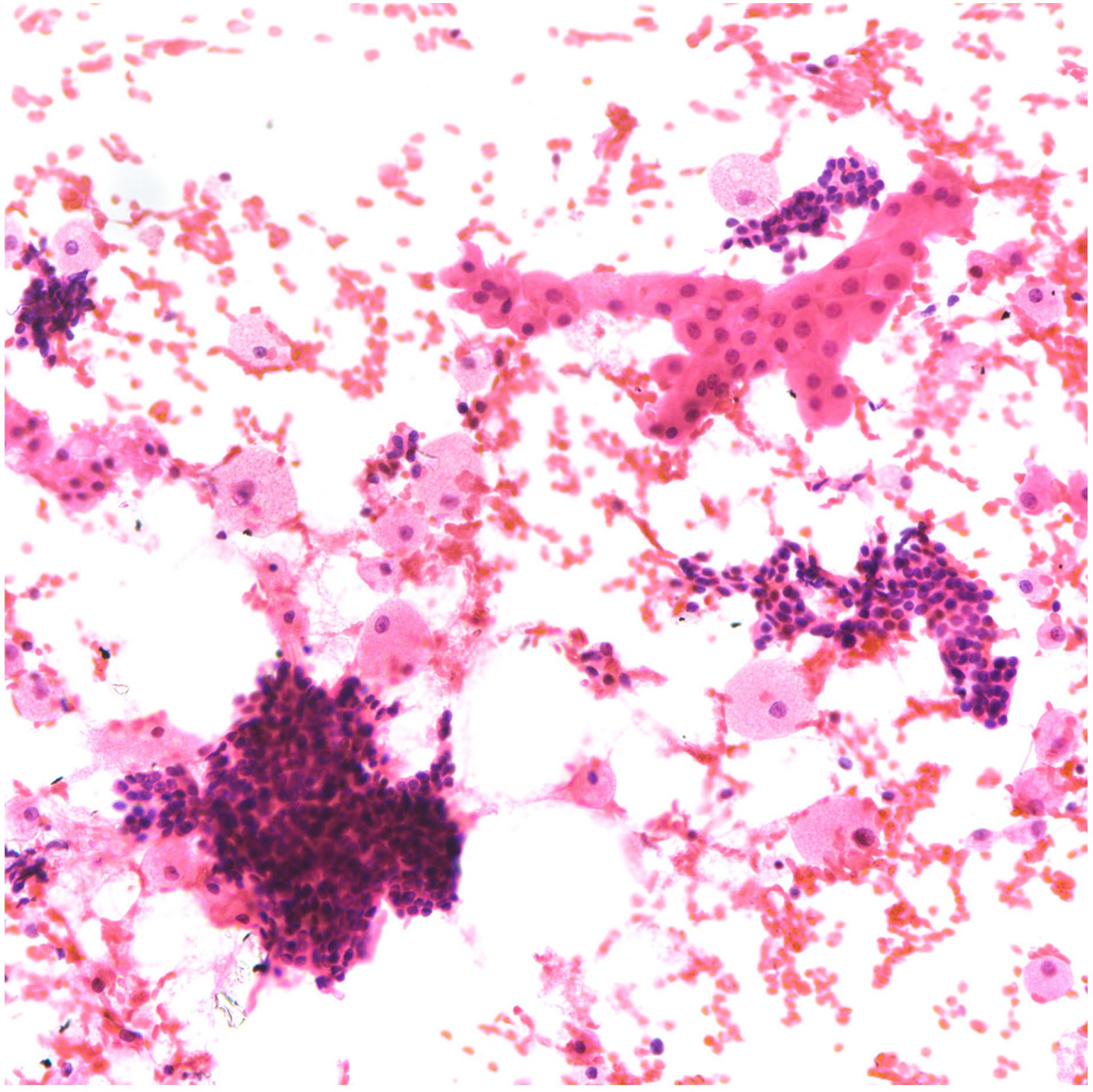
Feature	Benign	Malignant	Total	*P*
Bare bipolar nuclei				<.001
Absent	7	36	43	
Present	97	3	100	
Histiocytes				<.001
Absent	8	12	20	
Few	41	19	60	
Moderate	33	5	38	
Many	22	3	25	
Hemosiderophages				.683
Absent	73	29	102	
Present	31	10	41	
Columnar cells				<.001
Absent	14	25	39	
Few	38	8	46	
Moderate	24	2	26	
Many	28	4	32	
Apocrine metaplastic cells				<.001
Absent	44	39	82	
Present	60	0	61	
Calcifications				1.00
Absent	99	38	137	
Present	5	1	6	

