11th Annual CAP-ACP Annual Residents Review Course

Thoracic Pathology Review

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Learning Objectives

- At the end of the session, the participants will be able to:
  - Differentiate the common subtypes of lung carcinomas according to the 2015 WHO classification
  - Identify the most common types of interstitial lung disease
  - Have an approach to diagnosing suspicious pleural lesions
  - Discuss the differential diagnosis of anterior mediastinal tumours

Disclosures

- I have the following financial relationships to disclose:
  - Bayer, Novartis, Roche (Honoraria for consulting or speaking engagements)
  - Novartis, Amgen (Advisory Boards)
  - Novartis, Astra-Zeneca, Boehringer-Ingelheim, Merck, Takeda (Grants)

- I will not discuss off label use and/or investigational use in my presentation.

Learning Objectives

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  - Recognize the most common types of interstitial lung disease
  - Have an approach to diagnosing suspicious pleural lesions
  - Discuss the differential diagnosis of anterior mediastinal tumours

Lung tumours

- Classification
  - Primary pulmonary neoplasms
    - 2015 WHO Classification

  - Metastatic tumours
    - Common metastases to the lungs include
      - > Colorectal adenocarcinoma
      - > Renal cell carcinoma
      - > Sarcomas (various sites of origin)
      - > Melanoma (various sites of origin)

Lung Cancers

- Carcinomas
  - Adenocarcinoma
  - Squamous cell carcinoma
  - Neuroendocrine tumours
  - Large cell (undifferentiated) carcinoma
  - Other (uncommon) subtypes

- Other cancers
  - Sarcomas
  - Lymphomas
  - Metastatic

Lung Adenocarcinoma

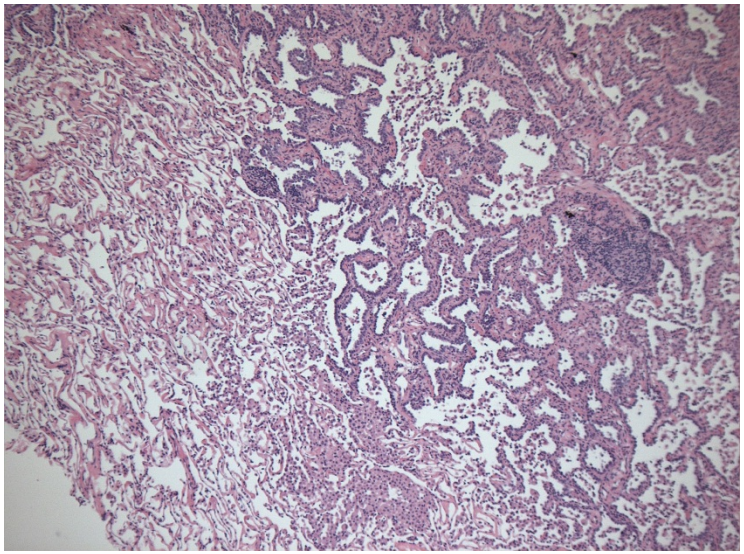
- Adenocarcinoma in situ (≤3.0 cm, no invasion)
- Minimally invasive ADC (≤3.0 cm, with ≤0.5 cm invasion)
- Invasive ADC (>0.5 cm invasive components)
  - Lepidic (≤3.0 cm + >0.5 cm invasion; or >3.0 cm total size)
  - Acinar
  - Papillary
  - Solid
  - Micropapillary
  - Others (e.g. invasive mucinous adenocarcinoma)

- IHC: Typically TTF-1 & Napsin A positive (~80% of cases)

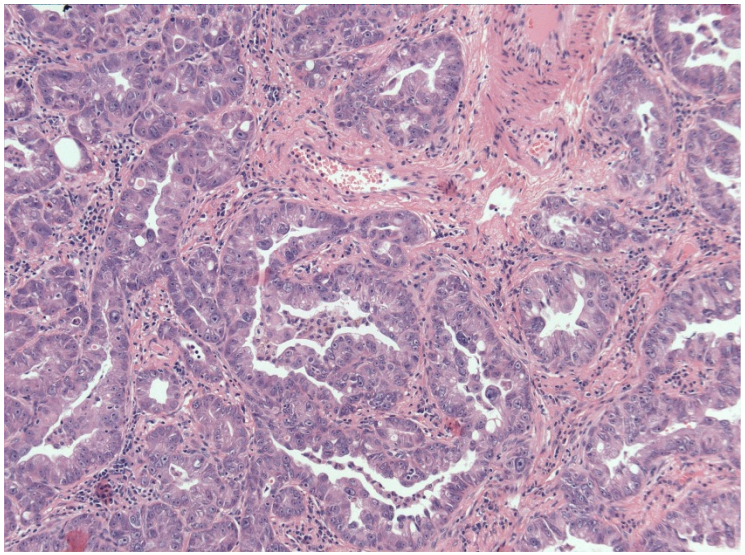
Lung Adenocarcinoma

- Subtypes

Lepidic

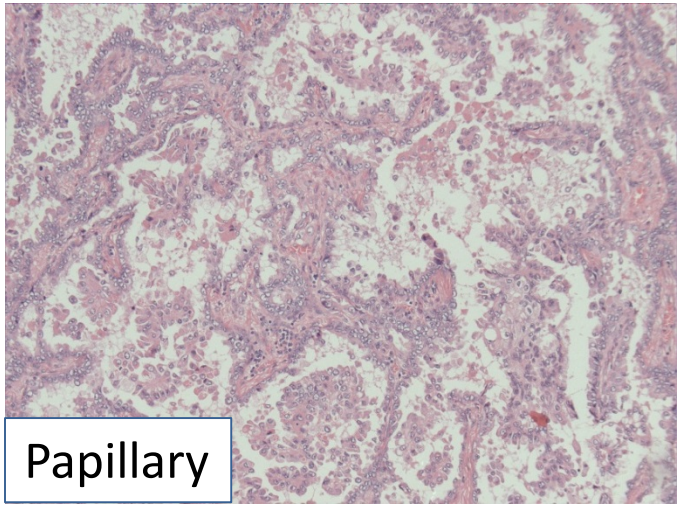


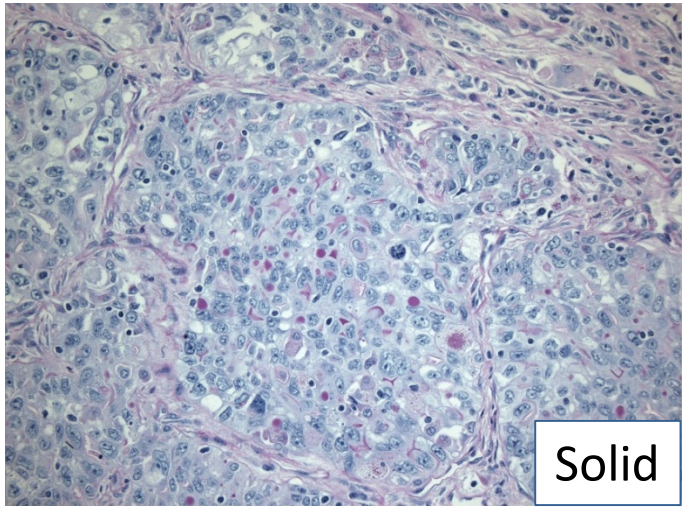
Acinar

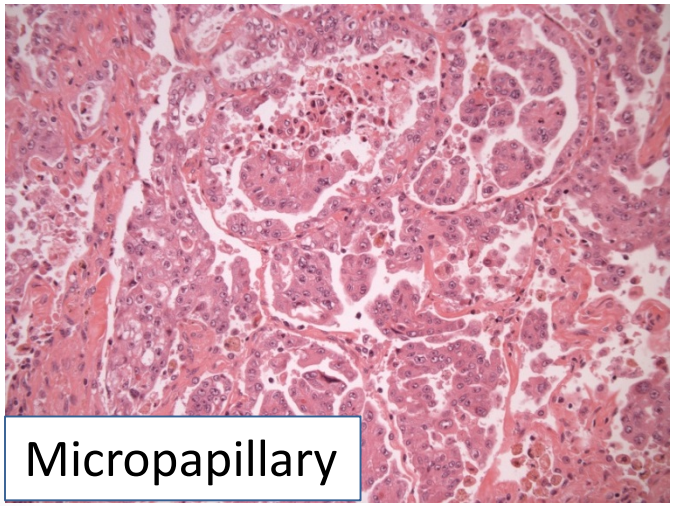


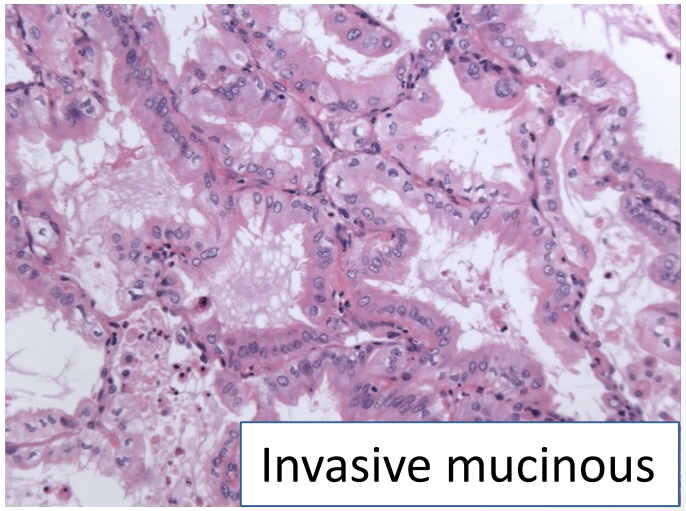
Lung Adenocarcinoma

- Subtypes


Papillary

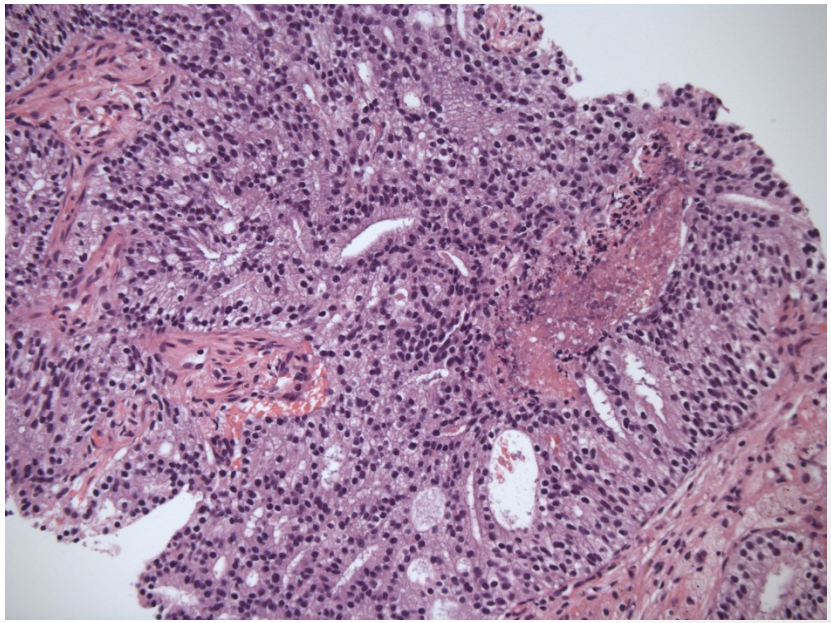

Solid


Micropapillary


Invasive mucinous

Adenocarcinomas

- Remember metastases!
  - History (previous/concurrent malignancy/mass)
  - Imaging
    - Multiple rounded nodules
    - Lymphangitic carcinomatosis pattern
  - Morphology
    - **Mets may sometimes show lepidic growth**
  - IHC, where appropriate
    - (e.g. TTF1-neg tumors)



Lung Adenocarcinoma Staging
Invasive size matters in 8th ed. TNM!!

- For invasive adenocarcinomas, staging of lung ADC in 8th ed. TNM is based on invasive tumor size

Size (cm)*	7th edition*	8th edition**
<1 cm	T1a	T1a
>1 cm to ≤2 cm		T1b
>2 to ≤3cm	T1b	T1c
>3 to ≤4 cm	T2a	T2a
>4 to ≤5 cm		T2b
>5 to ≤7 cm	T2b	T3
>7 cm	T3	T4

*Total size used in 7th edition

**Invasive tumor size used in 8th edition

Lung Adenocarcinoma Staging
Invasive size matters in 8th ed. TNM!!

- For invasive adenocarcinomas, staging of lung ADC in 8th ed. TNM is based on invasive tumor size
  - Direct measurement of invasive component on histologic slides (MIA's and smaller invasive tumors)

OR

  - Estimated invasive size by multiplying proportion of invasive (non-lepidic) histologic components by the total tumor size
    - e.g. 6.0 cm tumor with 40% acinar, 20% papillary, 10% solid, 30% lepidic
      - Invasive tumor size ~ (0.40 + 0.20 + 0.10) * 6.0 cm = 4.2 cm (pT2b, 8th ed. TNM)

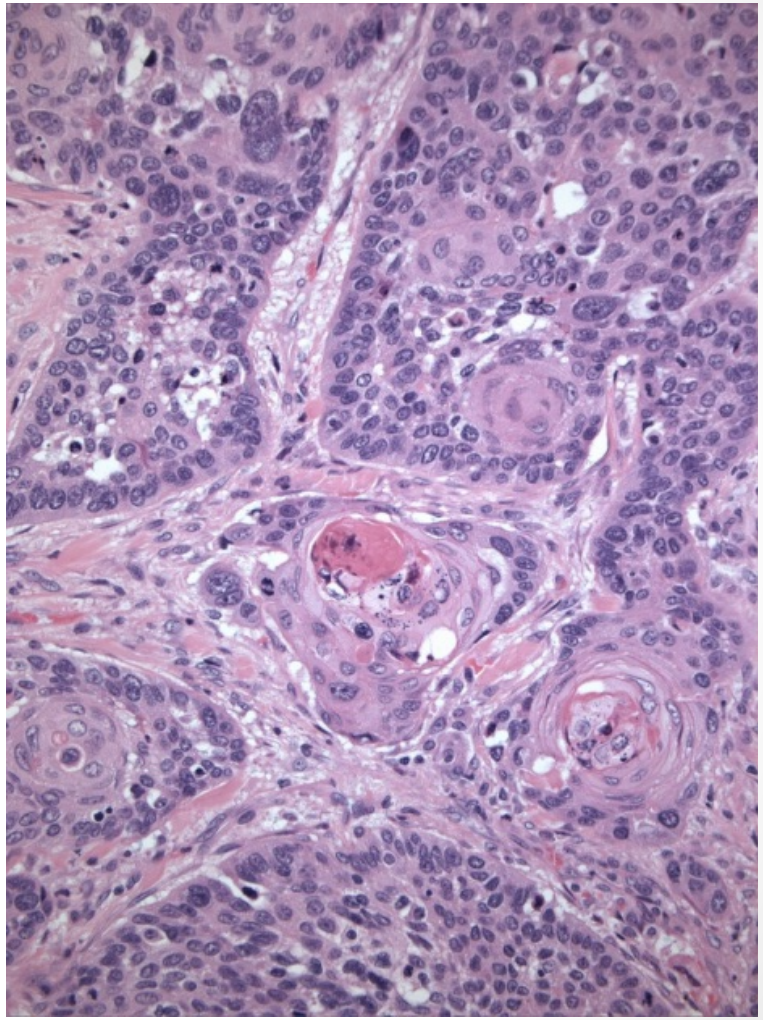
Lung Adenocarcinoma

- Predictive biomarkers for precision medicine
  - EGFR mutations (exons 18-21) – response to EGFR TKIs
    - Activating: exon 19 deletions; L858R (exon 21); others
    - Resistance: T790M, C797S (exon 20)
  - ALK gene rearrangements – response to ALK TKIs
    - IHC testing using 5A4 or D5F3 antibodies
  - PD-L1 IHC – response to PD-1/PD-L1 inhibitors
    - Multiple different antibodies used for different inhibitors
  - Others, including
    - KRAS, BRAF, HER2 mutations
    - ROS1, RET rearrangements
    - MET exon 14 skipping

Squamous cell carcinoma

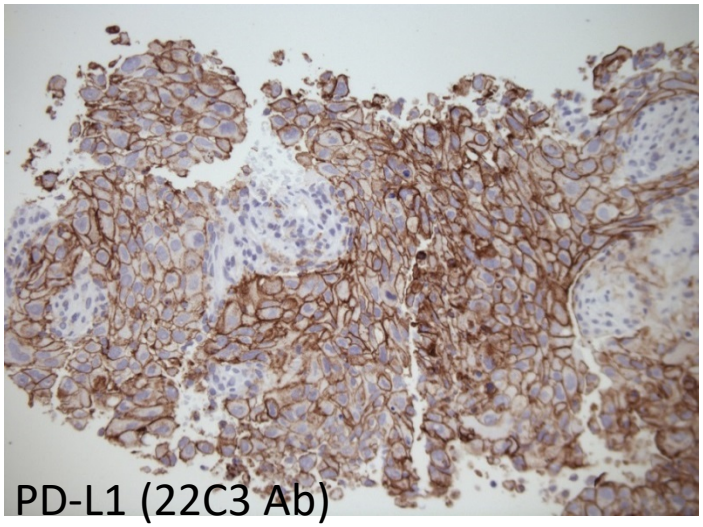
- Keratinizing SqCC
- Non-keratinizing SqCC
- Basaloid SqCC

- IHC:
  - P63/P40-positive
  - TTF-1/Napsin negative
  - No IHC to reliably differentiate primary lung vs. metastatic SqCC



Squamous cell carcinoma

- Predictive biomarker testing
  - PD-L1 IHC – response to PD-1/PD-L1 inhibitors
    - Multiple different antibodies used for different inhibitors



PD-L1 (22C3 Ab)

