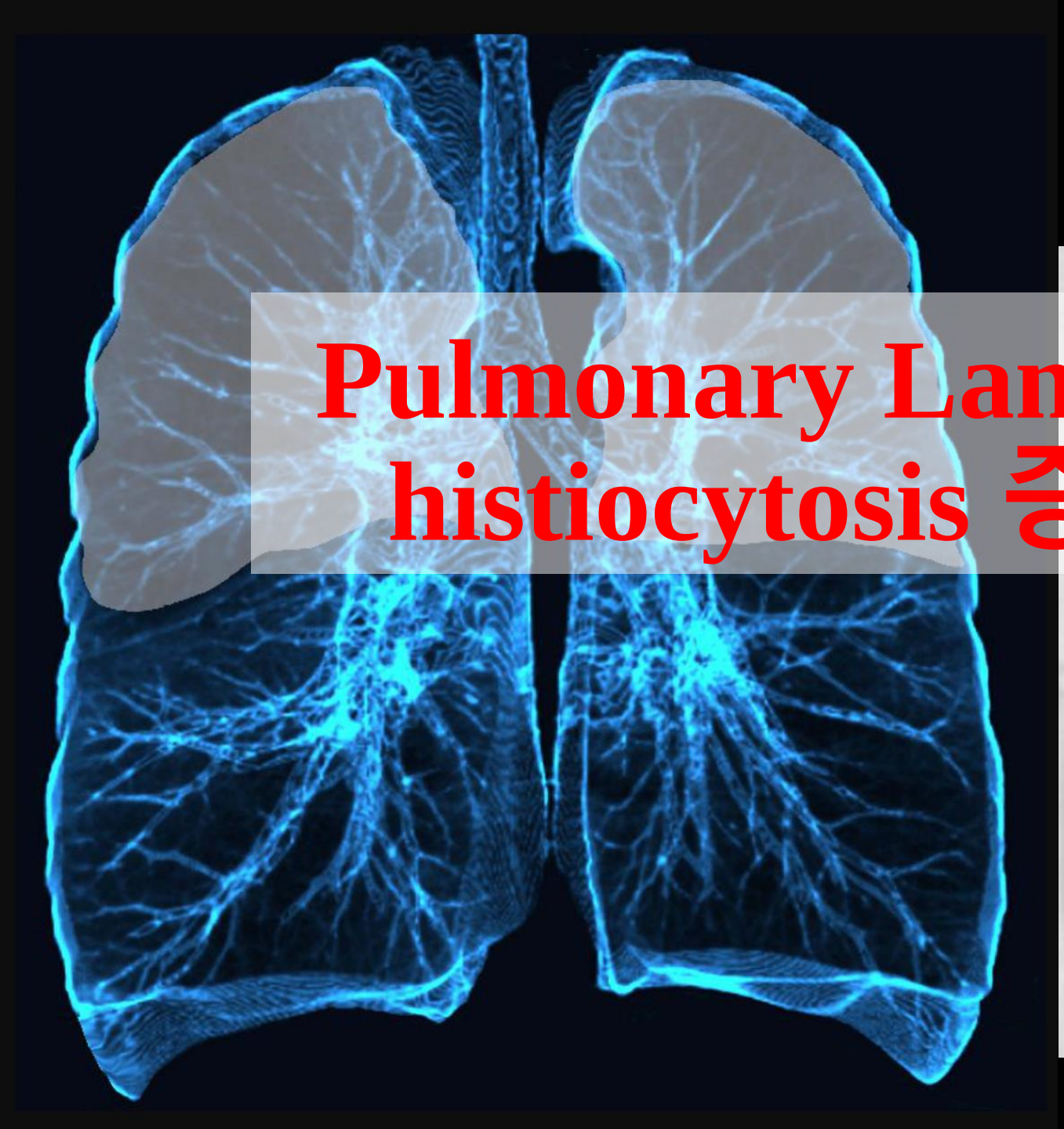


금연연구회 집담회
2023.7.17(월)

Pulmonary Langerhans-Cell histiocytosis 증례 및 고찰

전남대학교병원
호흡기내과
신홍준

40세 남자환자

- **C/C:** Chest pain (duration: 1 month)

- **Past medical history:**
  - No known history of diabetes, hypertension, tuberculosis, hepatitis
  - No known history of operation

- **Social history:**
  - Smoking: Current smoker, 20 PYs
  - Alcohol: Social alcohol drinker
  - Occupation: Business of billiard rooms

- **Family history:** non-specific
- **Bowel habit:** as usual
- **Urinary habit:** as usual
- **V/S:**

BP 120/80 mmHg	PR 90 /min
RR 15 /min	BT 37.0 ℃

Present illness

- 상기 환자는 특이 기저질환 없는 자로, 내원 1개월 전부터 발생한 우측 흉통 및 기침을 주소로 호흡기내과 외래 내원함.

Review of System

- General Weakness/Poor Oral Intake : (-/-)
- Fever/Chillness/Myalgia : (-/-/-)
- Cough/Sputum/Rhinorrhea : (+/+/-)
- Chest Pain/Dyspnea : (+/-)
- Anorexia/Nausea/Vomiting : (-/-/-)
- Diarrhea/Constipation : (-/-)
- Weight gain/loss : (-/-)
- Abdominal Pain/Discomfort/Distension : (-/-/-)
- Urinary frequency/Urgency/Dysuria : (-/-/-)

Physical examinations

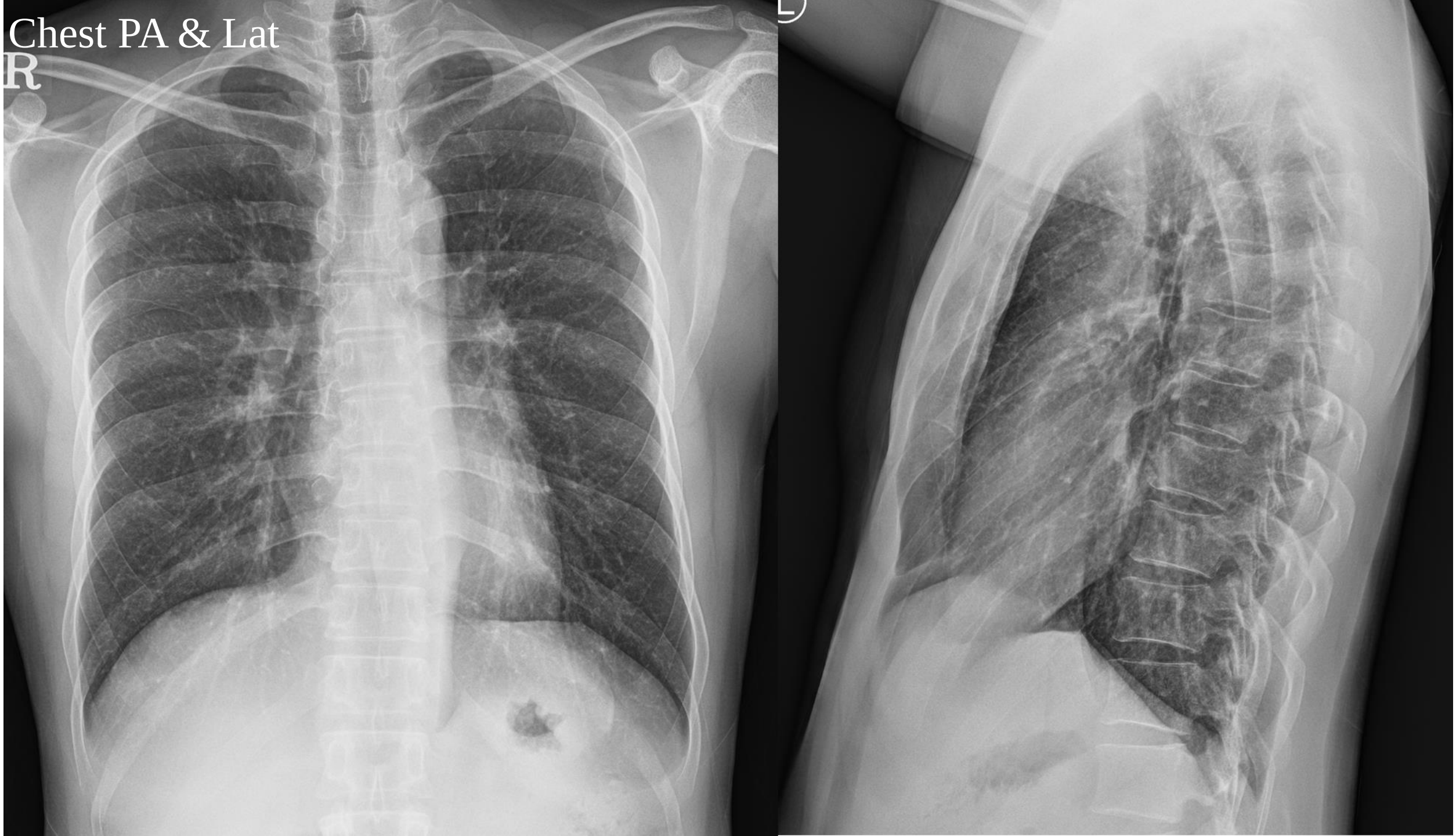
G/A	Not so ill appearance
H/S	No Scar and No Deformity
E/ENT	Not Anemic Conjunctiva Not Icteric Sclera
Neck	No JVE, No LAP
Chest	Mild crackles on both lung fields Regular heart beat without murmur
Abdomen	Soft Abdomen No Tenderness & Rebound tenderness Normal Bowel Sound
Extremitites	No edema

Impression

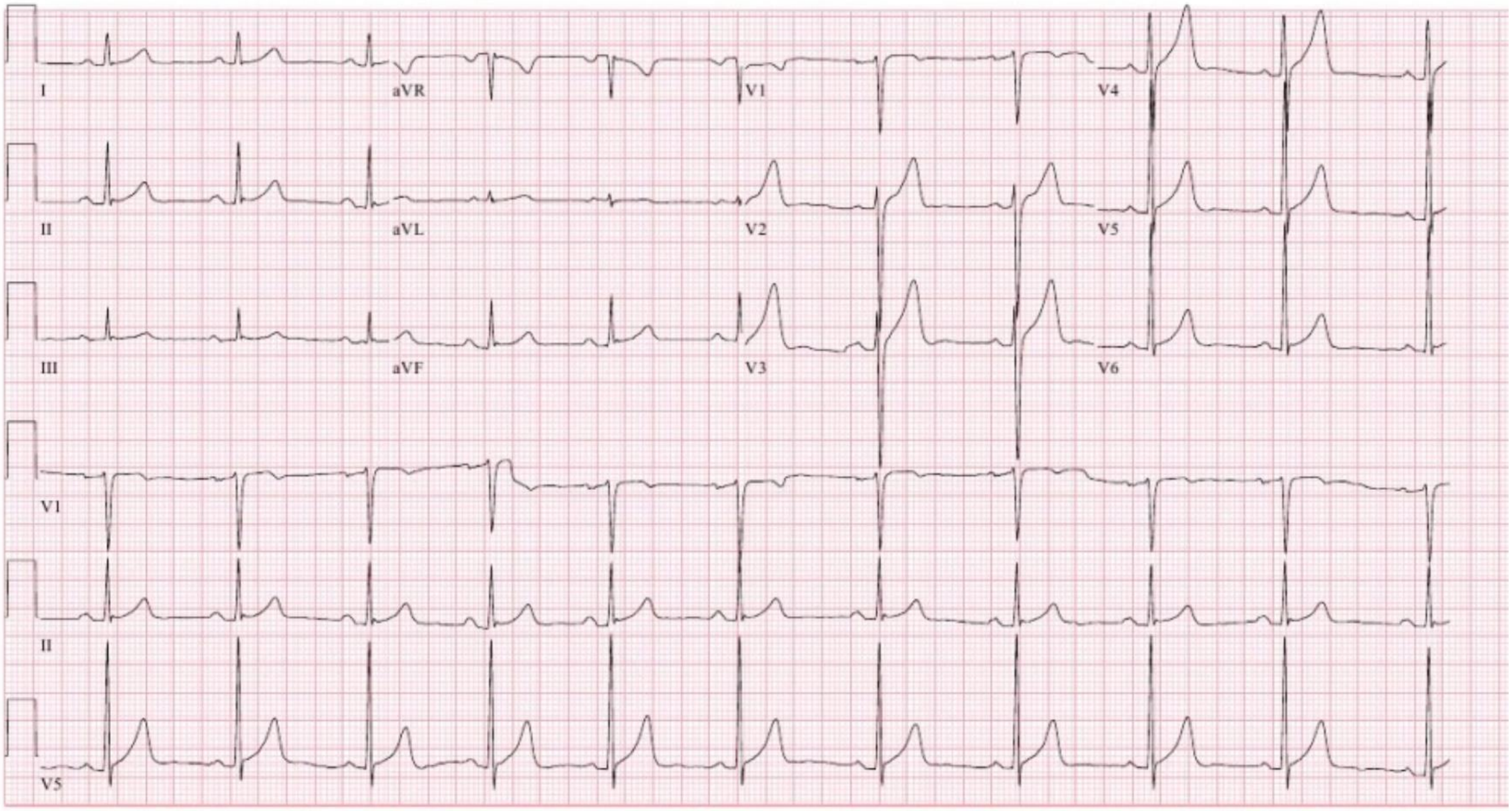
1. Pneumothorax
2. Acute bronchitis
3. R/O Pulmonary embolism
4. R/O Interstitial lung disease

Diagnostic plans

1. Chest X-ray
2. EKG
3. Routine lab
4. Pulmonary function test
5. HRCT or Chest CTA


Chest PA & Lat
R

EKG



Laboratory findings
CBC & D/C

WBC count, /uL	7800	4800 ~ 10800
Neutrophil, %	49.9	50 ~ 75
Lymphocyte, %	40.5	20 ~ 40
Eosinophil, %	1.5	0 ~ 5
Hemoglobin, g/dL	15.7	12 ~ 18
RBC count, 10^6/uL	4.75	4.20 ~ 6.10
Hematocrit, %	47.3	37 ~ 52
Platelet count, 10^3/uL	272	130 ~ 450

Laboratory findings
Liver function tests

Total protein, g/dL	7.0	6.0 ~ 8.3
Albumin, g/dL	4.4	3.5 ~ 5.2
AST, U/L	20	10 ~ 37
ALT, U/L	20	10 ~ 37
Gamma-GTP, U/L	41	5 ~ 61
ALP, U/L	76	35 ~ 129
Total bilirubin, mg/dL	0.59	0.22 ~ 1.30
Glucose, mg/dL	99	60 ~ 100
LDH, U/L	290	218 ~ 472

Laboratory findings
Renal function tests

BUN, mg/dL	10.1	8 ~ 23
Creatinine, mg/dL	0.87	0.5 ~ 1.3
Sodium, mEq/L	140	136 ~ 146
Potassium, mEq/L	4.5	3.5 ~ 5.1
Chloride, mEq/L	107	98 ~ 110
Uric acid, mg/dL	6.3	2.5 ~ 8.3
Total calcium, mg/dL	9.7	8.4 ~ 10.2
Ionized calcium, mEq/L	2.3	2.2 ~ 2.6
Osmolality, mOsm/Kg	280	280 ~ 295

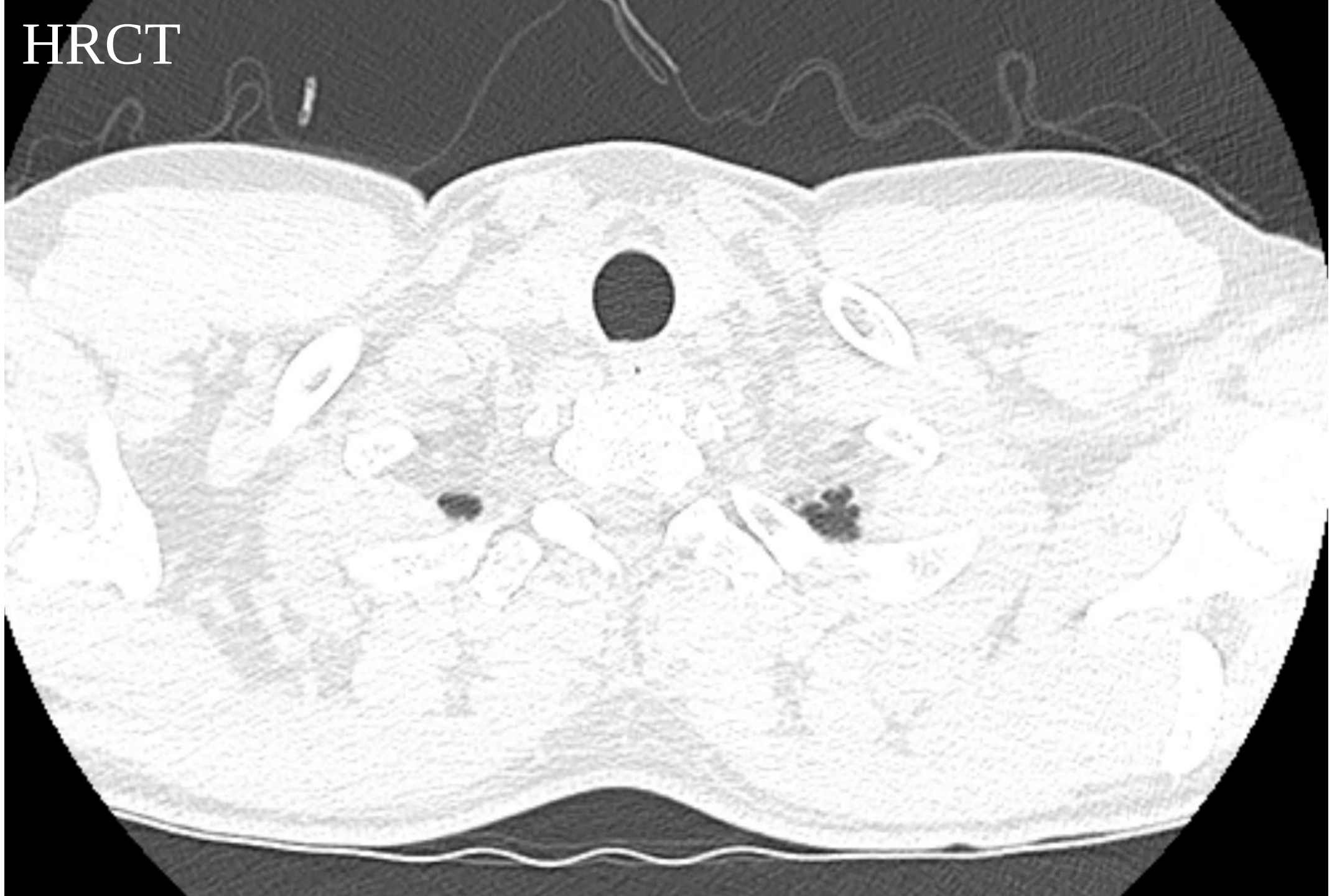
Laboratory findings
Urinalysis

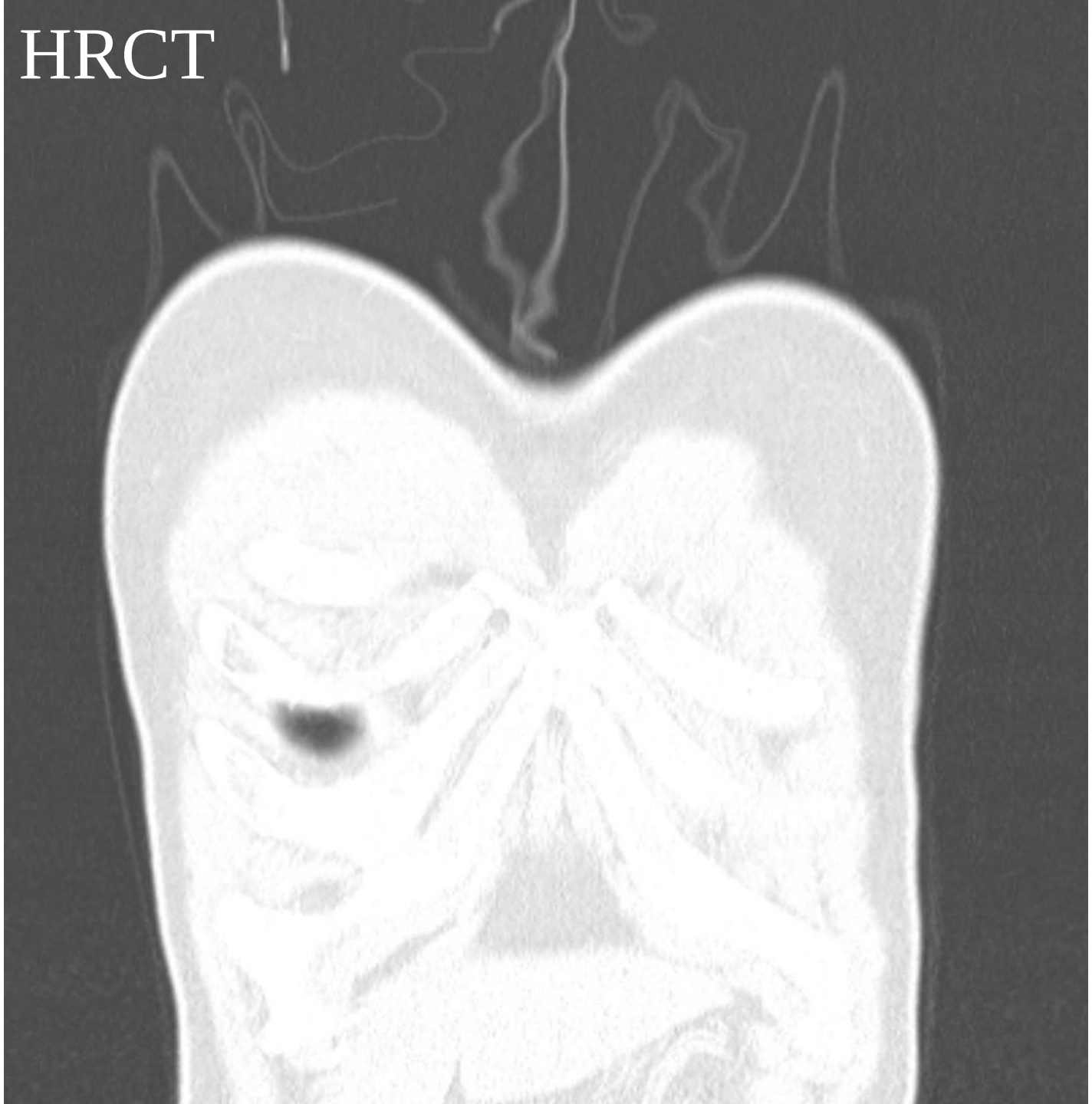
Specific gravity	1.010	1.005 ~ 1.030
pH	6.5	5 ~ 8
Protein, mg/dL	Negative	
Glucose, mg/dL	Negative	
Ketone, mg/dL	Negative	
Bilirubin, mg/dL	Negative	
RBC, /uL	Negative	
Nitrite	Negative	
Urobilinogen, mg/dL	0.2	0.1 ~ 1
WBC, /HPF	0-1	0 ~ 4

