An Update on Inflammatory and Fibrotic Lung Diseases

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Outline

- Organizing pneumonia
- Small granulomas in new places
  - Connective tissue disease vs. hypersensitivity pneumonitis
  - Immunodeficiency
  - Primary biliary cholangitis
- Check point inhibitor lung toxicity

BRONCHIOLITIS OBLITERANS ORGANIZING PNEUMONIA

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Abstract In 50 of 94 patients with bronchiolitis obliterans we found no apparent cause or associated disease, and the bronchiolitis obliterans occurred with patchy organizing pneumonia. Histologic characteristics included polypoid masses of granulation tissue in lumens of small airways, alveolar ducts, and some alveoli. The fibrosis was uniform in age, suggesting that all repair had begun at the same time. The distribution was patchy, with preservation of background architecture. Clinically, there was cough or flu-like illness for 4 to 10 weeks, and crackles were heard in the lungs of 68 per cent of the patients. Radiographs showed an unusual pattern of patchy densities with a "ground glass" appearance in 81 per cent. Physiologically, there was restriction in 72 per cent of the patients, and 86 per cent had impaired diffusing capacity. Obstruction was limited to smokers. The mean follow-up period was four years. With corticosteroids, there was complete clinical and physiologic recovery in 65 per cent of the subjects; two died from progressive disease. This disorder differs from bronchiolitis obliterans with irreversible obstruction. It was confused most often with idiopathic pulmonary fibrosis. In view of the benign course and therapeutic response, a histologic distinction is important. (N Engl J Med 1985; 312:152-8.)

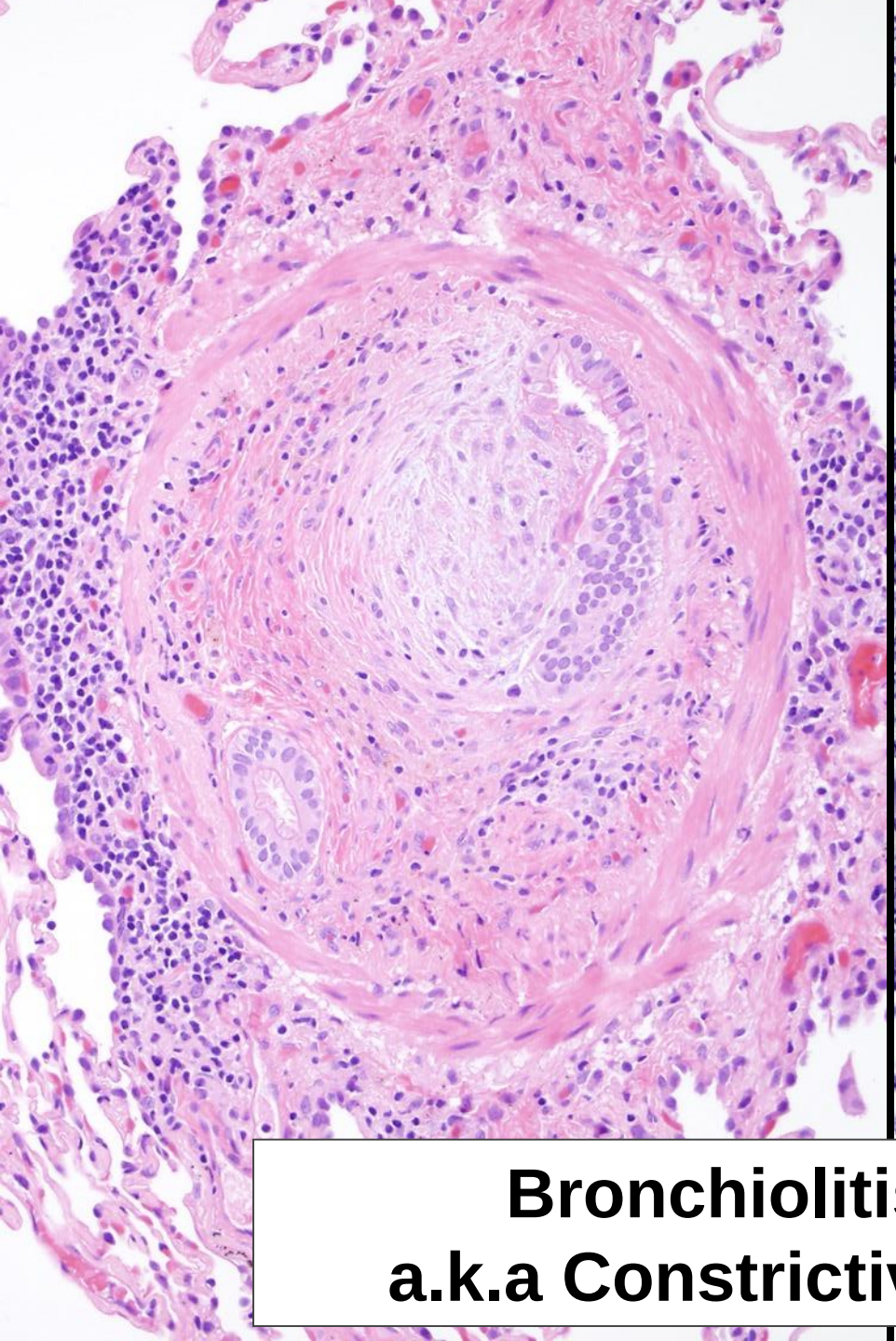
- **Not pure bronchiolitis obliterans (obliterative bronchiolitis)**
- **Not idiopathic pulmonary fibrosis**
- **Good prognosis with steroids**

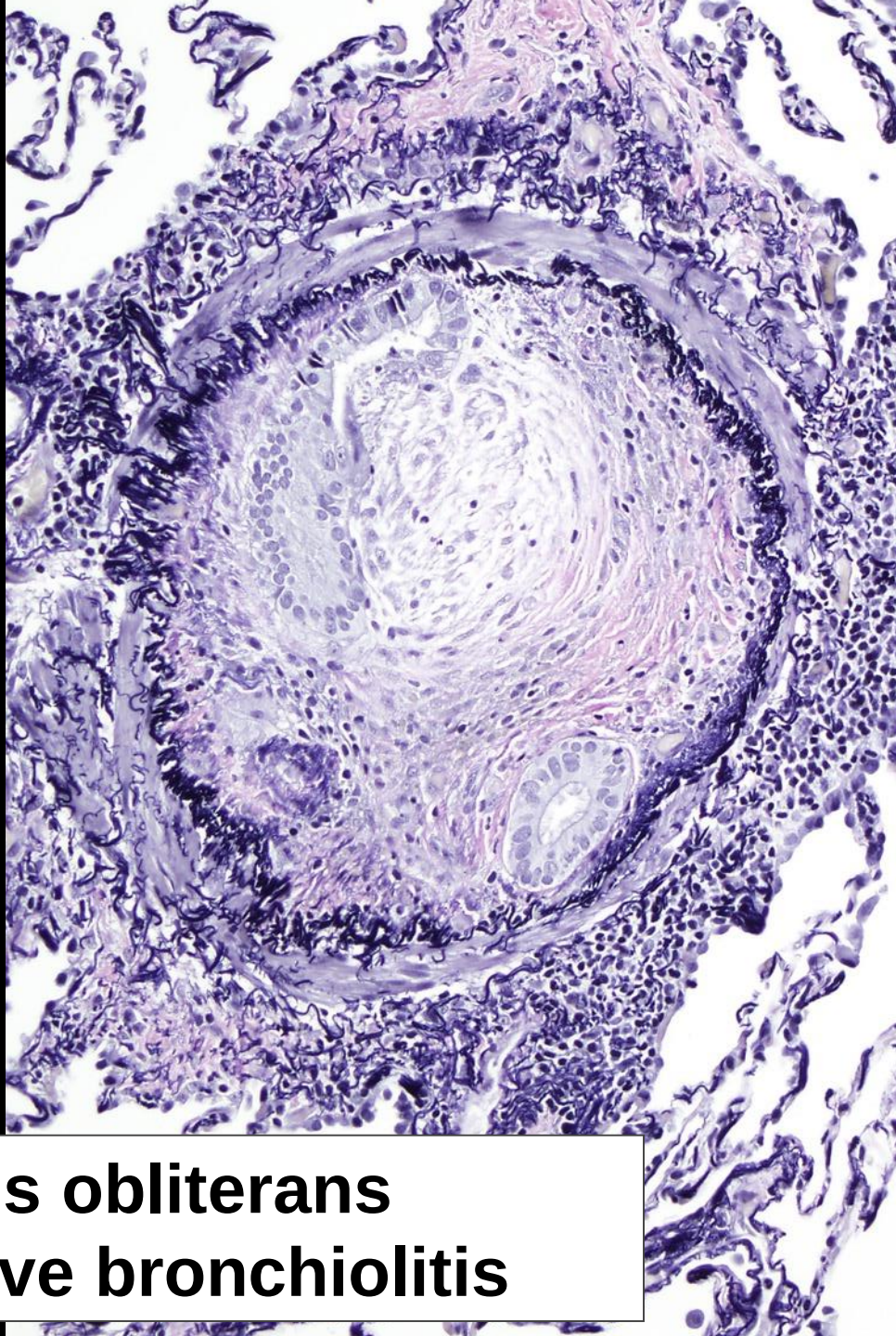
ATS/ERS Classification

CRYPTOGENIC ORGANIZING PNEUMONIA

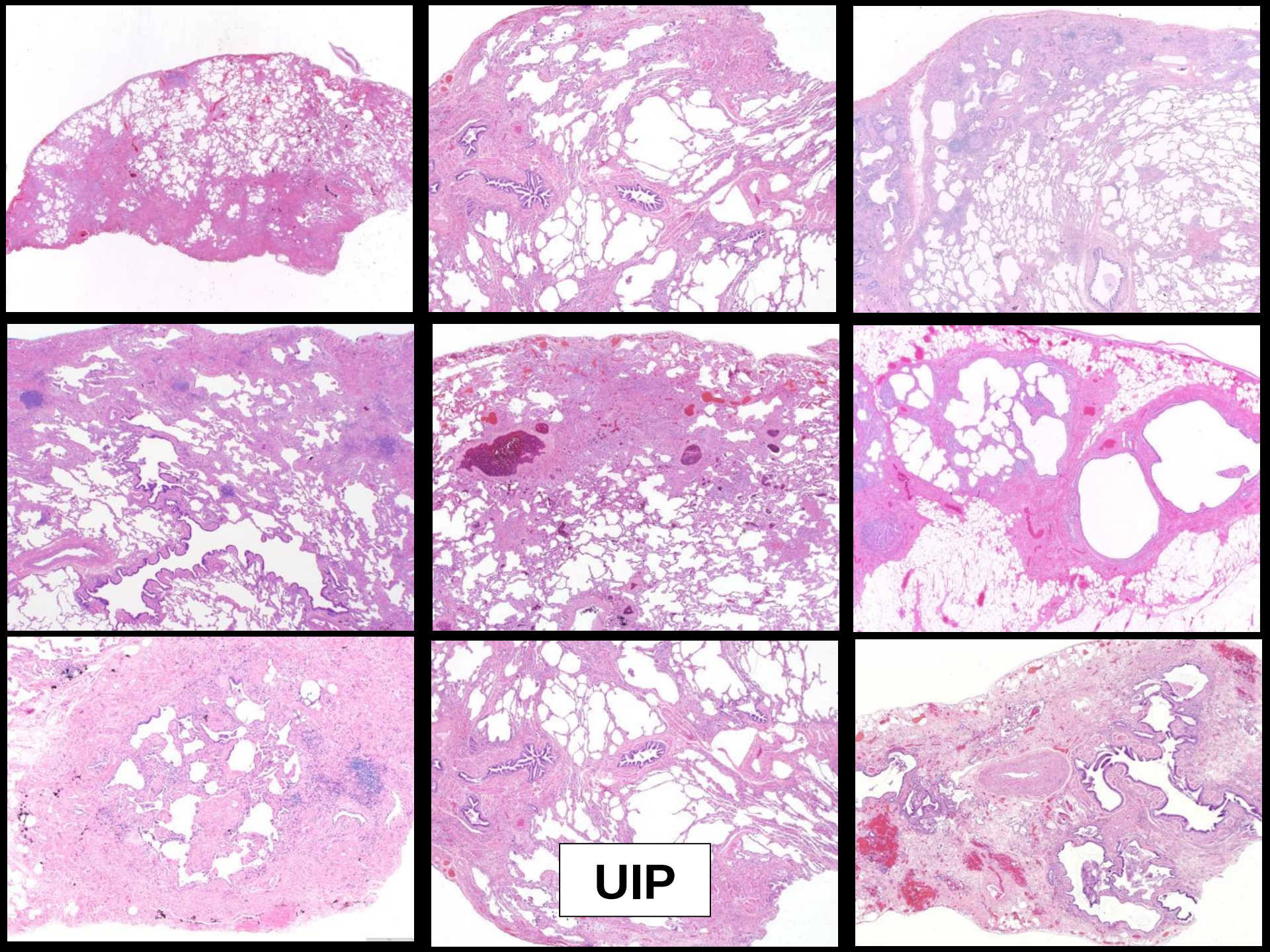
Cryptogenic organizing pneumonitis (COP) is a clinicopathologic entity described by Davison and coworkers in 1983 (38). In 1985, Epler and colleagues described the same entity under the term bronchiolitis obliterans organizing pneumonia (BOOP), and that latter term came into common usage (sometimes referred to as idiopathic BOOP) (37). The term cryptogenic organizing pneumonitis (COP) is preferred because it conveys the essential features of the syndrome described below and avoids confusion with airway diseases such as constrictive bronchiolitis obliterans, which can be problematic with the term BOOP. Features of the organizing pneumonia pattern are organization

Travis WD et al Am J Resp Crit Care Med 2002;165:277-304





Bronchiolitis obliterans
a.k.a Constrictive bronchiolitis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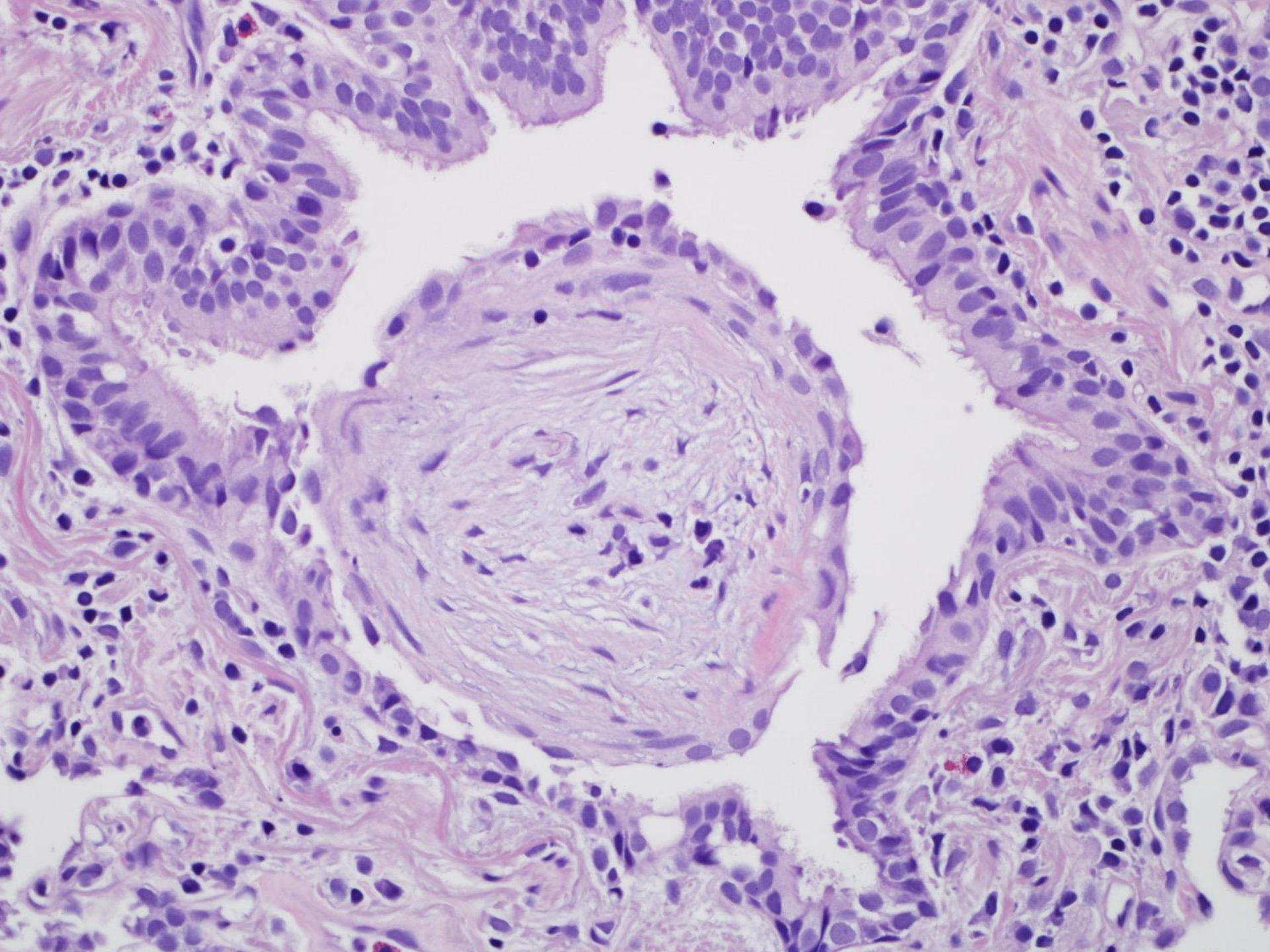
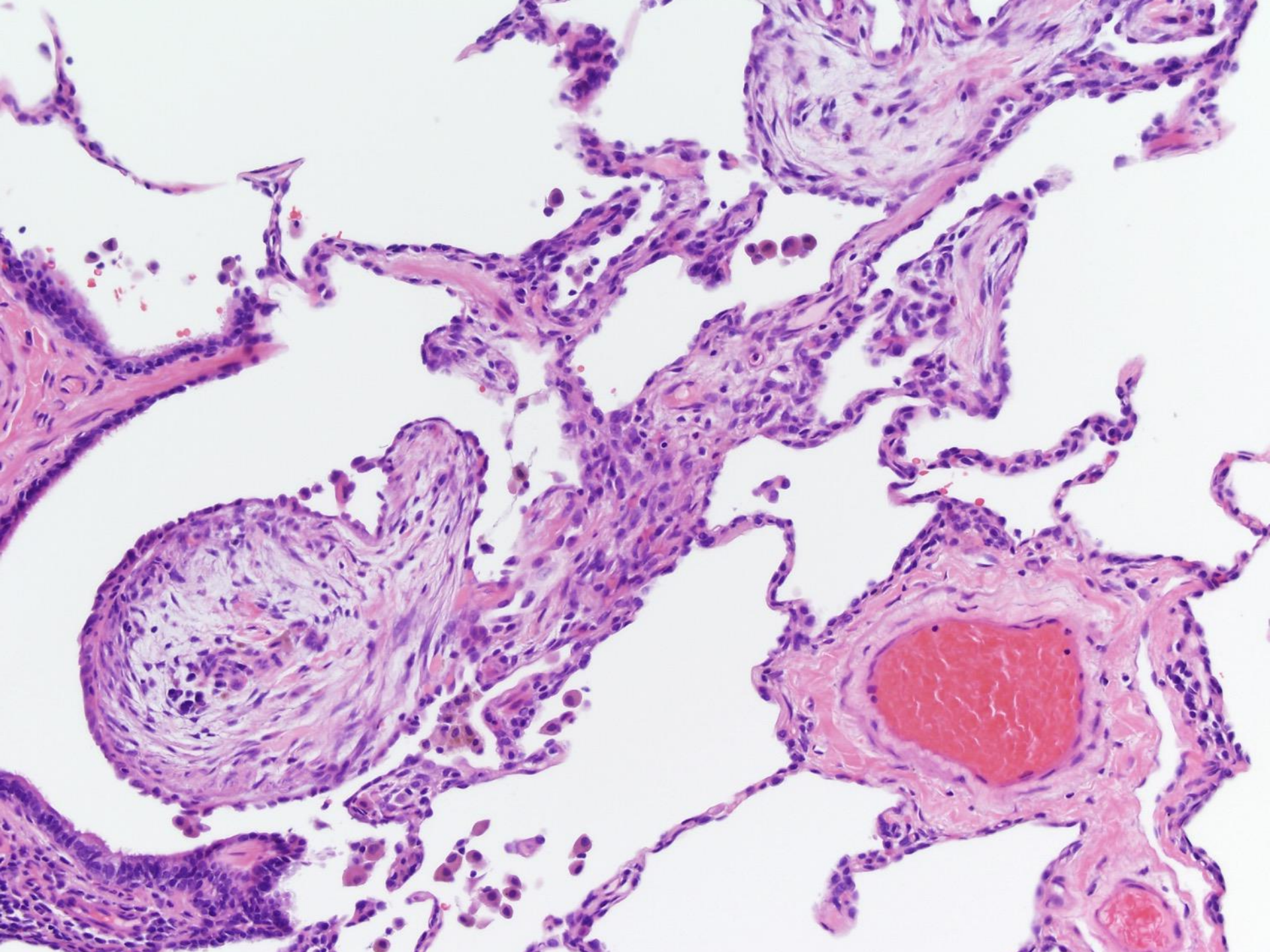
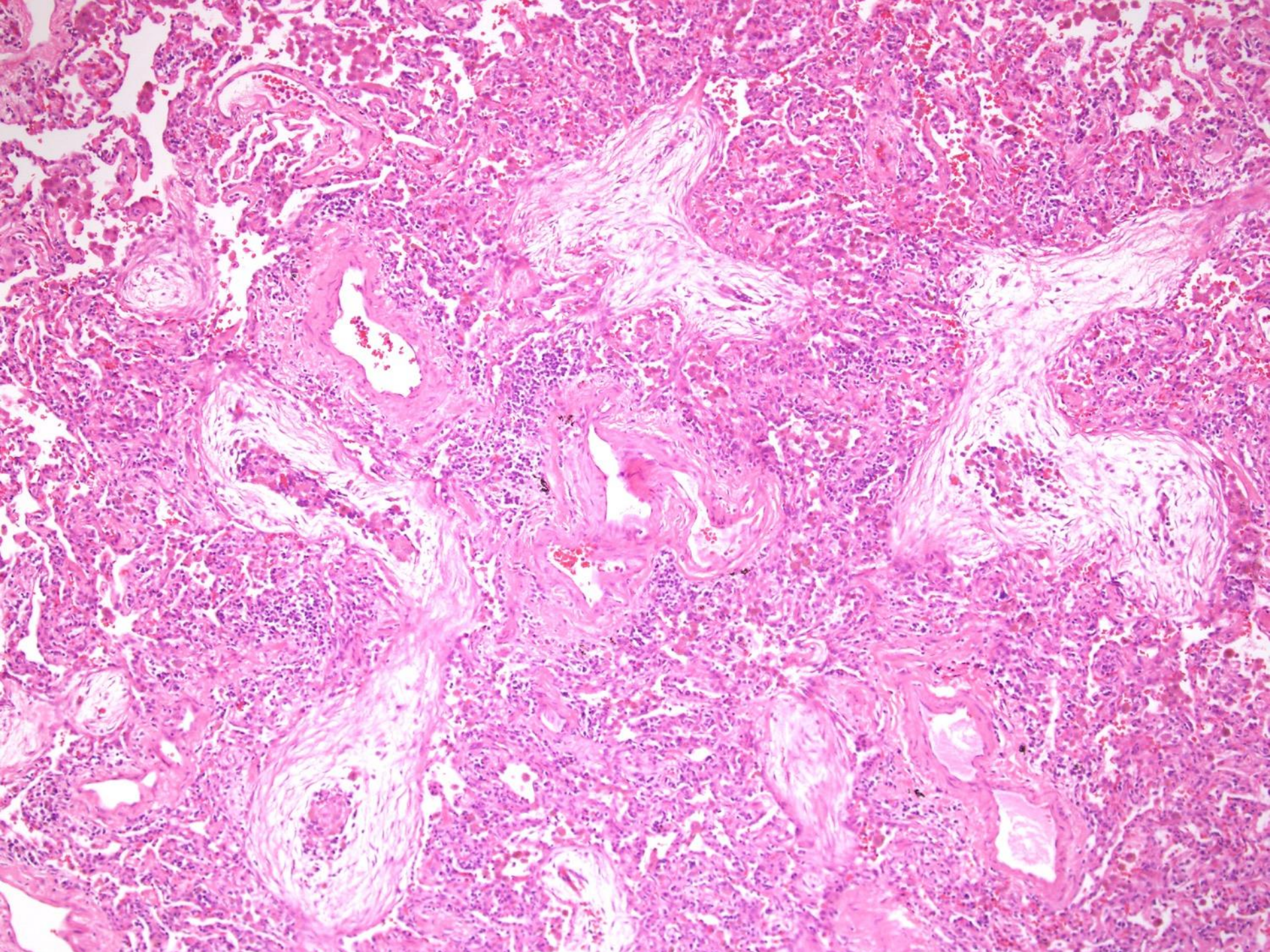
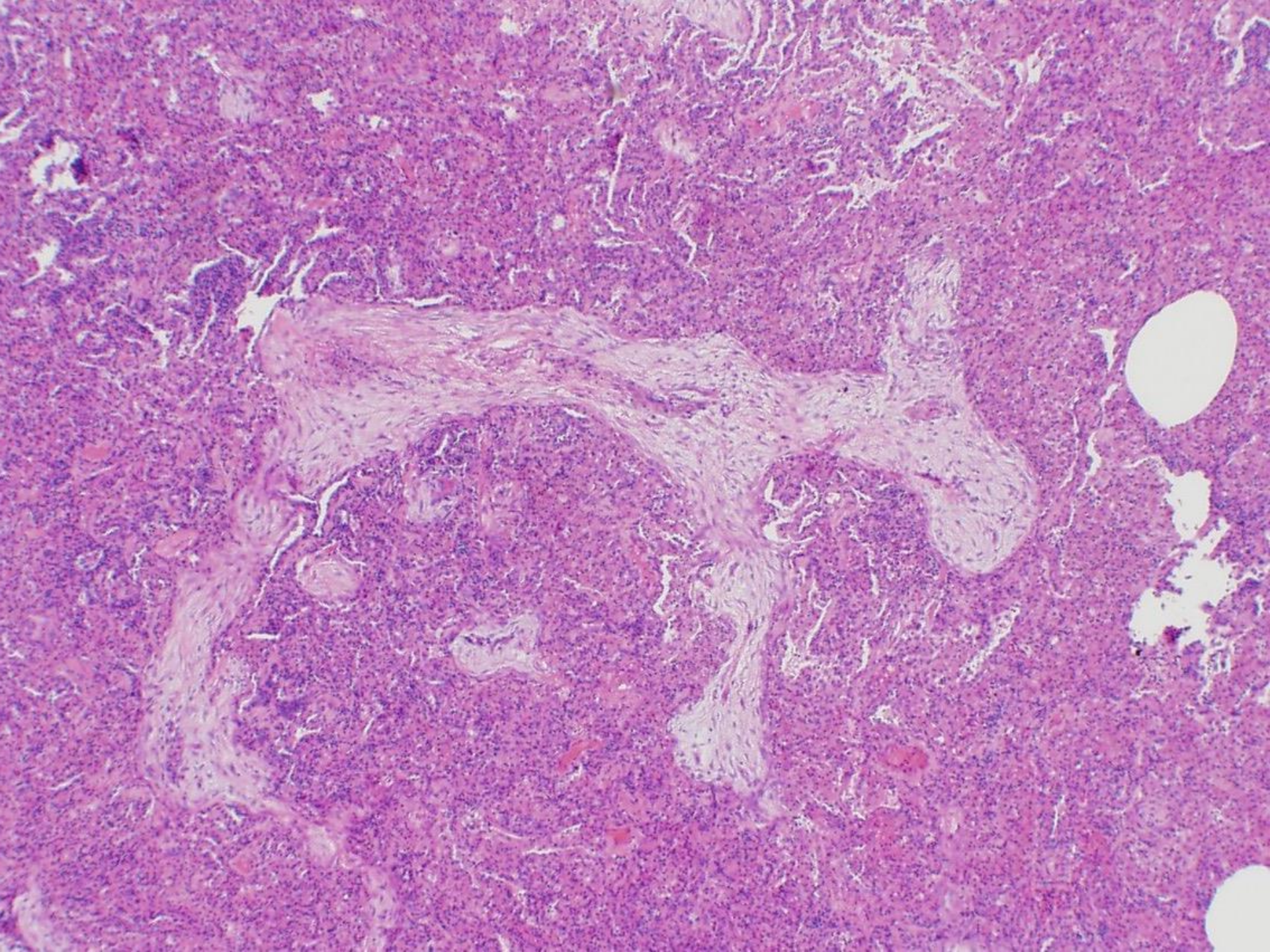
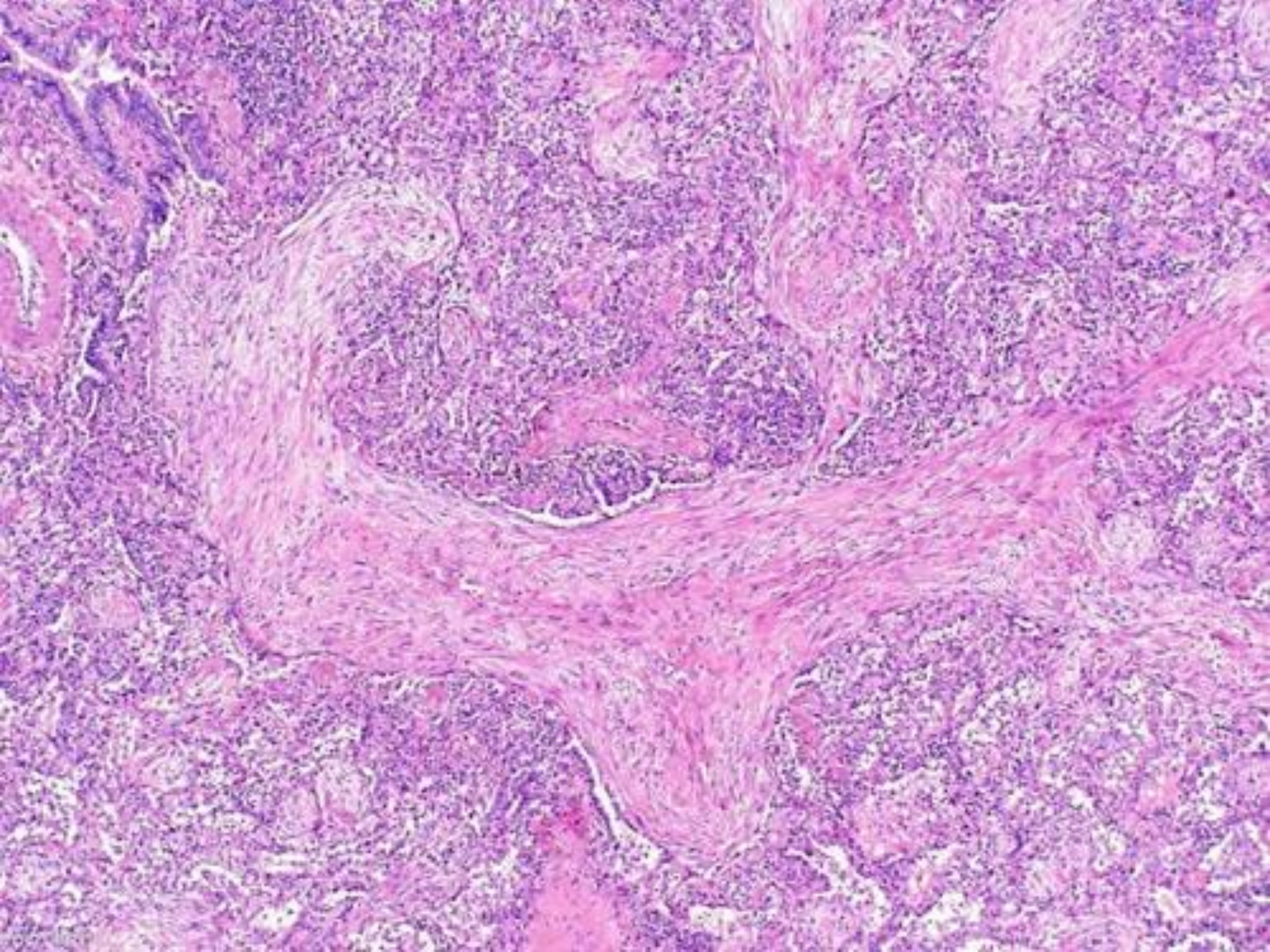
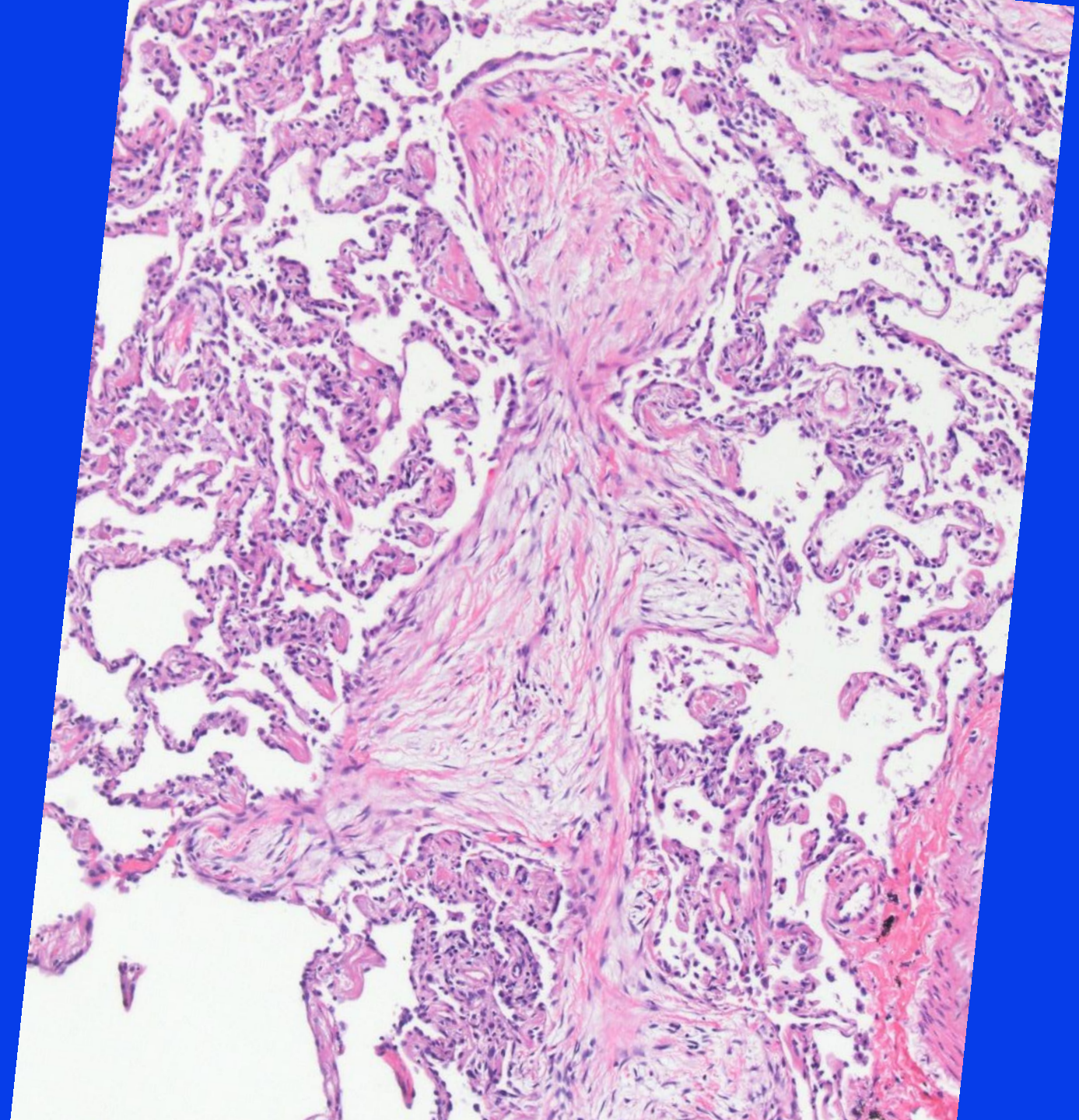