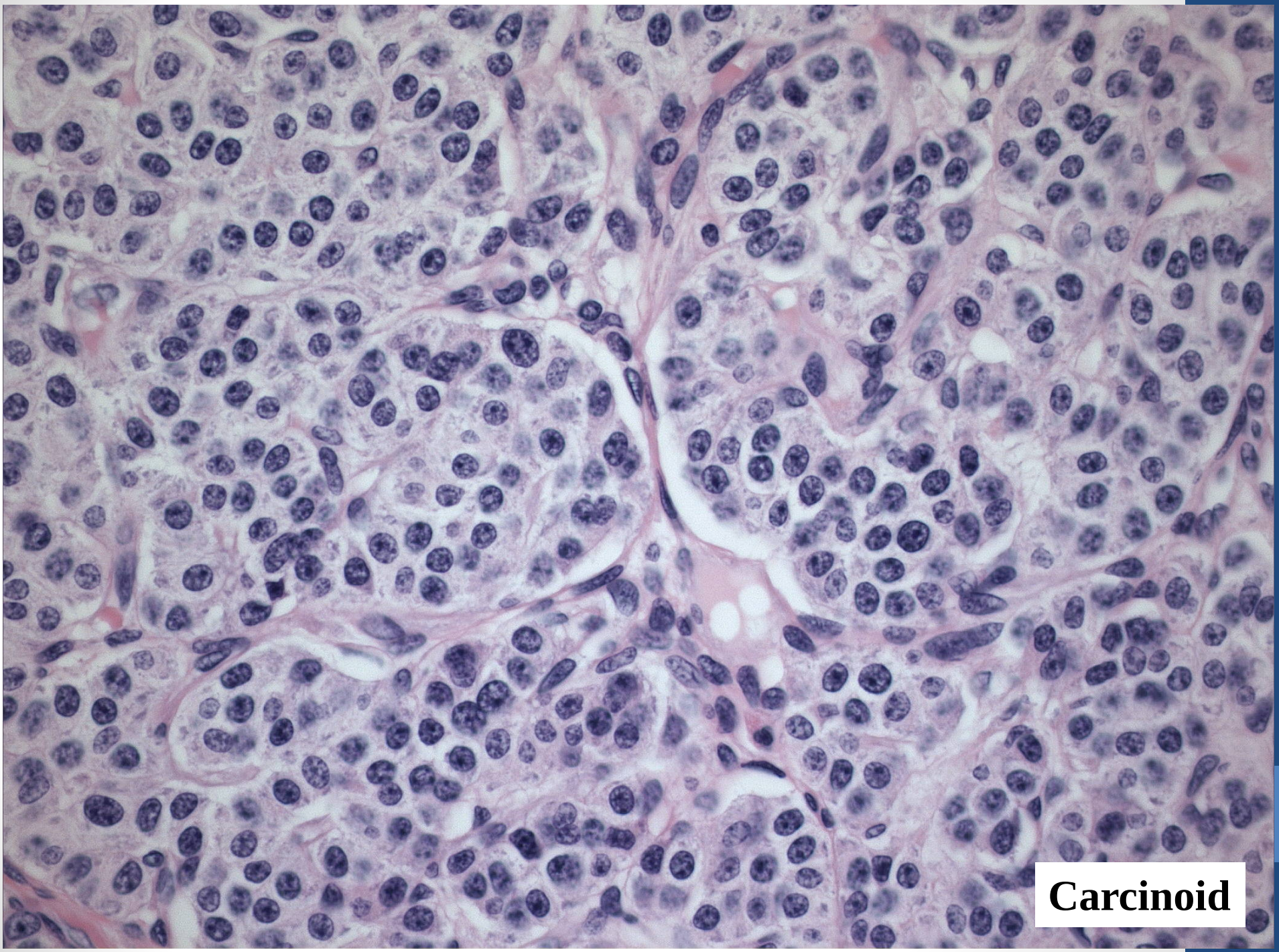
  - Currently no predictive molecular diagnostics tests for pulmonary squamous cell carcinoma

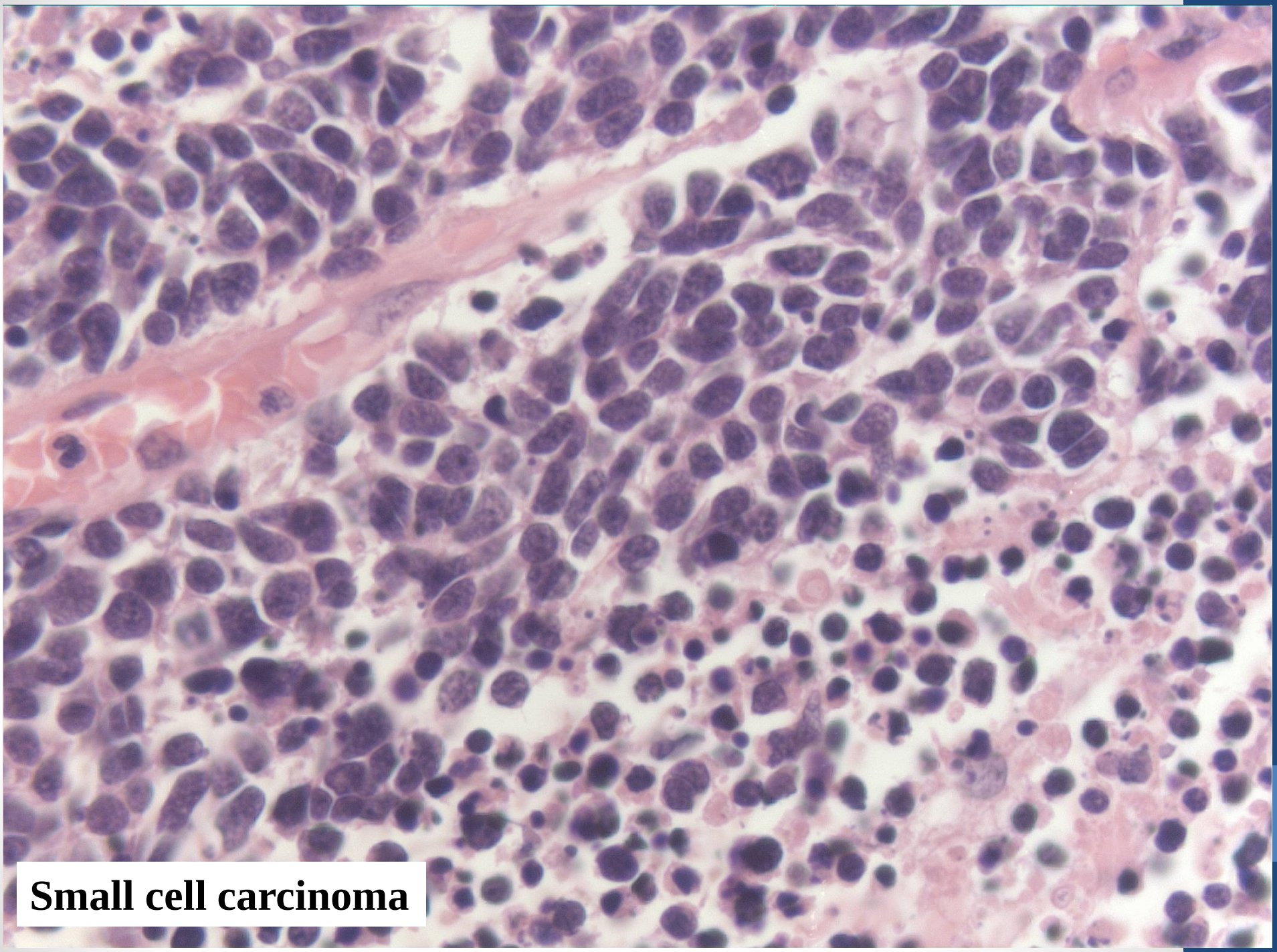
Large Cell Carcinoma

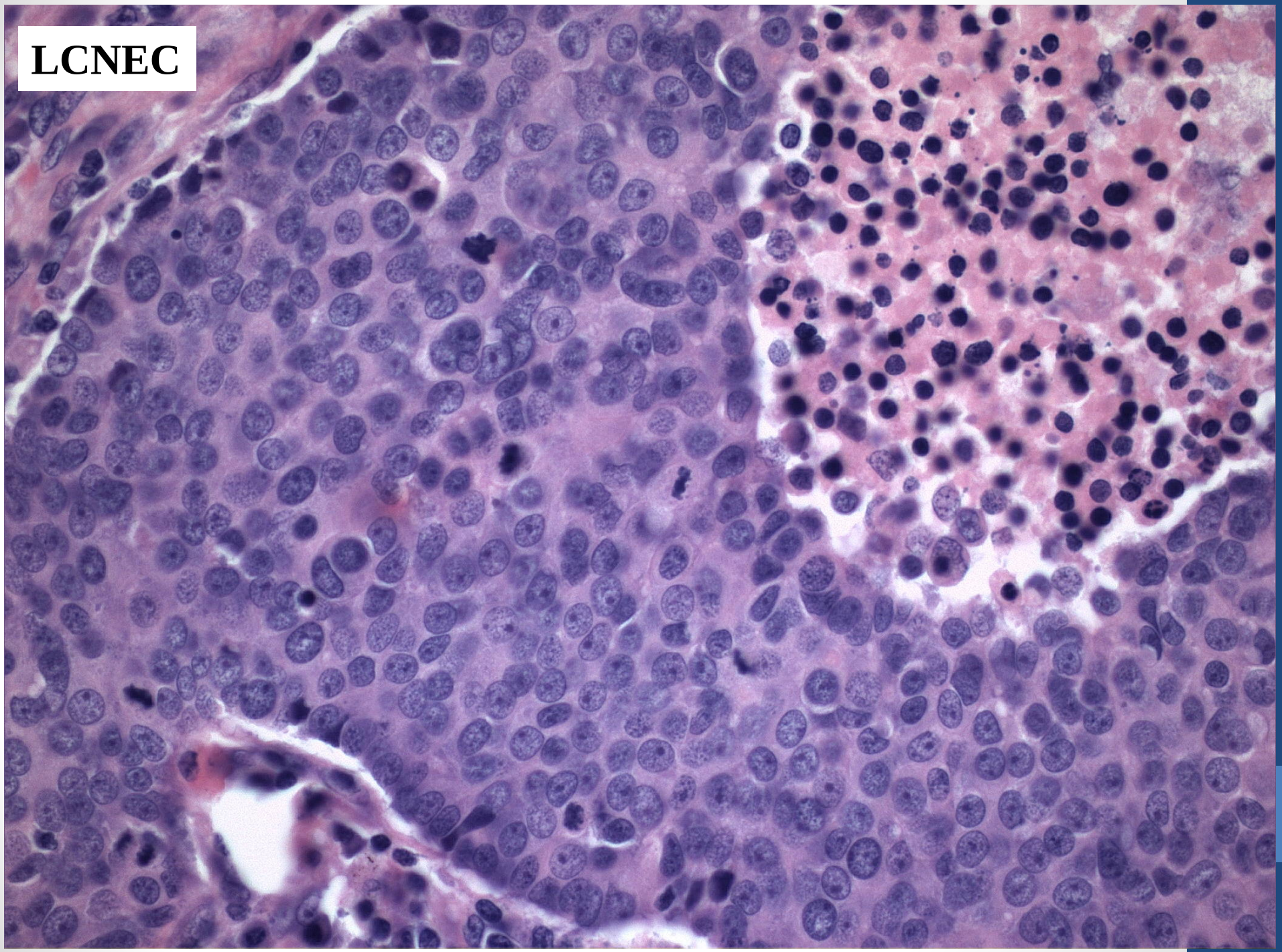
- An undifferentiated non-small cell carcinoma
  - Lacking morphologic & immunohistochemical features of squamous, glandular, or neuroendocrine differentiation
  - Large cell carcinoma designation reserved for resected tumors
    - In small biopsy material, report as non-small cell carcinoma
  - Molecular profile more similar to poorly differentiated lung adenocarcinomas
    - Warrants lung adenocarcinoma biomarker profiling

Neuroendocrine tumours

- Low grade:
  - Typical carcinoid (>0.5cm; <2mitoses/2 mm^2; no necrosis)
- Intermediate grade:
  - Atypical carcinoid (2-10 mitoses/2 mm^2 or necrosis)
- High grade:
  - Small cell carcinoma (DDx: lymphoma, basaloid squamous)
  - Large cell neuroendocrine carcinoma
  - Combined high grade NE carcinoma

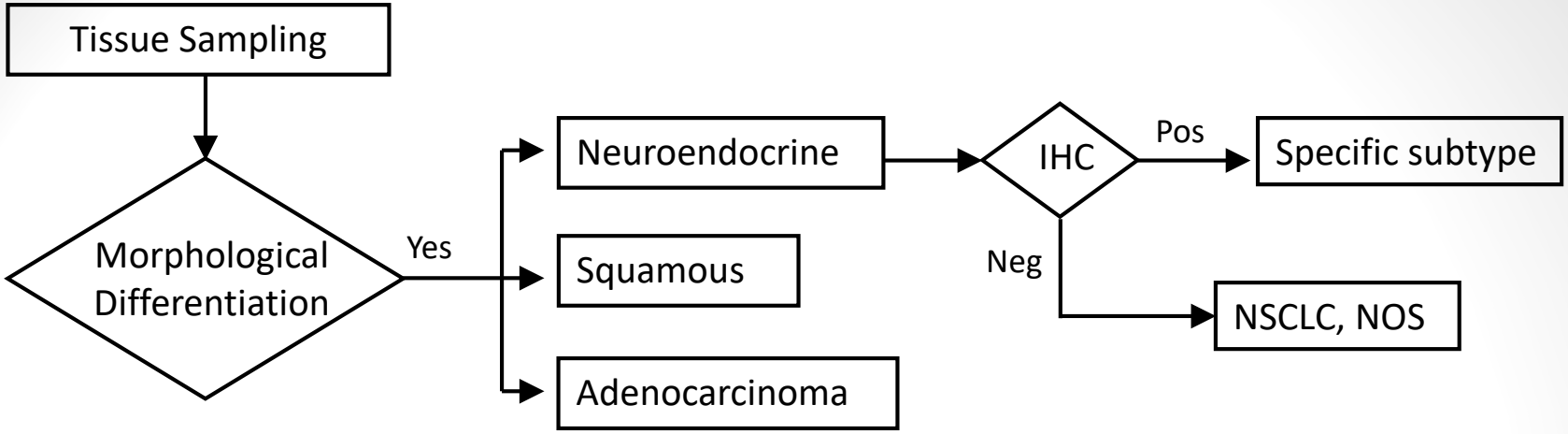

Carcinoid

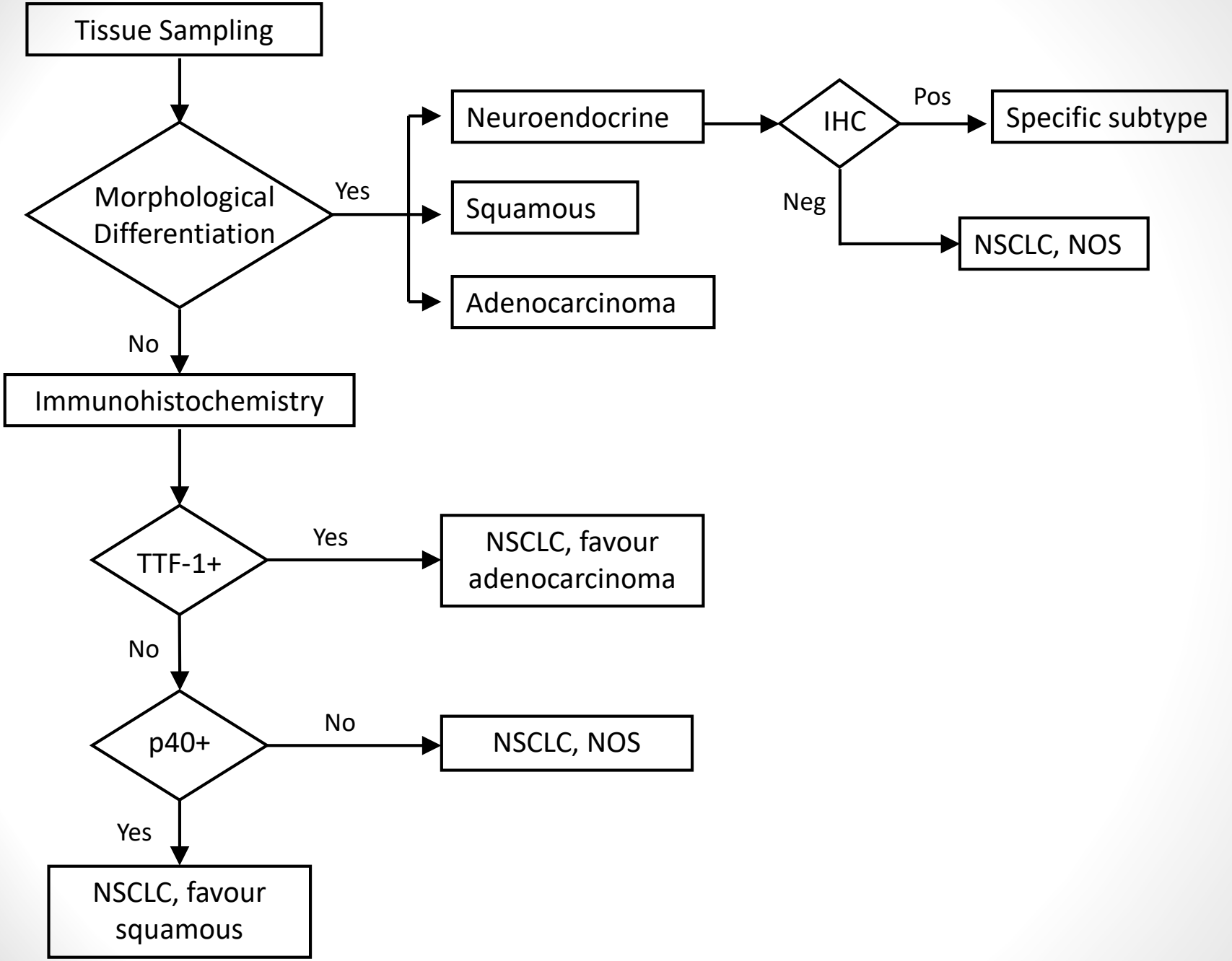

Small cell carcinoma


LCNEC

Lung Cancer Diagnosis in Biopsy Material

- In small biopsies, when morphologic features aren't definitive, a ***limited*** panel of IHC is indicated
  - TTF-1 & P40/P63
    - TTF-1-positive (with or without P40/P63 staining) → "*Non-small cell carcinoma, favour adenocarcinoma*"
    - P40/P63-positive, TTF-1-negative → "*Non-small cell carcinoma, favour squamous cell carcinoma*"
    - P40/P63 & TTF-1-negative → "*Poorly differentiated non-small cell carcinoma*"
      - 'Large cell carcinoma' – reserved for resection specimens


Tissue Sampling
Morphological Differentiation
Yes
Neuroendocrine
Squamous
Adenocarcinoma
IHC
Pos
Specific subtype
Neg
NSCLC, NOS


