흔히 경험하는
간질성 폐질환 치료의 실제

가톨릭대학교 의과대학
호흡기 내과 김용현

Introduction

TABLE 1. REVISED AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIAS: MULTIDISCIPLINARY DIAGNOSES

Major idiopathic interstitial pneumonias
Idiopathic pulmonary fibrosis
Idiopathic nonspecific interstitial pneumonia
Respiratory bronchiolitis–interstitial lung disease
Desquamative interstitial pneumonia
Cryptogenic organizing pneumonia
Acute interstitial pneumonia
Rare idiopathic interstitial pneumonias
Idiopathic lymphoid interstitial pneumonia
Idiopathic pleuroparenchymal fibroelastosis
Unclassifiable idiopathic interstitial pneumonias*

Am J Respir Crit Care Med 188;6:733–748, 2013

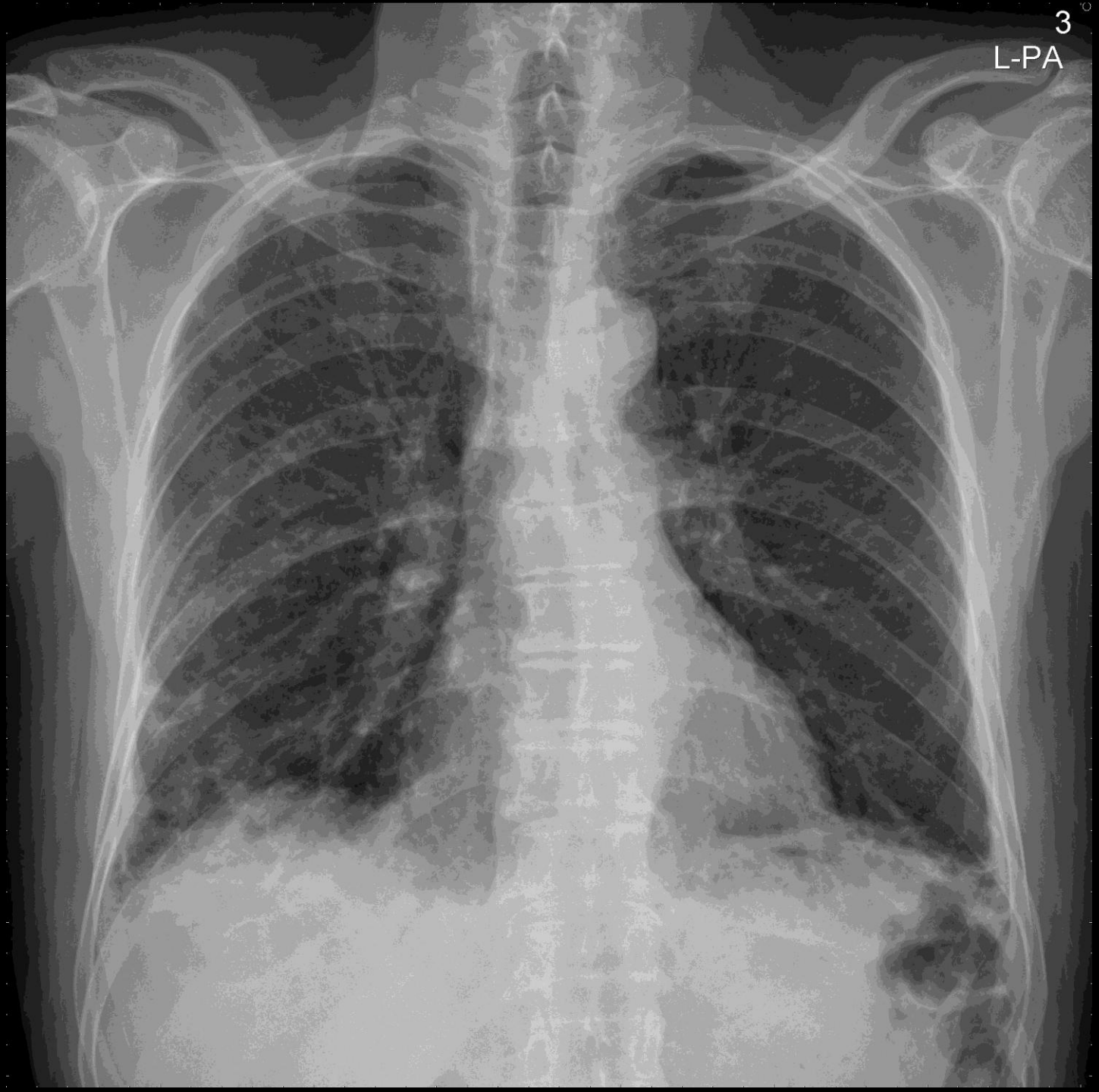
Topics of the presentation

- Which treatment and prognosis ?

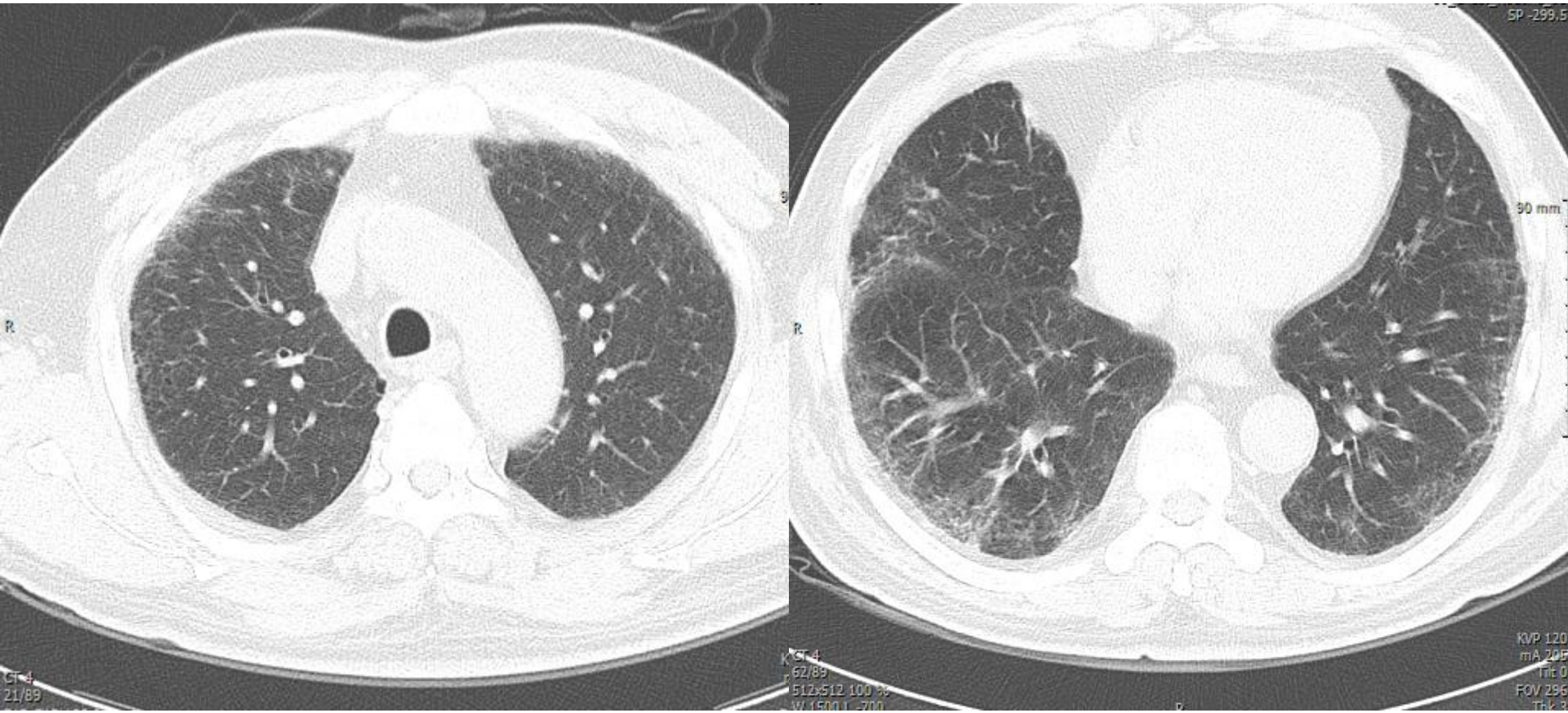
- Diseases of interest
  - Nonspecific interstitial pneumonia (NSIP)
  - Cryptogenic organizing pneumonia (COP)
  - Acute interstitial pneumonia (AIP)
  - Smoking-related interstitial pneumonia

CASE 1

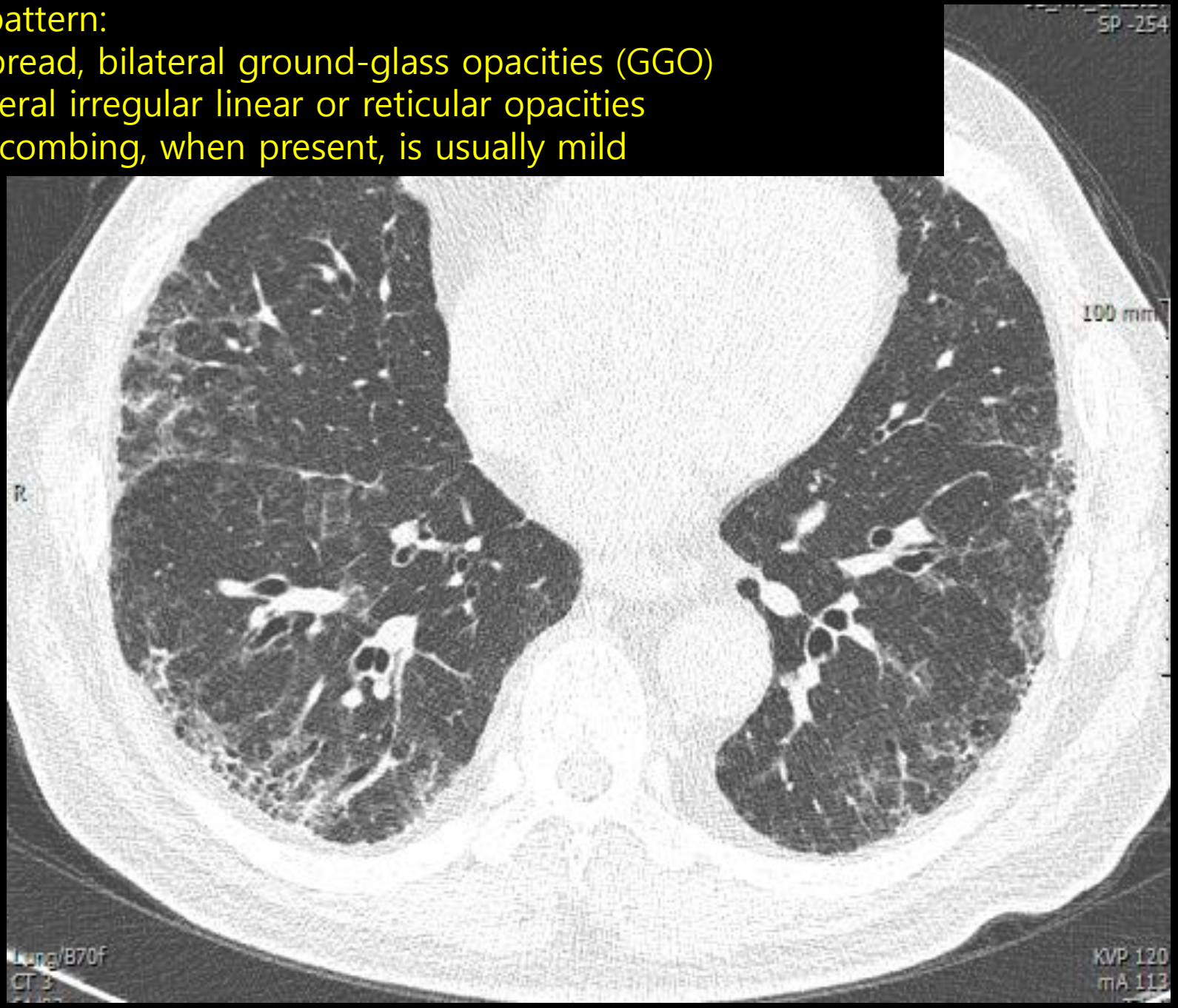
- 68세/남자
- 2-3 개월 전부터 시작된 호흡곤란
- Ex-smoker
- Crackle on both lung bases

