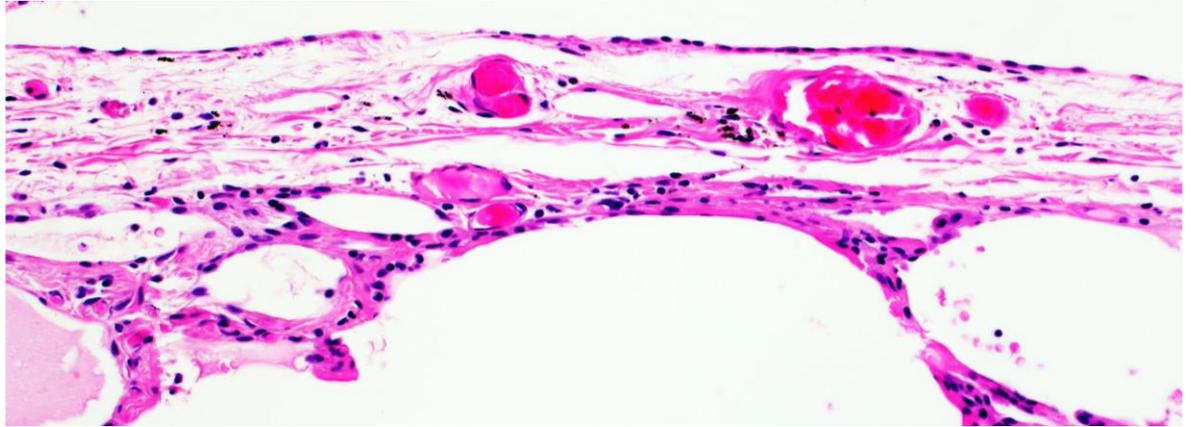


Serous Effusions

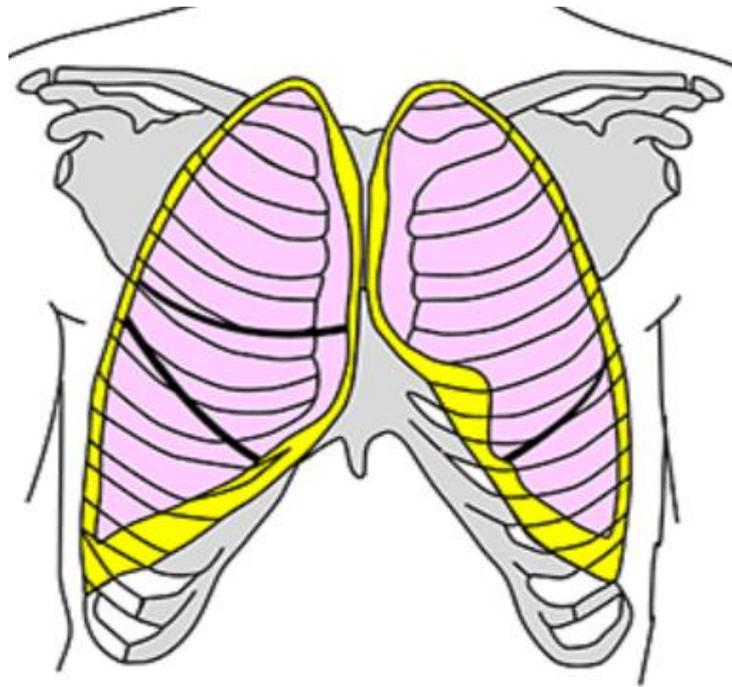
Spasenija Savic Prince, MD
Pathology, University Hospital Basel, Switzerland

Serous membrane



Body cavities:

- Pleural
- Pericardial
- Peritoneal



Effusion
=
Excess of fluid

80% ↓

Benign

20% ↓

Malignant

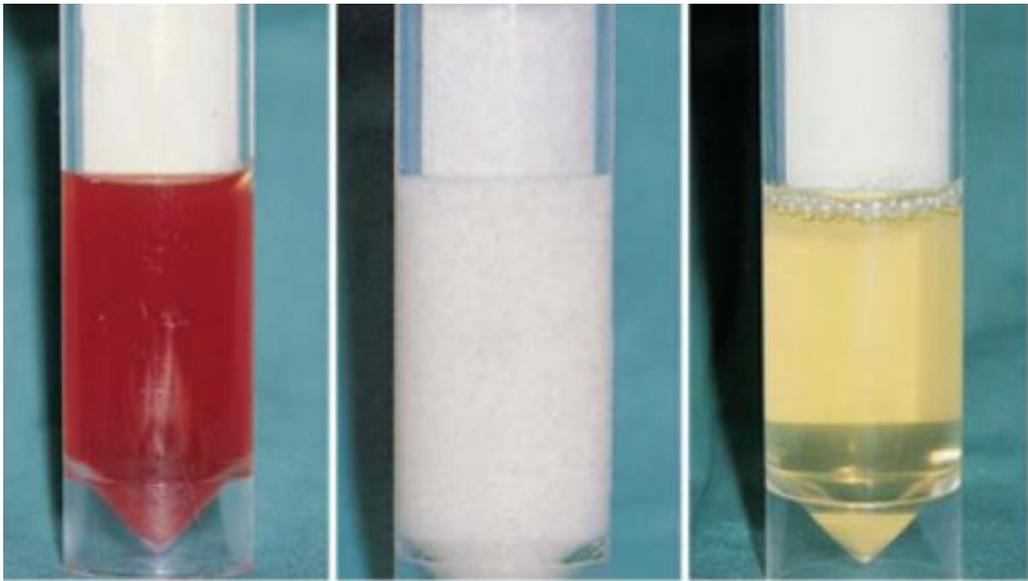
Outline

- Pre-analytics
- Non-neoplastic effusions
- Malignant effusions
 - Morphological features of the most common malignancies
 - Predictive marker testing
- Ancillary techniques
 - Immunocytochemistry
 - FISH

Collection and Processing

- Get as much as possible
- No additives
- Effusions are good cell media
 - at 4° C (for days)
- Centrifuge whole volume
- PAP (4x) and MGG (1x)
- Cell block

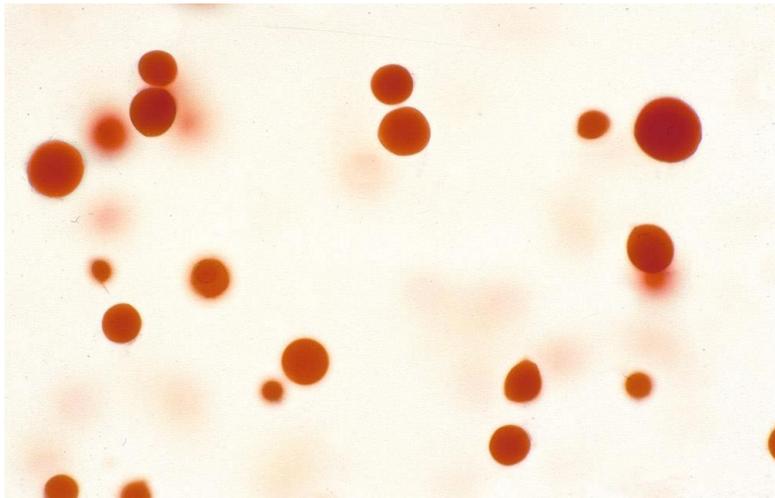




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Stain for neutral fat (Sudan)



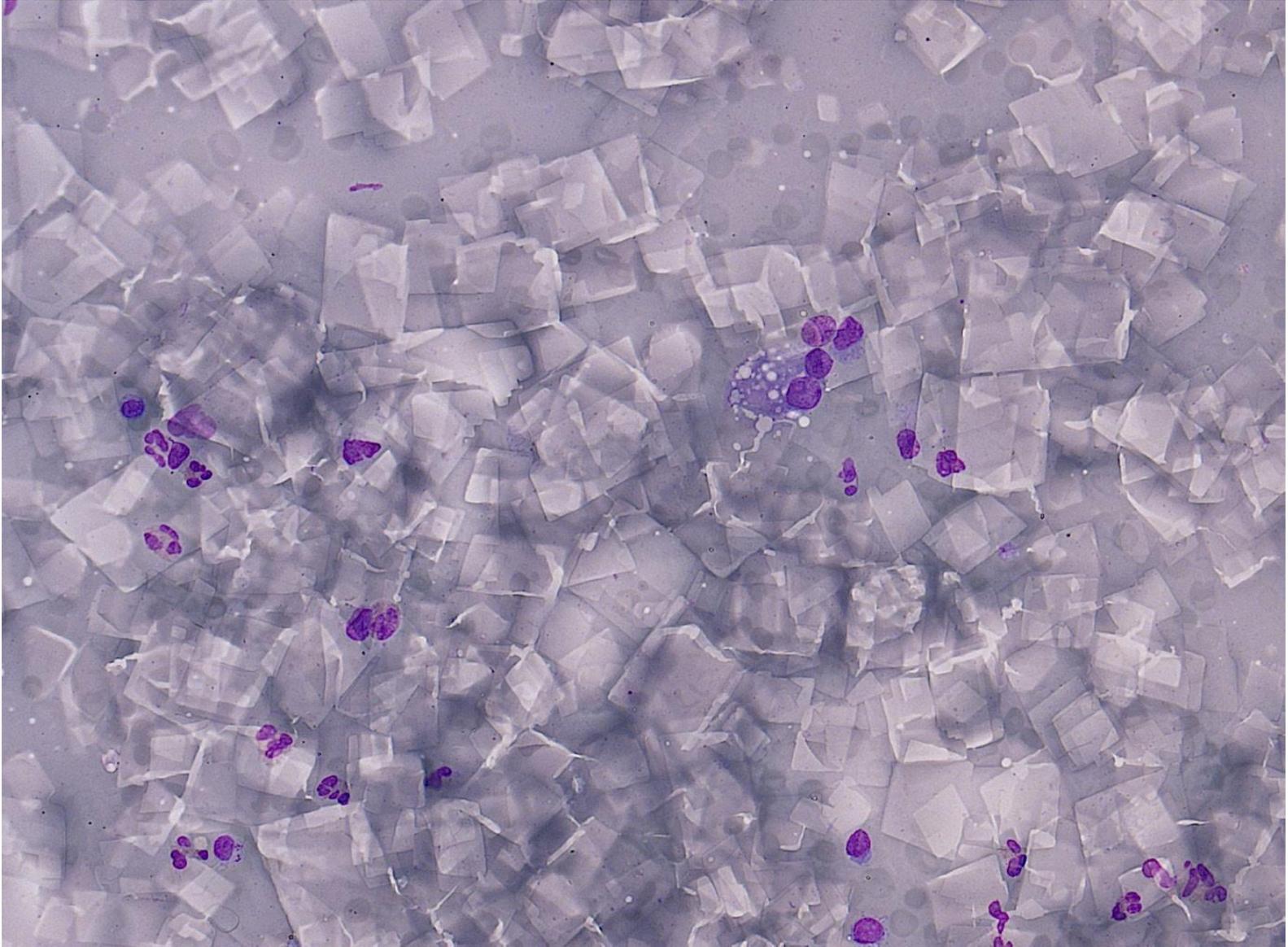
Chylous effusion

- rich in triglycerides (chylomicrons)

DD Pseudochylous effusion

- > pericardial
- rich in cholesterol

Cholesterol crystals



Cell Block

Coagulation



FFPE cell block



Cytology Slide

(Smear, Cytospin, Liquid based)

- Optimal cell morphology
- Intact cell nuclei
- Well preserved DNA

+

- Limited amount
- Adjustment of cut-off values (FISH)

Cell Block

- Validated FFPE protocols
 - e.g. IHC, FISH
- Serial sections
- Archiving
 - retransp. analyses

-

- Not always available
- Formalin fixation
- Truncated cell nuclei
- Hindered morphology

