CASE DISCUSSION

Pathologic finding

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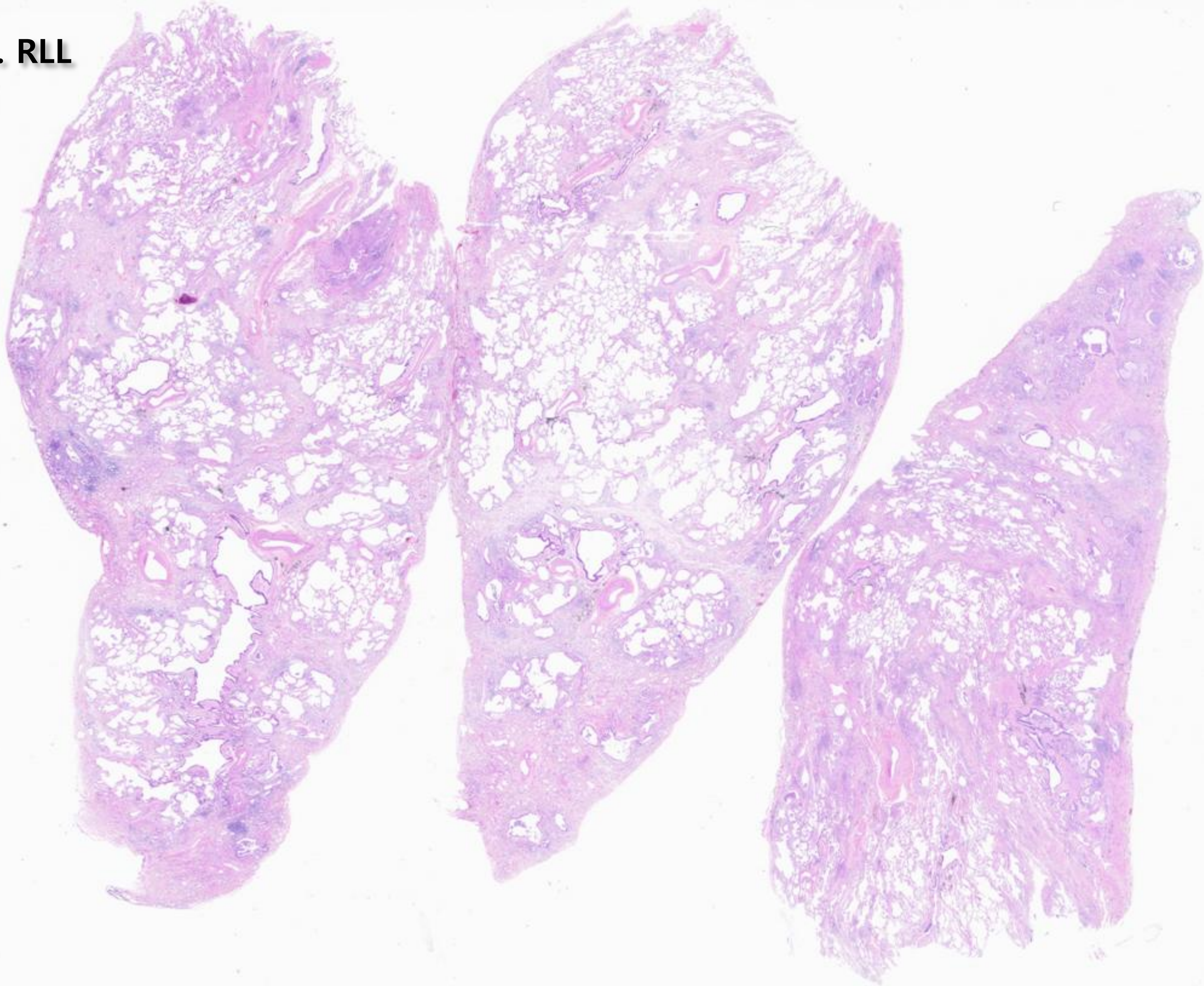
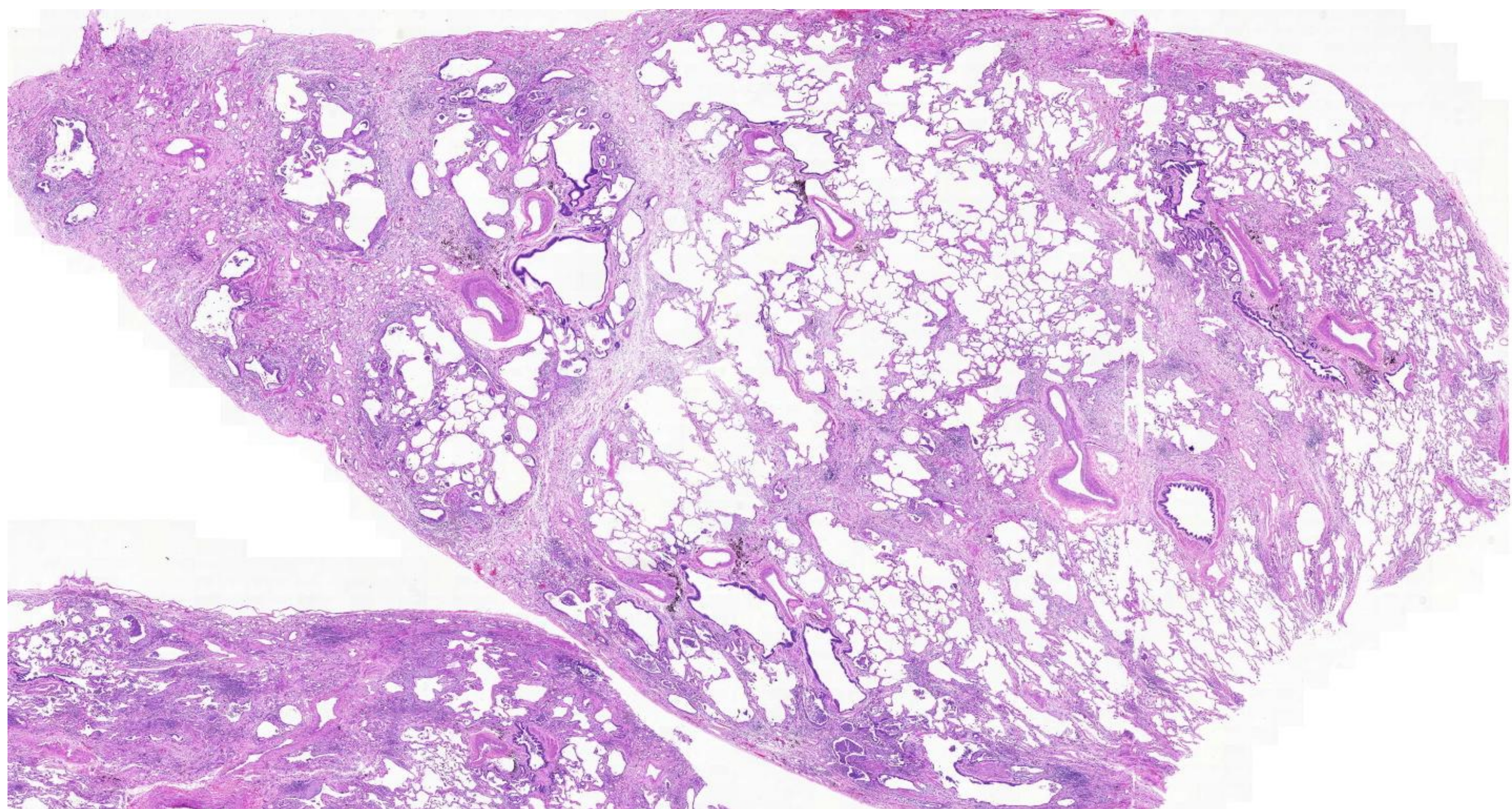
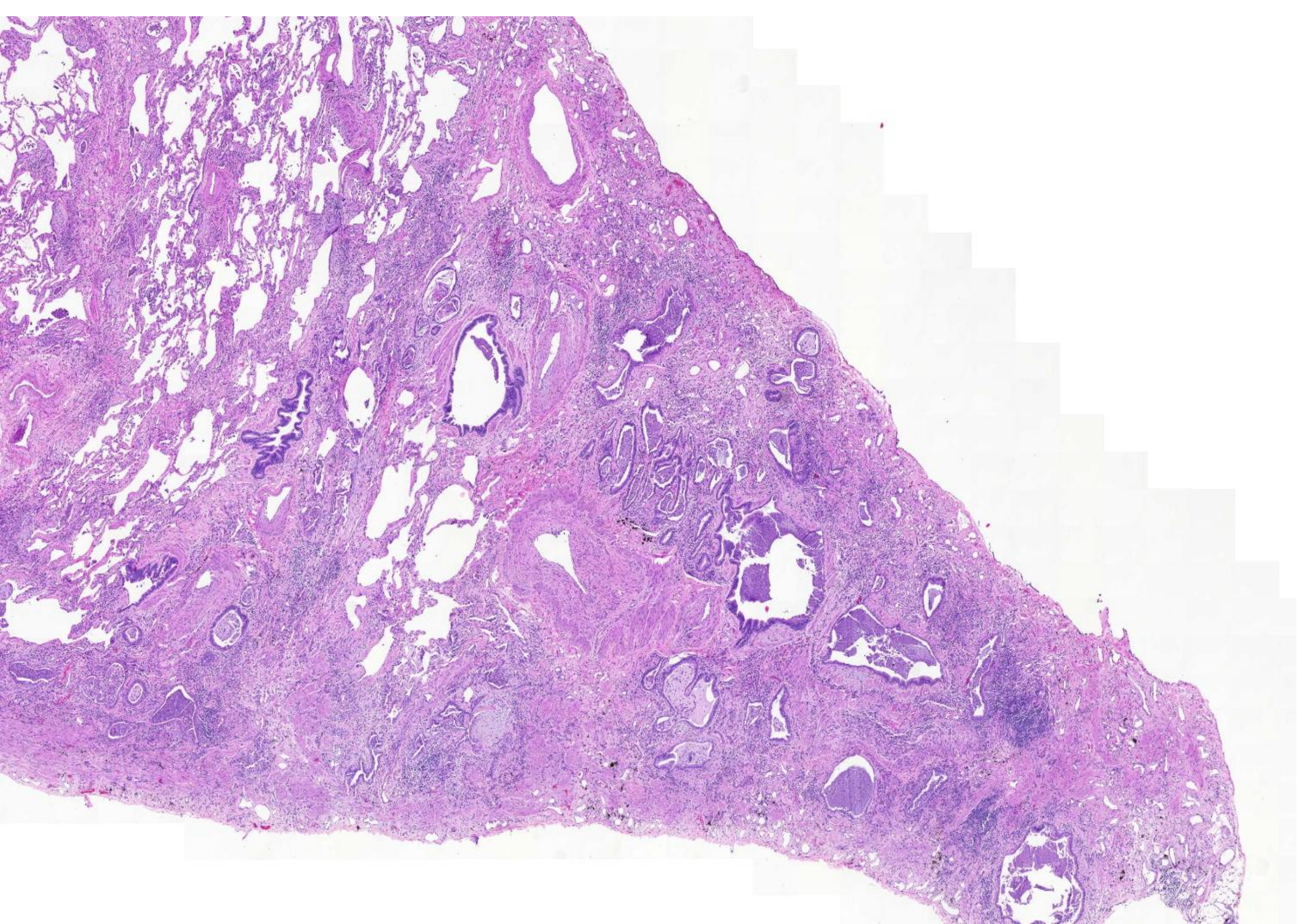
Case 1