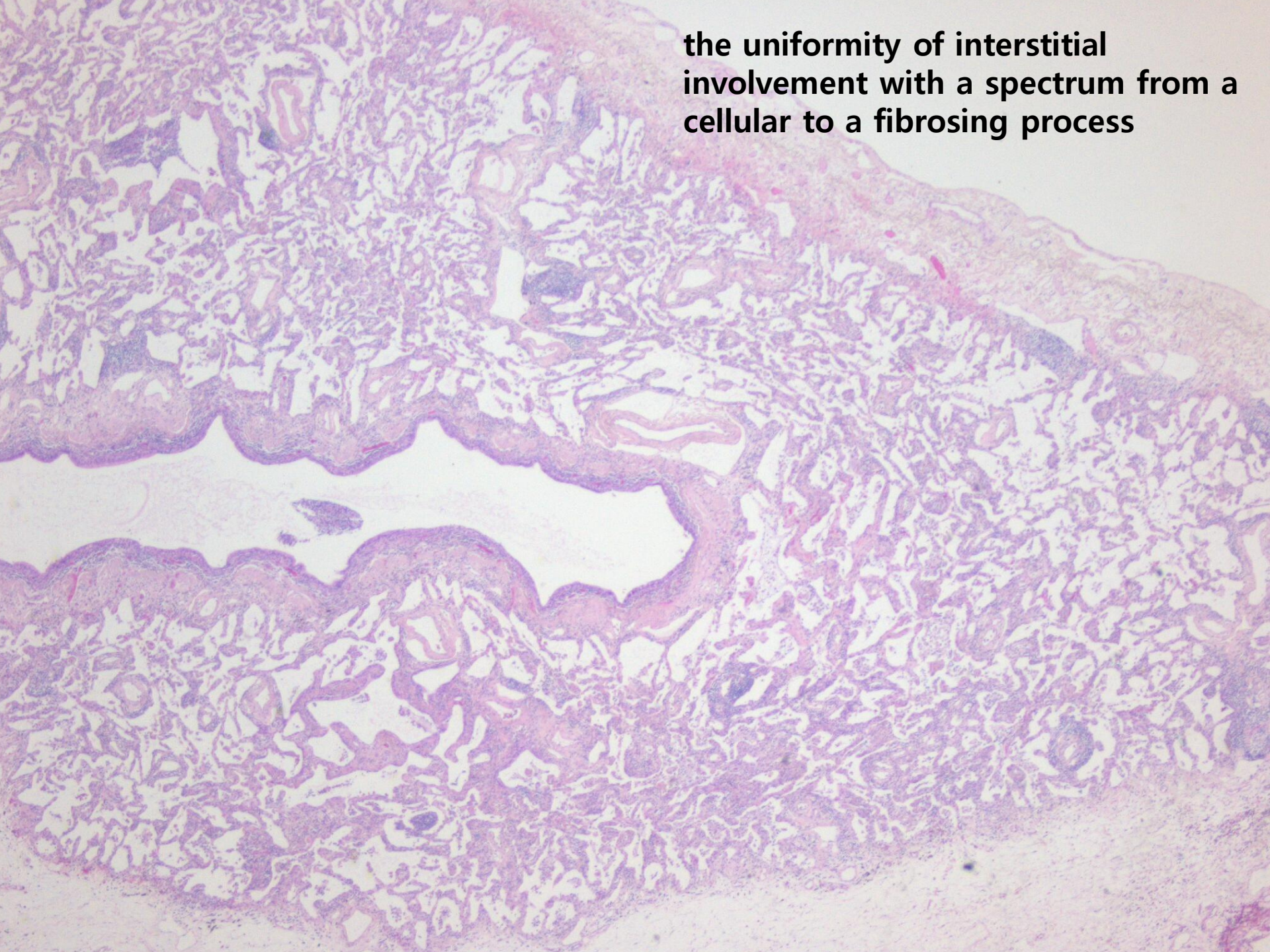

3
L-PA

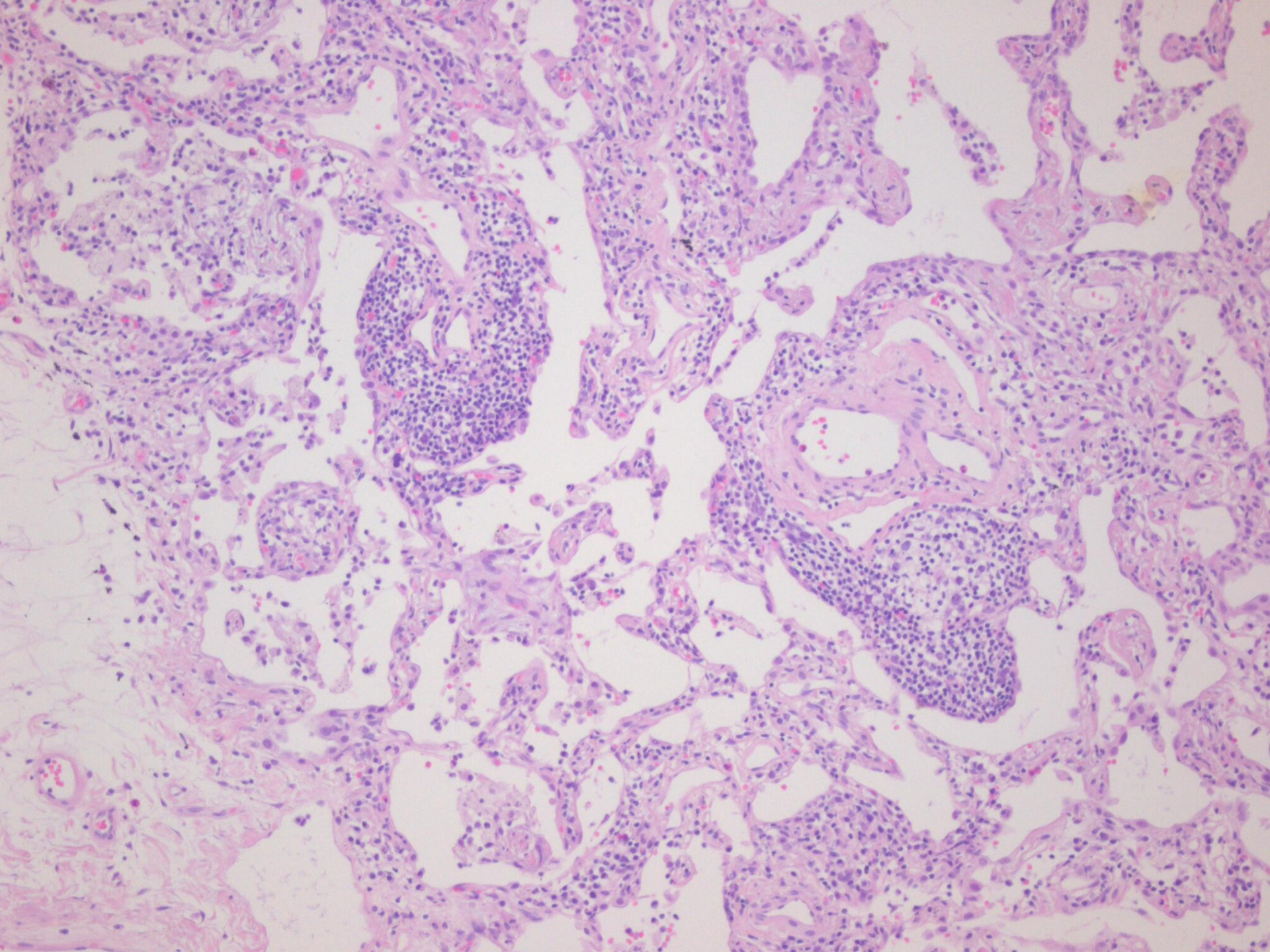
- Subpleural, basal predominance
- Reticular abnormality



NSIP pattern:
widespread, bilateral ground-glass opacities (GGO)
peripheral irregular linear or reticular opacities
Honeycombing, when present, is usually mild




the uniformity of interstitial involvement with a spectrum from a cellular to a fibrosing process



Clinical conditions associated with radiologic NSIP pattern

Collagen vascular disease
Hypersensitivity pneumonitis
Drug-induced pneumonitis
Infection (e.g., Pneumocystis jiroveci)
Immunodeficiency including HIV infection
Chronic eosinophilic pneumonia
Desquamative interstitial pneumonia (DIP)
Lymphoproliferative lung disorders (low grade)

Idiopathic and NSIP, really?

TABLE 1. REVIEW PROCESS FOR SELECTION OF FINAL 67 NONSPECIFIC INTERSTITIAL PNEUMONIA CASES

I. Review of 305 Cases with 193 Cases Selected for Further Evaluation
1. July 2001: Initial pathologic review of 305 cases
   (i) Six pathologists and two pulmonologists
2. September–December 2001: Initial CT review of 305 cases
   (i) Each case reviewed by three of six radiologists

II. Multidisciplinary Iterative Review of 193 Selected Cases and Detailed Radiologic Review with Selection of 67 Definite or Probable NSIP Cases
1. December 2001: Interactive workshop using a dynamic integrated approach with clinical-radiologic-pathologic review of 63 of the 193 cases
   (i) Six pathologists, 11 pulmonologists, and three radiologists
2. January–June 2002: Detailed NSIP CT data. Each case reviewed by three of six radiologists
3. June 2002: Interactive workshop using a dynamic integrated approach with clinical-radiologic-pathologic review of remaining 130 of the 193 cases
   (i) Seven pathologists, 12 pulmonologists, three radiologists

III. Detailed Clinical, Radiologic, and Pathologic Review of the Selected 67 NSIP Cases, Data Analysis, and Manuscript Preparation
1. December 2002: Interactive workshop using a dynamic integrated approach with clinical-radiologic-pathologic review of final 67 NSIP cases
   (i) Three pathologists, two pulmonologists, two radiologists
2. February 2003: Detailed review of pathology data from 67 definite and probable NSIP cases
   (i) Three pathologists
3. May 2003: Report of the ATS Workshop on Idiopathic Nonspecific Interstitial Pneumonia, symposium presentation at the ATS meeting, Seattle, Washington
4. May 2006: Writing committee meeting: final summary for this manuscript

Definition of abbreviations: ATS = American Thoracic Society; CT = computed tomography; NSIP = nonspecific interstitial pneumonia.

67 NSIP cases : definite (N=17) and probable (N=50)

Prognosis

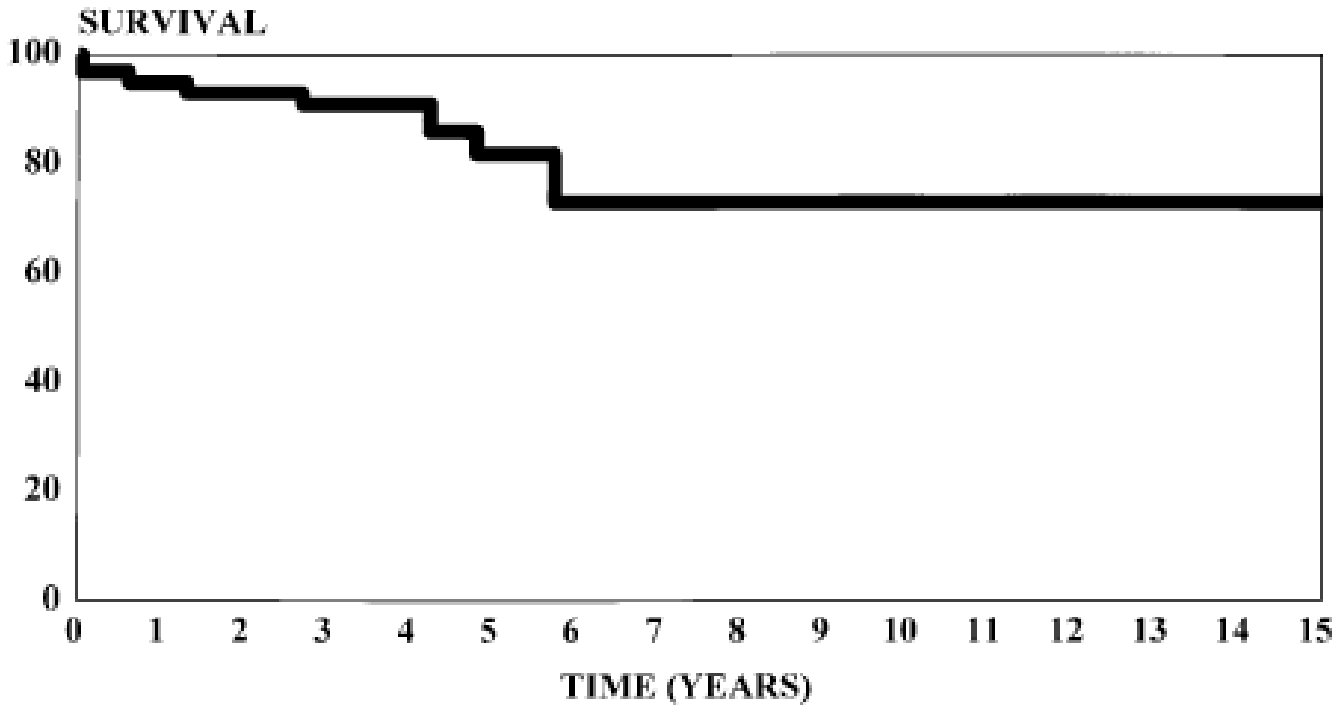
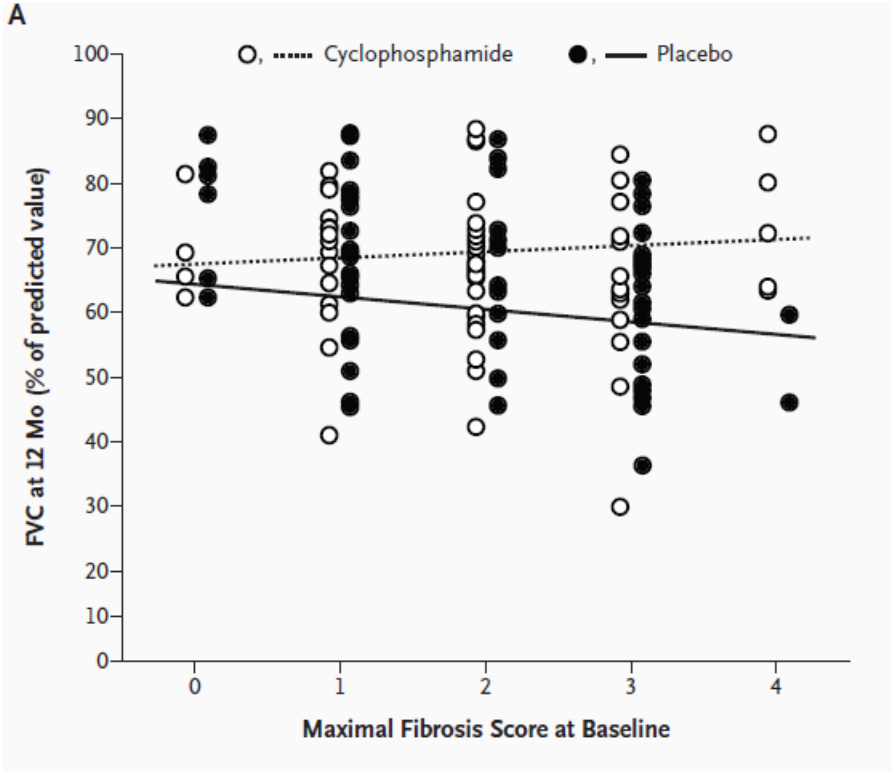


Figure 1. Survival in nonspecific interstitial pneumonia. Survival at 5 years was 82.3% and at 10 years was 73.2%.

Am J Respir Crit Care Med 177; 1338–1347, 2008

Cyclophosphamide versus Placebo in Scleroderma Lung Disease

- 158 ILD patients with scleroderma



N Engl J Med 2006;354:2655-66

Cyclophosphamide and low-dose prednisolone in fibrosing NSIP

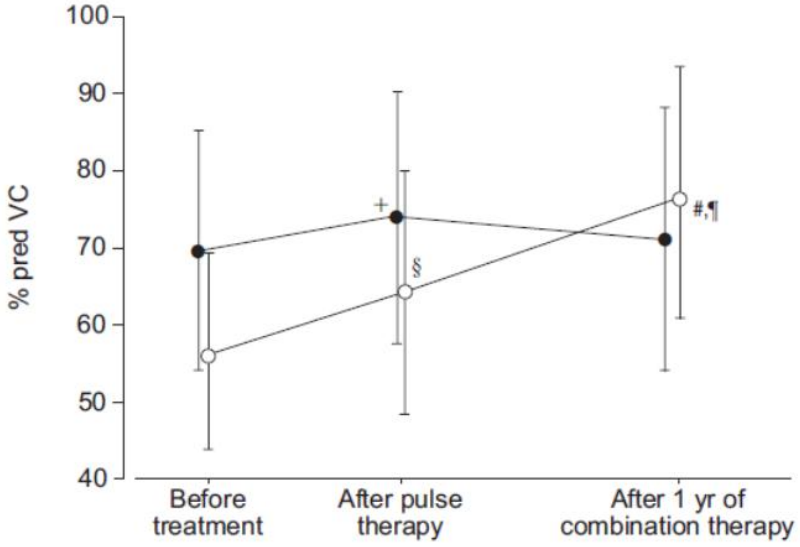
- Subject: fibrosing NSIP patients (n=12)

- Treatment protocol
  - Methylprednisolone pulse (1,000 mg/day for 3 days at 1-week intervals x 4 times)
  - followed by combination therapy for 1 yr with cyclophosphamide 1–2mg/kg/day + low-dose prednisolone (20 mg on alternate days)

Eur Respir J 2005; 25: 528–533

- **Results**

Changes in mean vital capacity



Five of 12 (42%) remained improved,

four of 12 (33%) unchanged,

three of 12 (25%) had worsened

(mean F/U 91.8 months; range 60–148)

Eur Respir J 2005; 25: 528–533

A long-term prospective randomized controlled study of NSIP treatment in scleroderma

- 18 biopsy-proven NSIP patients
  - Groups 1. CYC 1 g/m^2 IV with monthly during 12 months
  - Group 2. CYC + prednisone 60mg/day during 1 month followed by 10 mg/day on the end of the second month and maintaining the same dose until the end of the treatment

Clin Rheumatol (2011) 30:223–229

Baseline features in the two groups

Clinical features	CYC (n=9)	CYC+PRED (n=9)	P
Age (yrs), (mean±SD)	46.66±7.90	41.22±10.63	0.23
SSc limited/diffuse subtype (%)	3 (33.3%)/6 (66.7%)	5 (55.6%)/4 (44.4%)	0.63
Disease Duration (years) (mean±SD)	5.82±3.94	6.02±2.35	0.45
Scl70 positive (%)	2 (22.22%)	4 (44.44%)	0.62
Cellular/fibrosing NSIP (%)	6 (66.7%)/3 (33.3%)	8 (88.9%)/1 (11.1%)	0.57
MRSS (mean±SD)	24.50±13.36	14.88±12.62	0.19

PFT (% predicted value)	CYC (n=9)	CYC+PRED (n=9)	P
TLC	76.66±14.29[a]	81.87±8.64[b]	0.68
FVC	67.33±16.43	64.77±7.77	0.47
FEV1	69.22±16.88	70.66±5.70	0.56
DLCO-Hb	61.86±16.83[c]	69.86±22.57[d]	0.67

Pulmonary function tests were similar in both groups after treatment (at 1 year and 3 years)

Table 3 Comparison of the PFT and MRSS before and after treatment in both groups: CYC versus CYC+PRED

PFT Mean±SD	CYC (n=9)		p	CYC+PRED (n=9)		p
	Before	After 1year		Before	After 1year	
FVC	67.33±6.43	65.22±17.54	0.76	64.77±7.77	64.00±9.74	0.40
FEV1	69.22±16.88	69.33±17.55	0.88	70.66±5.70[a]	68.87±10.0[a]	0.50
DLCO-Hb	56.40±9.15[b]	41.80±14.58[b]	0.54	64.17±16.75[c]	60.17±15.25[c]	0.28
MRSS	24.50±13.36	22.44±12.49	0.72	14.88±12.62	9.05±9.85	0.02

Table 4 Comparison of the PFT and MRSS at 3 years after completing 1-year of active therapy with CYC or CYC+PRED

PFT Mean±SD	CYC (n=9)		p	CYC+PRED (n=9)		p
	End of therapy	After 3years		End of therapy	After 3years	
FVC	65.22±17.54	62.88±18.95	0.39	64.00±9.74	65.43±8.73	0.61
FEV1	69.33±17.55	64.00±19.73	0.78	68.87±10.0[a]	66.57±6.80	0.22
DLCO-Hb	41.80±14.58	42.80±15.61	0.54	60.17±15.25	65.33±10.89	0.28
MRSS	22.44±12.49	20.13±9.43	0.68	9.05±9.85	10.63±9.23	0.11