Laboratory findings

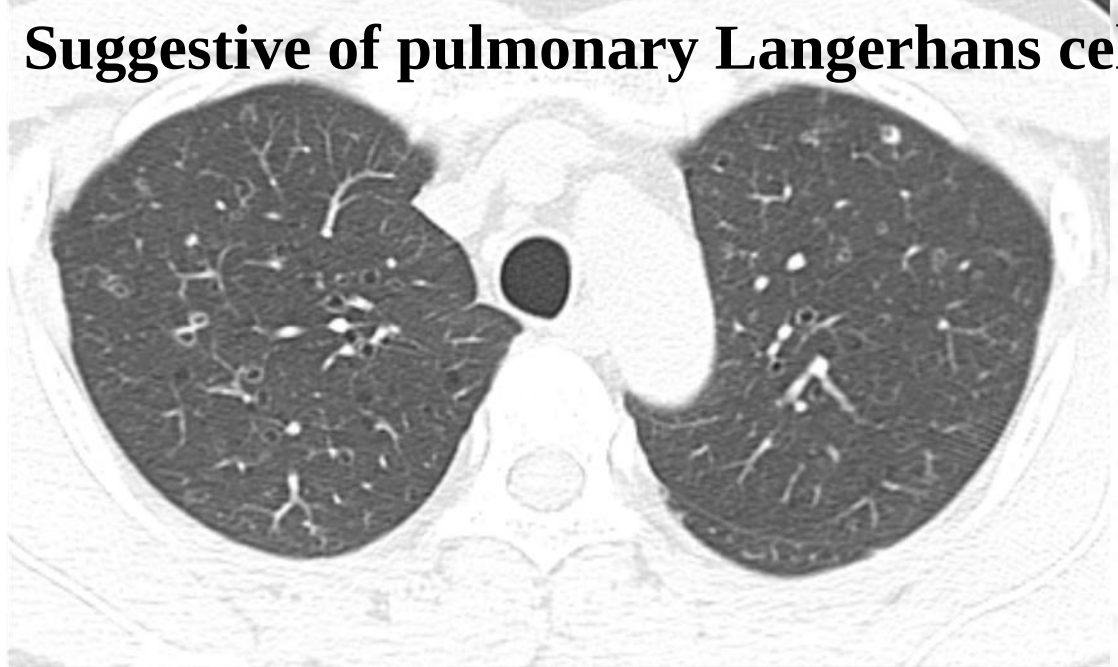
Coagulation profile & acute phase reactants

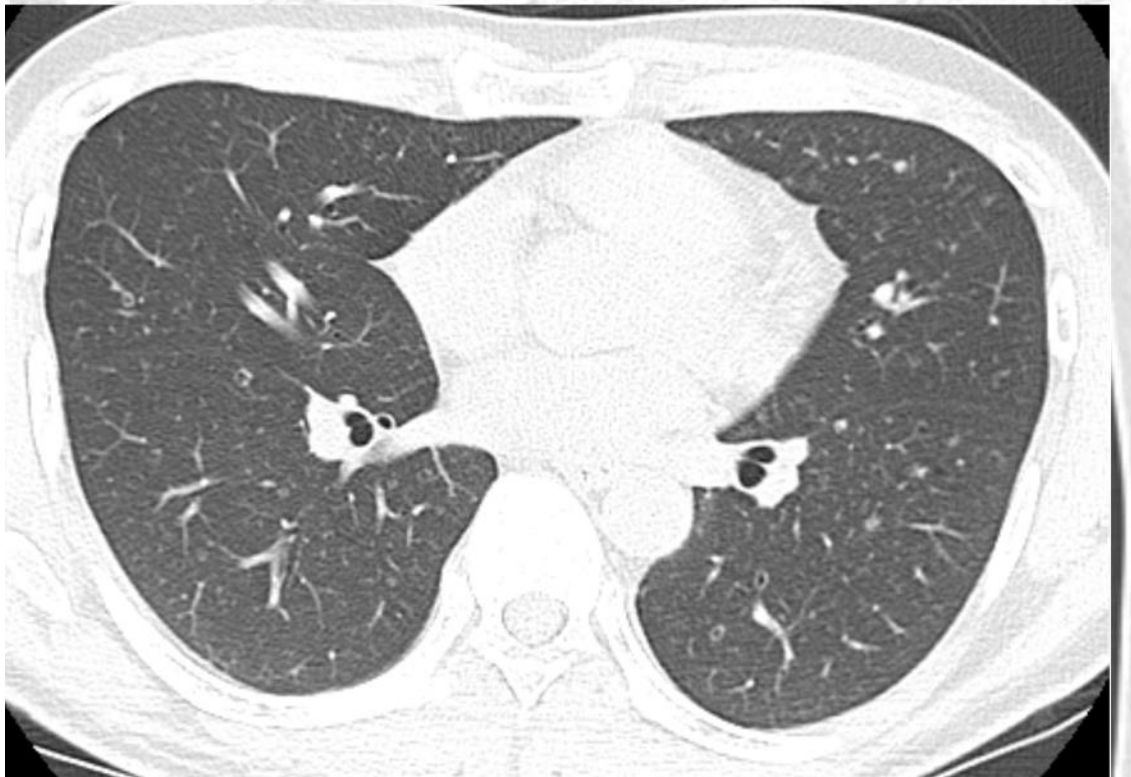
aPTT, sec	30.3	26.5 ~ 41
PT, sec	10.2	9.8 ~ 13
Fibrinogen, mg/dL	323	180 ~ 350
FDP, ug/mL	0.3	0 ~ 5
D-dimer, mg/L	0.10	0 ~ 0.55
CRP, mg/dL	0.04	0 ~ 0.3

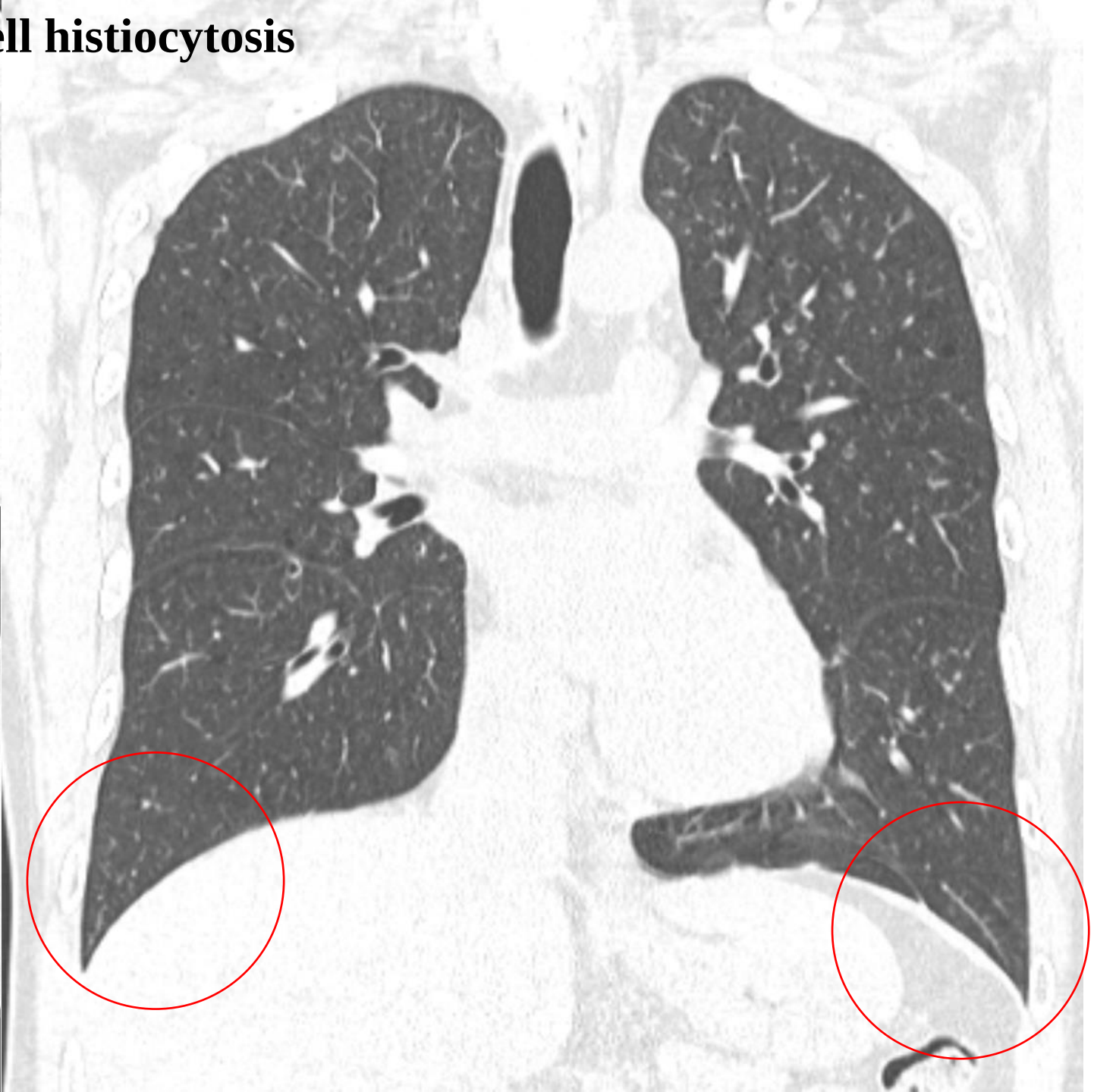

HRCT


HRCT

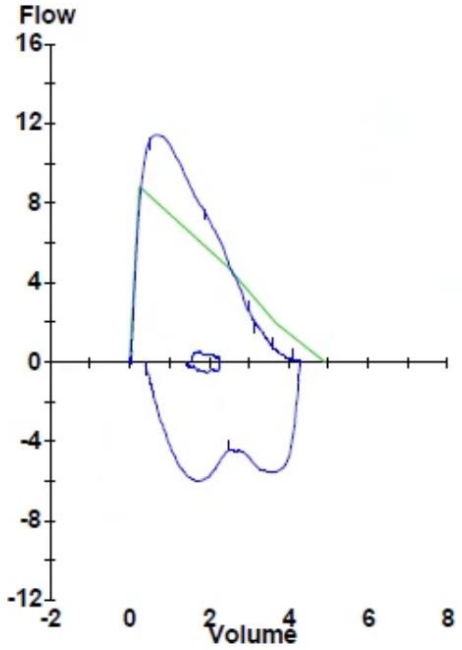
Suggestive of pulmonary Langerhans cell histiocytosis





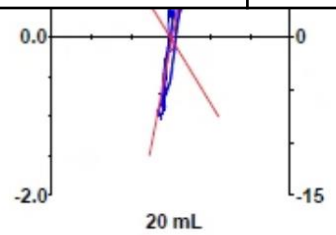


Pulmonary function test

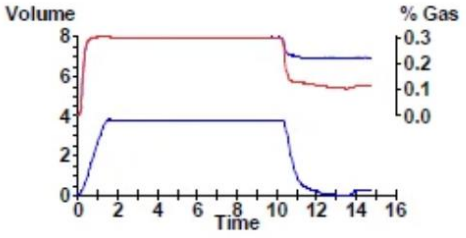


Spirometry		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
FVC	Liters	4.92	4.30	87			
FEV1	Liters	4.09	3.65	89			
FEV1/FVC	%	82	85				
FEF25-75%	L/sec	3.87	4.49	116			
PEF	L/sec	8.83	11.41	129			
FET100%	Sec		8.18				
FIVC	Liters	4.81	3.90	81			
FIF50%	L/sec		4.48				
FVL ECode			001000				
MVV	L/min	158	143	91			

FVC, %	FEV, %	FEV1/FCV	DLco, %
87	89	84	77



ERV	Liters	1.60	0.94	59
IC	Liters	3.20	3.26	102
RV/TLC	%	30	29	
Raw	cmH2O/L/sec	1.22	1.76	145
Vtg	Liters		3.87	
sGaw	L/s/cmH2O/L	0.224	0.146	65



Diffusion					Hb:
DLCO	mL/mmHg/min	28.6	22.0	77	
DL Adj	mL/mmHg/min	28.6	22.0	77	
VA	Liters		5.08		
DLCO/VA	mL/mHg/min/L	4.39	4.34	99	
DL/VA Adj	mL/mHg/min/L		4.34		
IVC	Liters		3.97		

Tentative diagnosis & further evaluation

1. Suggestive of pulmonary Langerhans cell histiocytosis

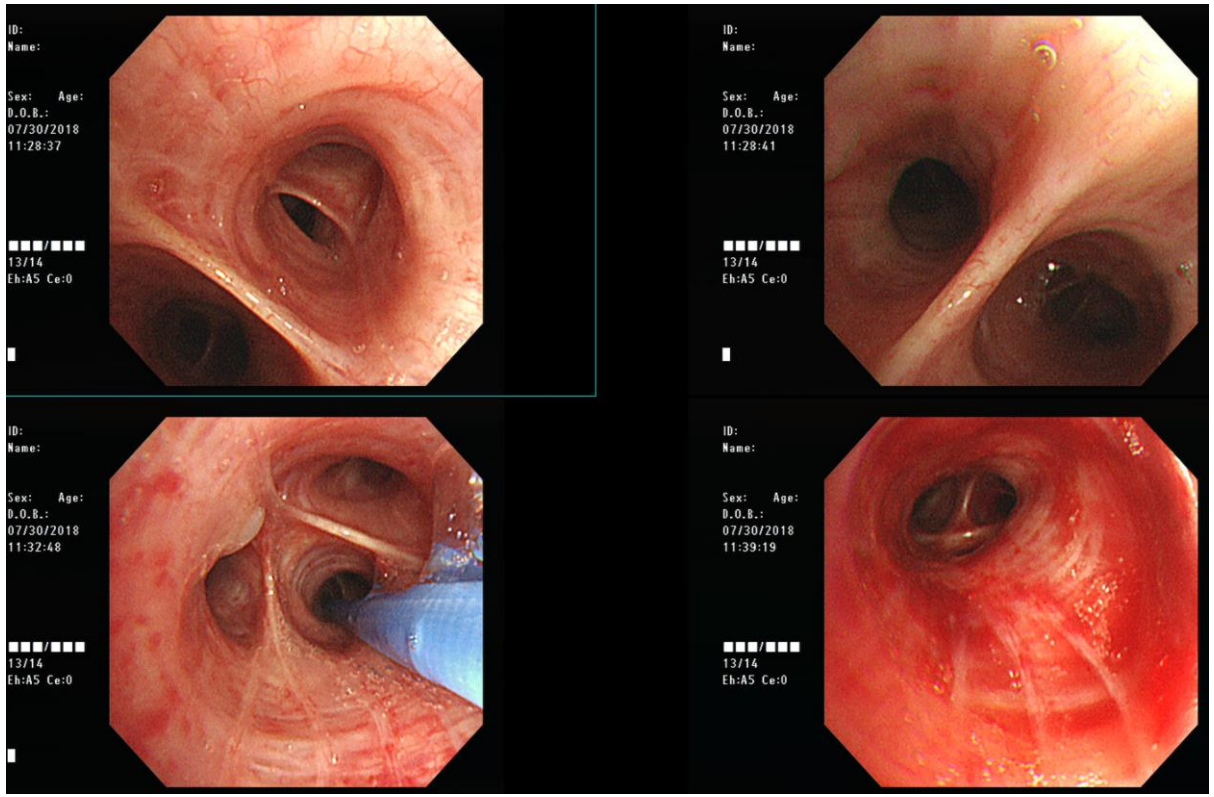
2. Further diagnostic plan

- Bronchoscopy (BAL & TBLB)
- Autoimmune marker

Laboratory findings
Autoimmune tests

Rheumatoid factor, IU/mL	4.4	0 ~ 14
Anti-CCP	0.5	0 ~ 5
ANA	Negative	
ANCA	Negative	

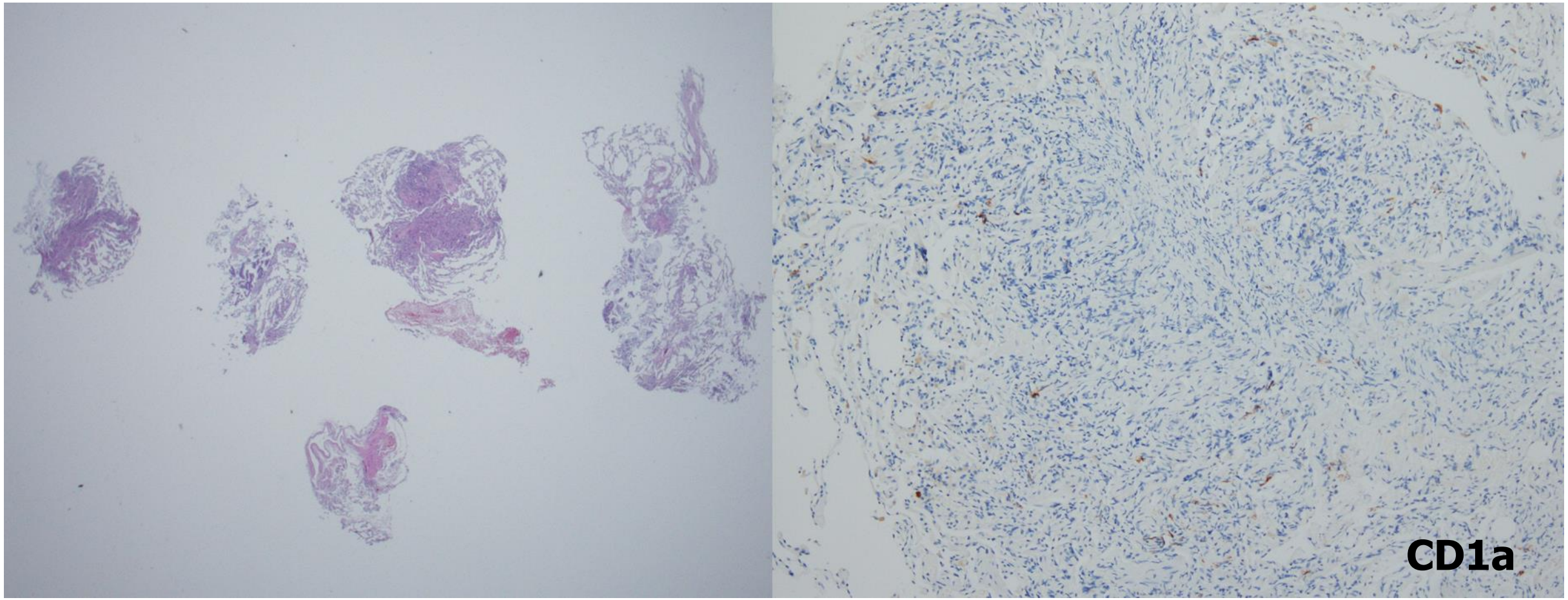
Bronchoscopy



<BAL findings>

Total nucleated cell, /mm^3	171
RBC, /mm^3	32
WBC, /mm^3	137
Neutrophil, %	21
Lymphocyte, %	74
Eosinophil, %	5

