

제 232회 대한결핵 및 호흡기학회 심포지엄 증례보고

Cho Eun Na

Division of Pulmonology

Department of Internal Medicine

Yonsei University College of Medicine

1885 제중원 창립

1904 세브란스병원

1913 세브란스의학교

1983 강남세브란스병원



1885 제중원 창립

한 O 택 M/45 (6588811)

- C.C : 우연히 발견된 이상엽의 젓빛 유리음영
- P.I : 45세 남환은 2013년 6월 건강검진 목적으로 외부병원에서 시행한 흉부전산화 단층촬영 상 관찰되는 다발성 흉막하 망상음영 및 간유리 음영의 정밀검진을 위해 본원 호흡기내과 내원함.

Past history

- Medical history

- HTN/DM (-/-), Old pul Tbc (-)

- 2012.12.14 s/p total thyroidectomy d/t PTC
- 2013.04 s/p I-131 RAIT

- No history of recent travel

- Medication : Levothyroxine 0.1mg qd, aspirin 100mg qd

- Social history

- Occupation : Police Officer

- Smoking : Never smoker

- Family history - none

Review of systems

- Cough / sputum / rhinorrhea / hemoptysis (-/-/-/-)
- Dyspnea / DOE (- / -)
- Fever / Chill (- / -)
- General weakness / Easy fatigue (- / -)
- Poor oral intake / Wt loss (- / -)
- Arthritis /Skin rashes (-/-) Lymphadenopathy (-)
- Abdomen pain/ Nausea/ Vomitting/ Diarrhea (-/-/-/-)
- Dysuria/ Urgency (-/-)

Physical examination

- Vital sign > BP 110/70mmHg PR 72/min
BT 36.0' RR 18/min
- G/A> Not so ill-looking, alert, oriented
- HEENT> not anemic, anicteric, neck op scar
PI(-) PTH(-/-)
LNE(-/-) V/E(-/-) carotid bruit(-/-)
- Chest> symmetric expansion without retraction
RHB without murmur
- Abdomen> Soft abdomen/ No tenderness

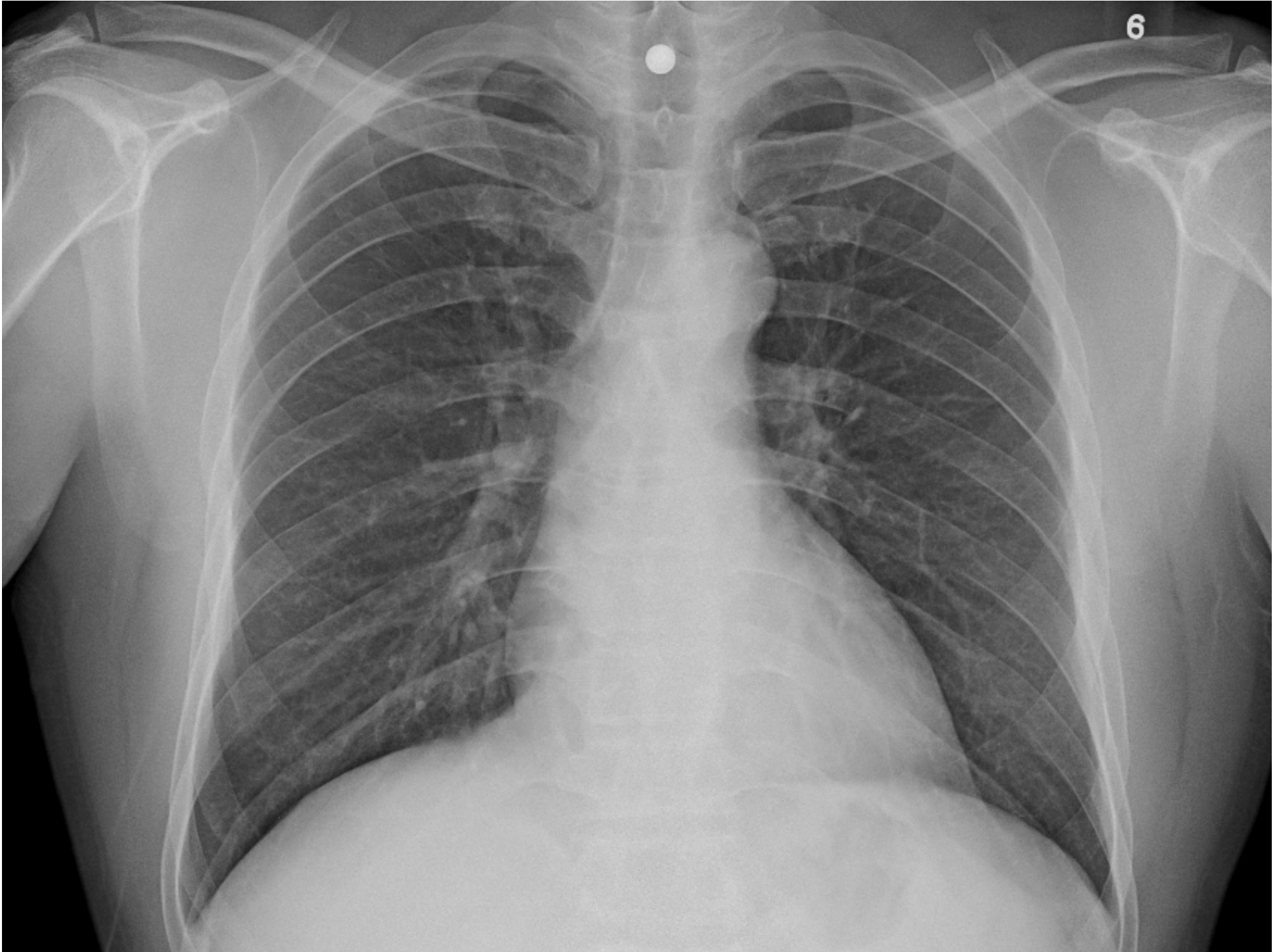
Laboratory findings

- CBC : 7460 (55.7%) / 16.9 / 230K
- BUN / Cr : 11.6 / 0.78 mg/dL
- Total protein / Albumin : 6.8 / 4.7 g/dL
- AST / ALT : 25 / 46 IU/L
- PT(INR) / aPTT : 0.91 / 28.0
- fT4 / TSH 2.1 / <0.01

