Cinquanta sfumature di grigio

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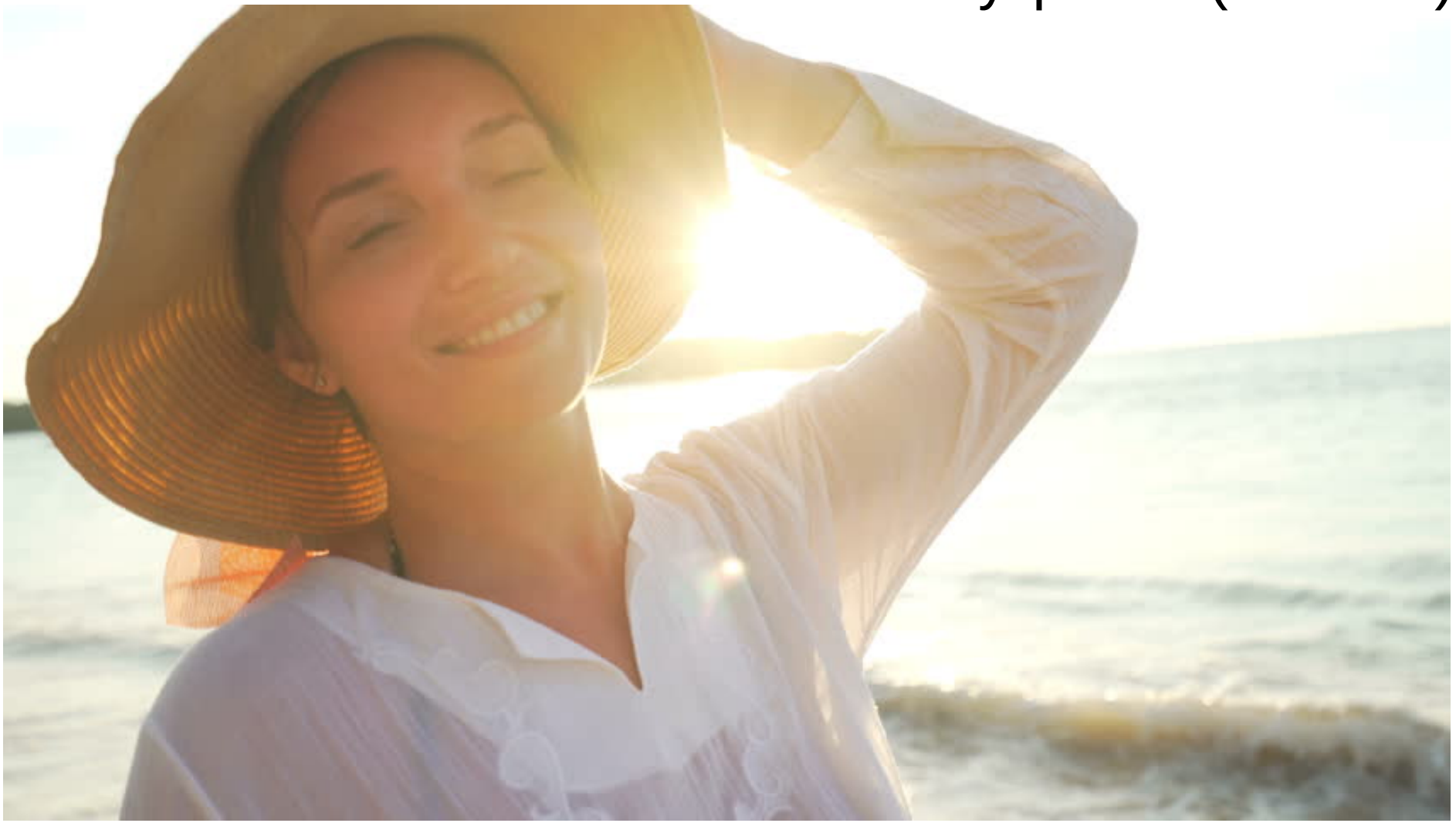
First evaluation

AL, woman, 47 years old, clerk
Ex smokers (5 p/y), stop on 1990

Chronic exertional dyspnoea (NHYA II)



Comorbidities:

Systemic hypertension ⟶ treatment with irbesartan + hydrochlorothiazide

From the age of 15 yrs, rheumatoid factor positive; rheumatological disease excluded, only follow-up

Physical examination:

- Velcro crackles on lung auscultation
- Normal pulse, HR 68
- Normal blood pressure 120/70
- No signs of collagen vascular disease

Lung function measurements

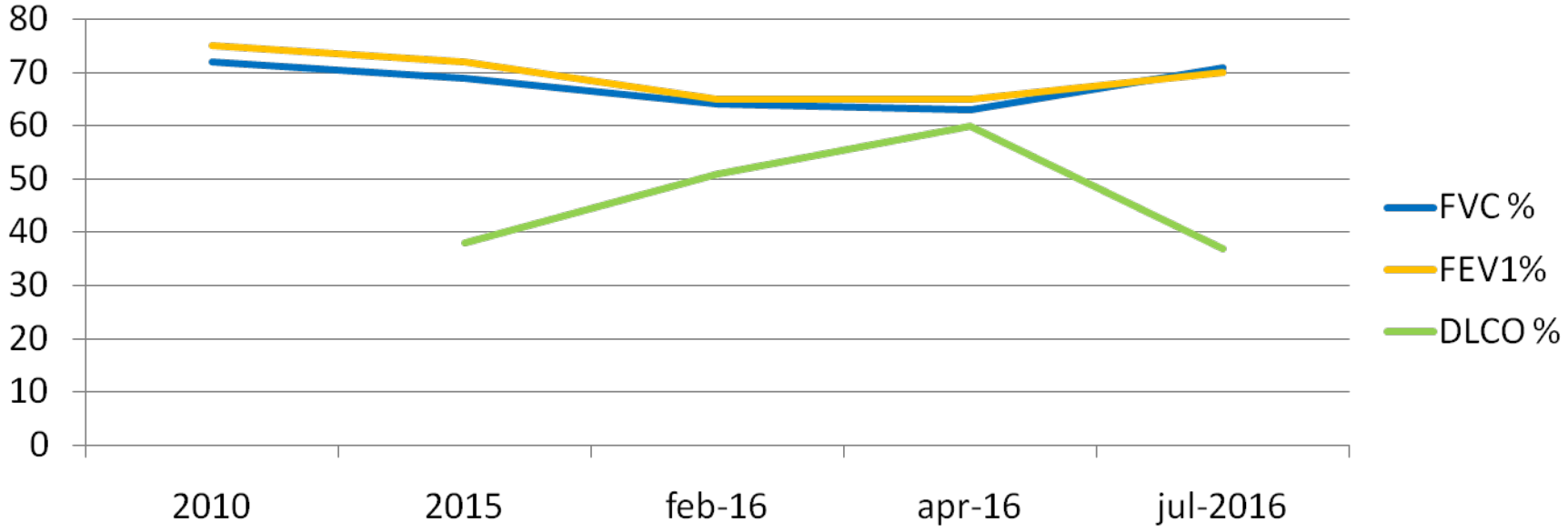
Parameter	Absolute value	% of predicted
FVC	2.11L	71%
FEV1	1.77L	70%
FEV1/FVC		81%
TLC	3.61L	76%
RV	1.42L	86%
DLCO	8.8 mL/mmHg/min	37%

ABG on room air: pO2 93 mmHg, pCO2 36 mmHg

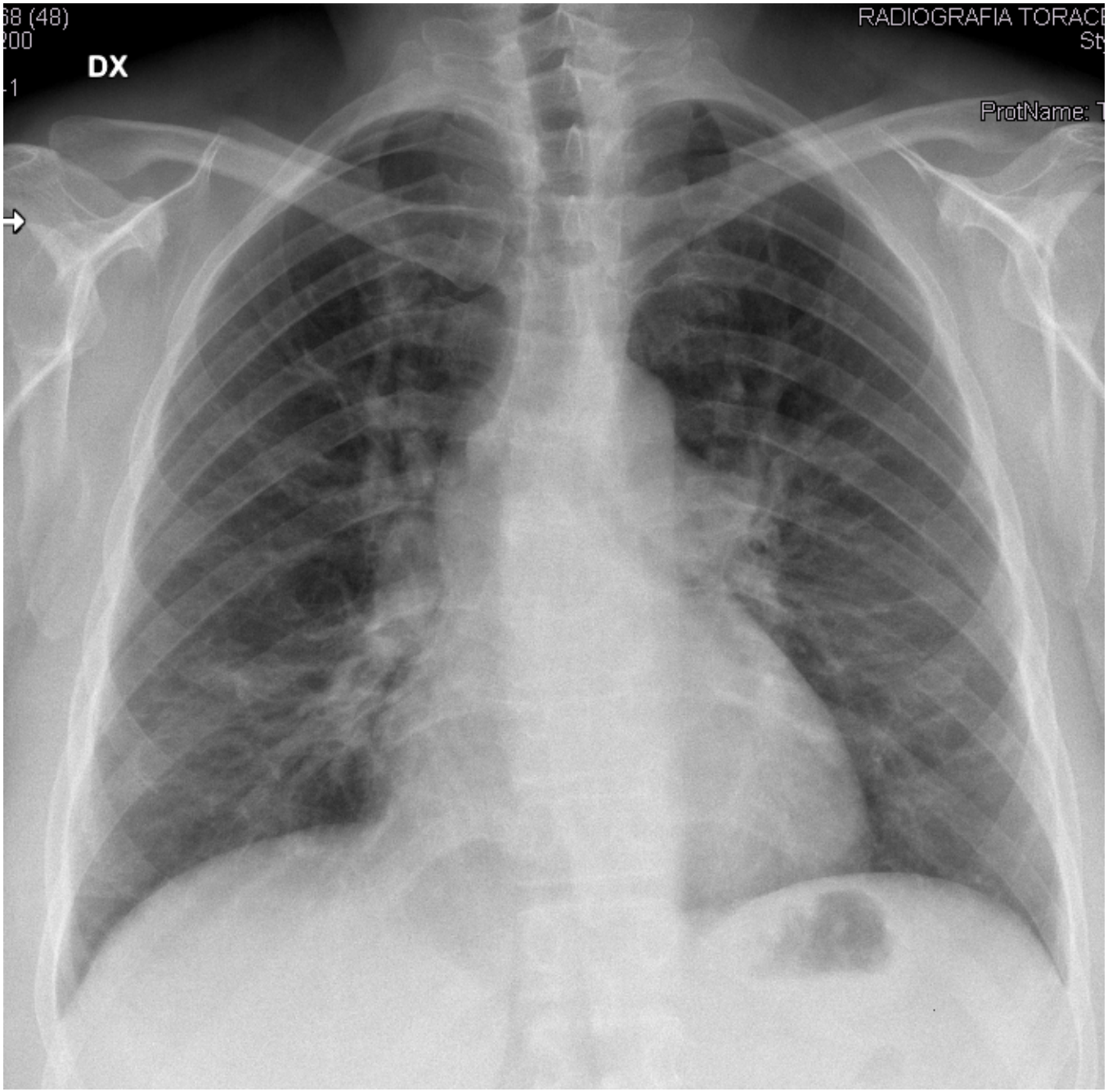
6MWT on room air: meters 500, Sat.O2 97% → 90%

Our evaluation

	2010	2015	Feb 2016	Apr-2016	Jul-2016
FVC	2.25	2.09	1.91	1.89	2.11
FVC %	72	69	64	63	71
FEV1	2.03	1.86	1.67	1.66	1.77
FEV1 %	75	72	65	65	70
FEV1/FVC		85	105	81	81
TLC %		82		77	76
DLCO %		36	51	60	37



