



Pulmonary Pathology



**7th Annual Board Review and Update in Pulmonary and
Critical Care Medicine**

**Pulmonary and Critical Care Medicine Division
Brigham and Women's Hospital, Harvard Medical School**

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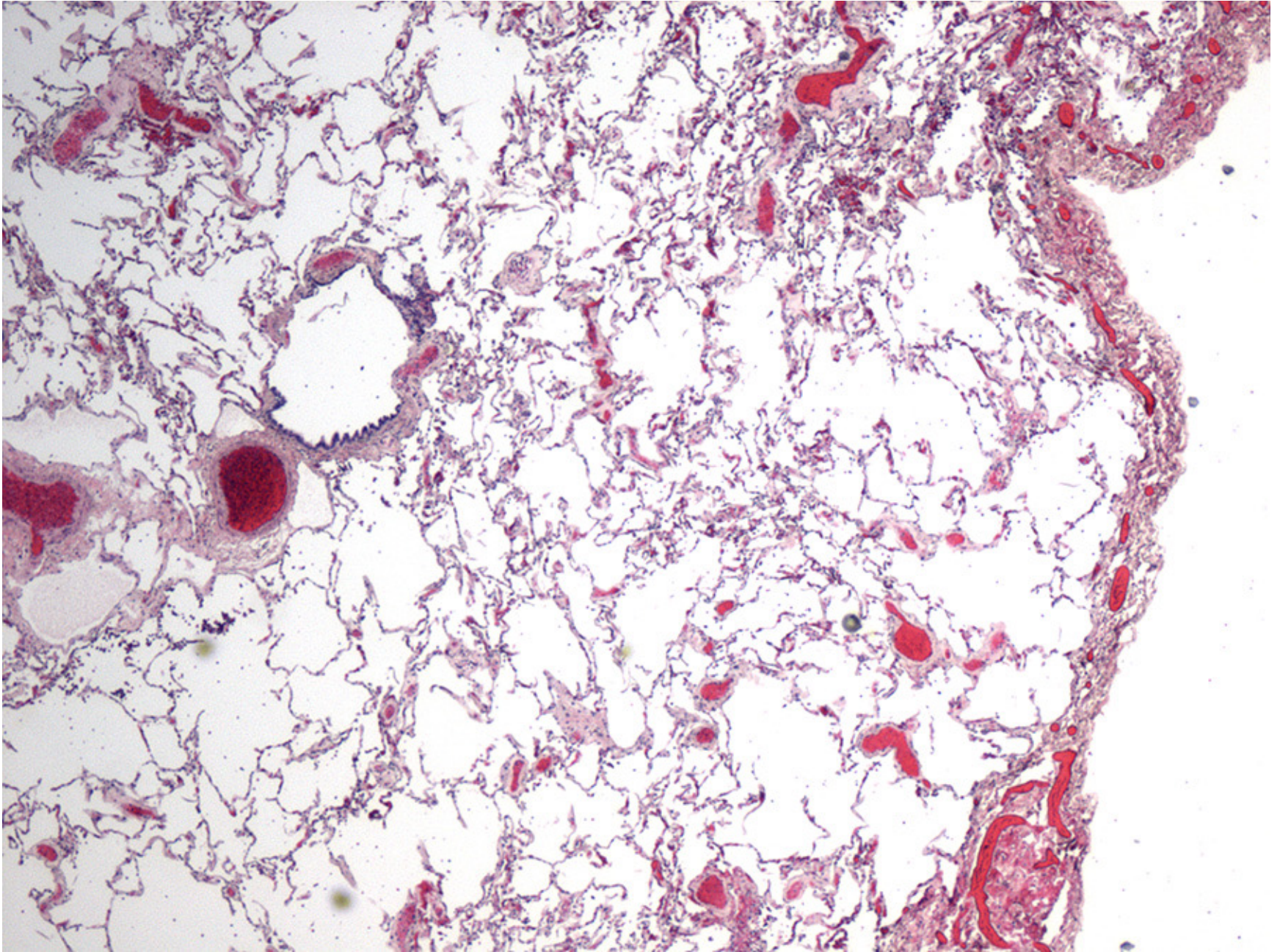
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Conflict of Interest Disclosure:
None

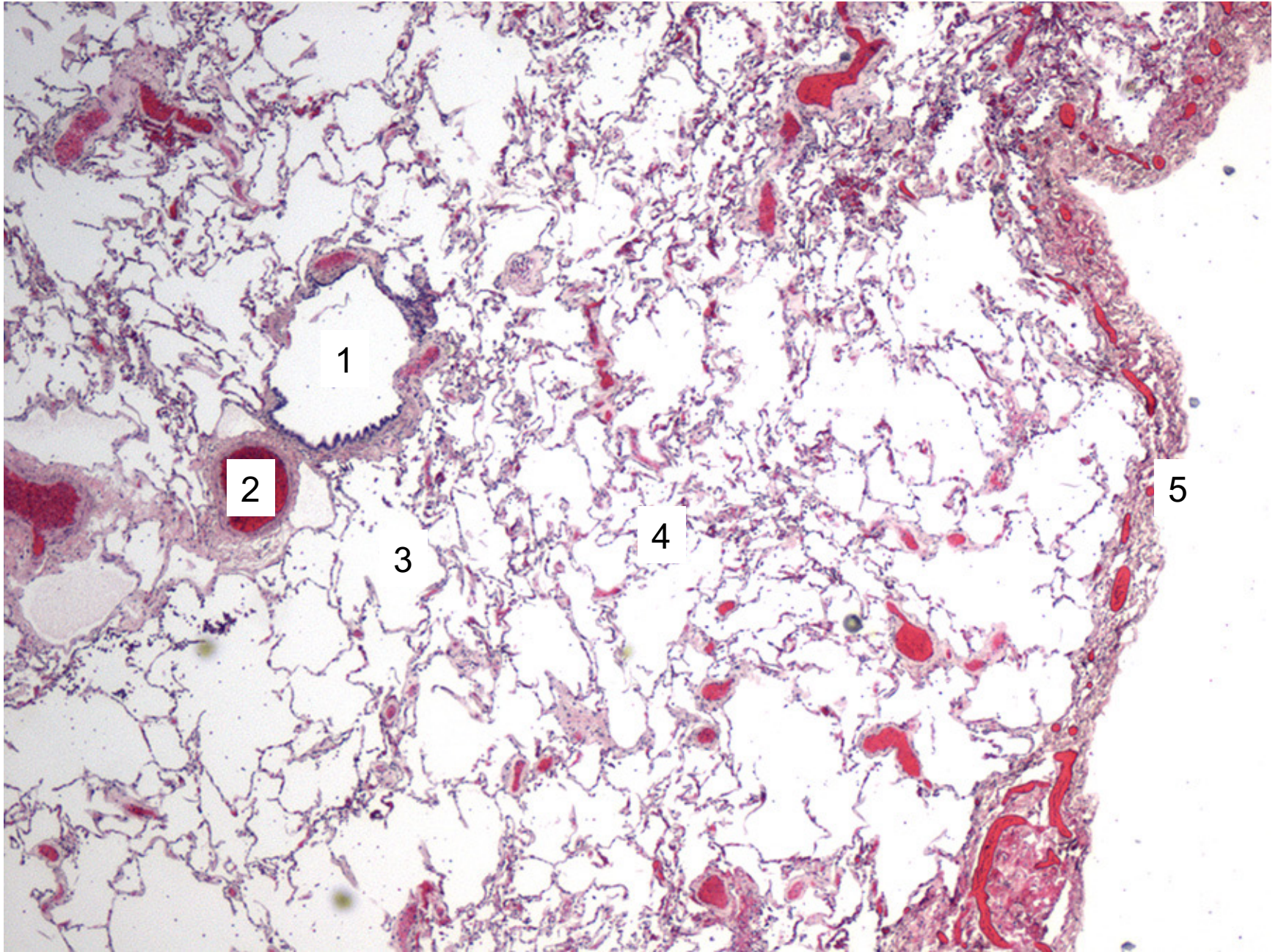
Goals

- ~~To teach you everything about pulmonary pathology~~
- To review commonly encountered non-neoplastic and neoplastic pulmonary pathology that might be encountered on the boards

Normal Anatomy



Normal Anatomy



Outline



- Interstitial lung disease
- Infection
- Malignancy
- Pathology special stains and buzzwords

Interstitial Lung Disease

- Usual interstitial pneumonia (UIP)
- Nonspecific interstitial pneumonia (NSIP)
- Acute interstitial pneumonia (AIP)
- Cryptogenic organizing pneumonia (COP)
- Hypersensitivity pneumonitis (HP)
- Sarcoidosis

- Not a comprehensive list

ILD – General Comments

- Clinical-radiologic-pathologic correlation
 - Multidisciplinary meeting
- Histologic patterns of disease
- Significant infidelity
 - One etiology can give rise to several patterns
 - Same pattern can be present in multiple diseases
- Surgical vs. transbronchial biopsy

Usual Interstitial Pneumonia - Gross

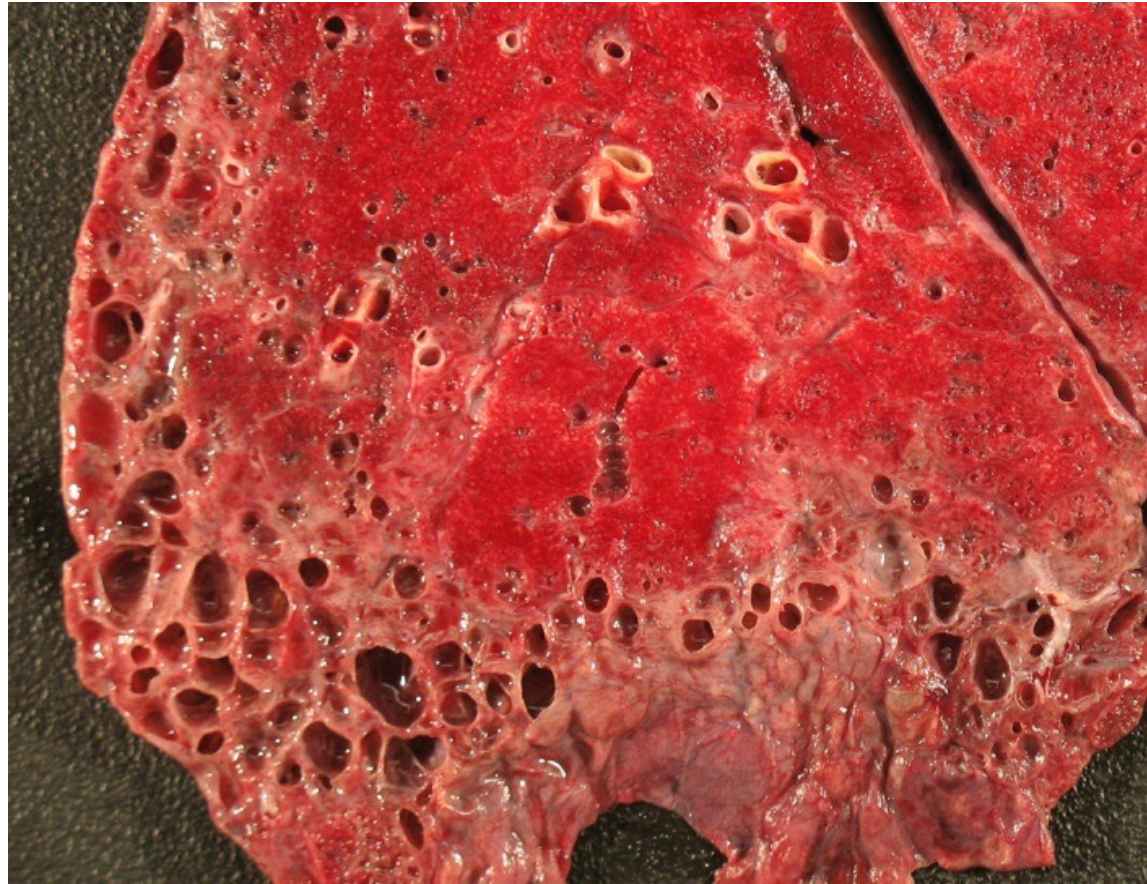
- Honeycombing, most severe/earliest in lower zones, subpleural areas



Usual Interstitial Pneumonia - Gross

Pleural surface

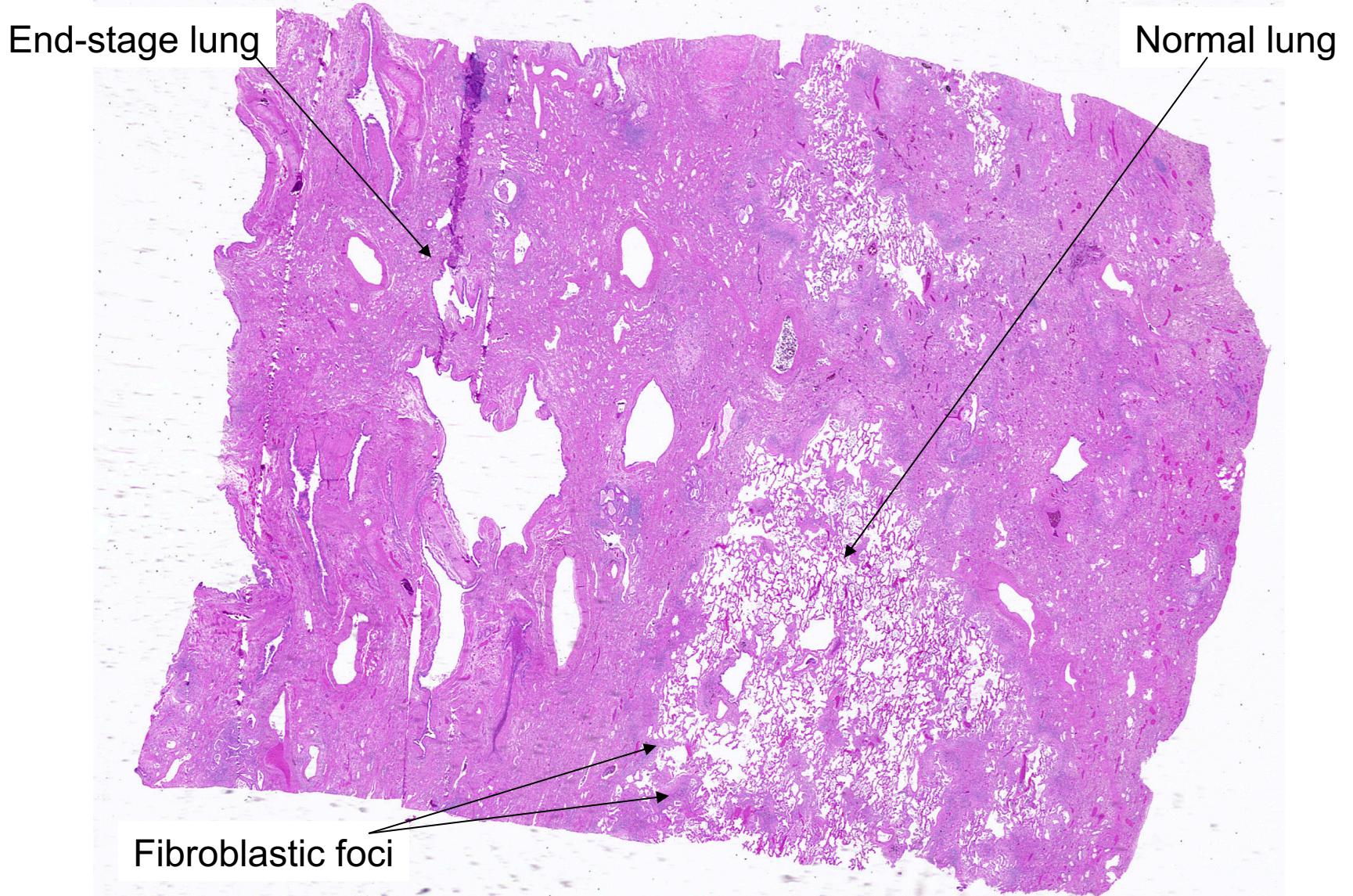
Heterogeneity



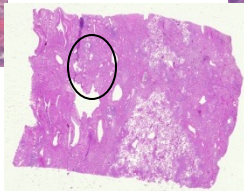
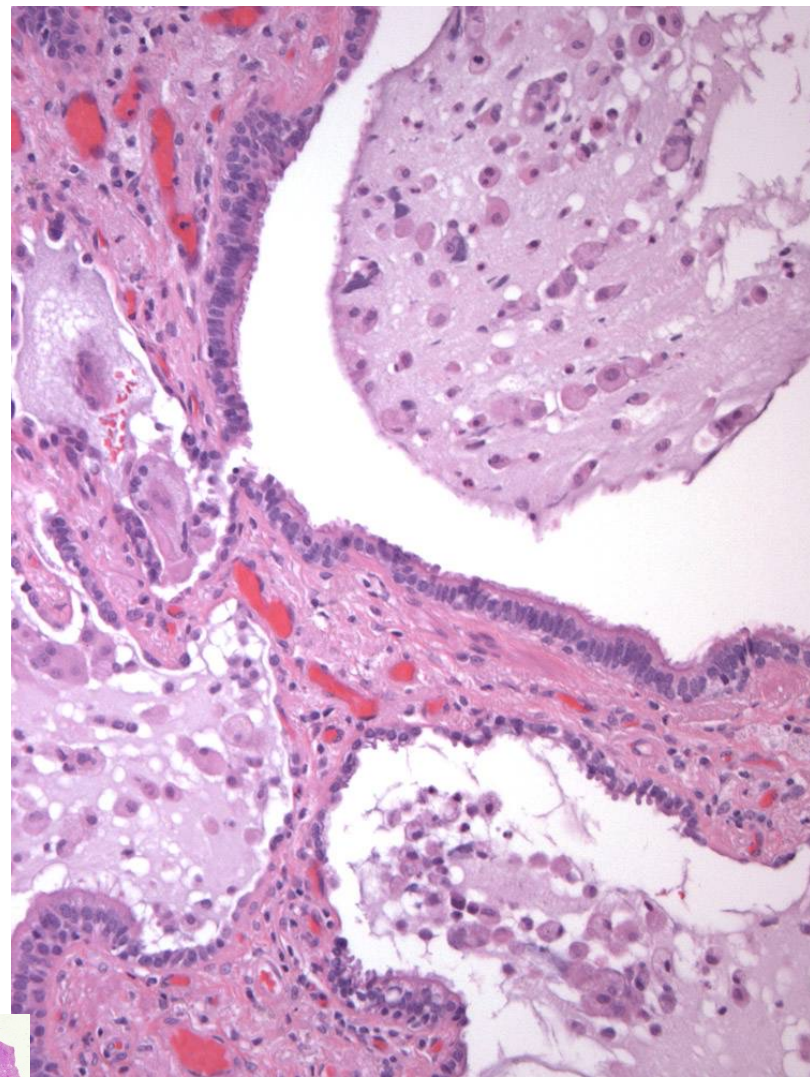
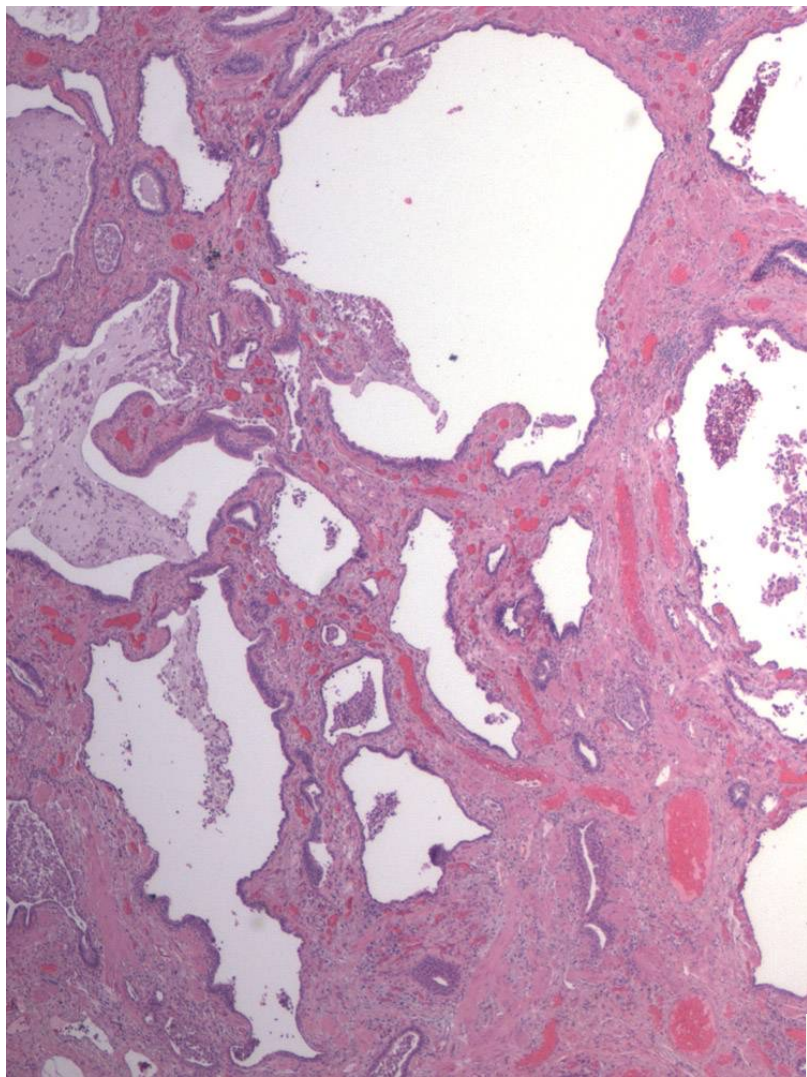
UIP - Microscopic

- Surgical biopsies – multiple lobes/areas
- Temporal and spatial *heterogeneity* - patchy
 - End-stage (“honeycomb”) lung
 - Fibroblastic foci
 - Normal lung
 - Minimal active inflammation (usually)
- Architectural distortion – fibrosis
- Absence of other specific findings (e.g., granulomas, vasculitis, aspirated material)

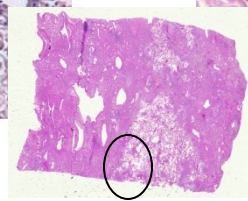
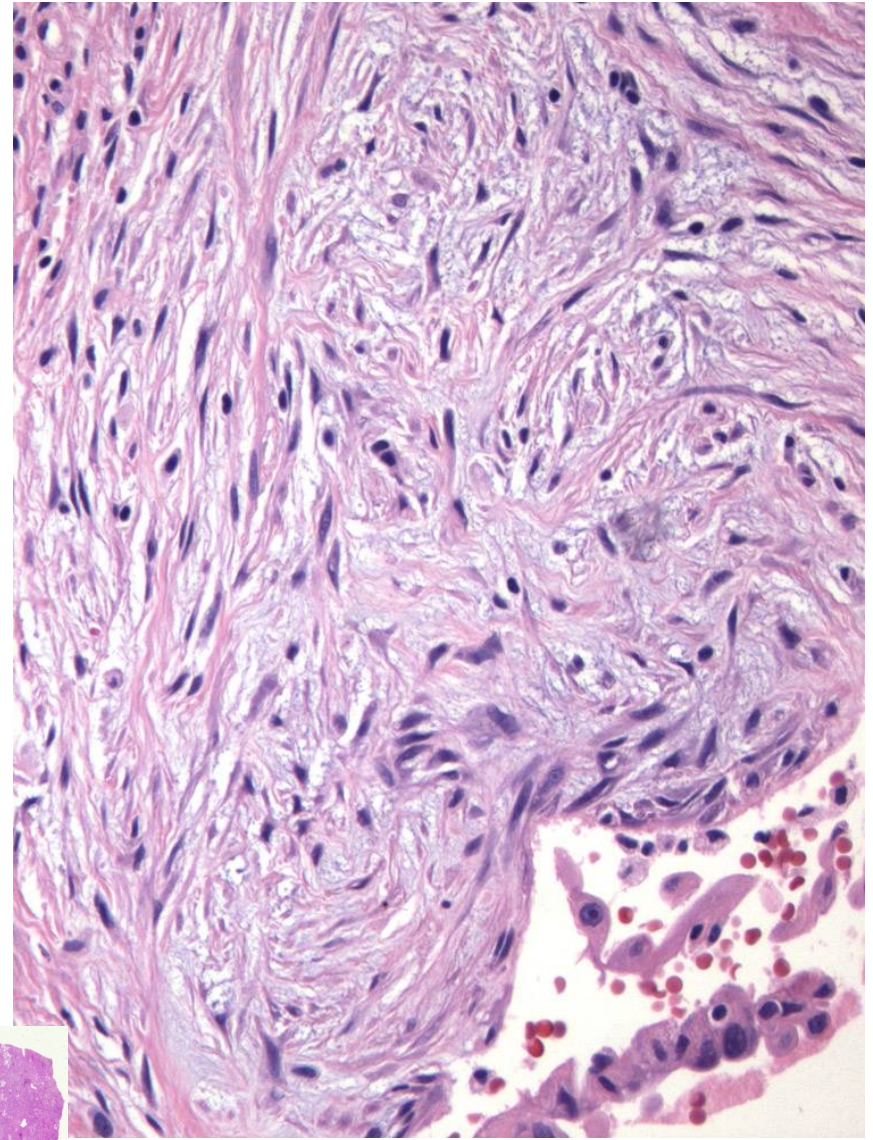
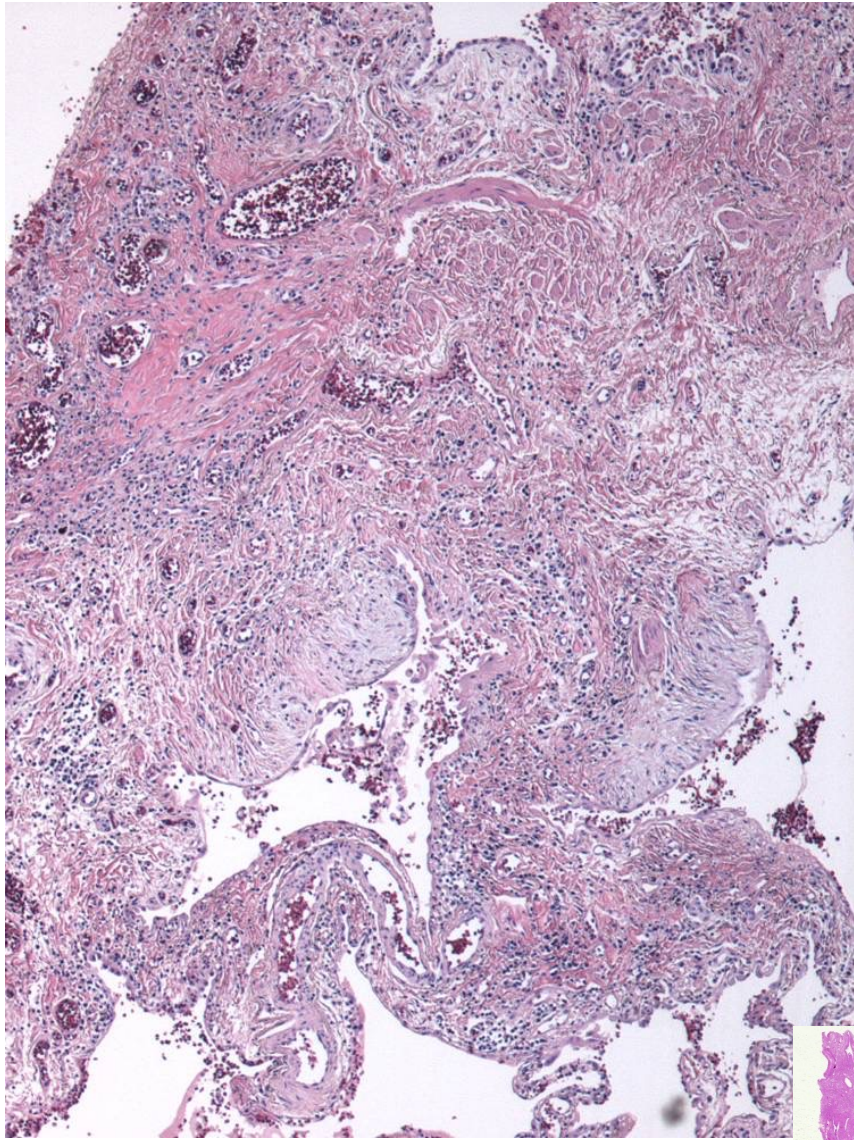
UIP - Microscopic