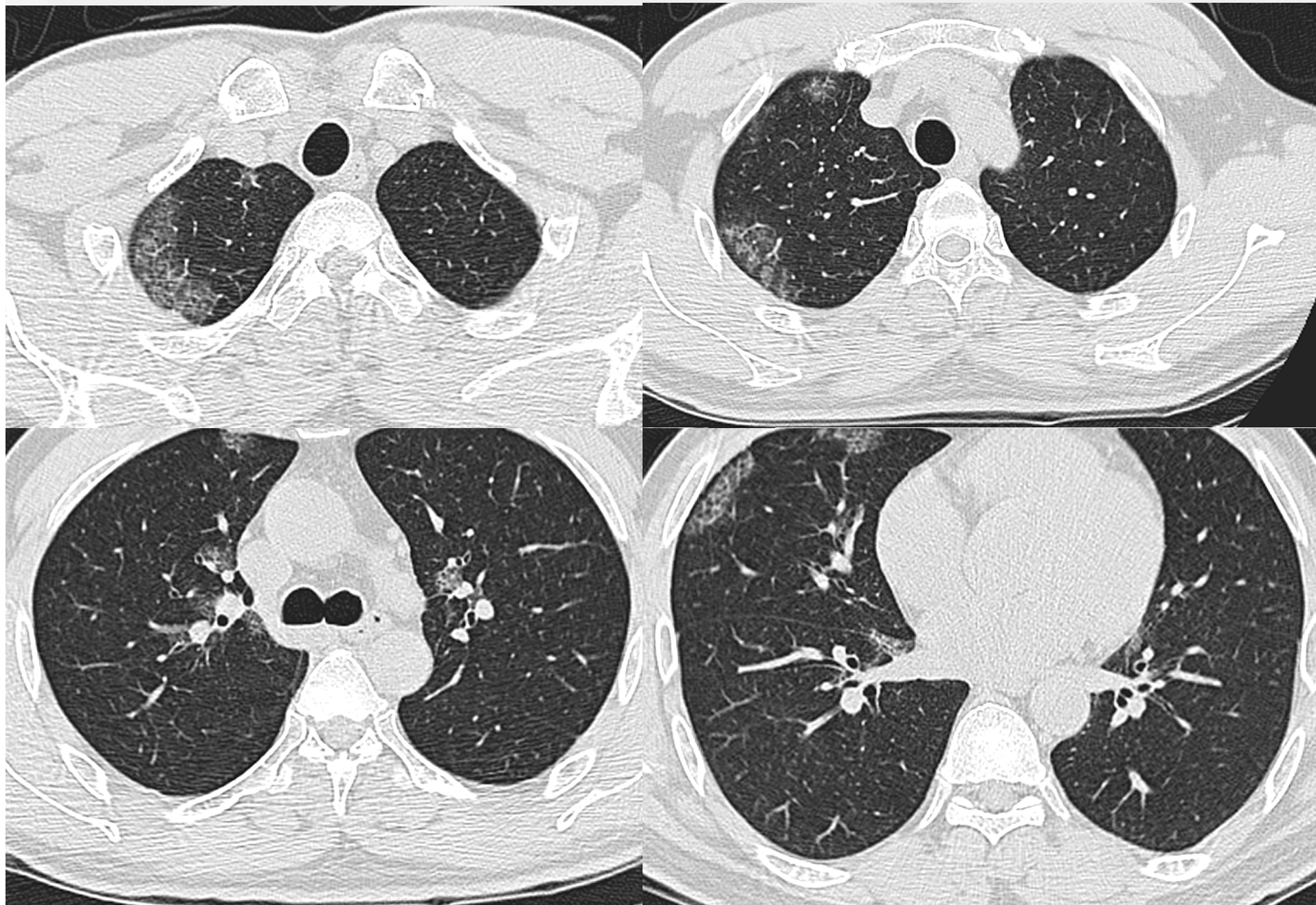
Image findings

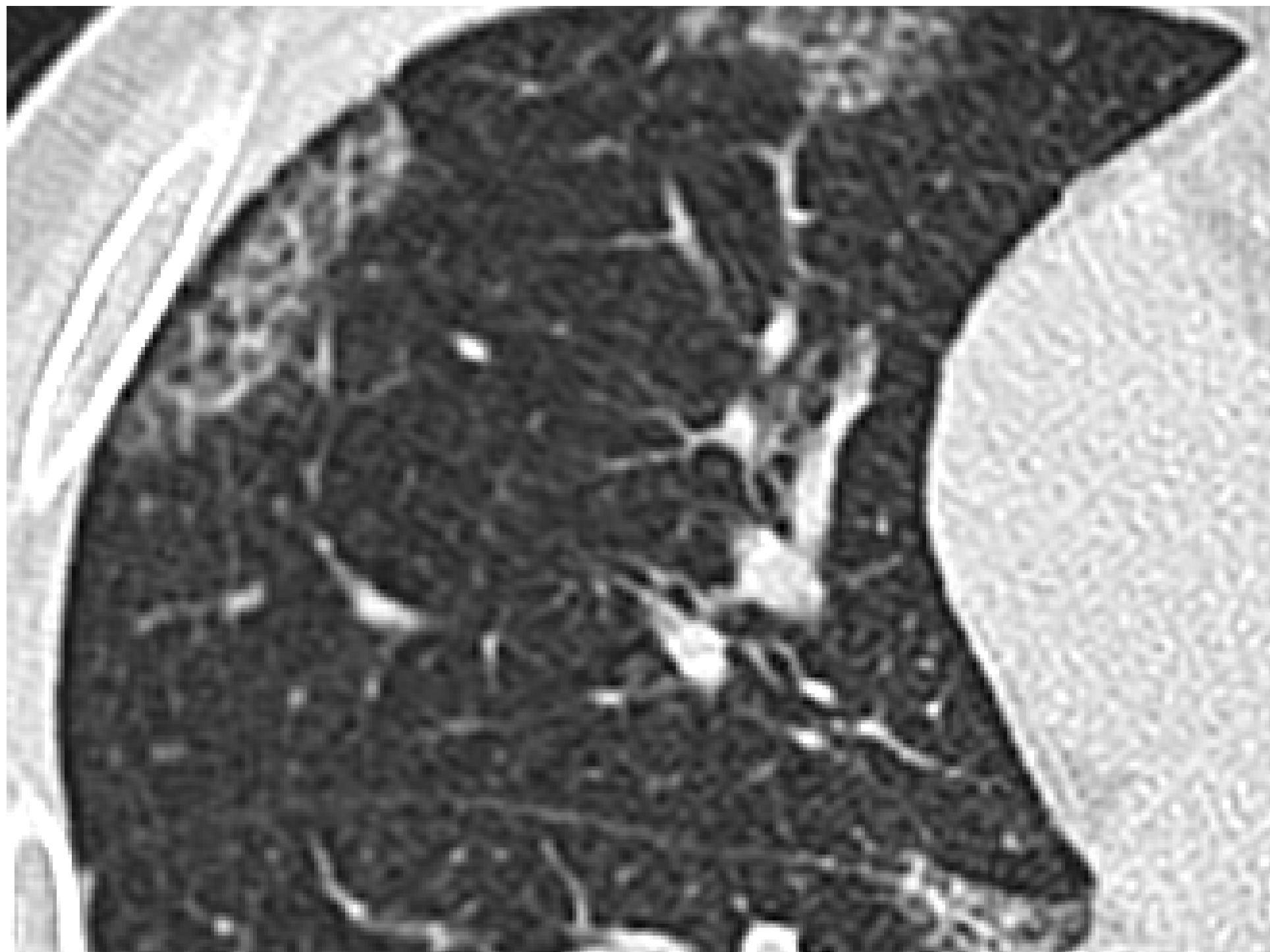
- Initial CT chest
non specific findings
→ 1 month CT chest f/u
- Persistent, multiple GGO in RUL

