Schweizerische Gesellschaft für Zytologie
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Fine Needle Cytology of the Breast
Why should we keep doing it?

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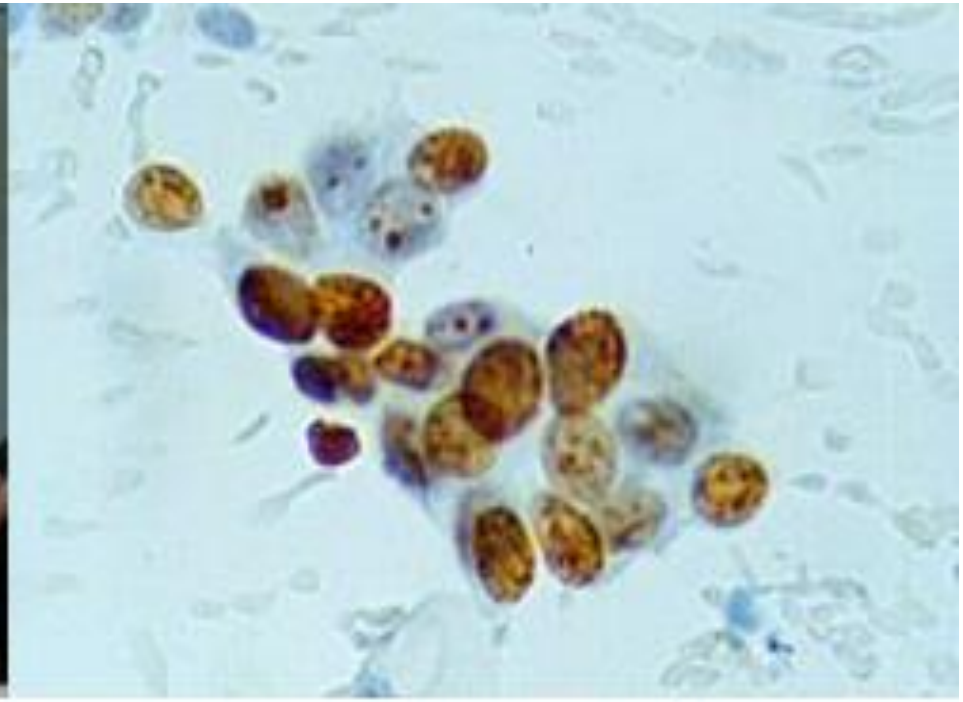
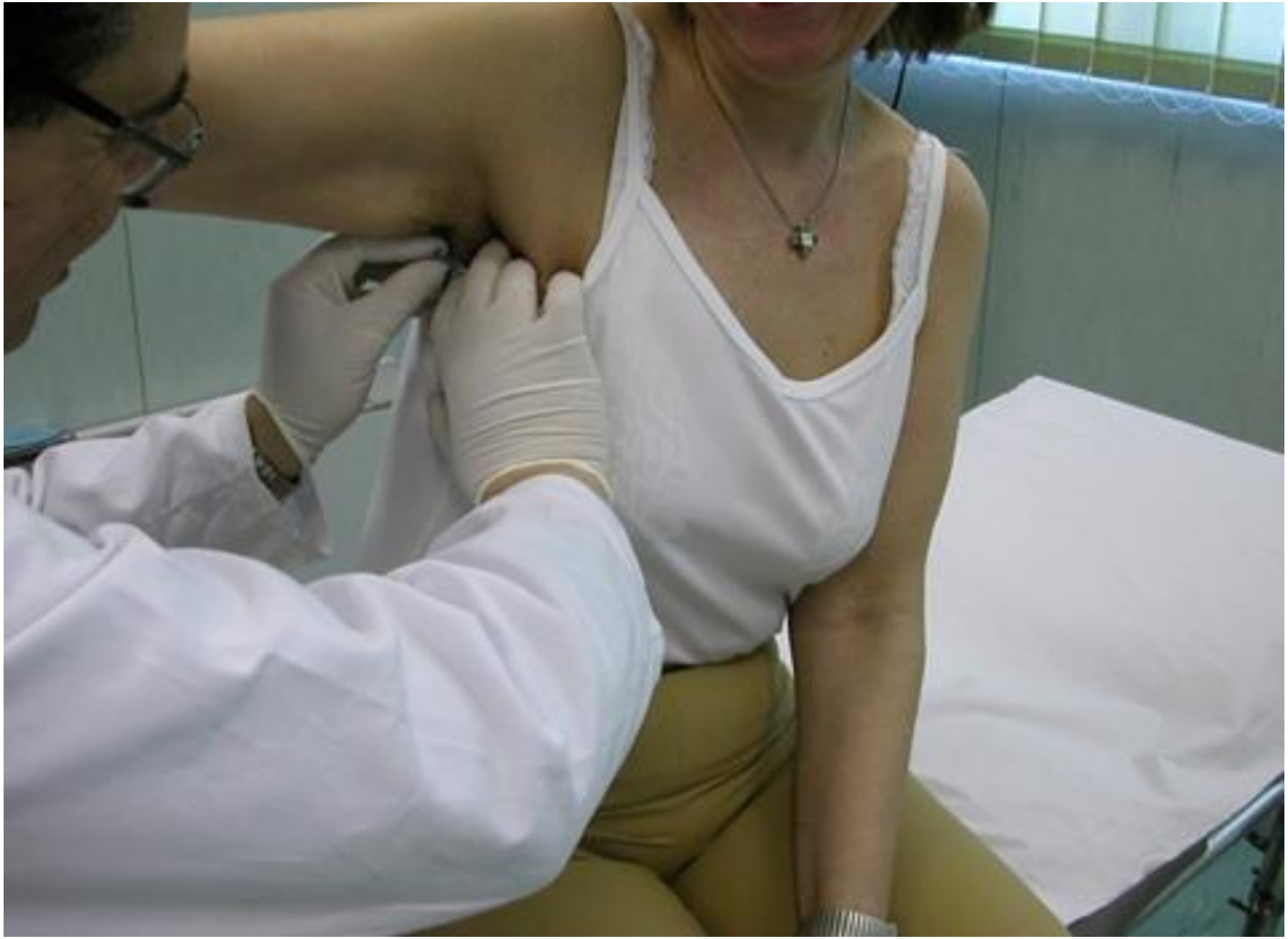
Fine Needle Cytology of the breast: facts

- **Explosive growth from 1970's to late 1990's;**
- **Extensively verified diagnostic accuracy;**
- **Progressive change of the cytopathologist's attitude (from clinical, palpation driven, to ultrasound/stereotaxic guided technique;**
- **Strict collaboration with radiologists.**

- **Progressive decrease in the 2000's with increasing transition to invasive procedures;**
- **Increasing medico-legal issues;**
- **Radiologists' egotism and excessive self confidence;**
- **High and fast patient turnover in high throughput Centers;**
- **Compensation issues;**
- **Lack of sense of belonging to an interdisciplinary group.**

Clinical Cytopathology= Diagnostic vs. screening cytology





Reprinted from CANCER, Vol. 61, No. 11, June 1, 1988.

Fine-Needle Aspiration Biopsies of Breast Masses

A Critical Analysis of 1956 Cases in 8 Years (1976–1984)

LUCIO PALOMBINI, MD, FRANCO FULCINITI, MD, ANTONIO VETRANI, MD, GAETANO DE ROSA, MD, GIUSEPPE DI BENEDETTO, MD, PIO ZEPPA, MD, AND GIANCARLO TRONCONE, MD

A series of 1956 fine-needle aspiration biopsies (FNAB) of breast masses is described. The diagnostic accuracy of this series (sensitivity, 95.7%; specificity, 89.6%; predictive value of positivity, 95.9%; and efficiency, 94.0%) was compared with that published in the literature. Statistically significant differences were found between the level of diagnostic accuracy in series published by pathologists who diagnosed smears prepared by clinicians and surgeons (Group A), and those published by pathologists who performed palpation and aspiration, and made the cytologic diagnosis by themselves (Group B). These differences mainly consisted of a lower number of false-positives and "unsatisfactory" samples in Group B series.

Cancer **61:2273–2277, 1988.**

TABLE 5. Analytical Cross-Comparison Among Data Published in Some of the Main Series: Group A. Pathologists Who Interpreted Smeared Samples Biopsied by Different Staff Members

	Investigator (Group A)						
	Kline	Pilotti	Bell	Wollenberg	Ulanow	Barrows	Total (A)
Reference No.	5	6	3	8	7	2	
Series	3545	4834	1680	321	449	1283	12,112
Controlled cases	1084	1173	584	184	318	1283	4626
True-positives	349	534	244	113	188	689	2117
True-negatives	735	639	340	71	128	594	250[illegible]
Unsatisfactory (%)	NR	30.86	13.69	7.6	7.4	21.20	16.15
Suggestive cyt./neg. hist.	60	9	112	45	15	53	294
Pos. cyt./neg. hist.	0	2	0	0	1	2	5
False-positives	60	11	112	45	16	55	299
Neg. cyt./pos. hist.	35	63	27	11	19	48	125
Uns. cyt./pos. hist.	4	112	15	1	9	72	213
False-negatives	39	175	42	12	28	120	41[illegible]
Sensitivity (%)	89.95	75.32	85.31	90.40	87.04	85.17	85.53*
Specificity (%)	92.45	98.31	75.22	61.21	88.89	91.53	84.60*
Pred. value pos. res. (%)	85.33	97.98	68.54	71.52	92.16	92.61	84.69*
Efficiency (%)	91.63	86.31	79.13	76.35	87.78	88.00	84.86*

NR: not reported.

* Expressed as a mean value.

TABLE 6. Analytical Cross-Comparison Among Data Published in Some of the Main Series: Group B. Pathologists Who Personally Performed FNAB and Smearing, and Made Cytologic Diagnosis

	Investigator (Group B)				
	Zajicek[10]	Zajdela[9]	Frable[4]	Palombini	Total (B)
Series	2111	2772	853	1956	7692
Controlled cases	2111	2772	853	674	6410
True-positives	1089	1745	311	492	3220
True-negatives	1022	1027	542	182	3668
Unsatisfactory cyt. (%)	0	5.59	5.39	5.11	4.02
Suggestive cyt/neg. hist	33	42	13	21	109
Pos. cyt/neg. hist.	5	3	1	0	9
False-positives	38	45	14	21	118
Neg. cyt/pos. hist.	118	63	27	15	223
Uns. cyt/pos. hist.	0	89	7	7	103
False-negatives	118	152	34	22	[illegible]
Sensitivity (%)	90.22	91.99	90.14	95.72	92.02*
Specificity (%)	96.42	95.80	97.48	89.66	94.84*
Pred. value pos. res. (%)	96.63	97.49	95.69	95.91	96.43*
Efficiency (%)	93.12	93.36	94.67	94.00	93.79*

FNAB: fine-needle aspiration biopsy.

* Expressed as a mean value.

Certainties: Can this technique be taught?

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Fine-Needle Aspiration Biopsies of Breast Masses

An Additional Experience With 1153 Cases (1985 to 1988) and a Meta-Analysis

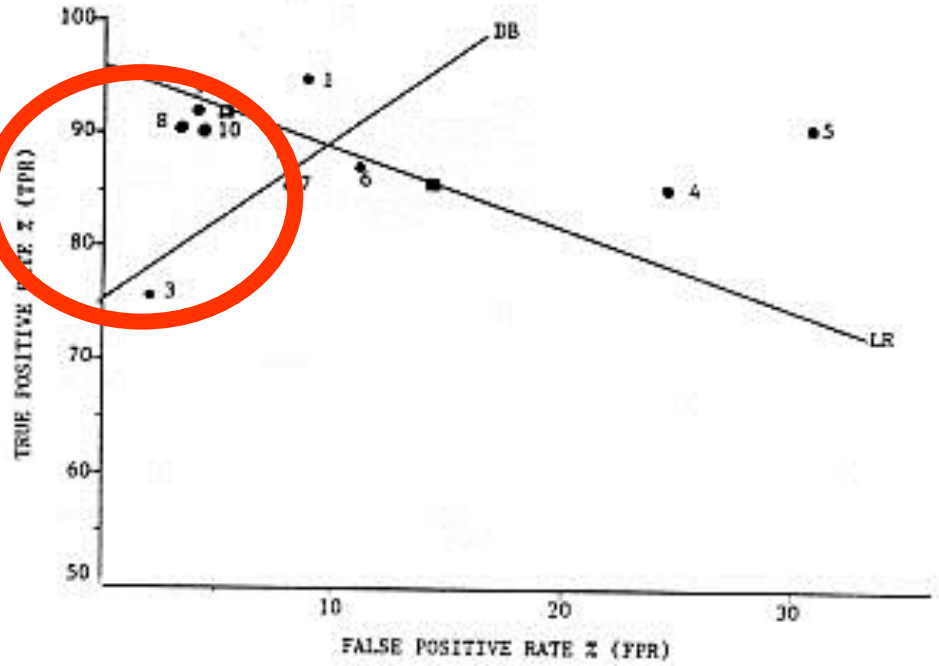
Antonio Vetrani, MD, Franco Fulciniti, MD, Giuseppe Di Benedetto, MD, Pio Zeppa, MD, Giancarlo Troncone, MD, Amedeo Boscaino, MD, Gaetano de Rosa, MD, and Lucio Palombini, MD

Table 6. Evaluation of the Statistical Significance Between the Totals of False, Suggestive, and Unsatisfactory Examinations in the Two Series

	(1976 to 1984)	(1985 to 1988)	Chi-square
True diagnoses (TP + TN)	674	236	
False diagnoses (FP + FN)	39	19	0.98 ($P > 0.10$)
Total	813	255	
True diagnoses (TP + TN)	674	236	
Suggestive diagnoses	127	54	0.98 ($P > 0.10$)
Total	801	290	
True diagnoses	674	236	
Unsatisfactory diagnoses	100	61	9.1 ($P > 0.001$)
Total	774	297	

TP: true-positive; TN: true-negative; FP: false-positive; FN: false-negative.
Confidence limit of significance = 0.001.

ROC analysis of accuracy



Best accuracy area

Diagnostic accuracy: Jan 2005 - March 2008

		H			
	Test result	+	-	Controlled cases	%
C	+	225 TP	11 FP	236	3.4 FP
	-	8 FN	76 TN	84	2.5 FN
		233	87	320	

Sensitivity= 96.5% (95.7)
Specificity= 87.3% (89.6%)

PPV= 95.3%;(95.9%)
NPV= 90.5%;
EFF= 94% (94%)

Crucial points: false positives

- Every FP is a potential litigation case;
- Every FP is potentially avoidable;
- About 50% of FP show scanty atypical cells;
- Over 80% of FP display a mixture of benign and atypical cells.

Points in favor of Fine Needle Cytology

- Ideal as first level technique: a definitive diagnosis may be reached in a high number of cases;
- Cost-effectiveness (120-150 USD vs. 480-600 USD for Core biopsy);
- Negligible number of complications vs. Core Biopsy;
- Well tolerated and repeatable technique.

Complications of breast core biopsy

- There are very few systematic studies in the literature;
- Potentially serious ones: Arterio-venous aneurysm, Pseudoaneurysm, Hematoma, Pneumothorax, Mondor's mastitis (sclerosing thrombophlebitis), Needle tract neoplastic seeding.

Fine Needle Cytology: possibilities

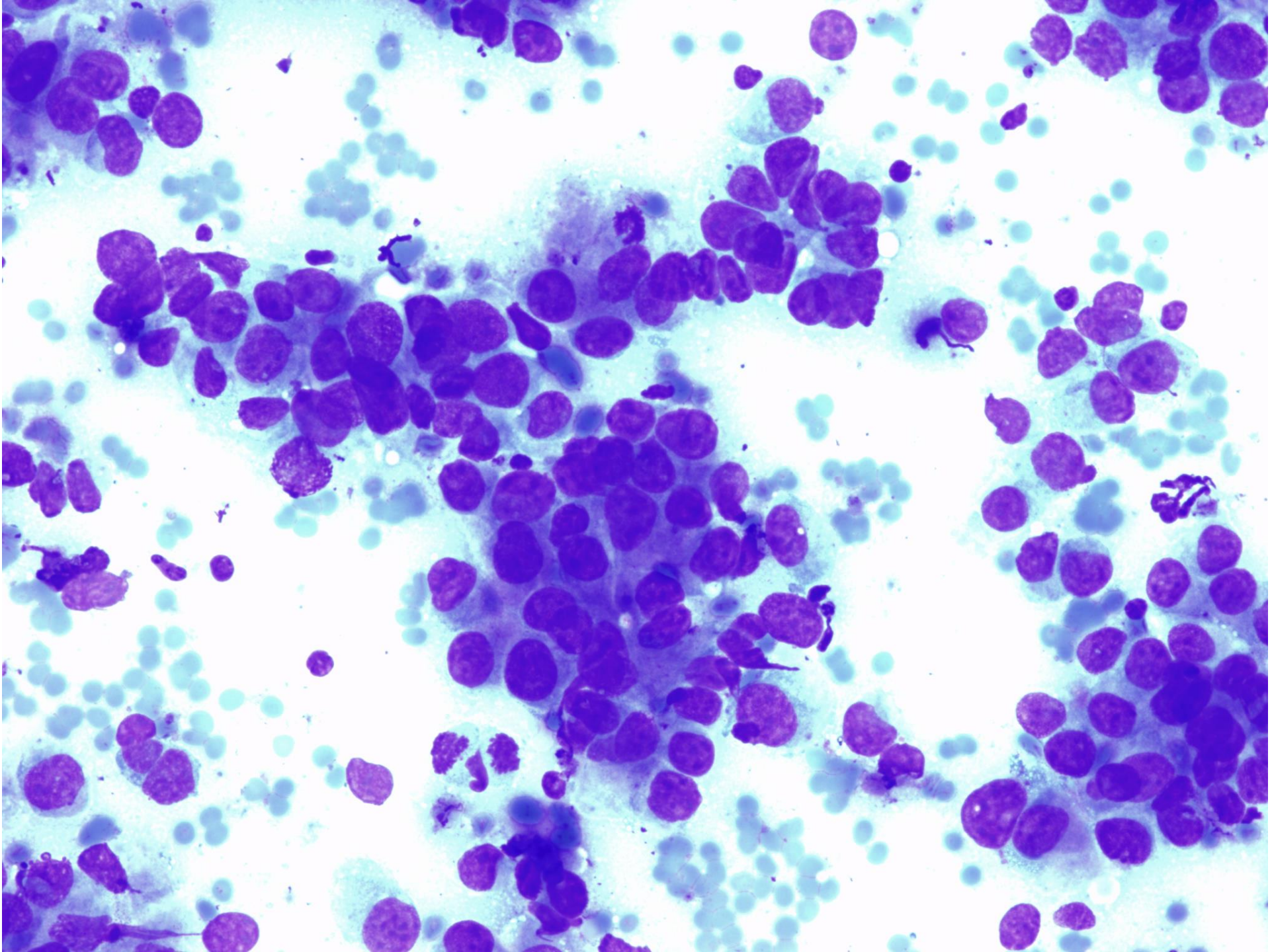
- Frequent correct recognition of main histotypes of breast carcinoma;
- Biomarker studies and Her-2 FISH/CISH possible on FNC samples;
- Additional prognostic studies possible on FNC samples possible (e.g. Endo-Predict);
- Correct typing of metastatic sites of breast carcinoma;
- Metastases to the breast usually correctly detected in a multidisciplinary setting.

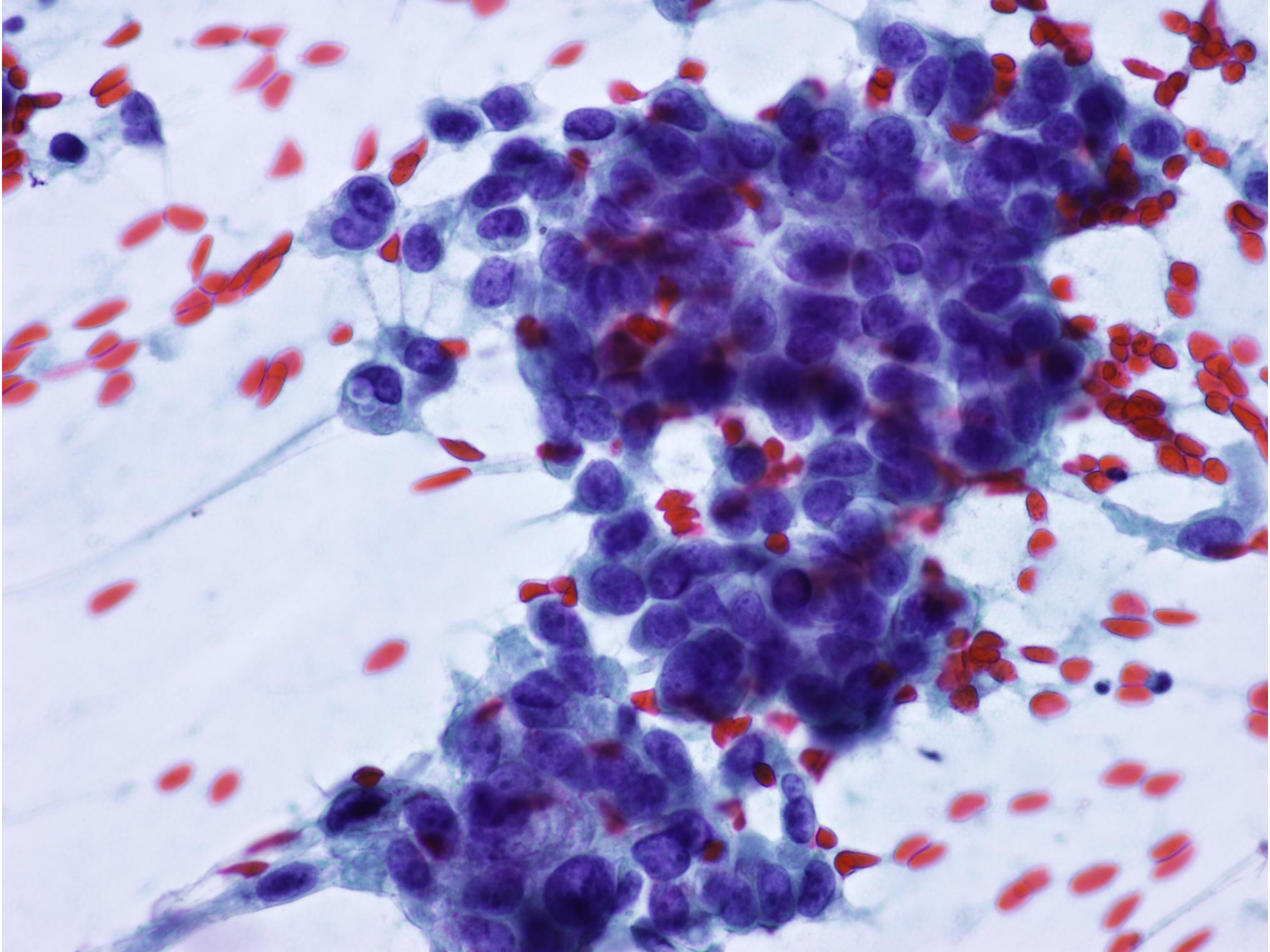
Ductal carcinoma

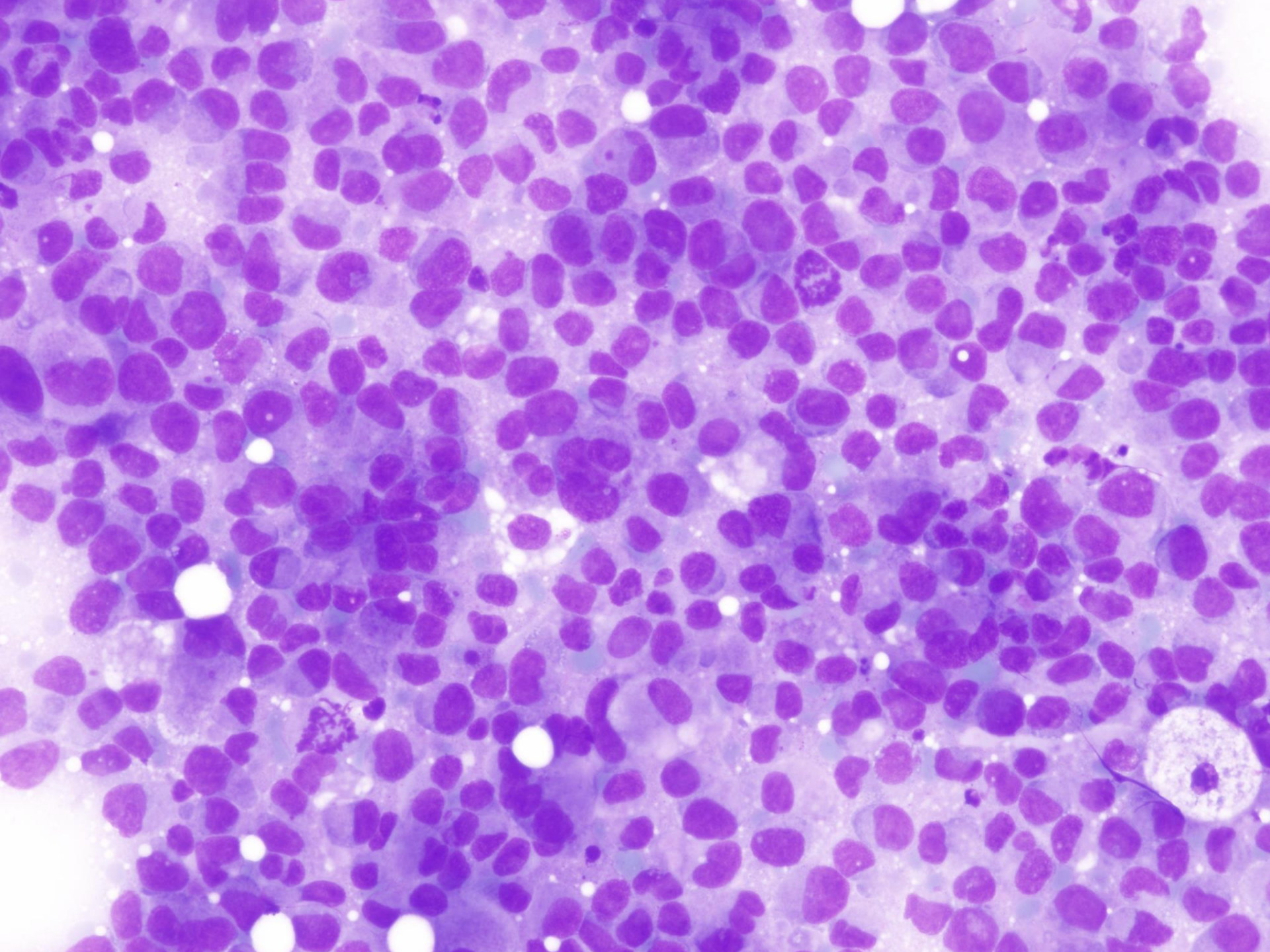
- Small to large atypical neoplastic cells with well-delimited, polygonal cytoplasms;
- Cytoplasms may be homogeneous, granular (apocrine-type), may show regressive or secretion vacuoles. Intracytoplasmic lumina seen both in ductal and lobular carcinoma;
- Nuclei are round-ovoid, nucleoli from small to large according to malignancy grade;
- N/C ratio variable according to grade; small cell duct carcinoma has a generally very high N/C ratio;
- Mitoses may be seen, mainly in high grade carcinomas.