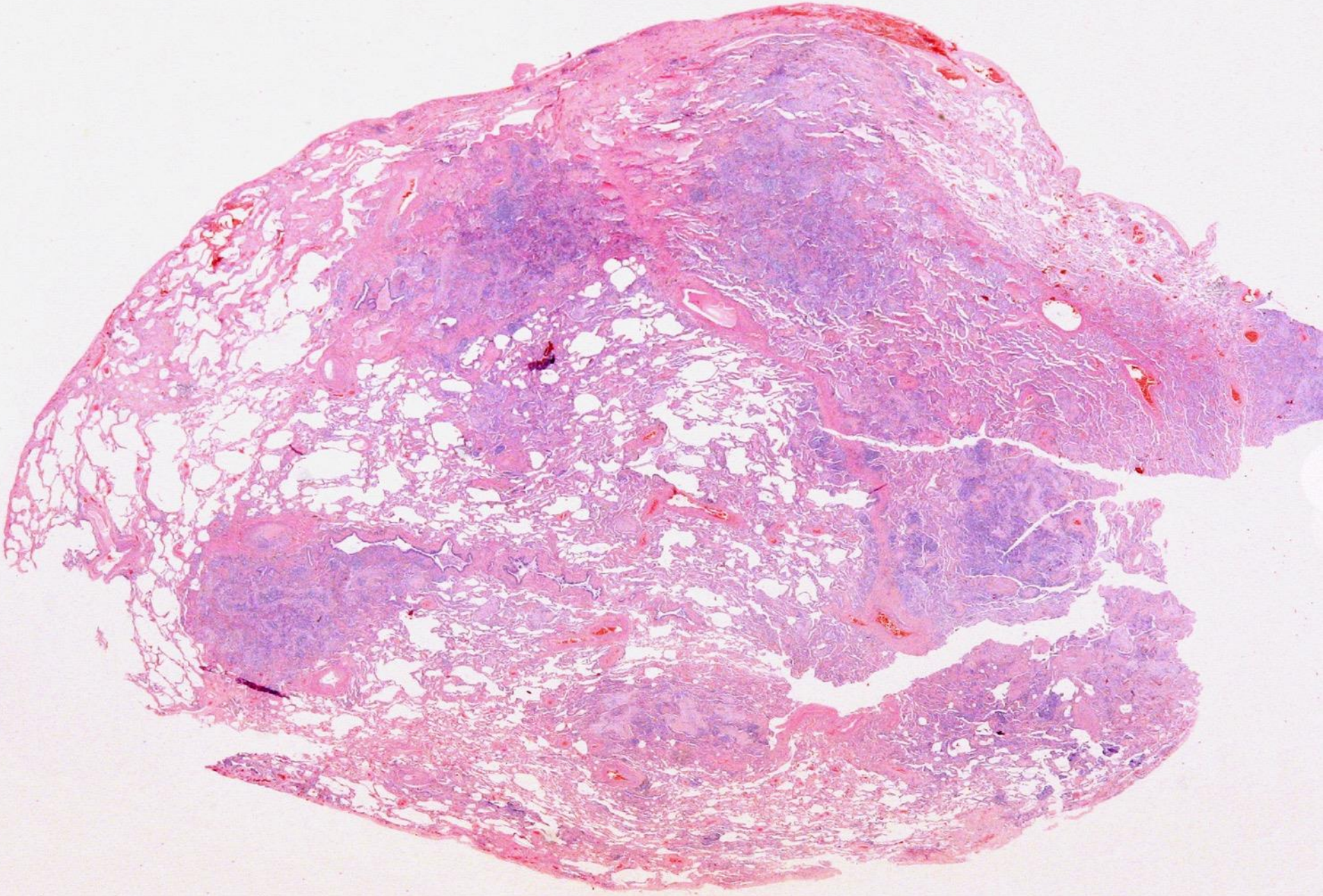




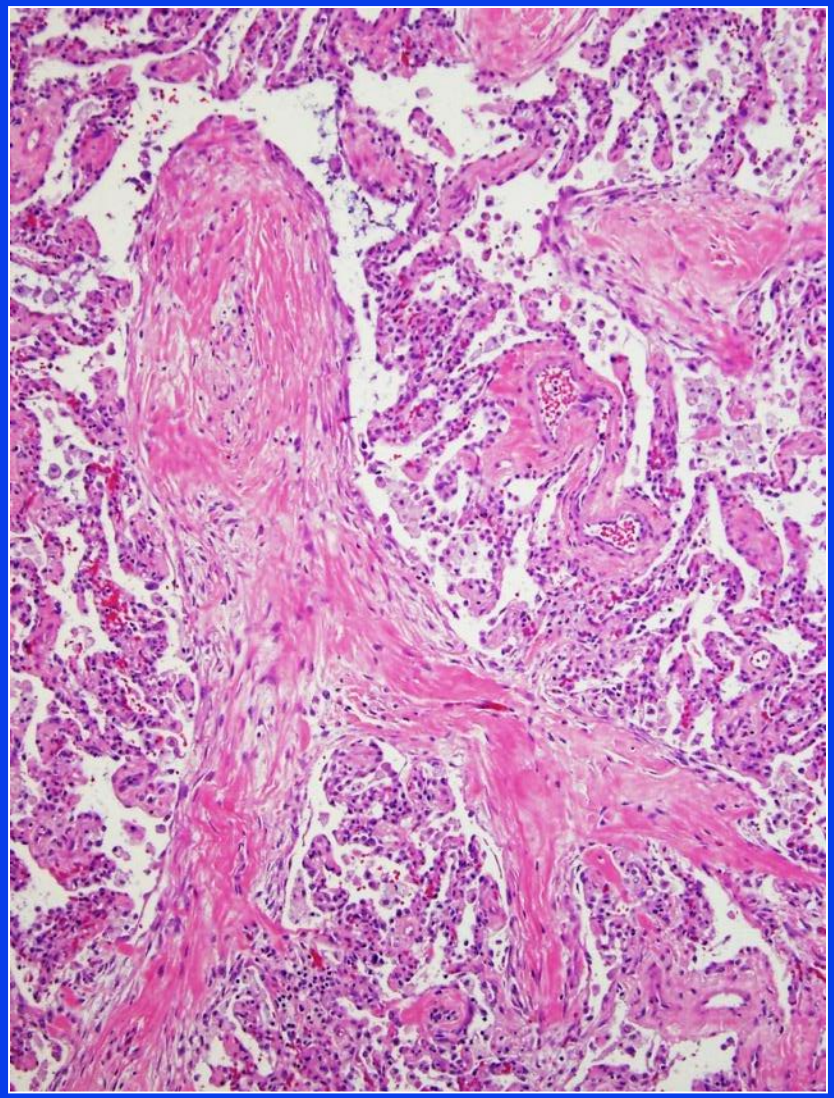


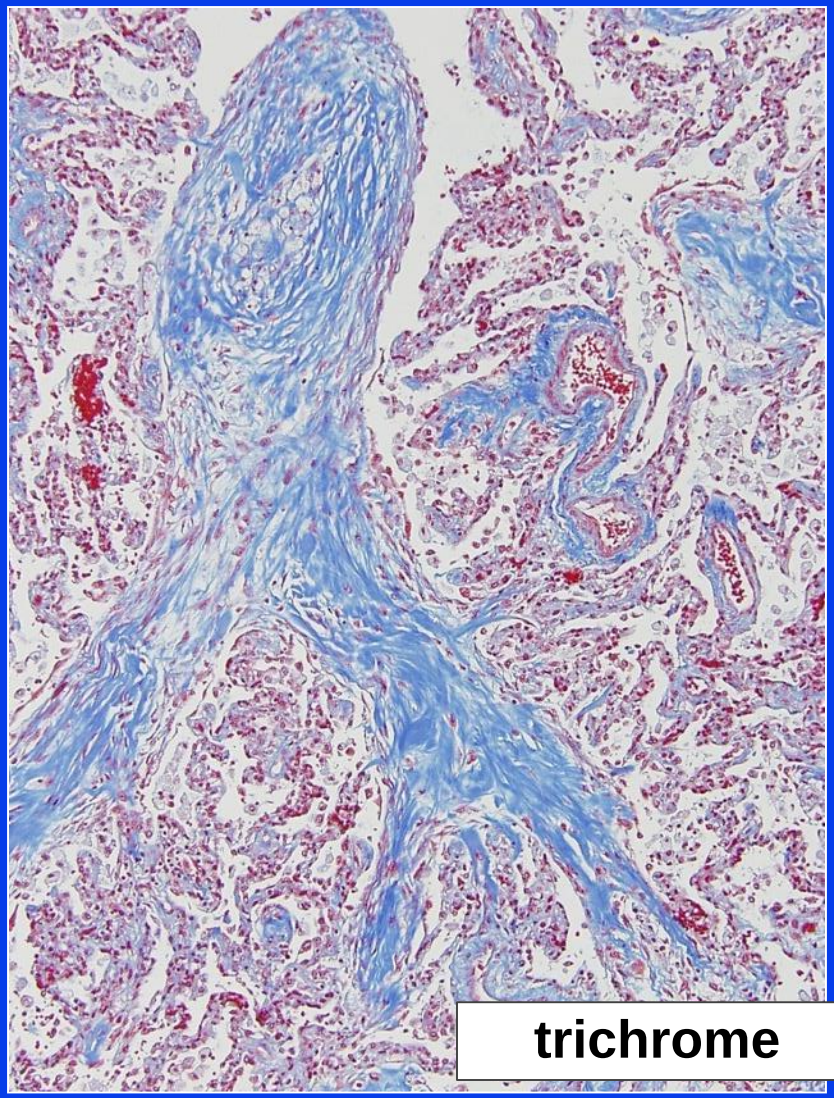
Bronchiolitis Obliterans *with* Organizing Pneumonia

- Despite sometimes long history, changes were of “same age”
- Some alveolar interstitial fibrosis-peribronchiolar
- Honeycombing never seen



Hyalinized Organizing Pneumonia





Yousem SA et al Mod Pathol 1997;10:864-871

Hyalinized/Cicatricial/Fibrosing Organizing Pneumonia

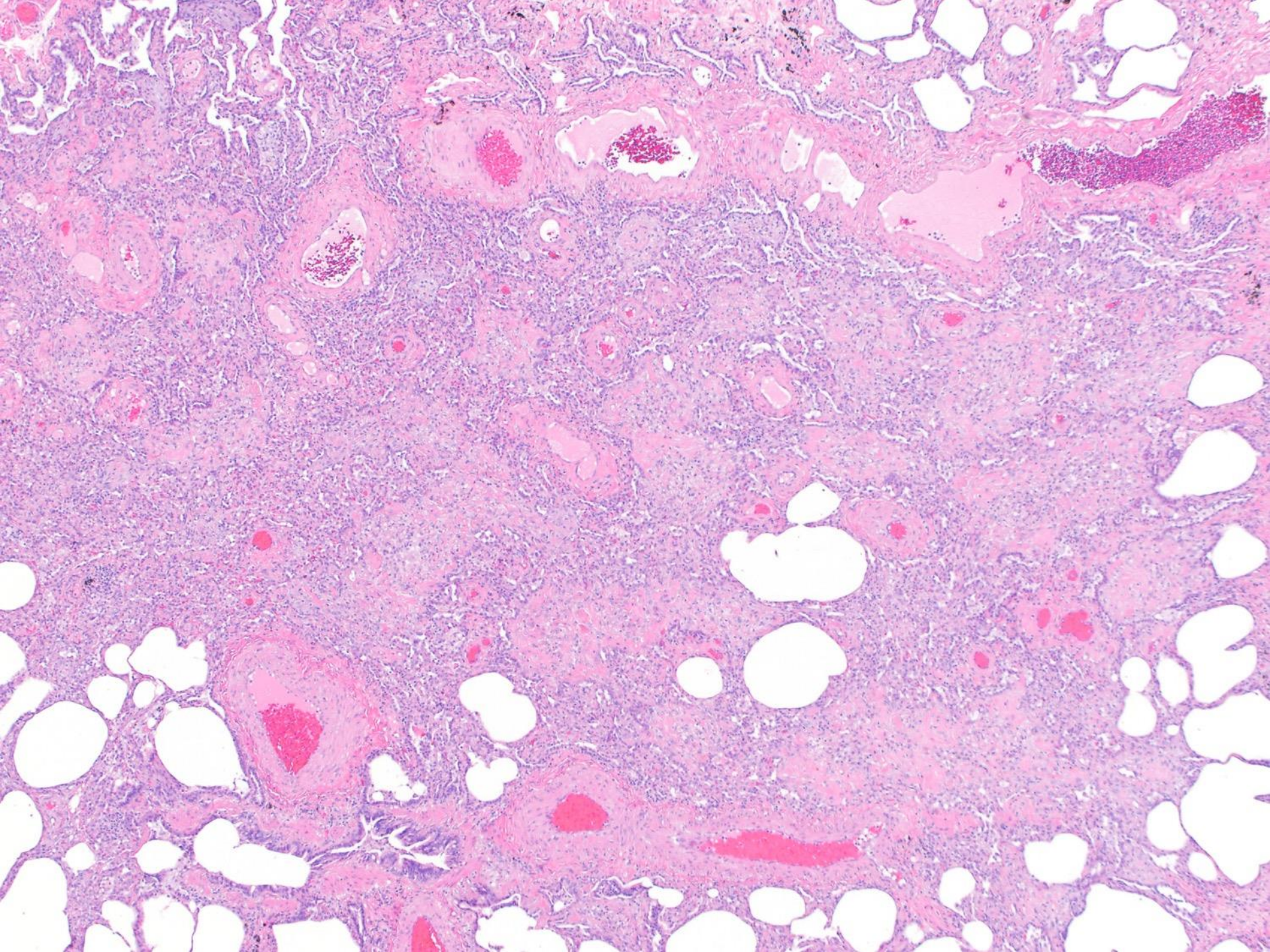
- 12 pts with cryptogenic disease
- 55% had progressive or persistent CT infiltrates
- 25% assoc. osseous metaplasia
- Contribution of pre-existing non fibrotic lung ds, like emphysema which impairs healing?
- Suggested poor steroid response

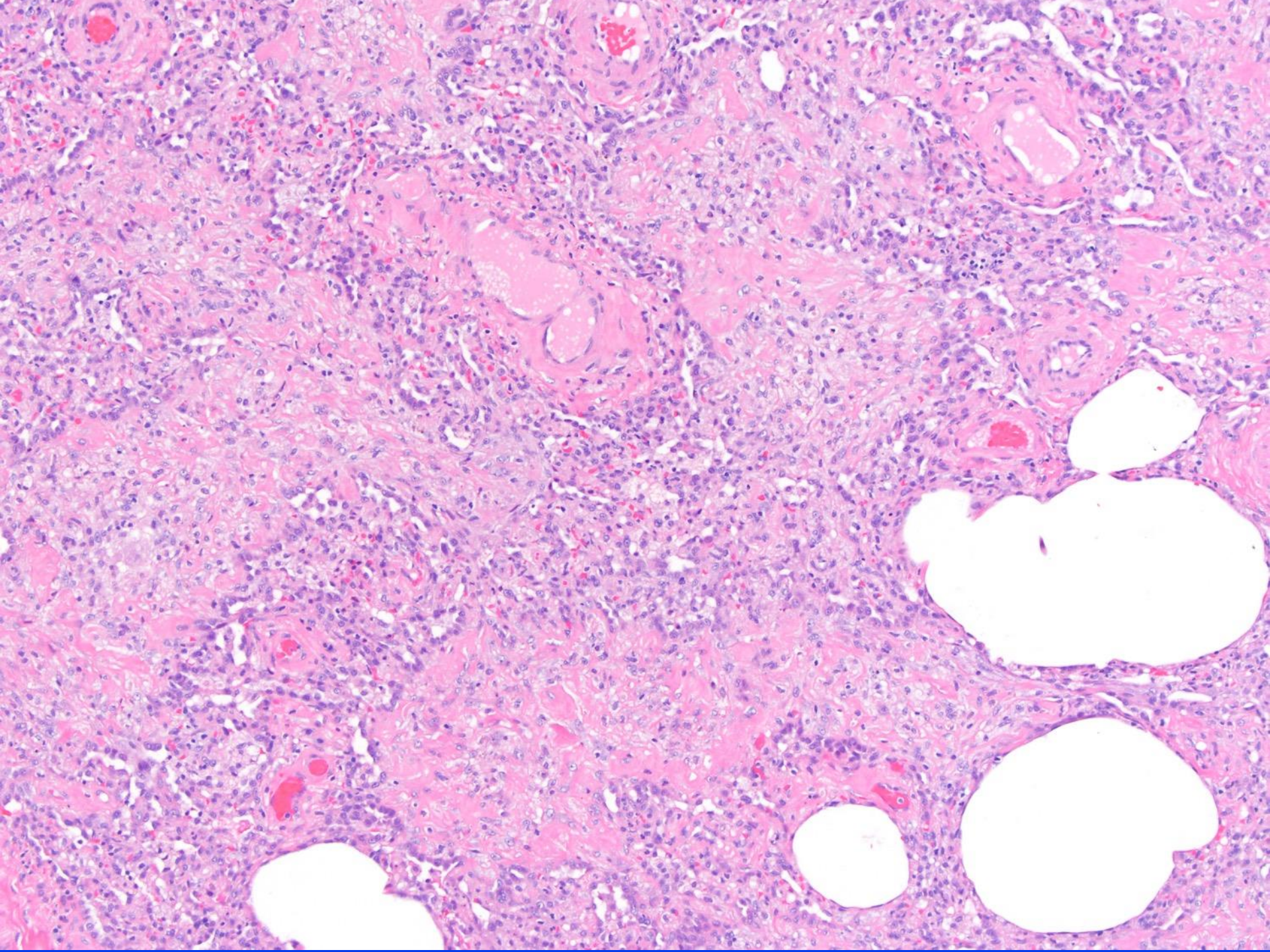
Yousem SA Hum Pathol 2017; 64:76-82

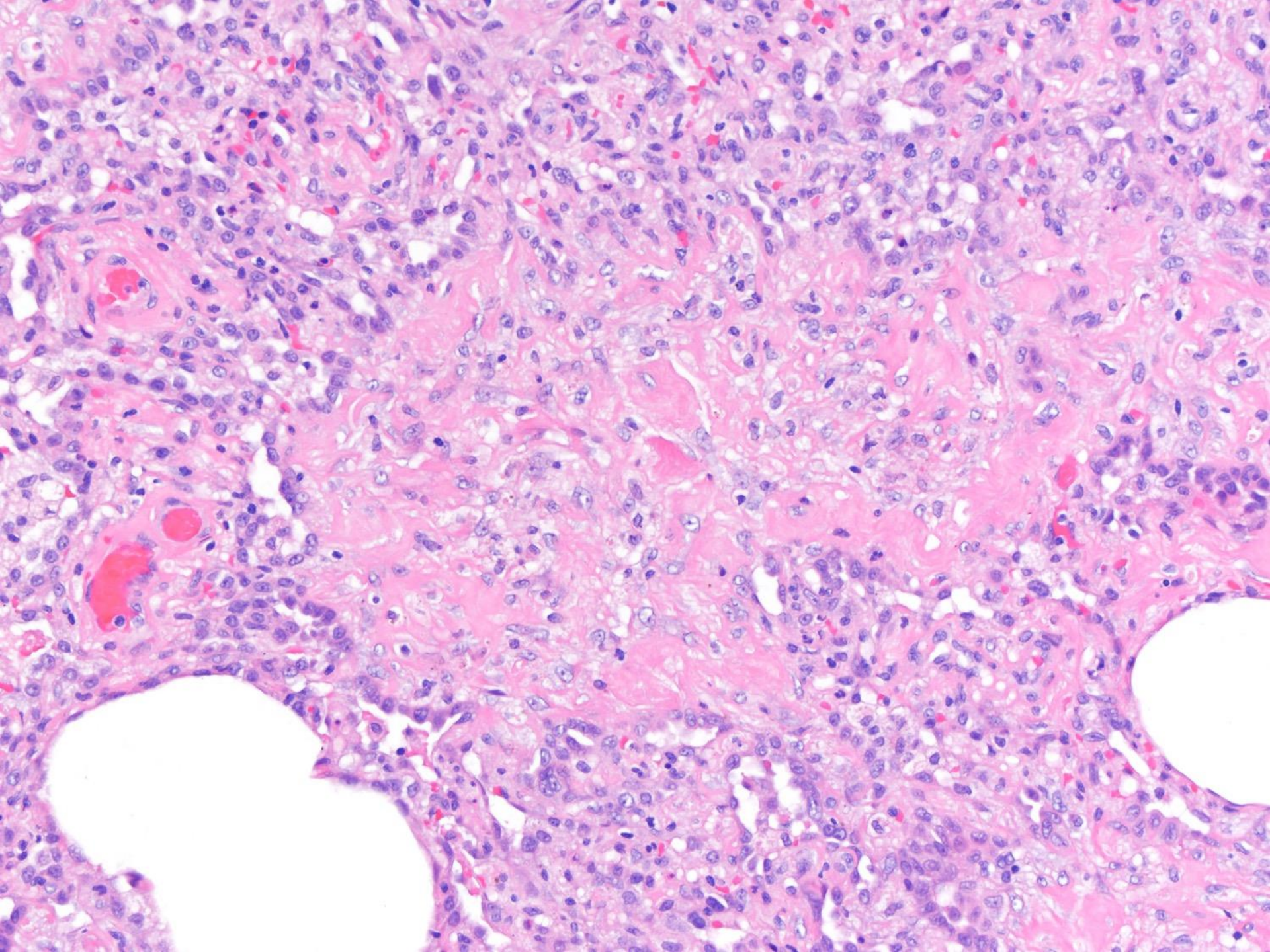
Hyalinized/Cicatricial/Fibrosing Organizing Pneumonia

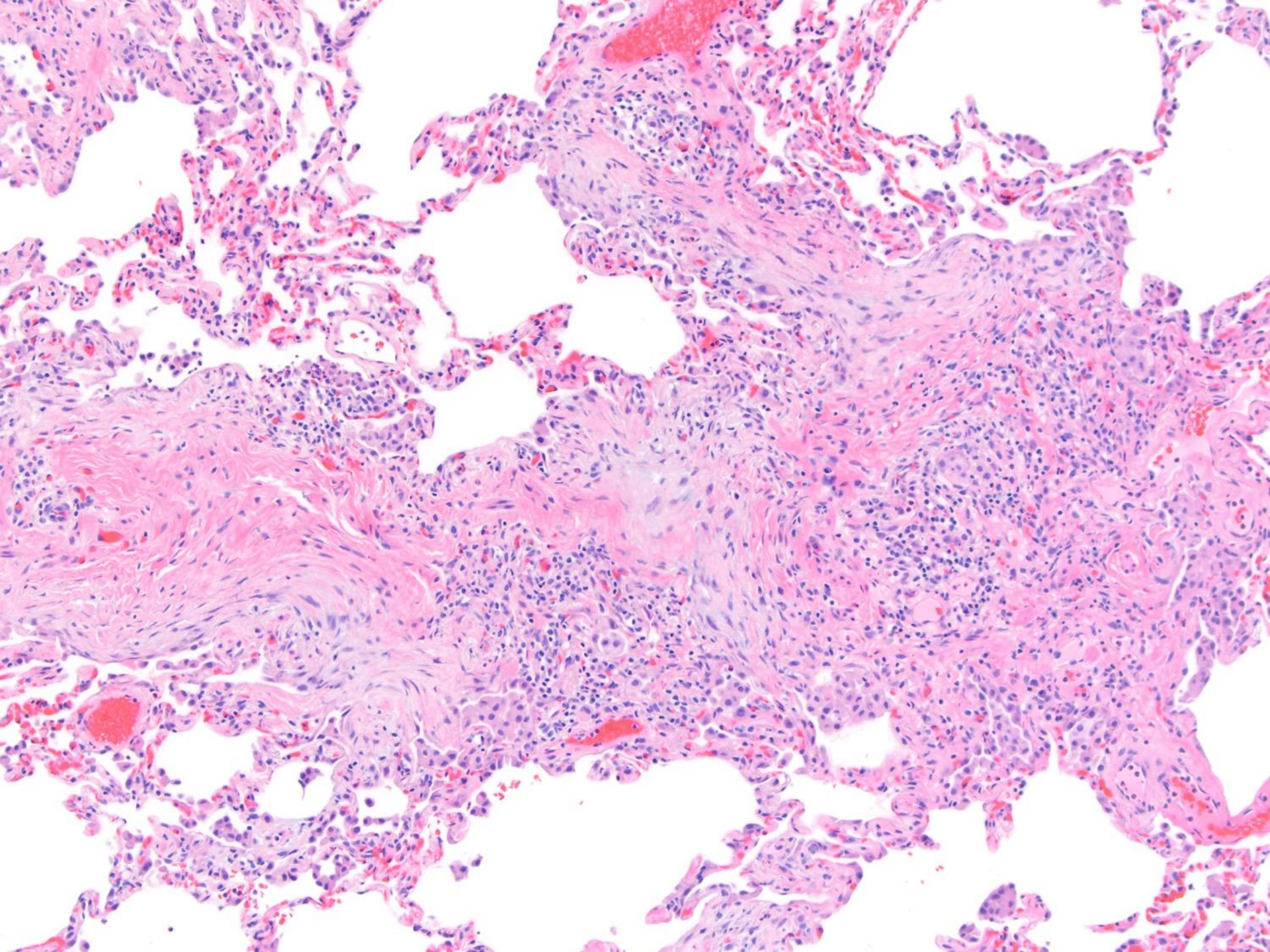
- 10 pts identified by pattern
- 20% assoc with radiologic ossification
- Mimic of fibrotic NSIP
- Non-progressive disease
- Ehlers Danlos-1 pt