6



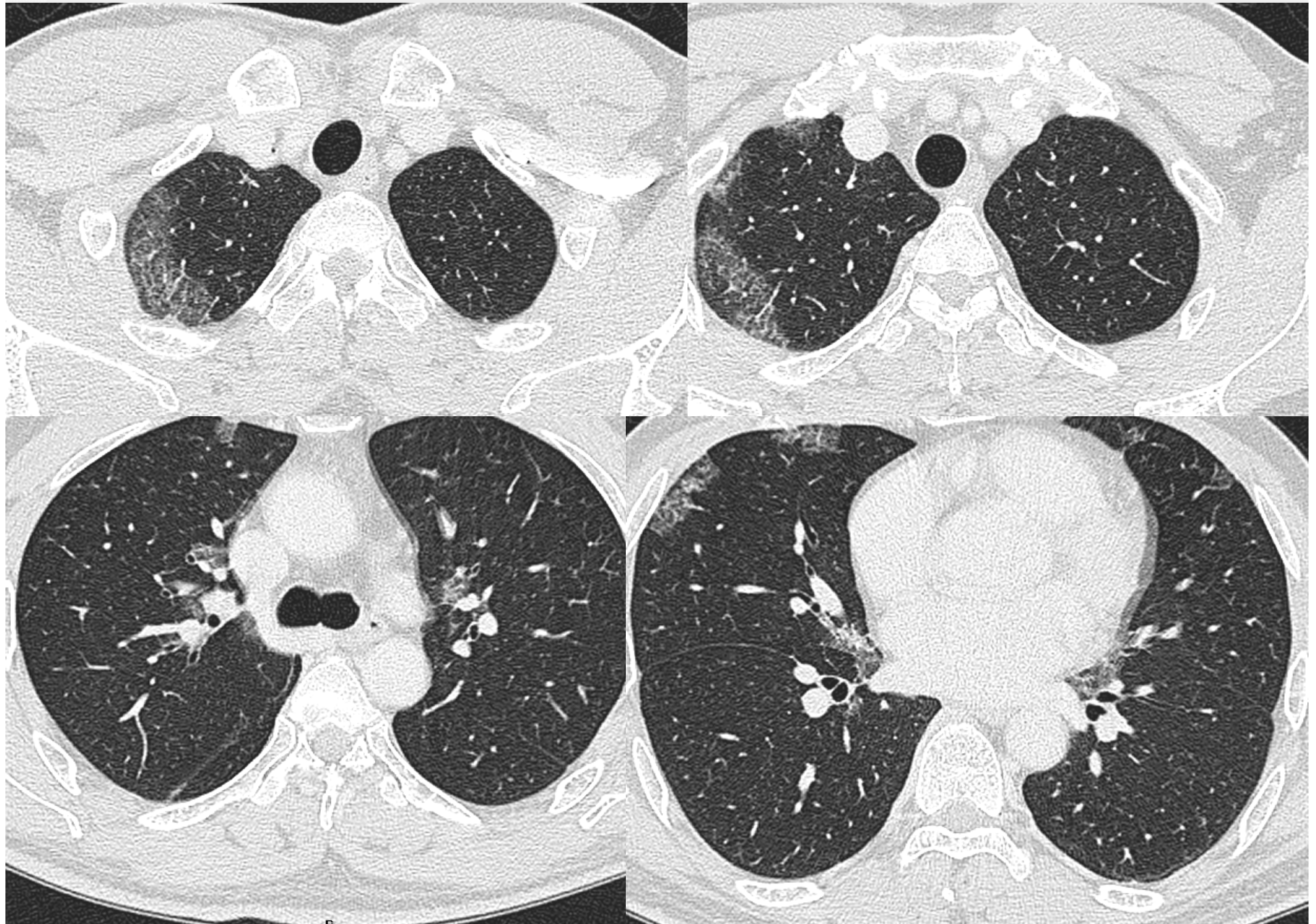
2013.06.19







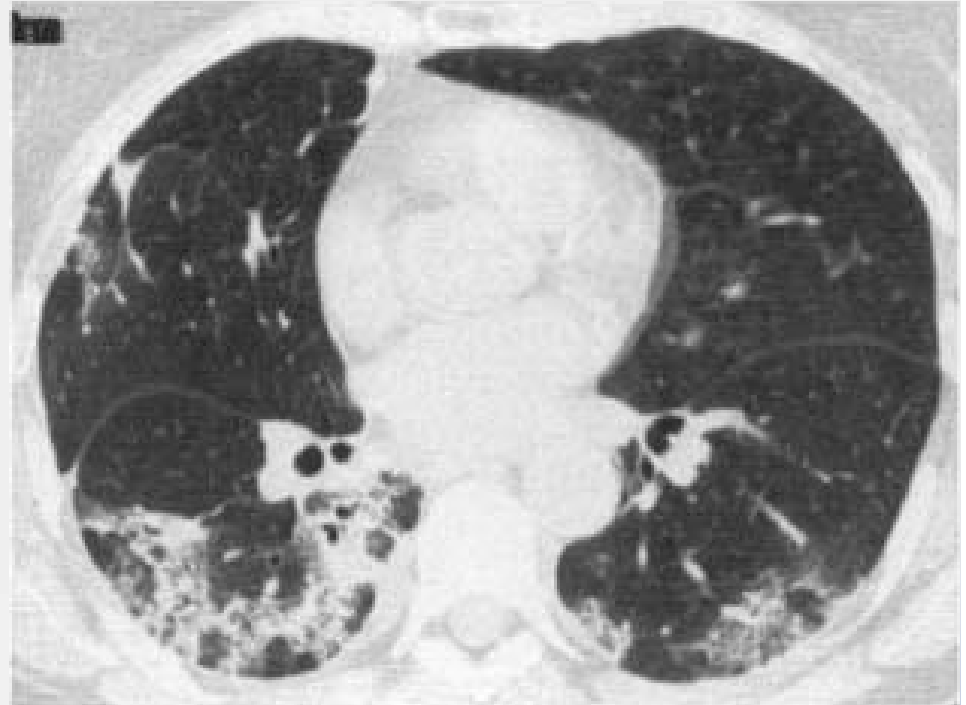
2013.07.24



Differential diagnosis (1)

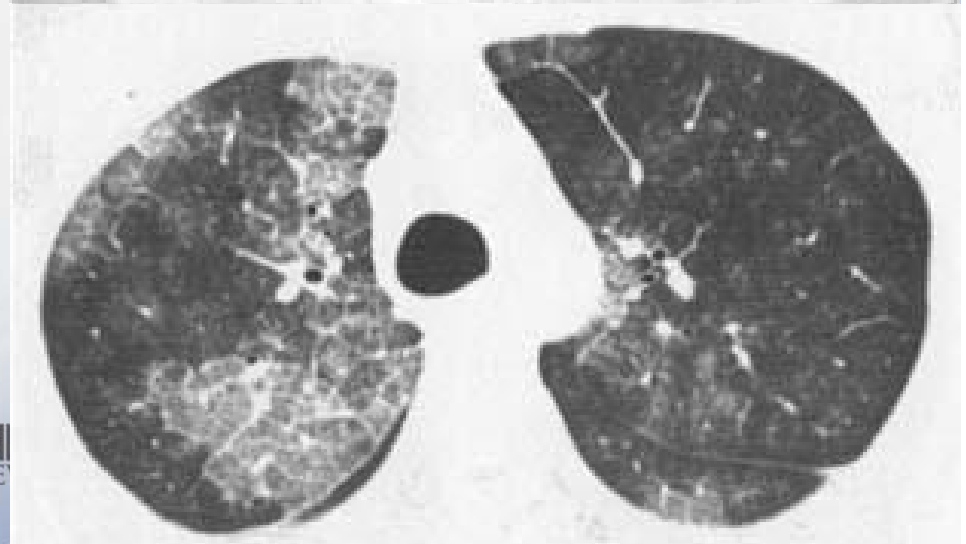
○ Chronic eosinophilic pneumonia

- Consolidation > GGO
- Peripheral, middle and upper-lung predominance
- Nonsegmental distribution.
- Alveolar and / or blood eosinophilia



○ Alveolar proteinosis

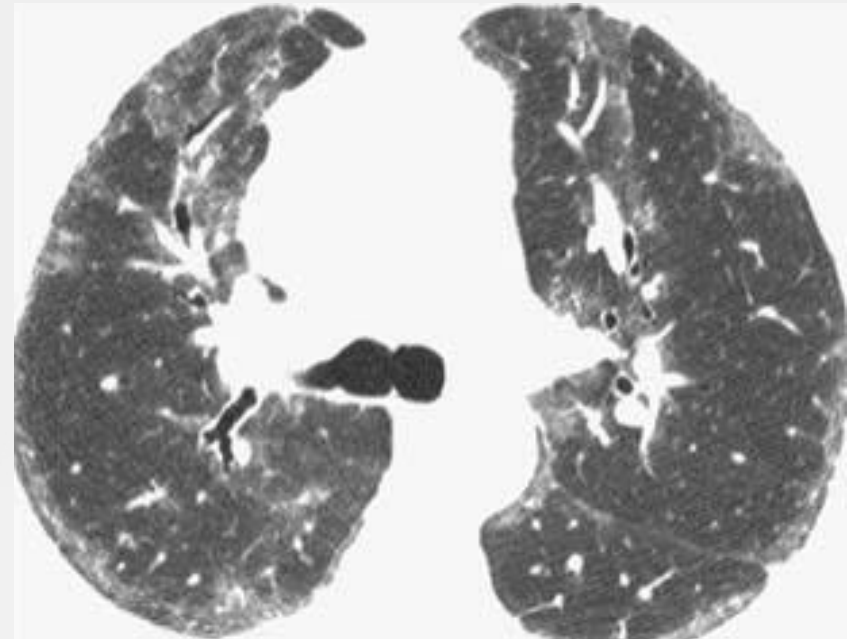
- Crazy-paving (GGO and smooth septal thickening in abnormal areas)
- Patchy or geographic distribution
- Bilateral, central, random



Differential diagnosis (2)

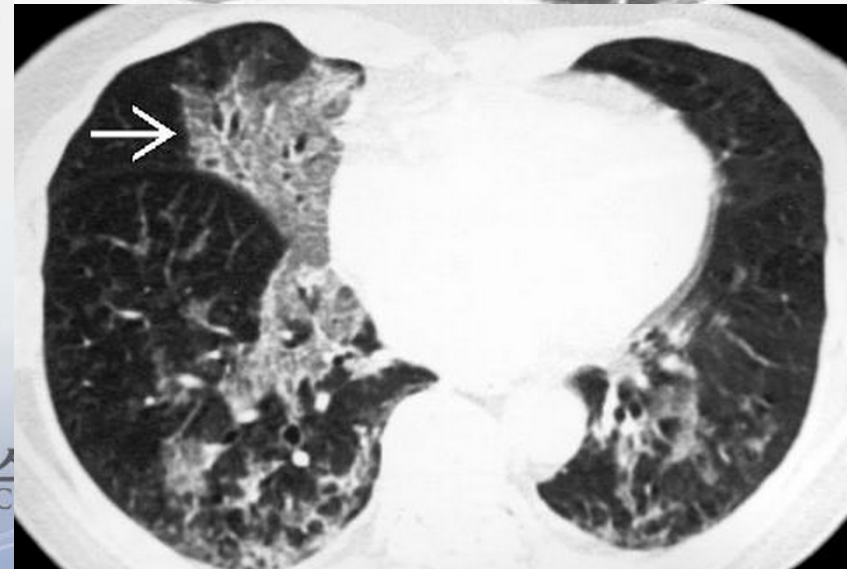
○ NSIP

- GGO, reticular opacities
- Traction bronchiectasis
- Lower lung zone predominance
- Concentric subpleural predominance