Tissue Sampling
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Neuroendocrine
IHC
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Specific subtype
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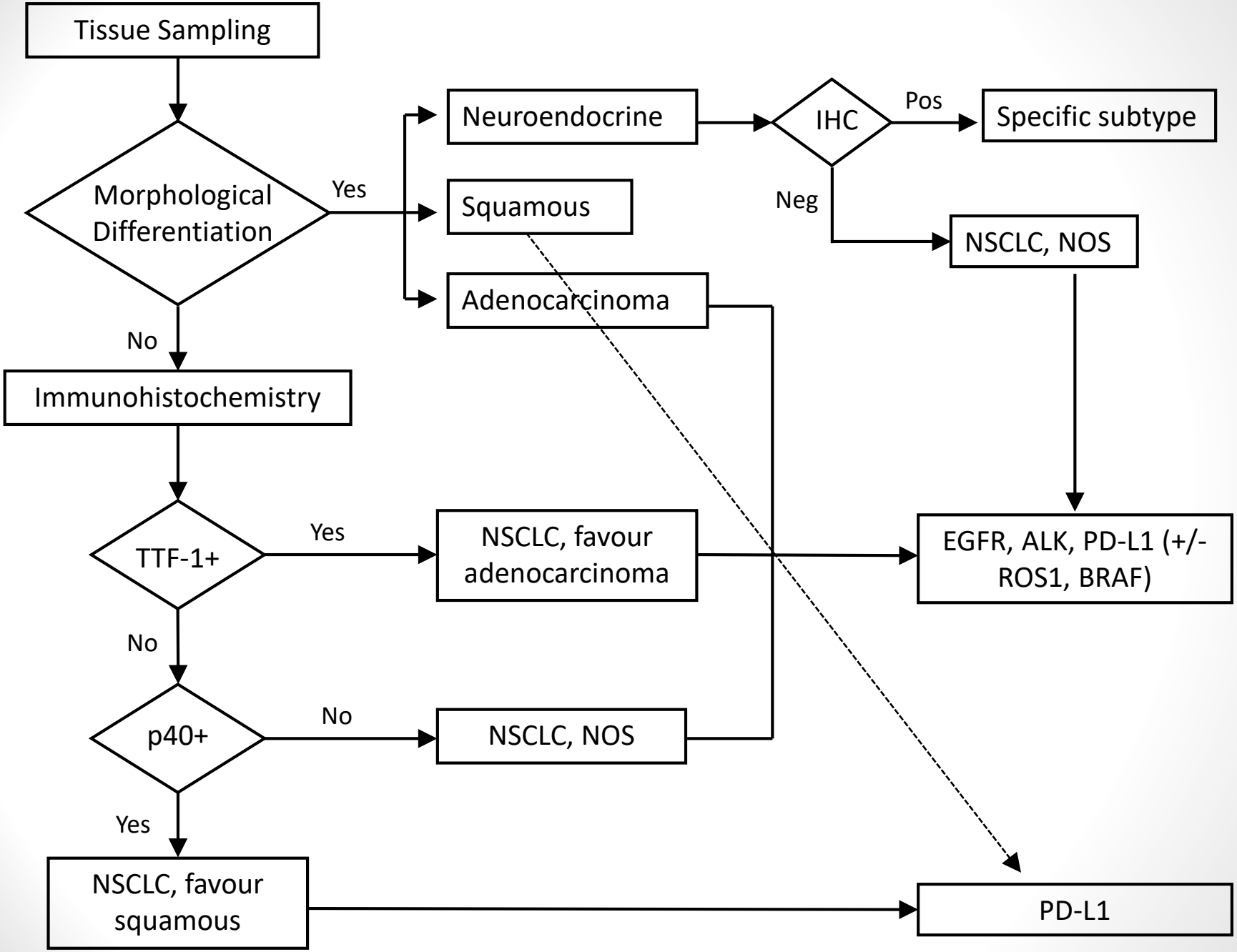
NSCLC, NOS
Squamous
Adenocarcinoma
No
Immunohistochemistry
TTF-1+
Yes
NSCLC, favour adenocarcinoma
No
p40+
No
NSCLC, NOS
Yes
NSCLC, favour squamous


Tissue Sampling
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Specific subtype
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NSCLC, NOS
Adenocarcinoma
No
Immunohistochemistry
TTF-1+
Yes
NSCLC, favour adenocarcinoma
EGFR, ALK, PD-L1 (+/- ROS1, BRAF)
No
p40+
No
NSCLC, NOS
Yes
NSCLC, favour squamous
PD-L1

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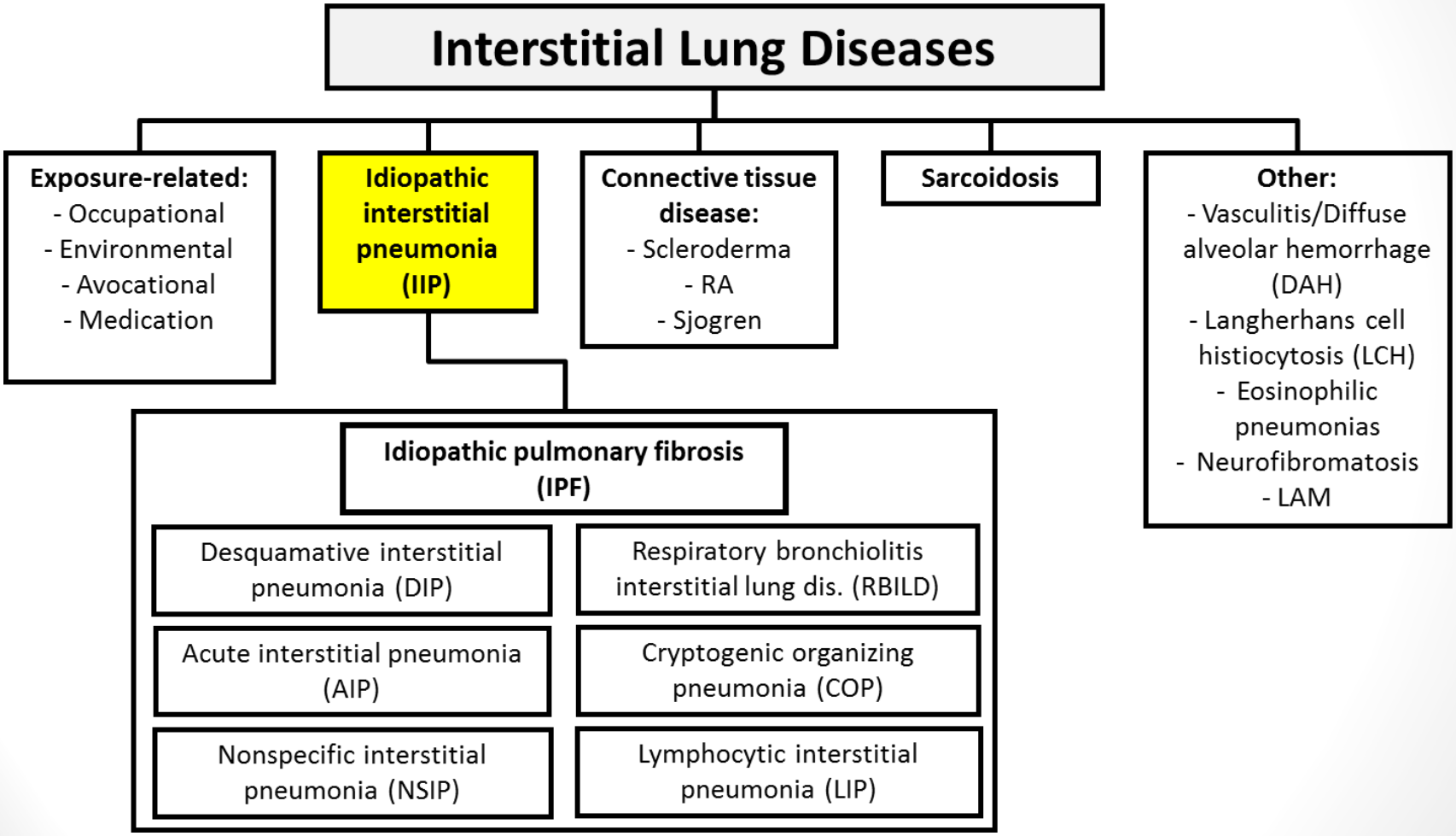
Non-Neoplastic Lung Disease

- General considerations
  - Typically dealing with ***patterns*** of histologic change, for example…
    - Interstitial fibrosis +/- honeycomb change
    - Interstitial inflammation
    - Organizing pneumonia
    - Alveolar macrophage accumulation
    - Granulomas
  - A single ***pattern*** may be present in multiple different conditions
  - Multiple patterns may be present in a single condition

Non-Neoplastic Lung Disease

- General considerations
  - Diagnosis of non-neoplastic lung disease is informed by clinical, radiologic, and pathologic findings
    - Importance of multidisciplinary approach
    - Etiology often not discernible histologically
      - Multiple etiologies may give rise to similar histopathologic findings
        - e.g. hypersensitivity pneumonitis vs. drug toxicity
    - ***Connective tissue diseases can result in any pattern (except RB-ILD?), or mixed patterns***

Non-Neoplastic Lung Disease



Am J Respir Crit Care Med 2002;165:277–304.

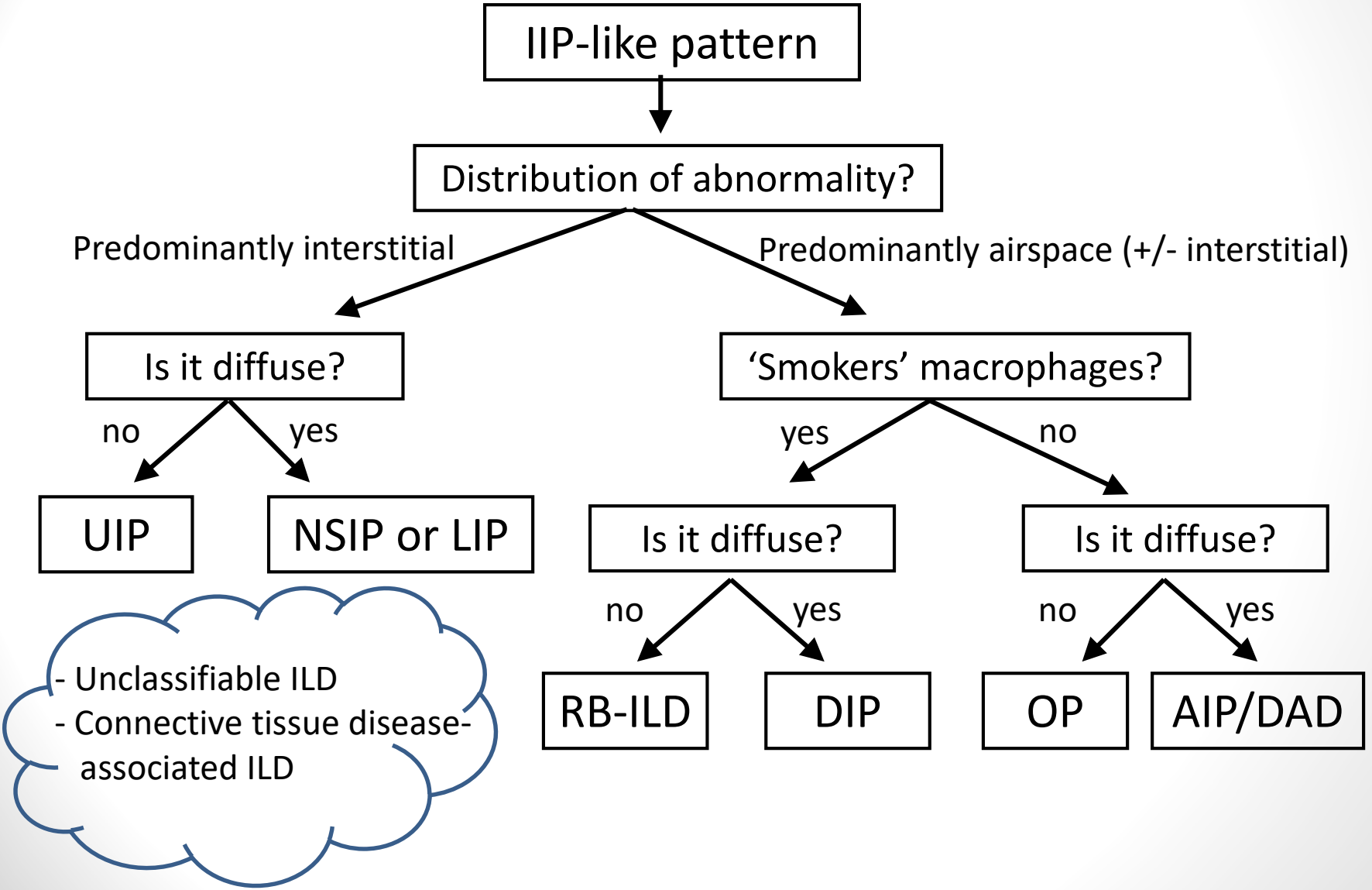
Idiopathic Interstitial Pneumonias

- Clinical Diagnosis vs. Histologic Patterns

Clinical-Radiologic-Pathologic *Diagnosis*	**Histologic *Pattern***
Idiopathic pulmonary fibrosis (IPF/UIP)	Usual interstitial pneumonia (UIP)
Non-specific interstitial pneumonia (NSIP)	Non-specific interstitial pneumonia (NSIP)
Cryptogenic organizing pneumonia (COP)	Organizing pneumonia (OP)
Acute interstitial pneumonia (AIP)	Diffuse alveolar damage (DAD)
Respiratory bronchiolitis interstitial lung disease (RB-ILD)	Respiratory bronchiolitis (RB)
Desquamative interstitial pneumonia (DIP)	Desquamative interstitial pneumonia (DIP)
Lymphocytic interstitial pneumonia (LIP)	Lymphocytic interstitial pneumonia (LIP)

Idiopathic Interstitial Pneumonias

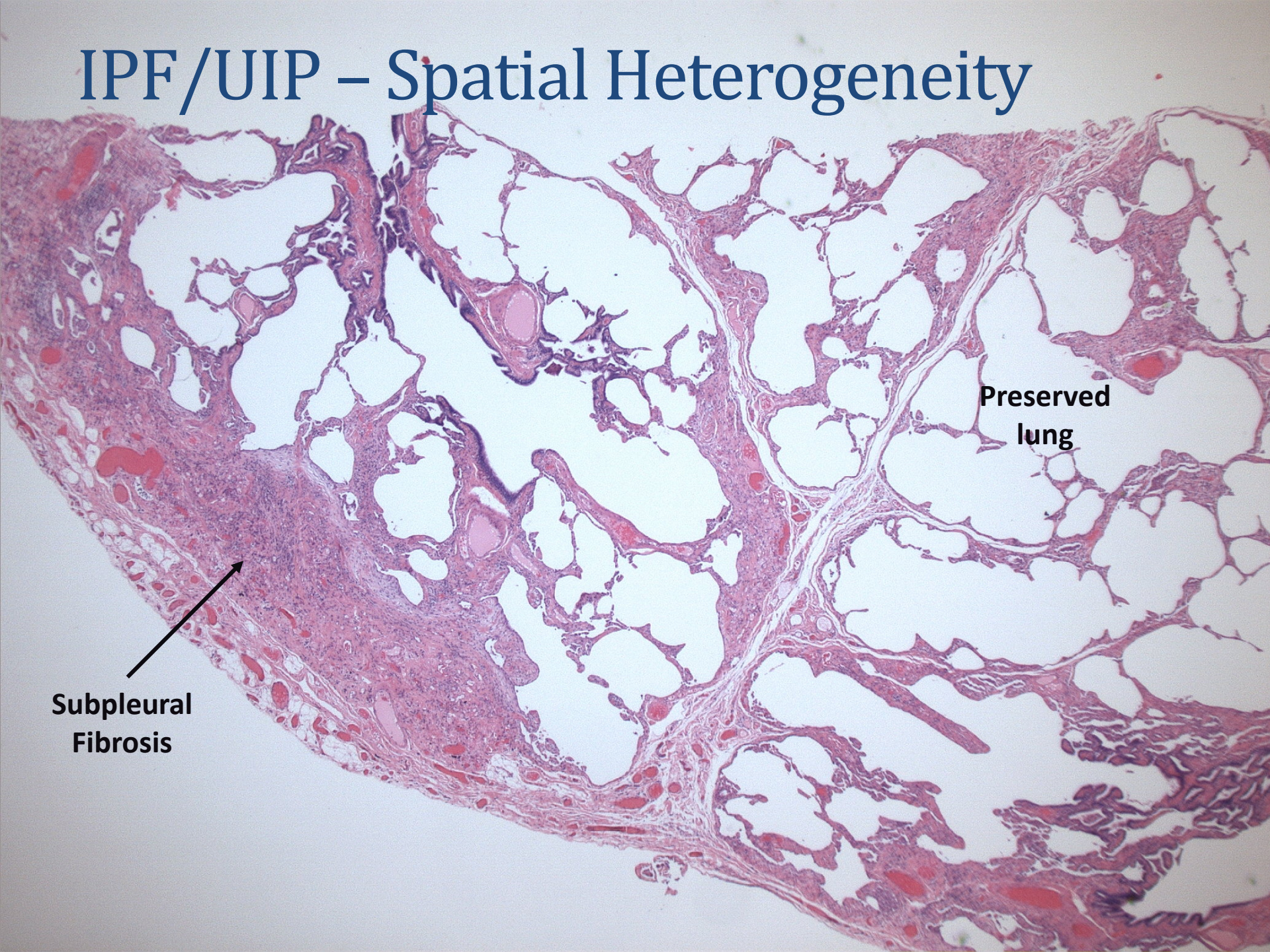
A (Very) Basic Approach



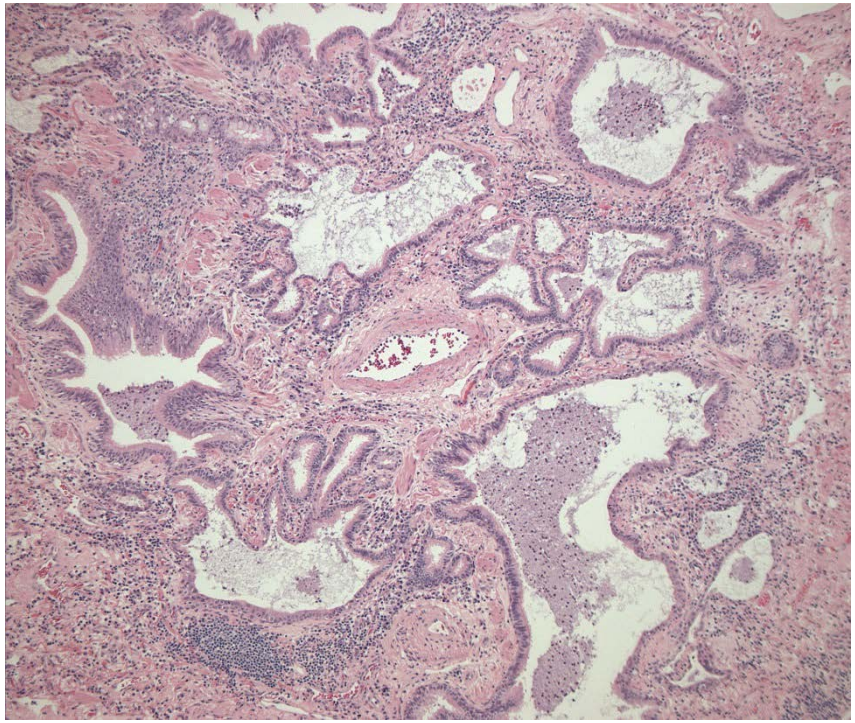
IPF/UIP

- Idiopathic Pulmonary Fibrosis (IPF) / Usual Interstitial Pneumonia (UIP)
  - ***Spatial heterogeneity*** of interstitial fibrosis
    - ***Patchy*** fibrosis admixed with normal/less fibrotic lung
    - Peripheral/subpleural predominance of fibrosis
    - Lower lung zones > upper lung zones
  - ***Temporal heterogeneity*** of fibrosis
    - End-stage fibrosis (microscopic honeycomb change) and
    - Active fibrosis (fibroblastic foci)