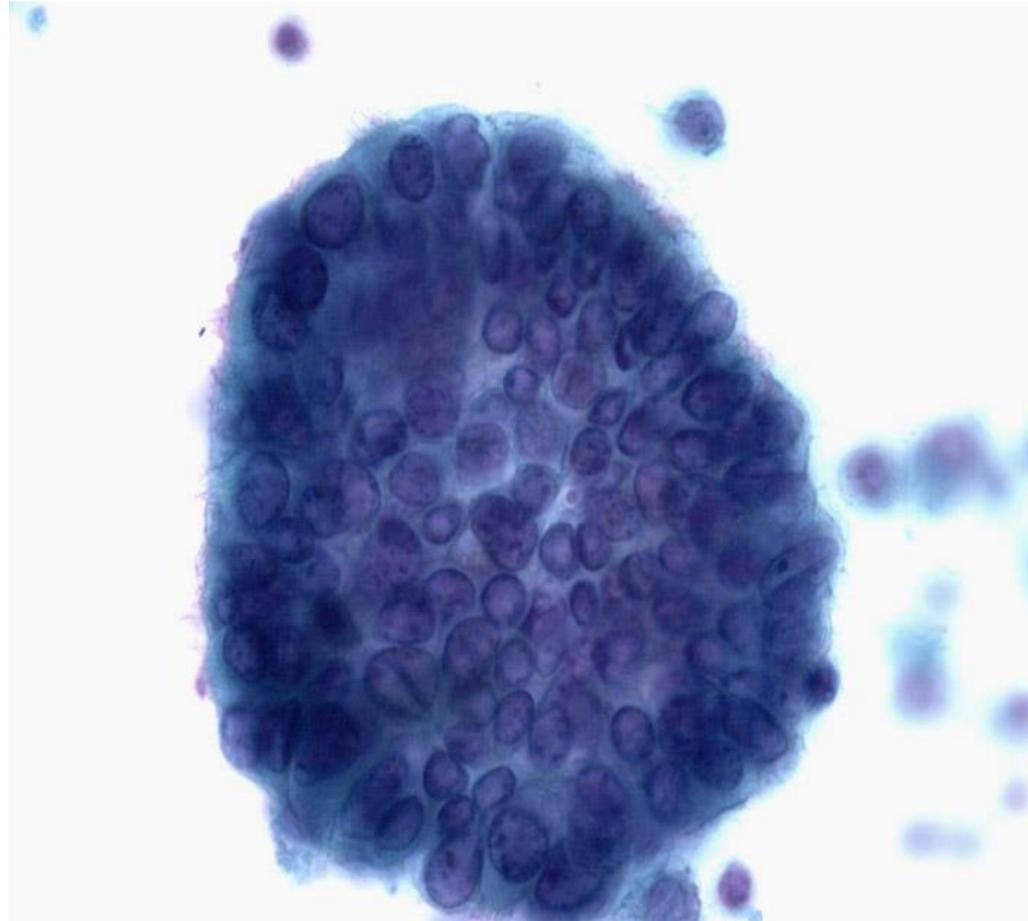
Mesothelial cells



„hugging“

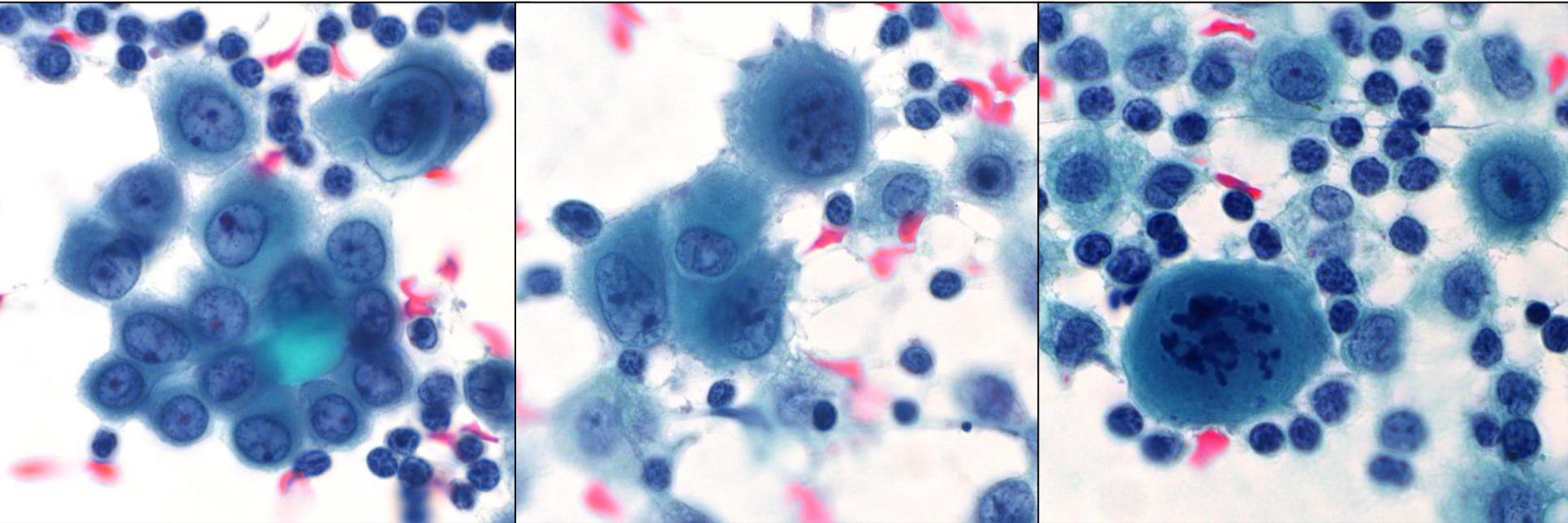
„skirt“

Mesothelial proliferation



pericard - douglas/peritoneal lavage - drainage

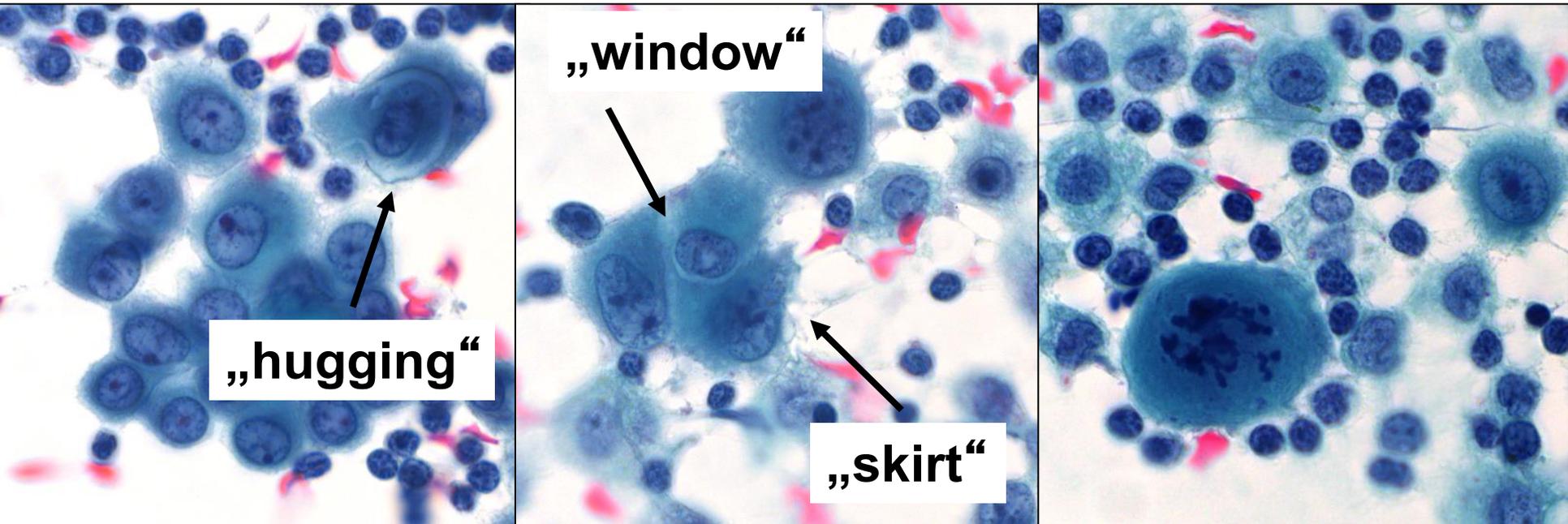
Reactive mesothelial cells



mimics of adenocarcinoma and malignant mesothelioma

pericard - radiation/chemotherapy - cirrhosis

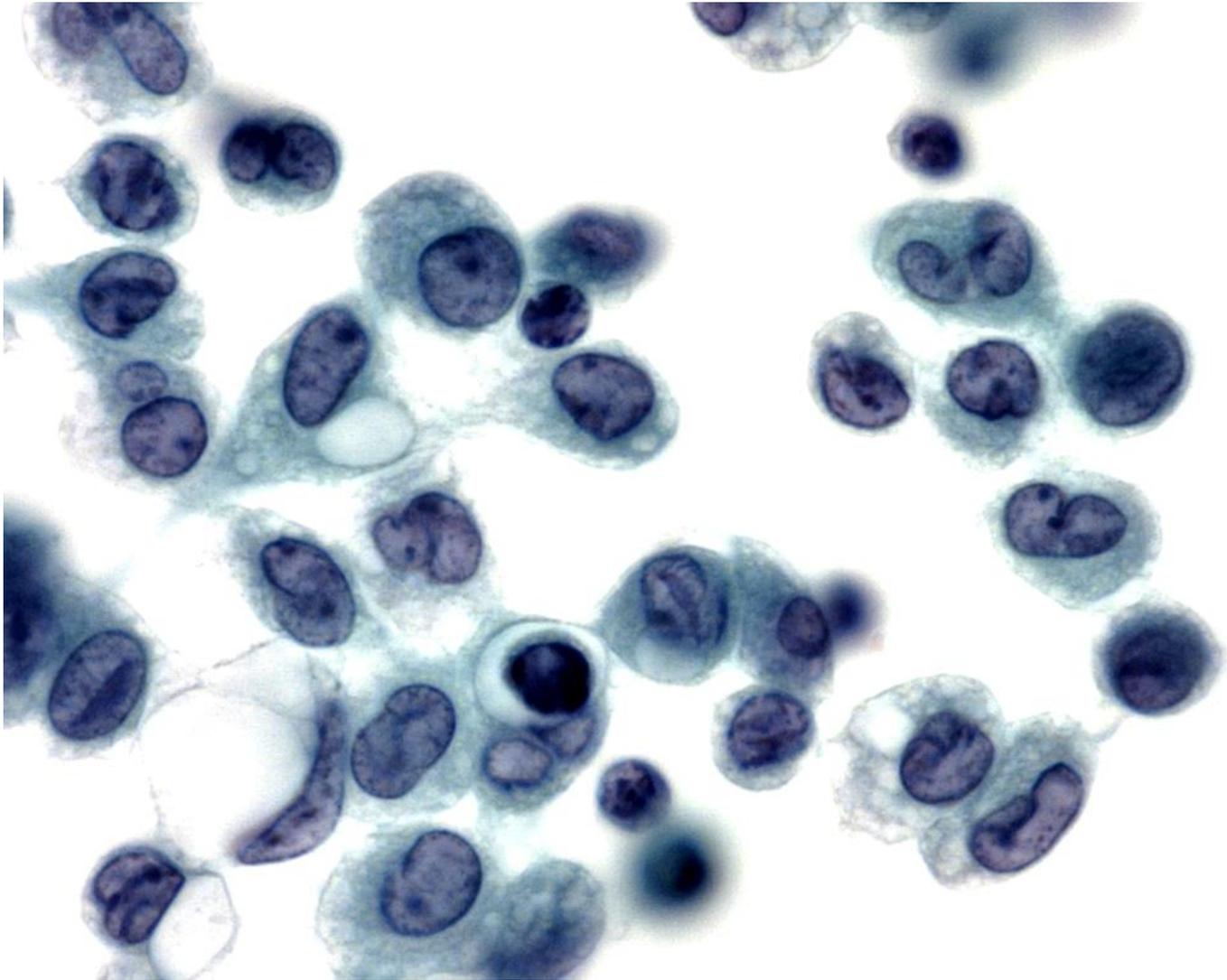
Reactive mesothelial cells



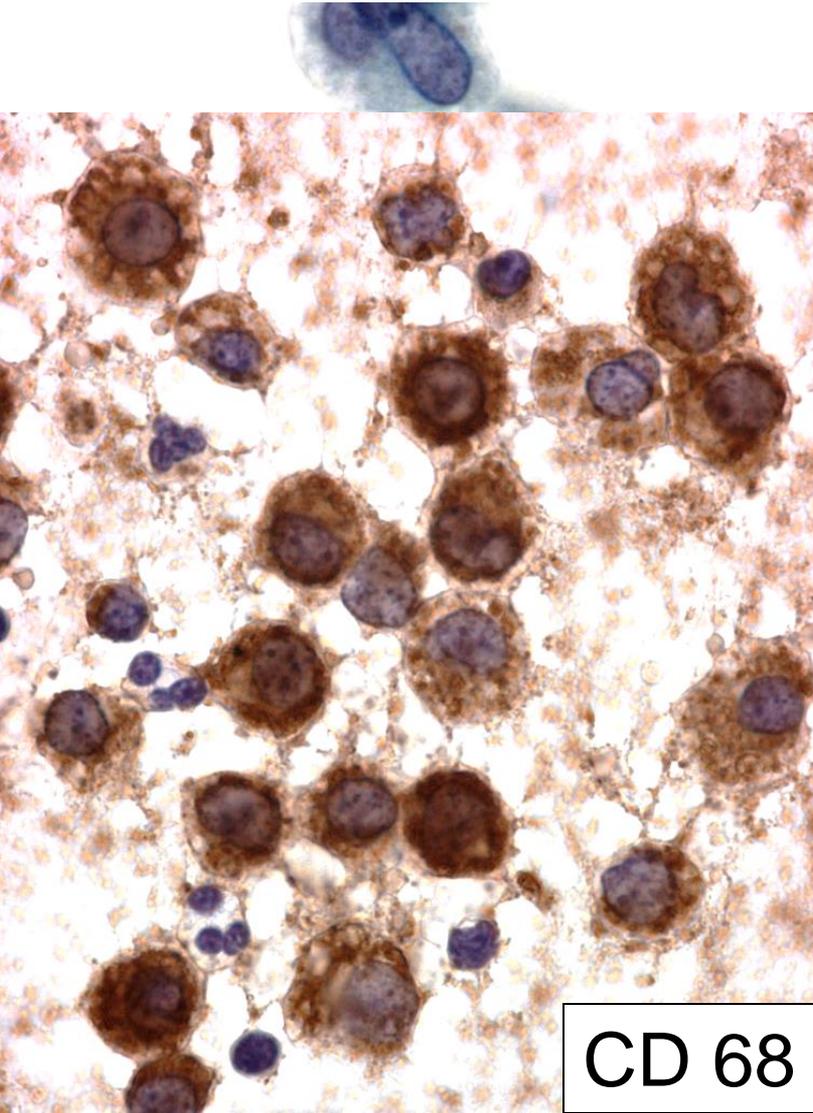
mimics of adenocarcinoma and malignant mesothelioma

pericard - radiation/chemotherapy - cirrhosis

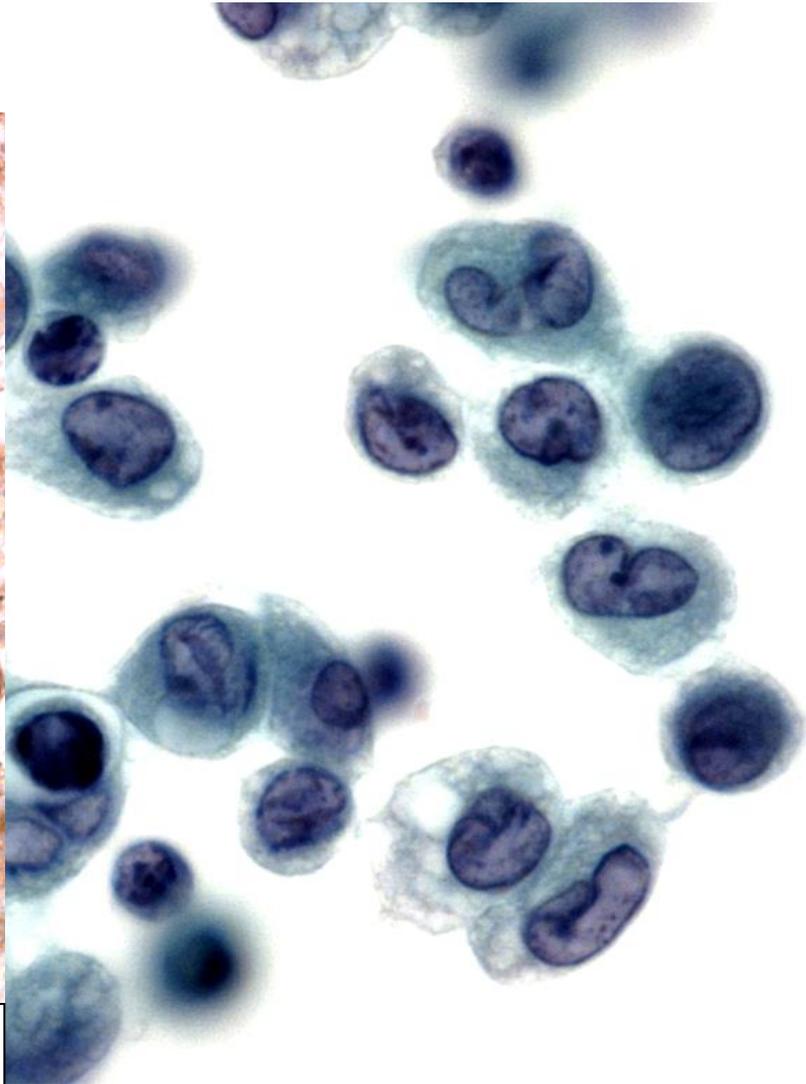
Macrophages



Macrophages



CD 68



Effusion

80%



Benign

20%



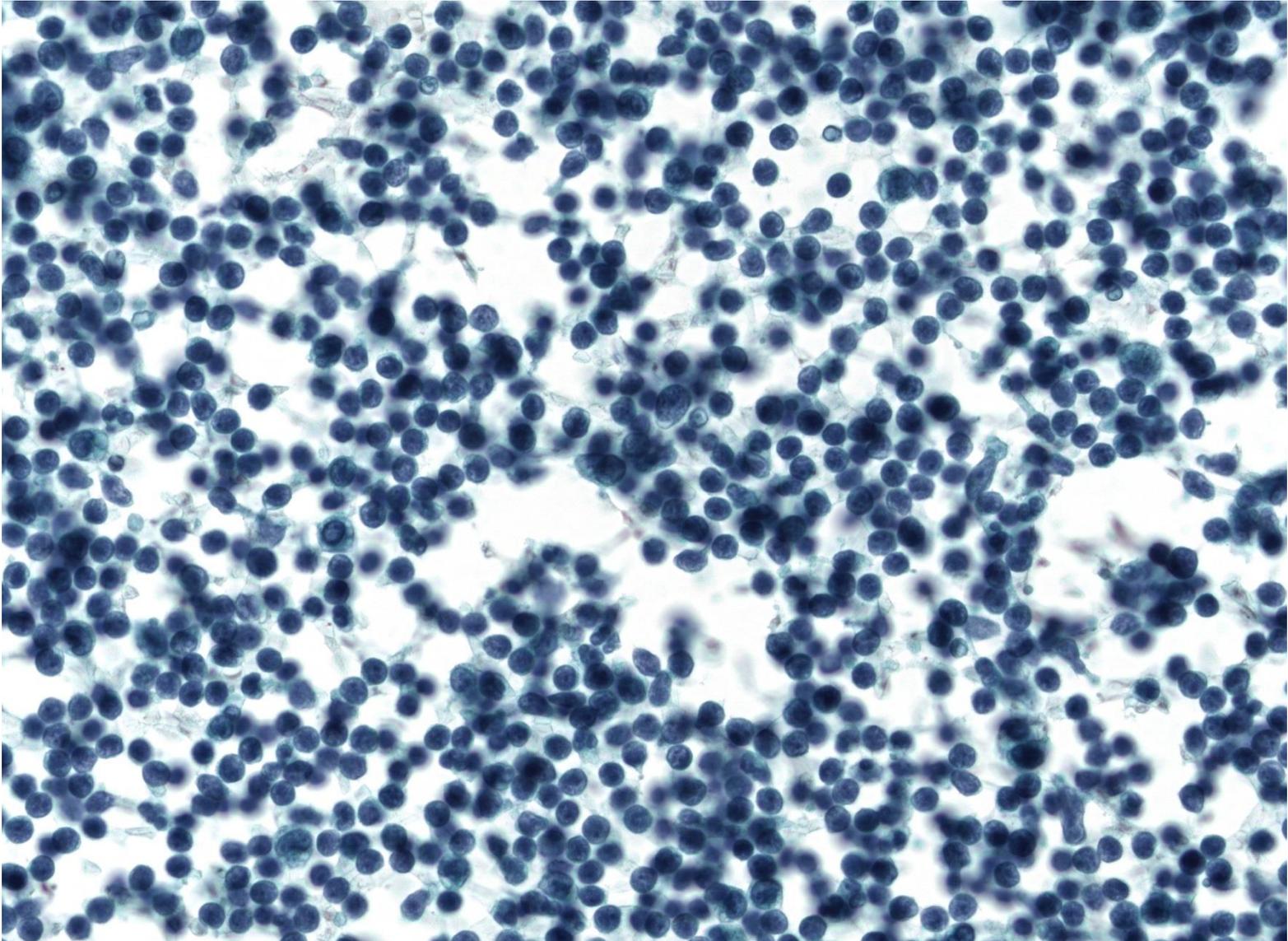
Malignant

- Inflammatory
Infectious / non-infectious
- Non-inflammatory
Hydro- / hemato- / chylothorax

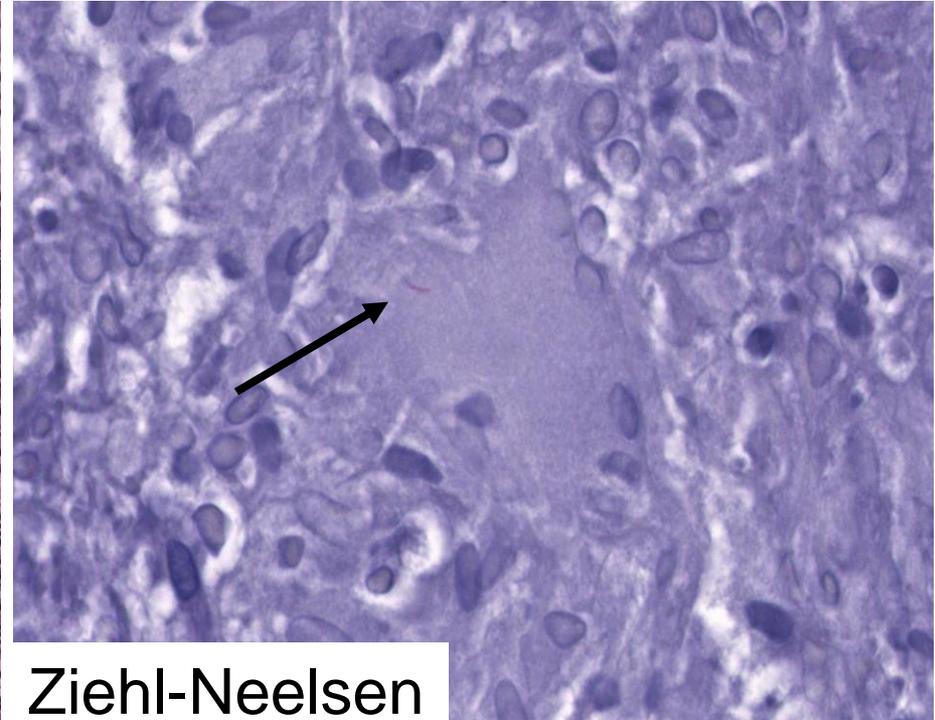
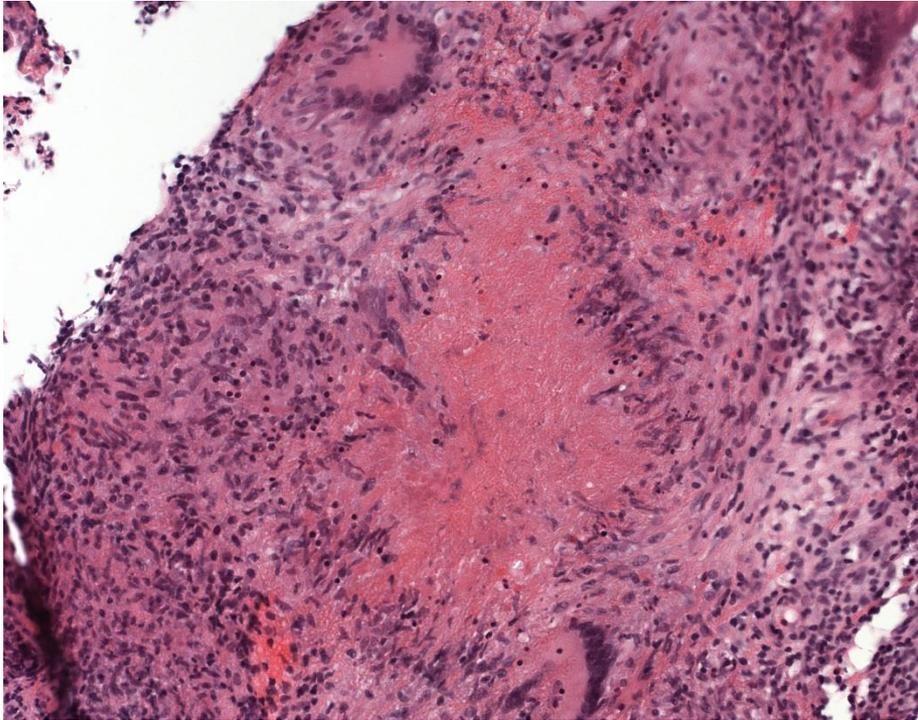
Inflammatory effusions

Lymphocytic	> 50% lymphocytes
Granulocytic	50- 90% neutrophils
Empyema	90% neutrophils detritus, foamy cells
Eosinophilic	> 10% eosinophils

Lymphocytic effusion in 27y male



Pleural biopsy



Ziehl-Neelsen

Rapid-PCR and culture: Mycobacterium tuberculosis

Tuberculous pleuritis

- Extrapulomal manifestation of Tbc
 - In 5-20%, especially in HIV
 - >80% pulmonary infiltrate on imaging
- Lymphocytic effusion (mostly >75% Ly)
 - after 1-2 weeks (initially neutrophils)
 - MBT antigenes → CD4+ Ly → Ly-inflammation
 - **cellular, unilateral**
 - **scant mesothelial cells: <10%** (except in HIV)
 - **no granulomas** (tuberculous empyema)