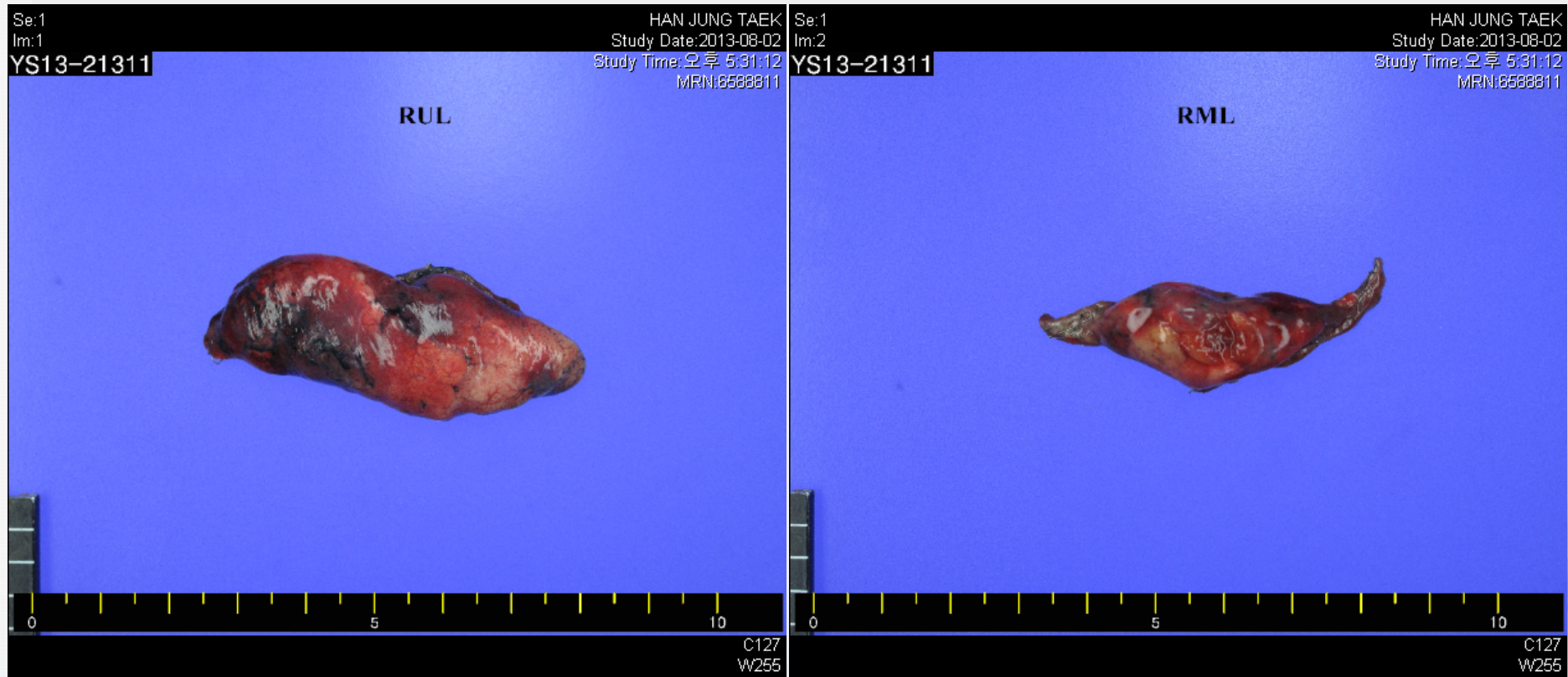


○ Lipoid pneumonia

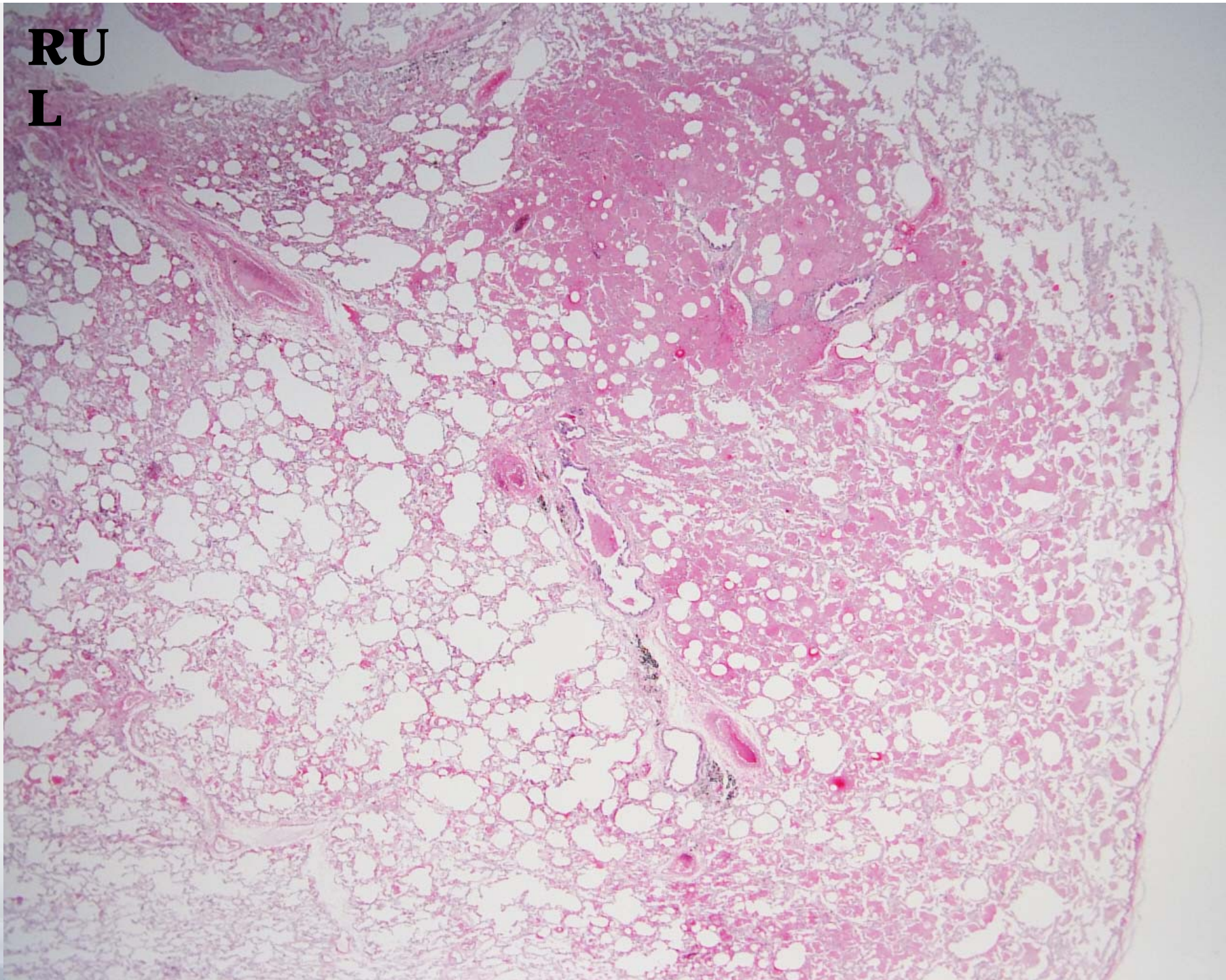
- Crazy-paving
- low density (fat) lesions