Imaging


DX
RADIOGRAFIA TORACE
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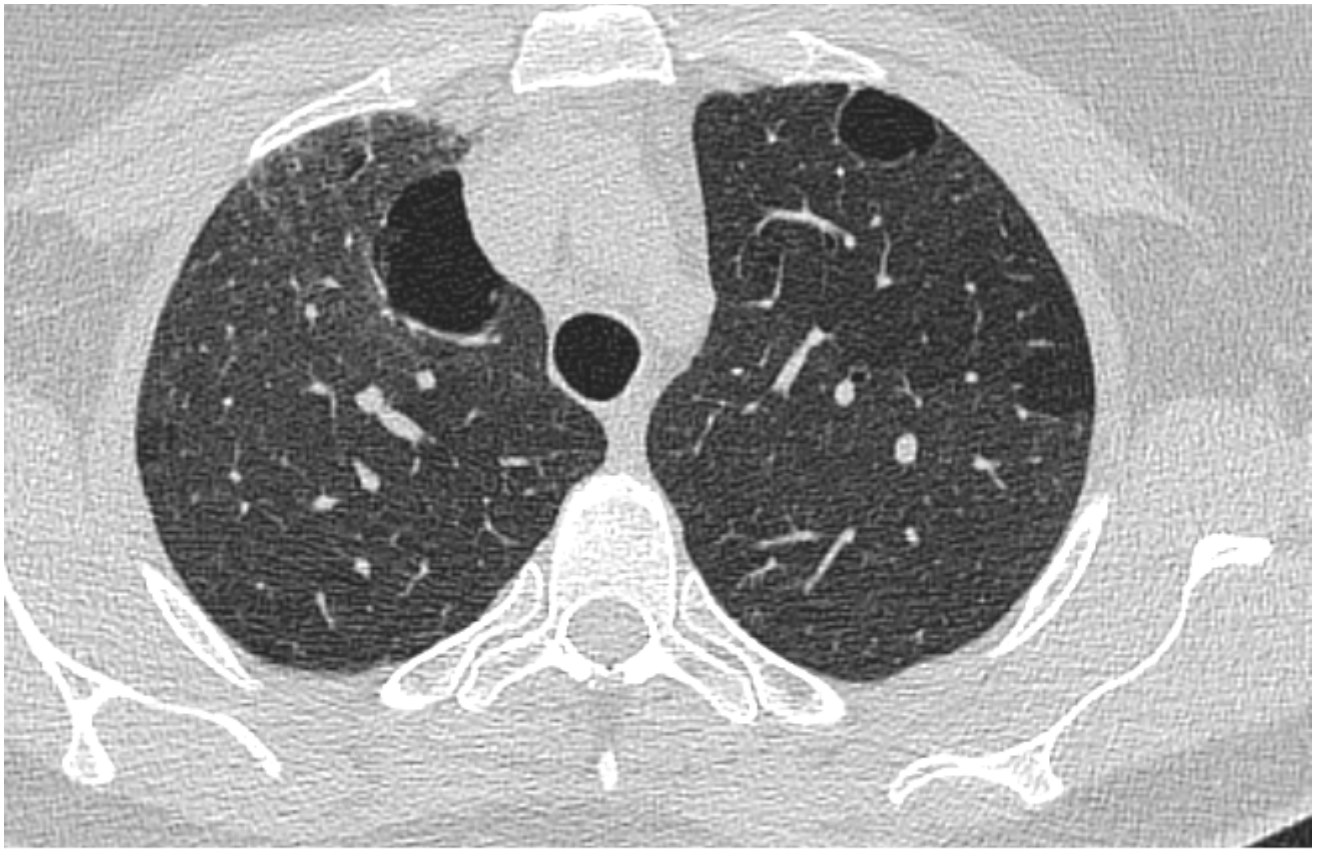
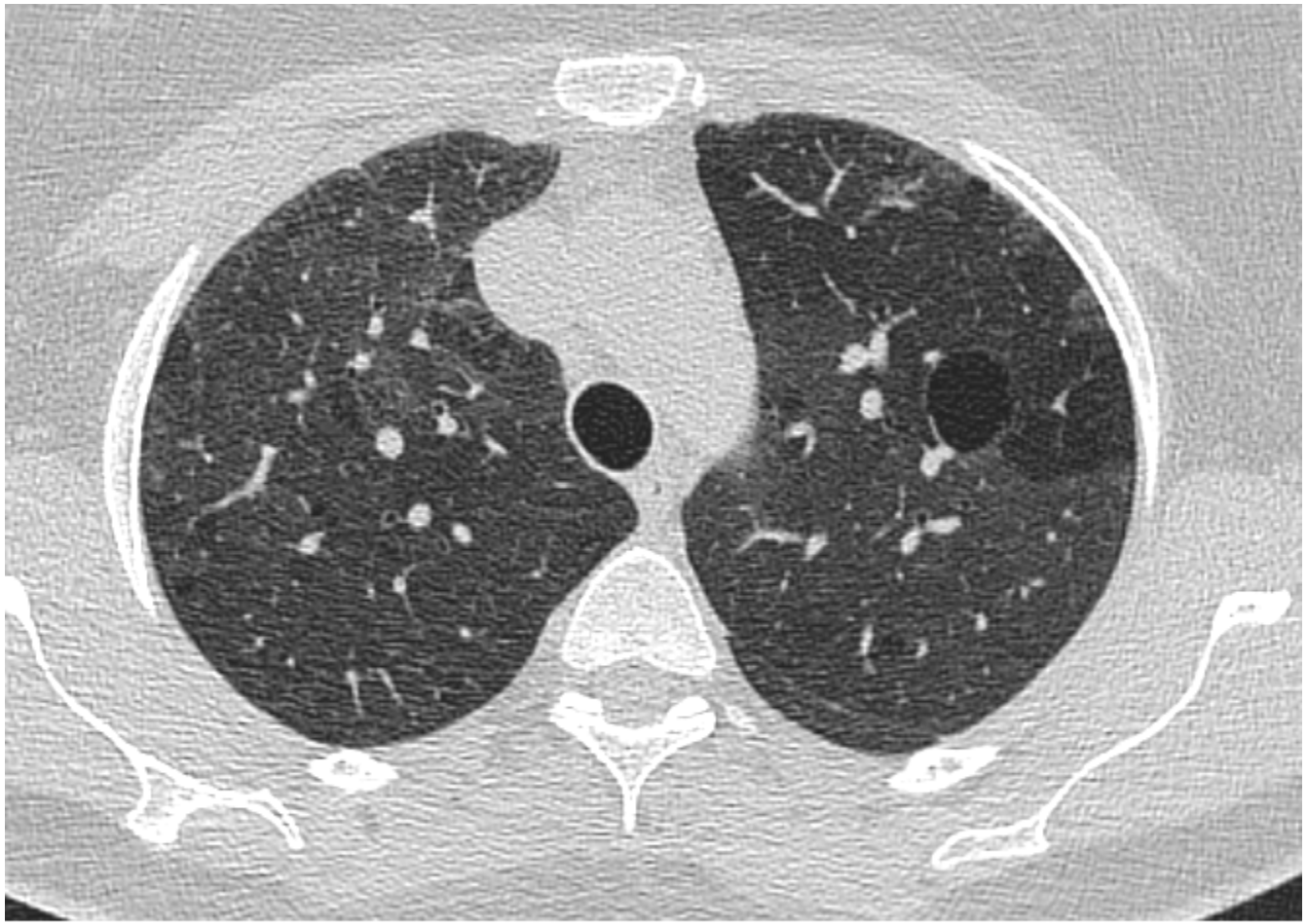
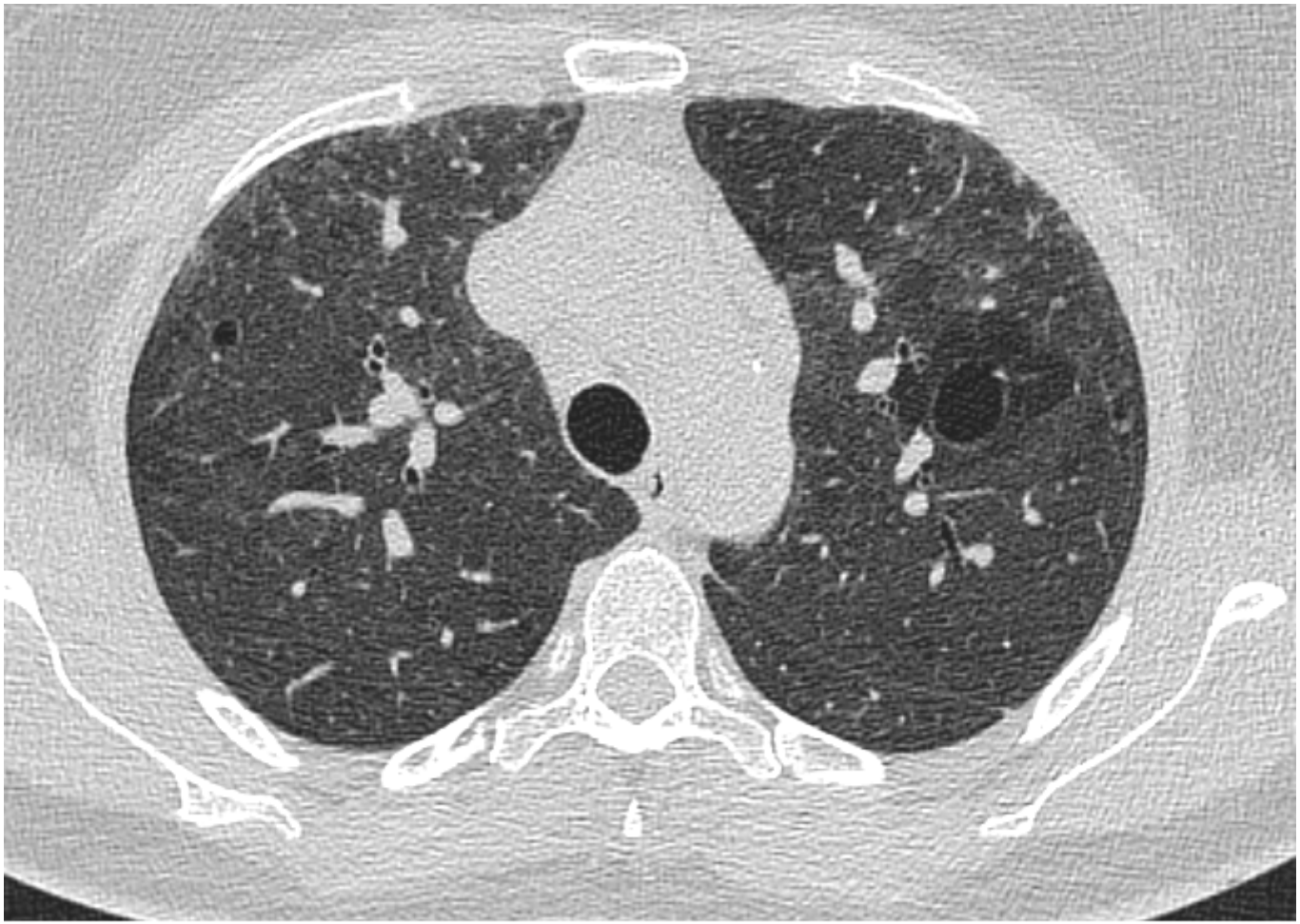
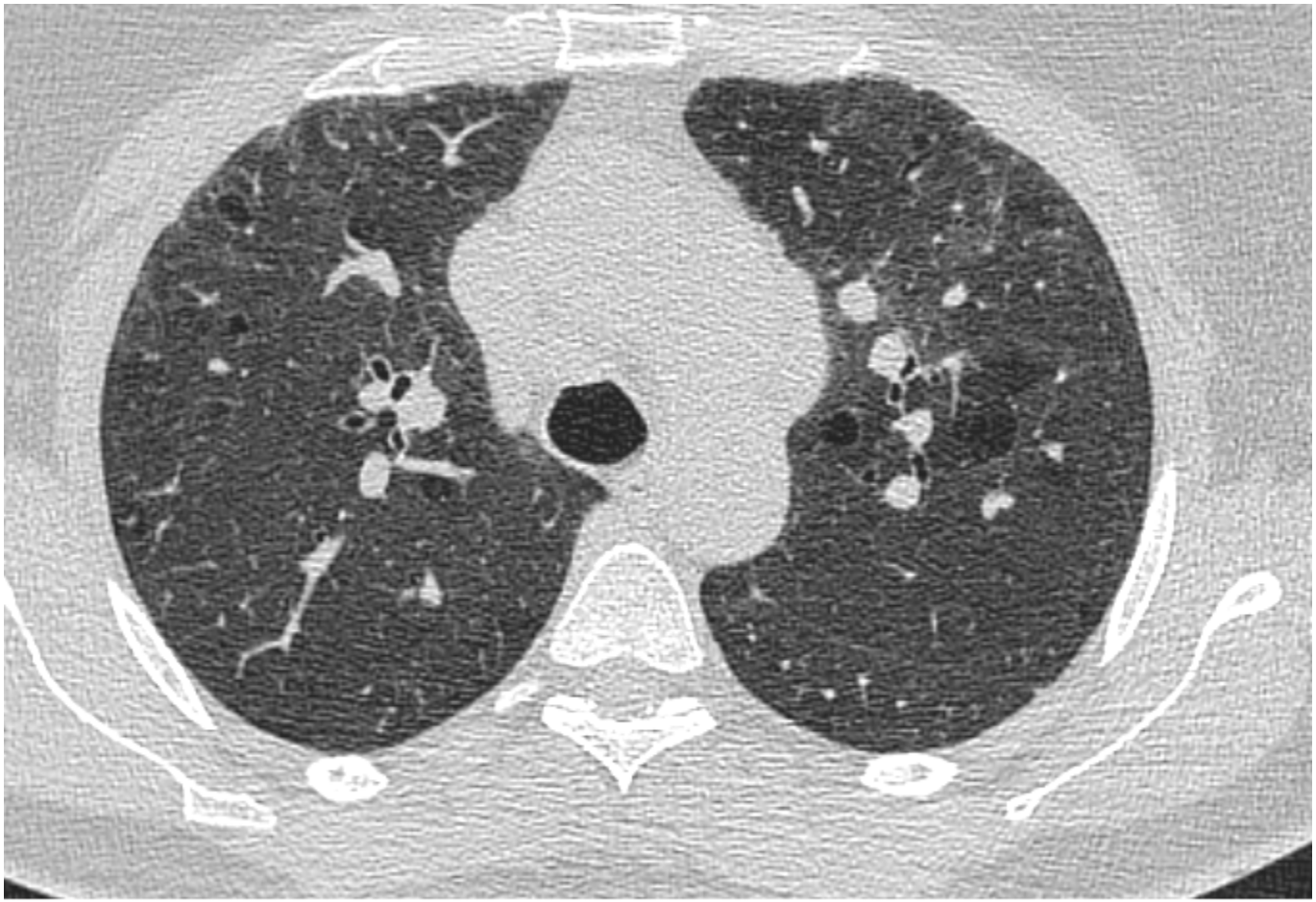
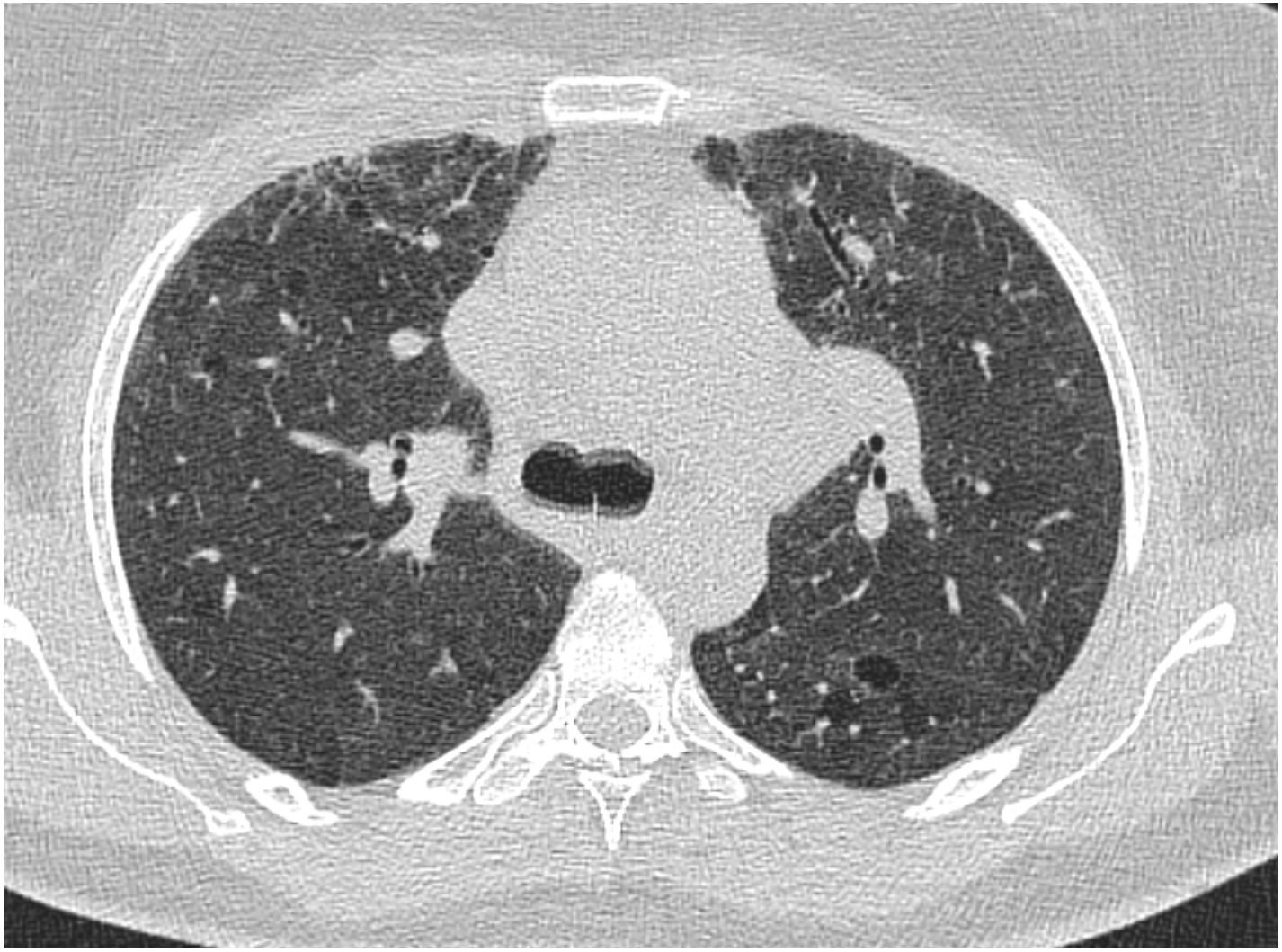
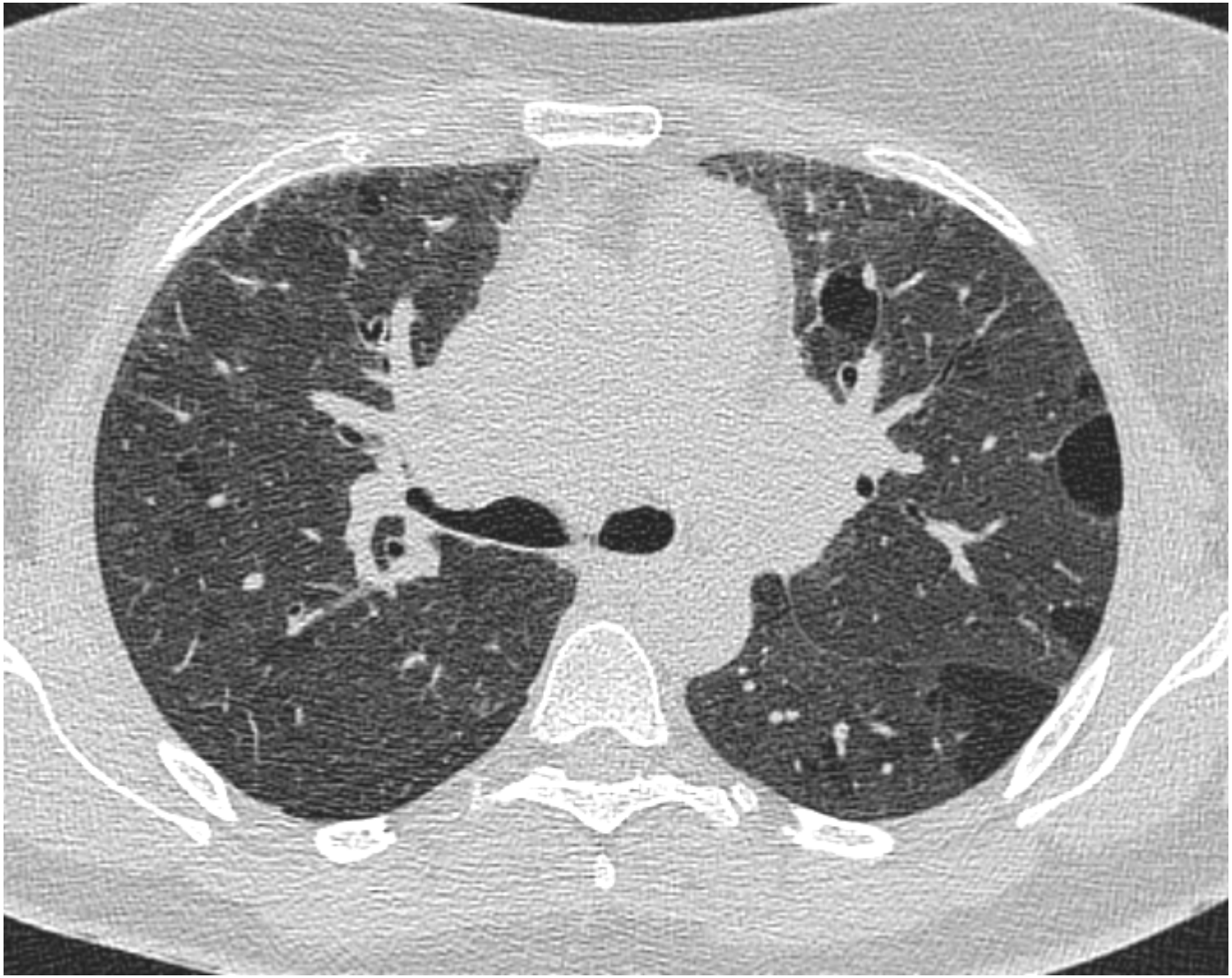