Bronchoscopy: TBLB findings

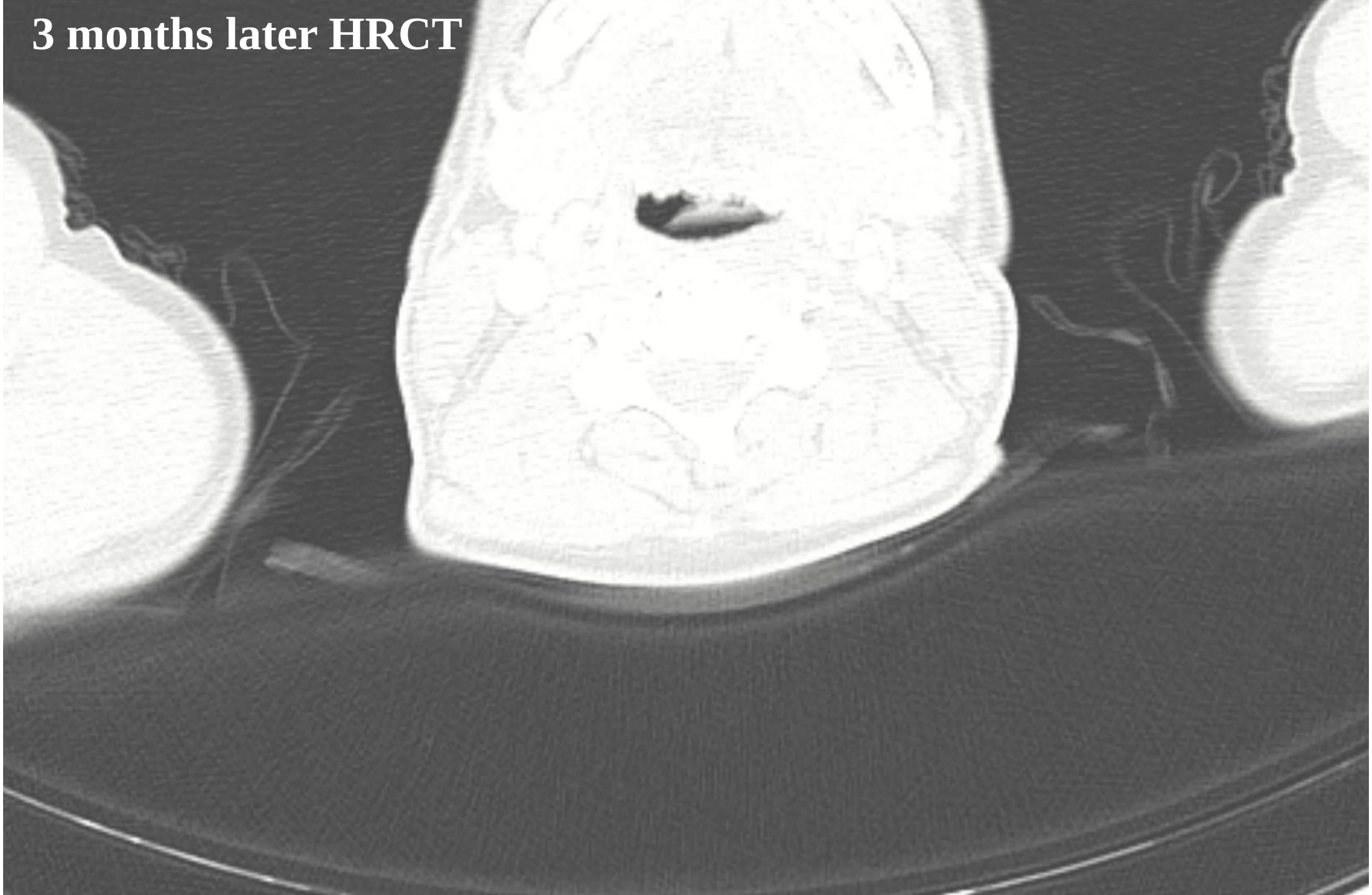


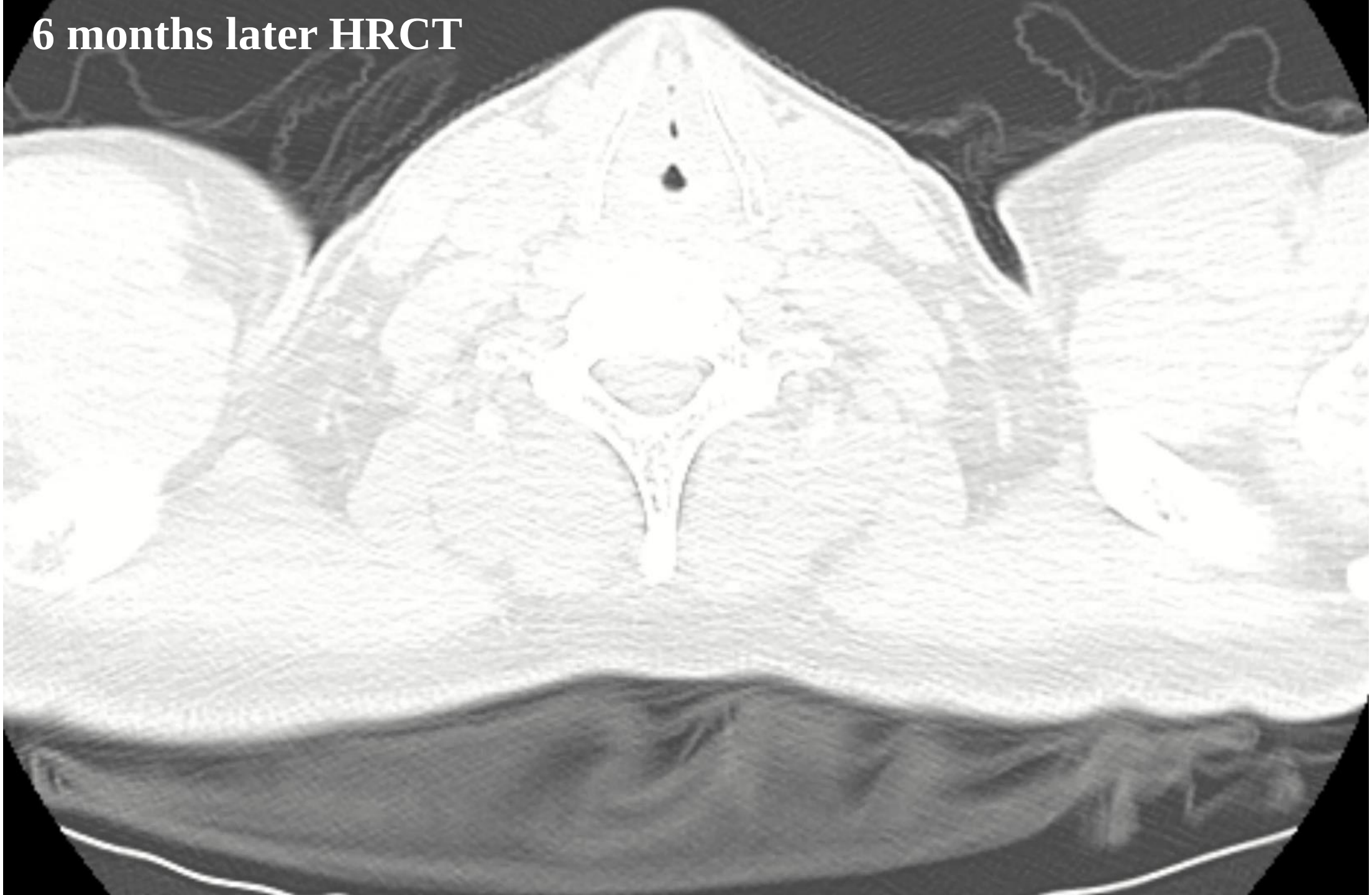
Tentative diagnosis & treatment plan

1. Suggestive of pulmonary Langerhans cell histiocytosis

2. Treatment plan

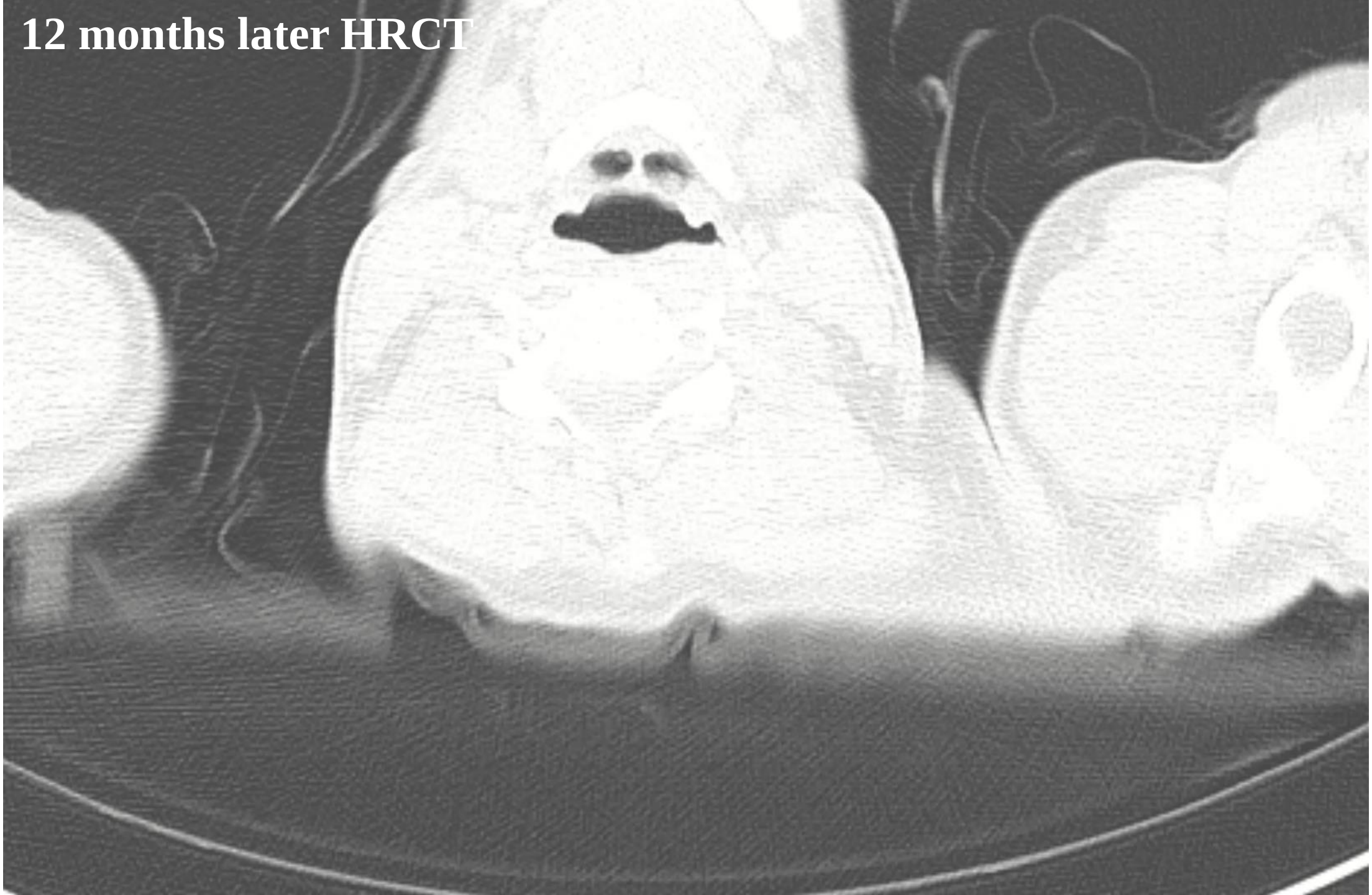
- Stop smoking
- Regular follow-up


3 months later HRCT


6 months later HRCT

Pulmonary function tests

Date	FVC, %	FEV, %	FEV1/FCV	DLco, %
2018.7.16	87	89	84	77
2019.4.30	87	87	82	73

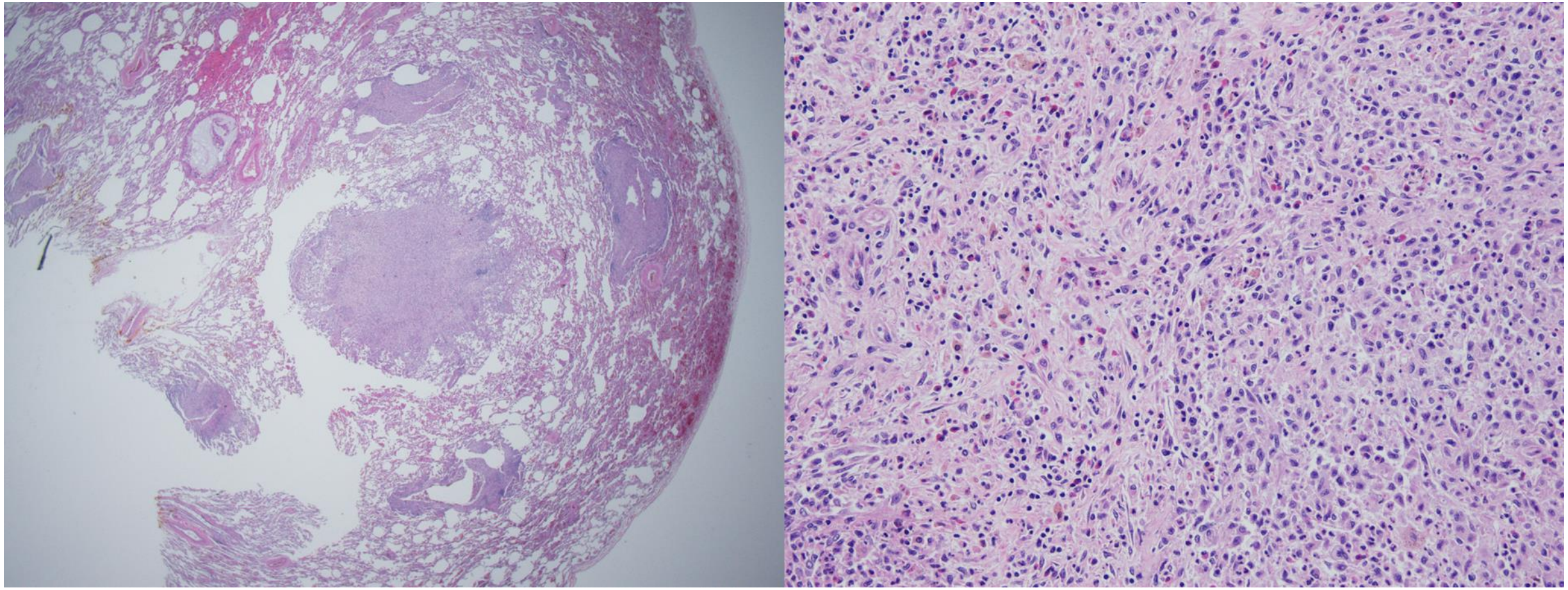

12 months later HRCT

Pulmonary function tests

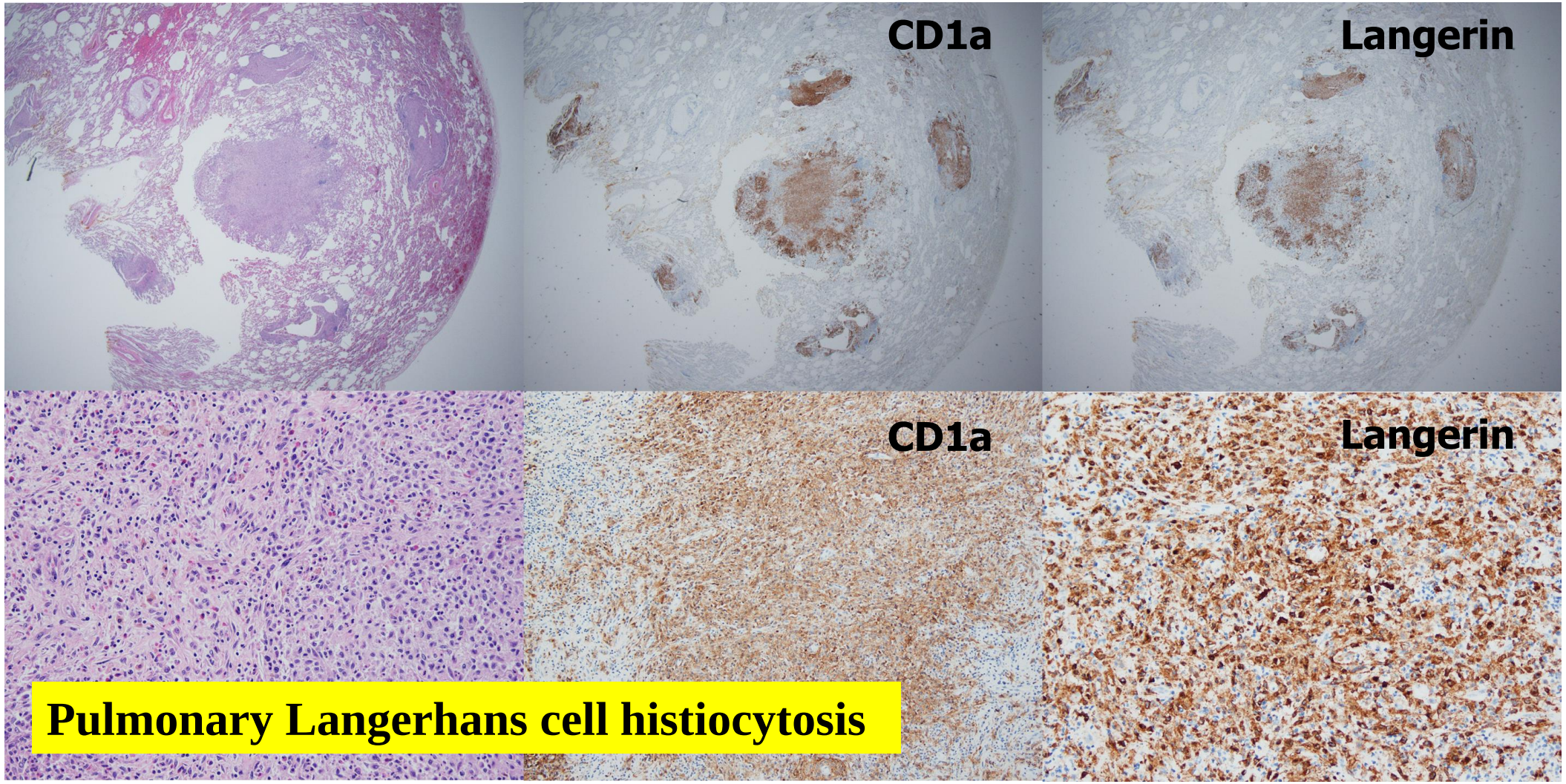
Date	FVC, %	FEV, %	FEV1/FCV	DLco, %
2018.7.16	87	89	84	77
2019.4.30	87	87	82	73
2020.5.12	89	88	82	68

- 금연 recommend 하였으나, 소량의 smoking 및 간접흡연 지속됨.
- mMRC 1~2의 호흡곤란, 기침 및 객담 동반됨.
- 약물적 치료를 고려하여 surgical biopsy recommend 함.

VATS (wedge resection): RUL, RML, RLL



VATS (wedge resection): RUL, RML, RLL



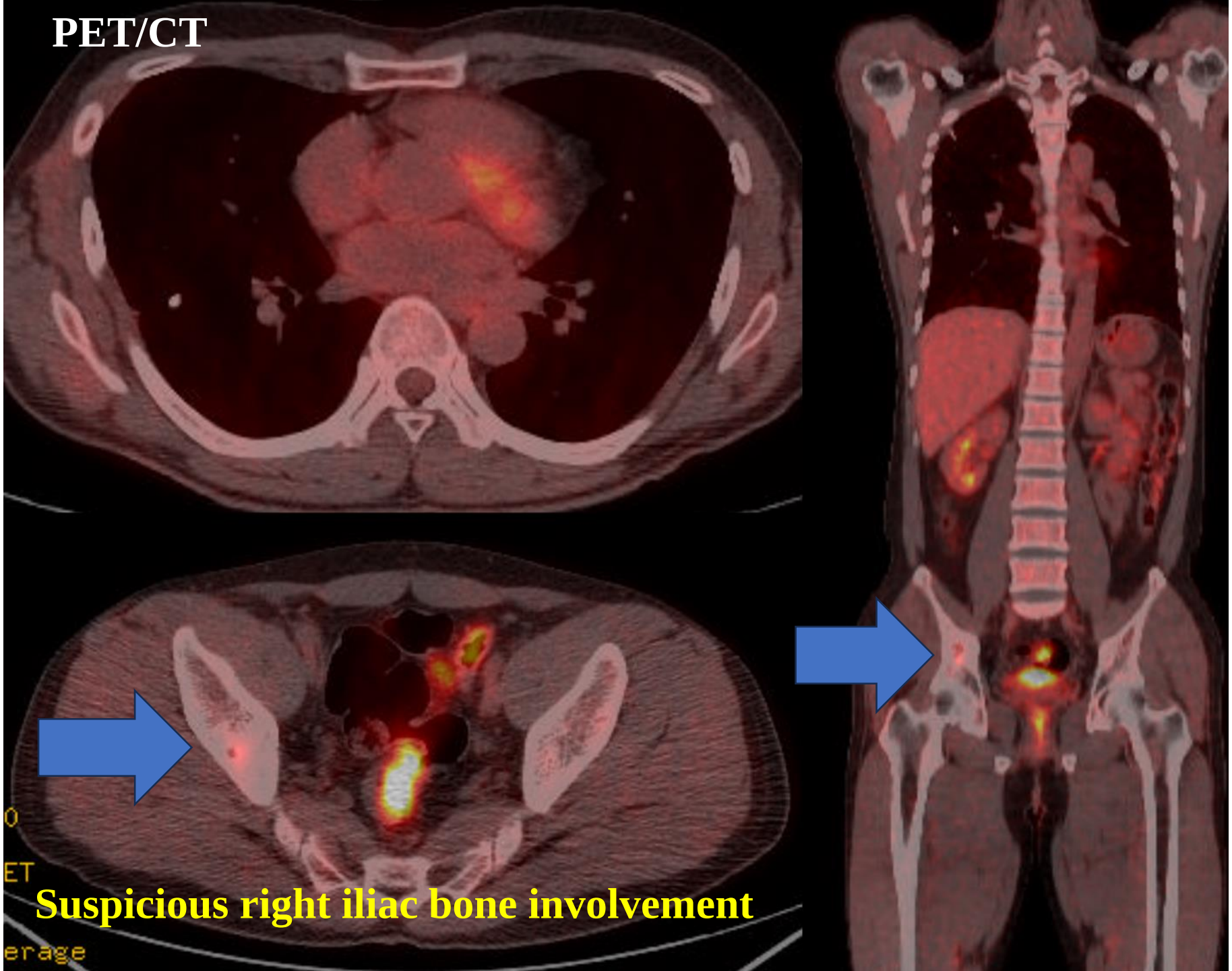
Final diagnosis, further evaluation, and treatment plan

1. **Pulmonary Langerhans cell histiocytosis**

2. **PET/CT**

3. **Oral glucocorticoid**

   -Solondo 30 mg qD start

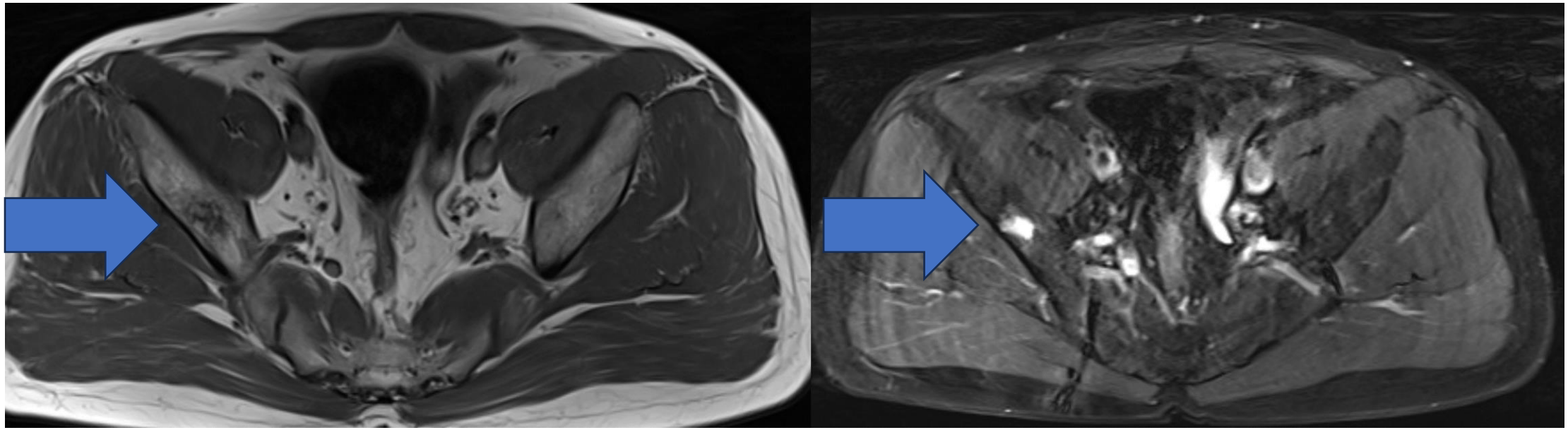

PET/CT
Suspicious right iliac bone involvement

Treatment plan

1. **Steroid 유지**

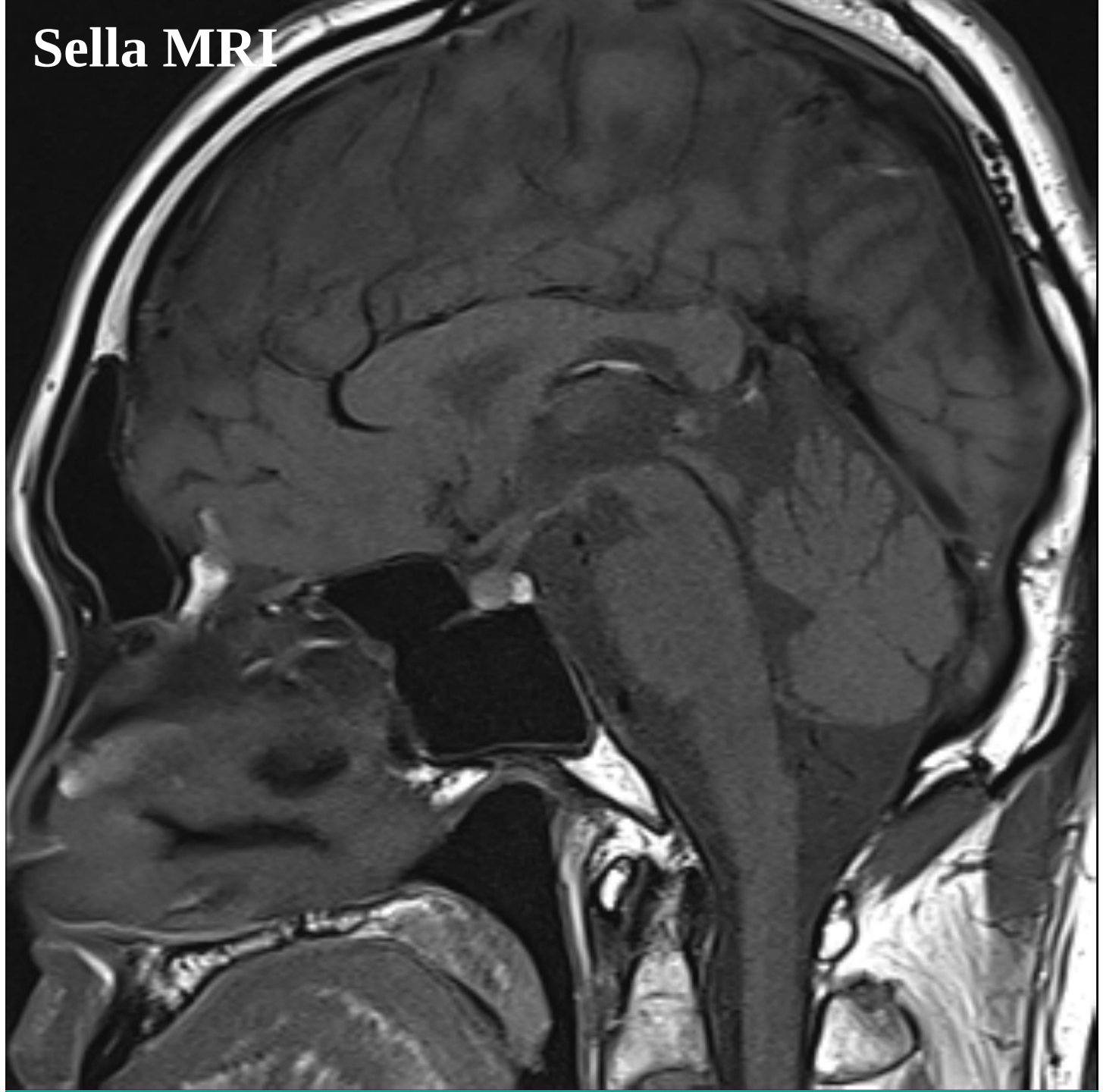
2. **OS & ONCO consult**

Pelvis MRI(E)



Ill-defined 2.8 x 1.6 x 1.6 cm osteolytic lesion with T2 heterogenous high and T1 low SI in right ilium.