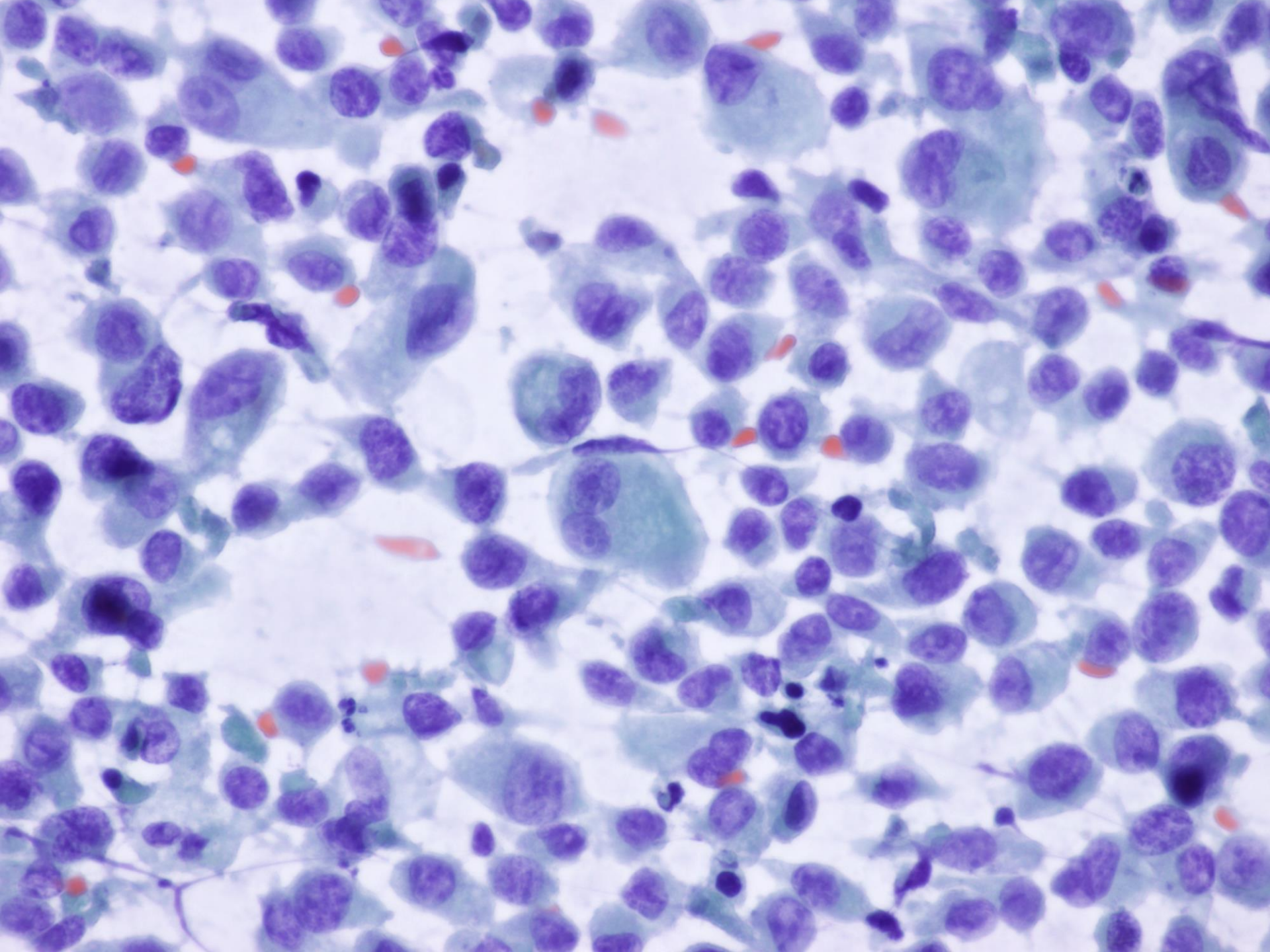
Ductal carcinoma

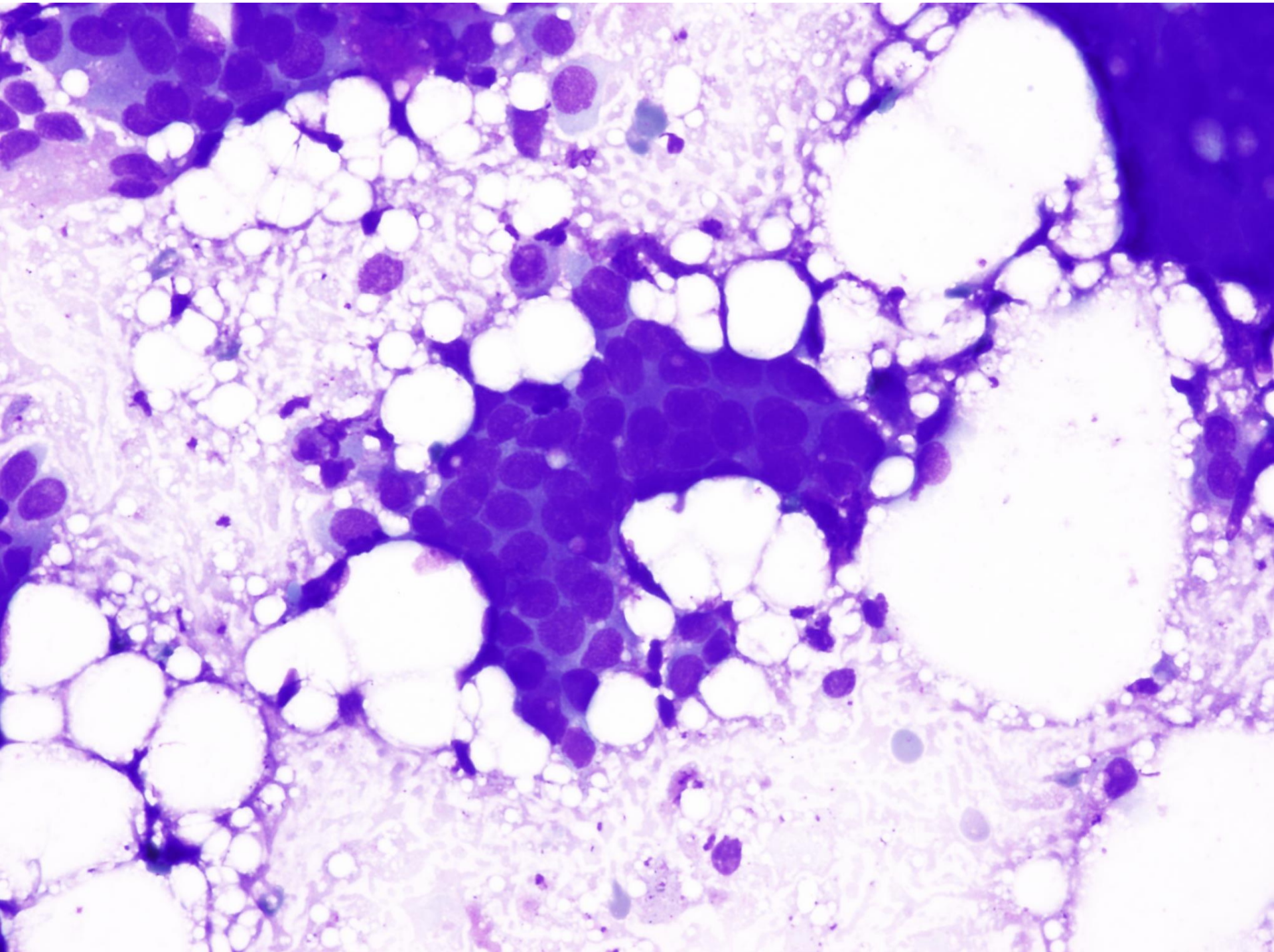
- Cohesion may vary from a dyshesive (dispersed) cell pattern to mixed pattern to mainly cohesive pattern;
- Acinar, duct-like, cribriform or solid clusters may be observed;
- Cellular necrosis, microcalcifications and cribriform clusters correlate to intraductal growth of variable degree;
- Lymphoid infiltration may be observed; when coupled to anaplastic cytomorhology it may be predictive of medullary carcinoma.