IPF/UIP – Spatial Heterogeneity

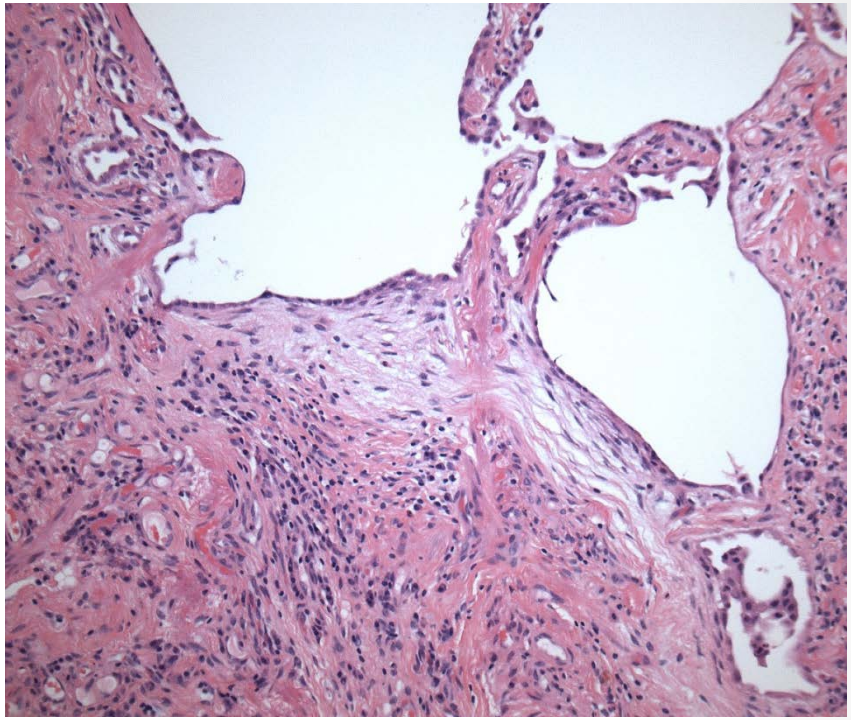


IPF/UIP – Temporal Heterogeneity



Microscopic honeycomb change

- Dense interstitial fibrosis with destruction/ remodeling of parenchymal architecture
- Cystic changes with epithelial peribronchiolar metaplasia
- +/- smooth muscle metaplasia



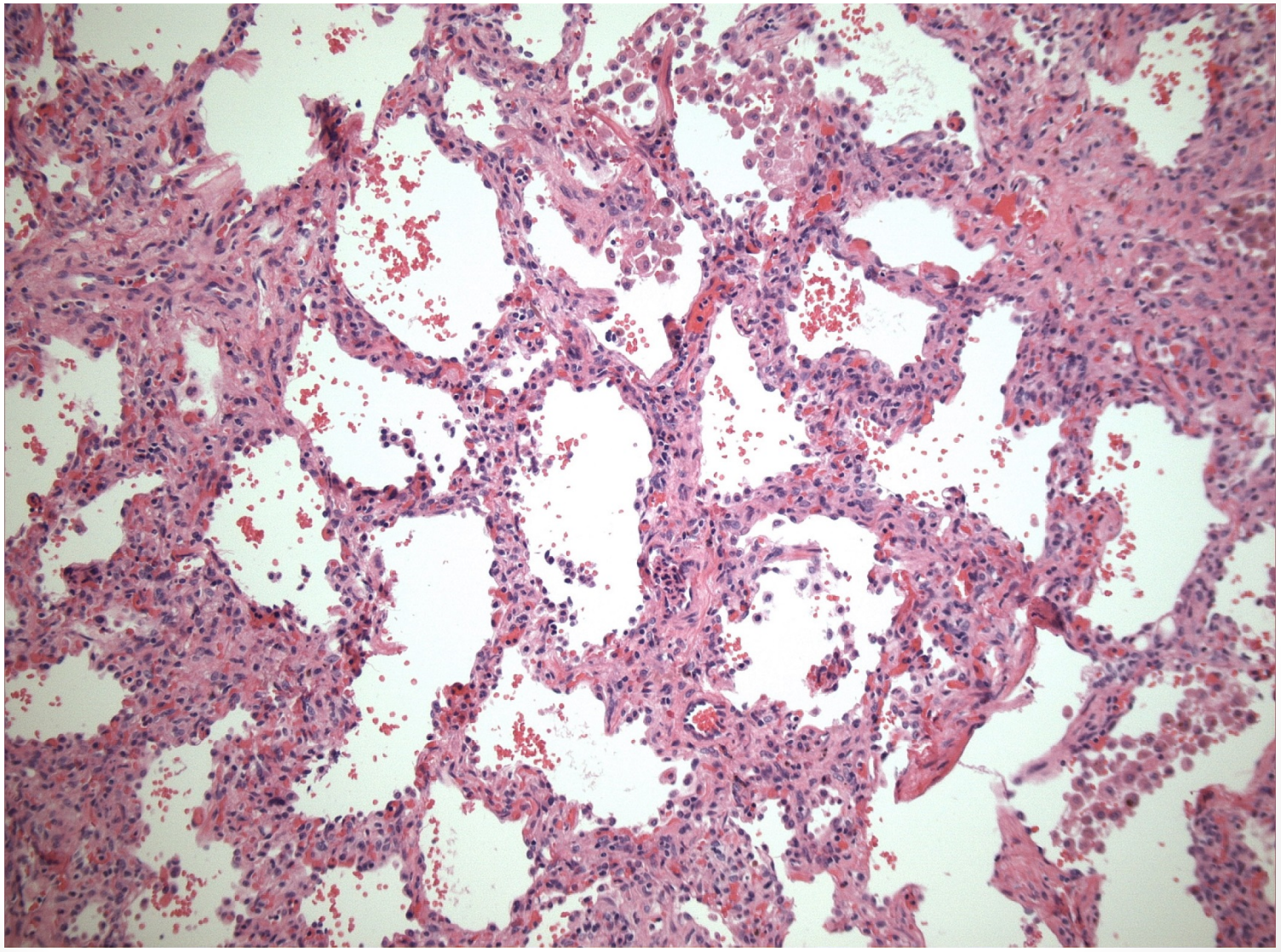
Fibroblastic foci

- Areas of fibroblastic proliferation suggestive of “active” fibrosis
- Often present at interface of fibrotic and preserved lung tissue

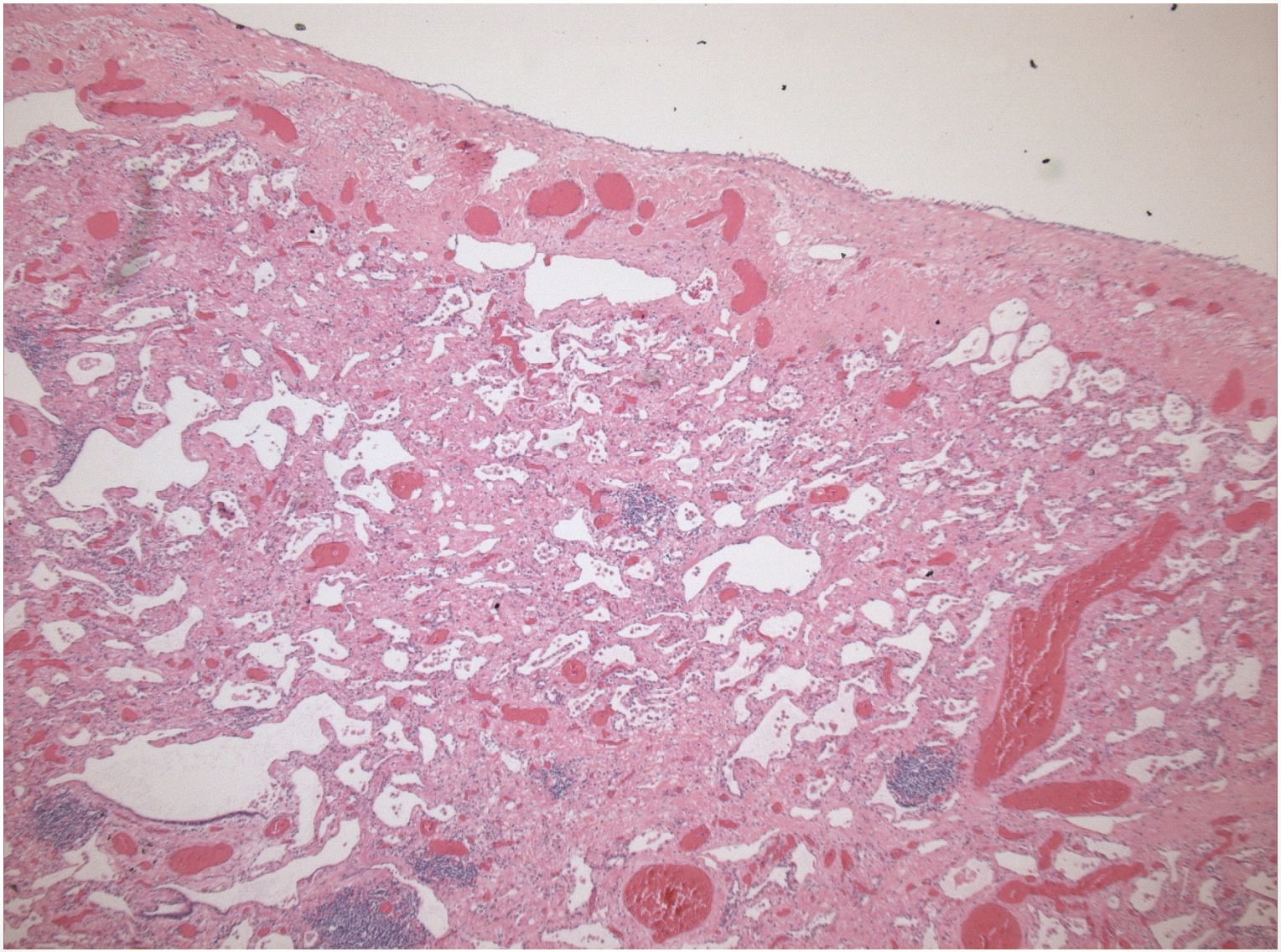
NSIP

- Non-Specific Interstitial Pneumonia (NSIP)
  - (Generally) diffuse interstitial inflammation and/or fibrosis
    - +/- foci of organizing pneumonia
  - Without destruction/remodeling of the underlying lung parenchymal architecture (as in UIP)
  - Subtypes
    - Cellular NSIP – predominantly inflammation
    - Fibrotic NSIP – predominantly fibrosis
    - Mixed NSIP

Cellular NSIP



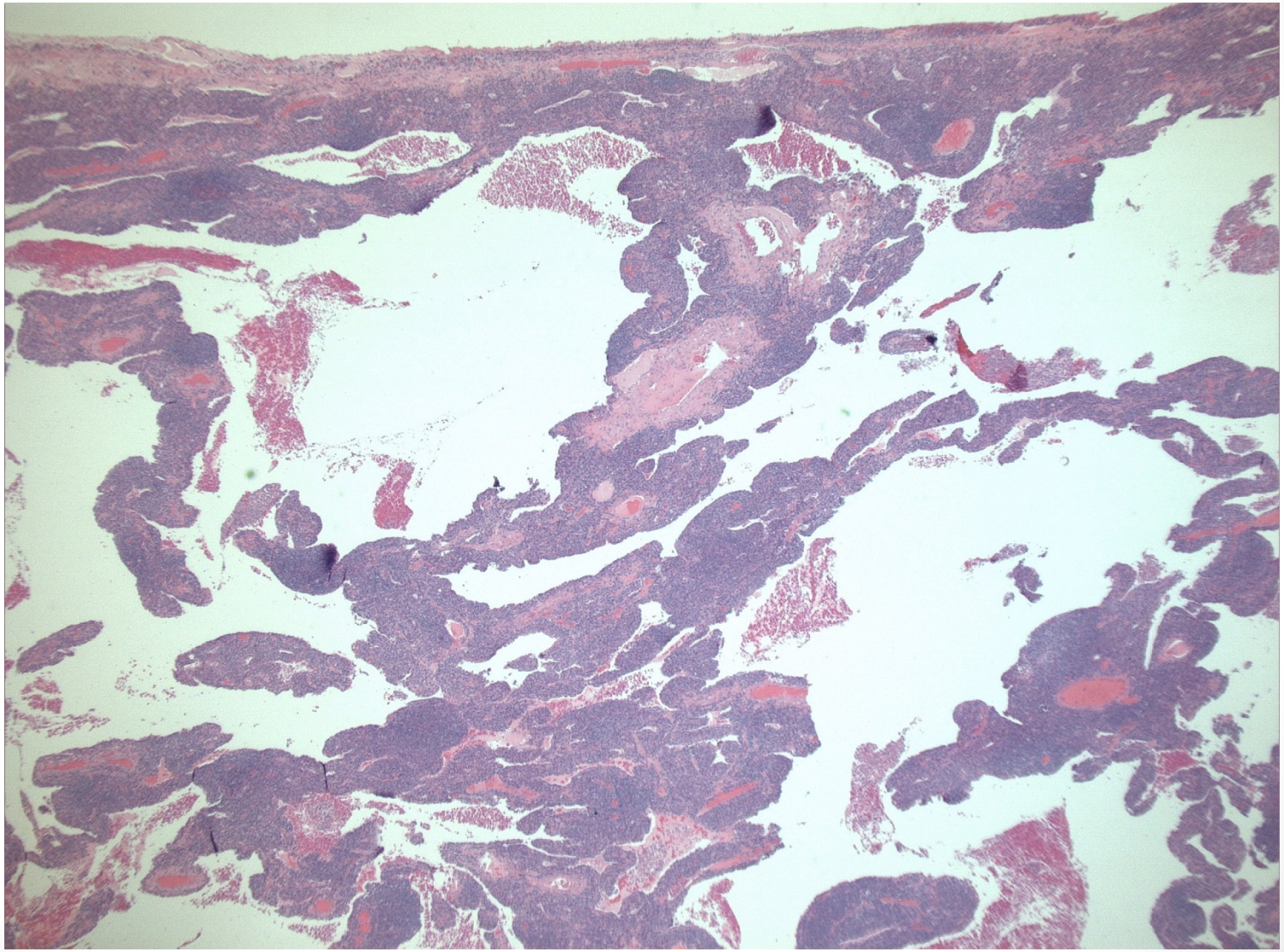
Fibrotic NSIP



LIP

- Lymphocytic Interstitial Pneumonia (LIP)
  - Pronounced, diffuse alveolar septal lymphoid infiltrates
    - Overlaps with cellular NSIP, but much more pronounced infiltrates
    - Often prominent lymphoid follicles
  - Truly idiopathic LIP is very rare
    - Most cases of LIP-pattern disease are secondary to
      - Connective tissue disease
      - Immunodeficiency states
      - Lymphoma (occasionally)