→ Radiation therapy on right iliac bone

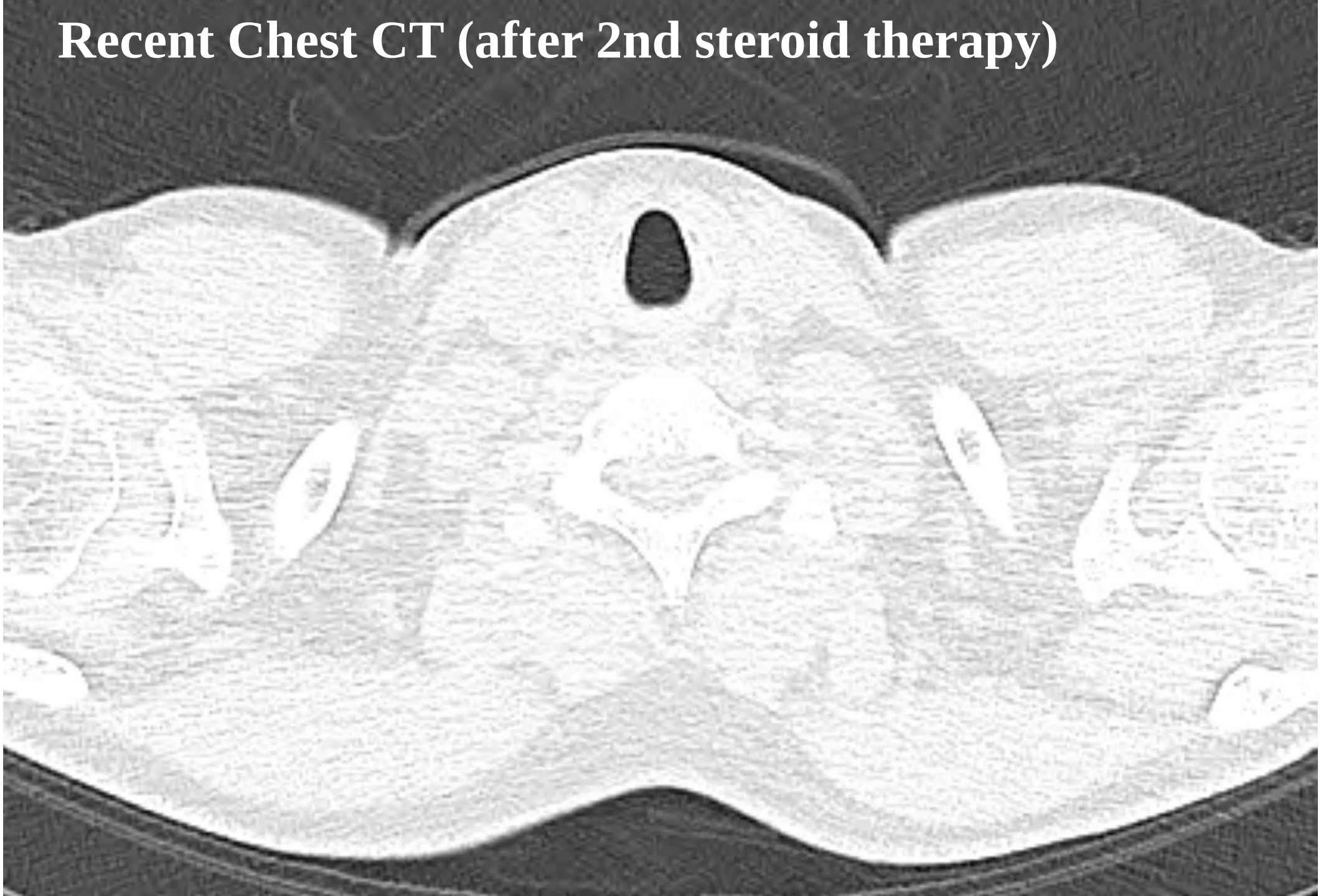

Sella MRI

Pulmonary function tests

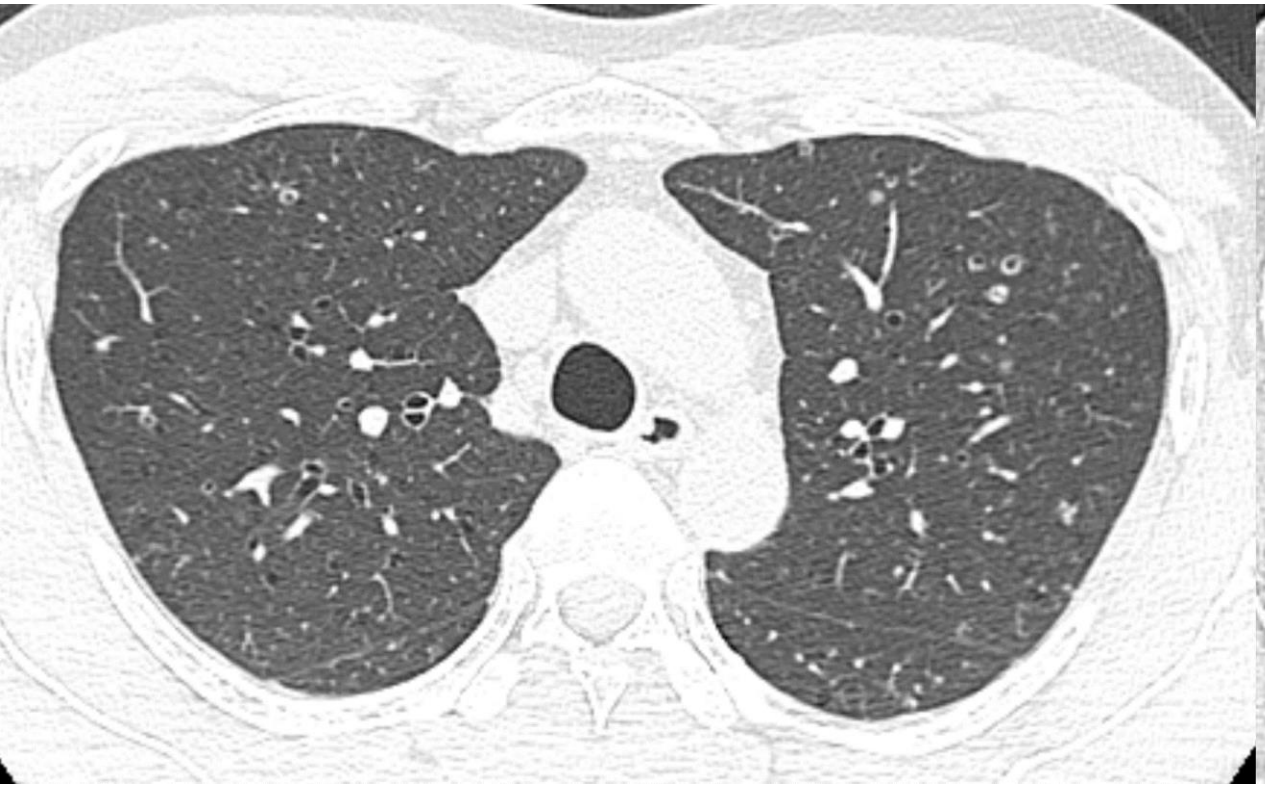
Date	FVC, %	FEV, %	FEV1/FCV	DLco, %
2018.7.16	87	89	84	77
2019.4.30	87	87	82	73
2020.5.12*	89	88	82	68
2020.9.2	81	84	86	82
2021.1.11	80	82	82	68
2022.3.28	83	87	87	81
2022.12.24*	77	77	83	69

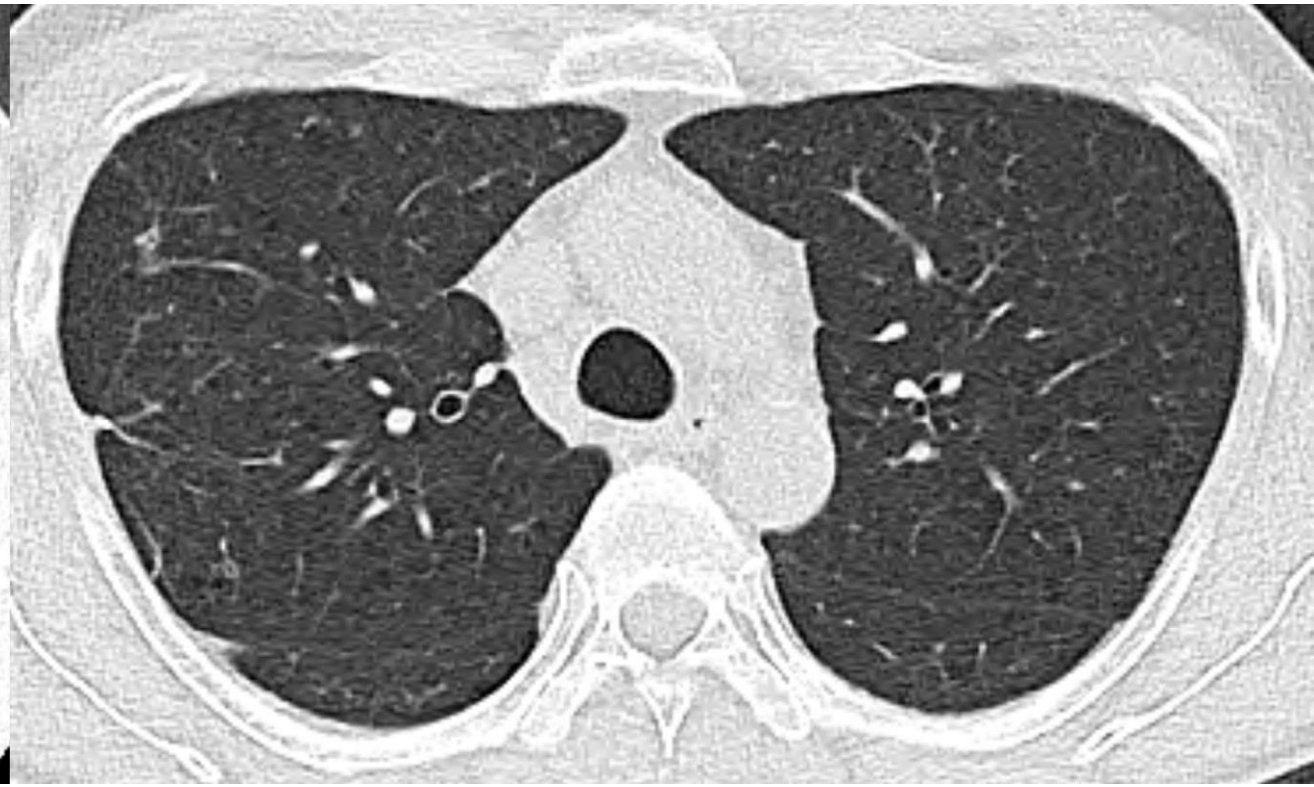
* Steroid therapy

Recent Chest CT (after 2nd steroid therapy)



Changes of chest CT findings



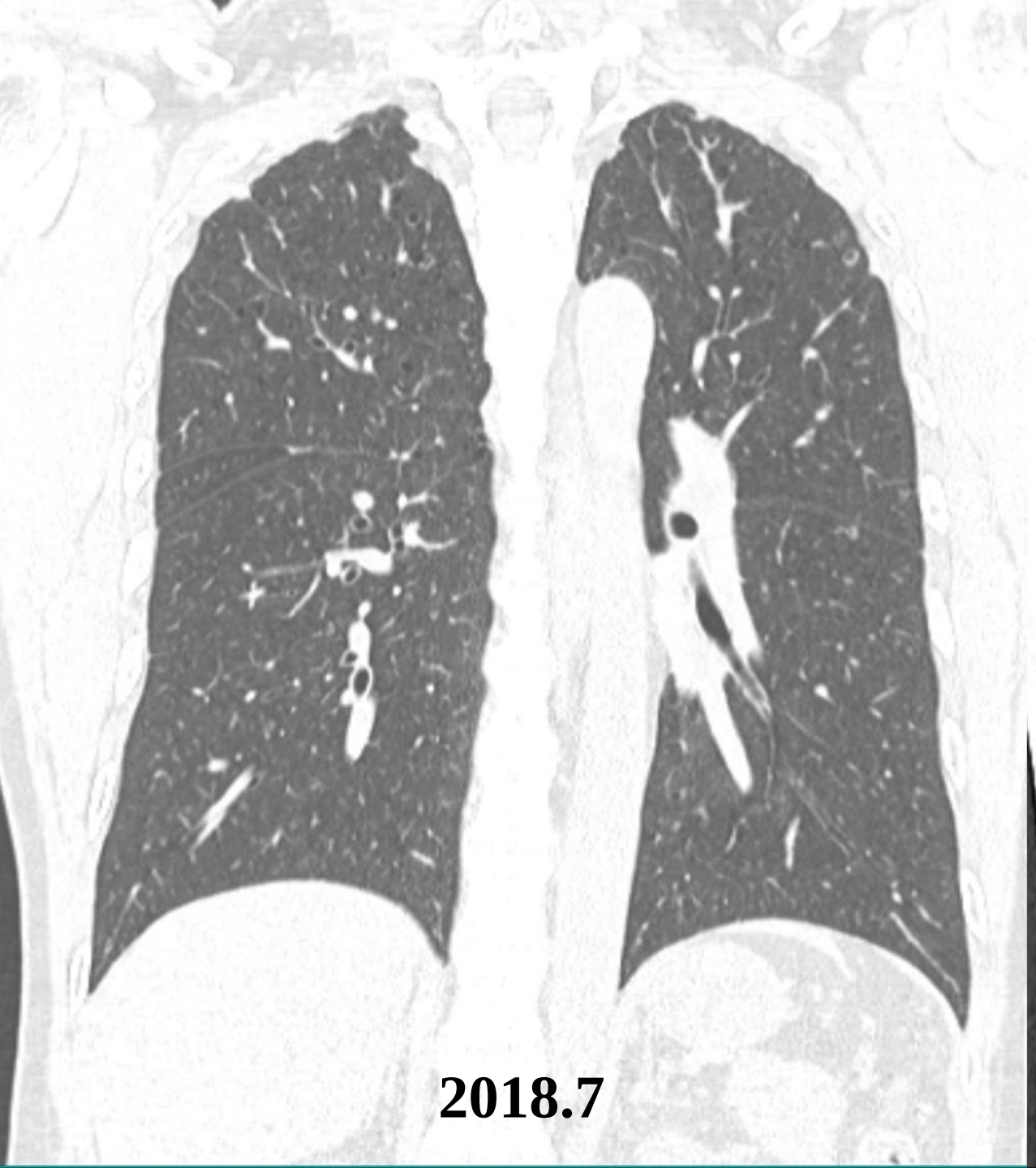


2018.7

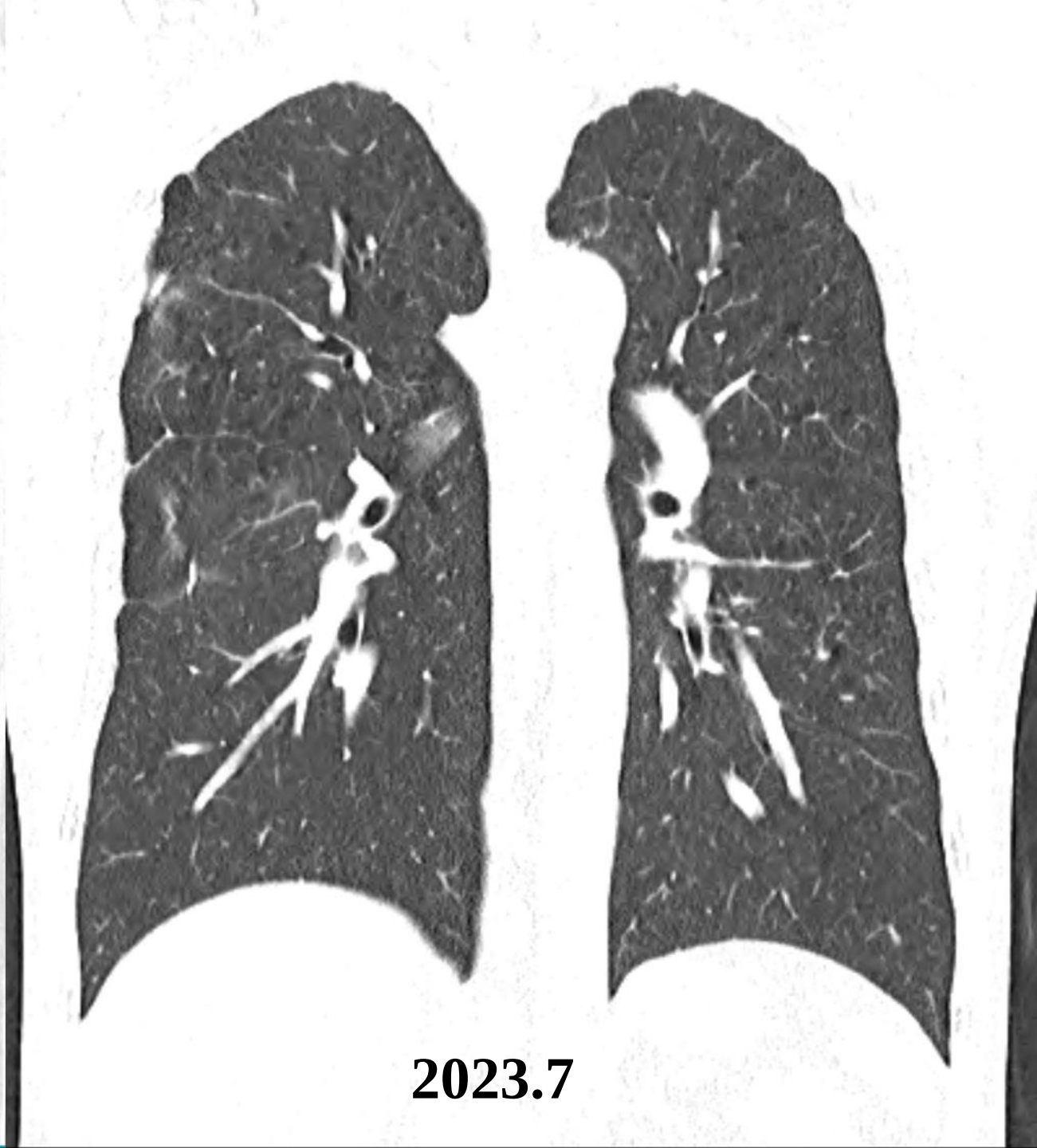
FVC 87%, FEV1 89%, DLco 77%

2023.7

?



2018.7



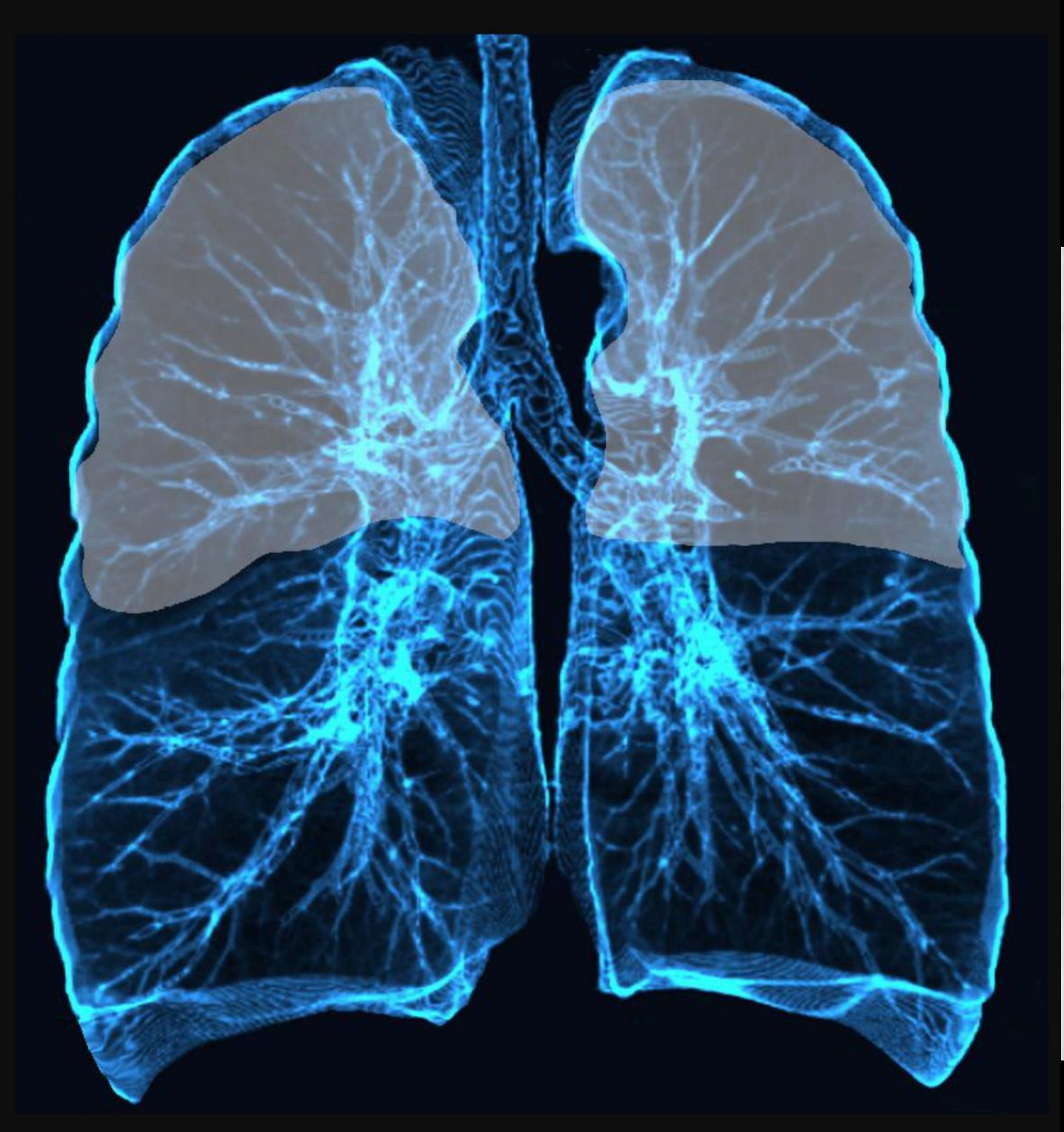
2023.7

Pulmonary function tests

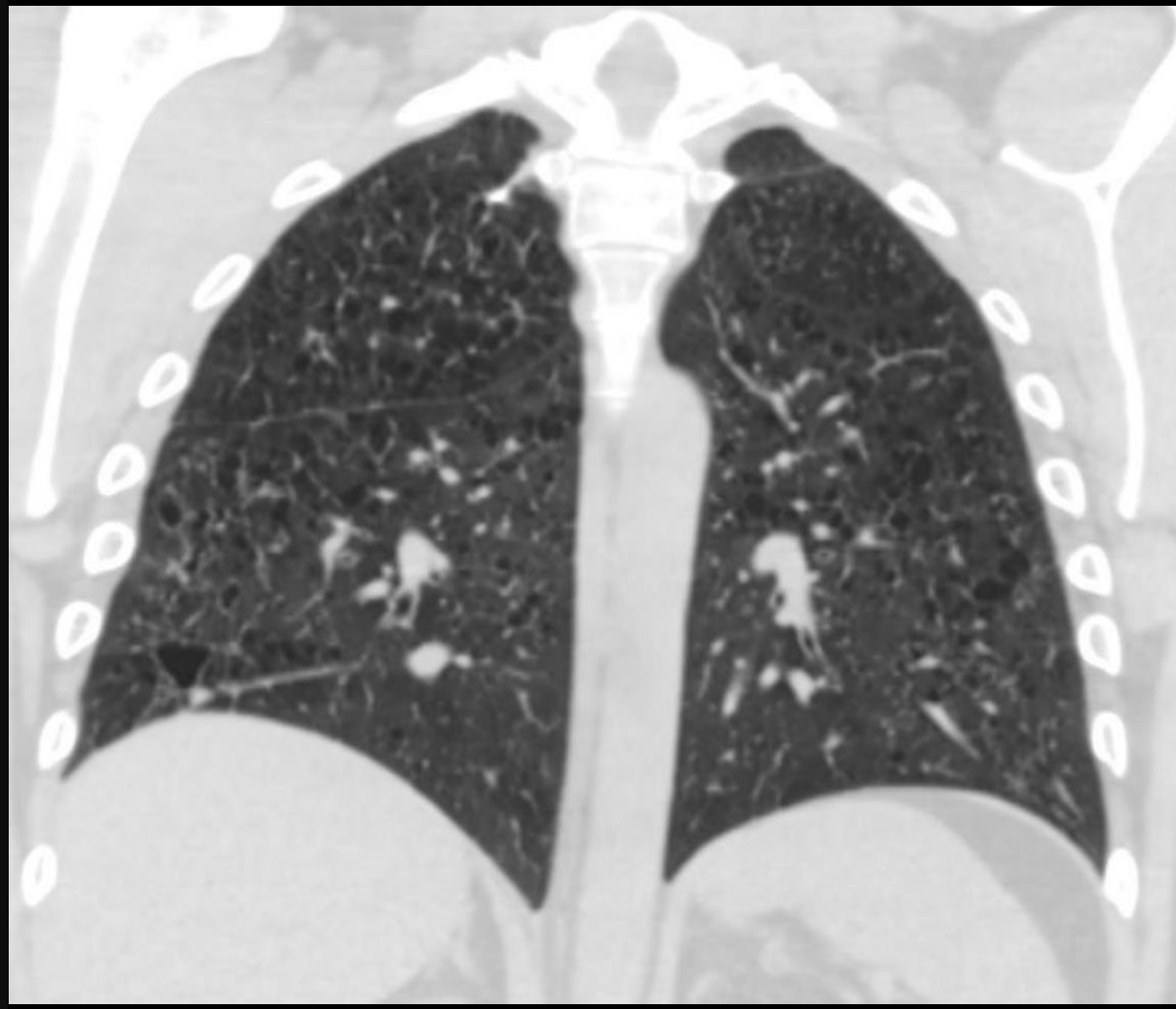
Date	FVC, %	FEV, %	FEV1/FCV	DLco, %
2018.7.16	87	89	84	77
2019.4.30	87	87	82	73
2020.5.12*	89	88	82	68
2020.9.2	81	84	86	82
2021.1.11	80	82	82	68
2022.3.28	83	87	87	81
2022.12.24*	77	77	83	69
????	**????**	**????**	**????**	**????**

* Steroid therapy

악화된다면 어떤 치료를?