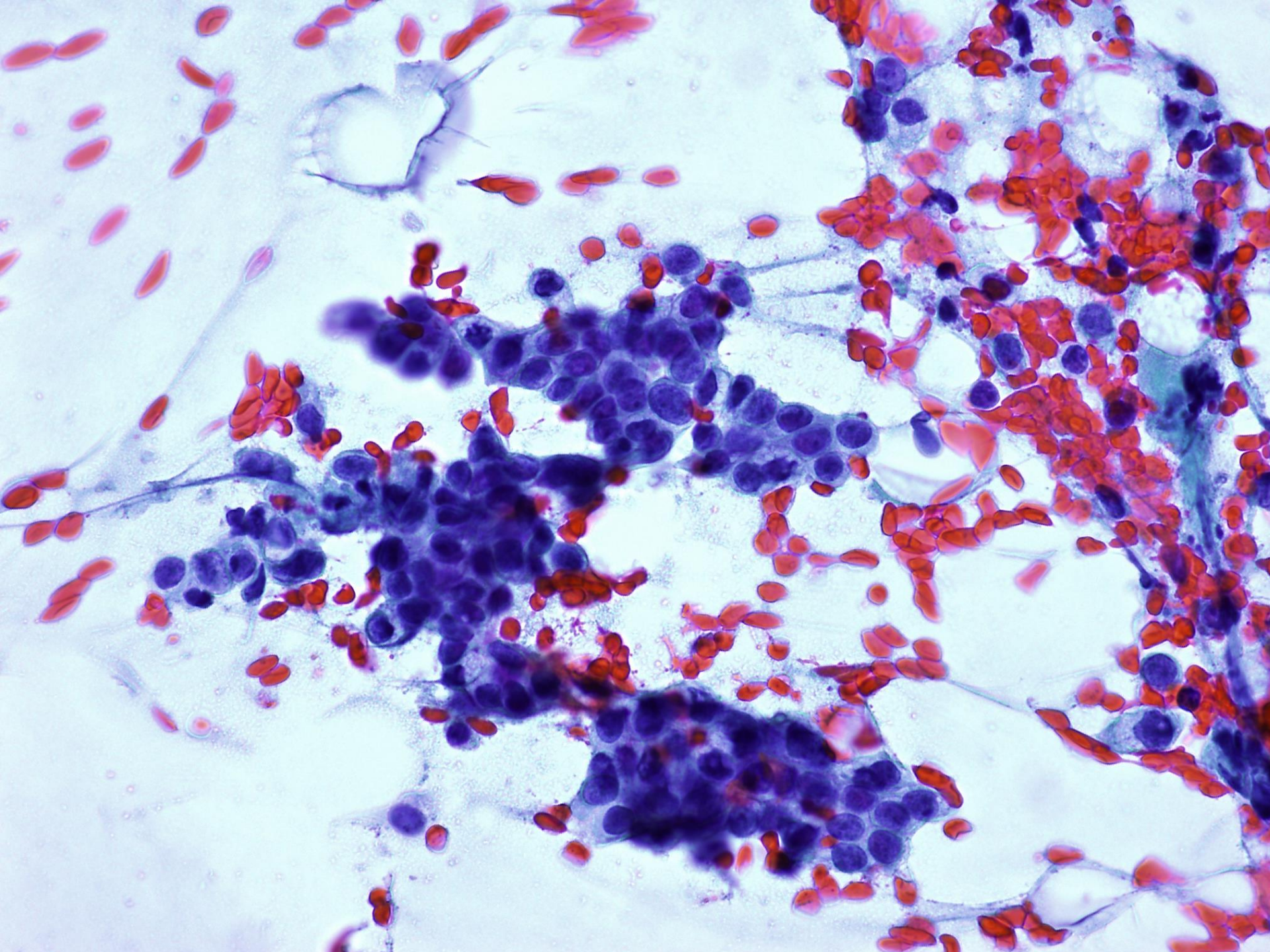


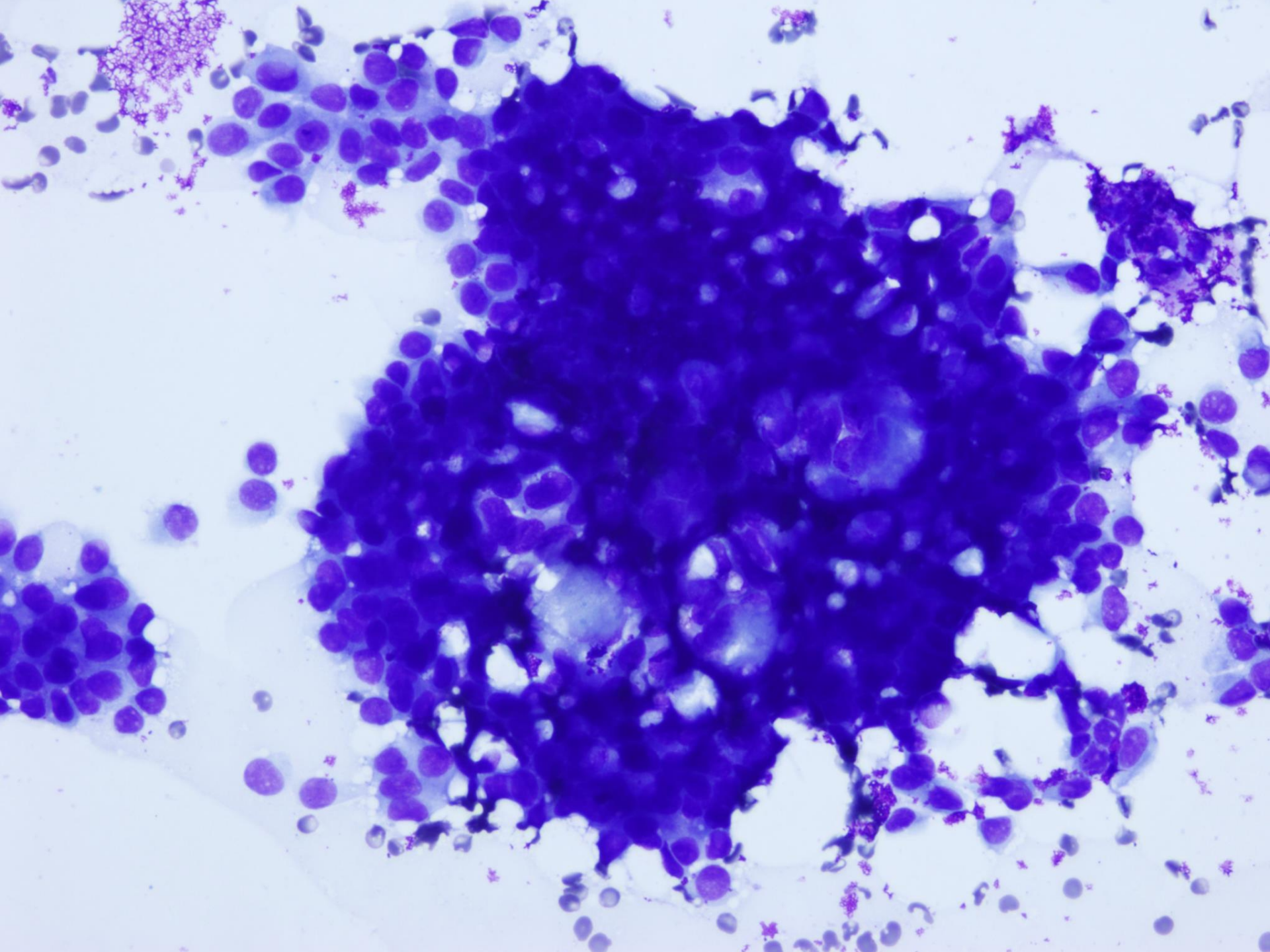


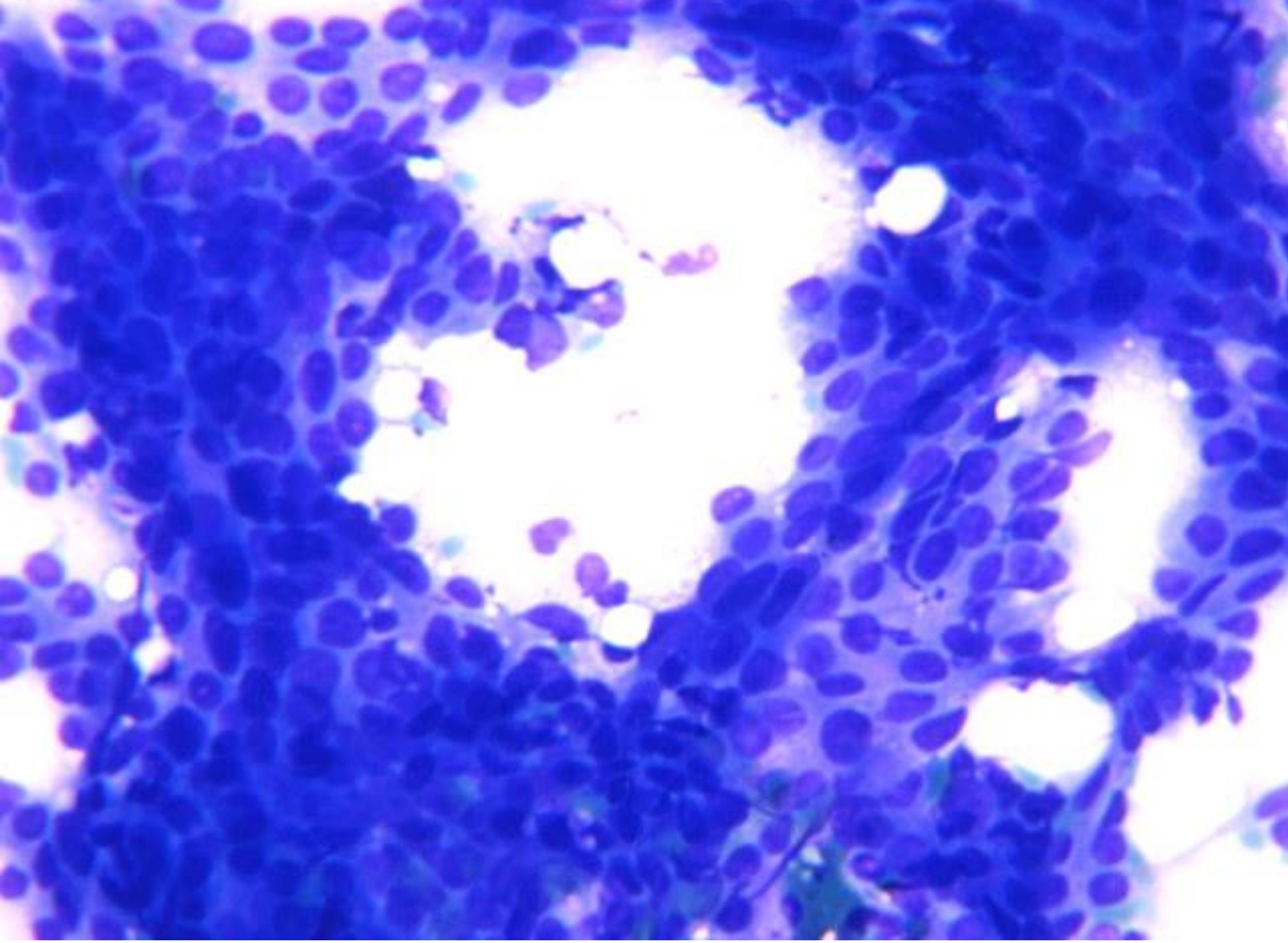


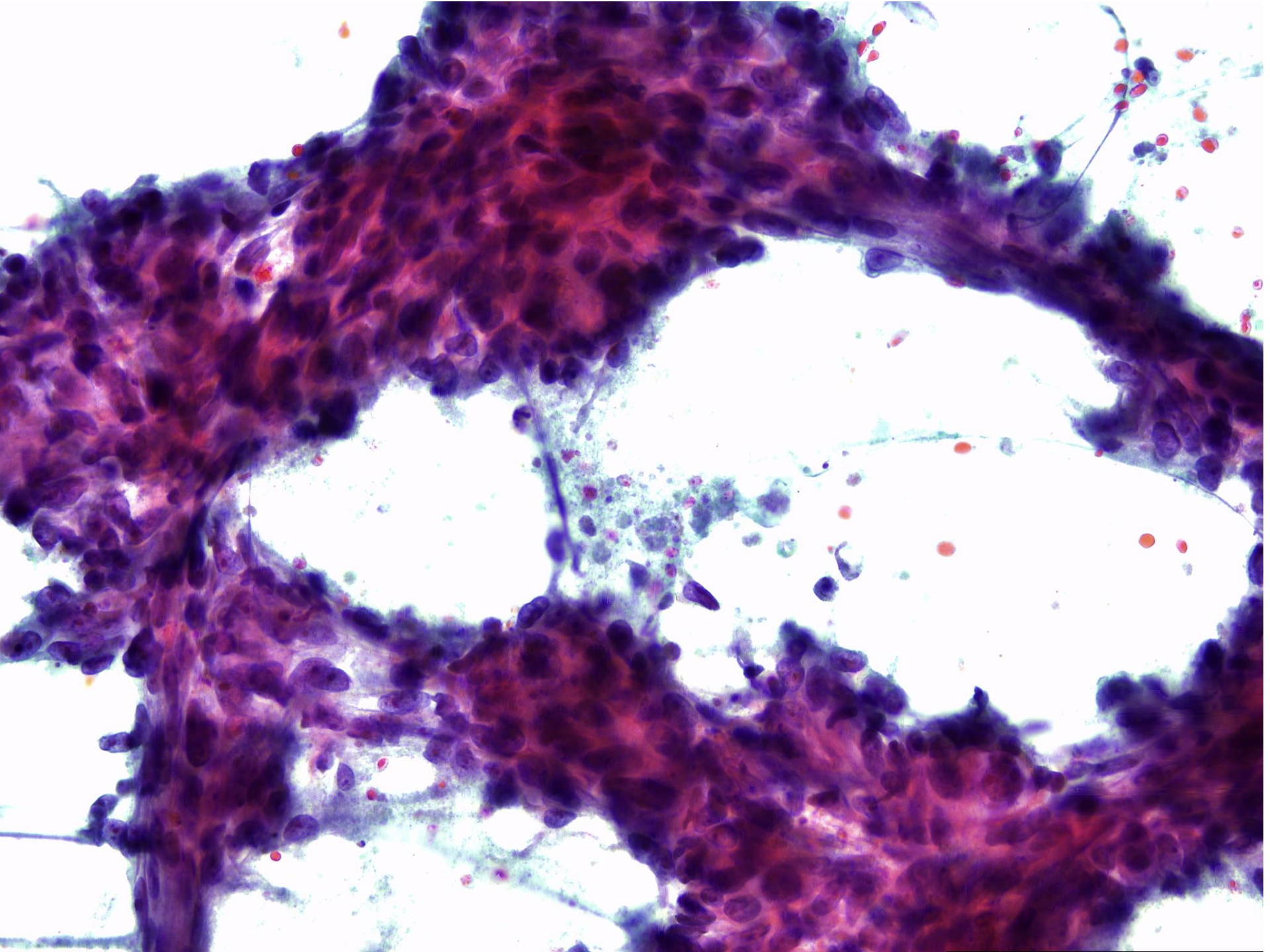


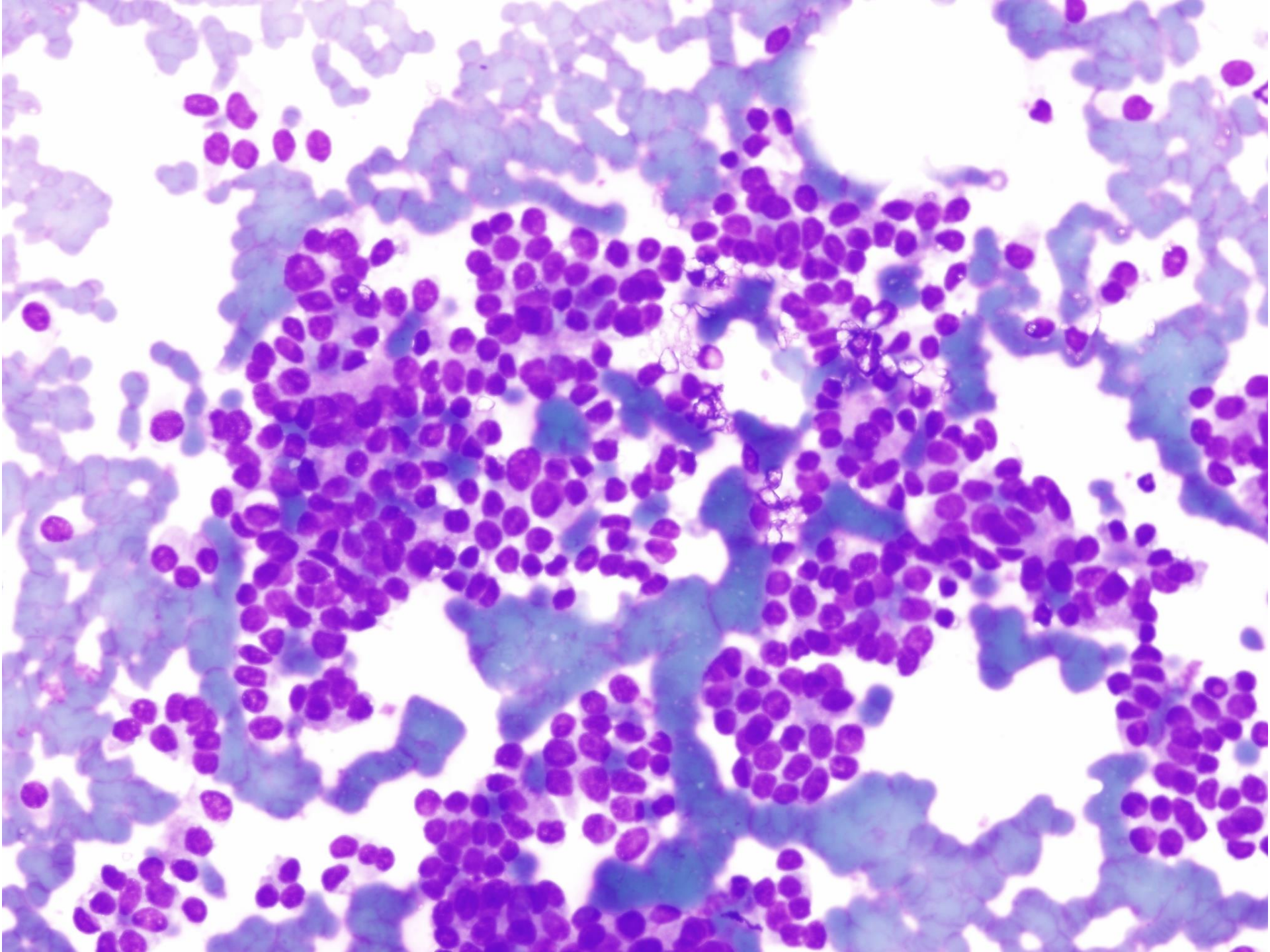


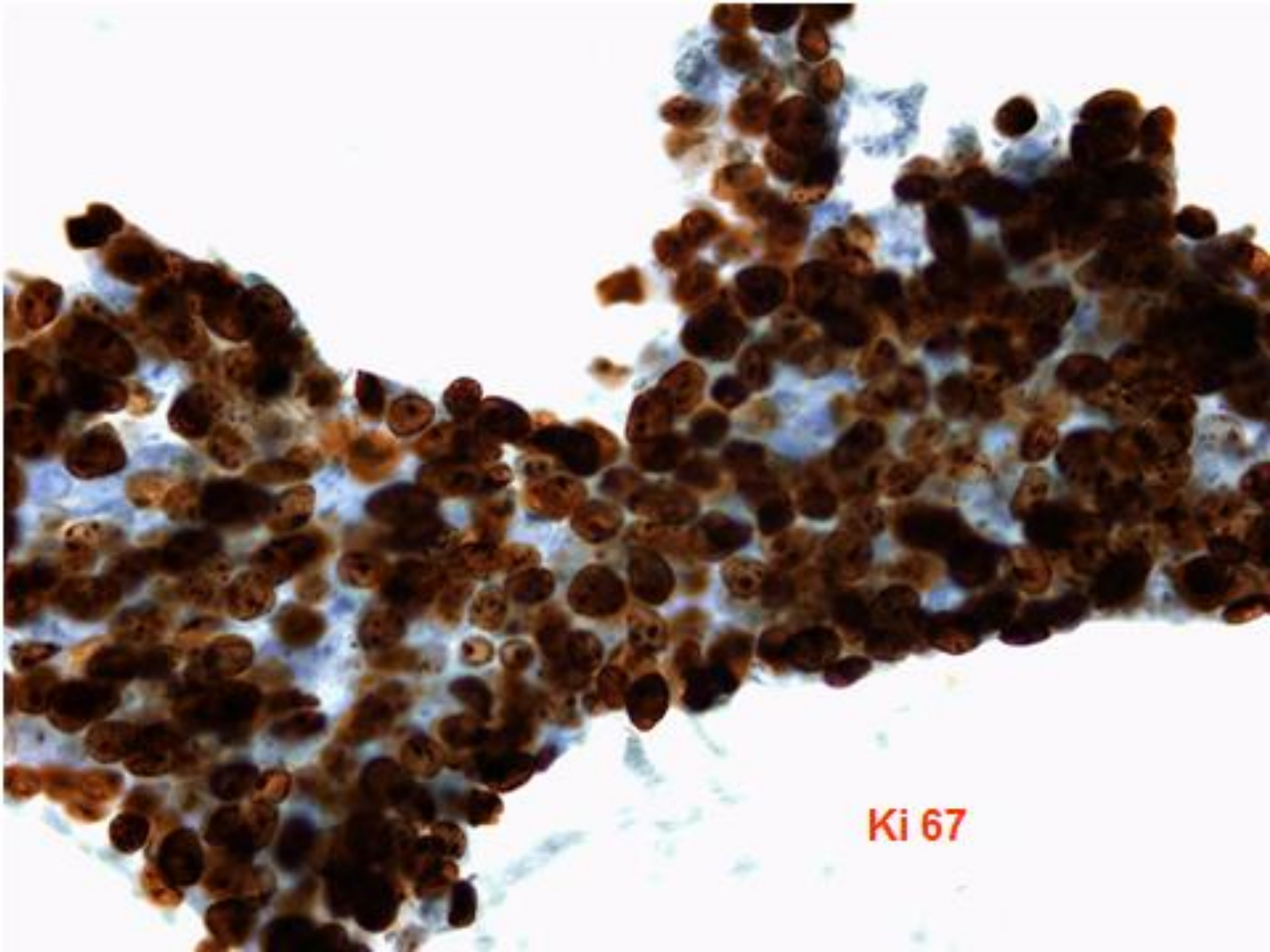








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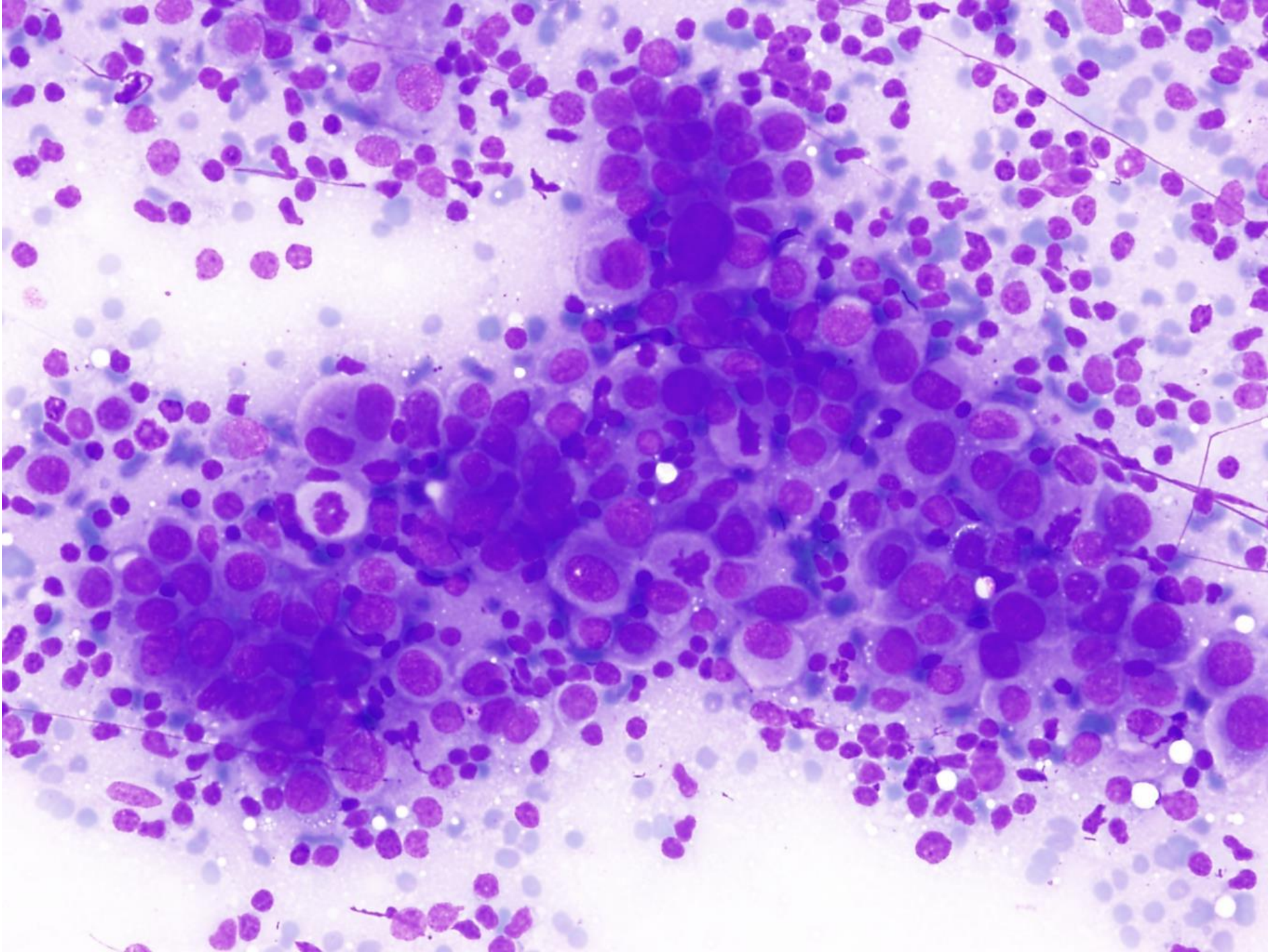

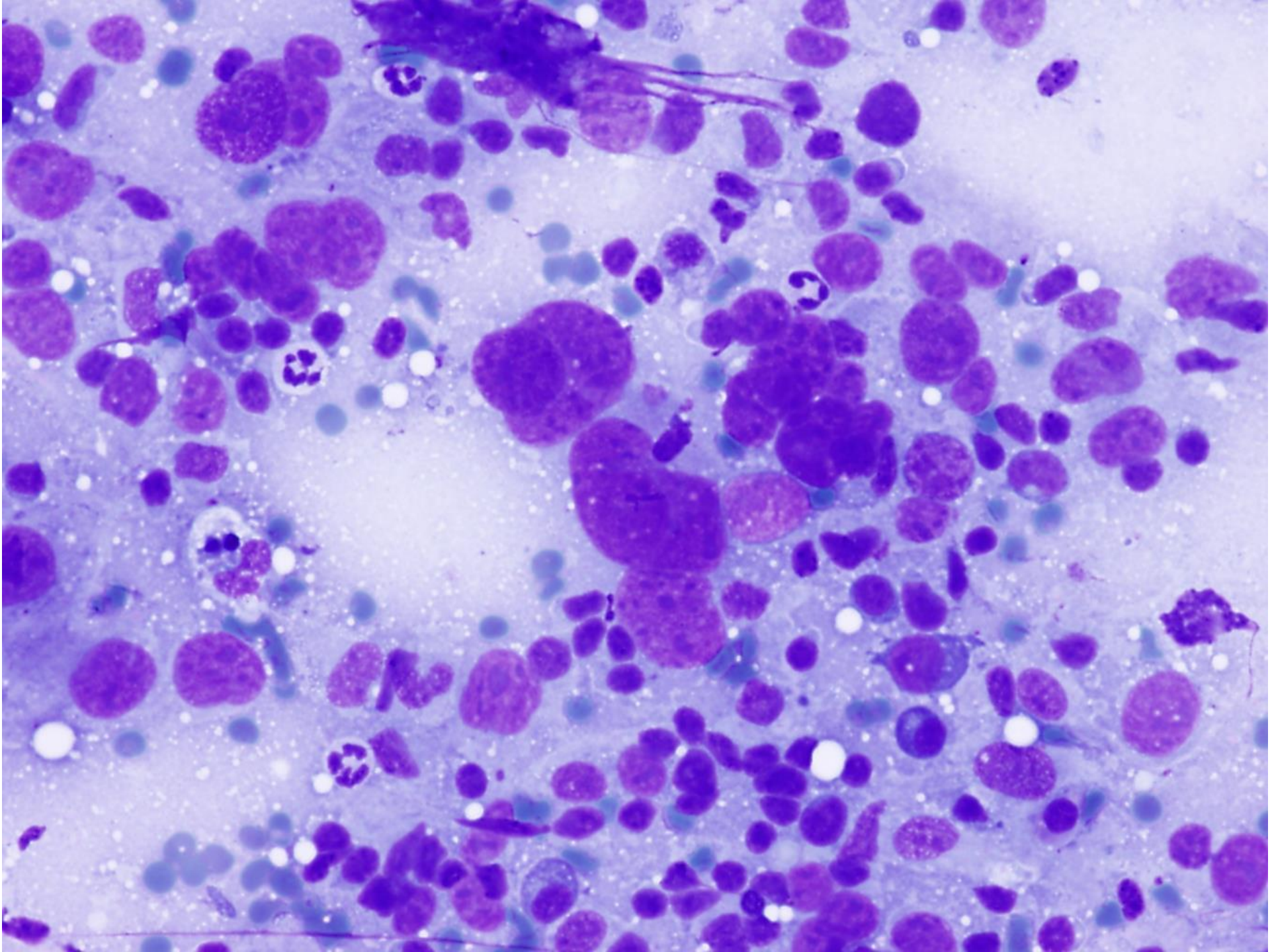

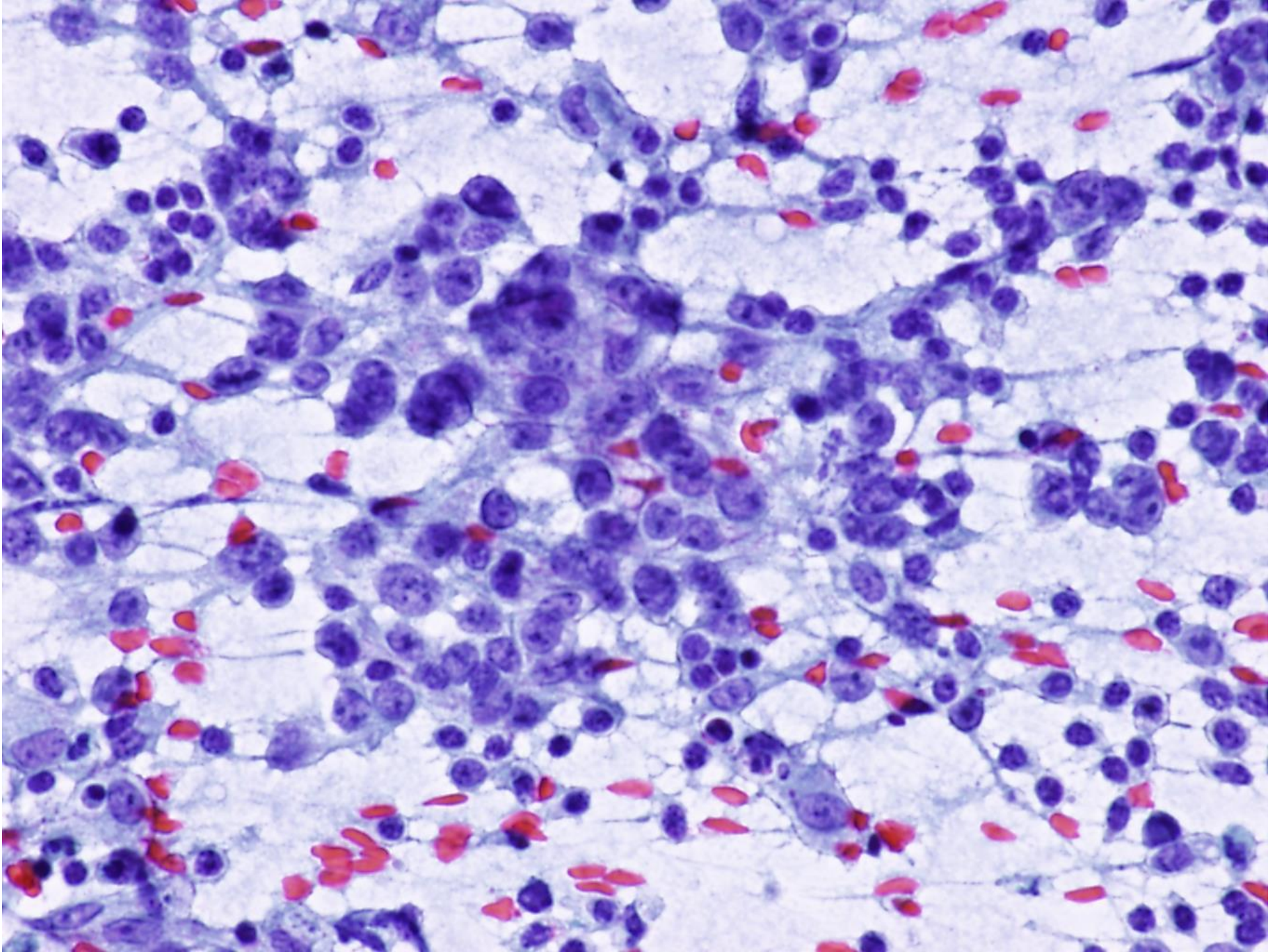

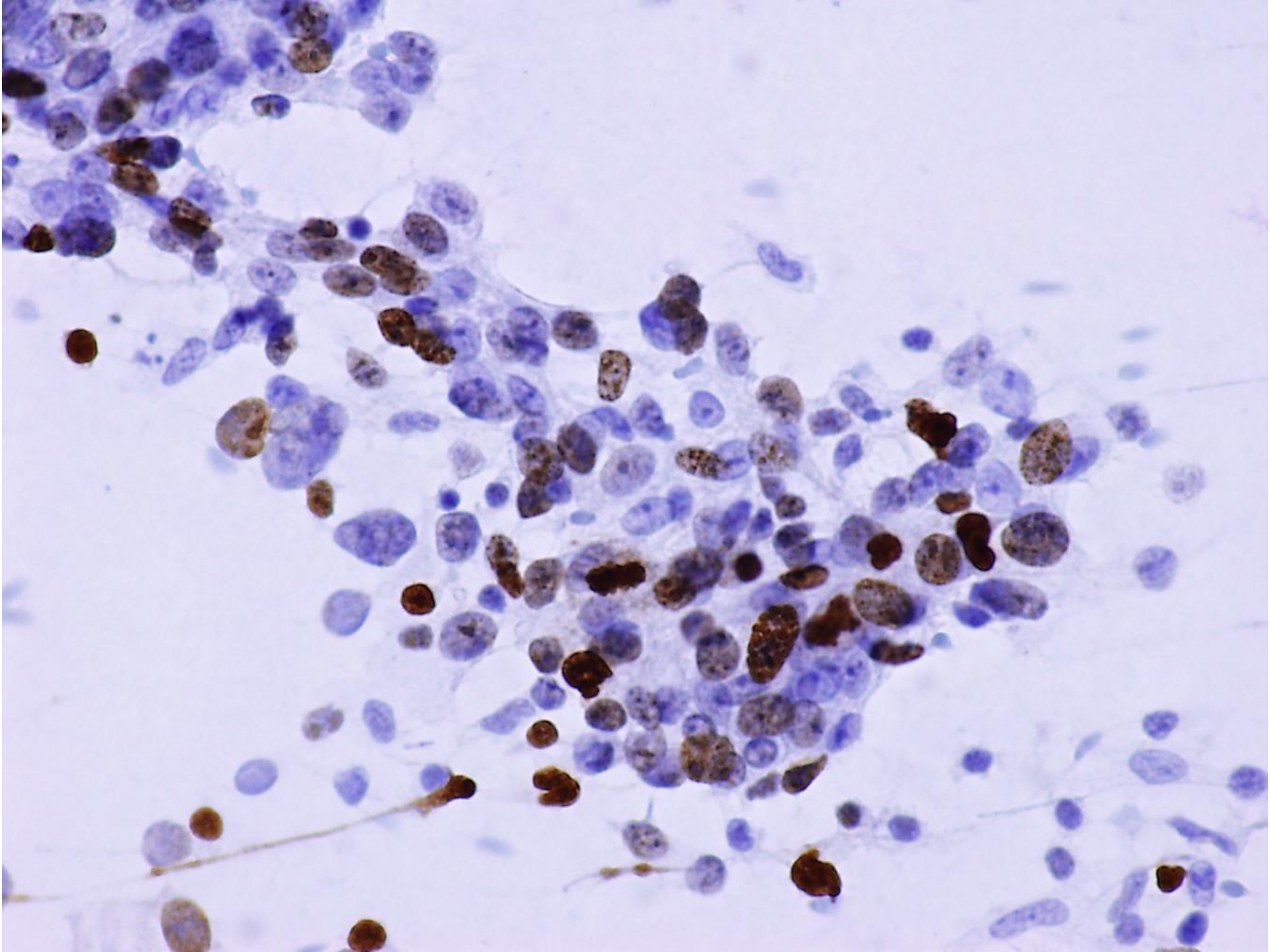

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Fine Needle Aspiration Cytology of Lobular Breast Carcinoma and Its Variants

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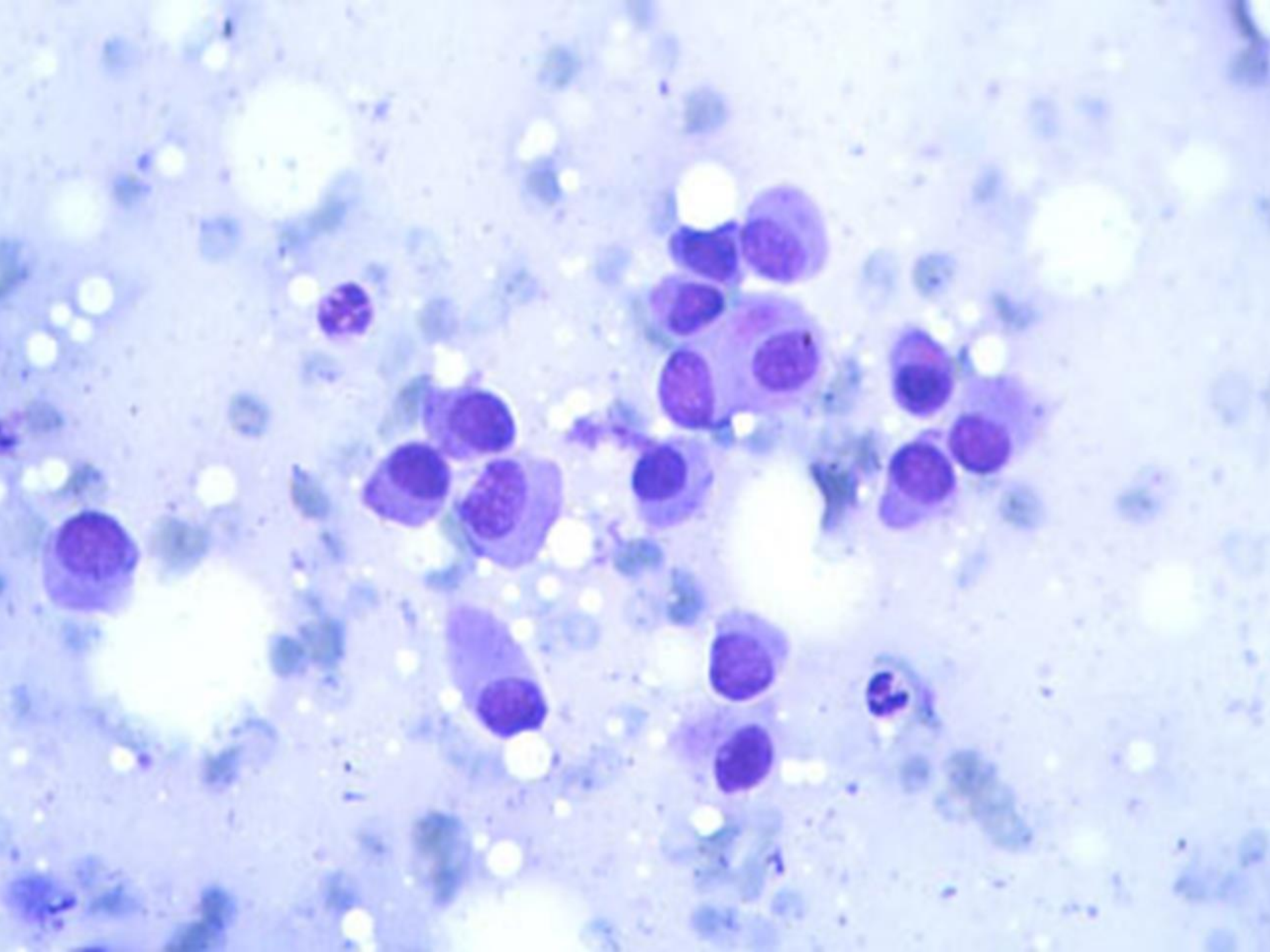
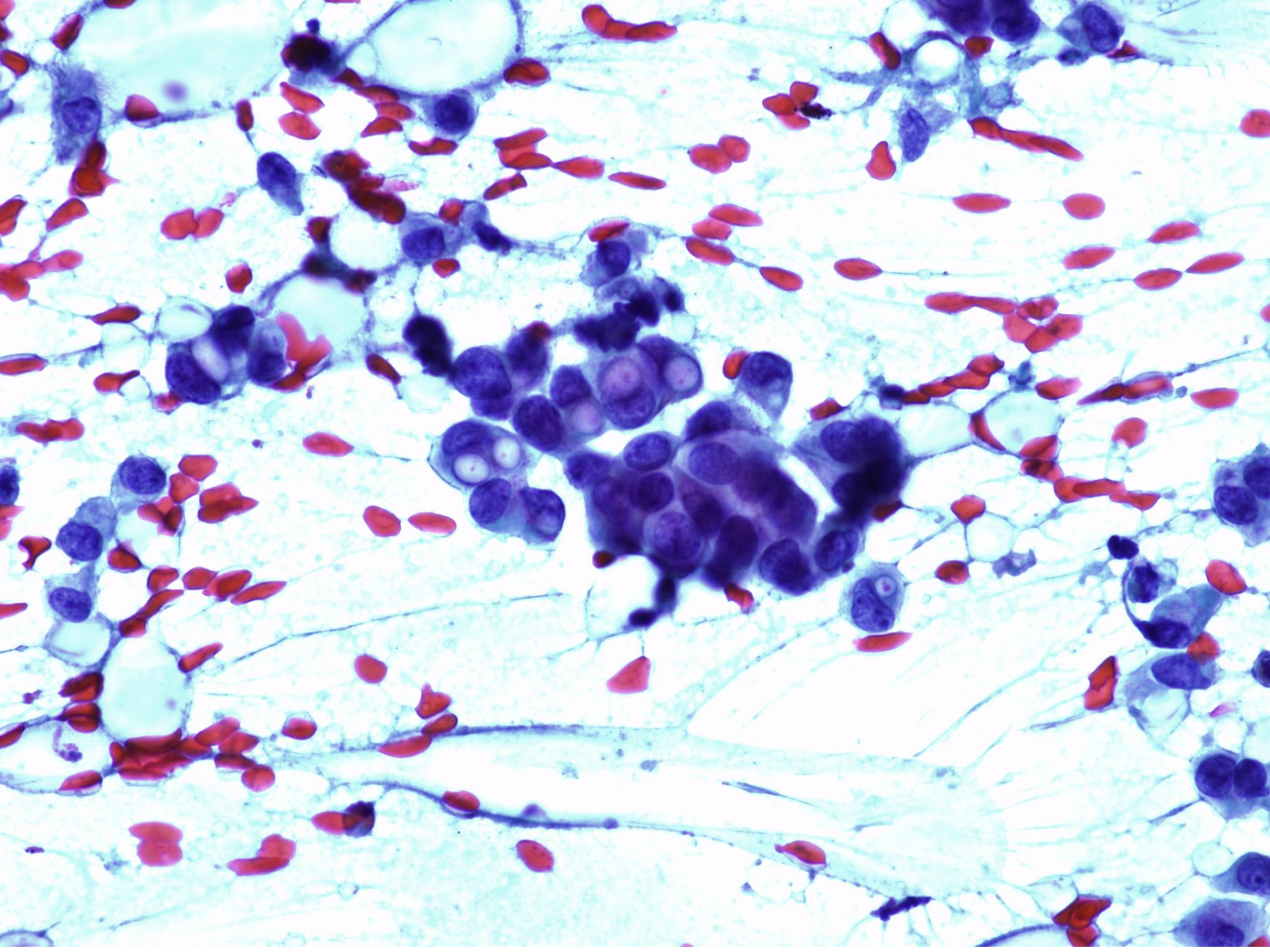
Lobular carcinoma

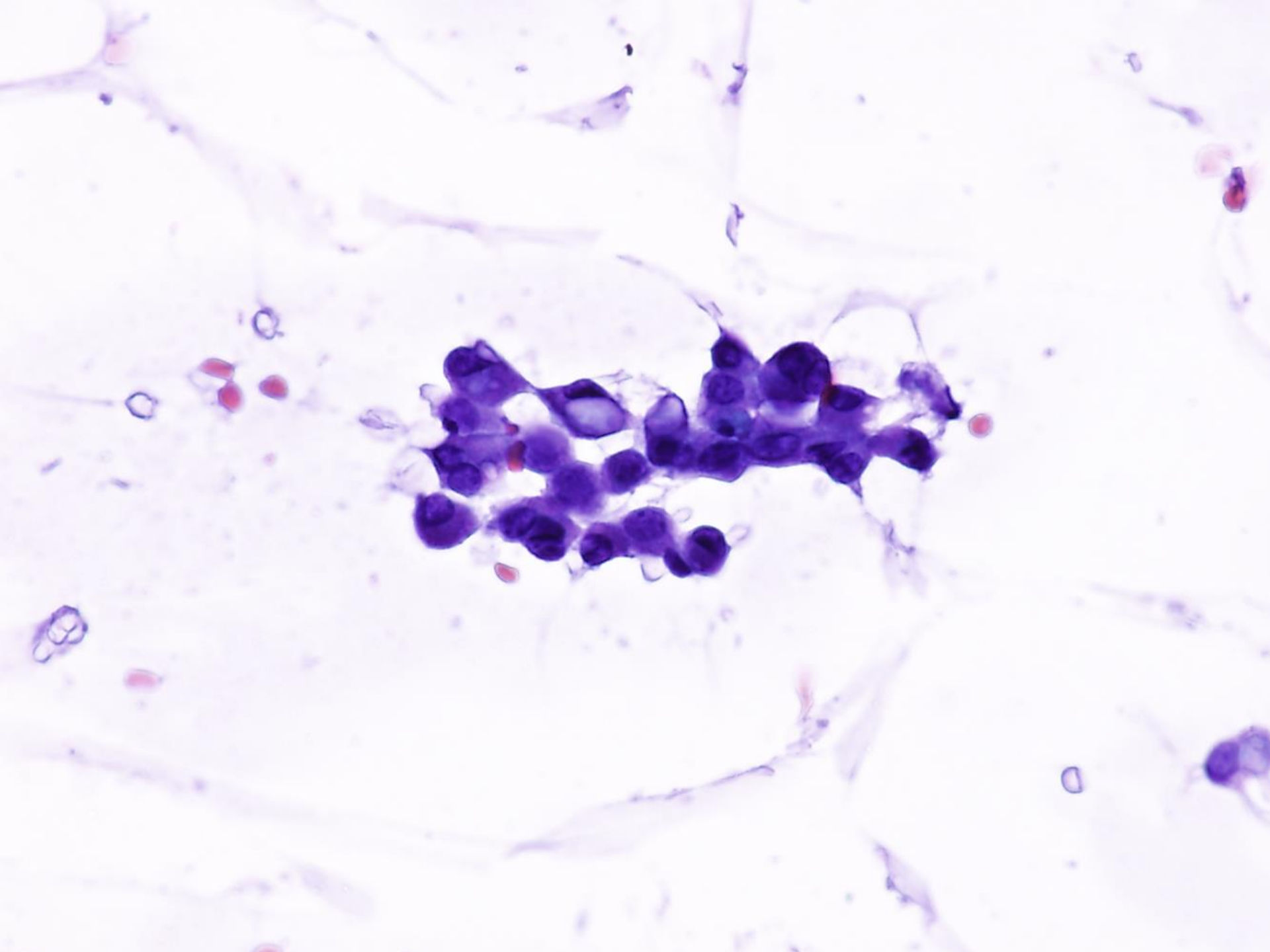
- Smaller cell size in ordinary type;
- Dispersed or finger-like aggregates;
- Indian lines;
- Intracytoplasmic lumina (not specific, but frequent);
- Plasmocytoid cells with basally located round-oval nucleus with small nucleolus, occasional nipple-like protrusion or nuclear lobulation and granular cytoplasm:
- E-Cadherin generally negative in ordinary types (high grade and special types of lobular ca. may express E-Cadherin).