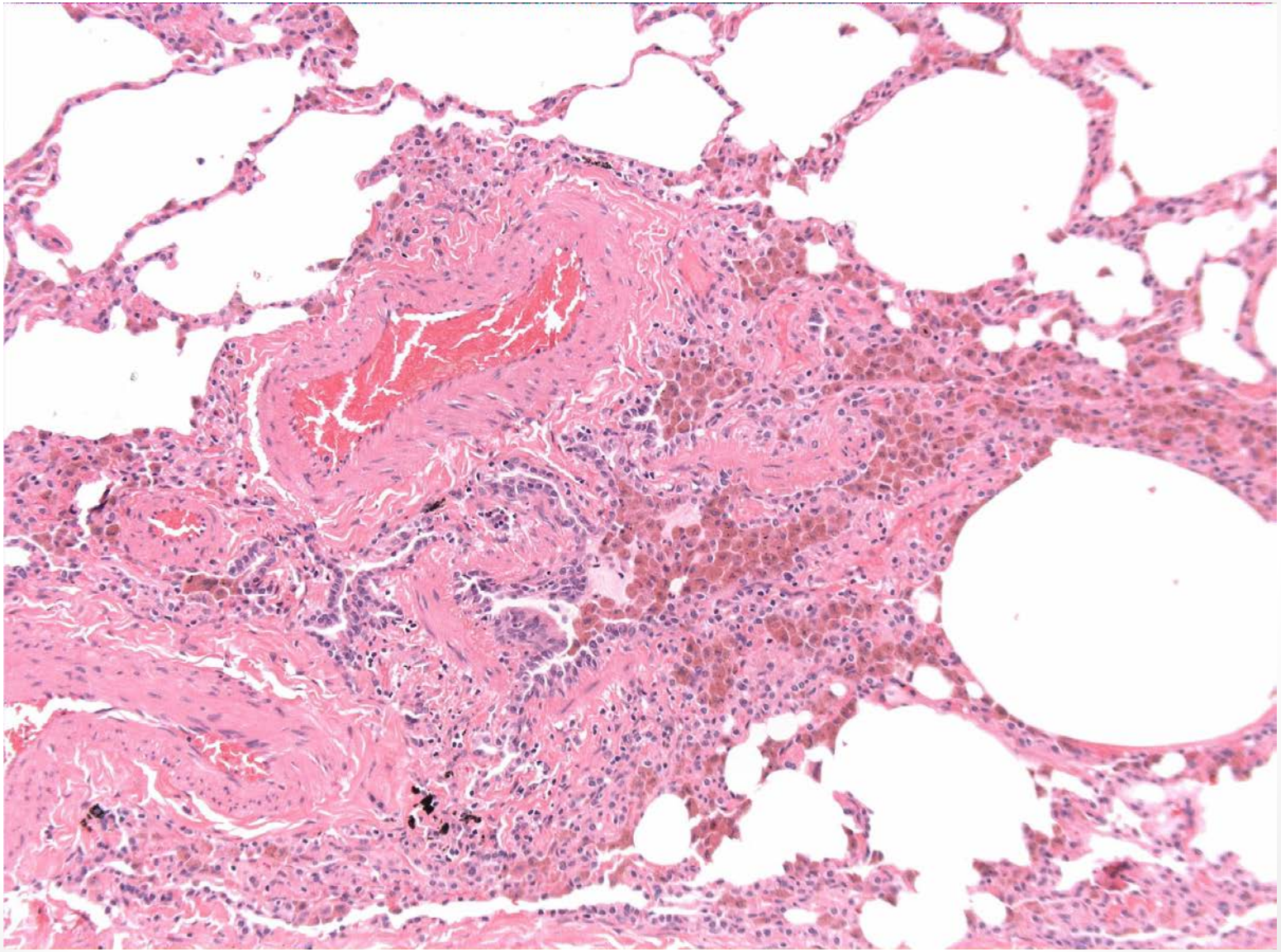
LIP



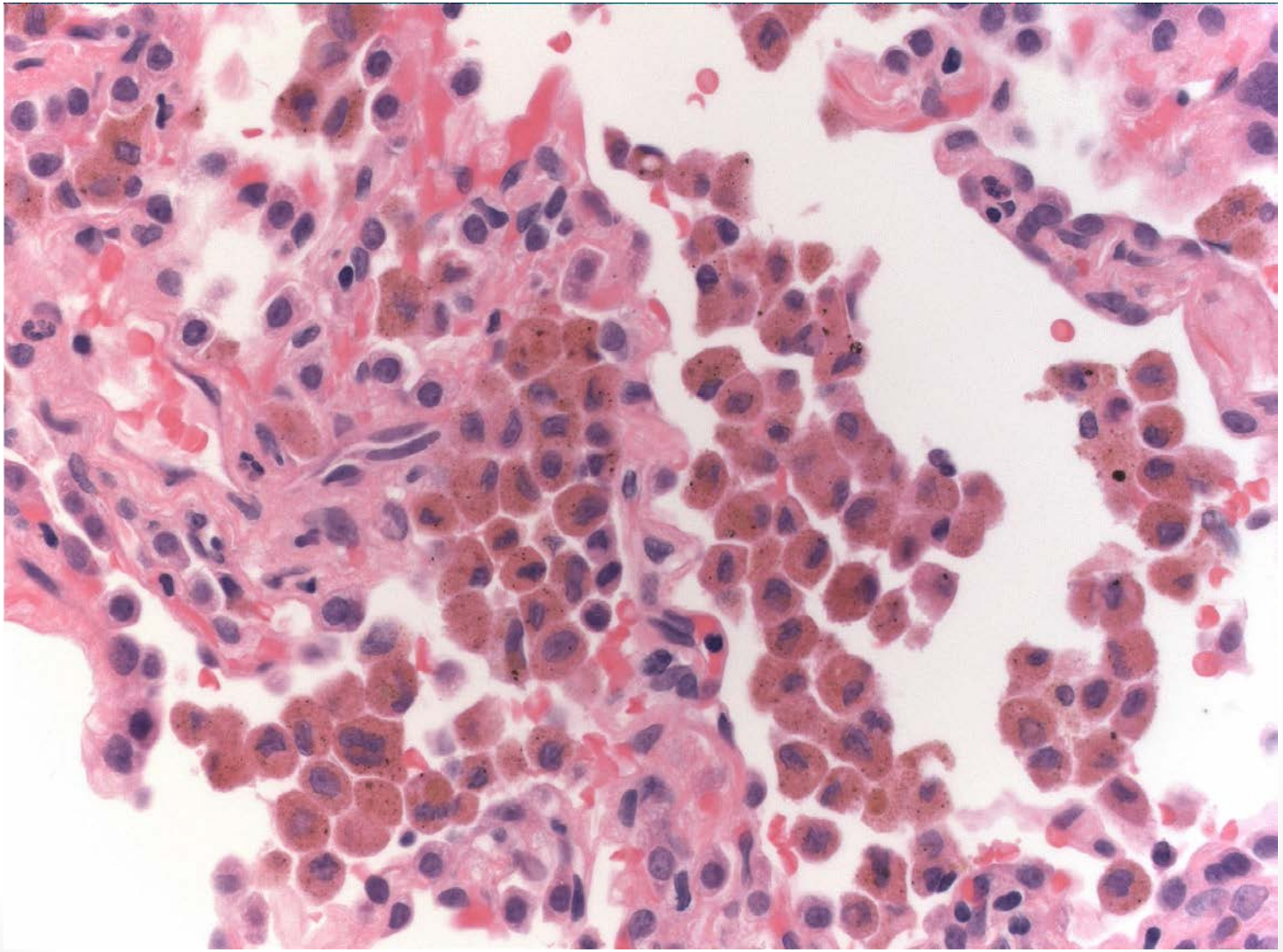
RB-ILD

- Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD)
  - Smoking-related disease
  - Characteristic “smokers’ macrophages” within small airway lumens and surrounding airspaces
    - Alveolar macrophages containing fine brown pigment
  - +/- concurrent interstitial fibrosis (but no honeycomb change)

RB-ILD



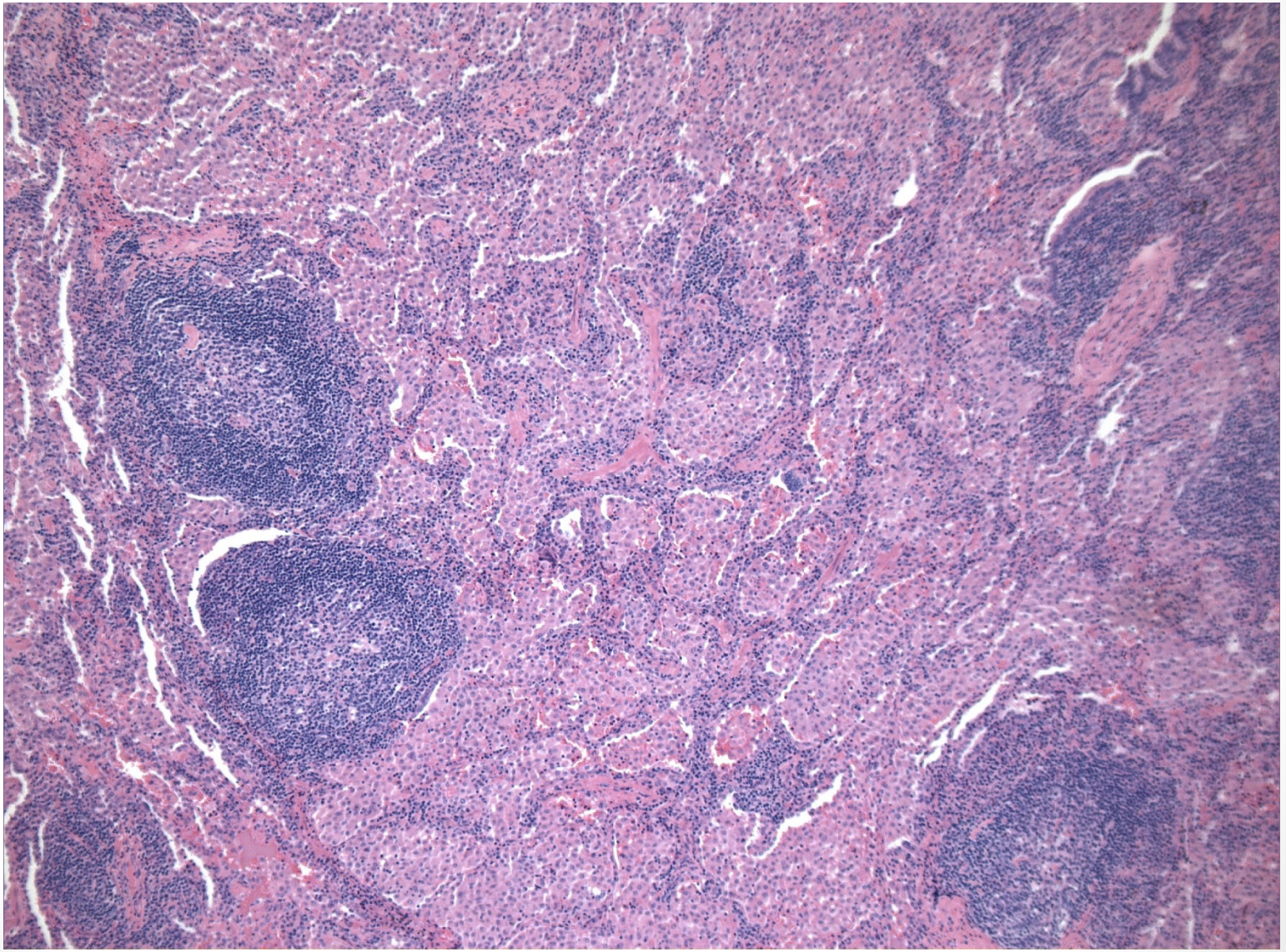
RB-ILD – Smokers' macrophages



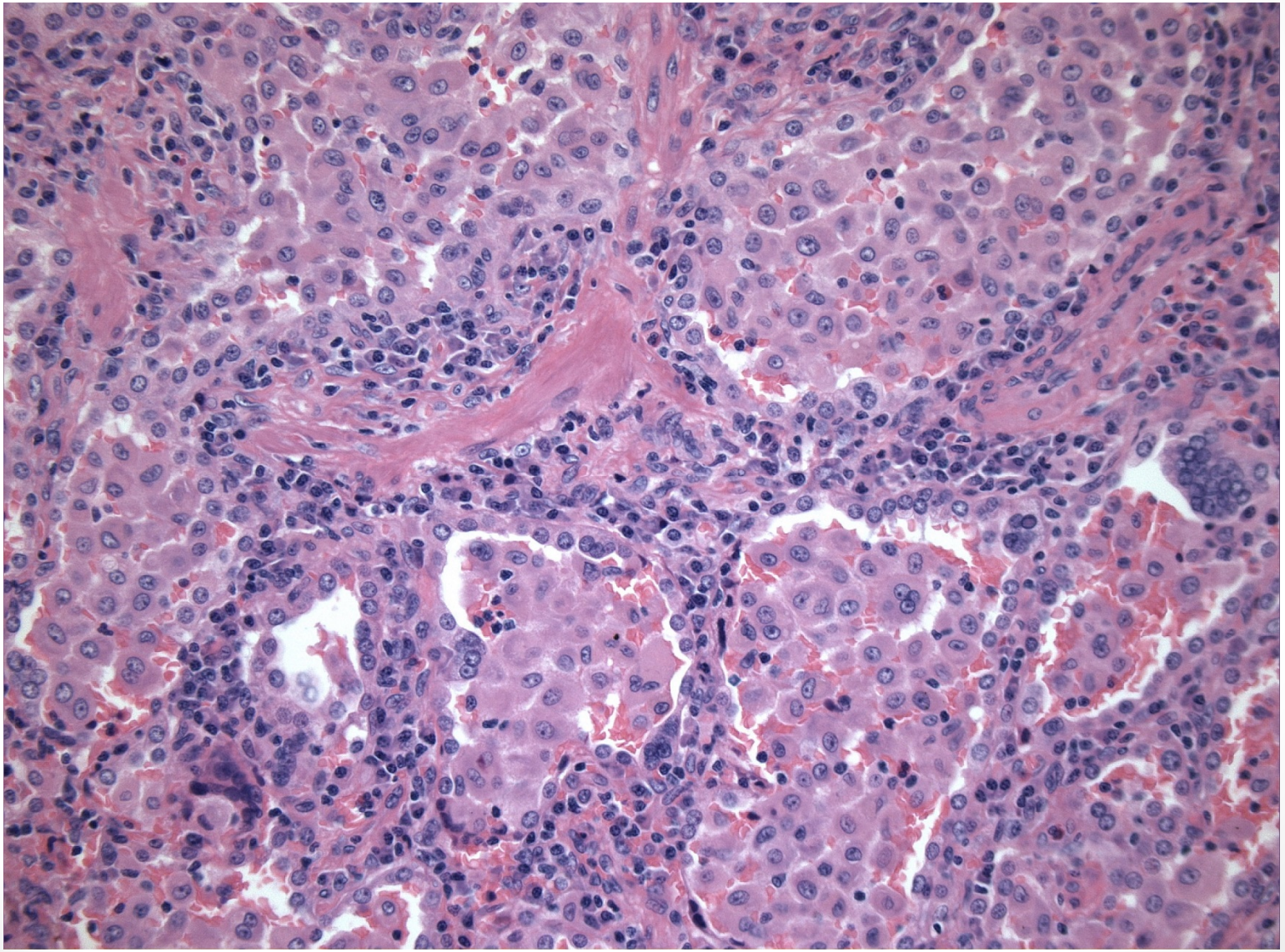
DIP

- Desquamative interstitial pneumonia (DIP)
  - In adults, a smoking-related disease
  - Diffuse, sheet-like alveolar filling by of finely pigmented alveolar macrophages
  - +/- mild to moderate interstitial inflammation or fibrosis
    - No microscopic honeycomb change

DIP



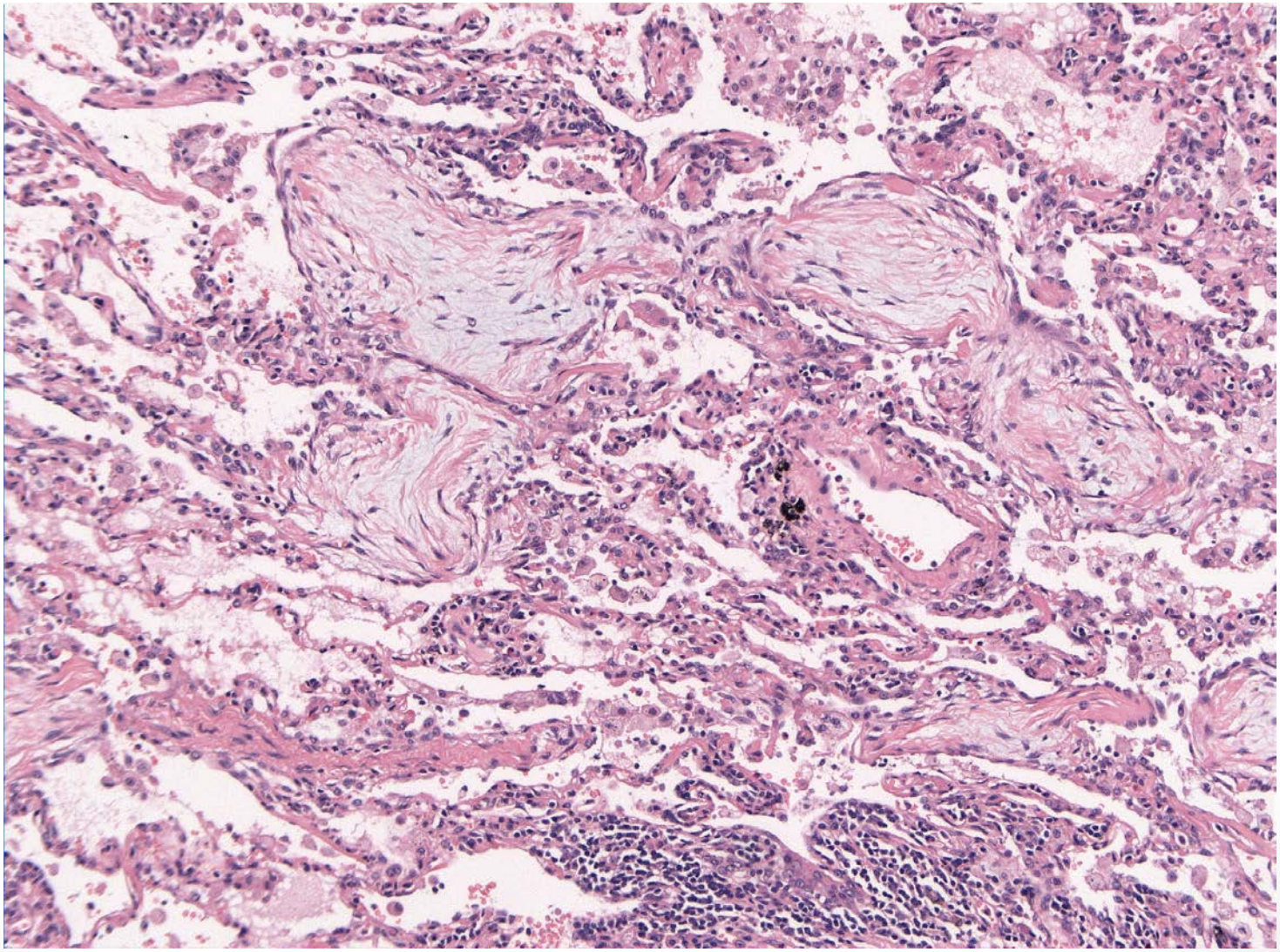
DIP



COP (formerly BOOP)

- Cryptogenic organizing pneumonia (COP)
  - Formerly called bronchiolitis obliterans-organizing pneumonia (BOOP)
  - Clinically, acute/subacute onset of respiratory symptoms
    - Unlike UIP/NSIP, which tend to be more chronic
    - Typically patchy radiologically, but may form nodule(s)
  - Histologically, characterized by organizing pneumonia (OP)
    - Polypoid fibroblastic plugs within alveolar ducts & alveolar spaces
    - +/- mild interstitial chronic inflammation

OP (Organizing pneumonia)



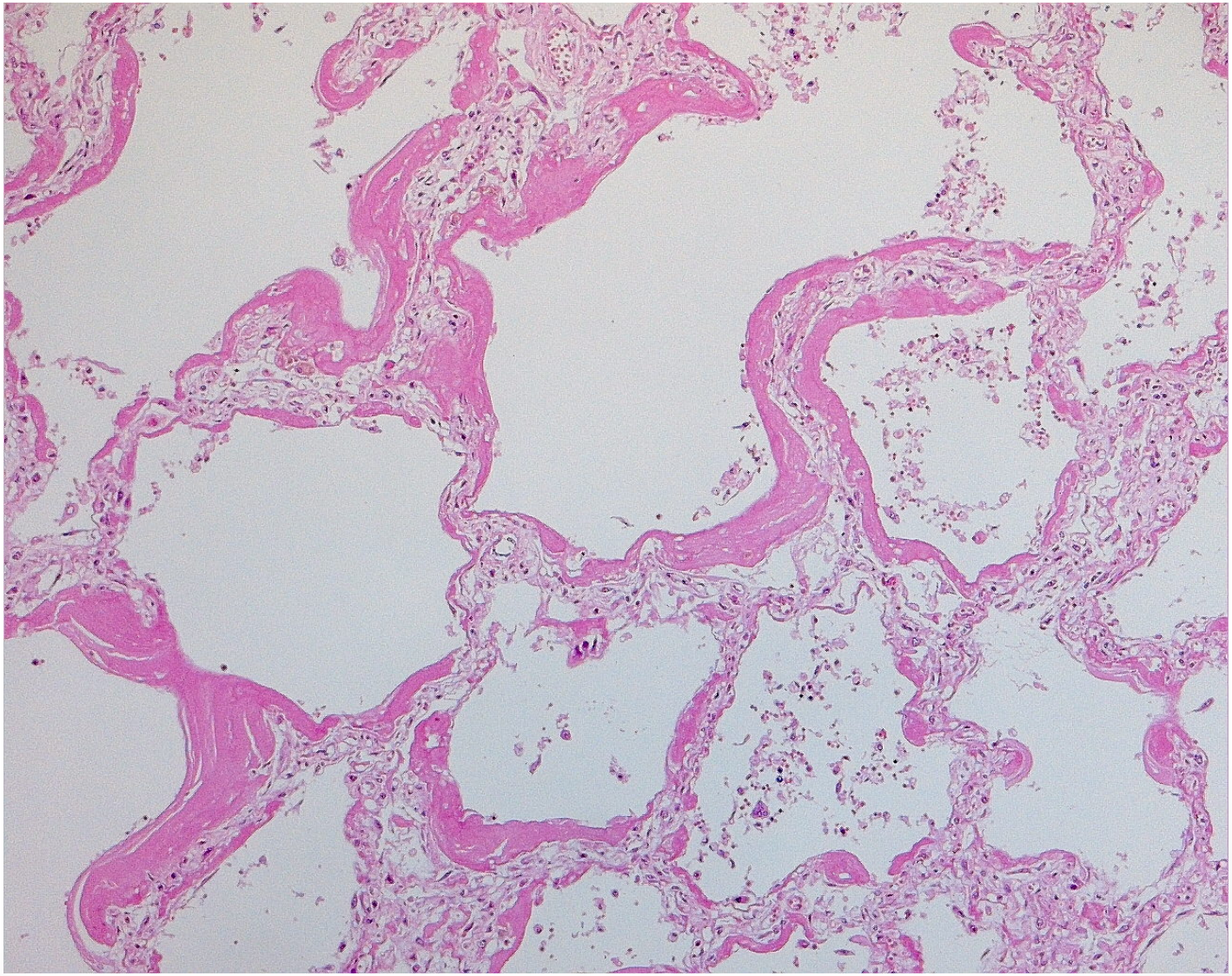
AIP/DAD

- Acute interstitial pneumonia (AIP)/Diffuse alveolar damage (DAD)
  - Clinically, acute rapidly progressive onset of respiratory distress/failure (ARDS)
  - Etiologically, many different causes of ARDS / DAD
    - e.g. infections, sepsis, toxic injuries, etc.
    - AIP = ARDS / DAD of unknown etiology (i.e. idiopathic)