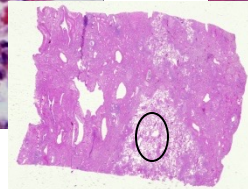
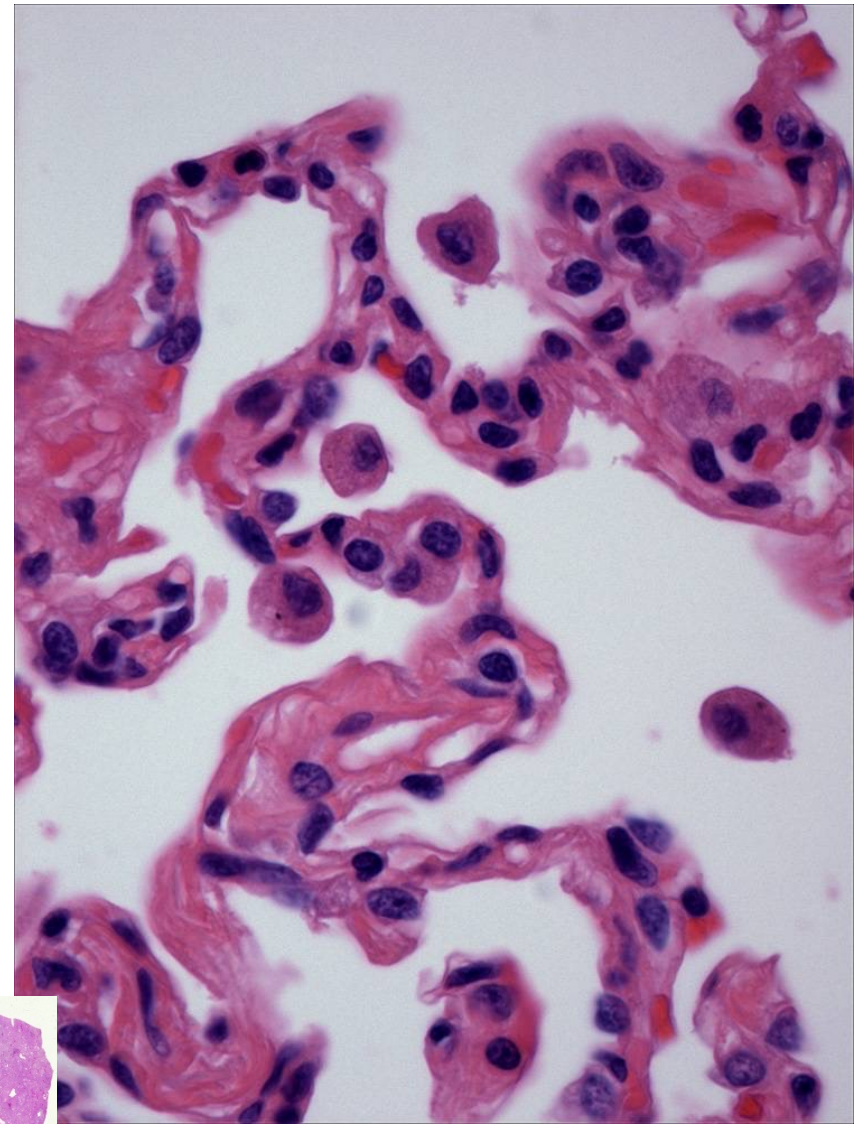
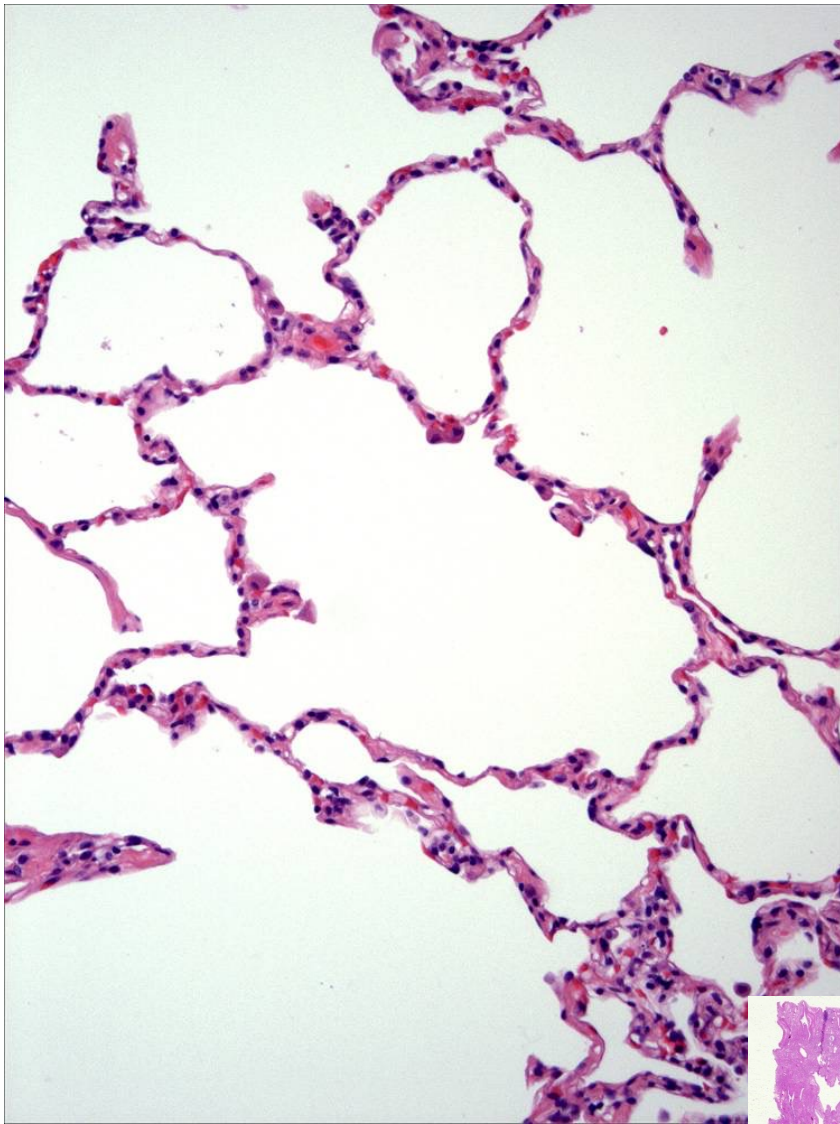
End Stage (“Honeycomb”) Lung



Fibroblastic Foci



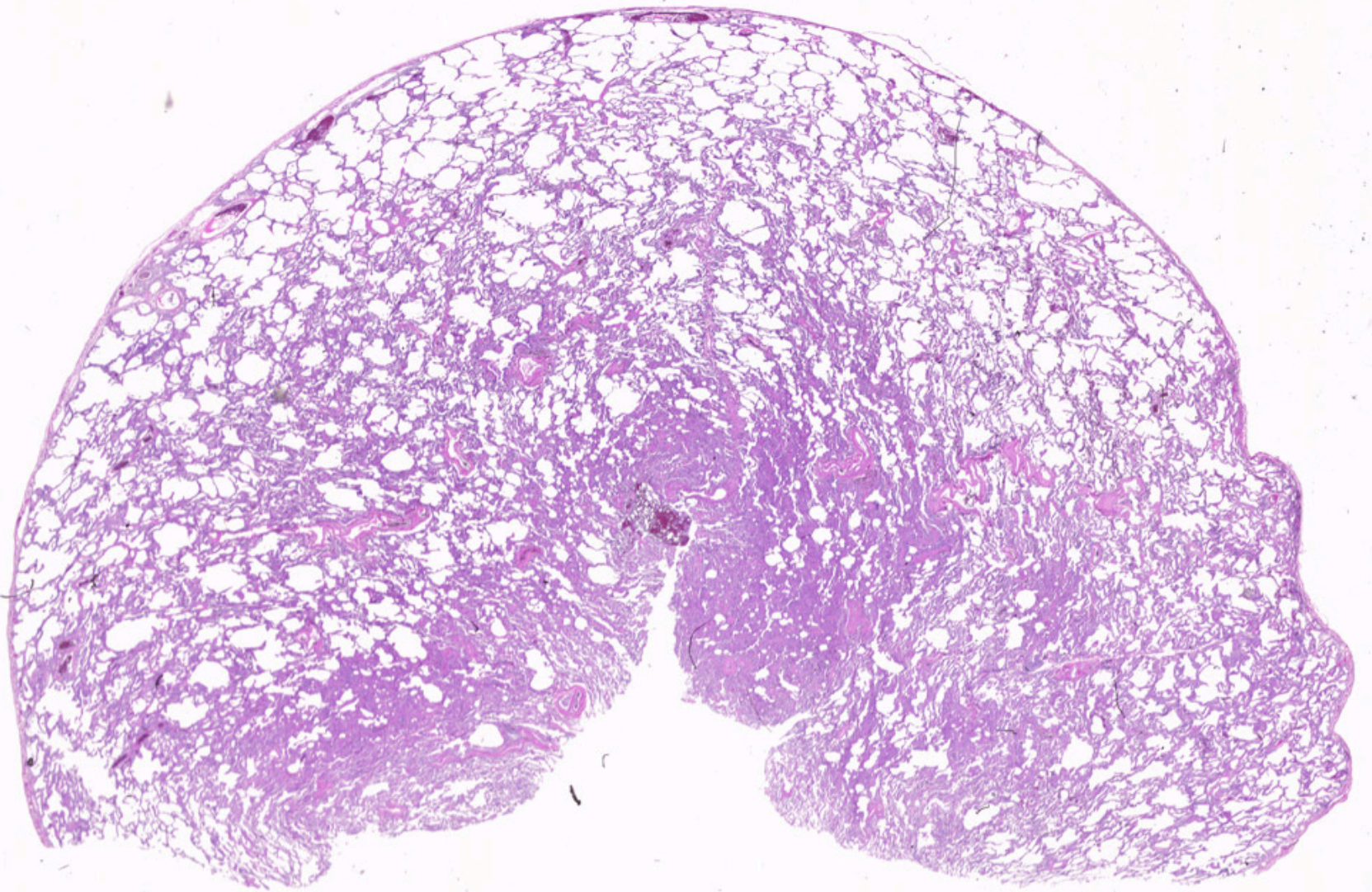
Normal Lung



Nonspecific Interstitial Pneumonia

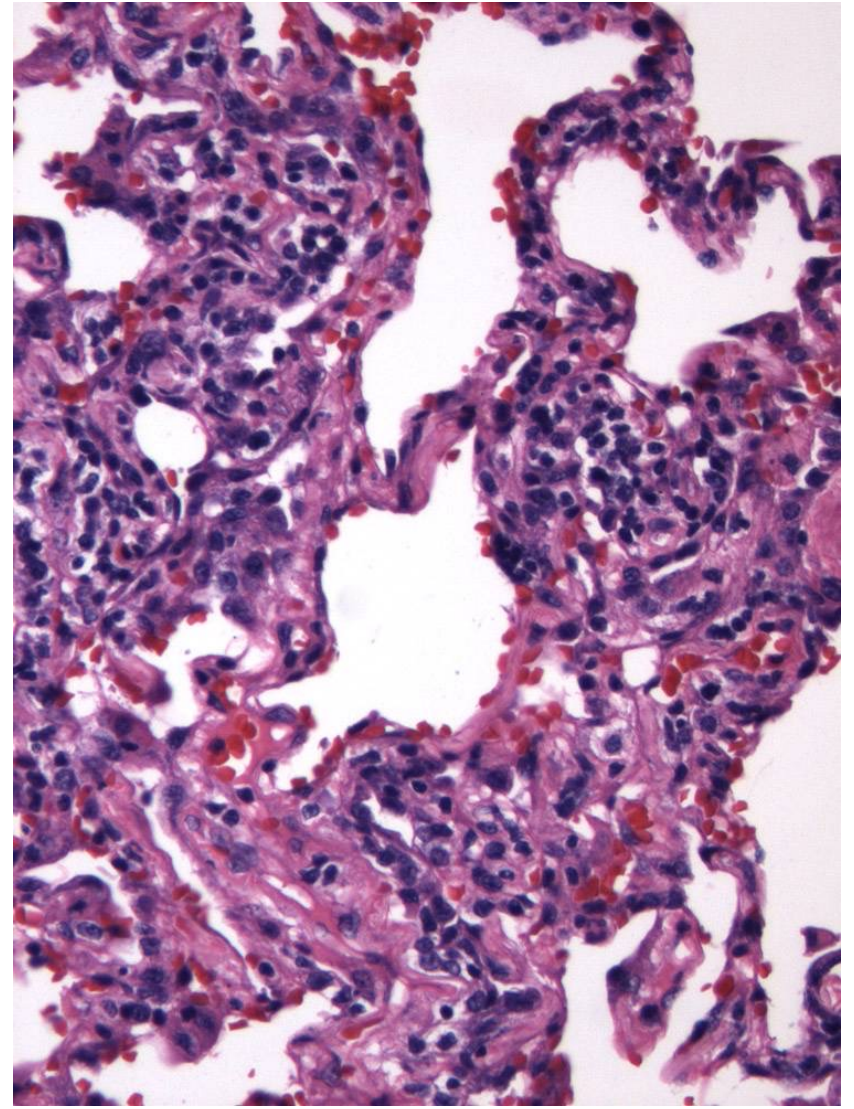
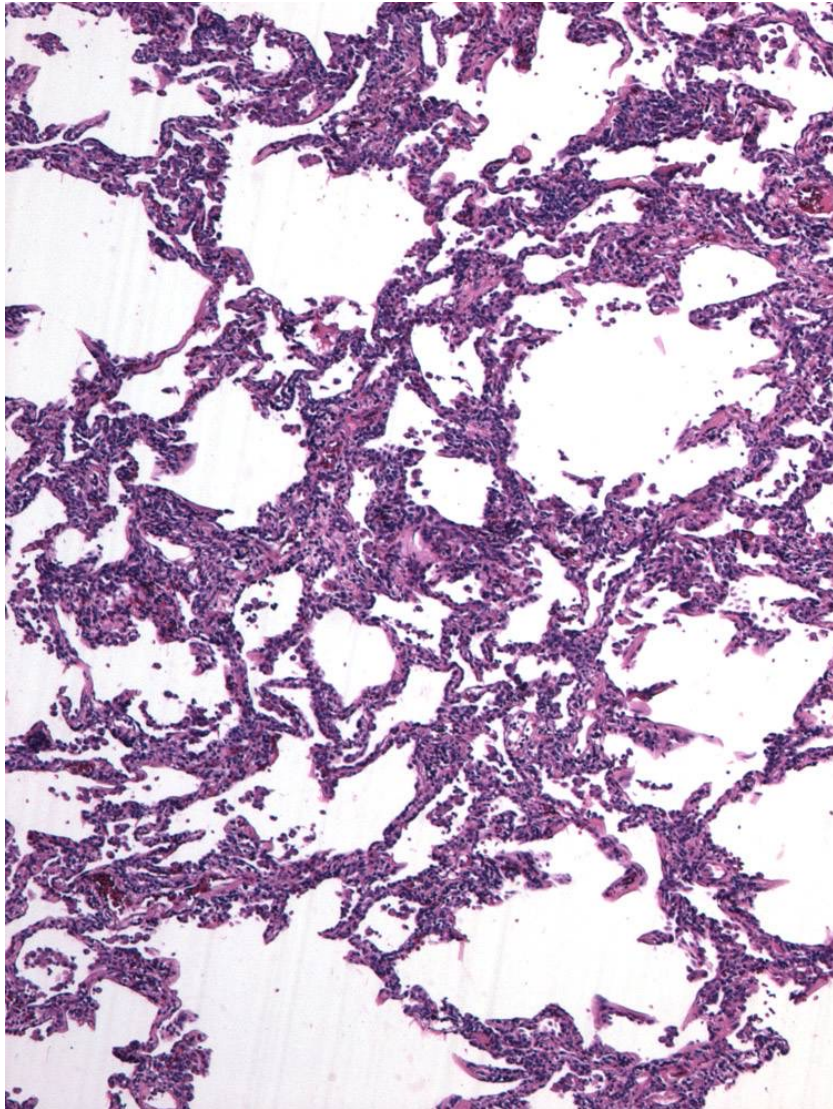
- Temporal and spatial *homogeneity*
- Cellular NSIP – chronic inflammation
- Fibrotic NSIP – fibrosis, less inflammation
- Architecture maintained

Cellular NSIP

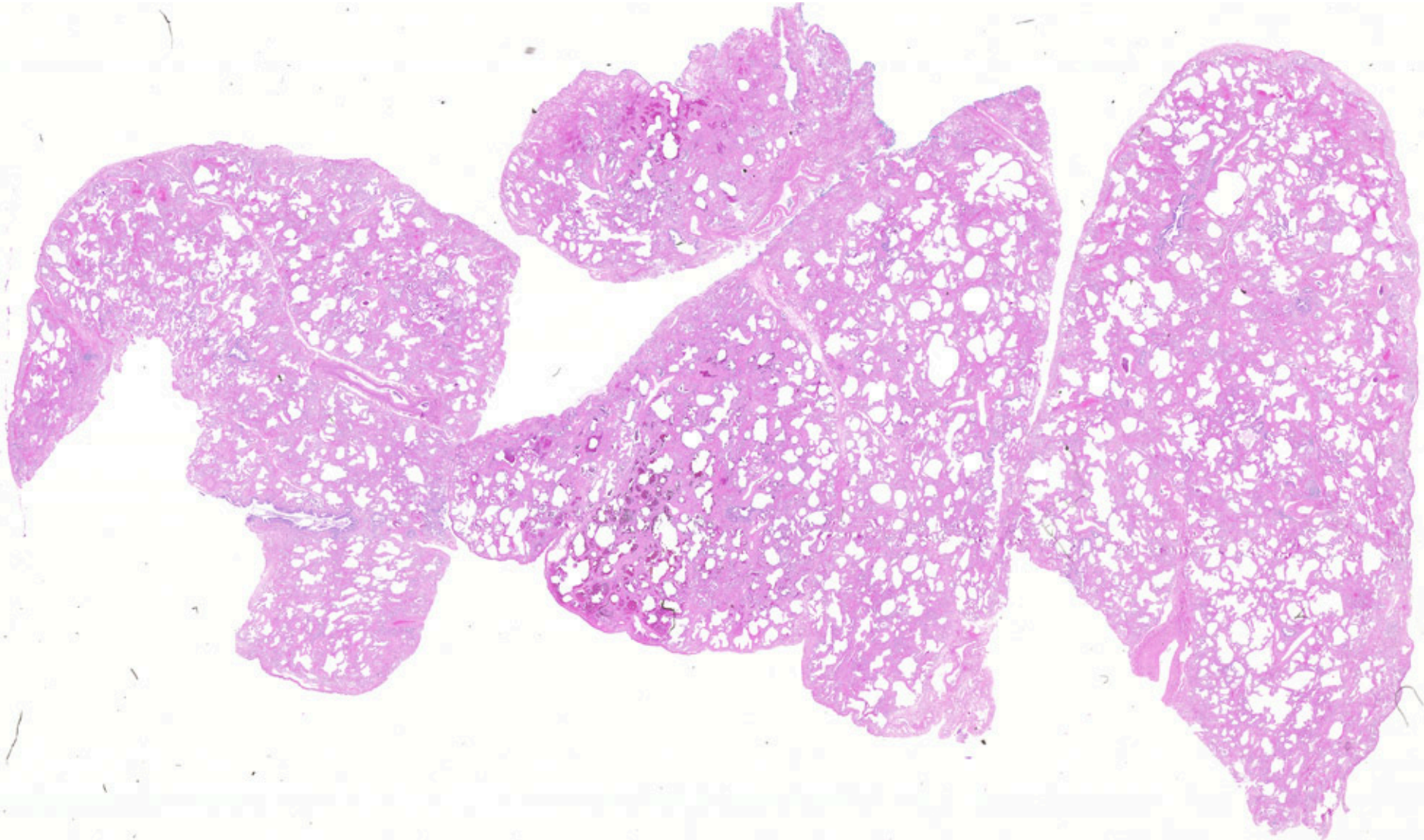


Cellular NSIP

Mild, diffuse, interstitial lymphocytic infiltrate

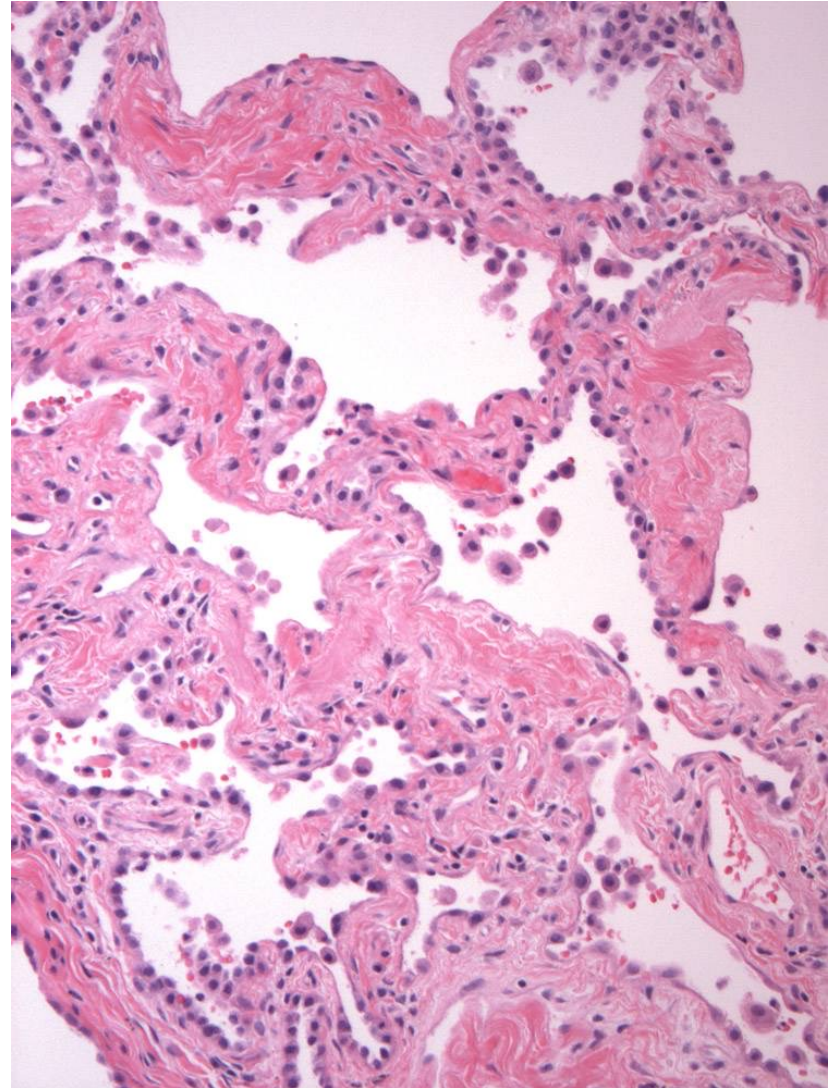
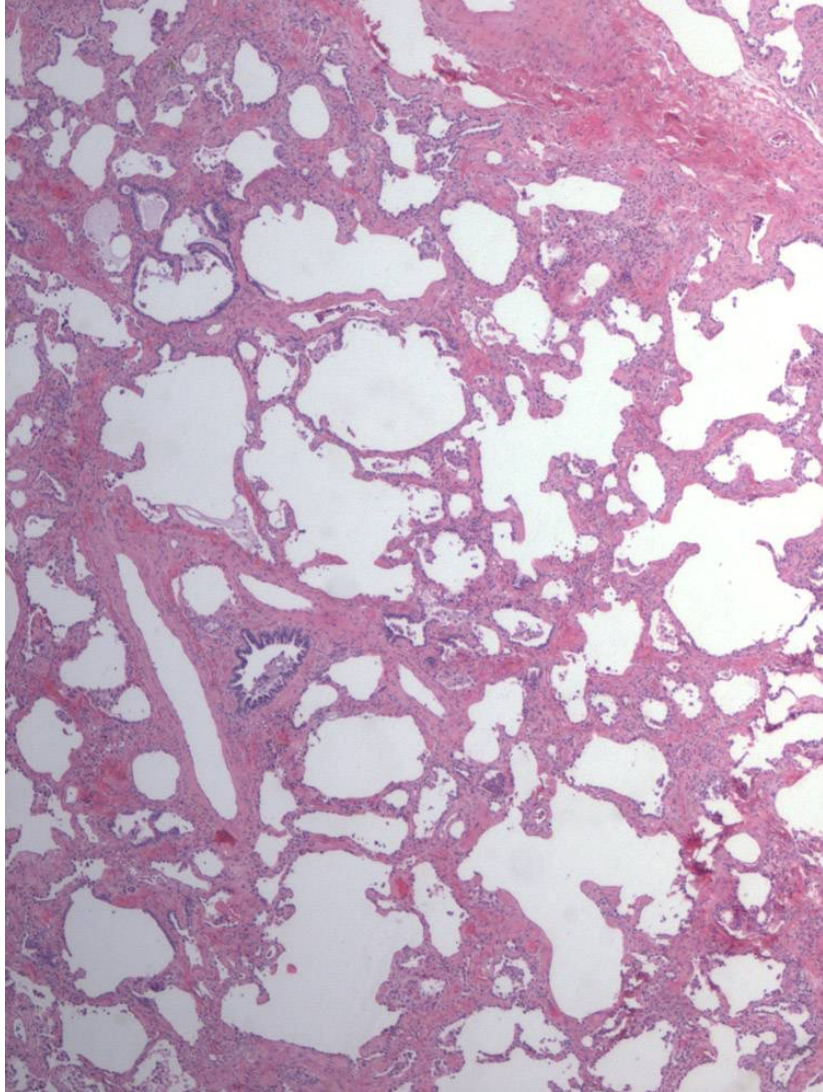