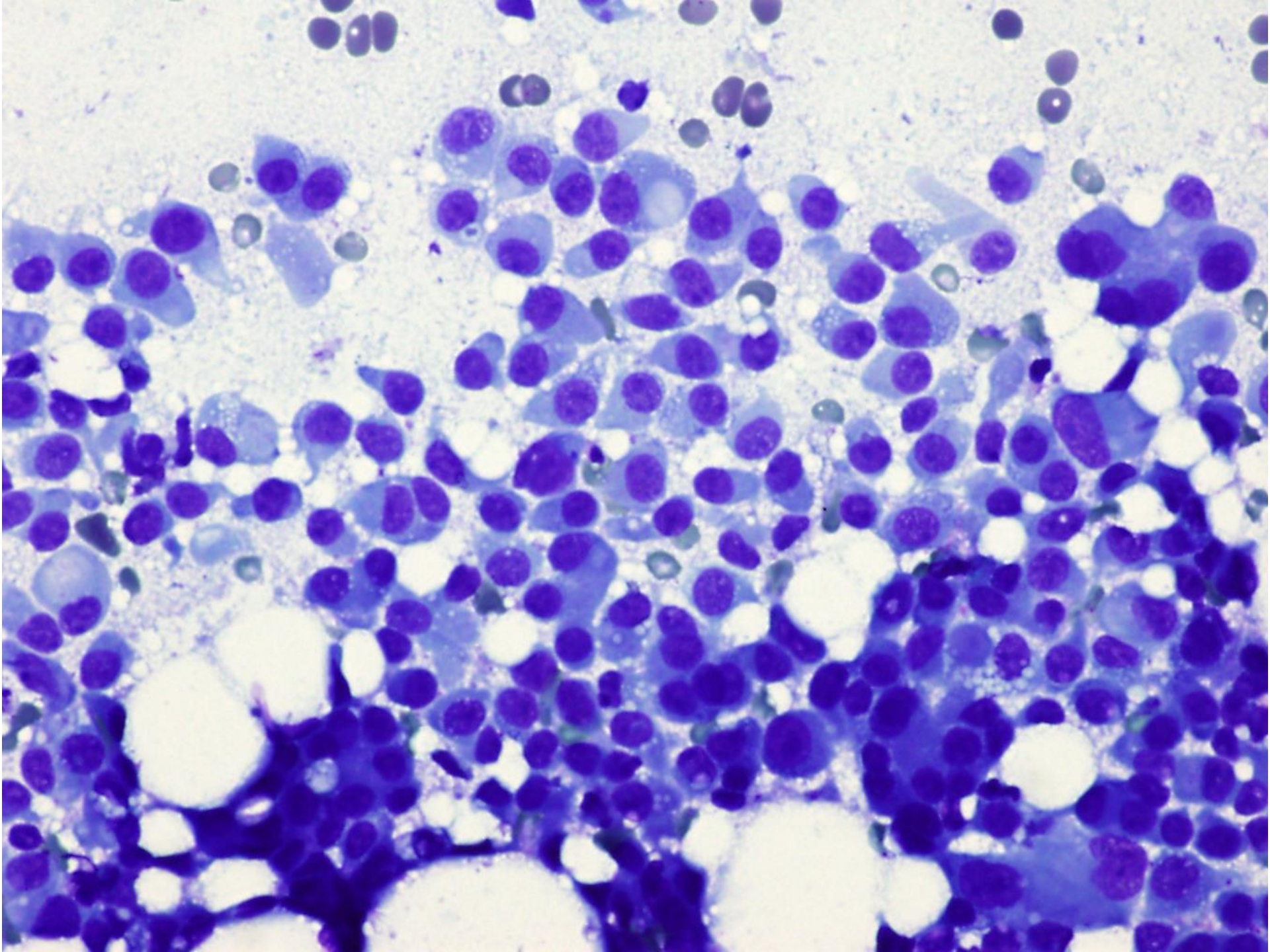
Lobular carcinoma

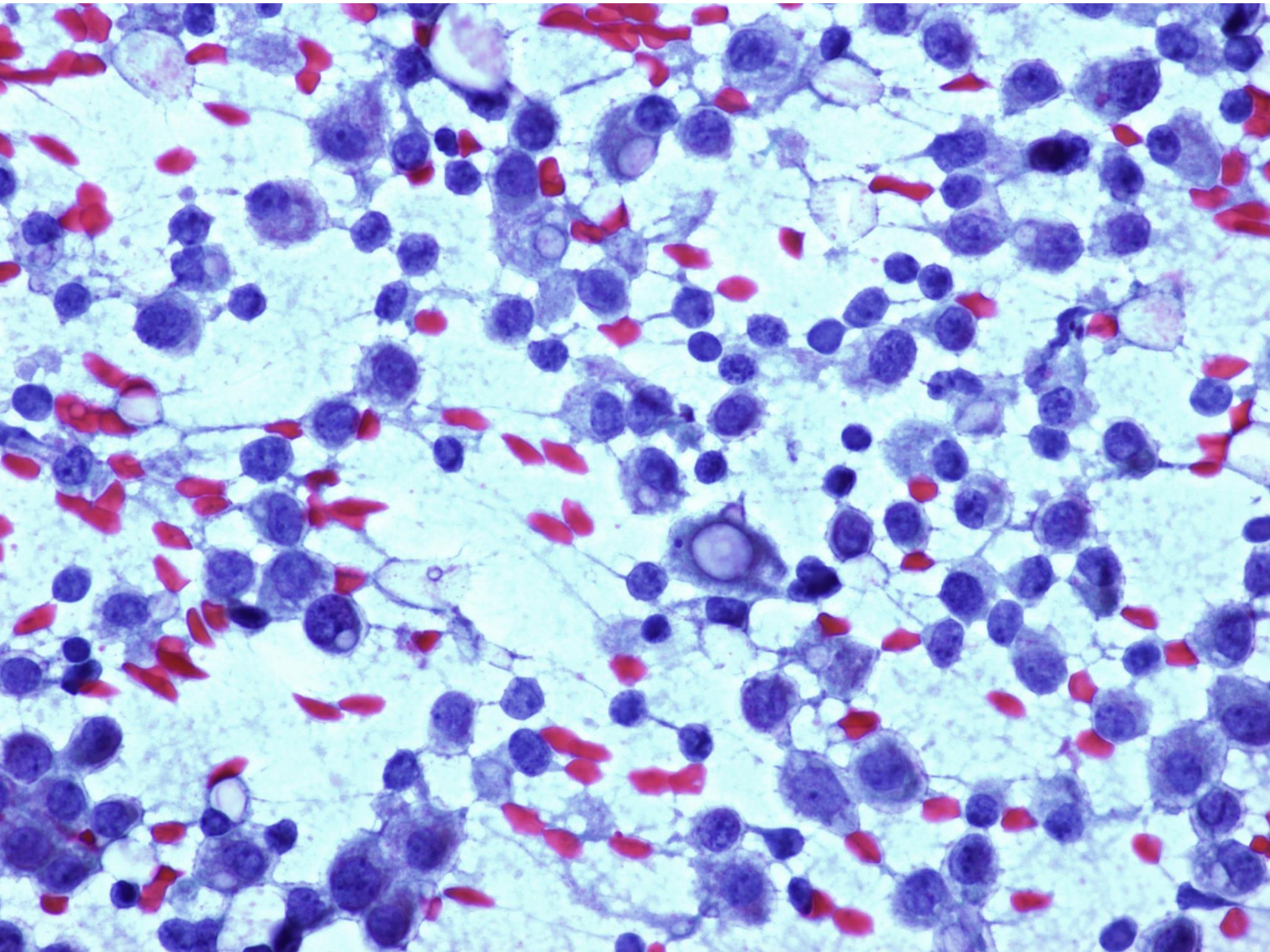
- Approximately 60 % can be recognized cytologically by their typical morphology;
- 40% hide in the ductulo-acinar and acinar cytological subtypes.
- Solid-alveolar/histiocytoid variants may sometimes be recognized on cytological samples.
- Frequent apocrine differentiation and GDFP15 expression in pleomorphic variant.

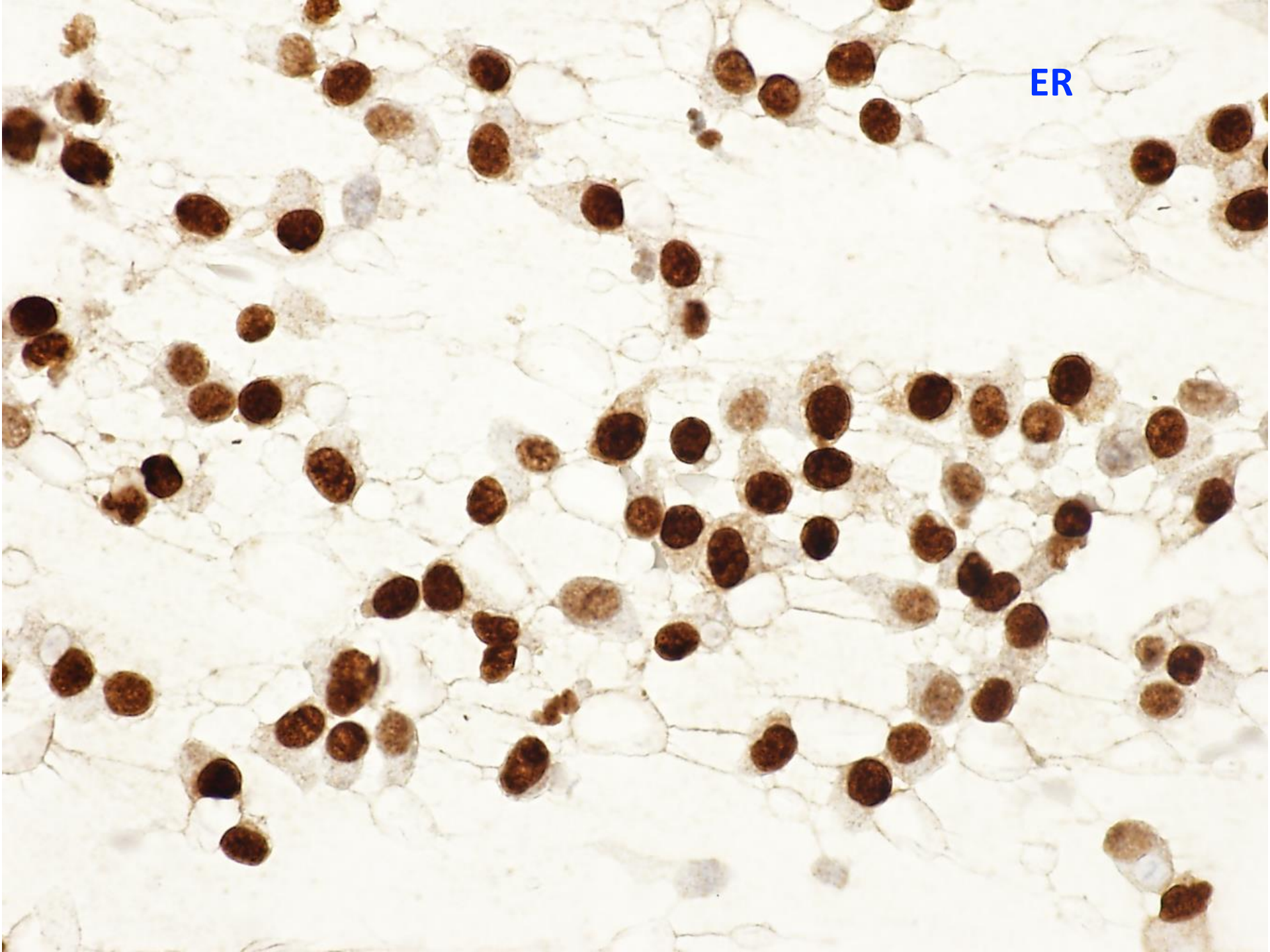








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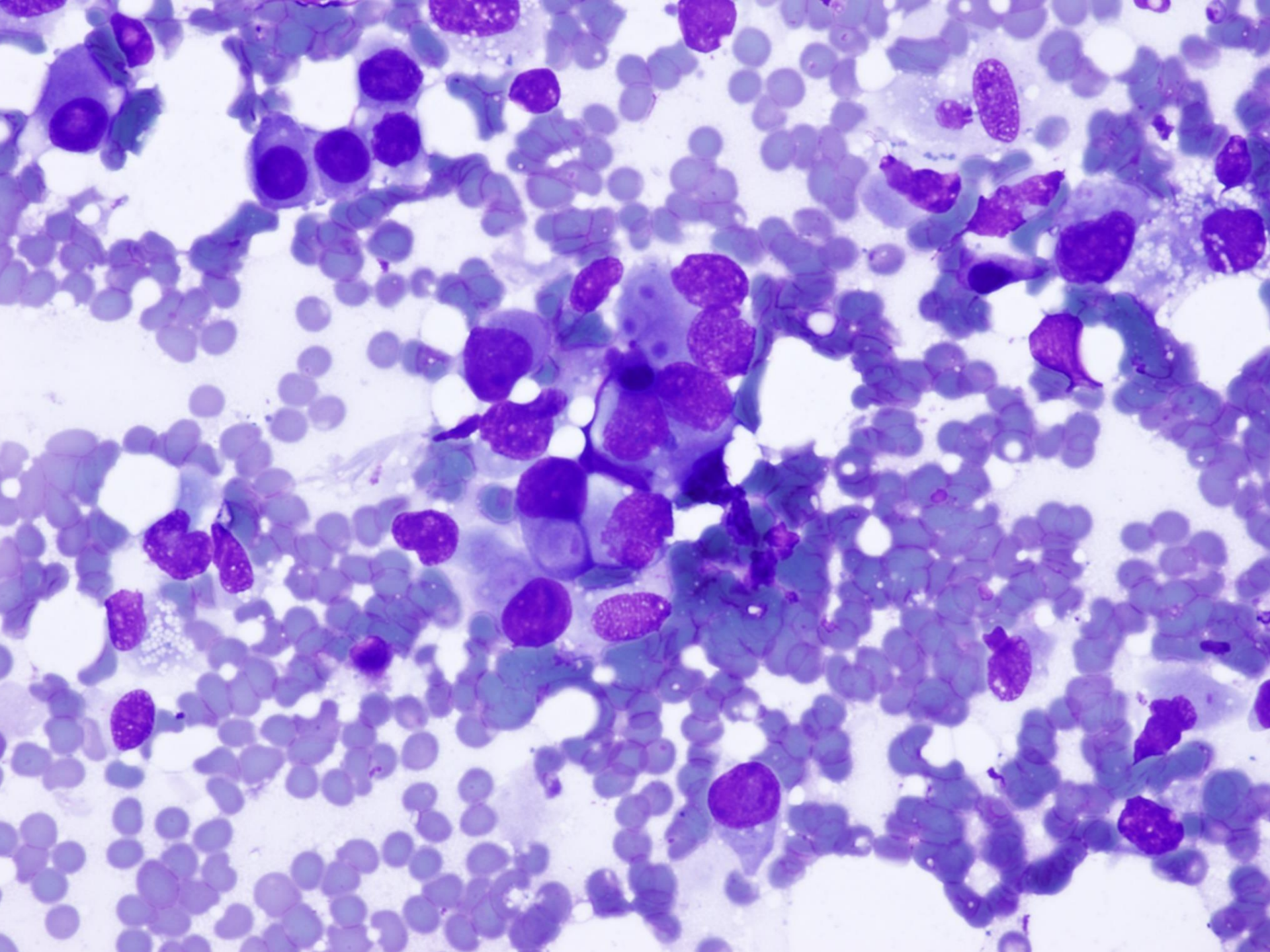
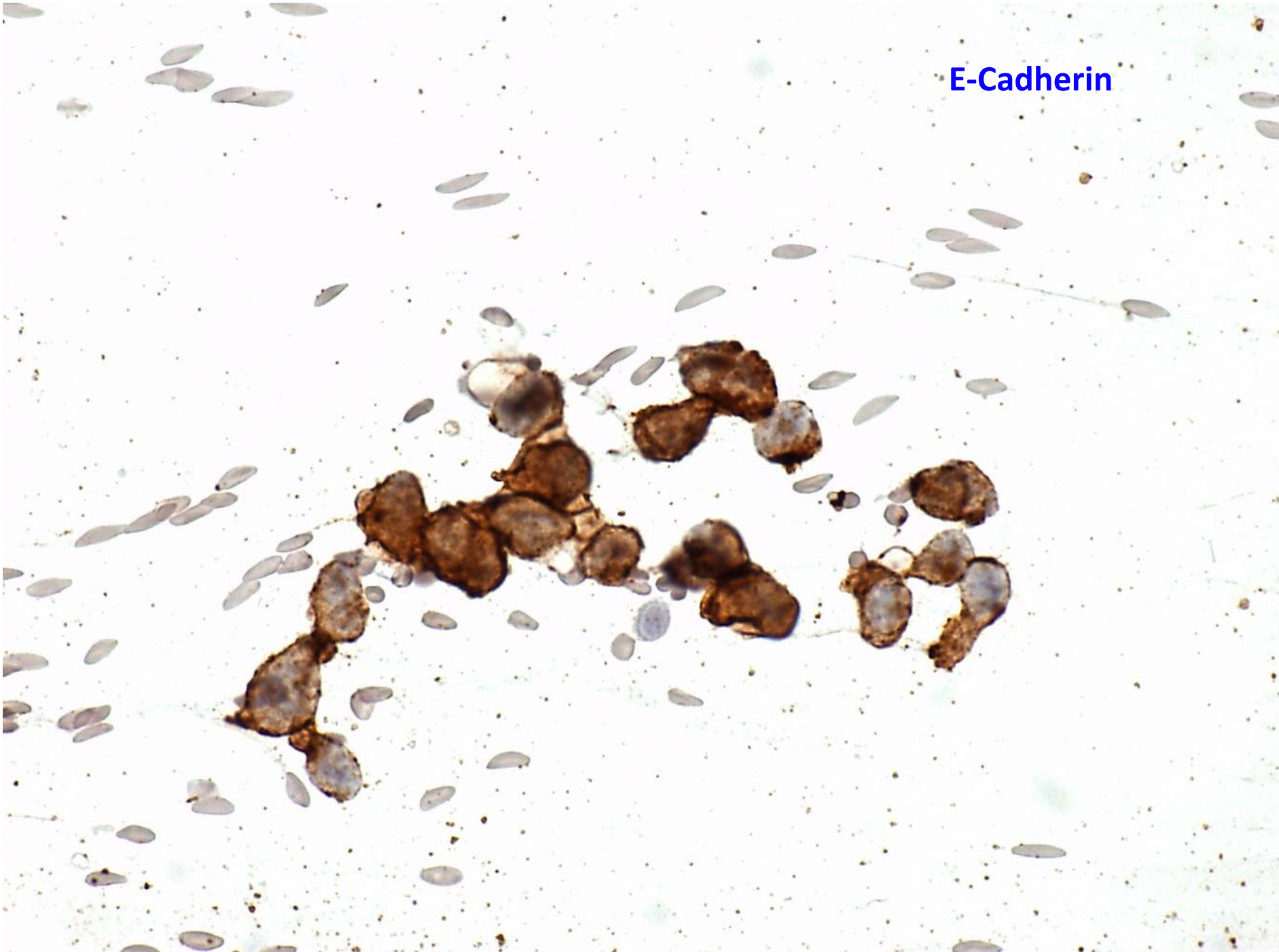
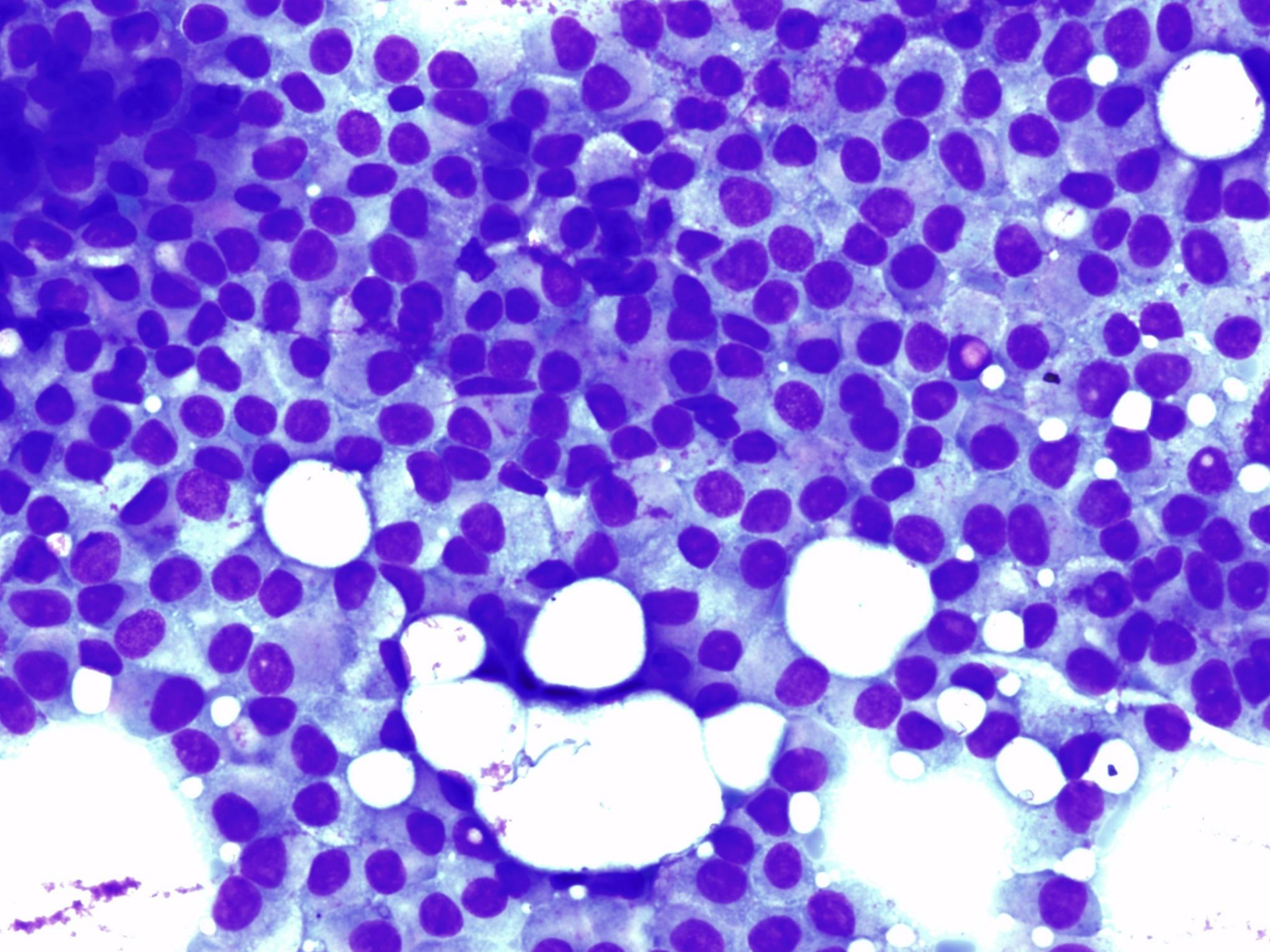
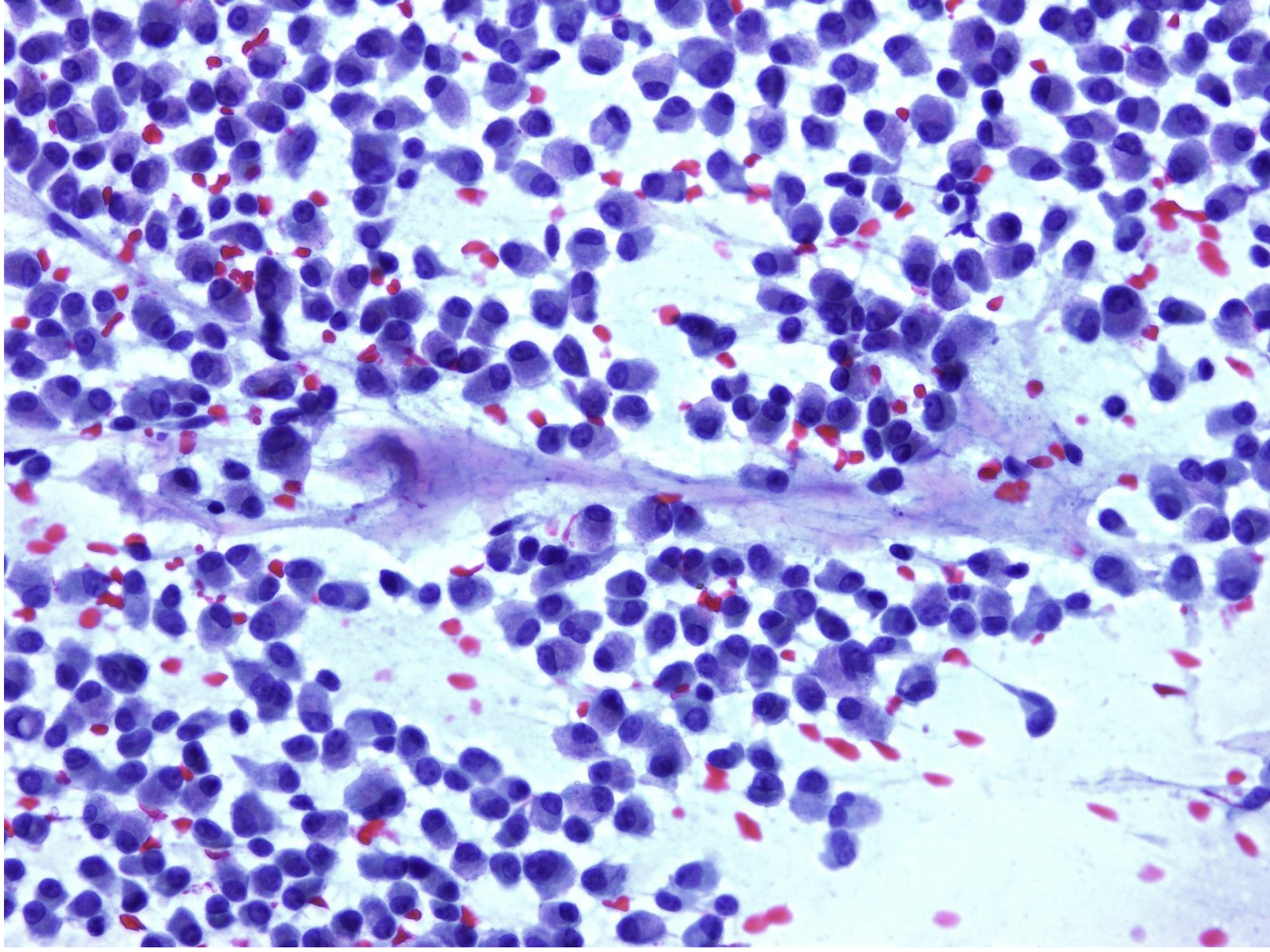
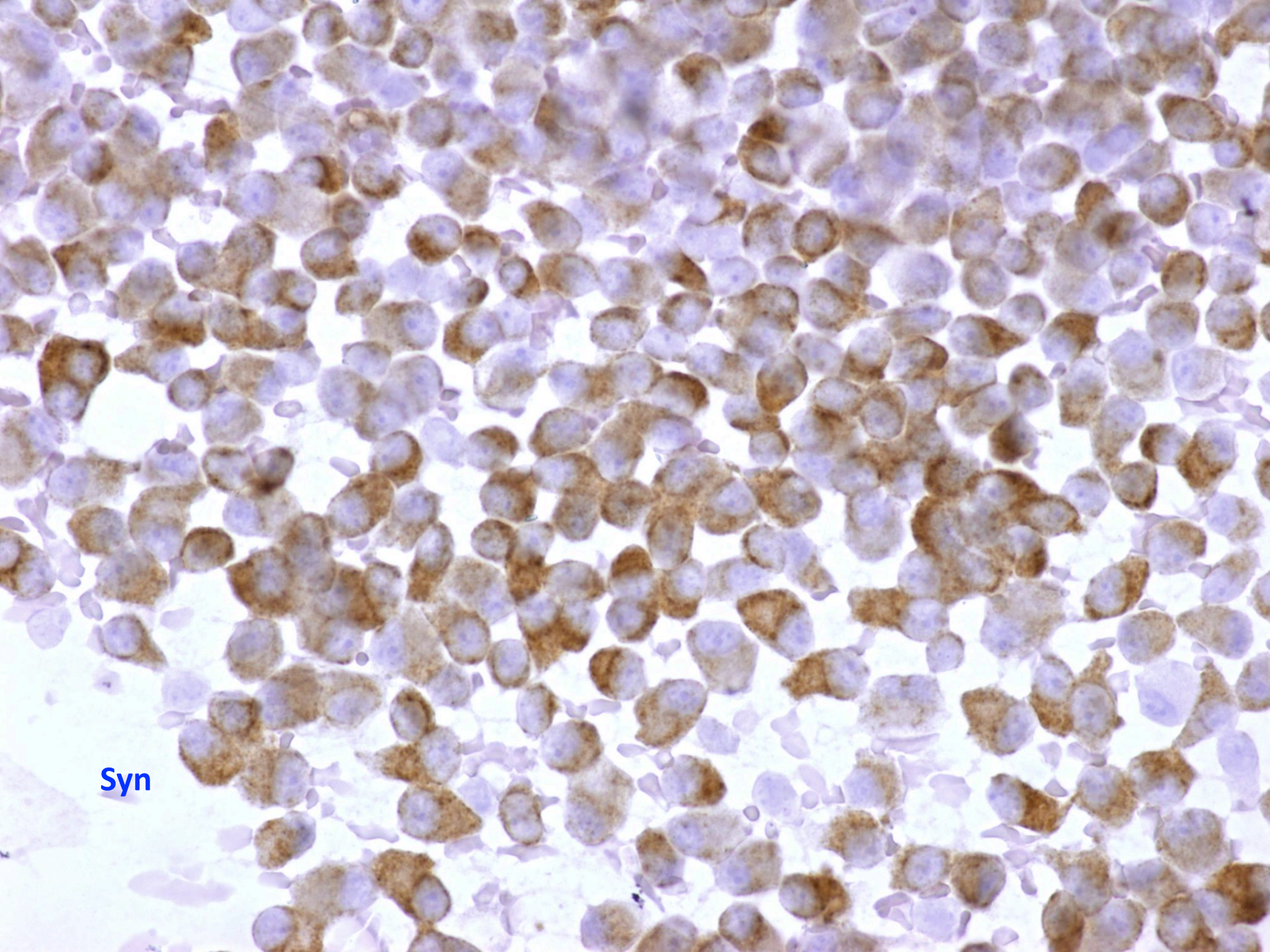