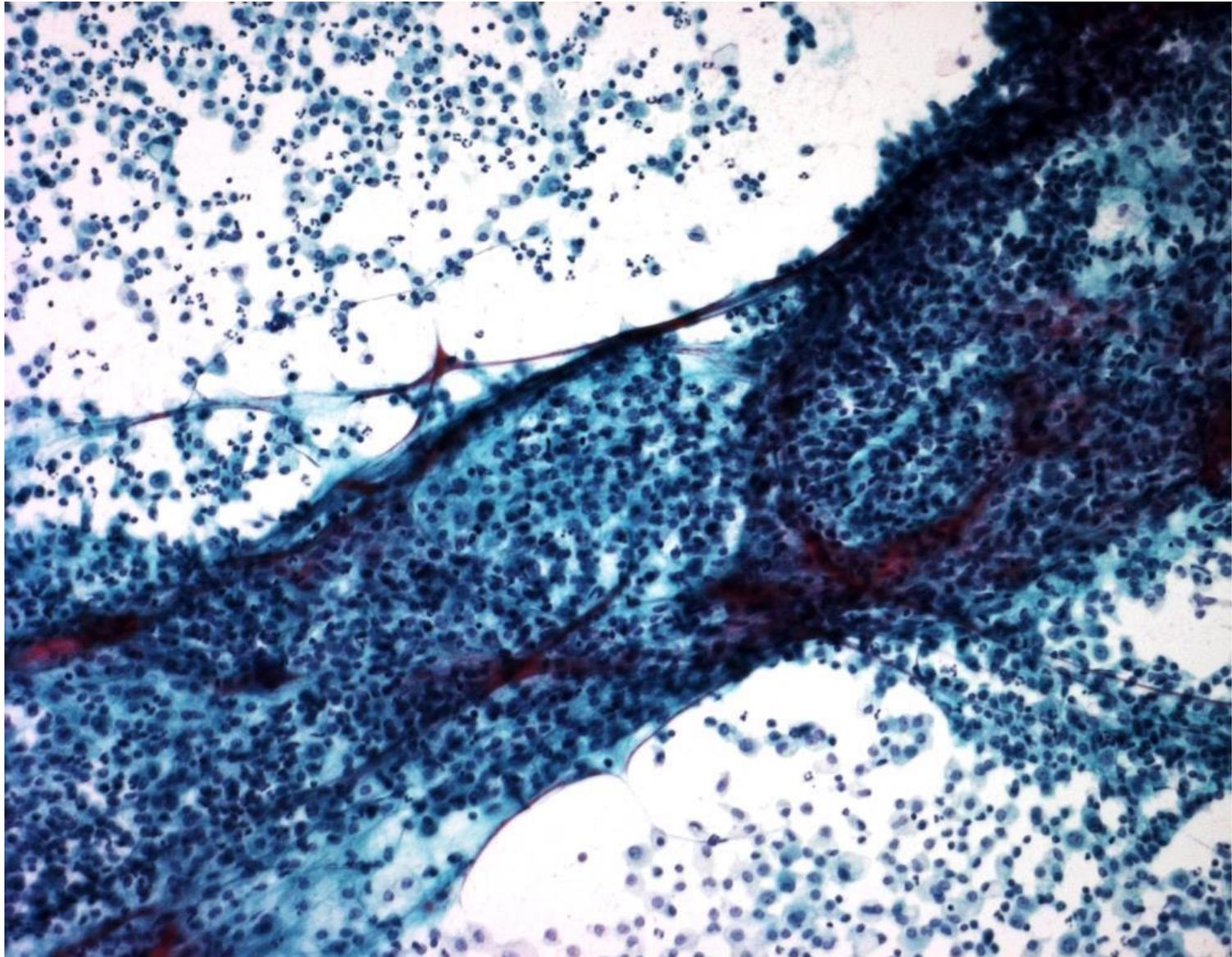
Tuberculous pleuritis

- Definitive diagnosis needs detection of mycobacteria:
 - direct staining (ZN, fluorochrome), culture or PCR
 - detection in pleural effusion in <10%
 - pleural biopsy often necessary

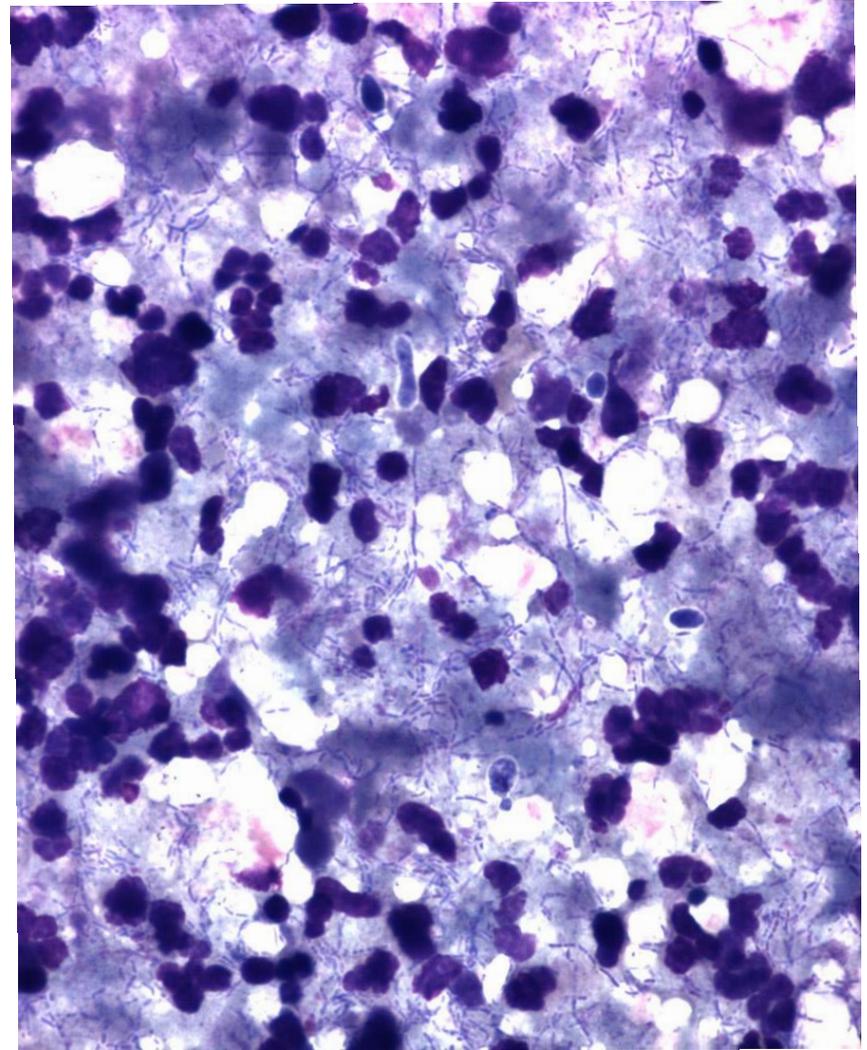
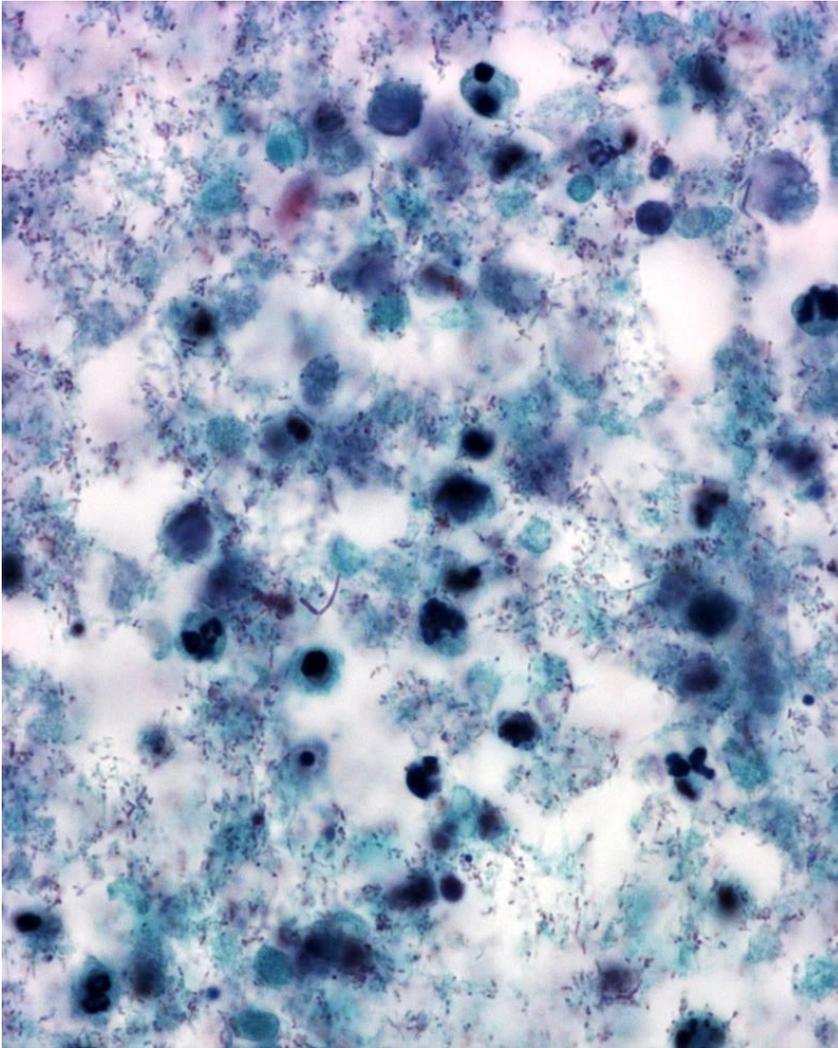
DD lymphocytic effusions

- Tuberculous pleuritis (<10% mesothelial cells)
- Carcinosis (> mesothelial cells)
- Lymphatic obstruction
 - Chylous effusion (trauma, malignancy)
- Lymphomas (CLL)
 - ICC CD20/CD3
 - CD20+ lymphocytes in >30%: B-cell lymphoma
- Sarcoidosis
- Congestive heart failure

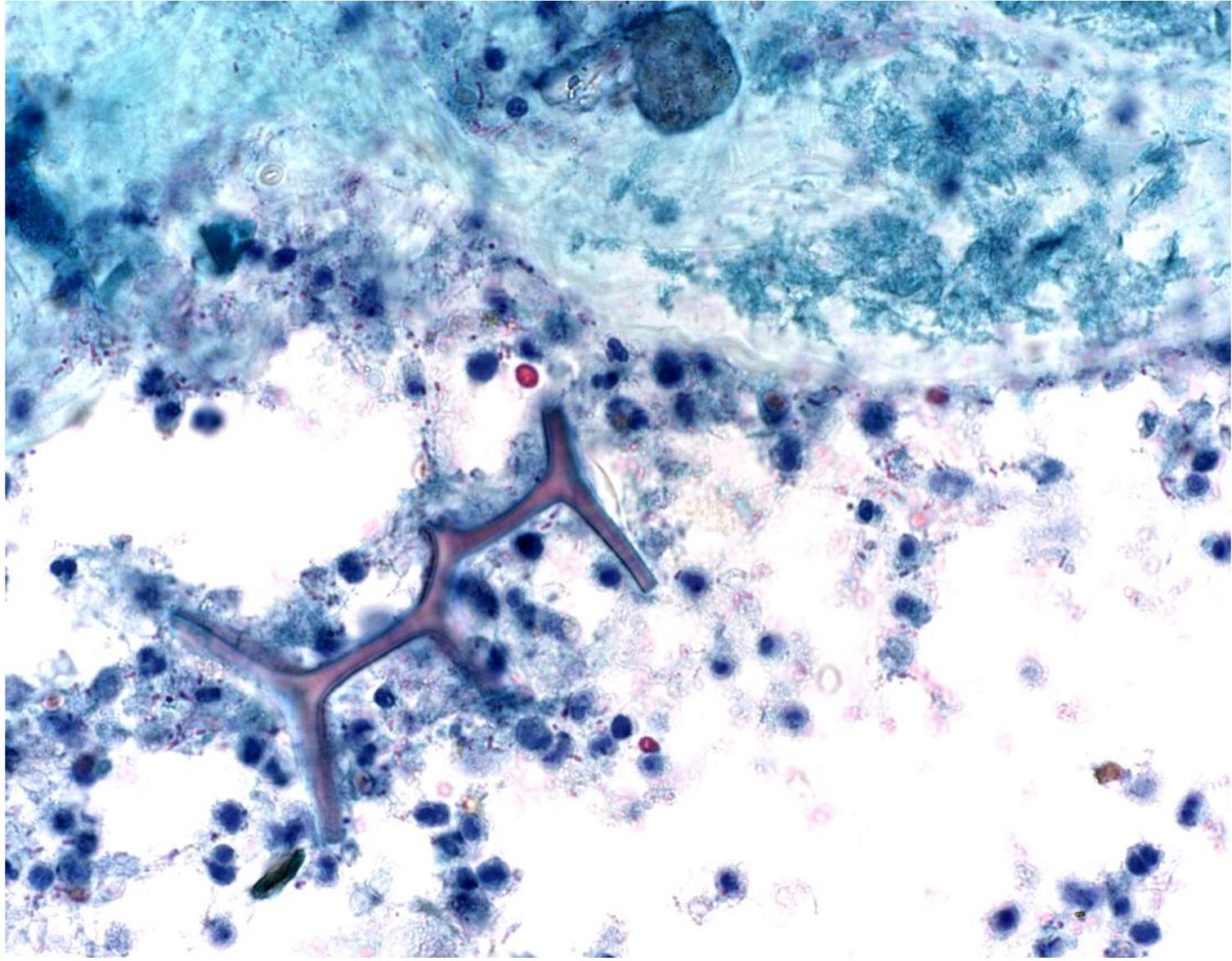
Fibrinous pleuritis



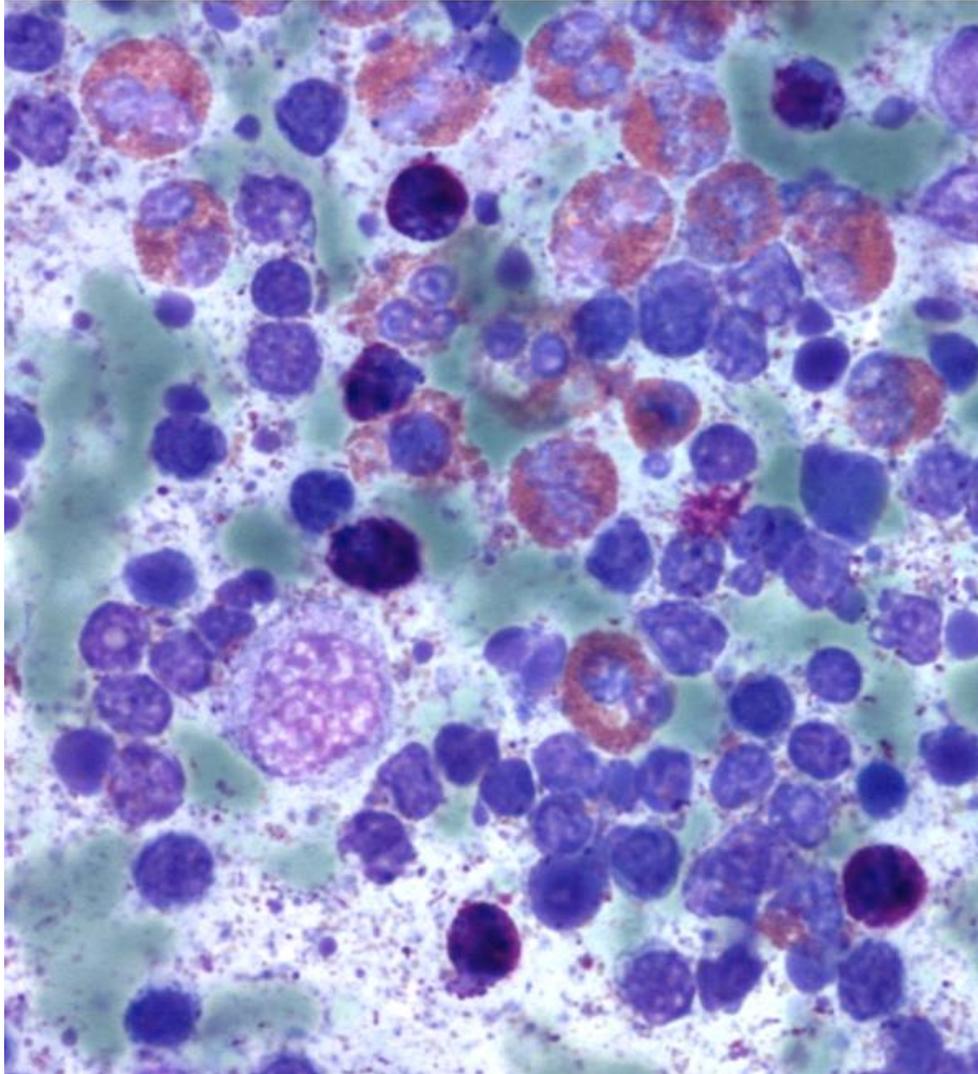
Empyema



Oesophagopleural fistula



Eosinophilic effusion

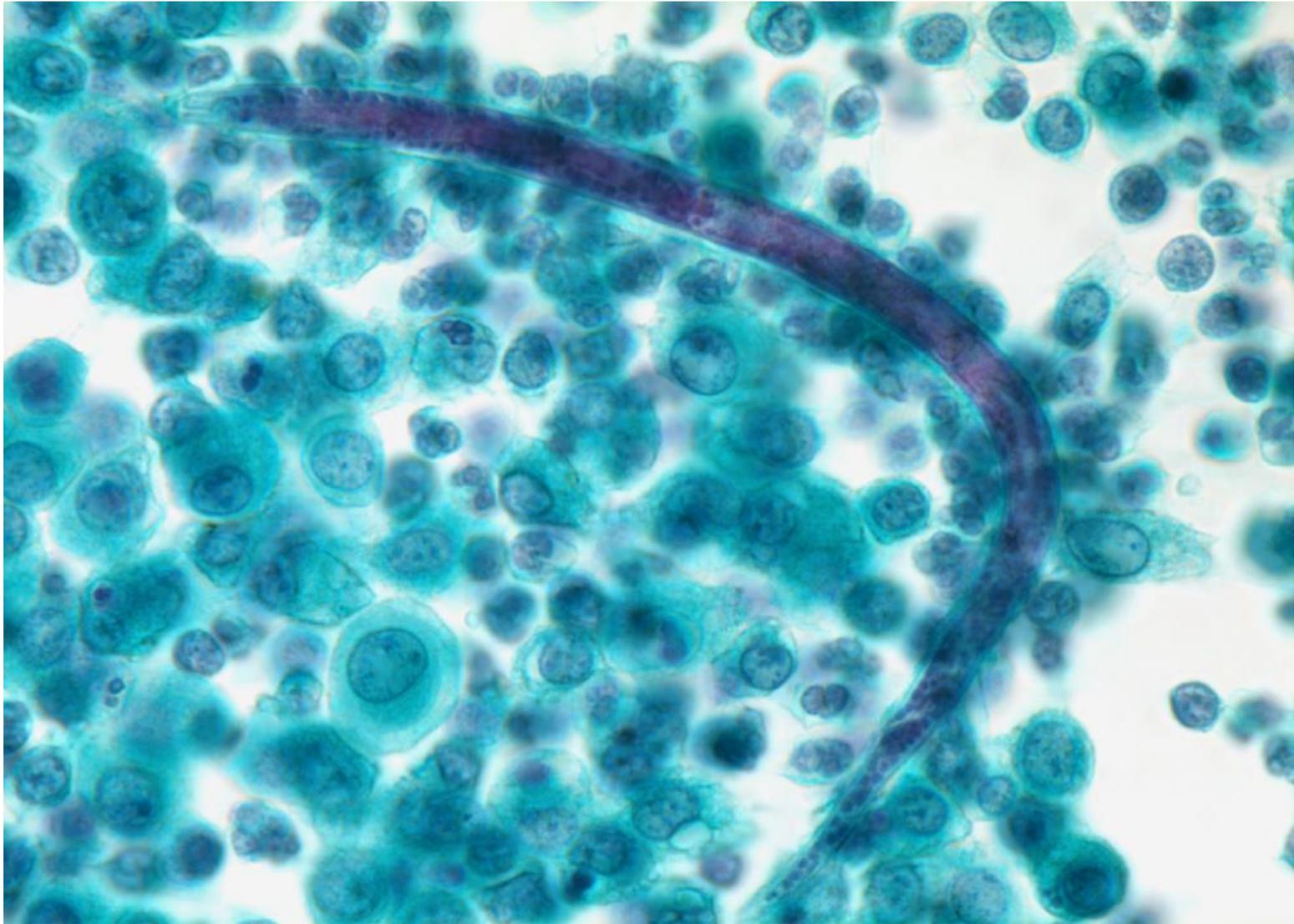


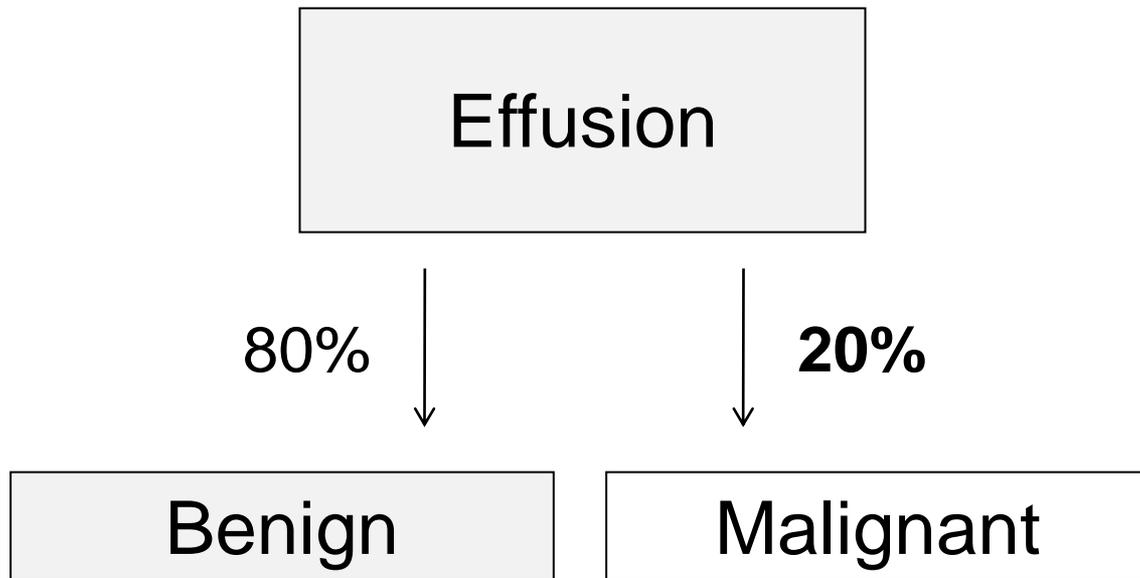
- **usually pleural, unilateral and non-specific**