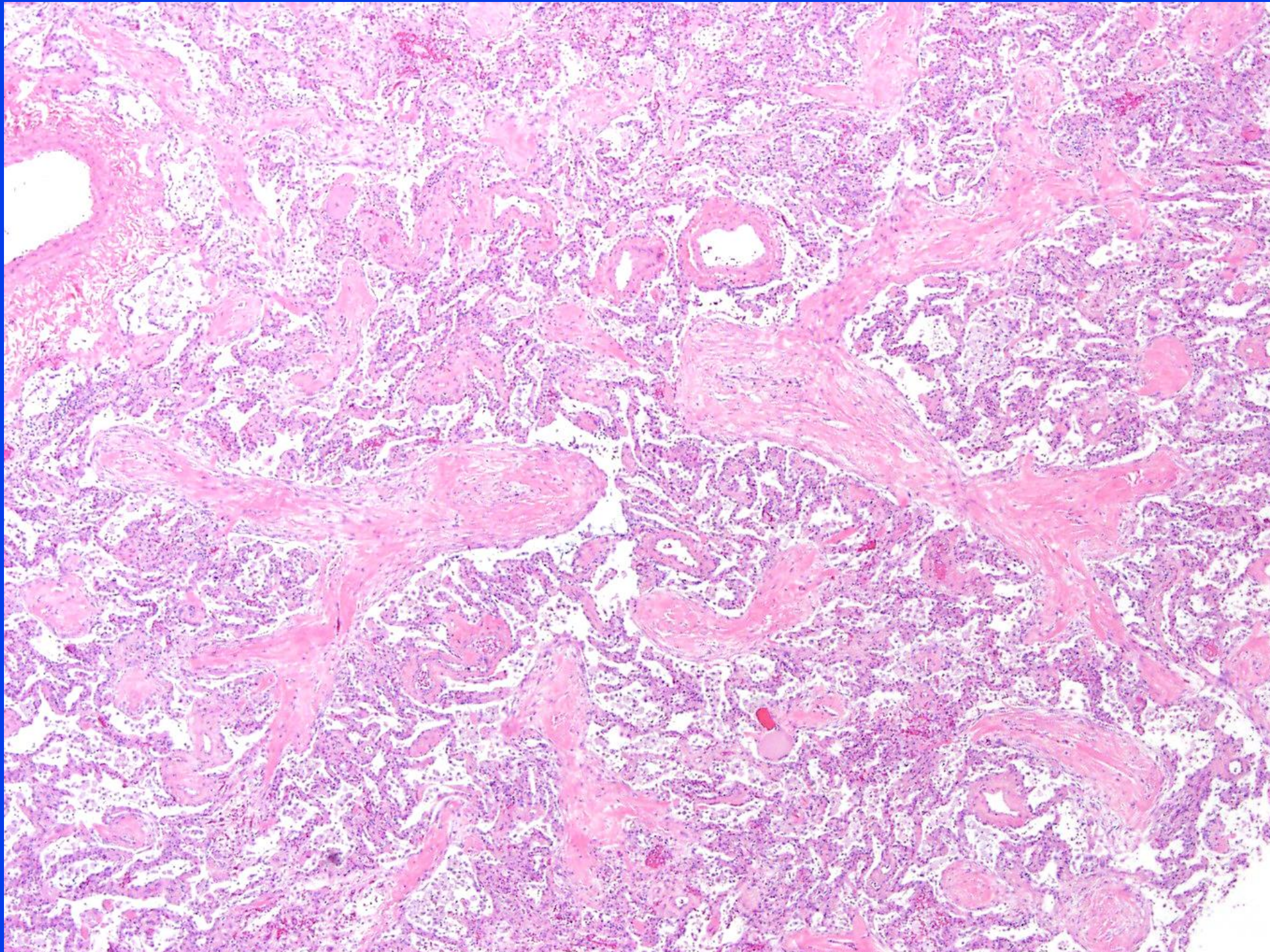
Churg A et al Histopathol 2018; 72:846-854

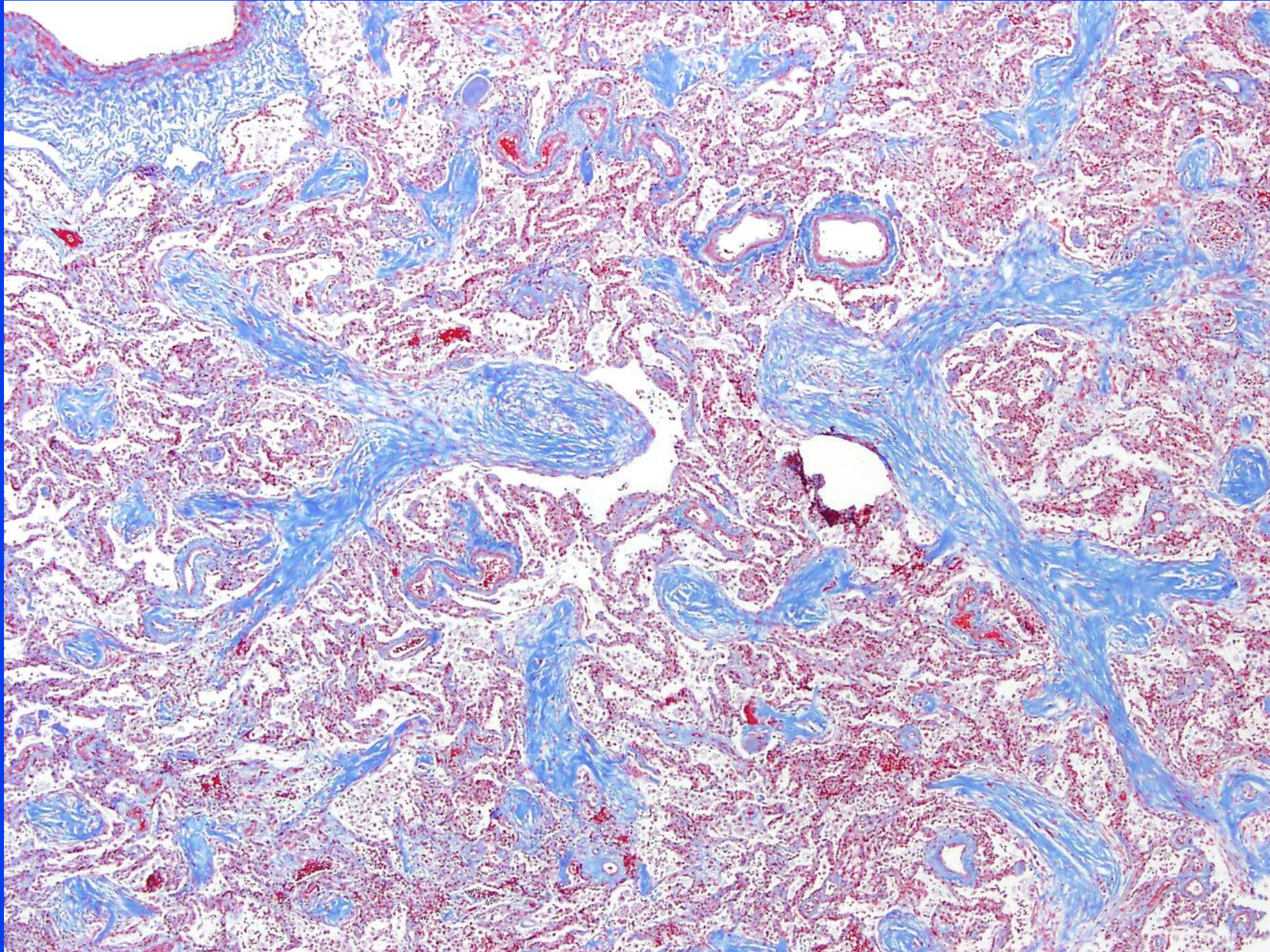


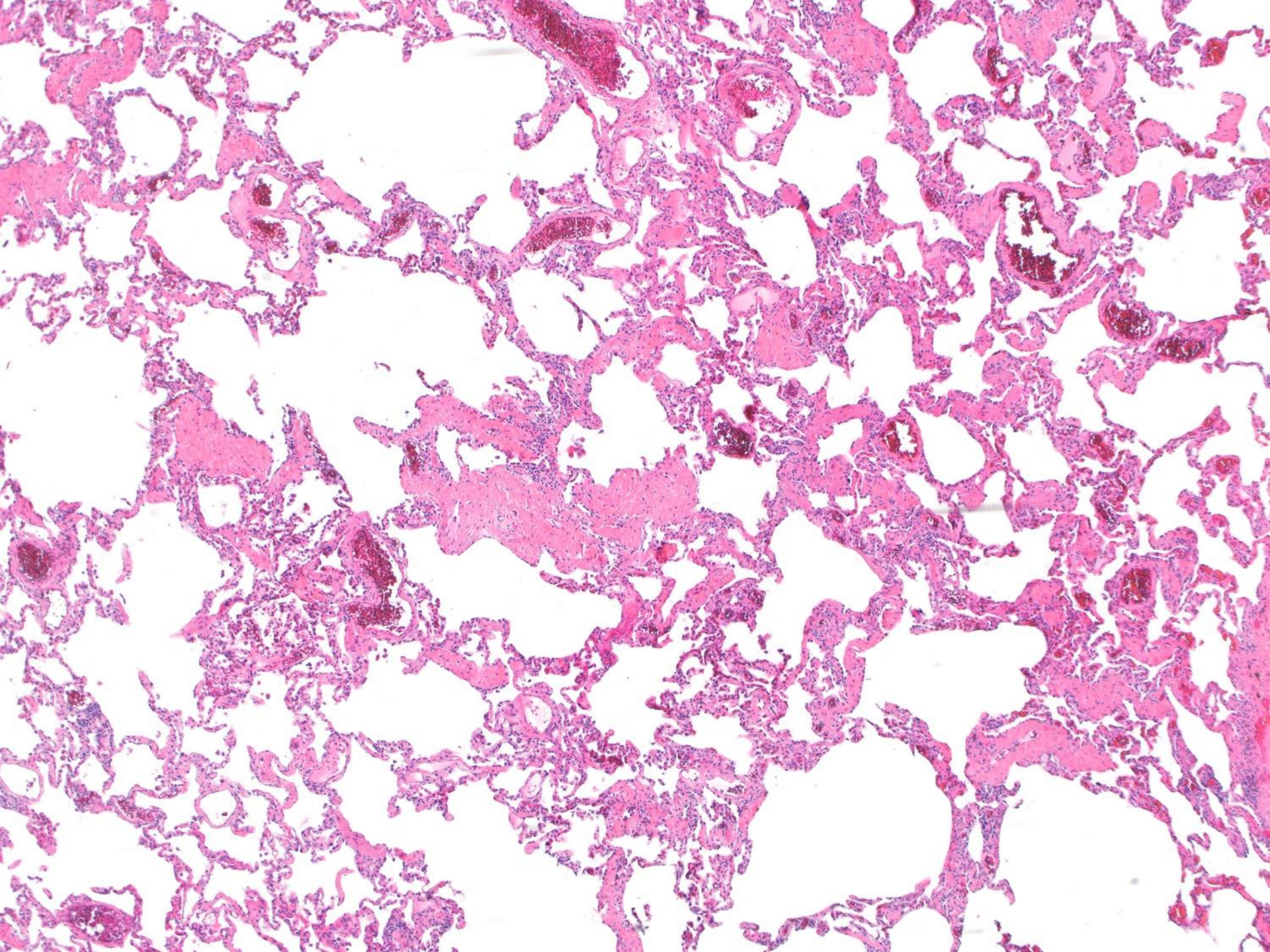


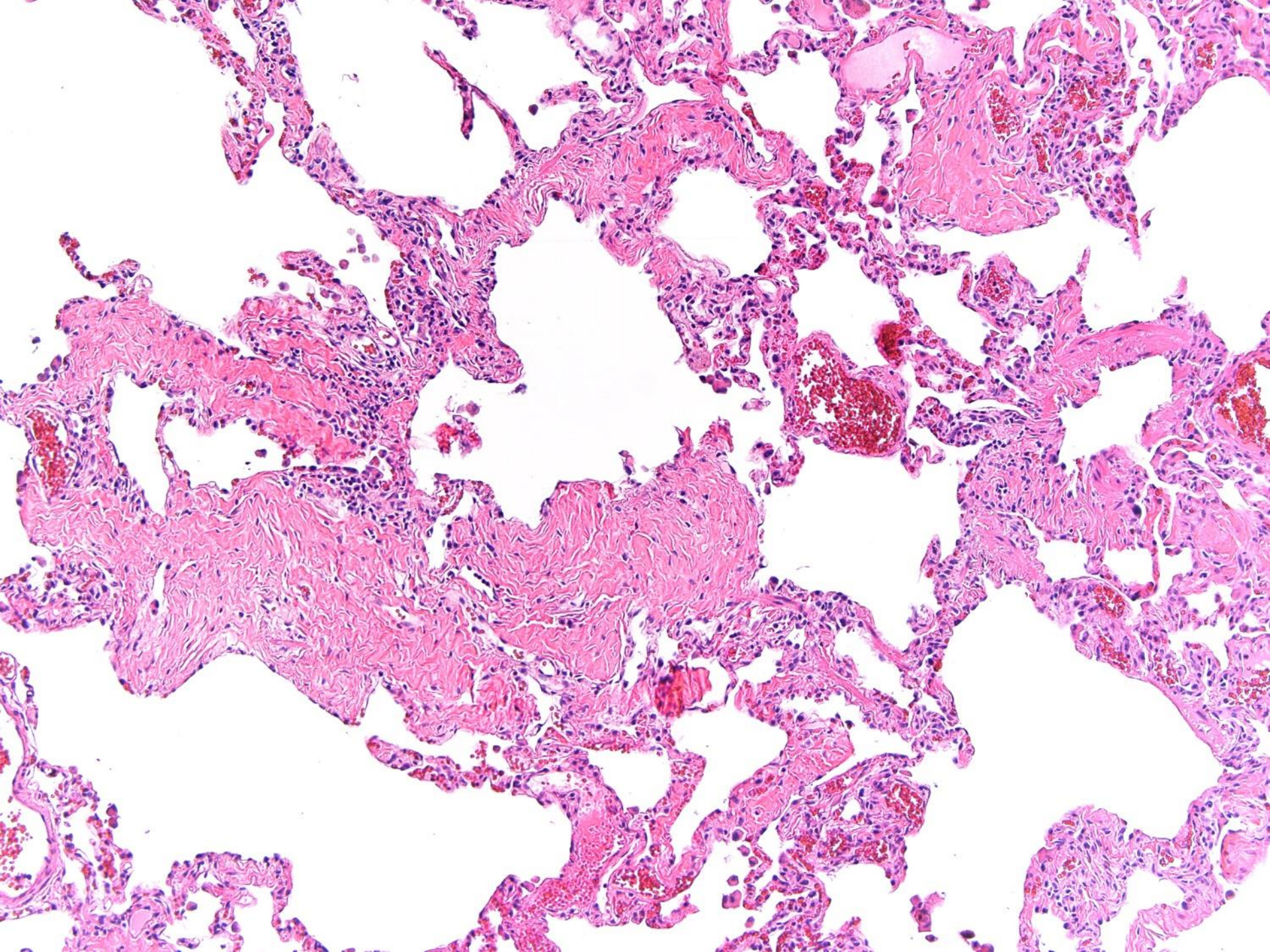






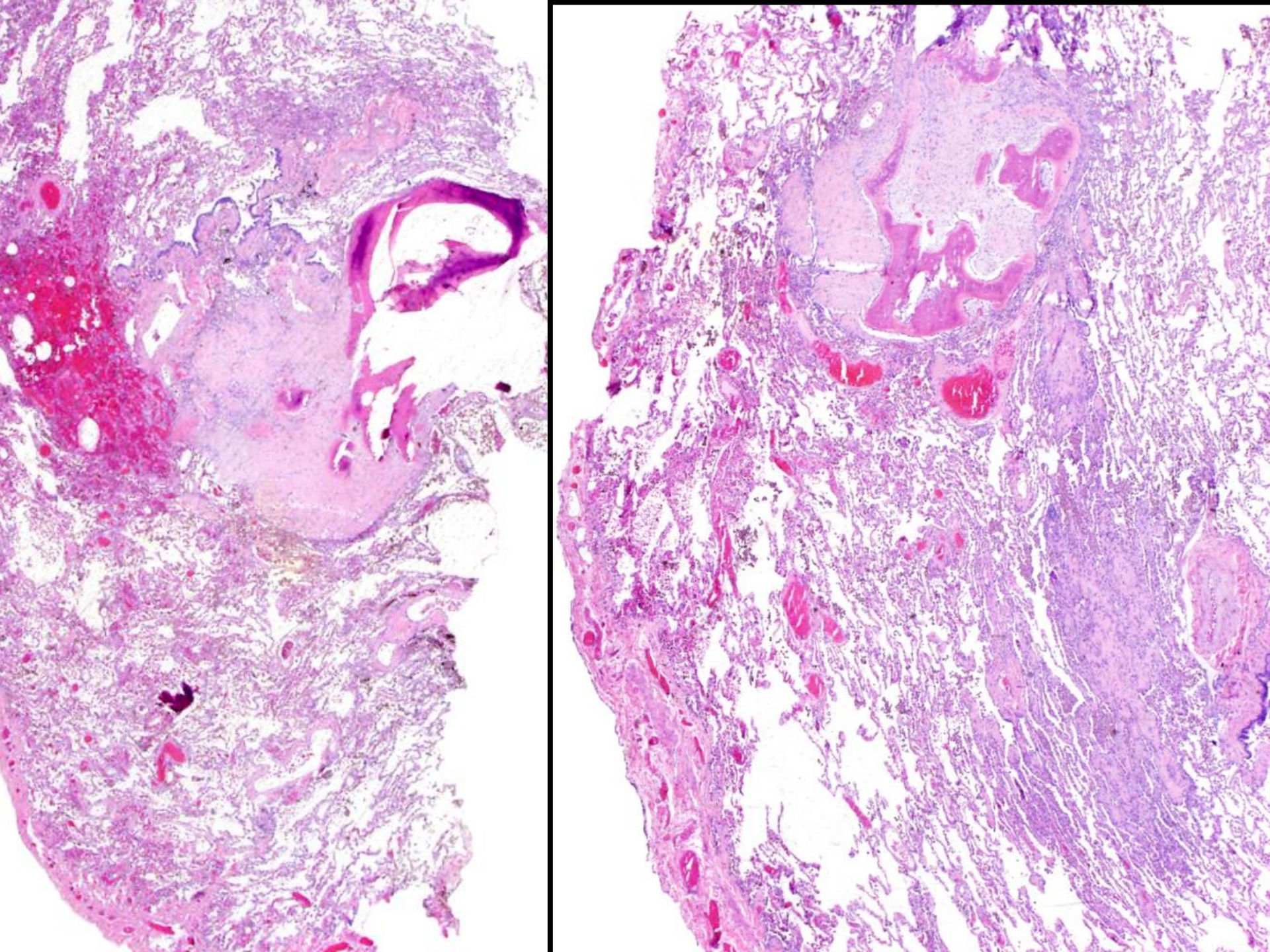


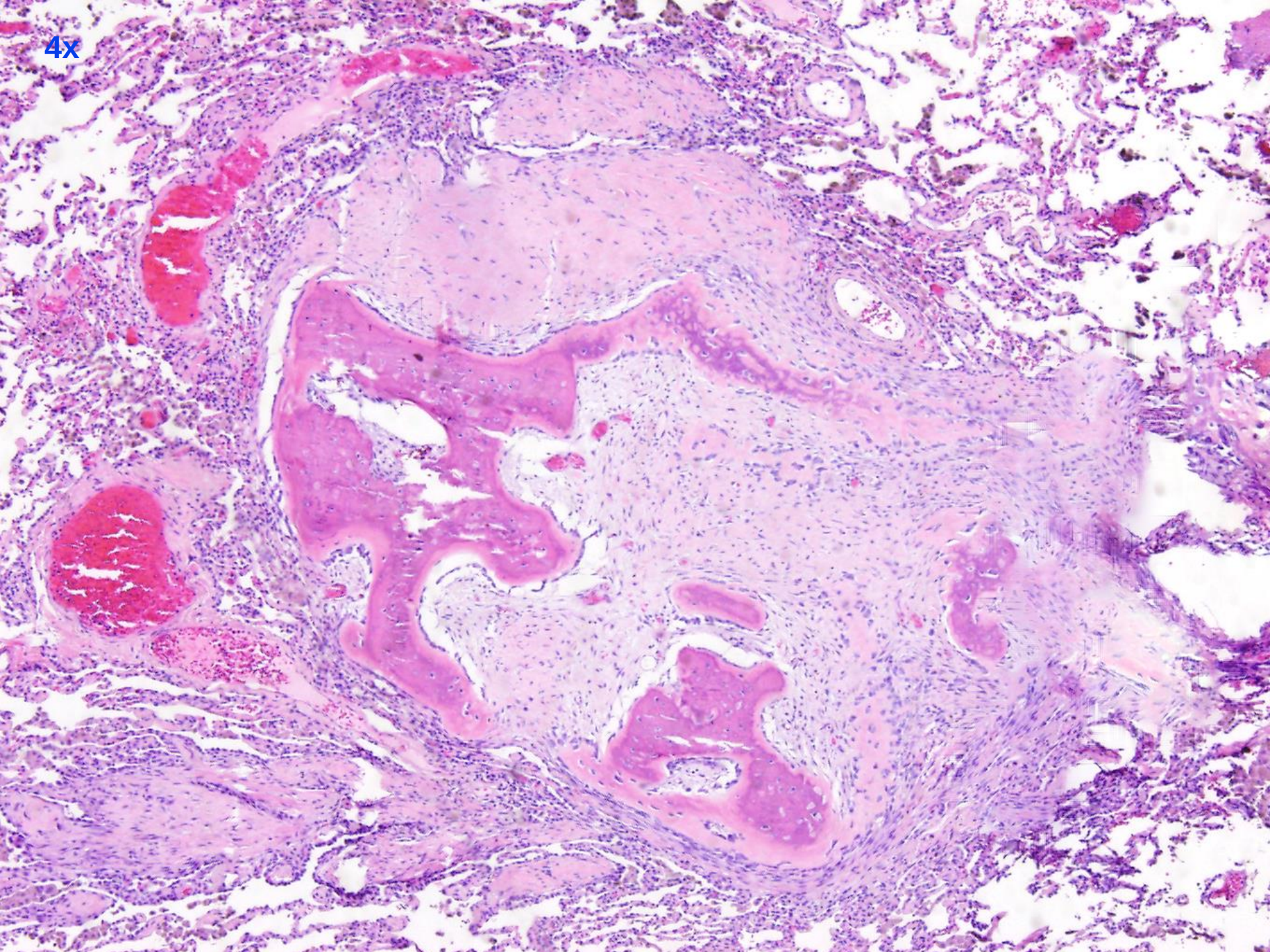




Ehlers Danlos Syndrome Patient History

- 41-year-old male real estate broker
  - CC: Cough and hemoptysis
- Past Medical History
  - Asthma
  - Recurrent pneumothorax
    - Unilateral January 2016
    - Bilateral October 2016
  - Autoimmune serologies negative

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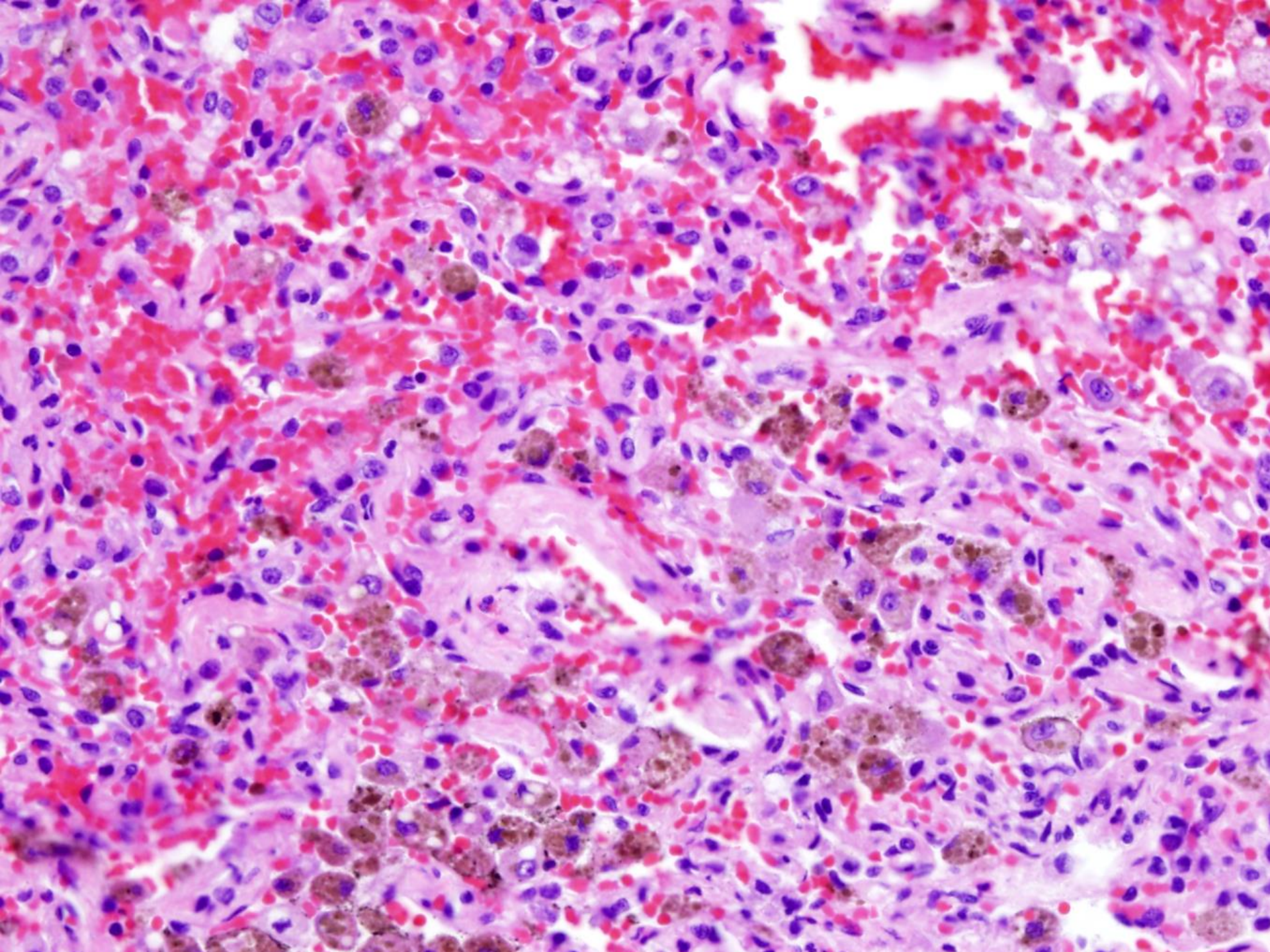


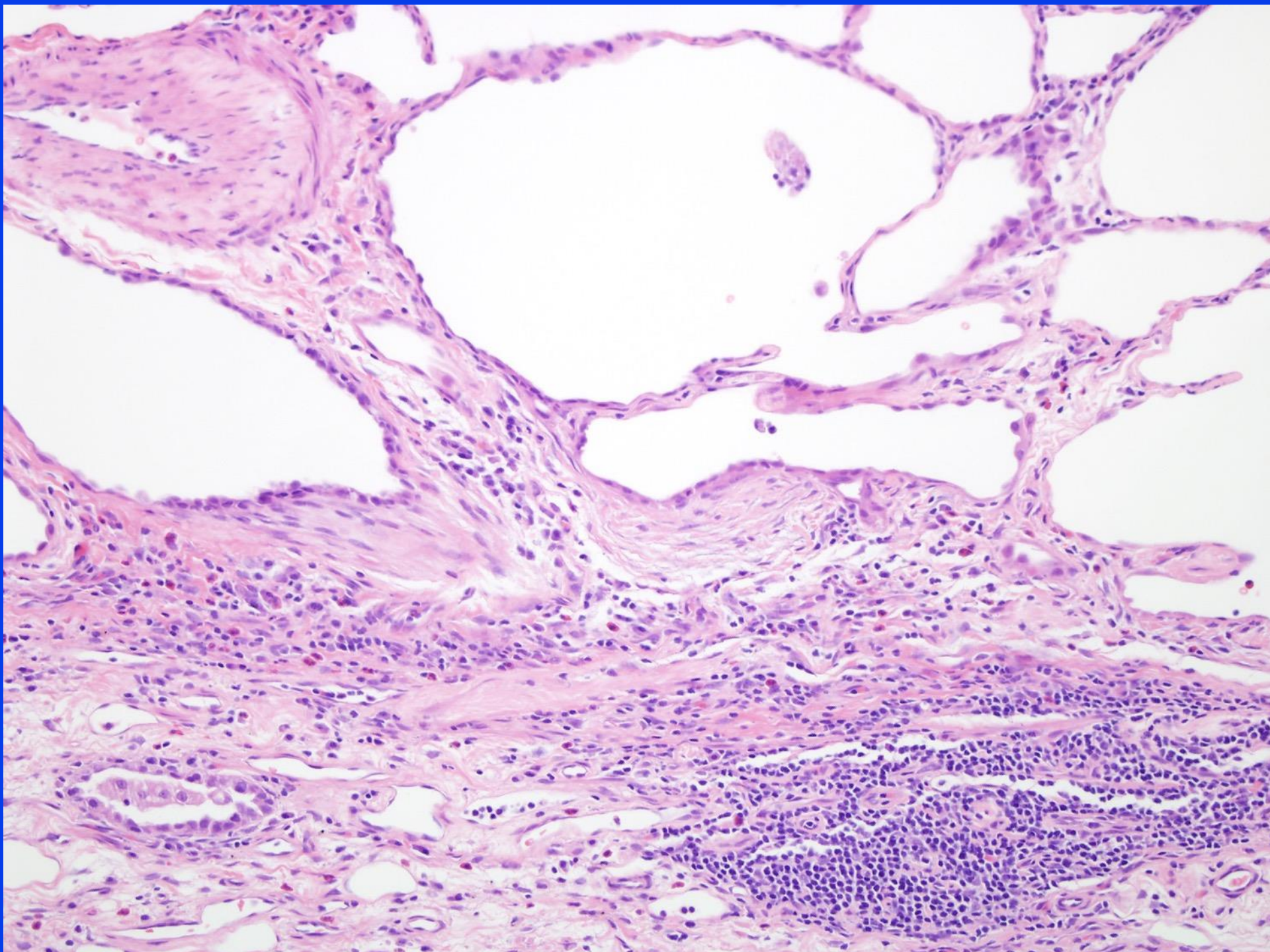
Ehlers-Danlos Syndrome

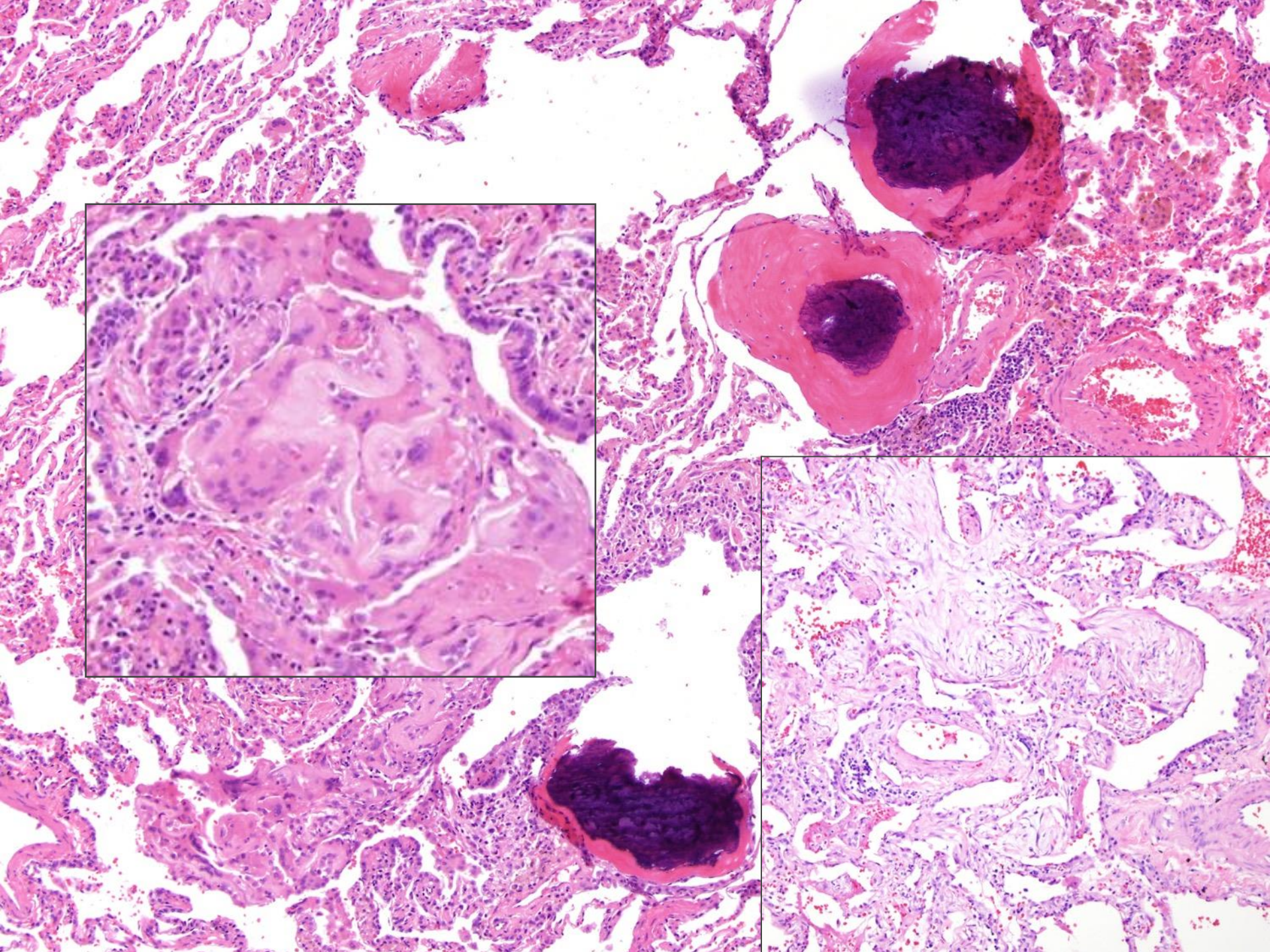
Villefranche classification[1]	Prior Nomenclature	Inheritance Pattern	Genes
Classic	Type I and II	AD	*COL5A1* and *COL5A2*
Hypermobility	Type III	AD (likely)[2]	Unknown[2]
Vascular	**Type IV**	**AD[3]**	***COL3A1***
Kyphoscoliosis	Type VI	AR	*PLOD1*
Arthrochalasia	Type VIIA and B	AD	*COL1A1* (VIIA) *COL1A2* (VIIB)
Dermatosparaxis	Type VIIC	AR	*ADAMTS2*

Beighton P et al Am J Med Genet 1998;77(1):31-7

Differential Diagnosis for Hyalinizing OP

- Ehlers Danlos syndrome
- OP in NSIP
- Fibroblast foci of UIP
- Aspiration pneumonia with OP pattern and ossification





Hyalinized/Cicatricial/Fibrosing Organizing Pneumonia

- New pattern to recognize
- Prognostic significance unclear
- Likely also occurs in association with other disease e.g. CTD
- Other features may point to etiology-EDS, aspiration

Churg A et al Histopathol 2018; 72:846-854

Q. A 58 year old woman with a history of Sjogren syndrome, gastroparesis, MALT lymphoma (treated with Rituximab and radiation) presented with a two day history of increasing shortness of breath. A CT about 1 month prior (done for cough and dyspnea) showed a stable infiltrate or scarring in the lingula….