Fibrotic NSIP



Fibrotic NSIP

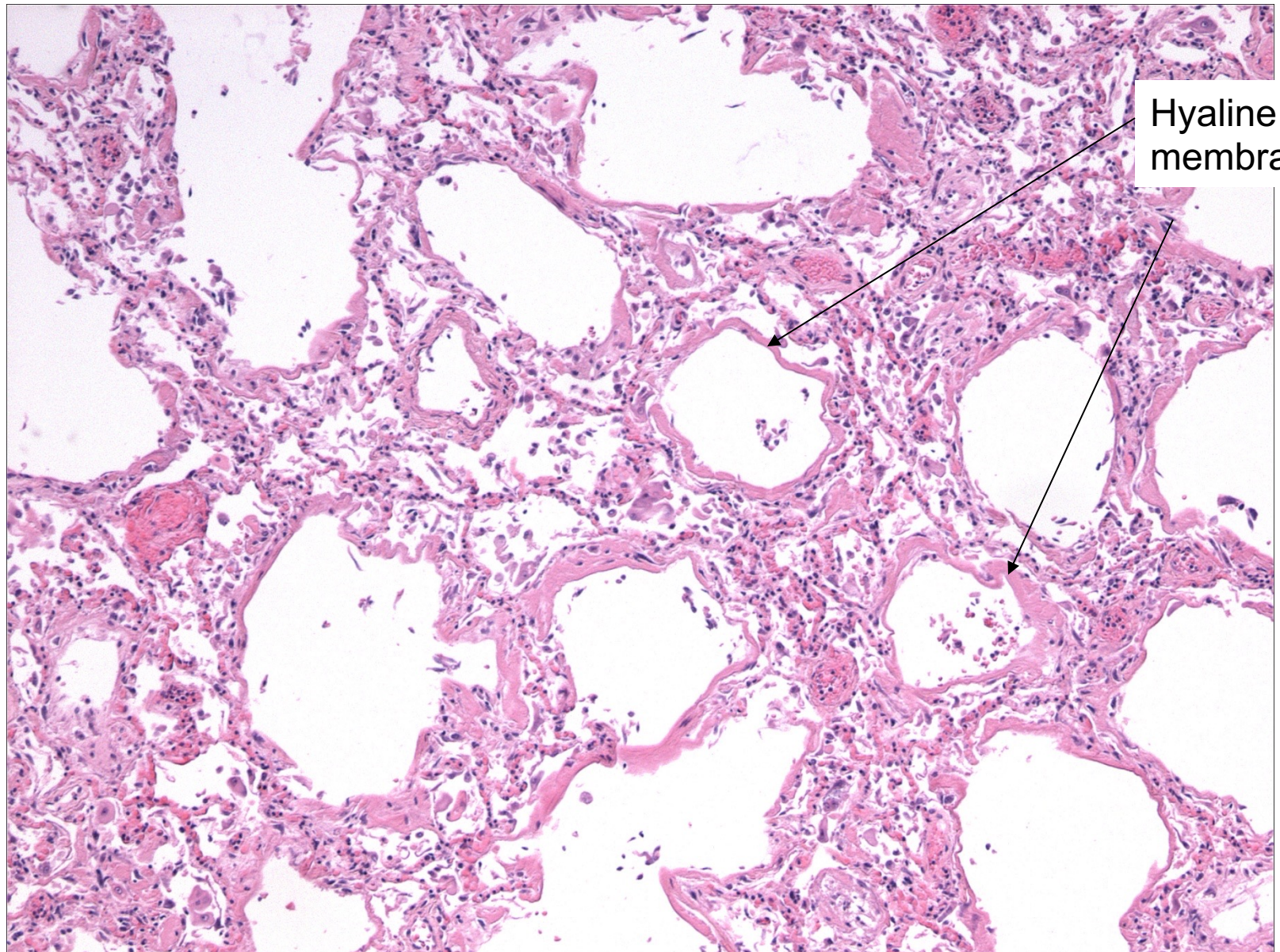
Diffuse interstitial fibrosis – all looks same age



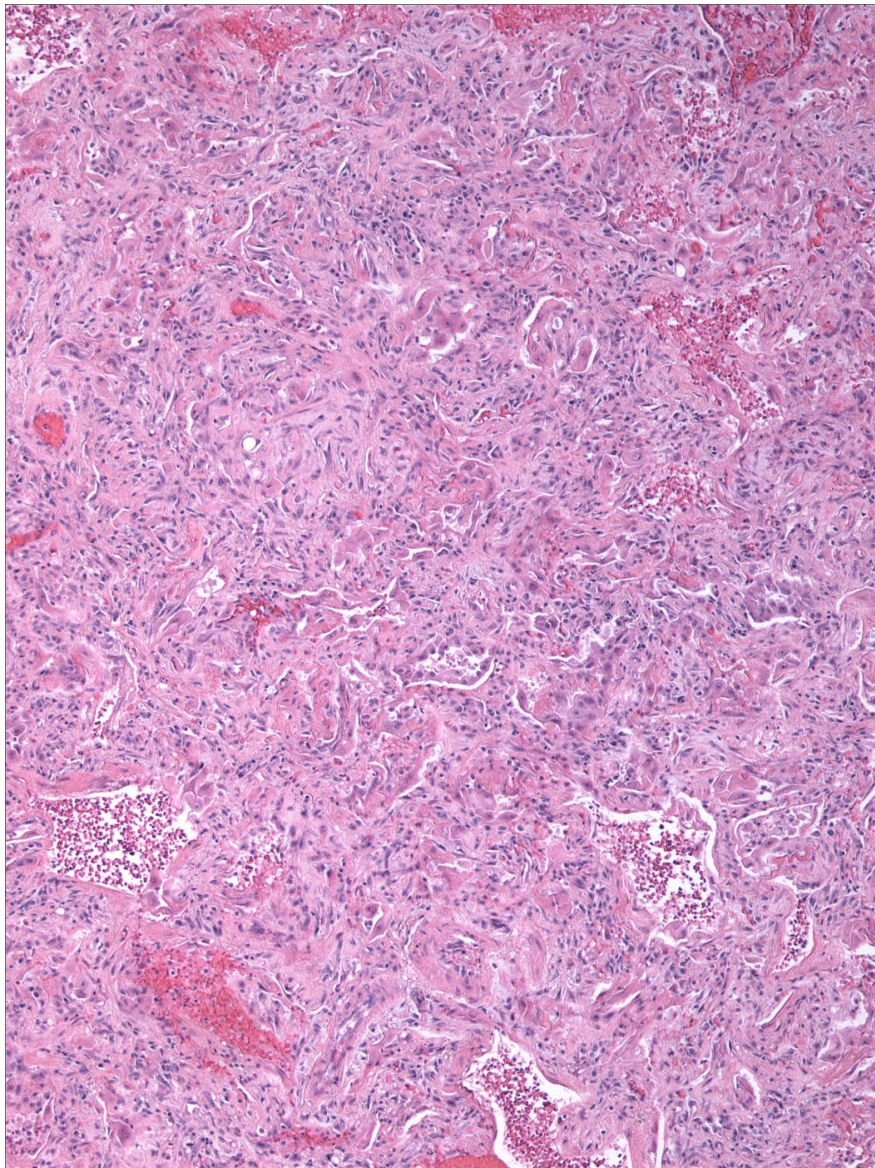
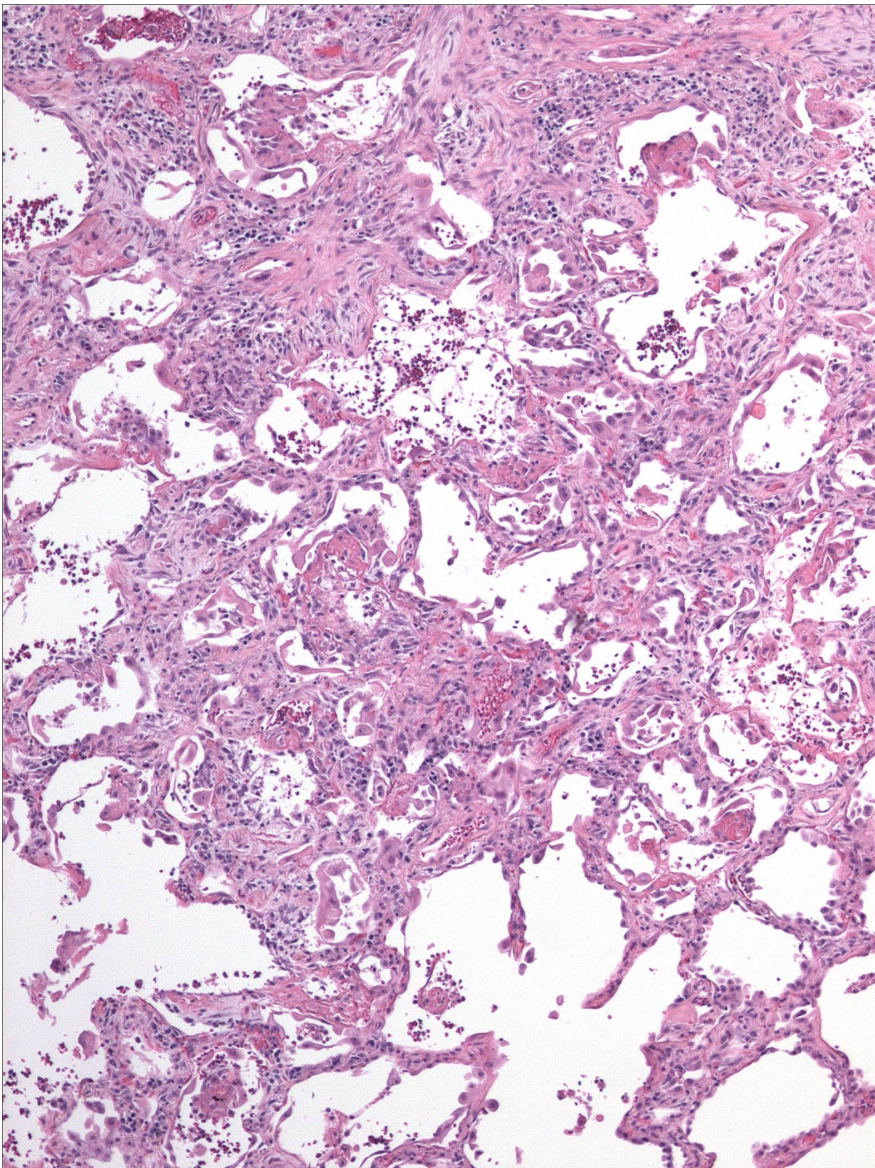
Acute Interstitial Pneumonia

- “Idiopathic” acute respiratory distress syndrome – no underlying cause (e.g., sepsis, toxic inhalation, pancreatitis)
- Pathologic findings – acute/exudative, organizing, fibrotic *diffuse alveolar damage* without morphologic clues as to etiology

AIP-Exudative Phase



AIP- Organizing and Fibrotic Phase

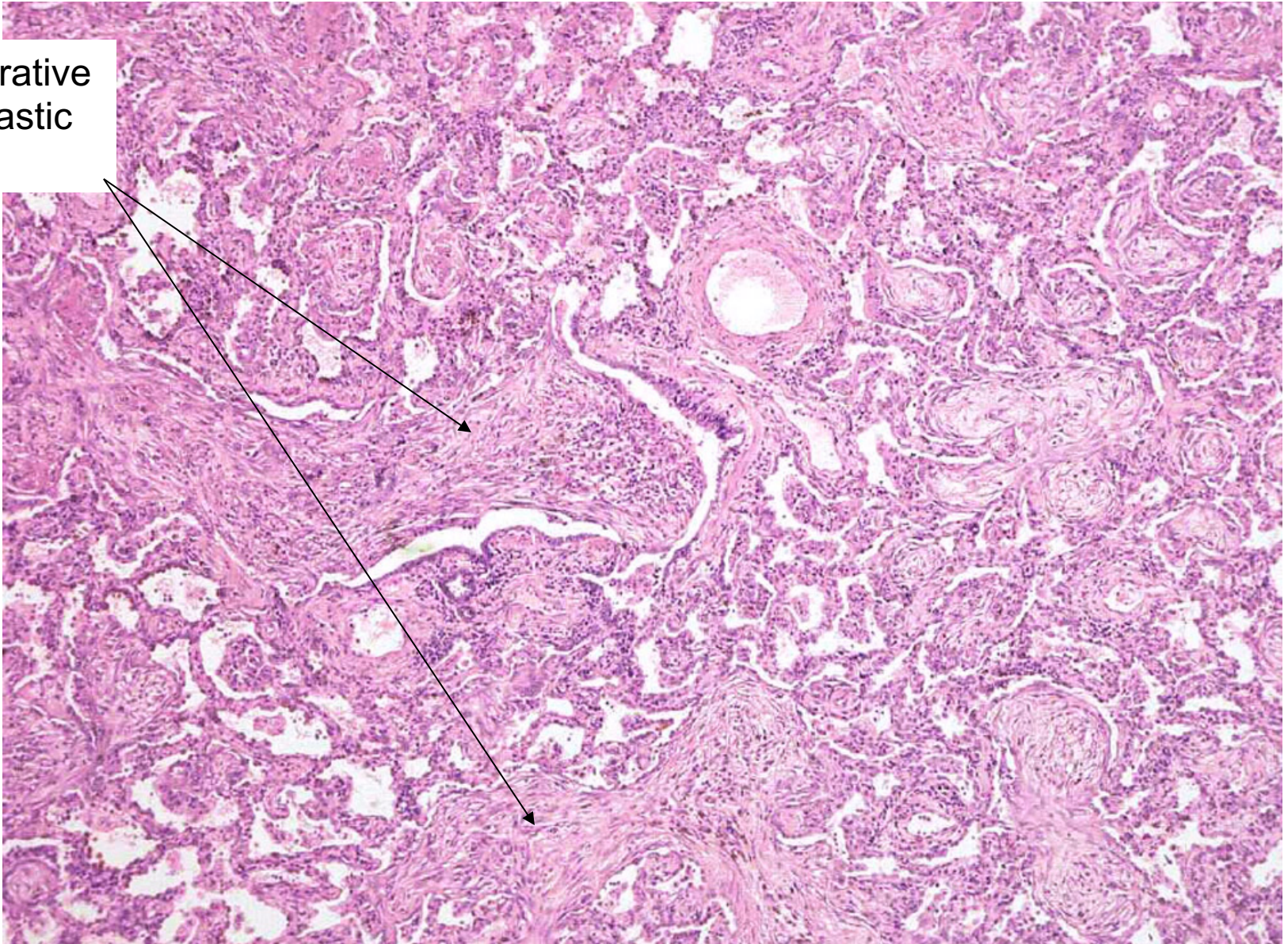


Cryptogenic Organizing Pneumonia

- “Idiopathic” bronchiolitis obliterans and organizing pneumonia
- Proliferative fibroblastic plugs within respiratory bronchioles, alveolar ducts, alveolar spaces
- Variable interstitial chronic inflammation
- Temporally homogeneous with preservation of underlying lung architecture
- Histologic pattern can be seen in various clinical scenarios and as part of other specific pathologic entities (e.g., hypersensitivity pneumonitis, at periphery of malignancies, resolving infection)

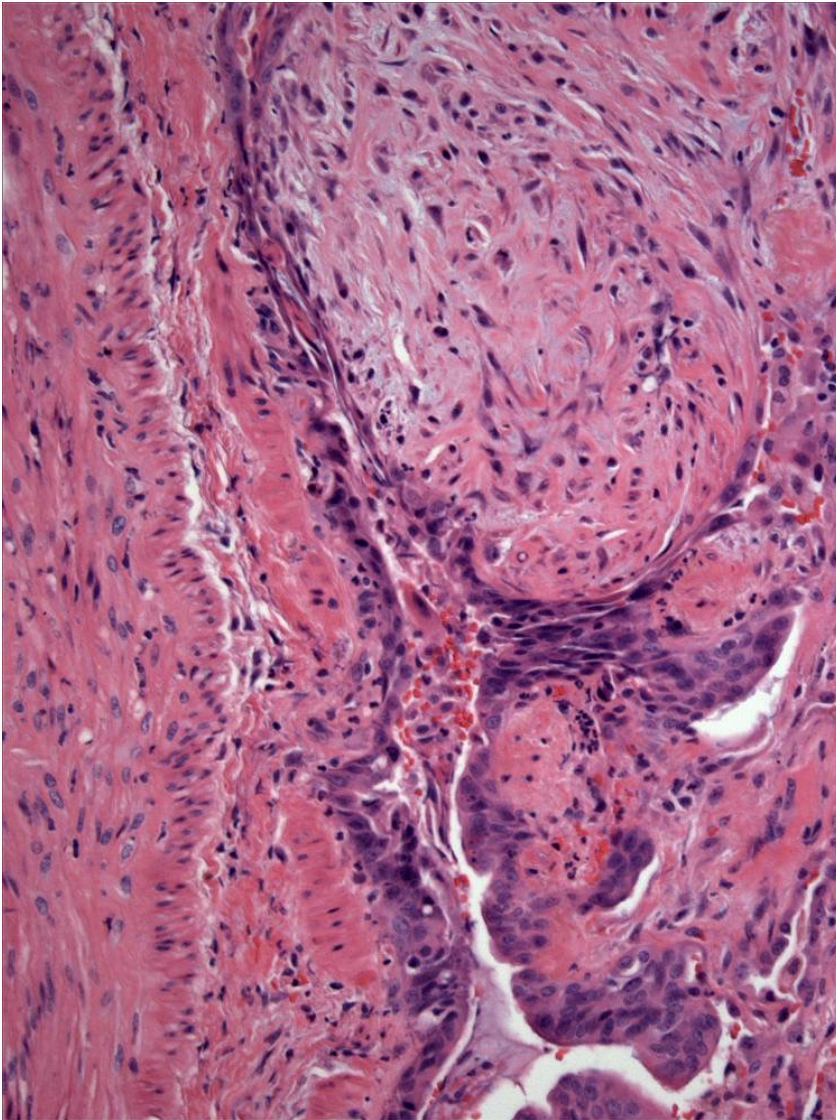
Cryptogenic Organizing Pneumonia

Proliferative
fibroblastic
plugs

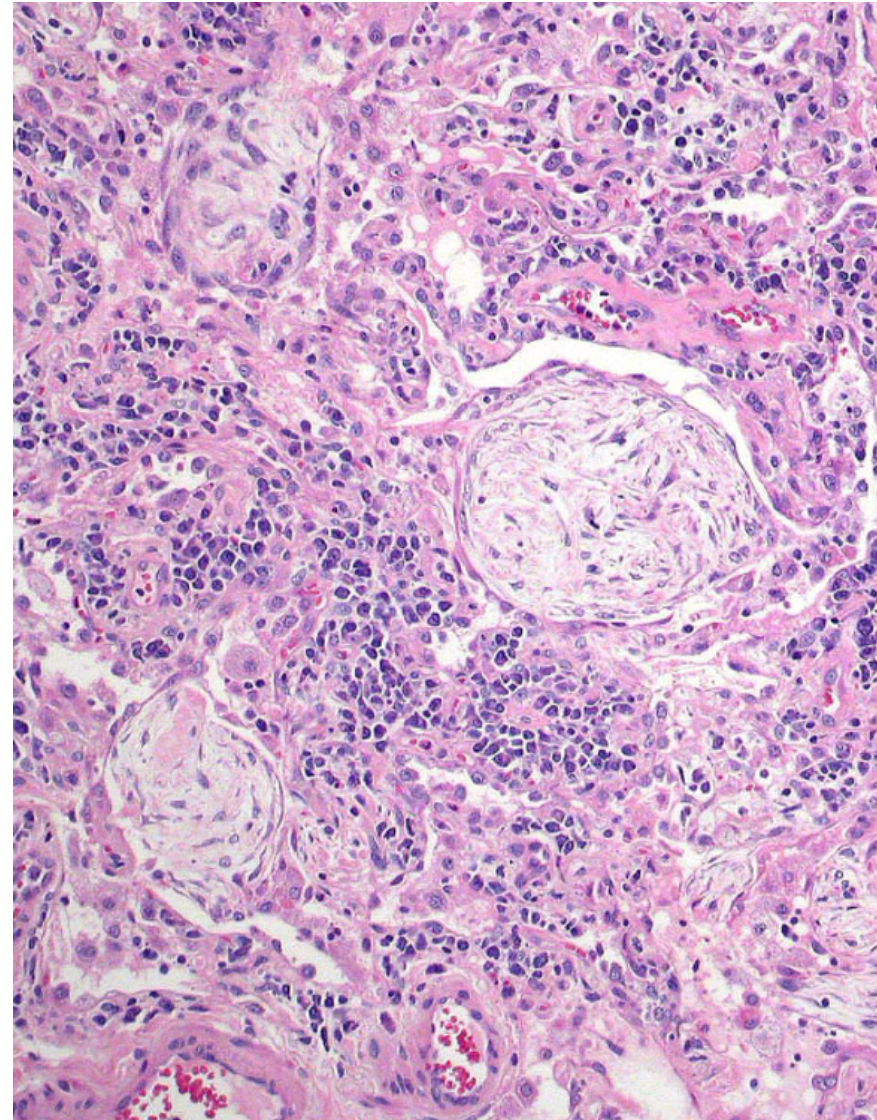


Cryptogenic Organizing Pneumonia

Bronchiolitis obliterans



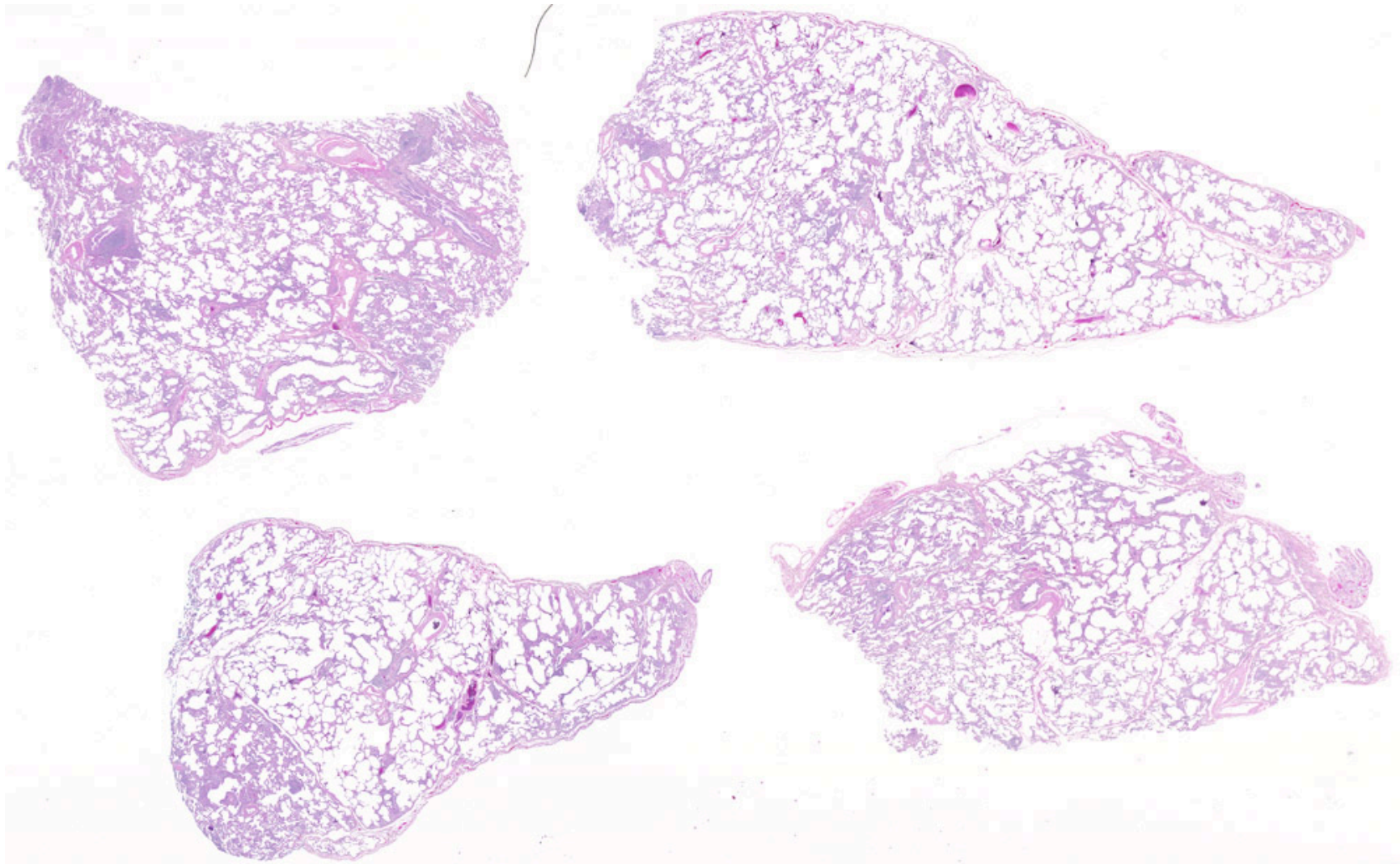
Organizing pneumonia



Hypersensitivity Pneumonitis

- Patchy interstitial pneumonitis with lymphocytes and plasma cells, accentuated around small airways
- Loosely formed non-necrotizing granulomas
- Foci of organizing pneumonia