E-Cadherin






Syn

Invasive lobular carcinoma with extracellular mucin production—a novel pattern of lobular carcinomas of the breast. Clinico-pathological description of eight cases

Virchows Archiv

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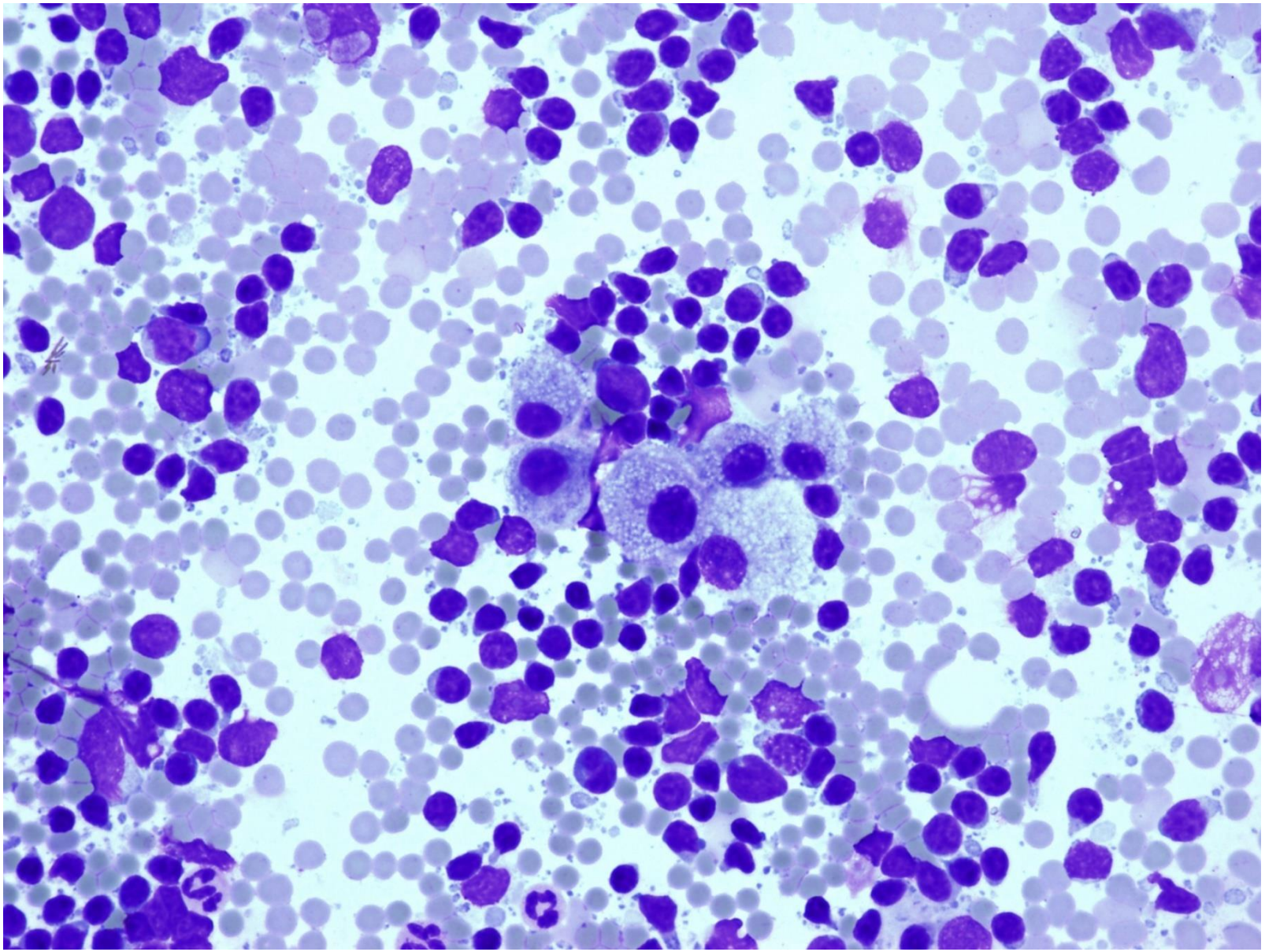
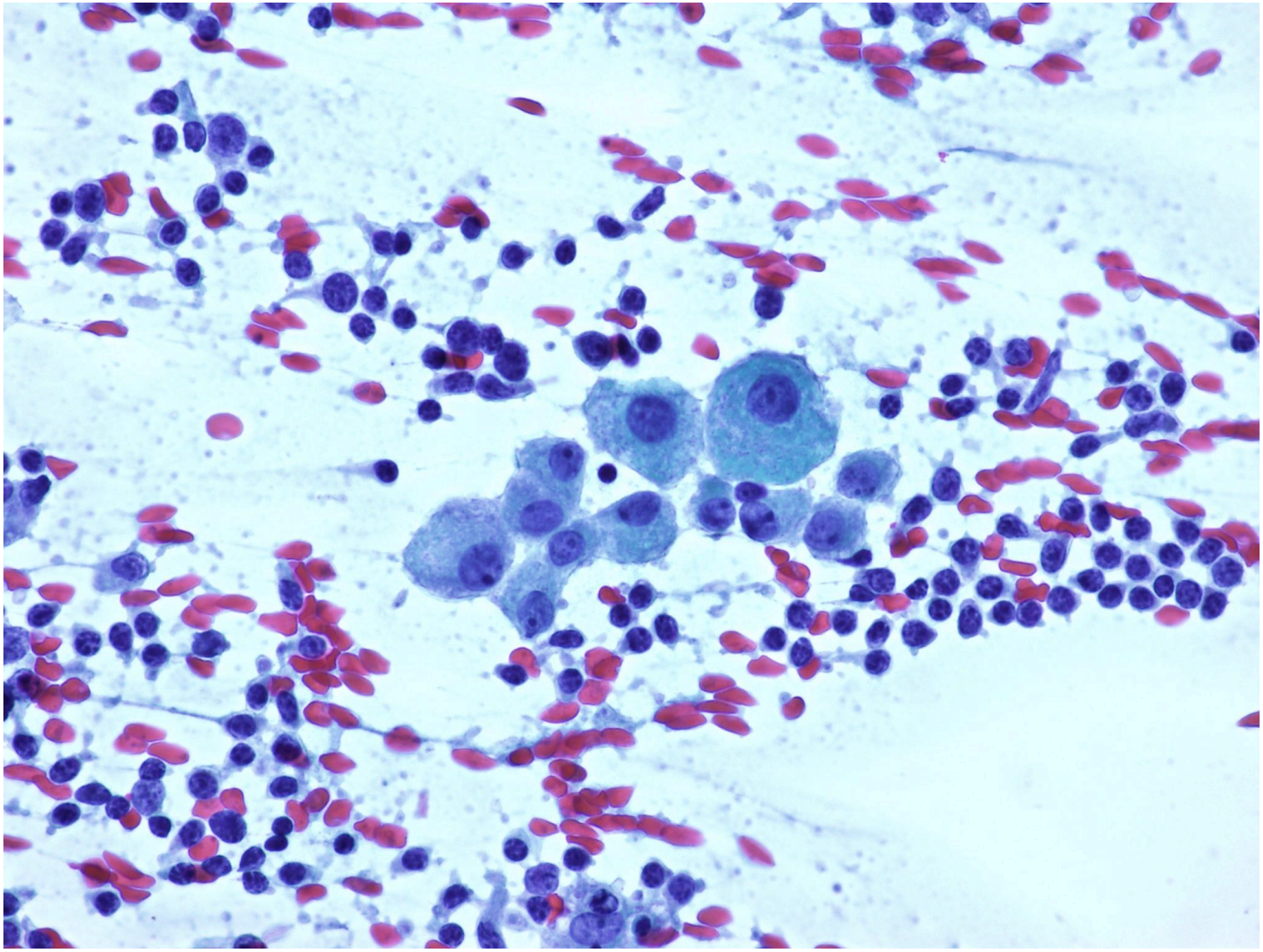
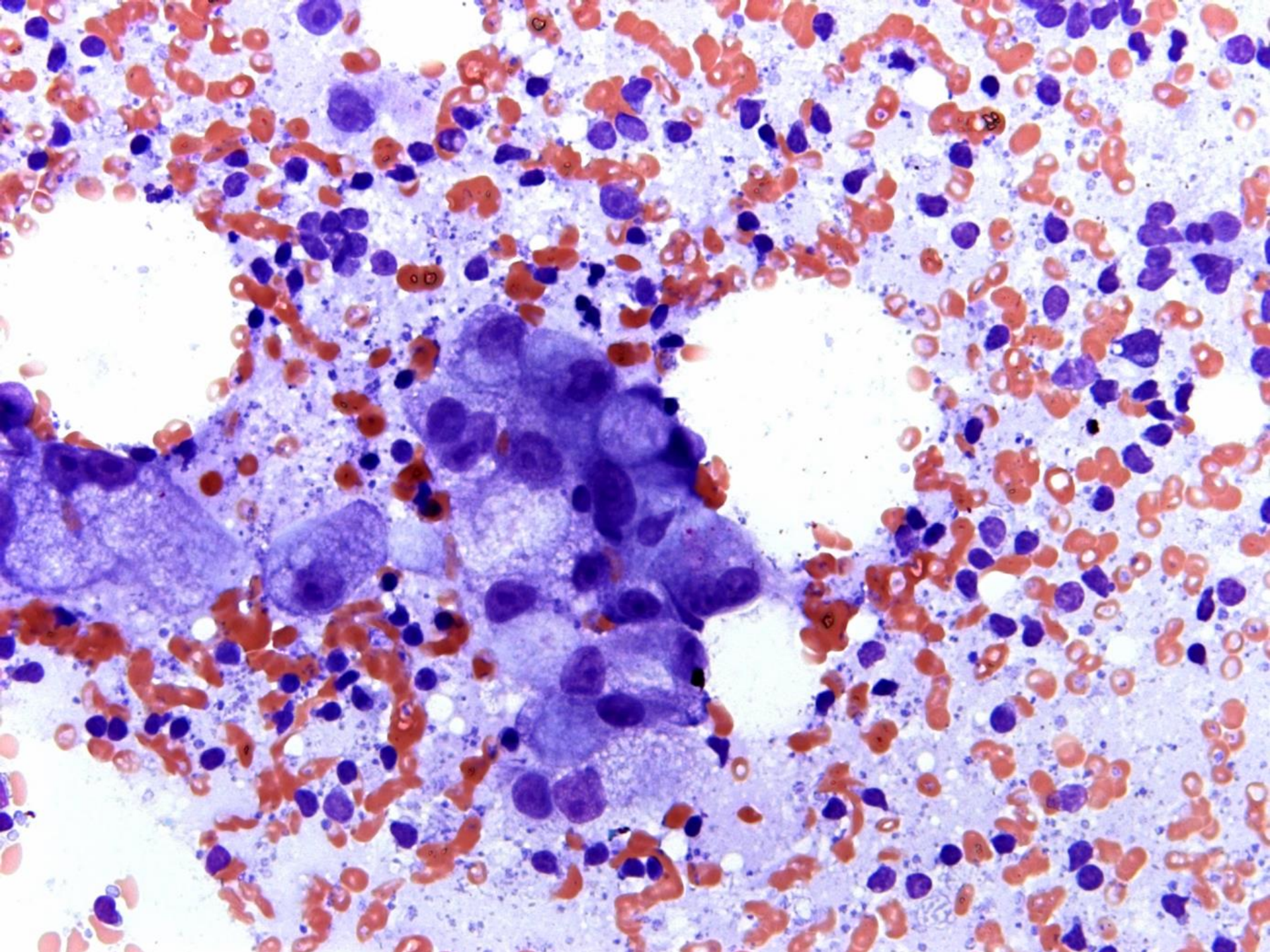
Abstract

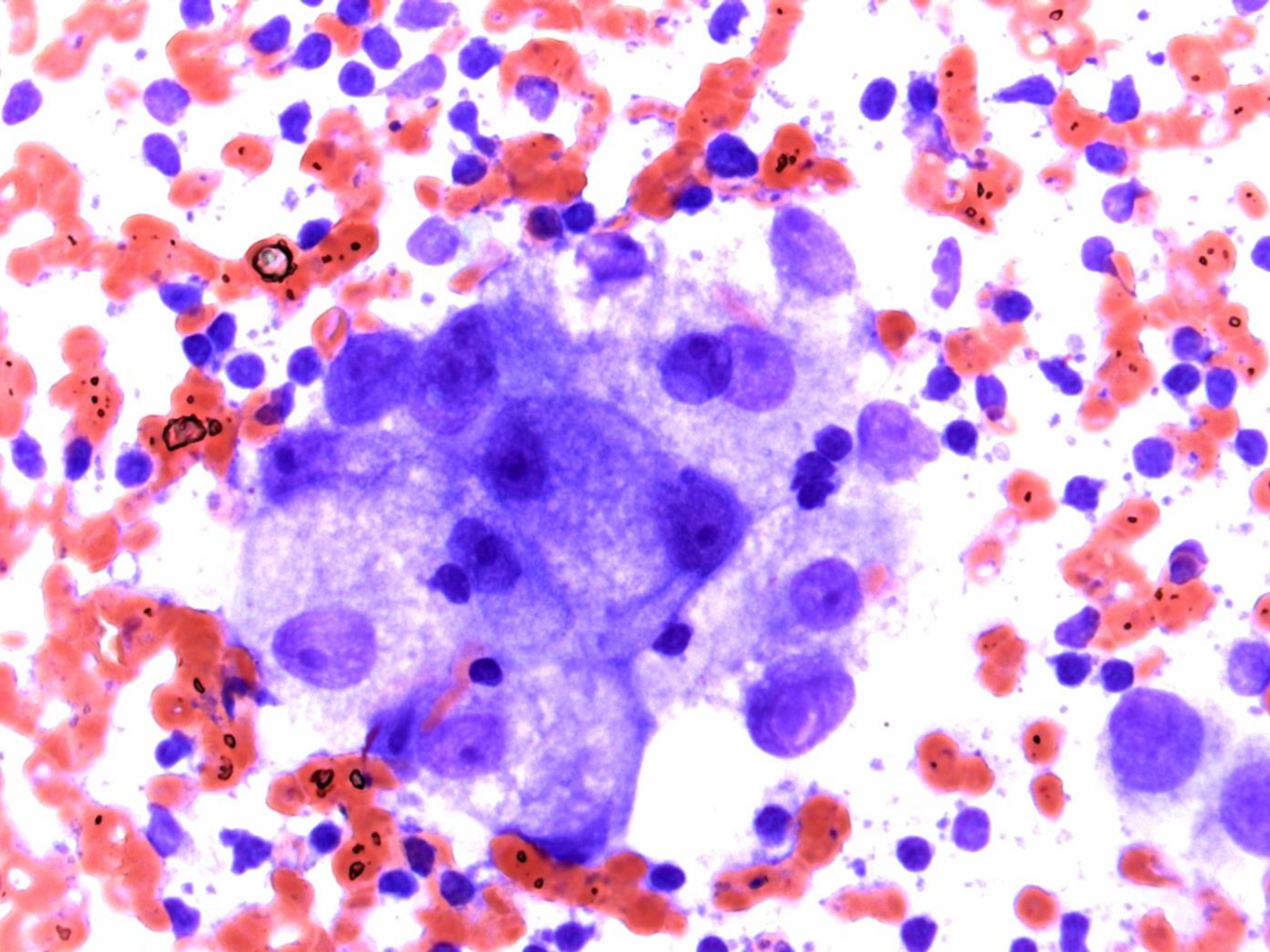
Invasive lobular carcinoma of the breast is known to produce intracellular mucin and has been recognized in single-case reports to show extracellular mucin production, as well. This latter morphology is not only rare but must also be under- or misdiagnosed. The aim was to better characterize this entity. Cases of lobular cancers demonstrating extracellular mucin formation were identified in a multi-institutional effort and their clinical and morphologic features were assessed. Immunohistochemistry was used to characterize the E-cadherin-membrane complex, neuroendocrine differentiation, and to some extent, mucin formation. All but one of the eight cases occurred in postmenopausal patients. Extracellular mucin production was present in 5 to 50% of the tumour samples and rarely also appeared in nodal and distant metastases. The tumours were completely E-cadherin negative and showed cytoplasmic p120 positivity. The majority (n = 6/8) was also completely negative for β-catenin, but two tumours displayed focal β-catenin positivity in the mucinous area. MUC1 and MUC2 expression was observed in all and 7/8 tumours, respectively; neuroendocrine differentiation was present in only one. Invasive lobular carcinoma with extracellular mucin formation is a rare morphologic variant of lobular carcinoma prone to be misdiagnosed and warranting further studies.