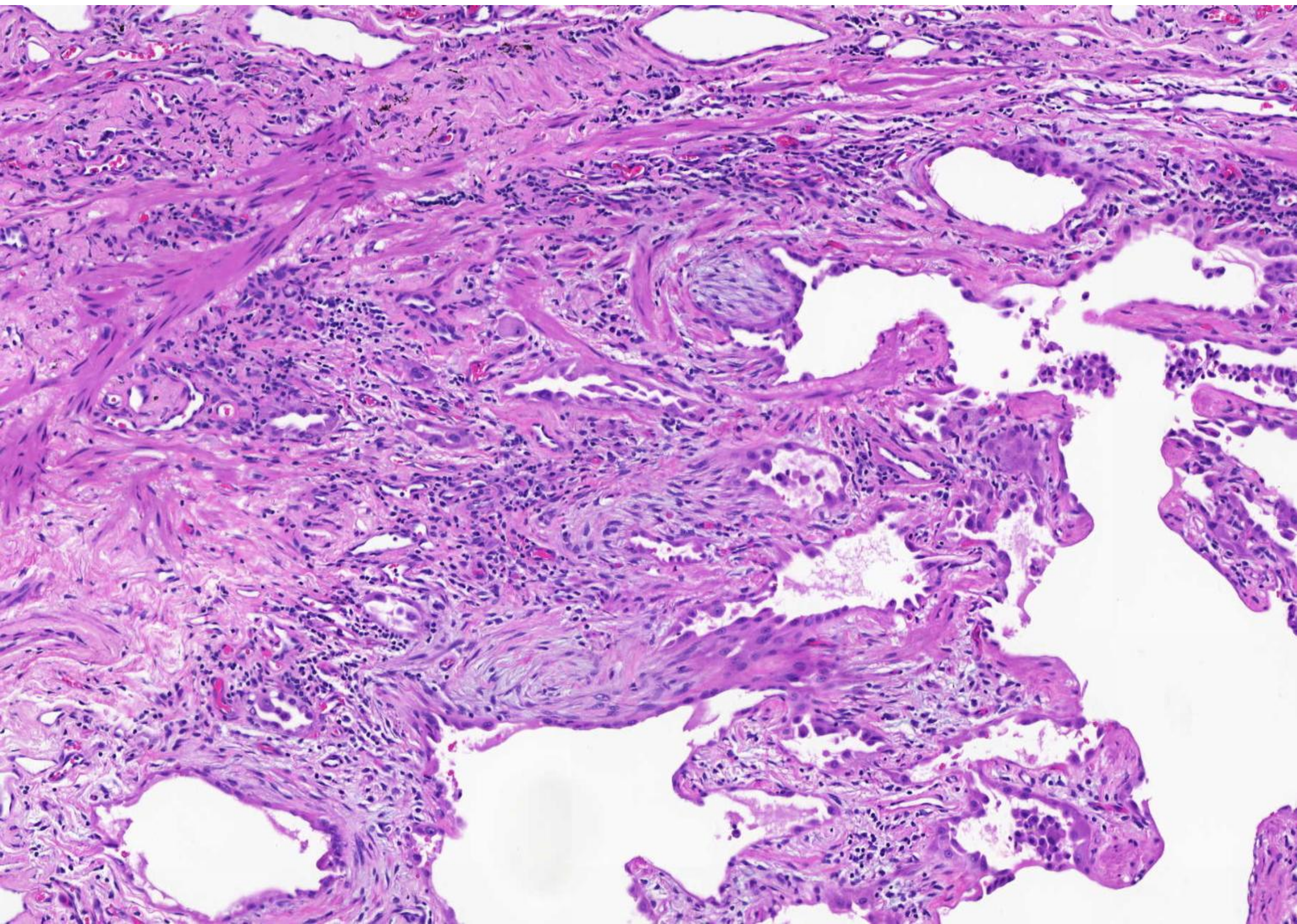
유 0 열 M/55

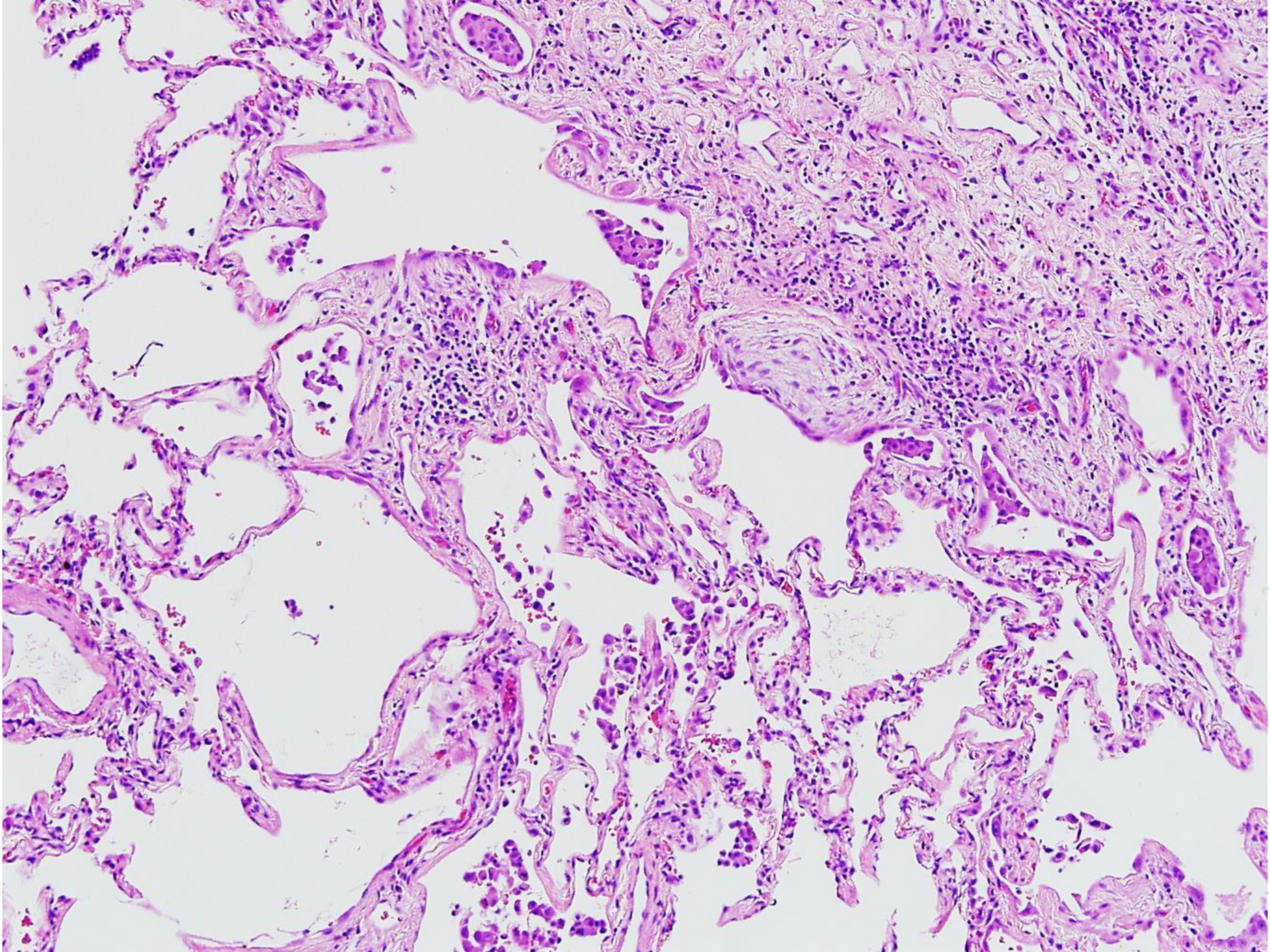
2011. RLL

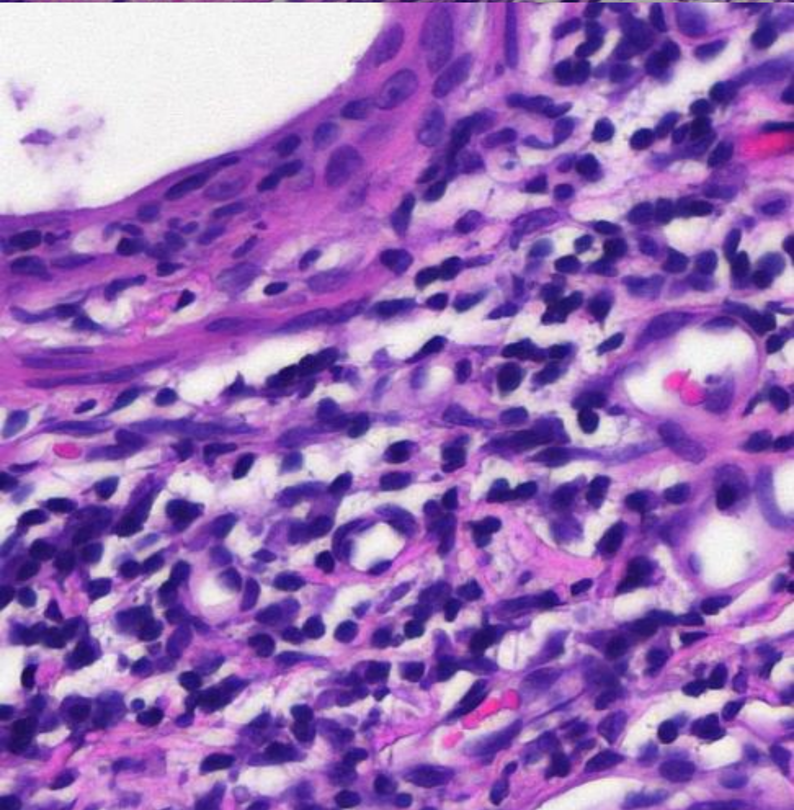












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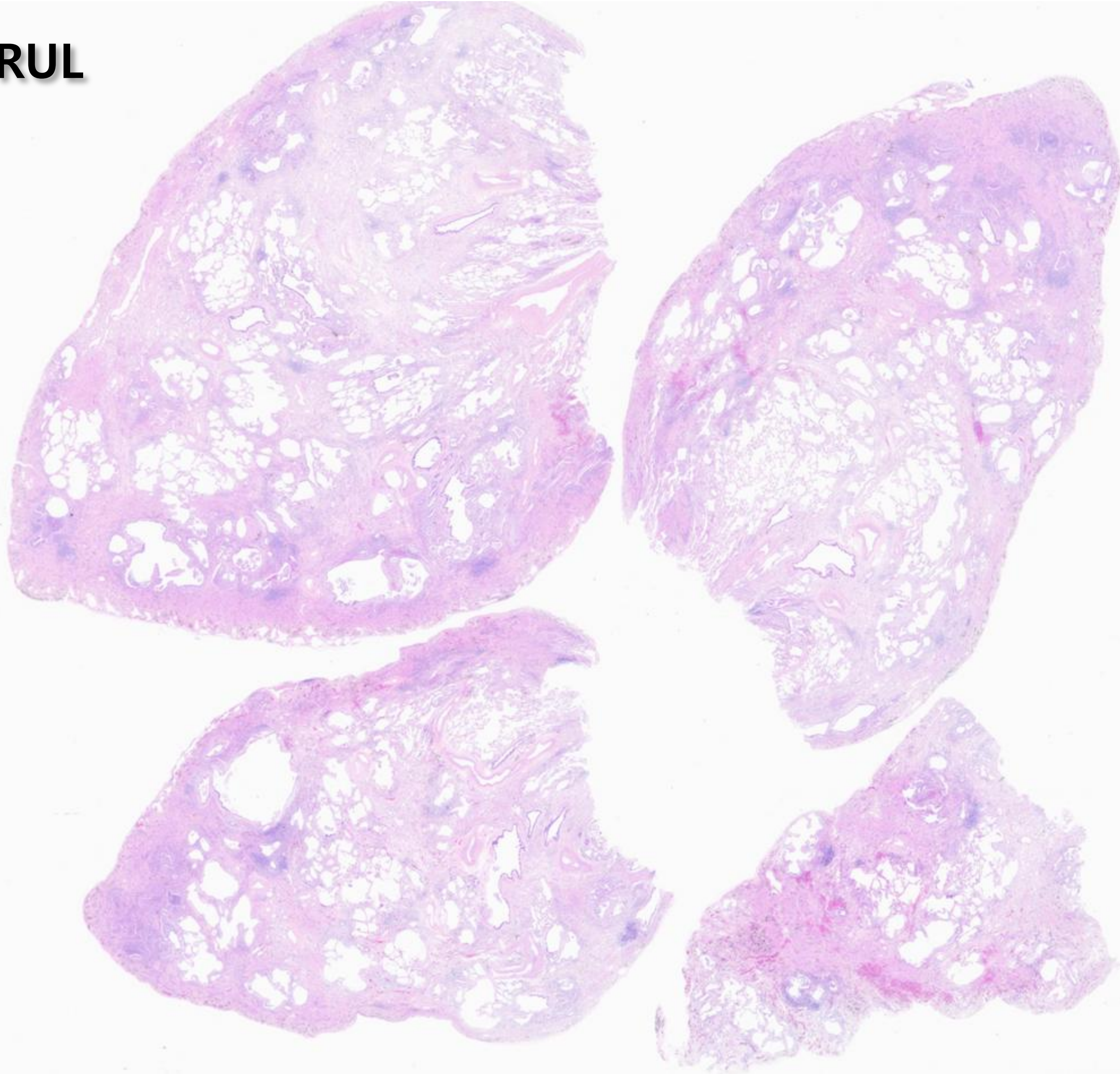
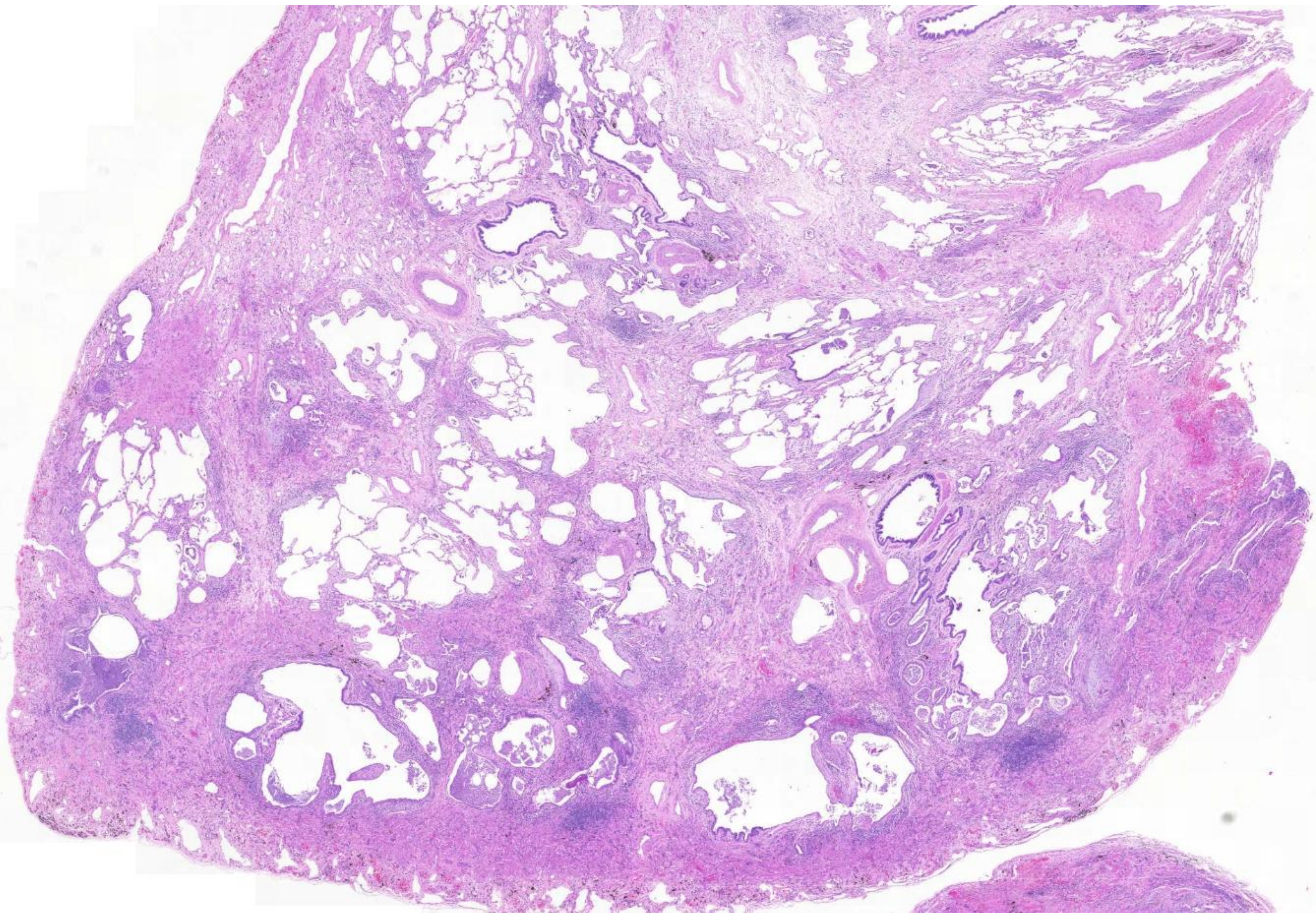
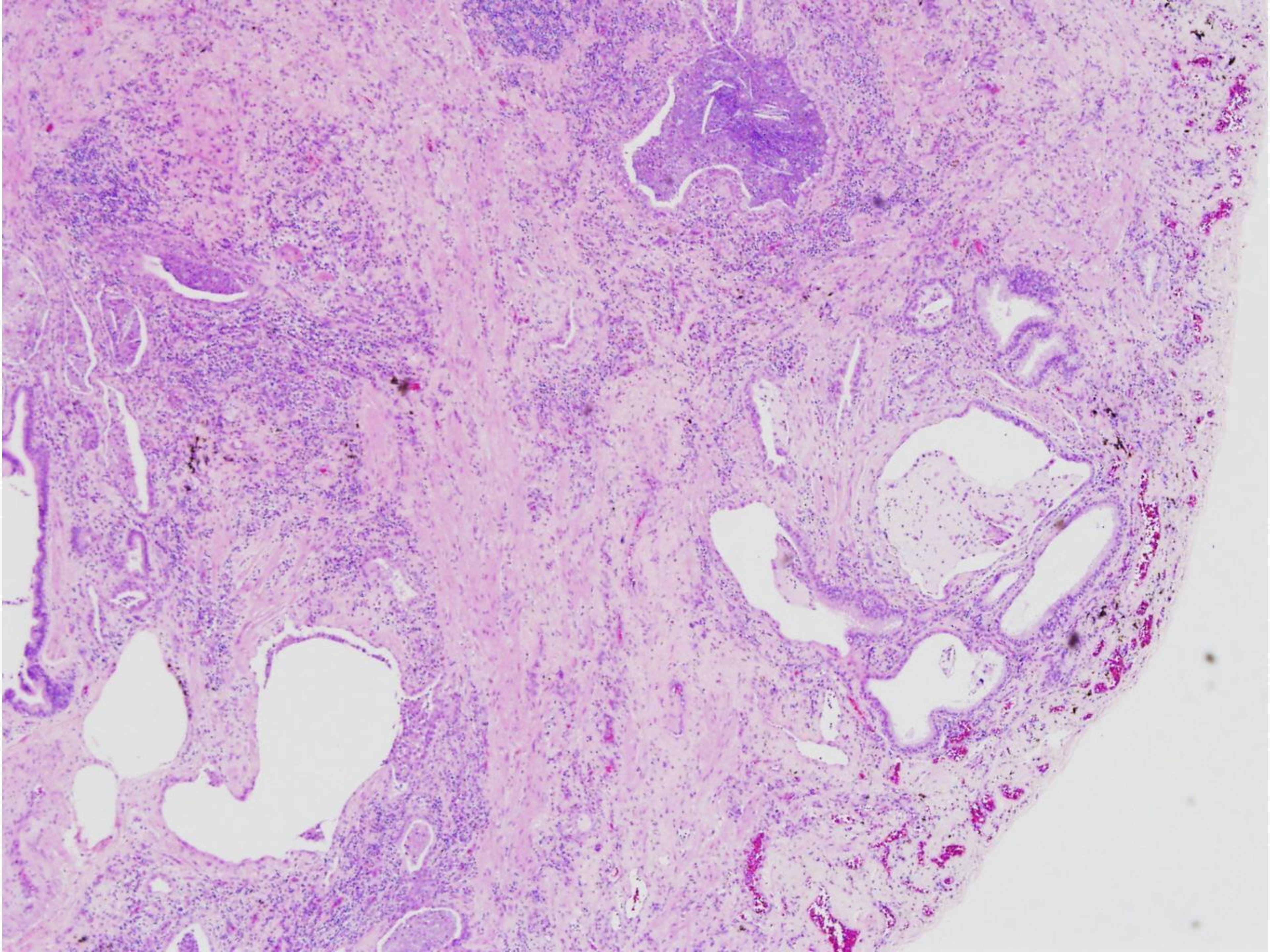
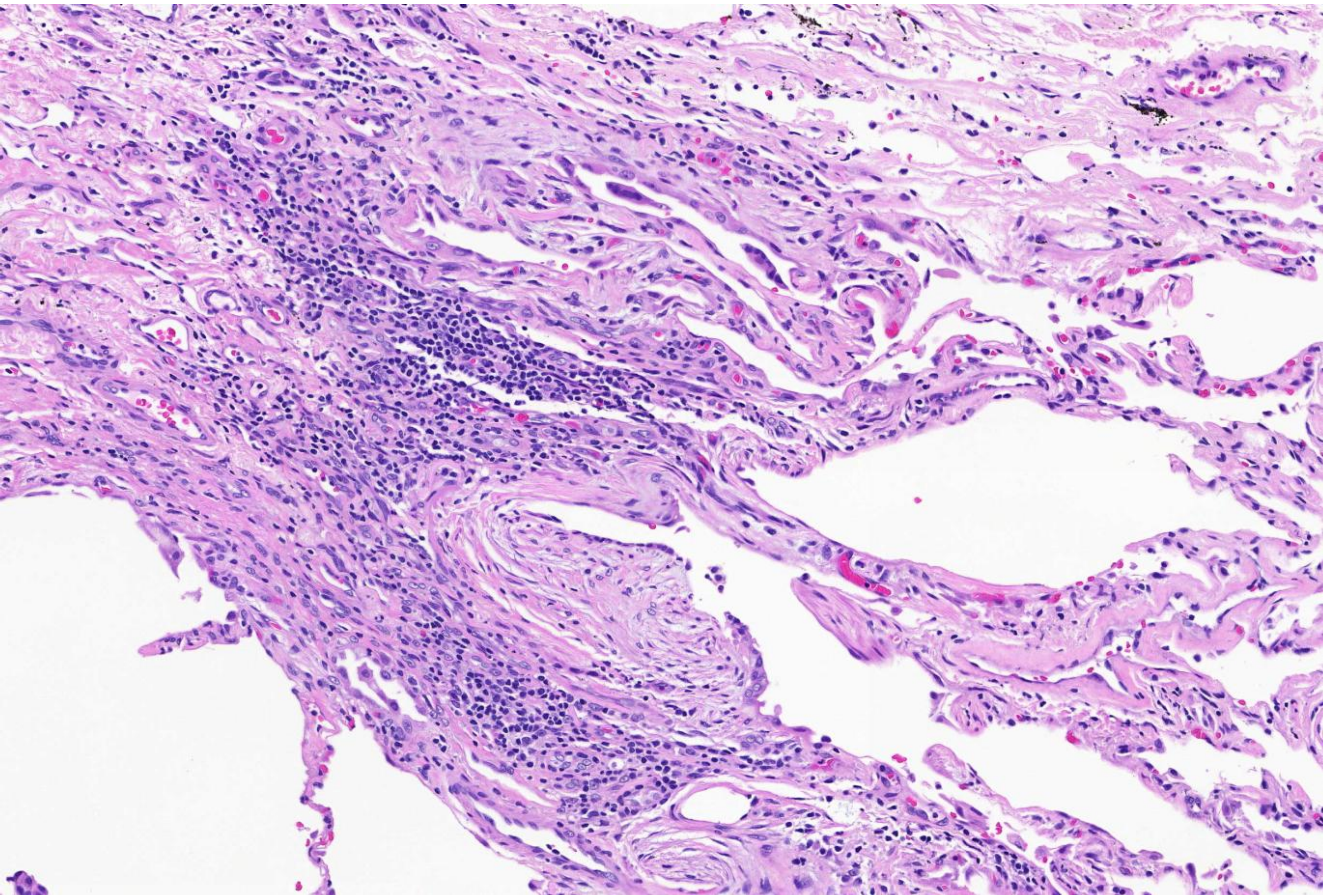
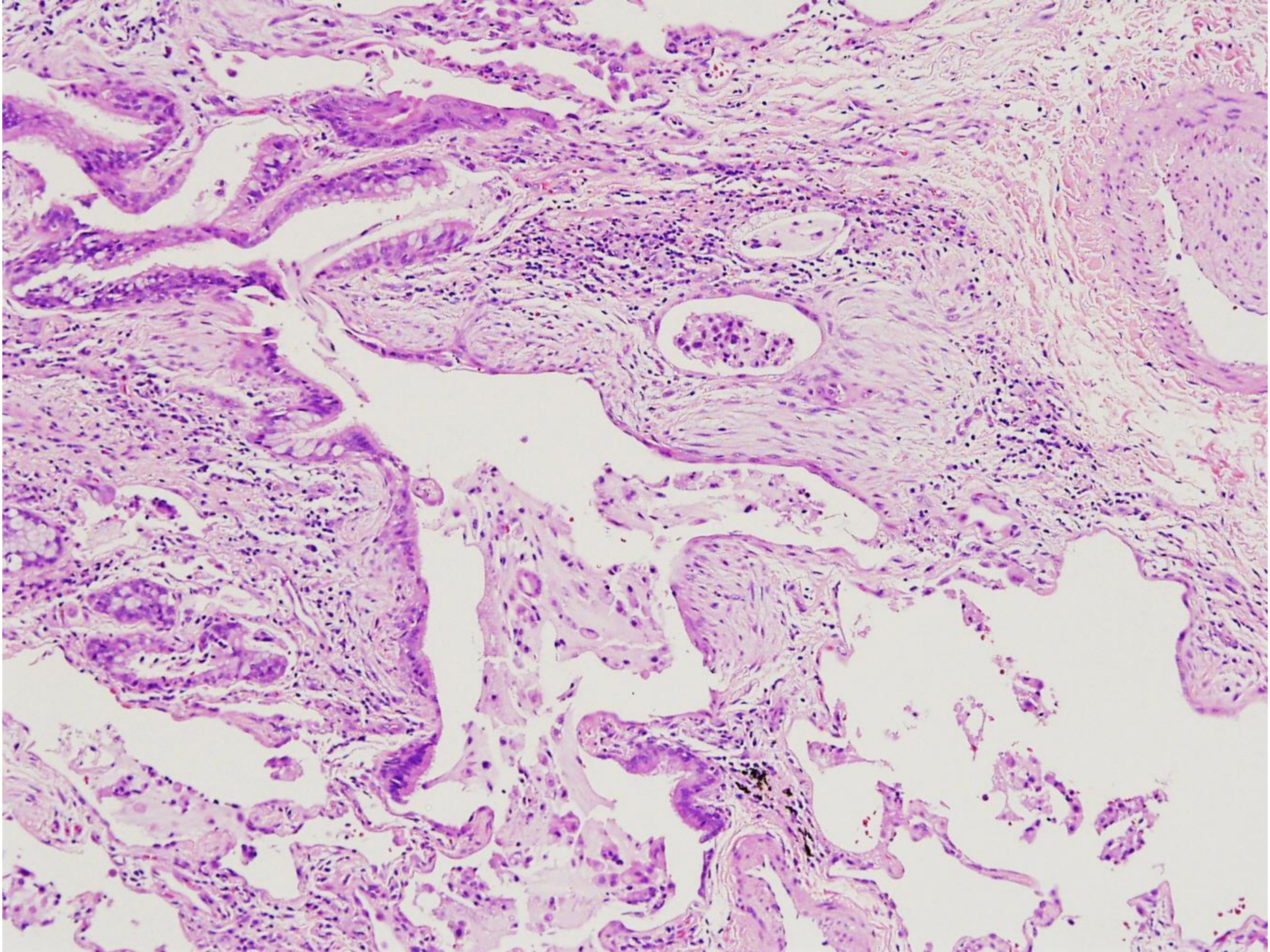
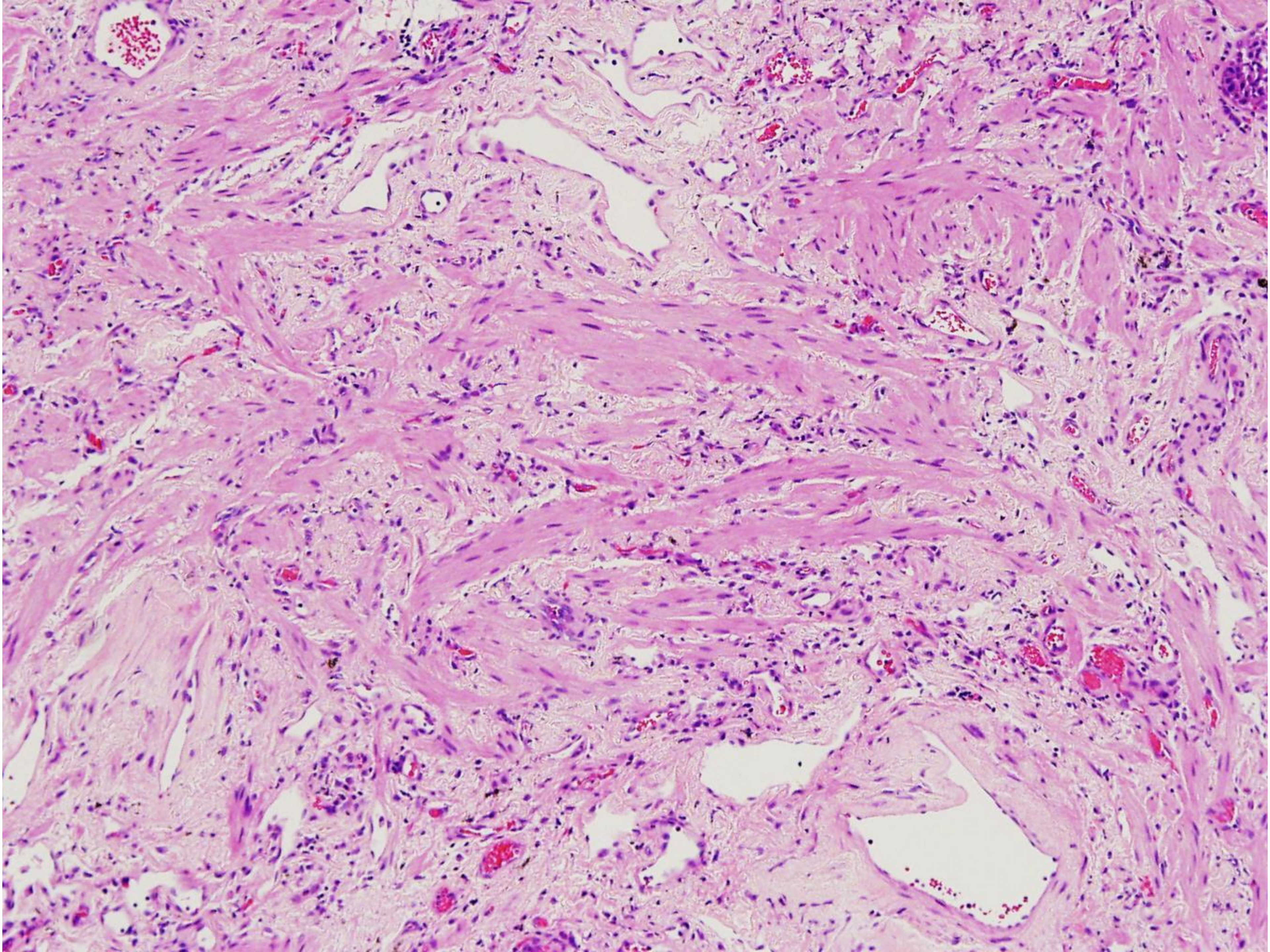












Diagnosis

Lung, (right upper and lower lobe), wedge resection :

- Fibrosing interstitial pneumonia

  with (1) subpleural predominancy

  (2) spatial and temporal heterogeniety

  (3) microscopic honeycomb change

  (4) moderate fibroblastic foci

  (5) moderate lymphoplasmacytic infiltration and lymphoid aggregates

  c/w usual interstitial pneumonia

An Official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias

William D. Travis, Ulrich Costabel, David M. Hansell, Talmadge E. King, Jr., David A. Lynch, Andrew G. Nicholson, Christopher J. Ryerson, Jay H. Ryu, Moisés Selman, Athol U. Wells, Jurgen Behr, Demosthenes Bouros, Kevin K. Brown, Thomas V. Colby, Harold R. Collard, Carlos Robalo Cordeiro, Vincent Cottin, Bruno Crestani, Marjolein Drent, Rosalind F. Dudden, Jim Egan, Kevin Flaherty, Cory Hogaboam, Yoshikazu Inoue, Takeshi Johkoh, Dong Soon Kim, Masanori Kitaichi, James Loyd, Fernando J. Martinez, Jeffrey Myers, Shandra Protzko, Ganesh Raghu, Luca Richeldi, Nicola Sverzellati, Jeffrey Swigris, and Dominique Valeyre; on behalf of the ATS/ERS Committee on Idiopathic Interstitial Pneumonias

Am J Respir Crit Care Med 188(6) 733-748

TABLE 2. CATEGORIZATION OF MAJOR IDIOPATHIC INTERSTITIAL PNEUMONIAS

Category	Clinical–Radiologic–Pathologic Diagnoses	Associated Radiologic and/or Pathologic–Morphologic Patterns
Chronic fibrosing IP	Idiopathic pulmonary fibrosis	Usual interstitial pneumonia
	Idiopathic nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia
Smoking-related IP*	Respiratory bronchiolitis-interstitial lung disease	Respiratory bronchiolitis
	Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Acute/subacute IP	Cryptogenic organizing pneumonia	Organizing pneumonia
	Acute interstitial pneumonia	Diffuse alveolar damage