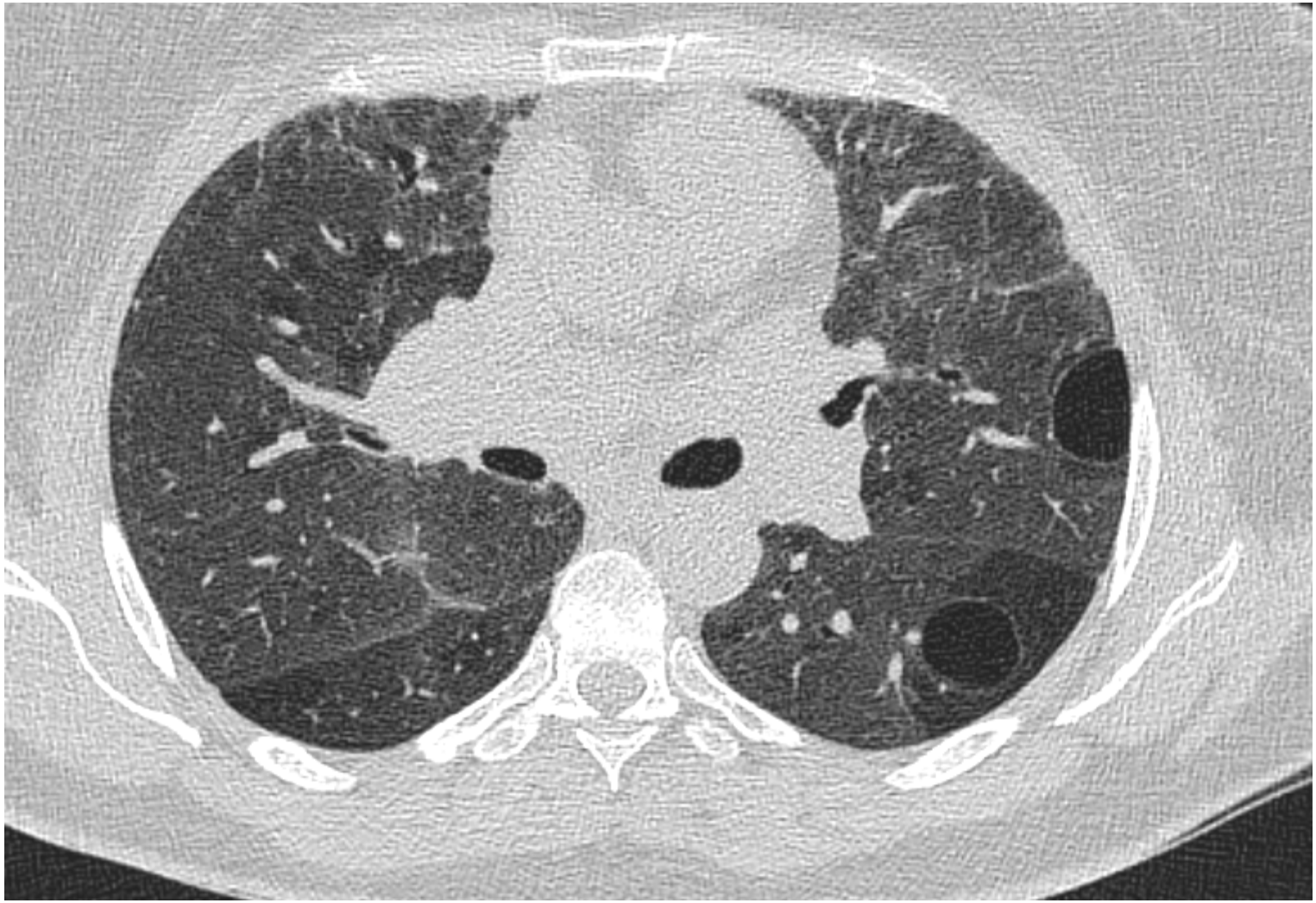


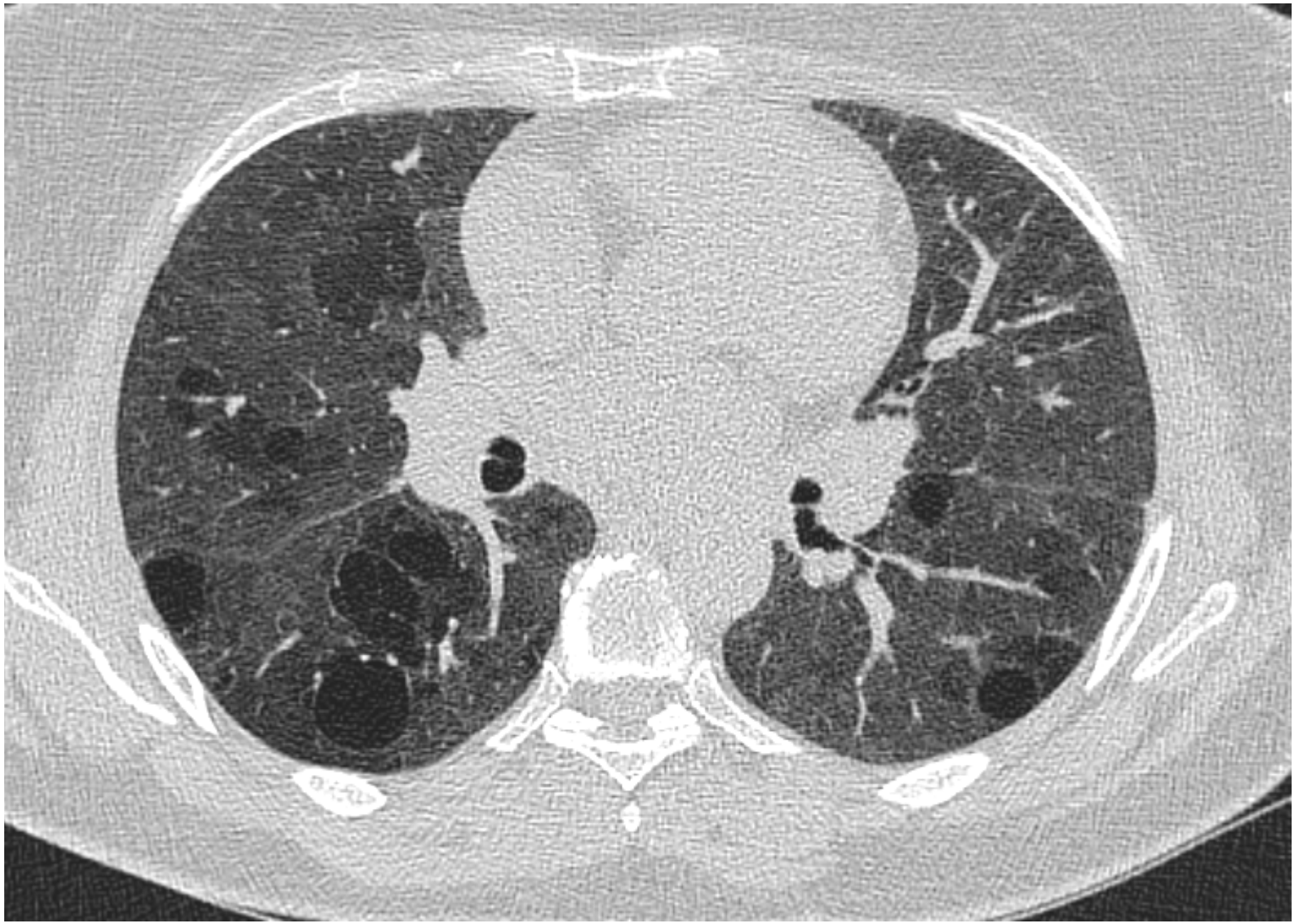


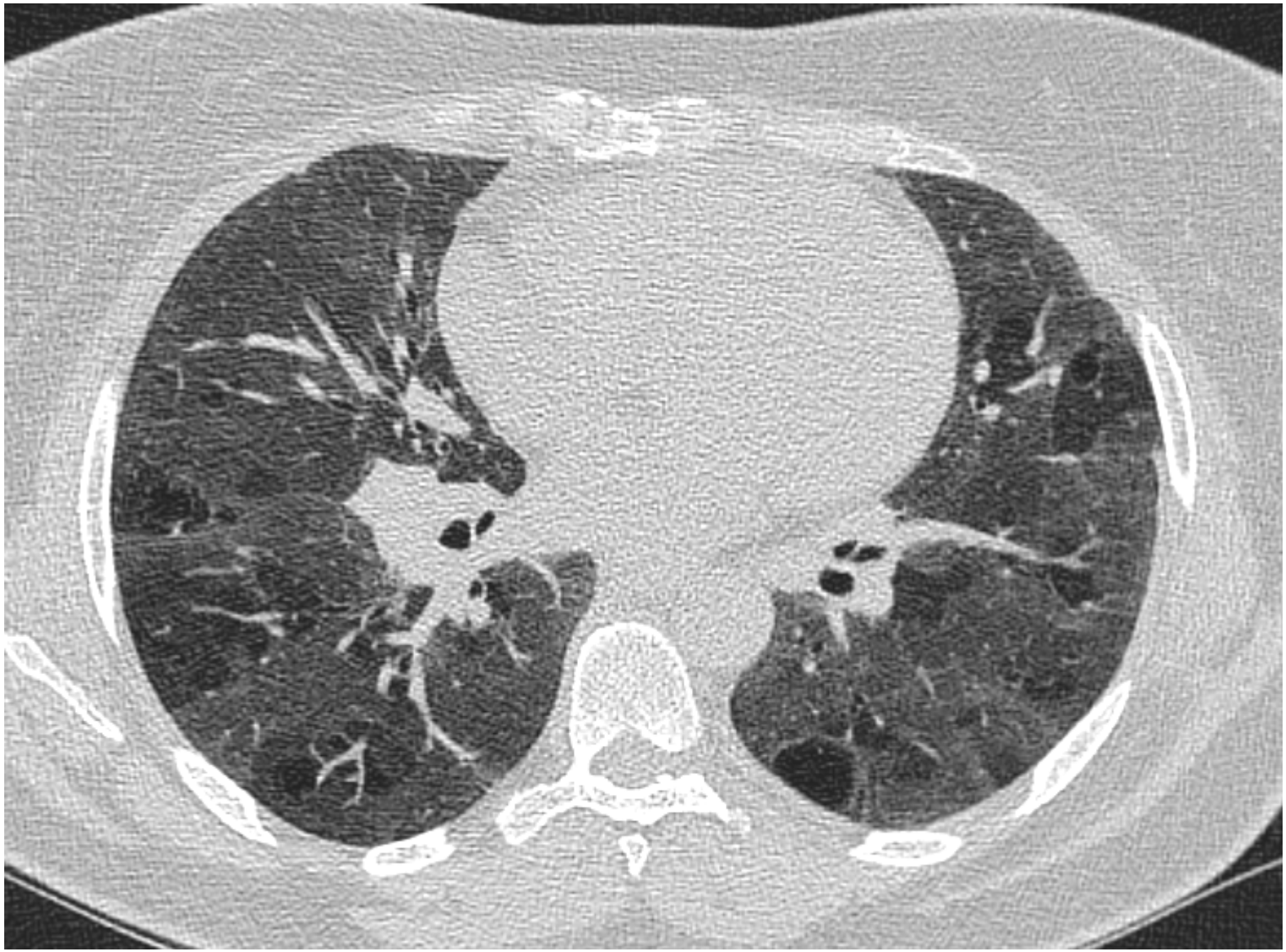


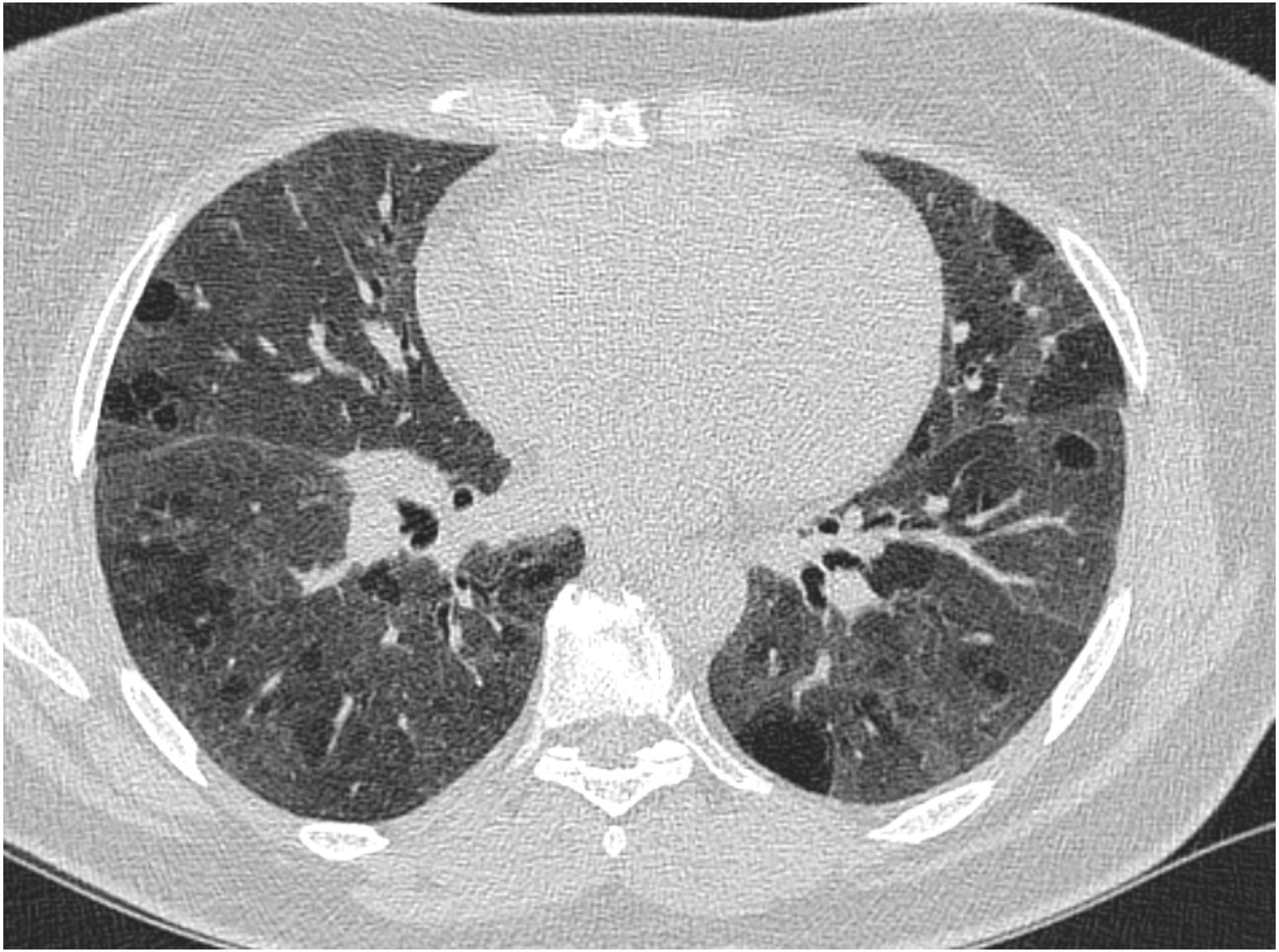


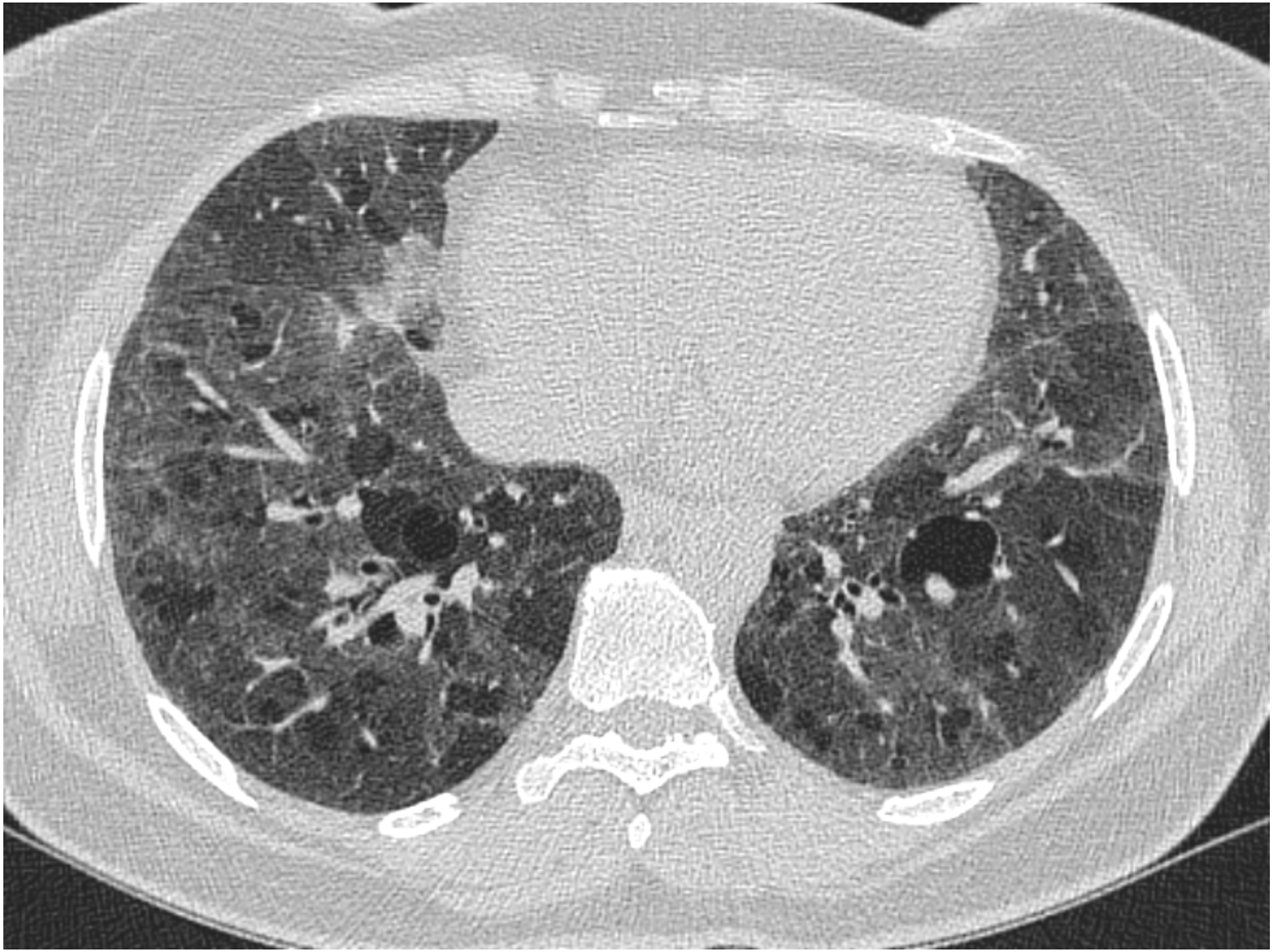


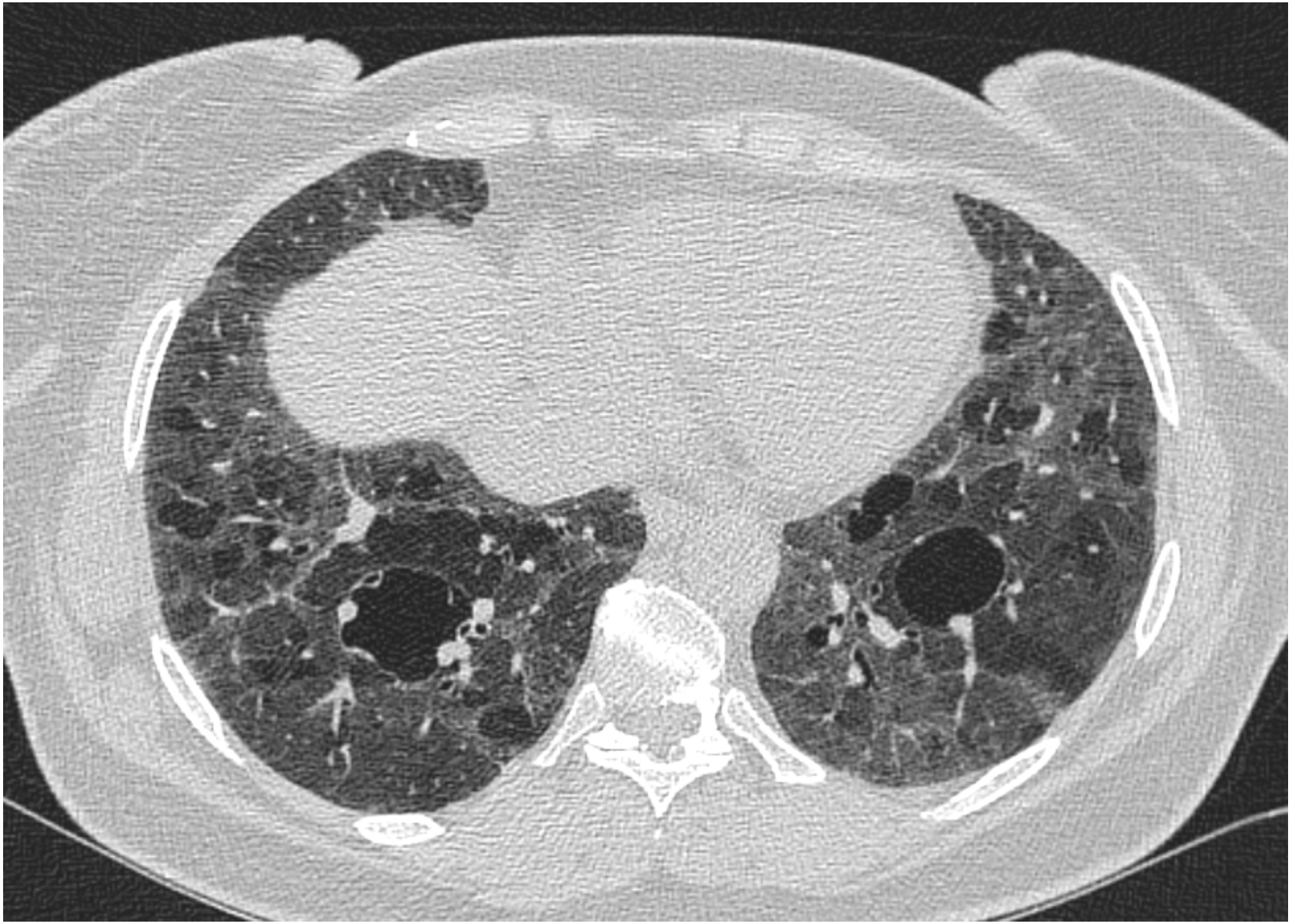


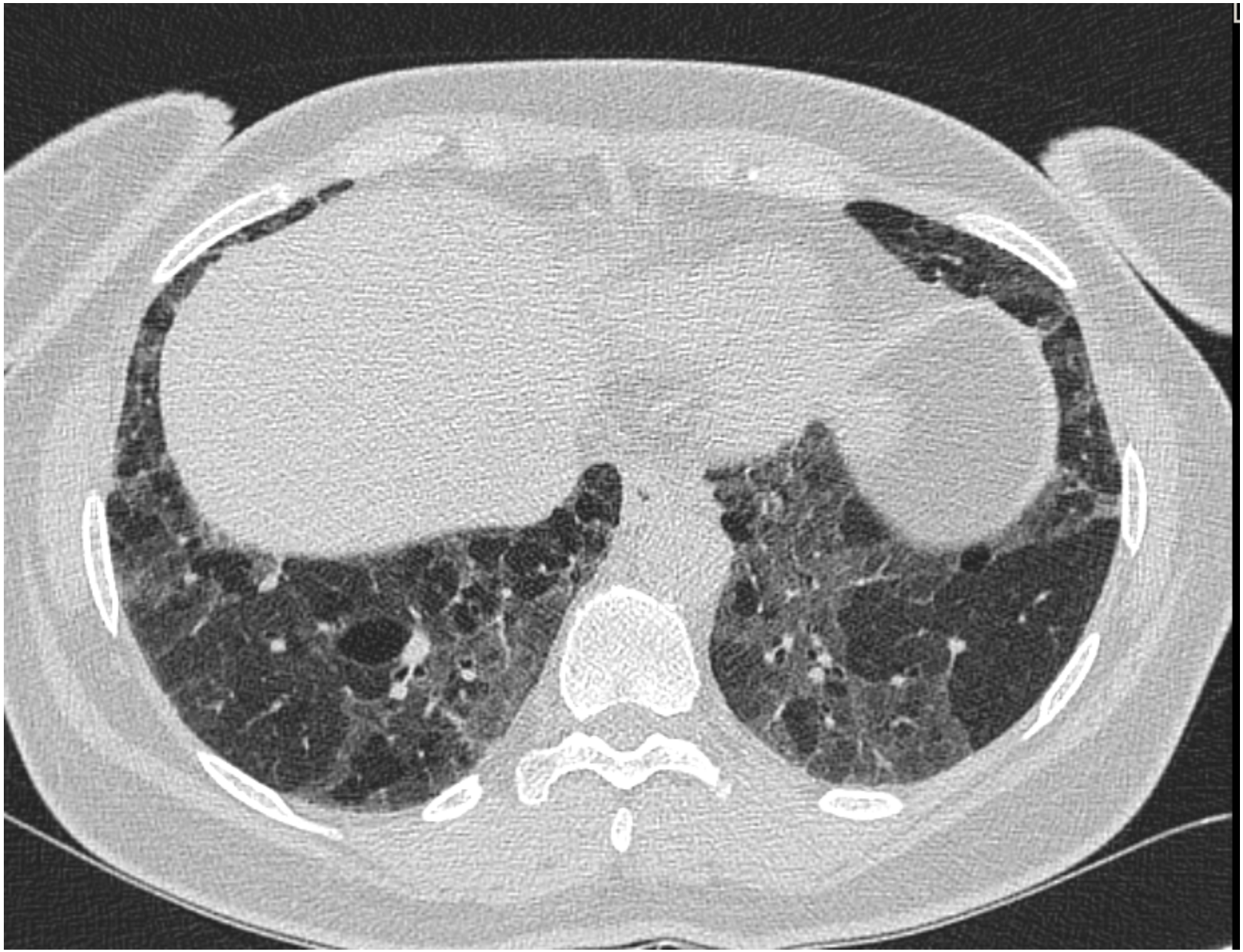


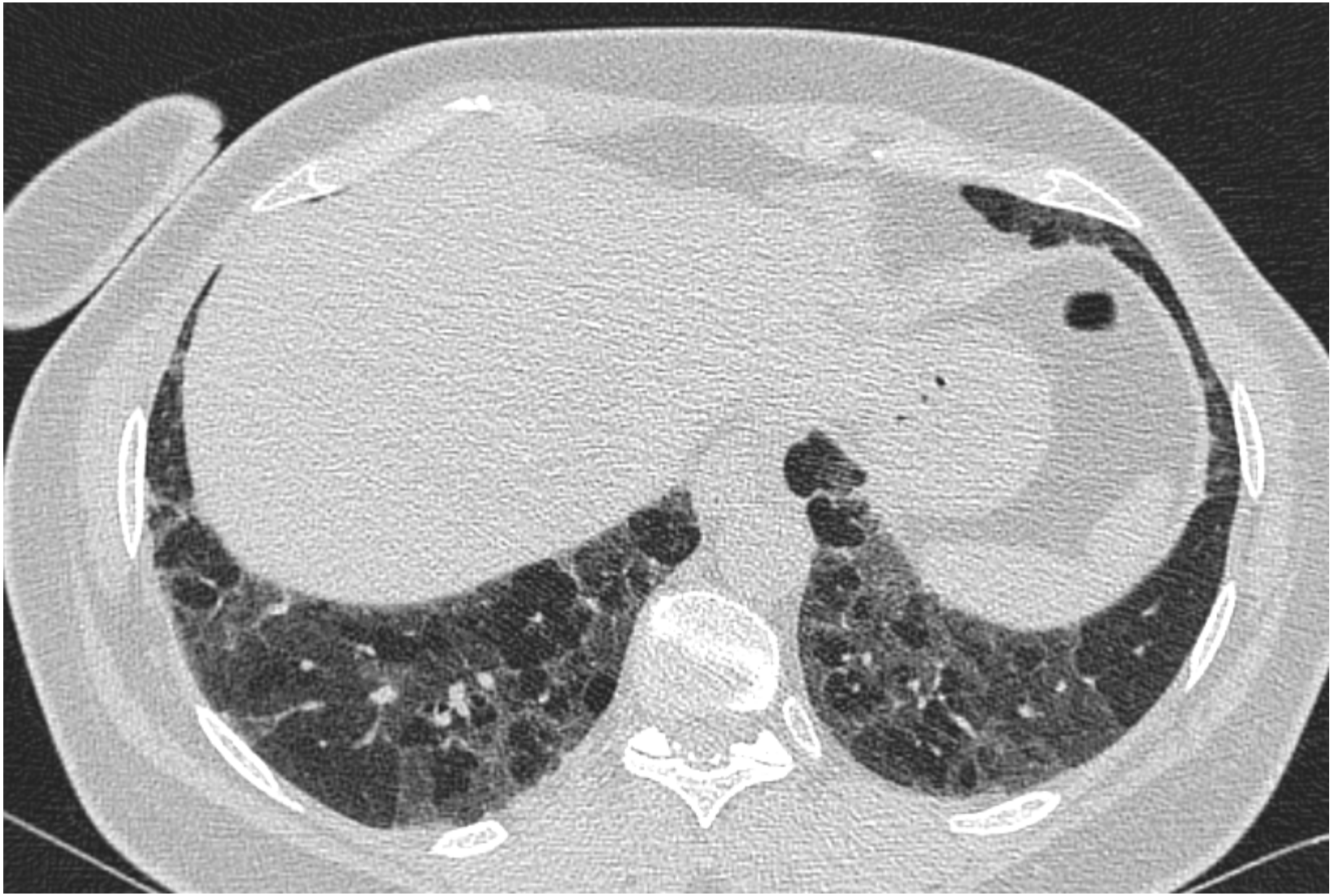












What's the radiological prevalent pattern?

- Cystic pattern
- Ground glass with mosaic attenuation
- Mixed cystic and ground glass pattern
- NSIP pattern

What's your radiological diagnosis?

- Lymphangioleiomyomatosis
- Pulmonary Langherans cell histiocytosis
- Cystic lung disease
- Other diagnosis

The patient was followed at another hospital for cystic lung disease and was adressed to our institution in suspicion of lymphangioleiomyomatosis

Classification of Diffuse Cystic Lung Diseases

Gupta N et al, AJRCCM 2015

1. *Neoplastic*	**Lymphangioleiomyomatosis** (S-LAM or TSC-LAM) **Pulmonary Langerhans cell histiocytosis**, and non-Langerhans cell histiocytoses including Erdheim Chester disease Other primary and metastatic neoplasms such as sarcomas, adenocarcinomas, pleuropulmonary blastoma, etc.	5. *Associated with interstitial lung diseases*	Hypersensitivity pneumonitis Desquamative interstitial pneumonia
2. Genetic Developmental Congenital	Birt-Hogg-Dubé syndrome Proteus syndrome, neurofibromatosis, Ehlers-Danlos syndrome Congenital pulmonary airway malformation, bronchopulmonary dysplasia,etc.	6. *Smoking related*	**Pulmonary Langerhans cell histiocytosis** Desquamative interstitial pneumonia
3. *Associated with lympho-proliferative disorders*	Lymphocytic interstitial pneumonia Follicular bronchiolitis Sjögren syndrome Amyloidosis Light chain deposition disease	7. *Other/ Miscellaneous*	Post-traumatic pseudocysts Fire-eater's lung Hyper IgE syndrome
4. *Infectious*	Pneumocystis jiroveci Staphylococcal pneumonia Recurrent respiratory papillomatosis Endemic fungal diseases Paragonimiasis	8. *DCLD mimics*	Emphysema Alpha-one antitrypsin deficiency Bronchiectasis Honeycombing seen in late stage scarring interstitial lung diseases

What's LAM?