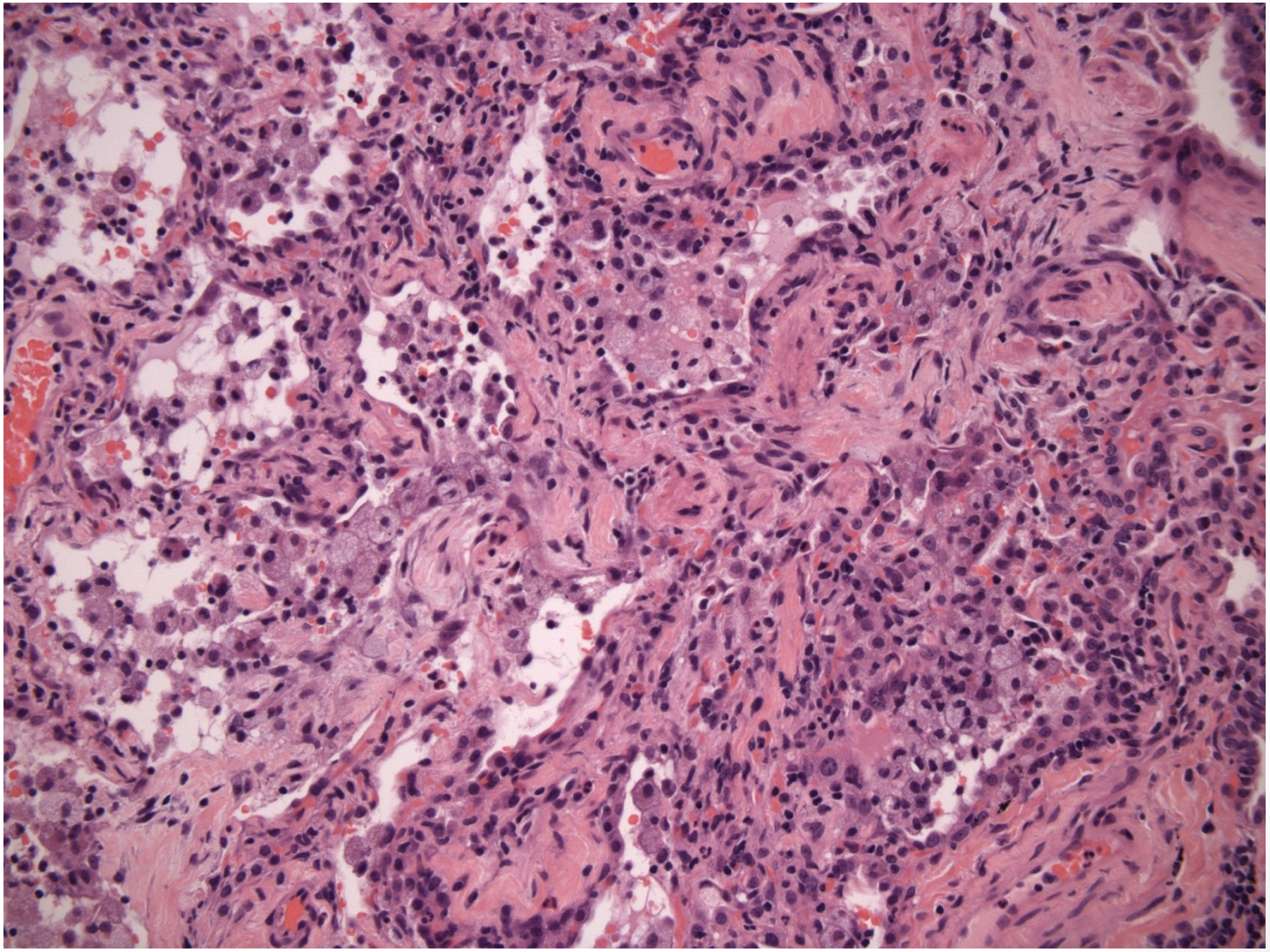
AIP/DAD

- Histologic features - 3 overlapping phases
  - Acute phase (0-14 days)
    - Intra-alveolar fibrinous exudates / hyaline membranes
  - Organizing/proliferative phase (1-4 weeks)
    - Organizing pneumonia
    - Diffuse interstitial inflammation or organizing fibrosis
    - Reactive pneumocyte hyperplasia
    - May resemble NSIP or OP
  - Resolution or fibrotic phase (>4 weeks)
    - Lung returns towards normal; or residual interstitial fibrosis

AIP/DAD – Acute phase



AIP/DAD – Organizing phase



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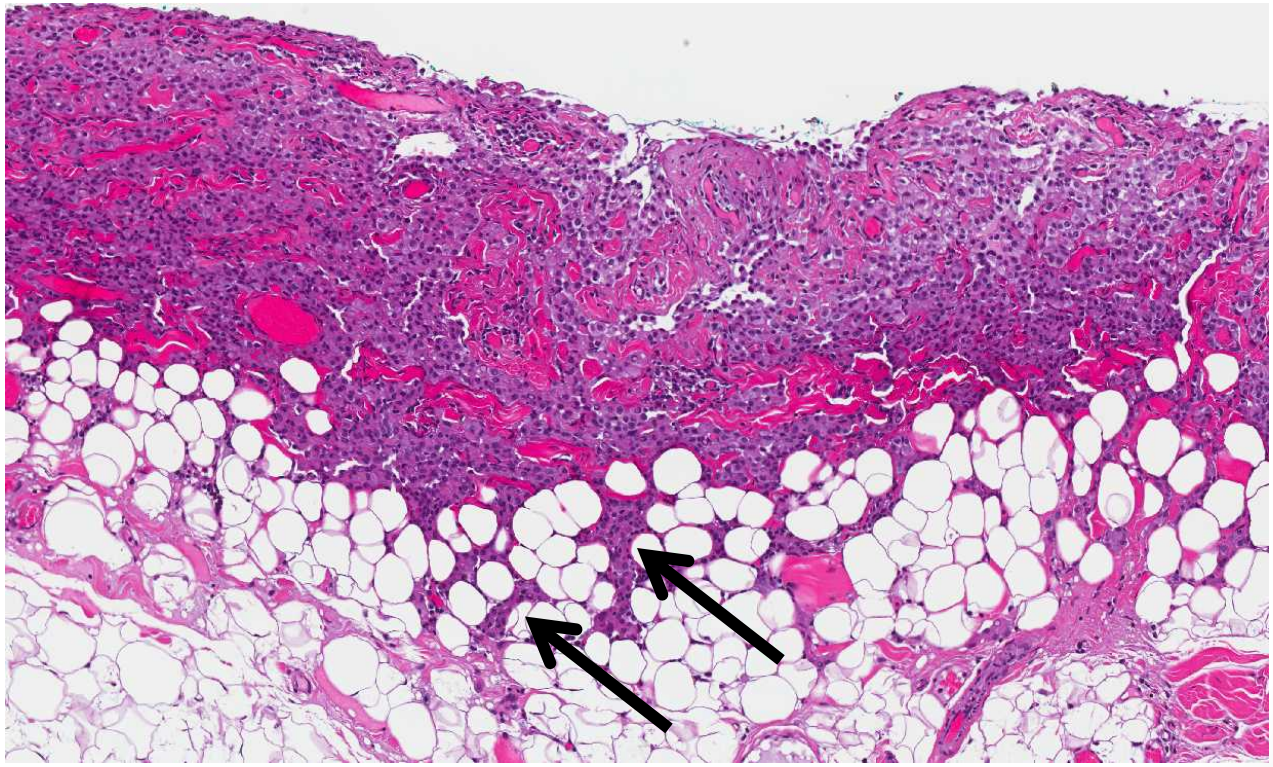
Pleural lesions

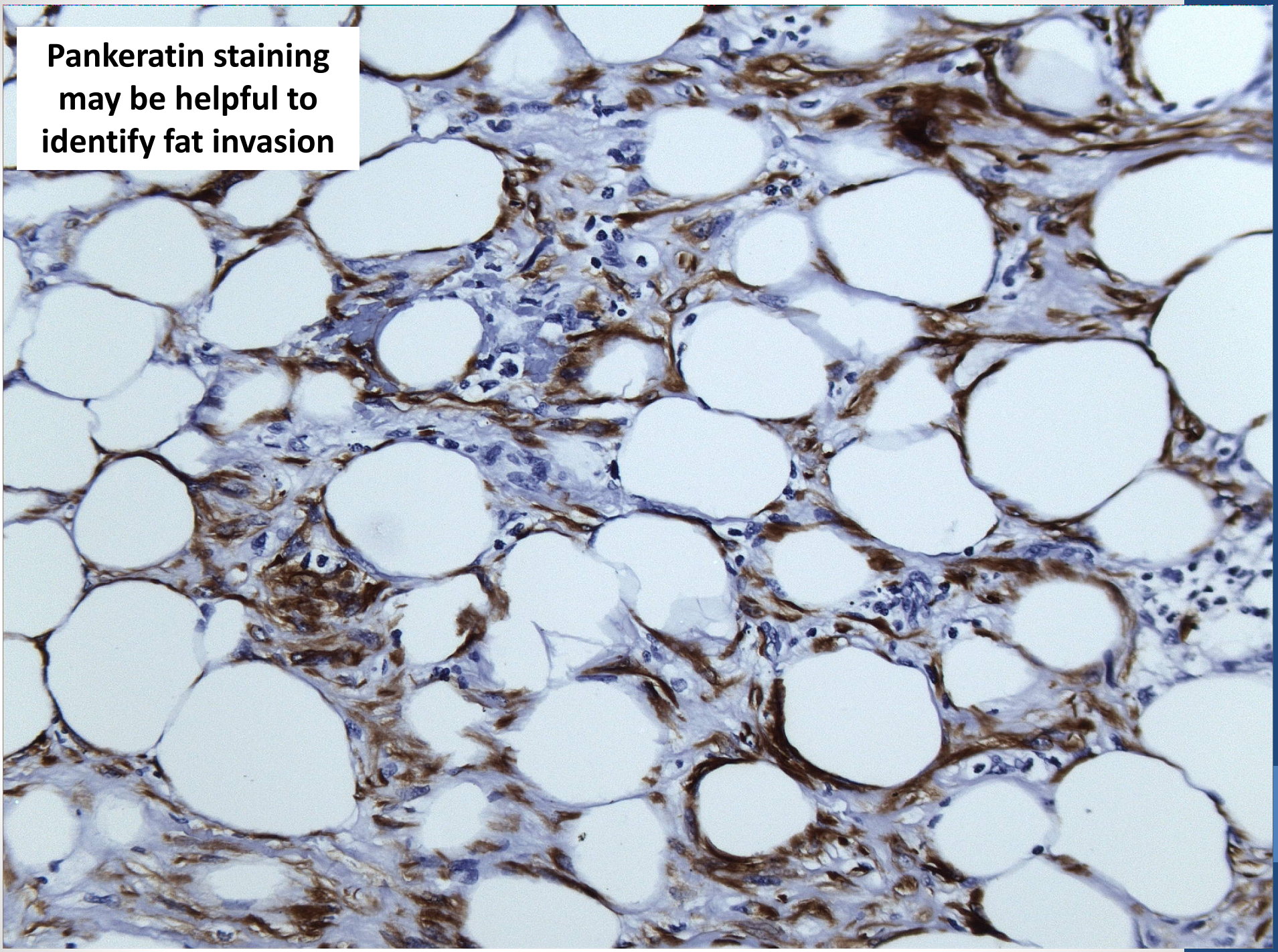
- Common differential diagnostic questions:
  - Reactive pleuritis/mesothelial proliferation vs. malignant mesothelioma?
    - Epithelioid malignant mesothelioma
    - Sarcomatoid malignant mesothelioma (including desmoplastic mesothelioma)
    - Biphasic malignant mesothelioma
  - Metastatic carcinoma vs. malignant mesothelioma?

Pleural lesions

- Reactive vs. malignant?
  - **Definitive**:
    - Invasion of fat or skeletal muscle = malignant

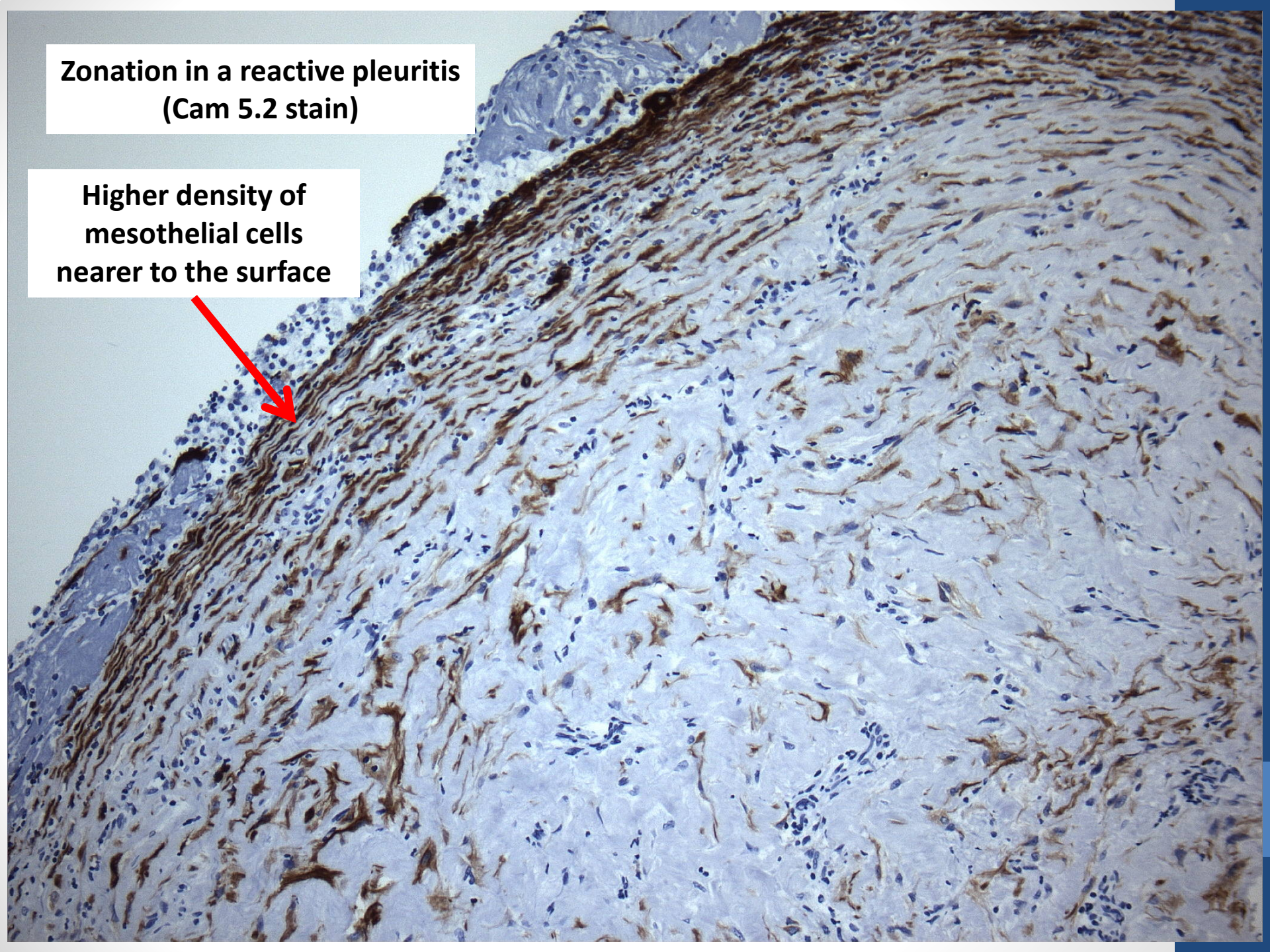


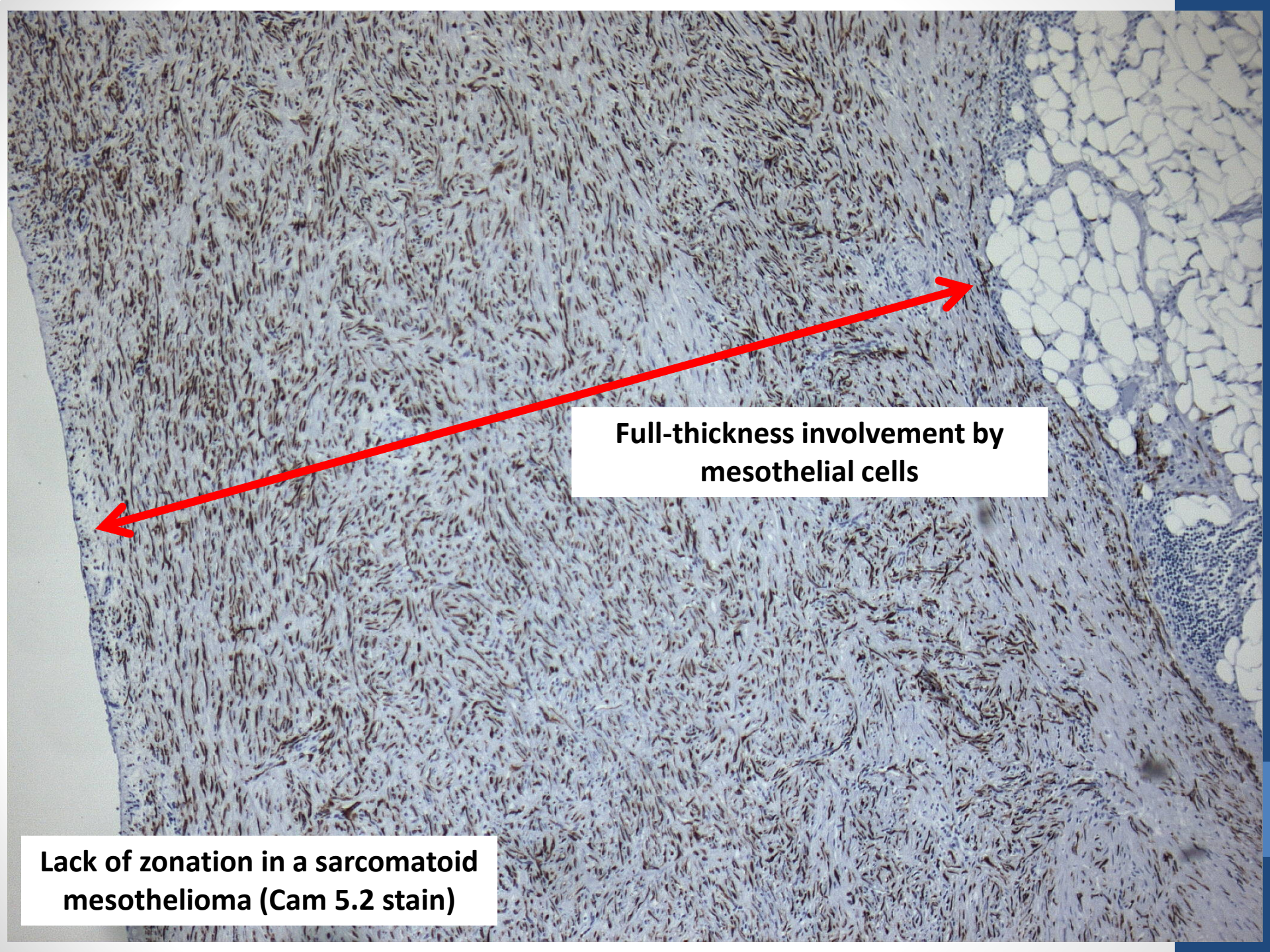
Picture courtesy of Dr. M. Gomes, University of Ottawa.