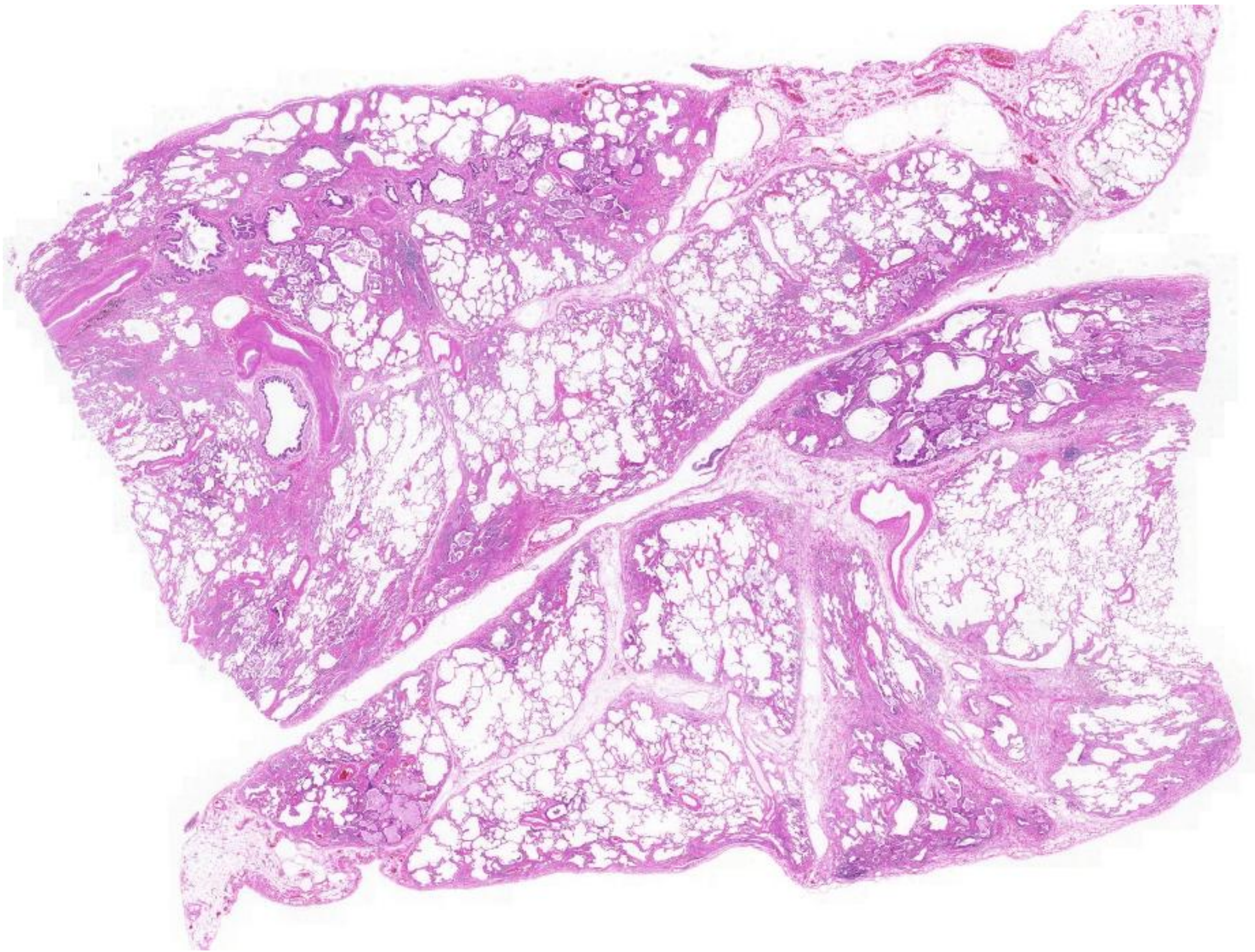
Usual Interstitial Pneumonia (UIP)

- Patchy fibrosis

- More pronounced beneath the pleura and along interlobular septa

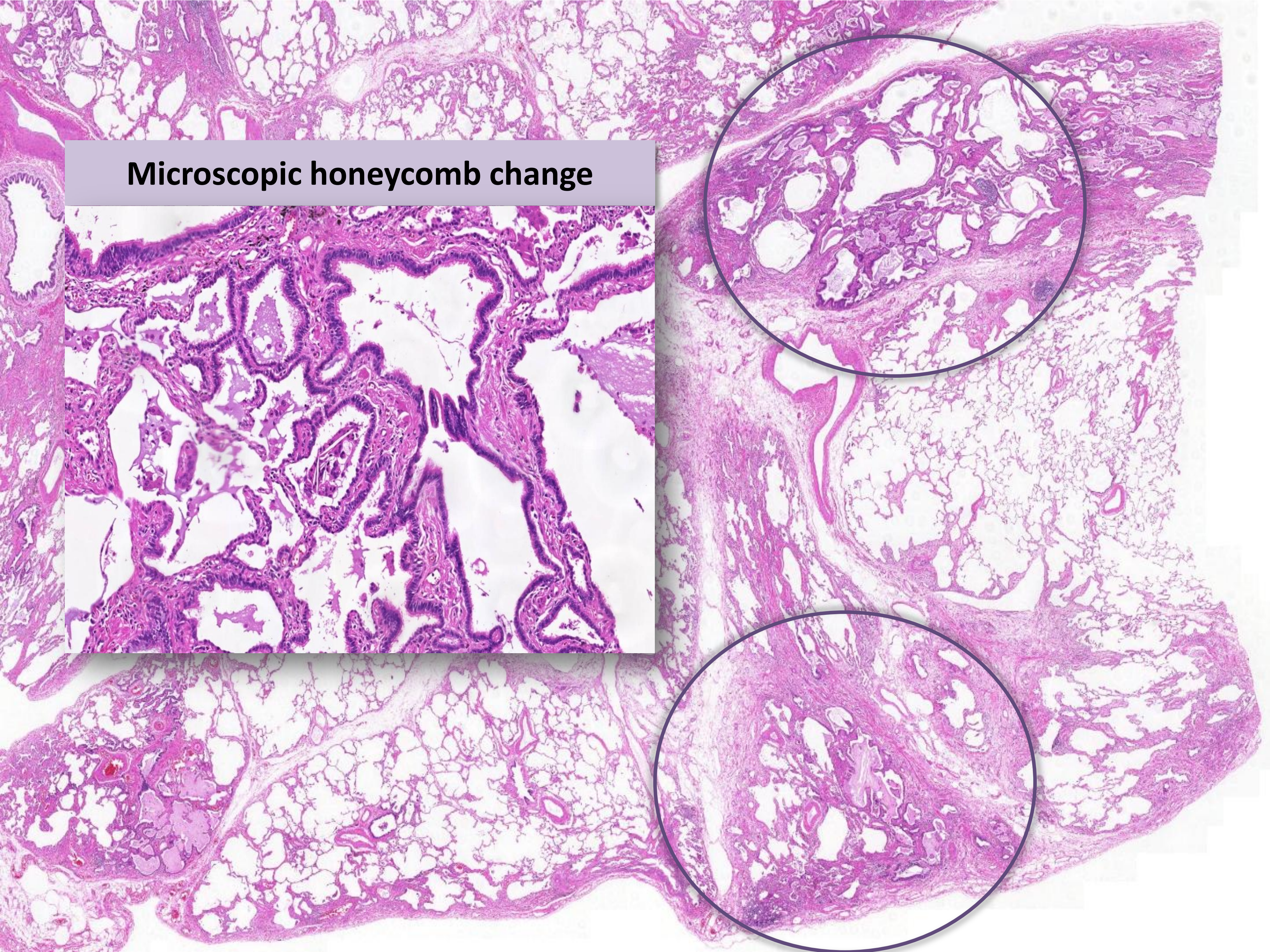
- End stage fibrosis alternates with areas of relatively spared parenchyma and areas of intermediate fibrosis
- Temporal heterogeneity in form of fibroblast foci

- Loose myxoid fibroblastic tissue juxtaposed adjacent to dense collagen fibrosis



Spatial heterogeniety: patchy involvement of subpleura and interlobular septa

Temporal heterogeneity
: young fibroblast and smooth muscle metaplasia (old fibrosis)


Microscopic honeycomb change

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Ganesh Raghu, Harold R. Collard, Jim J. Egan, Fernando J. Martinez, Juergen Behr, Kevin K. Brown, Thomas V. Colby, Jean-François Cordier, Kevin R. Flaherty, Joseph A. Lasky, David A. Lynch, Jay H. Ryu, Jeffrey J. Swigris, Athol U. Wells, Julio Ancochea, Demosthenes Bouros, Carlos Carvalho, Ulrich Costabel, Masahito Ebina, David M. Hansell, Takeshi Johkoh, Dong Soon Kim, Talmadge E. King, Jr., Yasuhiro Kondoh, Jeffrey Myers, Nestor L. Müller, Andrew G. Nicholson, Luca Richeldi, Moisés Selman, Rosalind F. Dudden, Barbara S. Griss, Shandra L. Protzko, and Holger J. Schünemann, on behalf of the ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis

Am J Respir Crit Care Med 183(2) 788-824

2002 ATS/ERS IIP Classification	2011 ATS/ERS/JRS/ALAT statement
Distinct type of chronic fibrosing interstitial pneumonia of unknown cause limited to the lungs and associated with a **surgical lung biopsy showing a histological patterns of UIP**	Specific form of chronic, progressive fibrosing, interstitial pneumonia of unknown cause, occurring primarily in **older adults**, limited to the lungs and associated with the **histopathologic and/ or radiologic pattern of UIP**

TABLE 4. HIGH-RESOLUTION

UIP Pattern (All Four Features)	ttern (Any of the Seven Features)
• Subpleural, basal predominance • Reticular abnormality • Honeycombing with or without t bronchiectasis • Absence of features listed as inco UIP pattern (*see* third column)	edominance redominance s abnormality (extent > (bilateral, predominantly e, bilateral, away from areas ation/air-trapping (bilateral, s) chopulmonary segment(s)/lobe(s)

Clear evidence of scarring, architectural distortion, +/- honeycomb change

Presence of fibroblastic foci

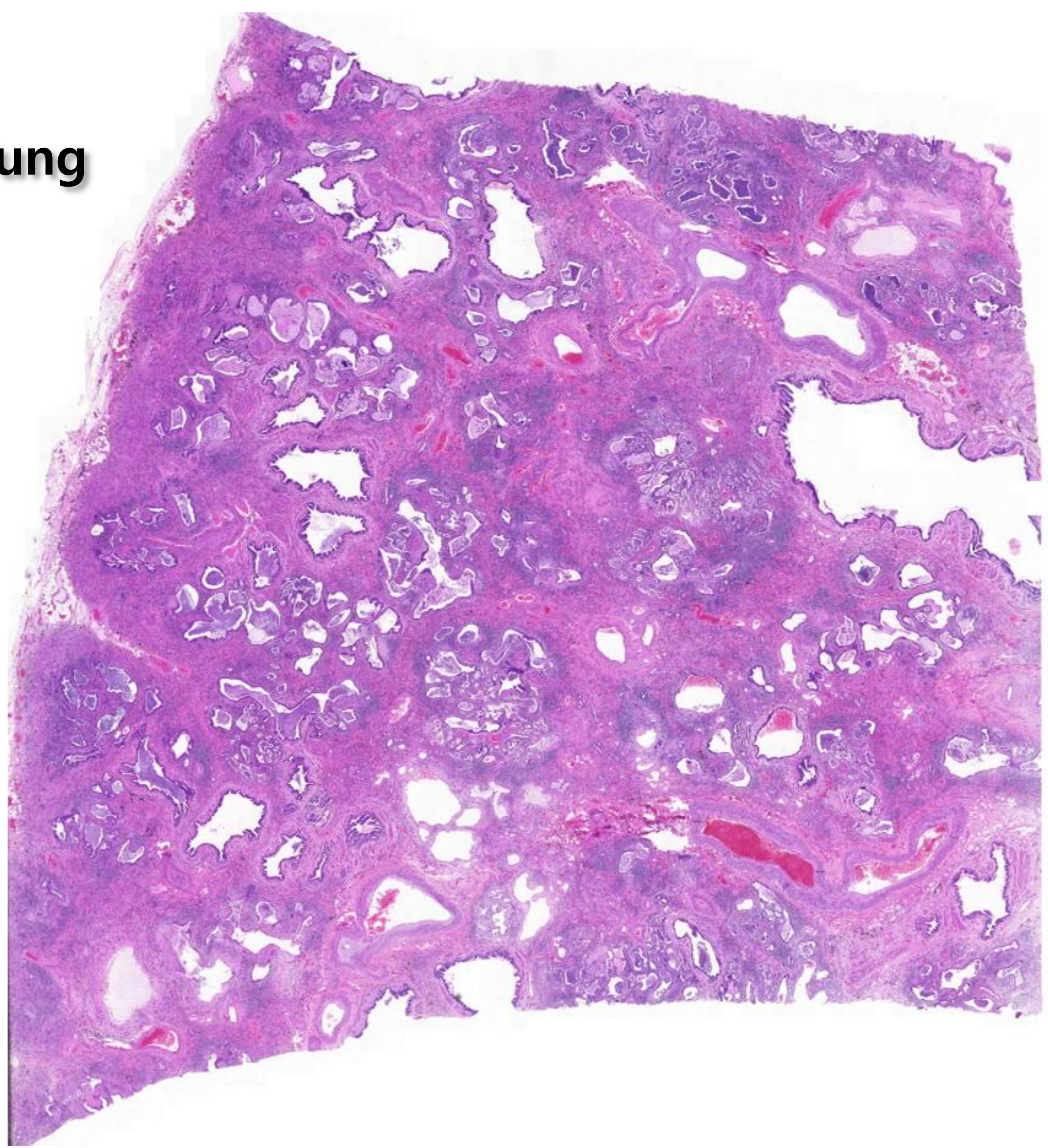
Presence of patchy involvement of lung parenchyme

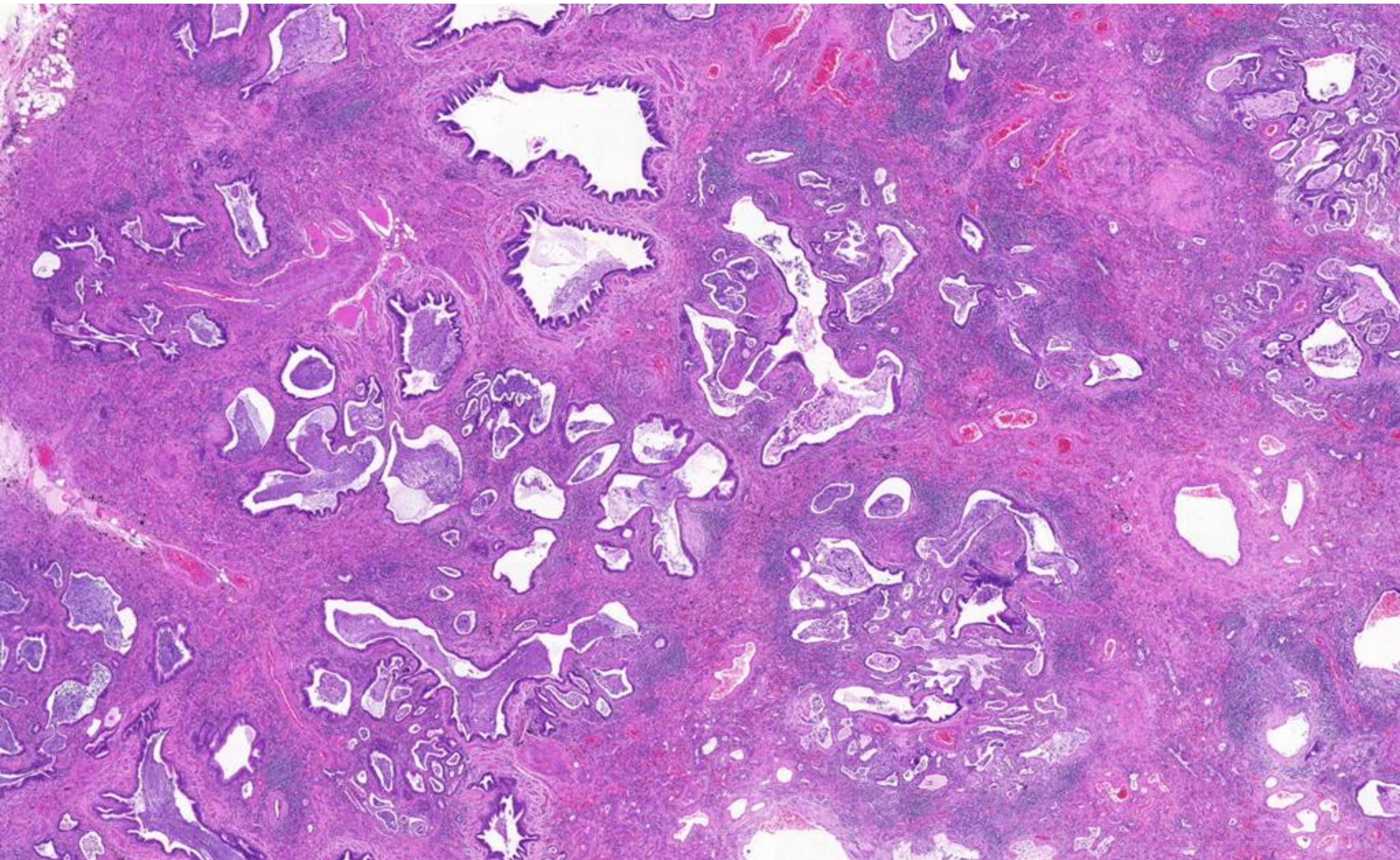
Absence of features against a diagnosis of UIP

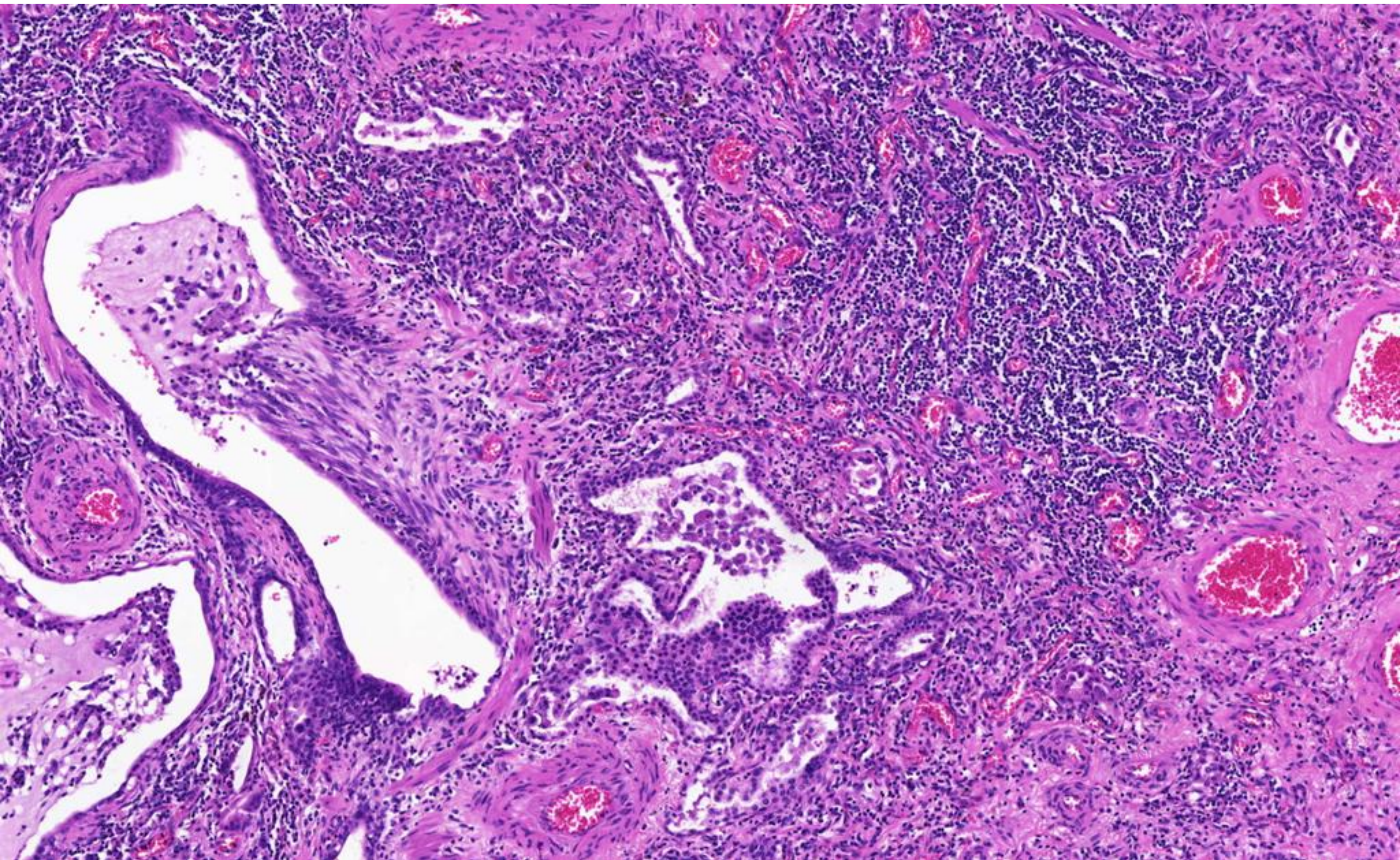
TABLE 5. HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN

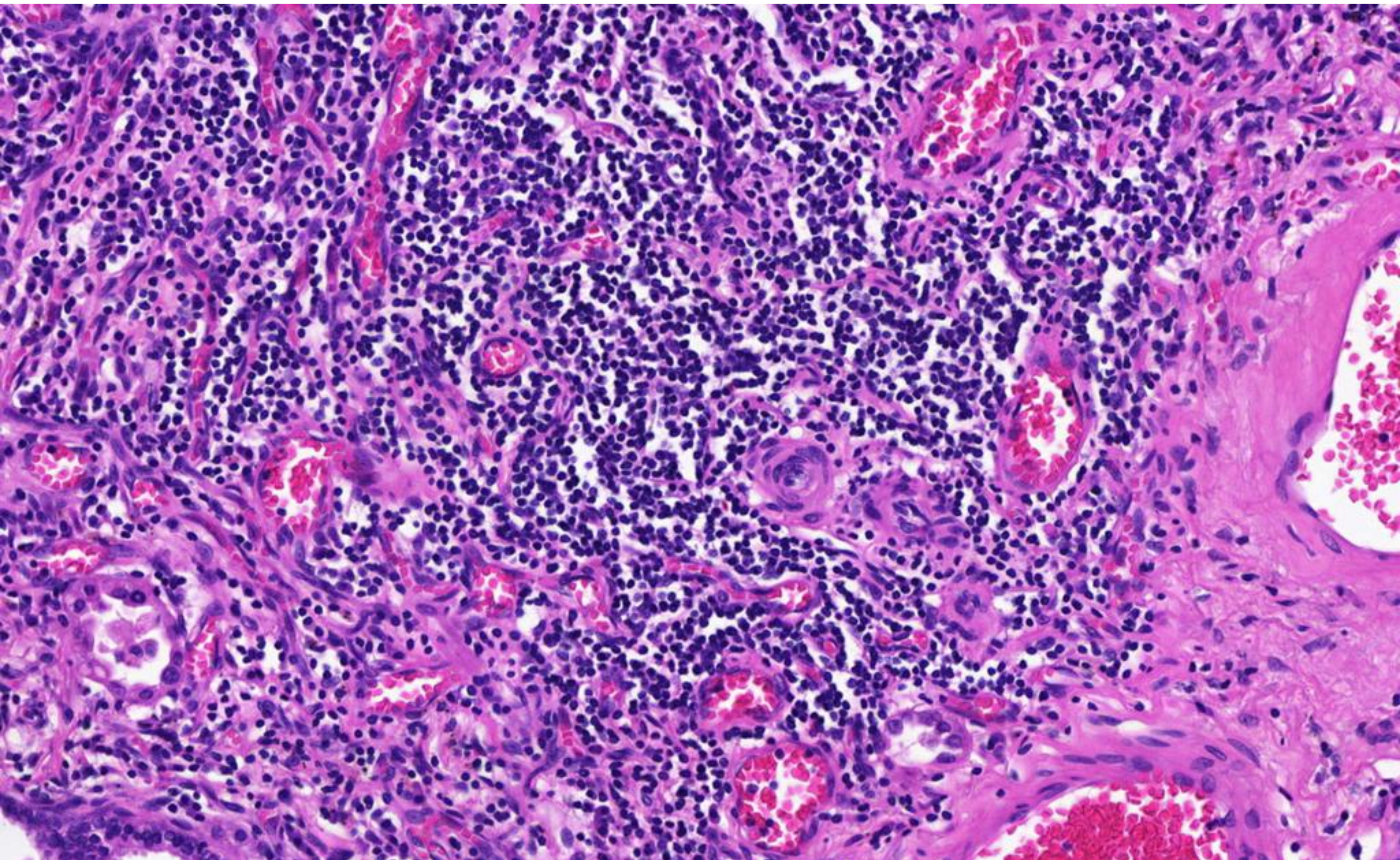
UIP Pattern (All Four Criteria)	Probable UIP Pattern	Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Criteria)
• Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution • Presence of patchy involvement of lung parenchyma by fibrosis • Presence of fibroblast foci • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)	• Evidence of marked fibrosis / architectural distortion, ± honeycombing • Absence of either patchy involvement or fibroblastic foci, but not both • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column) OR • Honeycomb changes only‡	• Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation • Absence of other criteria for UIP (*see* UIP PATTERN column) • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column)	• Hyaline membranes* • Organizing pneumonia*† • Granulomas† • Marked interstitial inflammatory cell infiltrate away from honeycombing • Predominant airway centered changes • Other features suggestive of an alternate diagnosis