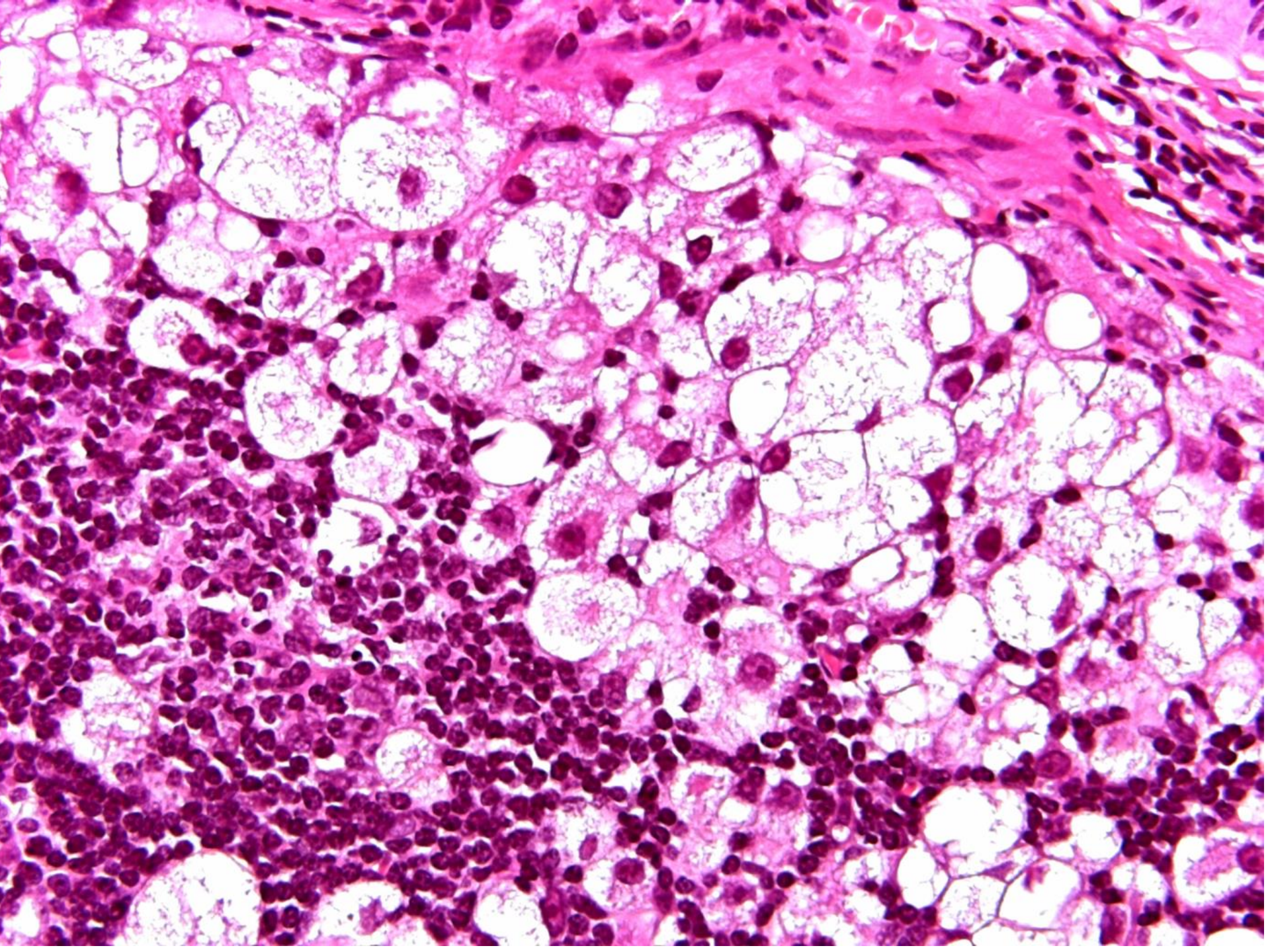
Histiocytoid Lobular Carcinoma

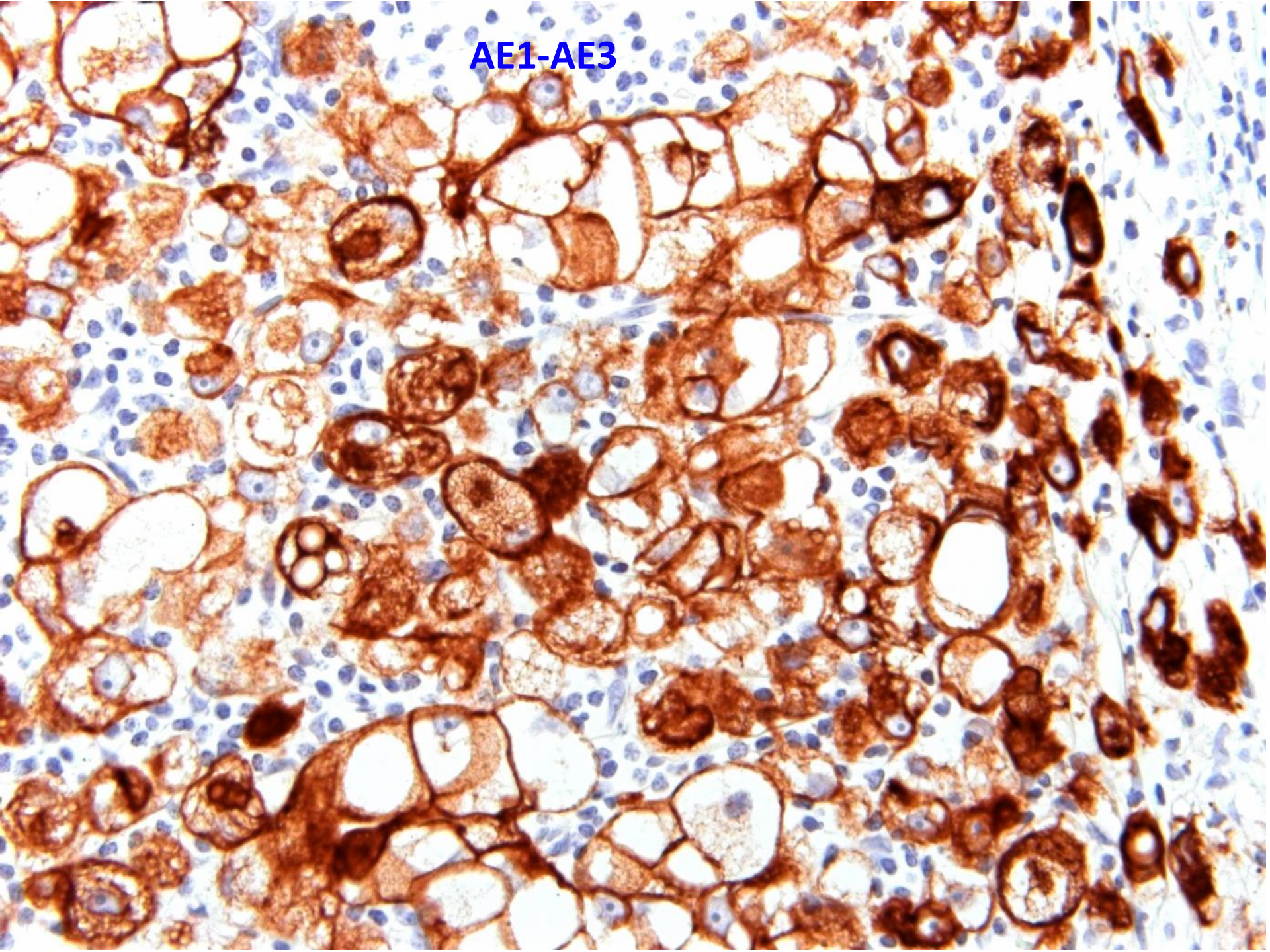




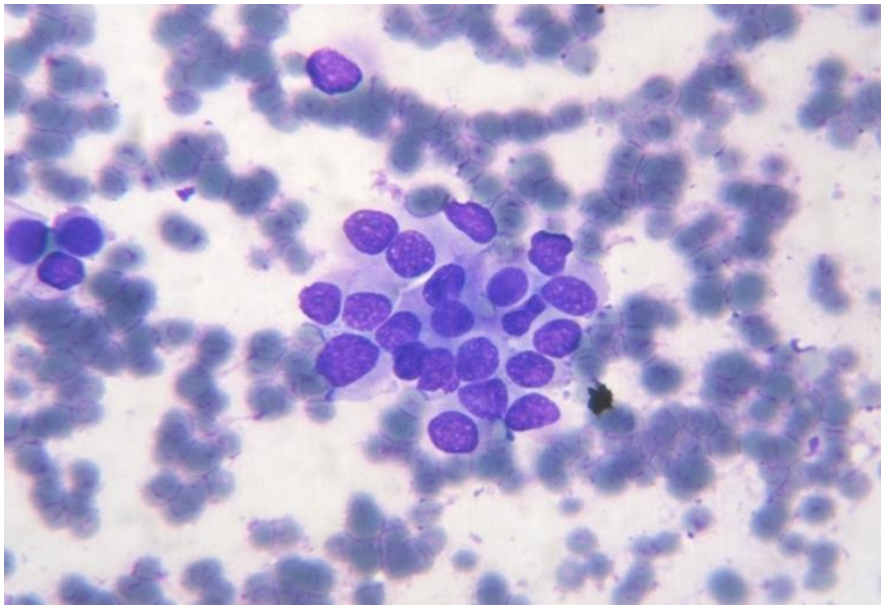


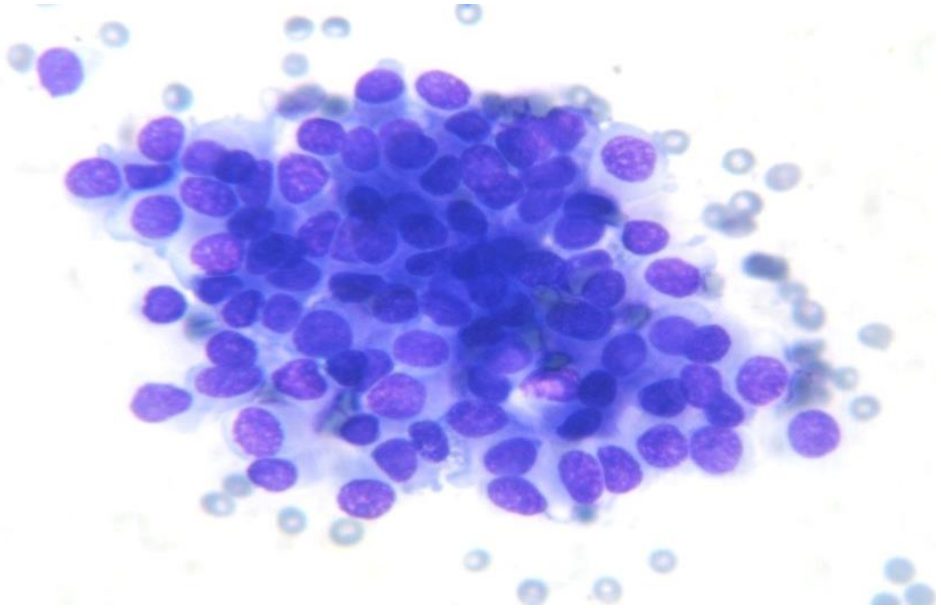





AE1-AE3

LCIS: a Difficult Diagnosis on FNC Samples





Ustün M, Berner A, Davidson B, Risberg B Fine-needle aspiration cytology of lobular carcinoma in situ. Diagn Cytopathol. 2002 Jul;27(1):22-6.

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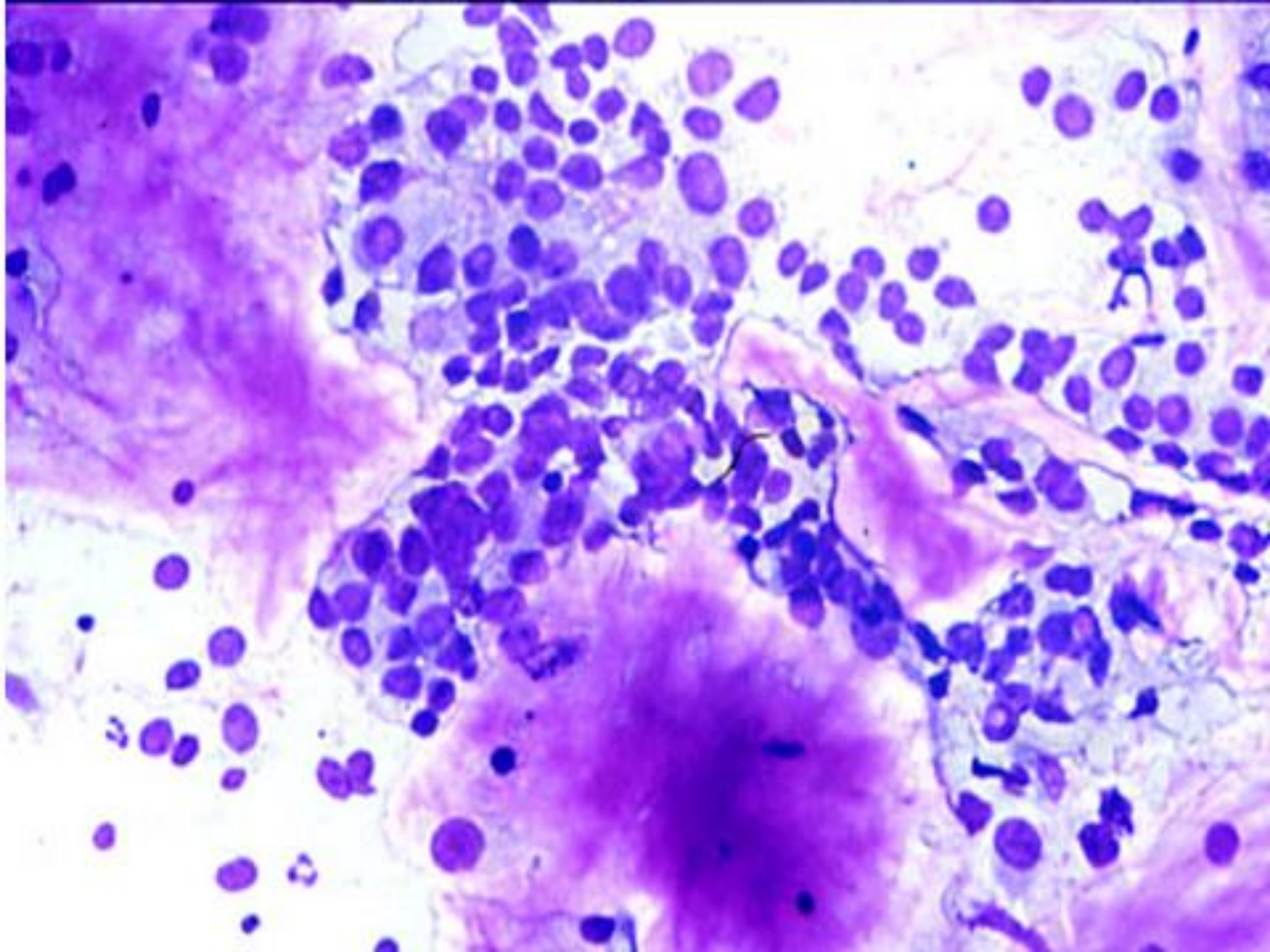
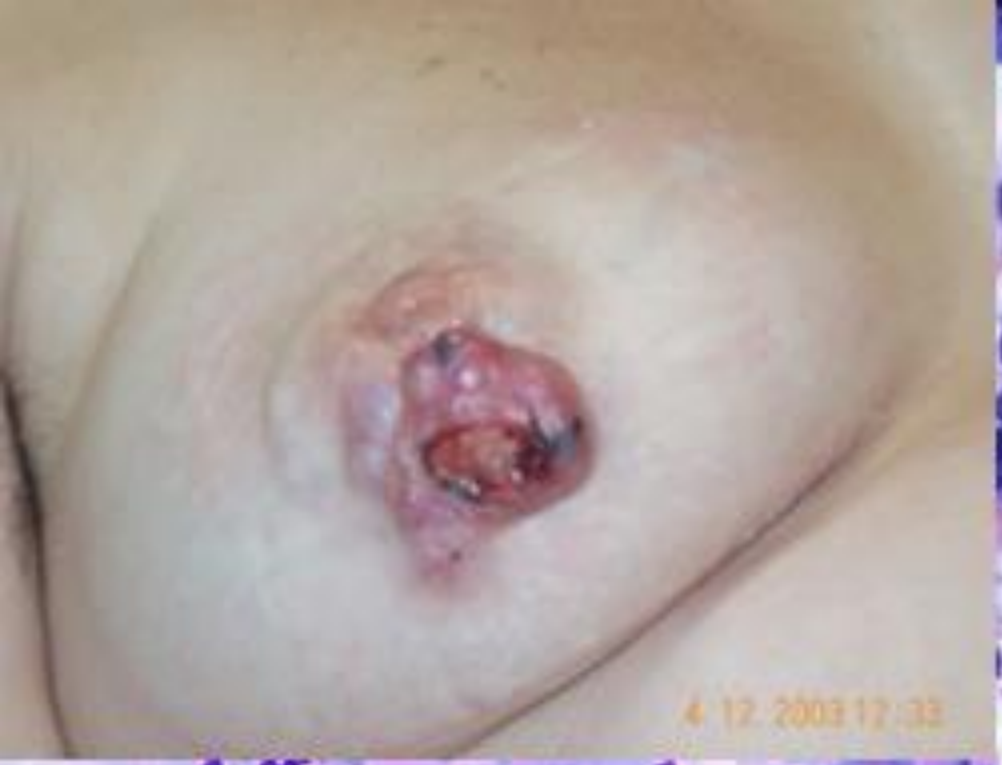
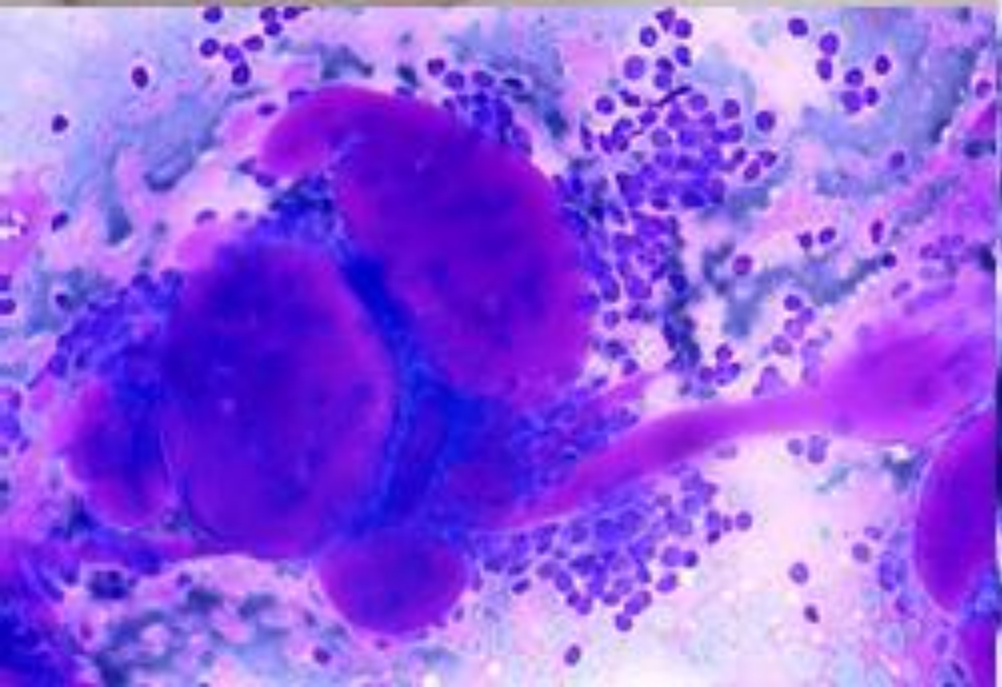
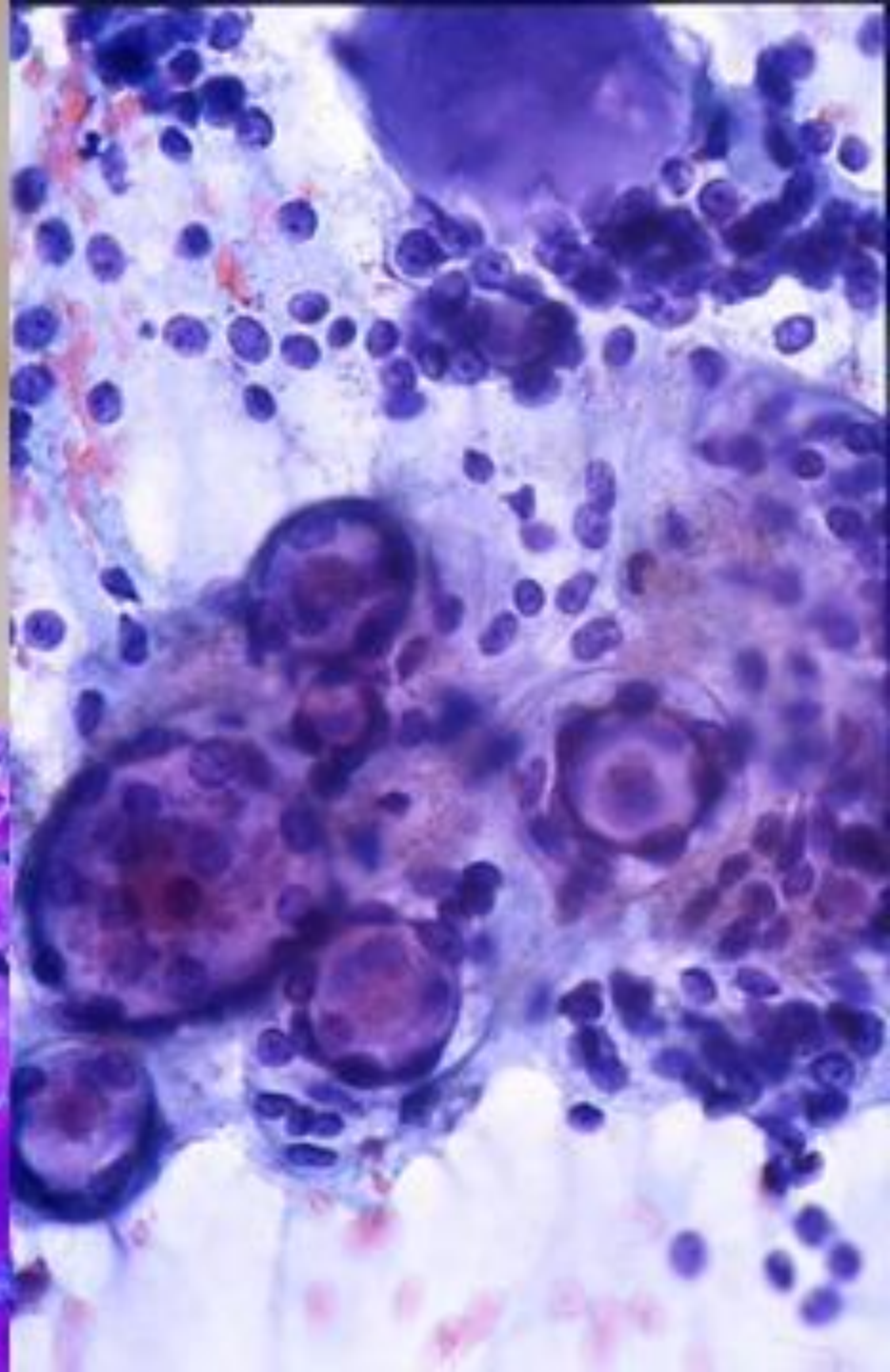
Special types of breast carcinoma

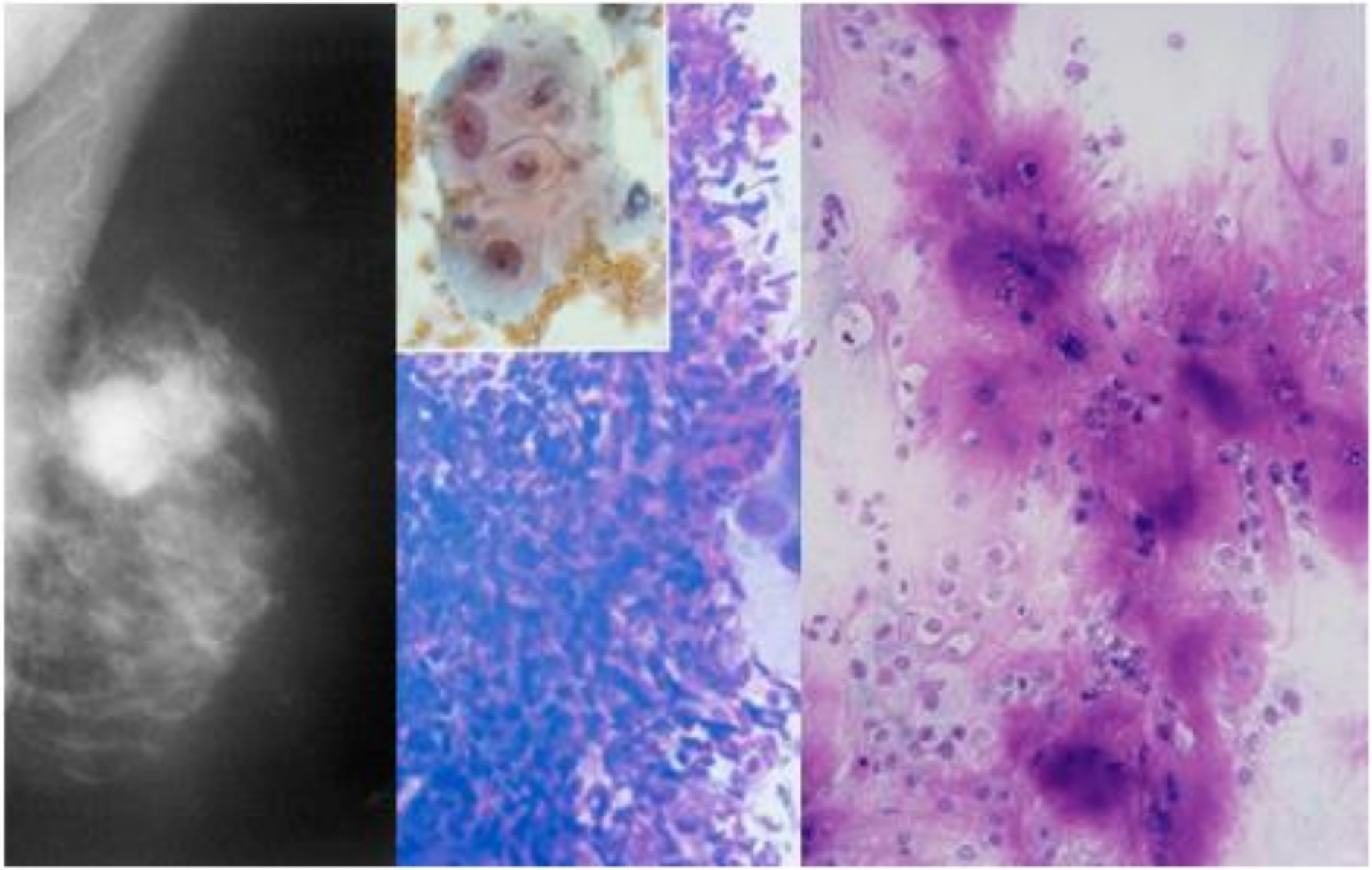
- Mucinous carcinoma
- Adenoid-cystic carcinoma
- Metaplastic carcinoma
- Papillary carcinoma
- Micropapillary carcinoma
- Other entities (carcinoma with osteoclast-like cells, with choriocarcinomatous elements etc..)











Metaplastic Breast Carcinoma on Fine-Needle Cytology Samples:
A Report of Three Cases

Franco Fulciniti, M.D.,[1*] Gelsomina Mansueto, M.D.,[1]
Antonio Vetrani, M.D.,[1] Antonello Accurso, M.D.,[2]
Adriana Fortunato, M.D.,[1] and Lucio Palombini, M.D.[1]

Metaplastic breast carcinoma (MBC) may have a varied presentation on fine-needle cytology samples. We herewith describe three cases of MBC found in our series. One of these cases showed a peculiar mixture of malignant ductal, apocrine type, and squamous epithelial cells with fascicles of spindle cells with variable degree of atypia and was diagnosed as metaplastic carcinoma of the carcino-sarcomatous type. The other two lesions were characterized by an abundant chondroid extracellular matrix to which were variably admixed carcinomatous and chondroid-type cells, with variable degree of atypia. Both these latter cases were defined as matrix-producing metaplastic carcinomas. Because of the various presentation of MBC on fine-needle cytology samples and the possible influence of needle "sampling" on the cytological specimen, the spectrum of differential diagnoses to be considered may encompass a number of benign and malignant entities, like keratinous subareolar cysts, malignant fibroepithelial lesions with myxo-chondroid stroma, and true sarcomas of the breast, with cartilaginous metaplasia. It is the Authors' feeling that, with optimal samples, the cytomorphological findings of this rare variant of breast carcinoma permit its accurate pre-operative diagnosis. Diagn. Cytopathol. 2005;33: 205–209.

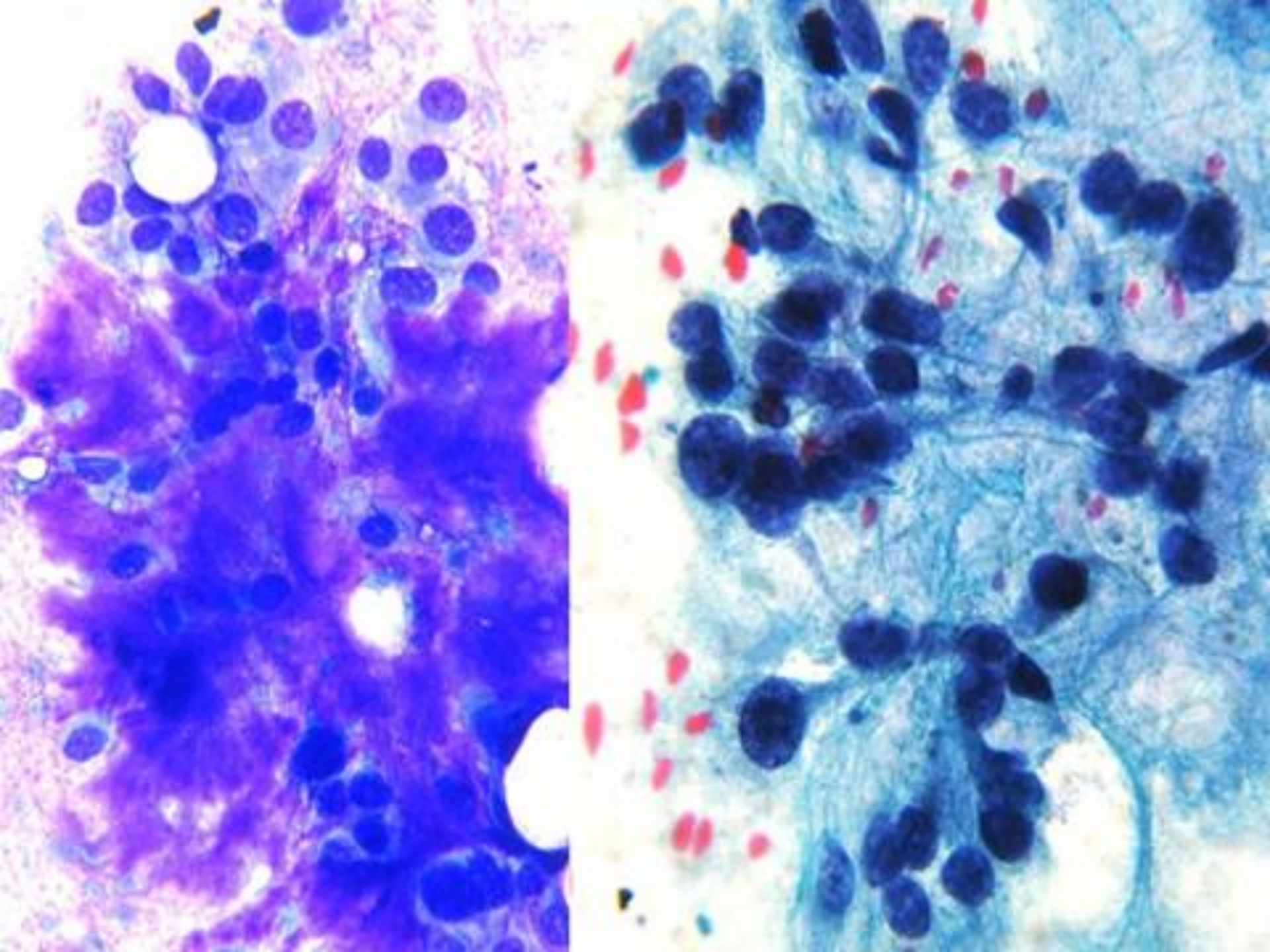
Key Words: Metaplastic breast carcinoma; fine-needle cytology; breast cancer diagnosis

In this neoplasm, the varied composition of the stromal component is supposed to derive from metaplasia of the epithelial cells, as testified also by the frequent expression of both epithelial and mesenchymal cell markers,[1] hence the term "metaplastic" carcinoma. Moreover, the pathological features of the stromal component may range from cytologically differentiated mesenchymal cells to pleomorphic, sarcomatous cell types.[6–14]

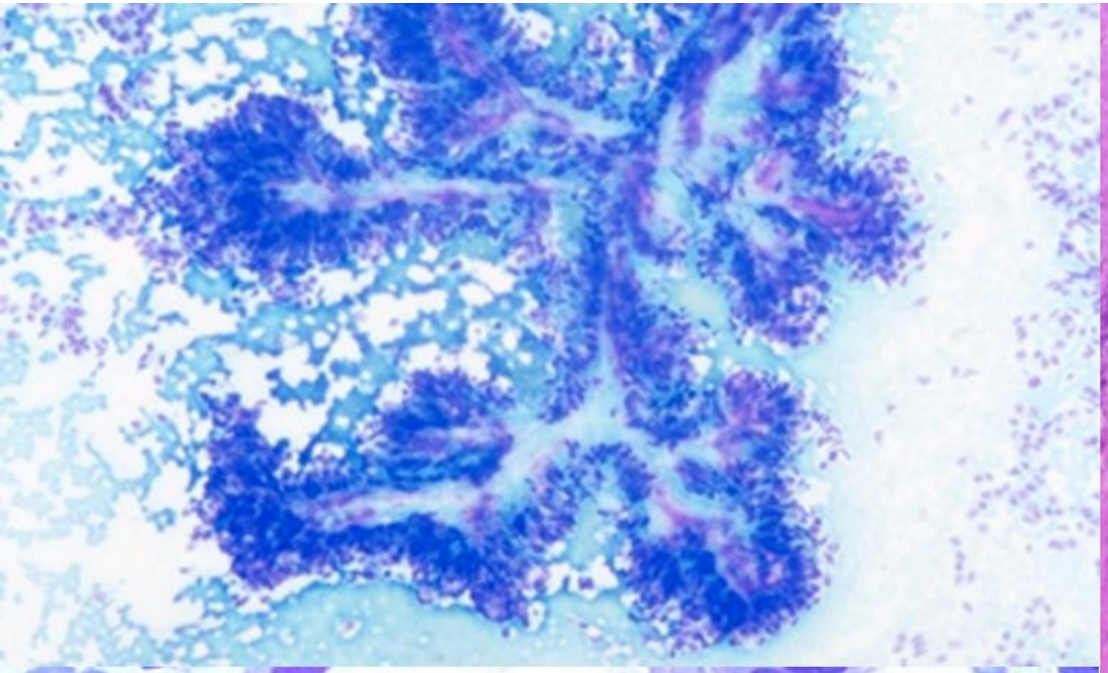
The peculiar mixture of cell types showing various degrees of cytological atypia makes the cytopathological diagnosis of MBC particularly challenging, with differential diagnoses encompassing a spectrum of benign and malignant entities.[2–19]