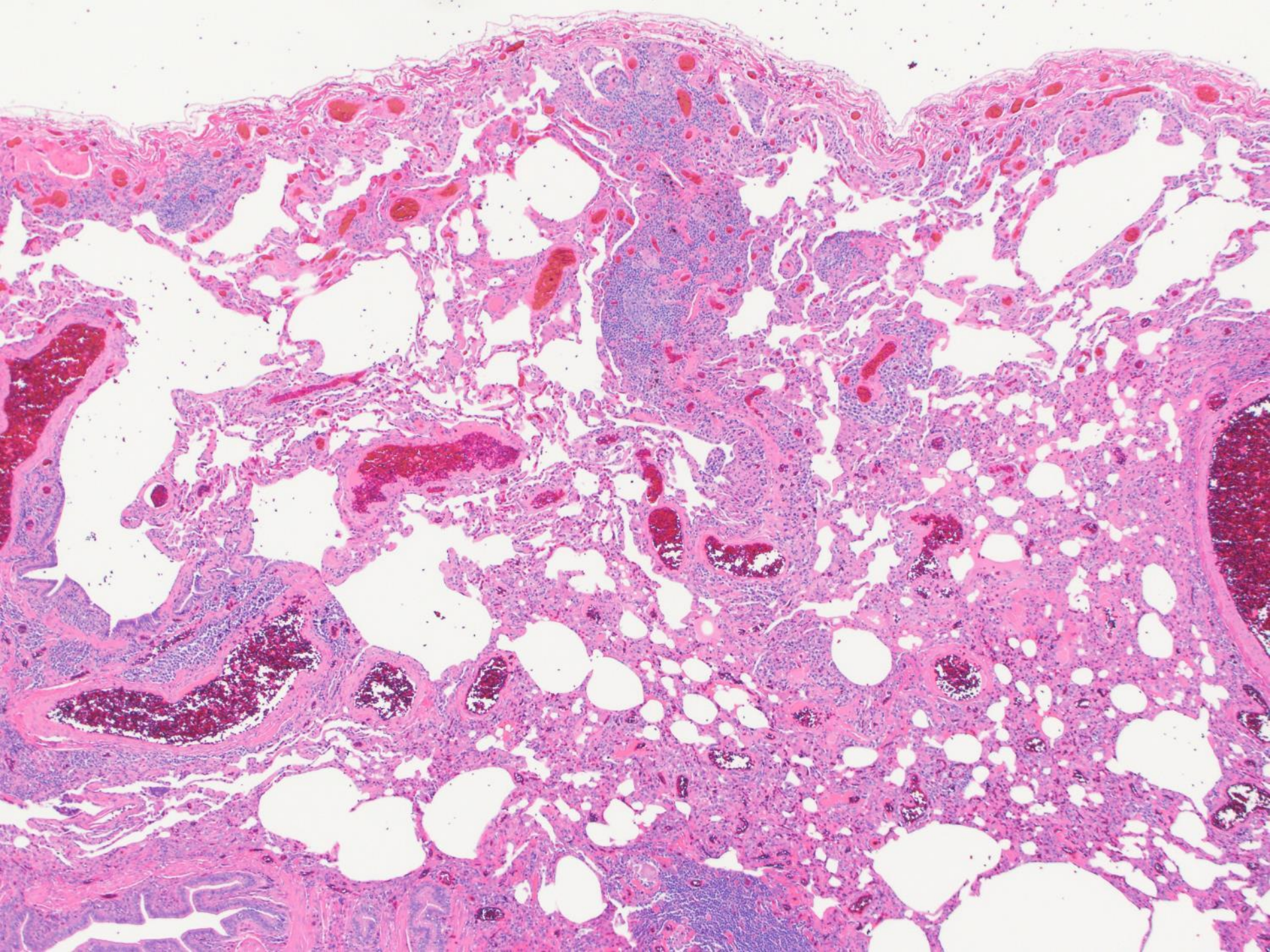
a. Aspiration bronchiolitis

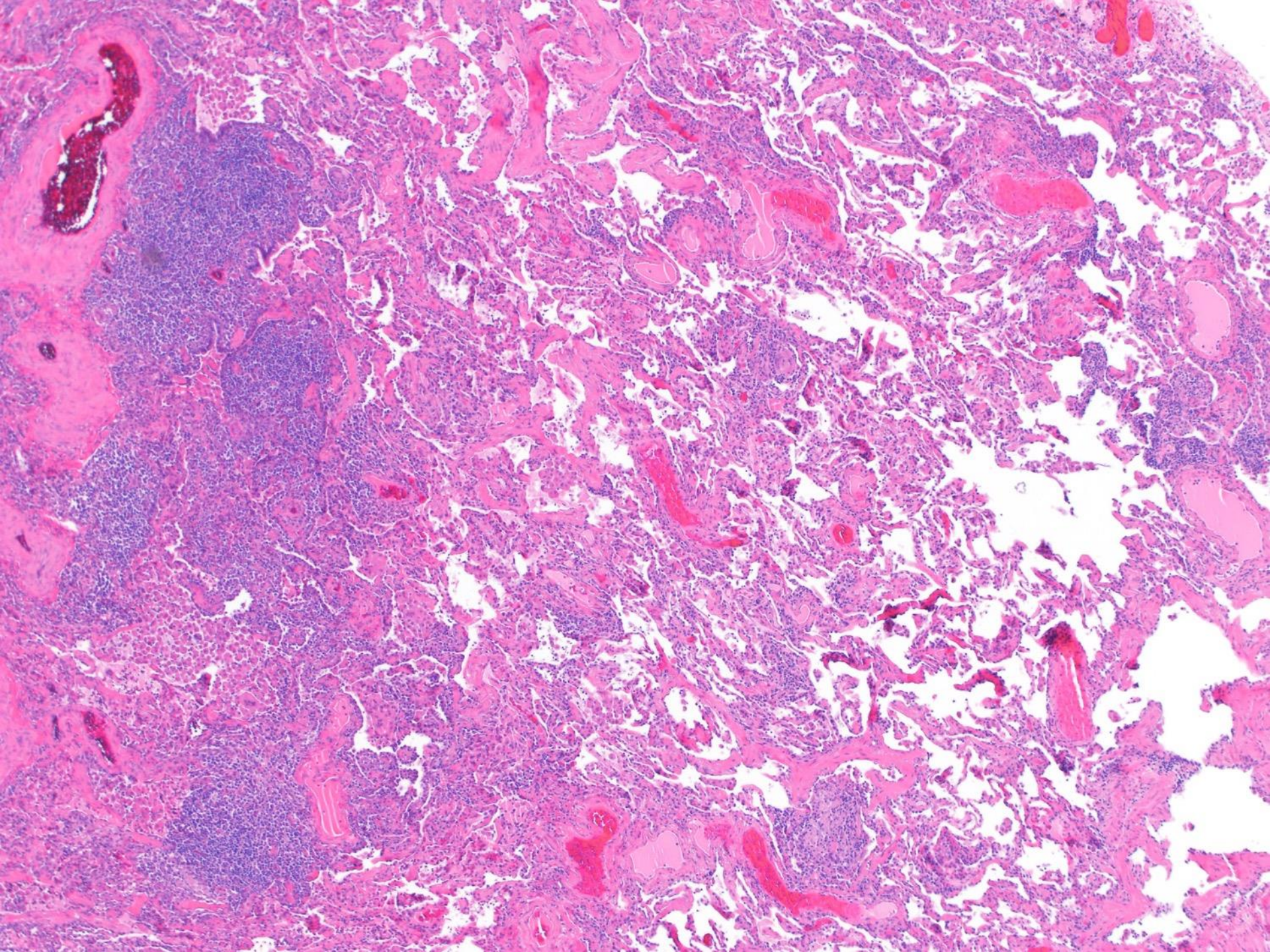
b. CTD related changes

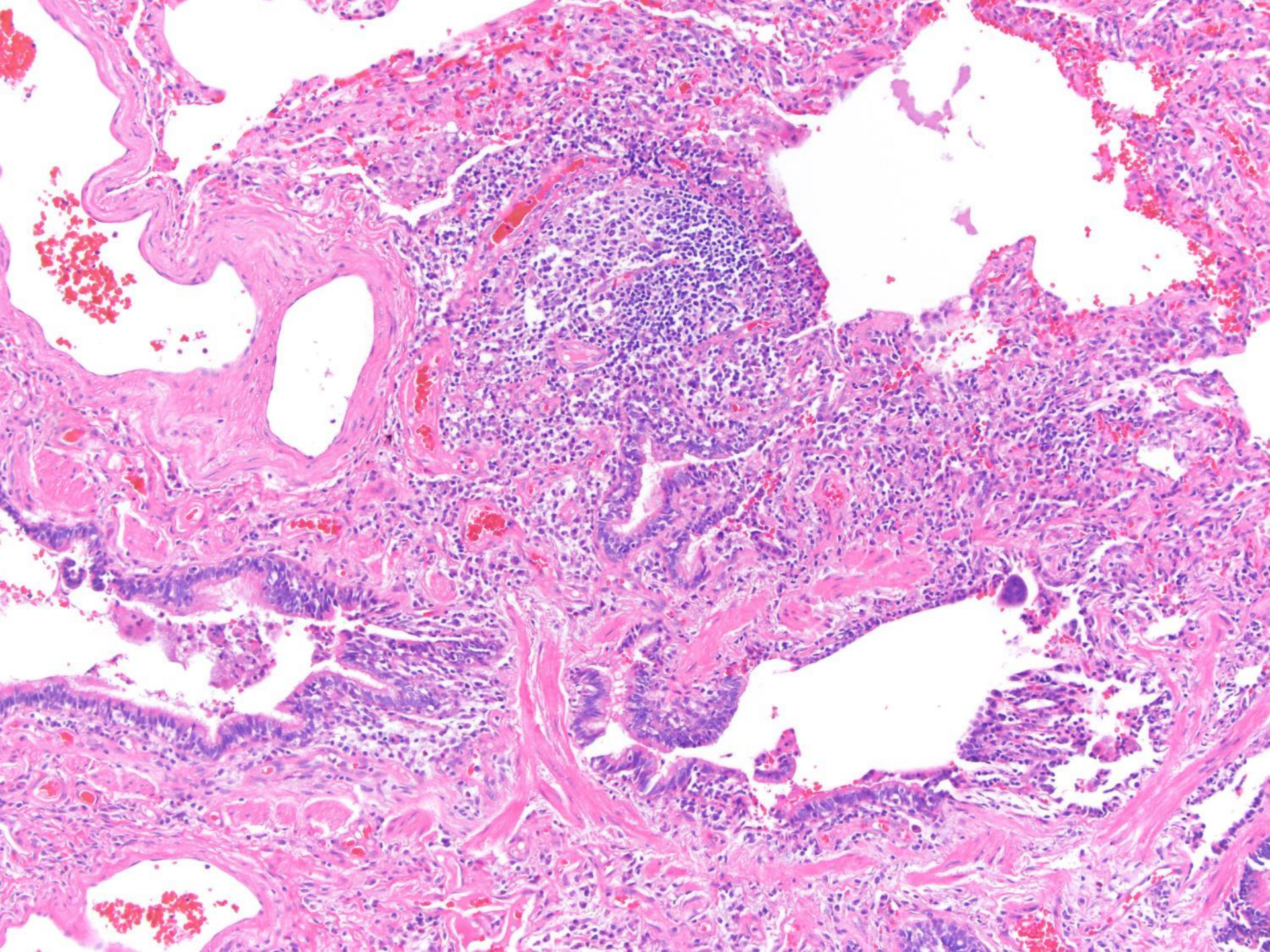
c. Drug toxicity

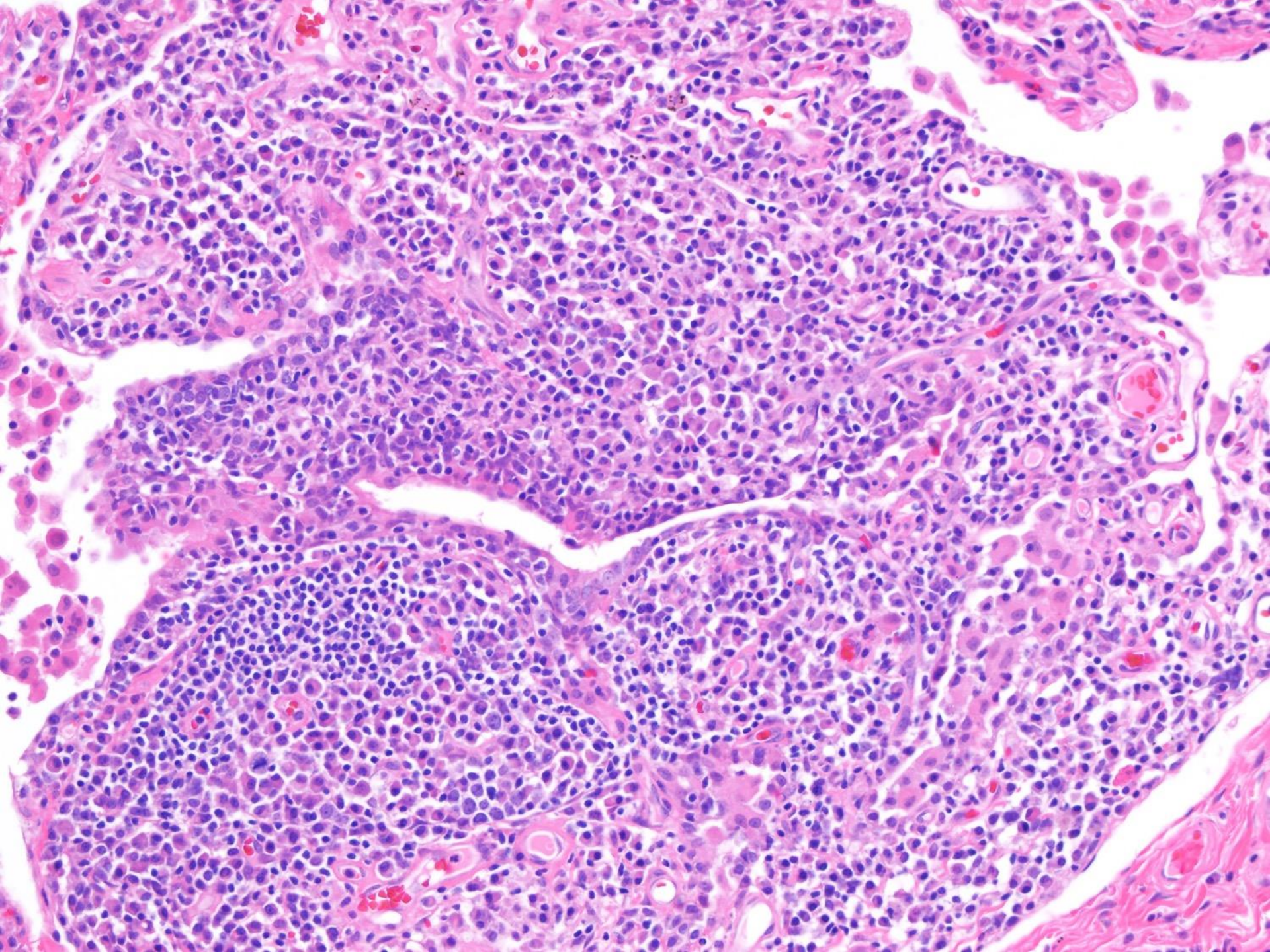
d. Hypersensitivity pneumonitis

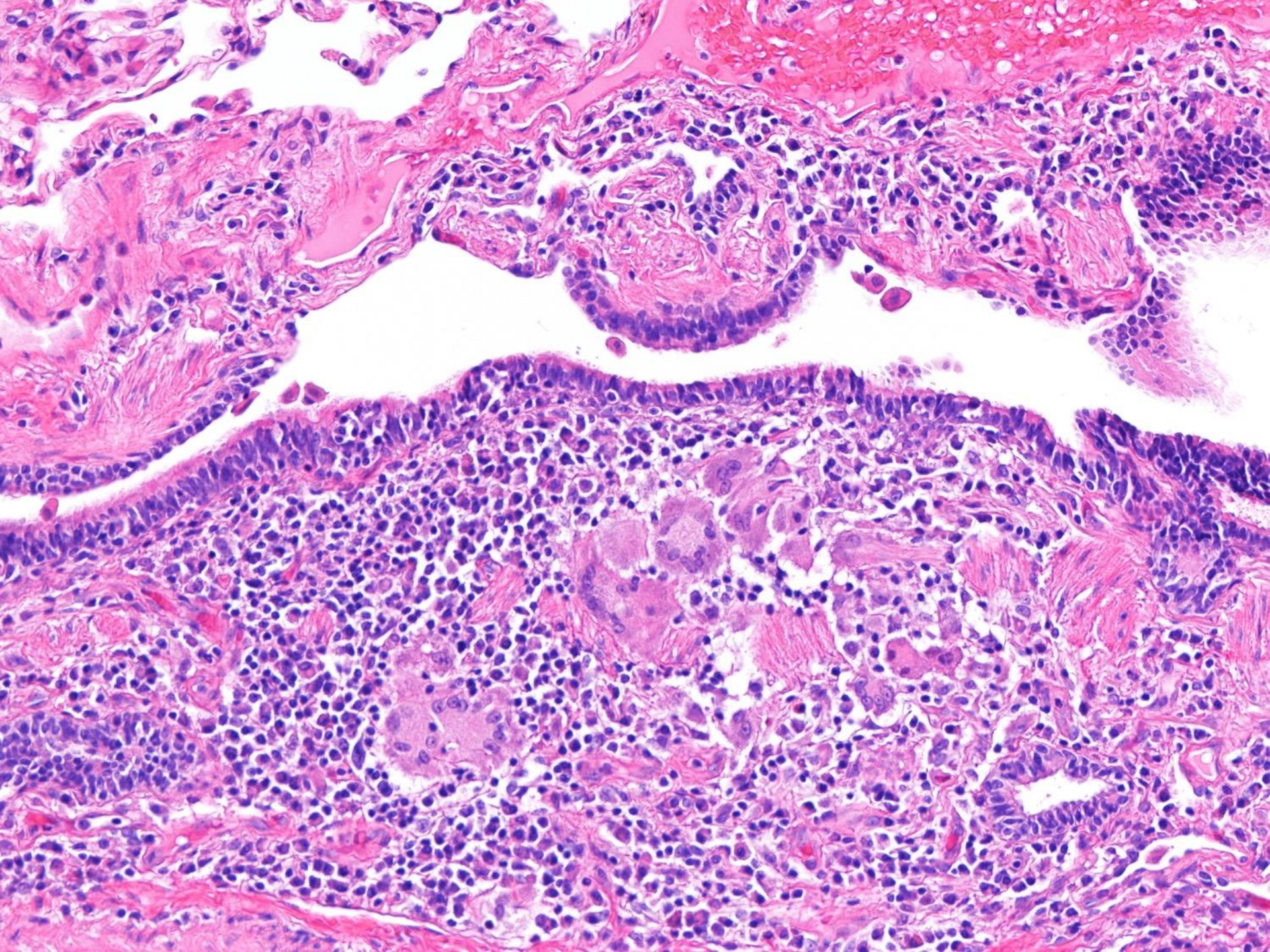
e. Non specific interstitial pneumonia

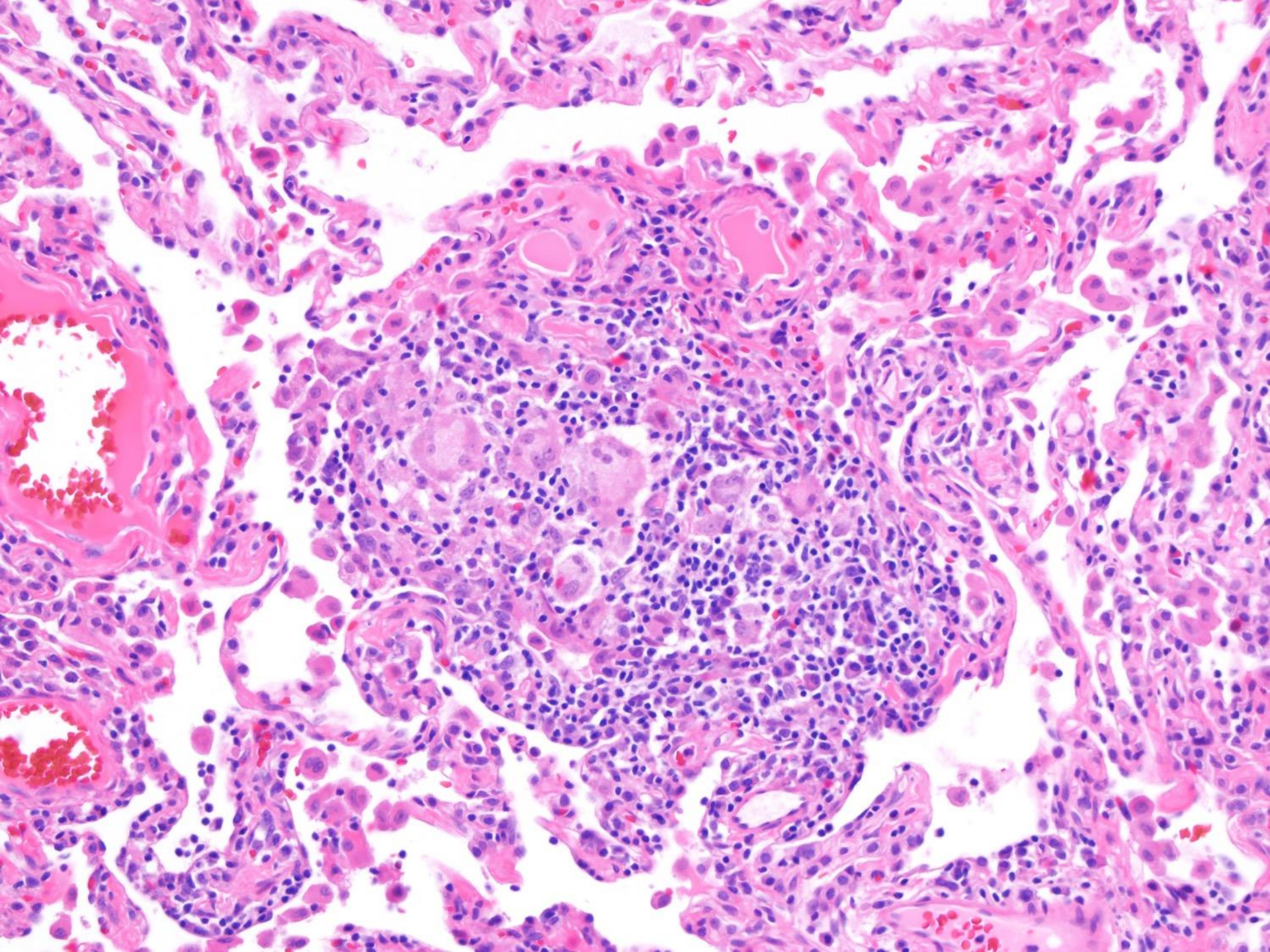












Q. A 58 year old woman with a history of Sjogren syndrome, gastroparesis MALT lymphoma (treated with Rituximab) presented with a two day history of increasing shortness of breath. A CT about 1 month prior (done for cough and dyspnea) showed a stable infiltrate or scarring in the lingula….

a. **Aspiration bronchiolitis**
b. **CTD related changes**
c. **Drug toxicity**
d. **Hypersensitivity pneumonitis**
e. **Non specific interstitial pneumonia**