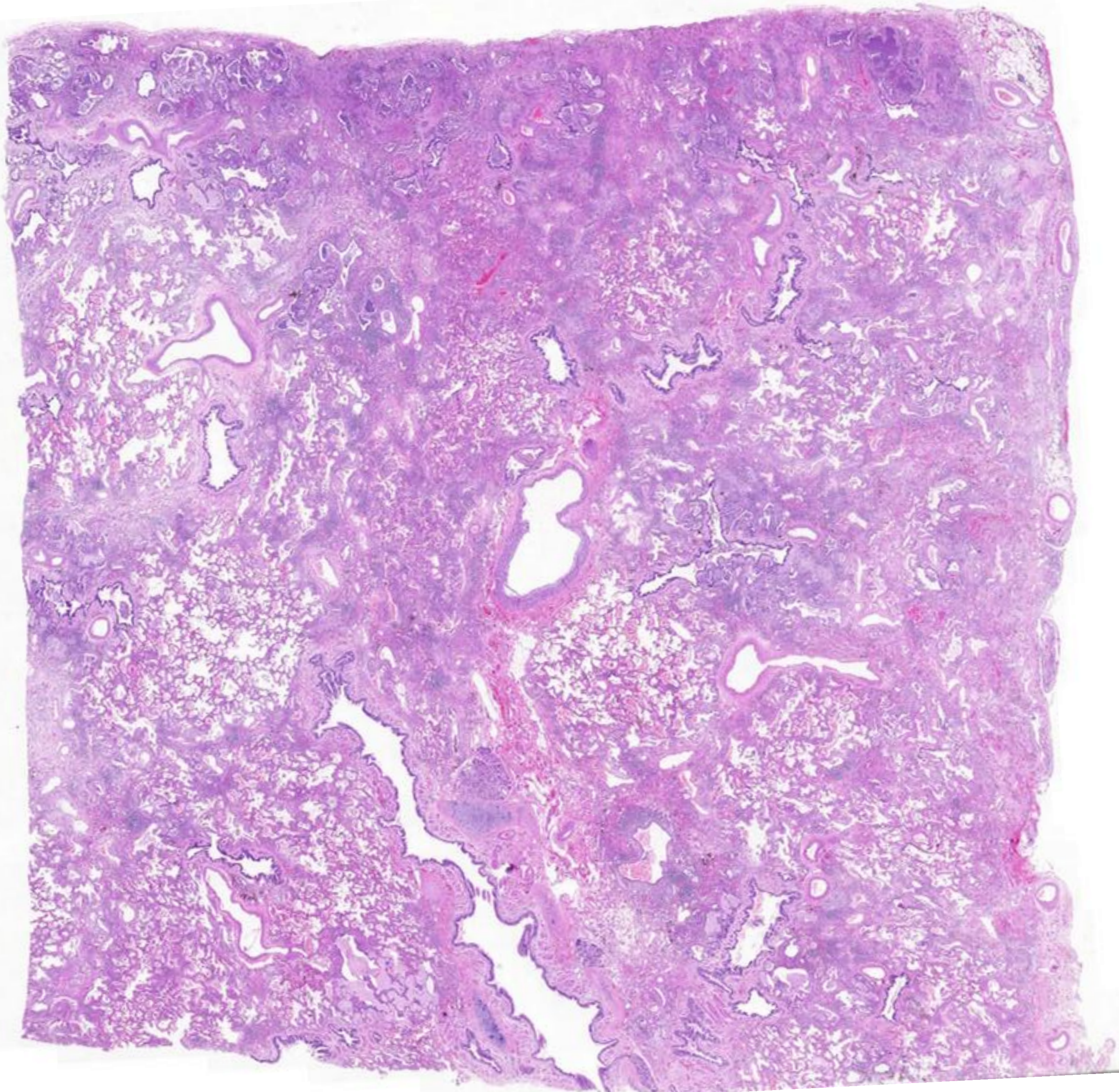
2014
Explanted lung

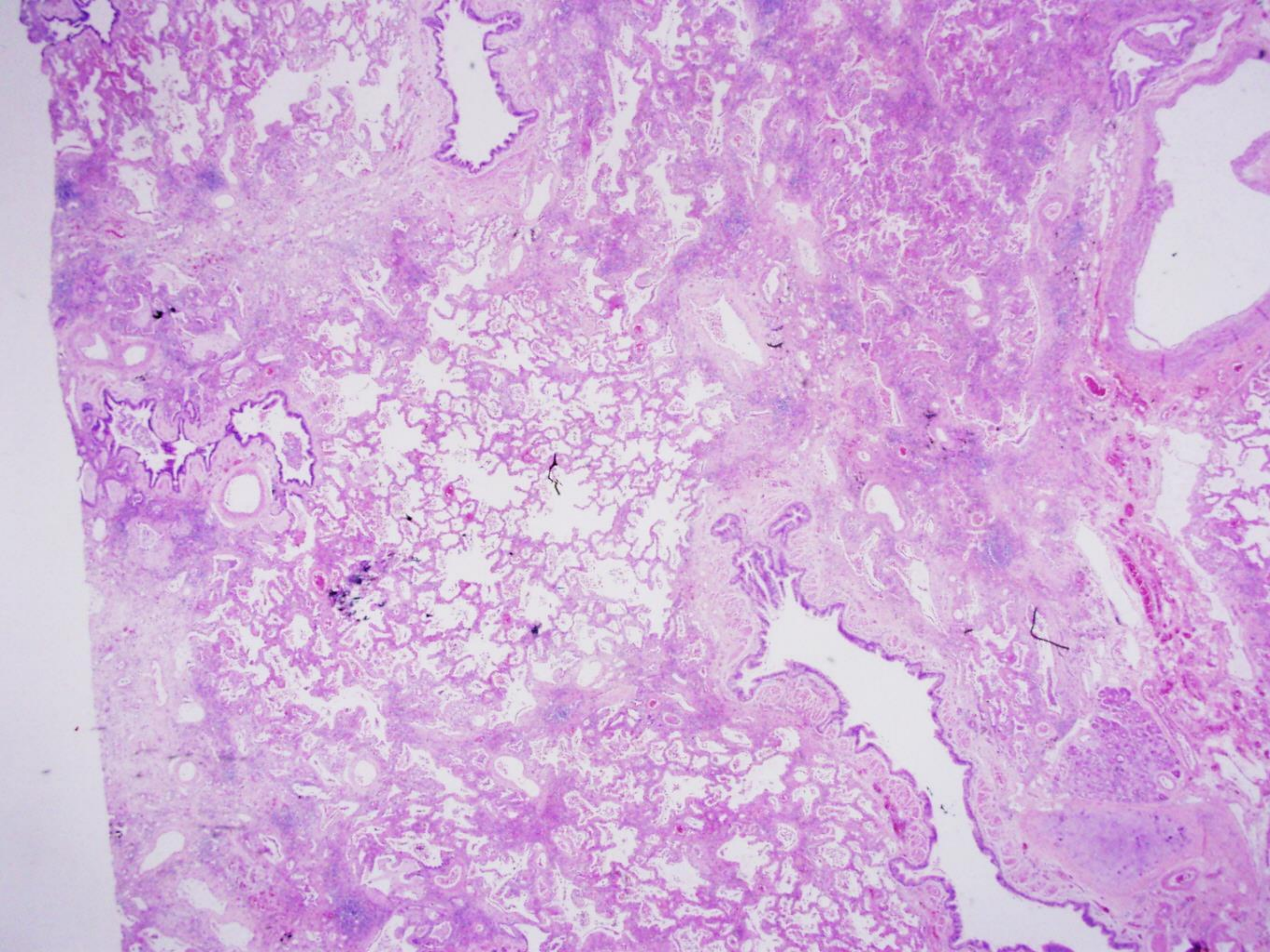


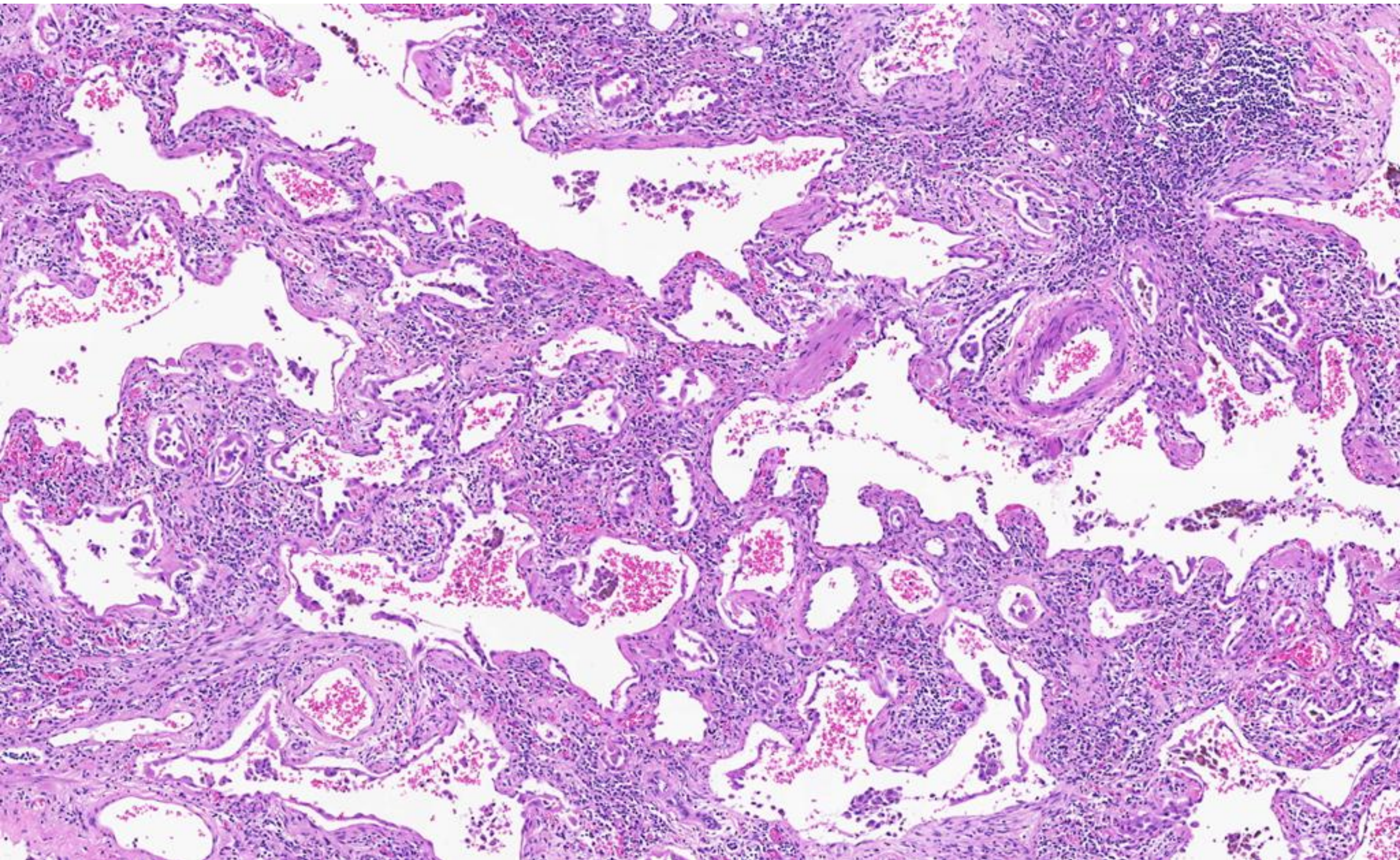


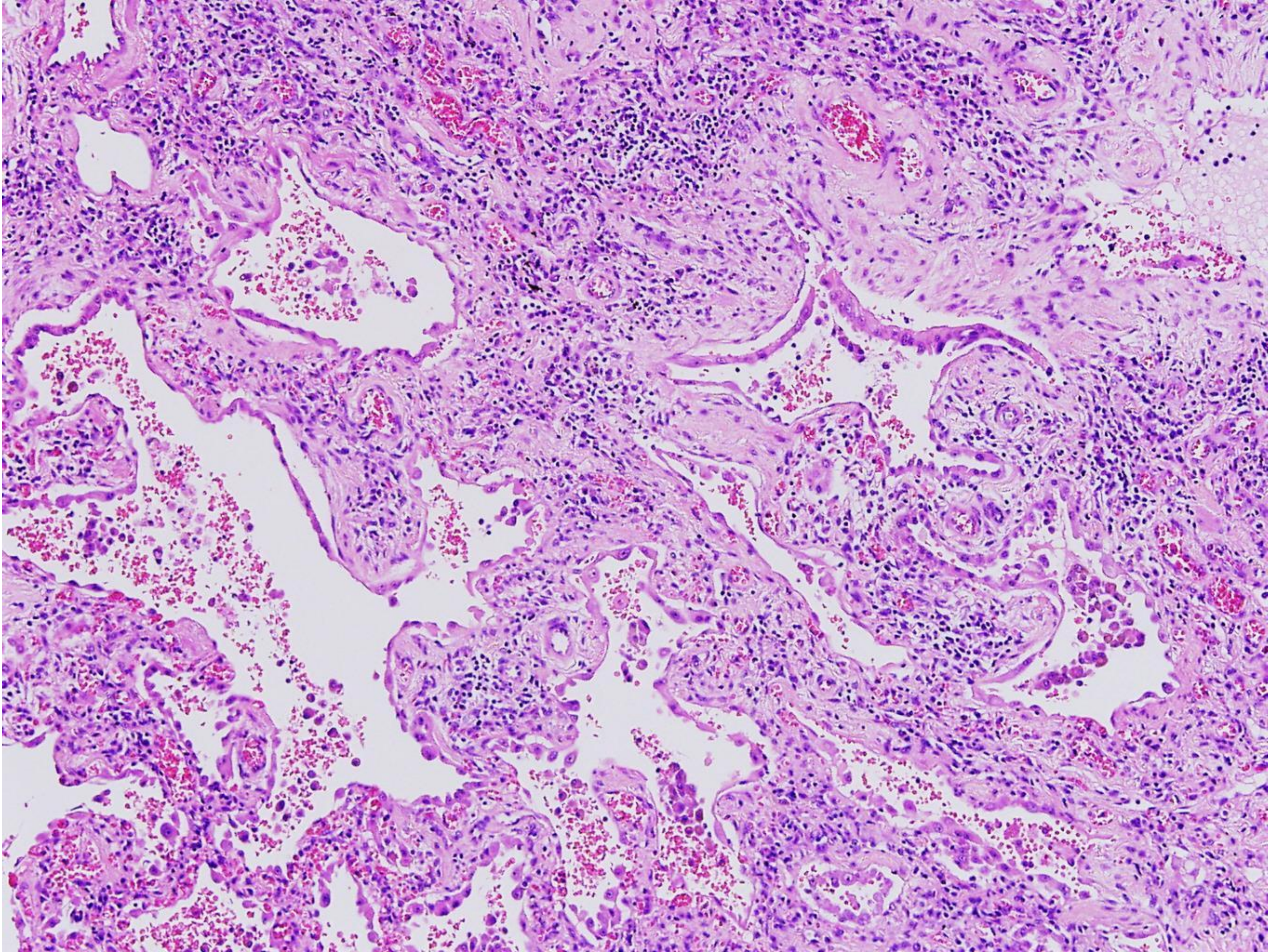


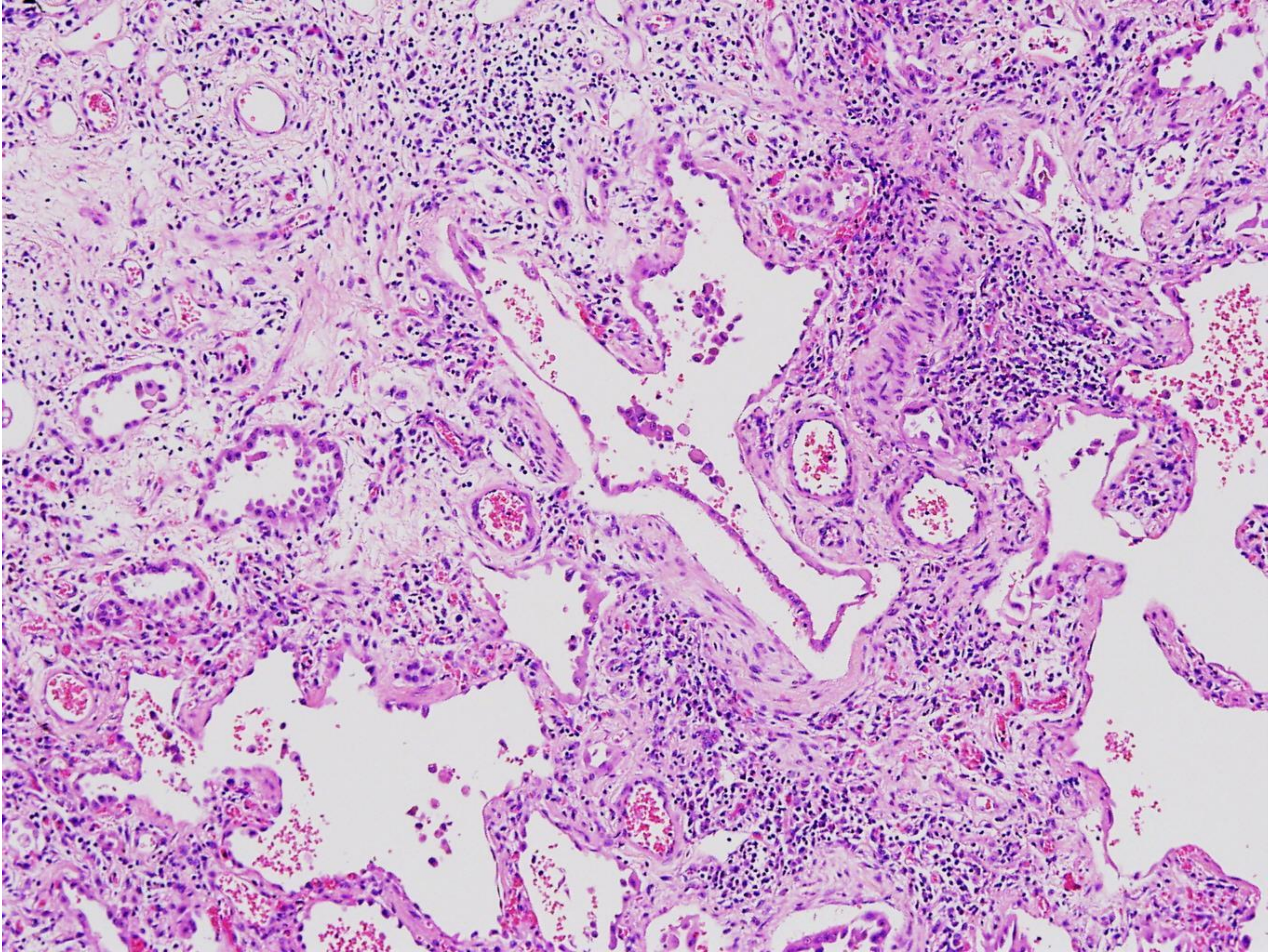


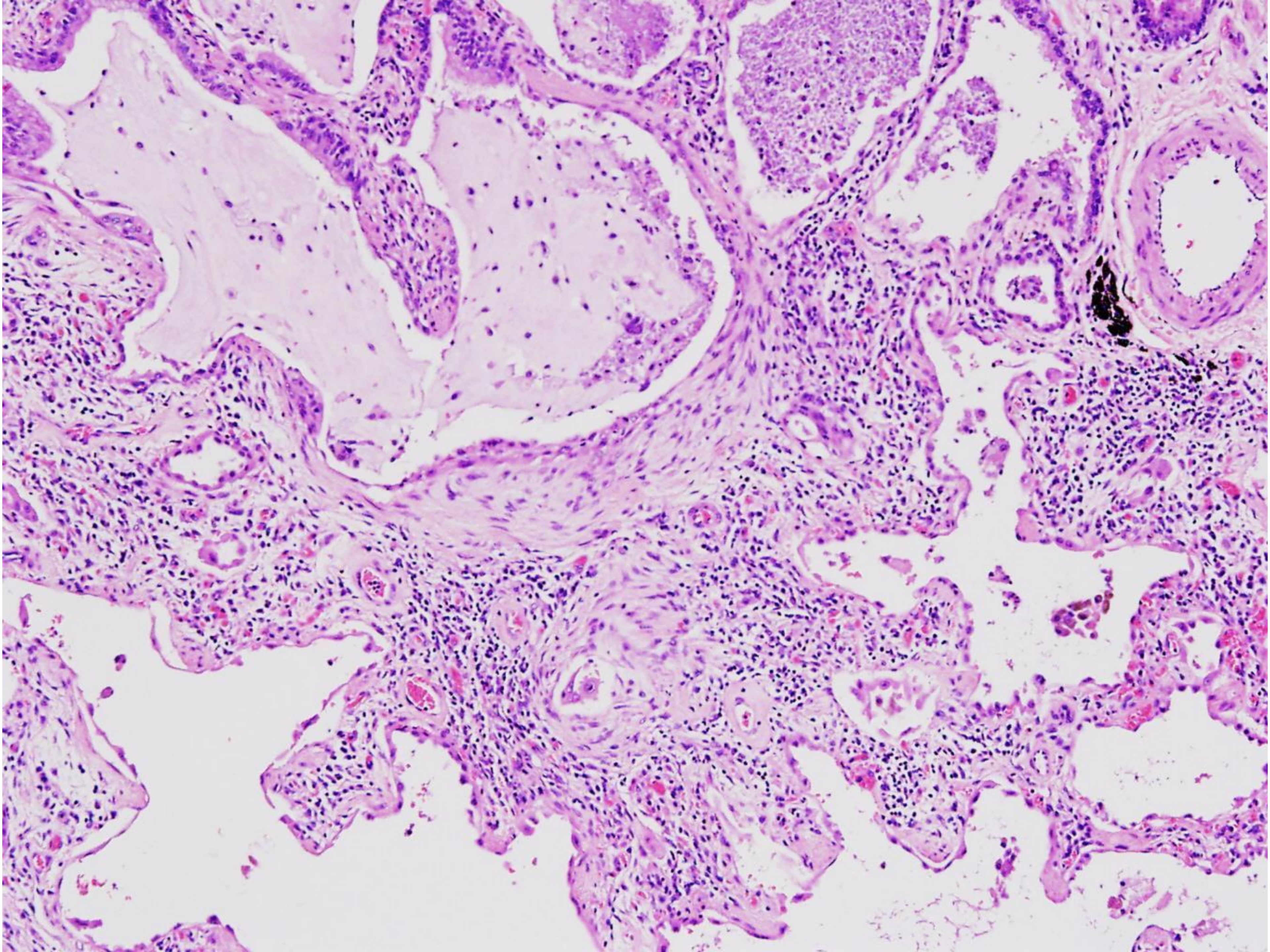


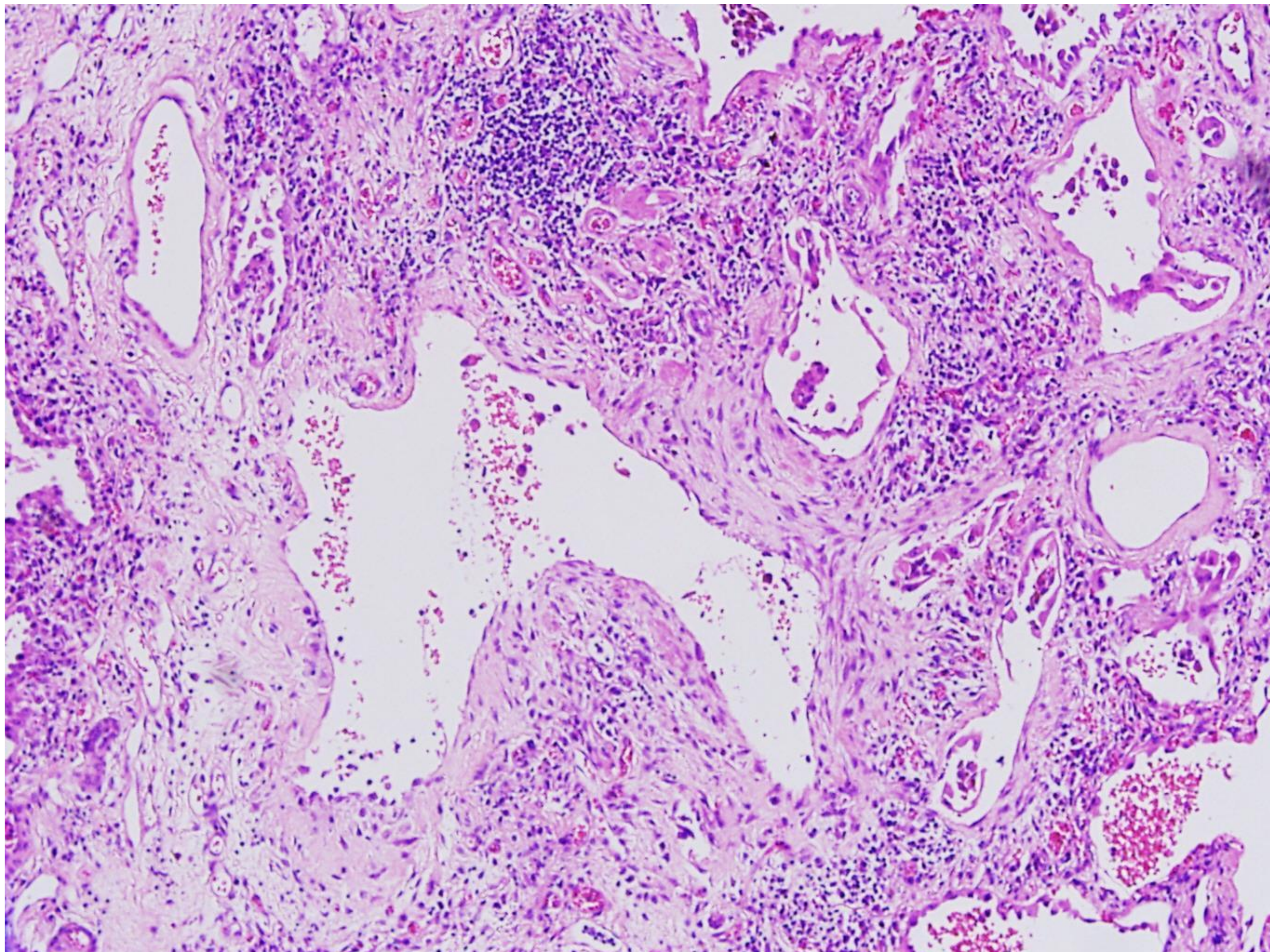


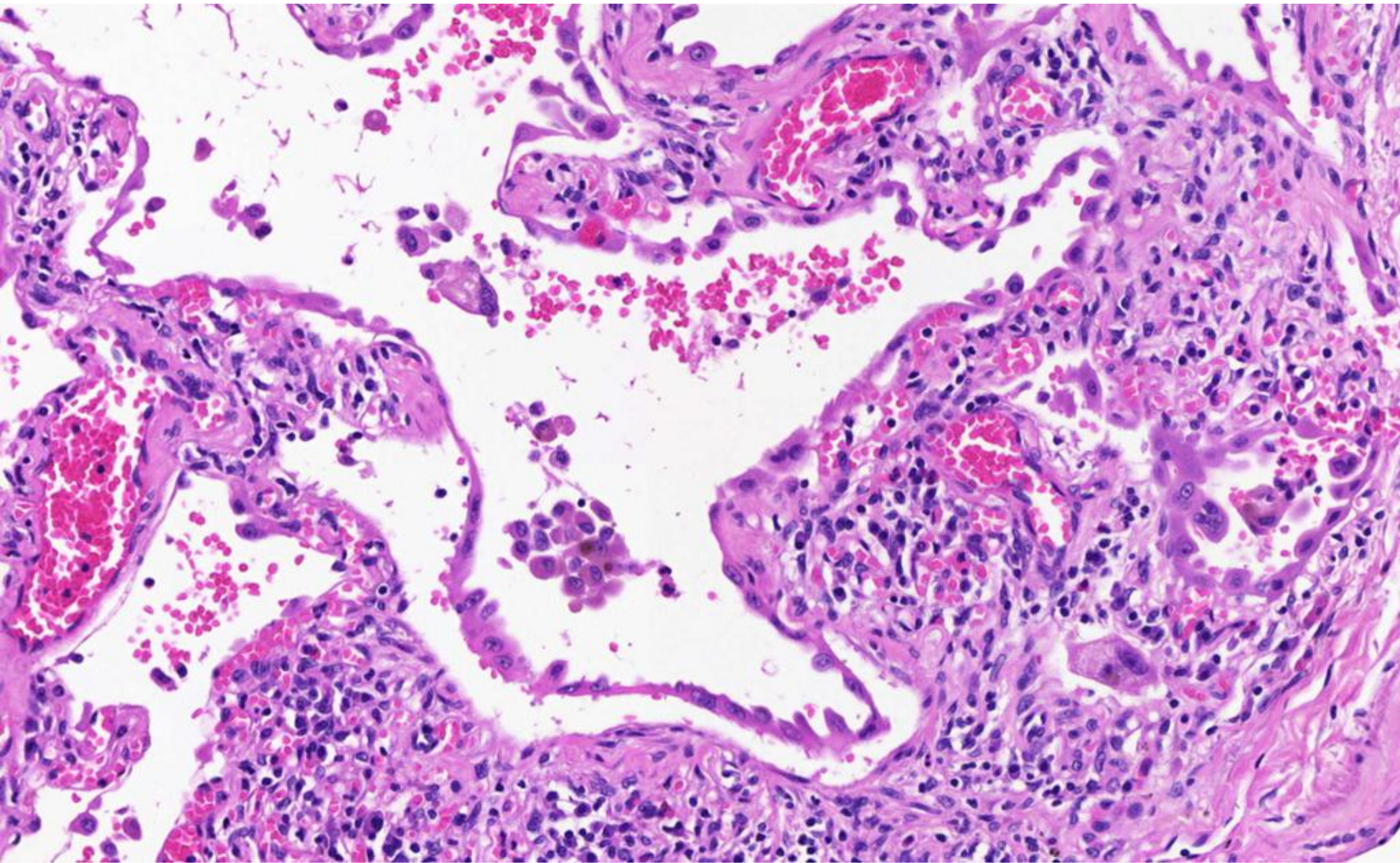


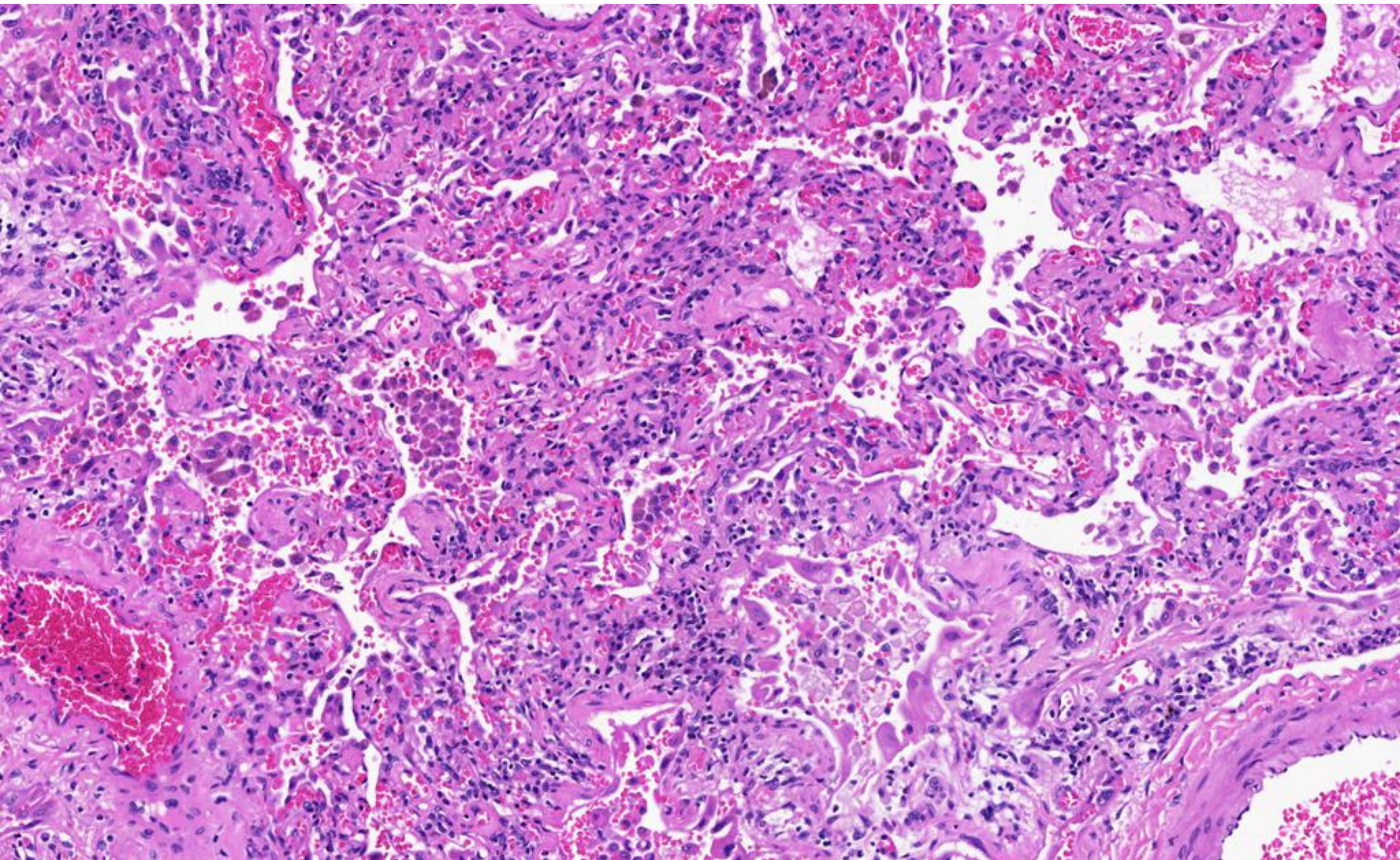


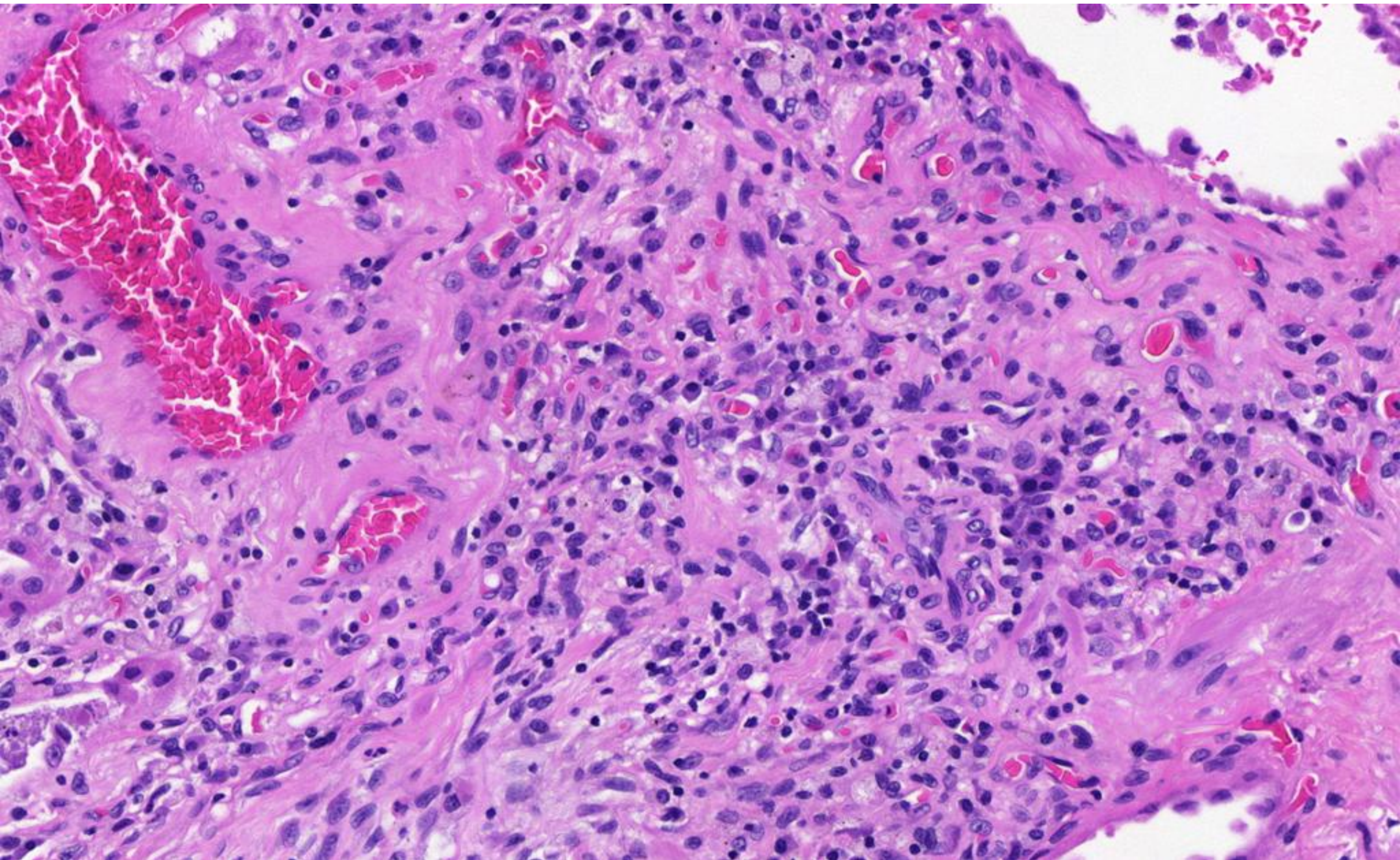












Diagnosis

- **Lung, explantation;**

  - Diffuse interstitial pneumonia

  with 1) marked microscopic honeycomb change

  2) marked fibroblastic foci

  3) atypical type II pneumocytes hyperplasia

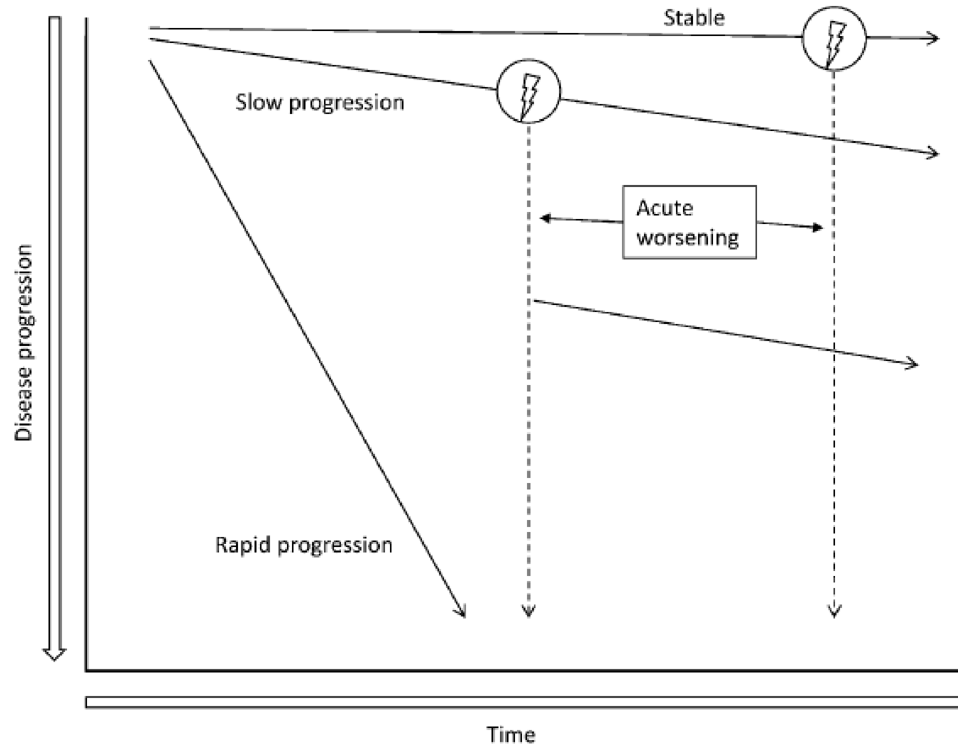
  4) marked interstitial lymphoplasmacytic infiltration and lymphoid aggregation

  5) focal ring fibrosis

  6) absence of hyaline membrane

c/w usual interstitial pneumonia with focal organizing phase of acute lung injury pattern.

Acute exacerbation of UIP/IPF