Review of Disease



Smoking-related ILD

- Cigarette smoke is associated with the development of several diffuse parenchymal lung diseases ➔ smoking-related ILD

  - Pulmonary Langerhans cell histiocytosis (PLCH)
  - Respiratory bronchiolitis-associated ILD (RB-ILD)
  - Desquamative interstitial pneumonia (DIP)
  - Acute eosinophilic pneumonia (AEP)
  - Combined pulmonary fibrosis and emphysema (CPFE)

Smoking cessation is a major component of the management strategy for patients with smoking-related ILD

Immunol Allergy Clin N Am 43 (2023) 273–287

Smoking-related ILD

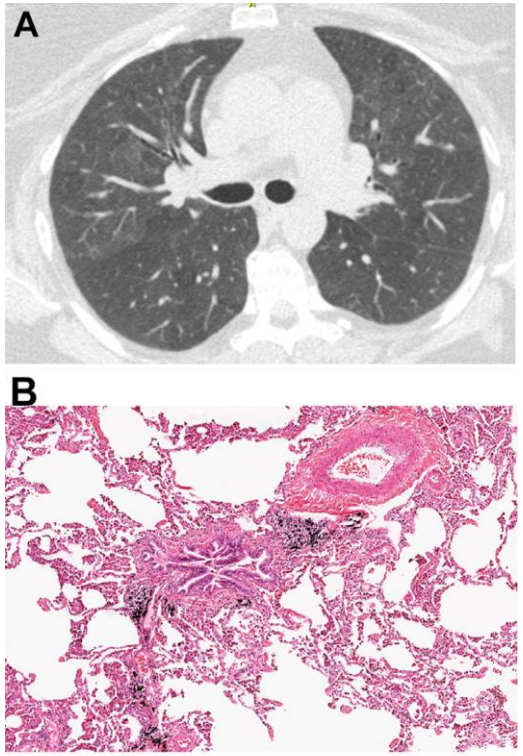
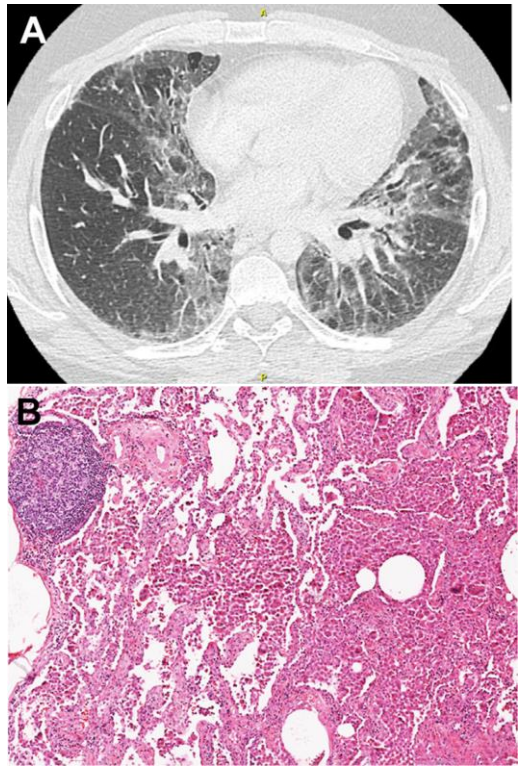


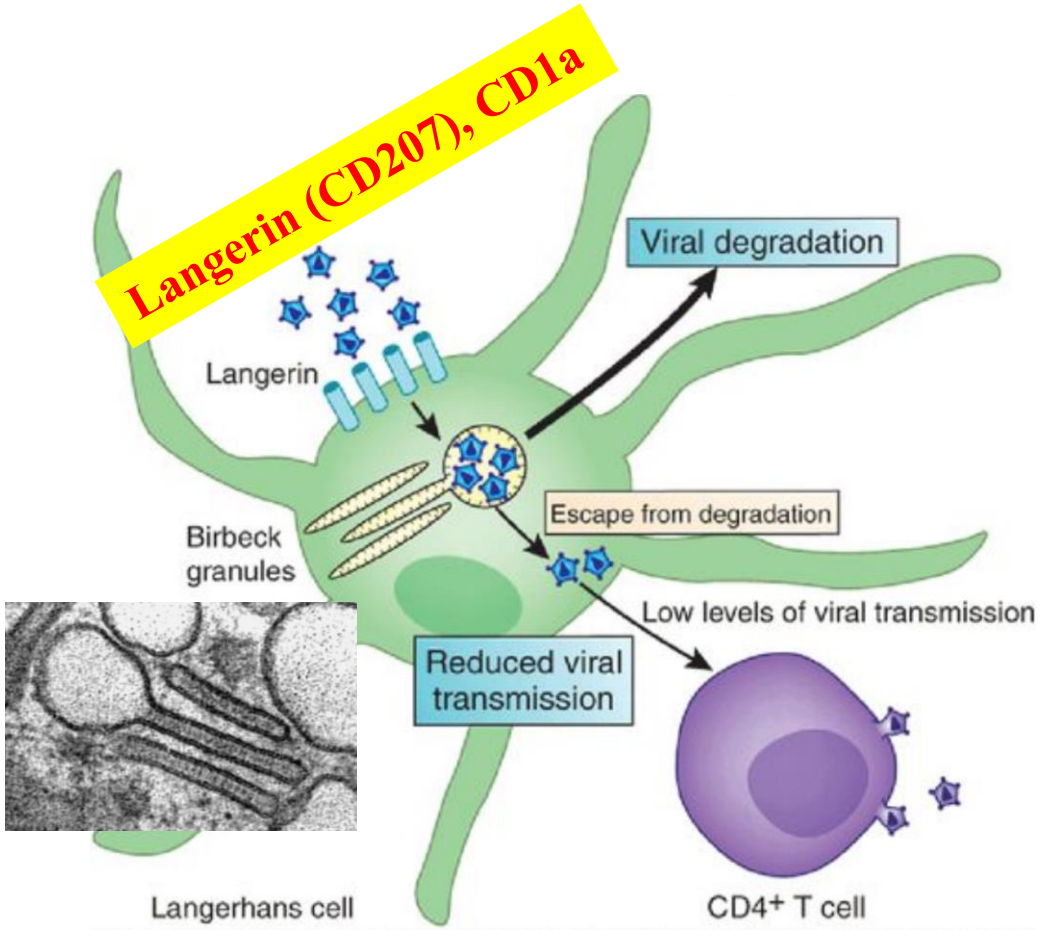
Table 1
Clinical characteristics of respiratory bronchiolitis-associated interstitial lung diseases and desquamative interstitial pneumonitis

	RB-ILD	Desquamative Interstitial Pneumonitis
Demographics	Age: 30 to 60 years old	Age: 40 to 50 years old Slight male predominance
Associations	Smoking >95%	Smoking 80% Occupational exposures Connective tissue Infection
Imaging	Centrilobular nodules Bronchial wall thickening	Ground glass opacities, lower lobe predominant. Reticular pattern
Pulmonary function tests	Variable. May be normal Decreased diffusion capacity (mild)	Restriction is more common, although other patterns can be present. Decreased diffusion capacity (moderate-severe)
Treatment	Smoking cessation	Smoking cessation Corticosteroids



Immunol Allergy Clin N Am 43 (2023) 273–287

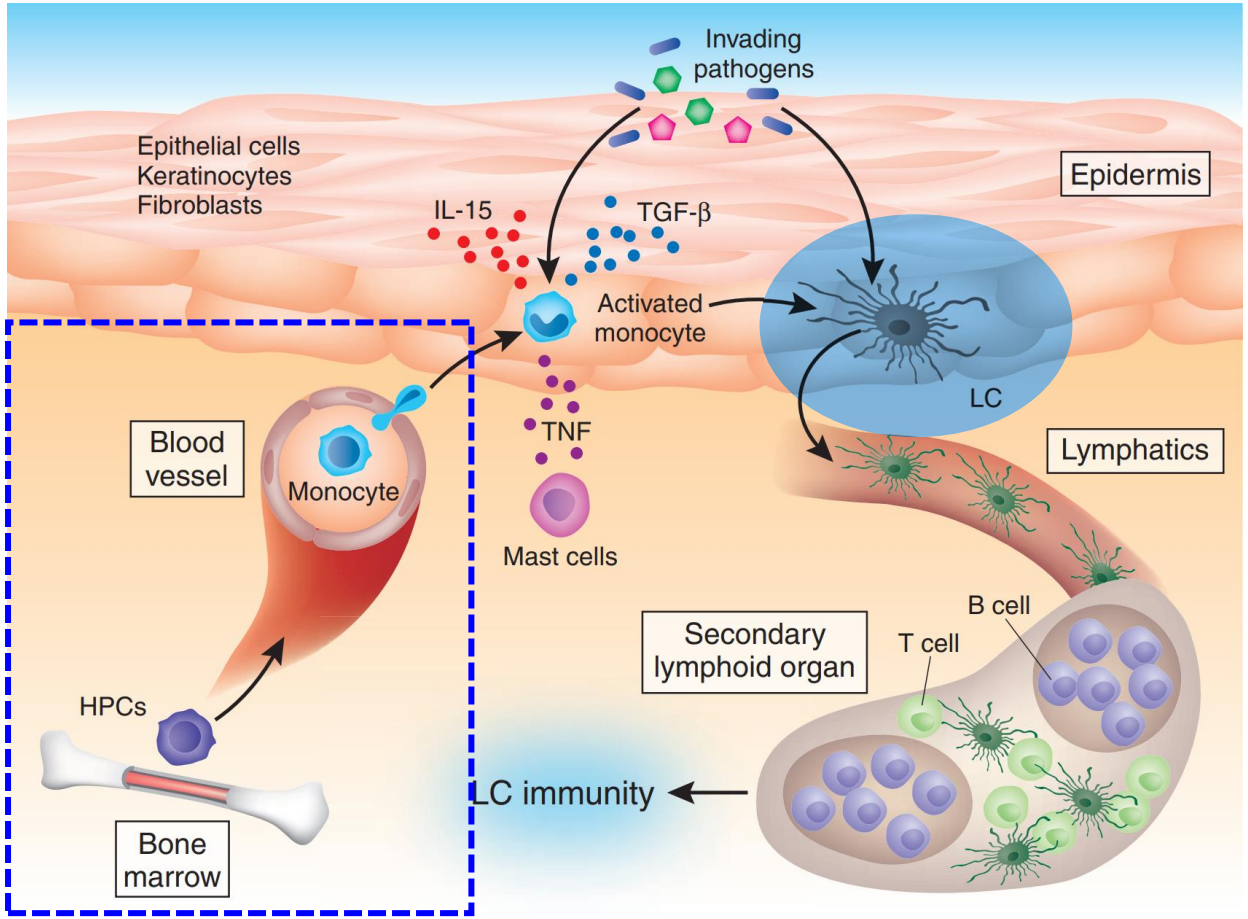
Langerhans Cell histiocytosis (LCH)

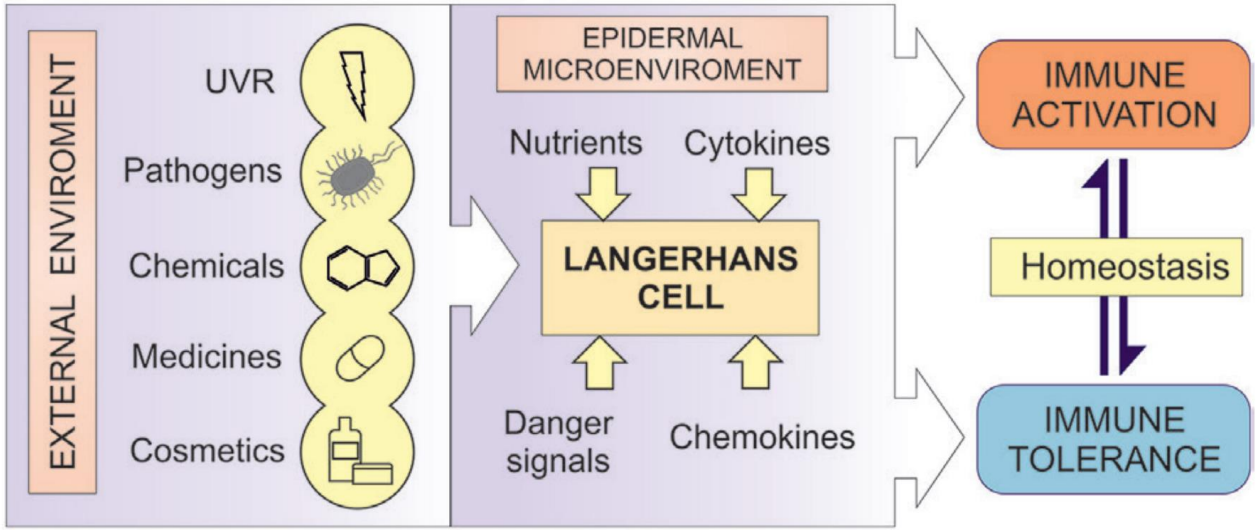


- Encompasses conditions characterized by aberrant function and differentiation or proliferation of cells of the mononuclear phagocyte system.
- Langerin-positive (CD207+) histiocytes + inflammatory infiltrates
- **Any organ system:** bone, skin, the lungs, and the pituitary.
- Single indolent lesions ~ explosive multisystem disease.

N Engl J Med 2018;379:856-68.

Langerhans cell



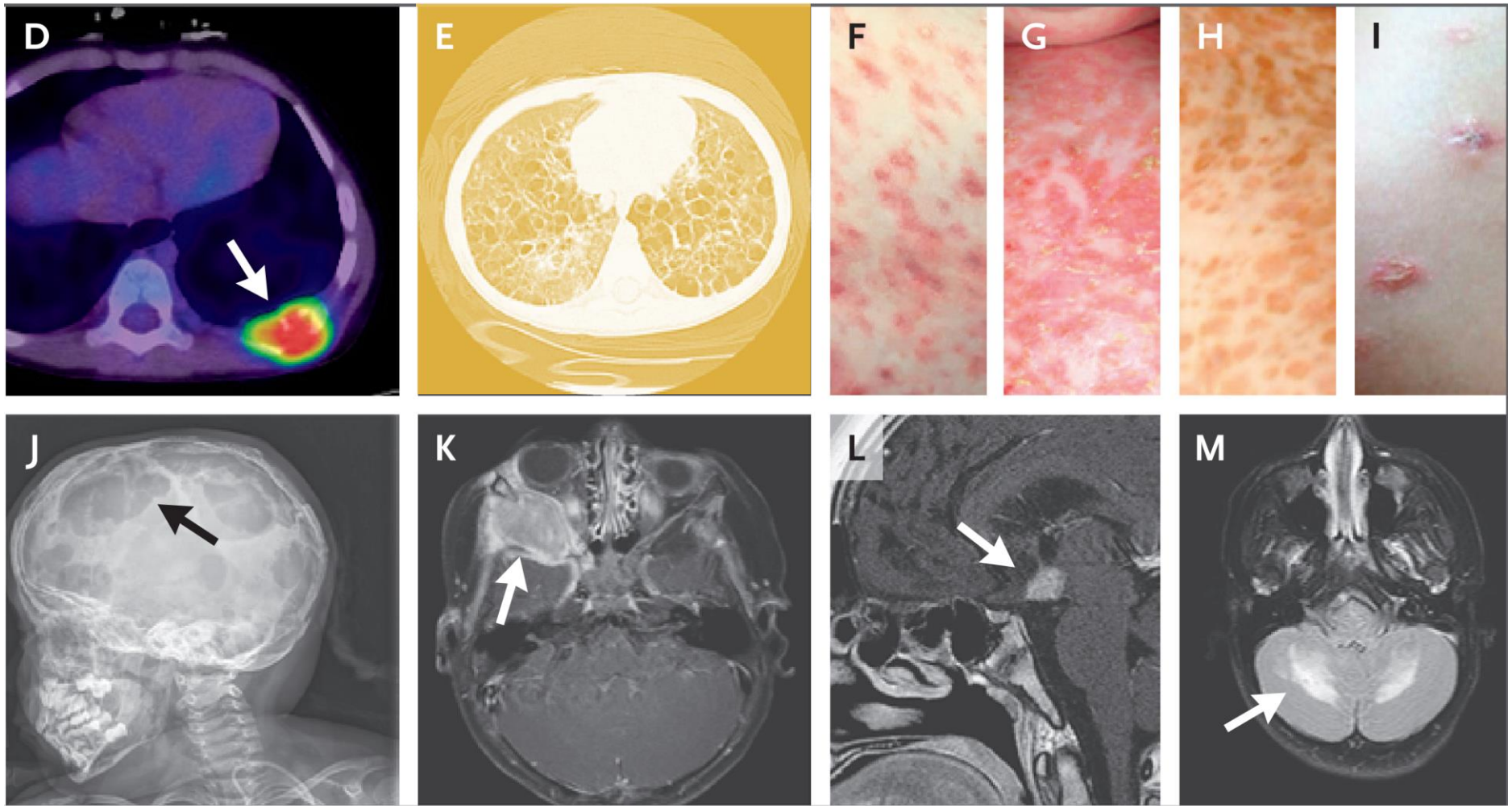


- Reside in the epidermis as a dense network of immune system sentinels
- Determine the appropriate adaptive immune response (inflammation or tolerance)
- Coordinate a continuous state of immune tolerance, preventing unnecessary and harmful immune activation

Nat Immunol . 2006 Mar;7(3):223-4.

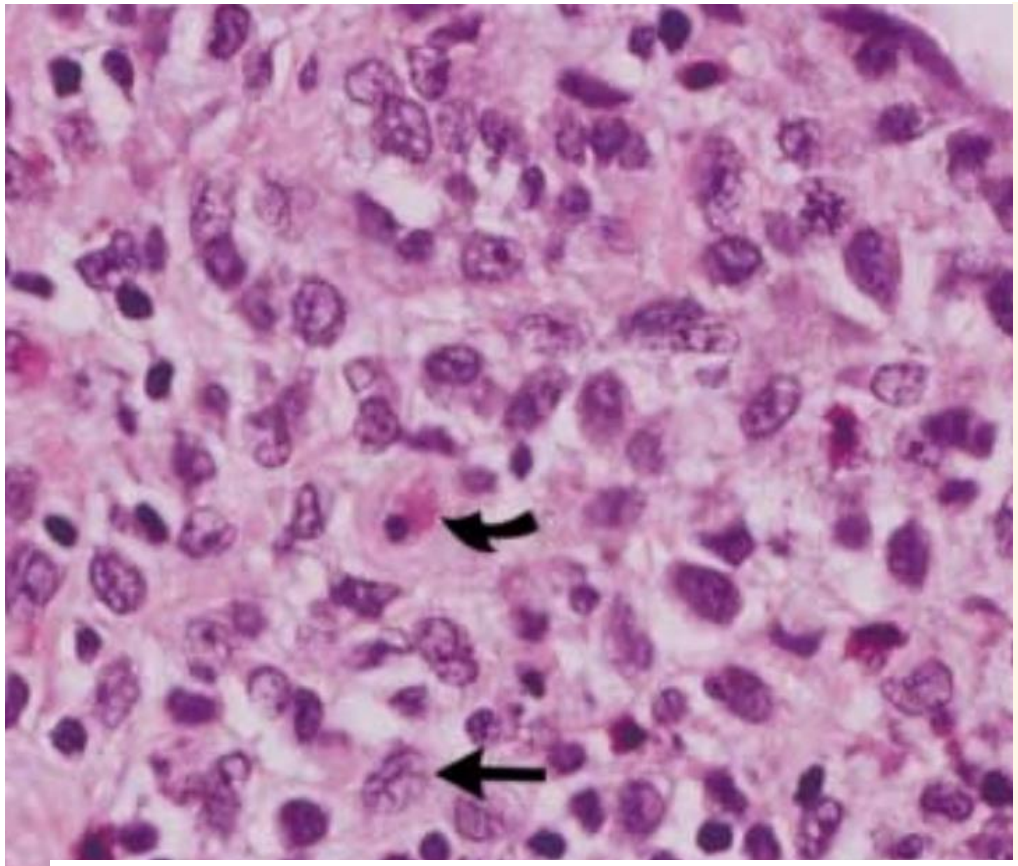
Front Immunol . 2017 Nov 29;8:1676.

Clinical spectrum of LCH

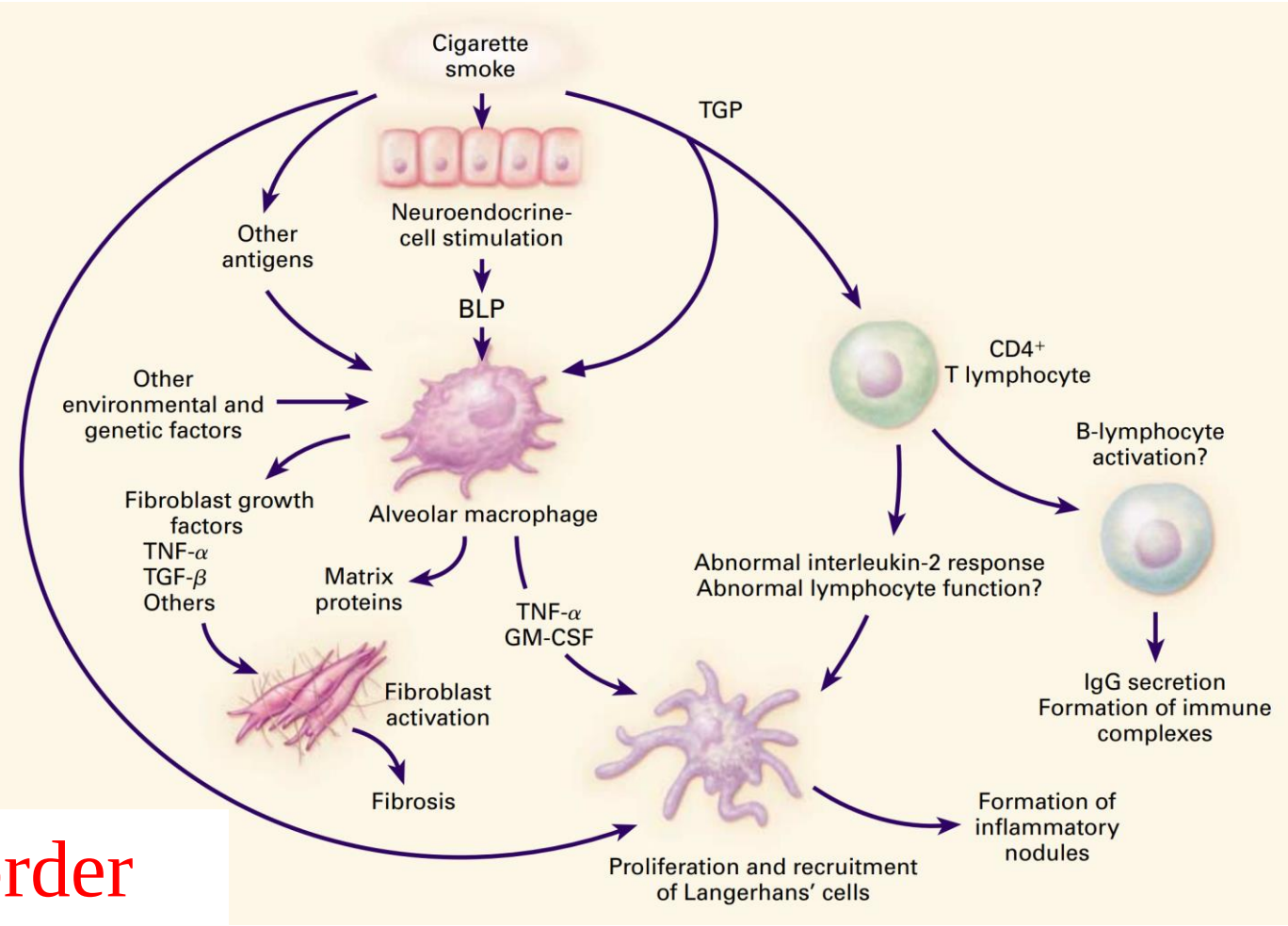


N Engl J Med 2018;379:856-68.