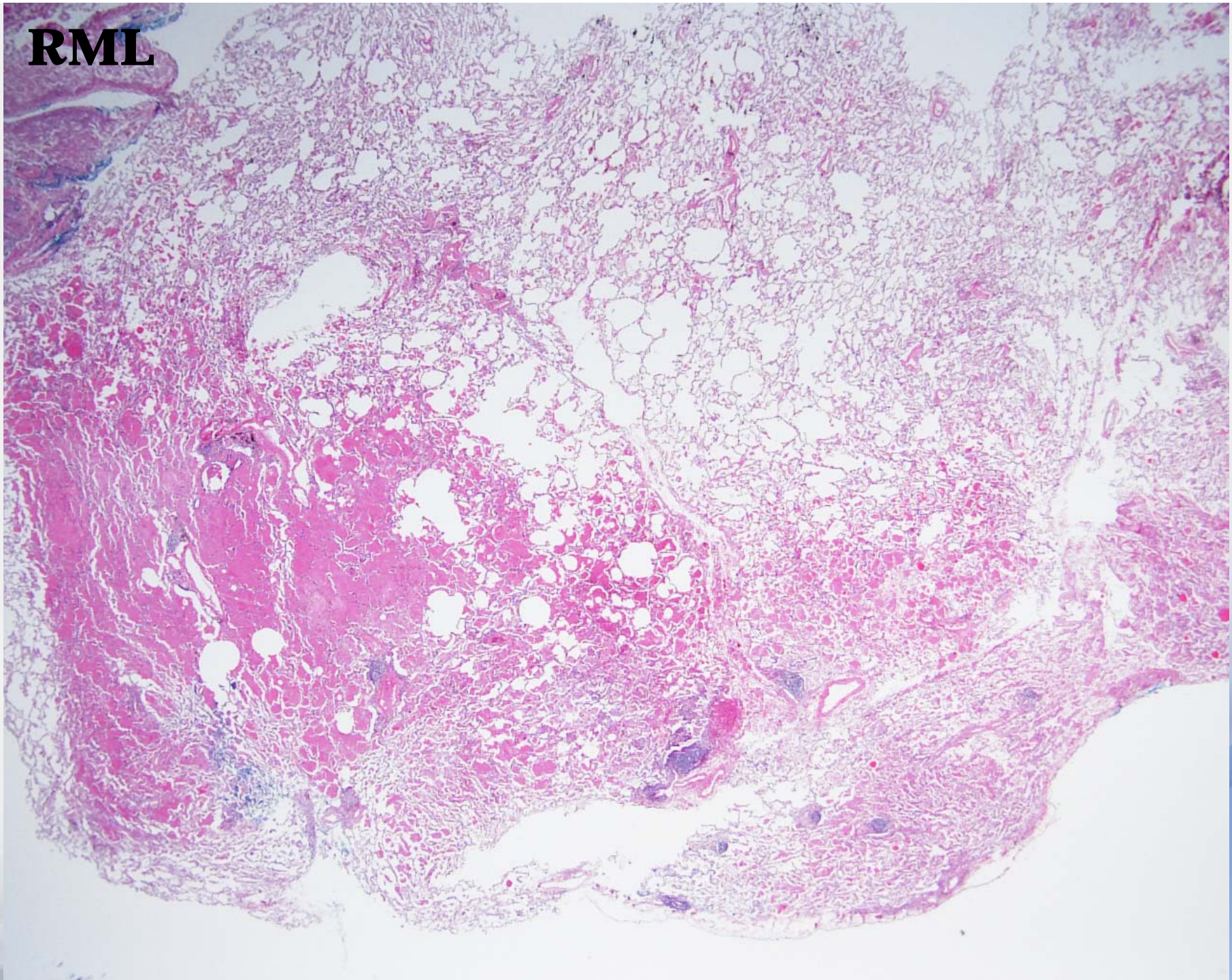
Wedge biopsy (2013-08-02)