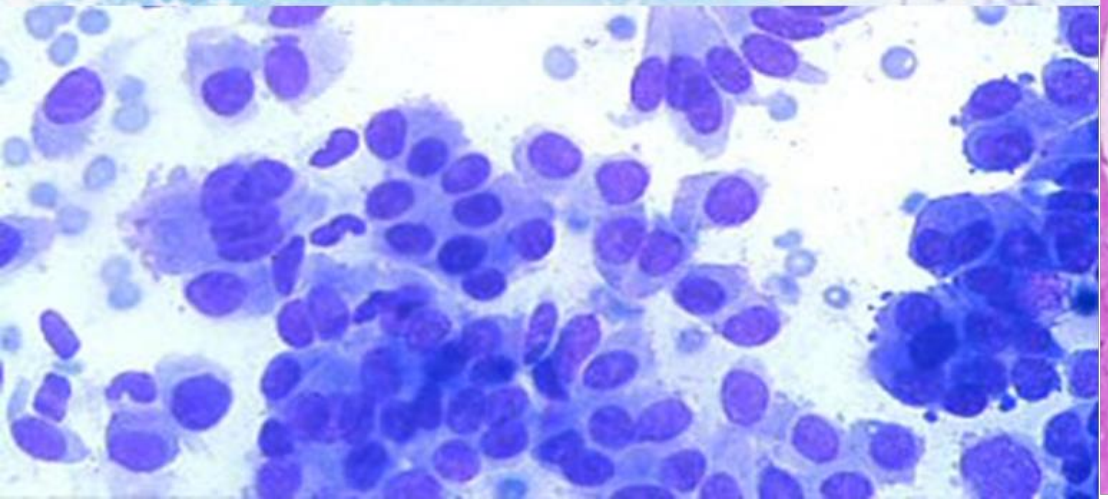
About forty cases of MBC have been described on fine-needle cytology (FNC) samples in the last decade, and the criteria required on cytologic material so as to diagnose MBC are represented by the identification of a mixture of various combinations of malignant ductal or squamous cells and mesenchymal cell components of different derivation.[2,4–8,19]

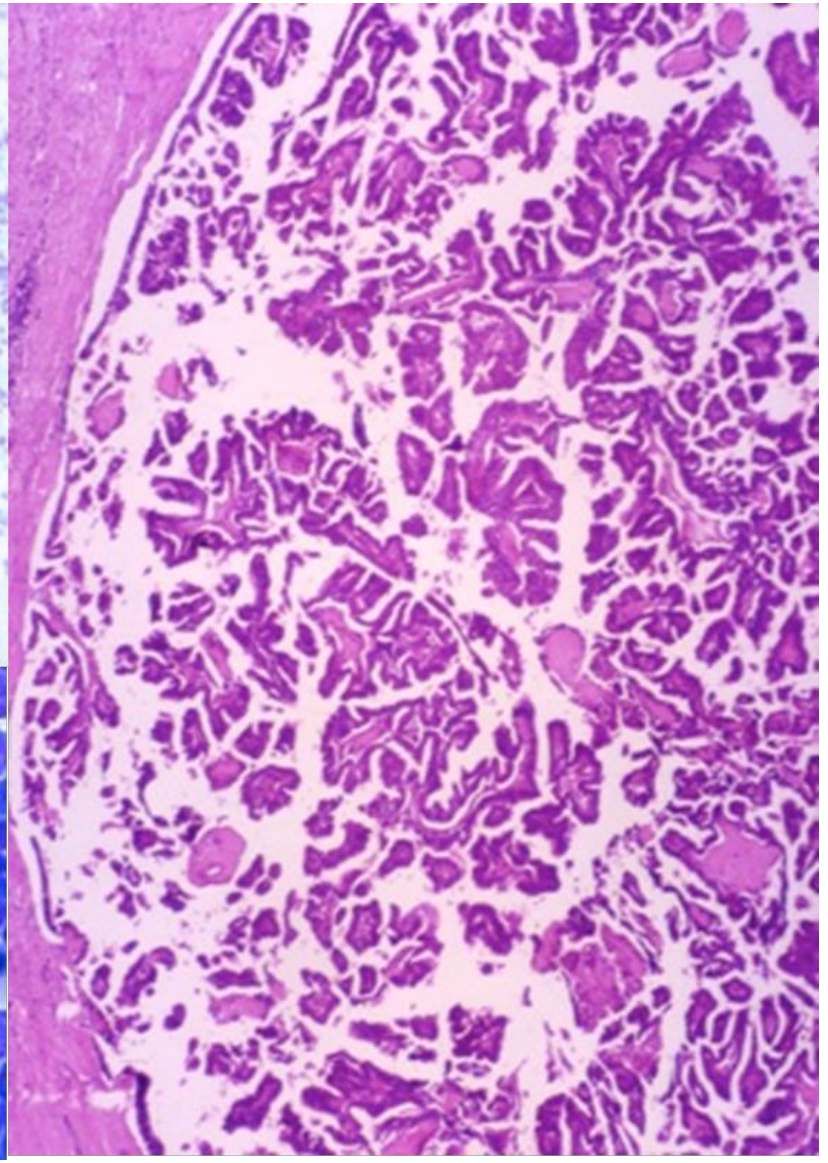
In this paper, three further cases of MBC diagnosed cyto-



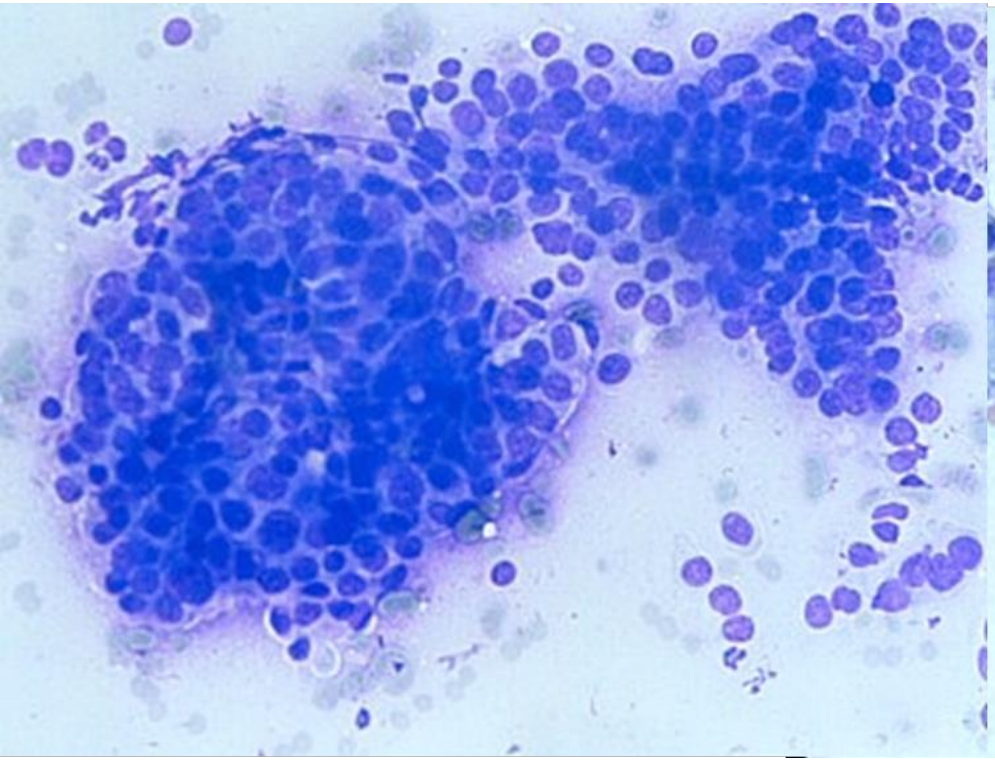
Papillary carcinoma

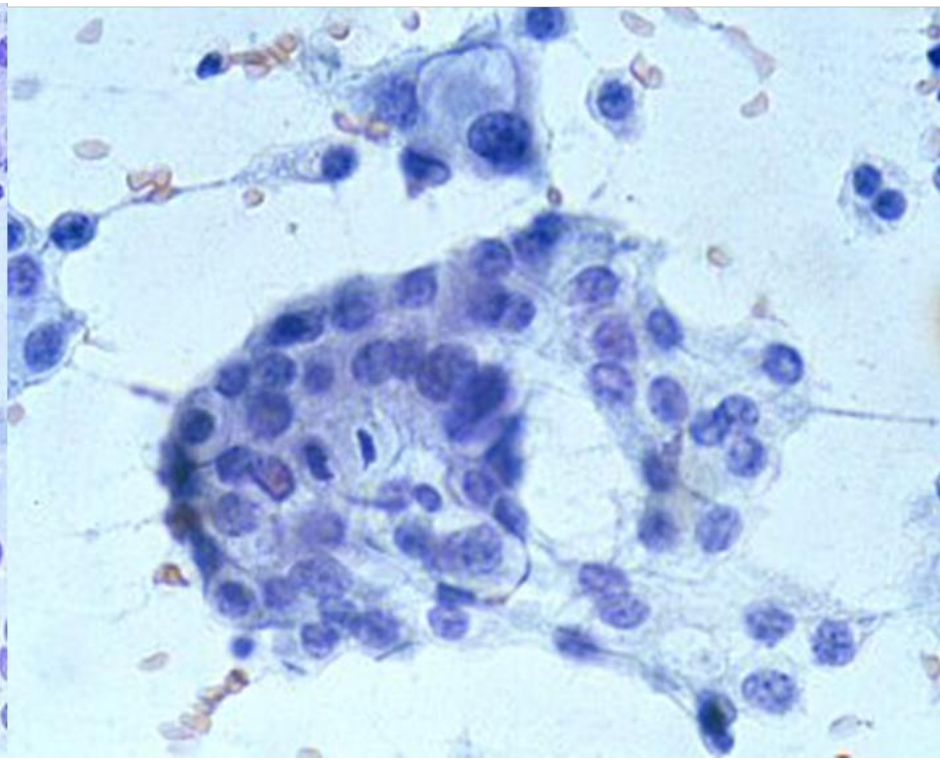


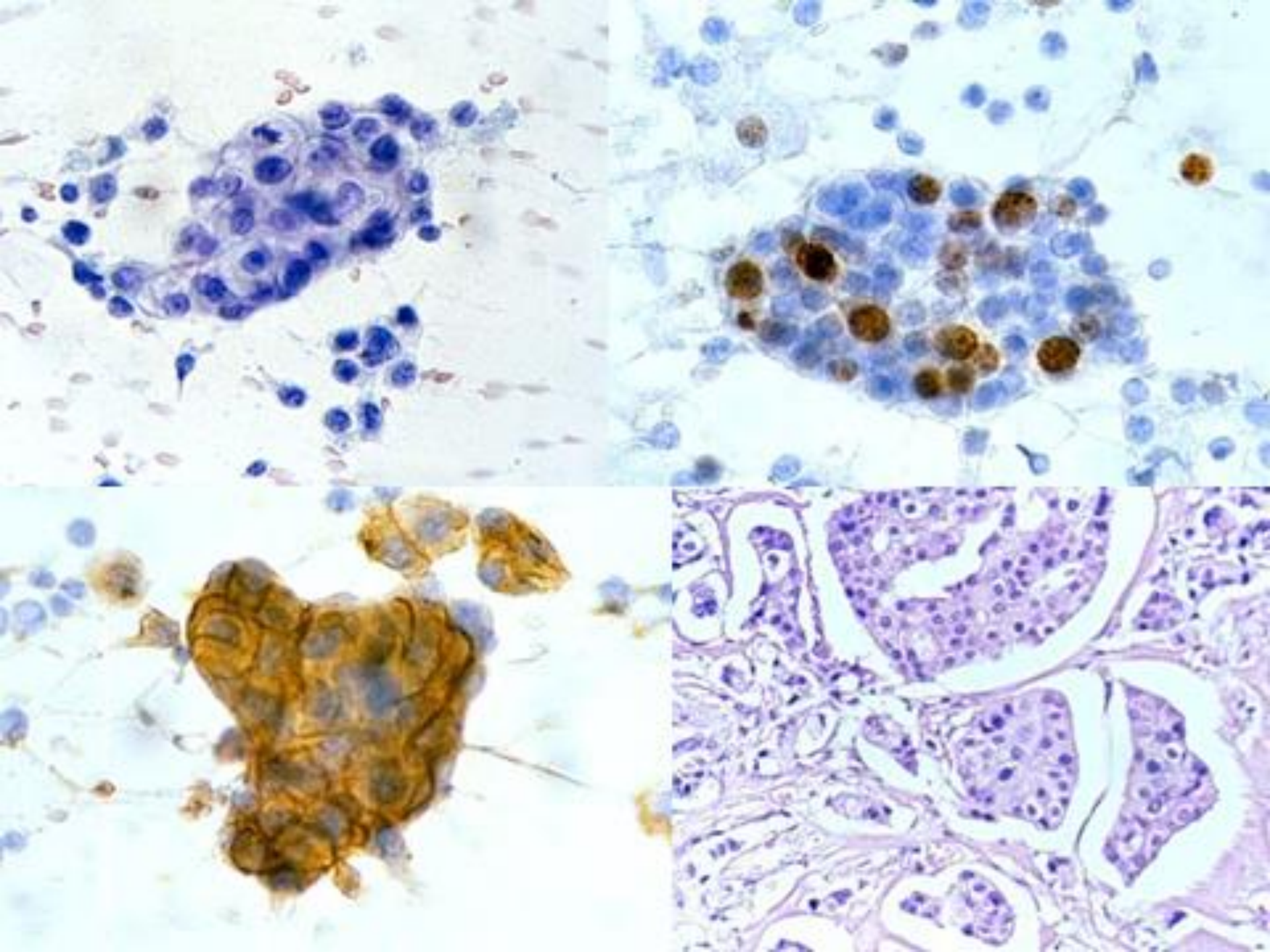




Micropapillary carcinoma







original article

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Metastases to the breast: role of fine needle cytology samples. Our experience with nine cases in 2 years

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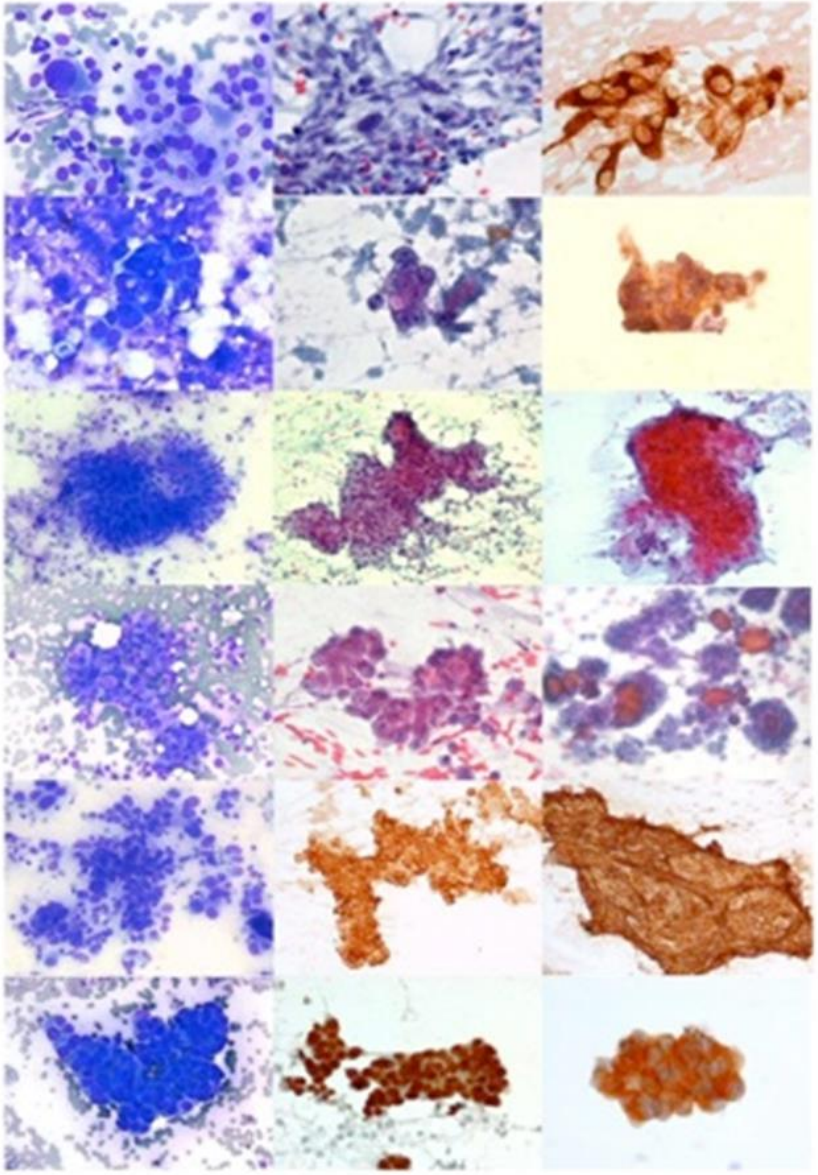
Background: The increased survival due to the introduction of effective antineoplastic regimens has caused a modification of the natural history of numerous malignancies. Follow-up of neoplastic patients often includes the evaluation of masses in various body sites by fine needle cytology (FNC) in order to rule out cancer recurrence. Besides primary neoplasms, the breast can host a number of metastases: these rarely do have a typical presentation, so FNC is requested for their cytomorphological assessment.

Patients and methods: This report describes nine consecutive cases in which a cytopathological diagnosis of metastasis to the breast was carried out on FNC samples.

Results: Primary sites were identified on cytomorphological and immunocytochemical bases and were represented by the ovary (three cases), melanoma (two cases), endocervix (one case), endometrium (one case), lung (one case) and prostate (one case).

Conclusion: The cytopathological diagnosis of metastatic neoplasms to the breast is not always straightforward, especially in the absence of a clinical history of cancer. The usage of improved cytopathological criteria combined with immunocytochemistry may be of great diagnostic help in the identification of breast metastases.

Key words: breast neoplasms, clinical cytology, diagnostic cytopathology of tumors, fine needle cytology, metastases to the breast

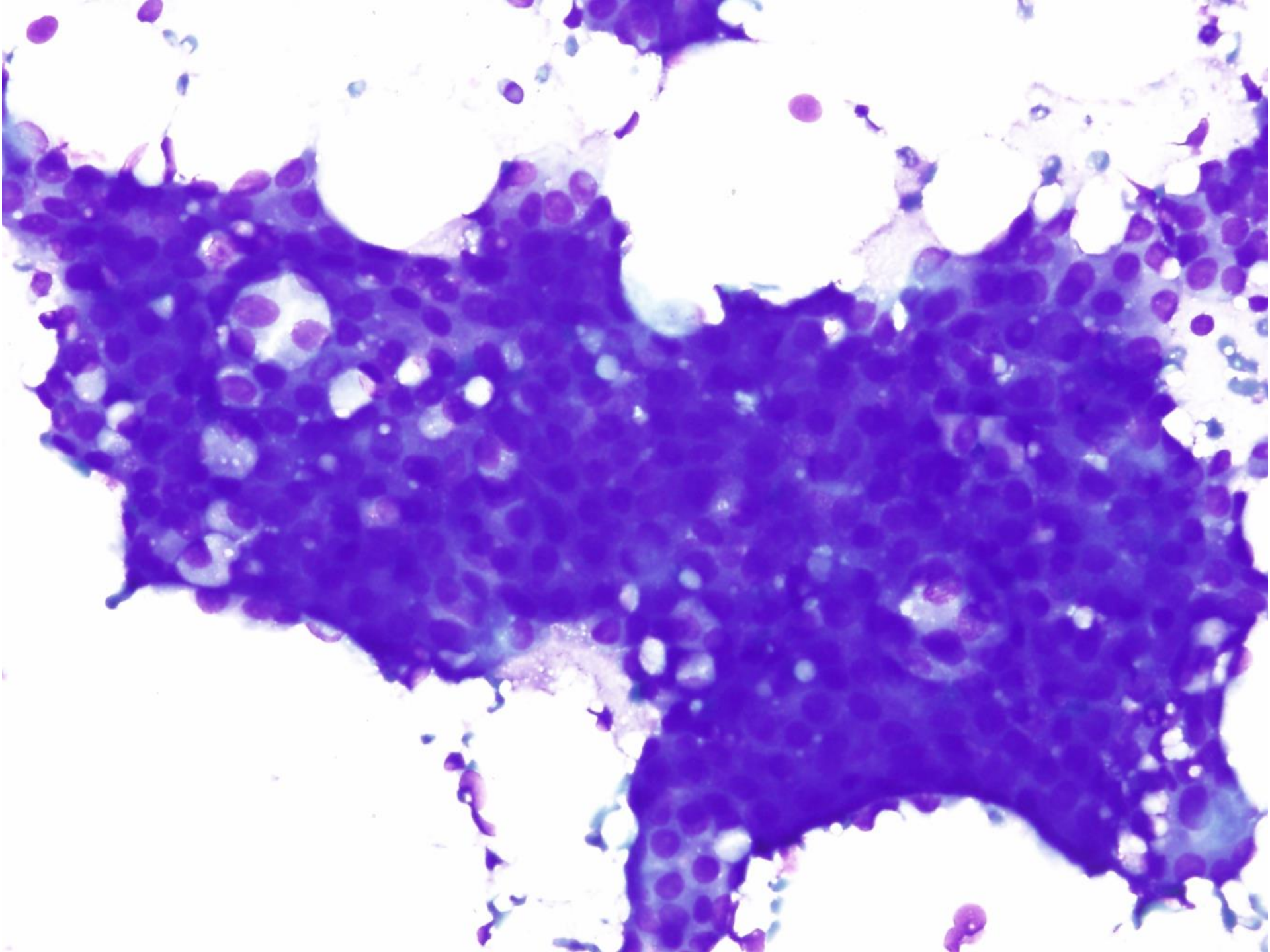


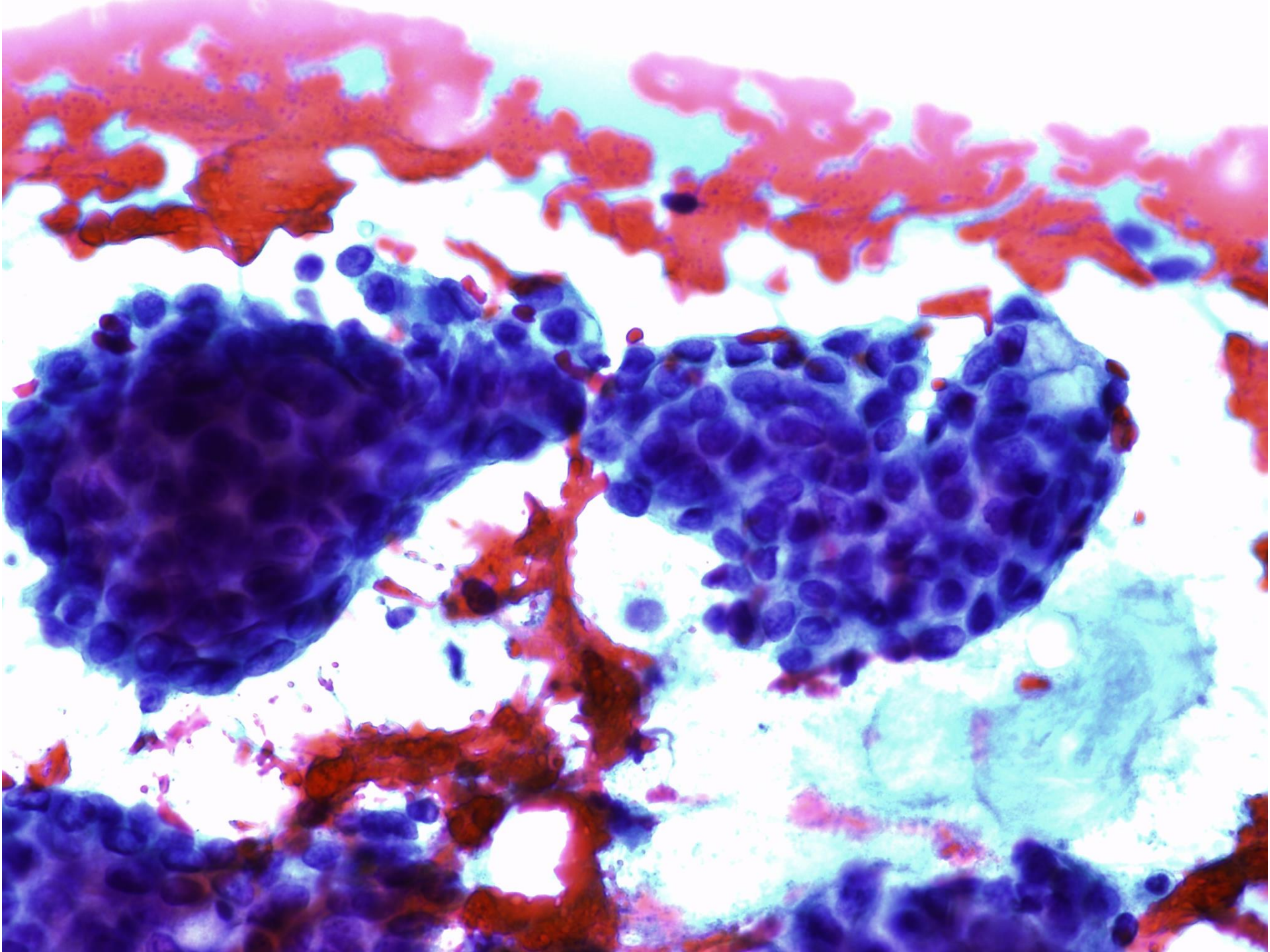
FNC of the breast: limitations and problem areas