DD:

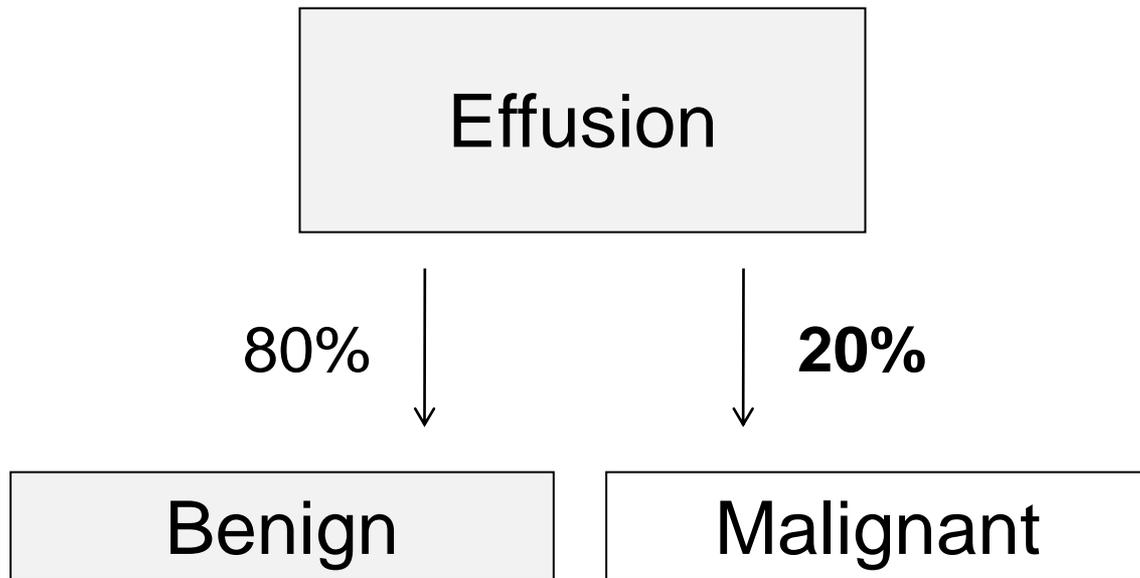
- air
- Idiopathic (1/3)
- post pneumonia
- with peripheral eos:
 - parasitic infections
 - immunologic
 - malignancies

Strongyloides





- Reactive vs malignant
- Origin (organ, tissue)
- Predictive markers



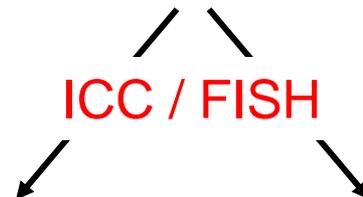
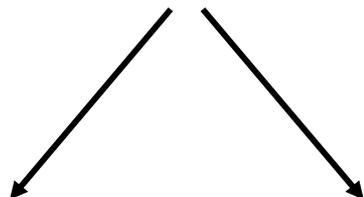
- Reactive vs malignant **ICC, FISH**
- Origin (organ, tissue) **ICC**
- Predictive markers **ICC, FISH, PCR**

ICC

Epithelial



Mesothelial



Carcinoma

Endometriosis
Follapian tube
Endosalping.

Reactive
mesothelial
cells

Malign.
mesothel.



Origin?

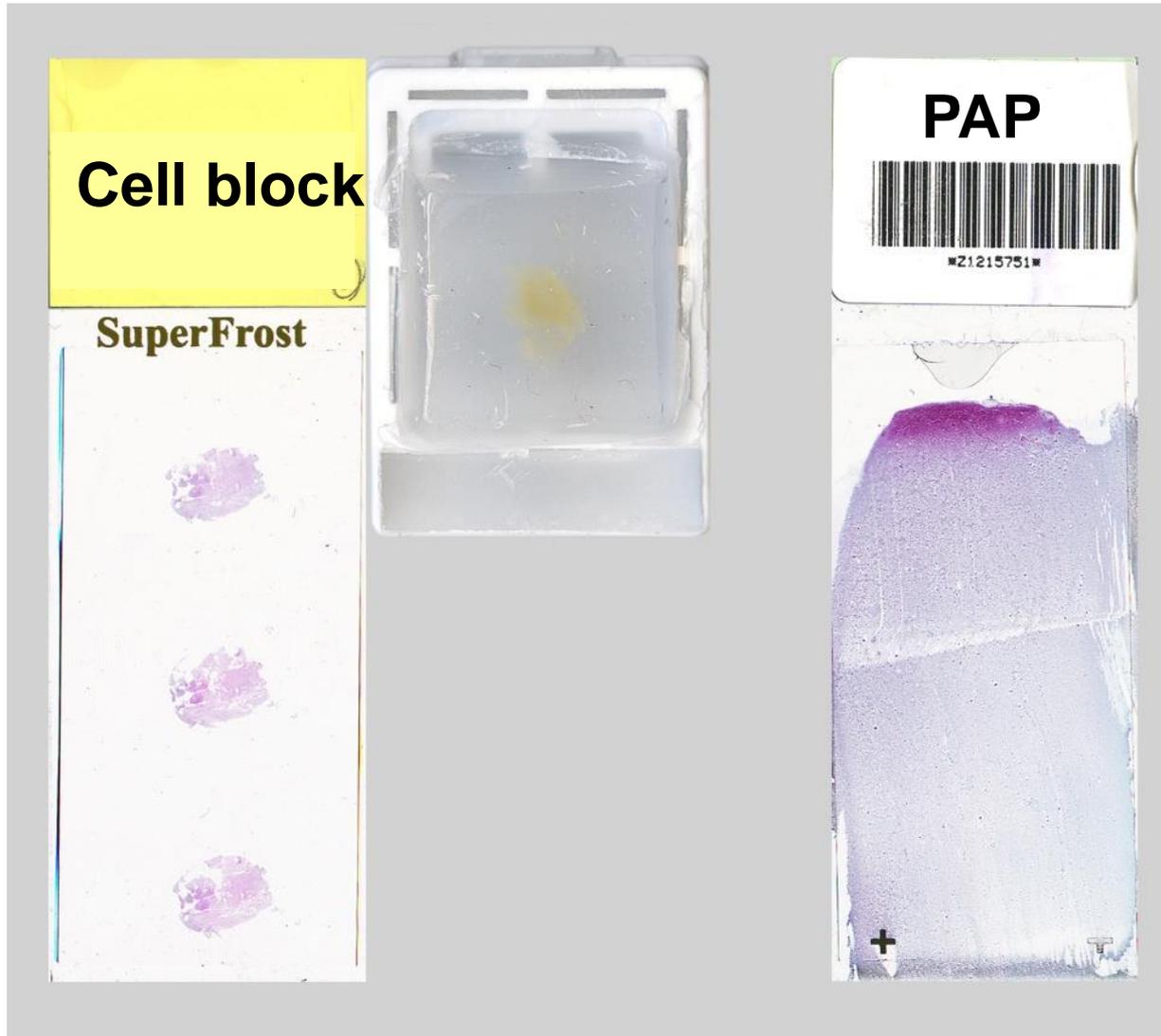
ICC, history, clinical info

Lymphoma, melanoma, sarcoma ICC

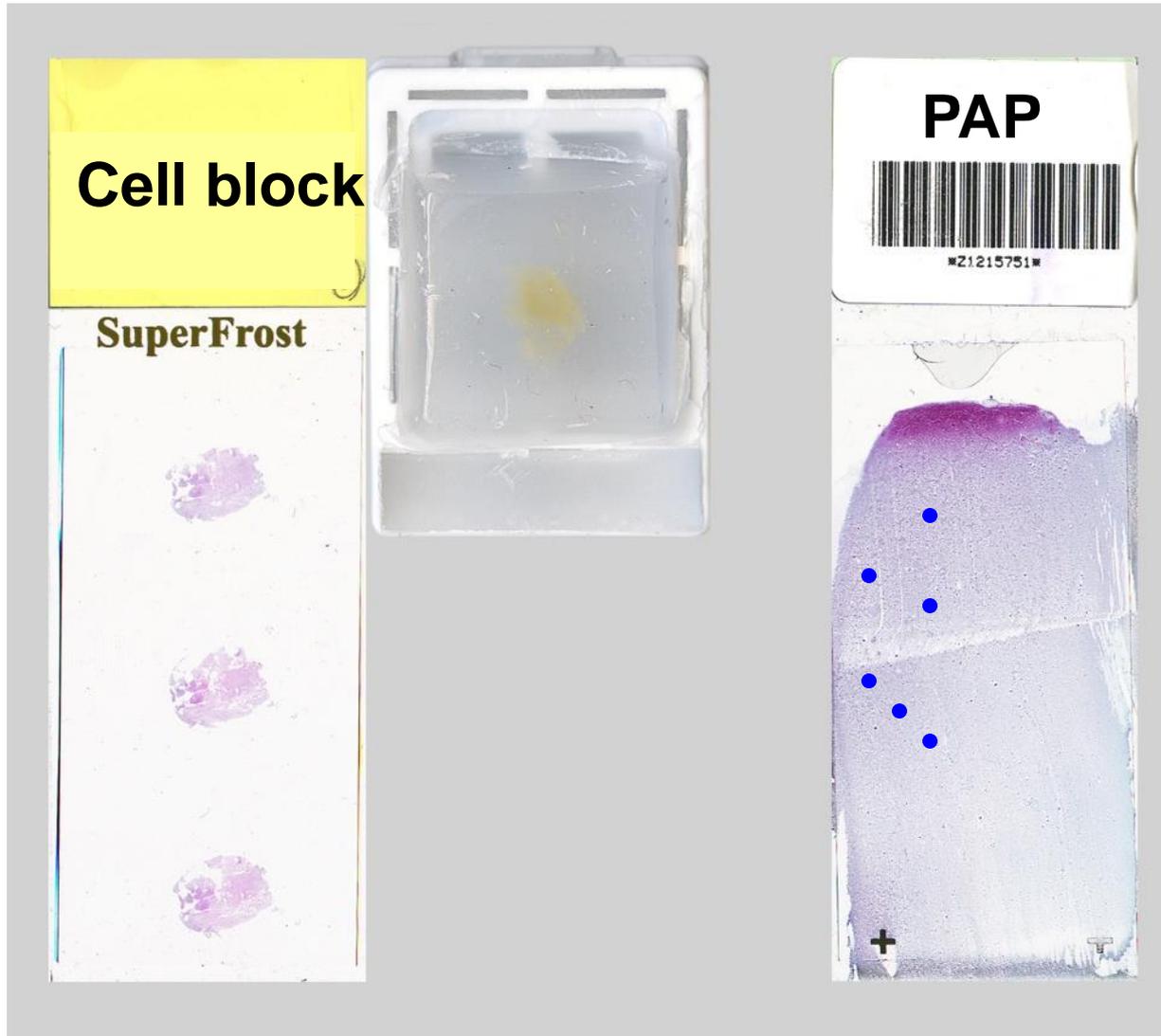
Immunocytochemistry

- On PAP stained specimens or from cells blocks
- Automated immunostainers
 - BondMax (Leica)
- Positive controls
 - Cytospins from pleural effusions
 - Commercially available cell cultures
 - Fresh tissue scrapings from resection specimens

Immunocytochemistry



Immunocytochemistry



Top list of ICC markers

BerEp4, Calretinin	Epithelial vs mesothelial cells
CK7, CK20	Cancer origin
TTF-1	Lung adenocarcinoma
GATA-3	Breast and urothelial cancer
ER, PR	Breast cancer (diagnostic and predictive)
ALK, ROS1	Lung cancer (predictive)
CD3, CD20	Reactive lymphocytes vs lymphoma

ICC

- Epithelial vs mesothelial: CK22 does not help
- Leading sources of malignant pleural effusions:
 - Pleural: Lung and breast cancers
 - Peritoneal: Ovarian, breast and pancreatic cancers } ADC
- Screening for origin of carcinoma cells
 - CK7+/CK20–: Lung, breast, gastric, pancreatic and cholangio
 - CK7–/CK20+: Colorectal
 - CK7+/CK20+: Urothelial, pancreatic and cholangio
 - CK7–/CK20–: Prostatic, renal cell and hepato cellular

ICC

- TTF1
 - Performance depends on clone
 - SPT24: more sensitive
 - 8G7G3/1: more specific
 - Cave TTF1+
 - extrapulm. high-grade NEC
 - -20% endometrioid CA
- Consider history and clinical presentation

Criteria for malignancy in effusions

- Foreign population of cells
- Malignant nuclear features
- Often large 3-D cell clusters
- Cytoplasmic features

Criteria for malignancy in effusions

- Foreign population of cells

Exeptions: Malignant mesothelioma, breast cancer

- Malignant nuclear features
- Often large 3-D cell clusters
- Cytoplasmic features

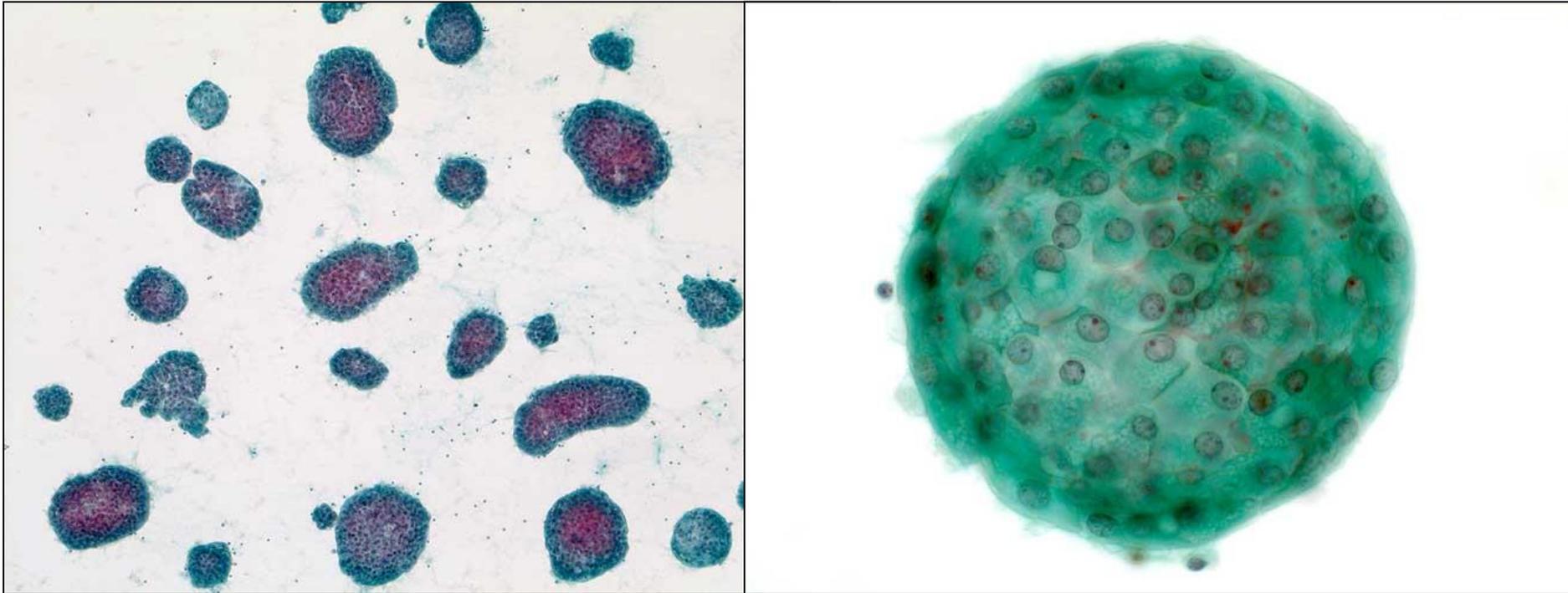
Criteria for malignancy in effusions

- **Foreign population of cells**
Exeptions: Mesotheliomas, breast cancer
- **Malignant nuclear features**
- Often large 3-D cell clusters
Exeptions: Lymphomas, breast, gastric, mesothel.
- Cytoplasmic features