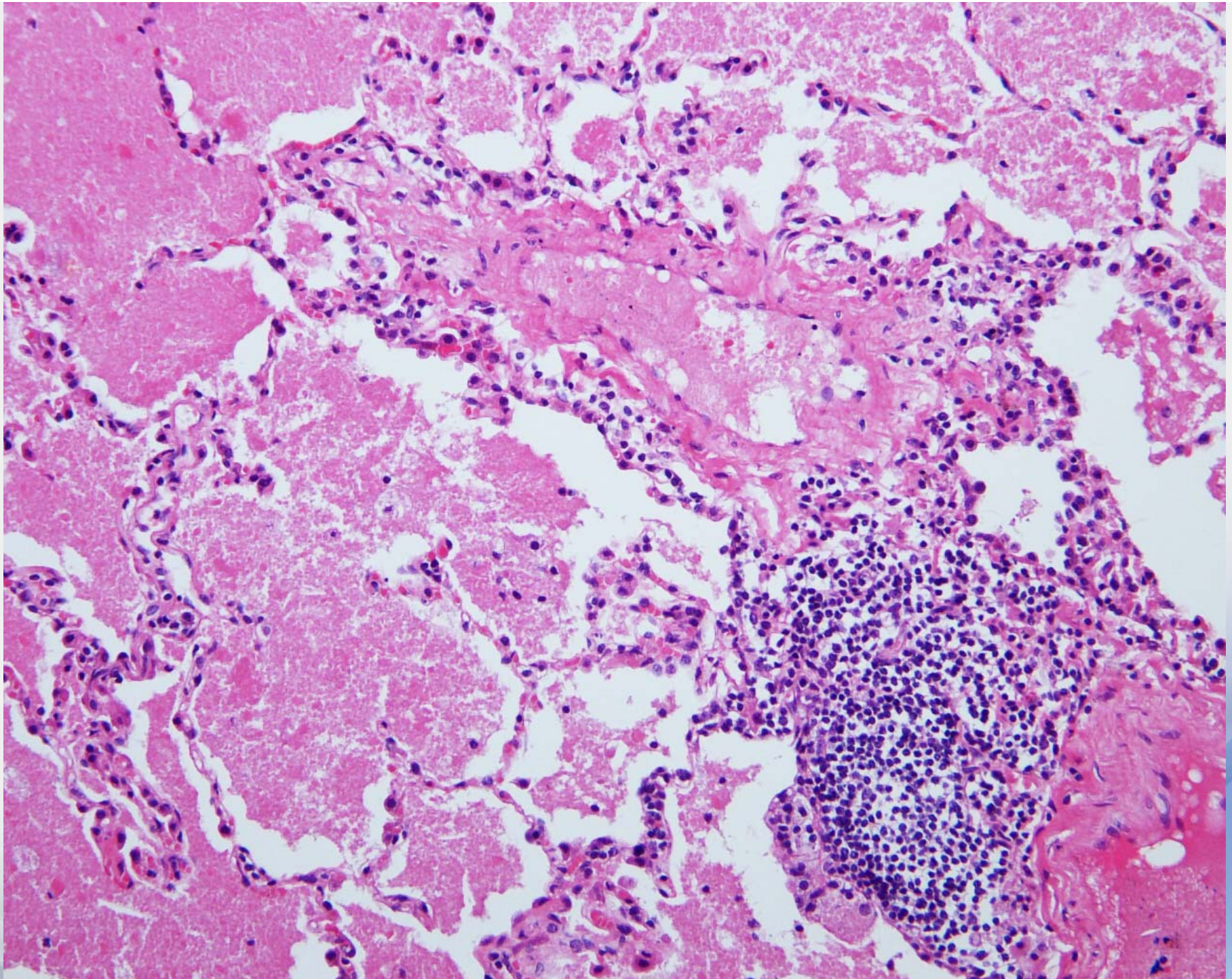


RU
L

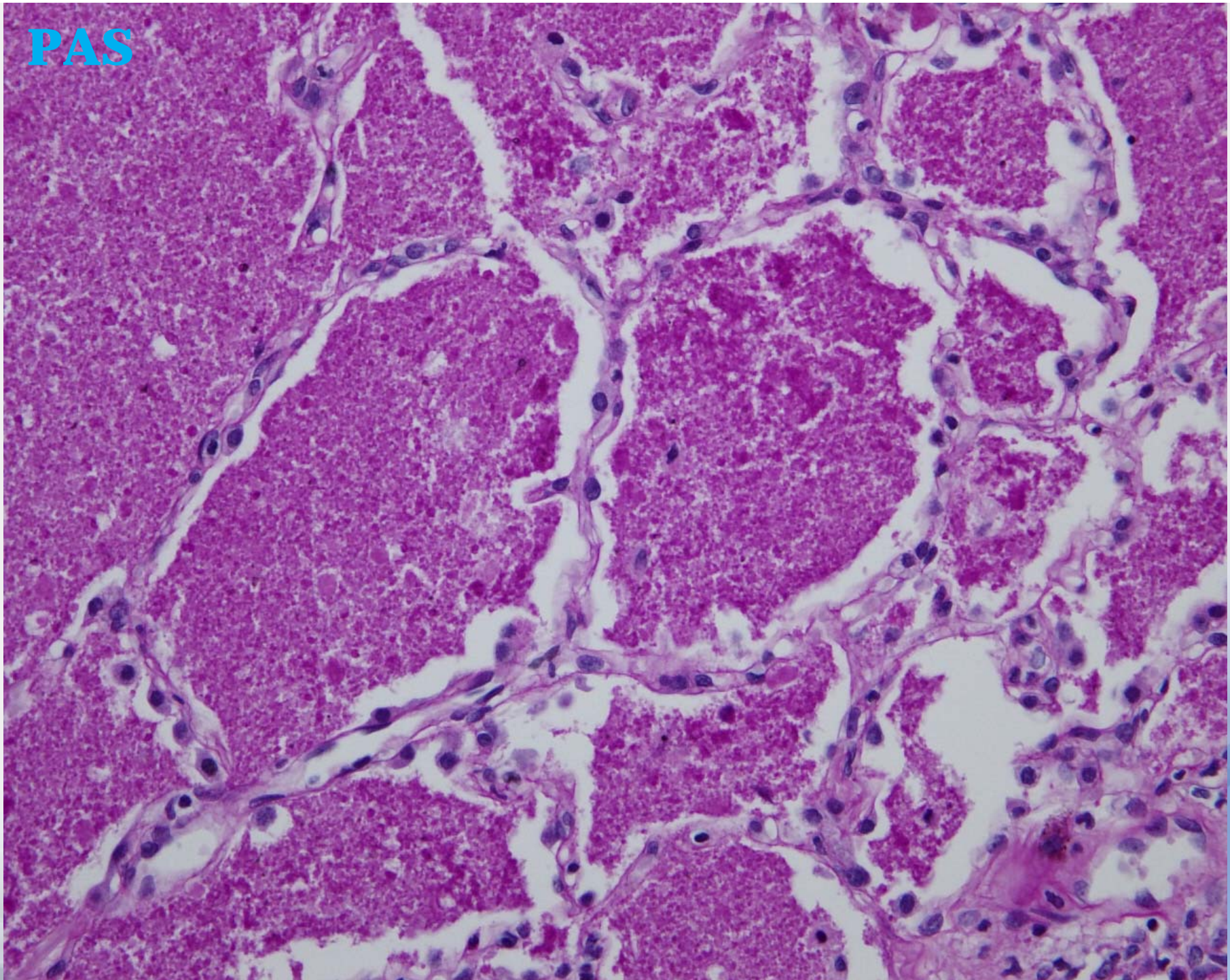


RML





PAS



YS13-21311

Lung, RUL & RML, wedge resection:

Intraalveolar collection of eosinophilic material with minimal lymphocytic infiltration

; consistent with pulmonary alveolar proteinosis, see note.

Note) The special stain results:

GMS and PAS: Negative for microorganism

REVIEWS

Pulmonary alveolar proteinosis

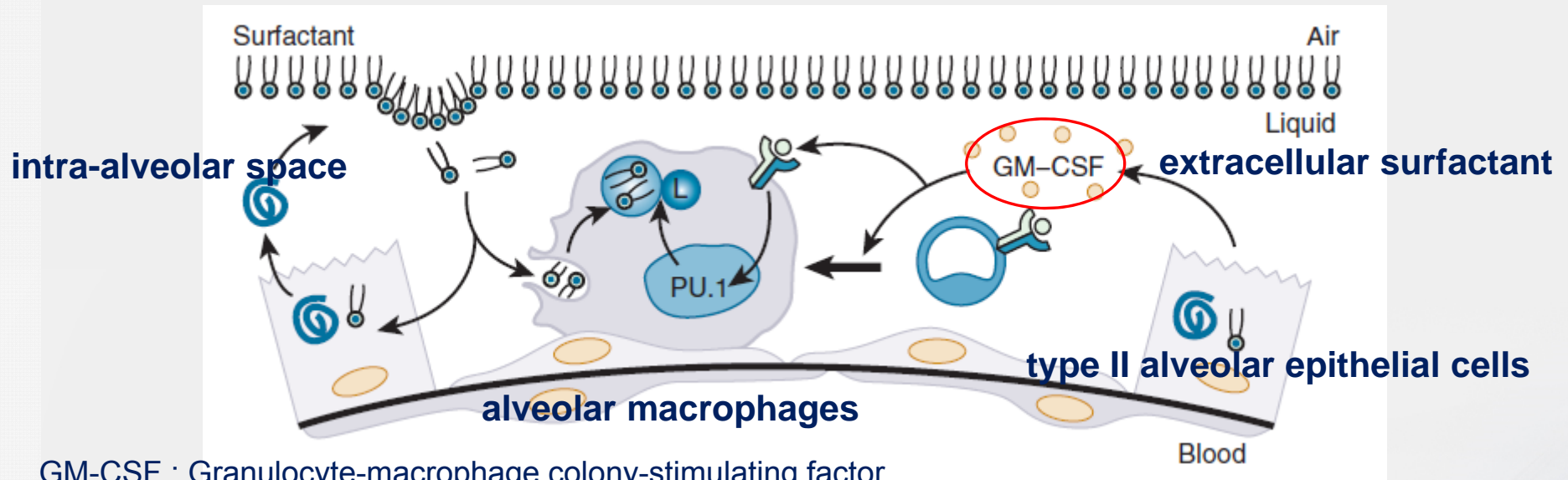
- **Pulmonary alveolar proteinosis (PAP)**

→ rare disorder characterized by **progressive accumulation of surfactant** within **pulmonary alveoli** resulting in **respiratory insufficiency** and, in severe cases, respiratory failure

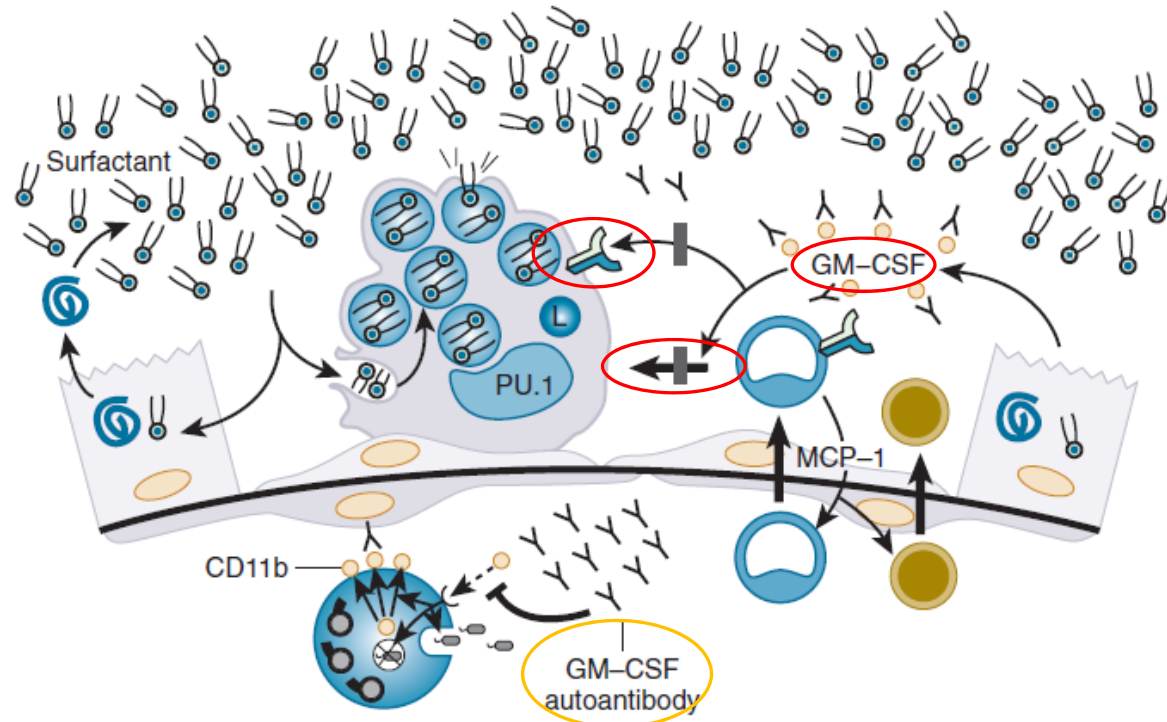
Disorders of Surfactant homeostasis

; production / **clearance** → 1', 2' (underlying disease)