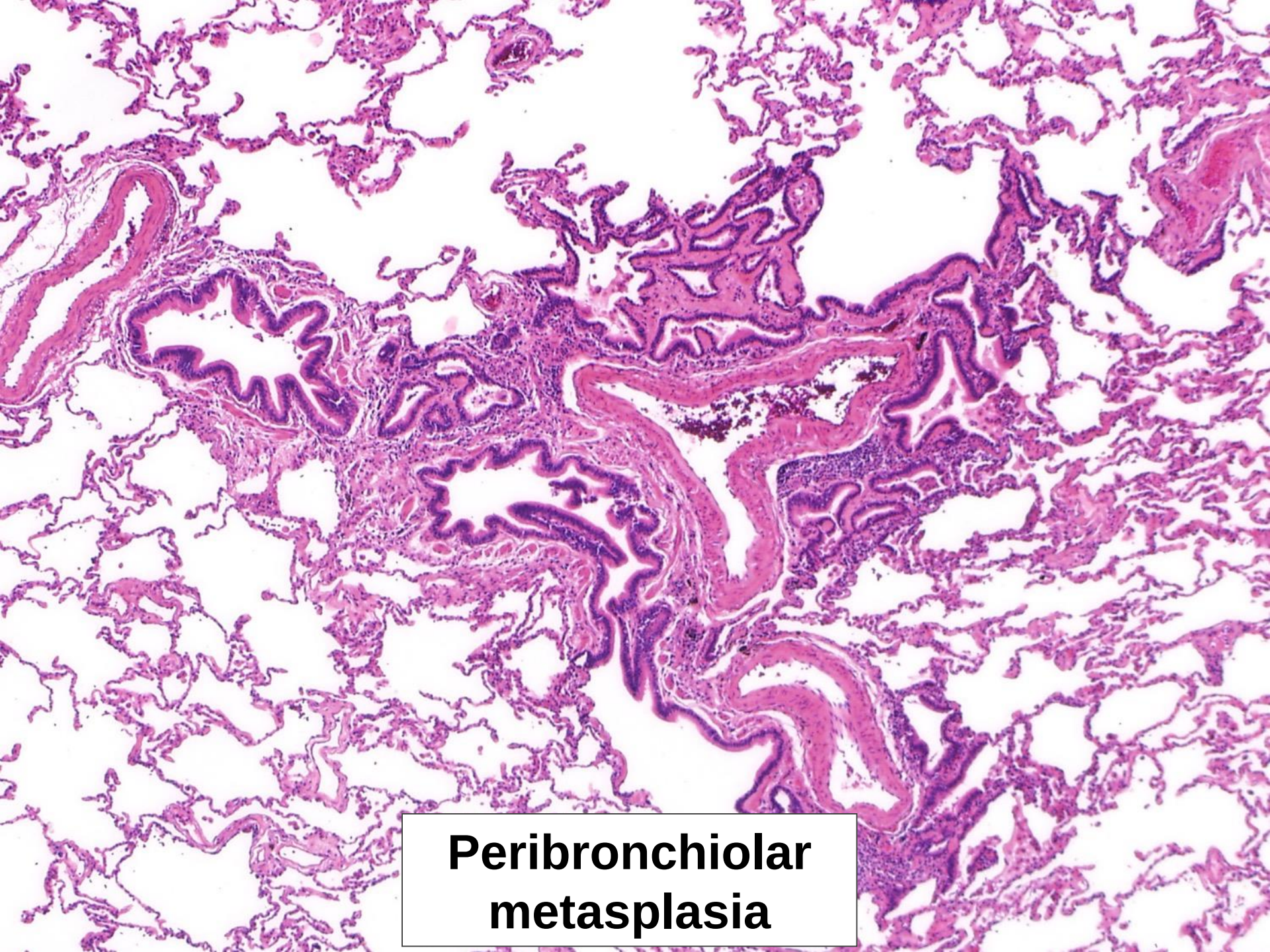
Diagnosis

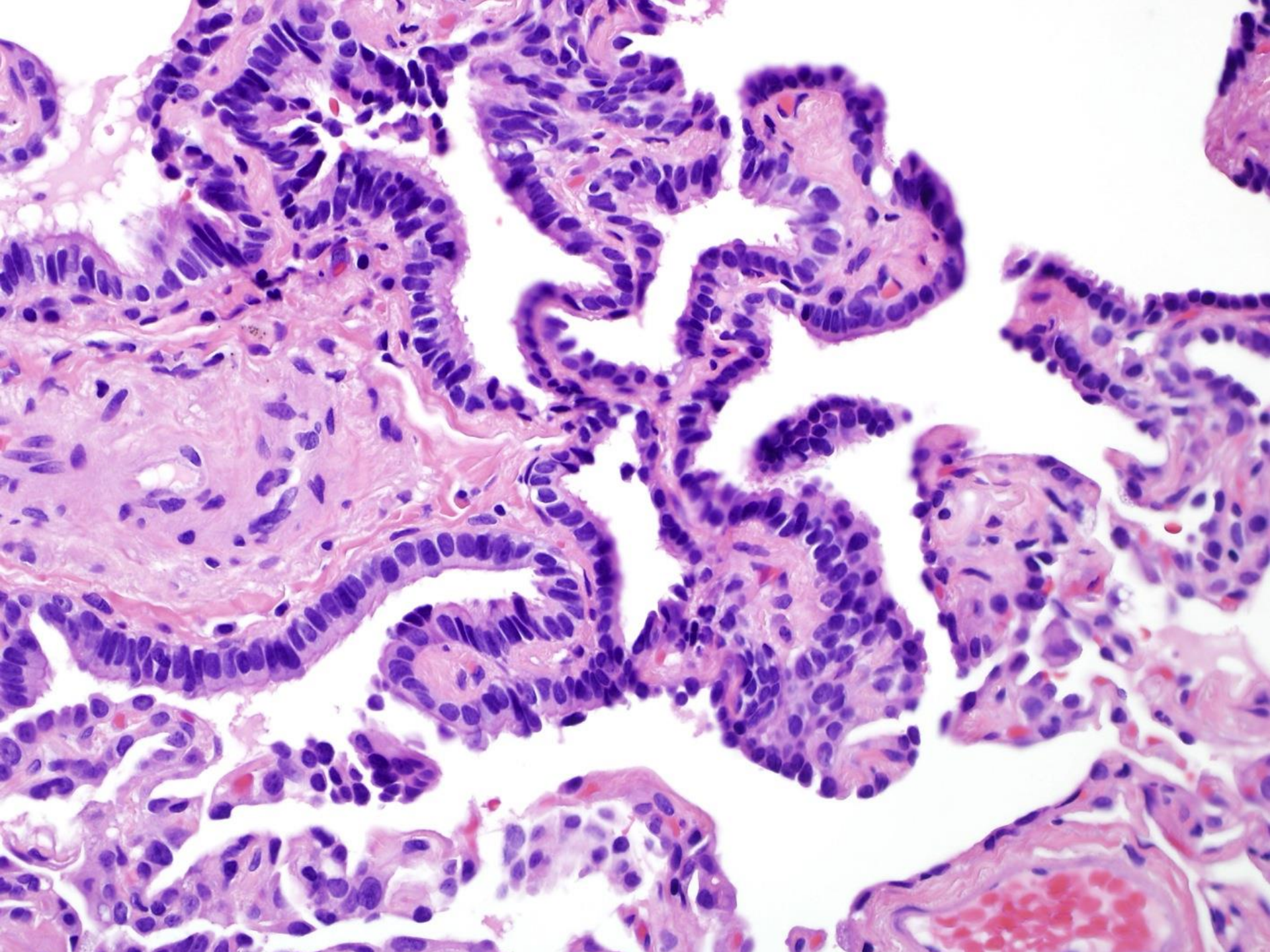
Chronic bronchiolitis with features of follicular bronchiolitis with non-necrotizing granulomatous inflammation, and patchy mild cellular and fibrotic interstitial pneumonia, most consistent with underlying connective tissue disease

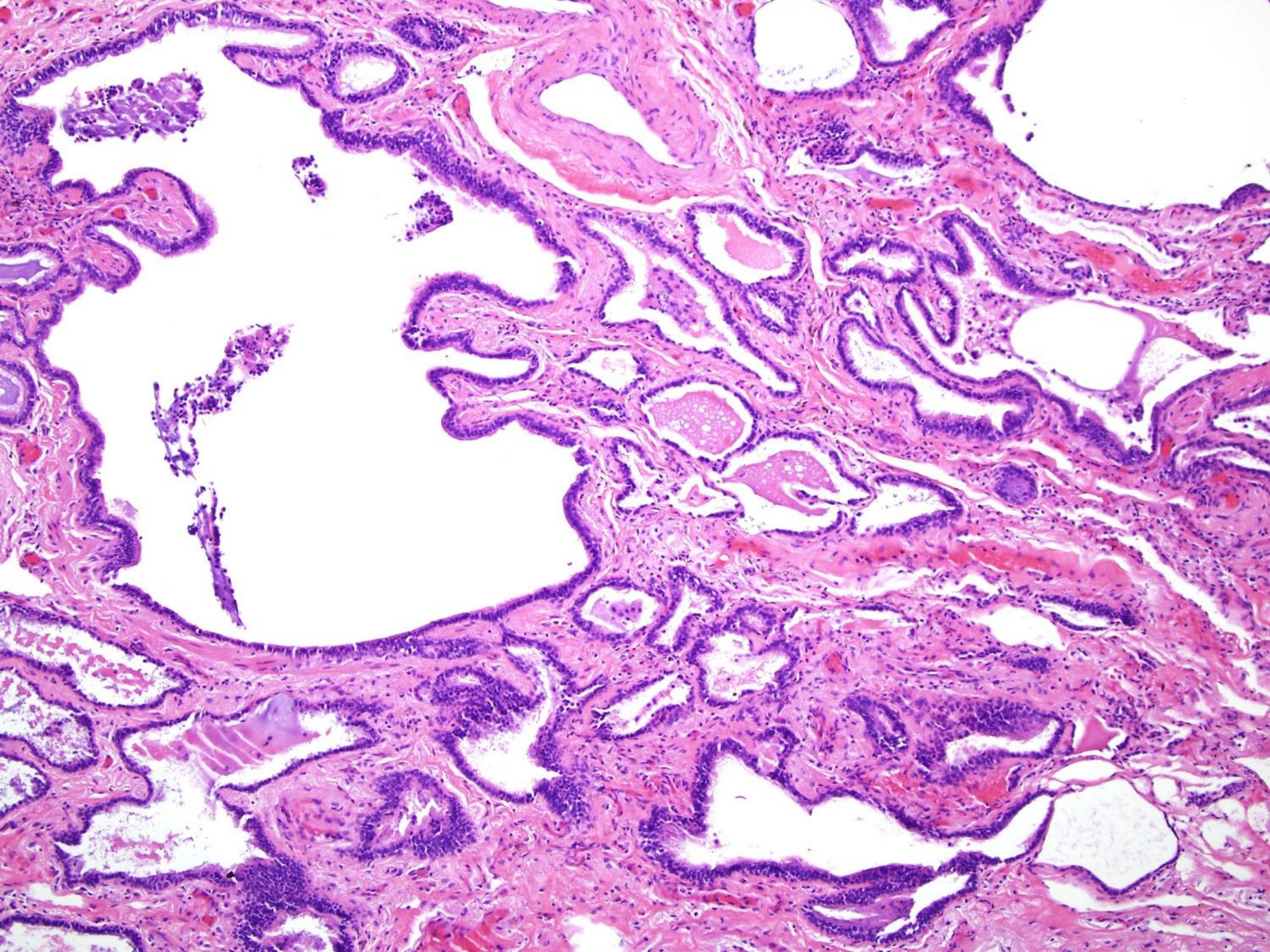
Chronic Hypersensitivity Pn'itis (CHP, n=16) vs. Fibrotic Disease due to Connective Tissue Disease (CTD, n=12)

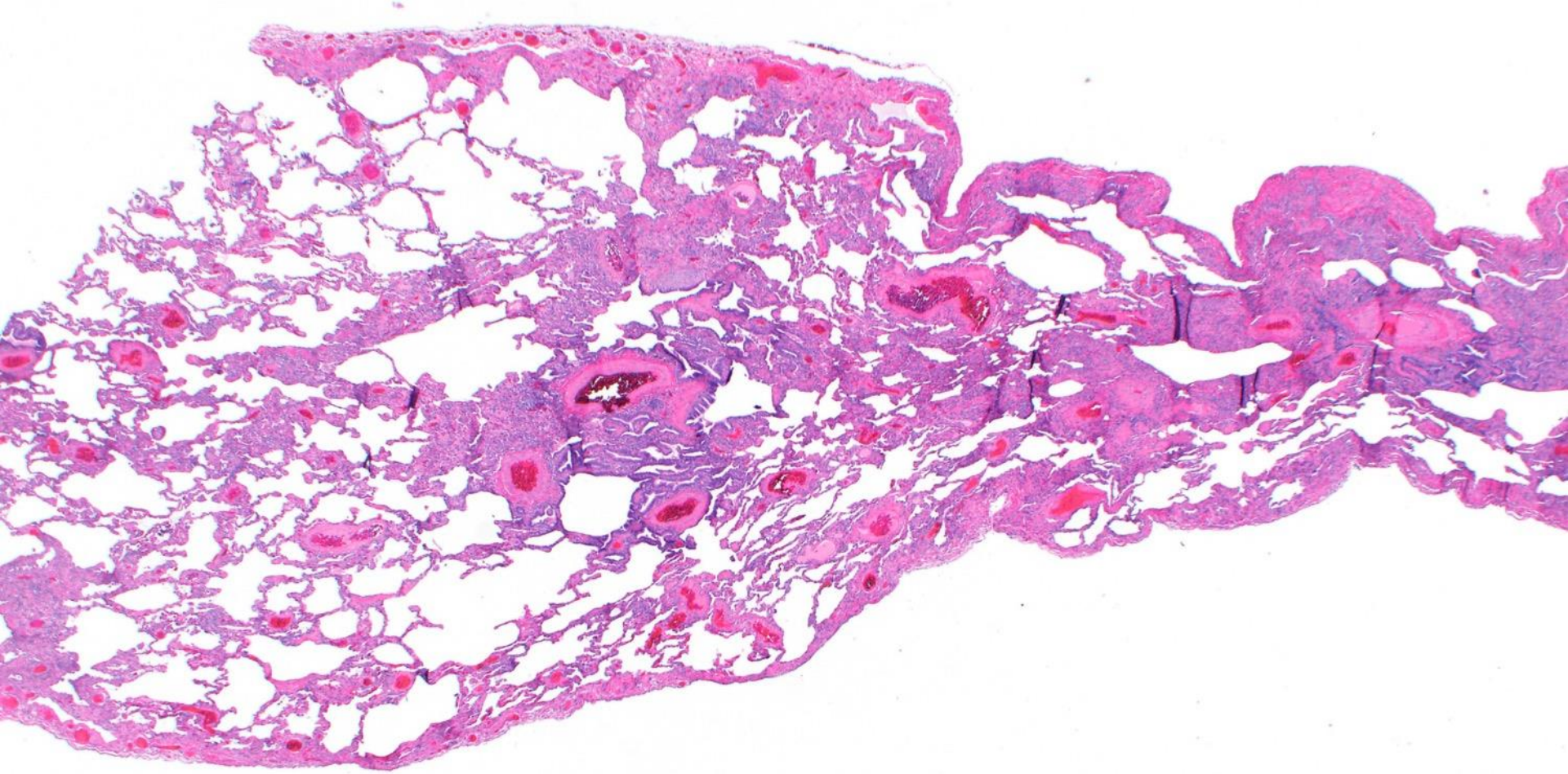
- Reviewed 15 parameters
- Germinal centers, prominent lymphoid aggregates and plasma cells favor CTD
- Peribronchiolar metaplasia favors HP
- Features that did not help: giant cells, granulomas, distribution of FiFo, pattern of fibrosis

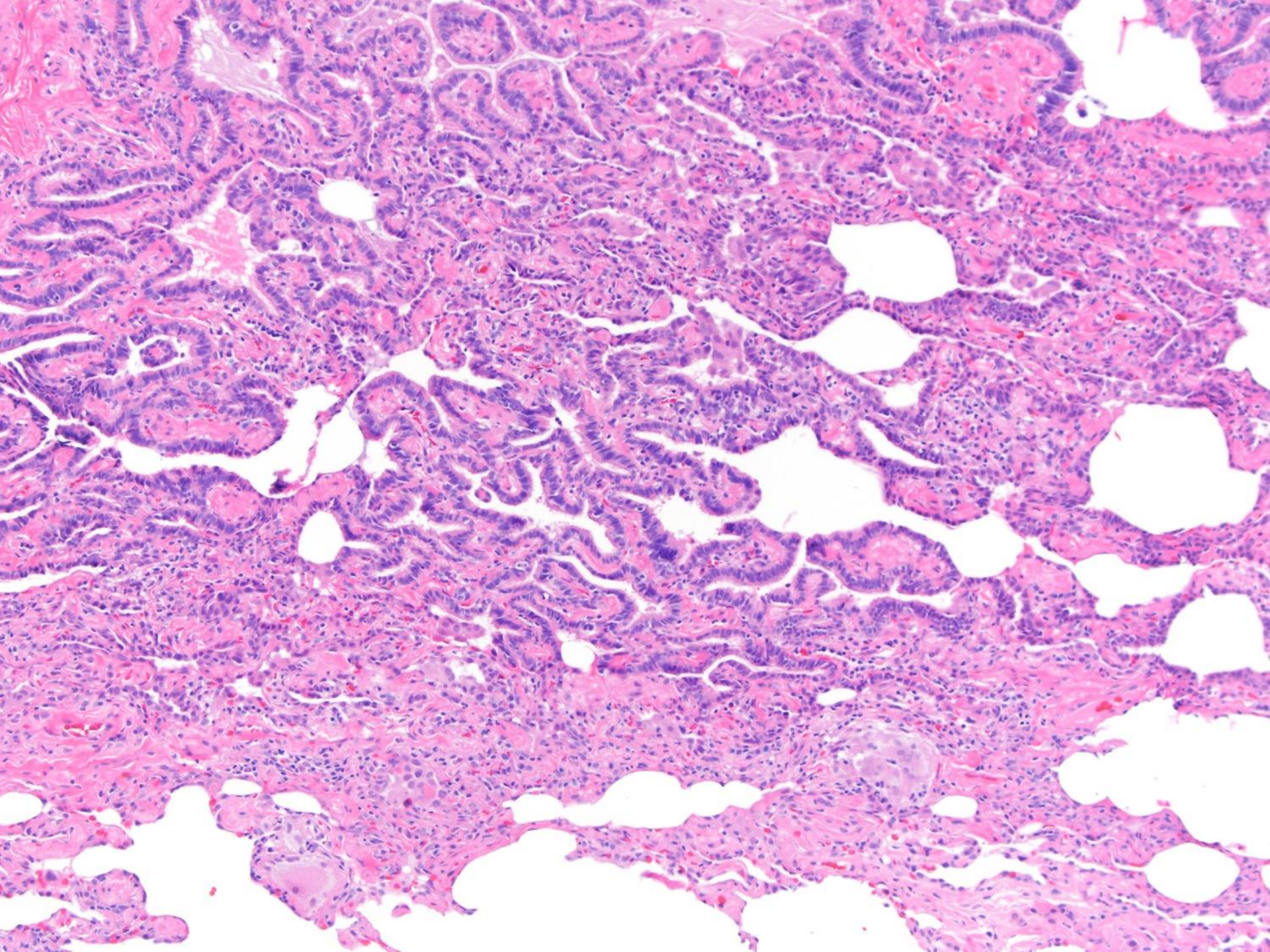
* Churg A et al Am J Surg Pathol 2017; 41:1403-1409


Peribronchiolar
metasplasia

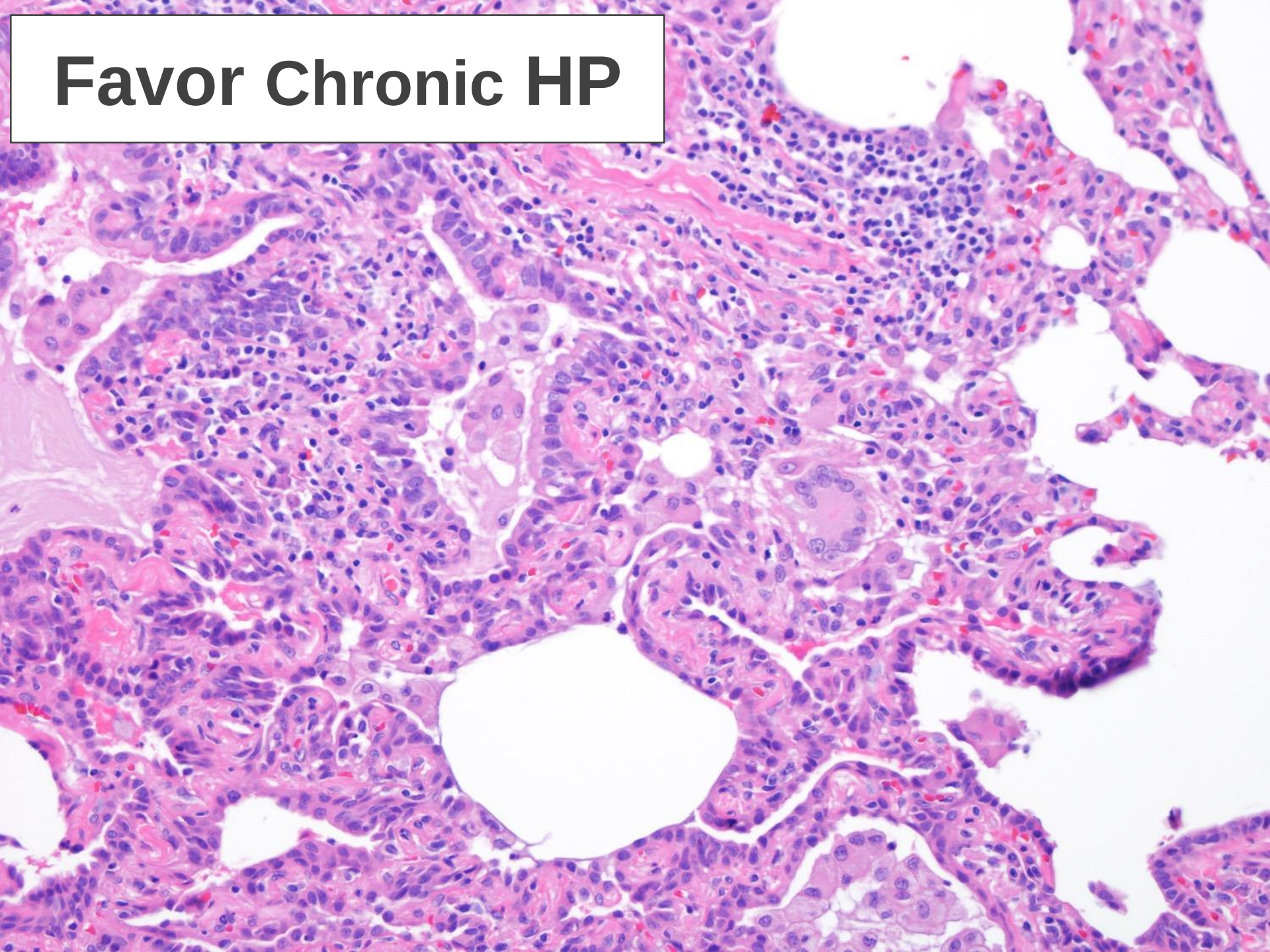








Favor Chronic HP



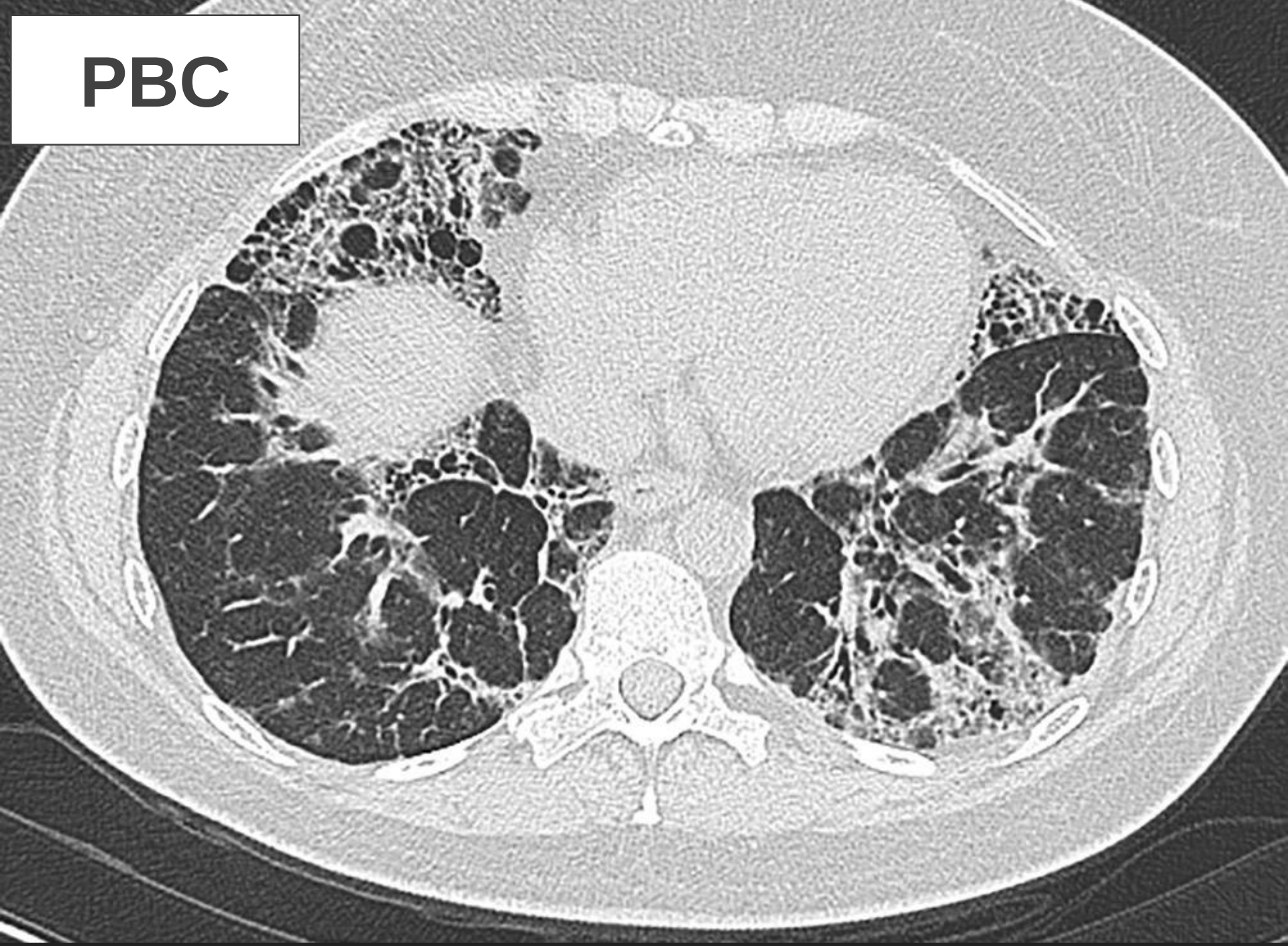
Chronic Hypersensitivity Pn'it is (CHP) vs. Fibrotic Disease due to Connective Tissue Disease (CTD)

- Challenging differential diagnosis
- Other features
  - Favor CHP: air trapping on HRCT, identifiable antigen
  - Favor CTD: multi-compartment disease e.g. pleuritis, vasculopathy

Lung in Primary Biliary Cholangitis
n=16, 94% women

Feature	Percent
Lymphocytic inflammation Mainly peribronchiolar	94
Non necrotizing granulomas	81
UIP/NSIP patterns	52
Organizing pneumonia	44
Eosinophils	33
MALT lymphoma with light chain deposition	6