Proposed Pathogenesis of Pulmonary Langerhans-Cell Histiocytosis.

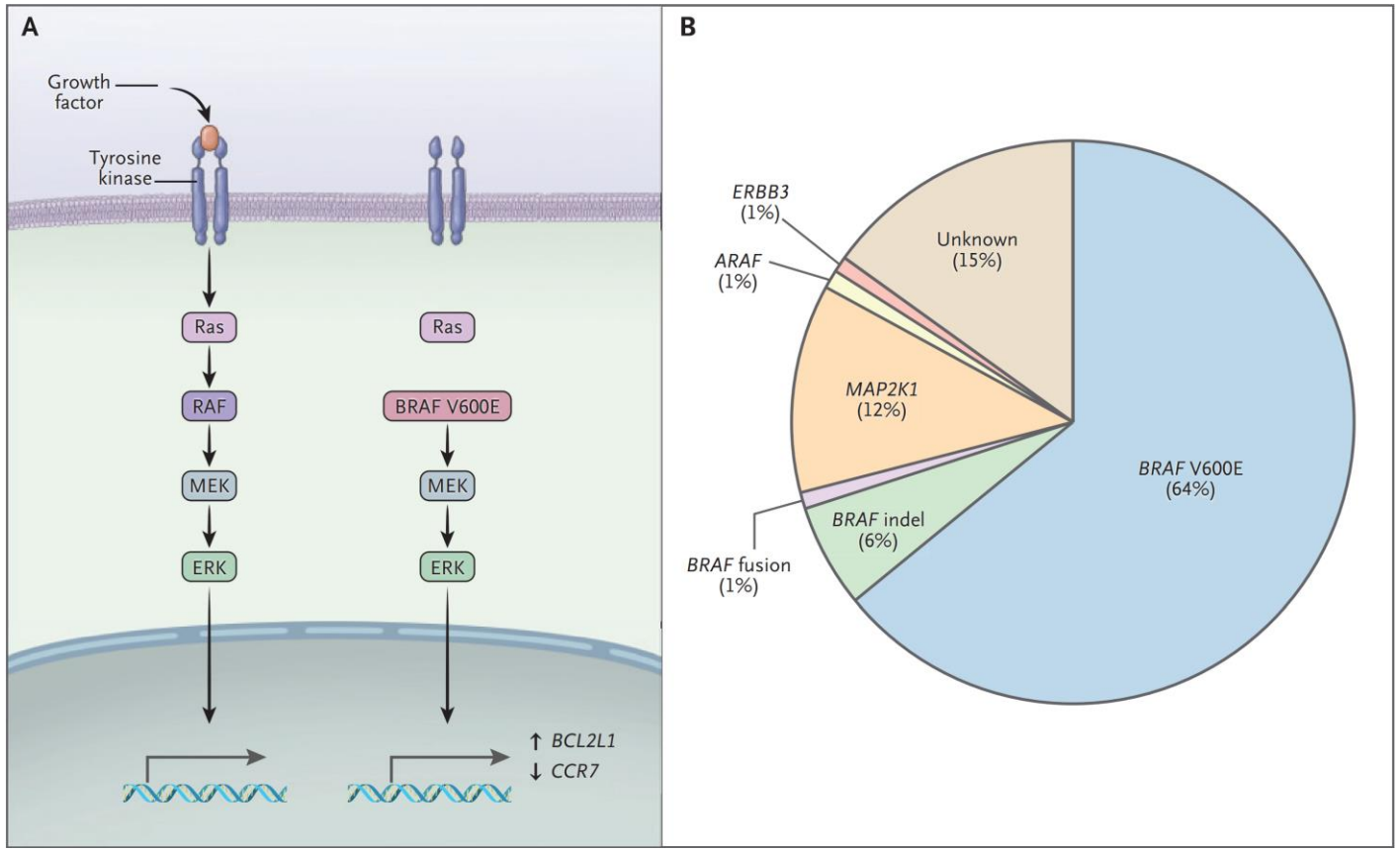


Immuno-dysregulatory disorder



N Engl J Med 2000; 342:1969-1978

Activating MAPK Pathway Mutations in LCH



Induce the expression of several transcription factors that regulate the gene expression involved in different cellular processes, including proliferation, survival, differentiation, migration, transformation, and apoptosis

N Engl J Med 2018;379:856-68.

Controversies of LCH

ELSEVIER

Hematology/Oncology Clinics of North America

Volume 12, Issue 2, 1 April 1998, Pages 339-357

CONTROVERSIES AND NEW APPROACHES TO TREATMENT OF LANGERHANS CELL HISTIOCYTOSIS

Robert J. Arceci MD, PhD [a], Malcolm K. Brenner MB, PhD, FRCP [b], Jon Pritchard FRCP [c]

https://doi.org/10.1016/S0889-8588(05)70514-1 ↗ Get rights and content ↗

Section snippets

- "lack of consensus is derived from a persisting ambivalence as to whether LCH is primarily a neoplastic disorder, an immuno-dysregulatory disorder, or a disorder with characteristics of both."

➔ Inflammatory myeloid neoplastic disorder

Hematol Oncol Clin North Am . 1998 Apr;12(2):339-57.

Classification of LCH in adults

Subtype	Definition
Unifocal	Solitary lesion involving any organ
Single-system pulmonary	Isolated lung involvement (predominantly smoking related)
Single-system multifocal	>1 lesion involving any organ
Multisystem	≥2 organ/system involvement

- **PLCH:** Accumulation of CD207+/CD1a^{+} cells in the lungs causes inflammatory cystic-nodular pulmonary parenchyma destruction in predisposed smokers

Blood . 2022 Apr 28;139(17):2601-2621

Pathogenesis of PLCH

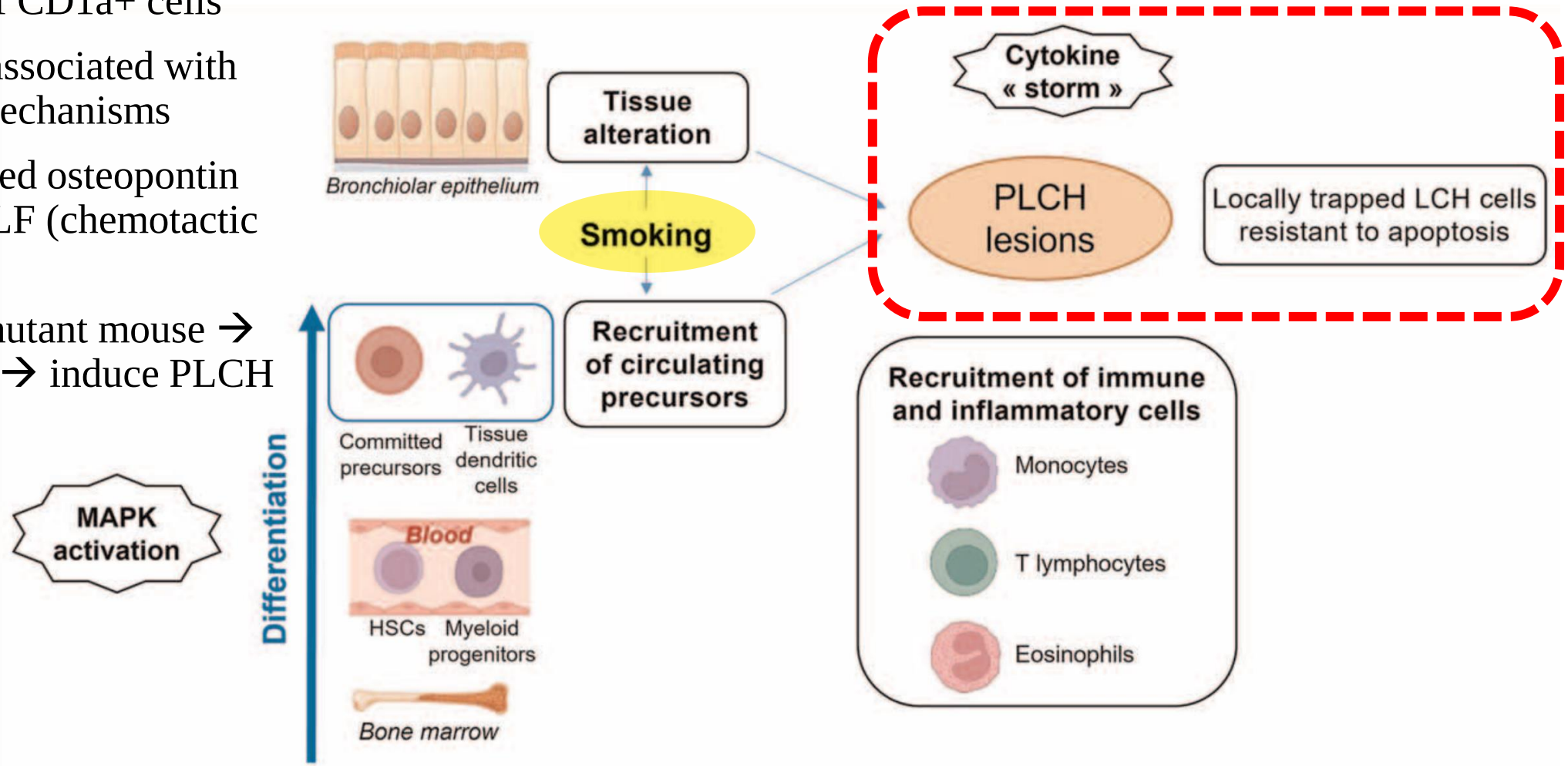
- **Smoking**

① Accumulation of CD1a+ cells

② Local cytokine associated with anti-apoptotic mechanisms

③ Nicotine increased osteopontin secretion in BALF (chemotactic effect)

④ BRAF V600E mutant mouse → cigarette smoke → induce PLCH like lesion



Curr Opin Pulm Med . 2023 Jul 7.

Epidemiology and clinical presentation

- **Prevalence:** Japan – male: 0.27/100,000, female: 0.07/100,000

- **The strongest risk factor (likely causal factor):** current or former tobacco smoking

- Often presents in the fourth decade of life
- Cough, dyspnea, chest pain, fever and general malaise
- Up to 50%: asymptomatic
- **Extrapulmonary manifestations (20%):** bone and pituitary gland

Eur Respir Rev 2023; 32: 220161

PLCH (n=206), 2004-2018 (age ≥ 18), histologic or clinical

EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
A. BENATTIA ET AL.

Long-term outcomes of adult pulmonary Langerhans cell histiocytosis: a prospective cohort

Amira Benattia[1], Emmanuelle Bugnet[1], Anouk Walter-Petrich[2,3], Constance de Margerie-Mellon[4,5], Véronique Meignin[6], Agathe Seguin-Givelet[7], Gwenaël Lorillon[1], Sylvie Chevret[2,3] and Abdellatif Tazi[1,8]

[1]Centre National de Référence des Histiocytoses, Service de Pneumologie, AP-HP, Hôpital Saint-Louis, Paris, France. [2]Biostatistics and Clinical Epidemiology Research Team (ECSTRRA), INSERM UMR-1153 (CRESS), Université de Paris, Paris, France. [3]Service de Biostatistique et Information Médicale, AP-HP, Hôpital Saint-Louis, Paris, France. [4]Université de Paris, INSERM UMR-1149, Paris, France. [5]Service de Radiologie, AP-HP, Hôpital Saint-Louis, Paris, France. [6]Service de Pathologie, AP-HP, Hôpital Saint-Louis, Paris, France. [7]Département Thoracique, Institut du Thorax Curie-Montsouris, Institut Mutualiste Montsouris, Paris, France. [8]Human Immunology Pathophysiology and Immunotherapy (HIPI) Unit, INSERM UMR-976, Institut de Recherche Saint-Louis, Université de Paris, Paris, France.

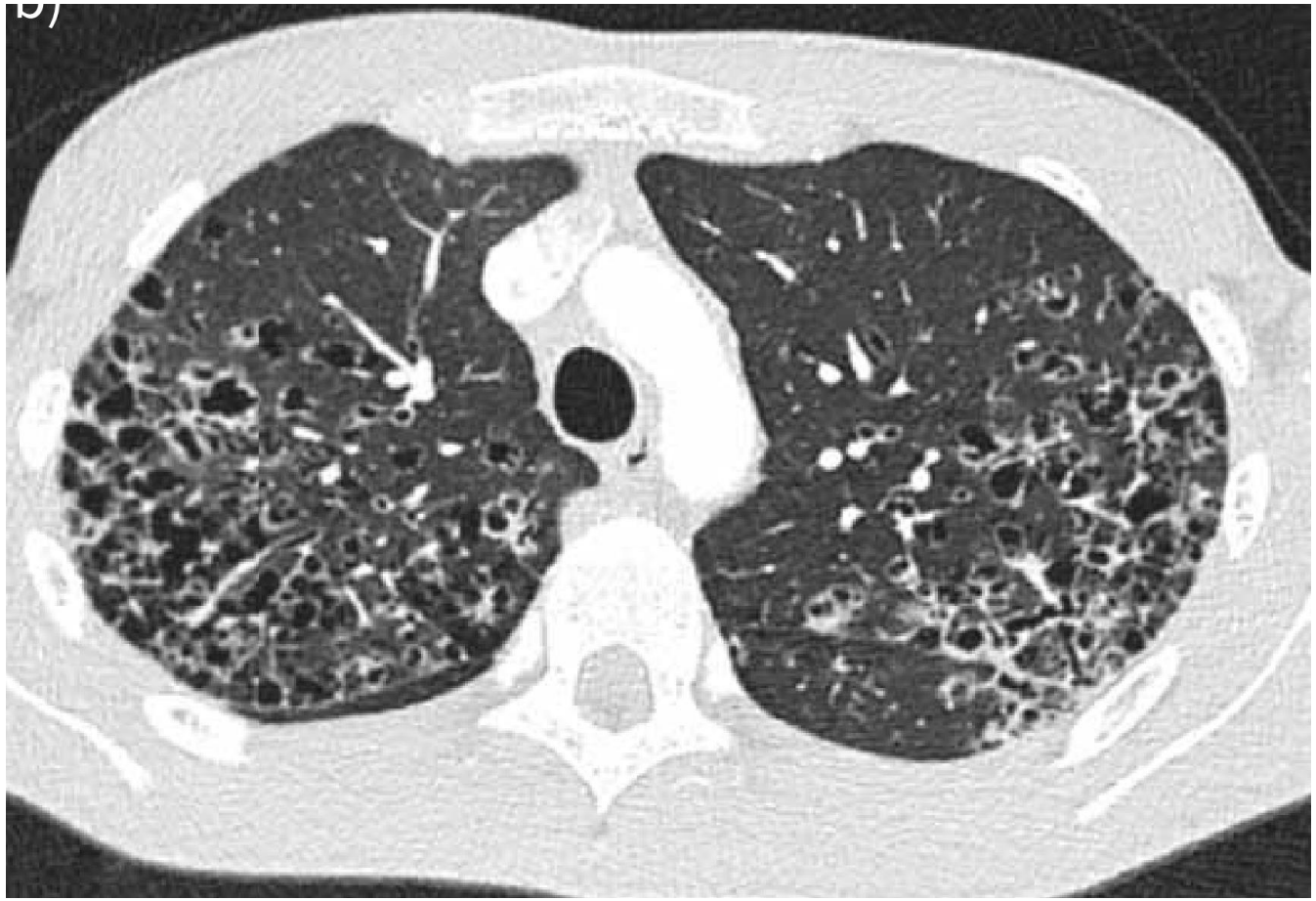
Eur Respir J . 2022 May 26;59(5):2101017

TABLE 1 Characteristics of the pulmonary Langerhans cell histiocytosis (PLCH) patients at the time of diagnosis

Characteristic	
Subjects, n	206
Age, years	39.3±12.8
Sex	
Female	123 (59.7)
Male	83 (40.3)
Smoking status	
Current smokers	196 (95.1)
Ex-smokers	8 (3.9)
Pack-years	21.7±15.9
Non-smokers[#]	2 (1)
Cannabis consumption[¶]	35 (17.0)
Histological diagnosis[+]	66 (32%)
LCH extent	
Isolated PLCH	157 (76.2)
Multisystem PLCH[§]	49 (23.8)
Bone	35
Diabetes insipidus	11
Skin	6
Liver	2
Other[f]	2

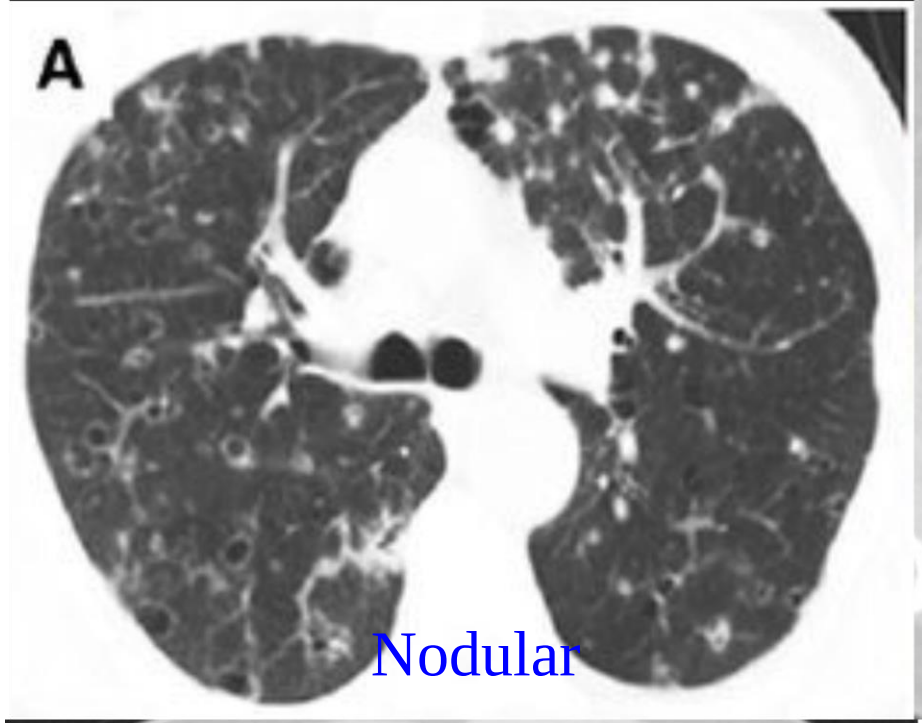
Eur Respir J . 2022 May 26;59(5):2101017

Radiologic findings

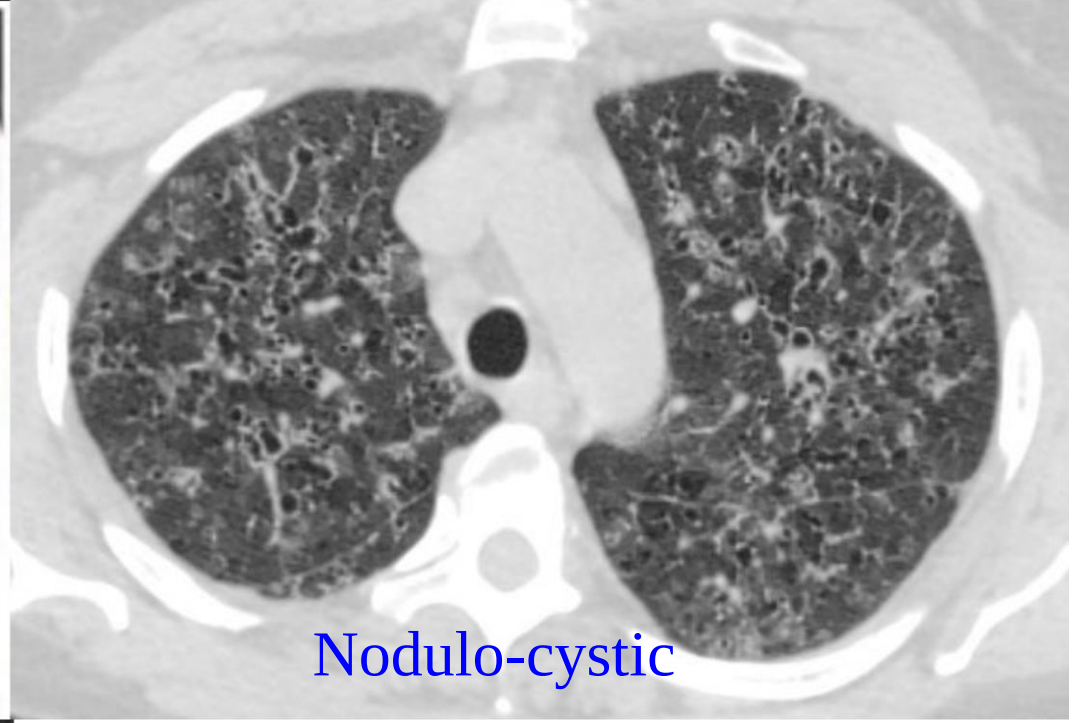


- Bronchiolocentric micronodular/nodular and cystic lesions with parenchymal destruction, of predominant upper and middle lobes distribution with typical sparing of costophrenic angles
- Cysts can be of various shapes (round, bilobed, clover-leafed, irregular or “bizarre”)