Mixed pattern of UIP and Diffuse alveolar damage

Diagnostic Criteria
Previous or concurrent diagnosis of Idiopathic Pulmonary Fibrosis *
Unexplained worsening or development of dyspnea within 30 days
High-resolution computed tomography with new bilateral ground glass abnormality and/or consolidation superimposed on Usual Interstitial Pneumonia pattern†
No evidence of infection by endotracheal aspirate or bronchoalveolar lavage‡
Exclusion of alternative causes, including: • Left heart failure • Pulmonary embolism • Identifiable cause of acute lung injury § (drug, pneumothorax, infection)

Patients with idiopathic clinical worsening who fail to meet all five criteria due to missing data should be termed “suspected acute exacerbations.”

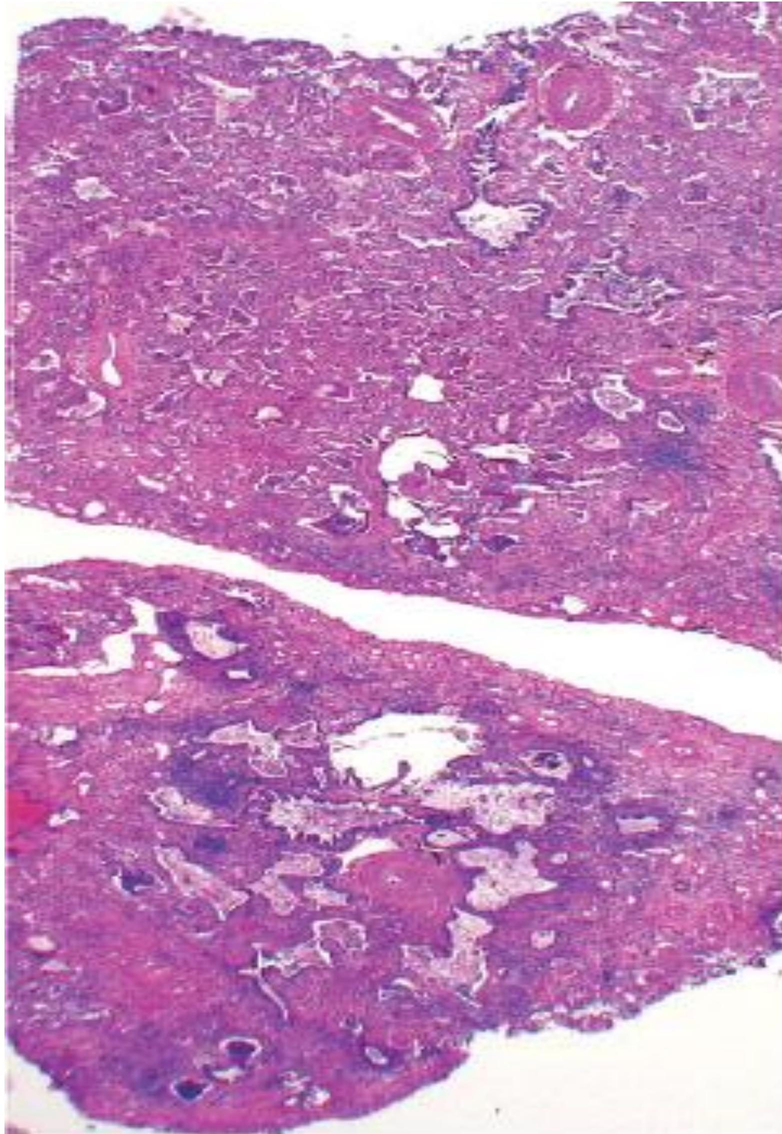
Am J Respir Crit Care Med 2007 :176(7):636-43

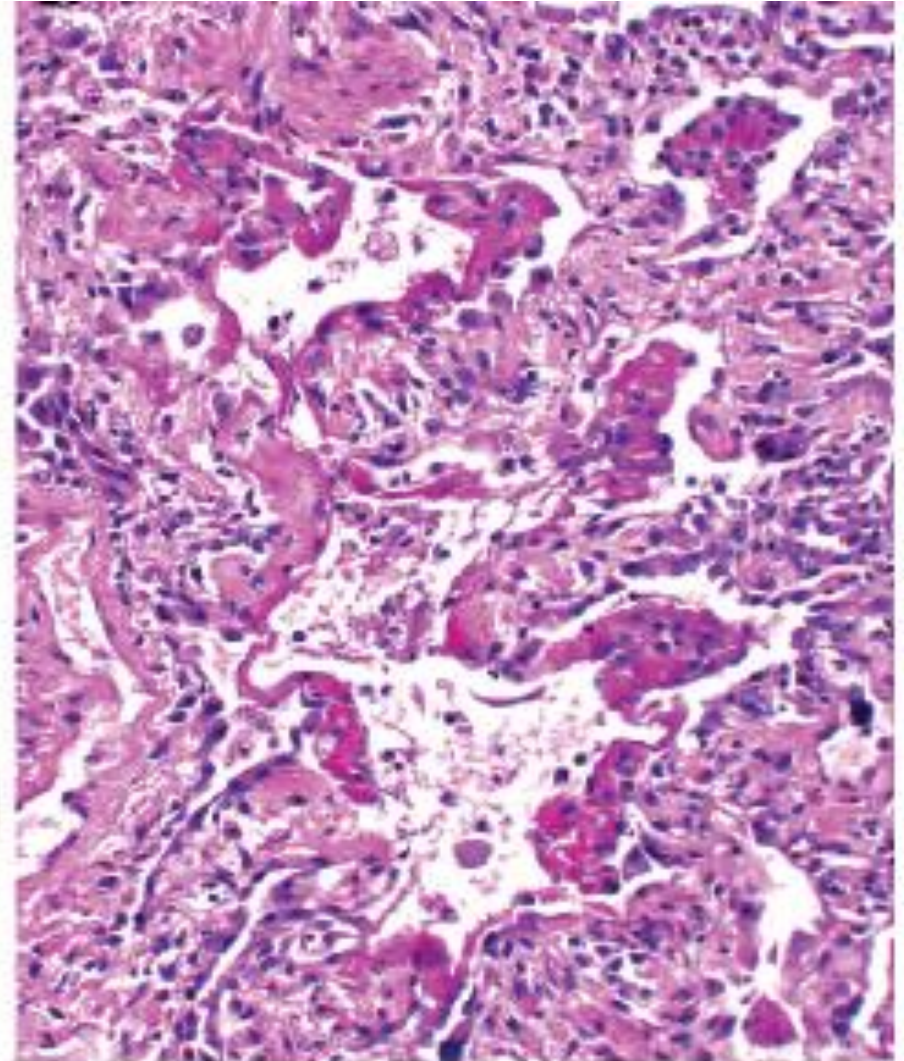
Histologic data on AE of UIP/IPF

- Diffuse alveolar damage (DAD) superimposed on underlying UIP is the most commonly described finding