Hypersensitivity Pneumonitis



Hypersensitivity Pneumonitis

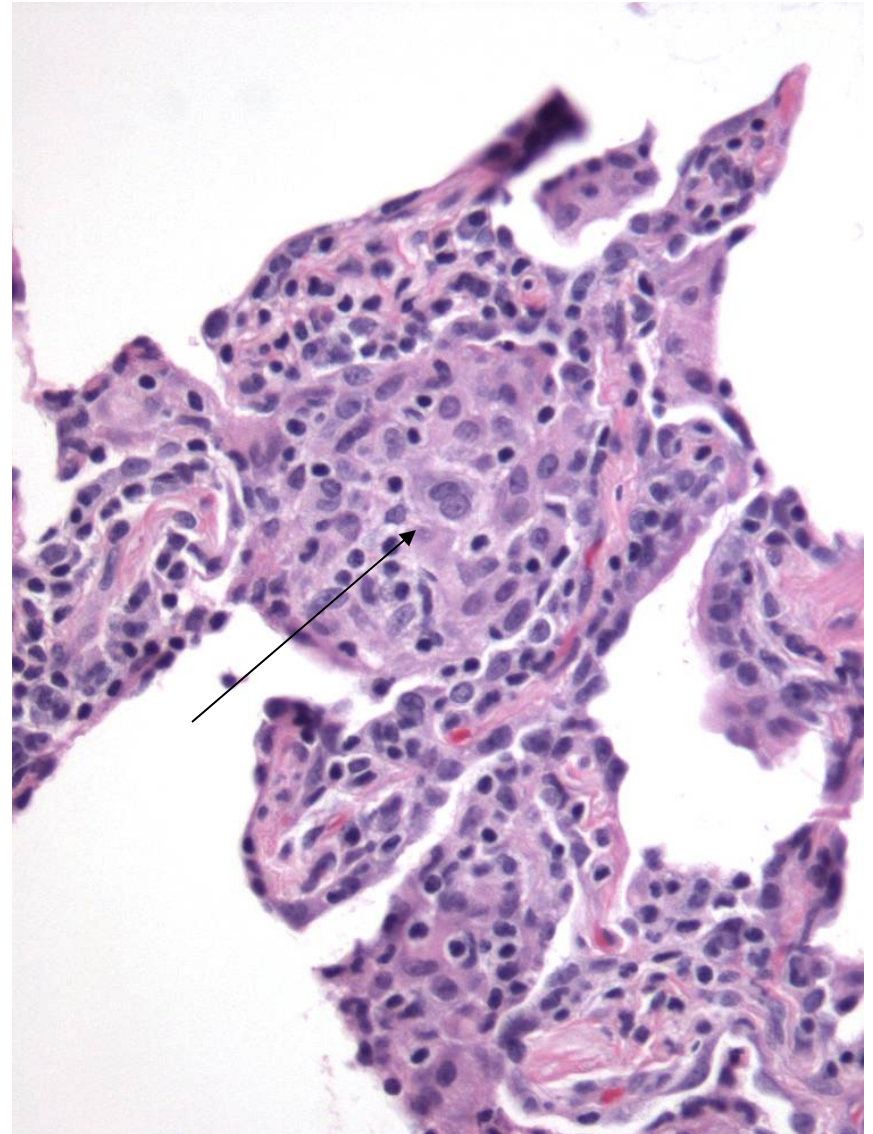
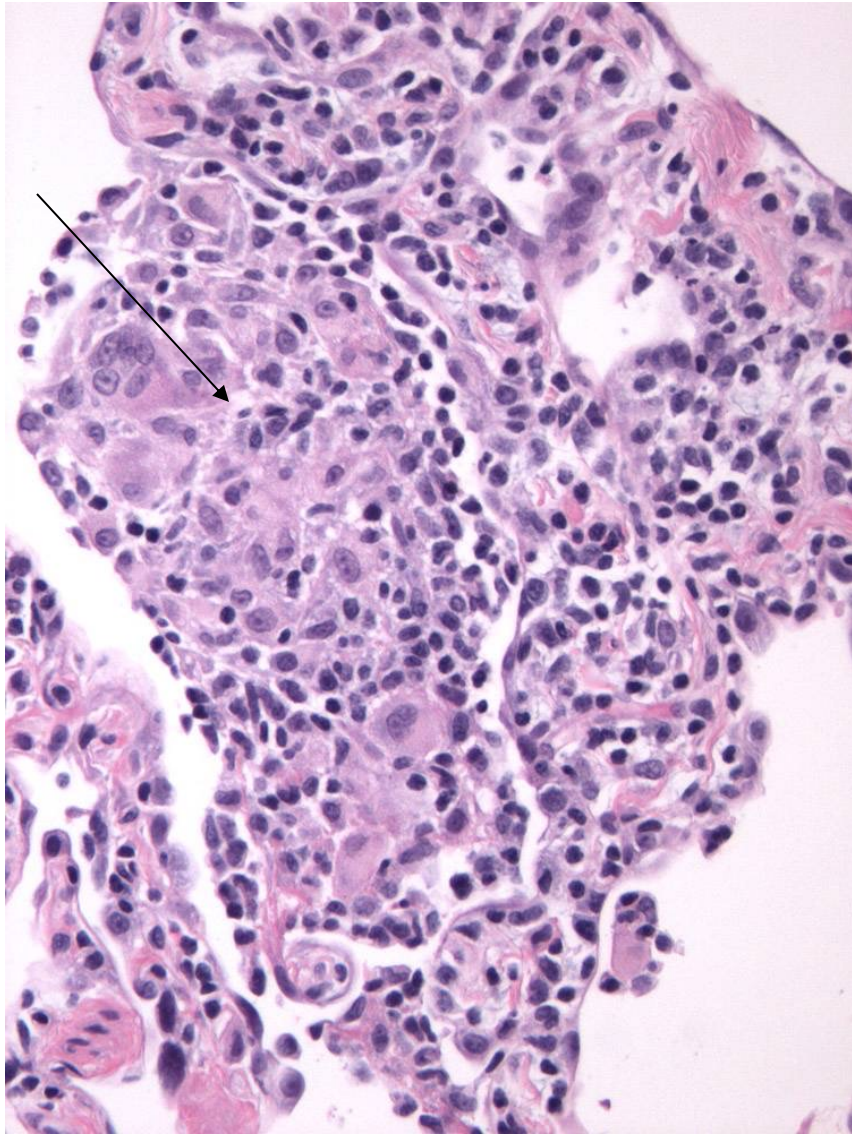


Chronic inflammation

Bronchiole

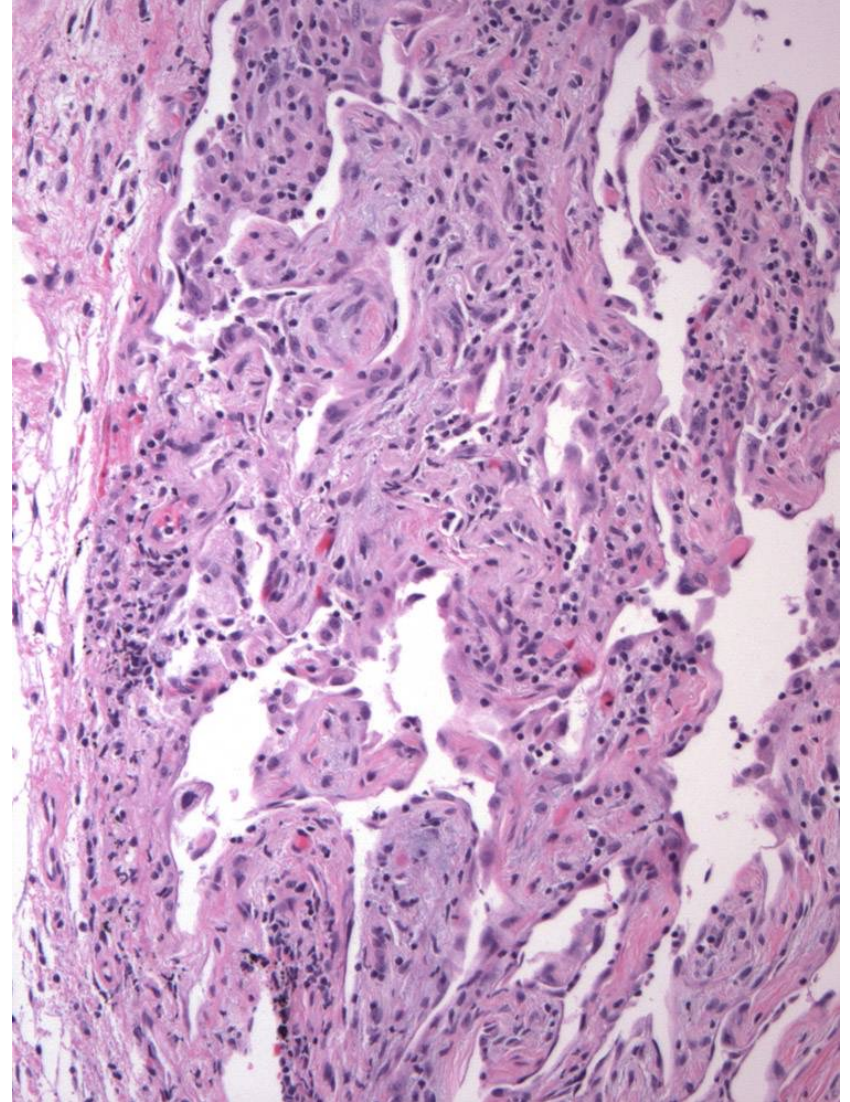
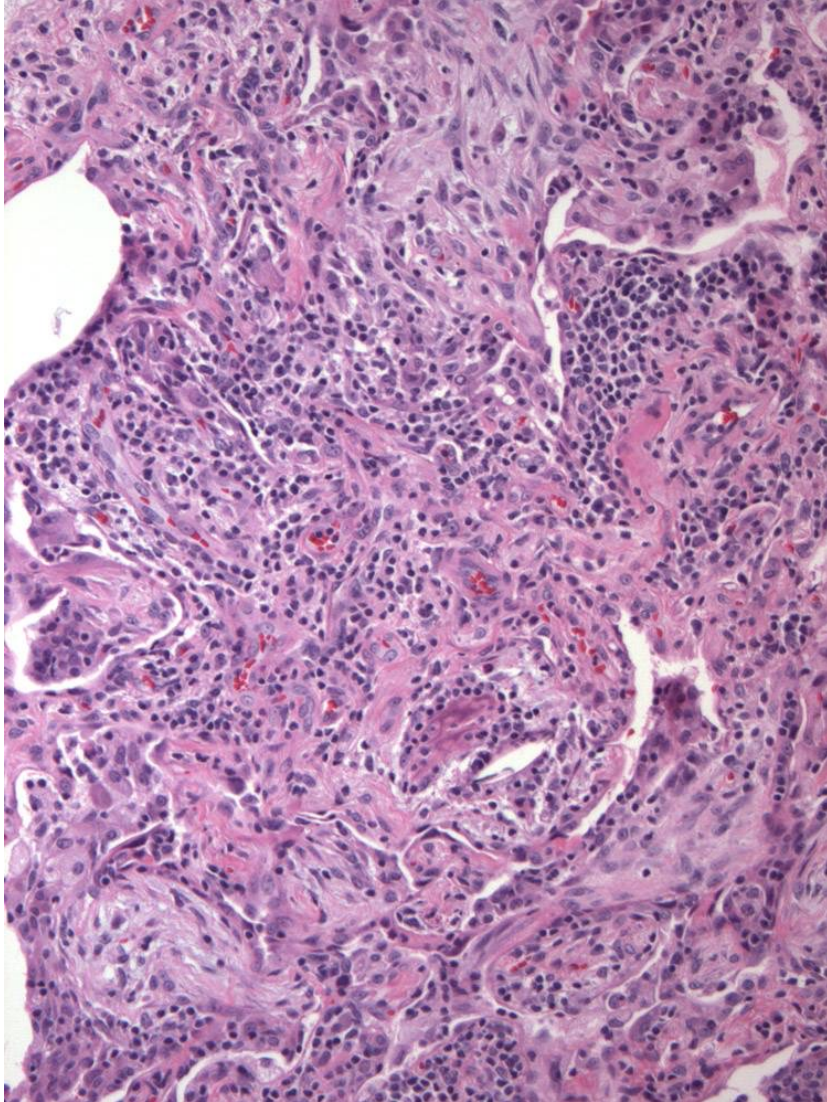
Hypersensitivity Pneumonitis

Loosely formed non-necrotizing granulomas



Hypersensitivity Pneumonitis

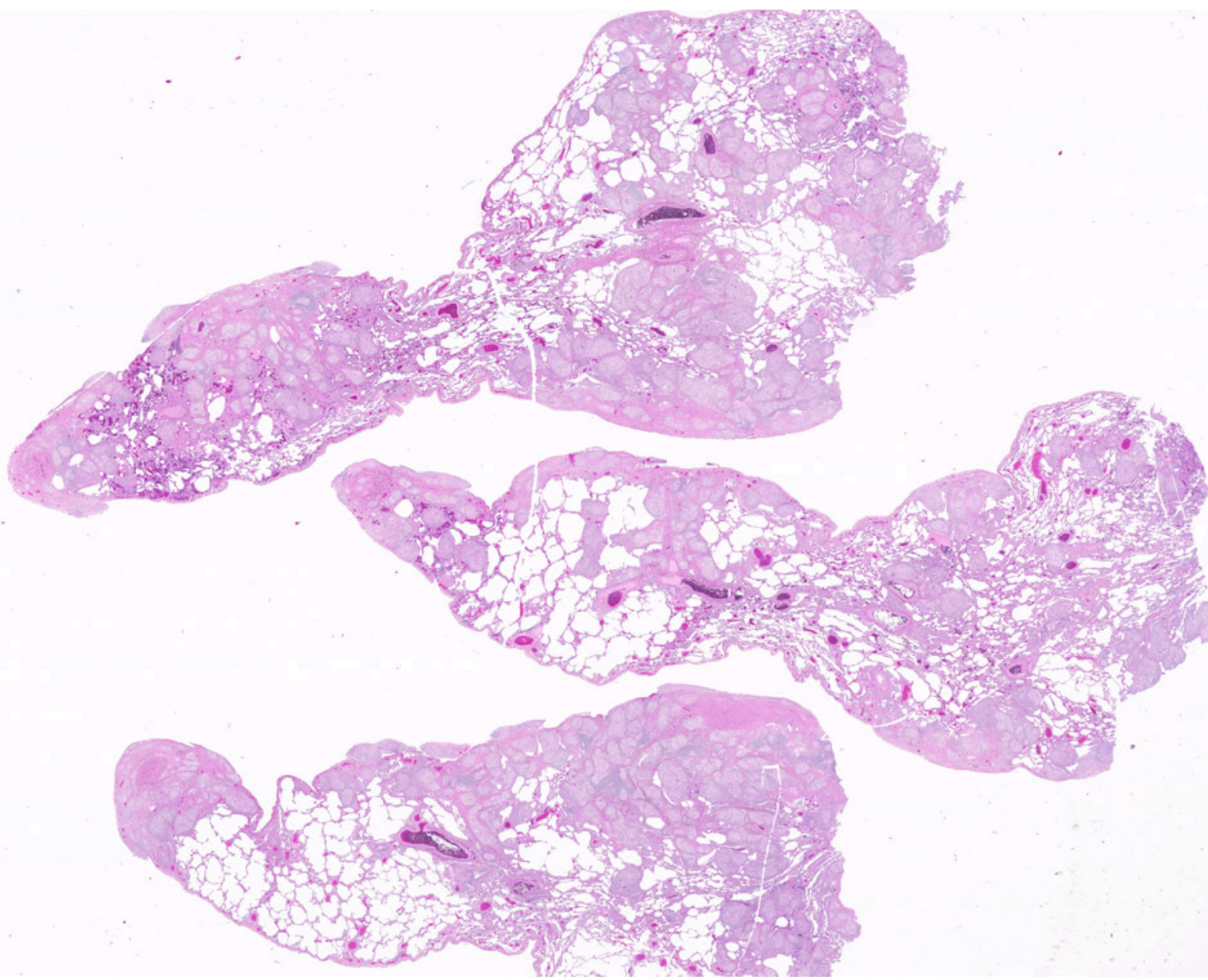
Areas of organizing pneumonia pattern



Sarcoidosis

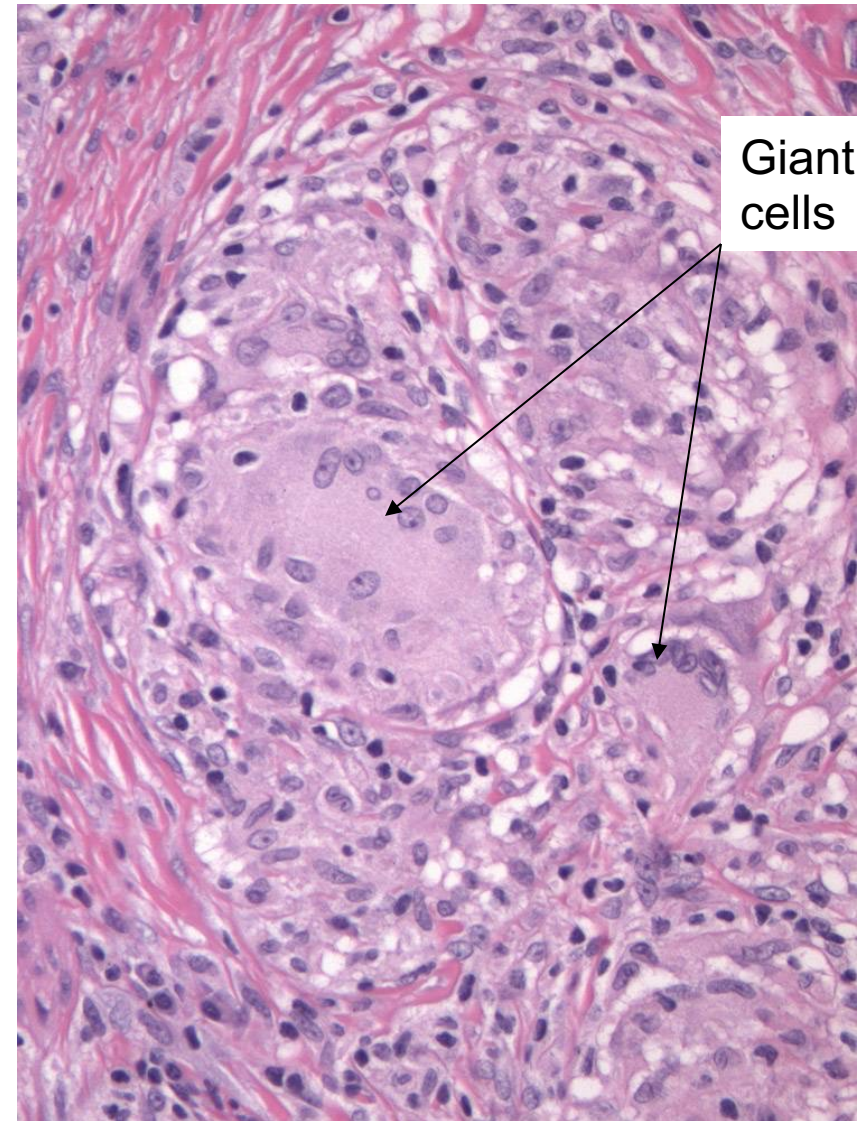
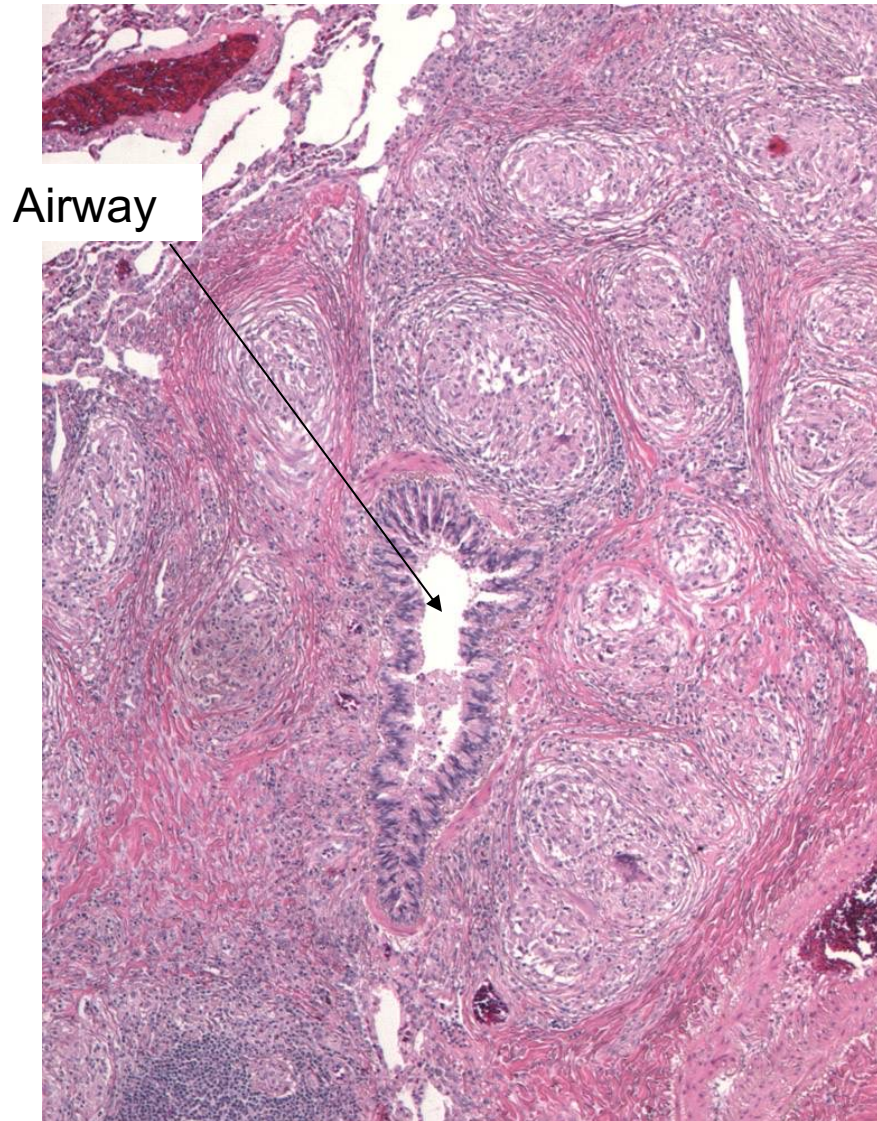
- Well-formed non-necrotizing granulomas
- Often with surrounding fibrosis and variable chronic inflammation
- Lymphatic distribution – peribronchiolar and septal/pleural
- Transbronchial biopsy can be diagnostic – multiple samples, multiple levels

Sarcoidosis



Sarcoidosis

Well-formed non-necrotizing granulomas



Sarcoidosis – Differential Diagnosis

- Infection – mycobacterial, fungal – special stains
- Foreign material (e.g., from IVDU)
- Hypersensitivity pneumonitis – different character of the granulomas
- Drug reaction
- Berylliosis – identical histology
- Other granulomatous lung diseases – granulomatosis with polyangiitis, rheumatoid nodules, bronchocentric granulomatosis

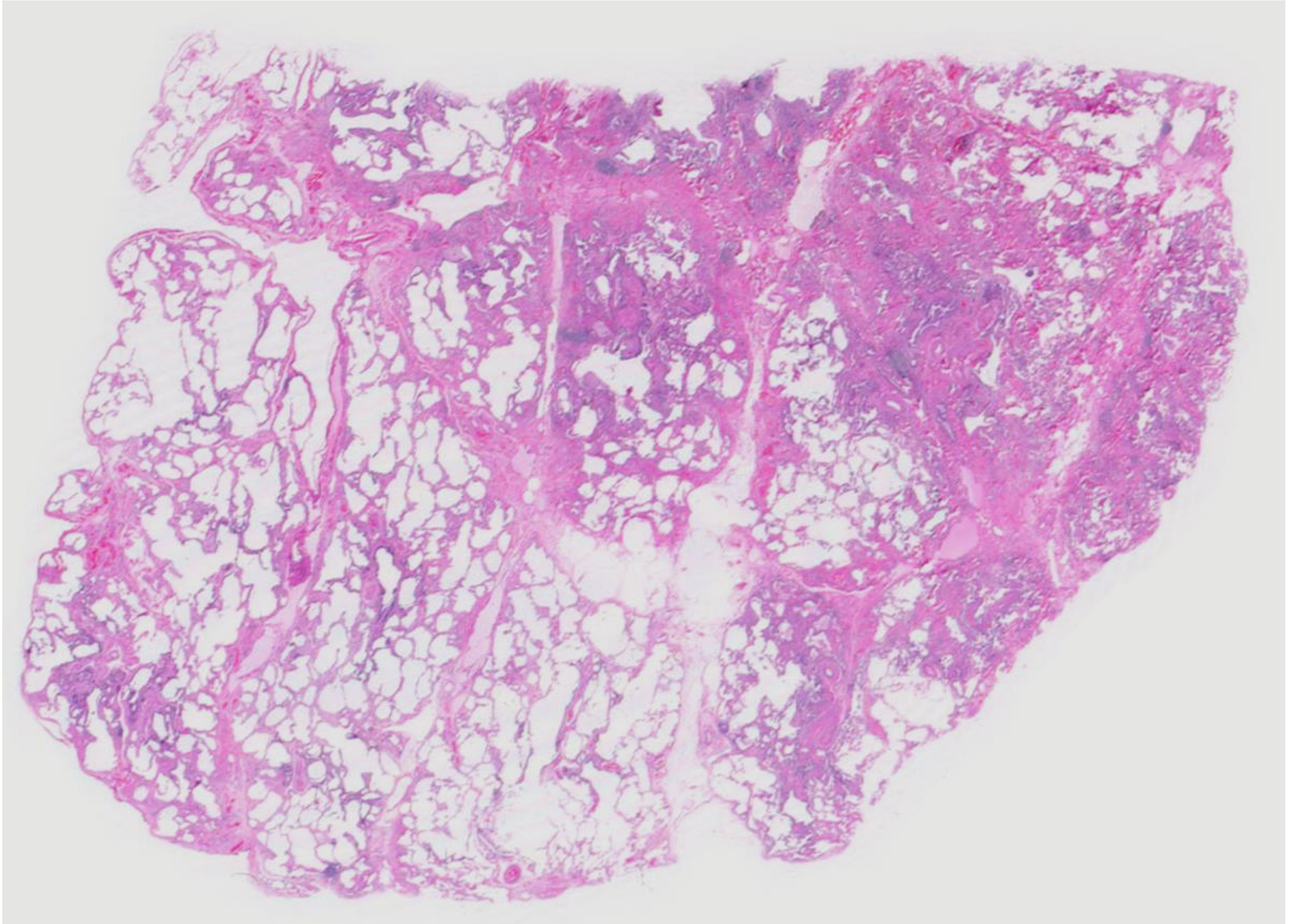
ILD – General Comments

- Clinical-radiologic-pathologic correlation
 - Multidisciplinary meeting
- Histologic patterns of disease
- Significant infidelity
 - One etiology can give rise to several patterns
 - Same pattern can be present in multiple diseases
- Surgical vs. transbronchial biopsy