Lee HE et al Hum Pathol 2018;82:177-186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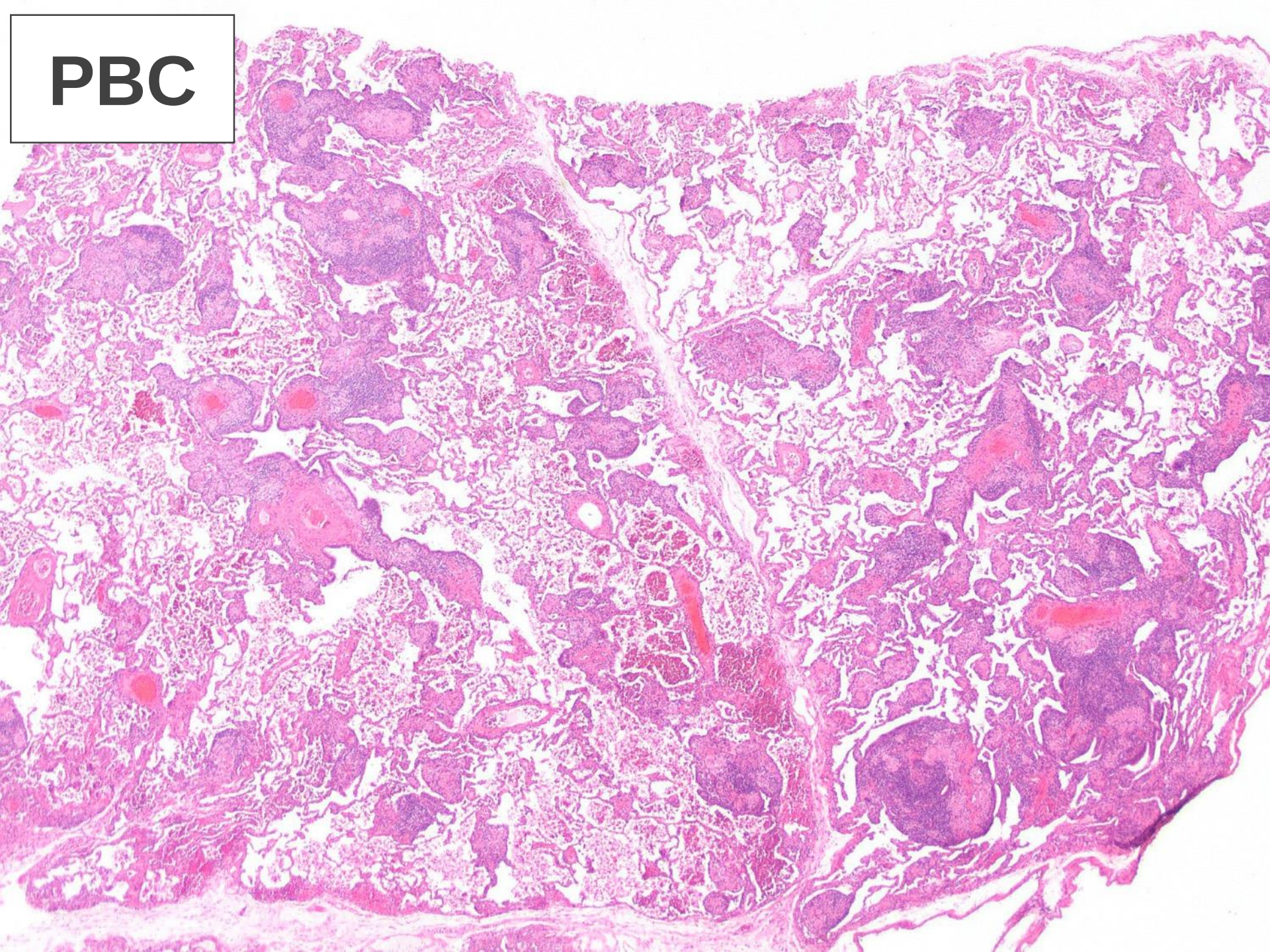
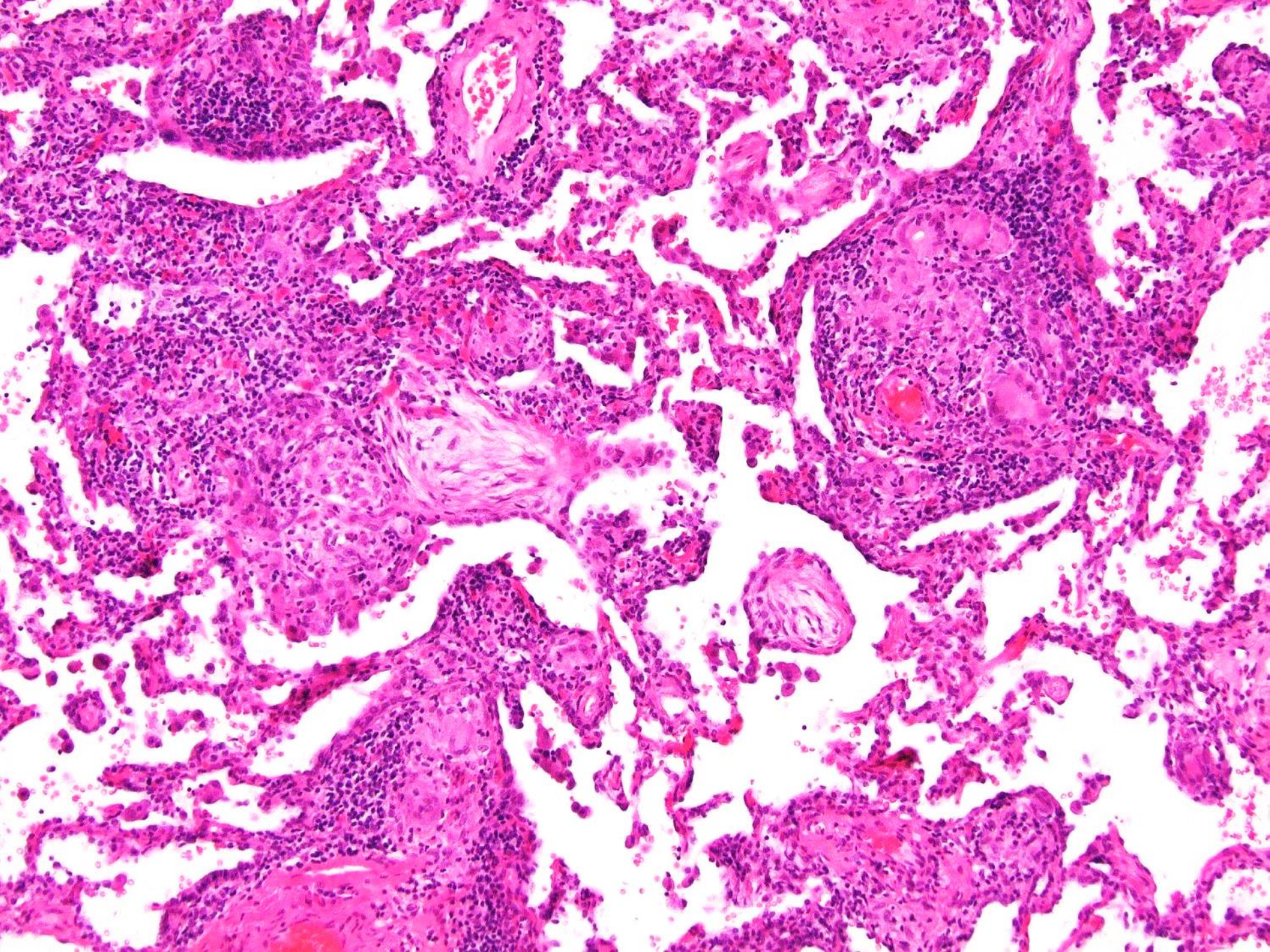
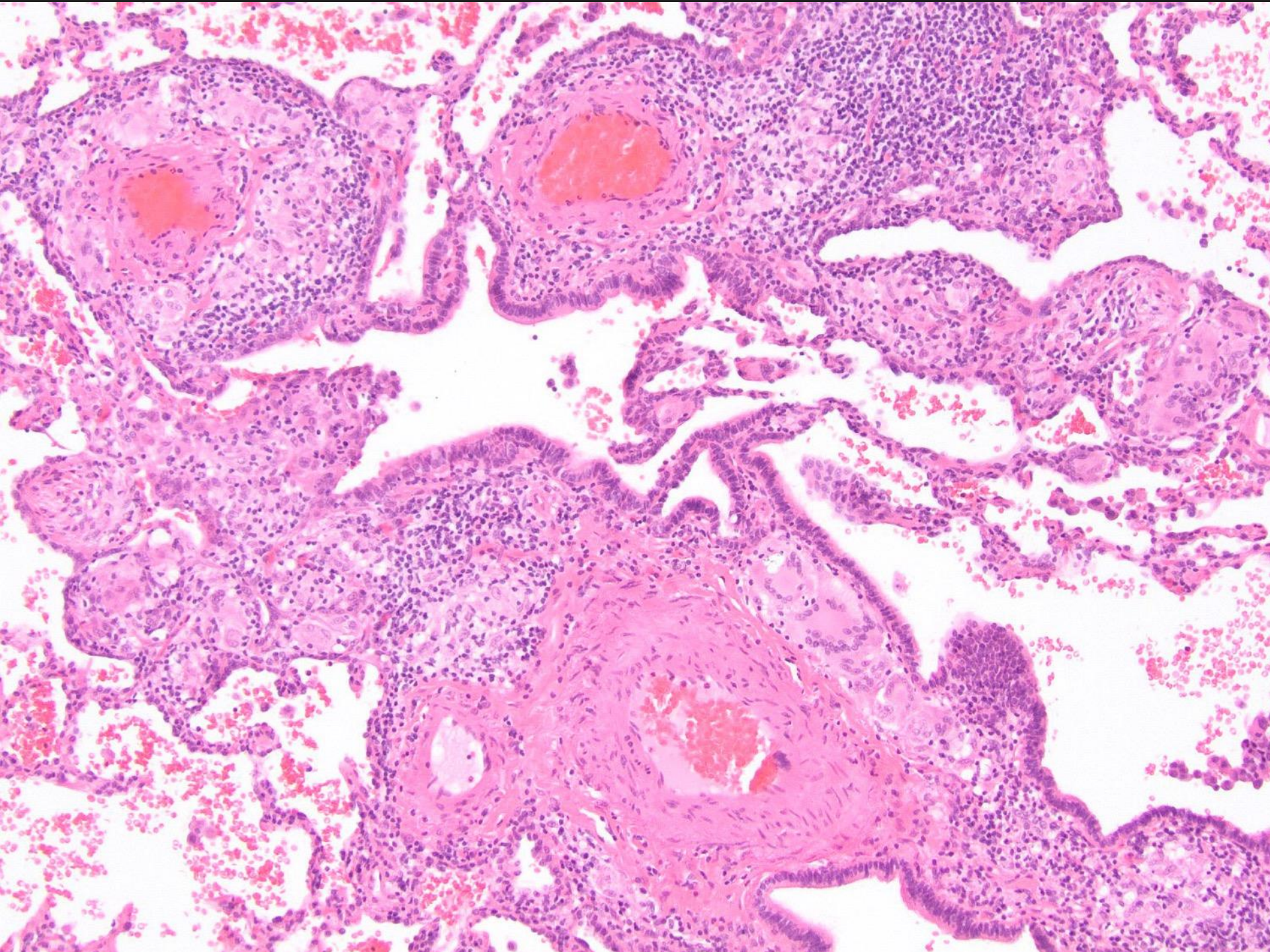
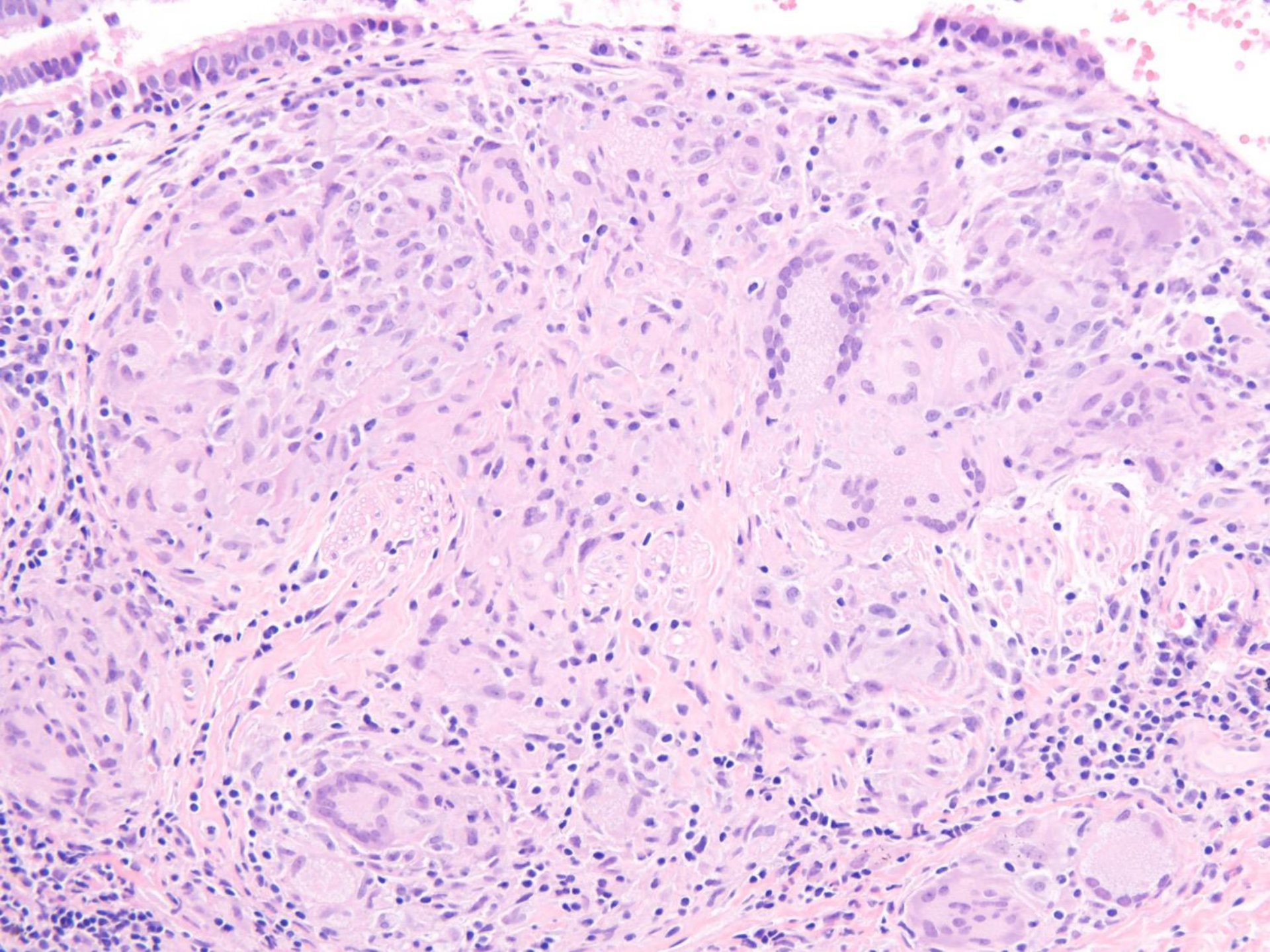
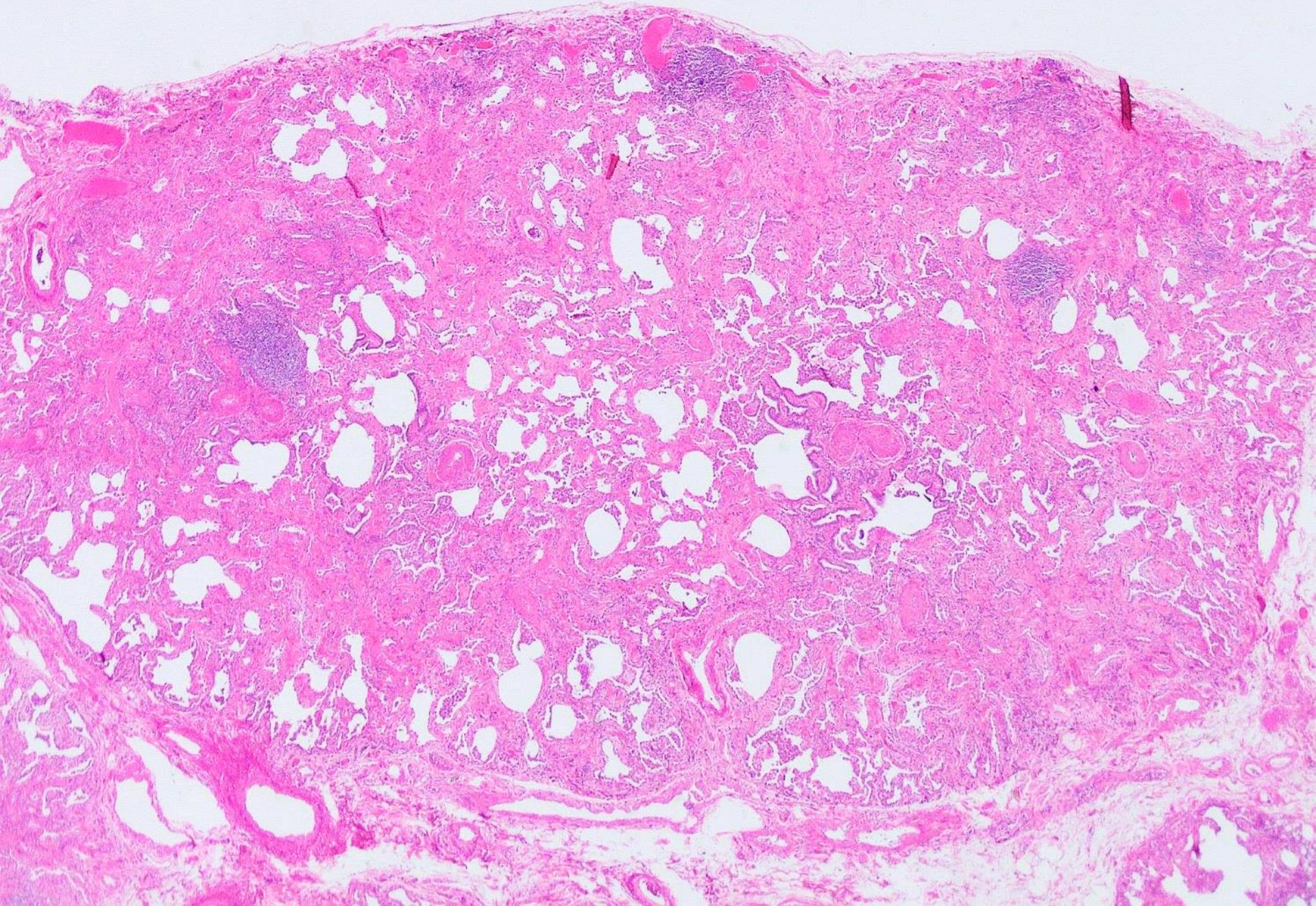
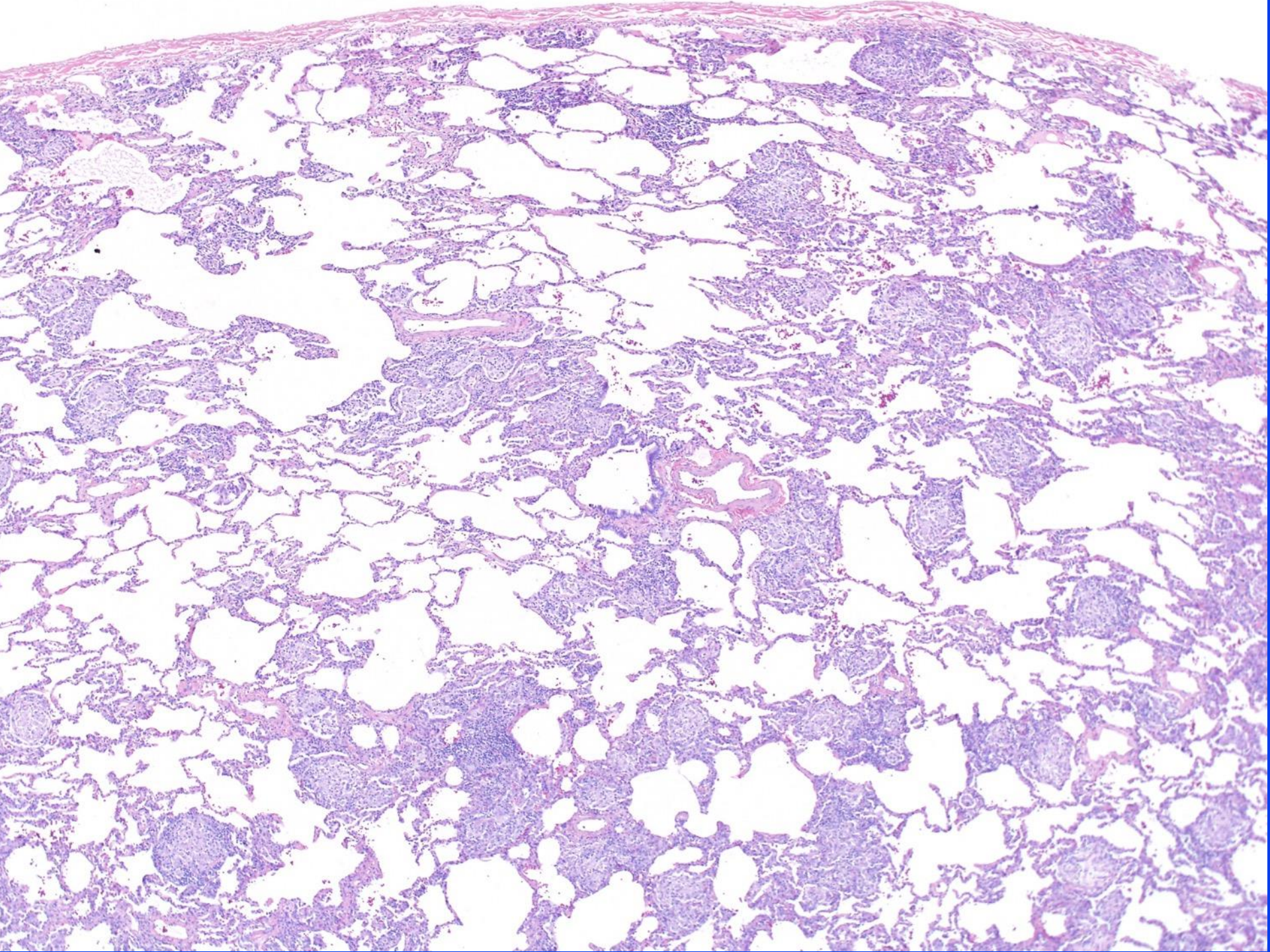


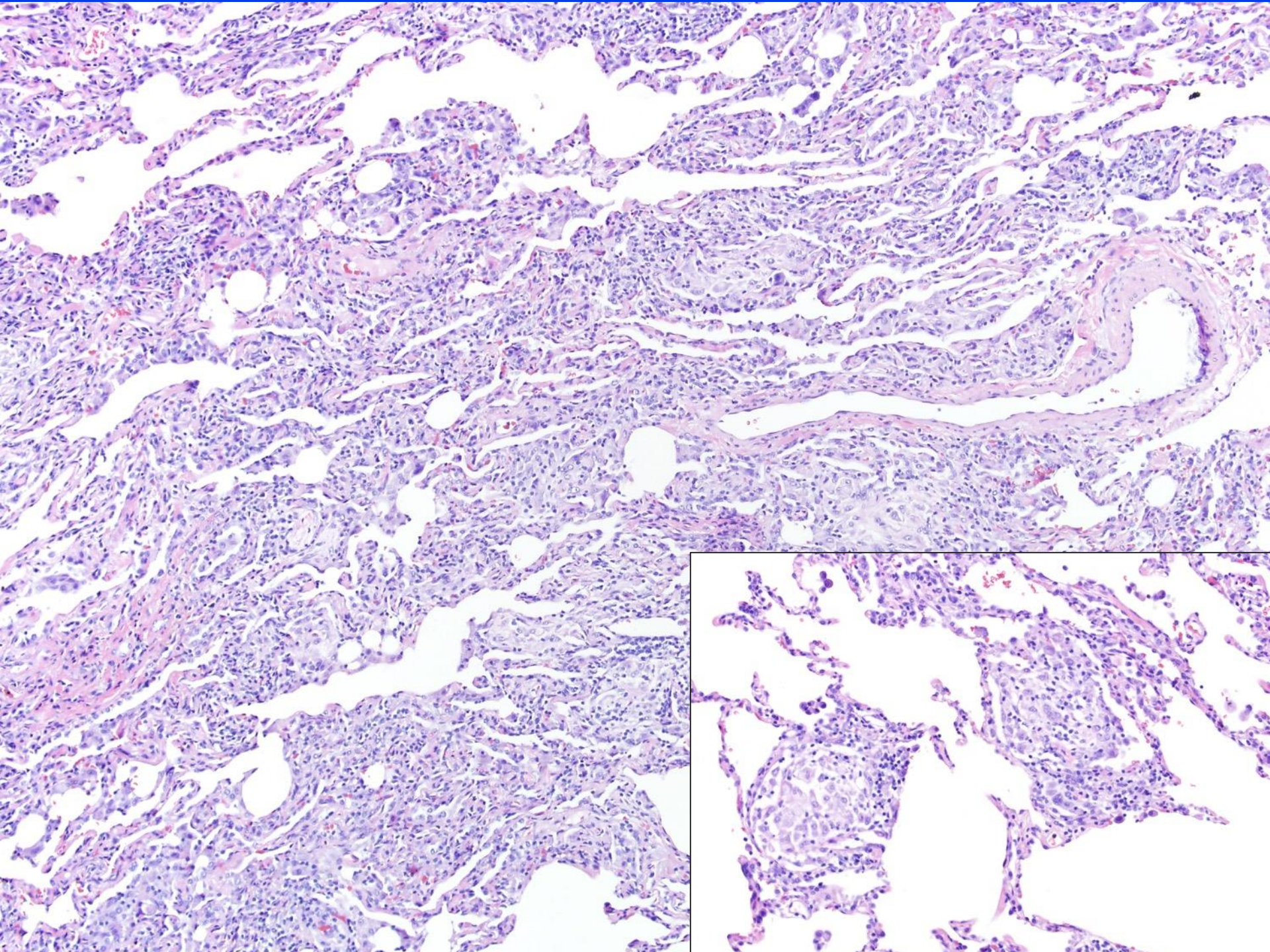












Common Variable Immunodefiency (CVID)

- Global immune dysfunction
- B cells, T cells, cytokines
  - Explains combination of infectious, inflammatory, autoimmune, and neoplastic conditions
  - Significantly reduced serum IgG
  - Low serum IgA and / or IgM

CVID Pulmonary Manifestations

- Infection-pneumonia, bronchitis
- Bronchiectasis
- Asthma
- Interstitial lung disease
  - Granulomatous-lymphocytic interstitial lung disease (GL-ILD)*
  - Organizing pneumonia

*Bates CA et al J Allergy Clin Immunol 2004; 114: 415-21

So- called GL-ILD

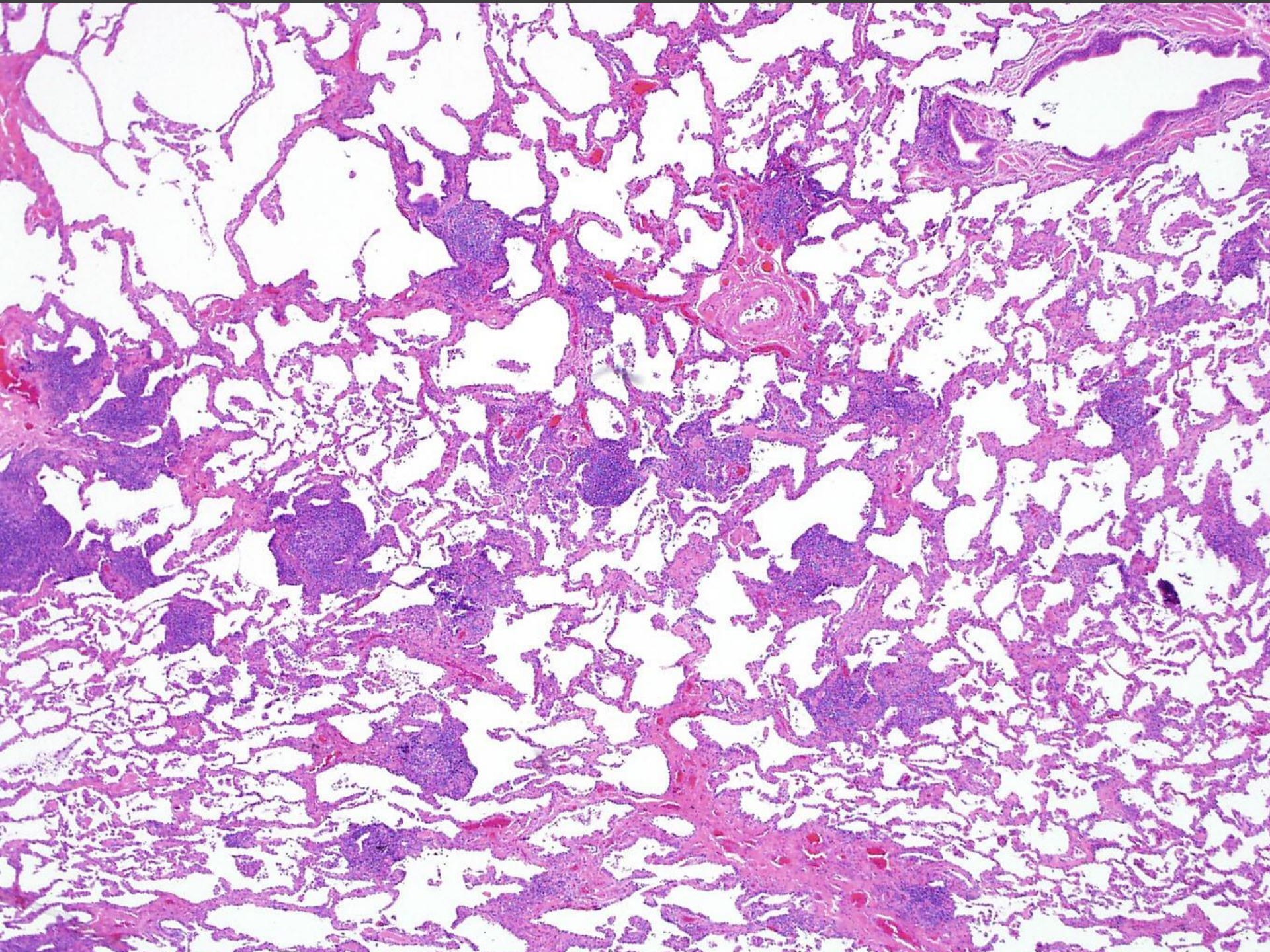
- Dyspnea
- Restrictive PFT's
- HRCT: consolidation, ground-glass opacities, reticular opacities
- Various histologies

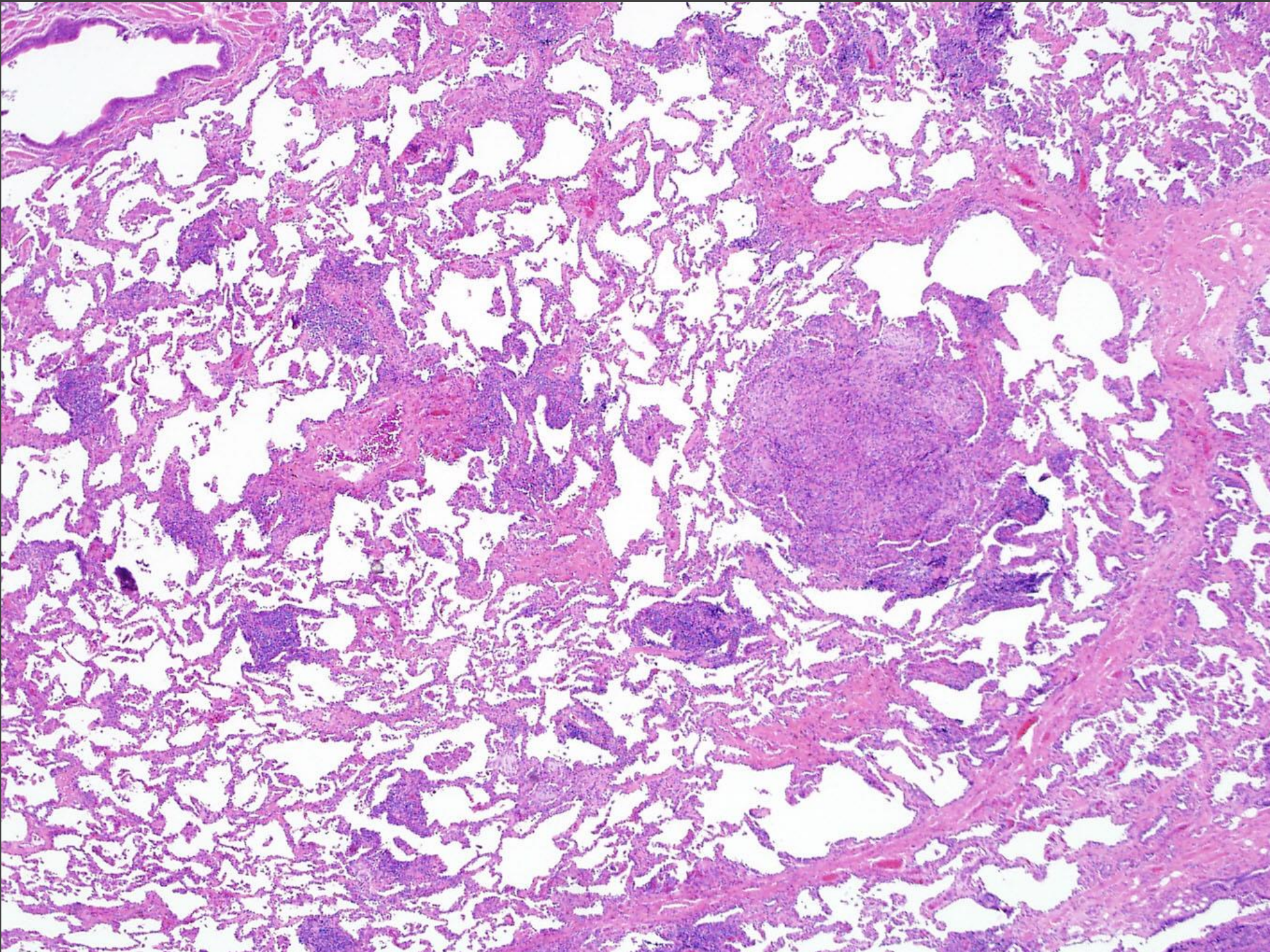
Bates CA et al J Allergy Clin Immunol 2004; 114: 415-21