Conclusion of this study

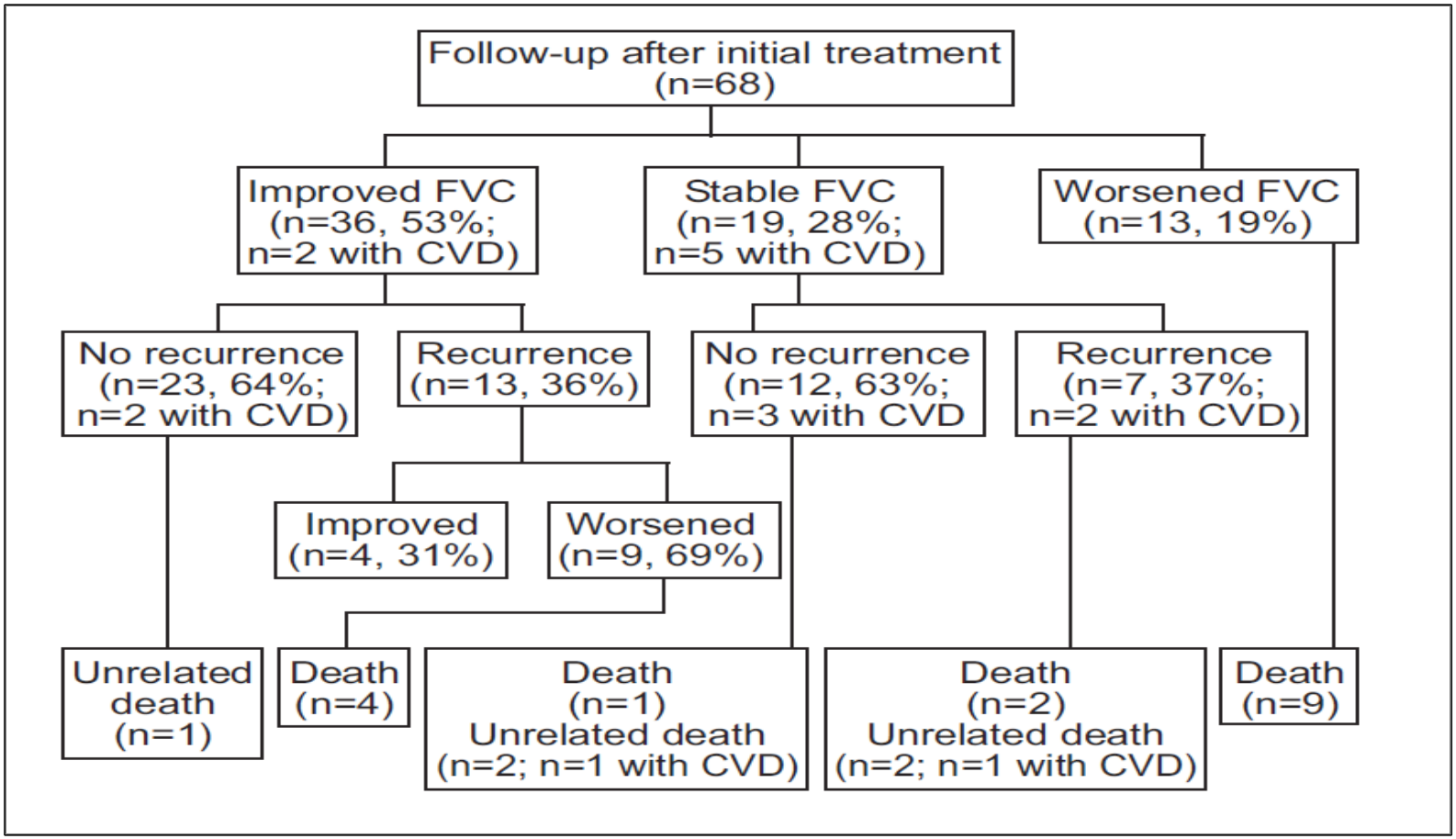
- Cyclophosphamide
  - effective to stabilize the lung function in NSIP of systemic sclerosis
  - A long-term effectiveness for 3 years after the 1-year treatment
  - The combination of prednisone did not bring further improvement

Reported experience, Korea treatment for NSIP

	Total (n=83)	Fibrotic NSIP (n=72)	Cellular NSIP (n=11)
Initial treatment			
Initial dose of PD mg	51.5±11.9	51.5±12.0	51.4±12.1
Combination with CX	62/79 (78%)	56/68 (82%)	6/11 (54%)
Time to 15 mg of PD months	6.8±7.2	5.7±3.7	12.8±15.5
Total duration months	17.2±12.1	17.4±12.1	15.8±12.4

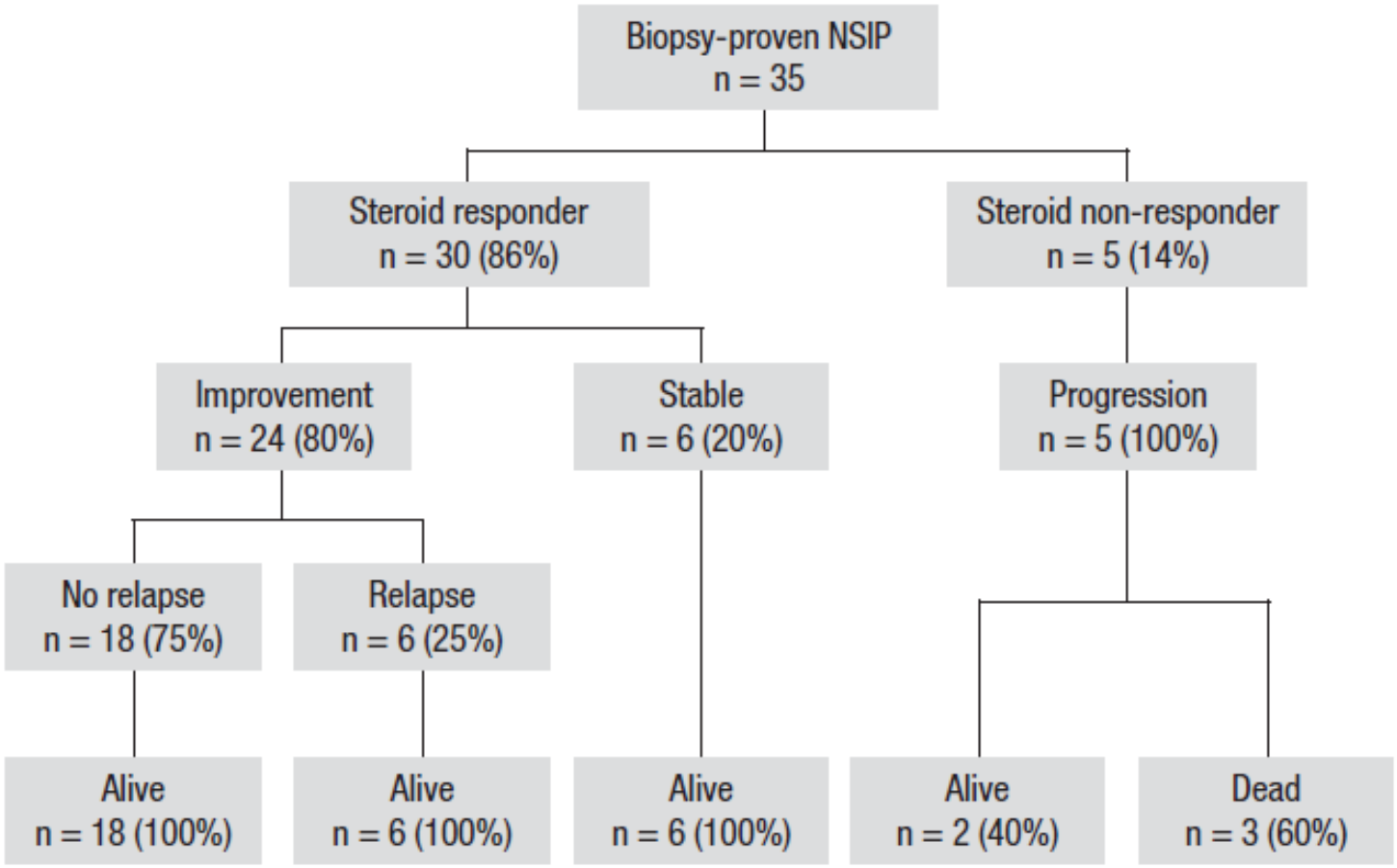
Eur Respir J 2009; 33: 68–76

Final outcomes of the patients with fibrotic NSIP after treatment



Eur Respir J 2009; 33: 68–76

Clinical courses of the patients with NSIP



J Korean Med Sci 2012; 27: 661-667

Mycophenolate Mofetil improves Lung Function in CTD-associated ILD

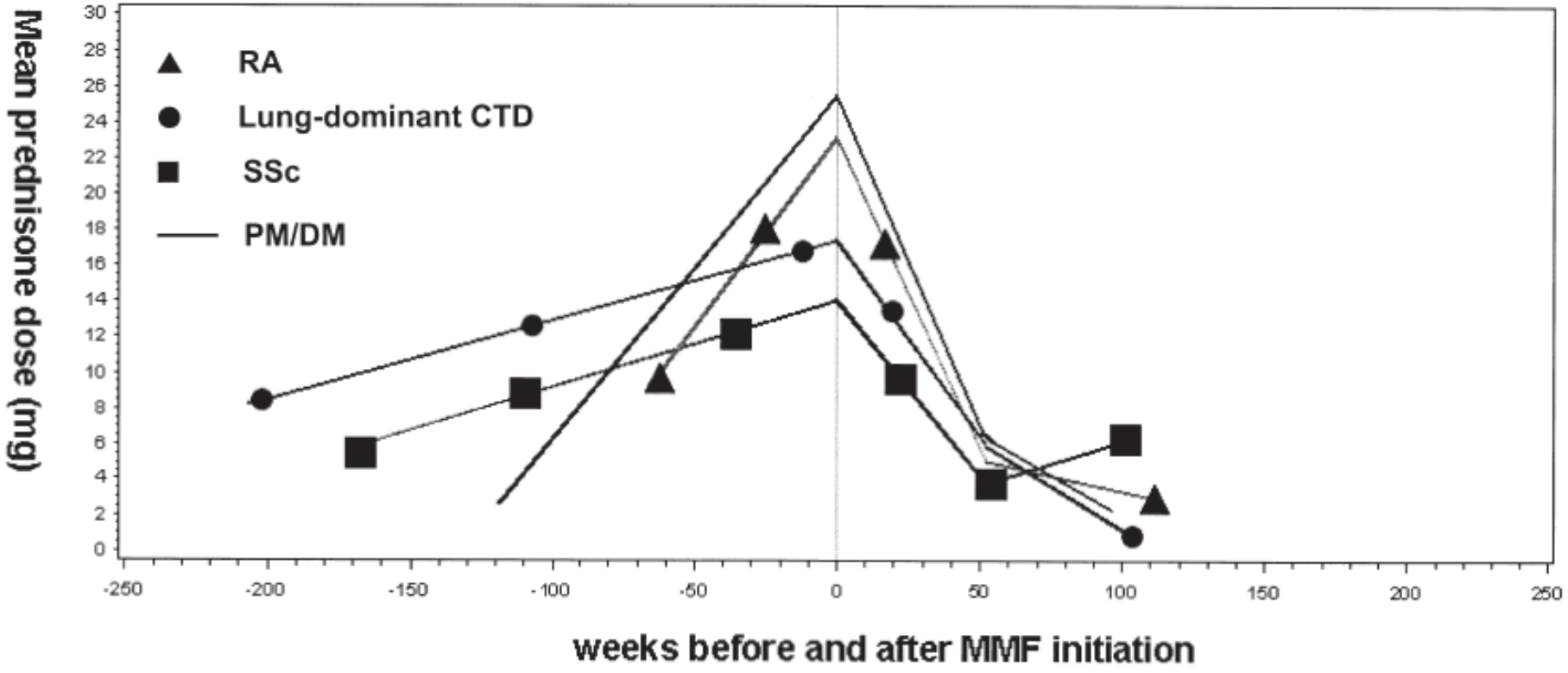
- **Mycophenolate mofetil (MMF)**
  - an immunosuppressant agent that inhibits proliferative responses of T and B lymphocytes
  - for prevention of organ rejection following allogeneic transplants and induction and maintenance therapy of lupus nephritis

J Rheumatol 2013; doi:10.3899/jrheum.121043

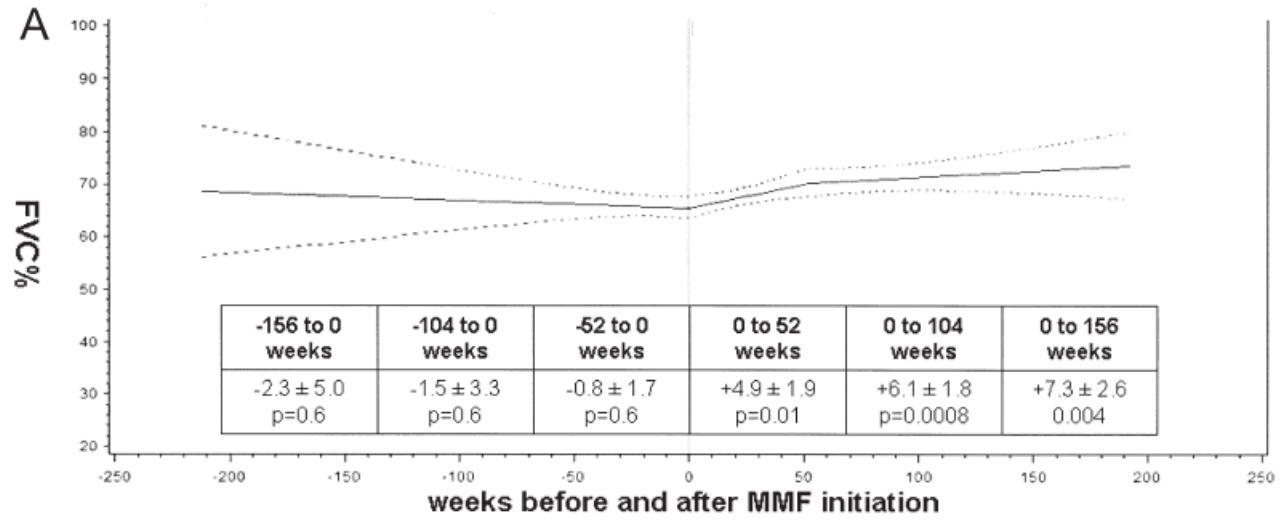
125 subjects treated with MMF for a median 897 days (41% of patients exposure to cyclophophamide or azathioprine)

Connective tissue disease, n	
Systemic sclerosis	44
Polymyositis/dermatomyositis	32
Lung-dominant connective tissue disease	19
Rheumatoid arthritis	18
Sjögren disease	5
Systemic lupus erythematosus	4
Mixed connective tissue disease	3
Mode of ILD diagnosis	
Clinical/HRCT, n (%)	74 (59)
Surgical lung biopsy, n (%)	51 (41)
Pathological pattern, n	
fNSIP	17
fNSIP + OP	10
UIP	14
UIP + OP	1
OP	8
DIP	1
Pulmonary physiology	
FVC%	66.7 ± 16.0
DLCO%	47.4 ± 16.4