LAM is a rare systemic neoplastic disease characterized by progressive proliferation of LAM-cells

LAM occurs in patients with and without evidence of TSC, a syndrome resulting from mutations in the *TSC1* or *TSC2* tumor suppressor genes.

LAM cells in the lung and angiomyolipomas (AMLs) from patients without overt TSC contain mutations in the TSC genes.

Is LAM a tumor?

LAM pathogenic mechanisms mirror those of many forms of human cancer

- Mutations
- Inappropriate growth and survival
- Metastasis via blood and lymphatic circulation
- Infiltration
- Tissue destruction
- Sex steroid sensitivity

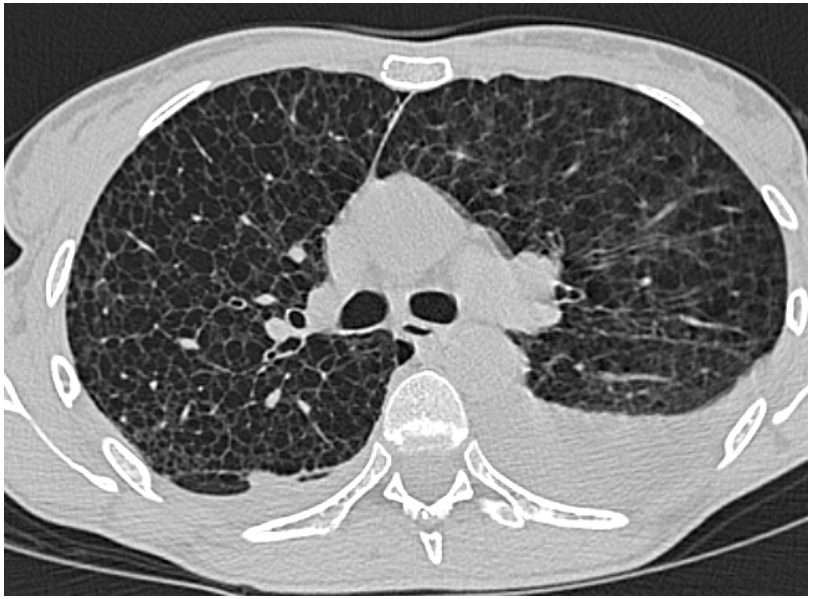
LAM has been included in PEComas

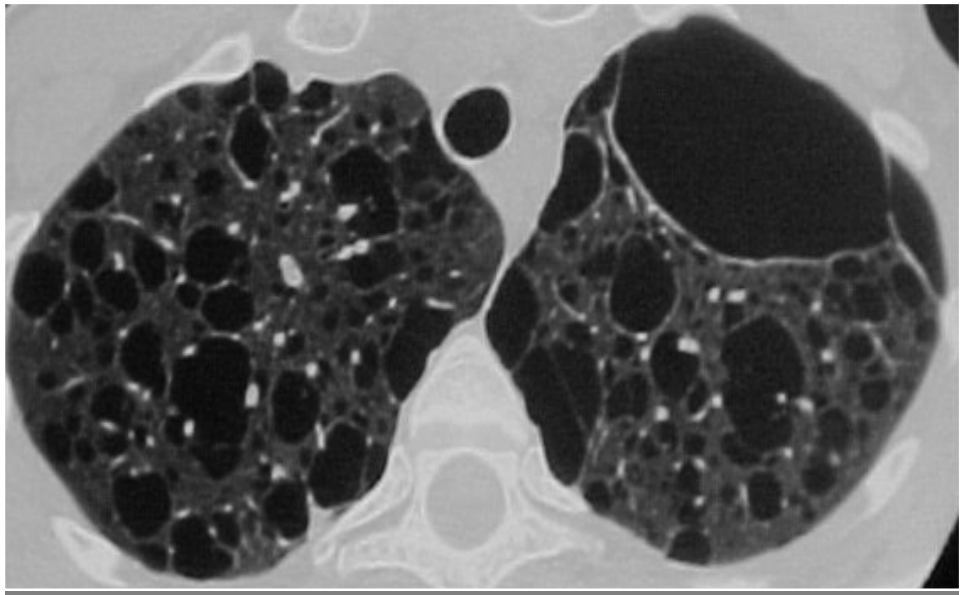
But the source of LAM cells is still unknown

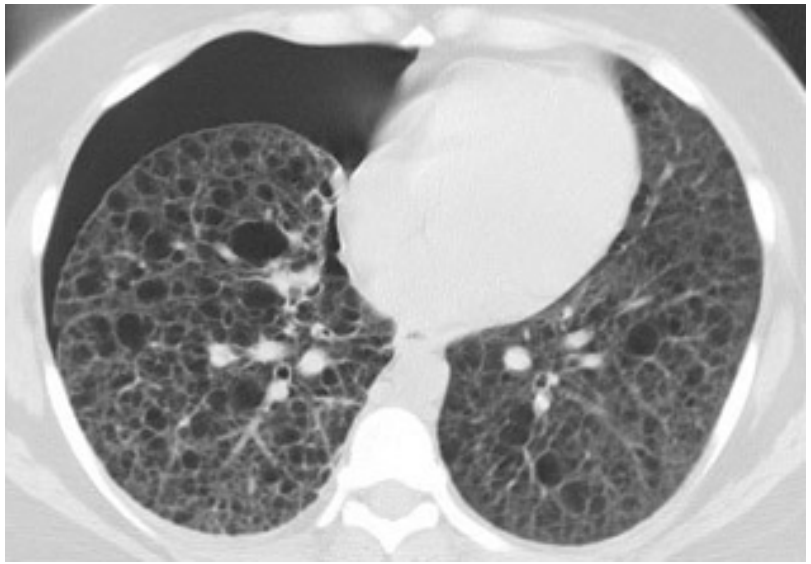
(Uterus? Kidneys? Lymphatics?)

LAM cells show no atypia

Henske EP, McCormack FX AJRCCM 2012
Harari S et al, ERJ 2015

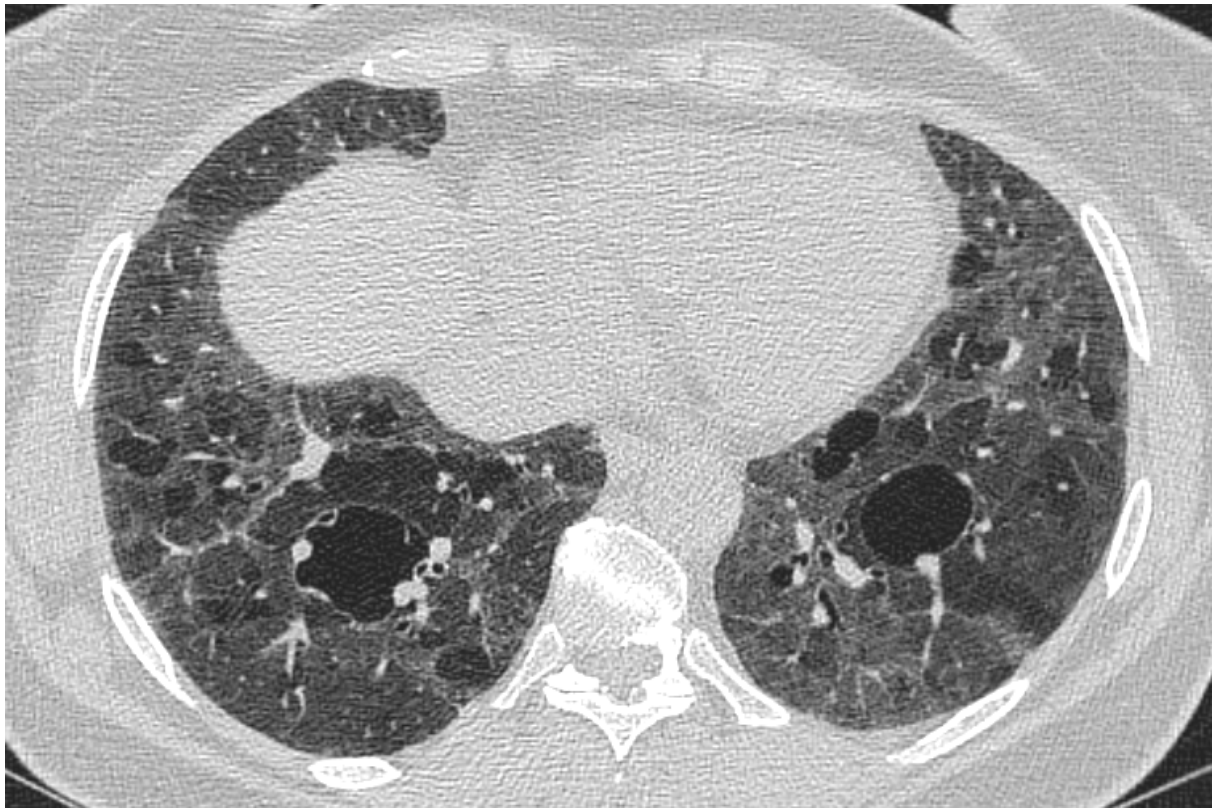






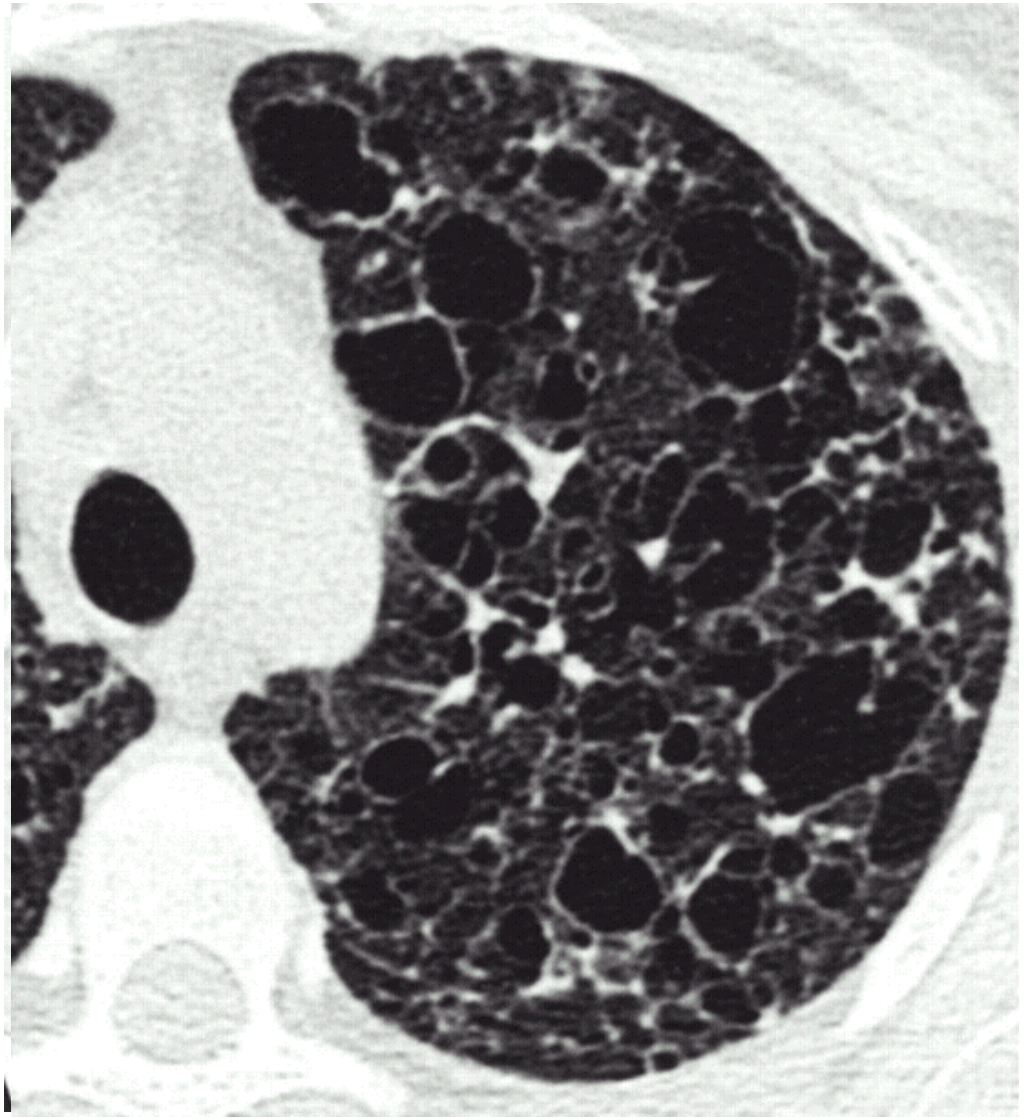
- Numerous thin-walled lung cysts
- These cysts usually range from 2 mm to 5 cm
- Their size tends to increase with disease progression

Is HRCT of our patient typical for LAM?



- Yes
- No
- I don’t know

PLCH



- Smokers
- Nodules in early disease
- Basal sparing

PLCH: a neoplastic or a reactive condition?

Is PLCH a clonal proliferative process or a reactive process induced by cigarette smoke ?

The NEW ENGLAND JOURNAL of MEDICINE

Volume 331:154-160 July 21, 1994 Number 3

Langerhans'-Cell Histiocytosis (Histiocytosis X) --

A Clonal Proliferative Disease

Cheryl L. Willman, Lambert Busque, Barbara B. Griffith, Blaise E. Favara, Kenneth L. McClain, Marilyn H. Duncan, and D. Gary Gilliland

The American Journal of Surgical Pathology *25(5): 630–636, 2001*

Pulmonary Langerhans' Cell Histiocytosis

Molecular Analysis of Clonality

Samuel A. Yousem, M.D., Thomas V. Colby, M.D., Yuan-Yuan Chen, B.S., Wen-Gang Chen, B.S., and Lawrence M. Weiss, M.D.

Mutations in PLCH

- BRAF mutations have been identified in up to 67% of cases of PLCH

- Identical but mutually exclusive MAPK/ ERK pathway mutations (BRAF, MAP2K1) were found supporting a neoplastic/clonal origin

Chilosi M et al, Leuk Lymphoma 2014
Kamionek M et al, Histopathology 2016

- NRAS mutations have been found

  BRAF and NRAS mutations can be present in different areas within the same lung lesion supporting a polyclonal nature of LCs

Mourah S et al, ERJ 2016

PLCH: a neoplastic or reactive condition?

At least a proportion of PLCH is a cigarette smoke induced or promoted dendritic cell neoplasm that is associated with a prominent immune-inflammatory component

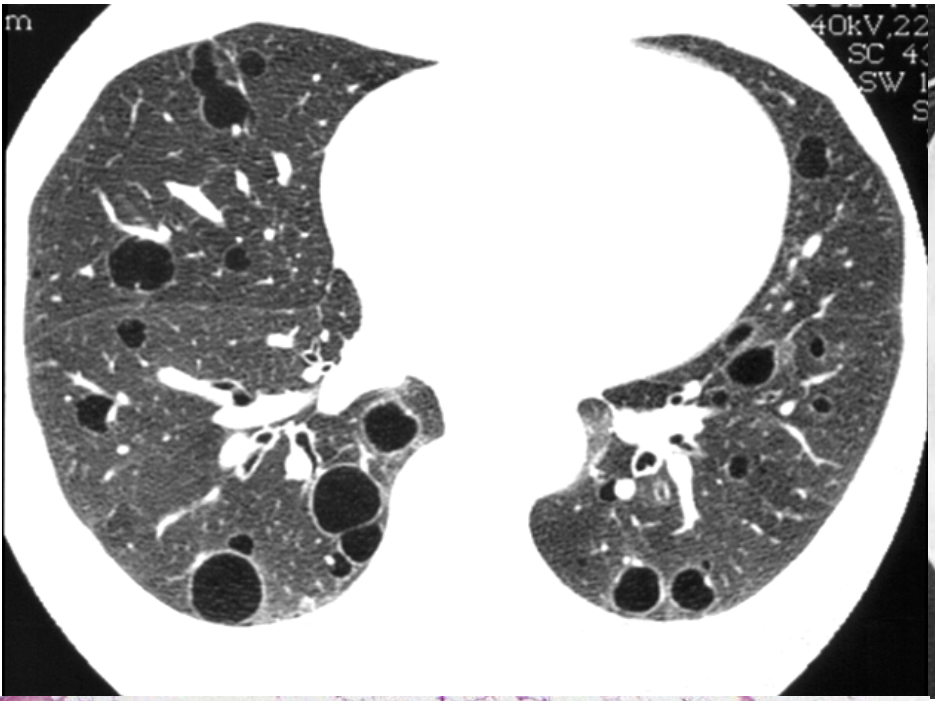
Gupta N et al, AJRCCM 2015

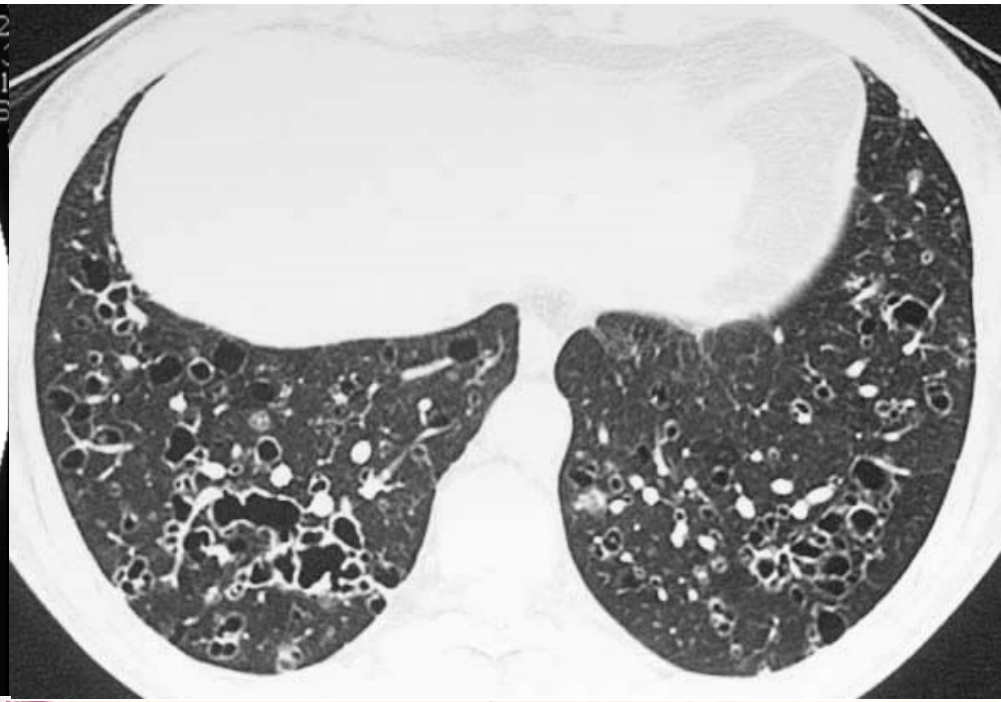
Role of smoking

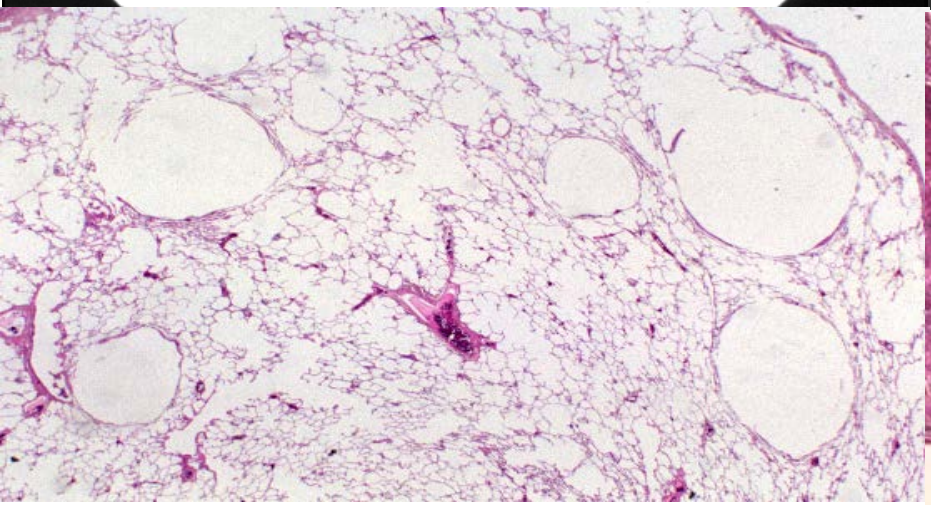
- Smoking induces accumulation of CD1a+ cells in the lungs
- Smoking stimulates local production of cytokines and osteopontin, which play a role in the recruitment, differentiation and activation of dendritic cells