Question

- Patient is a 60 year old man with cough and shortness of breath
- Surgical lung biopsy

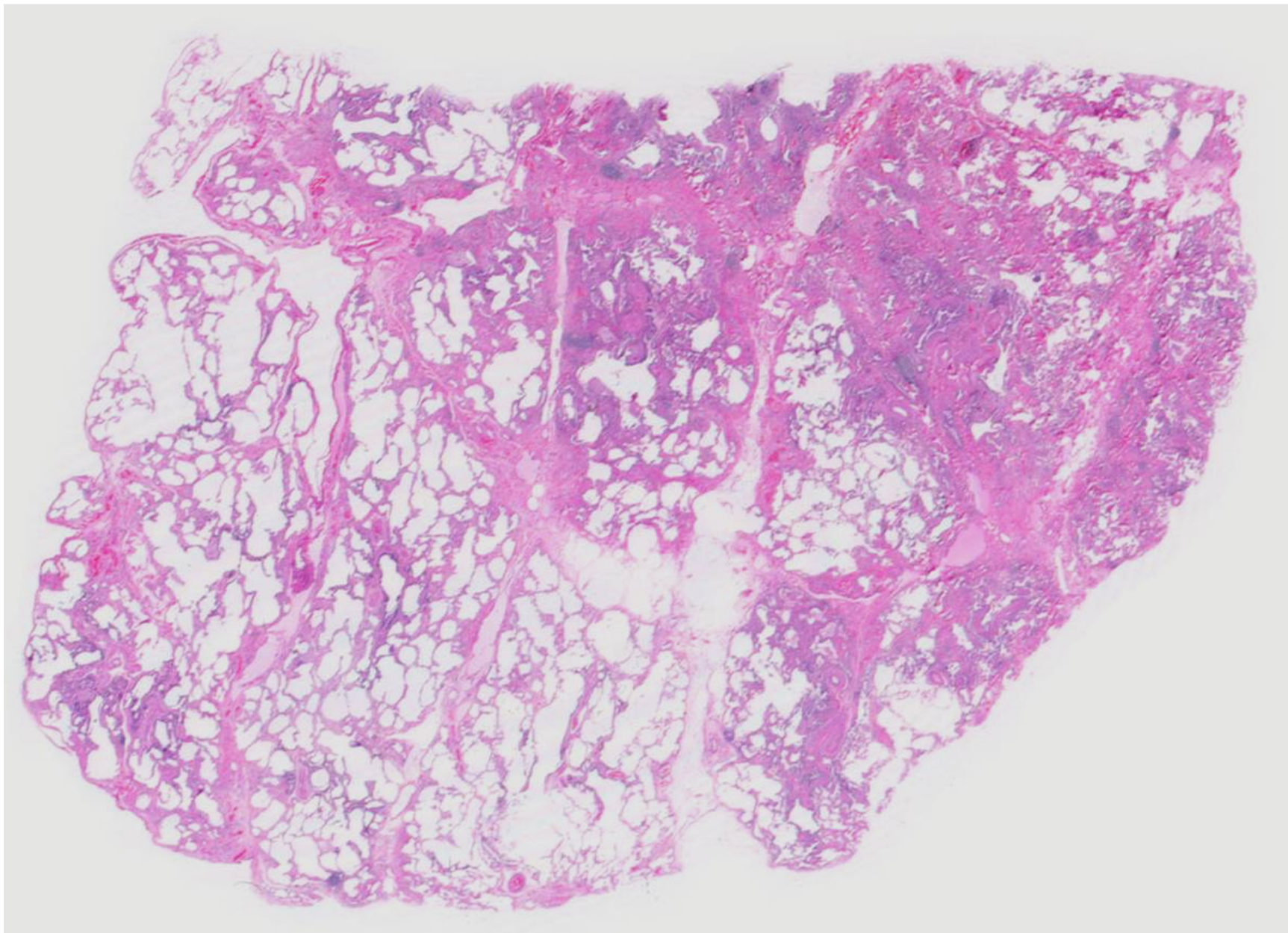
Question



Question – Which is correct?

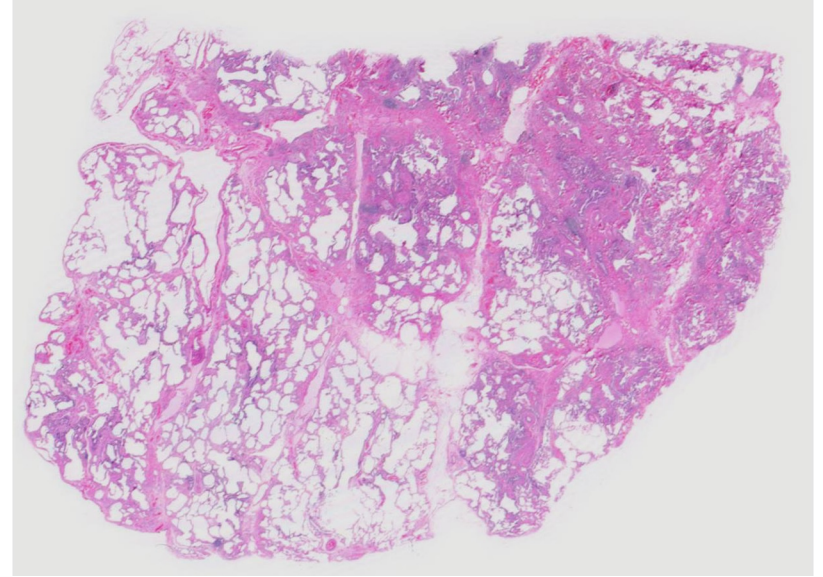
- A. This is a uniform process consistent with nonspecific interstitial pneumonia (NSIP)
- B. This is a patchy process consistent with usual interstitial pneumonia (UIP)
- C. There are hyaline membranes consistent with the exudative phase of diffuse alveolar damage; this would fit with acute interstitial pneumonia (AIP)
- D. This is an alveolar filling process consistent with cryptogenic organizing pneumonia (COP)
- E. A transbronchial biopsy could have made this diagnosis with certainty

Question



Question – Which is correct?

***This is a patchy process
consistent with usual
interstitial pneumonia (UIP)***



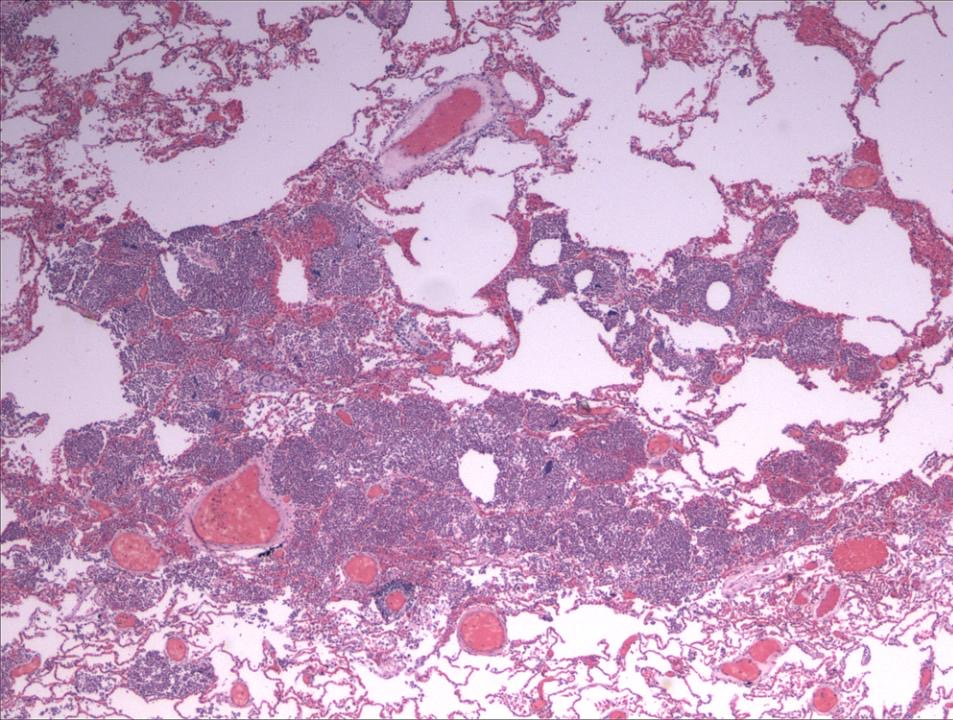
There are areas of dense fibrosis, areas of inflammation and areas of relatively normal lung. These are the histologic features of UIP.

Outline

- Interstitial lung disease
- • Infection
- Malignancy
- Pathology special stains and buzzwords

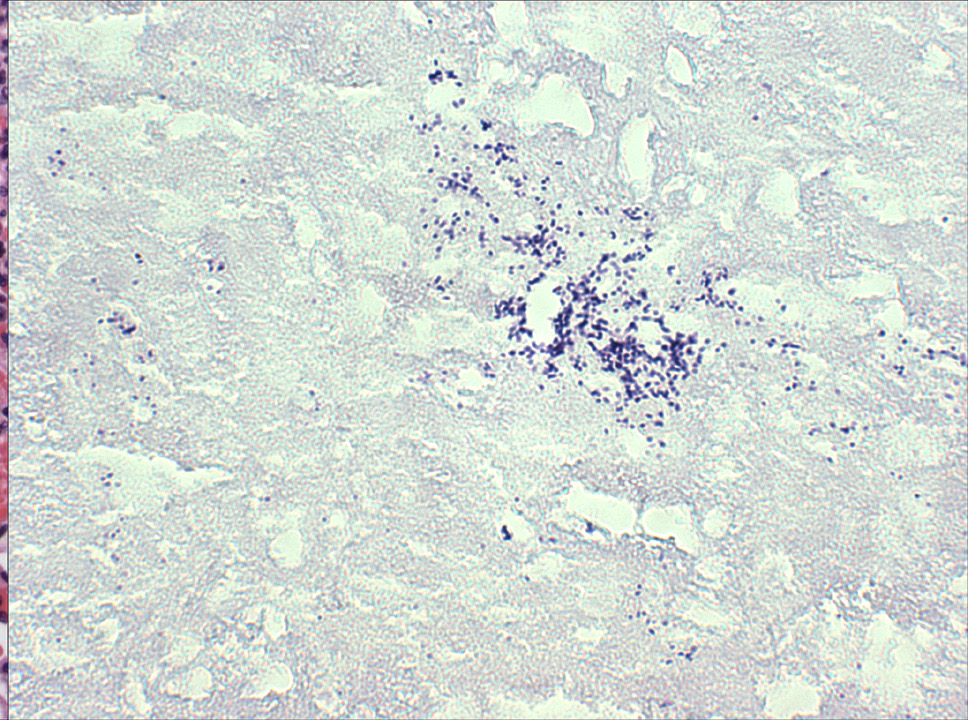
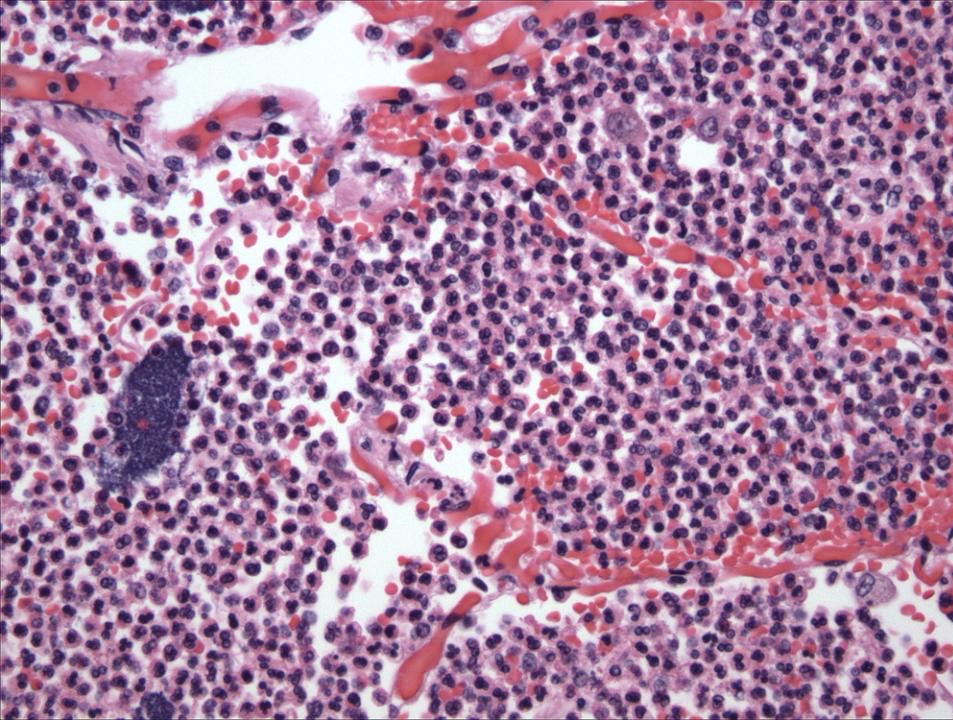
Bacterial Pneumonia

- Acute inflammation – neutrophils, fibrin, edema, bacteria in alveolar spaces
- Gram stain can highlight bacterial organisms in tissue sections and smears
- Progression to organizing pneumonia that resembles BOOP/COP discussed prior



Bacterial
Pneumonia

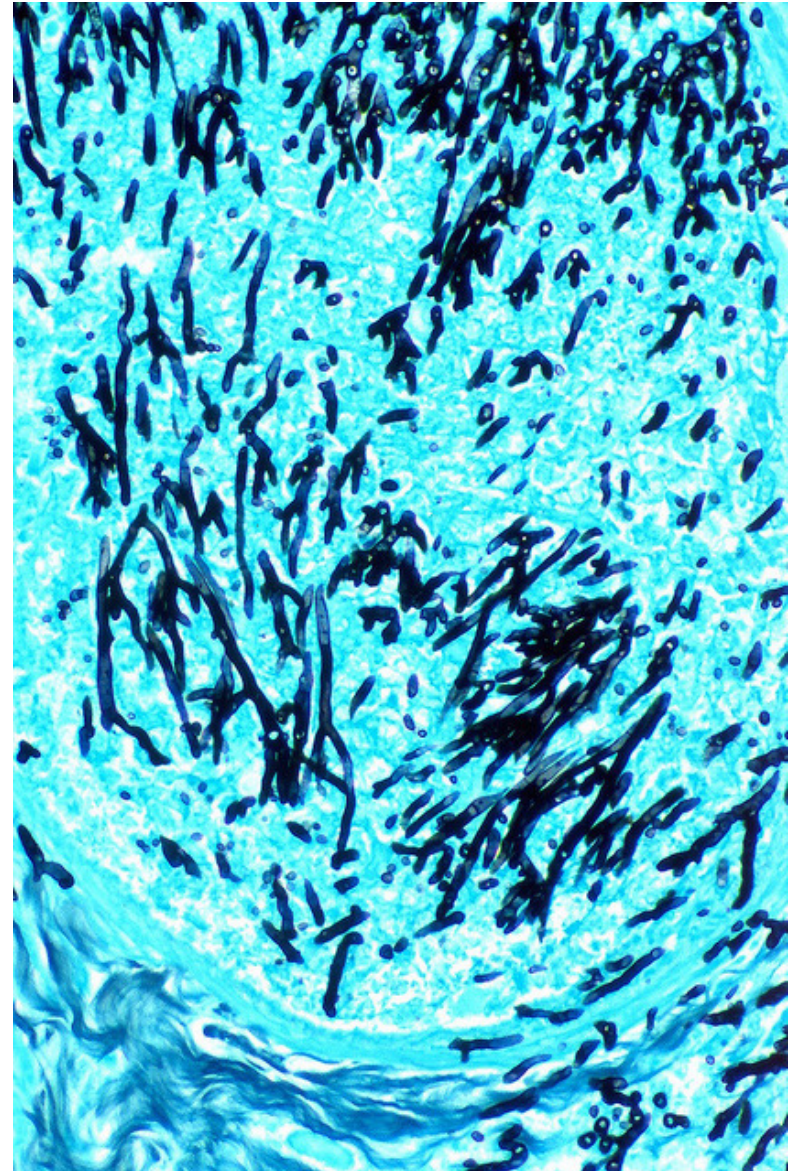
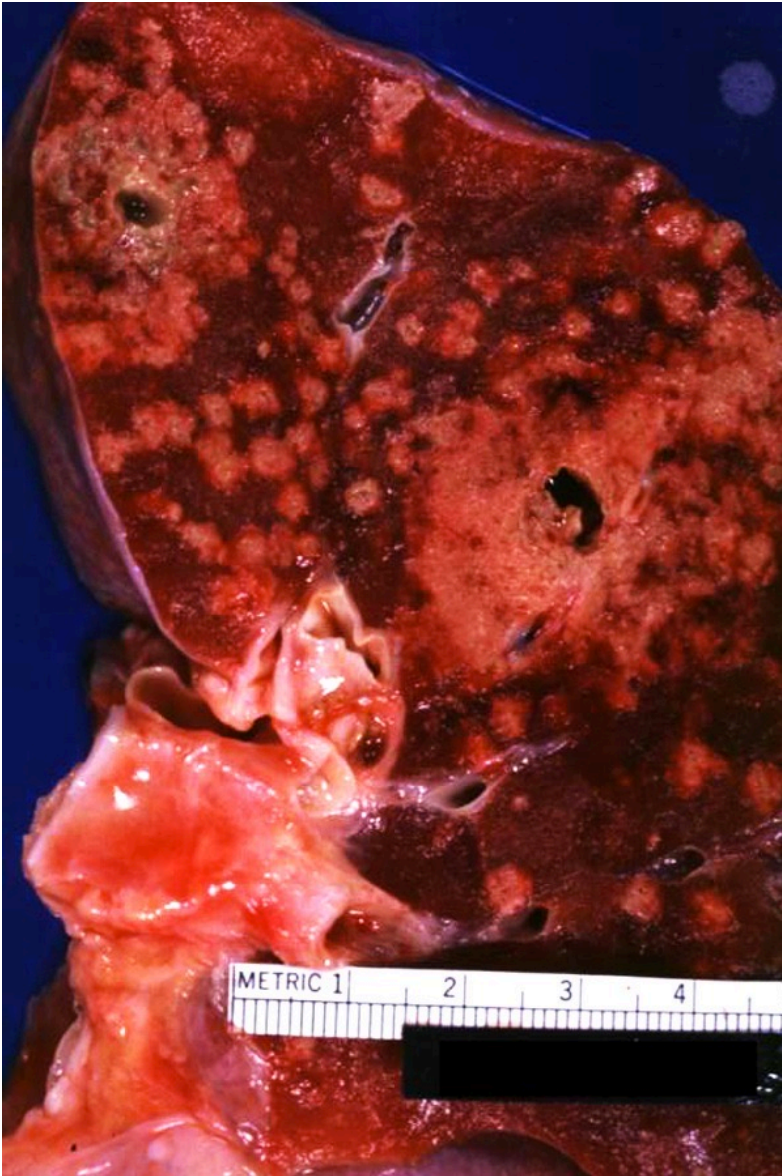
Gram stain



Fungal Pneumonia

- Many fungi will elicit a granulomatous reaction – may be necrotizing or not
- Special stains to identify organisms include methenamine silver stain (MSS), Gomori methenamine stain (GMS) and periodic acid-Schiff (PAS) stain
- *Pneumocystis jiroveci* produces a cell-poor, proteinaceous alveolar infiltrate

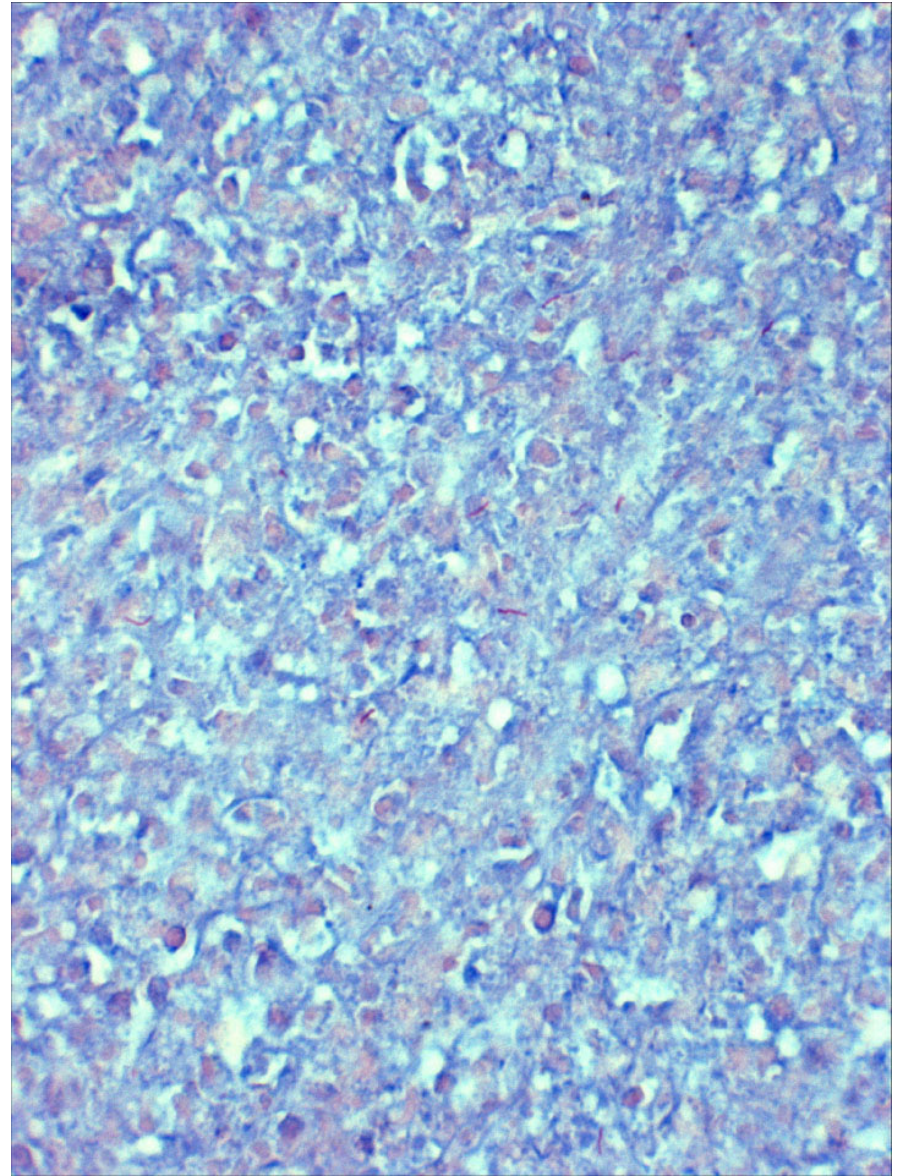
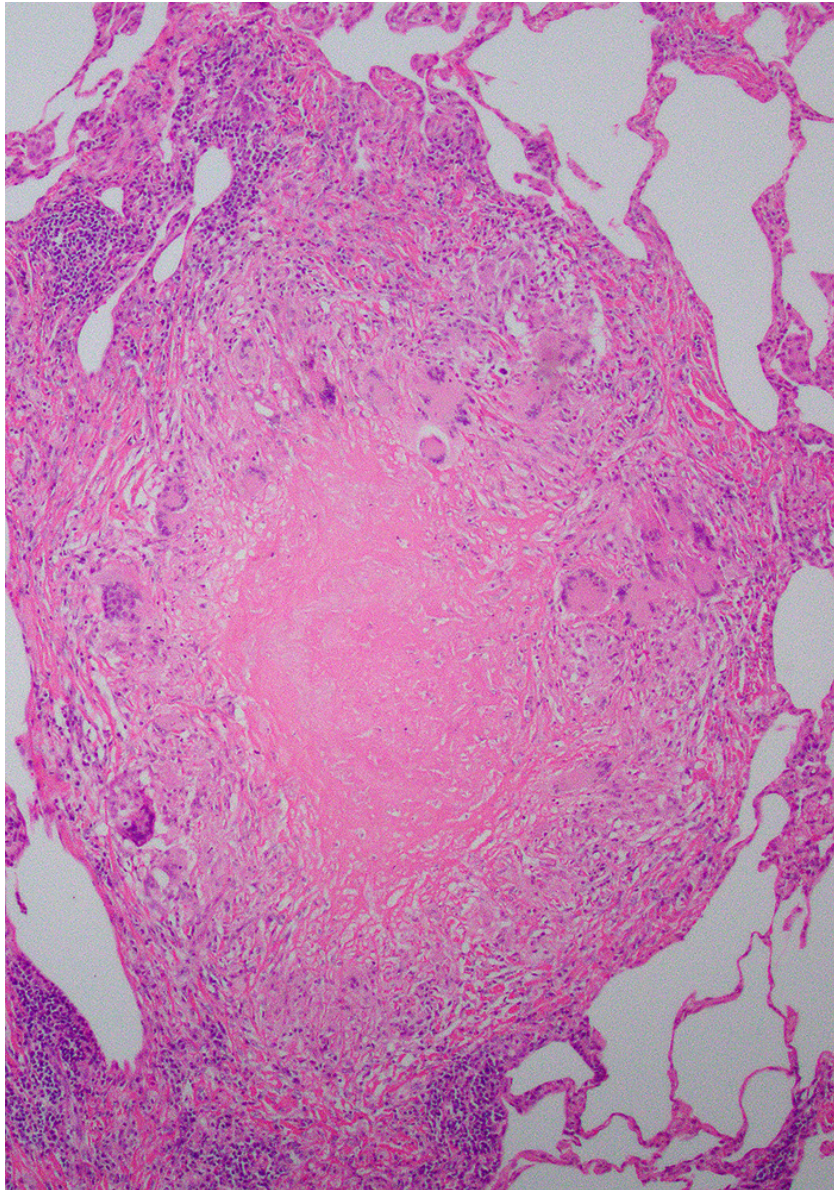
Aspergillus Pneumonia – MSS stain