- **DAD** was seen in 72%
  - in all but one associated with underlying UIP.
- **Organizing pneumonia** without other evidence of organizing DAD is seen in 12%
- Four specimens have been characterized as showing "active" (1) or "extensive" (3) **fibroblast foci**

Histologic finding on AE of UIP/IPF





Arch Pathol Lab Med 2012: 136:1234-1241

Case 2

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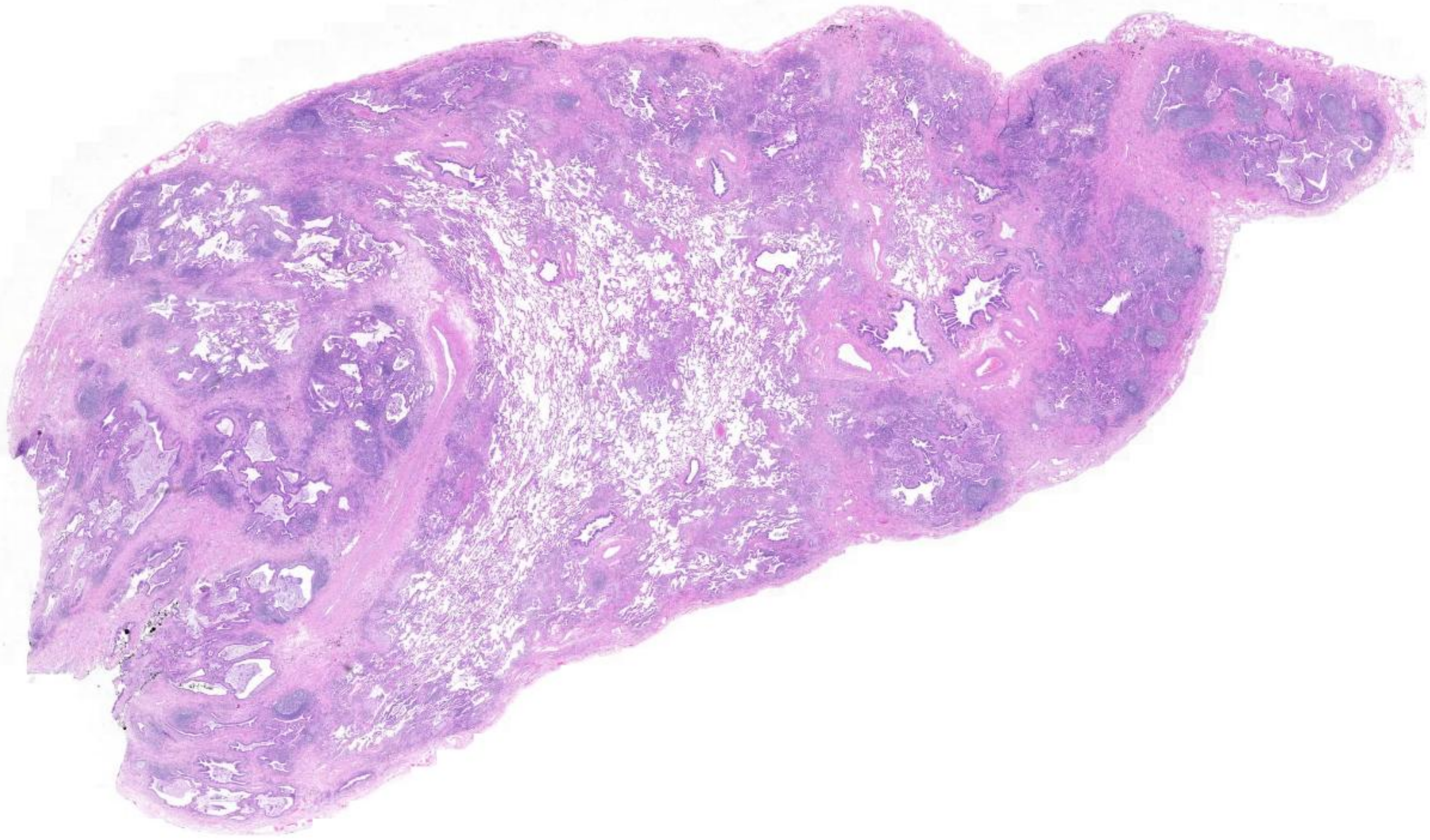
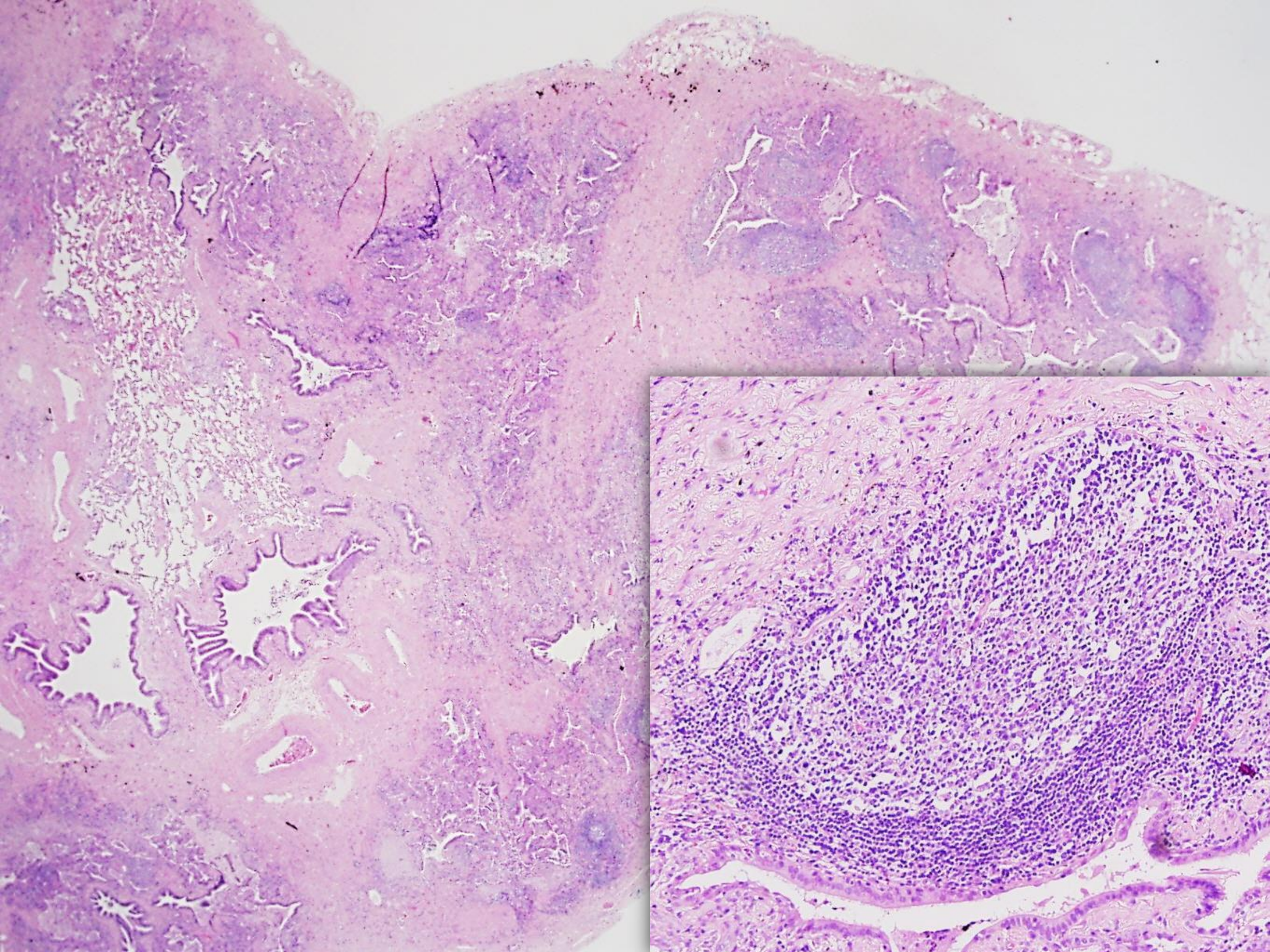
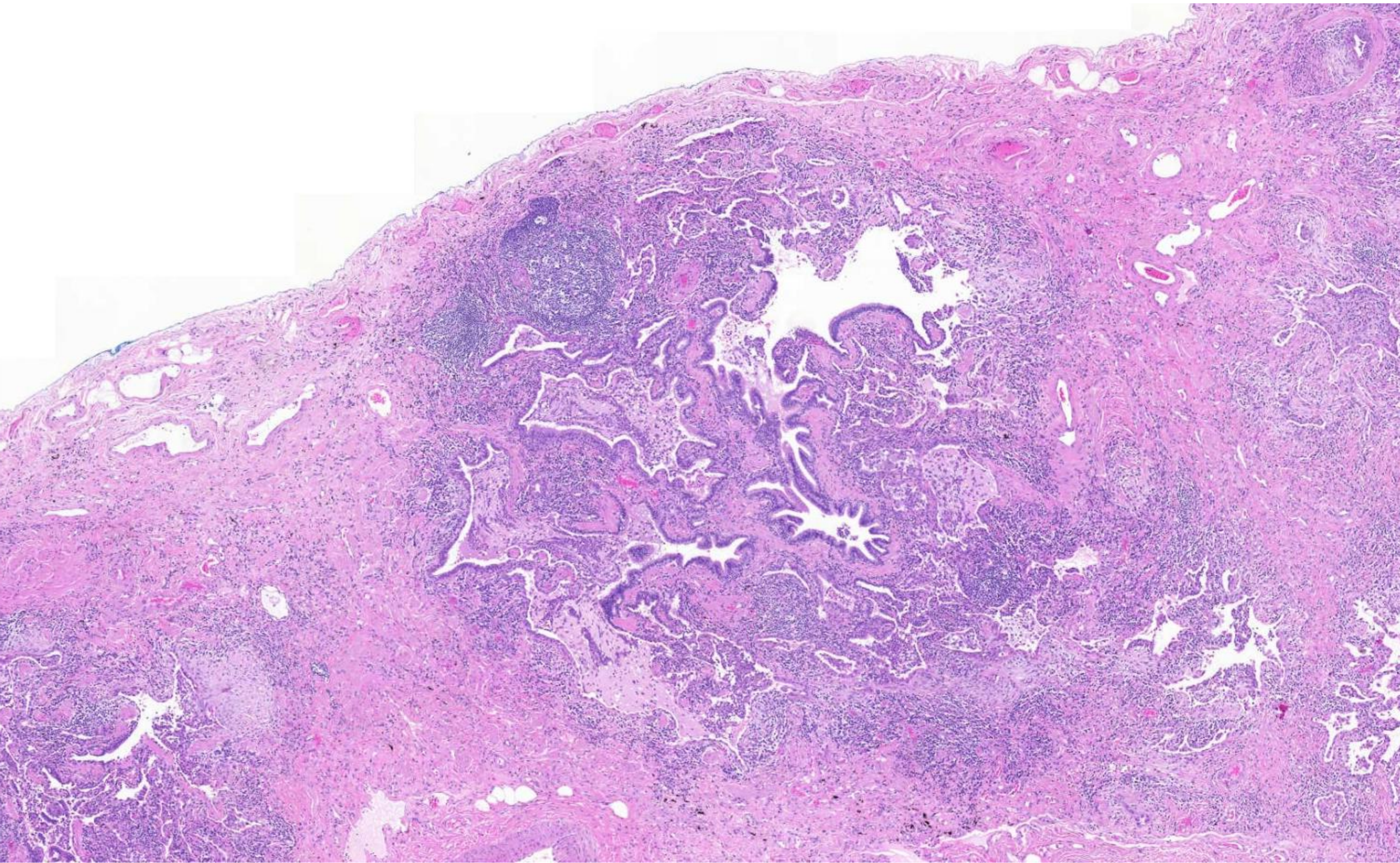
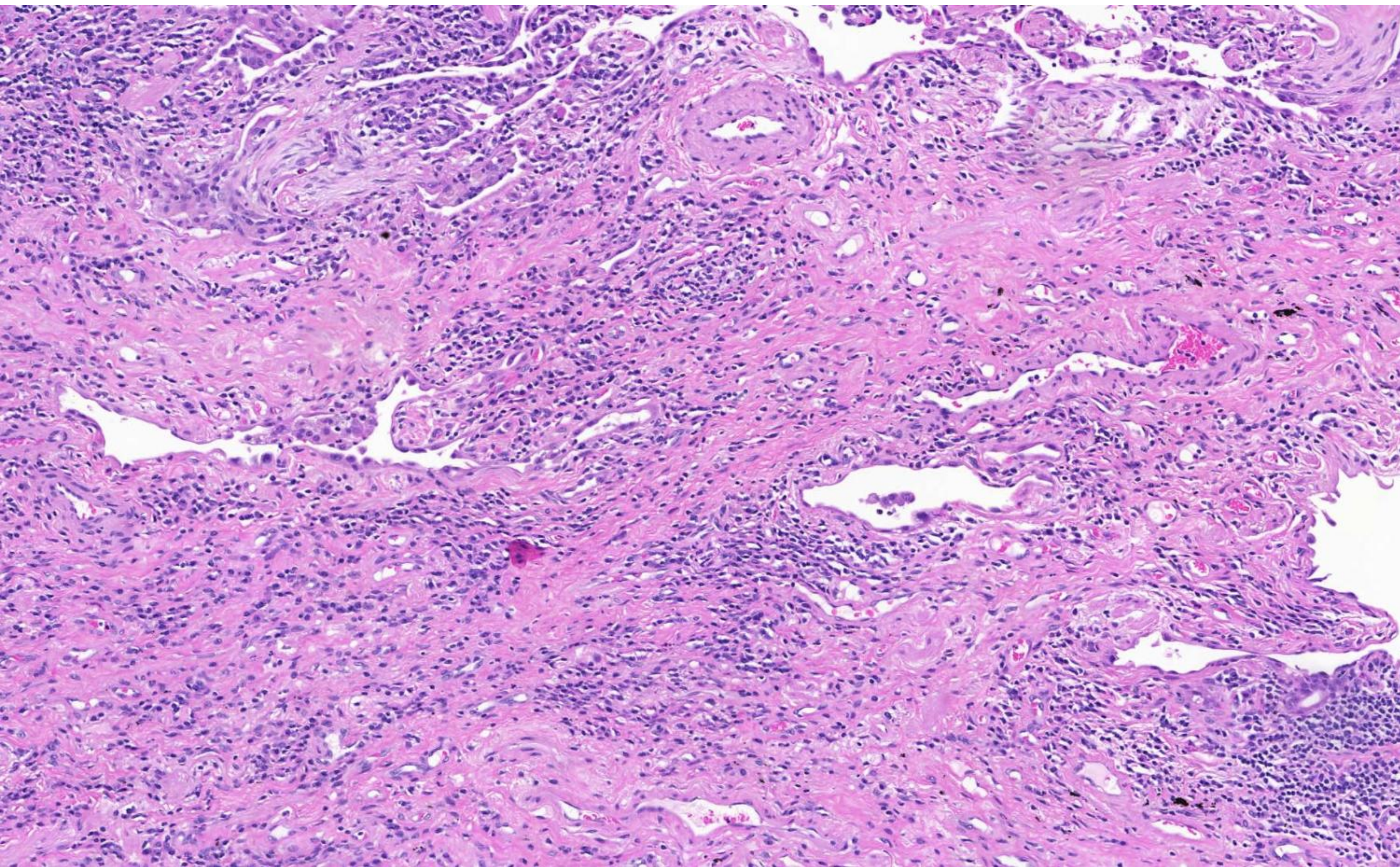
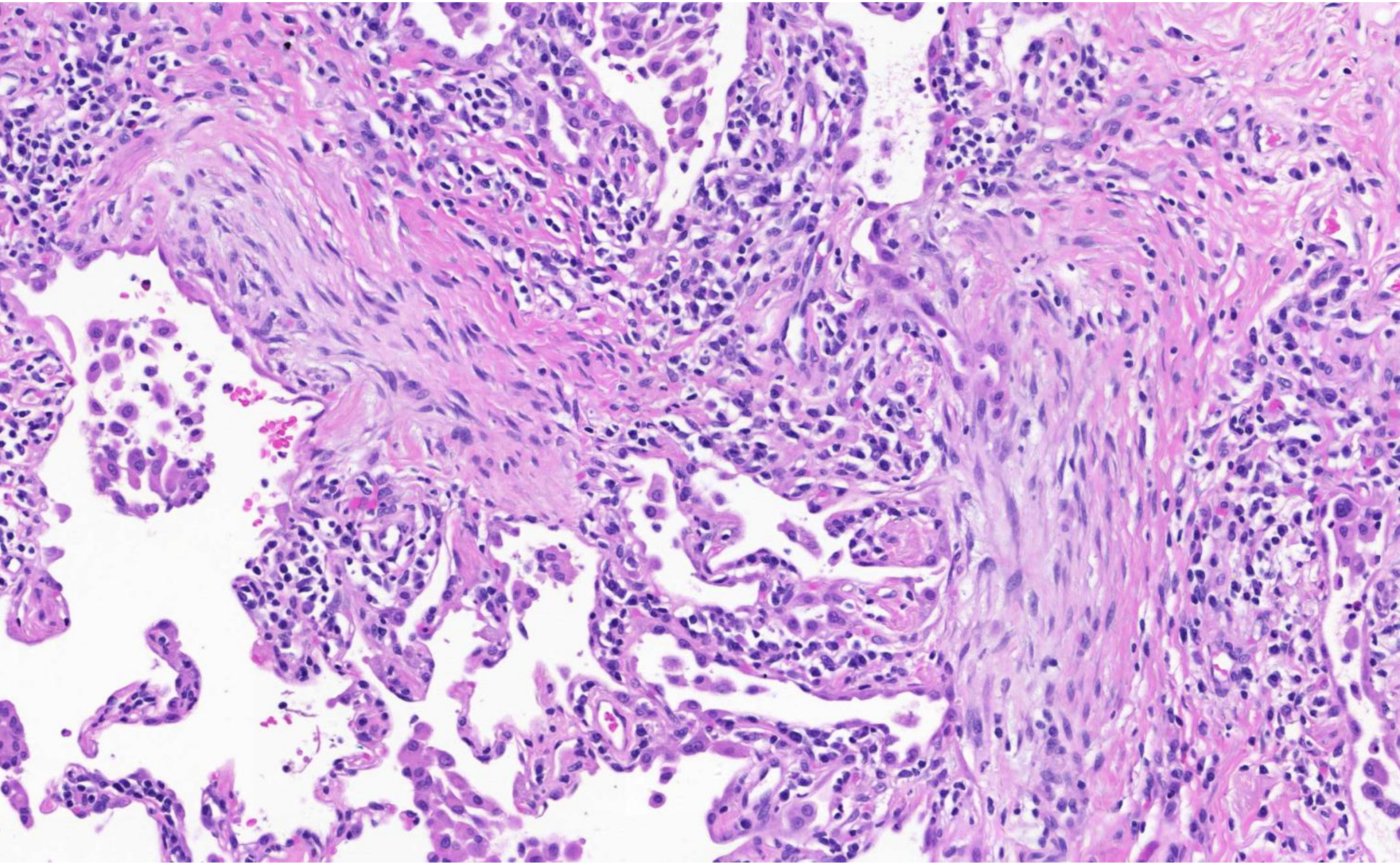
RLL