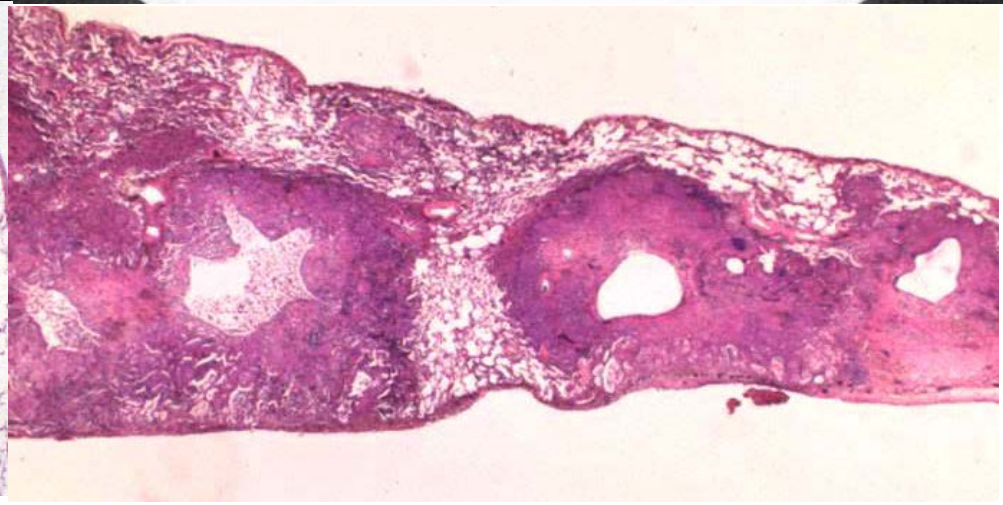
LAM

PLCH

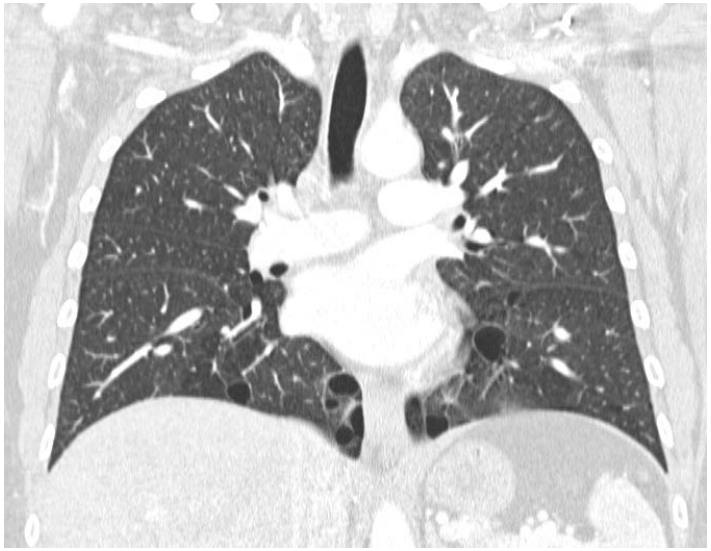


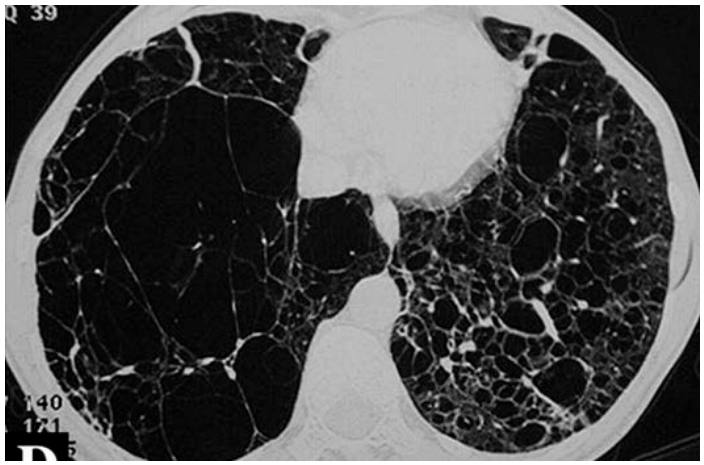






Others cystic lung diseases – BHD etc…





Colombat et al

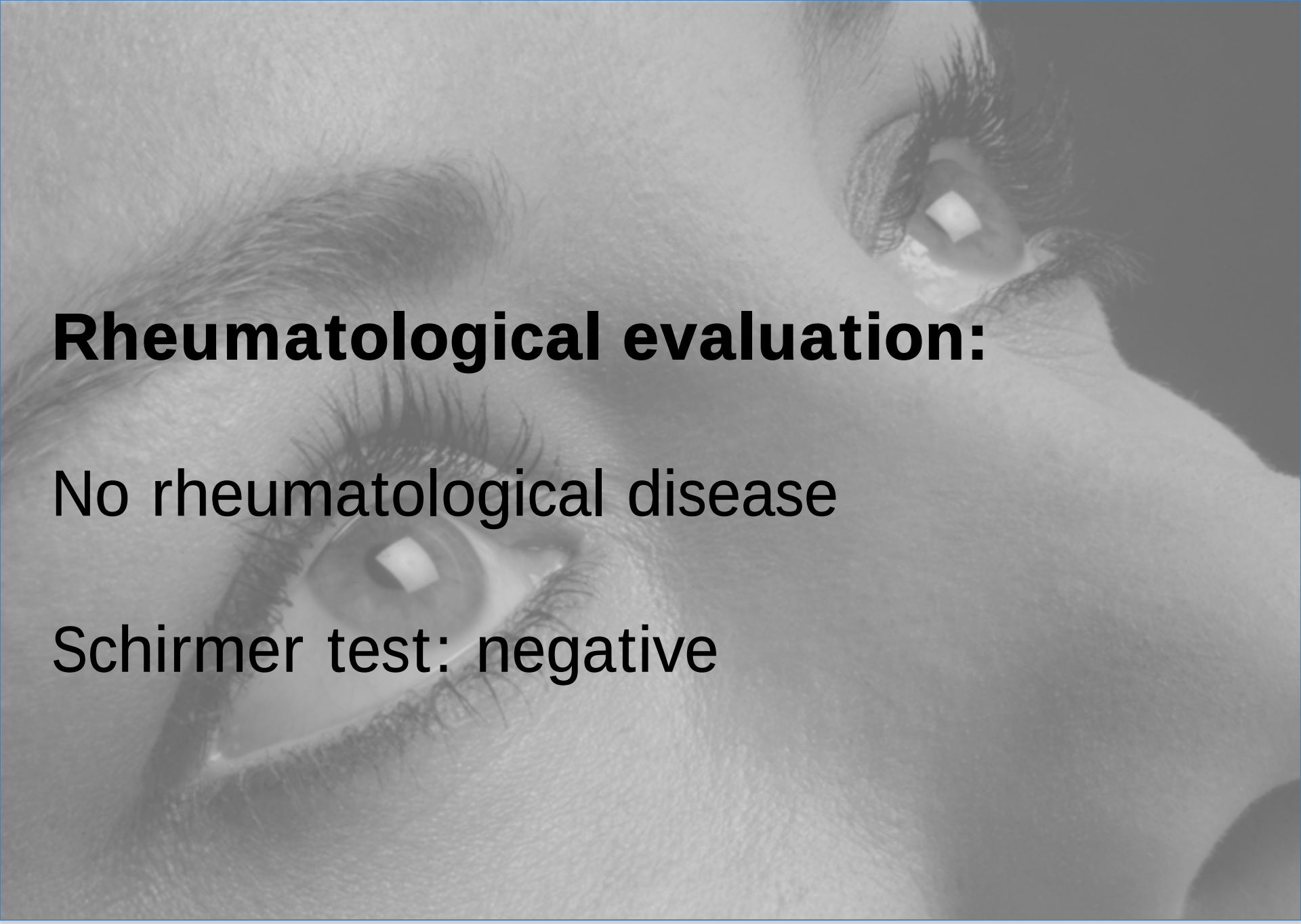
- Birt Hogg Dube
  - Autosomal dominant defect in the folliculin gene
  - Lung cysts, renal tumours and fibro-folliculomas
- LIP
- metastatic endometrial sarcoma
- light chain deposition
  - patchy deposition of eosinophilic material in alveolar walls, small airways, and vessels
- ……

Our patient…

Lab tests

Lab tests were within normal range

Parameter	Results
Antinuclear antibody	Positive 1:320
ENA	Negative
Rheumatoid factor	Positive
Anti-CCP	Negative



Rheumatological evaluation:

No rheumatological disease

Schirmer test: negative

Bronchoscopy

Macroscopic assessment showed no airway abnormality

Parameter	BAL differential cell count
Total cell count	280000 /mm3
Macrophages	24%
Neutrophils	8%
Lymphocites	68%
CD4/CD8	**2.3%**

BAS: microbiological analysis were all negative
no atypical cells

New tests were performed:

- Serum VEGF-D levels: 306 ng/mL

- Abdominal CT: normal

- Brain MRI: normal

What's the role of serum VEGF-D level in LAM?

- VEGF-D test is diagnostic in patients with compatible cystic changes on lung CT scan
- Sensitivity of test is low
- Serum VEGF-D levels seem to vary according to disease manifestations
- All the answers are correct

LAM – Biomarkers

VEGF-D

2006	Seyama K et al.	VEGF-D is increased in serum of patients with LAM
2008	Young et al.	VEGF-D serum levels are higher in LAM than in similar cystic or chylous lung diseases
2009	Glasgow et al	VEGF-D levels in LAM reflect lymphatic involvement
2010	**Young et al.**	**VEGF-D level higher than 800 pg/mL in a woman with typical changes on high-resolution CT scan is diagnostically specific for LAM, and identifies LAM in women with TSC**
2013	Young et al.	The results of an analysis of data from the MILES trial confirm that VEGF-D is a useful biomarker that correlates with disease severity and treatment response

2016

Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guidelines: Lymphangioleiomyomatosis Diagnosis and Management

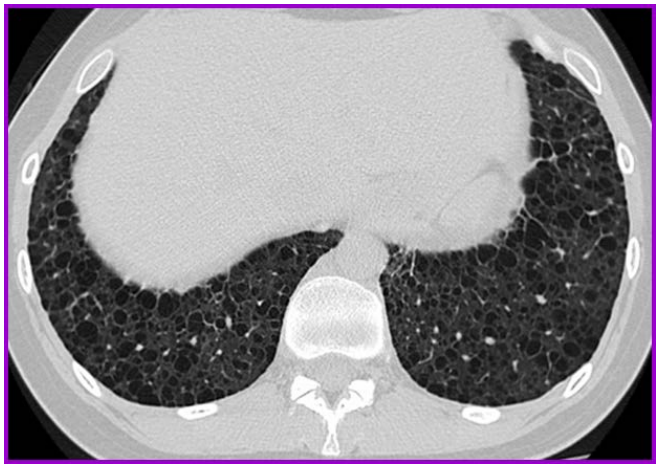
Francis X. McCormack, Nishant Gupta, Geraldine R. Finlay, Lisa R. Young, Angelo M. Taveira-DaSilva, Connie G. Glasgow, Wendy K. Steagall, Simon R. Johnson, Steven A. Sahn, Jay H. Ryu, Charlie Strange, Kuniaki Seyama, Eugene J. Sullivan, Robert M. Kotloff, Gregory P. Downey, Jeffrey T. Chapman, MeiLan K. Han, Jeanine M. D'Armiento, Yoshikazu Inoue, Elizabeth P. Henske, John J. Bissler, Thomas V. Colby, Brent W. Kinder, Kathryn A. Wikenheiser-Brokamp, Kevin K. Brown, Jean F. Cordier, Cristopher Meyer, Vincent Cottin, Jan L. Brozek, Karen Smith, Kevin C. Wilson, and Joel Moss; on behalf of the ATS/JRS Committee on Lymphangioleiomyomatosis

VEGF-D testing is recommended to establish the diagnosis of LAM

LAM diagnosis

Definite LAM: characteristic lung HRCT + any of the followings

	ERS guidelines 2010	ATS/JRS guidelines 2016
-	Tuberous Sclerosis Complex	✓
-	Chylous effusions	✓
-	Angiomyolipomas	✓
-	Lymphatic involvement	✓
		- Serum VEGFD levels ≥ 800 pg/mL



Characteristic lung HRCT
Numerous thin-walled lung cysts distributed diffusely throughout the lungs without sparing of lung bases

Johnson SR et al, ERJ 2010
McCormack FX et al, AJRCCM 2016

LAM – Biomarkers

VEGF-D

- Serum VEGF-D testing has a low false positive rate but a high false negative rate: a serum VEGFD value < 800 pg/mL does not exclude LAM.

- Serum VEGF-D can vary according to disease manifestations. It is usually higher in patients with lymphatic manifestations.

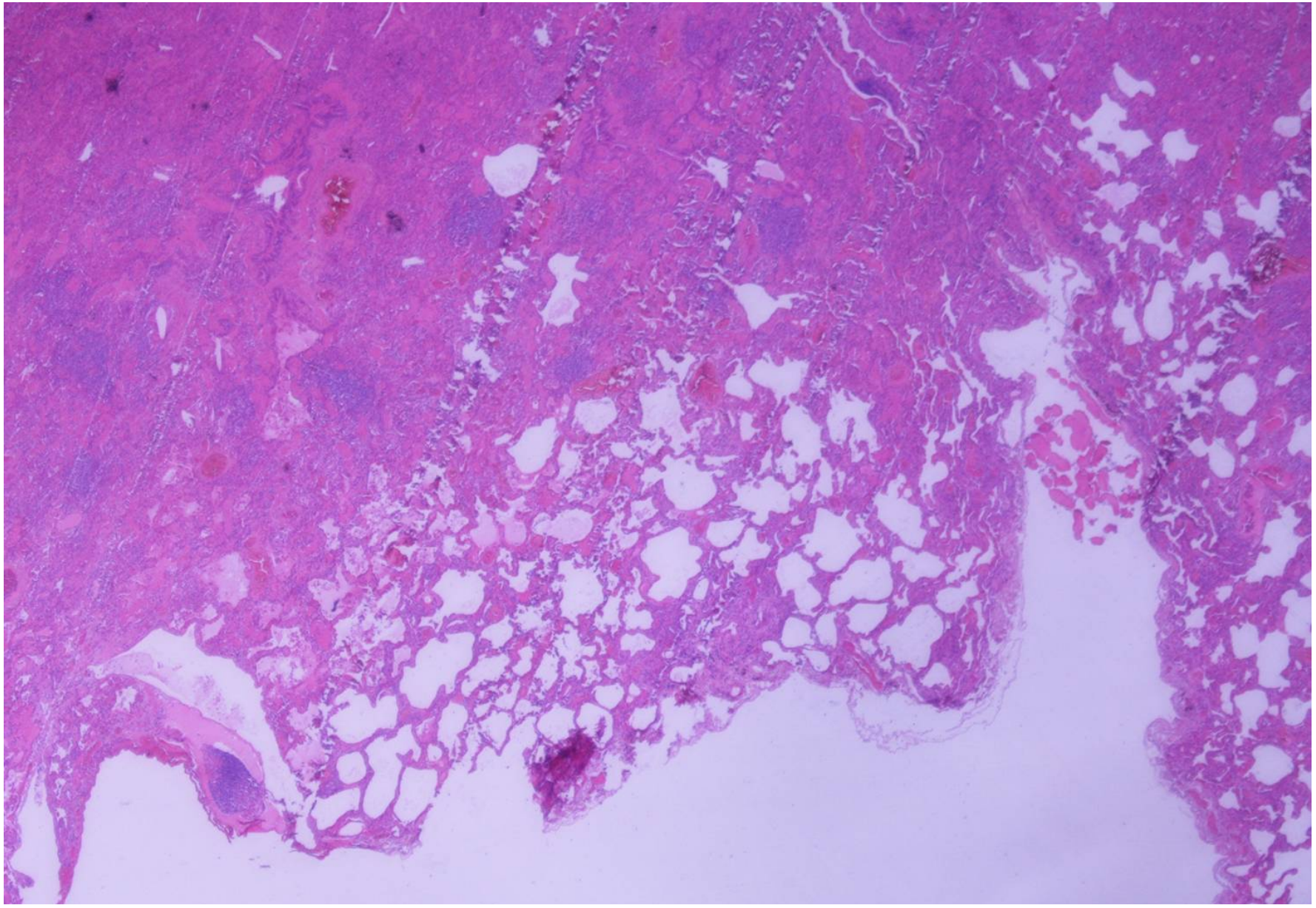
New biomarkers are still needed for diagnosis, follow-up, and designing of clinical trials

What is the next step which should be taken?

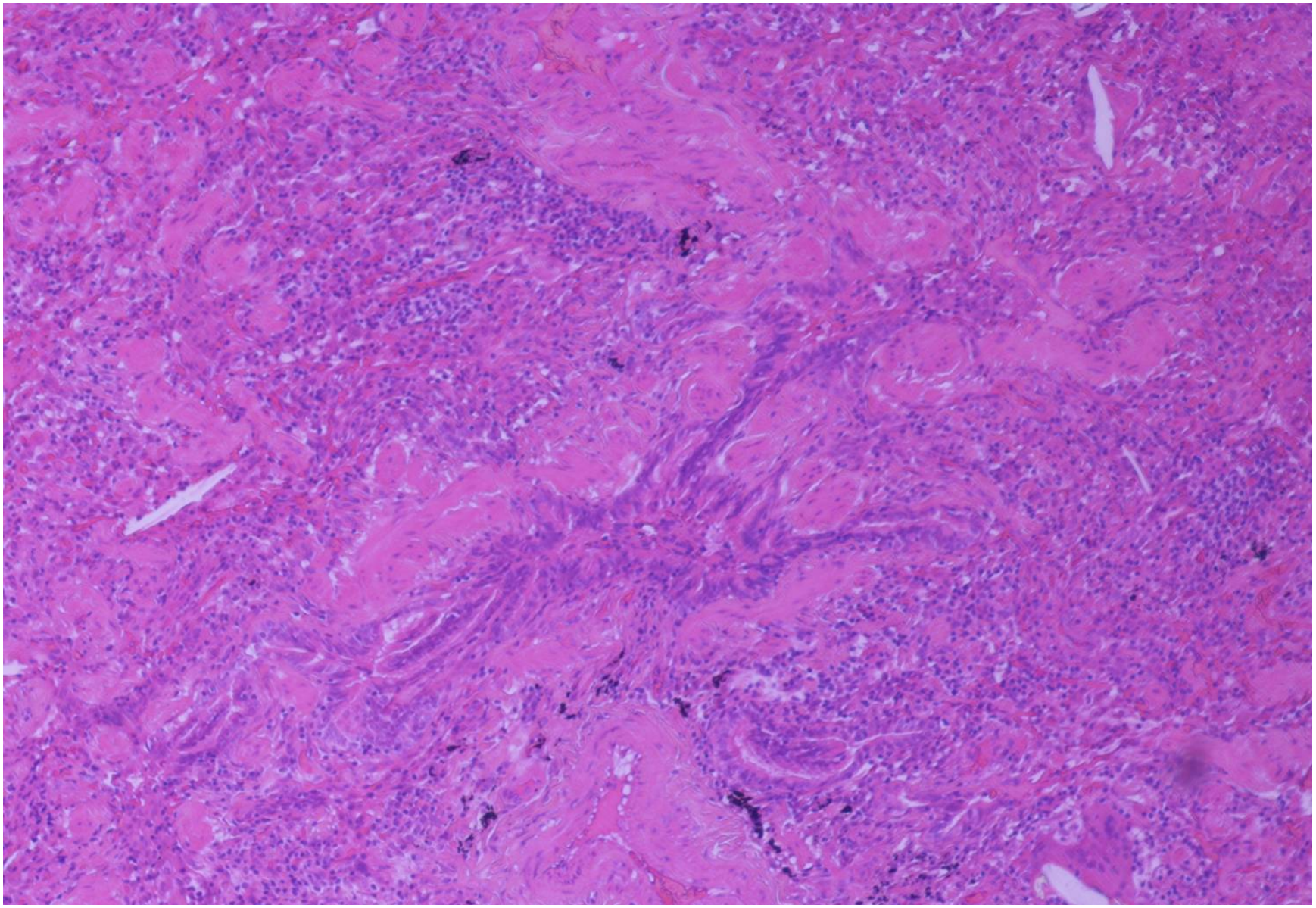
- Lung biopsy
- Cryobiopsy
- Clinical-radiological follow-up
- Medical therapy

VATS was performed

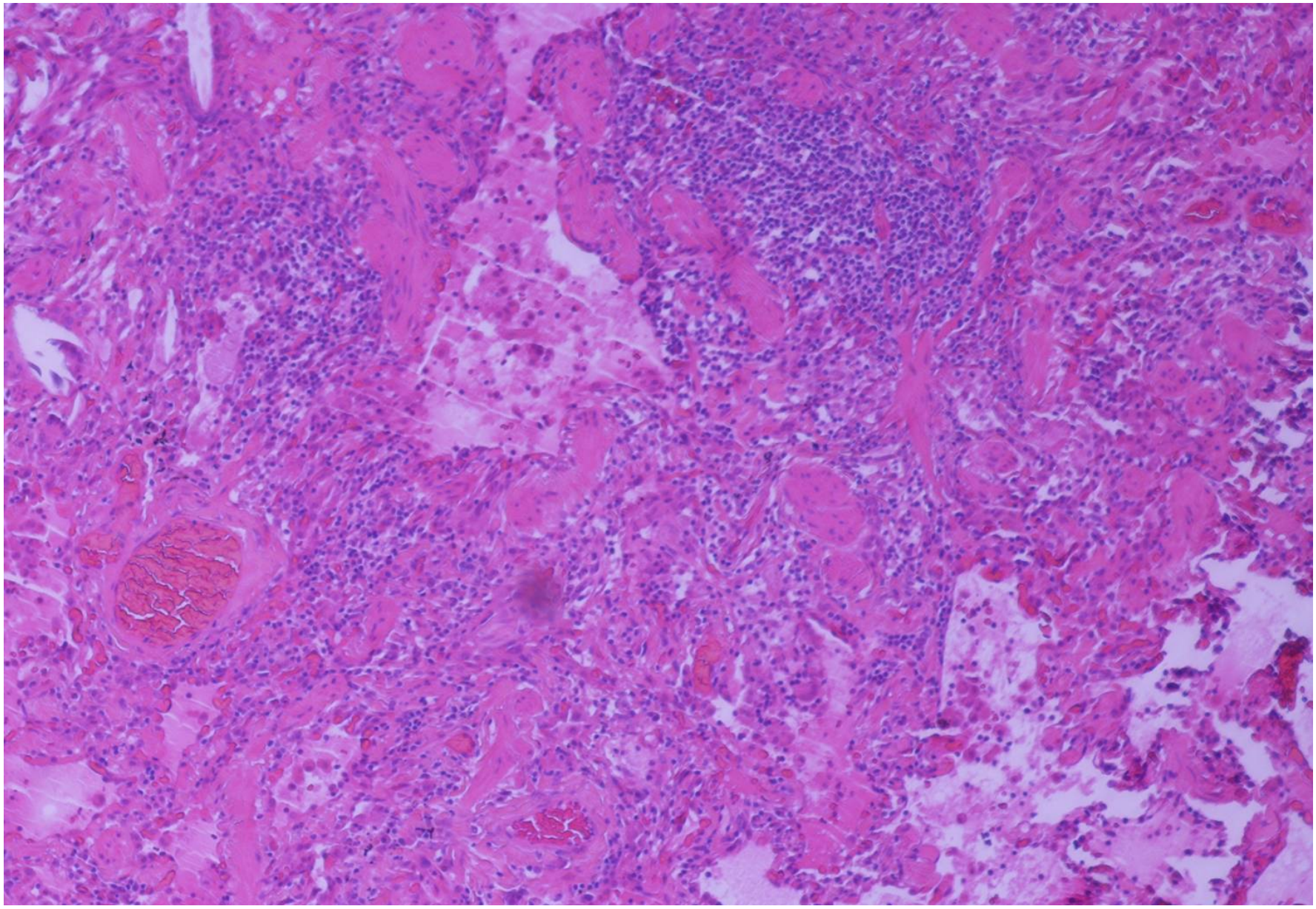
Samples were taken from upper and lower lobe of the left lung