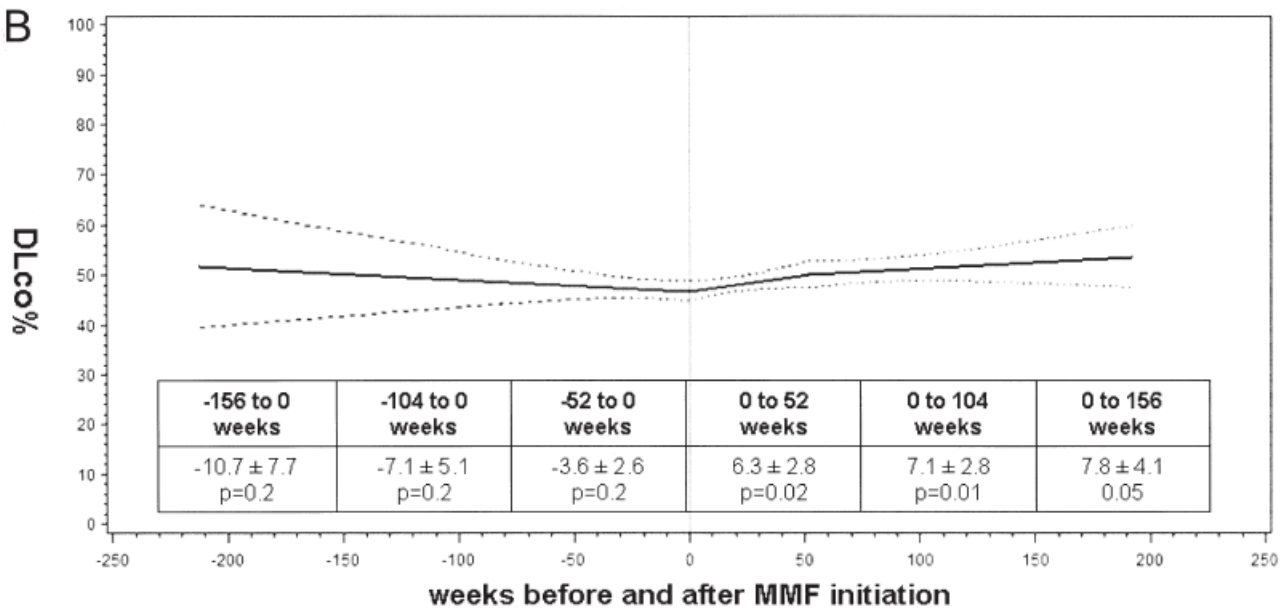
Corticosteroid sparing effect



Stable or improved pulmonary physiology over a median 2.5 years of follow up



-156 to 0 weeks	-104 to 0 weeks	-52 to 0 weeks	0 to 52 weeks	0 to 104 weeks	0 to 156 weeks
-2.3 ± 5.0 p=0.6	-1.5 ± 3.3 p=0.6	-0.8 ± 1.7 p=0.6	+4.9 ± 1.9 p=0.01	+6.1 ± 1.8 p=0.0008	+7.3 ± 2.6 0.004



-156 to 0 weeks	-104 to 0 weeks	-52 to 0 weeks	0 to 52 weeks	0 to 104 weeks	0 to 156 weeks
-10.7 ± 7.7 p=0.2	-7.1 ± 5.1 p=0.2	-3.6 ± 2.6 p=0.2	6.3 ± 2.8 p=0.02	7.1 ± 2.8 p=0.01	7.8 ± 4.1 0.05

Severe interstitial lung disease in connective tissue disease: rituximab as rescue therapy

- **Rituximab;**
  - A chimeric (human/mouse) monoclonal antibody for the CD20 expressed on pre-B and B-lymphocytes -> rapid depletion of B cells
  - Effective in non-Hodgkin's lymphoma, rheumatoid arthritis (RA), ANCA-associated vasculitis, pulmonary alveolar proteinosis and immune thrombocytopenic purpura

Eur Respir J 2012; 40: 641–648

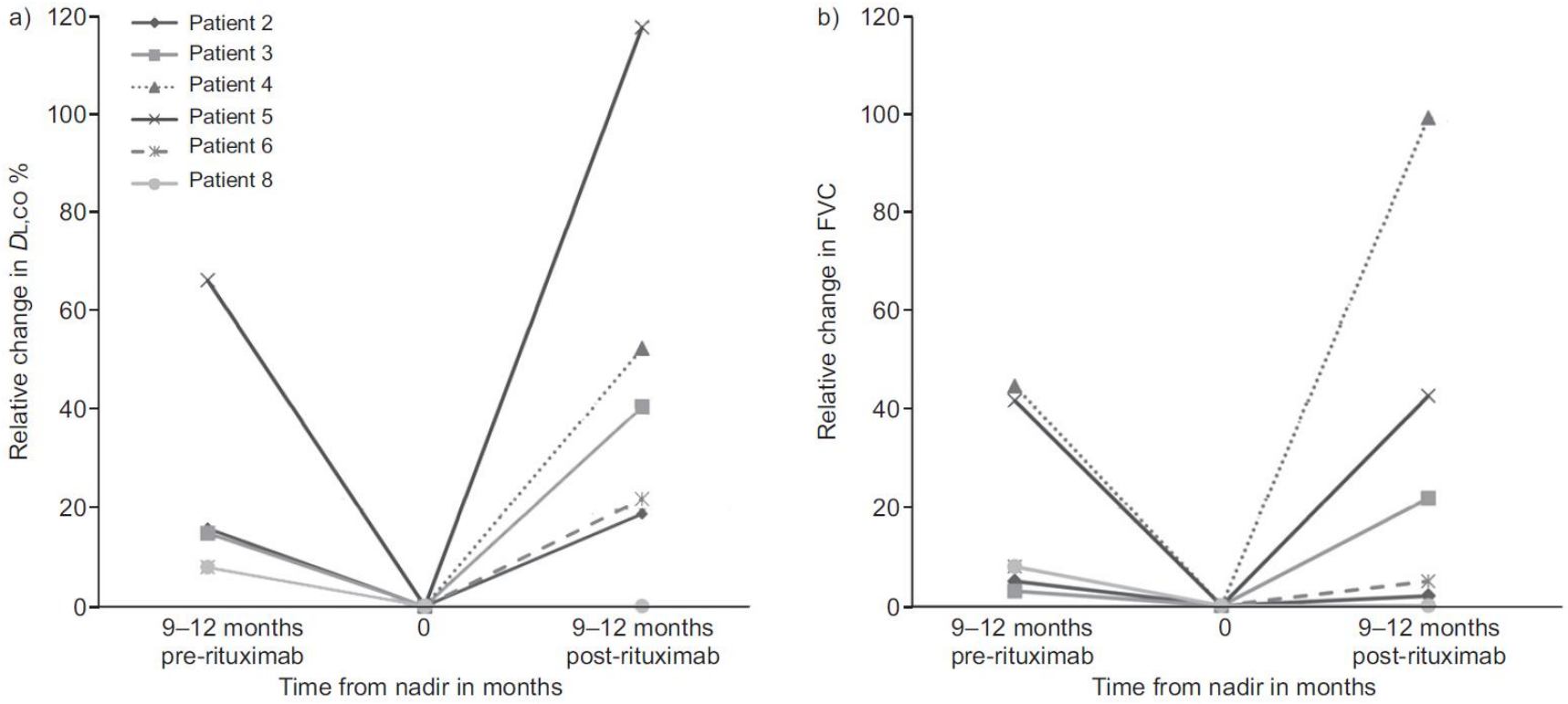
Subject : All patients (n=8, observational study) who had failed to respond to conventional immunosuppressive therapy

TABLE 1 Baseline characteristics of patients treated with rituximab, including immunosuppressive therapy in the previous 12 months

Patient	Age/sex	HRCT pattern	Year of ILD diagnosis	Serum auto-antibody/CTD features	Pre-rituximab immunosuppression
Polymyositis/dermatomyositis					
1	45/M	Organising pneumonia/DAD	2009	ENA, anti-Ro positive DM on muscle biopsy	*i.v.* methylprednisolone
2	60/M	Fibrotic NSIP*	2003	Anti-Jo 1, myositis	MMF, prednisolone, cyclosporine *i.v.* cyclophosphamide
3	60/F	Fibrotic NSIP	2000	Anti-Jo 1, myositis rheumatoid factor	MMF, prednisolone *i.v.* cyclophosphamide
4	29/F	Fibrotic NSIP	2009	Anti-Jo 1, myositis anti-Ro	MMF, prednisolone *i.v.* cyclophosphamide
5	51/M	Fibrotic NSIP	2005	Anti-Jo 1, myositis	MMF, prednisolone *i.v.* cyclophosphamide
Undifferentiated CTD					
6	49/M	Fibrotic NSIP	2006	ANA +++ (speckled) Raynaud's, GORD	*i.v.* cyclophosphamide prednisolone, MMF
7	37/F	Organising pneumonia/DAD	2009	Rheumatoid factor anti-CCP, anti-Ro	*i.v.* methylprednisolone
Systemic sclerosis					
8	63/M	Fibrotic NSIP	1999	ATA	MMF, prednisolone

Eur Respir J 2012; 40: 641–648

A median improvement in DLCO of 22% (range 0–119%; p=0.04) and FVC of 18% (range 0–100%; p=0.03)



Rituximab is an effective rescue therapy in some patients with severe CTD-ILD → may be effective for idiopathic NSIP ?

Official Journal of the Asian Pacific Society of Respirology
Respirology
2014:19, 353–359

ORIGINAL ARTICLE

Rituximab in severe, treatment-refractory interstitial lung disease

GREGORY J. KEIR,[1,2] TOBY M. MAHER,[1] DAMIEN MING,[1] REZA ABDULLAH,[1] ANGELO de LAURETIS,[3] M. WICKREMASINGHE,[4] ANDREW G. NICHOLSON,[1] DAVID M. HANSELL,[1] ATHOL U. WELLS[1] AND ELISABETTA A. RENZONI[1]

[1]Royal Brompton Hospital, [4]St Mary's Hospital, London, UK, [2]Princess Alexandra Hospital, Brisbane, Queensland, Australia, and [3]Department of Pneumonology, Carlo Poma Hospital, Mantua, Italy

Patients : Retrospective assessment of 50 patients with severe, progressive ILD

Results : a median improvement in FVC of 6.7%

and stabilization of DLco over the next 6–12 months

Assessing the response to Therapy

- Monitoring for treatment failure (progression)
  - dyspnea (objectively assessed)
  - A reduction in FVC or TLC by 10% or more
  - A reduction in DLco by 15% or more
  - Worsening of extent on HRCT findings, especially with development of honeycombing or signs of pulmonary hypertension
  - Decreased gas exchange at rest or with exercise (ex. 6-min walk test)

Summary I, NSIP

- No randomized and controlled studies in idiopathic NSIP
- A careful risk-benefit analysis for those patients who have mild to moderate symptomatic and physiologic impairment (not advanced) → monitoring for the disease progression without treatment
- Disease progression → start treatment

Summary II, NSIP

- First option
  - Methylprednisolone or cyclophosphamide IV pulse for induction (severe or progressive disease)
  - Corticosteroid alone (0.5-1mg/kg/d)
  - Corticosteroids (≤30mg/d) + azathioprine or cyclophosphamide or cyclosporine (50-150mg/d) orally at least for 1 year

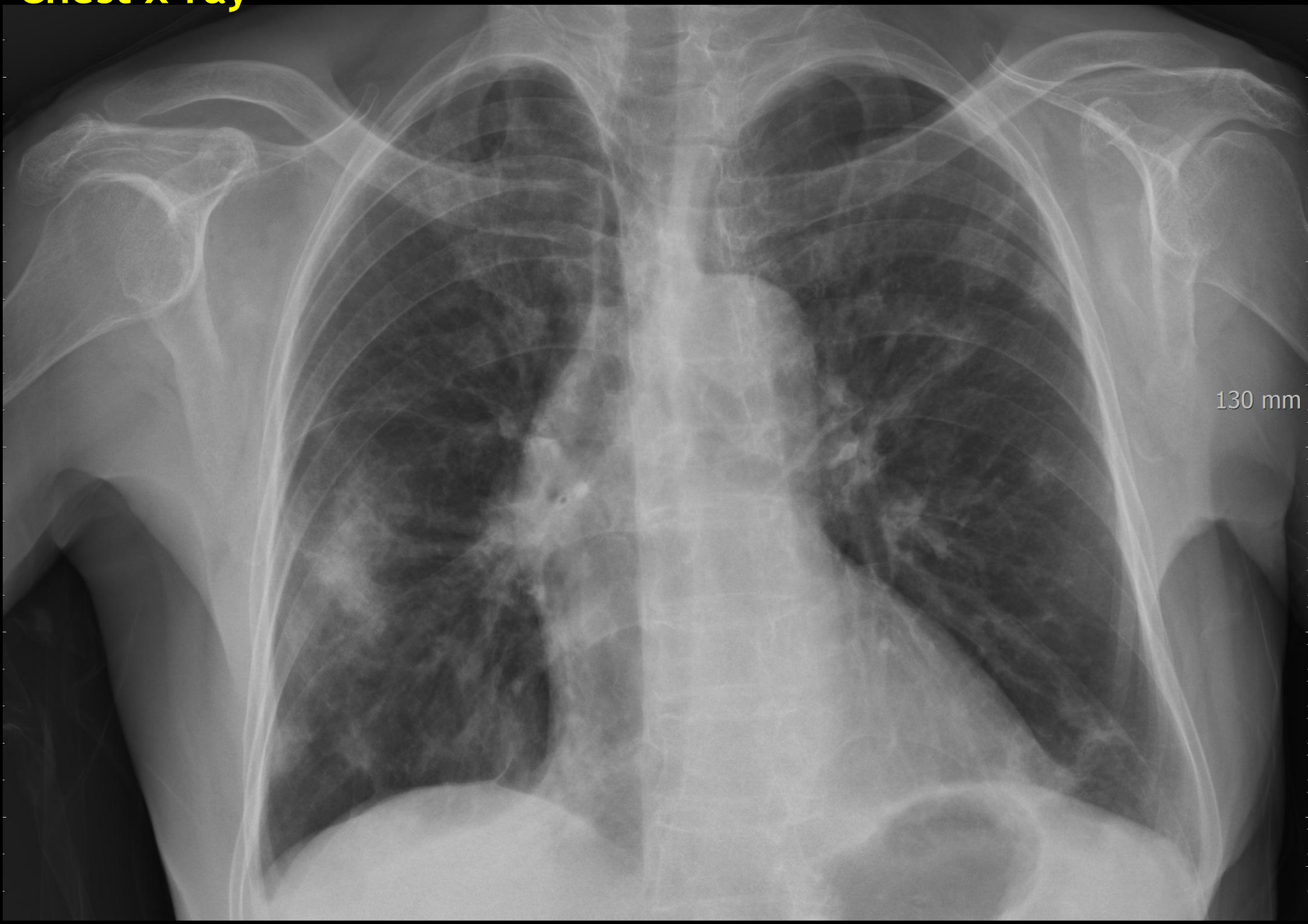
- Second option combination Therapy
  - Rituximab or Mycophenolate mofetil or Tacrolimus + low dose Corticosteroids

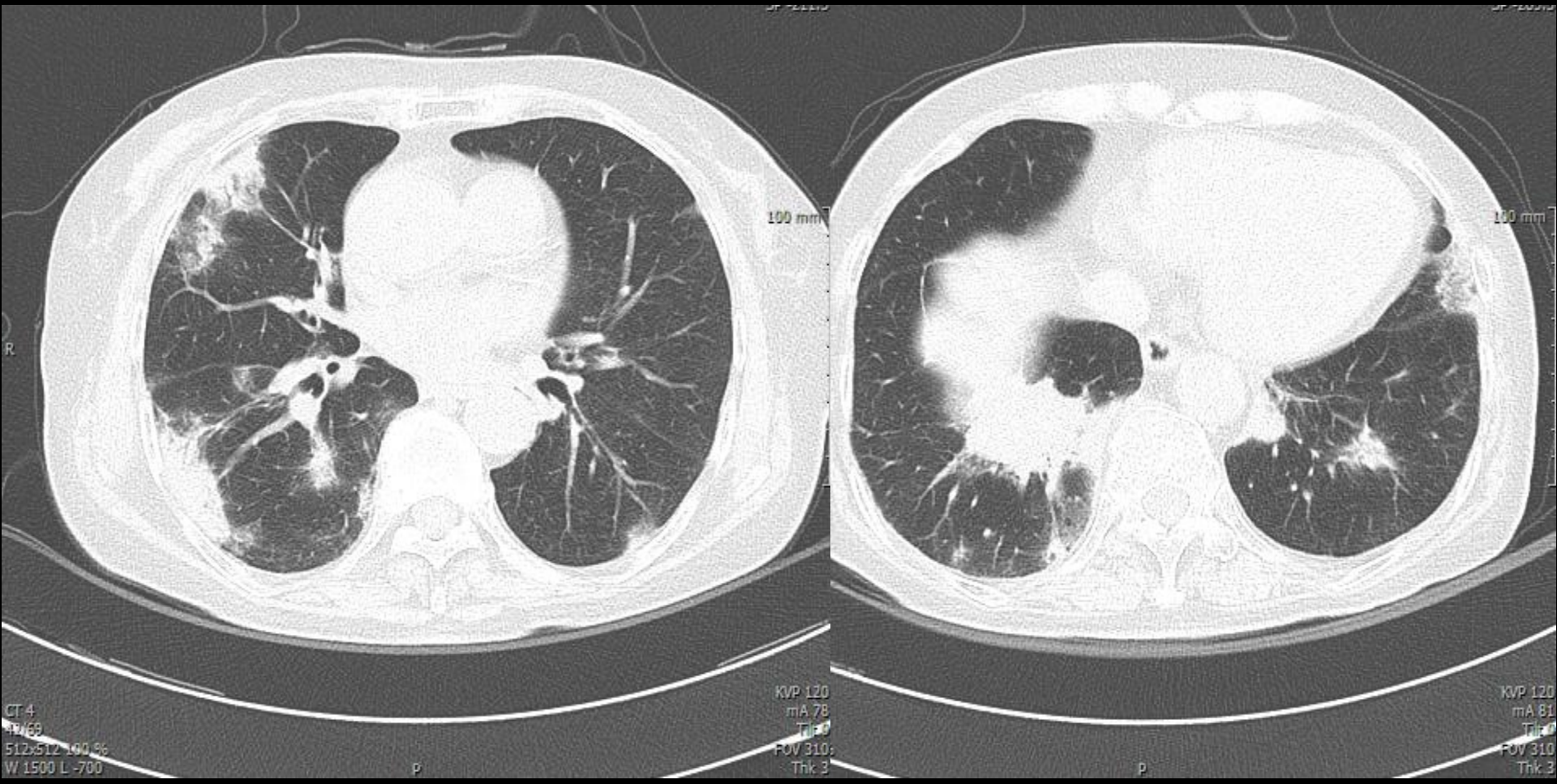
Medication	Dose	Disease	Monitoring and Precautions
Prednisone	0.5-1 mg/kg/d up to 60 mg/d	SSc, RA, DM, PM, SS	Monitor blood glucose level, bone mineral density, weight, and mental status. Taper after 8-12 wk. Doses .20 mg/d are not advised in SSc. If long-term use required, consider additional agents.
Methylprednisolone	1 g/d IV for 3 d	Acute worsening CTD-ILD	Monitor blood glucose level, bone mineral density, weight, and mental status. Rule out infection before administration.
Azathioprine	1-2 mg/kg/d	SSc, RA, DM, PM, SS	Monitor CBC and hepatic function every 2 wk for first month, then monthly. Measure TPMT; if low, use smaller dose adjustments.
Cyclophosphamide	1-2 mg/kg/d po or 500-1,000 mg IV pulse every 4 wk	SSc, RA	Monitor CBC, renal function, and urinalysis at baseline, then twice monthly. Salvage therapy because of serious toxicities.
Mycophenolate mofetil	1.0-1.5 g bid	SSc, RA, DM, PM	Monitor CBC weekly for first month, twice monthly second and third month, then monthly
Tacrolimus	1 mg bid	DM, PM	Monitor CBC, serum electrolytes/renal function, hepatic function, glucose level, and BP weekly for first month, twice weekly for second month, then monthly. Follow serum levels. (trough level of 5-10 ng/mL) Renal toxicity occurs over time.