Surfactant → 90% phospholipids
→ 10 %surfactant proteins



GM-CSF : Granulocyte-macrophage colony-stimulating factor



Classification

TABLE 63-3. Classification of Diseases Associated with Disruption of Surfactant Homeostasis

CLINICAL CATEGORY/DISEASE

Primary PAP

GM-CSF autoimmunity
CSF2RA dysfunction
CSF2RB dysfunction
GM-CSF mutations (mice)

Secondary PAP

Hematologic disease
Nonhematologic malignancy
Immune deficiency syndromes
Chronic inflammatory syndromes
Chronic infections

Pulmonary Surfactant Metabolic Dysfunction Disorders

SP-B deficiency
SP-C mutations
ABCA3 mutations

Secondary PAP

TABLE 63-1. Underlying Systemic Disorders Reported in Association with PAP Syndrome

Disease Category/Underlying Disease

HEMATOLOGIC DISORDERS

Acute lymphocytic leukemia
 Acute myeloid leukemia
 Aplastic anemia
 Chronic lymphocytic leukemia
 Chronic myeloid leukemia
 Myelodysplastic syndromes
 Multiple myeloma
 Lymphoma
 Waldenstrom's macroglobulinemia

NONHEMATOLOGIC MALIGNANCIES

Adenocarcinoma
 Glioblastoma
 Melanoma

IMMUNE DEFICIENCY AND CHRONIC INFLAMMATORY SYNDROMES

Acquired immunodeficiency syndrome
 Amyloidosis
 Fanconi's syndrome
 Agammaglobulinemia
 Juvenile dermatomyositis
 Renal tubular acidosis
 Severe combined immunodeficiency disease

CHRONIC INFECTIONS

Cytomegalovirus
Mycobacterium tuberculosis
Nocardia
Pneumocystis jirovecii (formerly *carinii*)

TABLE 63-2. Pulmonary Exposures Reported to Be Associated with PAP Syndrome

Exposure Category/Agent

DUSTS (INORGANIC)

Aluminum
 Cement
 Silica
 Titanium

알루미늄 분진, 티타늄, 석면, 시멘트, 유리섬유, 이산화규소, 절연체

ORGANIC DUSTS

Agricultural
 Bakery flower
 Fertilizer
 Sawdust

FUMES

Chlorine
 Cleaning products
 Gasoline/petroleum

Nitrogen dioxide

Paint
 Synthetic plastic fumes
 Varnish

Epidemiology

희귀난치성질환자 산정특례 대상 : J84.0 / 폐포단백질증(Alveolar proteinosis)

- 유병률 : 100만명당 3.7명
- 국내에서는 1986년 이후 증례 보고가 있고 2008년 전국실태조사를 통해 수 십명의 증례가 수집 보고됨
- 환자의 72%에서 흡연력이 있음
- 비흡연자에서는 남녀비가 유사
- 여성의 경우 35세 이상에서 발병한 경우 흡연자의 비율이 더 높음 (56% vs 21%)
- 환자의 1.7%에서 자가 면역성 질환과 동반 또는 혈청 검사상 자가 면역 항체를 보유 (합병된 자가 면역성 질환- 류마티스성 관절염, 면역글로불린 A 결핍증, 다발성 경화증 포함)

Clinical Presentation

주요증상

- 1) 점진적으로 진행되는 호흡곤란
- 2) 소량의 객담을 동반하기도 하는 기침
- 3) 피곤함

그 외 증상

; 체중감소, 미열
감염이 동반될 경우에는 고열 등의 증상

상당히 진행되기 전까지는
전혀 증상이 없는 경우도 적지 않다

신체검사상으로는 종종 정상

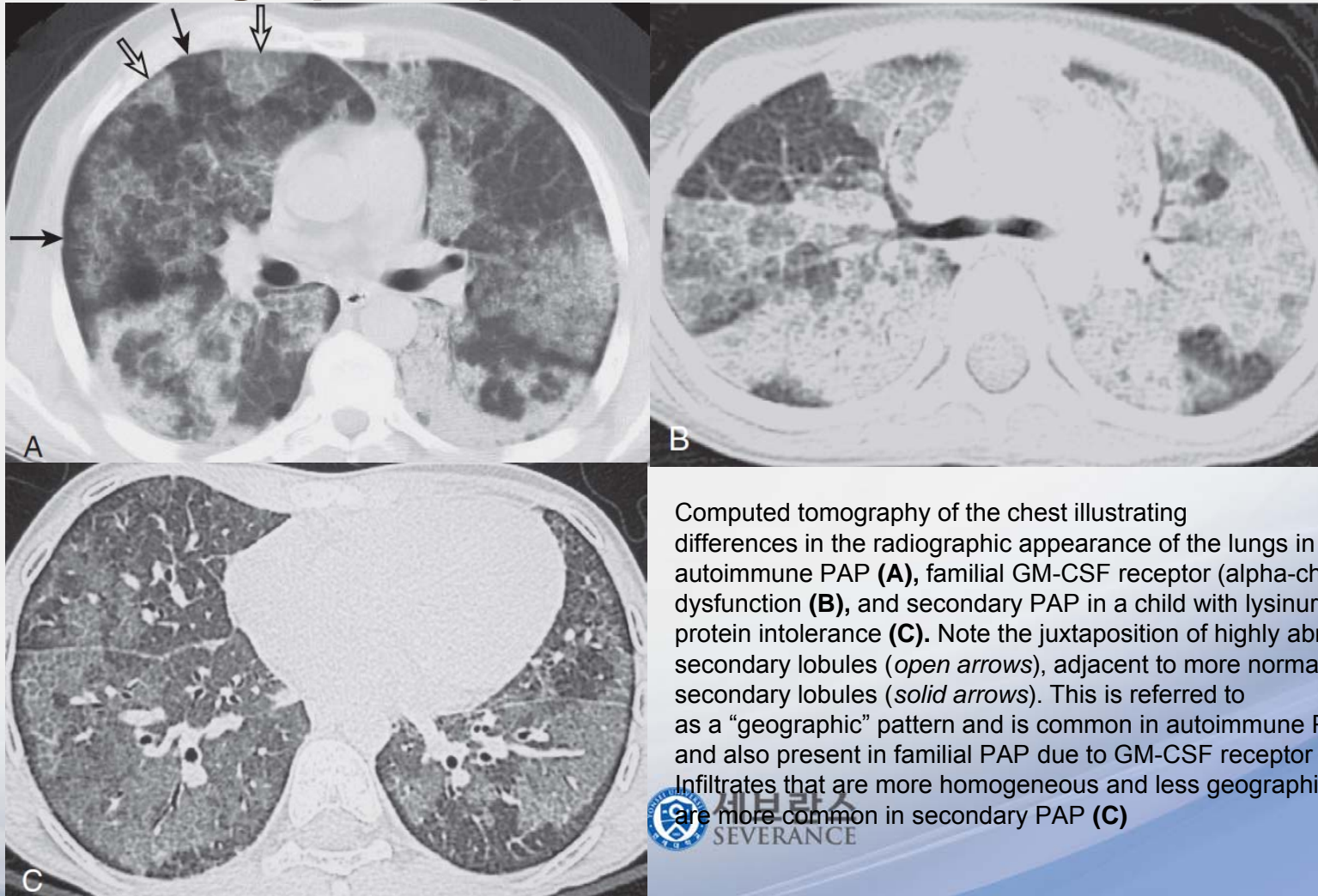
TABLE 63-4. Frequency of Symptoms among Patients with Autoimmune PAP*

Symptom	Frequency (%)
Dyspnea	54
Cough	23
Sputum	4
Other	4
None (asymptomatic)	31

*Data for a contemporaneous group composed of 220 patients.
From Inoue Y, Trapnell BC, Tazawa R, et al: Characteristics of a large cohort of autoimmune pulmonary alveolar proteinosis patients in Japan. Am J Respir Crit Care Med 177:752-762, 2008.

Evaluation and Differential Diagnosis

o Radiographic Appearance : HR CT



Radiologic finding

● Plain

- Air-space consolidation, ground-glass opacity
- Bilateral, symmetric, central, diffuse, or perihilar distribution
- More severe than clinical status

● HRCT

- Smooth interlobular septal thickening in GGO lesion (crazy paving)
- A patchy or random geographic distribution
- A sharply margin

Early PAP ?