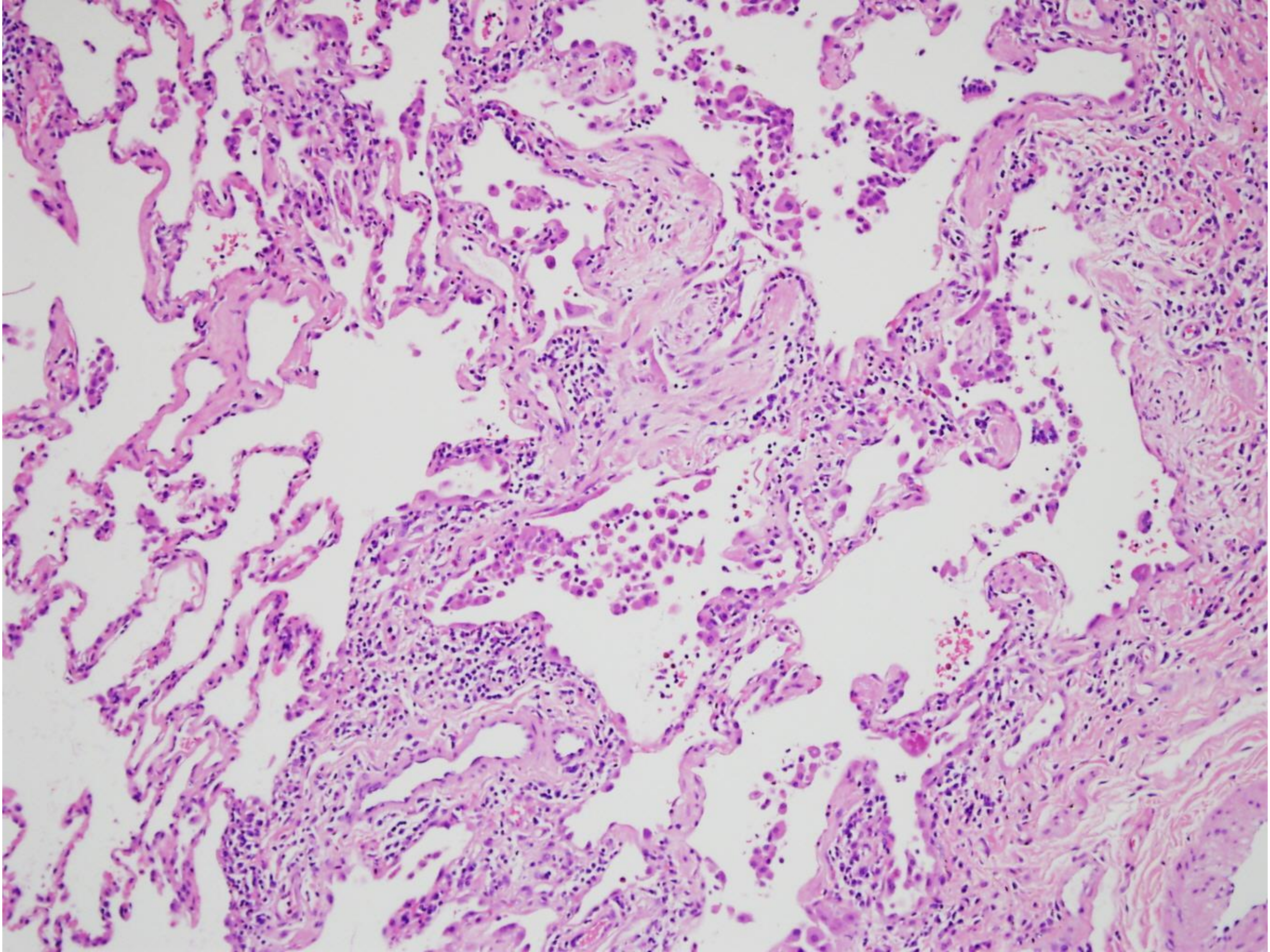


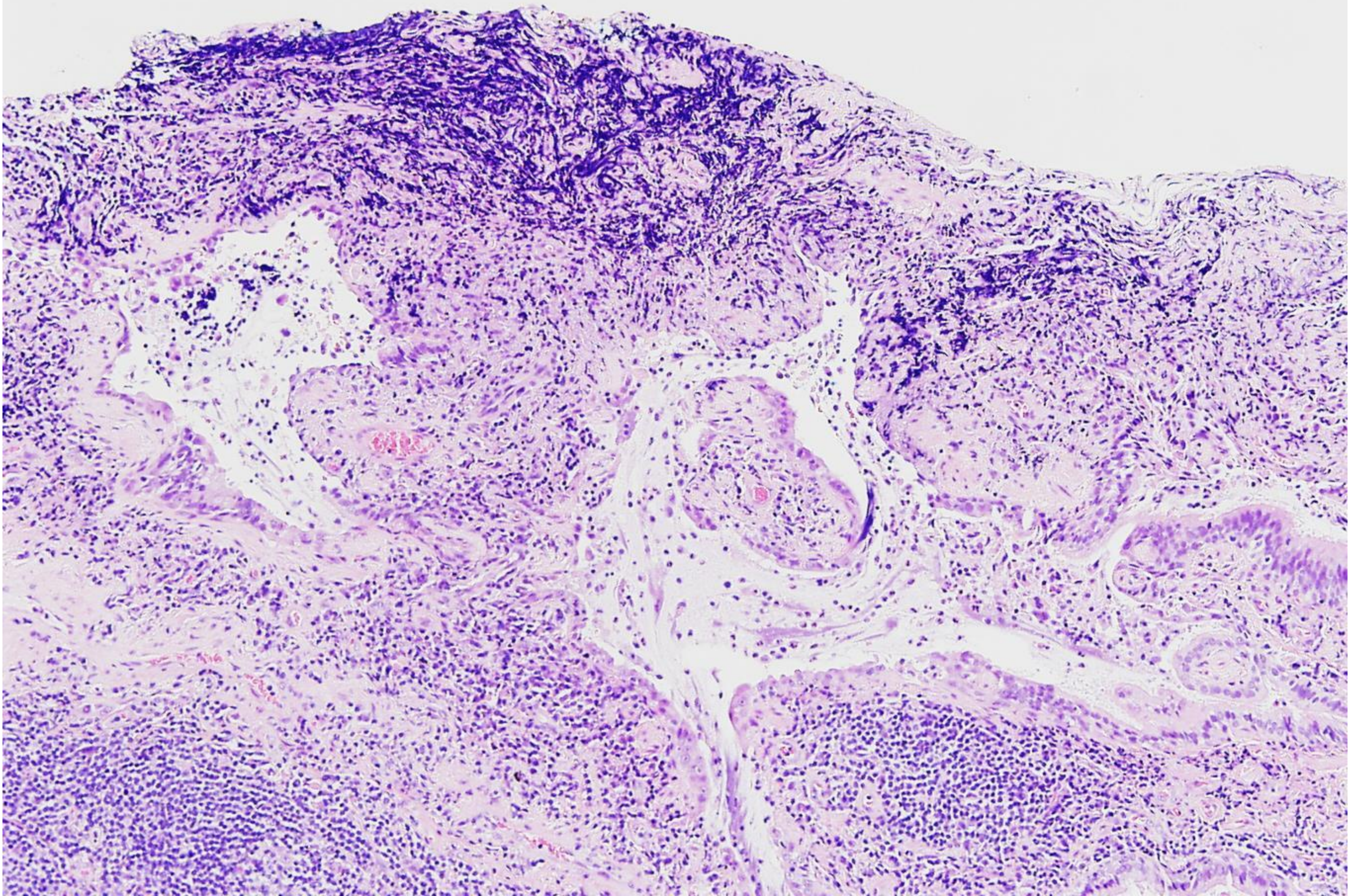


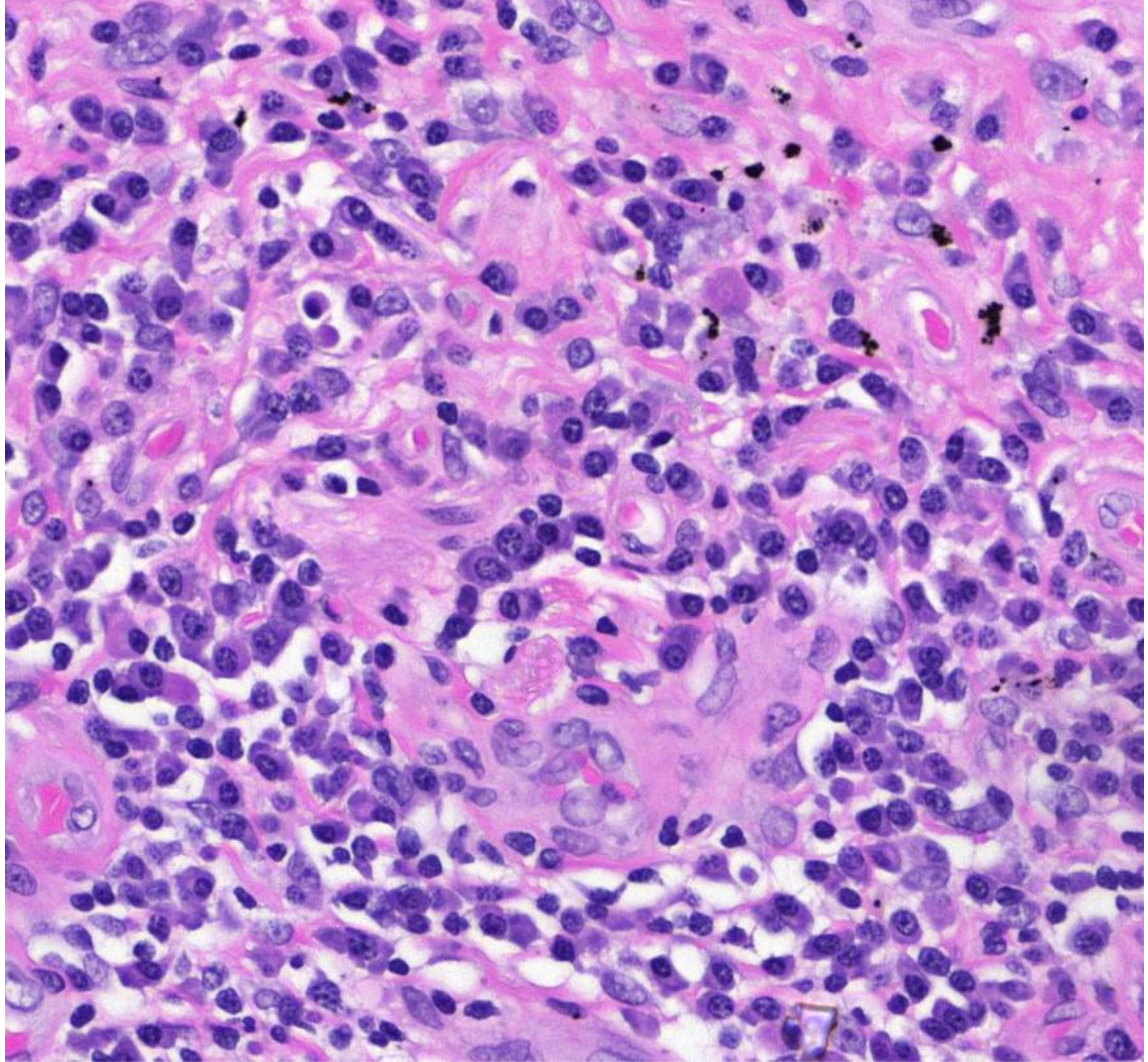


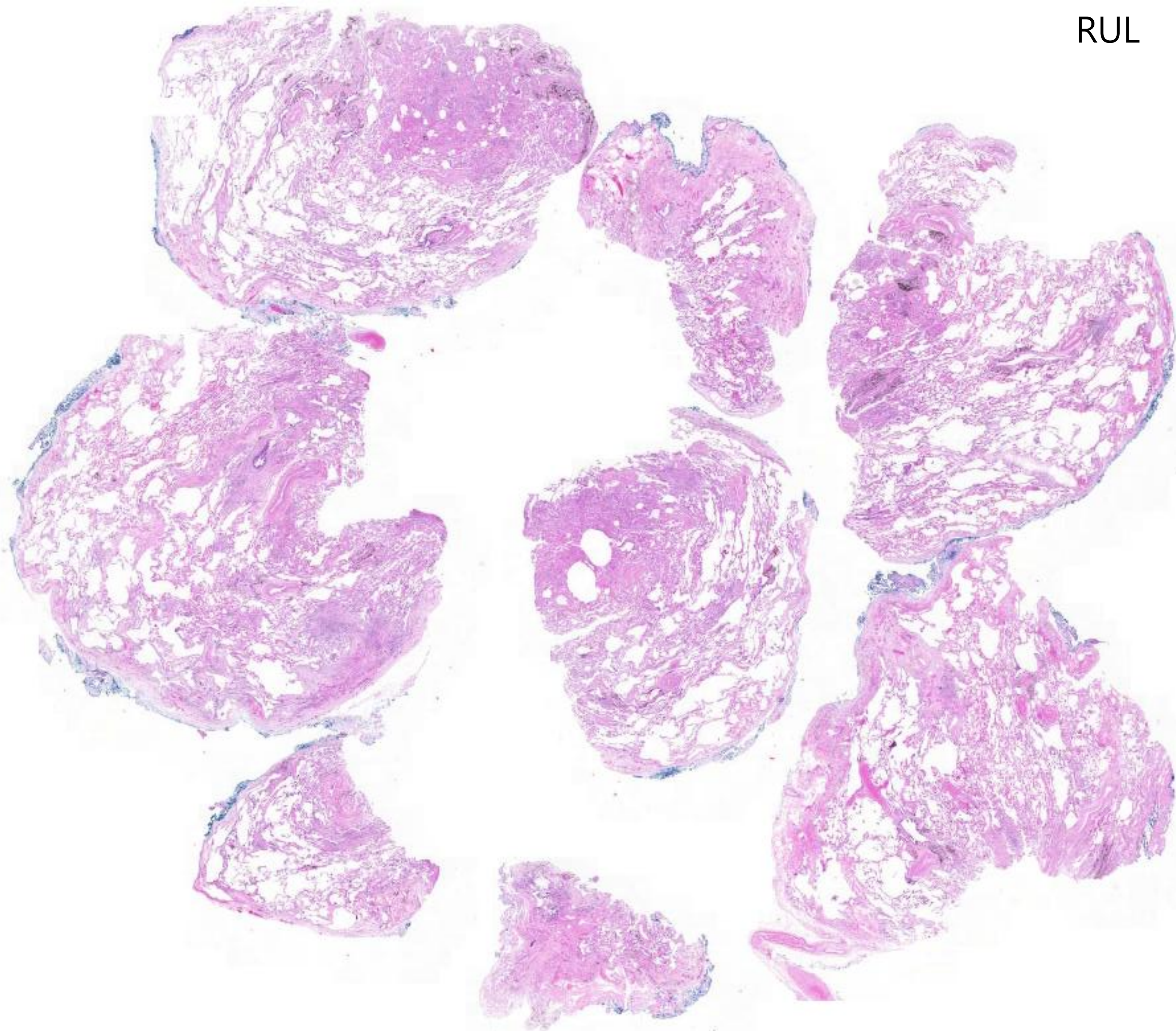








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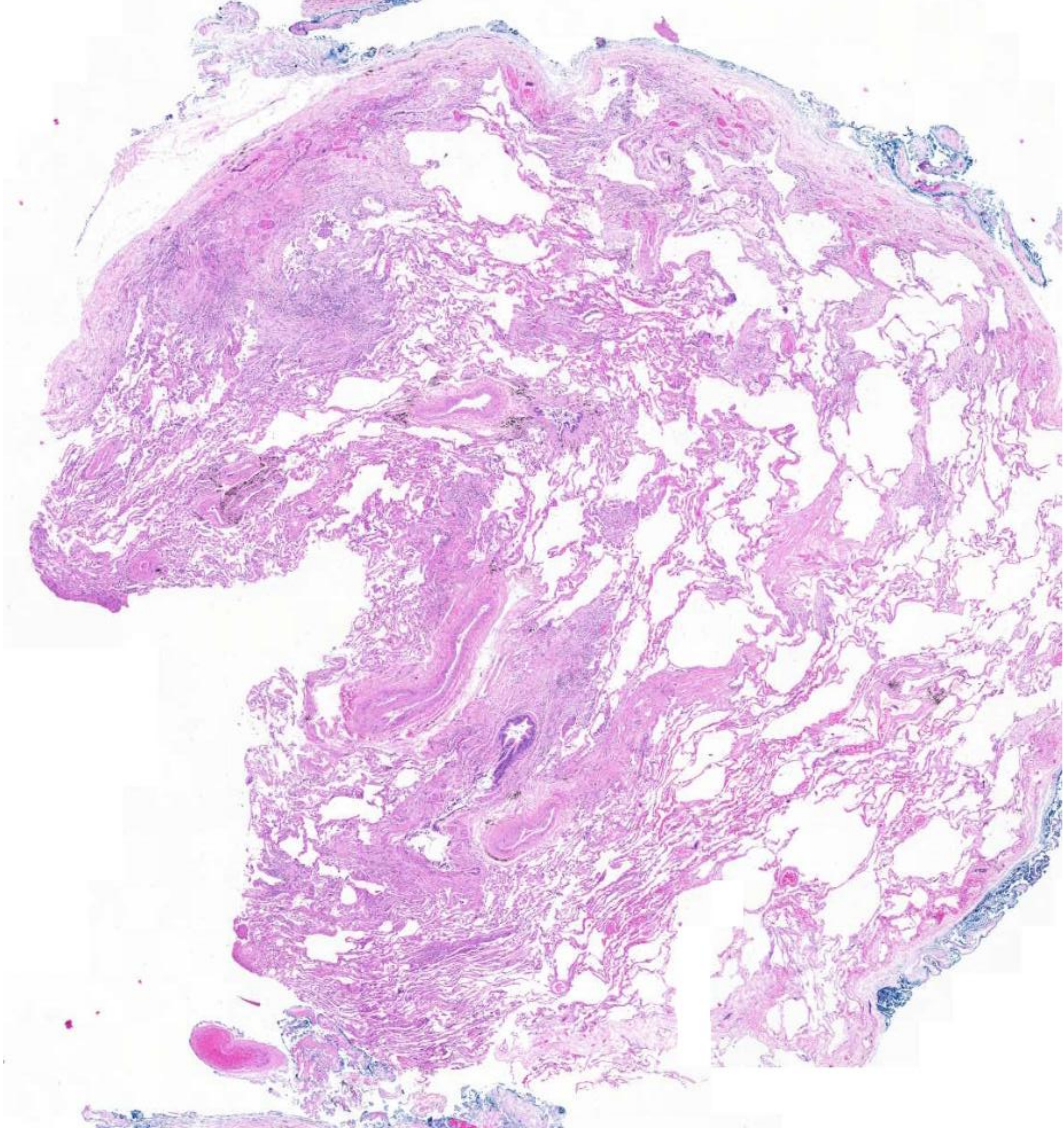
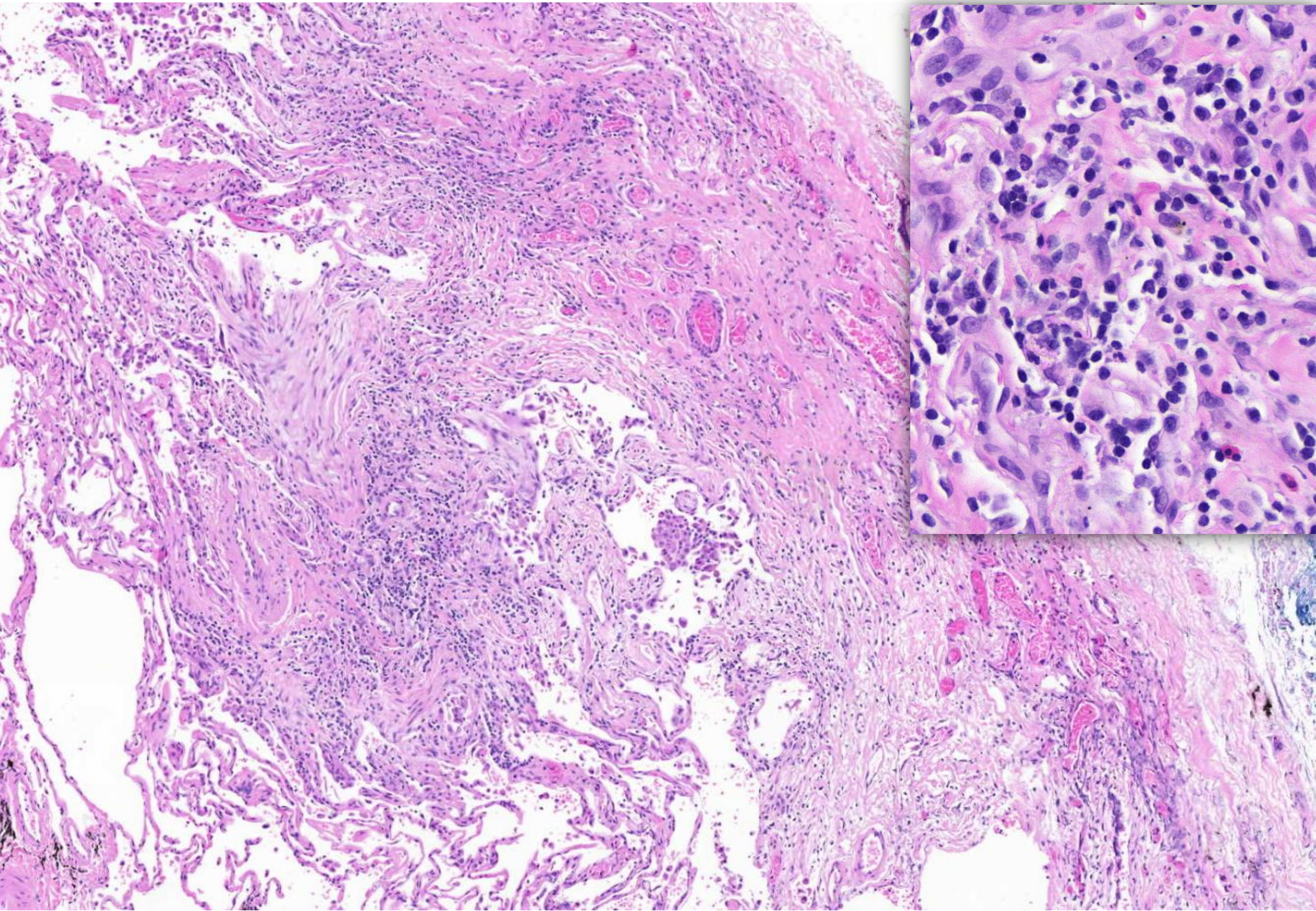


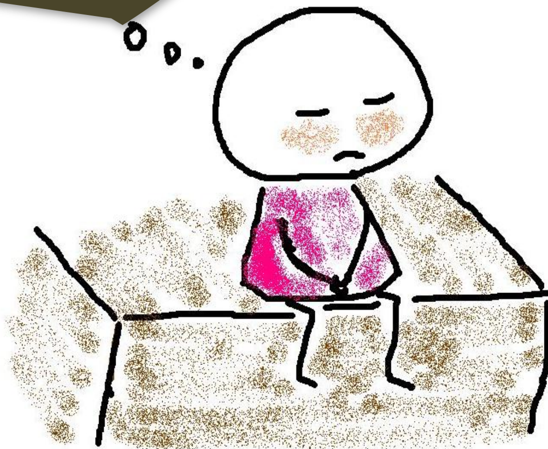


- **Subpleural fibrosis**
- **Heterogeneity**
- **Microscopic honeycomb change**
- **Fibroblastic foci**

일단은 UIP pattern인데,,

Lymphoid aggregation 과 germinal center 를 갖는 lymphoid follicle 이 많이 보이네....

- **환자의 혈액 검사 상 autoantibody 상태는?**
- **환자는 류마티스 증상은 없나?**



아무것도 없네..????
그래도
진단은 내야겠지?

Diagnosis

Lung, (right upper and lower lobe), wedge resection :

- Fibrosing and cellular interstitial pneumonia

with (1) subpleural predominancy

(2) spatial and temporal heterogeniety

(3) microscopic honeycomb change

(4) moderate fibroblastic foci

(5) moderate lymphoplasmacytic infiltration and lymphoid follicles

(6) chronic pleuritis

c/w usual interstitial pneumonia,

r/o connective tissue disease - associated interstitial pneumonia.

2012.12월 PIP joint pain & swelling

→ RF(+), anti-CCP(+)

(2011년 VATS시행 당시에는 negative)

→ 류마티스 내과에서 RA로 진단받음.

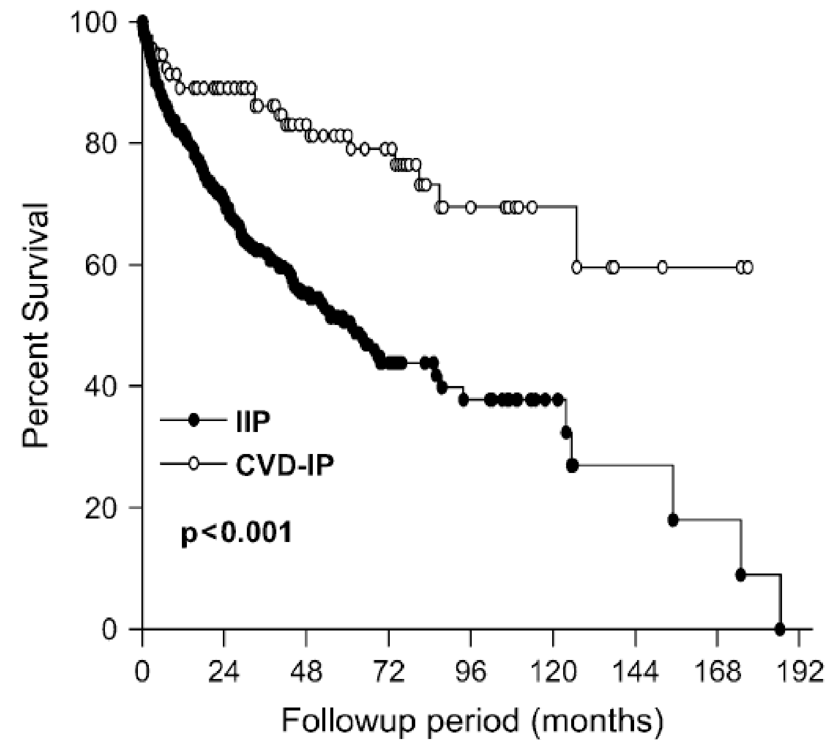
Idiopathic interstitial pneumonia (IIP) with connective tissue disease

1) **Interstitial lung disease in established connective tissue disease (CTD-ILD)**
2) Undifferentiated CTD (UCTD)
3) Lung dominant CTD (LD-ILD)
4) Interstitial disease with features of autoimmunity (IPAF)

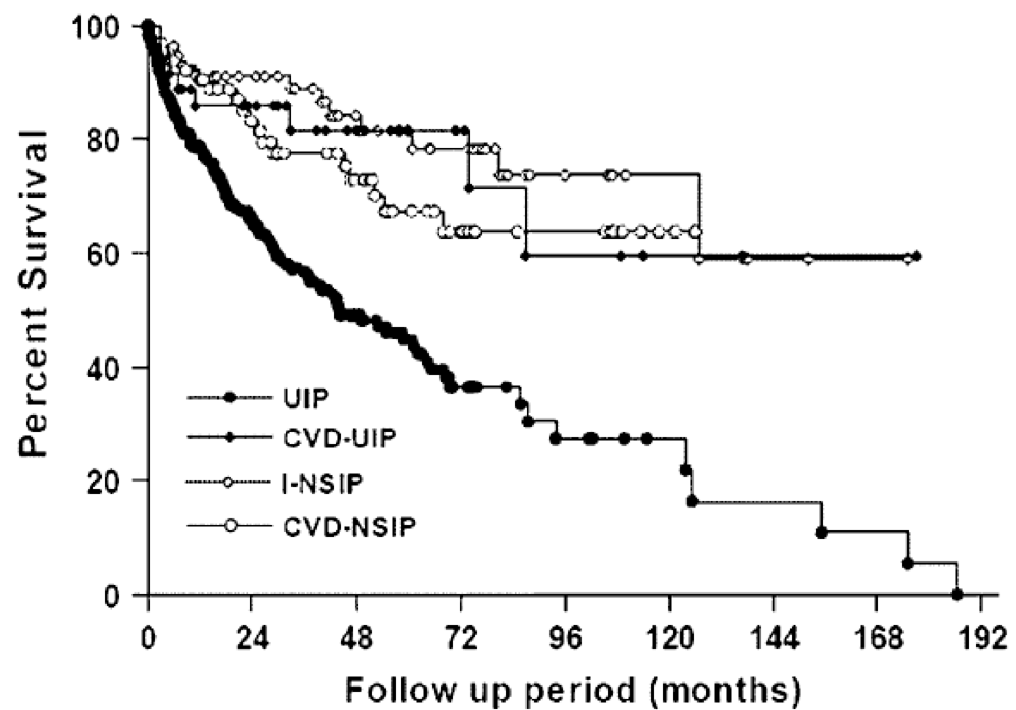
The prevalence of interstitial pneumonias in patients with connective tissue disease