CASE 2

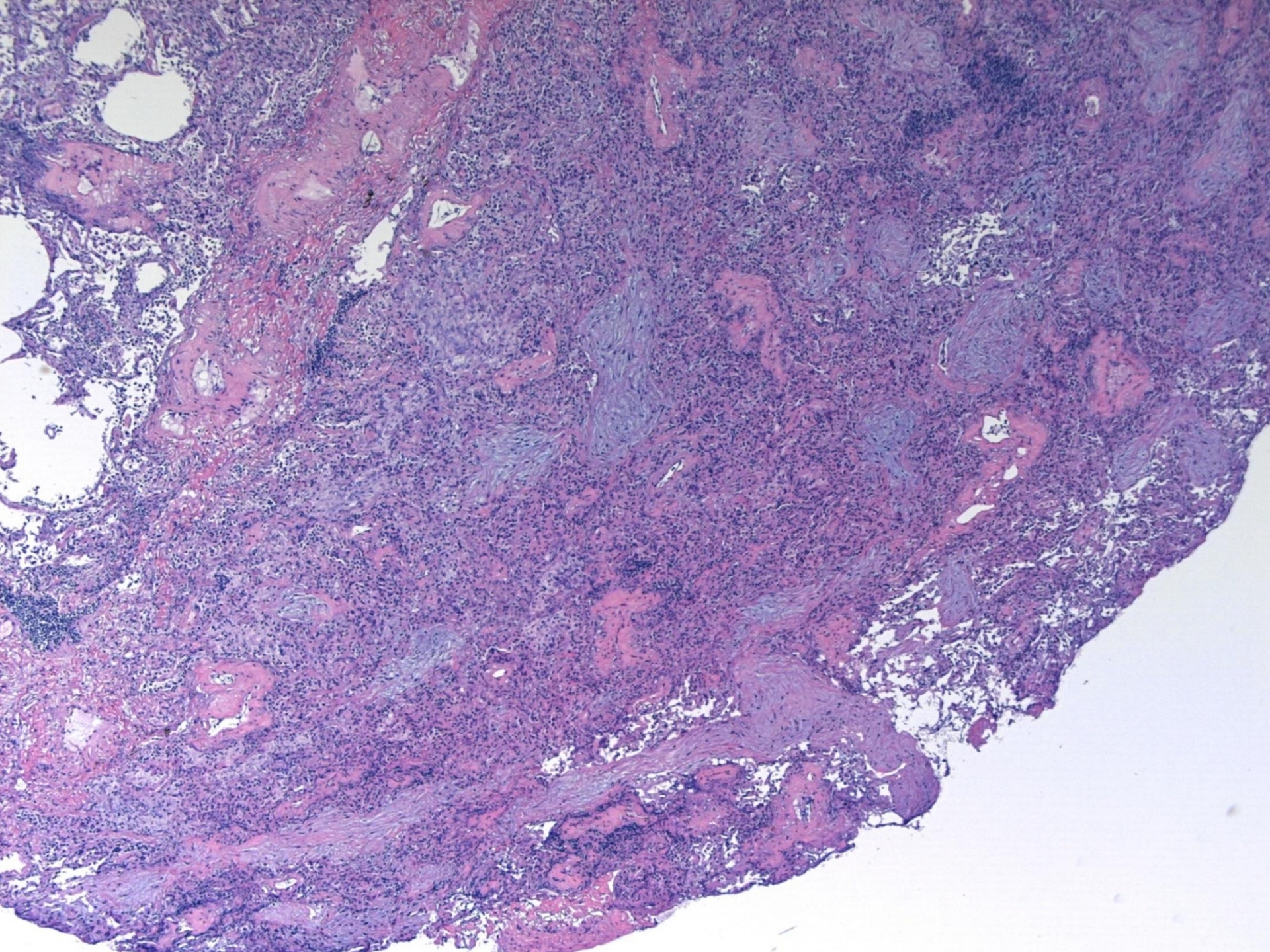
- 54/F
- 4 주전 부터 시작된 기침과 호흡곤란
- Never smoker
- Crackle on both lung bases
- Refractory to treatment for pneumonia

Chest x-ray





Patchy and often migratory consolidation in a subpleural, peribronchial, or band like pattern, commonly associated with GGO



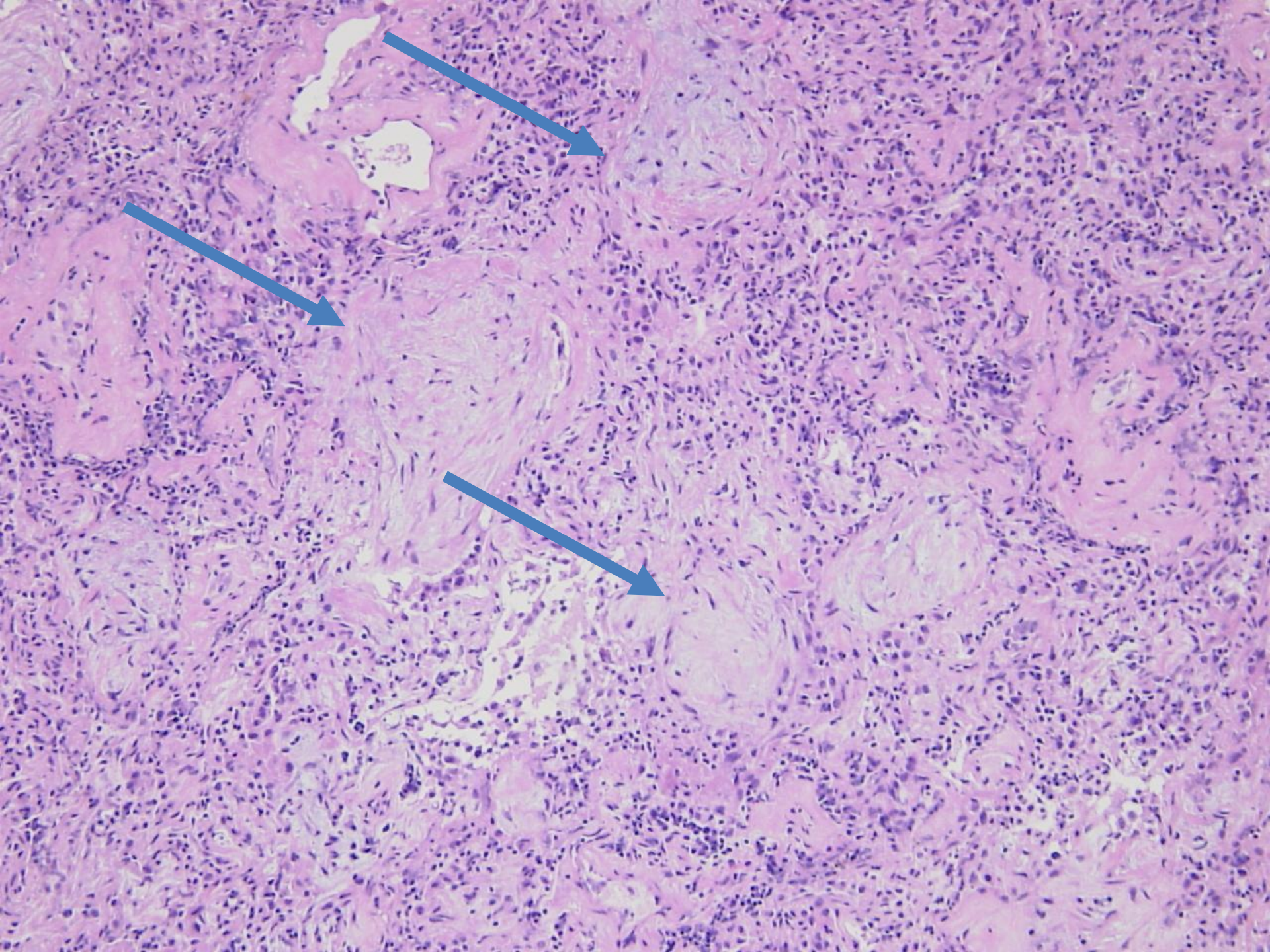


TABLE 9. CLINICAL SETTINGS ASSOCIATED WITH ORGANIZING PNEUMONIA PATTERN

As an idiopathic process that may be a localized nodule or infiltrative lung disease (COP)
Organizing diffuse alveolar damage
Organizing infections
Organization distal to obstruction
Organizing aspiration pneumonia
Organizing drug reactions, fume, and toxic exposures
Collagen vascular disease
Extrinsic allergic alveolitis/hypersensitivity pneumonitis
Eosinophilic lung disease
Inflammatory bowel disease
As a secondary reaction in chronic bronchiolitis
As a reparative reaction around other processes (including abscesses, Wegener's granulomatosis, neoplasms, and others)

Am J Respir Crit Care Med 165; 277–304, 2002

Prognosis in Patients with OP

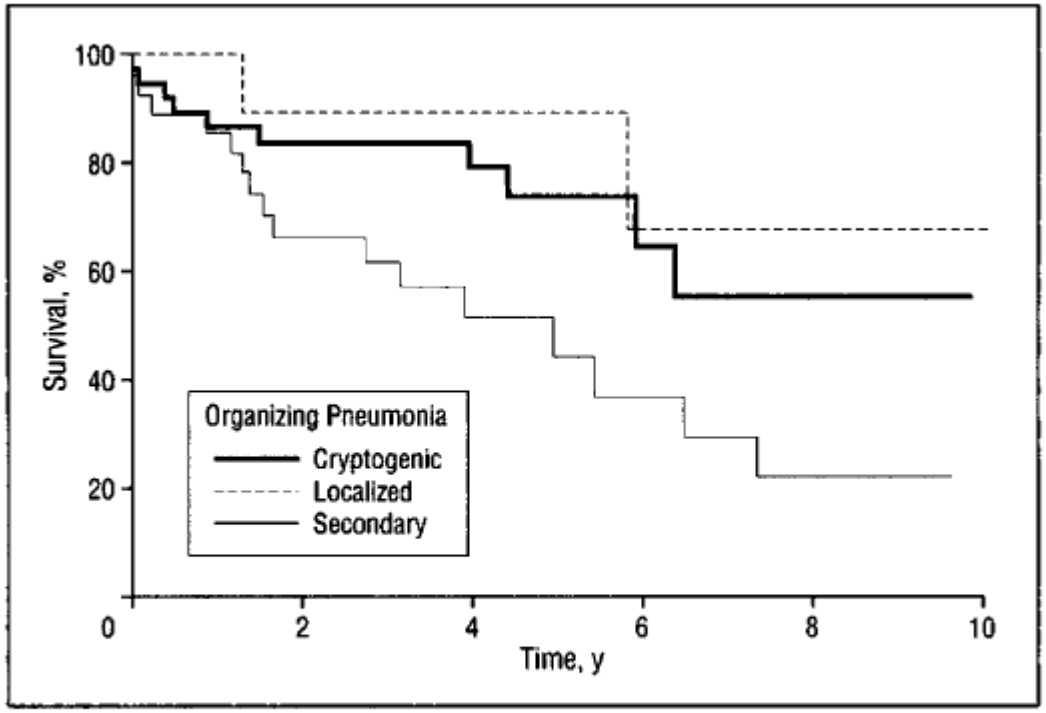


Figure 2. *Kaplan-Meier survival curve for 37 patients with cryptogenic organizing pneumonia, 27 patients with secondary organizing pneumonia, and 10 patients with focal organizing pneumonia.*

Arch Intern Med. 1997;157:1323-1329

Treatment for COP
in published literatures

- Epler and colleagues (first established BOOP, NEJM 1985)
  - 1 mg/kg/d prednisone for 1-3 month then decreases to 40 mg/d for 3 month, then 10 to 20mg/d for a total of 1 year

- King et el
  - 1 to 1.5 mg/kg/d prednisone for 4-8 wk, then tapering to 0.5-1 mg/kg/d for the ensuing 4-6 wk

Treatment for COP
in published literatures

CHEST 2011; 139(4):893–900

Treatment	OP	COP	Secondary OP
Corticosteroids	41 (77.4)	30 (81.1)	11 (68.8)
Macrolides	3 (5.7)	2 (5.4)	1 (6.3)
No treatment	9 (17)	5 (13.5)	4 (25.0)
Relapse	17 (37.8)	13 (38.2)	4 (36.4)
1-y mortality	5 (9.4)	2 (5.3)	3 (20)
In-hospital mortality	3 (5.7)	1 (2.6)	2 (13.3)

Values are presented as No. (%)

Cryptogenic Organizing Pneumonia

Characteristics of Relapses in a Series of 48 Patients

ROMAIN LAZOR, ANDRÉ VANDEVENNE, ANTOINE PELLETIER, PASCAL LECLERC, ISABELLE COURT-FORTUNE, JEAN-FRANÇOIS CORDIER and the Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P)

Centre d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires, Hôpital Cardiovasculaire et Pneumologique Louis Pradel, Université Claude Bernard, Hospices Civils de Lyon, Lyon; Service de Pneumologie, Centre Hospitalier Universitaire, Hôpital de Hautepierre, Strasbourg; Service de Pneumologie, Clinique St-Laurent, Rennes; Service de Pneumologie, Centre Hospitalier Privé des Yvelines, Sartrouville; Service de Pneumologie, Centre Hospitalier Universitaire de Saint-Etienne, Hôpital Nord, Saint-Etienne; and Service de Pneumologie, Hôpital Cardiovasculaire et Pneumologique Louis Pradel, Hospices Civils de Lyon, Lyon, France