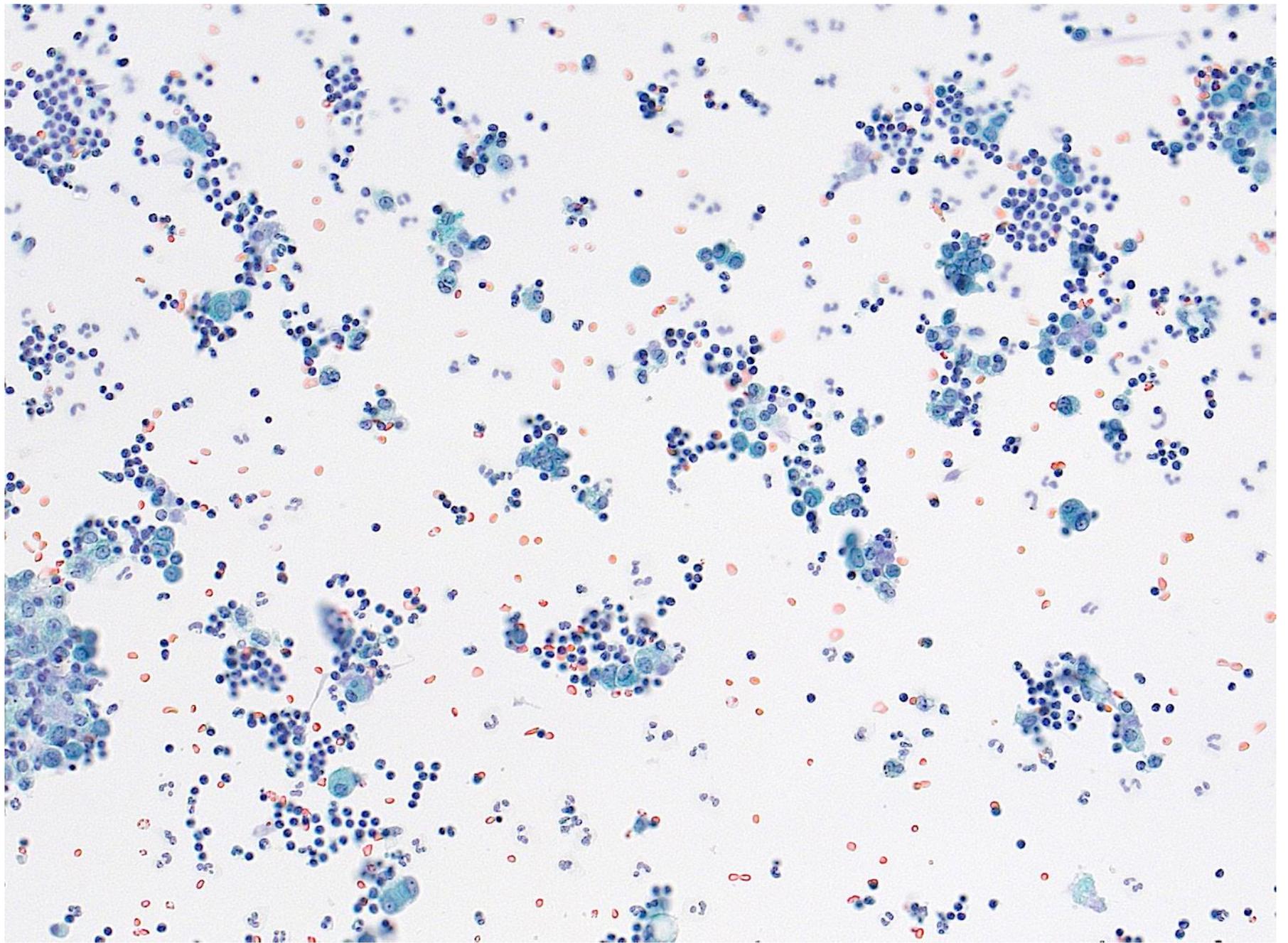
Criteria for malignancy in effusions

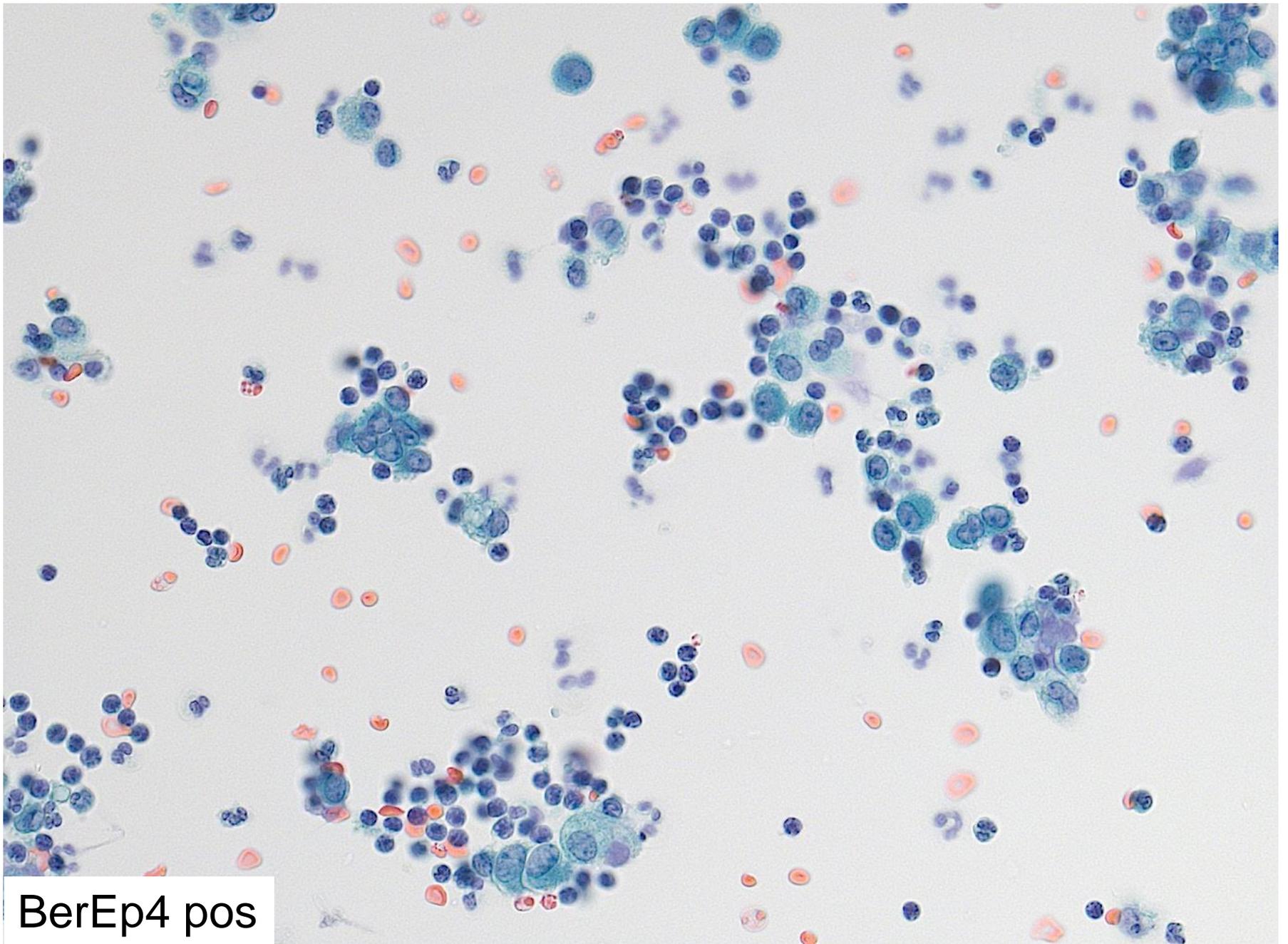
- Foreign population of cells
- Malignant nuclear features
 - ADC: Vesicular nuclei
- Often large 3-D cell clusters
 - ADC: Smooth community borders, acini, papillae
- Cytoplasmic features
 - ADC: Secretory vacuoles (mucin)

Breast cancer



„Cannon balls“



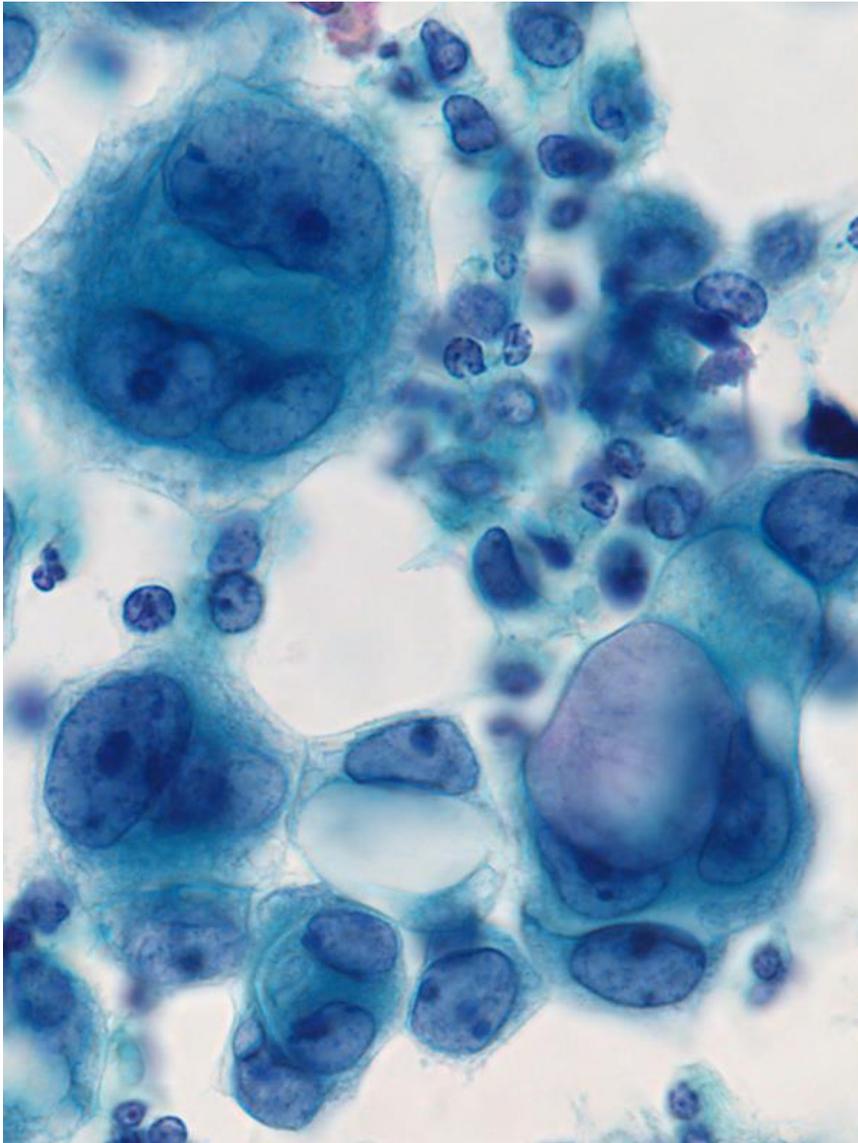


BerEp4 pos

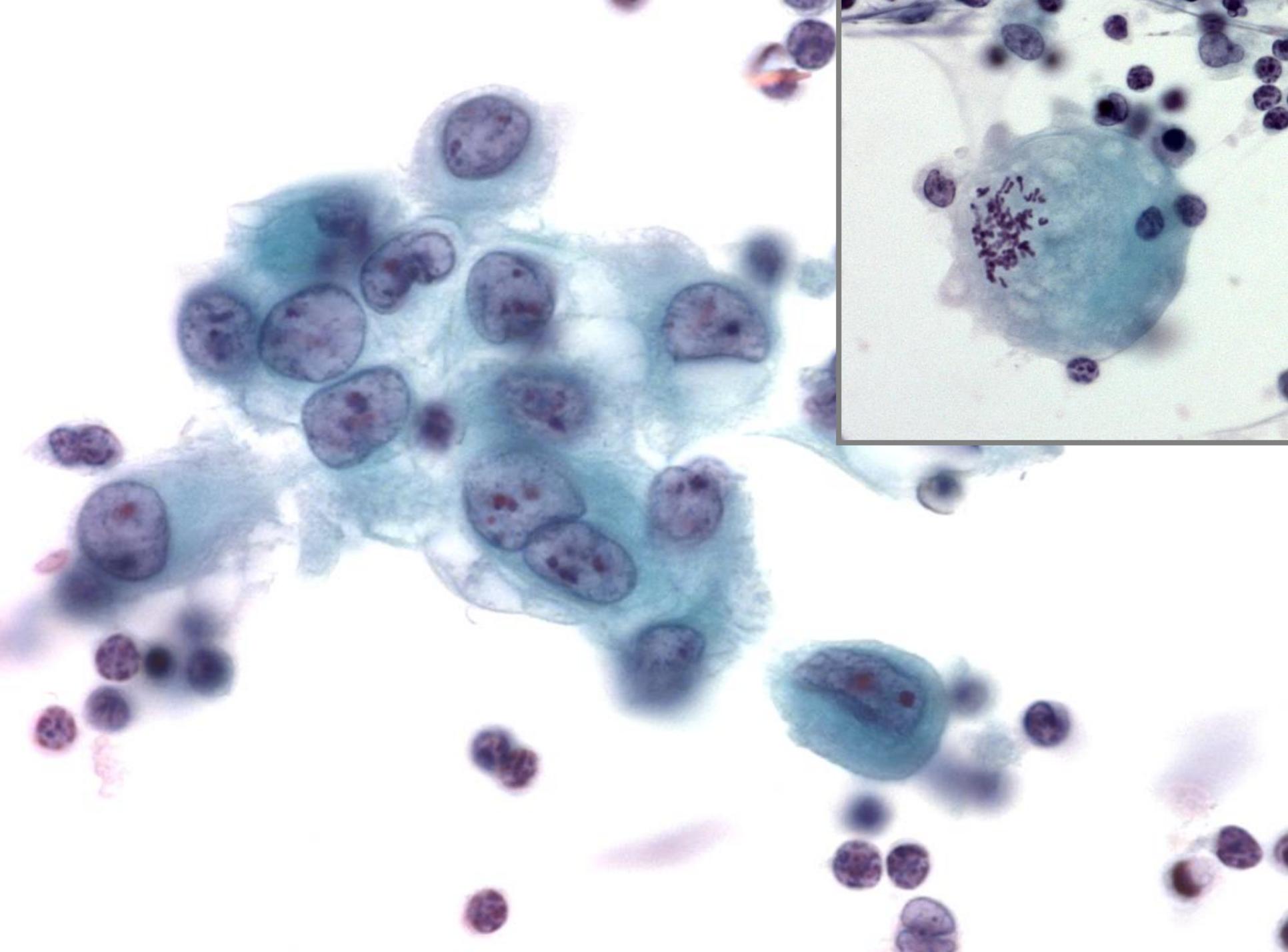
Lung Cancer: NSCLC (80%)

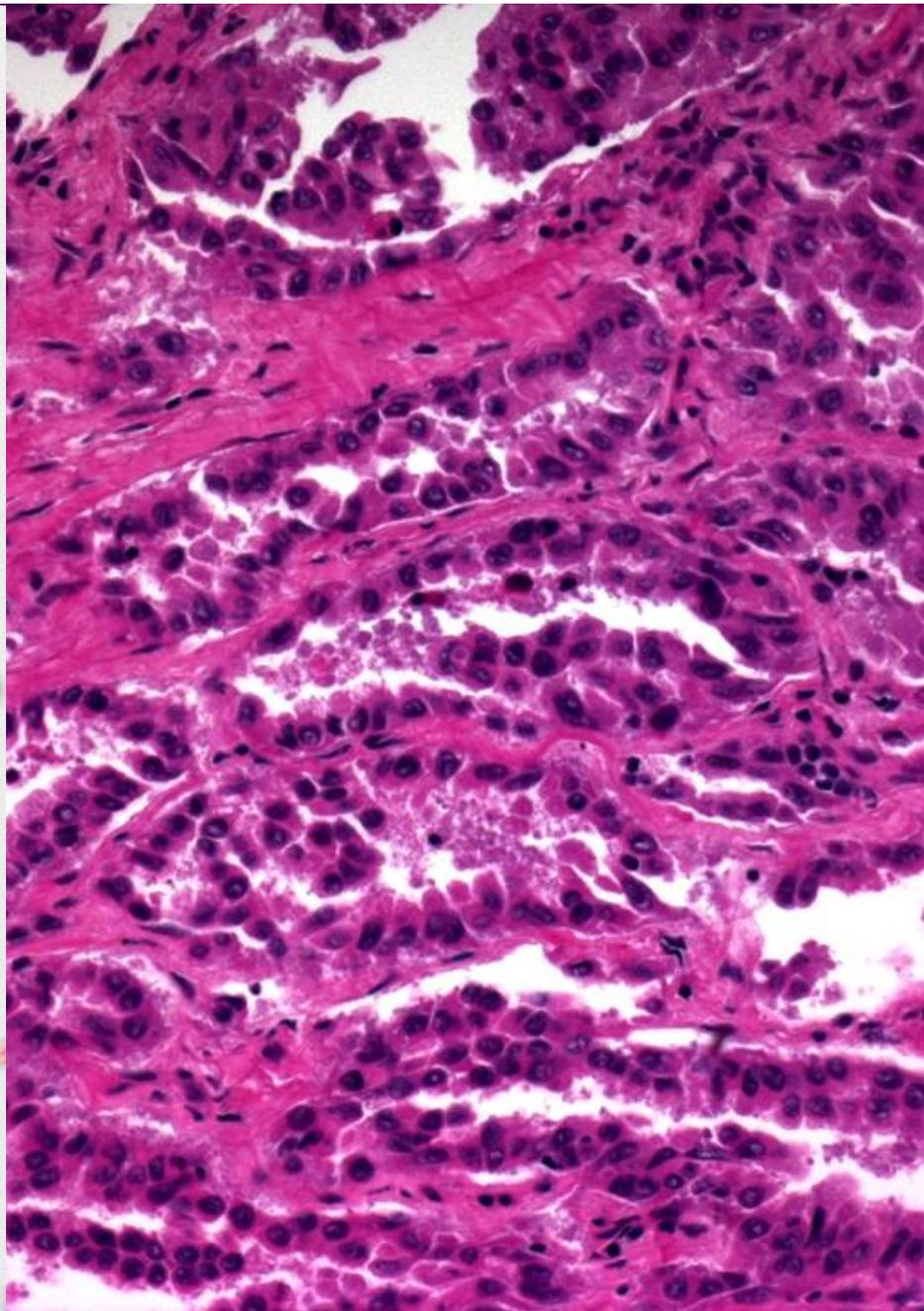
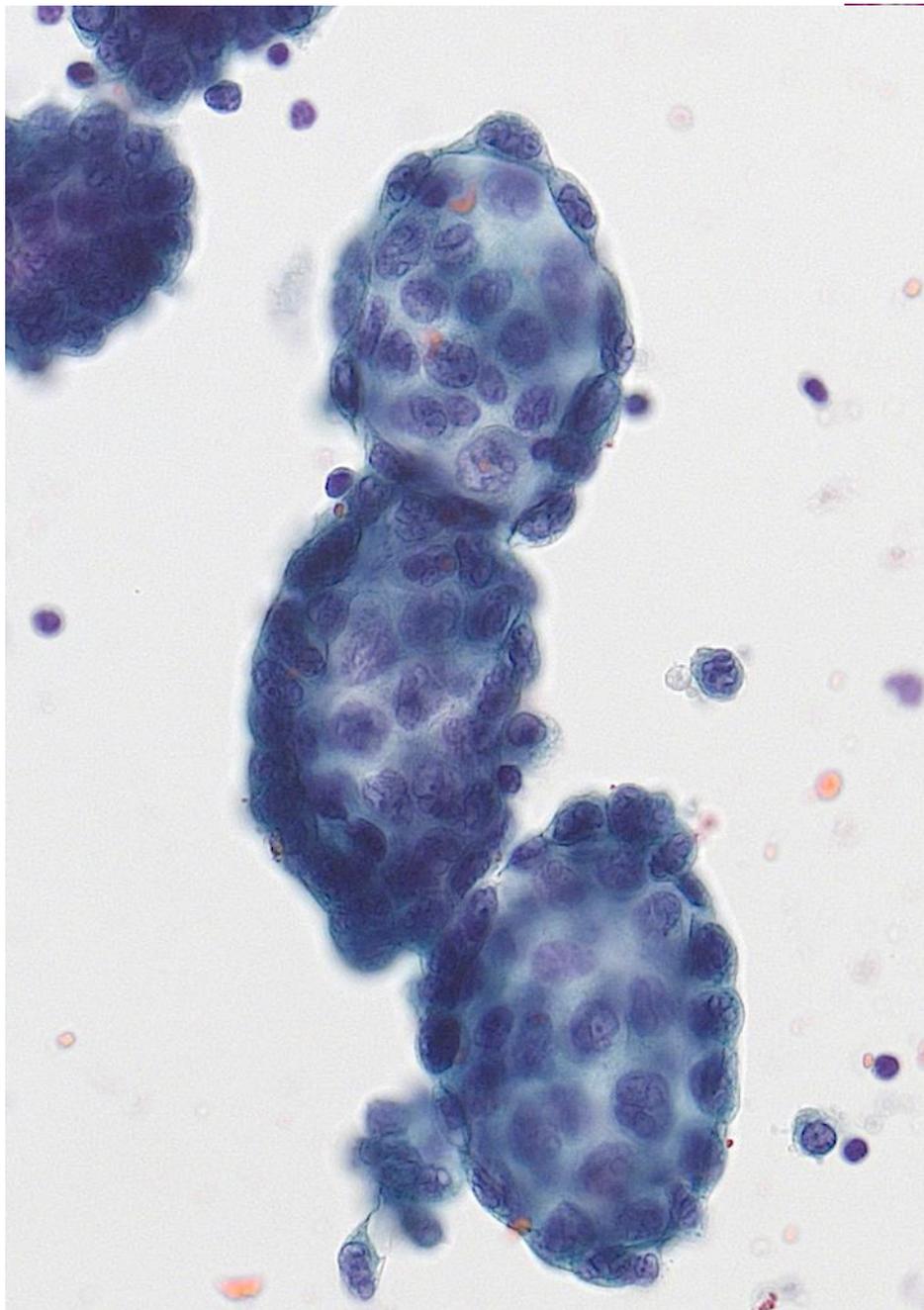
- Single most common cause of malignant effusions
- **Adenocarcinoma (60%)**
 - 80% TTF1+
 - Malignant effusion = stage IV disease
 - Predictive marker testing
- Squamous cell carcinoma (35%)
 - Rarely shed into effusions
 - Squamous diff. often not evident
 - P40+ → cave also in mesothelial cells
 - BerEp4 -