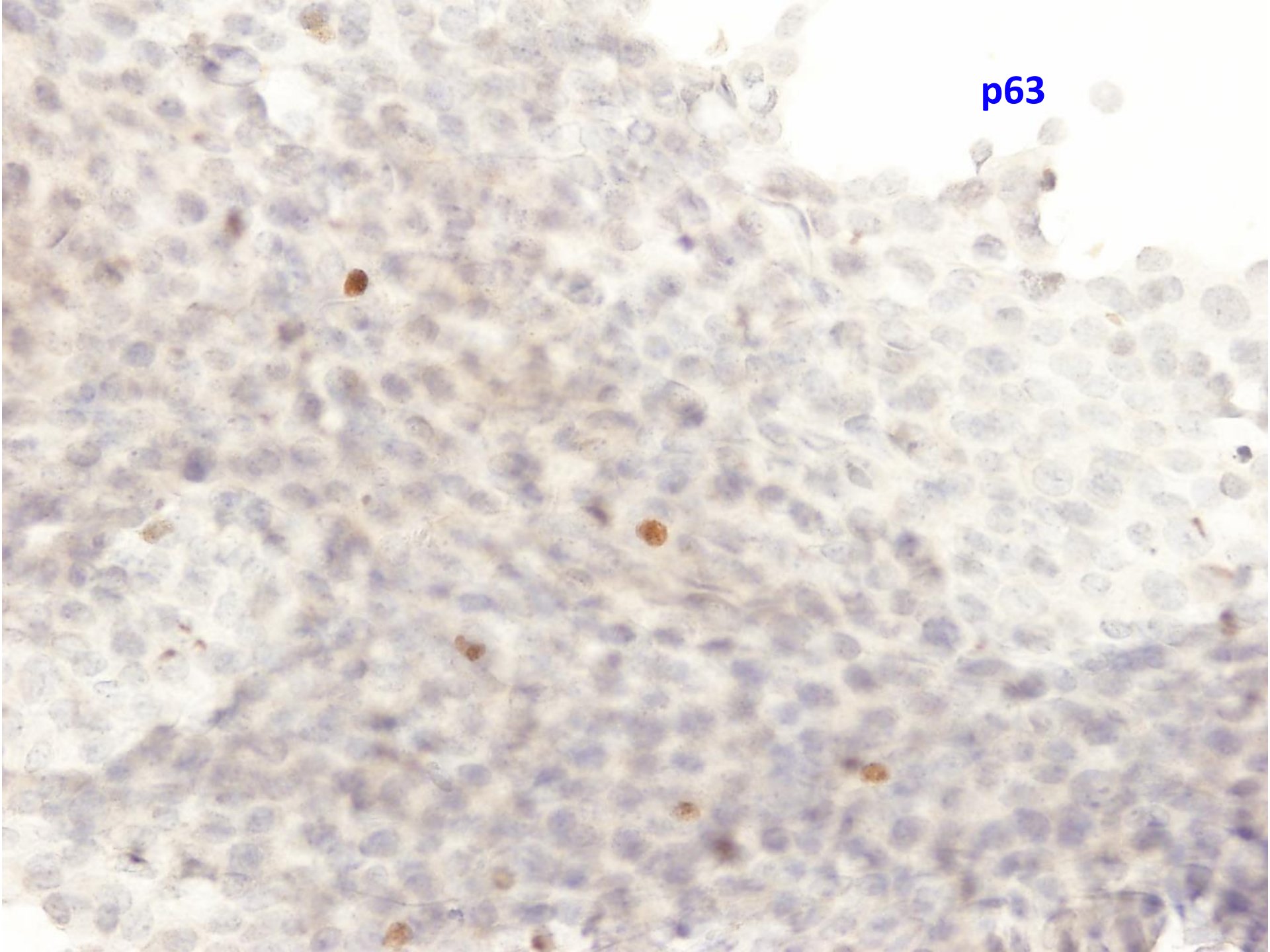
- Diagnosis of ADH;
- Diagnosis of columnar cell lesions;
- Cytologic grading of breast carcinomas

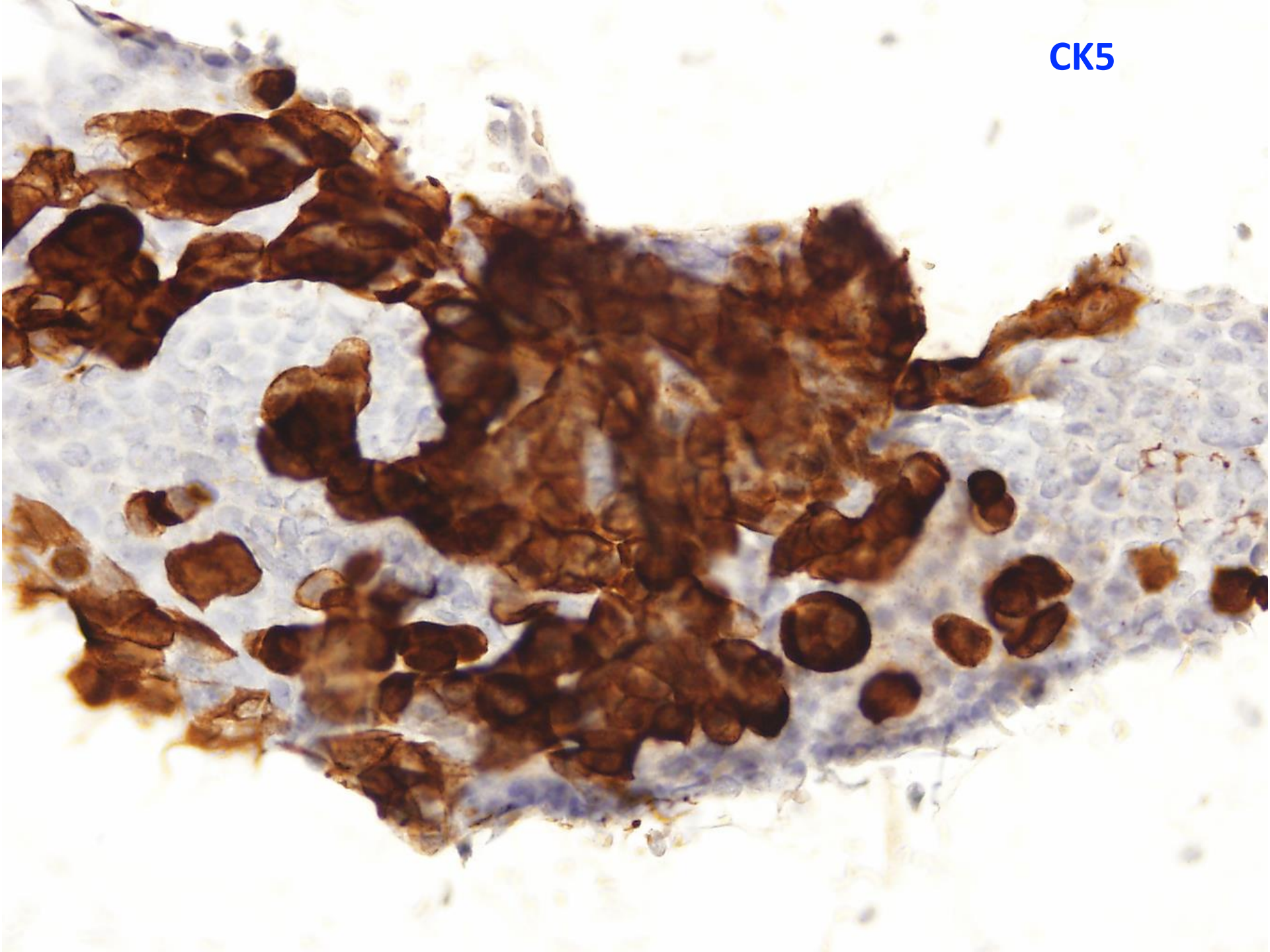
Atypical duct hyperplasia: diagnostic criteria

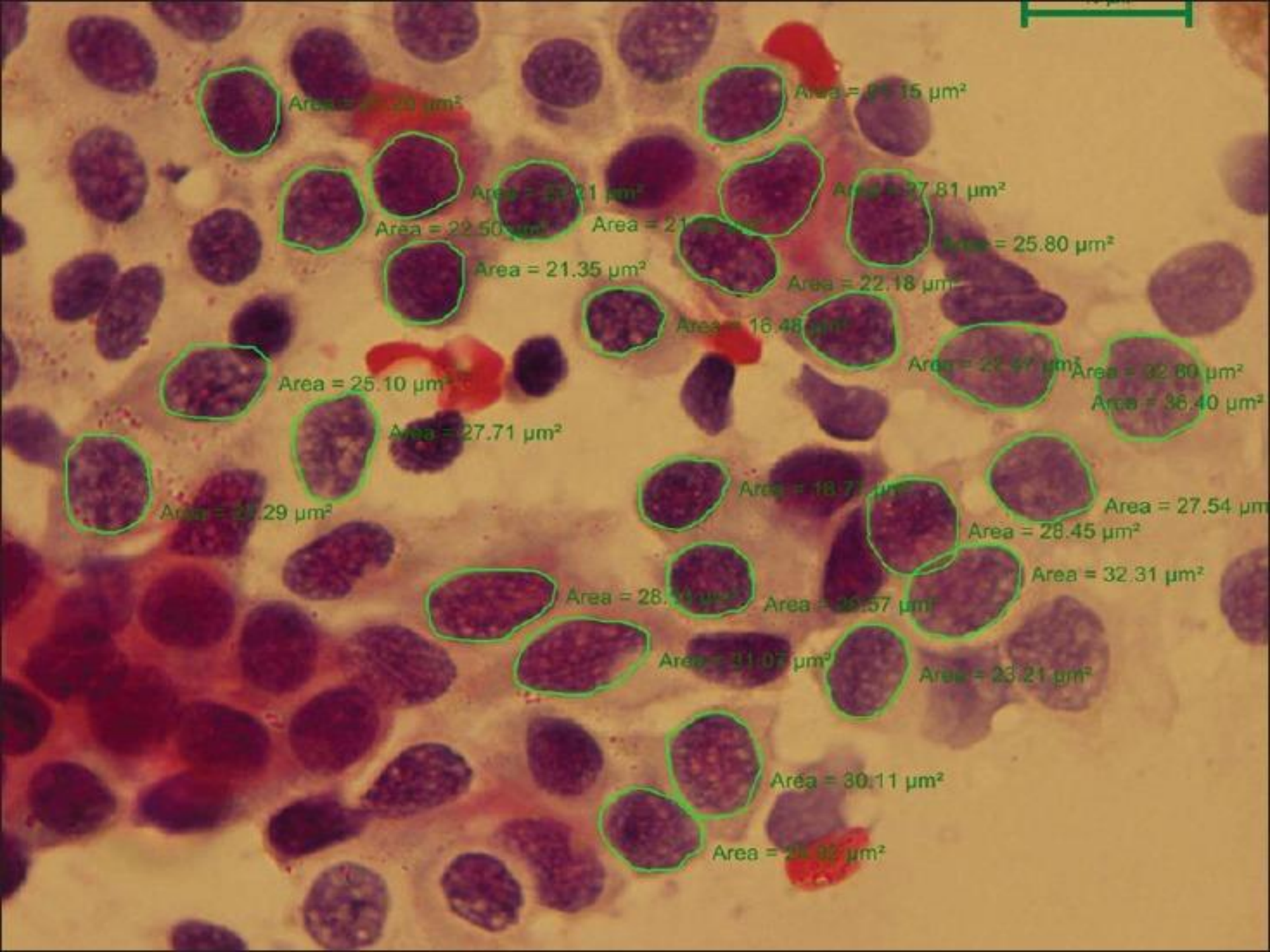
- There are no canonic criteria for cytological diagnosis of ADH;
- Traditionally, increased cellularity with architectural disorder, disturbed polarity and low number/absent myoepithelial naked nuclei are evaluated;
- Geographic loss of CK5 is a useful immunocytochemical criterion, coupled to p63/calponin staining for myoepithelial cells.
- DNA ploidy assessment/cytomorphometry could represent a useful tool






p63


CK5


Area = 21.35 µm²
Area = 25.10 µm²
Area = 27.71 µm²
Area = 25.80 µm²
Area = 22.18 µm²
Area = 27.54 µm
Area = 28.45 µm²
Area = 32.31 µm²
Area = 23.21 µm²
Area = 30.11 µm²

J Cytol. 2017 Jan-Mar; 34(1): 10–15.
doi: 10.4103/0970-9371.197591
PMCID: PMC5259923

Study of nuclear morphometry on cytology specimens of benign and malignant breast lesions: A study of 122 cases

Anamika Kashyap, Manjula Jain, Shailaja Shukla, and Manoj Andley[1]
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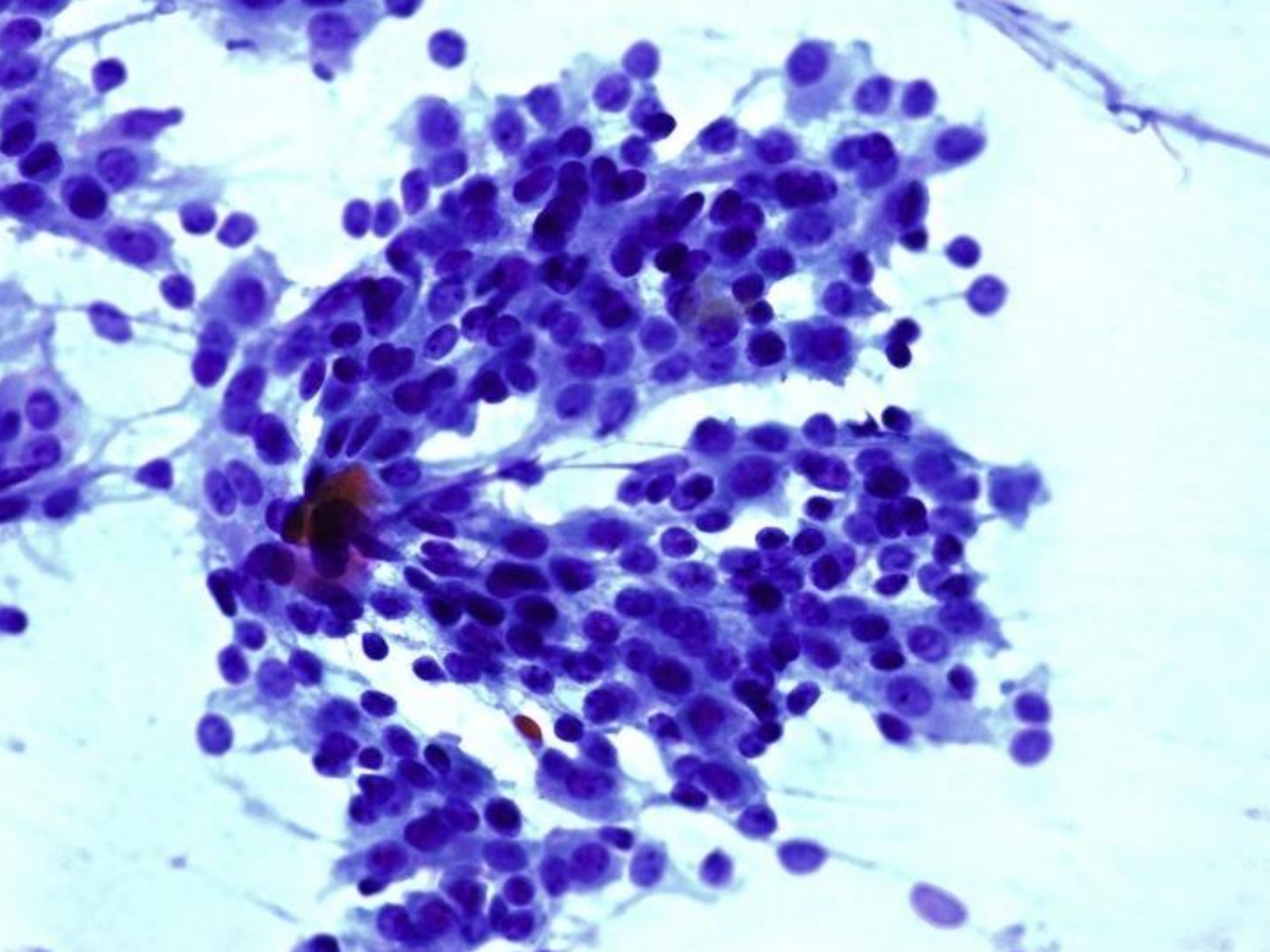
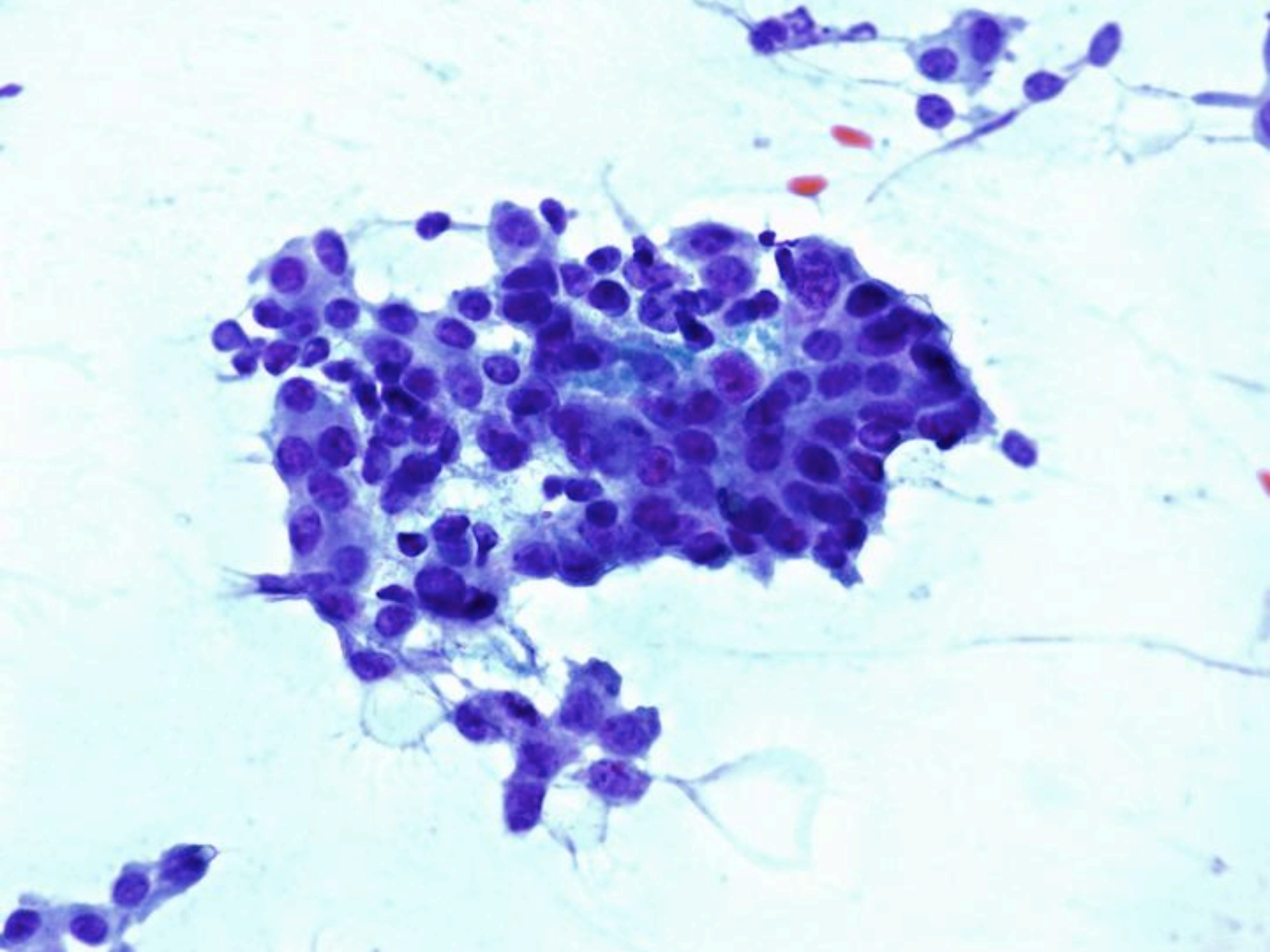
Nuclear morphometric parameters	BBD ($n=50$)	ADH ($n=8$)	Malignant ($n=64$)	ADH vs Carcinoma (P)
Area (μm^2)	24.86±3.59	29.44±3.51	51.43±20.47	0.0036
Equivalent diameter (μm)	5.59±0.41	6.08±0.36	7.87±1.50	0.0013
Min feret (μm)	5.07±0.40	5.39±0.43	7.09±1.29	0.0005
Max feret (μm)	6.51±0.3	7.26±0.42	9.26±1.81	0.0028
Perimeter (μm)	18.15±1.40	19.91±1.18	25.69±4.99	0.0018
Shape factor*	0.95±0.02	0.93±0.02	0.94±0.01	0.022
Roughness†	1.0033±0.002	1.0025±0.004	1.0033±0.003	0.495
Mean intensity	97.69±17.06	88.16±23.50	80.56±10.63	0.11
Sum intensity	677628.44±153651	717309.59±191745	1153390.65±532738	0.025
Mean brightness	38.35±6.73	34.57±9.21	31.53±4.08	0.098
Sum brightness	265768.80±60264.39	281297.88±75194.00	452250.92±20883.2	0.0001
Mean density	0.45±0.09	0.51±0.16	0.54±0.07	0.341
Sum density	3087.85±772.72	4139.20±1444.22	7519.18±2819.28	0.0014

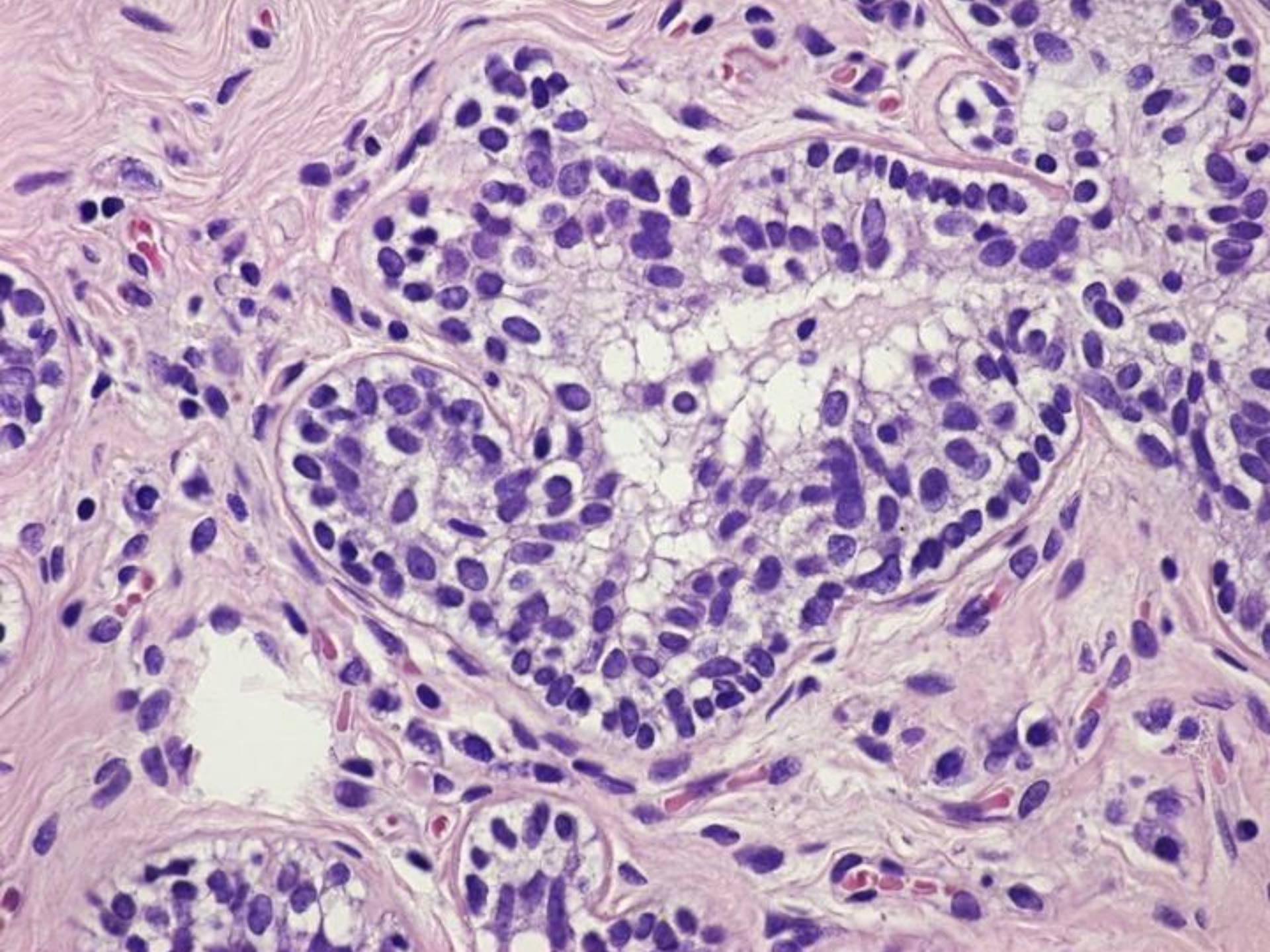
Columnar lesions*

- "columnar cell change (CCC) and columnar cell hyperplasia are lesions of the terminal duct lobular units that are characterized by enlarged, variably dilated acini, lined by columnar epithelial cells (WHO blue book, 2012);
- Recently, flat atypia has been separated from CCC, though they may be associated in the same area/nodule/lesion;
- *…of interest is that 18/20 (90%) cases of the cytological material was interpreted as atypical. However, on follow up surgical biopsy only 5 cases (20%) showed atypia.
- *….the high numbers of atypical cases suggest that we still do not have much experience and well-established cytological criteria to recognize CC changes.

- **Siziopikou K.P, Gattuso, P.: "The emerging biological and clinical significance of the columnar cell lesions of the breast." Editorial, Diagn Cytopathol 2007;35 (6):369.**
- **Jensen K.C., Kong CS. Cytologic diagnosis of columnar cell lesions of the breast. Diagn Cytopathol 2007, 35 (2): 73-9**







Cytologic grading systems of breast cancer

- Robinson's et al (1994)
- Mouriquand's and Pasquier (1986)
- Taniguchi et al. (2000)
- Fisher's modification of Black's nuclear grading (1980)
- Khan et al. (2003)
- Howell et al. (1994)

Arul P, Suresh Masilamani. Comparative evaluation of various cytomorphological grading systems in breast cancer. Indian J Med Paediatr Oncol. 2016; 37(2): 79-84;

Saha K et al. Comparative evaluation of six cytological grading systems in breast carcinoma. J Cytol. 2013; 30(2):87-93

Six grading systems of breast cancer

***Robinson's et al**: (score1-3)*
Cell dissociation
Cell size
Cell uniformity
Nucleoli
Nuclear margin
Chromatin

Grade I (6-11)
Grade II (12-14)
Grade III(15-18)
Nucleo-Cytoplasmic ratio
Mitoses
Necrosis

Mouriquand's and Pasquier
(score 0-3)
Cells (isolated,clusters, large size, anisokaryosis)
Nuclei (Naked,budding)
Chromatin (hypochromasia, hypercromasia)
Nucleoli (Red and Blue)
Mitosis

Grade I score>5
Grade II score 6-9
Grade III score >10

***Taniguchi et al**:* (score 1-3)
Cellular size
Nuclear-cytoplasmic ratio
Nuclear pleomorphism
Nucleoli
Chromatin granularity
Density of chromatin
Necrosis (score 0-1)

Grade I score 6-9
Grade II score 10-11
Grade III score 12-19

Fisher's modification of Black's nuclear grading
Anysonucleosis
Nuclear membrane
Nuclear chromasia
Chromatin
Nucleoli
Mitosis

Grade I
Grade II
Grade III

***Khan et al**:* (score 1-3)
Cellular pleomorphism
Nuclear size
Nuclear margin
Nucleoli
Naked tumor nuclei
Mitotic count

Grade I score 6-10
Grade II score11-14
Grade III score 15-18

***Howell et al**:*
Mitotic count (score1-3)
0-1/10 HPF score 1
2-4/10 HPF score 2
>5/10 HPF score 3

Grade I score 3-5
Grade II score 6-7
Grade III score 8-9

Arul P (2016) and Saha K (2013): «*Robinson's grading method as better choice due to its simplicity, specificity and better reproducibility*»

Conclusions

- FNC remains a simple, accurate and inexpensive diagnostic technique;
- It can be taught to residents in pathology, with good results;
- Its accuracy may be partially implemented by instrumental guidance;
- Its usage permits a considerable reduction of the number of invasive procedures and associated costs;
- Though a vast number of lesions may be accurately diagnosed, the technique has its limits and these latter should not be ignored or underestimated.