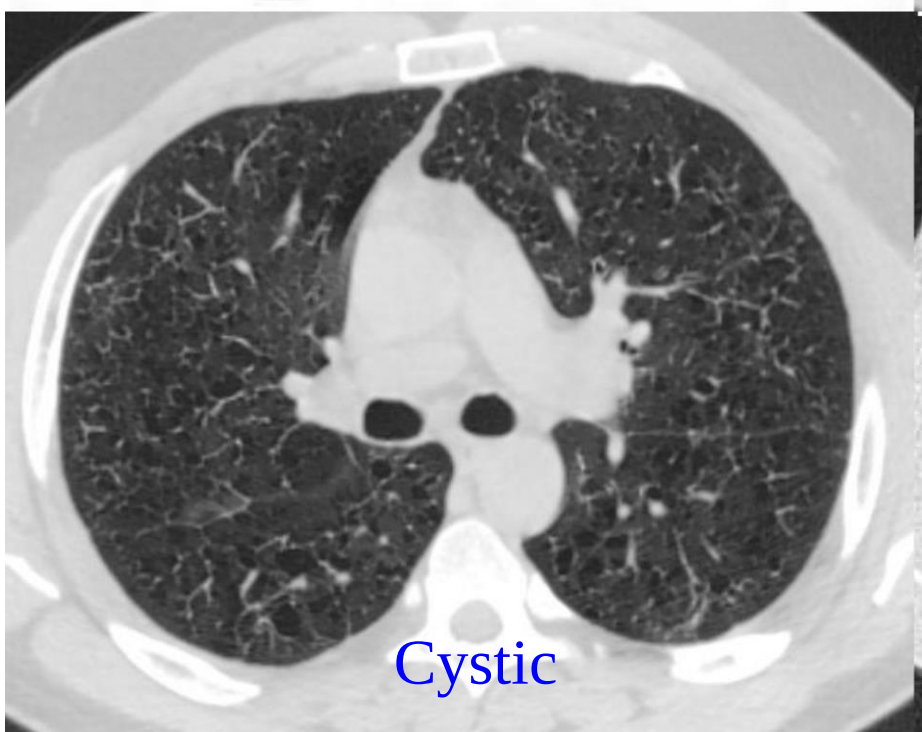
Eur Respir Rev 2023; 32: 220161



Nodular



Nodulo-cystic



Cystic

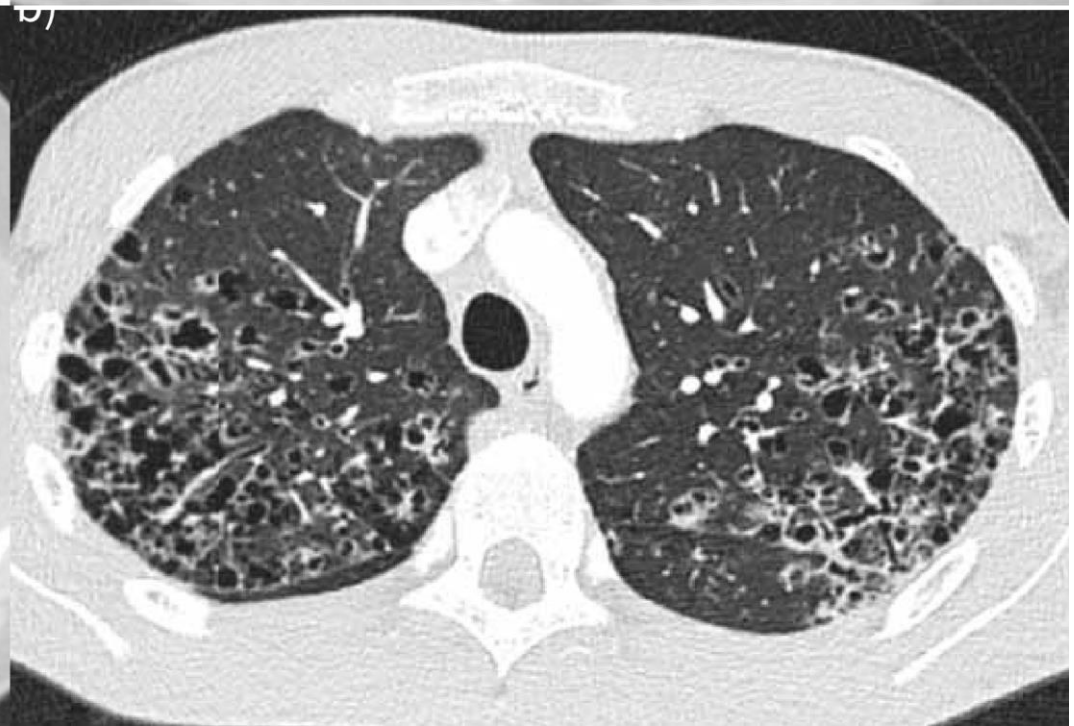


TABLE 1 Characteristics of the pulmonary Langerhans cell histiocytosis (PLCH) patients at the time of diagnosis

Characteristic	
HRCT pattern, n=196[¶¶]	
Nodulo-cystic	176 (89.8)
Nodular (cavitated)	6 (3.1)
Cystic	14 (7.1)
HRCT nodular score	6.8±4.8
HRCT nodular score subgroup	
Low (0–6)	116 (59.2)
Intermediate (7–12)	54 (27.6)
High (13–18)	26 (13.3)
HRCT cystic score	6.8±4.5
HRCT cystic score subgroup	
Low (0–6)	136 (69.4)
Intermediate (7–12)	39 (19.9)
High (13–18)	15 (7.7)
Very high (19–24)	6 (3.1)

Diagnosis

- A definite diagnosis requires confirmation either by BAL or sometimes histology, but a high-confidence diagnosis can often be made with a combination of a typical HRCT pattern and suggestive history, especially in smokers

TABLE 1 Characteristics of the pulmonary Langerhans cell histiocytosis (PLCH) patients at the time of diagnosis

Characteristic	
Histological diagnosis+	66 (32%)

+Surgical lung biopsy (n=44) and extra-thoracic LCH localization (n=22)

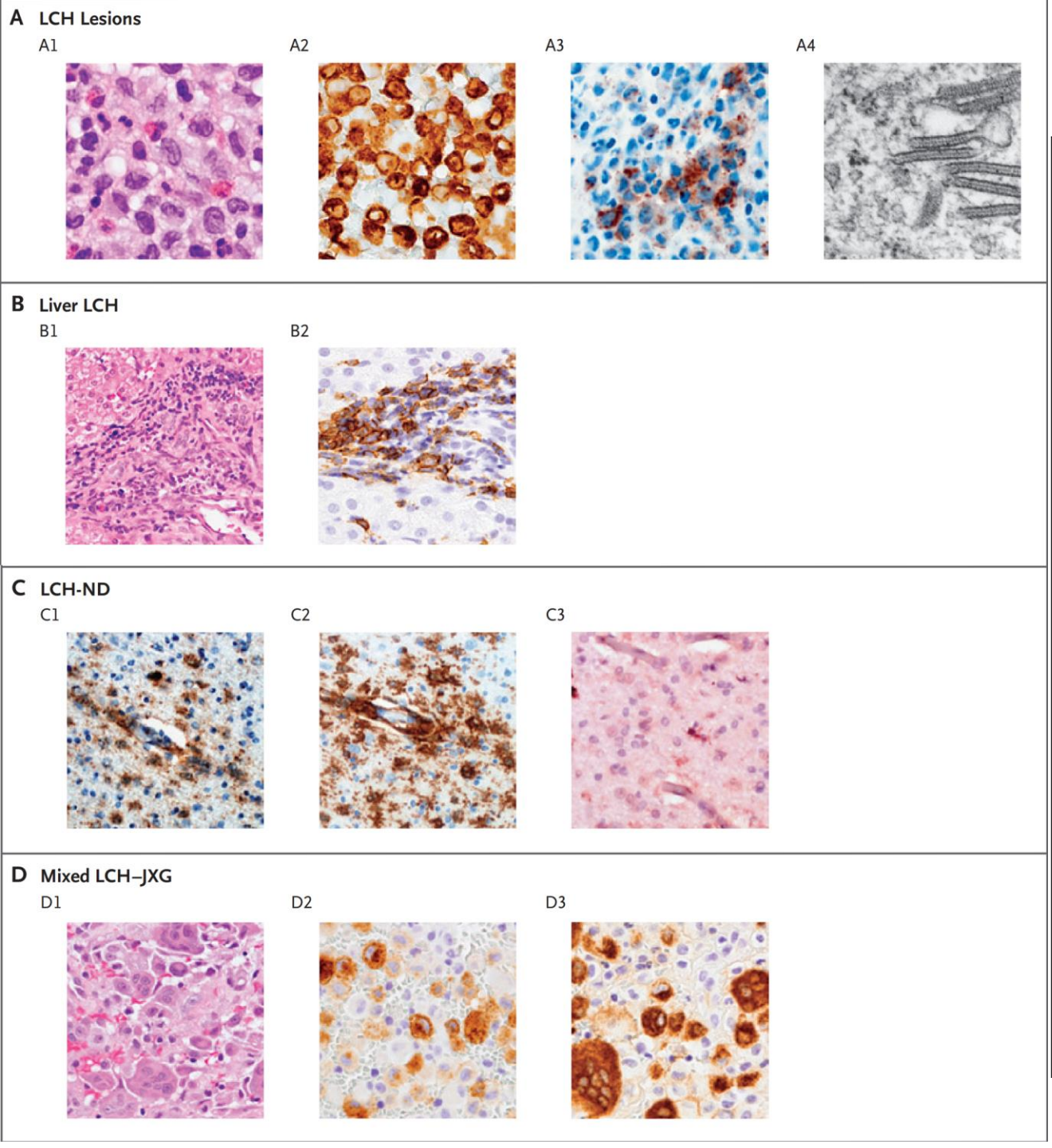
Eur Respir Rev 2023; 32: 220161

Bronchoscopy

- Exclude other disorders, especially infection

- **TBLB** – 10~50 % of diagnostic yield (nodular lesion)
- **TBLC** – case reports
- **BAL** – presence of >5% cells with CD1a expression (0~25% pts)

Immunol Allergy Clin N Am 43 (2023) 273–287



Diagnosis of LCH

Clinical and radiographic features

1. Upper lobe predominant nodular and cystic lung lesions in a smoker
2. Central diabetes insipidus
3. Punched-out lytic osseous lesions, often involving flat bones (skull, sternum, ribs, pelvis)

Histopathologic features

1. Lesional histiocytes with elongated, grooved nuclei, often with intermixed eosinophils
2. CD207 (langerin)- and CD1a-positive histiocytes in lesional tissue by IHC
3. Characteristic pattern of tissue involvement to exclude reactive Langerhans cells

Molecular features

1. *BRAF*-V600E mutation
2. Other activating mutations in the RAS-RAF-MEK-ERK pathway (*MAP2K1*, *BRAF*, *KRAS*, *NRAS*, *ARAF*, etc)
3. Activating kinase fusions

N Engl J Med 2018;379:856-68.

International expert consensus recommendation for the diagnosis and treatment of LCH in adults

Statement number	Consensus statements	Consensus recommendation category
Diagnosis		
1.	A biopsy of lesional tissue is recommended even in circumstances of highly suggestive clinical and imaging features to confirm LCH diagnosis and establish BRAF or another MAPK-ERK pathway mutational status. Cases of single-system PLCH with typical radiologic findings and clinical context are a reasonable exception, although a biopsy is recommended in these cases as well.	A
2.	LCH should be considered in the presence of characteristic clinical/radiologic features (Table 3), even when a histopathologic review is equivocal. Molecular analysis of tissue for BRAF and MAPK-ERK pathway mutations can be helpful in the diagnosis of questionable lesions.	B
3.	Baseline full-body (vertex-to-toes) FDG-PET/CT, including the distal extremities, is recommended to aid in diagnosis and defining the extent of disease.	B
4.	Organ-specific imaging (CT, MRI) is recommended to further assess involved sites of disease based on initial imaging studies.	A
5.	MRI of the brain with gadolinium, with a dedicated examination of the sella turcica, should be undertaken at diagnosis in cases with pituitary dysfunction or neurologic symptoms.	A

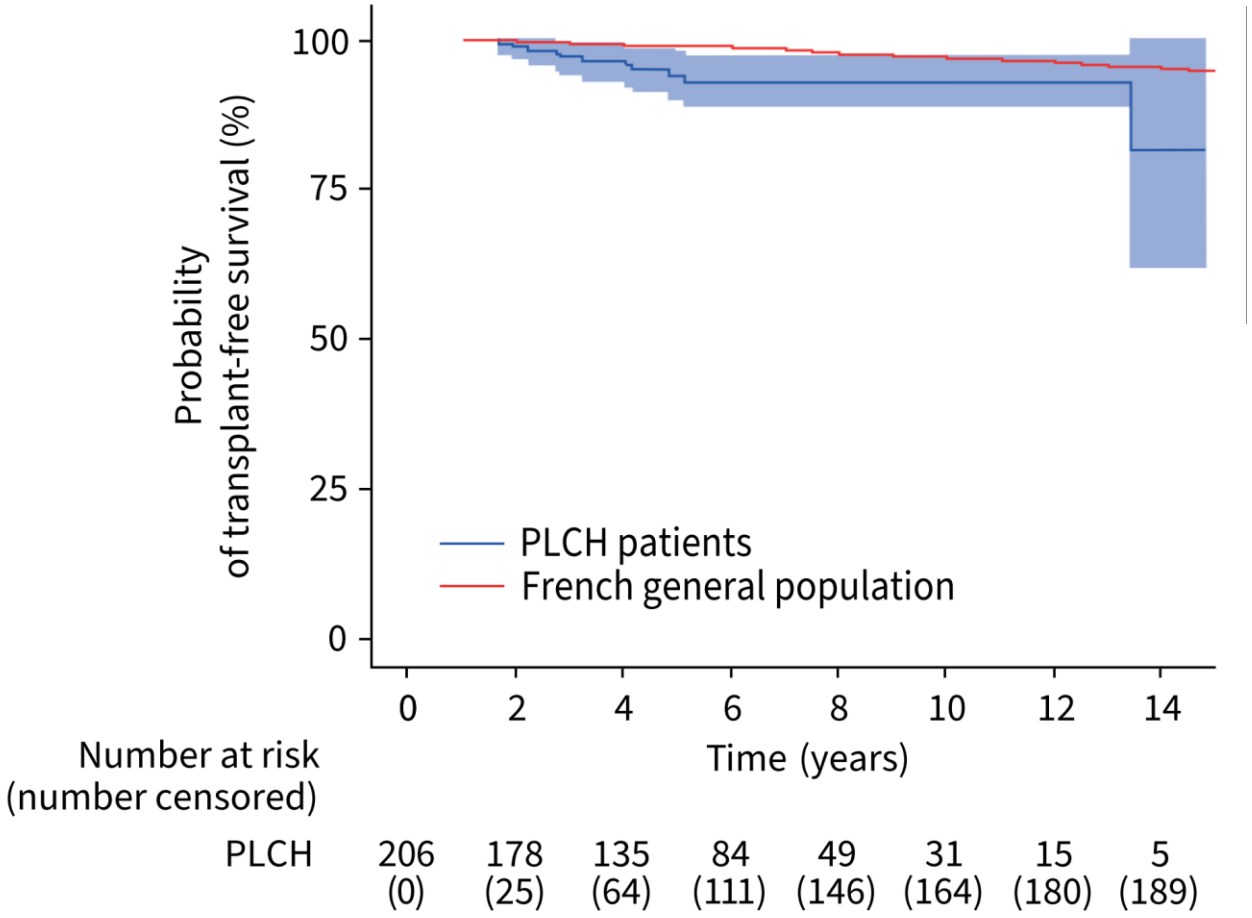
Blood . 2022 Apr 28;139(17):2601-2621.

Disease course

- Most of the cases experience regression with smoking discontinuation
- Around 20–30% of the cases the disease progresses to end-stage lung disease
- Between 12–32% of patients will present pneumothorax in their lifetime
- A prospective series followed newly diagnosed patients with PLCH for 2 years and found that 38% presented lung function decline, with predictors of deterioration being smoking status and baseline PaO2
- 10-year survival has been estimated at 93%

Eur Respir Rev 2023; 32: 220161

Long-term survival



Cox model with covariates at diagnosis

Characteristic	HR (95% CI)	p-value
Age	1.09 (1.03–1.16)	0.004
FEV_1 #	0.97 (0.94–1.00)	0.042
Smoking exposure, pack-years	1.00 (0.96–1.06)	0.85

Cox model with all characteristics introduced as time-dependent covariates

Characteristic	HR (95% CI)	p-value
Age	1.07 (1.01–1.13)	0.017
FEV_1	0.96 (0.92–1.00)	0.046
Smoking status	1.54 (0.42–5.60)	0.52
Systemic treatment ¶	1.53 (0.36–6.54)	0.57

Eur Respir Rev 2023; 32: 220161

Causes of death

TABLE 2 Characteristics of the 12 pulmonary Langerhans cell histiocytosis (PLCH) patients who died during the study period

Patient	Age at diagnosis, years	Sex	Smoking status at diagnosis	Pack-years at diagnosis	Extent of LCH	CRF	PH	Time to death, years	Cause of death
1	58	M	Former	20	Isolated	Yes	Yes	13	Lung cancer
2	35	M	Current	10	Isolated	No	No	5	Lung cancer
3	35	F	Current	14	Multisystem	No	No	5	Lung cancer
4	49	F	Former	20	Isolated	No	No	2	Lung cancer
5	33	M	Current	30	Isolated	Yes	Yes	2	Respiratory failure
6	47	M	Current	80	Isolated	Yes	Yes	2	Respiratory failure
7	48	M	Current	30	Isolated	Yes	Yes	4	Respiratory failure
8[#]	38	F	Former	20	Multisystem	Yes	Yes	4	Pulmonary mucormycosis
9[¶]	72	F	Current	50	Isolated	Yes	Yes	4	CMML
10	49	F	Current	60	Isolated	No	Yes	3	Acute coronary syndrome
11	79	M	Former	60	Multisystem	No	No	3	Bacterial pneumonia
12	87	M	Non-smoker	0	Multisystem	No	No	2	Heart failure

LCH: Langerhans cell histiocytosis; CRF: chronic respiratory failure; PH: pulmonary hypertension; M: male; F: female; CMML: chronic myelomonocytic leukaemia. [#]: died 1 year after lung transplantation; [¶]: treated with cladribine.

Eur Respir J . 2022 May 26;59(5):2101017

Treatment

- Smoking cessation alone can be sufficient to obtain stabilization or regression of PLCH
- Tobacco and marijuana weaning are sometimes temporary and are insufficient in approximately one-third of cases.
- Pharmacological treatment with cladribine has been shown to be effective and BRAF kinase/MEK inhibition represents promising leads in case for specific mutations.
- In advanced cases, lung transplantation is effective, but recurrence can occur

Eur Respir Rev 2023; 32: 220161

금연의 효과

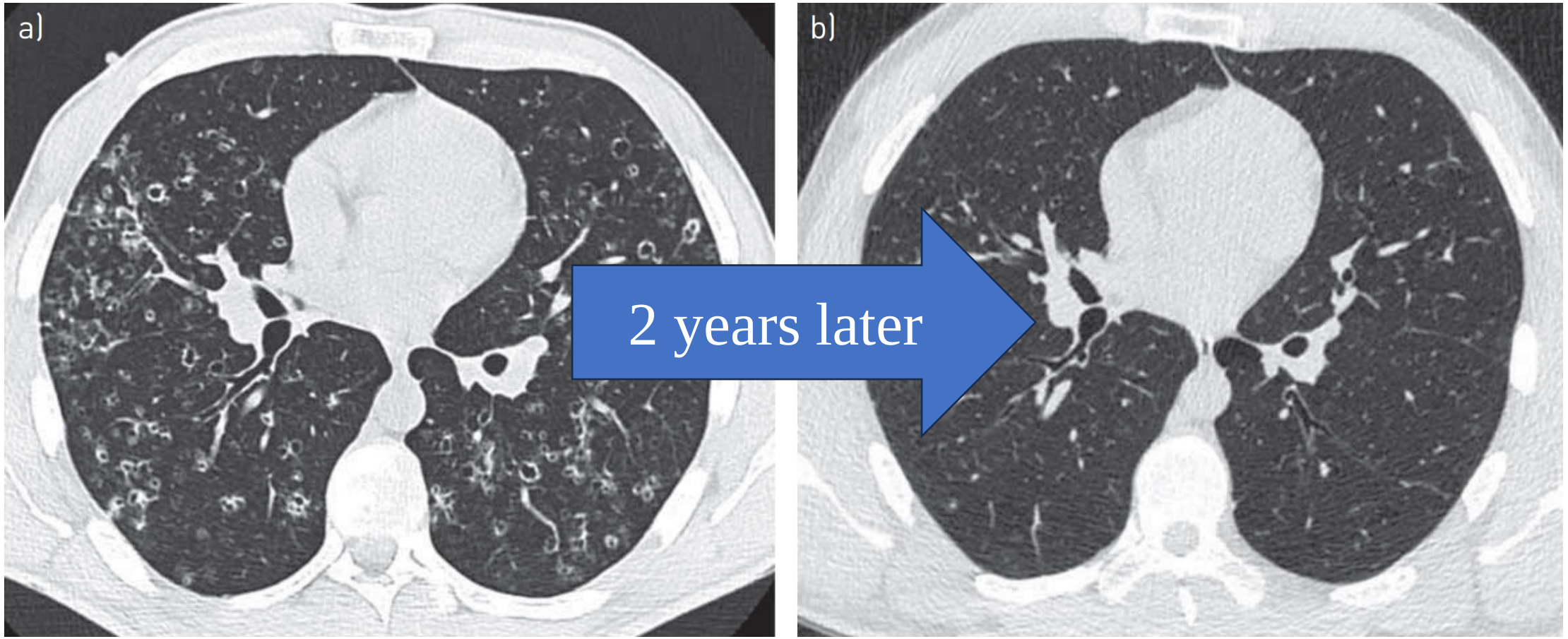
- **~50% of PLCH pts** – smoking cessation leads to partial regression and subsequent stabilization without immunosuppressive therapy.

- **Require systemic follow-up** because reactivation of LCH

- **Cessation of both cigarette smoking and marijuana smoking** is becoming a challenge for both patients and doctors

Front Med (Lausanne) . 2021 Mar 8;7:582581.

PLCH → stop smoking



Eur Respir Rev . 2017 Sep 6;26(145):170070.

Smoking status & lung function deterioration

Table 3 Univariate analyses of the predictive factors (measured at inclusion) of lung function deterioration*

Characteristic	Deterioration (n = 23)	No deterioration (n = 35)	HR (95% CI)	P value
Demographic features				
Age, yrs	41.1 ± 12.0**	32.0 ± 8.2	1.7 (1.2-2.4)†	0.002
Sex, n (%)				
Male	12 (52)	15 (43)	1.0	
Female	11 (48)	20 (57)	0.98 (0.4-2.3)	0.97
Smoking status, n (%)				
Smokers	20 (87)	19 (54)	1.0	
Non-smokers	3 (13)	16 (46)	0.25 (0.1-0.85)	0.027

Tazi et al. Orphanet Journal of Rare Diseases (2015) 10:30

Corticosteroids

- **Systemic corticosteroid therapy**→ symptomatic, radiological, and functional improvement (insufficient data)
- Dose ? Duration ?
- Possible effects of smoking cessation rather than steroid therapy
- This treatment is no longer recommended.

- For patients with symptomatic and progressive nodular PLCH despite smoking cessation, we suggest a trial of systemic glucocorticoids (eg, prednisone 0.25 to 0.5 mg/kg per day or 30 mg/day initially with gradual tapering over six months) -*Uptodate*

Front Med (Lausanne) . 2021 Mar 8;7:582581.

PLCH (n=36) + corticosteroids

Prednisolone 40 mg qD for mean 9.6 months → none of worsening of PLCH

Table 3. Lung function values of 17 patients with early-stage histiocytosis X before and during or after corticosteroid therapy (mean values and standard deviation)

	n	Before therapy	During or after therapy
VC, % pred.	17	101 ± 17	112 ± 19*
TLC, % pred.	17	100 ± 15	104 ± 16
RV, % TLC	15	30 ± 6	26 ± 9
FEV_1, % VC	16	73 ± 8	67 ± 11
$T_{L\,CO}$, % pred.	13	64 ± 14	67 ± 16
K_{CO}, % pred.	13	62 ± 11	59 ± 9

The observation period was 29.9 ± 24.1 months, the duration of therapy 9.5 ± 6.9 months. * $p < 0.01$ (paired t test). Abbreviations as

Respiration . 1993;60(1):38-44.