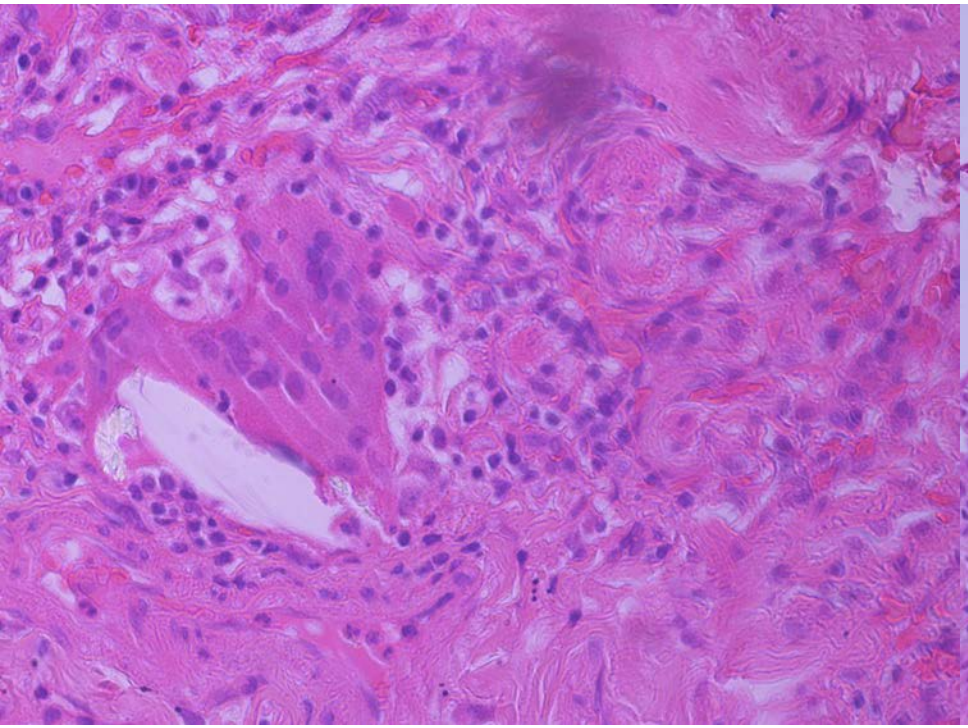
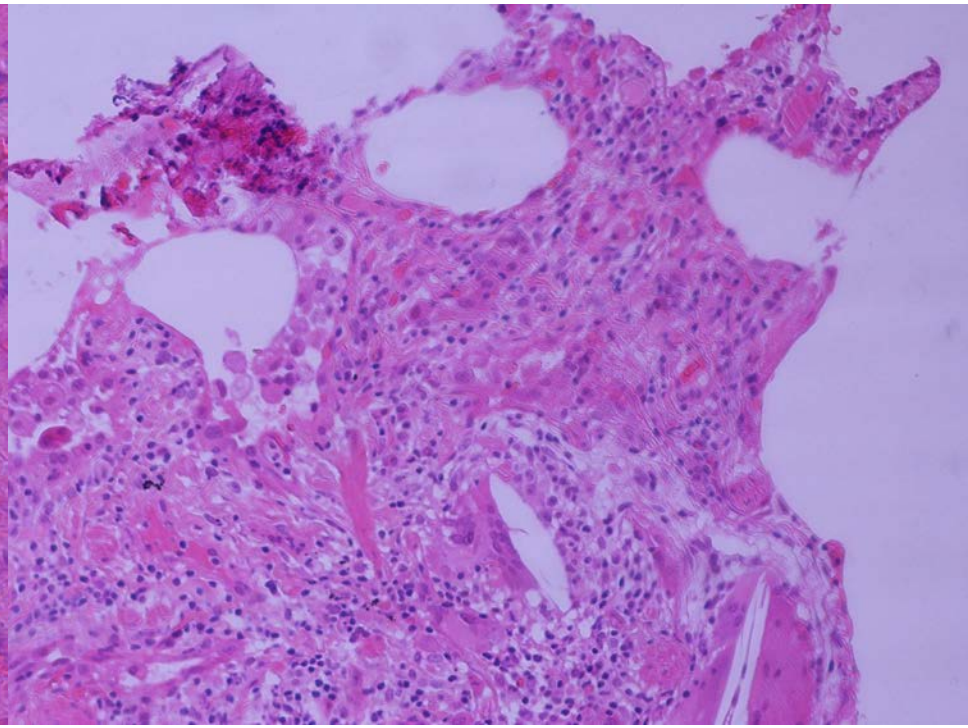
Diffuse lymphoplasmacytic interstitial infiltration



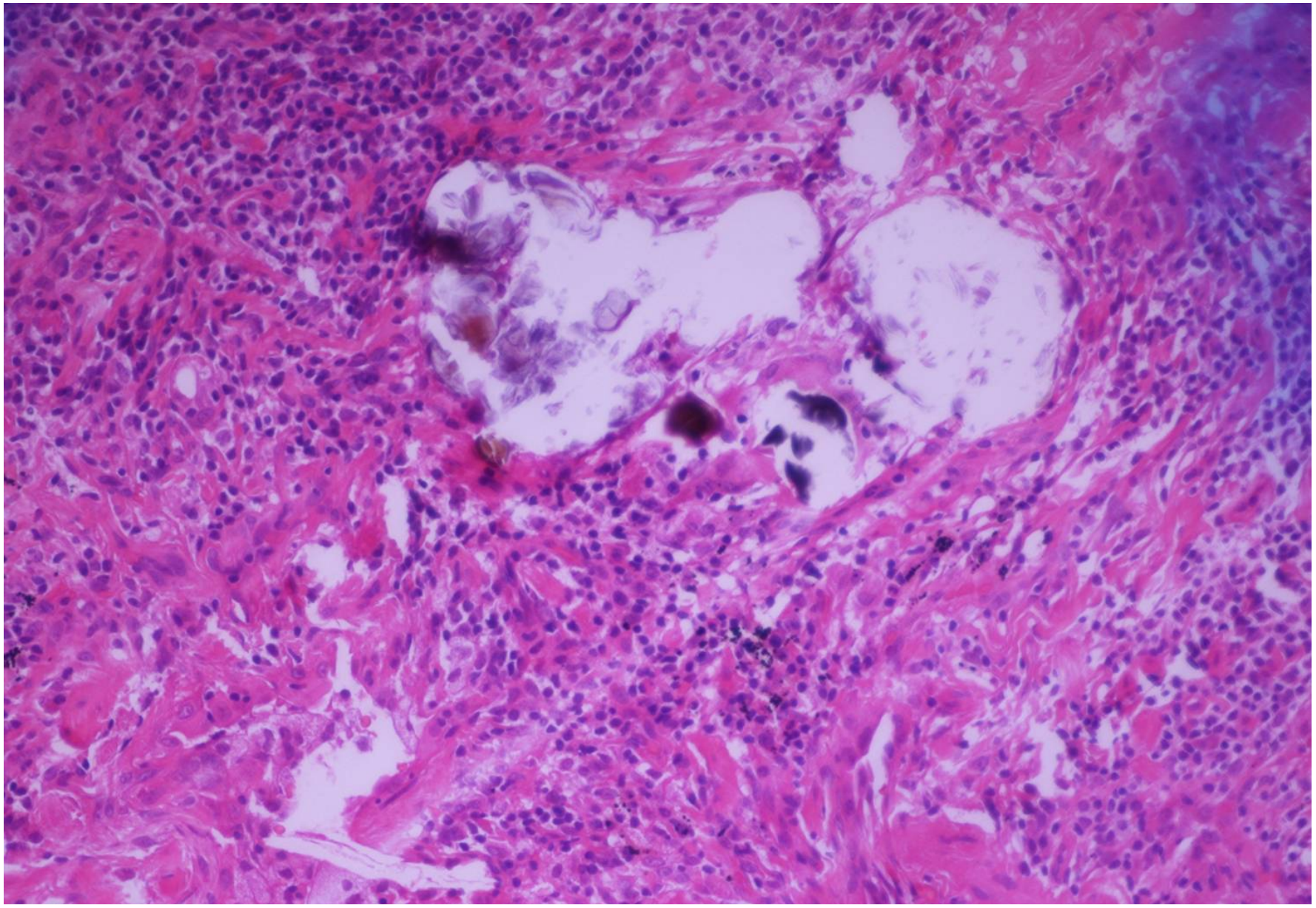
More intense peribronchiolar lymphocytic infiltration



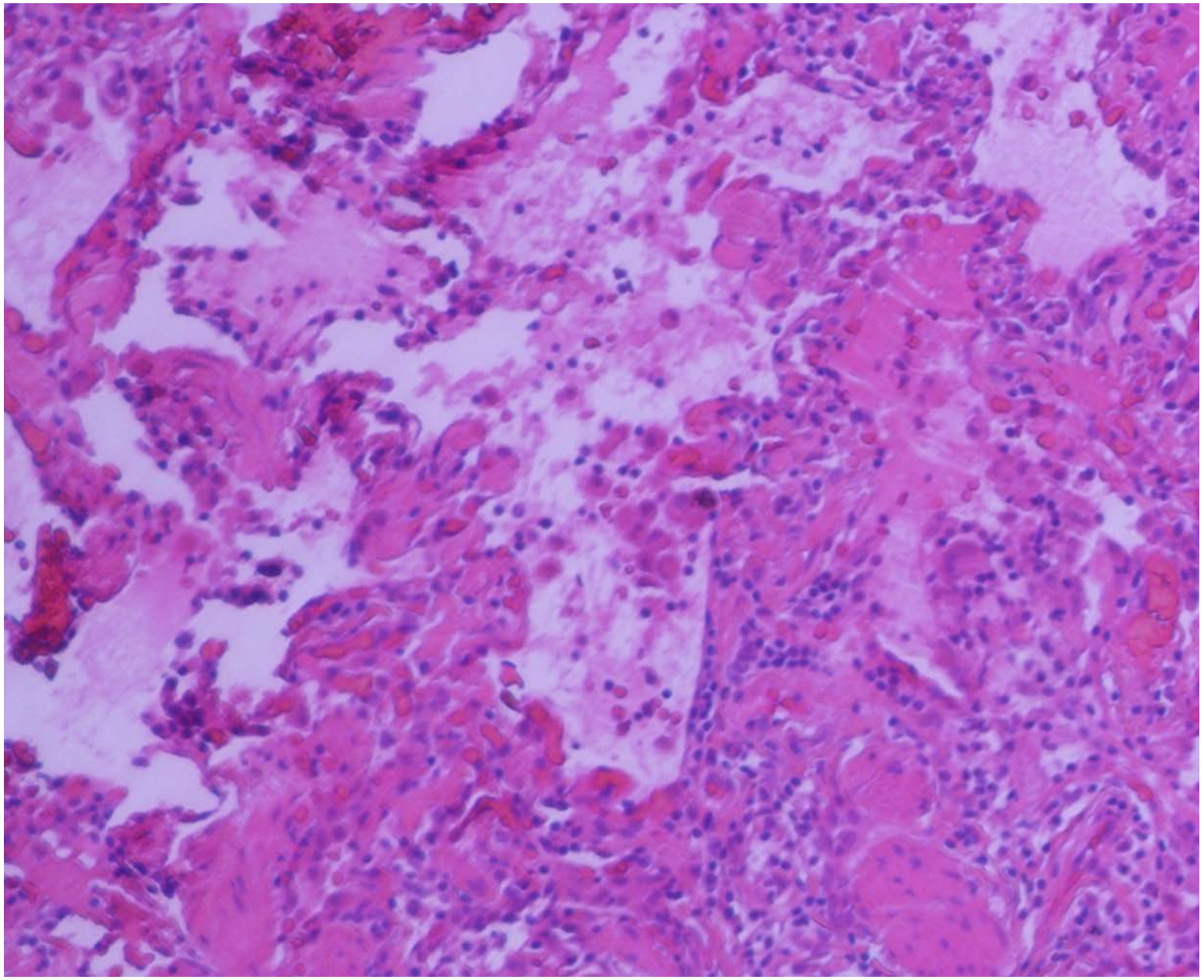
Cellular/follicular bronchiolitis

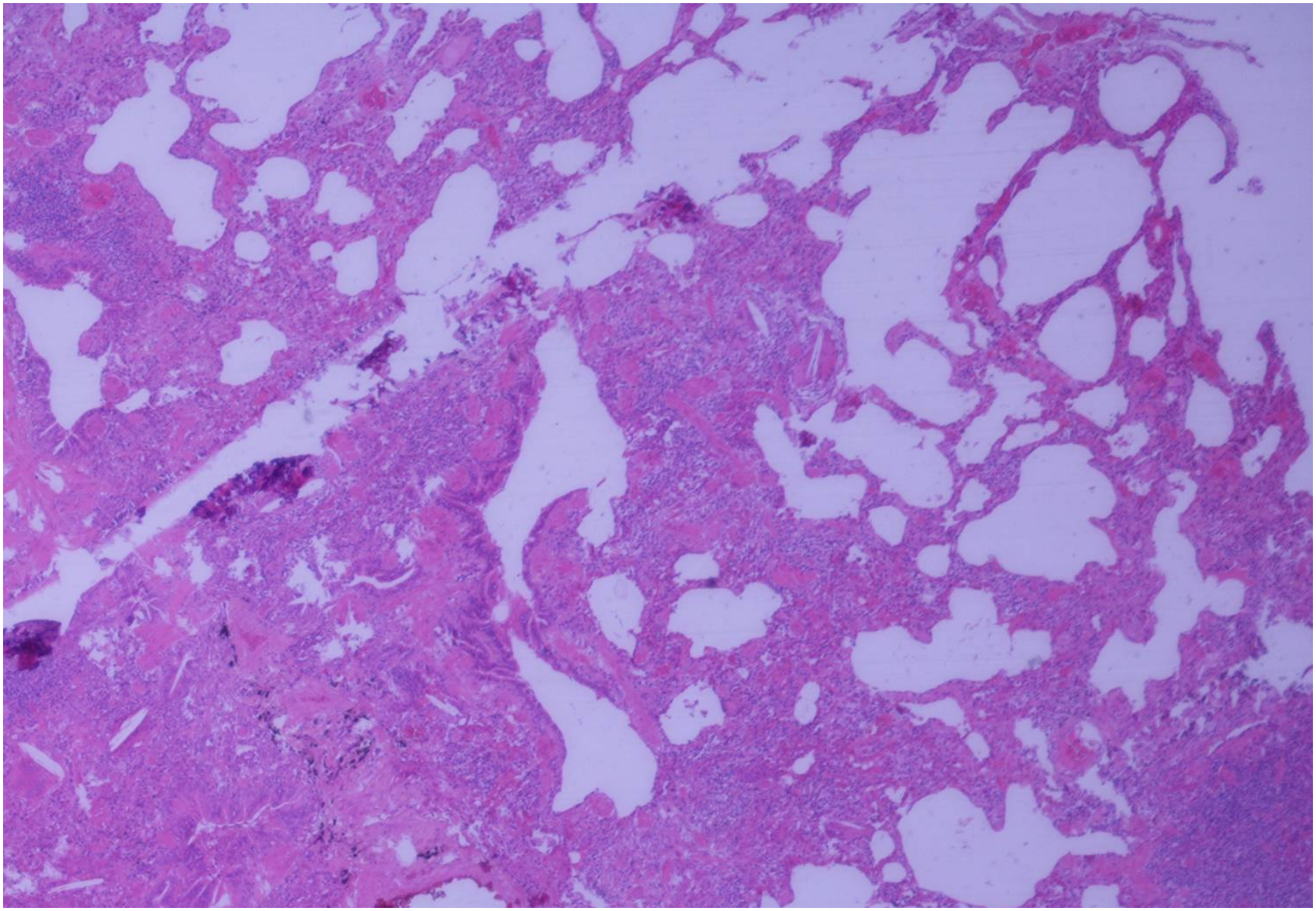
Giant cells



A Schaumann body



Small foci of organizing pneumonia and foamy macrophages



Cellular NSIP/LIP with giant cells and micro-granulomas

Histology:

Diffuse lymphoplasmacytic interstitial infiltration, more accentuated around the bronchioles with aspects of follicular/cellular bronchiolitis, is present

There are many interstitial micro-granulomas in the form of giant cells that incorporate cholesterol cleft, Schaumann bodies and aspect of organizing pneumonia

Conclusion: Pattern of cellular NSIP/LIP with micro-granulomas

What's your definitive diagnosis?

- IPAF
- Hypersensitivity pneumonitis
- NSIP
- Organizing pneumonia

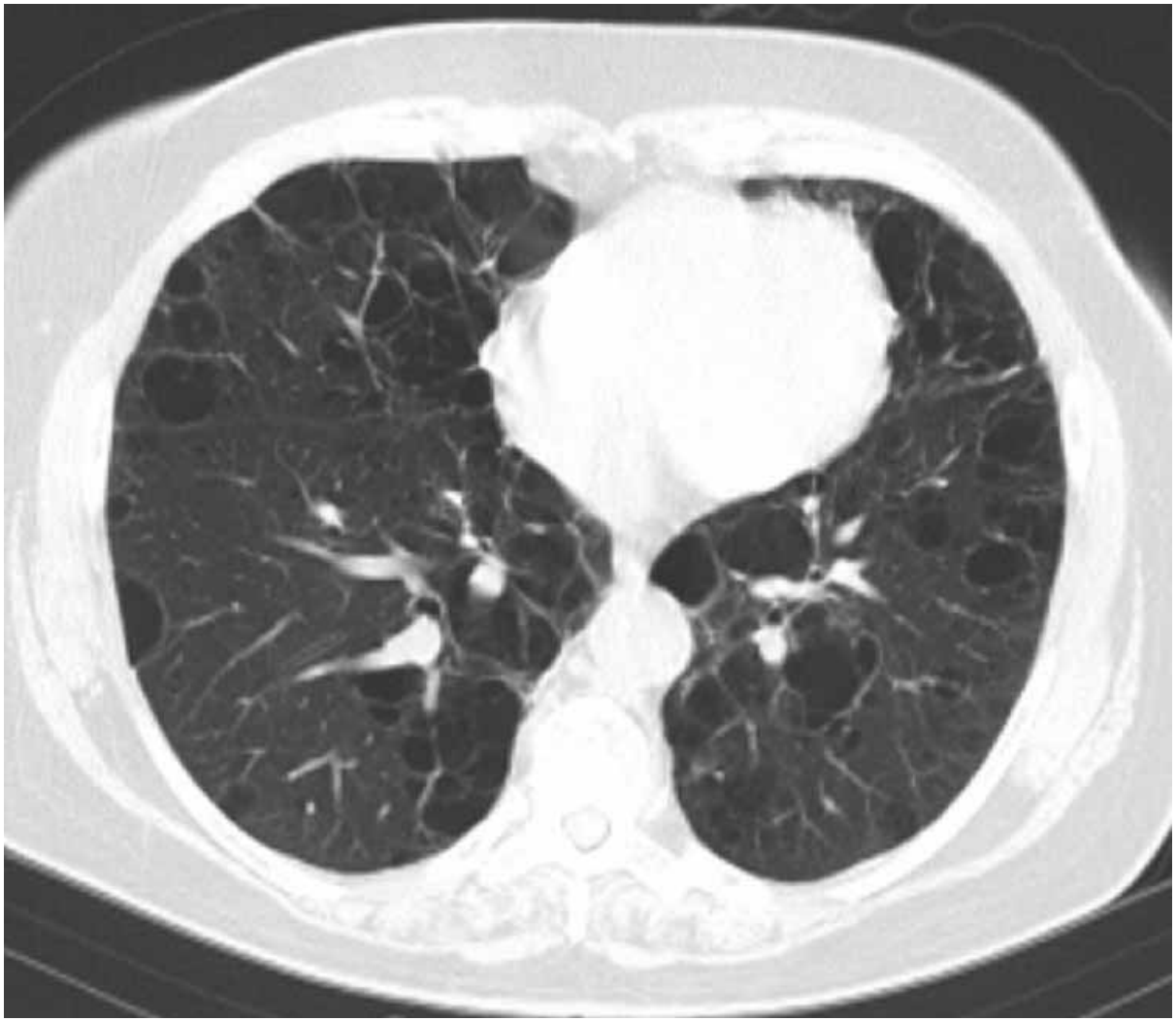
The criteria for IPAF are (1) the presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) and (2) the exclusion of alternative etiologies and (3) incomplete features of a defined CTD and (4) at least one feature from at least 2 domains (columns A, B, or C).