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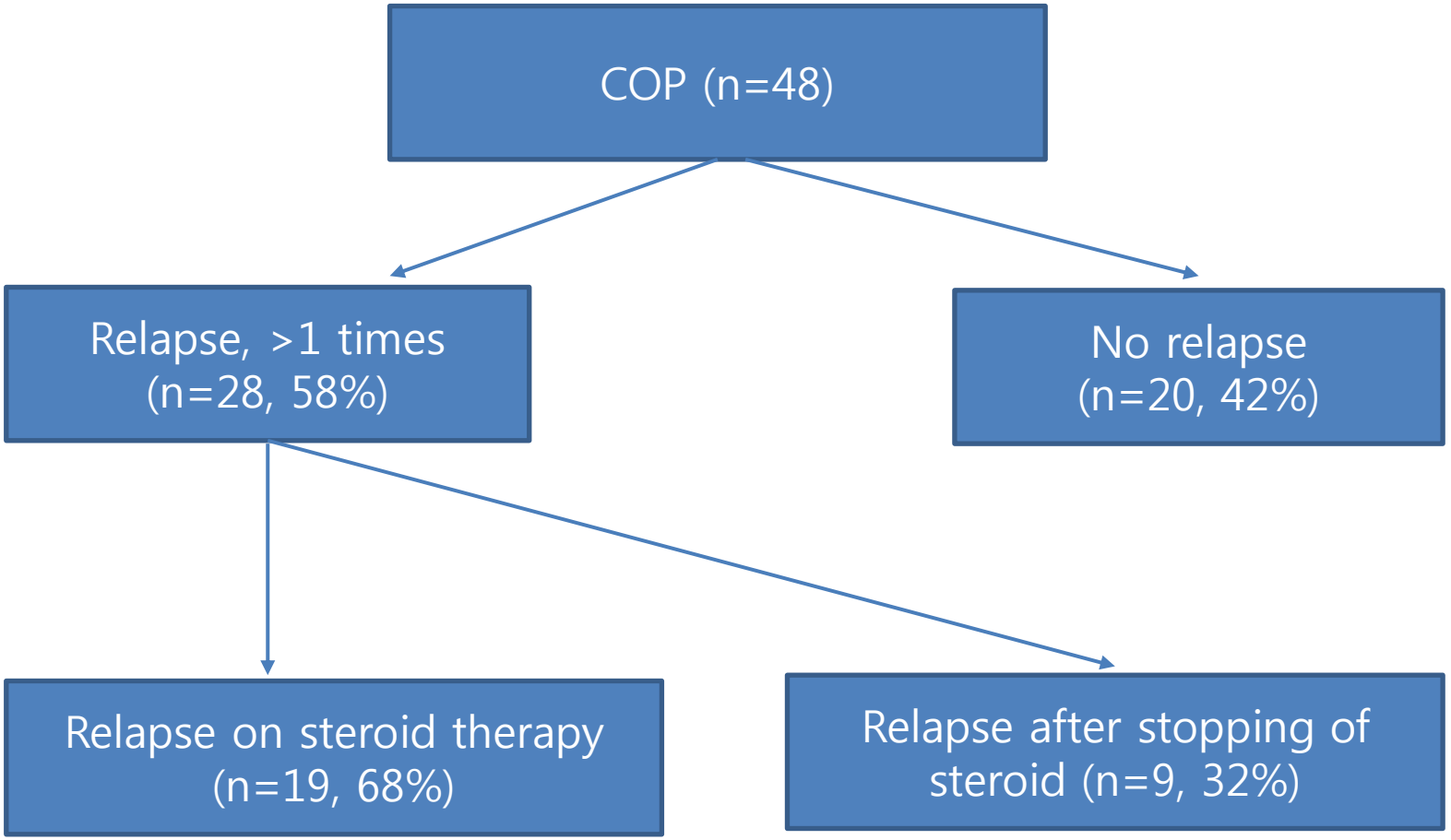
Clinical course of COP patients



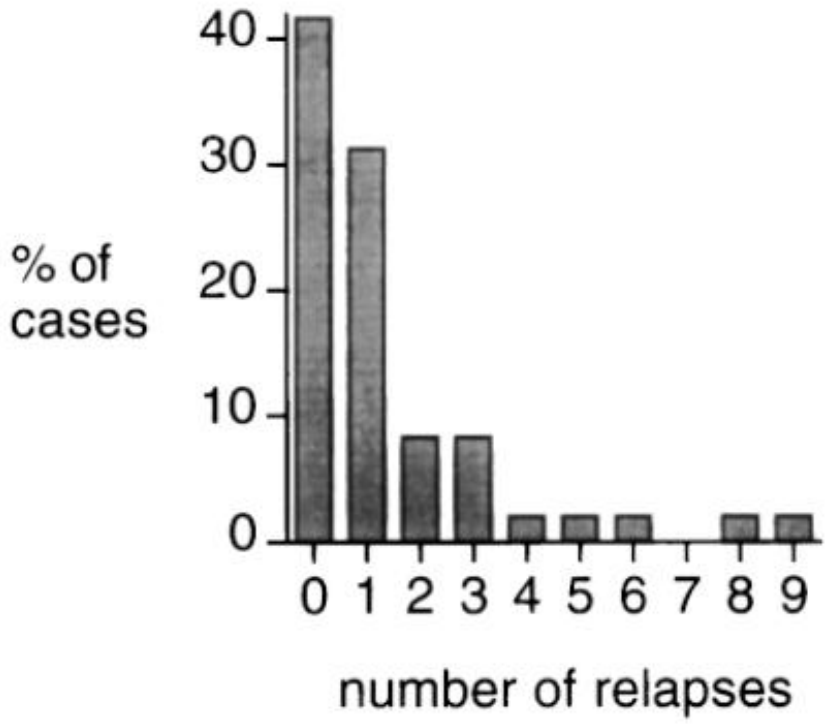


Figure 1. Distribution of 48 cases of COP according to the number of relapses. Values are expressed as percentage of the whole study population.

Treatment protocol in this study

- Prednisone by oral route (total duration 24weeks)
  - 0.75 mg/kg/d during 4 wk
  - 0.5 mg/kg/d during 4 wk
  - 20mg/d during 4 wk
  - 10 mg/d during 6 wk
  - 5 mg/d during 6 wk
- In the case of relapse (< 20mg prednisone)
  - treated by increasing prednisone to 20 mg/d
- In critical situations
  - IV boluses of methylprednisolone (2 mg/kg/d) during the first 3 to 5 d for the initial episode

Message from this study

- The Multiple Relapse subgroup
  - characterized by delayed treatment for the initial episode of COP and mild cholestasis
  - relapse occurrence was not the result of lower doses of corticosteroids

- Effect of Relapses on Morbidity and Mortality
  - All relapses were treated by resuming or increasing steroid retreatment
  - do not increase morbidity and mortality

- Frequent complications of corticosteroid
  - in 12 of 48 (25%) patients

Summary, COP

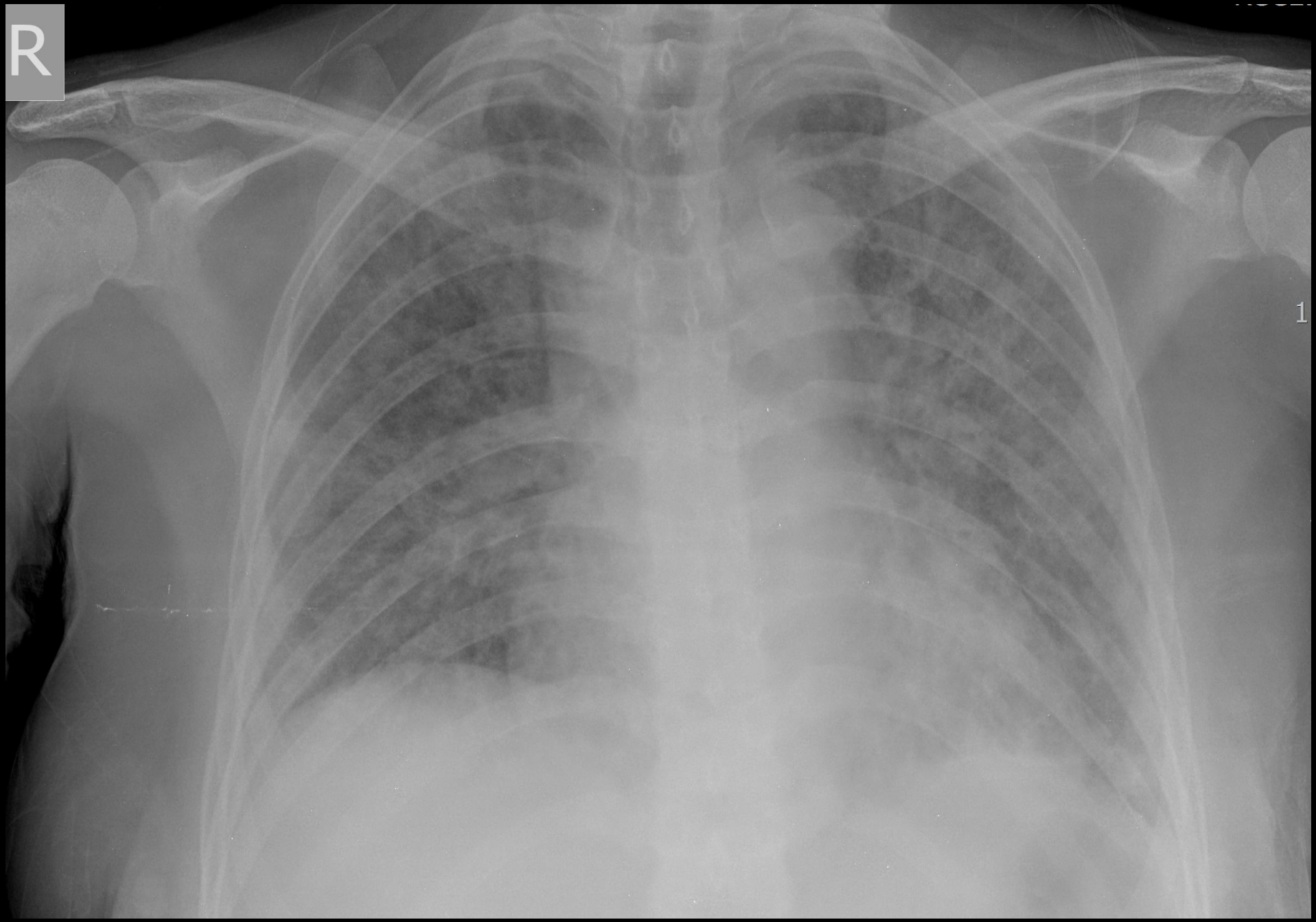
- Cryptogenic or secondary ?

- First option
  - Corticosteroid 0.5-0.75mg/kg/day, oral (<40-60mg Max)
  - Gradual tapering with 4 weeks interval
  - Total duration 24 weeks (or longer)

- In critical situations
  - IV methylprednisolone (2 mg/kg/d) during the first 3 to 5 d

CASE 3

- 50/F
- 4 주전 URI like illness
- 이후 시작된 기침과 2 주전부터 점점 심해지는 호흡곤란
- Never smoker
- Crackle on both lung bases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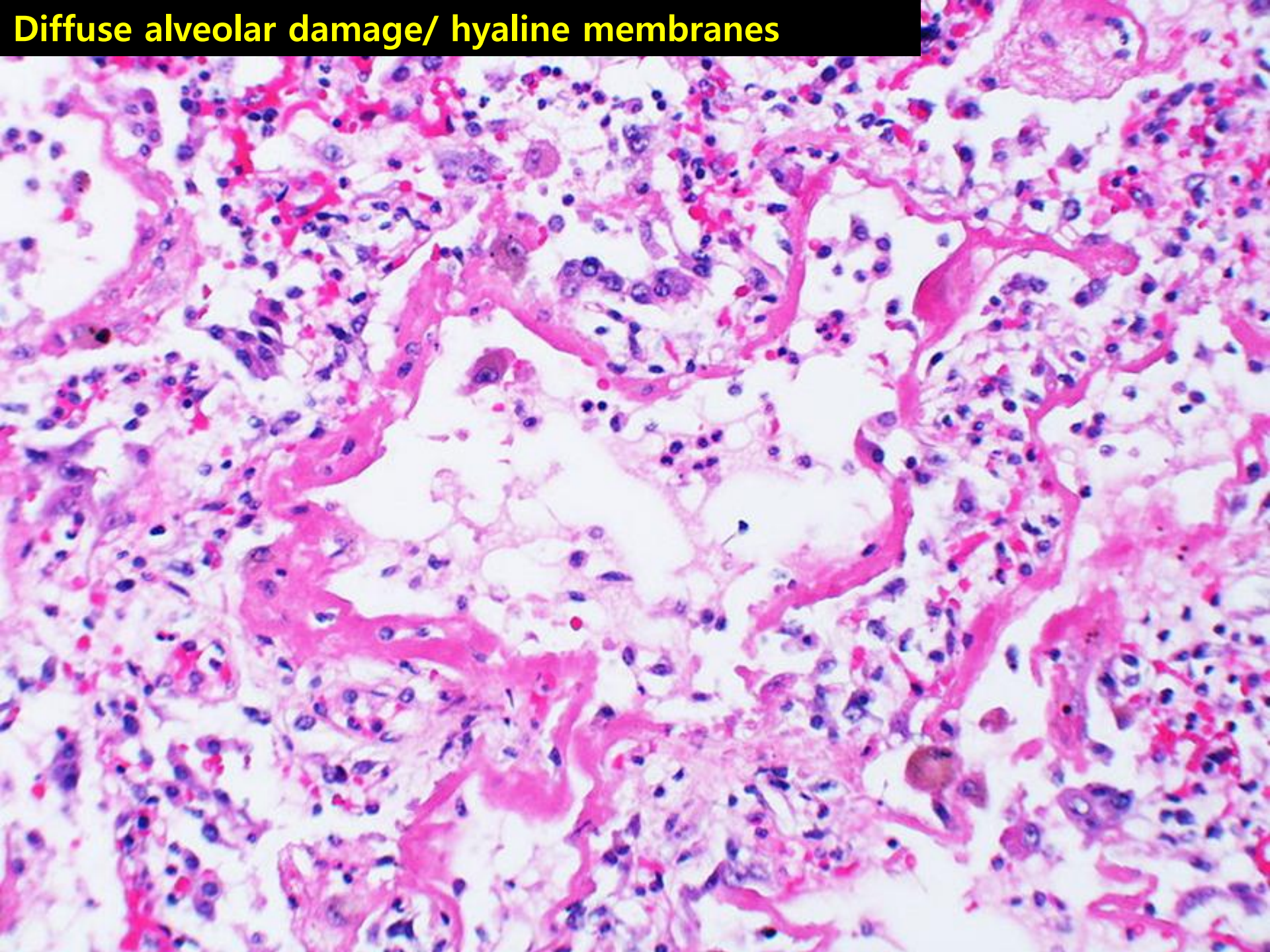
Bronchoscopy (BAL)

Body fluid	WBC **2265** ㎣
	RBC 60 ㎣
Diff. count	Neut 64%
	Lymp 13%
	Eosi 12%
	Macro 11%
CD4	11.5 %
CD8	47.4 %
CD4+/CD8+	0.7

Diffuse alveolar damage/ hyaline membranes



Acute interstitial pneumonia (AIP)

- Idiopathic form of acute lung injury
- characterized clinically by acute respiratory failure with bilateral lung infiltrates (compatible to ARDS)
- histologically diffuse alveolar damage (DAD)

Causes of and diseases associated with diffuse alveolar damage

Infection (viral , bacterial , fungal , parasitic)

Toxic inhalant

Drugs Radiation reaction (acute)

Haemodynamic disturbances

Alveolar hemorrhage syndromes

Connective tissue disease

Vasculitides

Idiopathic (acute interstitial pneumonia)

Published Series of AIP

First Author (Year)	Number of Patients	Outcome
Katzenstein (1986)	8	6 of 8 died; 2 survived to discharge (one died at 6 months)
Olson (1990)	29	17 of 29 died; 12 survived, some for up to 2 years; no histological features could discriminate survivors from nonsurvivors
Primack (1993)	9	8 of 9 died within 3 months of presentation
Ichikado (1997)	14	All patients died within 2 weeks to 6 months
Johkoh (1999)	36	Not available
Vourlekis (2000)	13	12 of 13 required mechanical ventilation; 4 died in hospital; 8 survived (hospital survival: 67%)
Quefatieh (2003)	8	7 of 8 survived to hospital discharge
Rice (2003)	6	All patients died (this was an autopsy series)
Bonaccorsi (2003)	4	3 of 4 died between 7 and 38 days
Suh (2006)	10	8 of 10 survived to hospital discharge; survivors were followed from 1 2 to 78 months; most were asymptomatic on follow-up
Parambil (2007)	12	6 of 12 died (50% hospital mortality)
Avnon (2009)	9	All patients died within 5.26 days of admission to intensive care unit (100% mortality)