Feature	Benign	Malignant	Total	*P*
Proteinaceous materials				.016
Absent	73	35	108	
Present	31	4	35	
Debris				.062
Absent	100	34	134	
Present	4	5	9	
Necrosis				.073
Absent	104	37	141	
Present	0	2	2	
Hemorrhage				.025
Mild	57	15	72	
Moderate	37	15	52	
Marked	10	9	19	
Lymphocytes				.472
Absent	1	1	2	
Present	103	38	141	
Neutrophils				<.001
None/few	89	17	106	
Many	15	22	37	

- Benignity associated with the presence of bare bipolar nuclei, numerous histiocytes, columnar cells, apocrine metaplastic cells, and proteinaceous material
- Malignancy associated with more background hemorrhage and neutrophils

Background cystic changes, including apocrine metaplastic cells, columnar cells, and histiocytes



Cytomorphologic features in papillary FNAC

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- All cytomorphologic features assessed were found to be significant predictors of malignancy
- The presence of mitosis correlated with malignancy
- None of the benign cases demonstrated a N:C ratio> 0.7

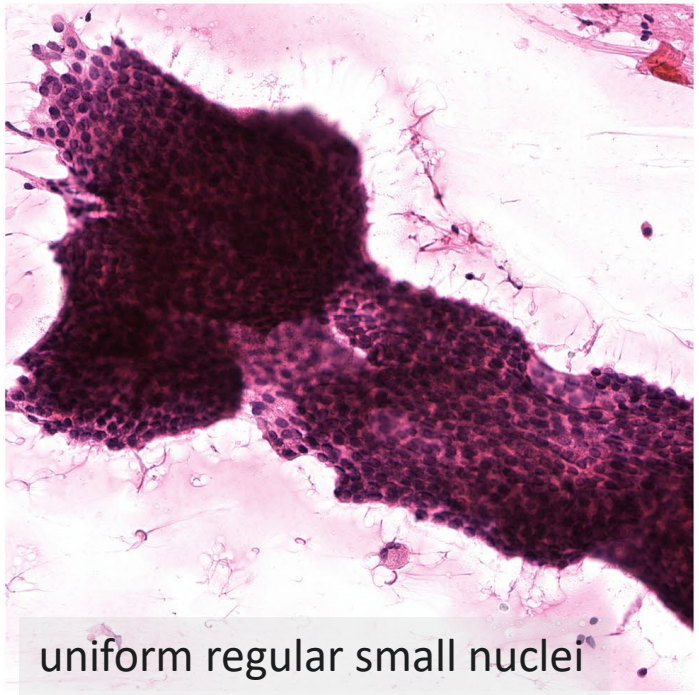
Feature	Benign	Malignant	Total	*P*
Nuclear to cytoplasmic ratio				<.001
0.6	2	17	19	
0.7	102	14	116	
≥0.8	0	8	8	
Nuclear enlargement				<.001
Absent	104	25	129	
Present	0	14	14	
Nuclear size variation				<.001
Mild	104	31	135	
Marked	0	8	8	
Nuclear placement				<.001
Center	103	13	116	
Eccentric	1	26	27	
Nuclear membrane				<.001
Smooth	101	26	127	
Not smooth	3	13	16	
Chromatin character				<.001
Fine	91	3	94	
Speckled	13	27	40	
Coarse	0	9	9	