Mycobacterial Infection

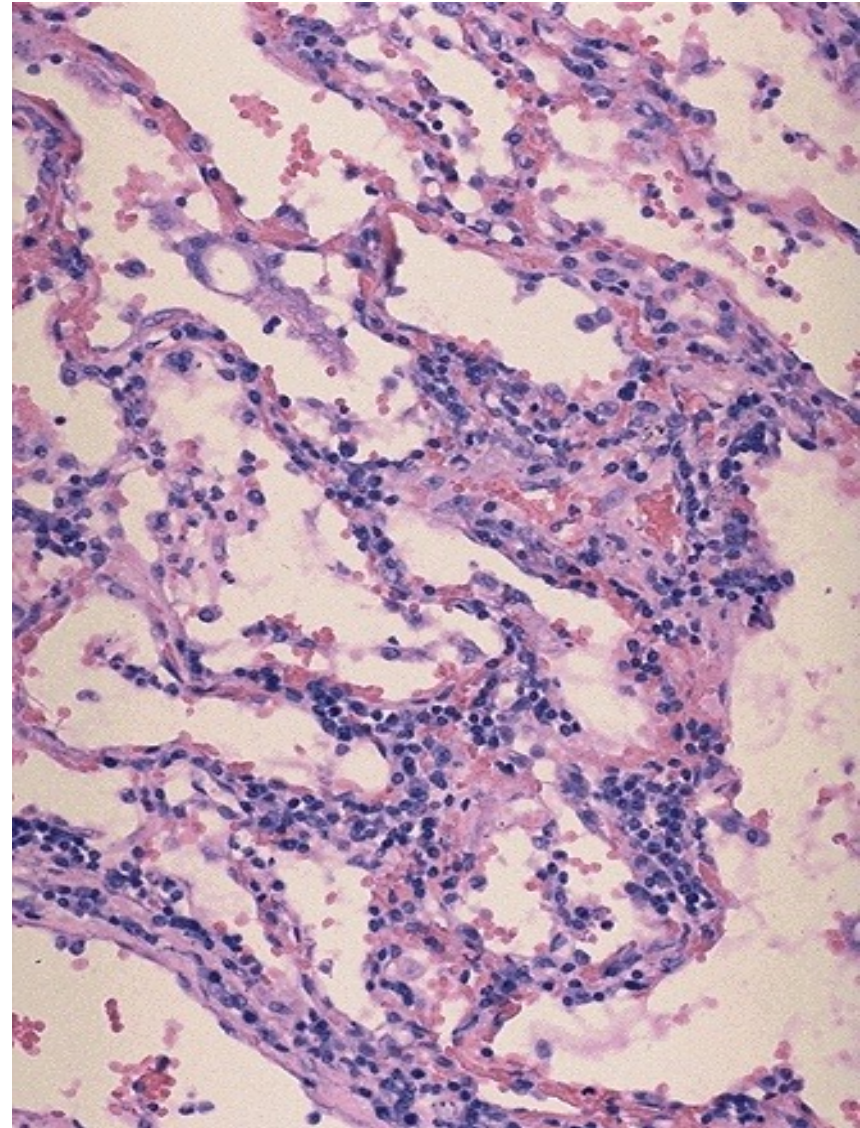
- Most mycobacteria will elicit a granulomatous reaction – may be necrotizing or not
- Special stains to identify organisms include acid-fast bacilli (AFB) stain and modifications thereof (e.g., Nocardia stain)
- Infiltrates of foamy macrophages may contain non-tuberculous mycobacteria in immunocompromised patients

Mycobacterial Infection - AFB



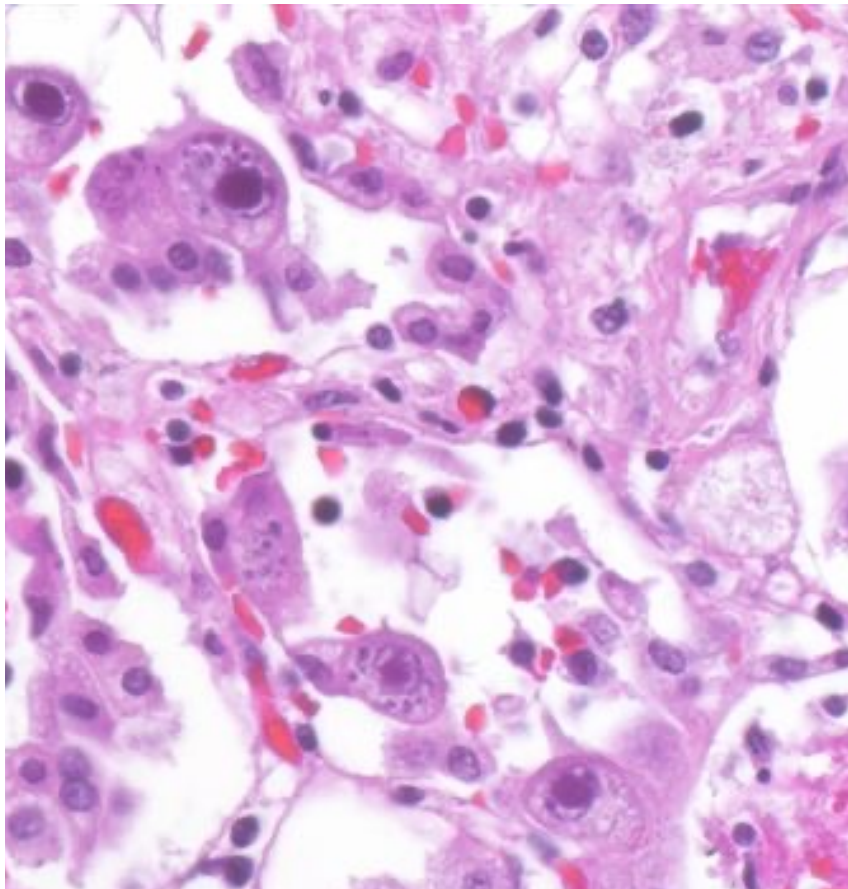
Viral Pneumonitis

- Milder injury pattern for many respiratory viral infections (RSV, parainfluenza, adenovirus, metapneumovirus, et al.)
- Variable interstitial mononuclear cell infiltrates, edema
- Severe viral infection may produce DAD/ARDS pattern (SARS-CoV-2)

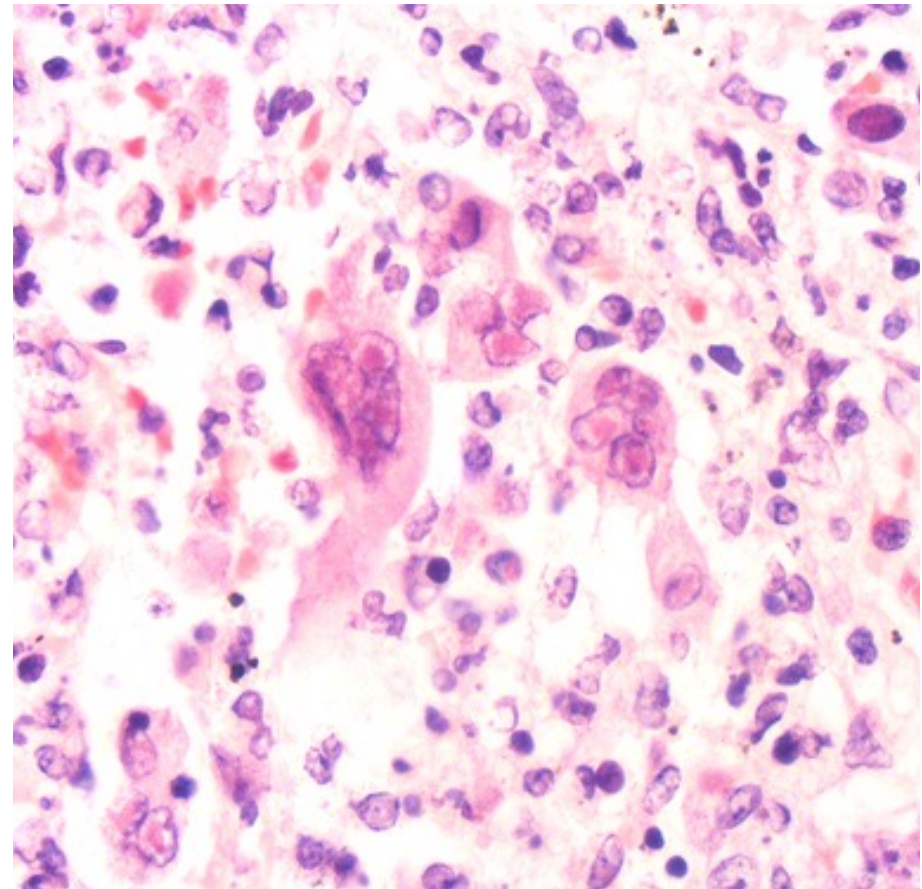


Diagnostic Viral Inclusions

Cytomegalovirus: Large cells, red nuclear inclusions



Herpes simplex: Giant cells with Cowdry type A inclusions



Outline

- Interstitial lung disease
- Infection
- • Malignancy
- Pathology special stains and buzzwords

Common malignancies

- Adenocarcinoma
- Squamous cell carcinoma
- Carcinoid/atypical carcinoid
- Small cell carcinoma
- (Metastasis)

Adenocarcinoma

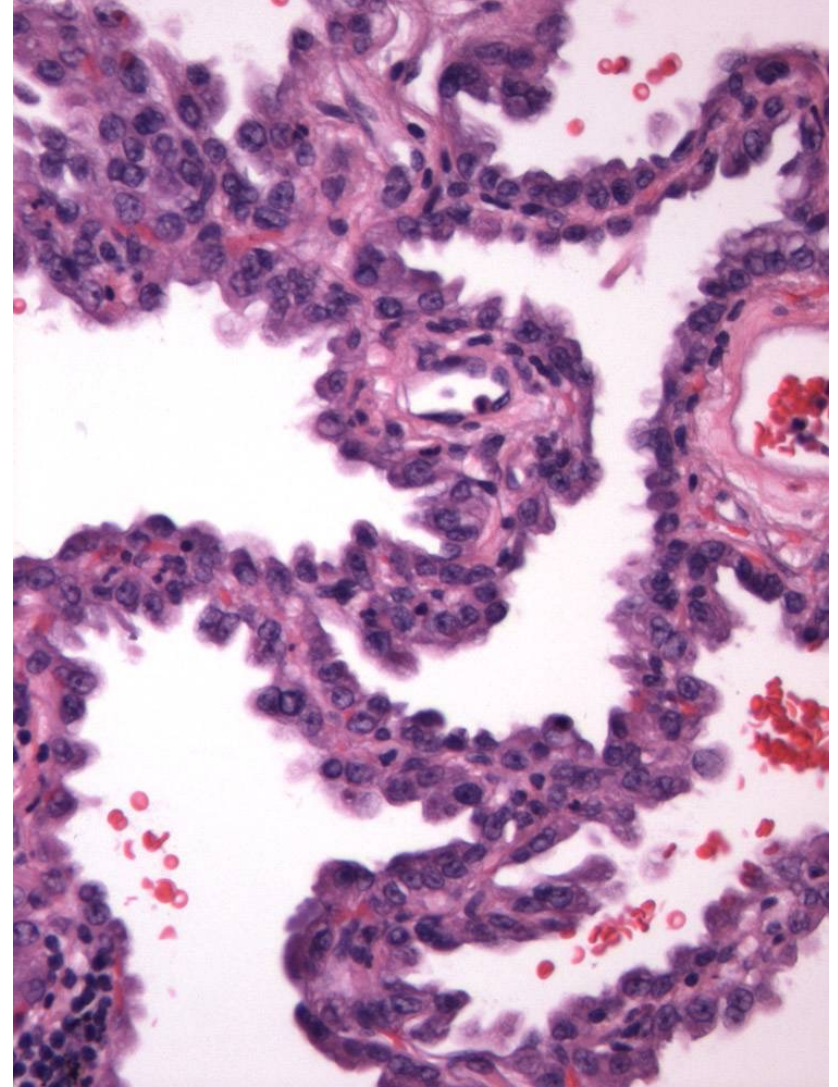
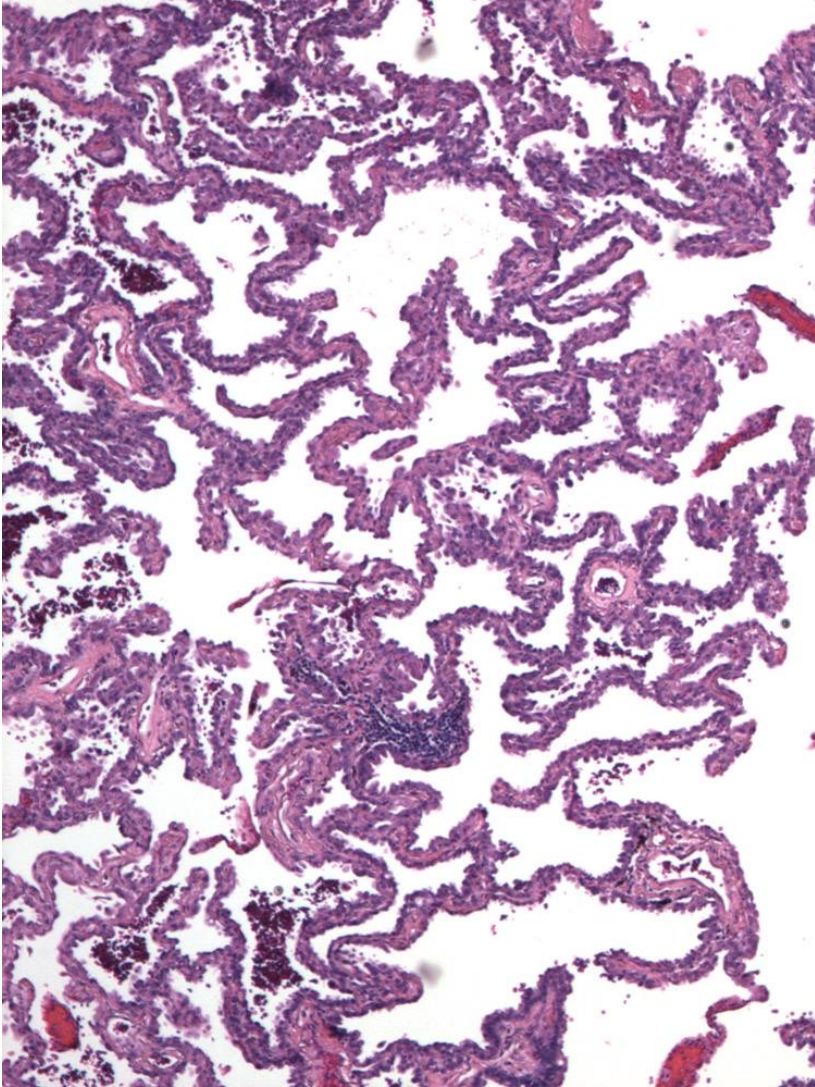
- Atypical adenomatous hyperplasia
- Adenocarcinoma in situ (formerly non-mucinous BAC)
- Minimally invasive adenocarcinoma
- Invasive adenocarcinoma, predominantly...
 - Lepidic, acinar, papillary, micropapillary or solid
- Variants
 - Invasive mucinous adenocarcinoma (formerly mucinous BAC)
- Genetic studies – EGFR, EML4-ALK, ROS1, KRAS

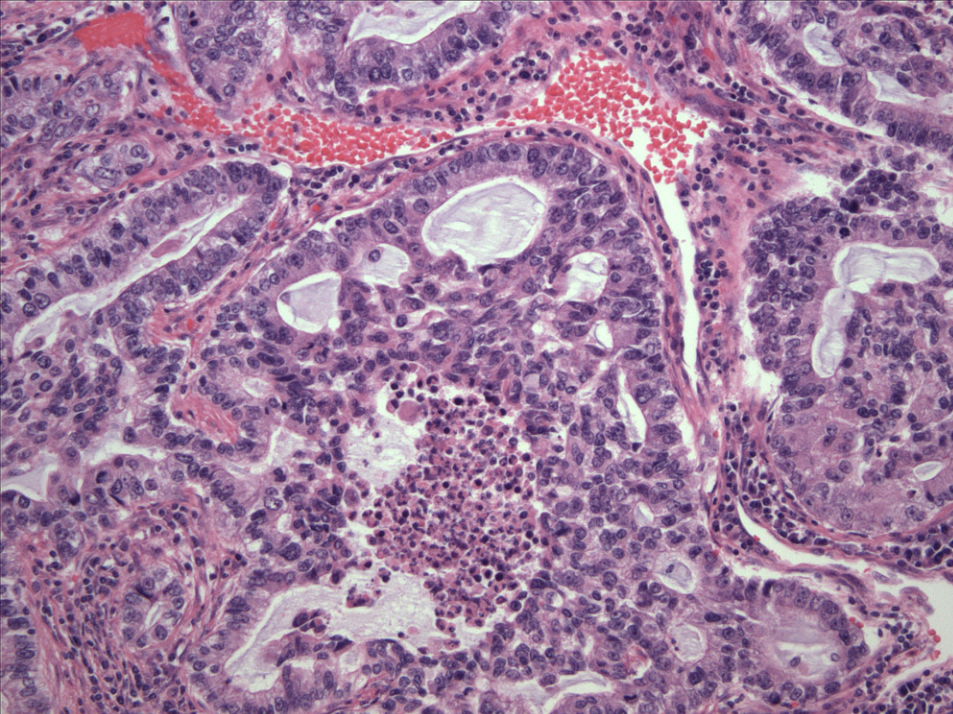
Adenocarcinoma



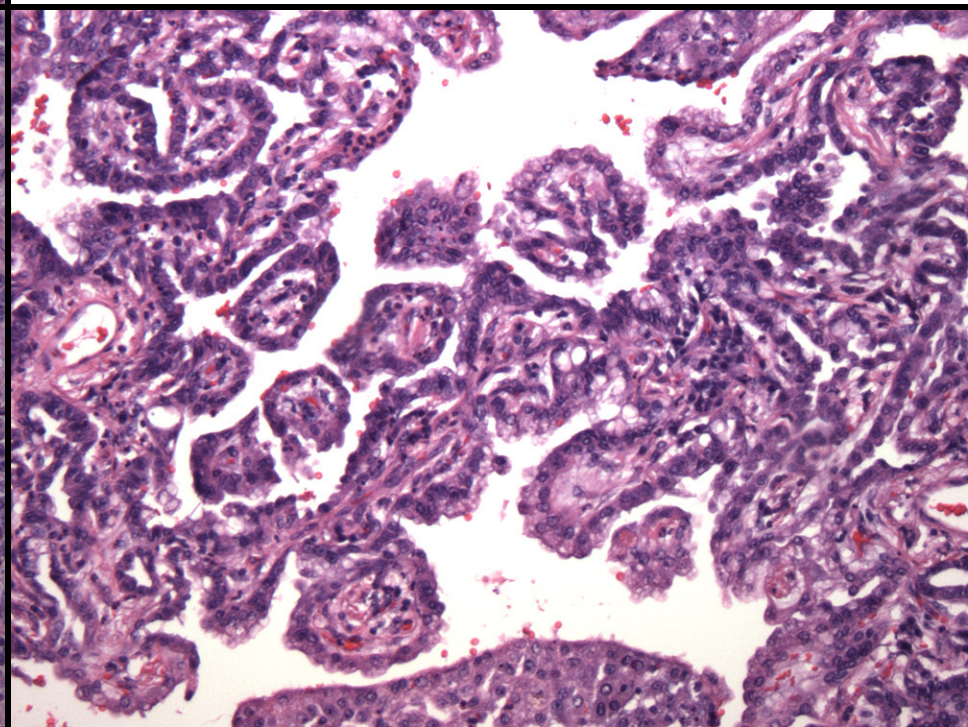
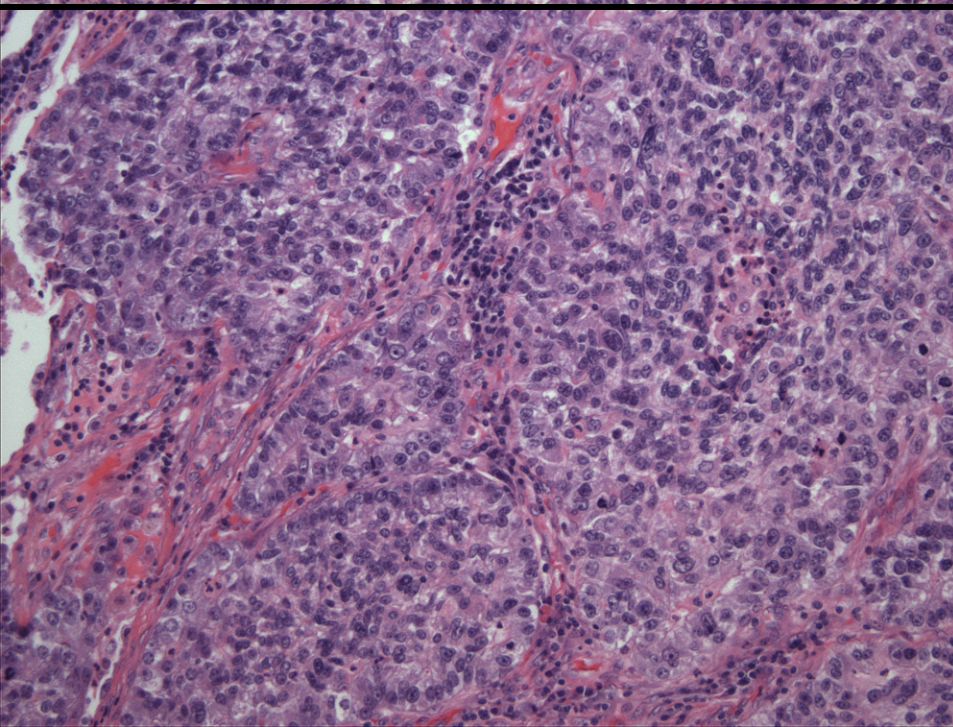
Adenocarcinoma In Situ