Lung Cancer: Adenocarcinoma

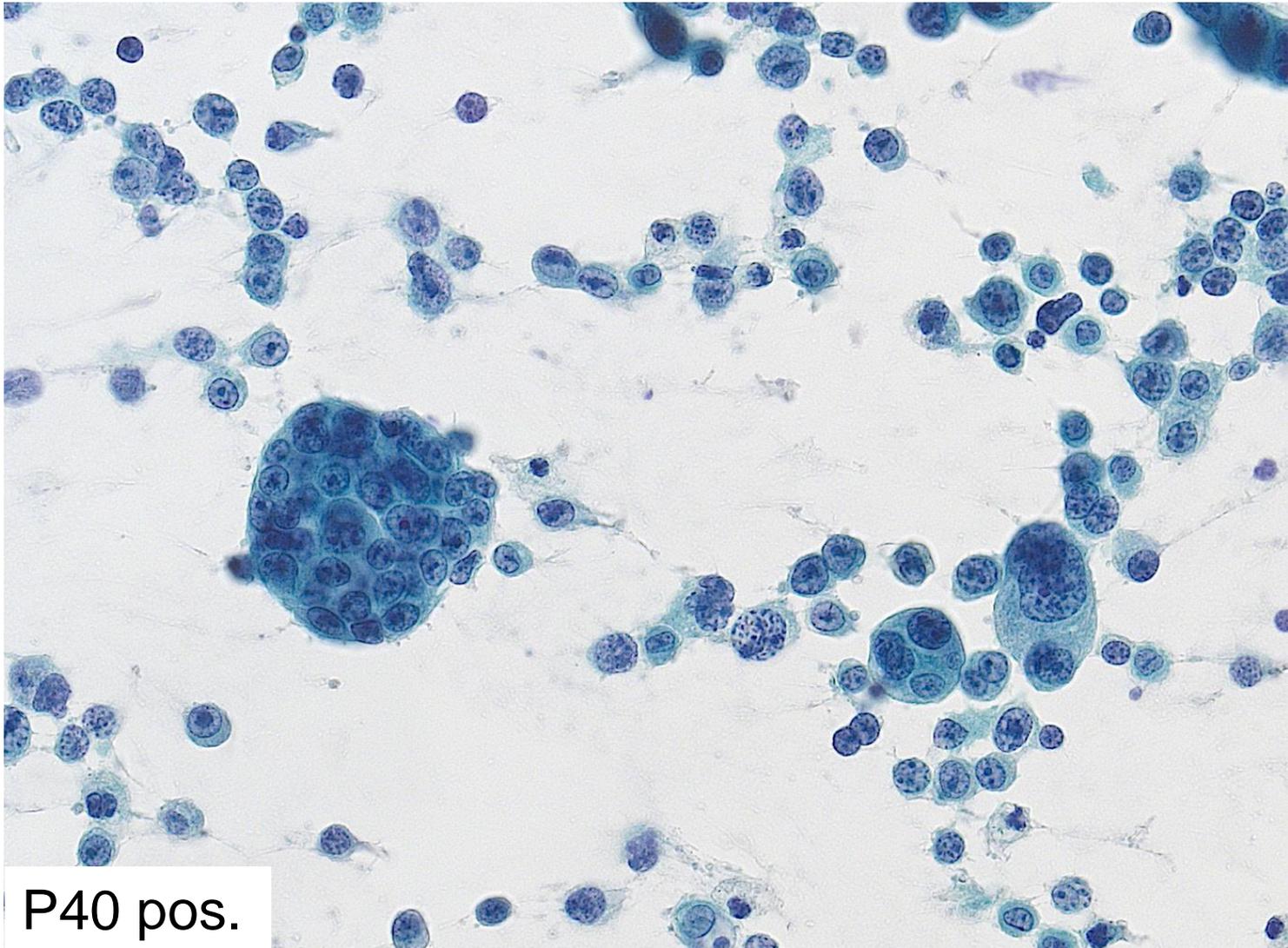


Mucin

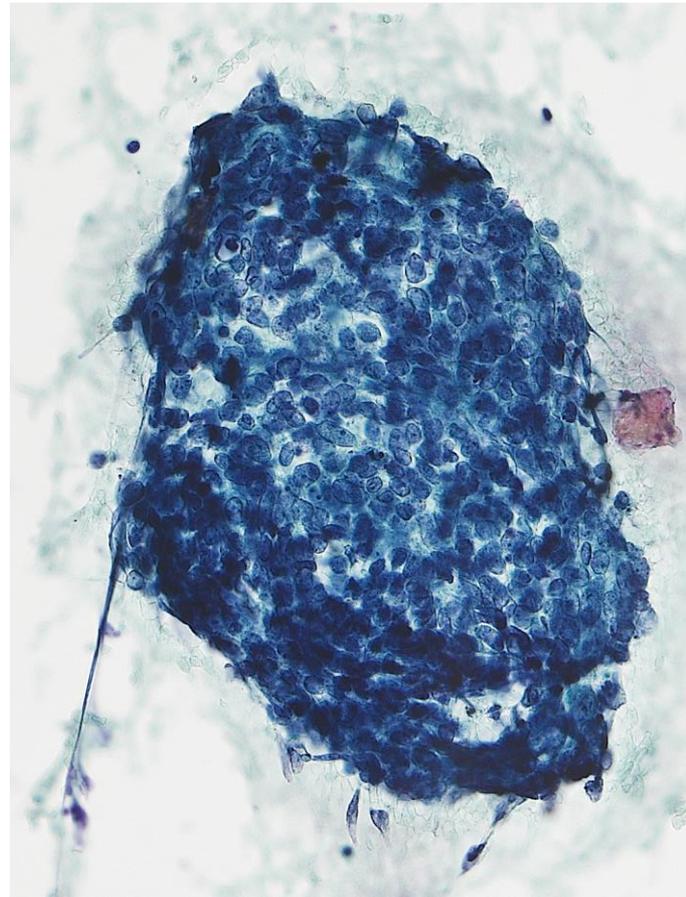
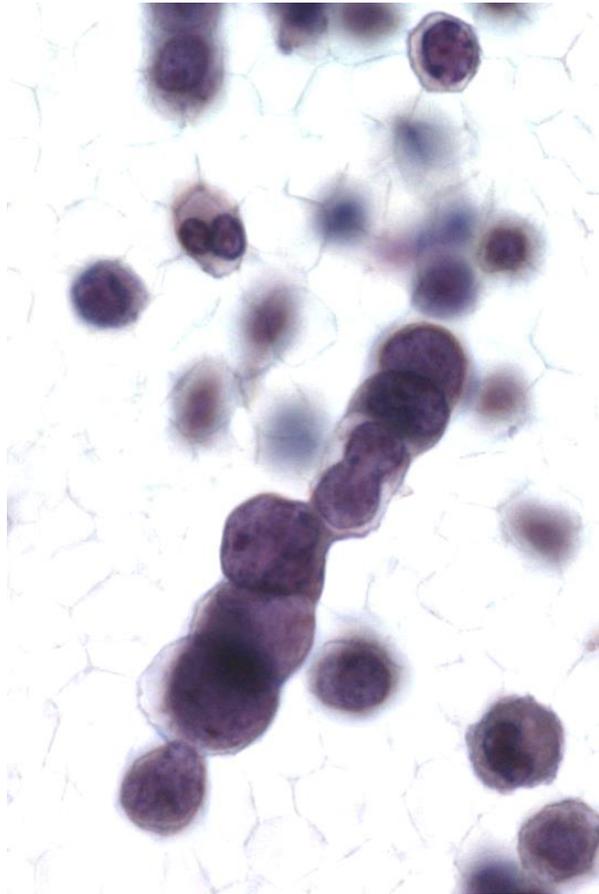




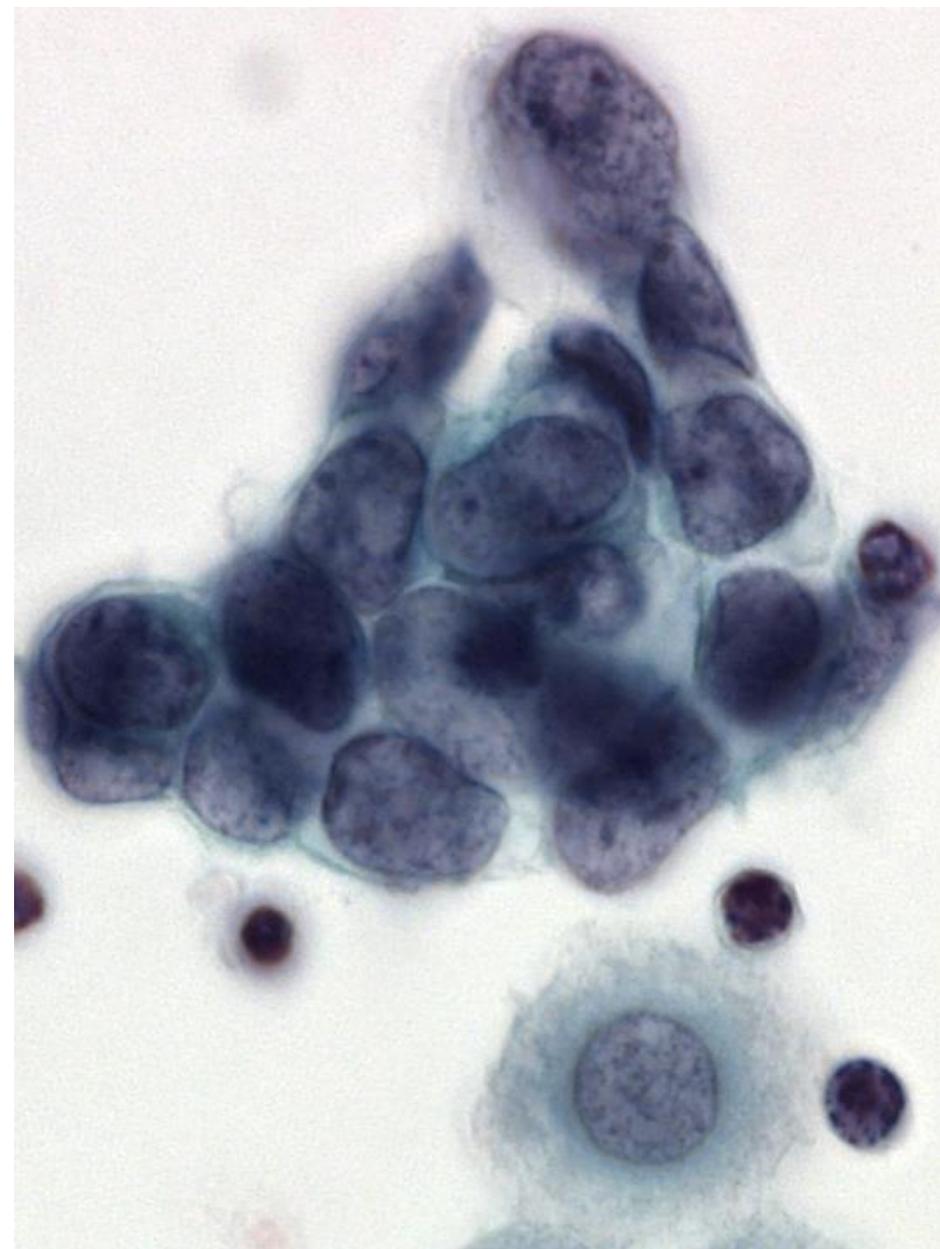
Lung Cancer: Squamous



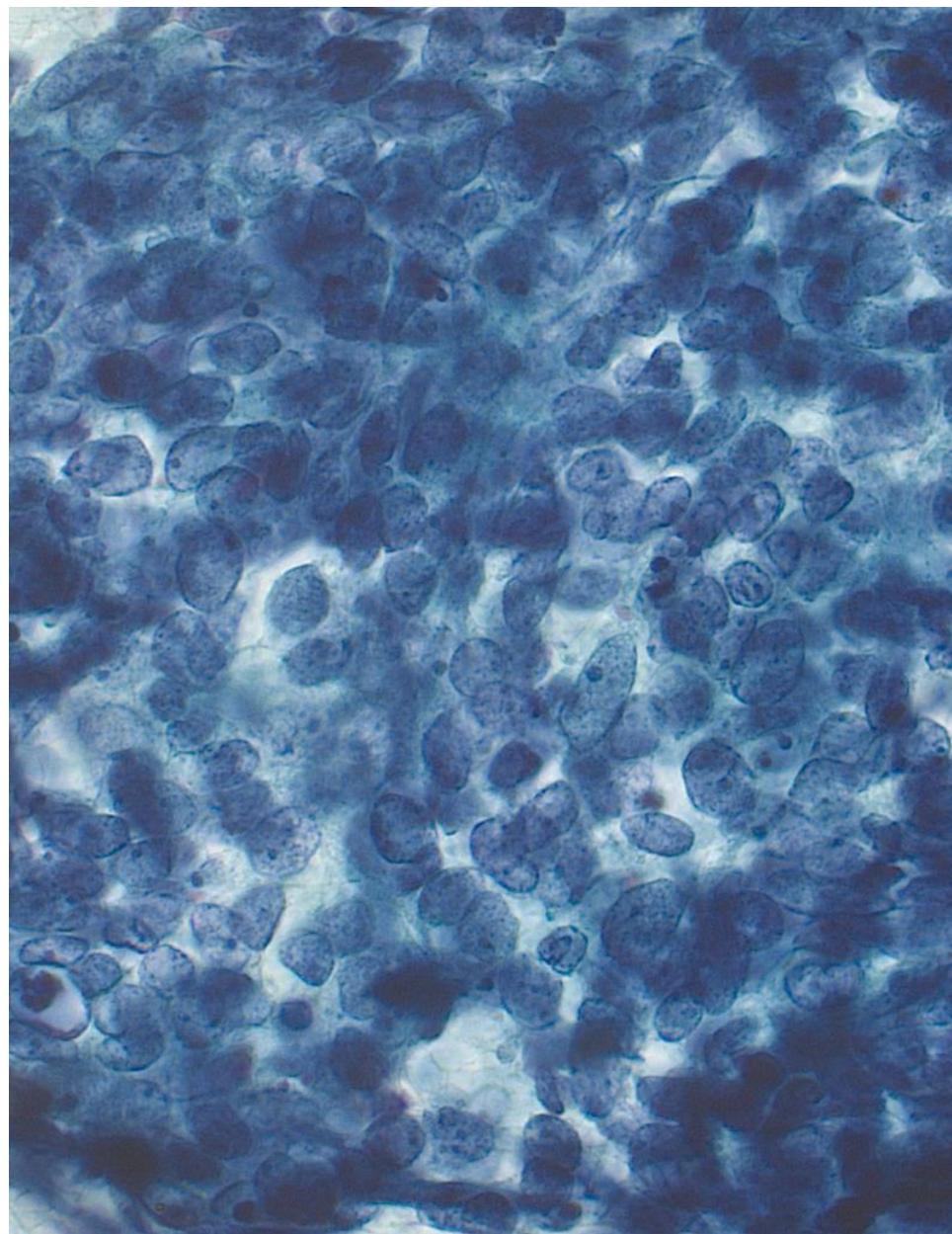
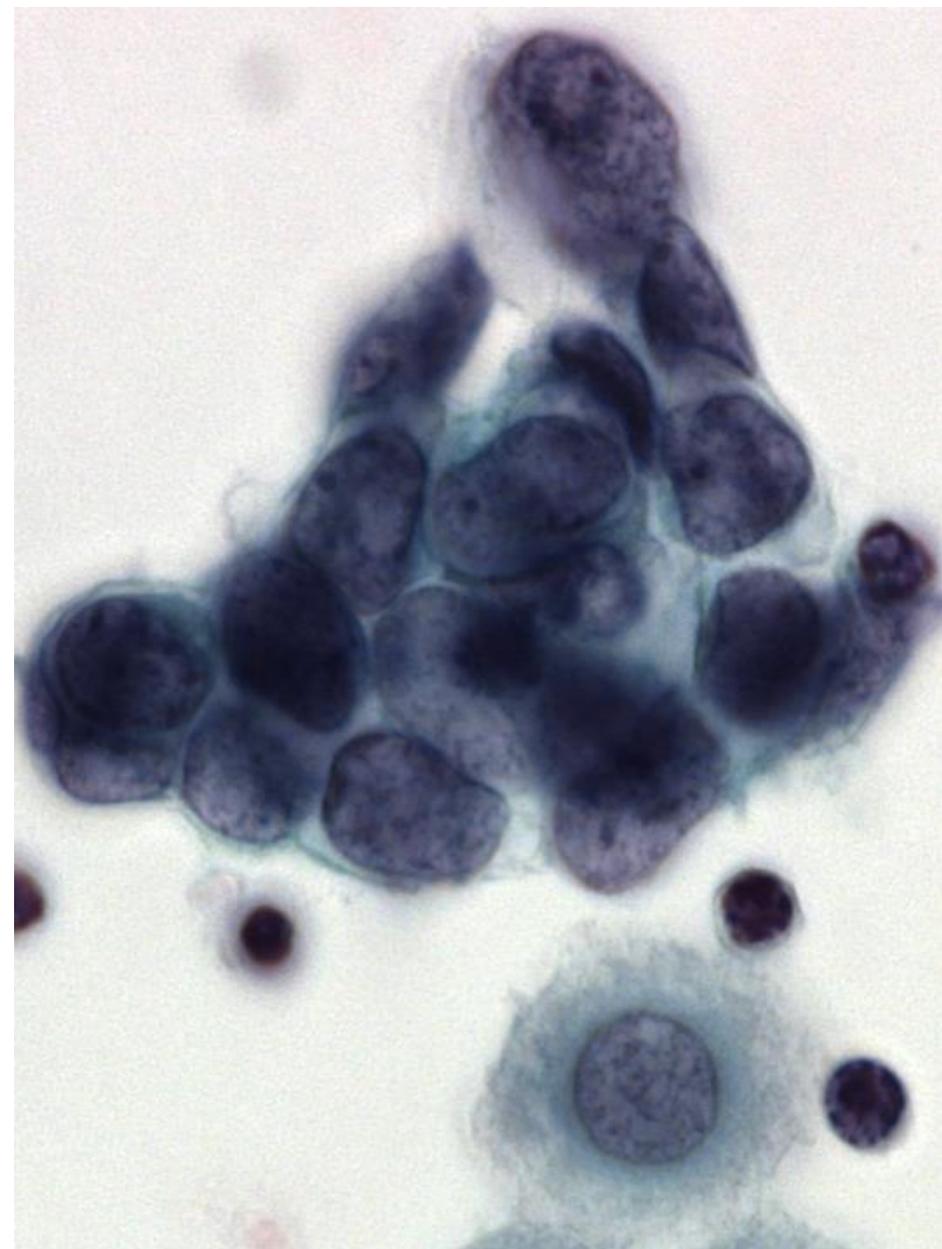
Lung Cancer: SCLC (20%)