Feature	Benign	Malignant	Total	*P*
Nucleoli				<.001
Absent	29	5	34	
Small	75	28	103	
Large	0	6	6	
Mitosis				.017
Absent	90	27	117	
Present	14	12	26	
Amount of cytoplasm				<.001
Decreased	1	3	4	
Normal	103	14	117	
Increased	0	22	22	
Cytoplasmic vacuolation				<.001
Absent	100	28	128	
Present	4	11	15	
Cytoplasmic granules				<.001
Absent	101	16	117	
Present	3	23	26	

Malignancy showed :

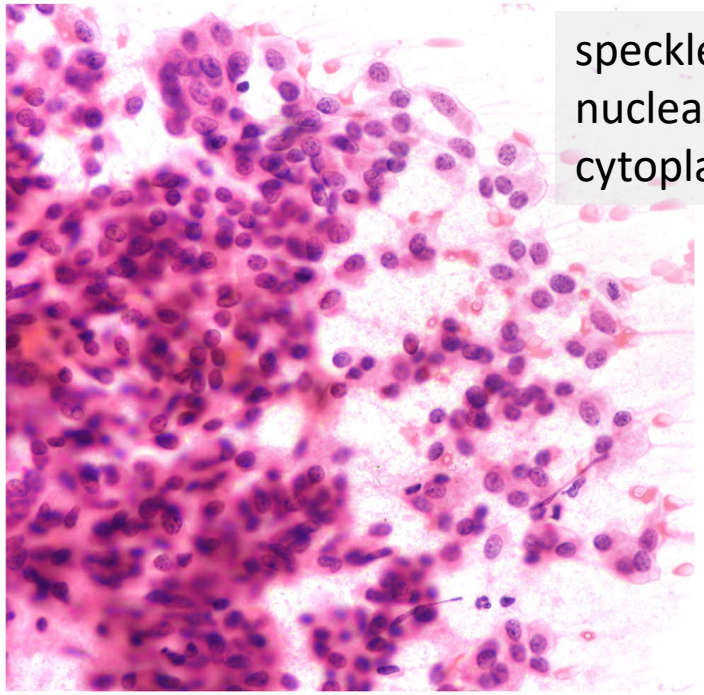
- nuclear enlargement
- nuclear size variation
- nuclear eccentricity
- nuclear membrane irregularity
- coarse chromatin pattern
- large nucleoli
- an increased amount of cytoplasm
- presence of cytoplasmic vacuolation, and cytoplasmic granules