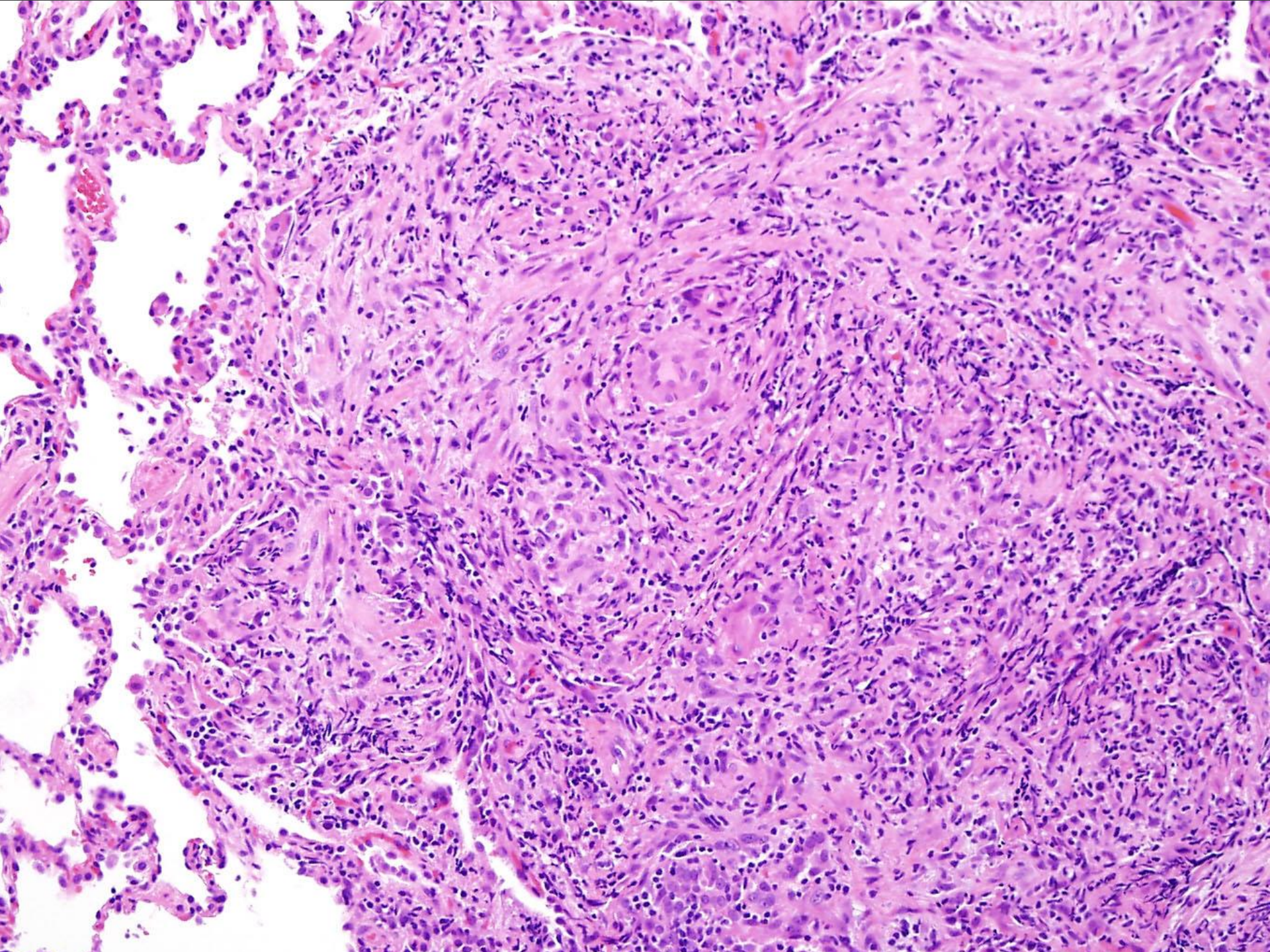
So- called GL-ILD Histologic Features

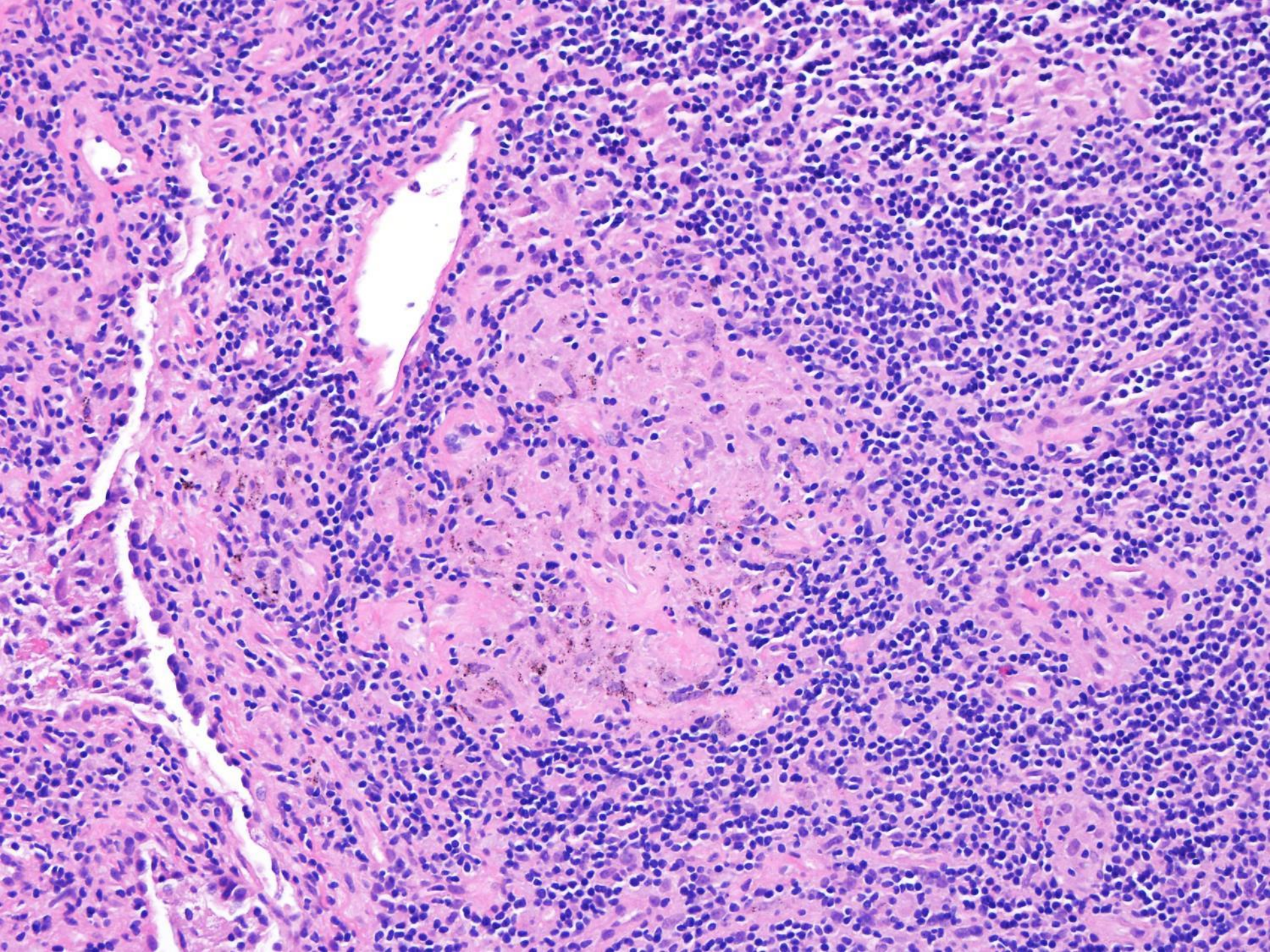
- Lymphocytic infiltrates/LIP
- Non necrotizing granulomas (most, but not all)
- Follicular bronchiolitis
- Diffuse lymphoid hyperplasia
- Prominent organizing pneumonia
- Fibrosis (including honeycomb)

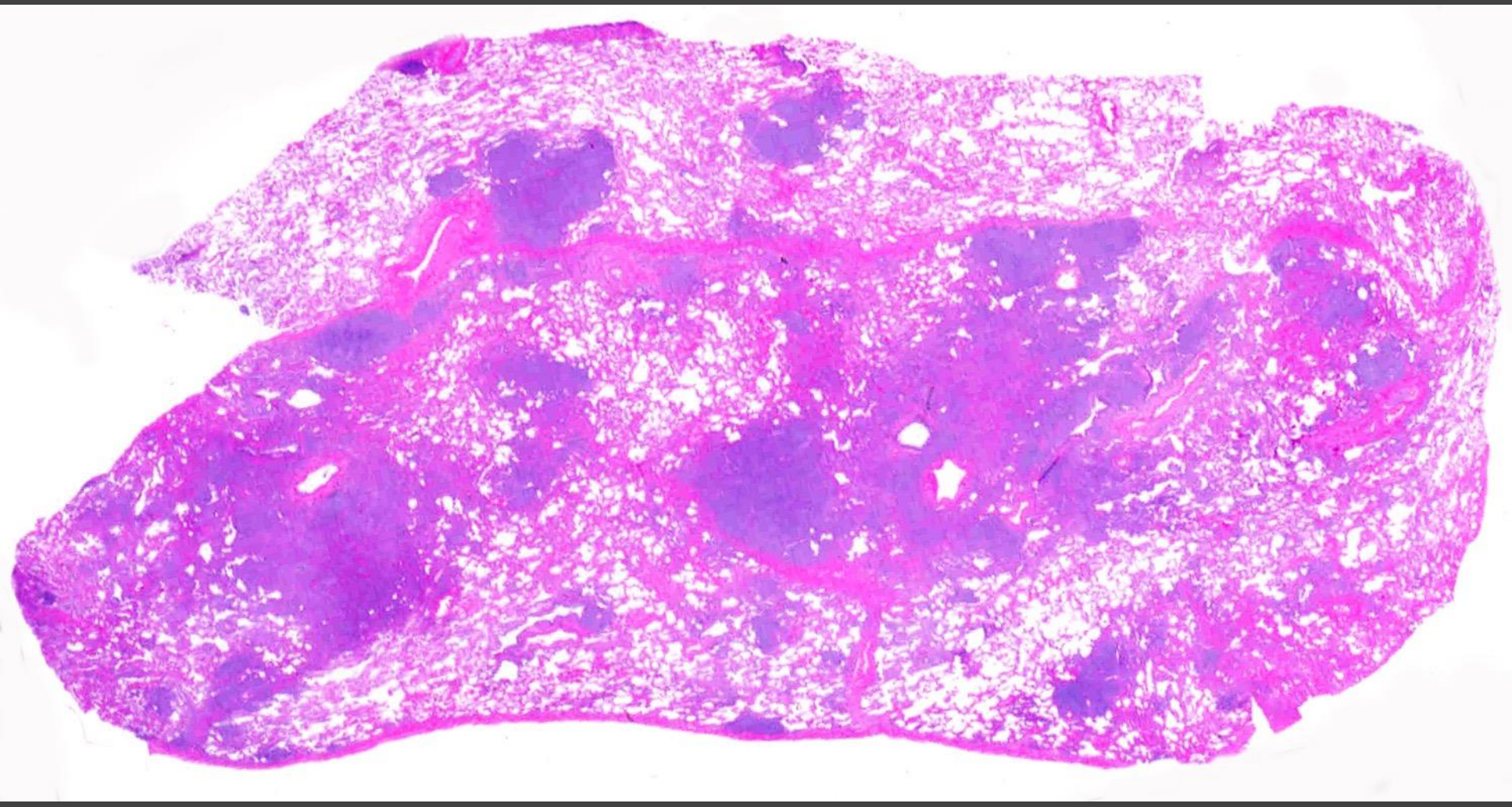
Rao N et al Hum Pathol 2015;46:1306-1314

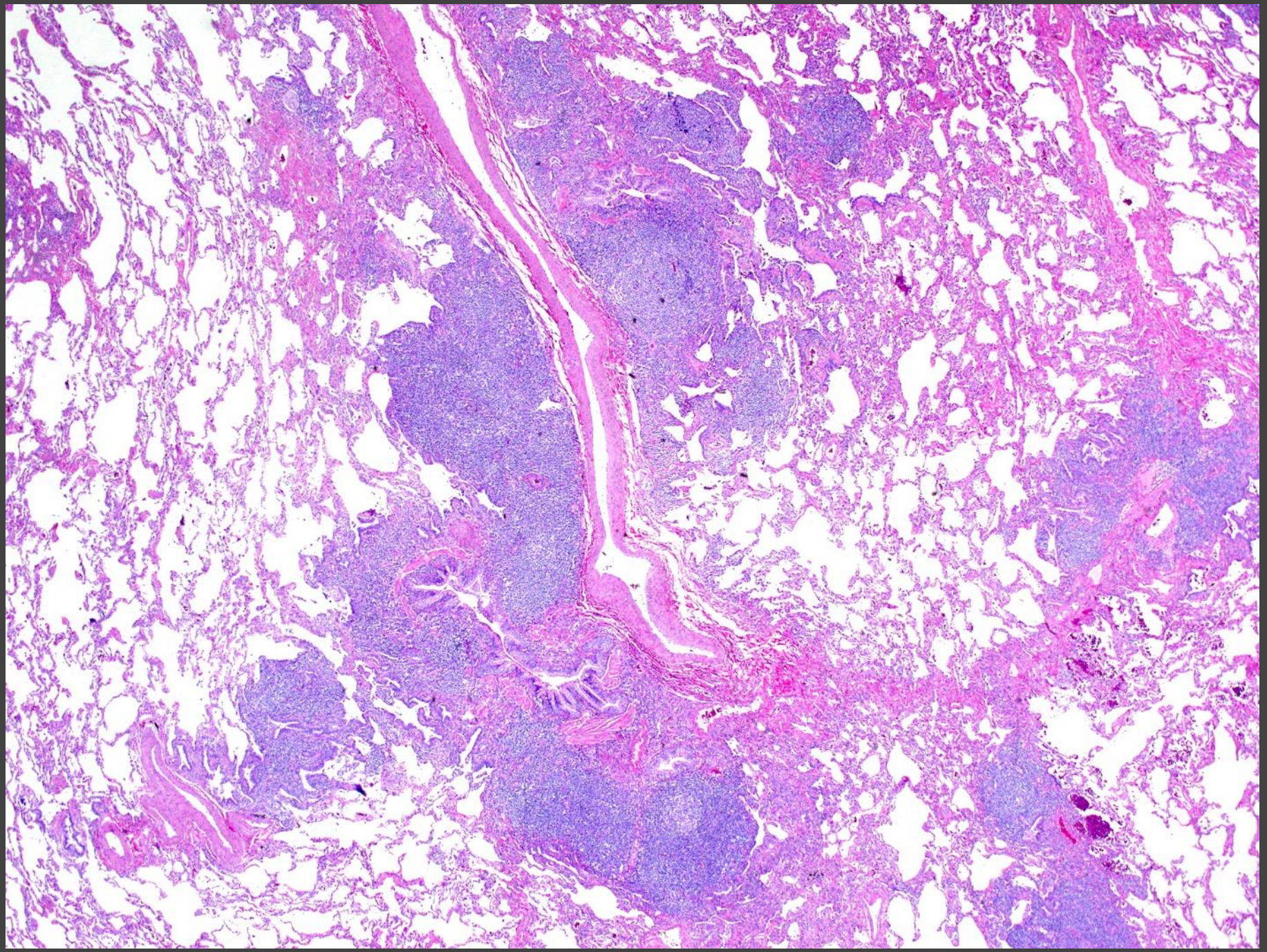


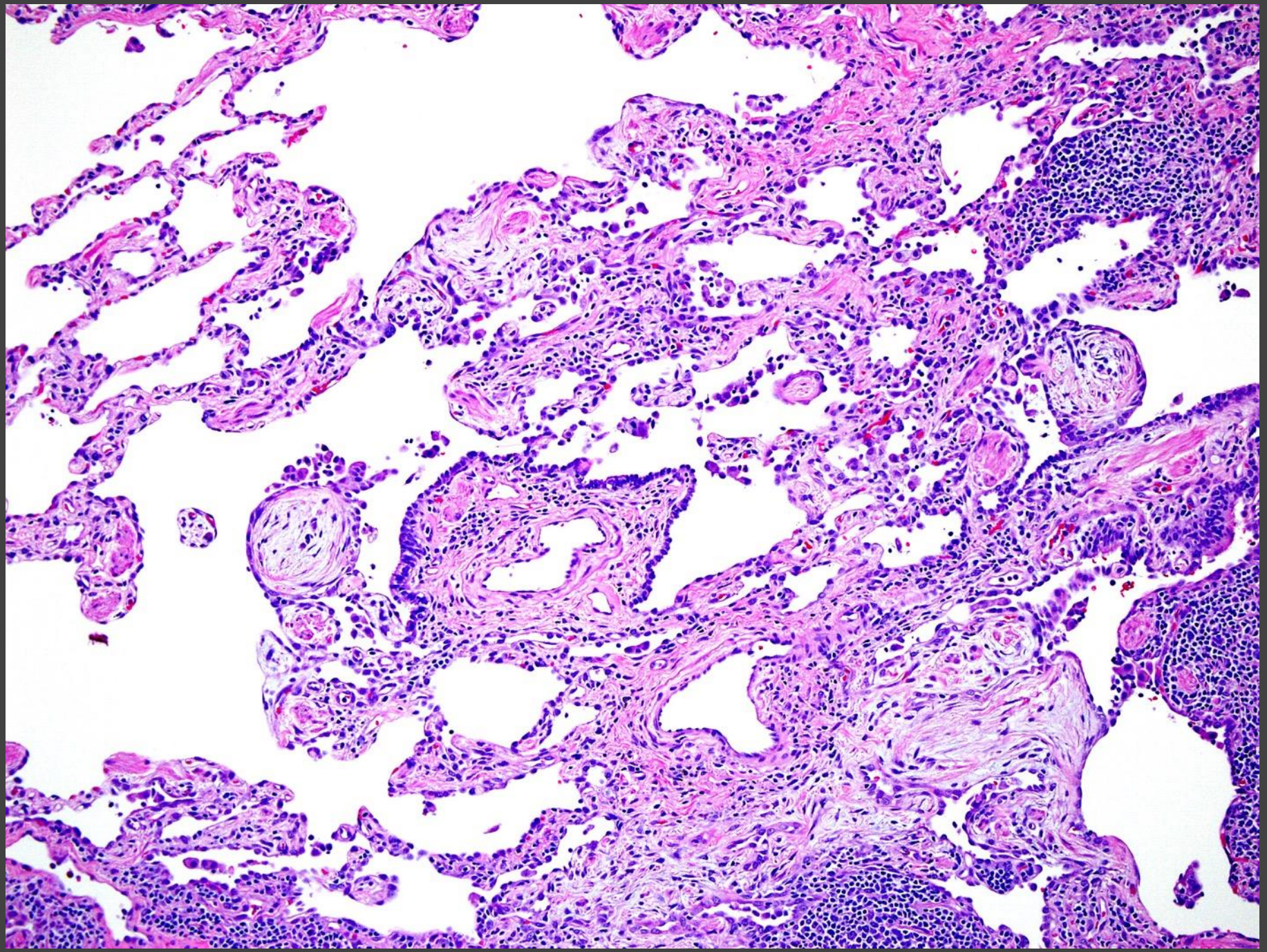


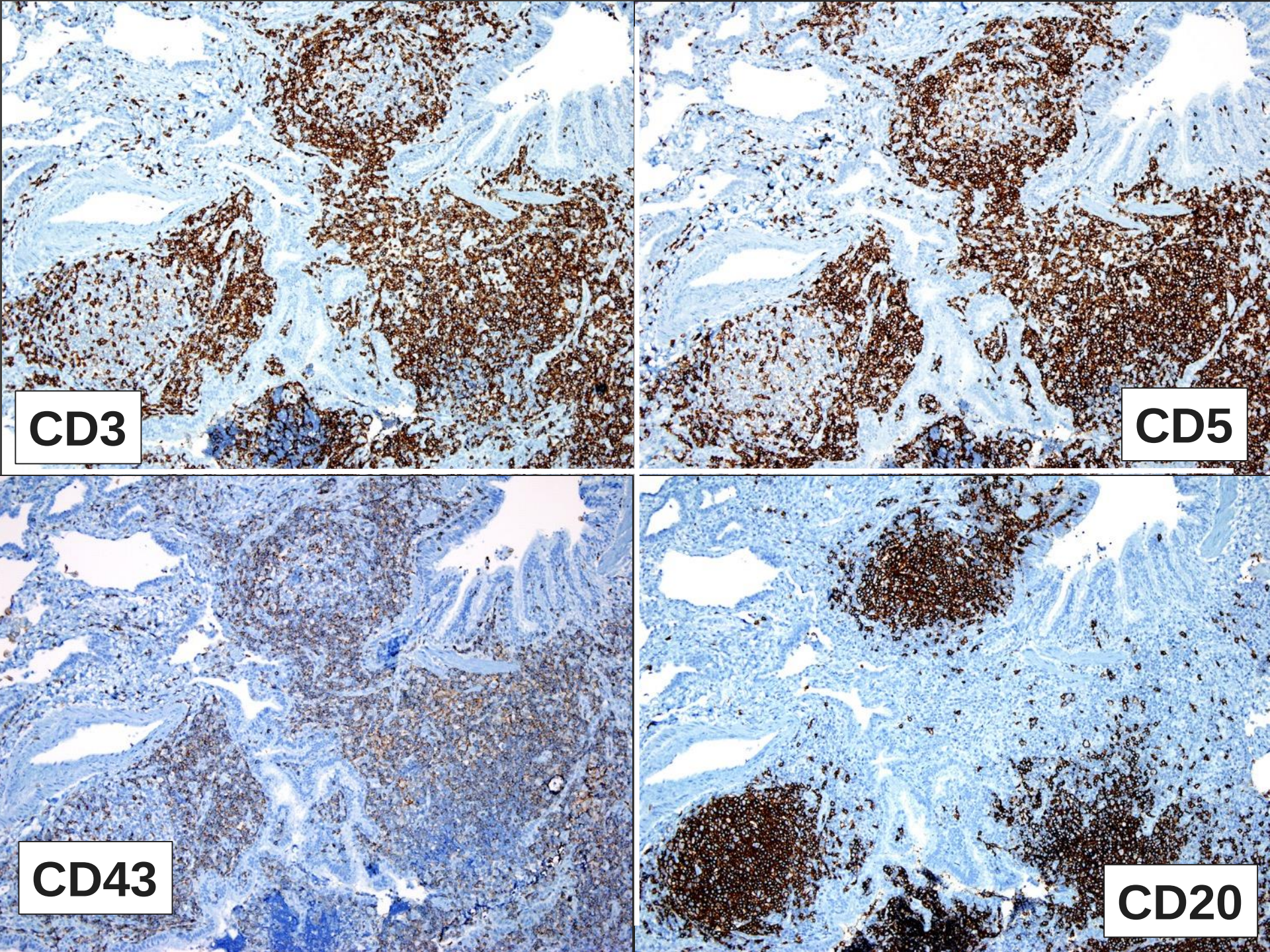








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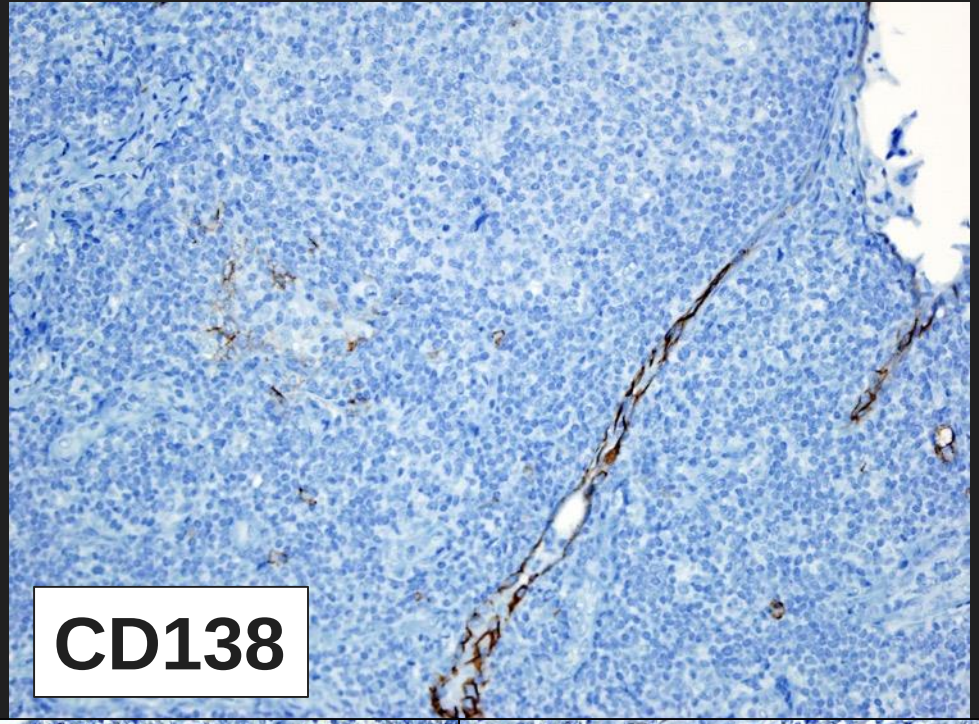
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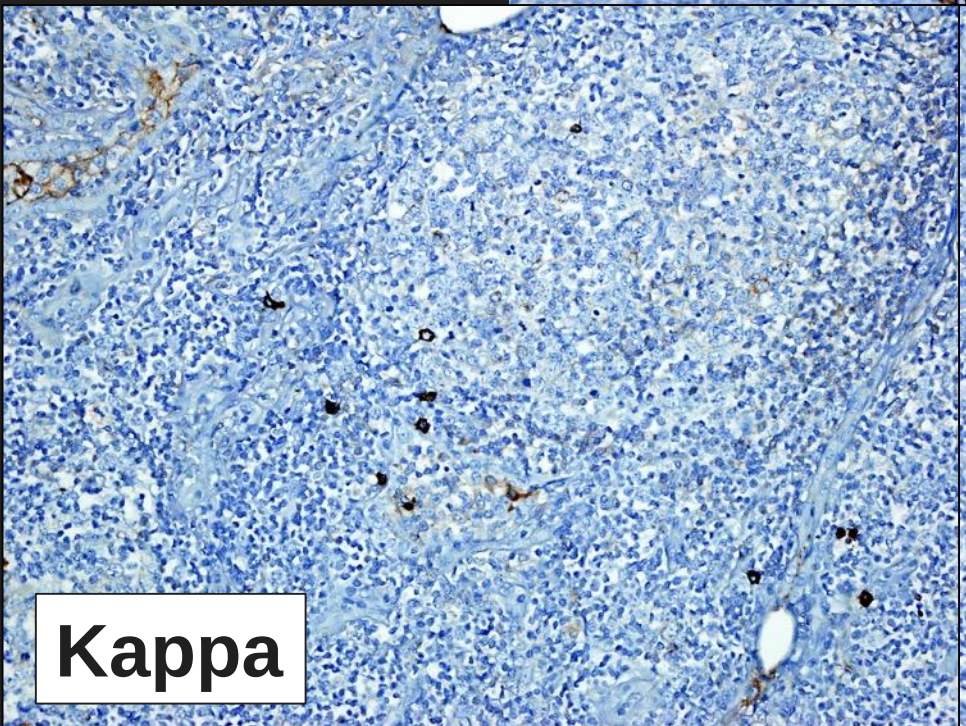
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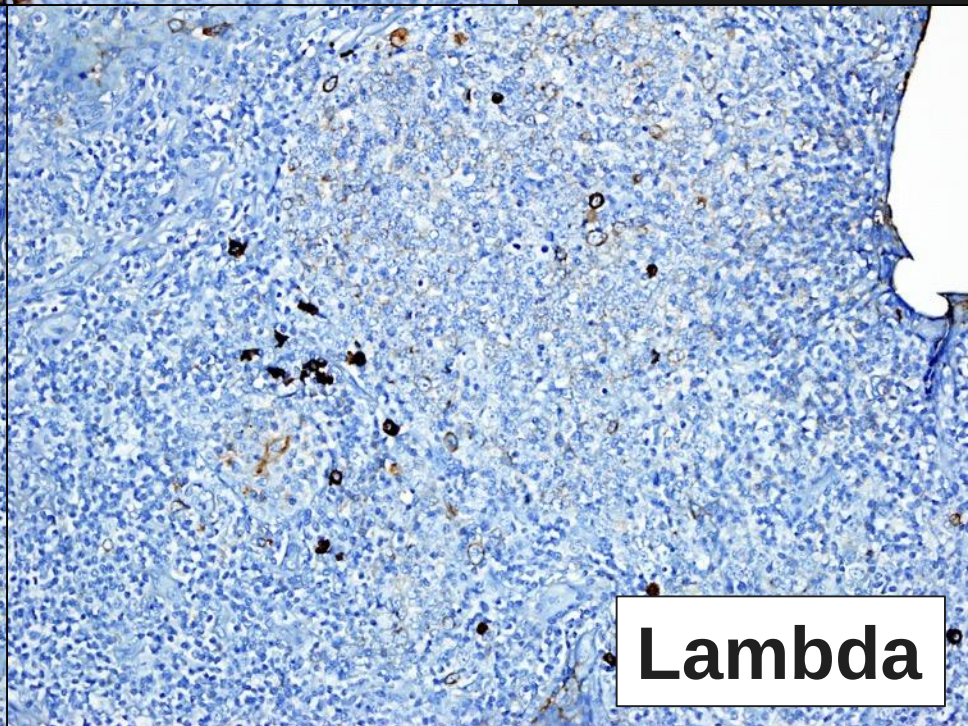

Lambda

So- called GL-ILD Histologic Features

- Wide spectrum of histologies
- Possibly useful as a clinical term, but very confusing for pathologists!
- Always need to exclude lymphoma
- Granulomas don’t exclude lymphoma (20% of pulmonary MALT lymphomas)