	RA	SLE	SSc	PM/DM	SjS
UIP	++?	+/-	+	+	+/-
NSIP	++?	+?	+++	++	++
LIP/FB	++	+/-	-	-	++
OP	+	+/-	+/-	++	+/-
DAD	+	++	+/-	+/-	-
DIP/ RB	+/-*	-	+*	-	-

++ = frequent, + = not infrequent, +/- = rare;
? = prevalence currently uncertain;
* = Probable incidental to pulmonary symptoms



100
80
60
40
20
0
Percent Survival
IIP
CVD-IP
p<0.001
0
24
48
72
96
120
144
168
192
Followup period (months)



100
80
60
40
20
0
Percent Survival
UIP
CVD-UIP
I-NSIP
CVD-NSIP
0
24
48
72
96
120
144
168
192
Follow up period (months)

Pathologic and Radiologic Differences Between Idiopathic and Collagen Vascular Disease-Related Usual Interstitial Pneumonia

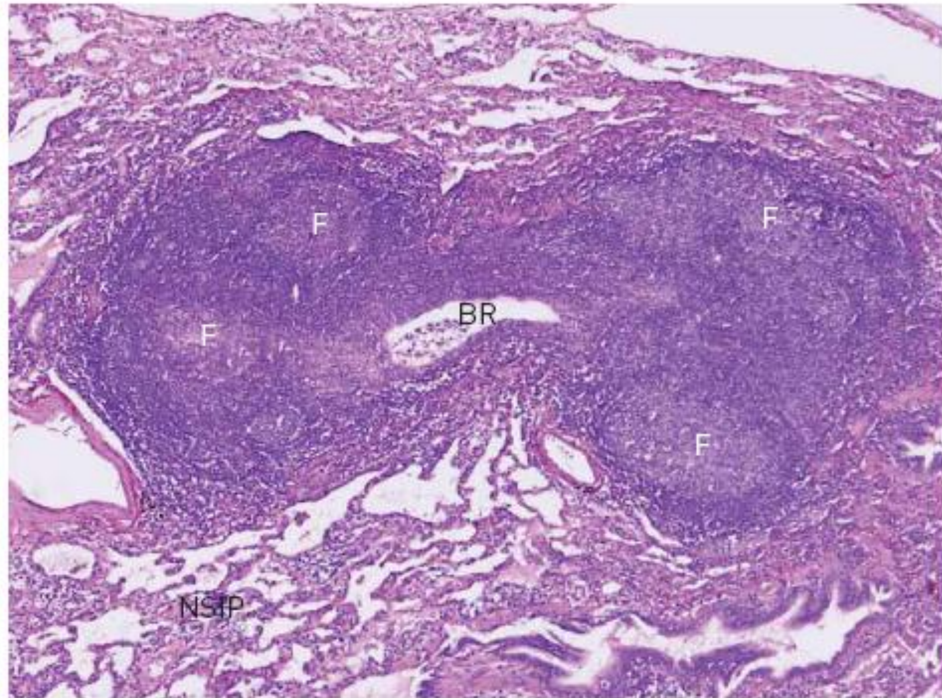
Jin Woo Song, MD; Kyung-Hyun Do, MD; Mi-Young Kim, MD; Se Jin Jang, MD; Thomas V. Colby, MD, FCCP; and Dong Soon Kim, MD, FCCP

CHEST 2009:136:23-30

Table 2—*Comparison of Pathologic Scores Between CVD-UIP and IPF/UIP*

Category	CVD-UIP Patients	IPF/UIP Patients	p Value
Fibroblastic foci	1.56 ± 0.74	2.01 ± 0.81	0.007
Germinal centers	1.04 ± 1.07	0.33 ± 0.61	< 0.001
Total inflammation	2.10 ± 0.69	1.74 ± 0.66	0.010
HC (size)*	1.71 ± 1.09	2.20 ± 1.09	0.034
Plasma cells	1.72 ± 0.68	1.43 ± 0.71	0.044
Organizing pneumonia	0.33 ± 0.53	0.38 ± 0.60	NS
Intraalveolar macrophages	0.76 ± 0.54	0.85 ± 0.45	NS
Pleural fibrosis, % of affected cases	4 (10.5)	7 (11.5)	NS

Data are presented as the mean ± SD or No. (%), unless otherwise indicated. See Table 1 for abbreviation not used in the text.
*See "Materials and Methods" section.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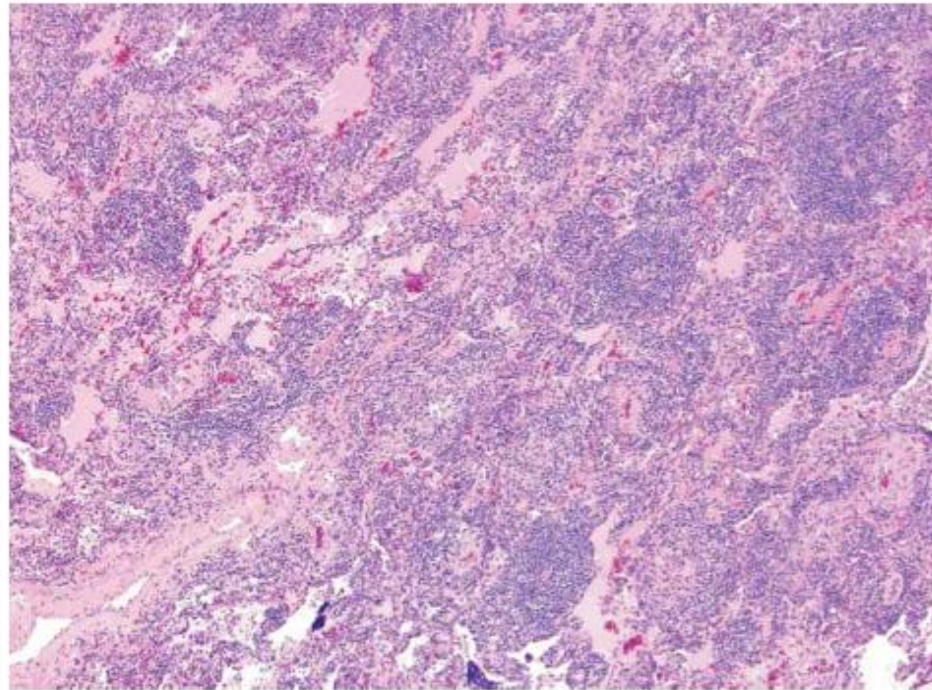
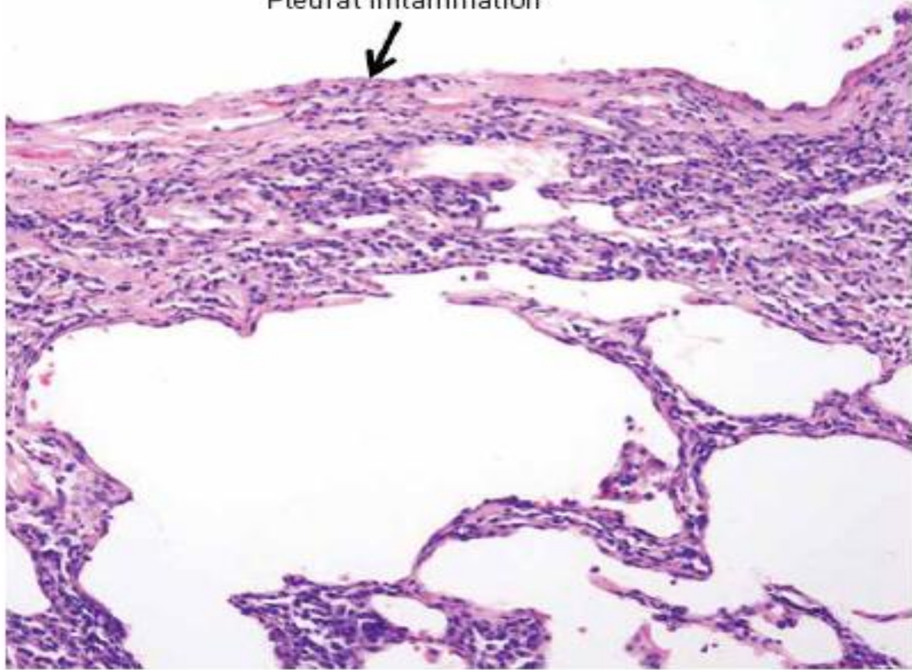
F
NSIP

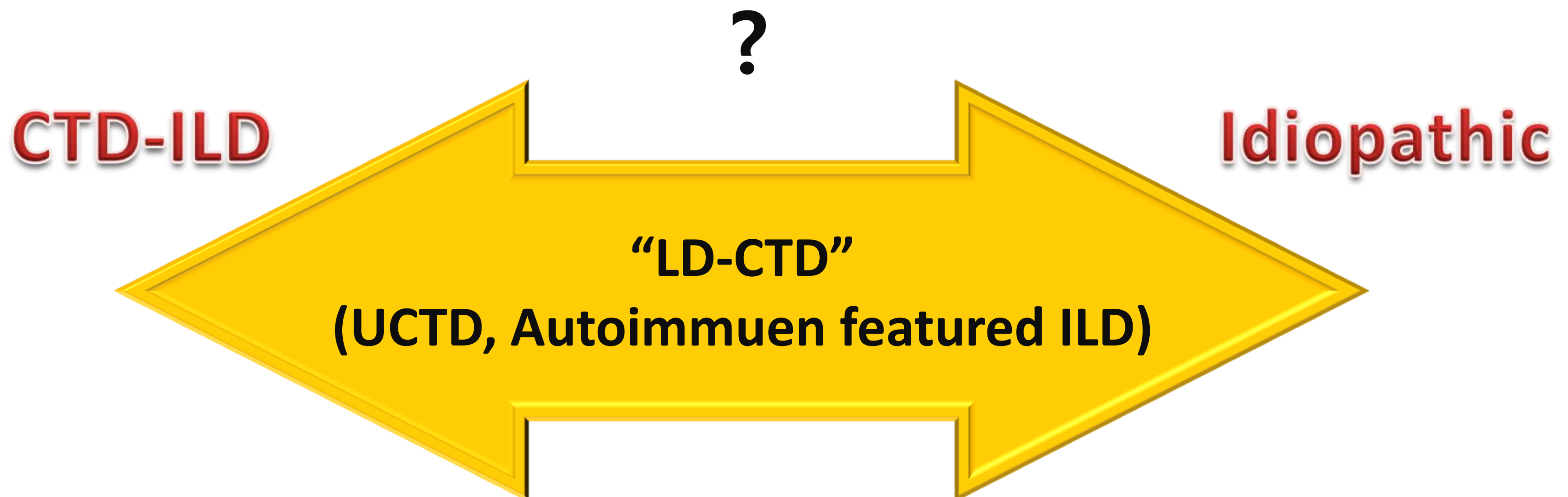



Pleural inflammation

Idiopathic interstitial pneumonia (IIP) with connective tissue disease

1) Interstitial lung disease in established connective tissue disease (CTD-ILD)
2) Undifferentiated CTD (UCTD)
3) Lung dominant CTD (LD-ILD)
4) Interstitial disease with features of autoimmunity (IPAF)

Lung dominant connective tissue disease (CTD) may, or may not, evolve into well-defined CTD



Am J Respir Crit Care Med. 2007;176:691-697, Courtesy of SJ Park

Diagnostic criteria of lung dominant CTD

1. NSIP, UIP, LIP, OP, and DAD (or DIP if no smoking history), as determined by surgical lung biopsy specimen or suggested by high-resolution CT *and*
2. Insufficient extrathoracic features of a definite CTD to allow a specific CTD designation *and*
3. No identifiable alternative etiology for IP *and*
4. Any *one* of the following autoantibodies or *at least two* of the histopathology features:

Autoantibodies	Histopathology features
a. High-titer ANA (>1:320) or RF (>60 IU/mL)	(a) Lymphoid aggregates with germinal centers
b. Nucleolar-ANA	(b) Extensive pleuritis
c. Anti-CCP	(c) Prominent plasmacytic infiltration
d. Anti-Scl-70	(d) Dense perivascular collagen
e. Anti-Ro	
f. Anti-La	
g. Anti-dsDNA	
h. Anti-Smith	
i. Anti-RNP	
j. Anti-tRNA synthetase (eg, Jo-1, PL-7, PL-12, and others)	
k. Anti-PM-Scl	
l. Anticentromere	

ANA = antinuclear antibody; CCP = cyclic citrullinated peptide; CTD = connective tissue disease; DAD = diffuse alveolar damage; DIP = desquamative interstitial pneumonia; IP = interstitial pneumonia; LIP = lymphocytic interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; RF = rheumatoid factor; RNP = ribonucleoprotein; UIP = usual interstitial pneumonia.

Histologic features

(a) Lymphoid aggregates with germinal center

(b) Extensive pleuritis

(c) Prominent plasamcytic infiltration

(d) Dense perivascular collagen

Fischer A et al, Chest. 2010;138(2):251-6

An official European Respiratory Society/ American Thoracic Society research statement: interstitial pneumonia with autoimmune features

Aryeh Fischer[1,17,18], Katerina M. Antoniou[2], Kevin K. Brown[3], Jacques Cadranel[4], Tamera J. Corte[5,18], Roland M. du Bois[6], Joyce S. Lee[7,18], Kevin O. Leslie[8], David A. Lynch[9], Eric L. Matteson[10], Marta Mosca[11], Imre Noth[12], Luca Richeldi[13], Mary E. Strek[12,18], Jeffrey J. Swigris[3,18], Athol U. Wells[14], Sterling G. West[15], Harold R. Collard[7,18,19] and Vincent Cottin[16,18,19], on behalf of the "ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD"

Eur Respir J 2015; 46: 976–987

TABLE 1 Classification criteria for "interstitial pneumonia with autoimmune features"

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) *and*,
2. Exclusion of alternative aetiologies *and*,
3. Does not meet criteria of a defined connective tissue disease *and*,
4. At least one feature from at least two of these domains:
   A. Clinical domain
   B. Serologic domain
   C. Morphologic domain

Interstitial pneumonia With autoimmune feature

A. Clinical domain
1. Distal digital fissuring (*i.e.* "mechanic hands")
2. Distal digital tip ulceration
3. Inflammatory arthritis *or* polyarticular morning joint stiffness ≥60 min
4. Palmar telangiectasia
5. Ray
6. Une
7. Une

B. Serolog
1. AN
   a.
   b.
2. Rh
3. An
4. An
5. An
6. An
7. An
8. An
9. An
10. An
11. An
12. Anti-MDA-5

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) *and*,
2. Exclusion of alternative aetiologies *and*,
3. Does not meet criteria of a defined connective tissue disease *and*,
4. At least one feature from at least two of these domains:
   A. Clinical domain
   B. Serologic domain
   C. Morphologic domain

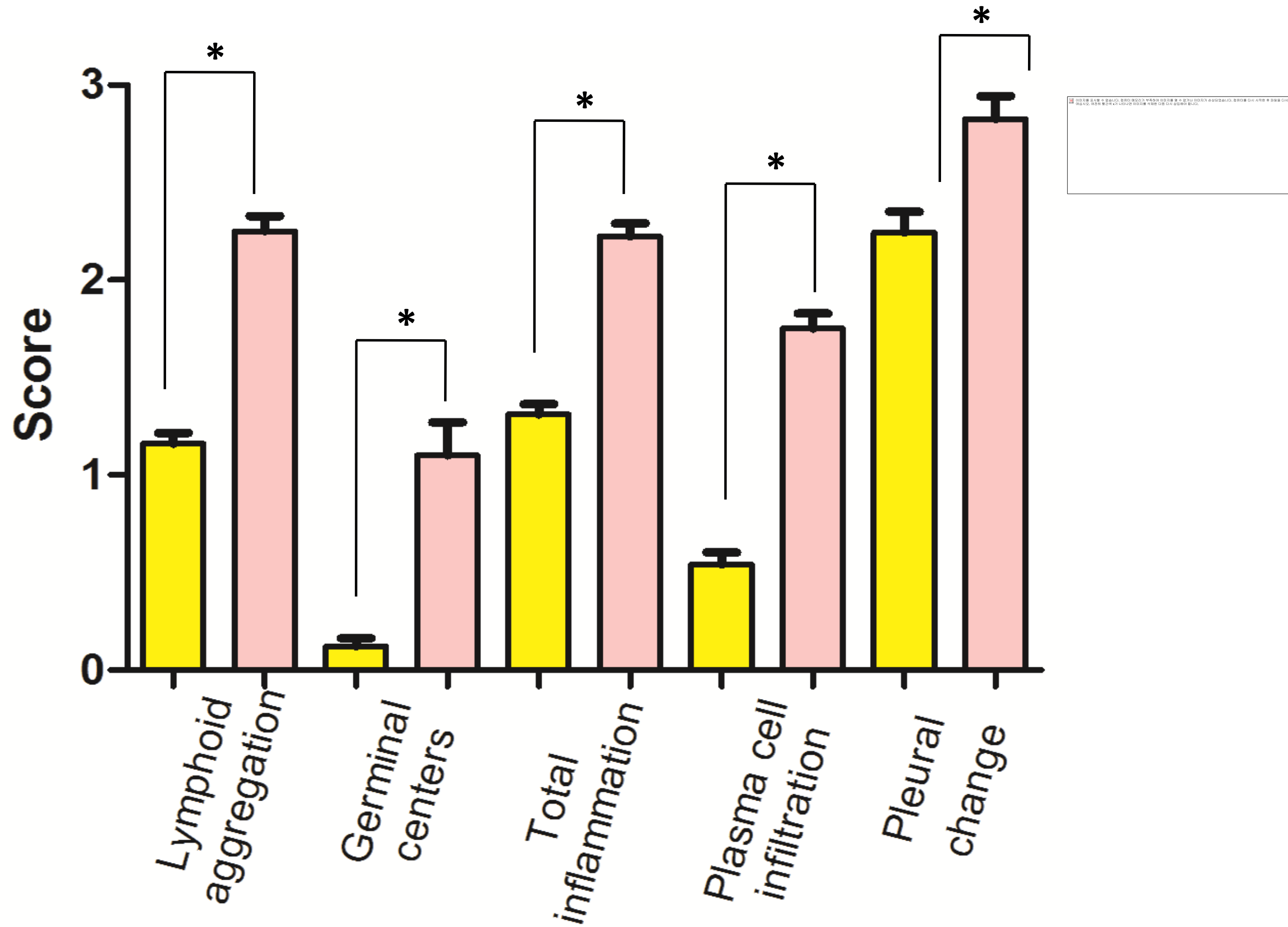
C. Morphologic domain
1. Suggestive radiology patterns by HRCT (see text for descriptions):
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
2. Histopathology patterns or features by surgical lung biopsy:
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
   e. Interstitial lymphoid aggregates with germinal centres
   f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
3. Multi-compartment involvement (in addition to interstitial pneumonia):
   a. Unexplained pleural effusion or thickening
   b. Unexplained pericardial effusion or thickening
   c. Unexplained intrinsic airways disease[#] (by PFT, imaging or pathology)
   d. Unexplained pulmonary vasculopathy

C. Morphologic domain

1. Suggestive radiology patterns by HRCT (see text for descriptions):
    a. NSIP
    b. OP
    c. NSIP with OP overlap
    d. LIP
2. Histopathology patterns or features by surgical lung biopsy:
    a. NSIP
    b. OP
    c. NSIP with OP overlap
    d. LIP
    e. Interstitial lymphoid aggregates with germinal centres
    f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
3. Multi-compartment involvement (in addition to interstitial pneumonia):
    a. Unexplained pleural effusion or thickening
    b. Unexplained pericardial effusion or thickening
    c. Unexplained intrinsic airways disease[#] (by PFT, imaging or pathology)
    d. Unexplained pulmonary vasculopathy

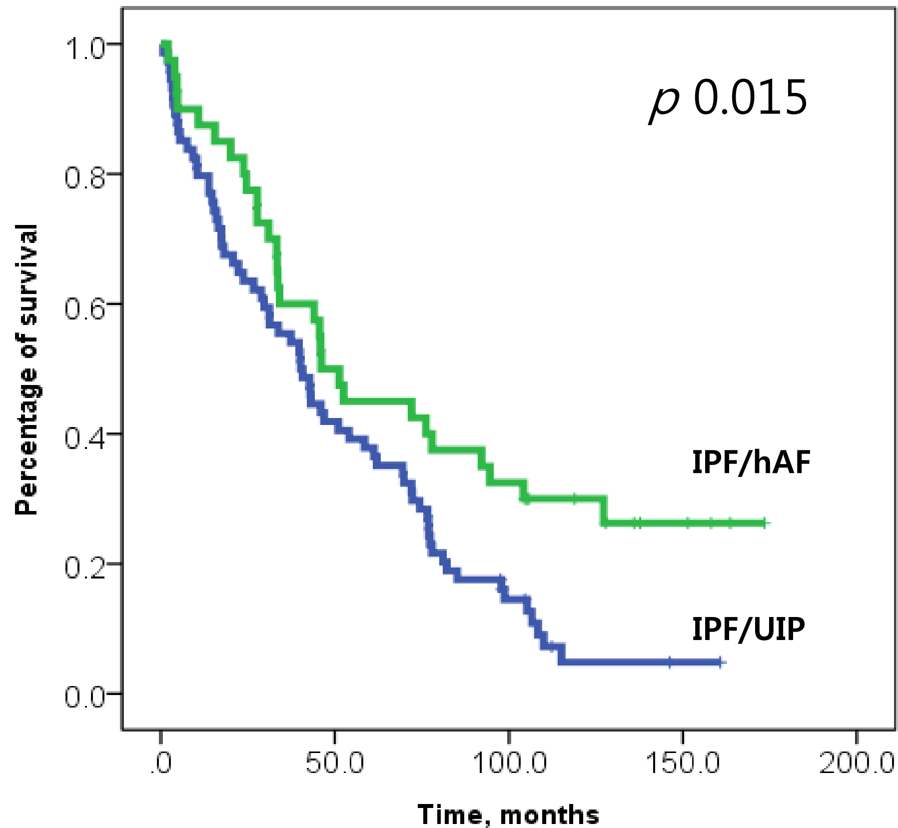
HRCT: high-resolution computed tomography; ANA: antinuclear antibody; NSIP: non-specific interstitial pneumonia; OP: organising pneumonia; LIP: lymphoid interstitial pneumonia; PFT: pulmonary function testing. [#]: includes airflow obstruction, bronchiolitis or bronchiectasis.

Pathologic Score



Unpublished data, Song et al 2015, Courtesy of SJ Park

Survival



Median survival duration, month, median (IQR)
48.7 (27.7-105.5) vs. 40.4 (15.1-77.5)

Unpublished data, Song et al 2015, Courtesy of SJ Park

FOR
YOUR ATTENTION!

Q&A