Pankeratin staining may be helpful to identify fat invasion

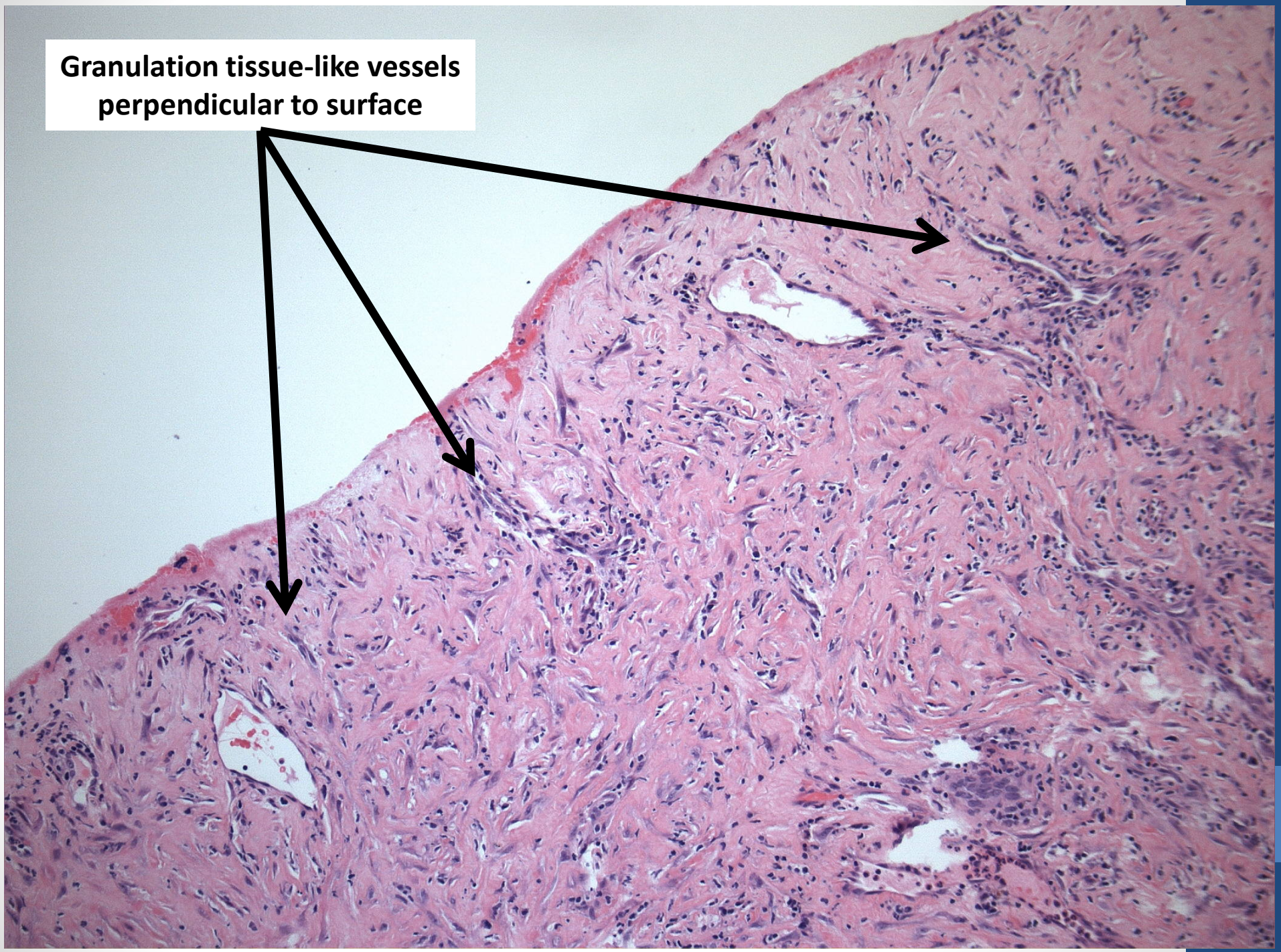
Pleural lesions

- Reactive vs. malignant?
  - Potentially **helpful** features (**but not definitive**):
    - Zonation: increased cellularity towards the pleural surface → favors reactive
    - Granulation tissue-like capillaries perpendicular to the pleural surface → favors reactive
    - Complex architectural features (complex branching glands or papillae) → somewhat favors malignant
    - Severe nuclear atypia → somewhat favors malignant
      - But nuclear atypia may be seen in reactive
    - Mitoses & necrosis → may be seen in both


Zonation in a reactive pleuritis
(Cam 5.2 stain)
Higher density of
mesothelial cells
nearer to the surface

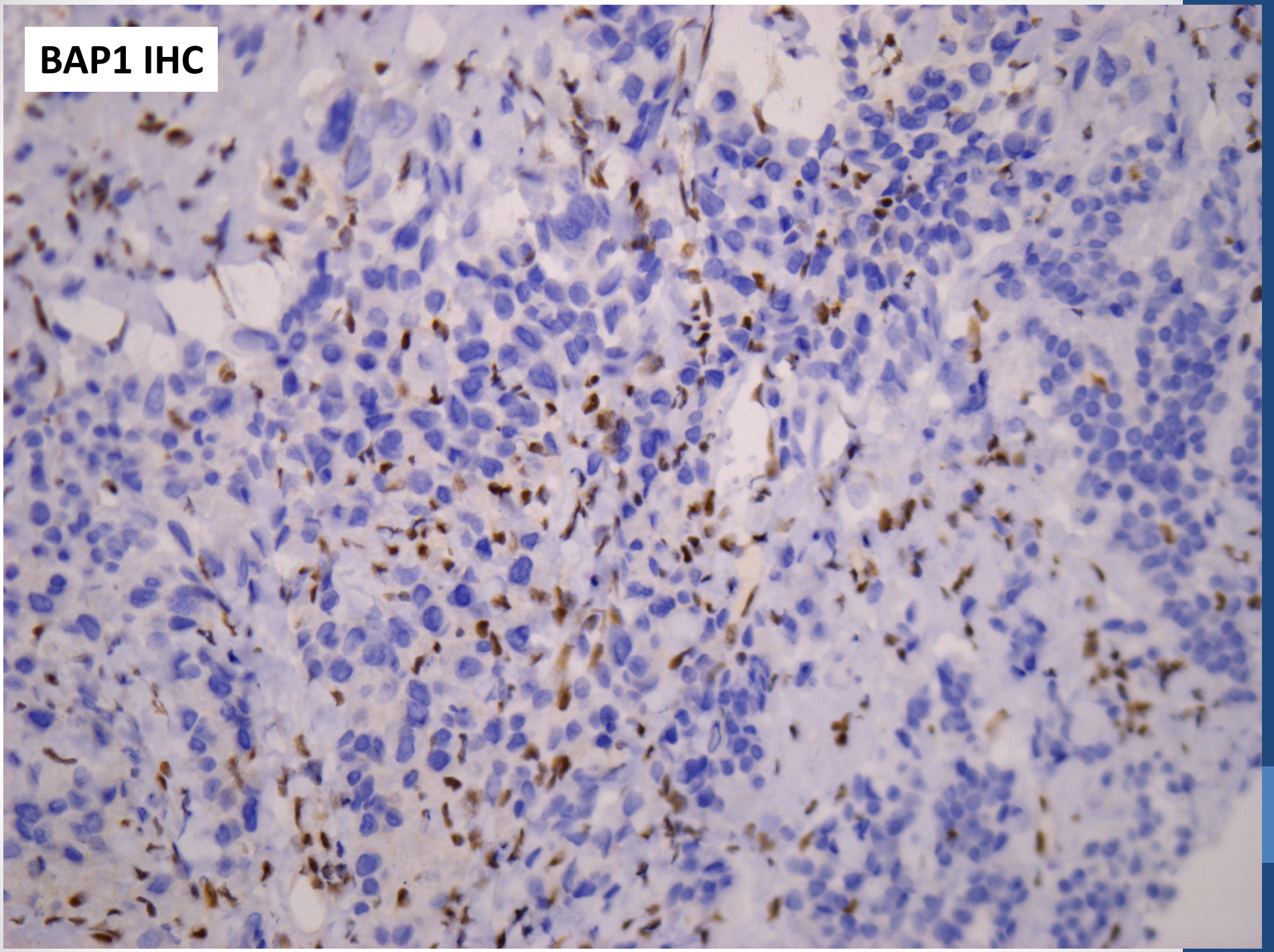


Lack of zonation in a sarcomatoid mesothelioma (Cam 5.2 stain)


Granulation tissue-like vessels perpendicular to surface

Pleural lesions

- Reactive vs. malignant – Ancillary testing
  - BAP1 IHC
    - Loss of nuclear BAP1 expression in a mesothelial proliferation is reported to be highly specific for mesothelioma
    - Retained BAP1 expression does not rule out mesothelioma
  - Deletion of p16/CDKN2A (chr. 9p21) by FISH
    - Reported in up to ~70-80% of malignant pleural mesotheliomas
    - Methylthioadenosine phosphorylase (MTAP) loss by IHC as a possible surrogate for homozygous CDKN2A deletion


BAP1 IHC

Pleural lesions

- Ddx: Metastatic carcinoma vs. malignant mesothelioma
  - Most commonly, pulmonary adenocarcinoma vs. epithelioid mesothelioma
  - WHO 2015 recommends using at least 2 ‘mesothelial markers’ and 2 ‘carcinoma markers’; for example,
    - Mesothelial: calretinin, WT-1 (nuclear), D2-40, CK5/6
    - Carcinoma: EpCAM (Ber-EP4, MOC31), Claudin-4, B72.3, monoclonal CEA
      - +/- TTF-1 or other site-specific carcinoma markers

Learning Objectives

- At the end of the session, the participants will be able to:
  - Differentiate the common subtypes of lung carcinomas according to the 2015 WHO classification
  - Recognize the most common types of interstitial lung disease
  - Have an approach to diagnosing suspicious pleural lesions
  - Discuss the differential diagnosis of anterior mediastinal tumours

Mediastinal tumors

- Differential depends on location
  - Anterior/superior – 4 T's
    - **T**hymoma (& other thymic epithelial tumors)
    - **T**hyroid (goiter or tumors)
    - **T**eratoma (& mediastinal other germ cell tumors)
    - (**T**errible) Lymphomas (e.g. Hodgkin; DLBCL)
    - (and don't forget Me**T**s!)
  - Posterior
    - Neurogenic tumors
    - Lymphomas
    - Esophageal tumors
    - Mets

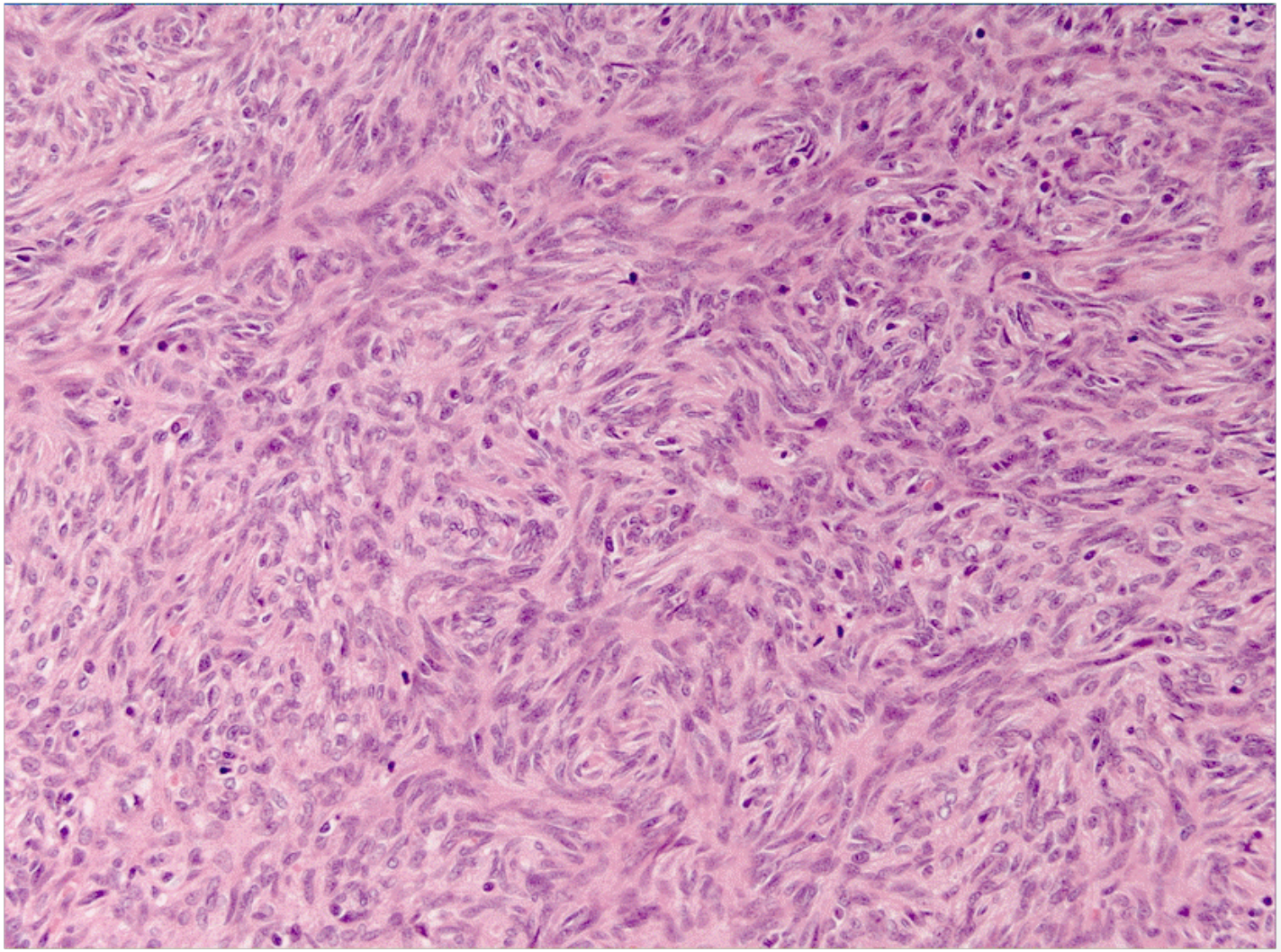
Thymic Epithelial Tumors

- Thymomas
  - Cytologically bland thymic epithelial cells
    - 'Medullary' type – ovoid to spindle cell morphology
    - 'Cortical' type
      - Polygonal/epithelioid morphology
      - Dendritic processes apparent by cytokeratin staining
    - Positive for cytokeratins & P63/P40
      - +/- PAX-8, depending on antibody used
    - Typically negative for CD5 & CD117
  - Variable numbers of reactive thymocytes
    - IHC positive for CD1a, TdT, CD99

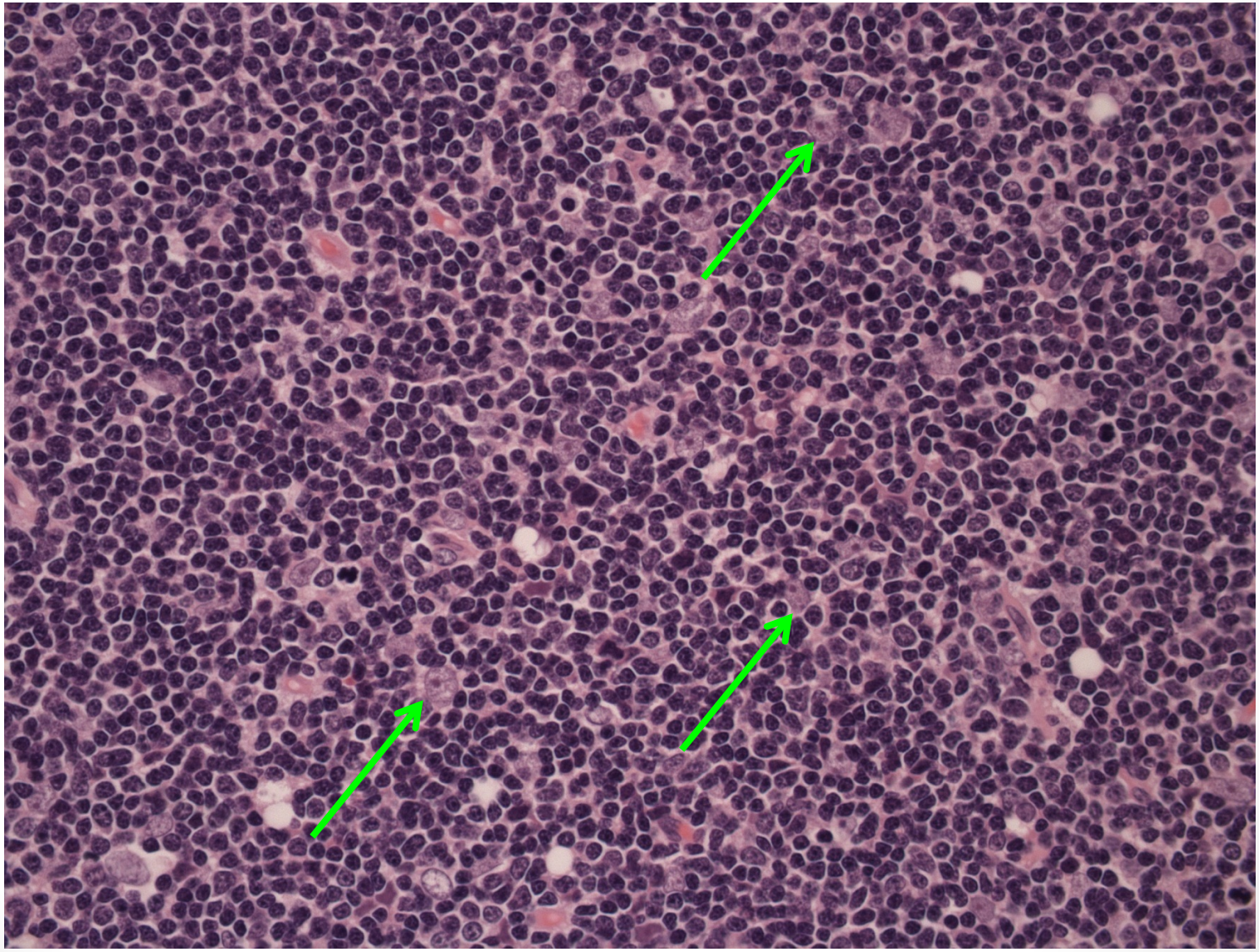
Thymic Epithelial Tumors

- Thymomas – WHO 2015 Classification
  - Type A – medullary-type epithelial cells; sparse to no lymphocytes
  - Type B1/B2/B3
    - B1 – predominantly lymphocytes, with scattered cortical-type epithelial cells
    - B2 – intermediate between B1 & B3 (“50:50”)
    - B2 – predominantly cortical-type epithelial cells, with few lymphocytes
  - Type AB – admixture of type A & B patterns