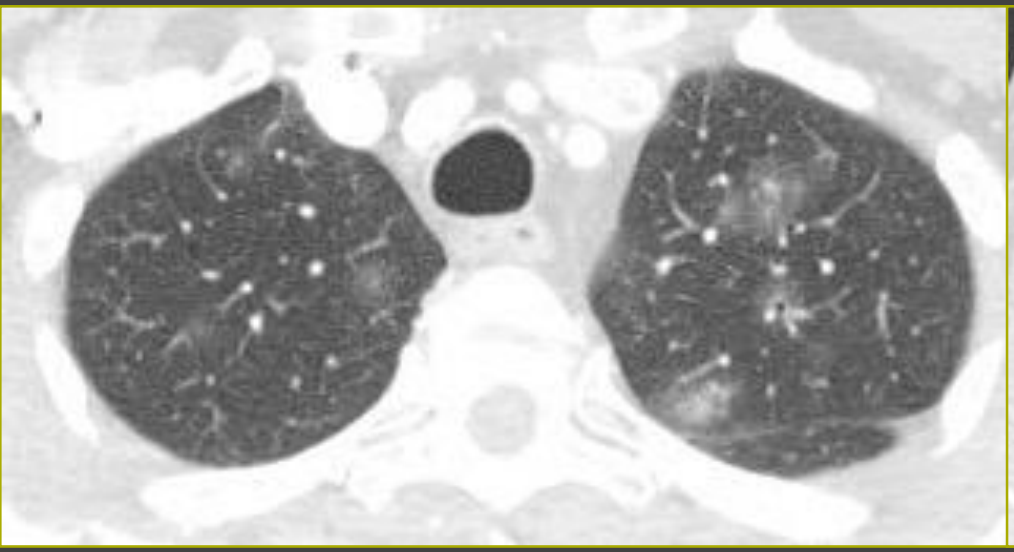
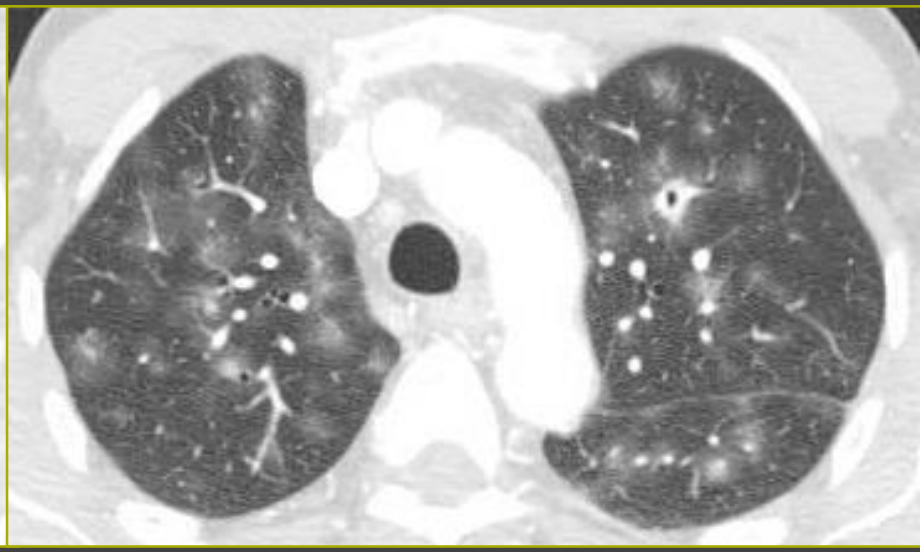
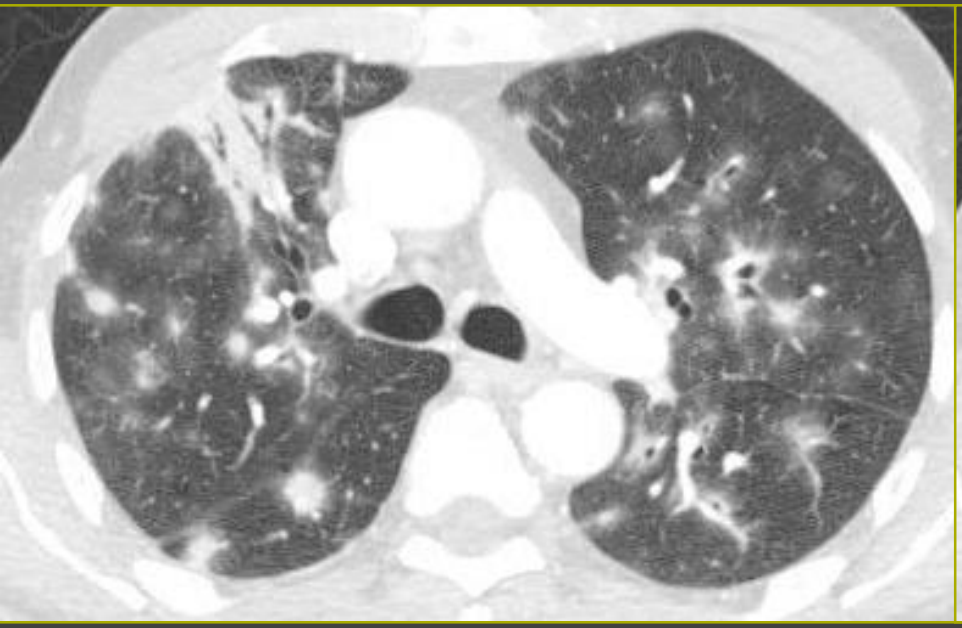
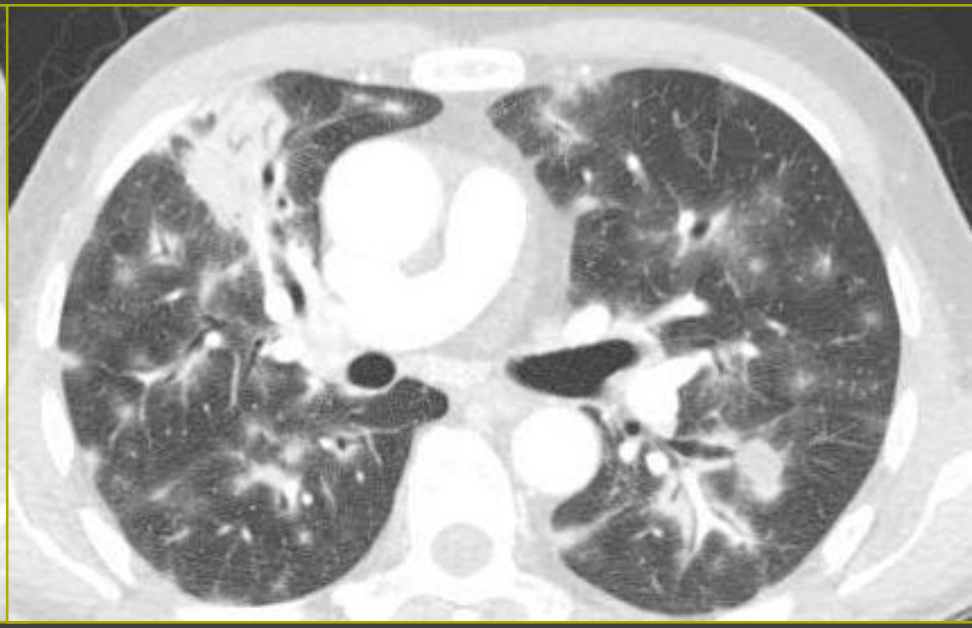
History

- 76 yr. old M 10 pack yr smoker
- Referred for possible bronchoscopy
- History of metastatic melanoma
- Started on Immunotherapy with Pembrolizumab 10 months ago

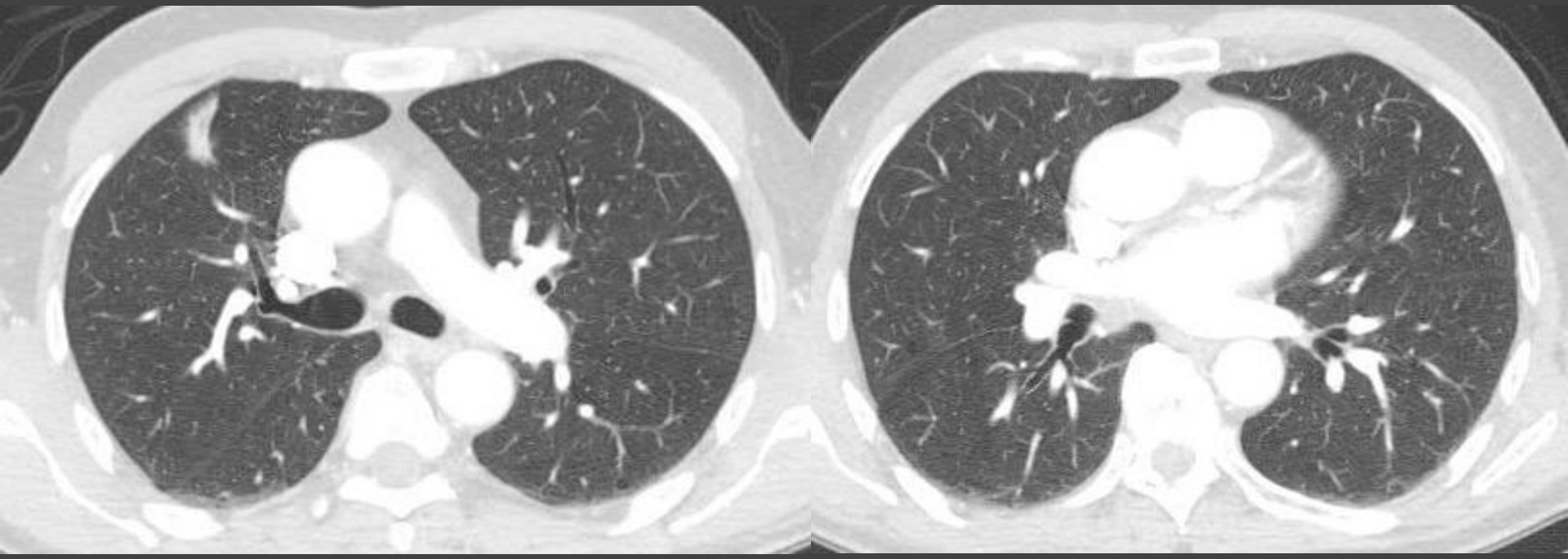
History

Hospitalized

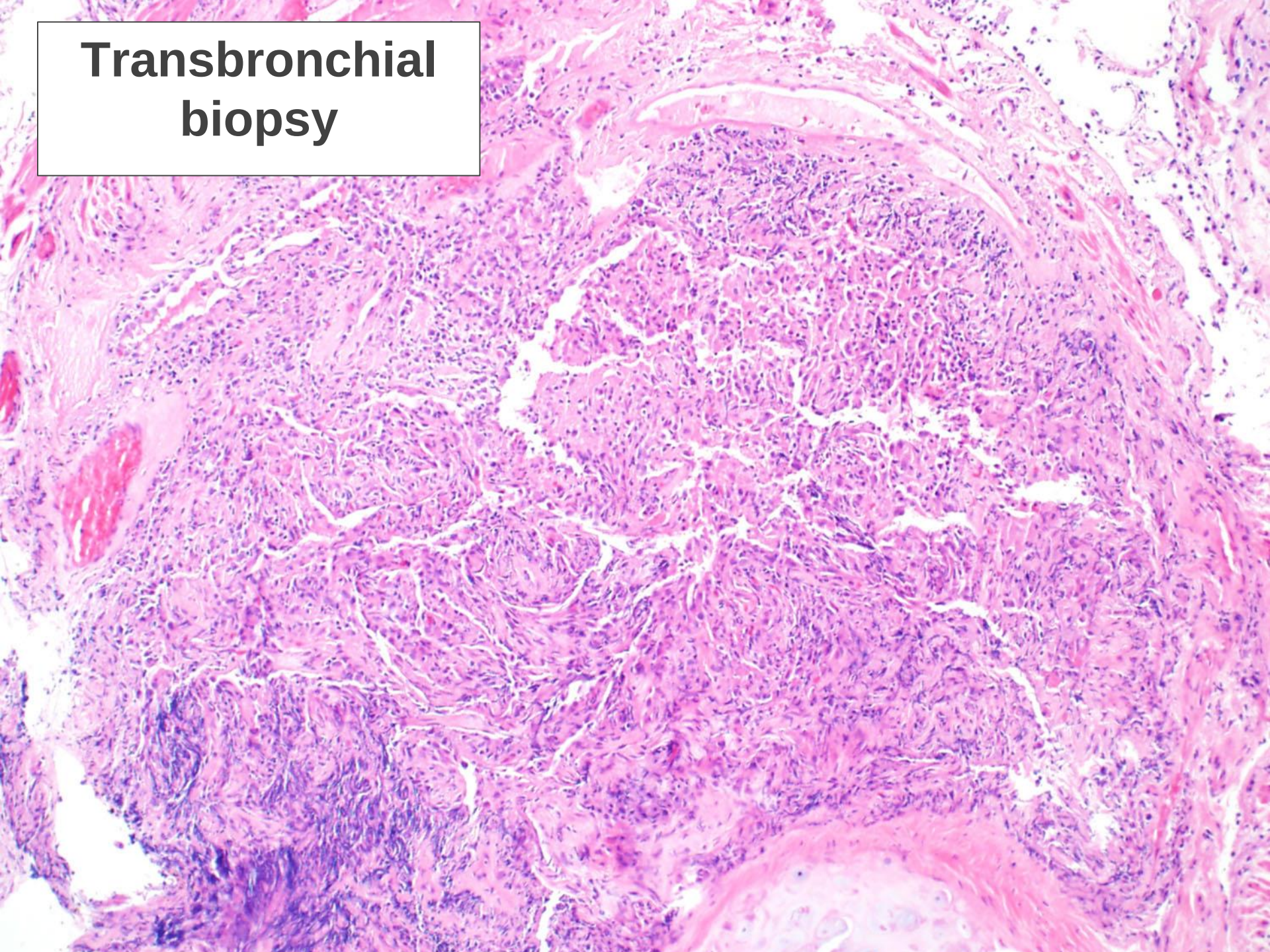
- **Weight loss of 6-8 lbs. over the last 4 weeks**
- **Noted dyspnea on exertion for 4 weeks**
- **Dry cough for 3 weeks**
- **Low grade fever and chills for the past 10 days**

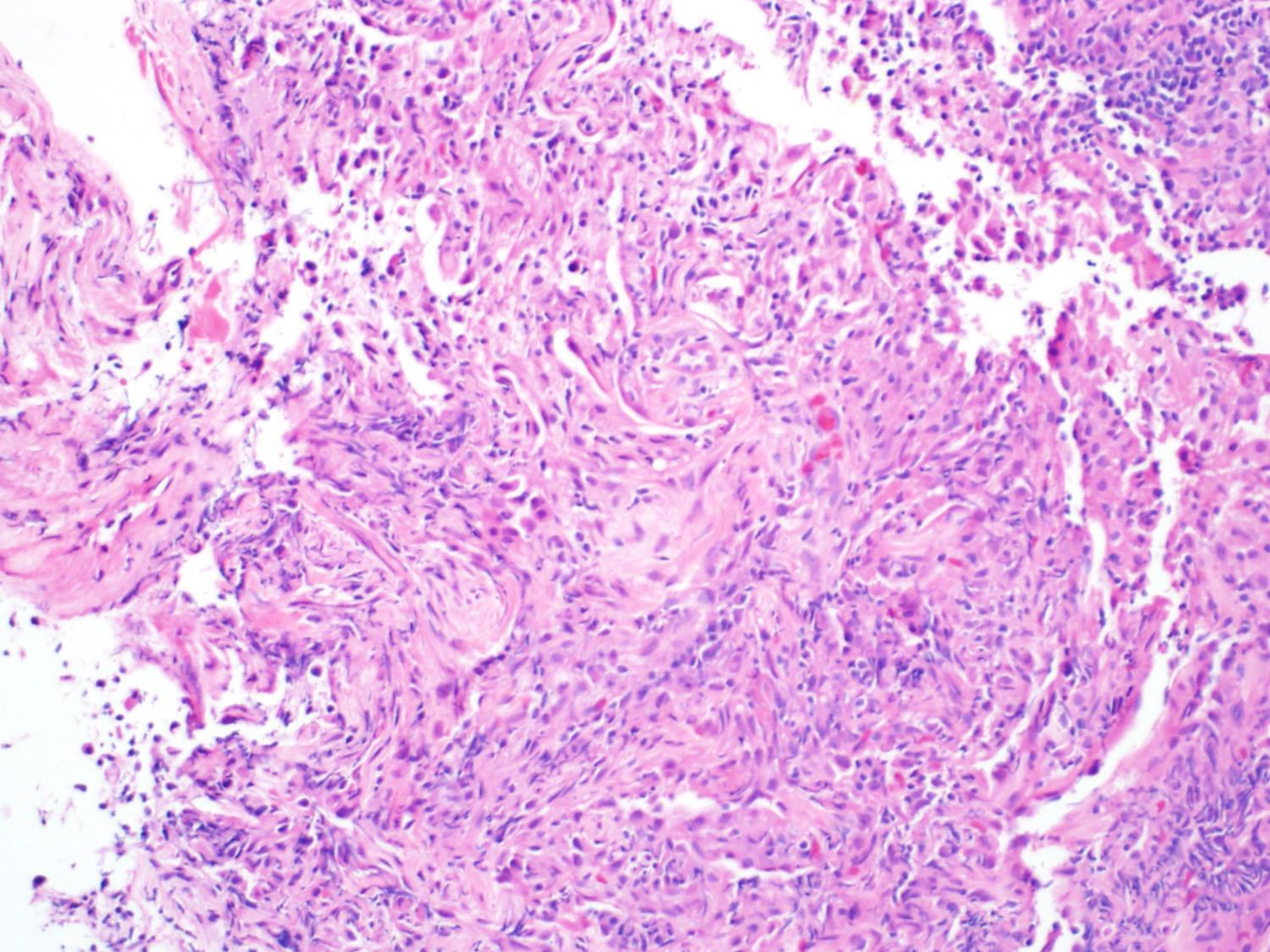





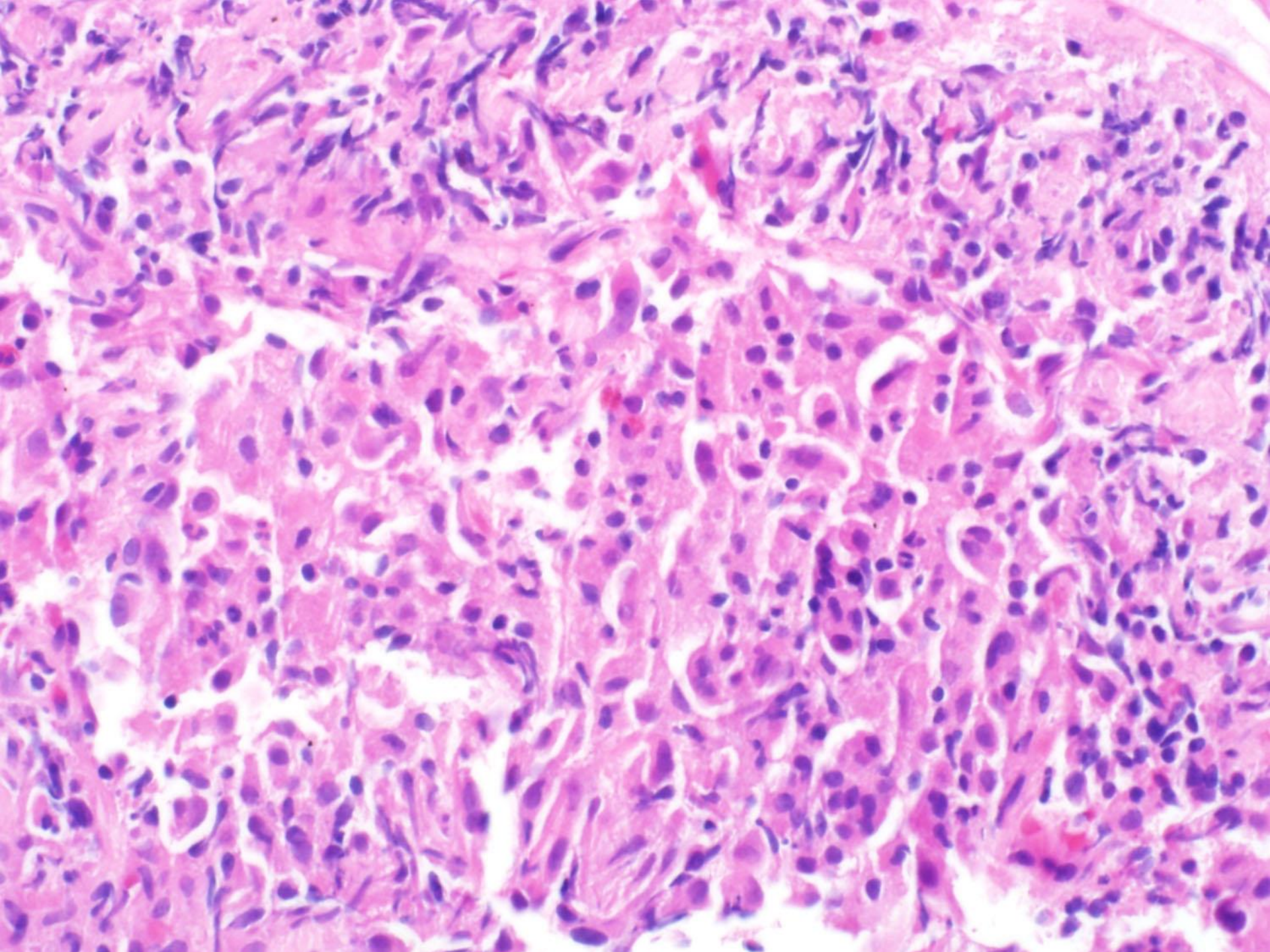
CT 3 Months Prior



Transbronchial biopsy







Pathologic Diagnosis?

- Organizing Pneumonia
  - DDx: infection, drug reaction, connective tissue disease, aspiration, and as an idiopathic entity (cryptogenic organizing pneumonia)

Final Clinical Diagnosis

- BAL and special stains negative for infection
- Pembrolizumab-induced organizing pneumonia
- Pt started on 60 mg of prednisone
- Improved over the next few weeks with tapering of steroids over 2 months

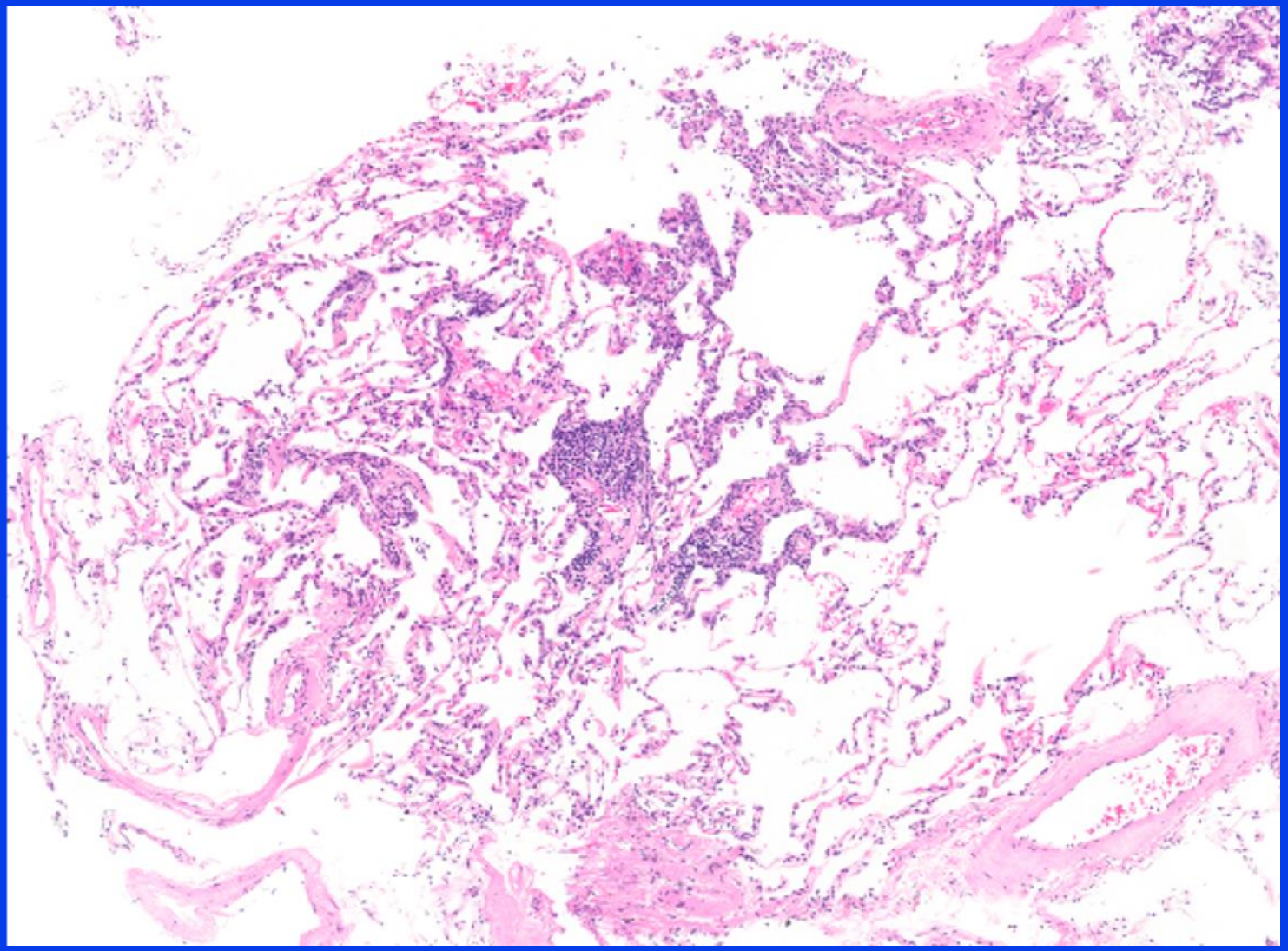
Check Point Inhibitor- Assoc ILD, n=64

Radiologic Patterns	%
Organizing pneumonia (OP)	23.4
Hypersensitivity Pneumonia	15.6
NSIP plus OP	9.4
NSIP	7.8
Bronchiolitis	6.3
NSIP plus bronchiolitis	1.6
Not classified	35.9

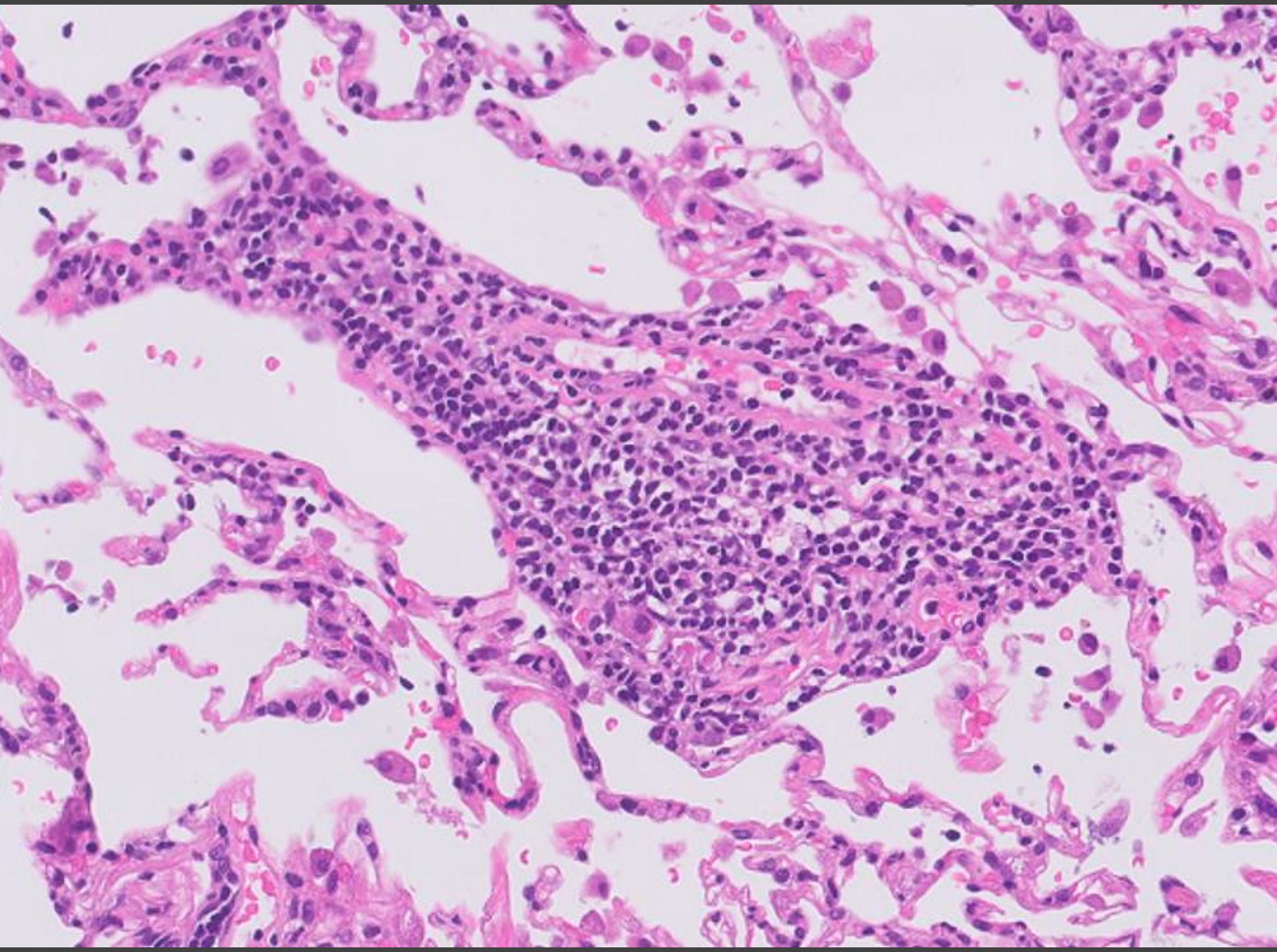
Delaunay M et al. Eur Resp J 2017;50:1700050

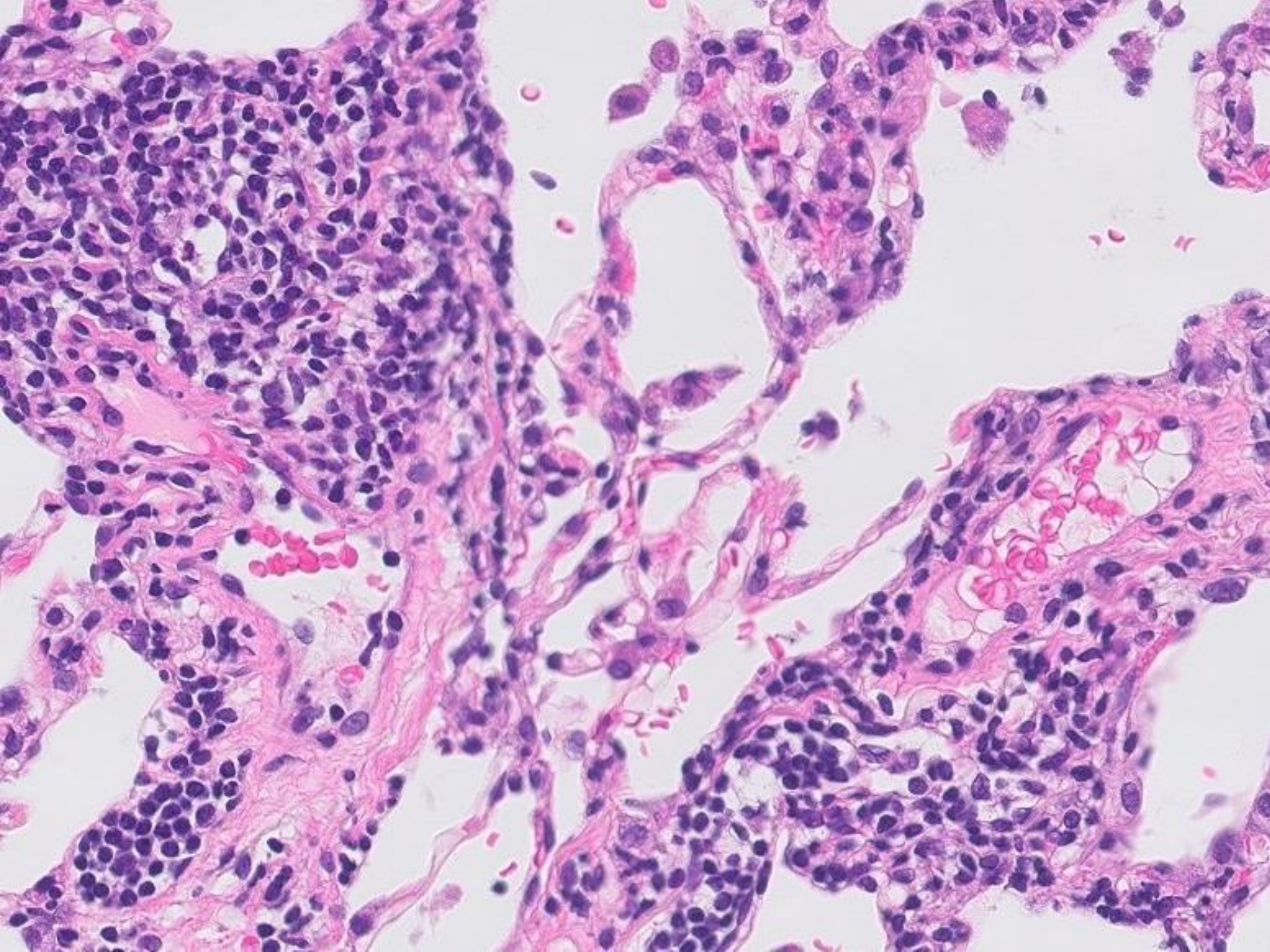
Check Point Inhibitor- Pathology Patterns
Diffuse alveolar damage
Organizing pneumonia (OP) +/- fibrin
Hypersensitivity pneumonitis/granulomatous pneumonitis
NSIP-cellular interstitial infiltrates
Bronchiolitis
Fibrosis
Eosinophilic pneumonia
Granulomatous lymphadenitis

TBBX from 68 year old man on 6th cycle of Pembrolizumab



Courtesy of Dr. Masahara Nemeto, Kameda, Japan





Summary

- Spectrum of OP histology broad
- CTD related lung disease and hypersensitivity pneumonitis have significant overlaps
- PBC and CVID can both cause granulomatous lung disease
- Immune check point inhibitors can cause variety of toxicity patterns

Thank you!