Growth along pre-existing alveolar walls with no stromal invasion

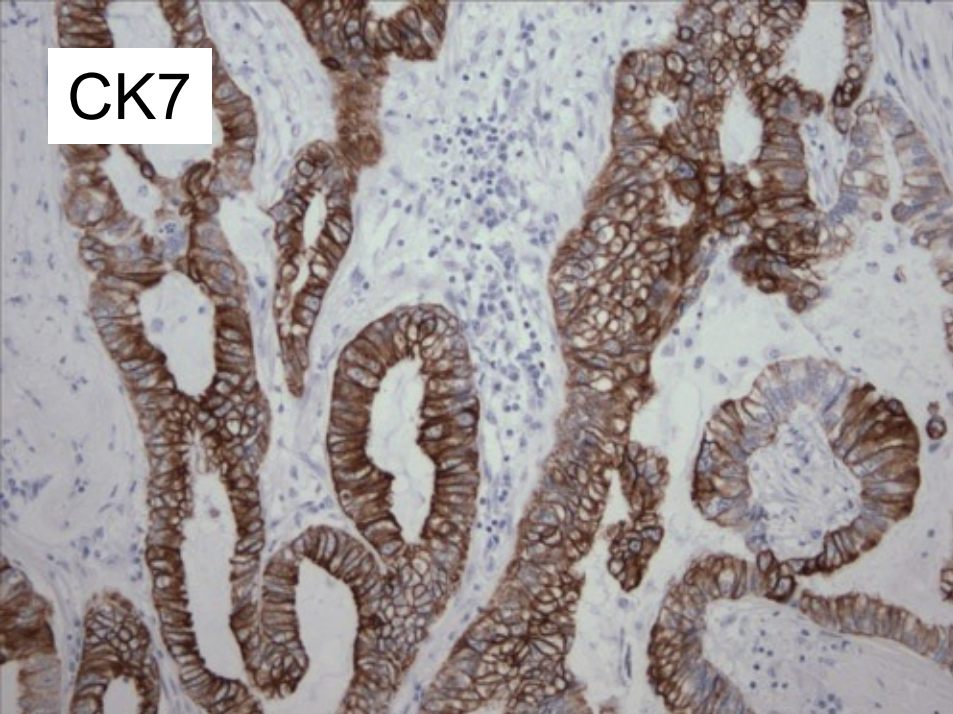




Acinar, solid, papillary
All from same tumor
Predominant pattern
reported

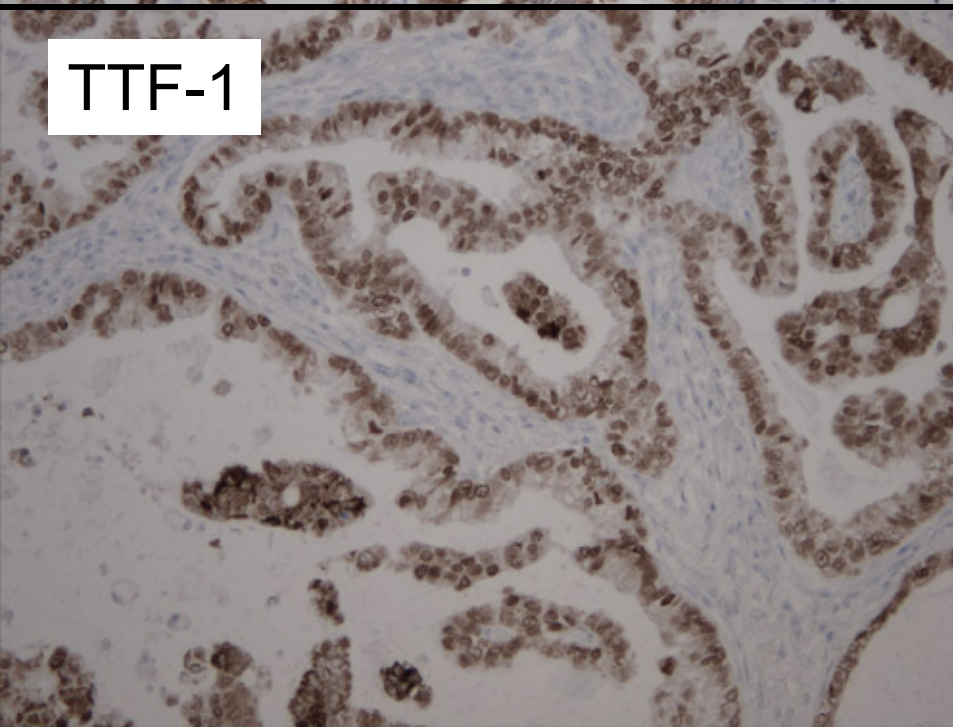


CK7

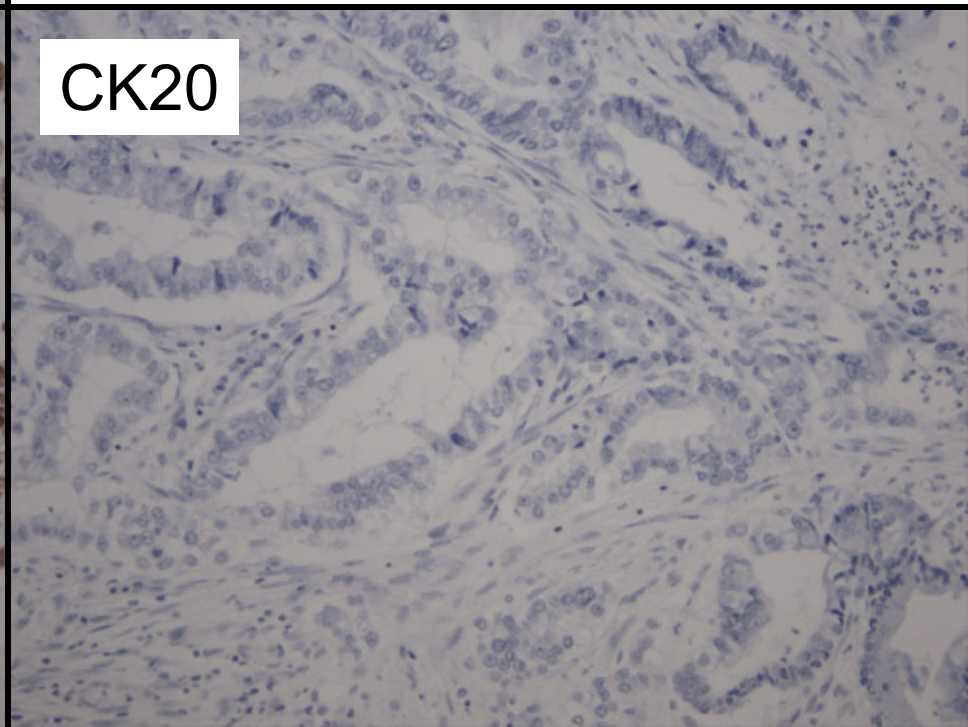


Immunohistochemistry
Primary vs. metastasis

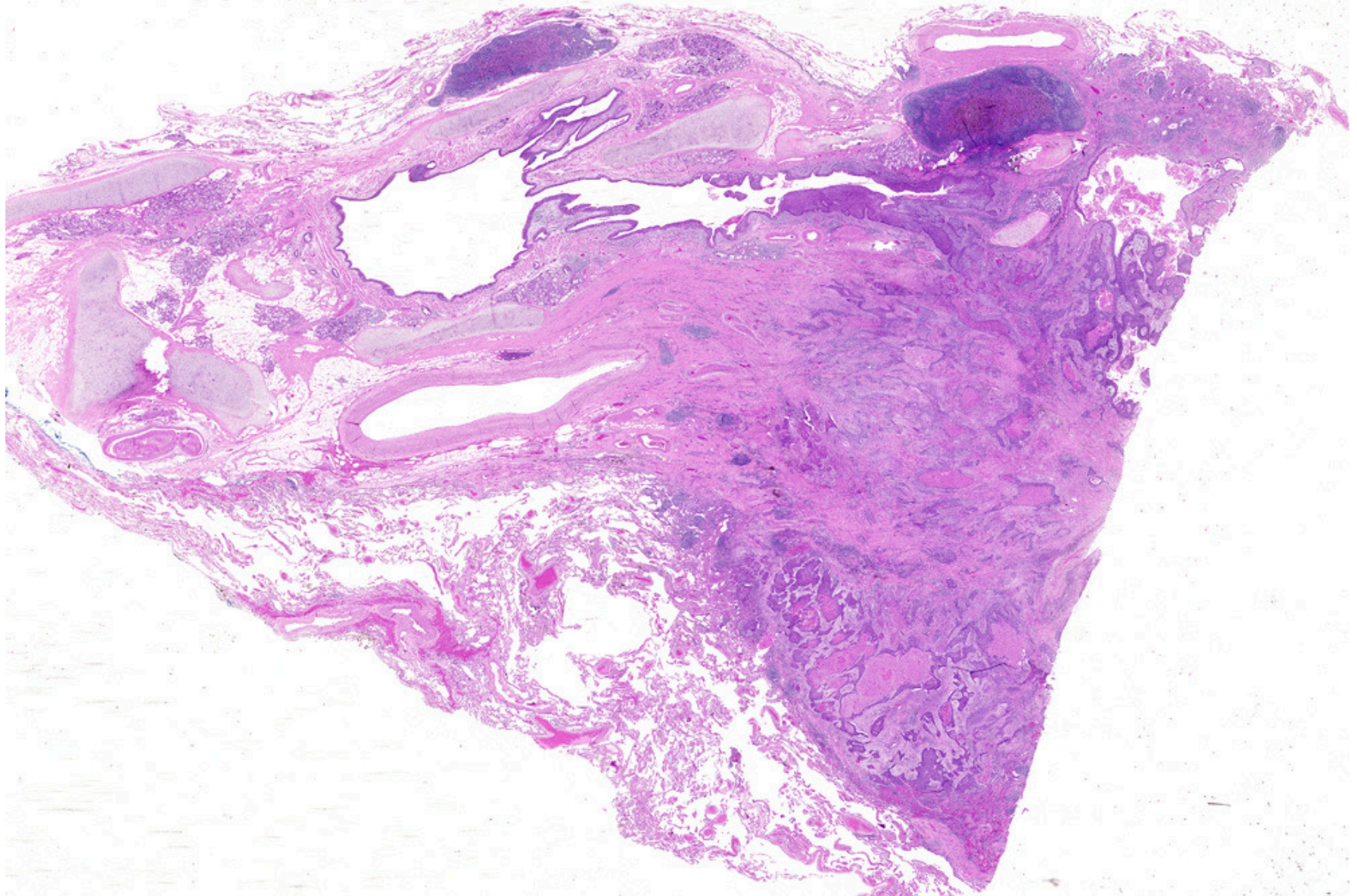
TTF-1



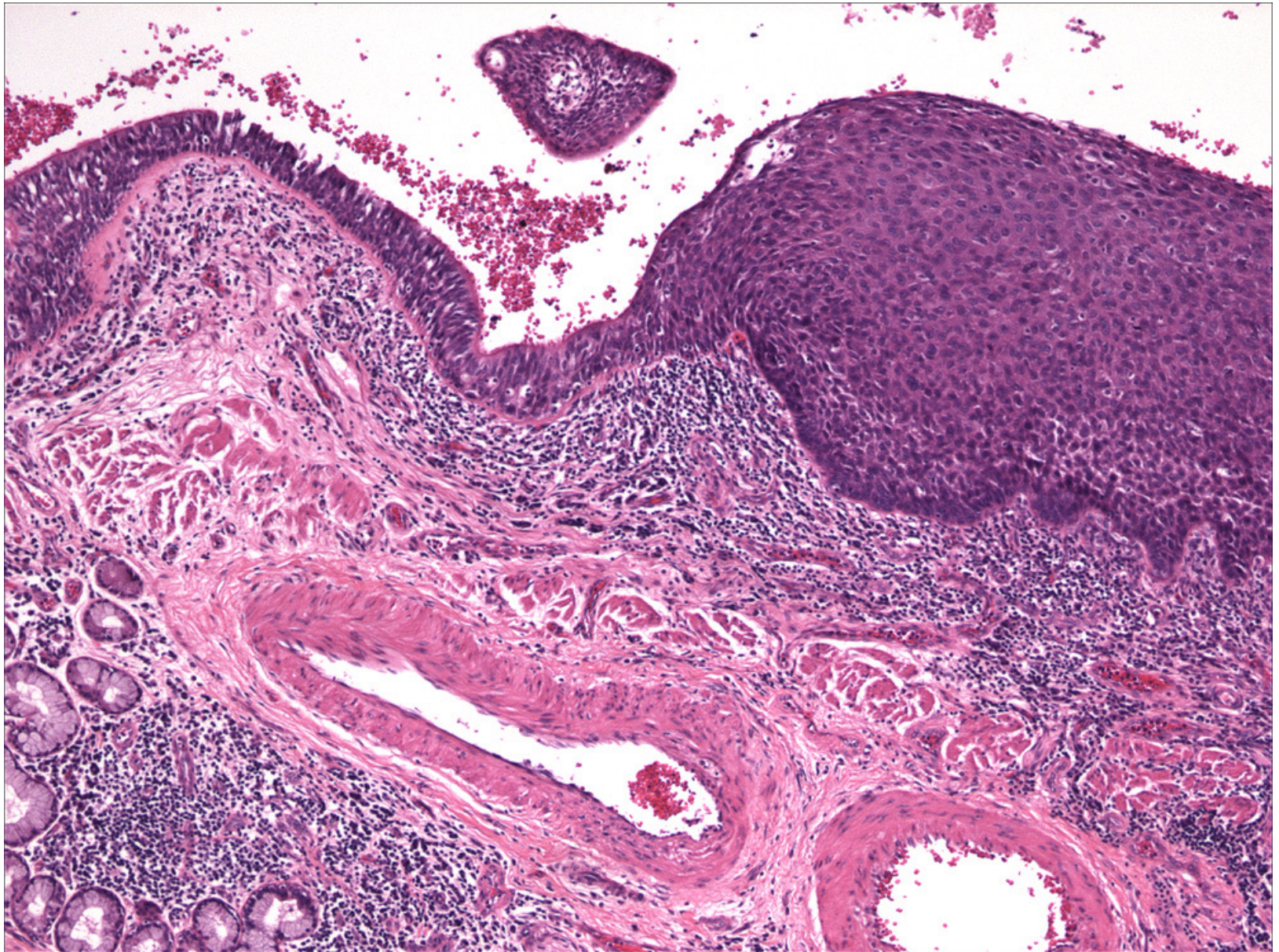
CK20



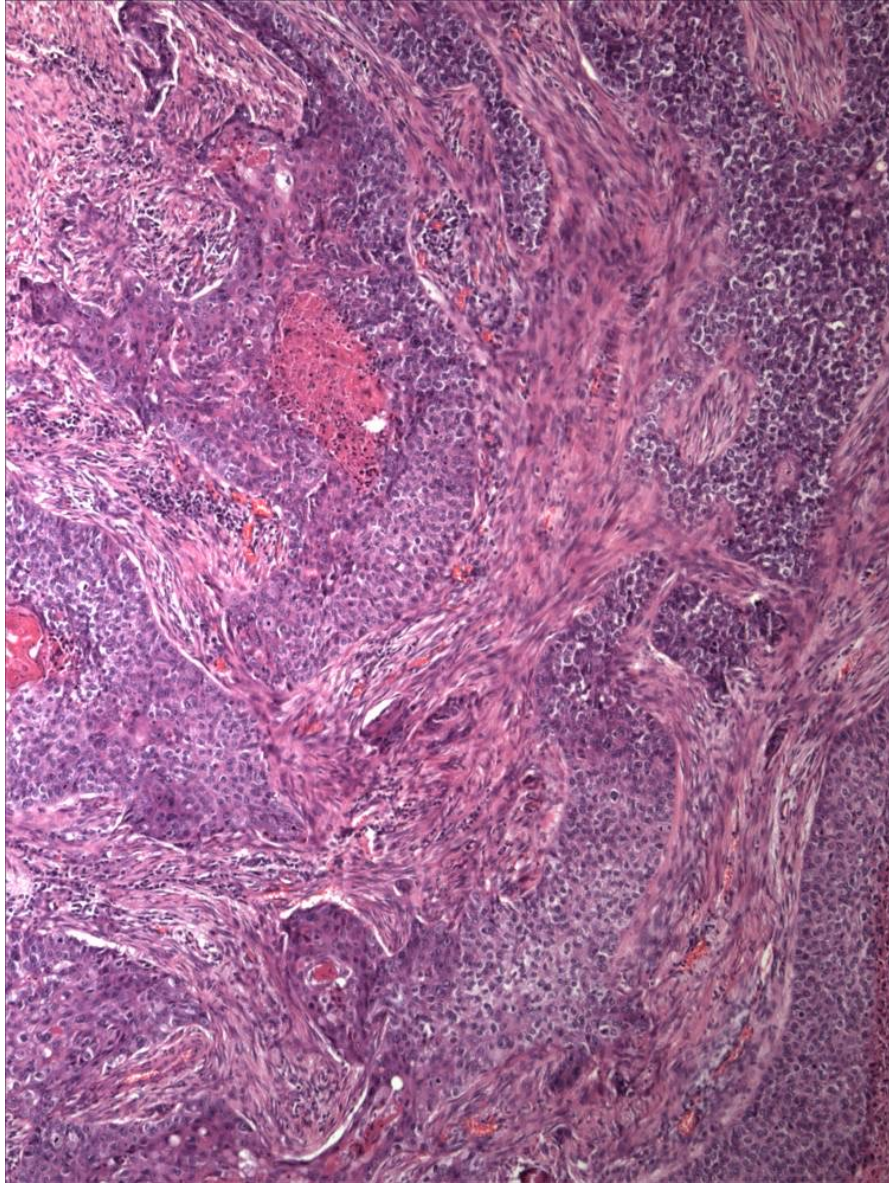
Squamous Cell Carcinoma



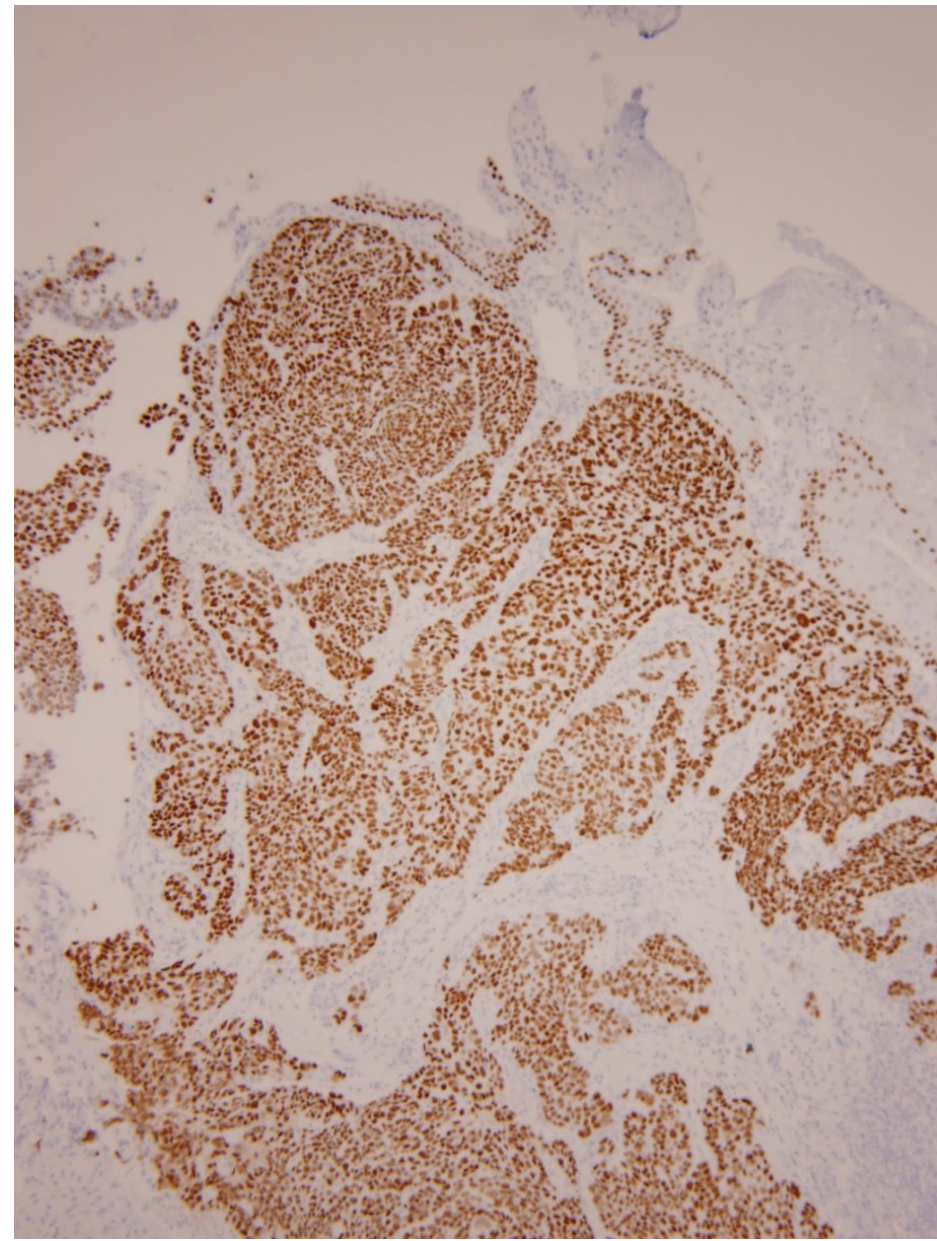
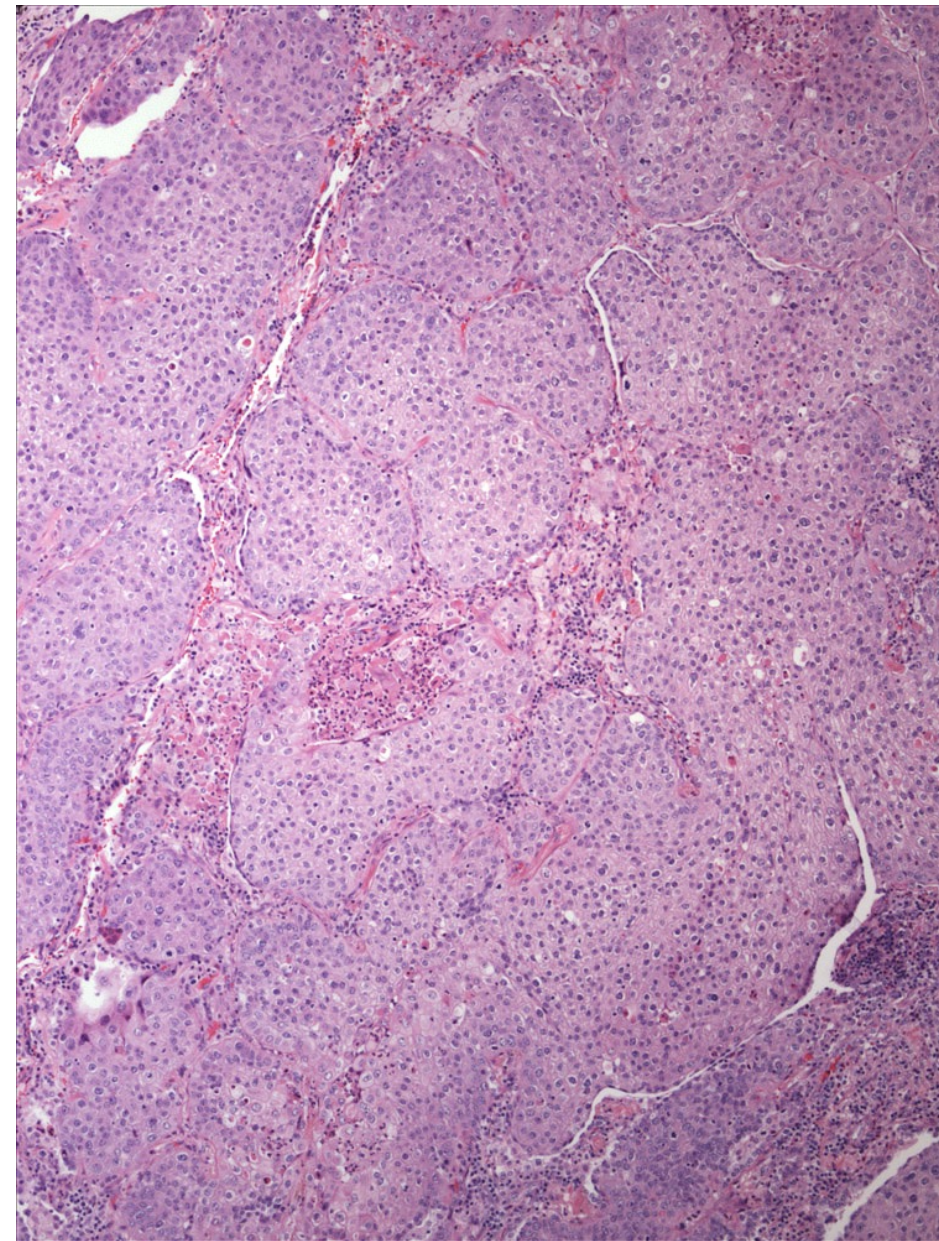
Squamous Cell – In Situ Component



Squamous Cell – Invasive



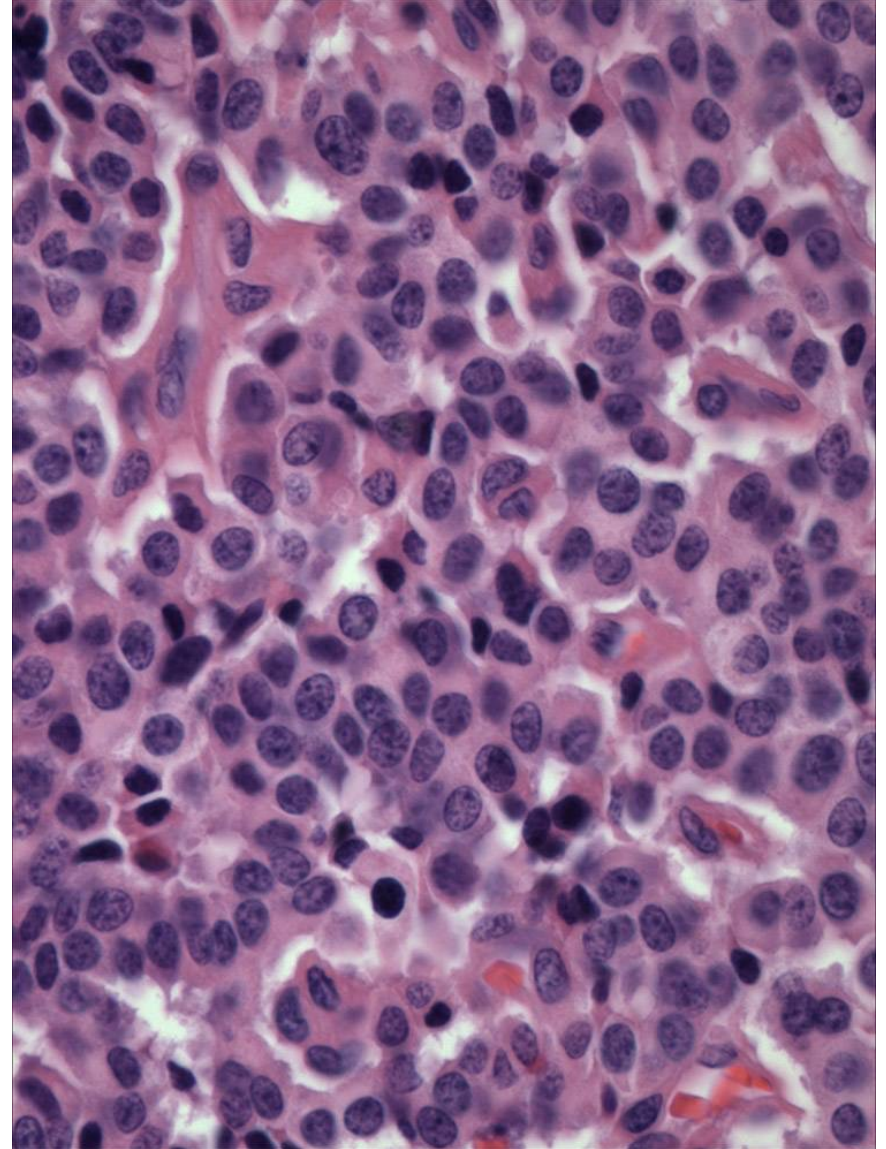
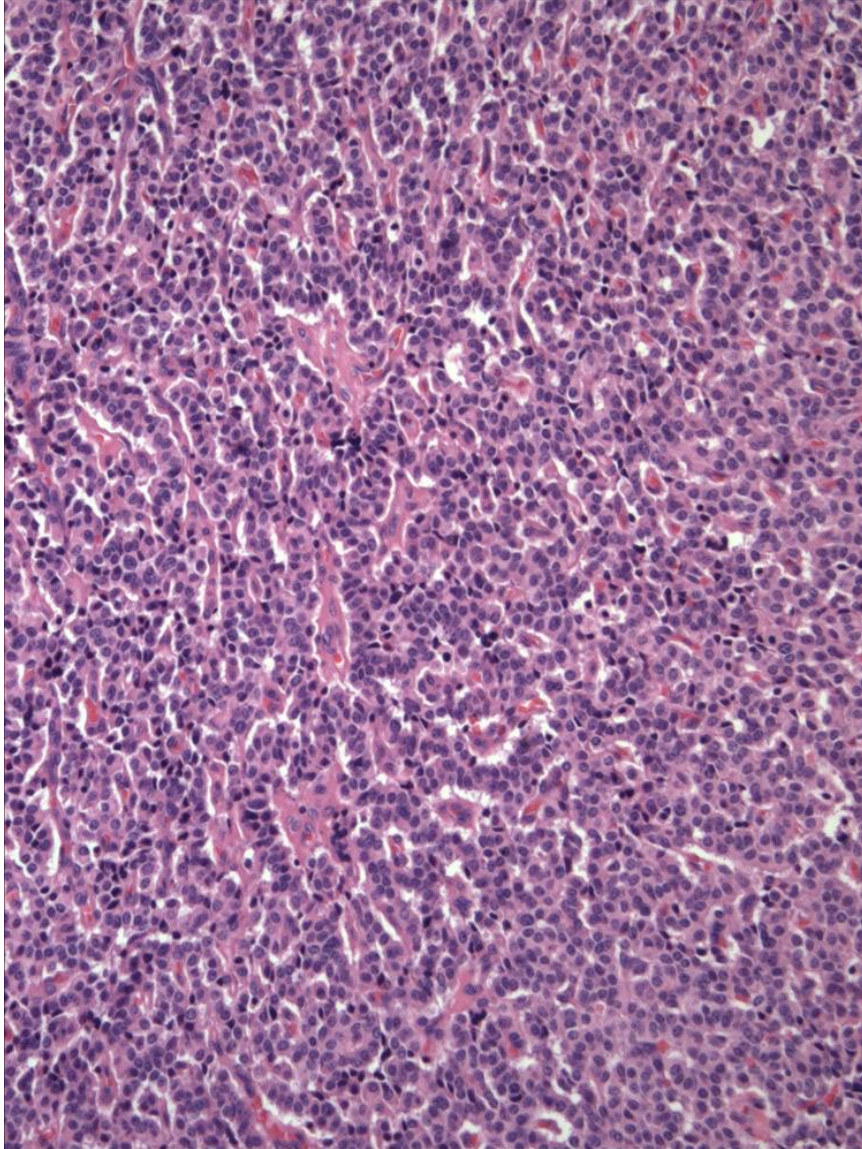
Squamous Cell – Invasive – p40, p63