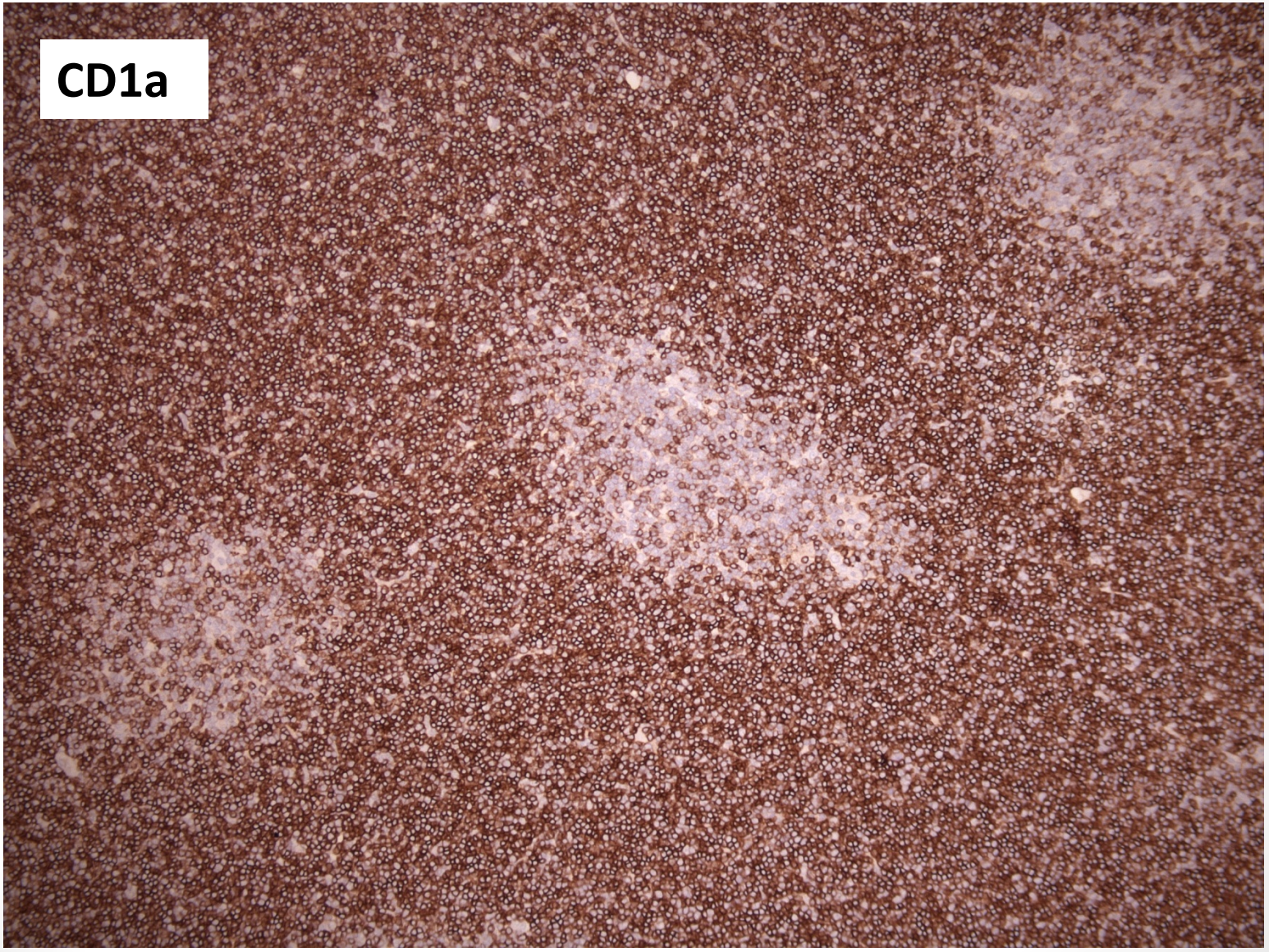
Thymoma – Type A



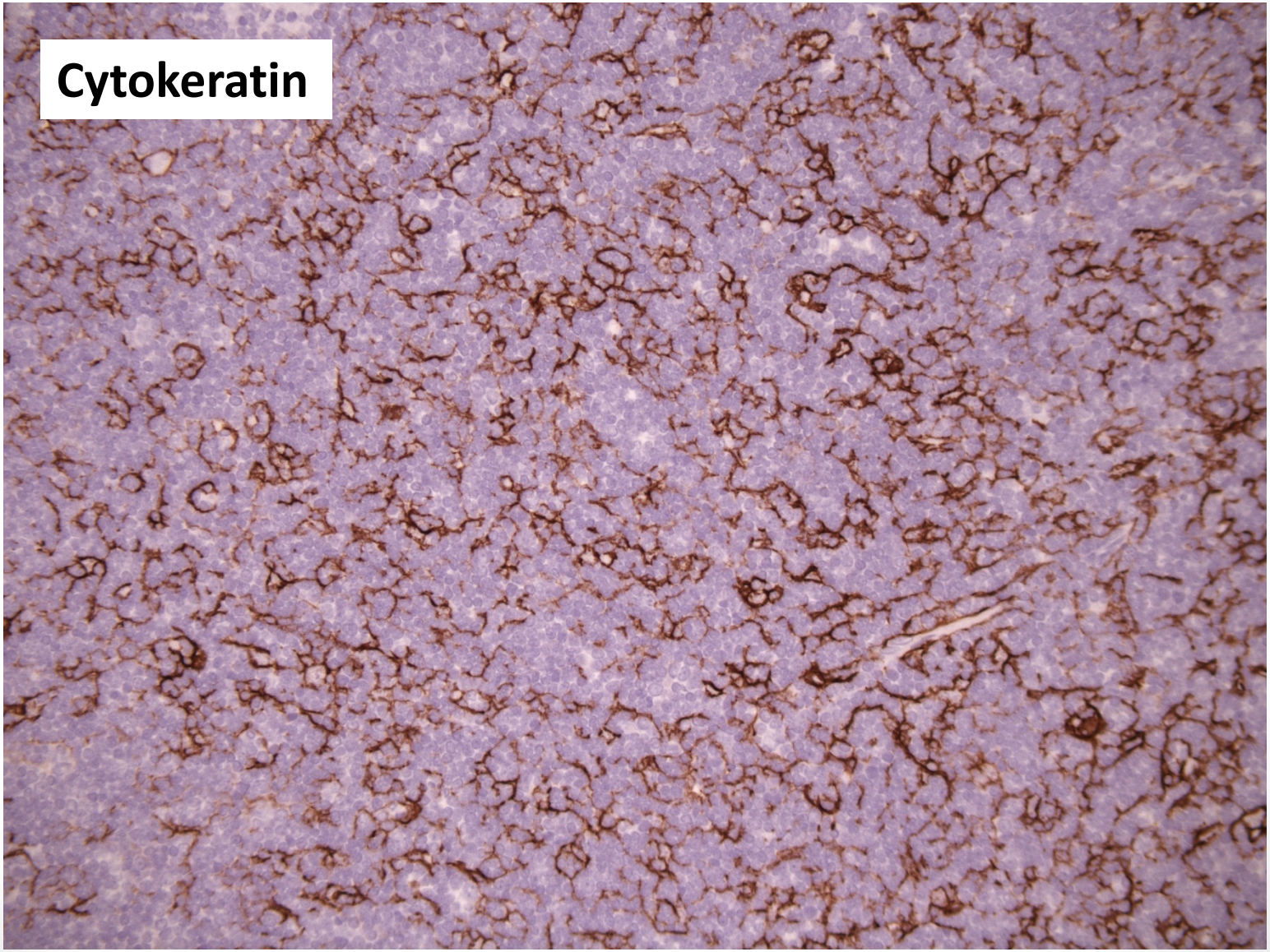
Thymoma – Type B1



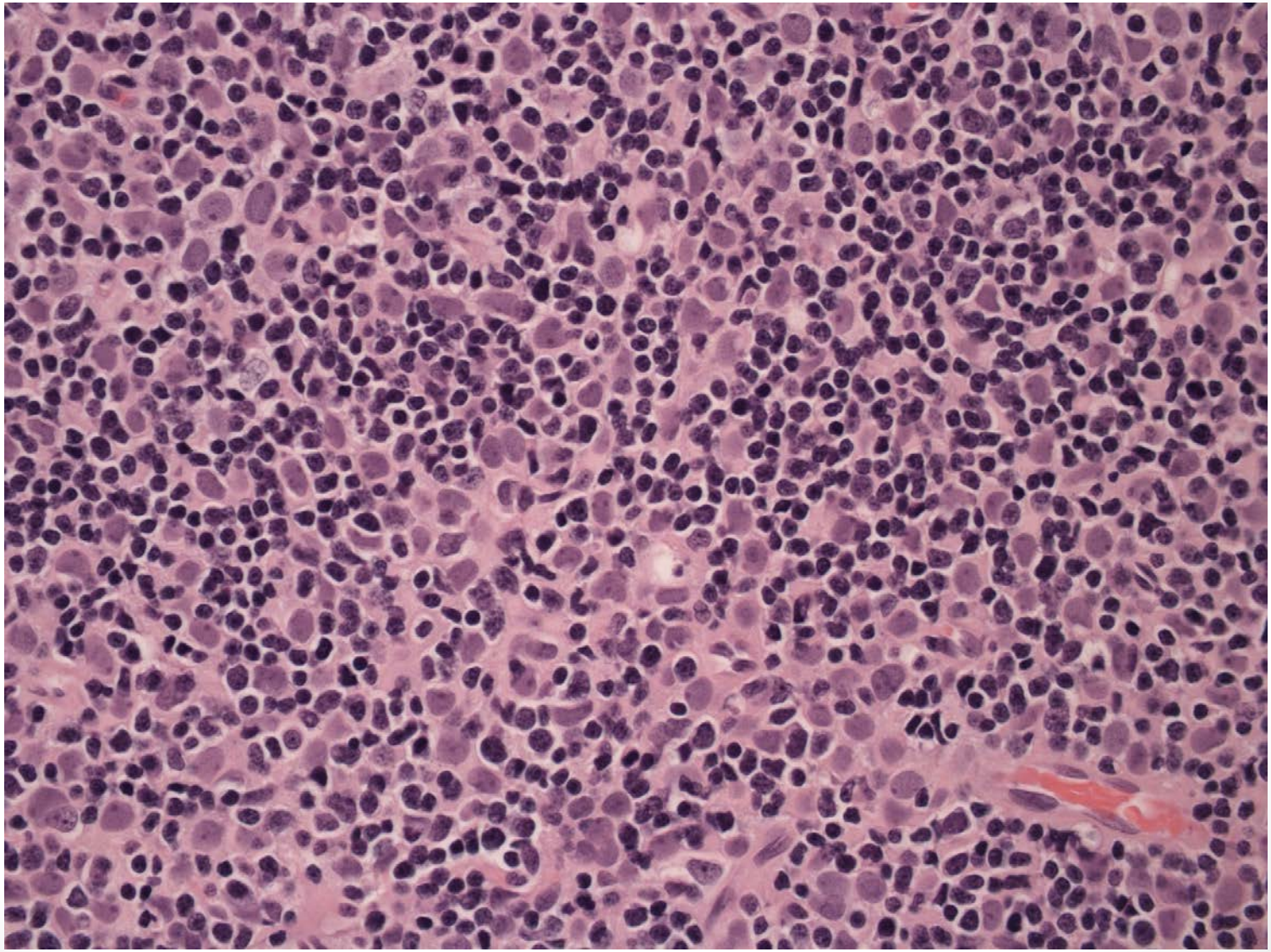
Thymoma – Type B1



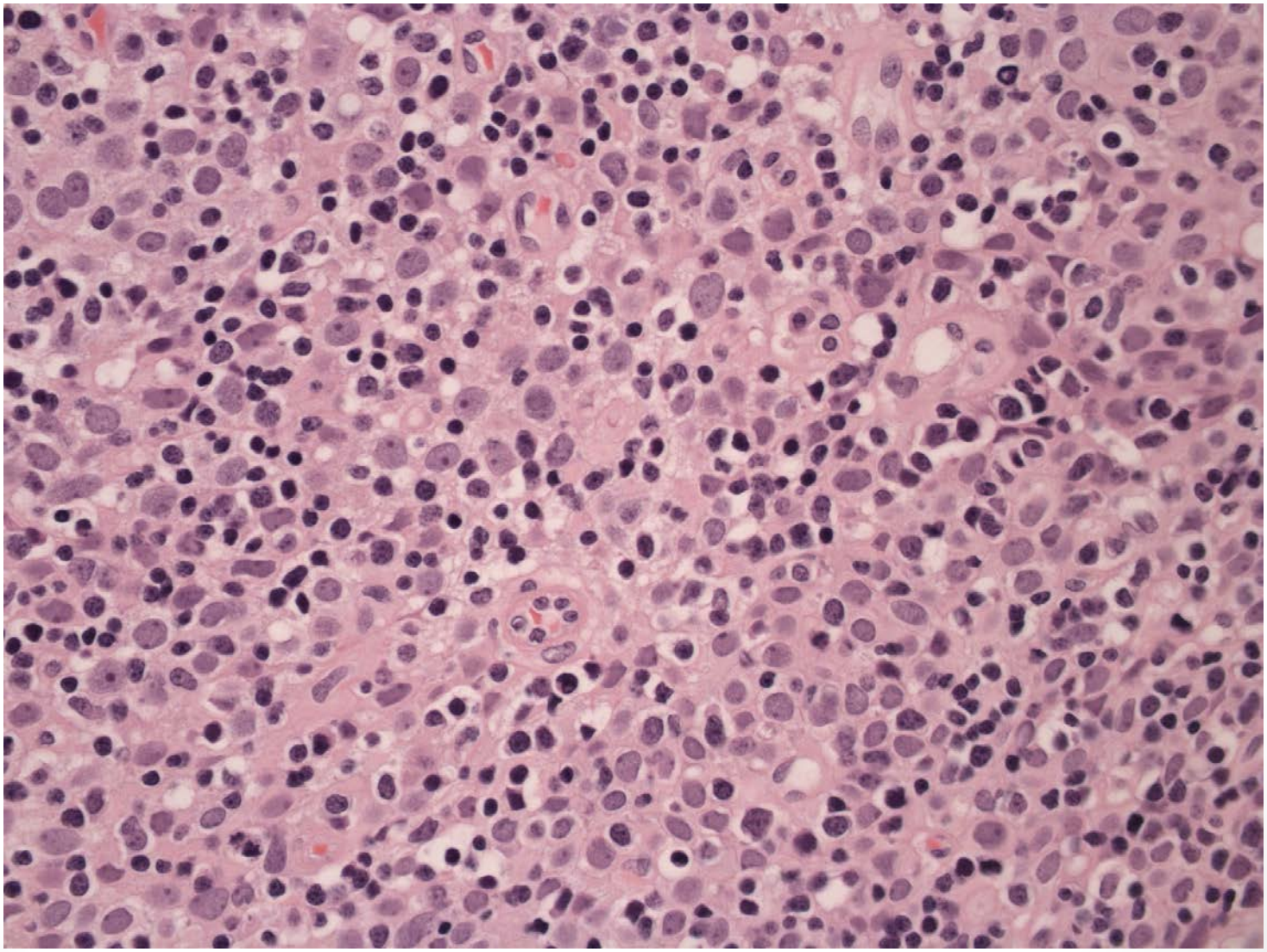
Thymoma – Type B1



Thymoma – Type B2



Thymoma – Type B3



Thymic Epithelial Tumors

- Thymic Carcinomas (aka Type C thymoma)
  - Cytologically malignant epithelial cells
    - No tumor-associated reactive thymocytes
  - Most commonly squamous cell carcinoma
    - Positive for P63/P40, and often for CD5 and CD117
  - Typically more aggressive behavior than thymomas
- Thymic Neuroendocrine Carcinomas
  - Classified similarly to pulmonary NE tumors
    - Typical/atypical carcinoids; small cell Ca; LCNEC

Thymic Tumors

- Differential Diagnostic considerations
  - Lymphomas
    - Always remember, esp. when considering type B1/B2 thymomas
    - Negative for cytokeratins
  - Metastatic tumors
    - Squamous cell carcinoma from other body sites – CD5 & CD117 ***not specific*** for thymic origin
    - Germ cell tumors – r/o testicular / ovarian origin

Learning Objectives

- At the end of the session, the participants will be able to:
  - Differentiate the common subtypes of lung carcinomas according to the 2015 WHO classification
  - Identify the most common types of interstitial lung disease
  - Have an approach to diagnosing suspicious pleural lesions
  - Discuss the differential diagnosis of anterior mediastinal tumours

Exam References

- 2015 WHO Classification of Tumours of the Lung Pleura, Thymus and Heart
  - Lung and thymic tumors
  - Classification of mesotheliomas
- Robbins and Cotran, Pathologic Basis of Disease, 9th edition
  - Probably good enough for medical lung disease
- Churg A, Galateau-Salle F. The separation of benign and malignant mesothelial proliferations. Arch Pathol Lab Med. 2012;136(10):1217-26.

Questions?