Summary of published English language cases of acute interstitial pneumonia

First author	Year published	Women	Men	Mean age (range)	Mean symptom duration (days)	**Acute case fatality ratio**
Katzenstein	1986	5	3	28 (13 . 50)	3.5 (0 . 11)	62.5
Olson	1990	15	14	50 (7 . 77)	18.3 (1 . 60)	59
Primack	1993	1	6	65 (46 . 83)	NA	86
Ash	1995	0	1	70	3	100
Robinson	1996	0	1	49	NA	0
Johkoh	1999	16	20	61 (22 . 83)	NA	89
Vourlekis	2000	7	6	54 (34 . 74)	9.9 (0 . 60)	50
Ichikado	2002	13	18	60 (29 . 77)	NA	68
Bonaccorsi	2003	3	1	57 (44 . 67)	36.8 (17 . 60)	75
Quefatieh	2003	5	3	48 (20 . 78)	16.8 (3 . 49)	12.5
Totals		65	73	55 (7 . 83)	15.2 (0 . 60)	68

Treatment for AIP

- No randomized and controlled studies
- There is no proven effective therapy in the literature (case or case series)
- Adopted from similar clinical condition (based on reports of lower mortality in ARDS) or expert's opinion

A Randomized Controlled Trial in ARDS

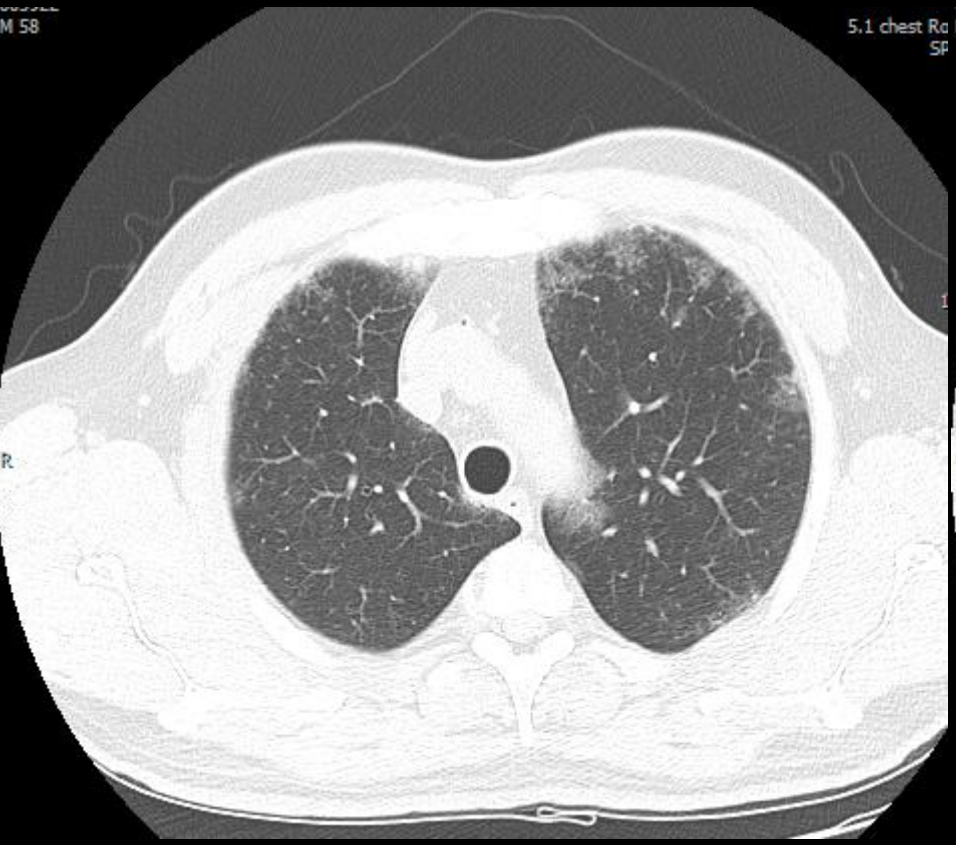
- Treatment protocol (JAMA 1998;280(2):159-165)
  - IV methylprednisolone every 6 hours
    - 2 mg/kg/d from 1 to 14 days
    - 1 mg/kg/d from day 15 to day 21
    - 0.5 mg/kg/d from day 22 to day 28
    - 0.25 mg/kg/day on days 29 and 30
    - 0.125 mg/kg per day on days 31 and 32

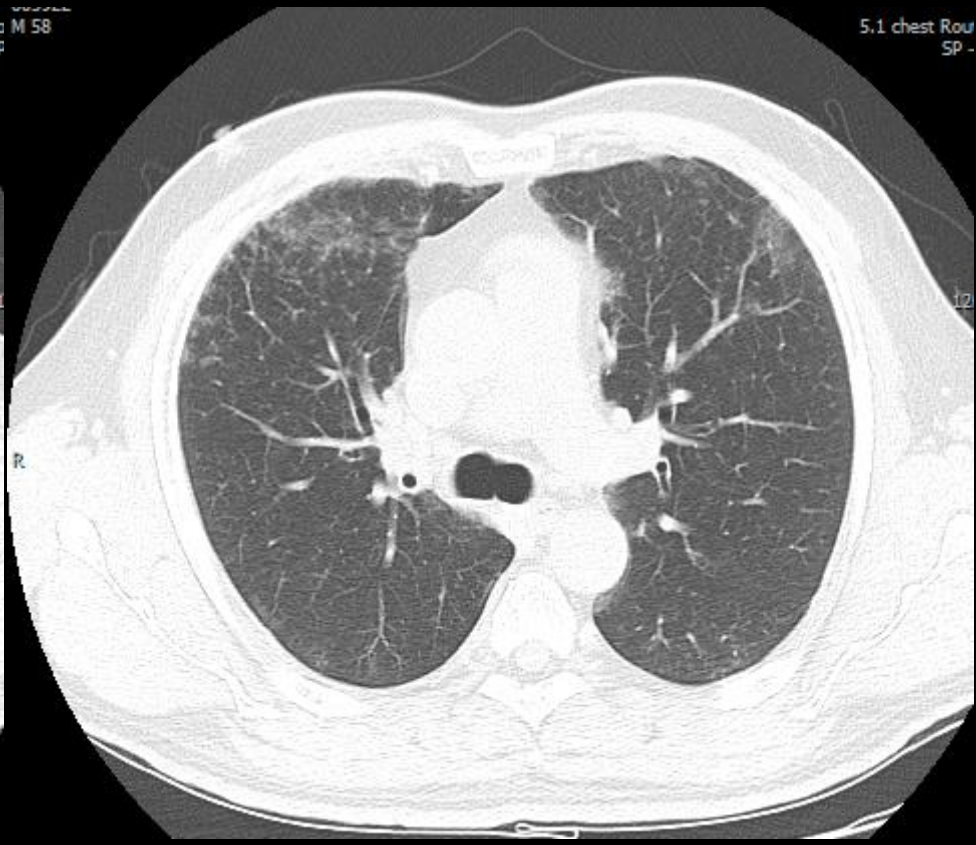
- Treatment protocol (NEJM 2006;354:1671-84)
  - A single dose of methylprednisolone 2 mg/kg
  - 0.5 mg/kg every 6 hours for 14 days
  - 0.5 mg/kg every 12 hours for 7 days

Summary, AIP

- High-dose intravenous corticosteroids
  - IV methylprednisolone (750–1000 mg/day for 3 days) by expert's opinion
  - IV low dose methylprednisolone : Adopted from treatment protocol for ARDS
- Antibiotics ± antiviral agents
- Mechanical ventilation (same strategy in ARDS)
- Best supportive care

M/58





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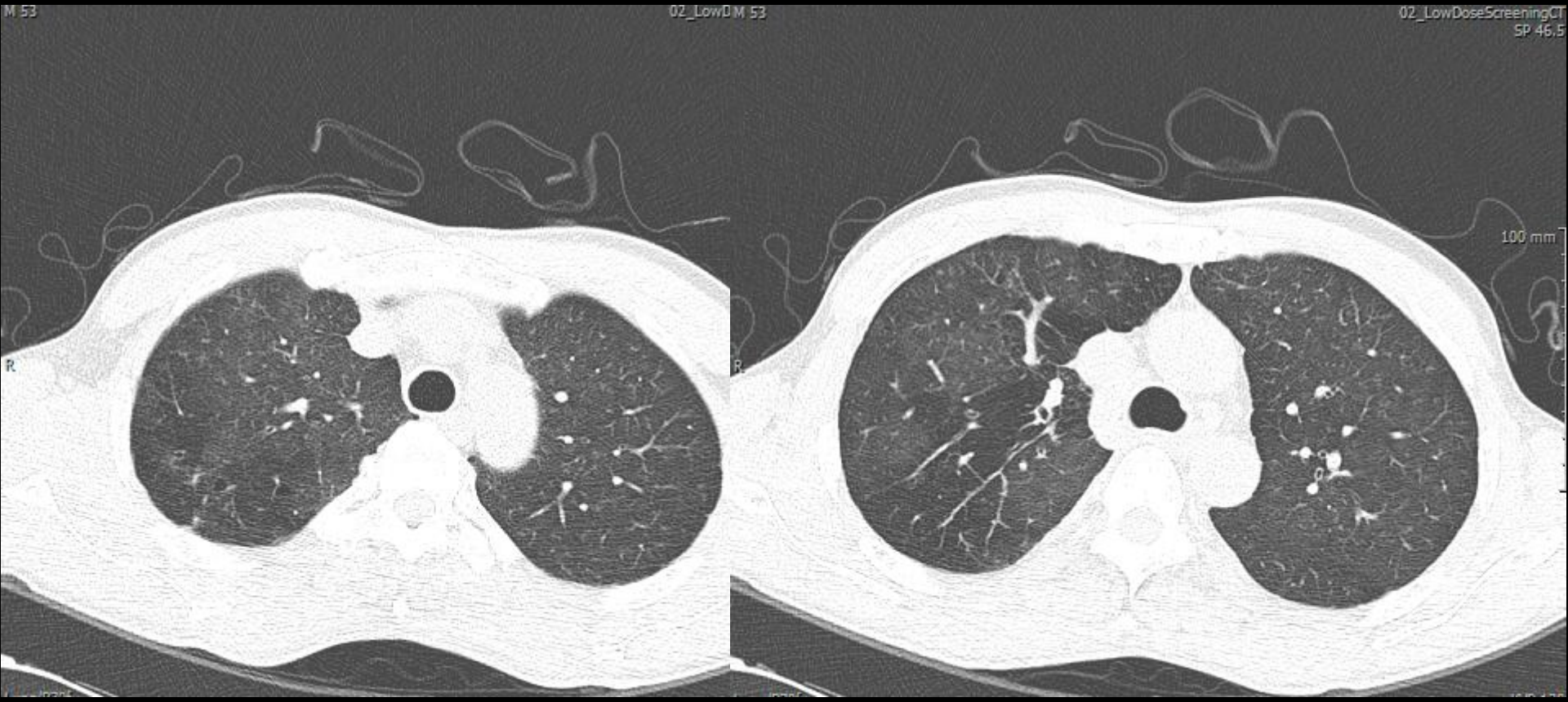

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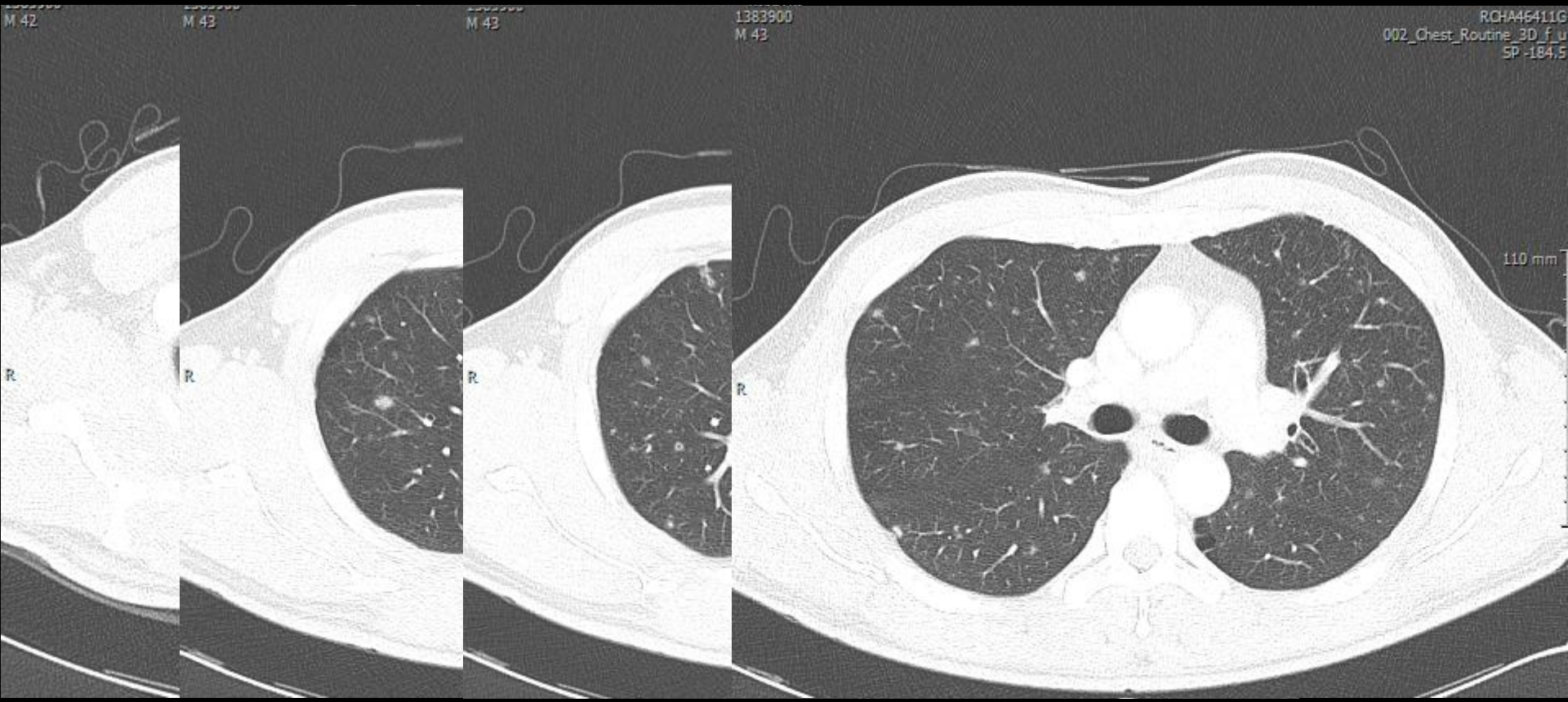
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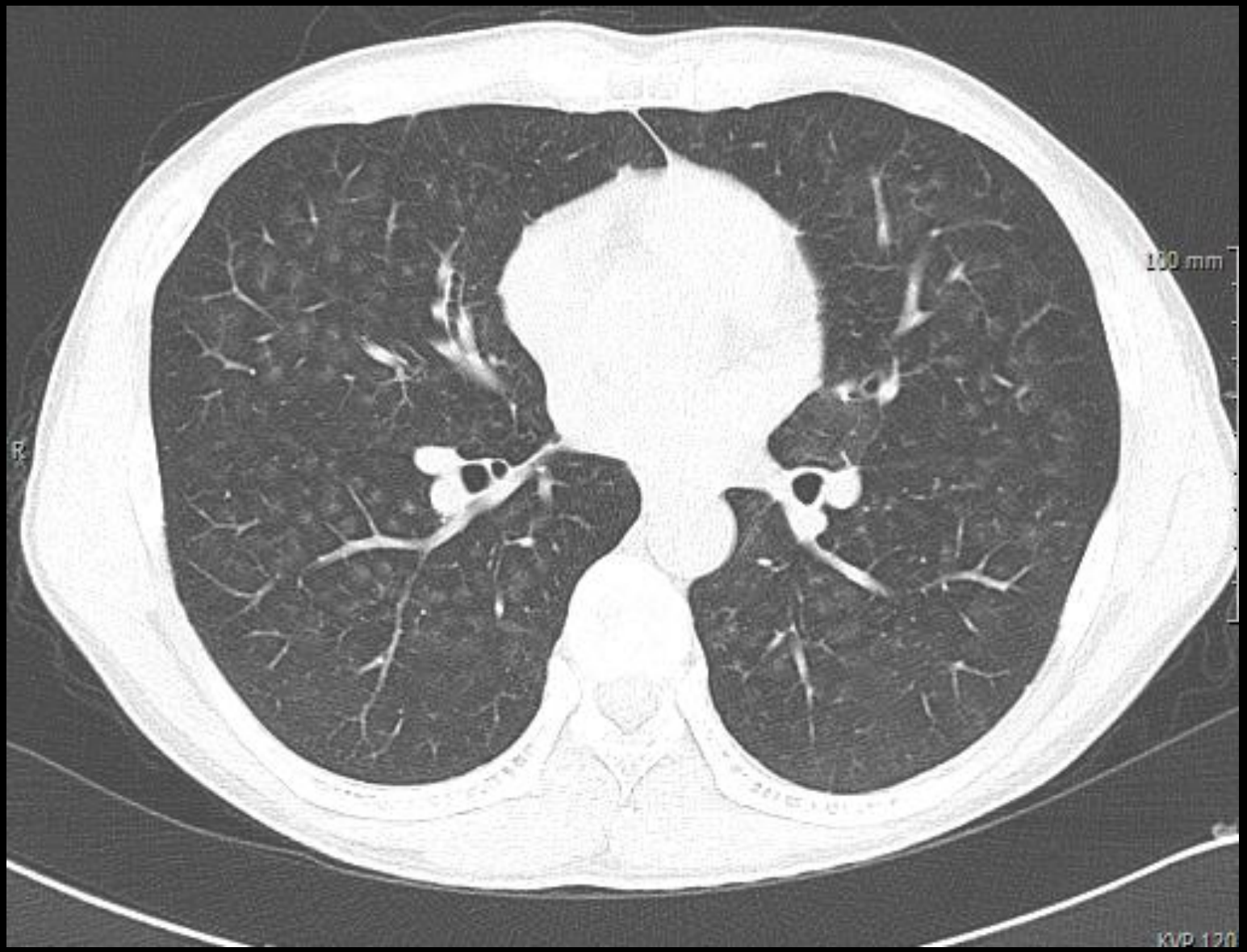