Carcinoid



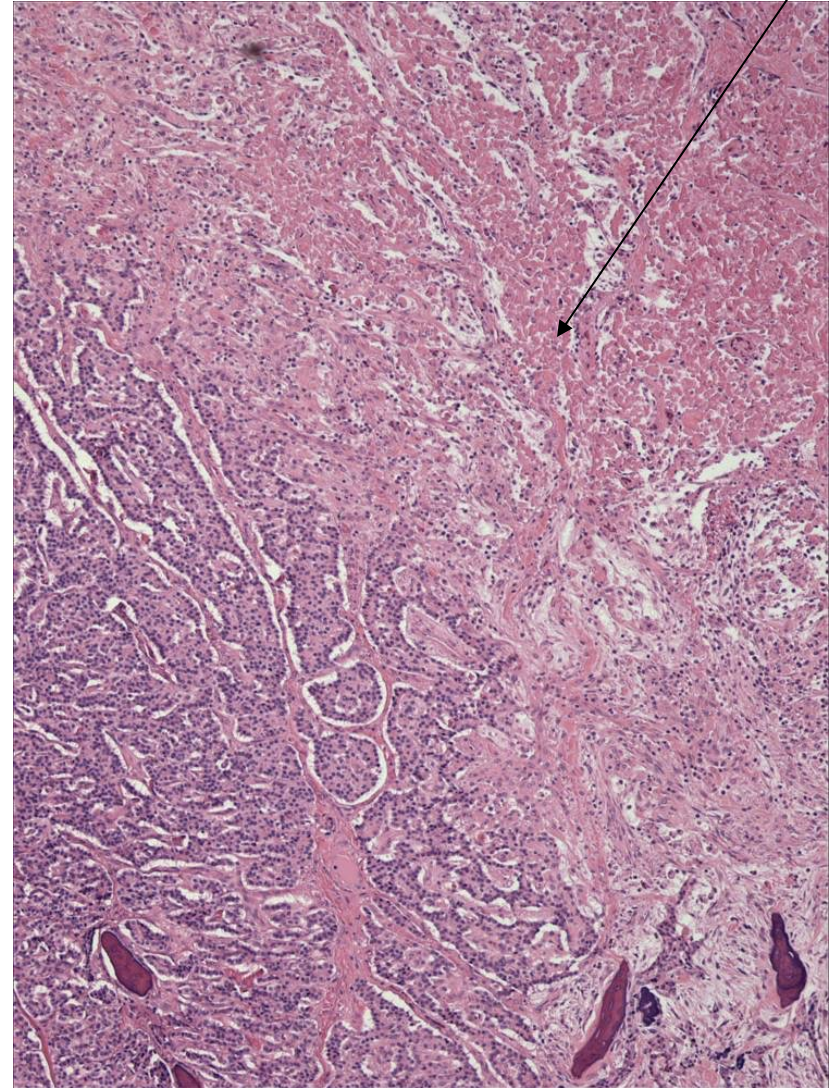
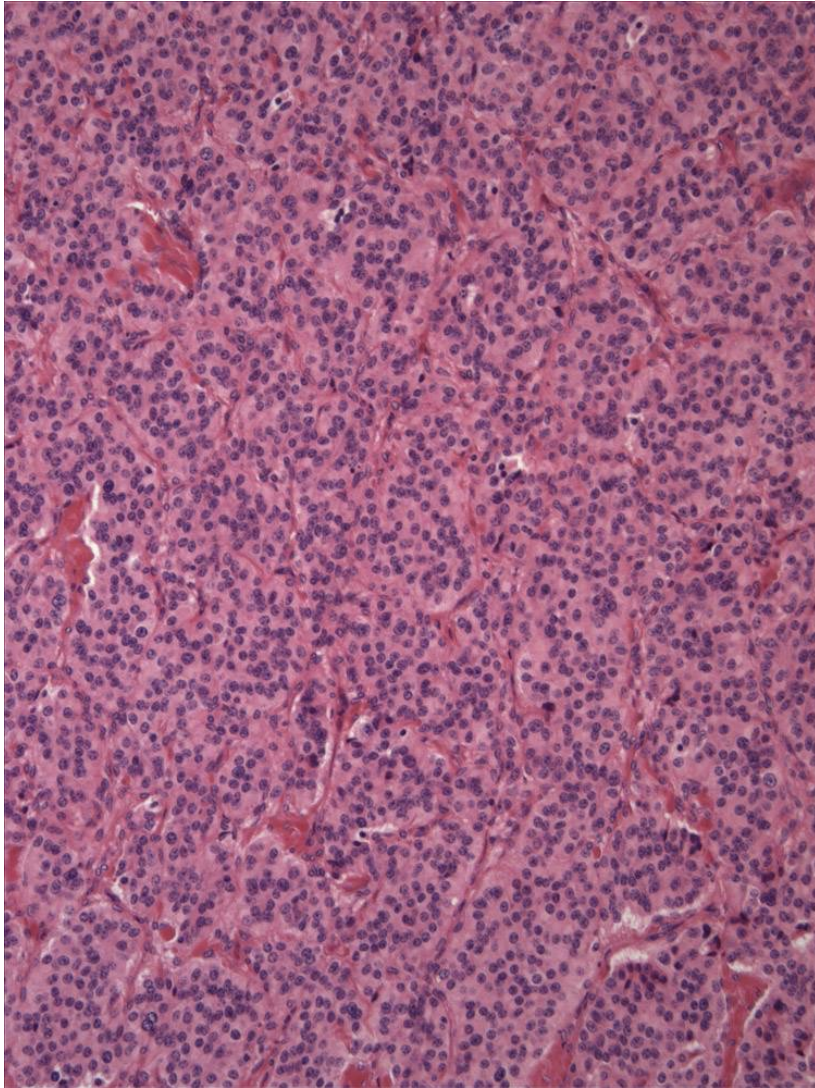
Carcinoid



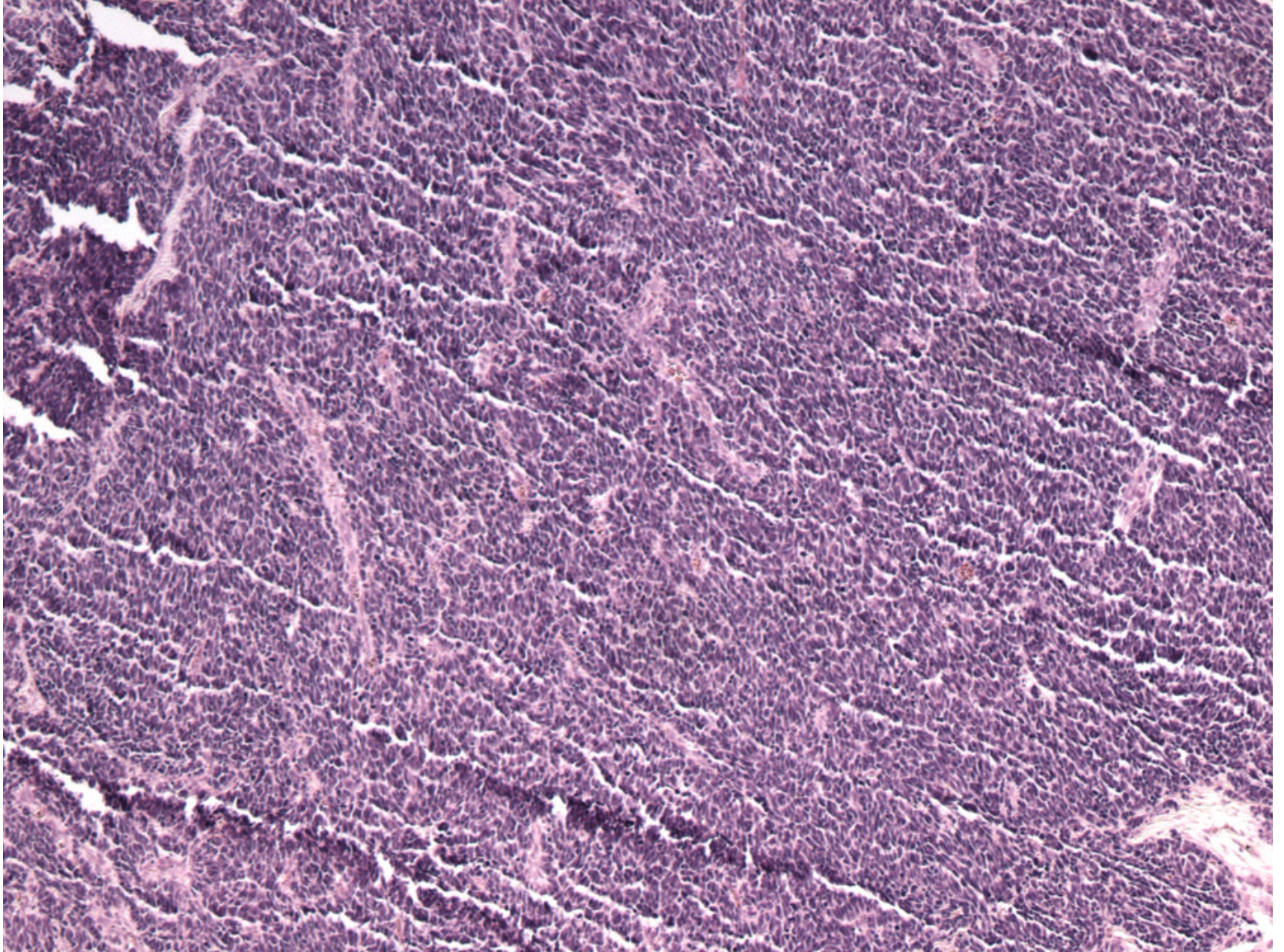
Atypical Carcinoid

Increased mitosis, pleomorphism, areas of necrosis

Necrosis

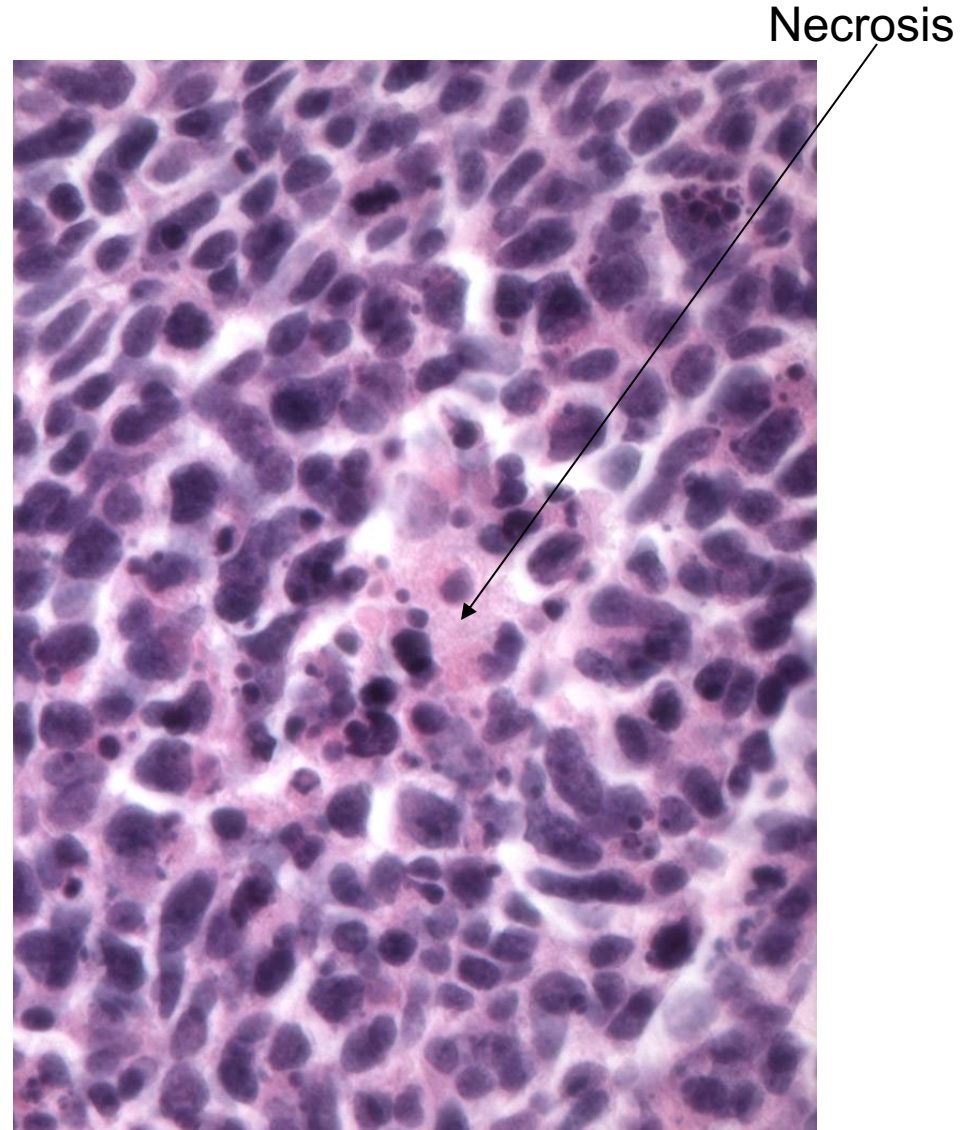
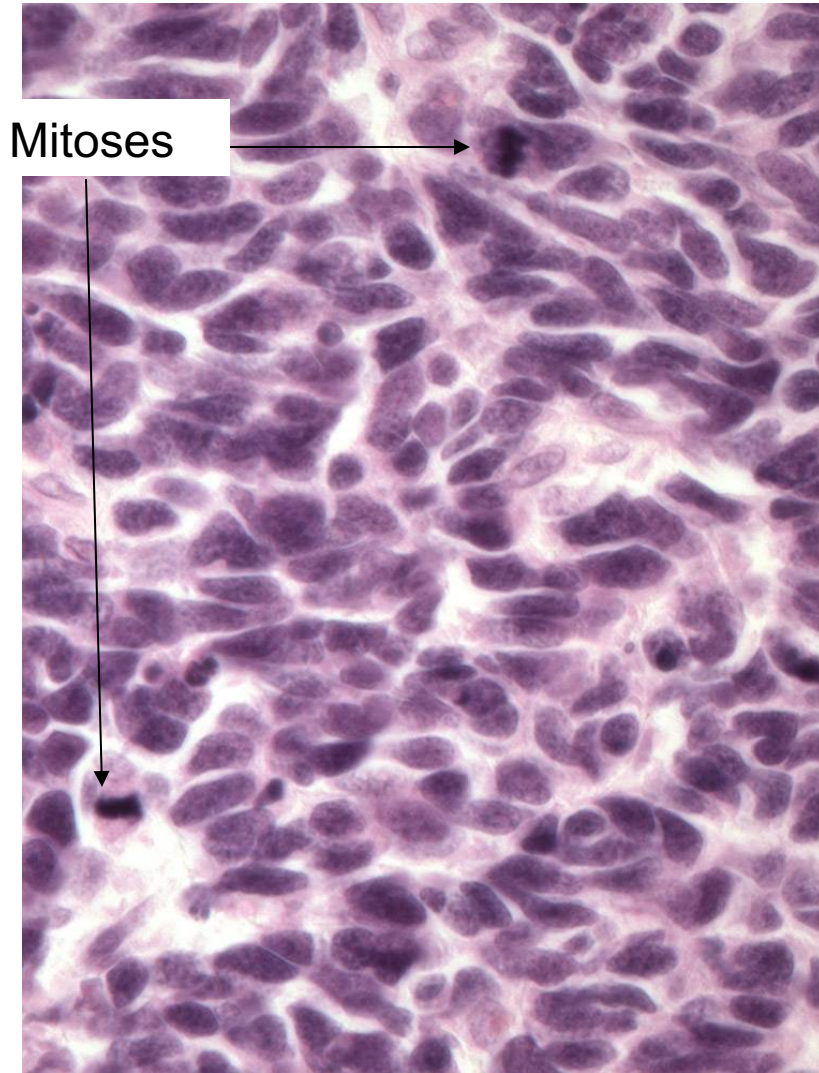


Small Cell Carcinoma

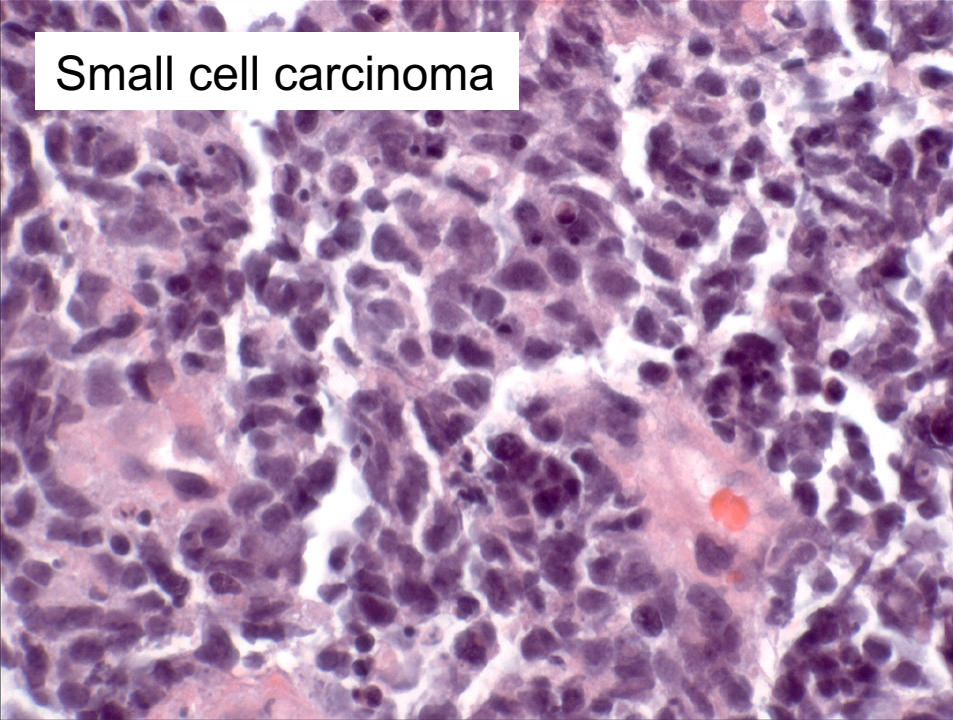


Small Cell Carcinoma

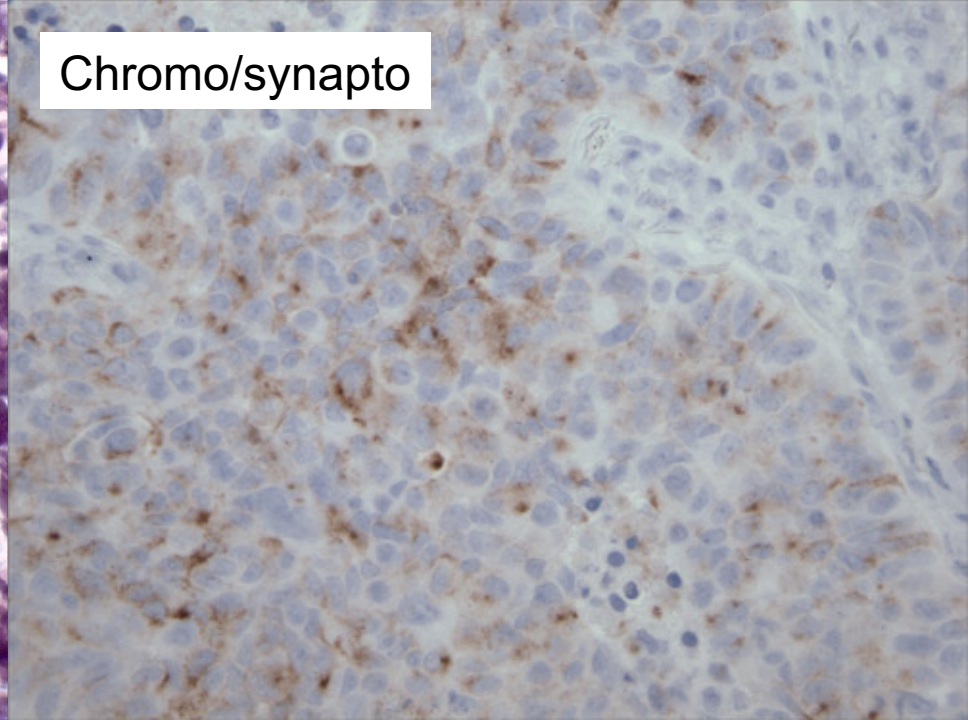
Hyperchromasia, nuclear molding, mitoses, single cell necrosis



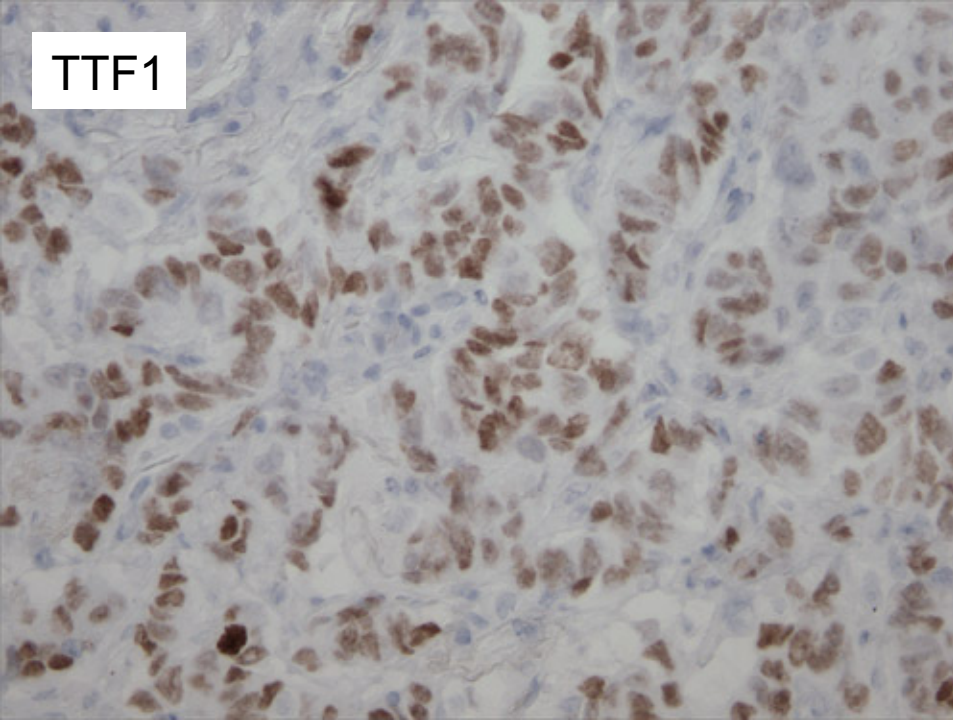
Small cell carcinoma



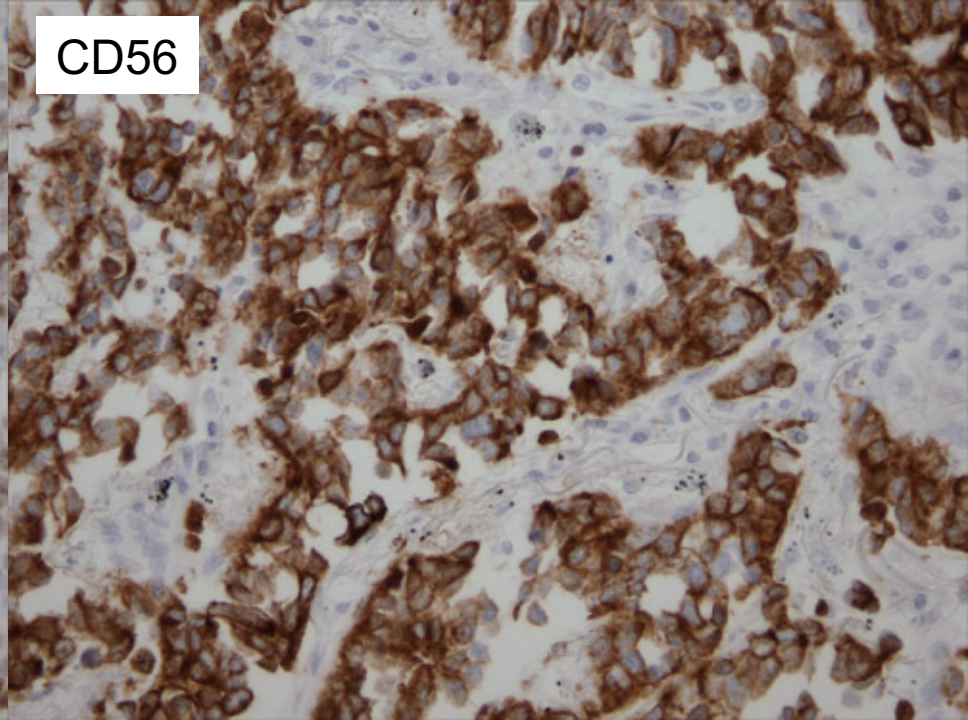
Chromo/synapto



TTF1



CD56



Outline

- Interstitial lung disease
- Infection
- Malignancy
- • Pathology special stains and buzzwords

Neoplastic Special Stains

- Pulmonary adenocarcinoma
 - TTF-1, napsin, CK7, mucicarmine positive
 - p40, p63 negative
- Squamous cell carcinoma
 - p40, p63, CK5/6 positive
 - TTF-1, napsin negative
- Small cell carcinoma
 - Keratin, TTF-1, CD56, synaptophysin (50%), chromogranin (50%) positive
- Immunohistochemistry for ALK, ROS1, PD-L1 (also some EGFR and BRAF mutants)

Non-neoplastic Special Stains

- Trichrome stain – fibrosis
- Congo red stain, apple green birefringence – amyloid
- AFB stain – mycobacteria, Nocardia
- MSS, GMS – fungus
- PAS – fungus; also for pulmonary alveolar proteinosis
- Gram stain – bacteria

Buzzwords

- Spatial/temporal heterogeneity, fibroblastic foci – UIP
- Hyaline membranes – DAD/AIP
- Loosely formed granulomas – HP
- Well-formed granulomas – sarcoid
- Necrotizing granulomas – TB, Fungus, GPA
- Nuclear molding, single cell necrosis – small cell carcinoma
- Central tumor in smoker – squamous cell or small cell carcinoma
- Central tumor in nonsmoker – carcinoid
- Peripheral tumor, lepidic growth - adenocarcinoma



Pulmonary Pathology



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