PLCH (n=45)

Median f/u: 6 yrs (1-29 yrs)
Death or LT: 12 (27%)

- **Diagnosis**
  - Lung biopsy: 25 (OL: 24, TBLB: 1)
  - BAL: 20
- **Age (mean)** 28 ± 10
- **Male** 71%
- **C-smoker** 96%

Table 3. – Treatment regimen for the study of subjects with pulmonary Langerhans' cell granulomatosis (LCG)

Treatment regimen	Subjects n	%
None	22	48
Corticosteroids alone	18	40
Corticosteroids and cyclophosphamids§	2	5
Polychemotherapy#	1	2
Chlorambucil*	1	2
Vinblastine and azathioprin‡	1	2

Table 5. – Effect of clinical and functional variables at the time of diagnosis and of steroid therapy during follow-up on evolution to terminal respiratory failure of the 45 patients with pulmonary LCG

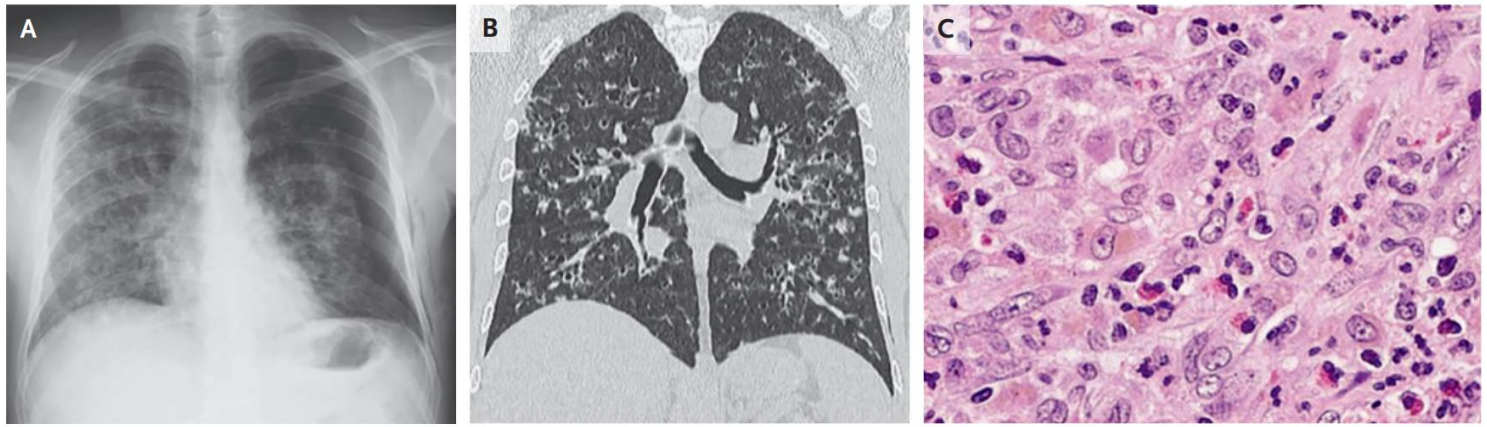
	HR	95% CI	p-value
Age	1.12	1.05–1.19	0.0005
Male gender	1.57	0.3–8.25	0.6
Pulmonary symptoms *vs* none	3.69	0.76–17.96	0.11
Cessation of tobacco consumption *vs* none	10.57	1.29–86.34	0.03
Treatment with corticosteroids *vs* none	2.44	0.50–11.28	0.03
ILO profusion category	1.7	0.80–4.12	0.16
FEV_1	0.99	0.94–1.00	0.07
FVC	0.98	0.94–1.03	0.5
FEV_1/FVC ratio	0.95	0.90–0.99	0.03
TLC	1.02	0.97–1.08	0.4
RV	1.01	0.99–1.03	0.2
RV/TLC ratio	1.11	1.02–1.21	0.01
$T_{L,CO}/V_A$	0.98	0.95–1.00	0.07
$T_{L,CO}/V_A$ <55%	0.21	0.05–0.89	0.03

Eur Respir J . 1996 Oct;9(10):2002

IMAGES IN CLINICAL MEDICINE

Stephanie V. Sherman, M.D., *Editor*

Pulmonary Langerhans-Cell Histiocytosis



A 40-YEAR-OLD MAN WITH A HISTORY OF SMOKING PRESENTED TO THE emergency department with a 2-week history of cough, dyspnea, night sweats, and pleuritic chest pain on the left side. Physical examination was notable for decreased breath sounds over the left lung fields. A chest radiograph showed a large pneumothorax on the left side and interstitial infiltrates in both lungs (Panel A). The pneumothorax was treated with chest-tube thoracostomy. Subsequent computed tomography of the chest showed multiple cysts and nodules, predominantly in the upper and middle lung fields, with sparing of the costophrenic angles (Panel B). A transbronchial lung biopsy was performed. Histopathological tests showed a lymphocytic lung infiltrate with interalveolar septal thickening, eosinophils, and large cells with foamy cytoplasm and large nuclei (Panel C). Immunohistochemical staining was positive for S-100 protein, CD1a, placental acid phosphatase, and langerin. A diagnosis of pulmonary Langerhans-cell histiocytosis was made. Further testing revealed no evidence of systemic histiocytosis. BRAF testing was not done. The patient was advised to stop smoking, and a tapering dose of prednisone was prescribed. At the 6-month follow-up, the patient had ceased smoking; he was still taking low-dose prednisone, and his symptoms had abated.

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This article was published on December 24, 2022, at NEJM.org.

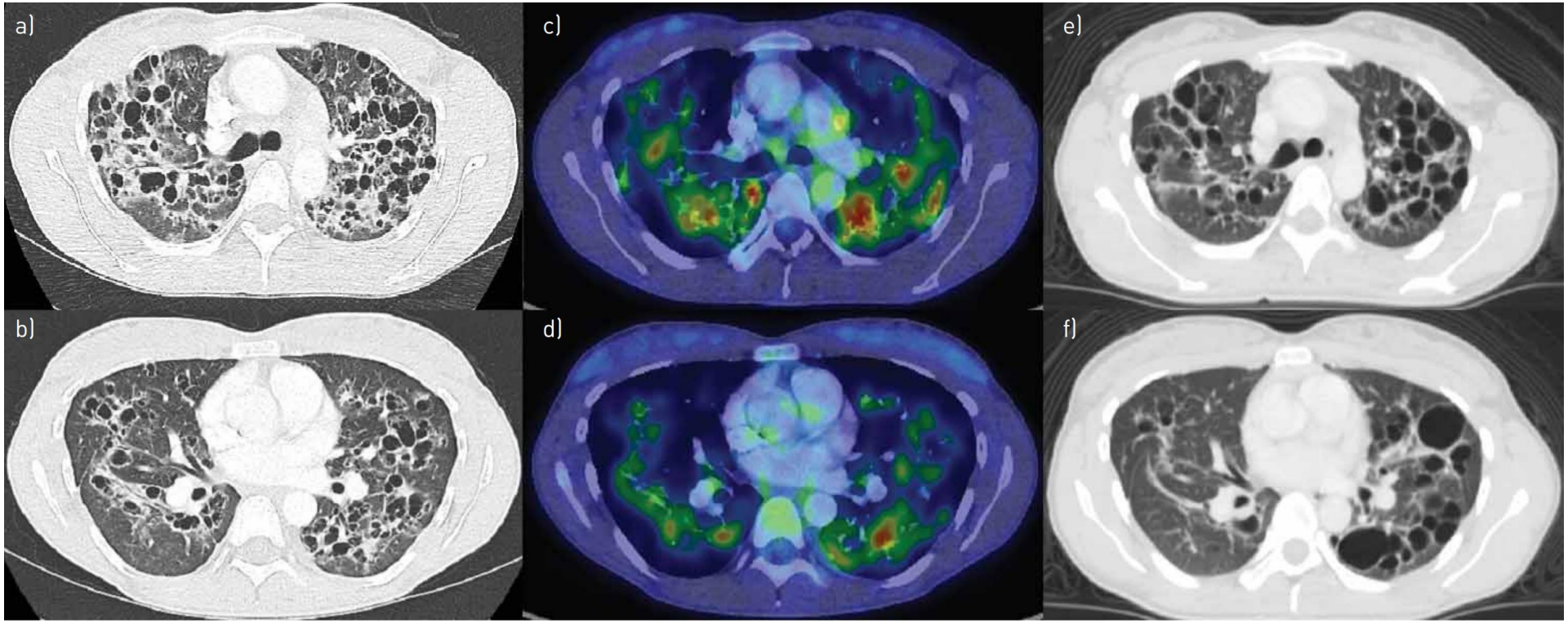
- 40/M, C-smoker
- **Chest CT:** pneumothorax, nodulo-cystic lesion
- **TBLB:** S-100+, CD1a+, Langerin+
- No evidence of systemic disease
- BRAF test (none)
- Smoking cessation
- Steroid therapy (tapering → low dose ≥ 6 months)

N Engl J Med . 2022 Dec 29;387(26):2449.

Chemotherapy

- **Cladribine** (2-chlorodeoxyadenosine): may induce remission or improvement of PLCH

<34/F, multi-system LCH, Cladribine for 5 days/month, Total 4 months treatment >



ERJ Open Res . 2018 Feb 23;4(1):00089-2017.

Cladribine

Evaluation of Efficacy and Tolerance of Cladribine in Symptomatic Pulmonary Langerhans Cell Histiocytosis (ECLA)

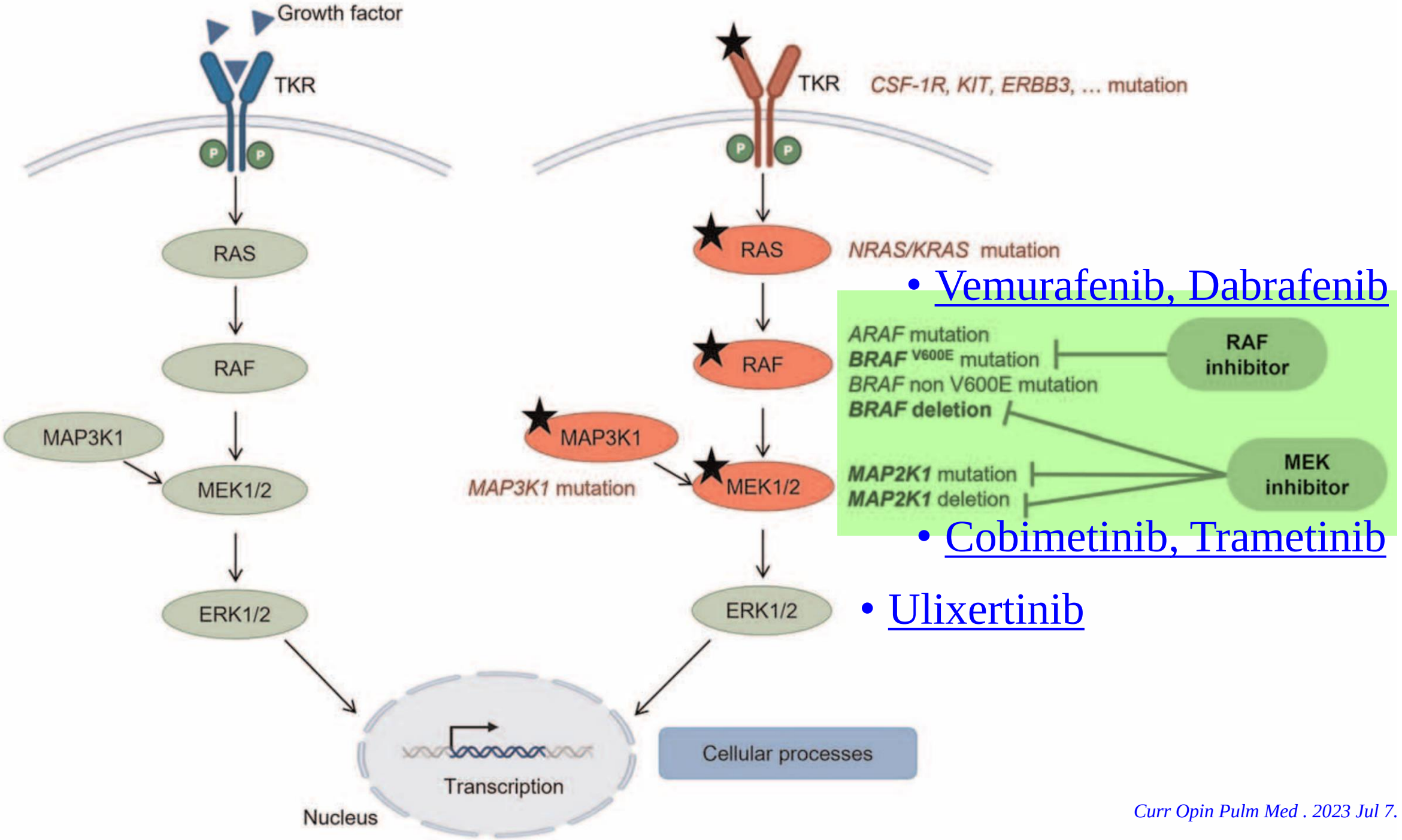
ClinicalTrials.gov ID NCT01473797

Sponsor Assistance Publique - Hôpitaux de Paris

Information provided by Assistance Publique - Hôpitaux de Paris (Responsible Party)

Last Update Posted 2021-02-18

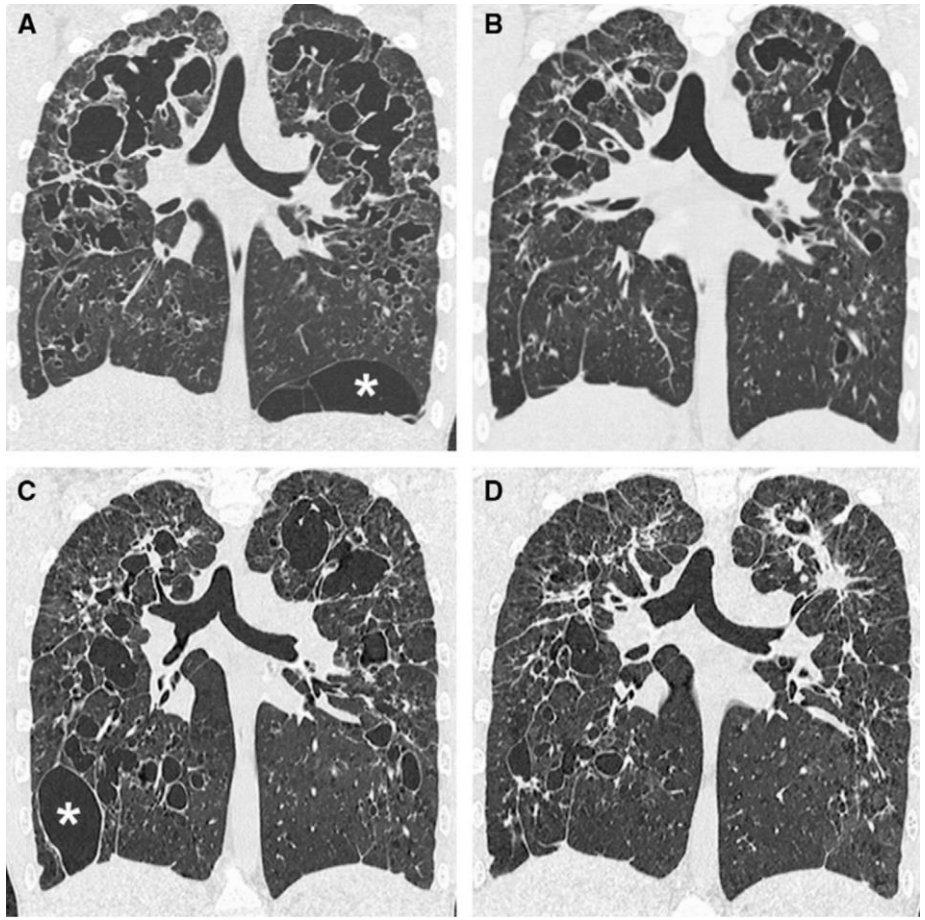
Participant Group/Arm	Intervention/Treatment
Experimental: cladribine	Drug: Cladribine • Subcutaneous injections, 0,1 mg/kg/day for 5 days, one course per month for 4 months



- Vemurafenib, Dabrafenib
- Cobimetinib, Trametinib
- Ulixertinib

Curr Opin Pulm Med . 2023 Jul 7.

Target therapy



- 18 yo/M
- Smoking + Cannabis
- Cladribine administration
- Genotyping (NGS): BRAF, MAP2K1 deletions
- MEKi trametinib for 9 months
- Improving dyspnea, 6MWD, and cystic lesions on HRCT

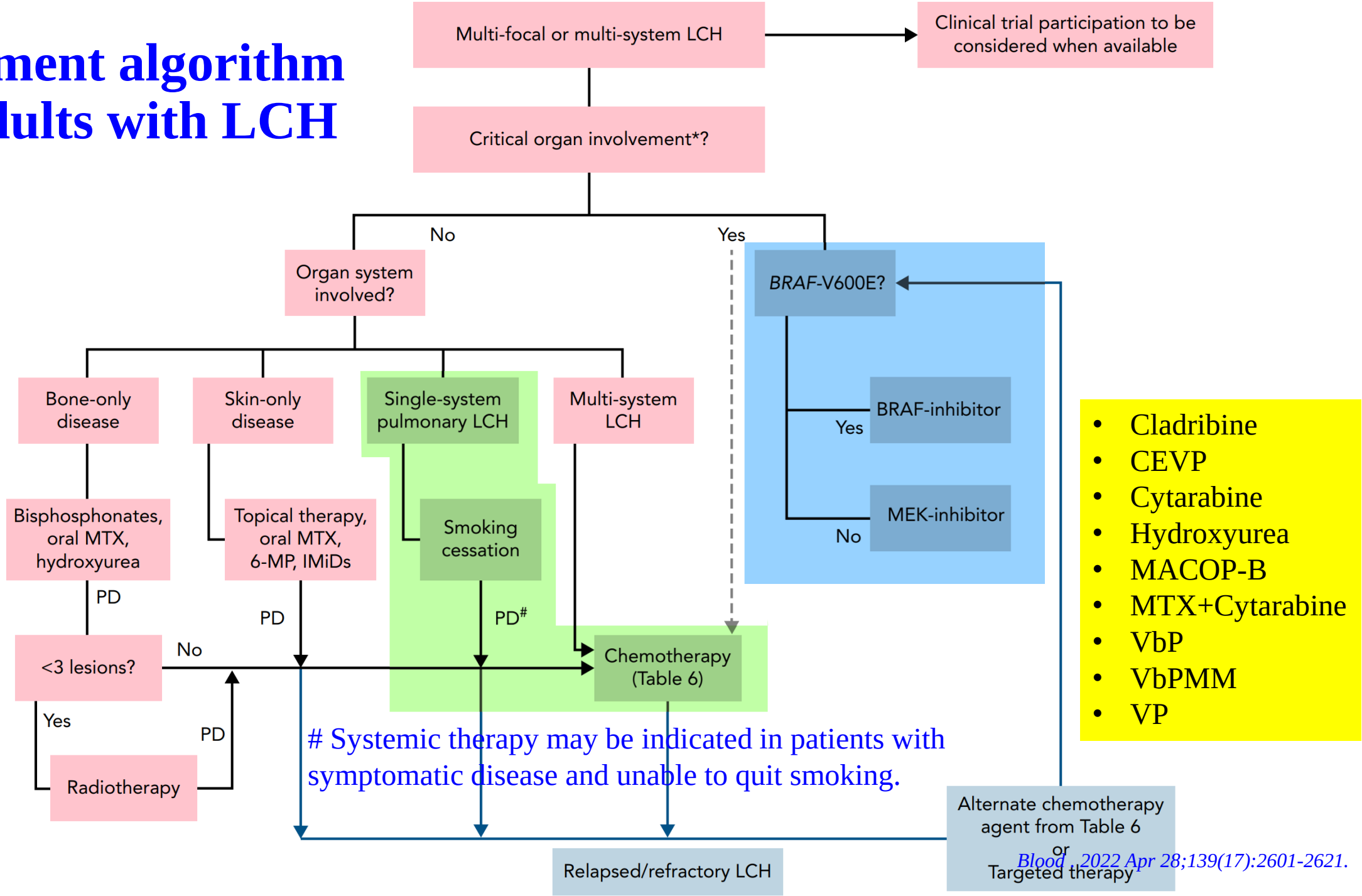
Am J Respir Crit Care Med . 2018 Sep 1;198(5):675-678.

International expert consensus recommendation for the diagnosis and treatment of LCH in adults

Statement number	Consensus statements	Consensus recommendation category
	Single-system pulmonary LCH	
23.	Cessation of smoking, vaping, inhalation of marijuana or other substances is recommended as first-line therapy for single-system PLCH.	A
24.	Systemic therapy is recommended for single-system PLCH in the presence of progressive disease (regardless of smoking status) or for stable disease with clinically significant respiratory symptoms or dysfunction.	A
25.	For patients who develop advanced single-system PLCH refractory to or ineligible for systemic treatments, lung transplantation referral should be undertaken.	A

Blood . 2022 Apr 28;139(17):2601-2621.

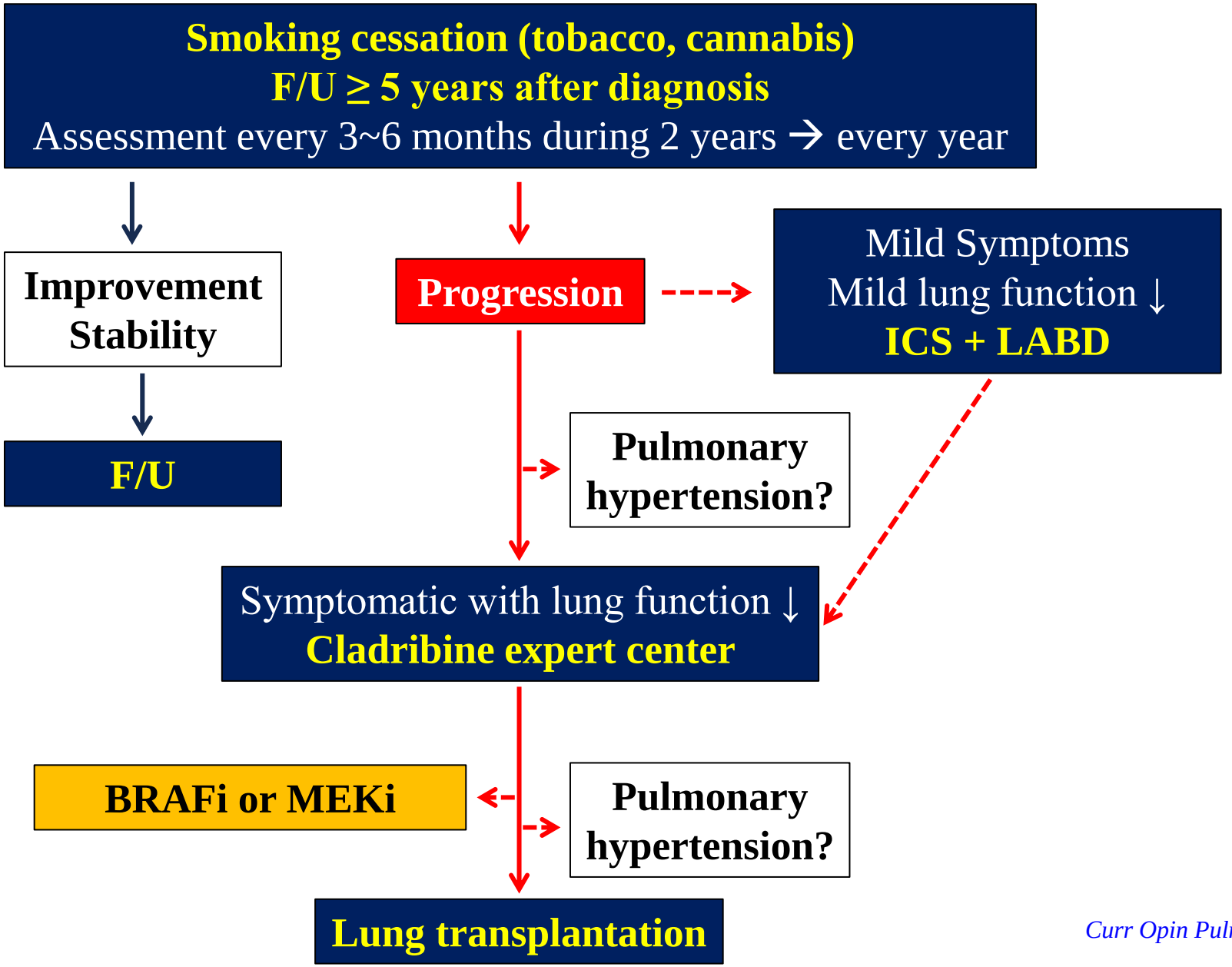
Treatment algorithm for adults with LCH



- Cladribine
- CEVP
- Cytarabine
- Hydroxyurea
- MACOP-B
- MTX+Cytarabine
- VbP
- VbPMM
- VP

Blood . 2022 Apr 28;139(17):2601-2621.

Management of adult PLCH in clinical practice



Curr Opin Pulm Med . 2023 Jul 7.

Summary

① Smoking is associated with several forms of ILD – PLCH, RB-ILD, DIP, AEP and CPFE.

② Tissue biopsy is required for the diagnosis of PLCH - TBLB, TBLC, VATS

③ Smoking cessation is a major component of smoking-related ILD management.

④ It is controversial to use corticosteroids in patients with progressive PLCH.

⑤ Target therapy and cladribine are promising treatments for PLCH.