Table 1. Criteria for Interstitial Pneumonia With Autoimmune Features (IPAF)[a,b]

A. Clinical Domain	B. Serologic Domain	C. Morphologic Domain
• Raynaud phenomenon • Palmar telangiectasia • Distal digital fissuring (ie, "mechanics hands") • Distal digital tip ulceration • Inflammatory arthritis *or* polyarticular morning joint stiffness >60 min • Unexplained digital edema • Unexplained fixed rash on the digital extensor surfaces (Gottron sign)	• ANA titer >1:320, diffuse, speckled, or homogeneous patterns *or* ANA nucleolar pattern (any titer) *or* ANA centromere pattern (any titer) • RF >2 × ULN • Anti-CCP • Anti-dsDNA • Anti-Ro antibodies (SS-A) • Anti-La antibodies (SS-B) • Antiribonucleoprotein • Anti-Smith antigen • Antitopoisomerase (Scl-70) • Anti-tRNA synthetase (eg, Jo-1, PL-7, PL-12 [others are EJ, OJ, KS, Zo, tRS]) • Anti-PM-Scl • Anti-CADM (MDA-5)	Radiology features • Suggested NSIP pattern • Suggested OP pattern • Suggested mixed NSIP/OP pattern • Suggested LIP pattern Histopathology features (SLB) • NSIP • OP • NSIP with OP overlap • LIP • Interstitial lymphoid aggregates with GCs • Diffuse lymphoplasmacytic infiltration (±lymphoid follicles) Multicompartment involvement • Unexplained pleural effusion or thickening • Unexplained pericardial effusion or thickening • Unexplained intrinsic airways disease (by PFT, HRCT, or pathology) • Unexplained pulmonary vasculopathy

Fischer A et al. Eur Respir J 2015; 46: 976

Fischer A et al. Eur Respir J 2015; 46: 976



But.....

Patient reports a previous exposure to molds (up to 2 years before) and parrots (up to 10 years before)

Lab tests

Lab test were within normal range

Parameter	Results
Antinuclear antibody	Positive 1:320
ENA	Negative
Rheumatoid factor	Positive
Anti-CCP	Negative
Precipitins	Positive

Radiological findings of sub-acute HP:

Patchy ground-glass opacities

Lobular areas of decreased attenuation and vascularity and air trapping (mosaic pattern)

Poorly defined centrilobular nodules in approximately 50% of patients

Lung cysts

A small percentage of patients with sub-acute and chronic HP show thin-walled cysts, usually in areas of ground-glass attenuation, resembling those observed in lymphocytic interstitial pneumonia

Selman M et al. Am J Respir Crit Care Med 2012; 186: 314

The presence of autoimmune features in patients with HP has only recently been formally recognized; up to 15% of patients with HP may have associated autoimmune features

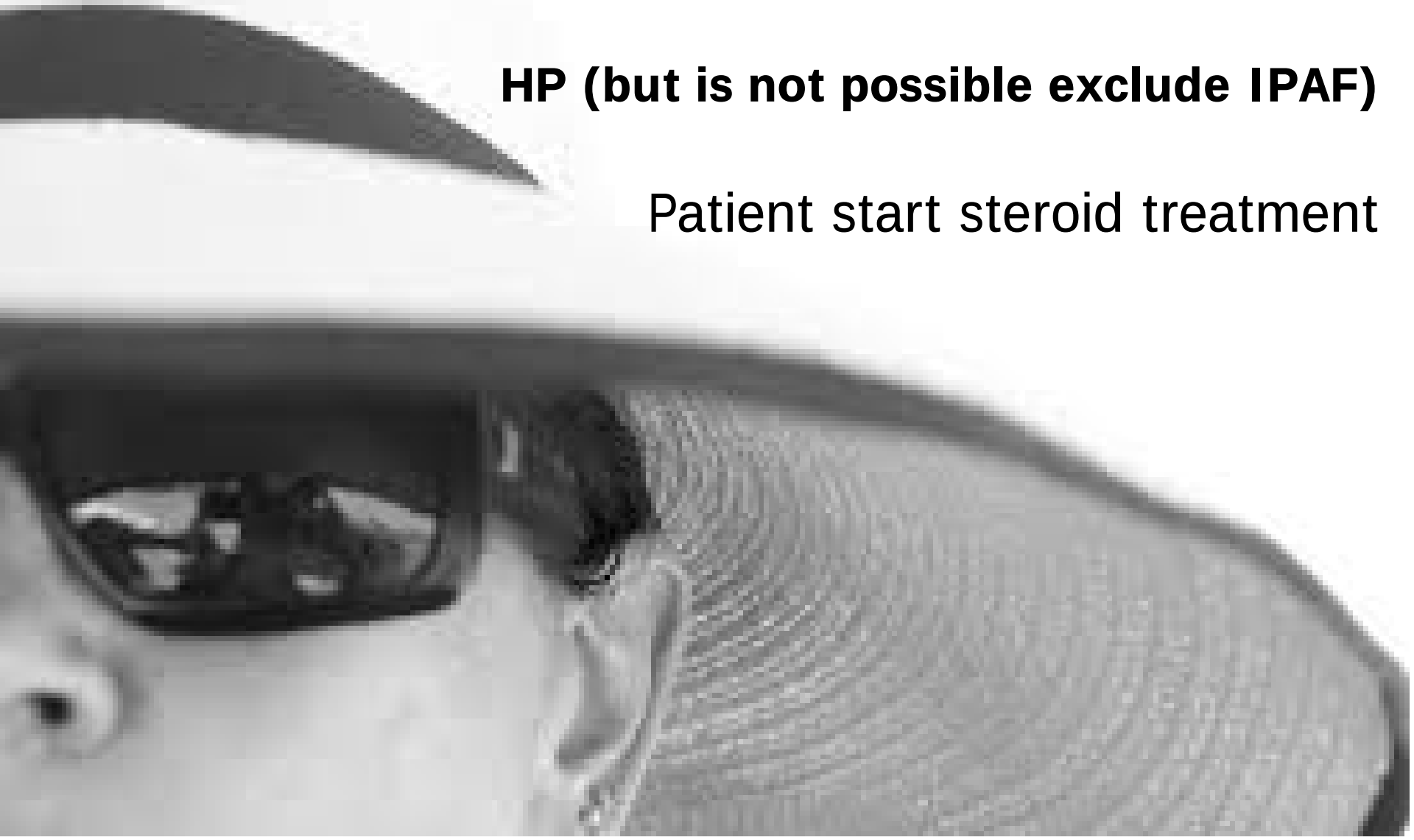
There is relationship between autoimmunity and HP

Chung JH et al. AJR 2017; 208:1229
Adegunsoye A et al. Respir Med 2016; 114: 53

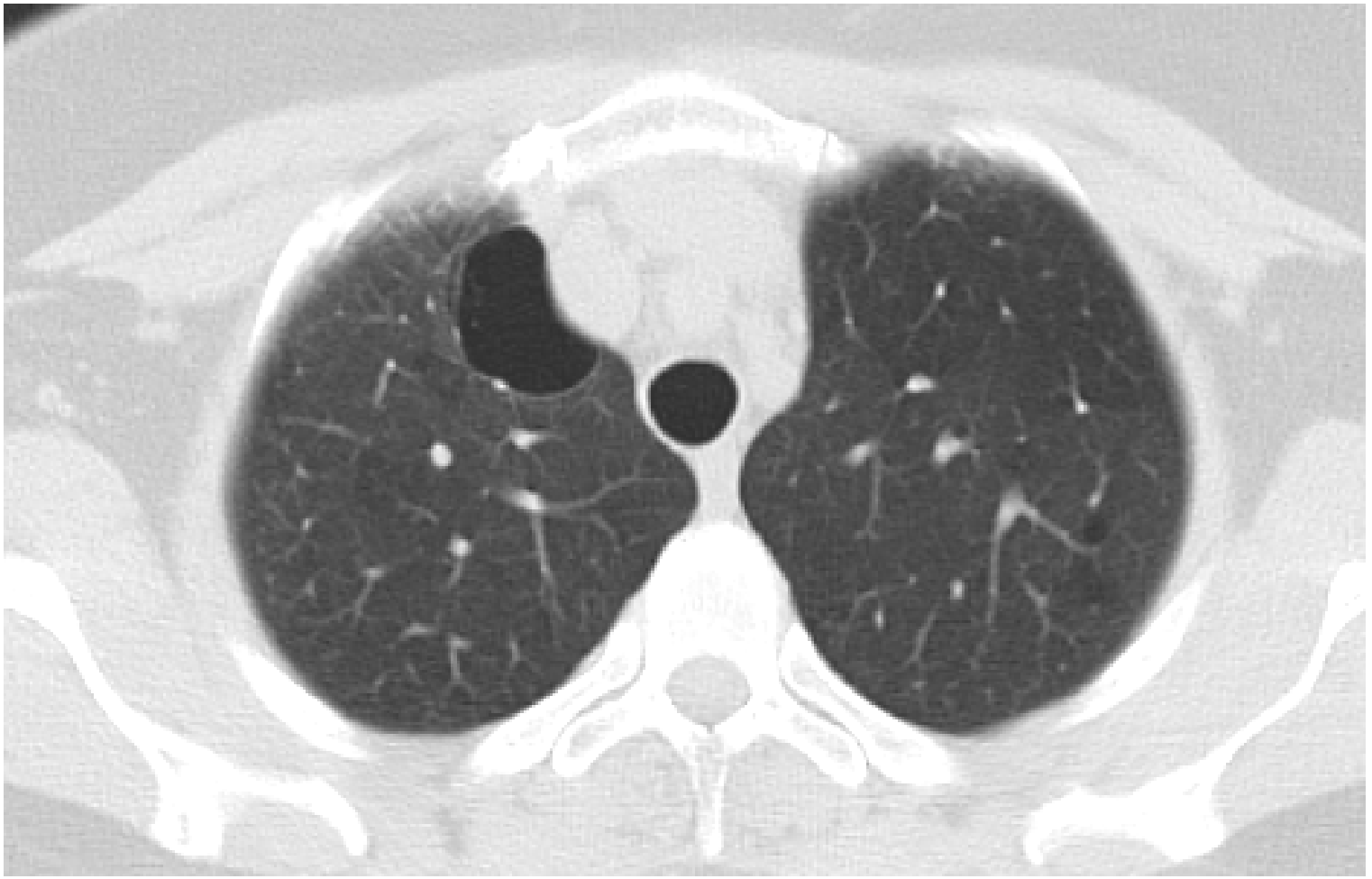
Multidisciplinary discussion

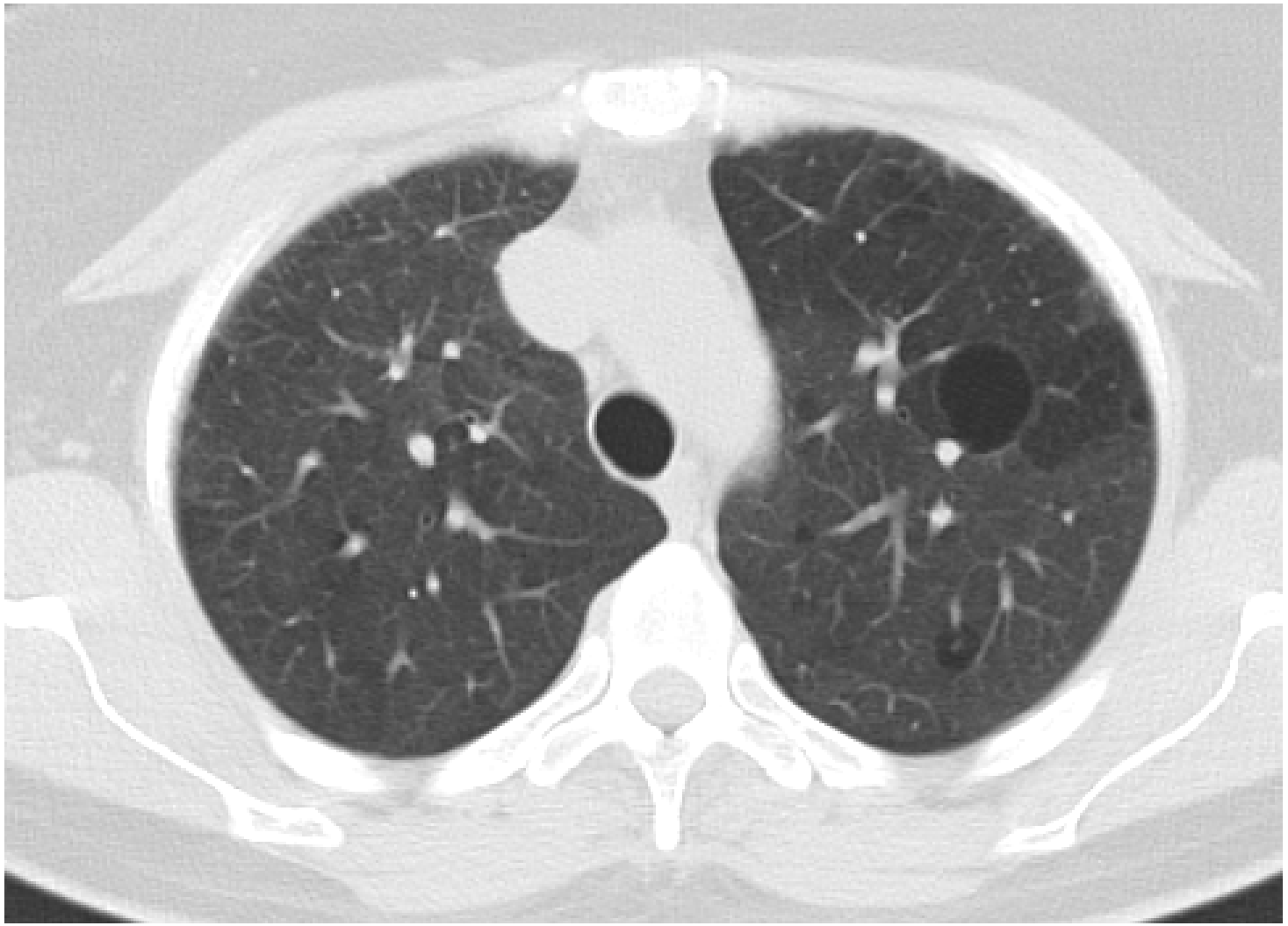
HP (but is not possible exclude IPAF)