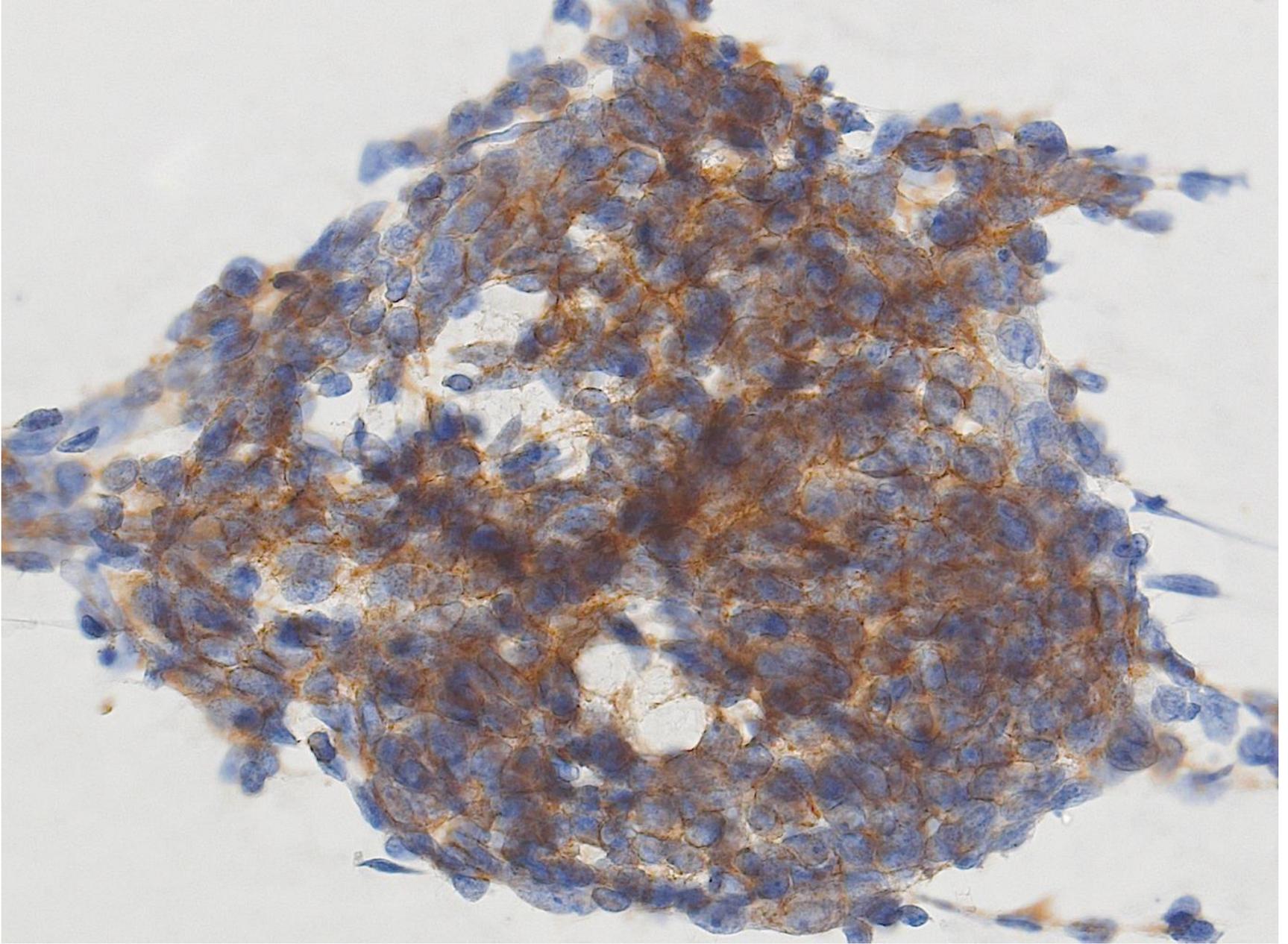
- Rarely shed into effusions
- Cells may be sparse in tightly packed clusters (can be overlooked)



- -4-6x a lymphocytes , variable in size and shape
- Charact.nuclear features (finely coarse chromatin, inconspicuous nuclei)

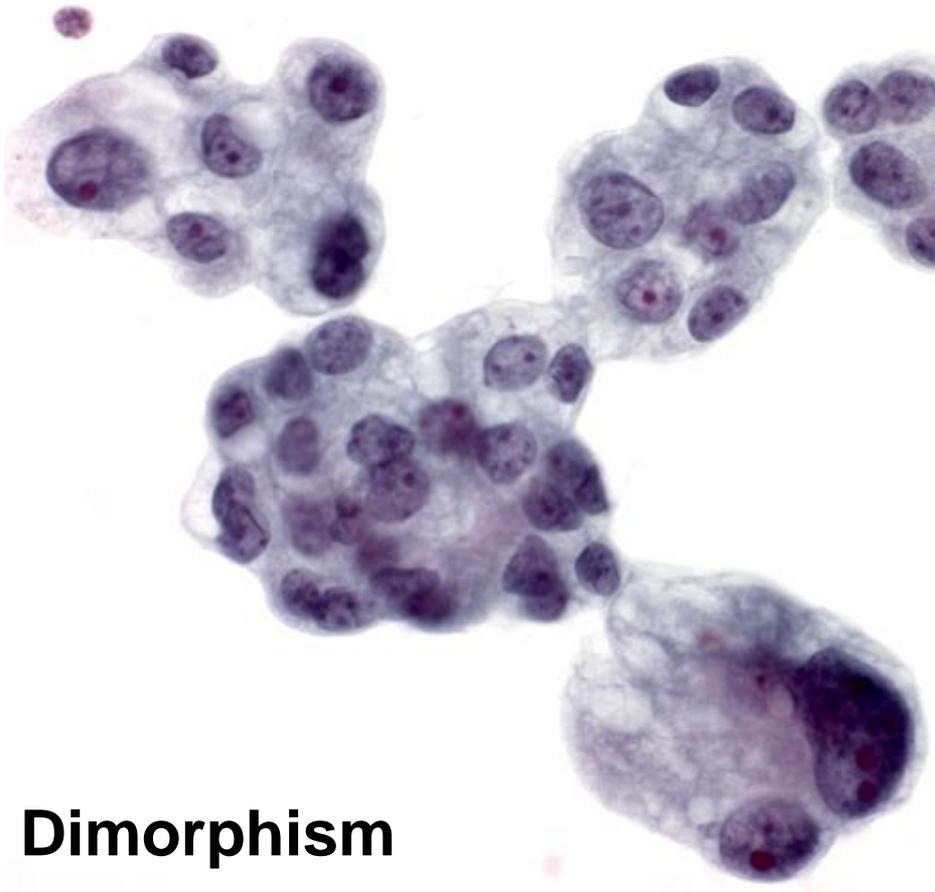


- -4-6x a lymphocytes , variable in size and shape
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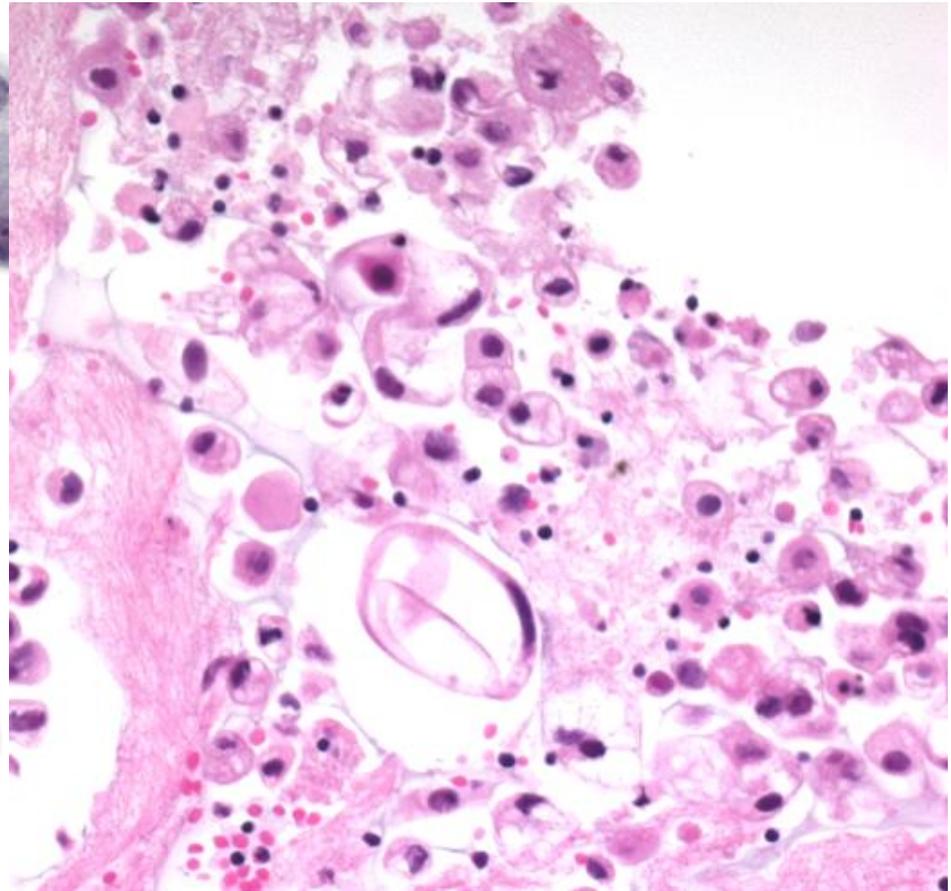


- positive for neuroendocrine markers: CD 56, chromogranin, synaptophysin
 - Ki67 >90%

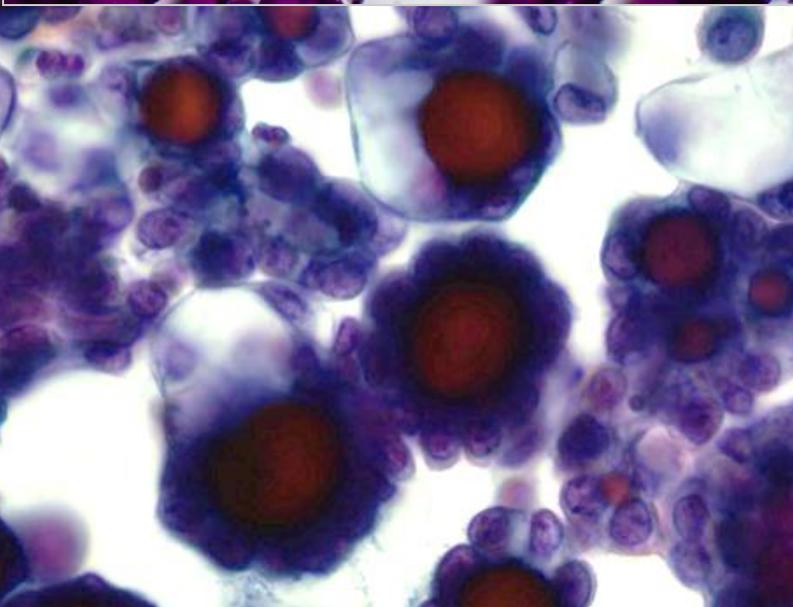
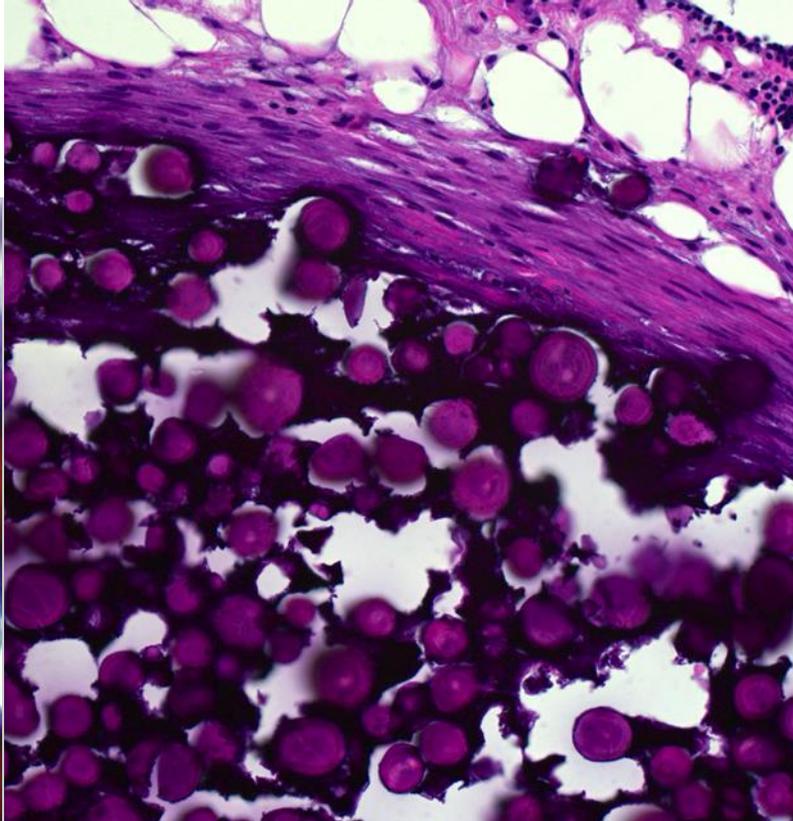
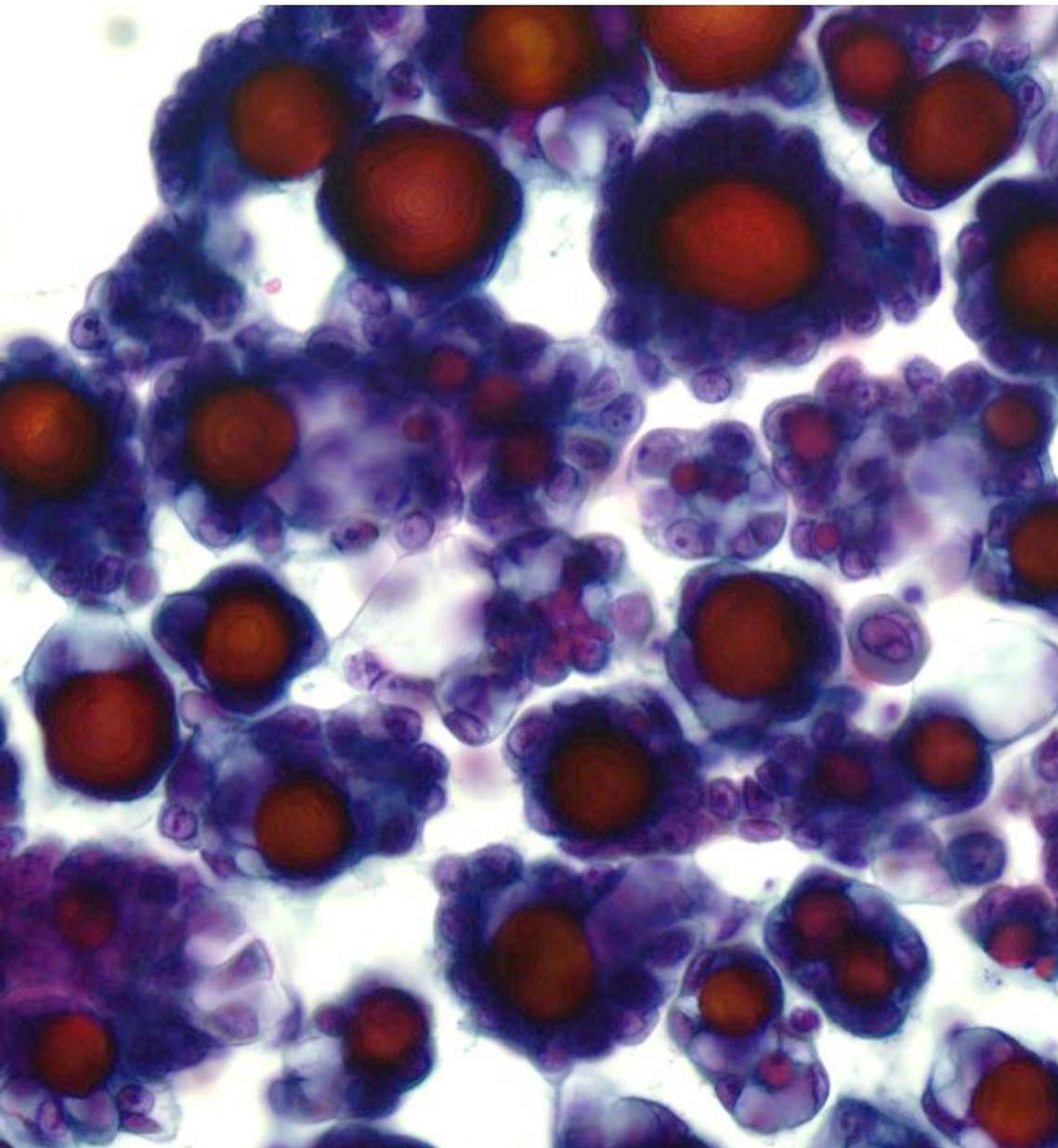
Ovarian high-grade serous carcinoma