A



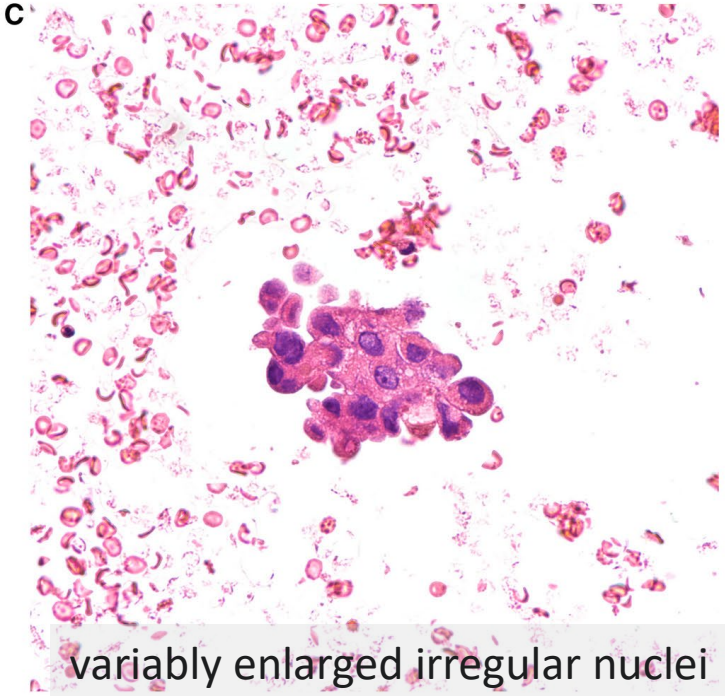
uniform regular small nuclei

B



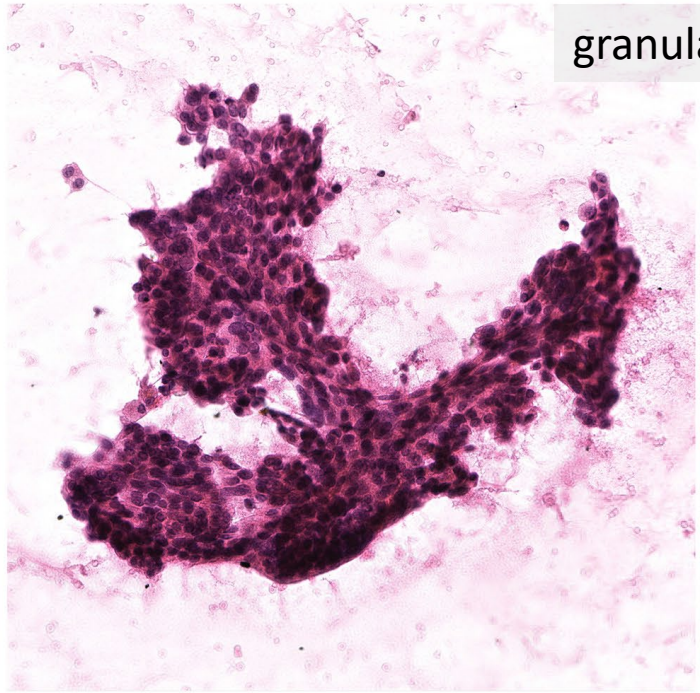
speckled chromatin, eccentric nuclear placement, and cytoplasmic granulation

C



variably enlarged irregular nuclei

D



granular cytoplasm

Papillae FNAC

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- The complexity and slenderness of the papillary fronds were associated with malignancy
- Naked papillary fronds, which show sclerotic or fibrotic broad papillary stromal fragments with minimal associated epithelial cells, correlated with IDPs

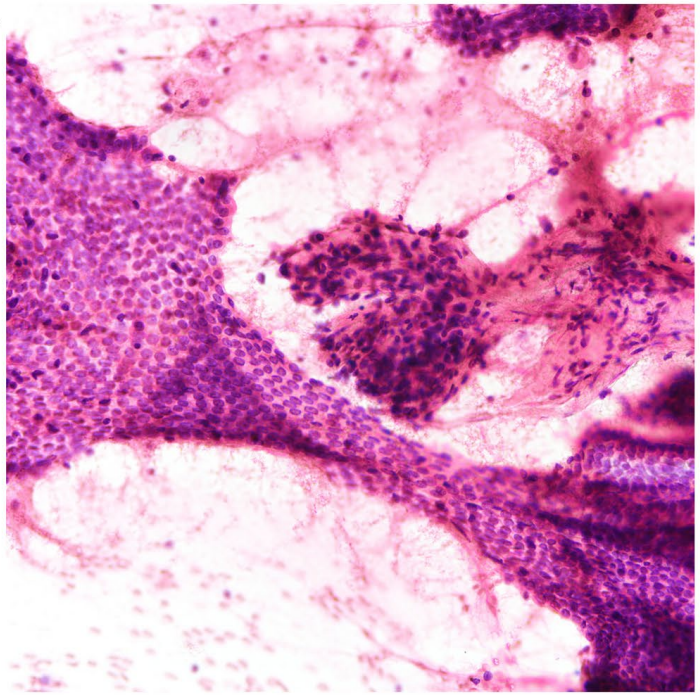
TABLE 5. Features of Papillary Structures in Fine-Needle Aspiration Cytology of Papillary Lesions of the Breast