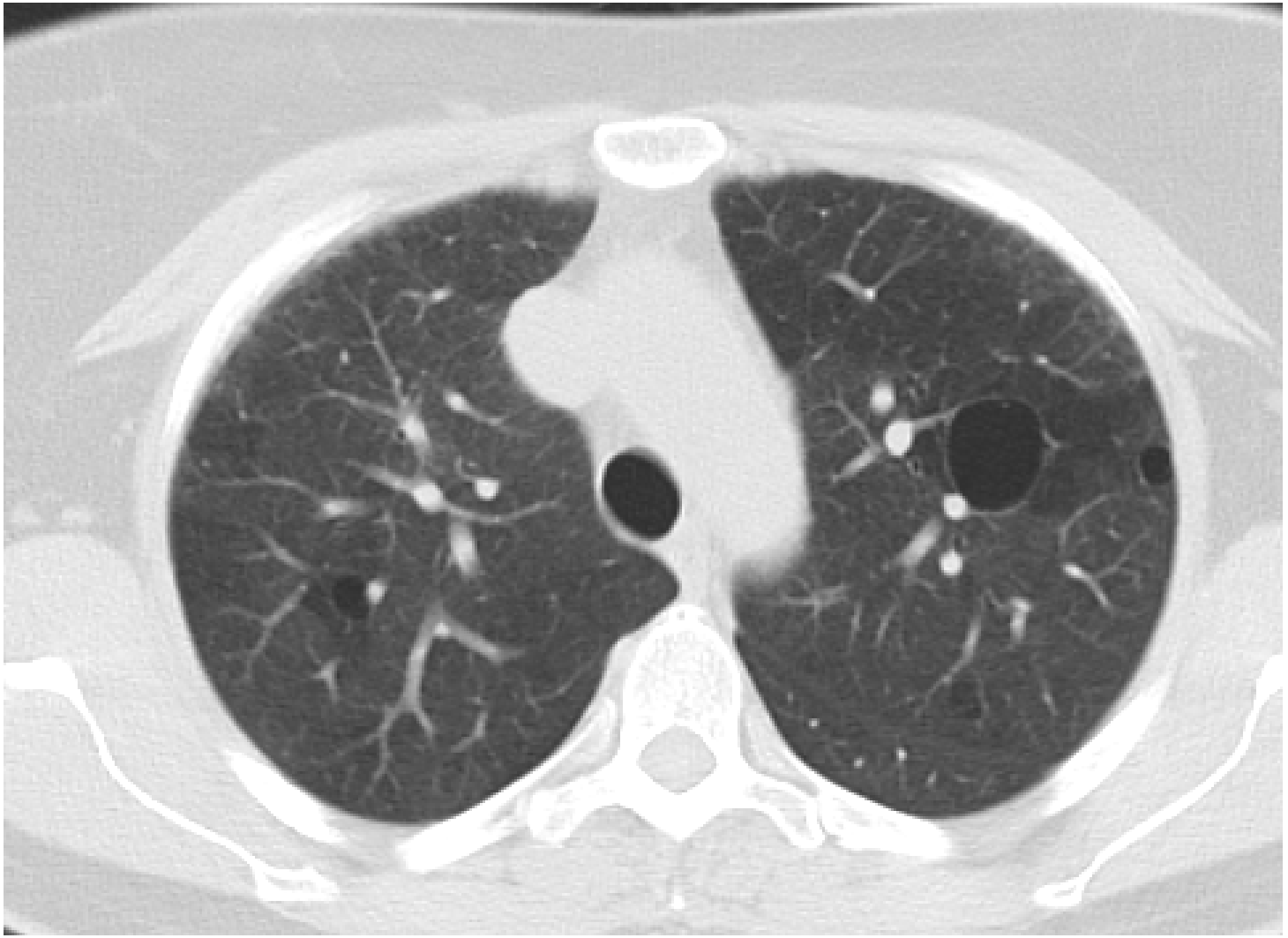
Patient start steroid treatment

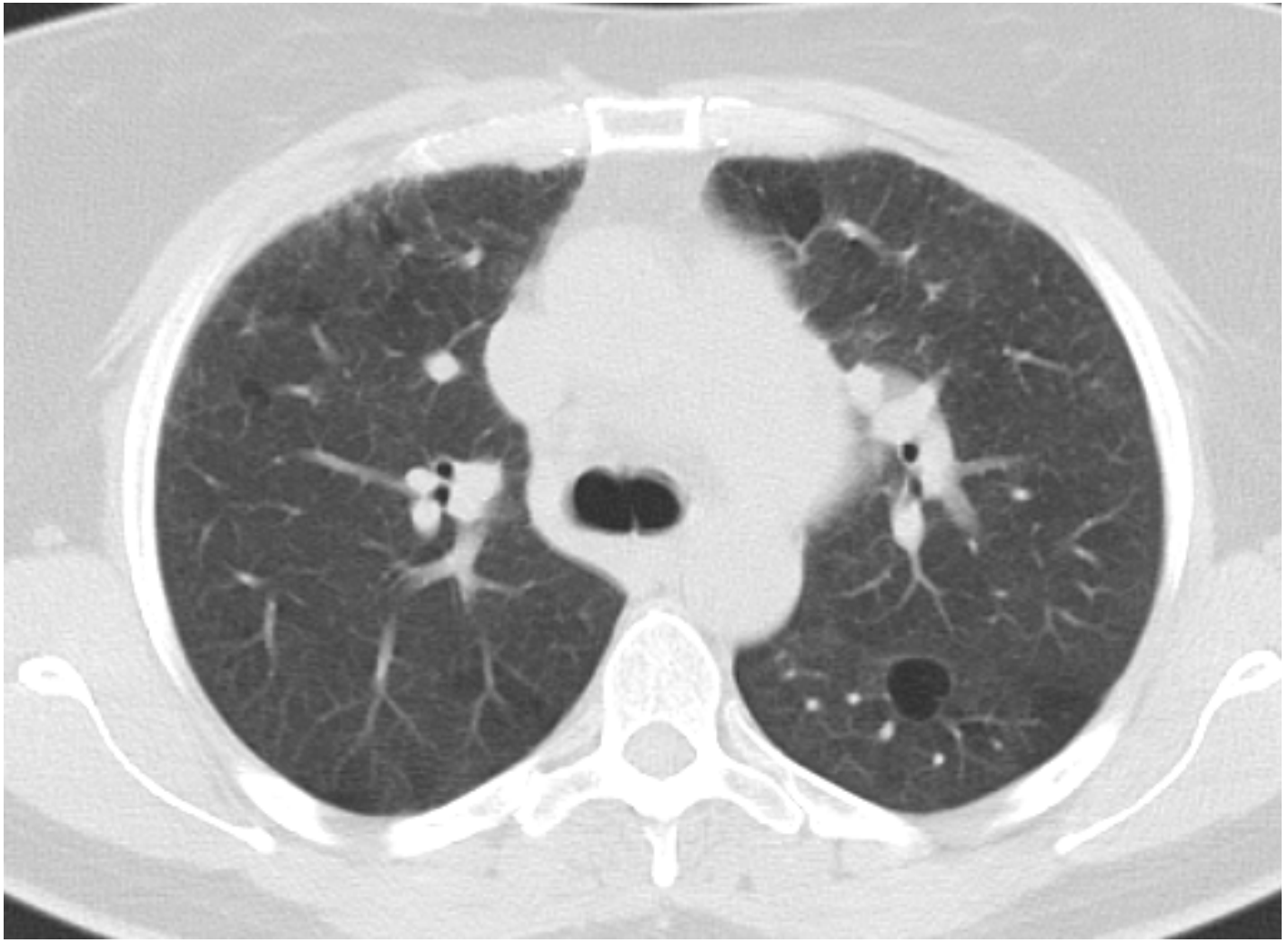


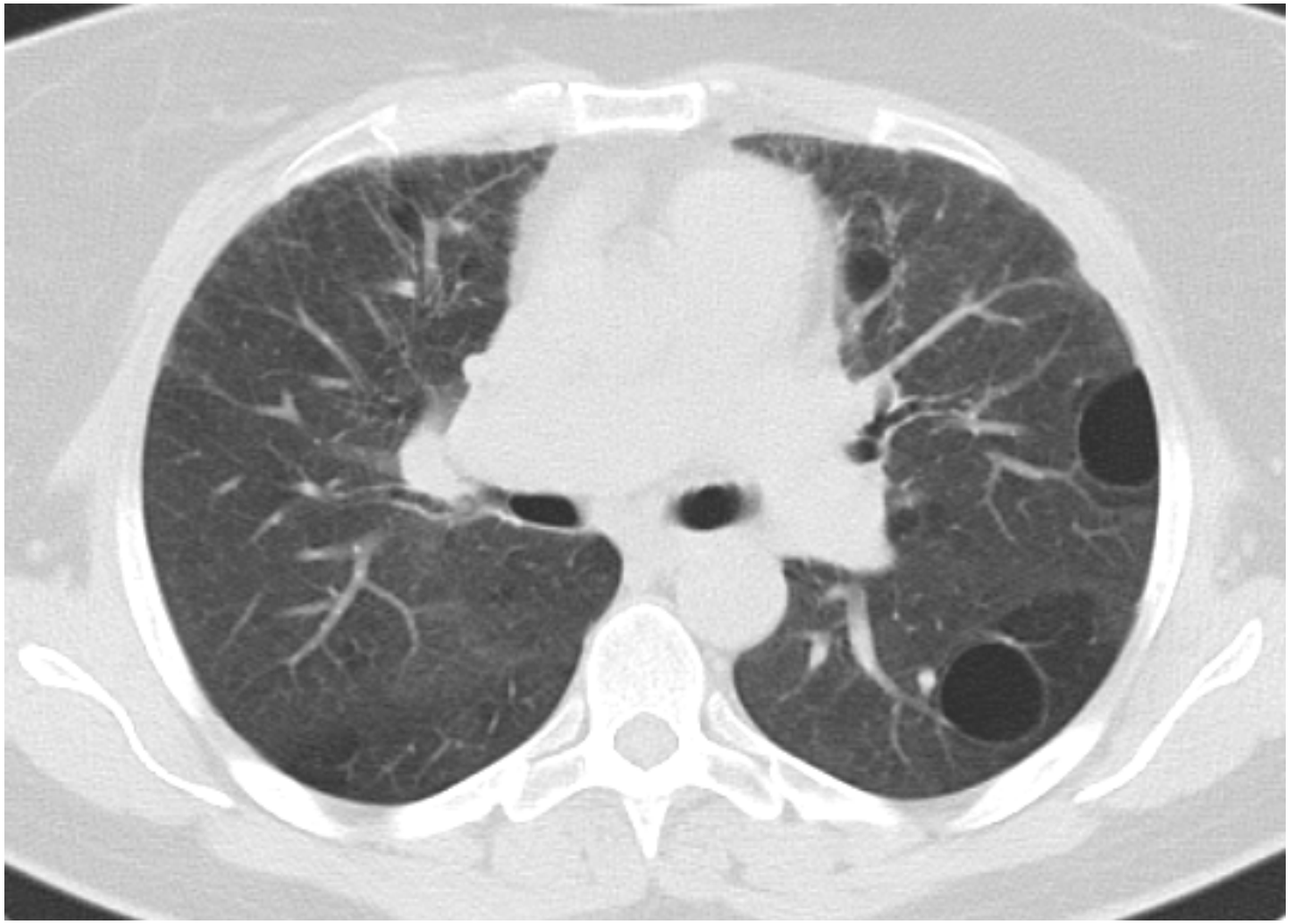
Four months after……

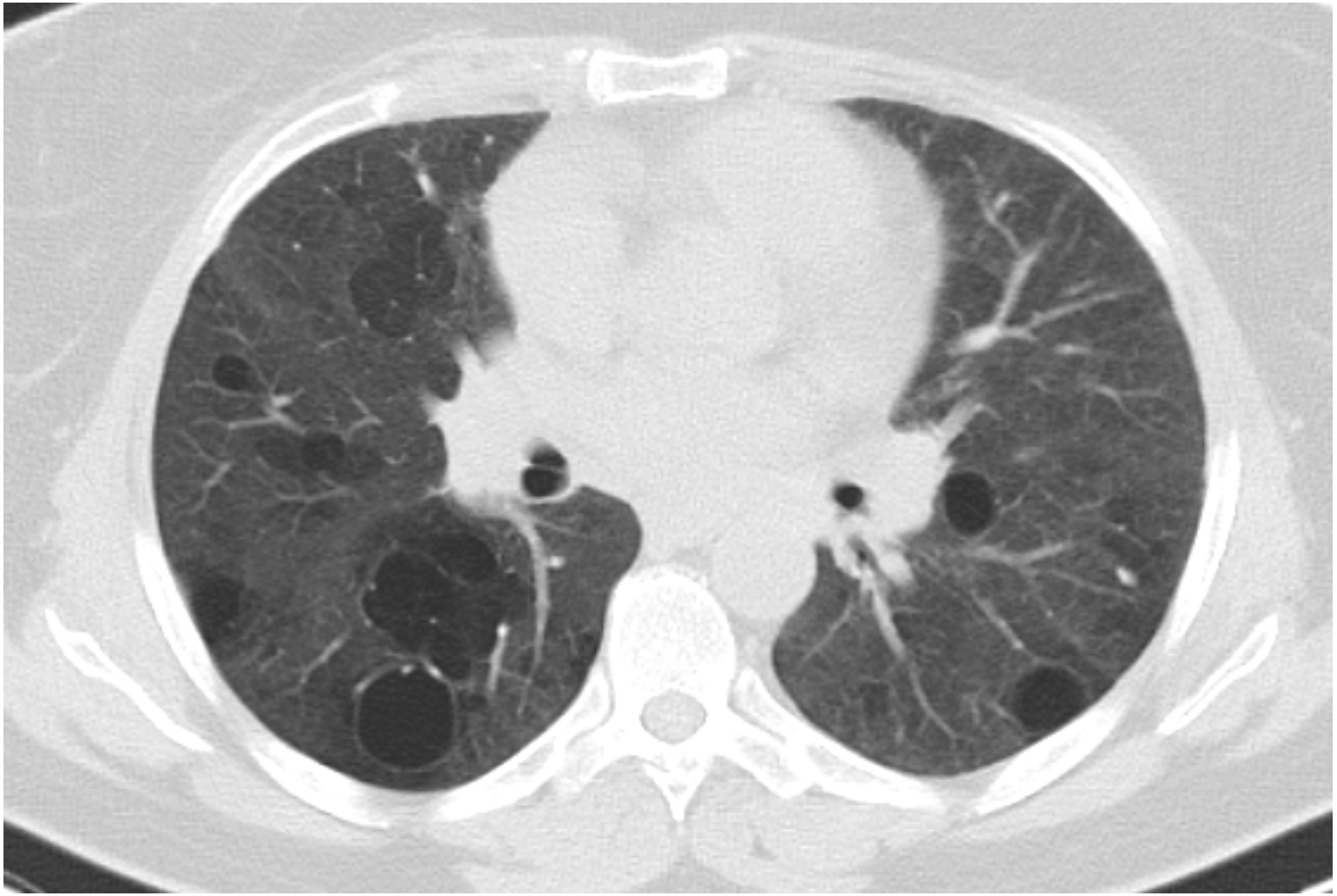


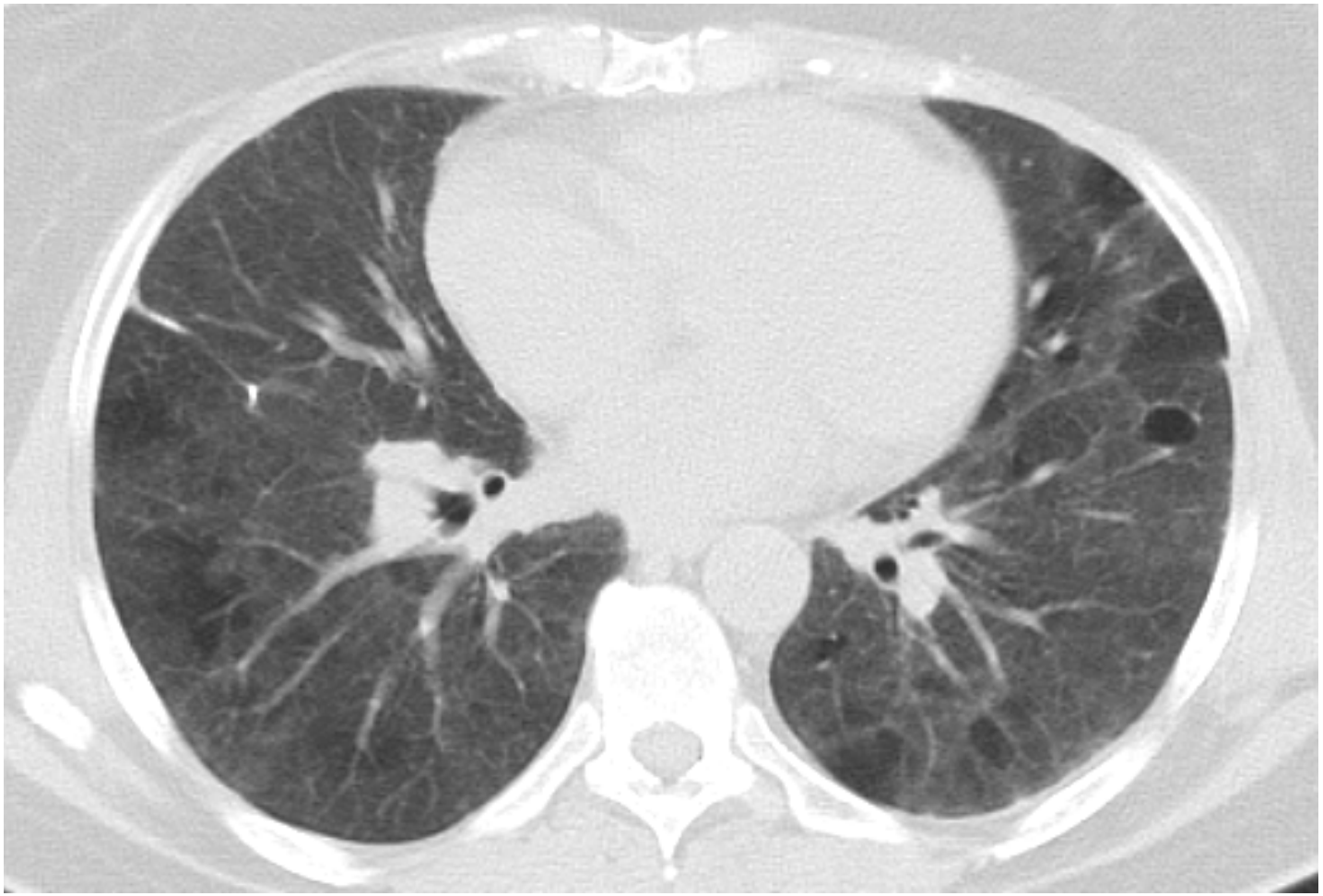


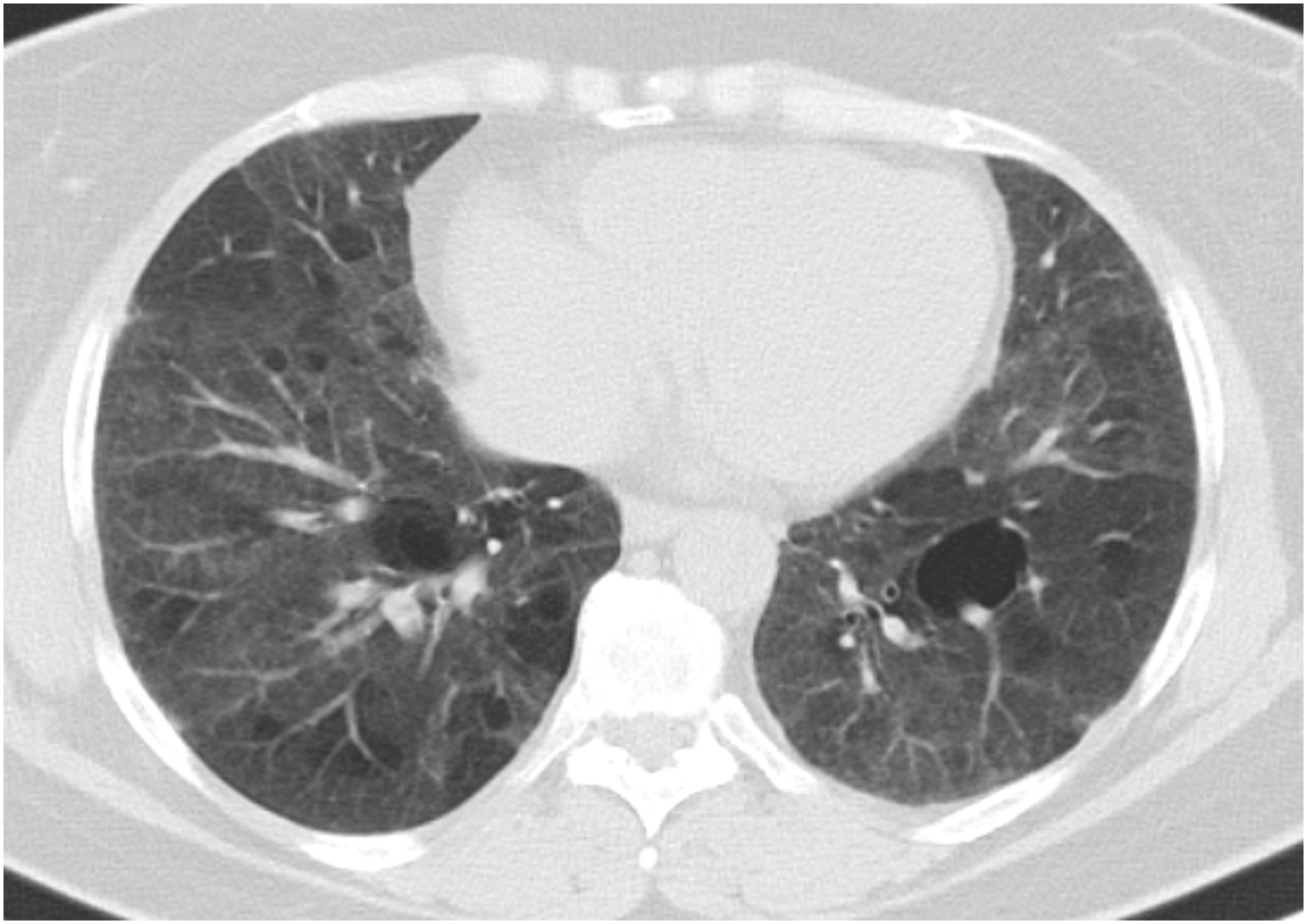


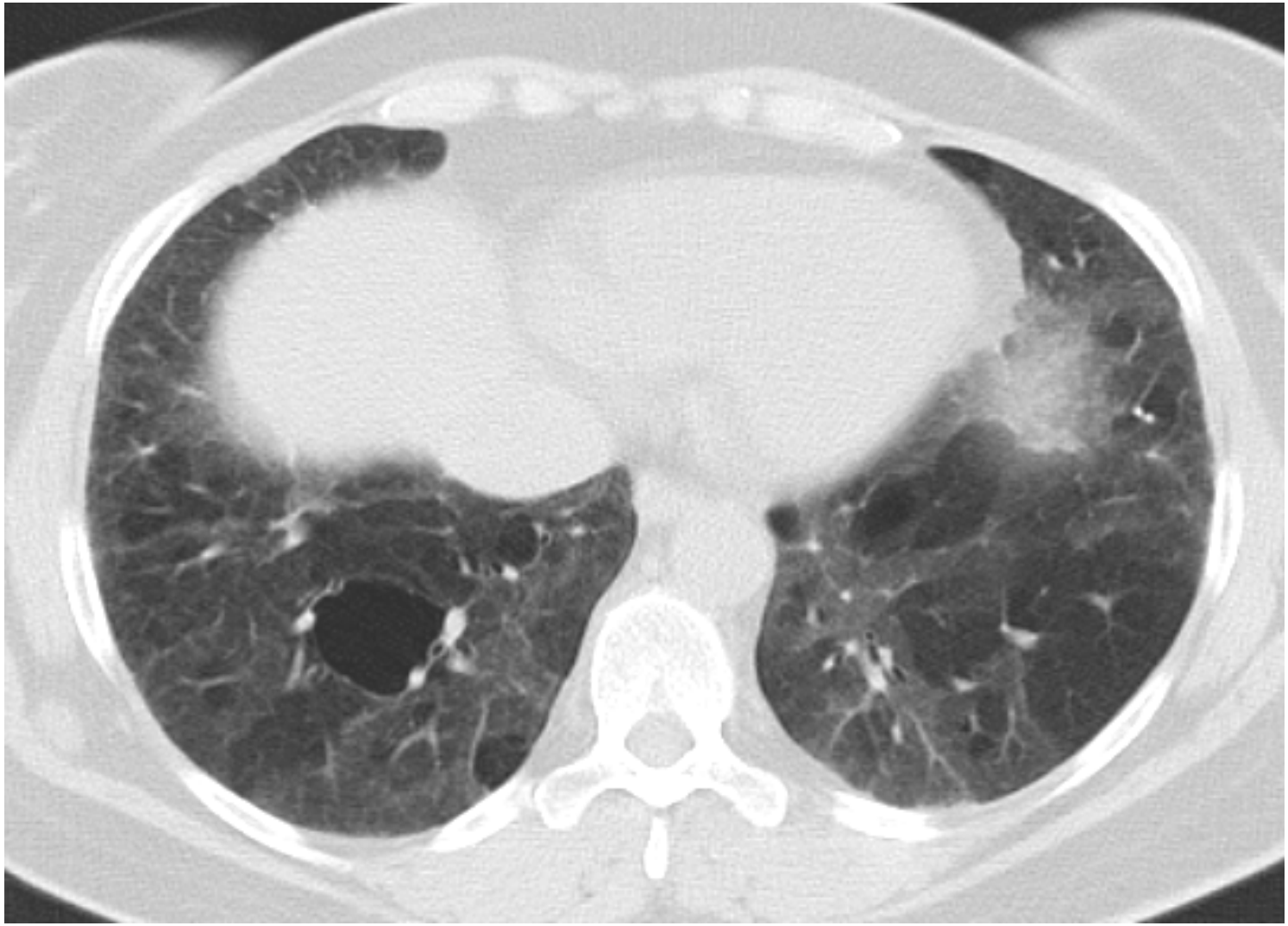


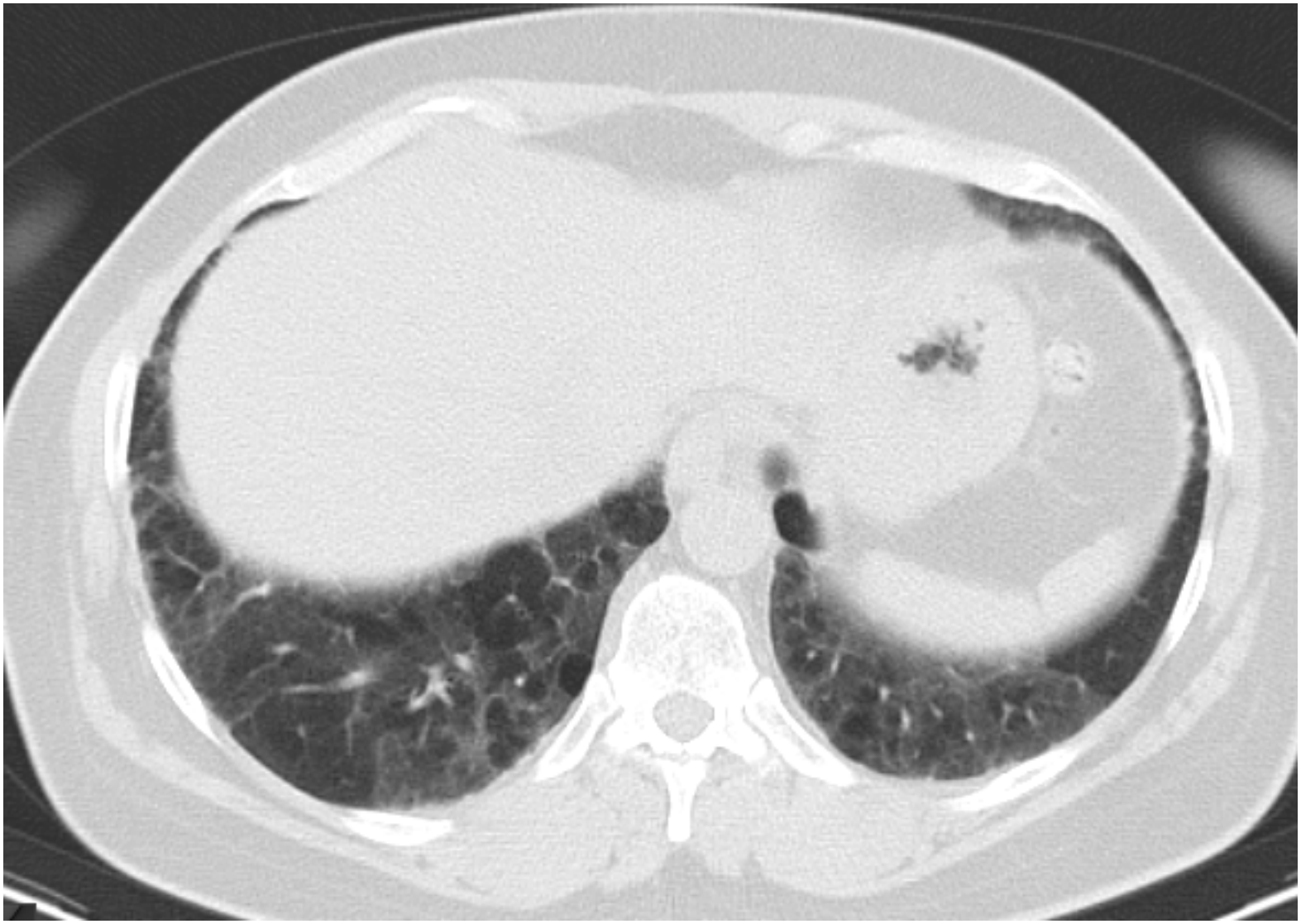












The importance of details

- HRCT ground glass opacities and mosaic attenuation: not “ancillary” aspects

- Ask the patient!

Time is gentleman