- A case of pulmonary alveolar proteinosis that showed solitary ground-glass opacity in the subpleural area.
 - Nihon Kokyuki Gakkai Zasshi. 2010 Jul;48(7):516-9. Japanese.
- Pulmonary alveolar proteinosis detected by a nodular lesion on chest computed tomography.
 - Kyobu Geka. 2011 Feb;64(2):139-41.
- A case of pulmonary alveolar proteinosis presenting with peripheral ground-glass opacity.
 - Nihon Kokyuki Gakkai Zasshi. 2009 Jan;47(1):71-5.
- A case of pulmonary alveolar proteinosis presenting with peripheral infiltrates.
 - Nihon Kokyuki Gakkai Zasshi. 1999 Apr;37(4):333-6.

Evaluation and Differential Diagnosis

○ Pulmonary Function Testing

→ can be normal

commonly show a restrictive ventilatory defect

Forced vital capacity & Total Lung Capacity : mild impairment

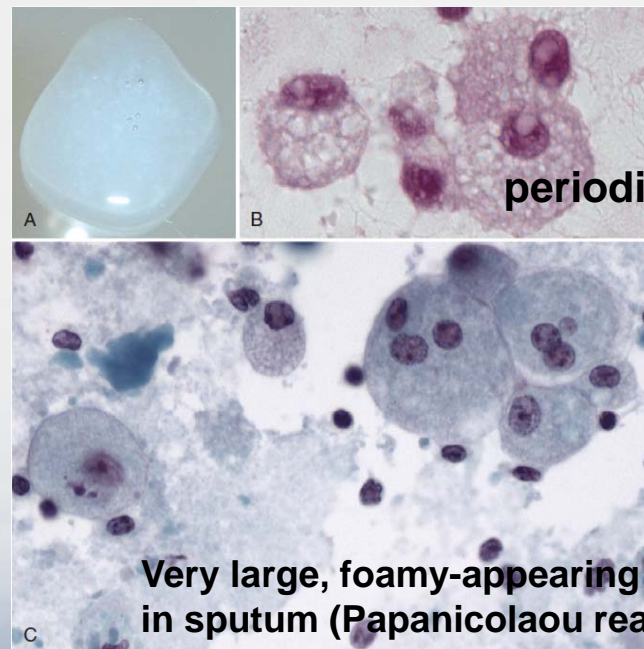
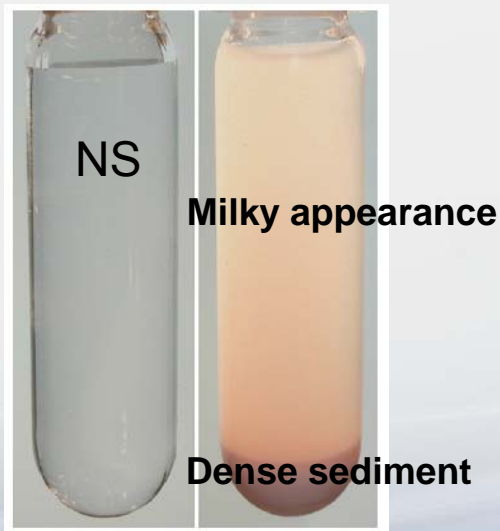
DLCO : disproportionate, severe reduction

Evaluation and Differential Diagnosis

- **Bronchoscopy** : typically unremarkable in PAP
- **Bronchoalveolar Lavage** ;

BAL fluid : “milky” or “waxy” appearance

Papanicolaou-stained specimens : granular, acellular, eosinophilic lipoproteinaceous material



Evaluation and Differential Diagnosis

- Transbronchial Biopsy
- Surgical Lung Biopsy

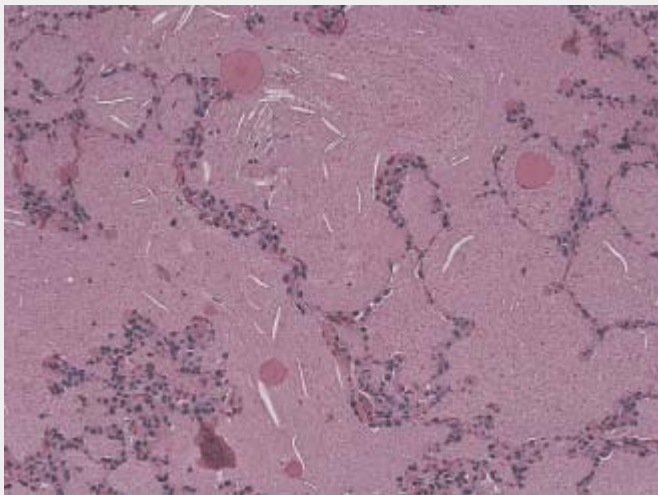
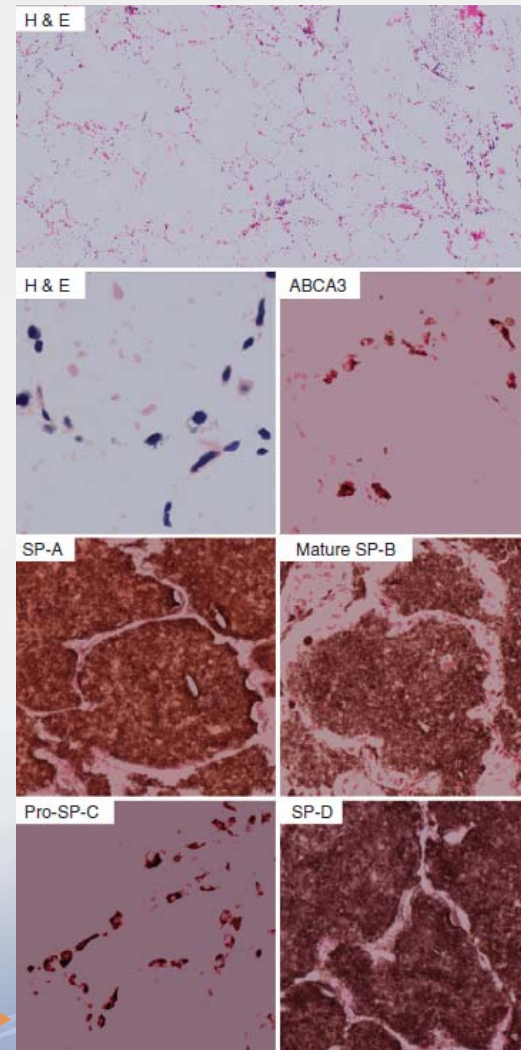


FIGURE 63-8 ■ Histopathologic appearance of the lung in autoimmune PAP. An open-lung biopsy was obtained from a patient with autoimmune PAP. The alveoli are completely filled with amorphous, acellular eosinophilic material contains cholesterol clefts and occasional eosinophilic bodies. The alveolar architecture is well preserved, and the alveolar walls are essentially unremarkable.



Familial PAP caused by function-altering mutations in the *CSF2RA* gene

Evaluation and Differential Diagnosis

○ Laboratory Studies

→ Routine laboratory studies are usually normal in PAP

Serum lactate dehydrogenase : ↑ non specific

Serum levels of

SP-A, SP-B, SP-D, C-reactive protein ↑
Krebs von den Lungen protein-6 (KL-6) ↑
(a mucin-like protein secreted by alveolar epithelium)

→ correlate with lung disease severity, dx 보다 monitoring에 유용

- A high serum level of GM-CSF autoantibodies : helpful for establishing a diagnosis of autoimmune PAP (> 3 µg/mL // 0.5 µg/mL)

Therapeutic Strategies

o Autoimmune PAP

; *Whole-Lung Lavage*

Granulocyte-Macrophage Colony-Stimulating Factor

1) **subcutaneous daily** doses of up to **6 µg/kg/day**

resulted in reduction of the alveolar-arterial oxygen gradient and improved exercise tolerance within 35 days

2) **daily inhaled** doses of GM-CSF ranging from **125 to 500 µg per patient per day**

3) **aerosolized** GM-CSF given as

induction therapy (**250 µg on days 1 to 8 of 14, ×6 cycles**) followed by **maintenance** therapy (**125 µg on days 1 to 4 of 14, ×6 cycles**) (35 Pts)

Other Approaches

plasmapheresis and B-lymphocyte depletion

(reduction in the level of GM-CSF autoantibodies)

Lung transplantation

Therapeutic Strategies

- **Familial PAP** (caused by *CSF2RA* mutations)

- ; *Whole-lung lavage*

- Bone marrow transplantation*

- **Secondary PAP**

- in some cases caused by hematologic disorders, can resolve with resolution of the underlying disorder.

- Nonresolving secondary PAP ; **whole-lung lavage**

Discussion point

- Progression or Flare up ?
- Genetic study ?
- Treatment plan → observation