Dimorphism



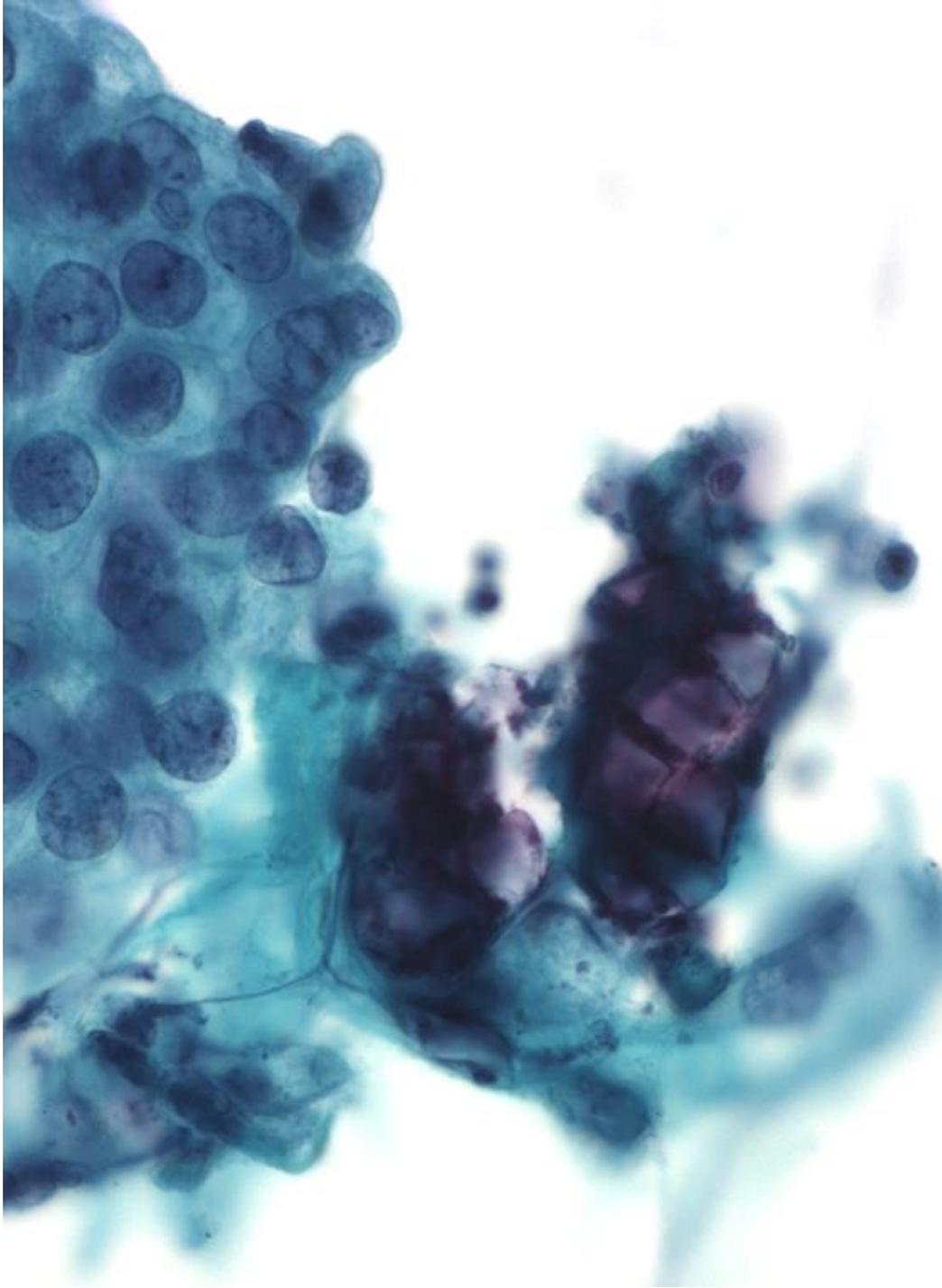
Serous Borderline Tumour



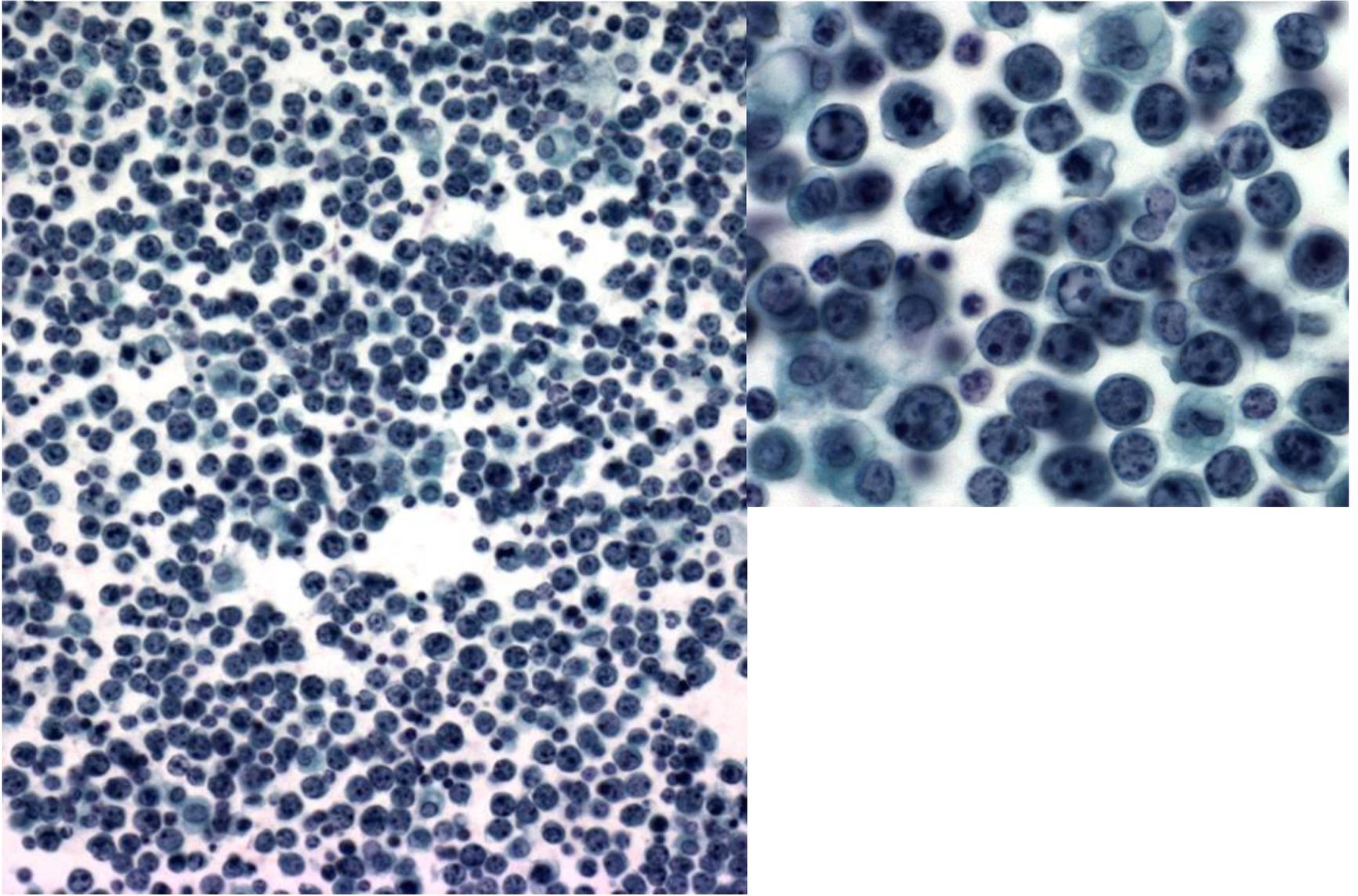
Psammoma bodies

DD

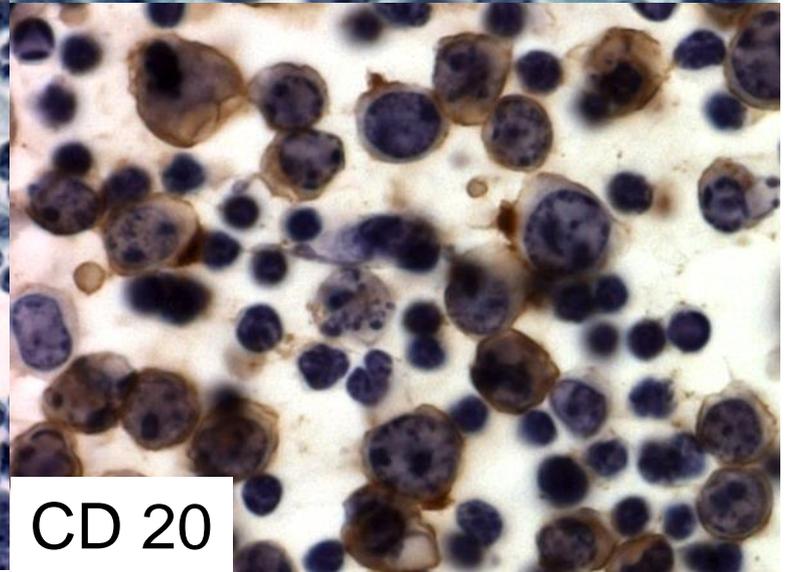
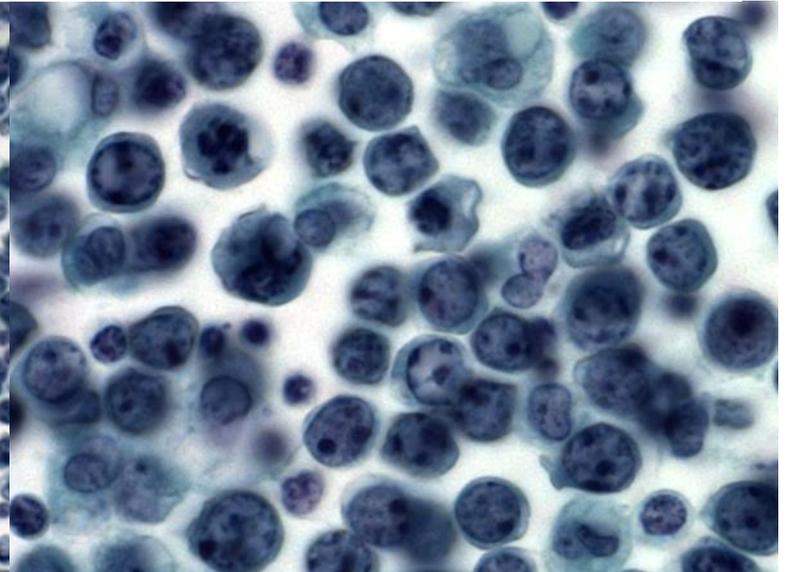
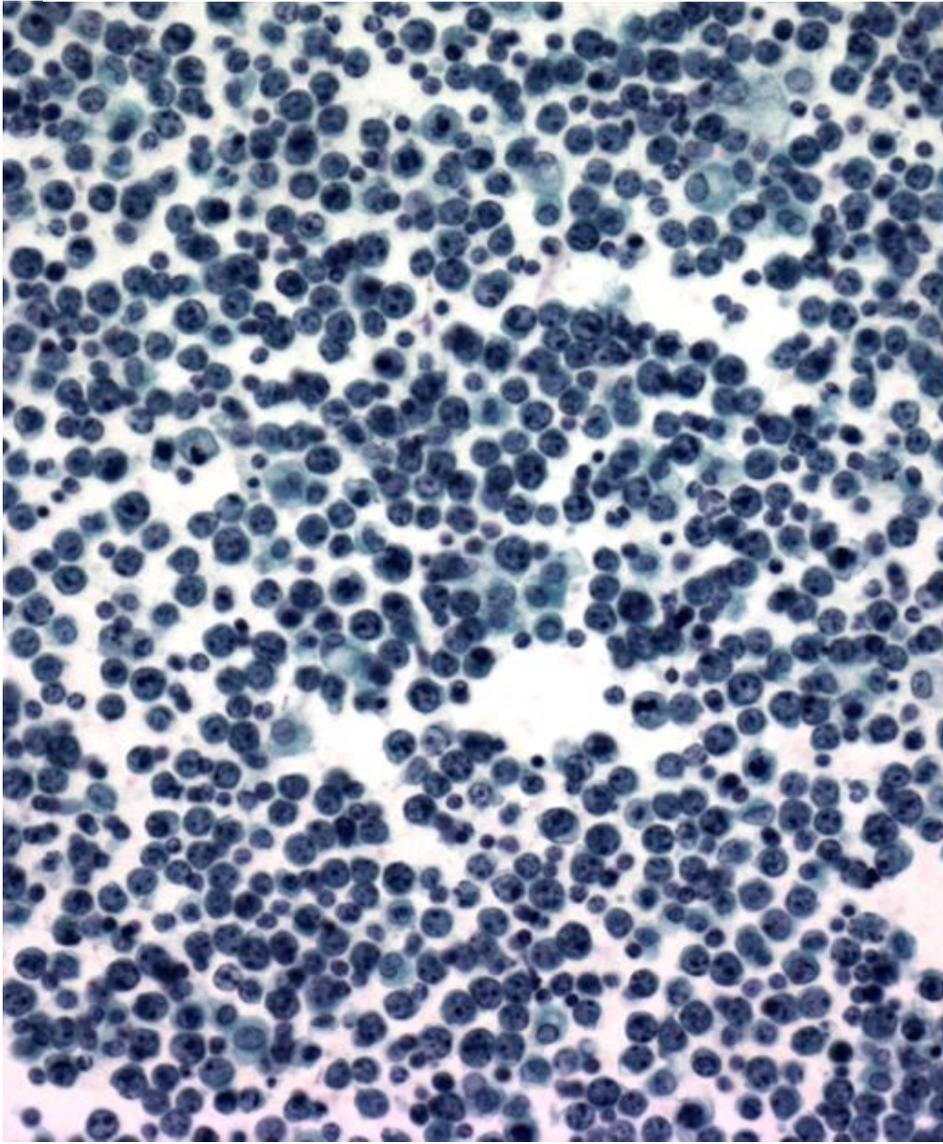
- Serous carcinoma
- Serous borderline tumour
- Mesothelioma
- (Papillary ADC lung)
- (Papillary thyroid CA)
- *Psammoma bodies in peritoneum:*
in 1/3 benigne



Single cell pattern



DLBCL

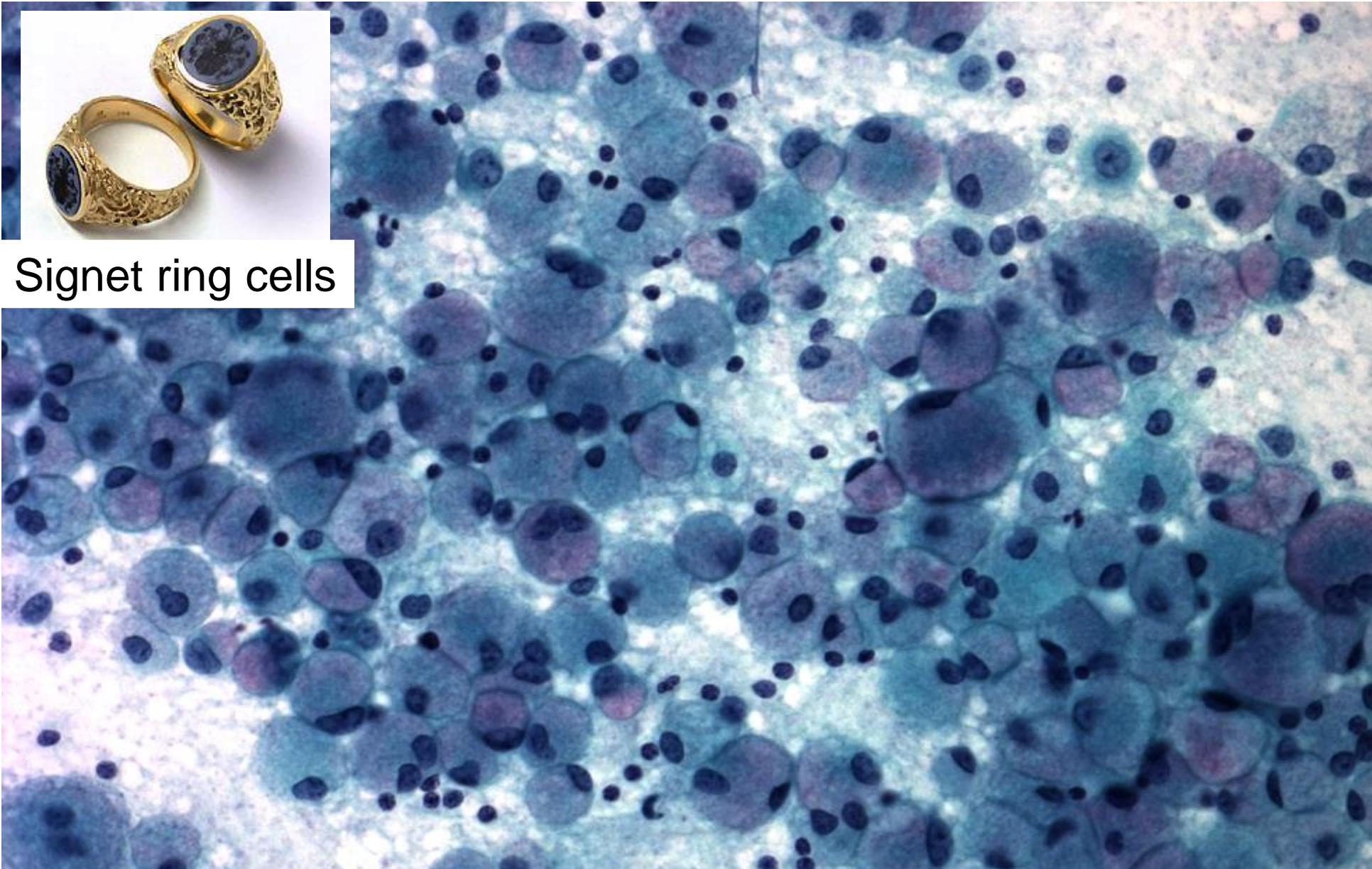


CD 20

Adenocarcinoma with signet ring cells



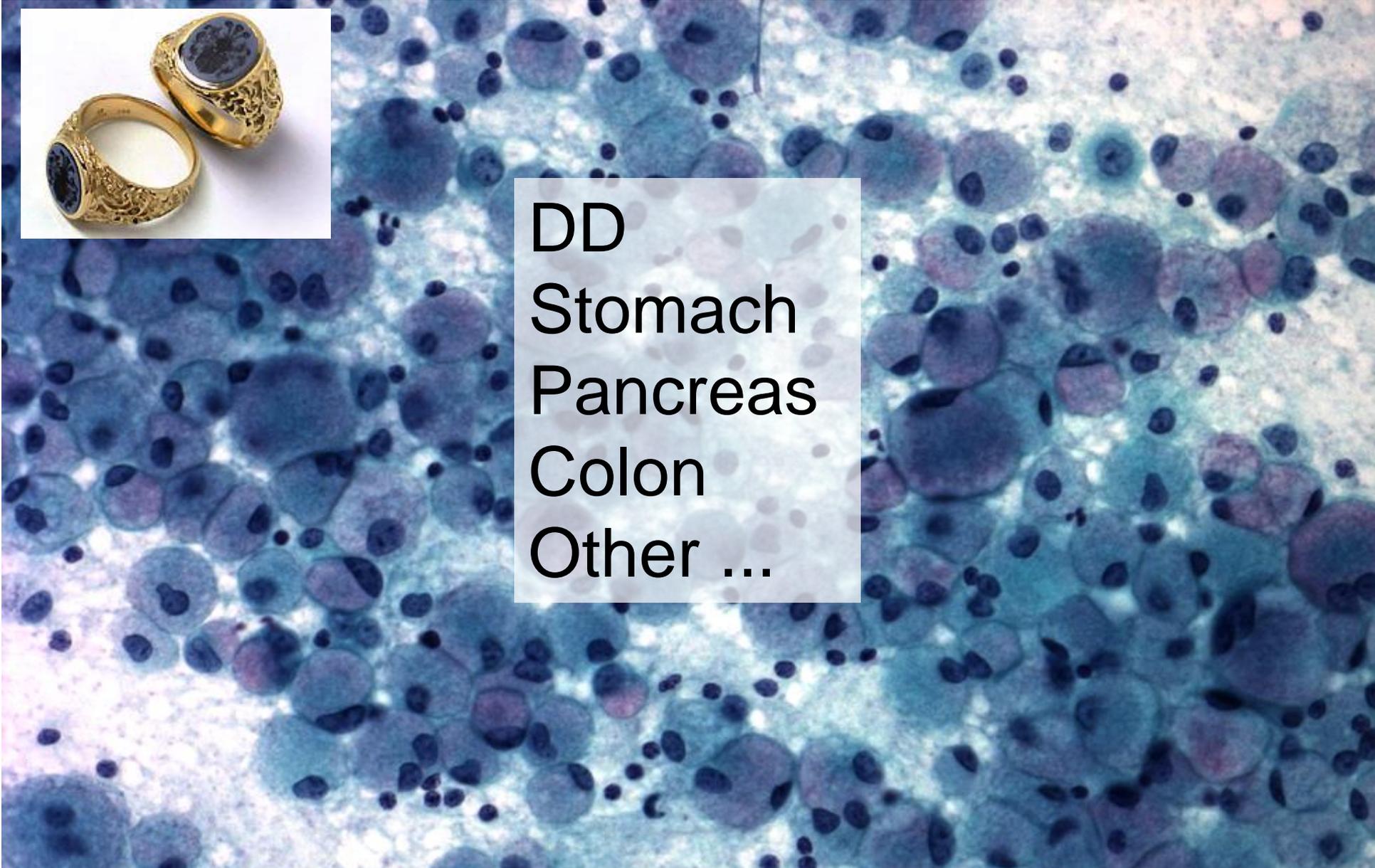
Signet ring cells



Adenocarcinoma with signet ring cells



DD
Stomach
Pancreas
Colon
Other ...



Summery: Part 1

- Malignant effusions are common and encompass a wide variety of malignant neoplasms
- Always consider clinical history and presentation
- Leading sources of malignant pleural effusions
 - Adenocarcinomas of lung and breast
 - Ancillary ICC
- Malignant cells are usually readily recognized as a foreign population
 - **Cave** breast cancer, malignant mesothelioma