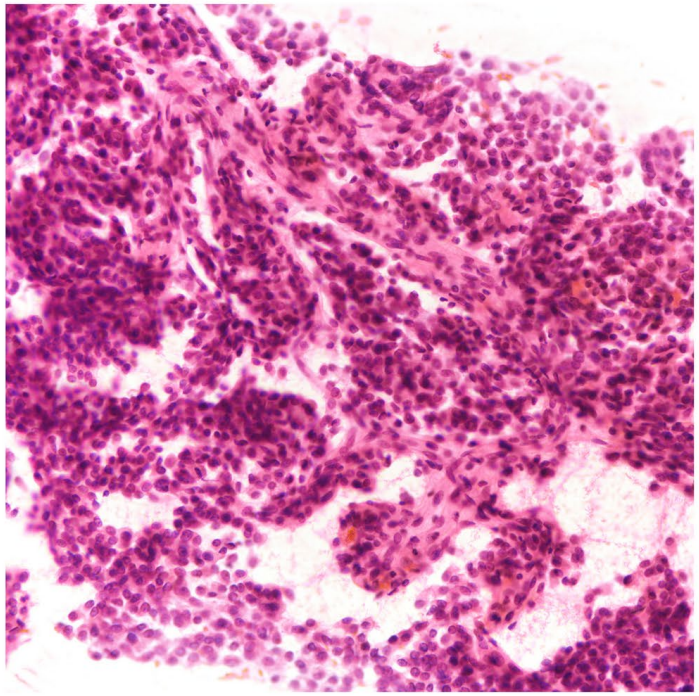
Feature	Benign	Malignant	Total	*P*
Complexity				.031
Simple	69	9	78	
Complex	10	5	15	
Size of fibrovascular stalk				.026
Slender	26	9	35	
Broad	53	5	58	
Naked papillary fronds				.043
Absent	93	31	124	
Present	27	2	29	

*benign papillary structure: IDPs, IDPs with ADH, and DCIS involving IDPs

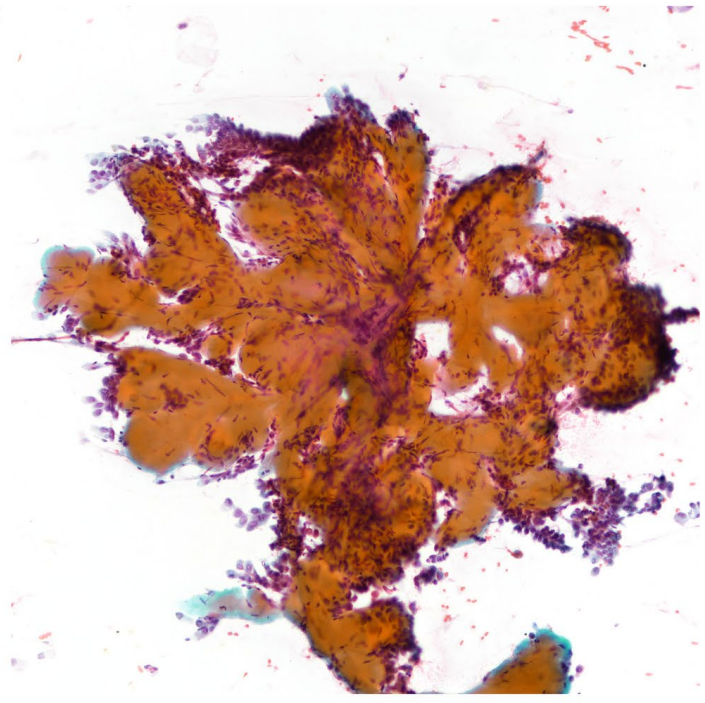
*malignant papillary lesions: IPCs, EPCs, and SPC

Simple papillae with preserved myoepithelial cells





Complex papillae with loss of myoepithelial cells



Naked papillary frond in benign papillary lesions
(Papanicolaou stain)

Summary

- Probablistic approach (Yokohama, WHO) C1-C5
- Triple test, ROSE, ROM
- Common breast lesions
  - Fibrocystic changes
  - Atypical hyperplasia
  - Fibroadenoma
  - Phyllodes tumor
  - Papillary lesions