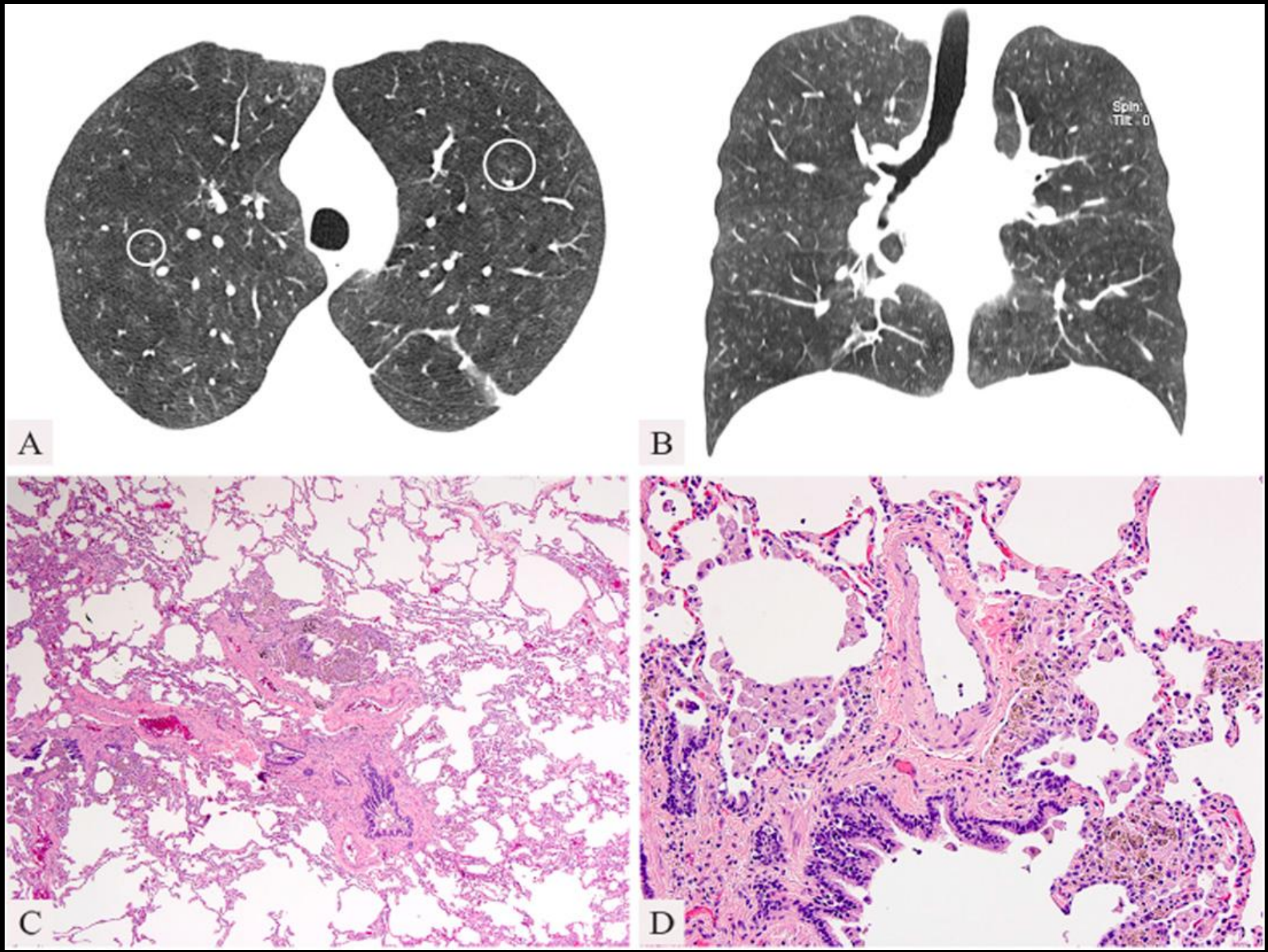
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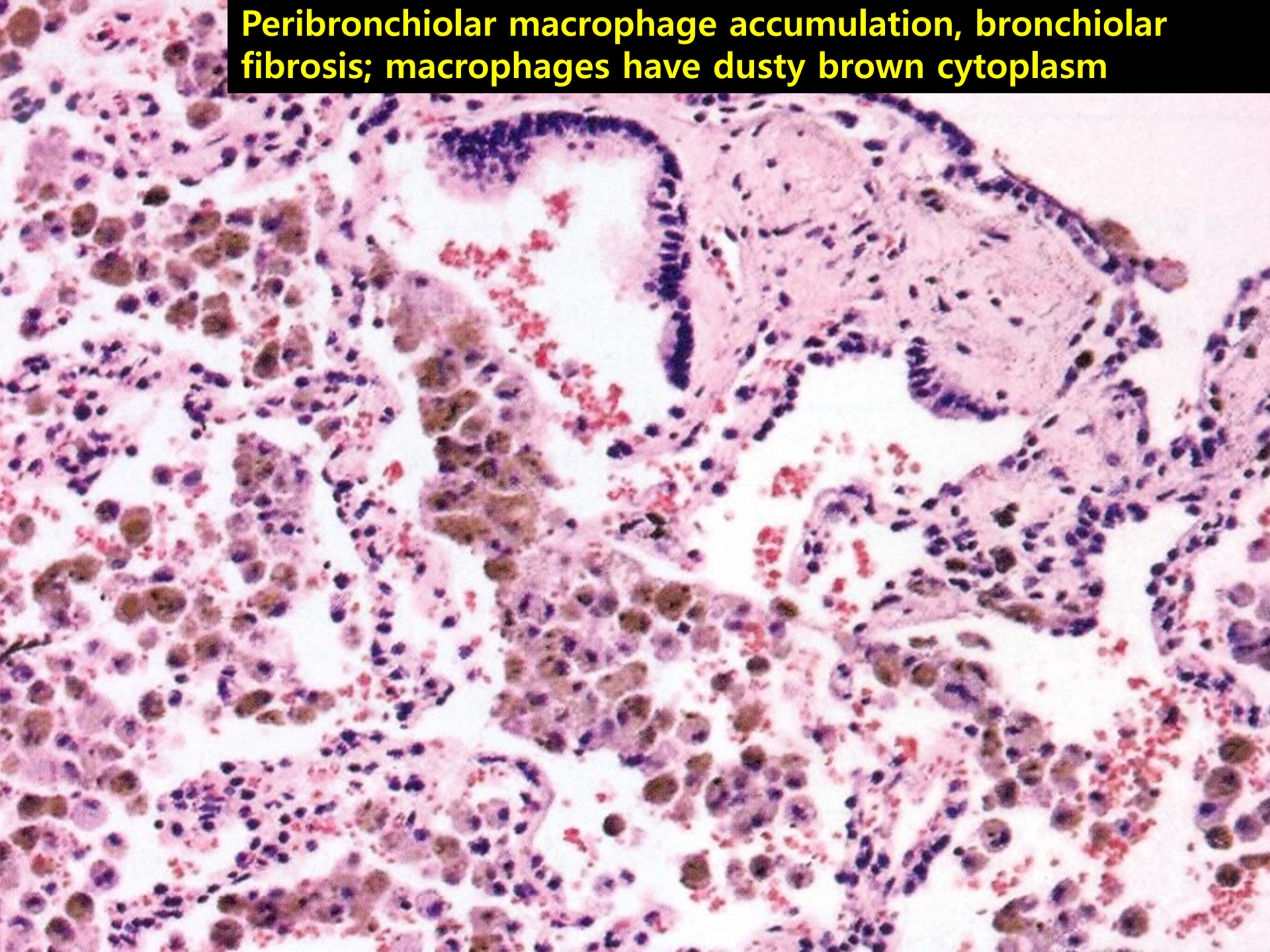
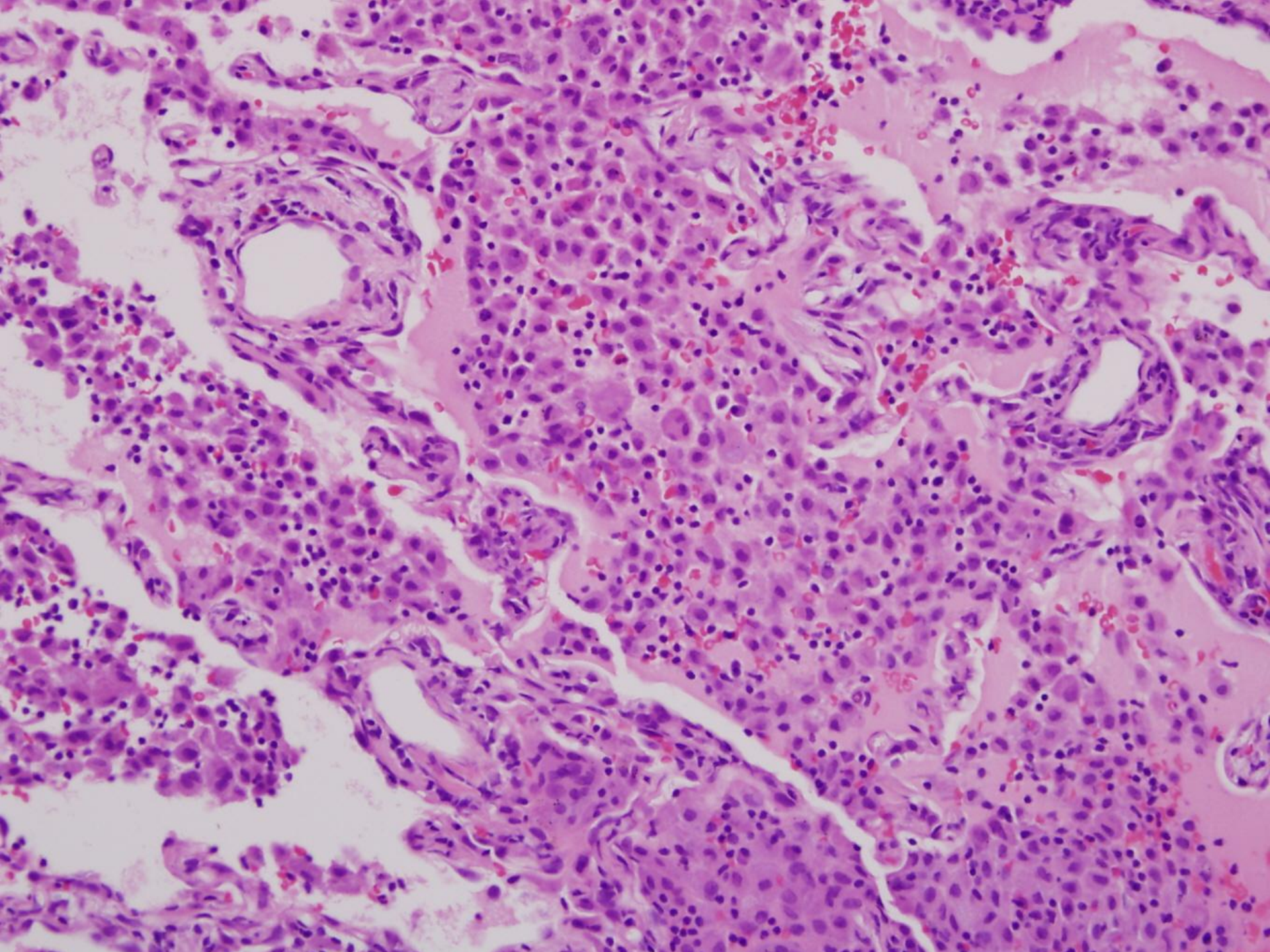

Peribronchiolar macrophage accumulation, bronchiolar fibrosis; macrophages have dusty brown cytoplasm



Smoking related ILD

Chronic ILDs strongly associated with cigarette smoking	Respiratory bronchiolitis-associated ILD Desquamative interstitial pneumonia Adult pulmonary Langerhans cell histiocytosis
Acute ILDs related to smoking	Acute eosinophilic pneumonia Pulmonary haemorrhage syndromes
ILDs that are more prevalent in smokers	Idiopathic pulmonary fibrosis Rheumatoid arthritis-associated ILD
ILDs that may be less prevalent in smokers	Hypersensitivity pneumonitis Sarcoidosis

Eur Respir Rev 2012; 21: 207–217

Published prognosis of RB-ILD

- *CHEST 2007; 131:664–671*
  - Total 32 RB-ILD patients
    - F/U assessment was available for 25 patients
  - Median follow-up of 7.0 years

Overall Outcome

Variables	No.	Better	Worse	Unchanged	p Value
Patient's overall subjective assessment — number (%)	25	7 (28)	11 (44)	7 (28)	0.56 *
Symptoms					
Cough	24	8 (33)	6 (25)	10 (42)	0.65
Sputum	24	6 (25)	4 (17)	14 (58)	0.03
Dyspnea	24	8 (33)	6 (25)	10 (42)	0.79
Dyspnea score	24	5 (21)	15 (63)	4 (16)	0.01
Physiologic assessment					
Spirometry	19	2 (11)	9 (47)	8 (42)	0.12
DLco	12	2 (17)	3 (25)	7 (58)	0.27
P(A-a)O2	9	3 (33)	5 (65)	1 (11)	0.32

* none of the comparisons were statistically significant

- Symptomatic and physiologic improvement occurs in only a minority of patients regardless of smoking cessation or immunosuppressive therapy
- 75% of patients are expected to survive ≥7 years

Comparison of Published RB-ILD Cases

	Myers et al	Yousem et al	Moon et al	Ryu et al	Current Study
Years of enrollment	1972-1984	Before 1989	1980-1998	1990-2001	1982-1999
Cases	6	17	6	12	32
Pack-yr	12-70 (38)	7-75 (30)	21-80 (54)	3-75 (29)	11-126 (39)
Patients treated with steroids	3		3	11	15
Patients who quit smoking	1	15	6	6	18
Follow-up, mo	14-66 (38.4)	1-240 (66.8)	6-89 (37.5)	11.8±16.5	25-169 (84)
Overall outcome	6	16	6	12	25
Improved or stable	6	16	5	11	14
Worse or deceased	0	0	1	1	11

Reported prognosis of DIP

- *NEJM 1978; 298: 801–9*
  - 40 patients with DIP
  - 26/40 of patients showed disease progression
  - 61% of patients with DIP responded to treatment (steroid)
  - the 5-year mortality 4.8%

- In other literatures
  - Reported mortality 6–30%

Reported prognosis of DIP

- *CHEST 1996; 110:378-82*
  - DIP patients (total n=11)
  - Treatment
    - 9 patient : corticosteroid
    - 1 patient : corticosteroid + cyclophosphamide
    - 1 patient : corticosteroid + azathioprine
  - Outcome (CT image analysis)
    - only two patients showed progression

Reported prognosis of DIP/RB-ILD

CHEST 2005; 127:178–184

Characteristic	DIP (n = 23)	RB-ILD (n=12)
Treatment		
None	2 (9)	1 (8)
Corticosteroids	21 (91)	11 (92)
Smoking cessation†		
Yes	4 (27)	4 (40)
No	11 (73)	6 (60)
Response to corticosteroid		
Subjective improvement	5 (24)	6 (55)
Objective improvement	7 (33)	7 (64)
Final clinical outcome‡		
Improved	1 (5)	3 (25)
Stable	12 (63)	8 (67)
Worsened	1 (5)	1 (8)
Dead	5 (26)	0 (0)

‡Final clinical outcome using the American Thoracic Society criteria

Treatment for RB-ILD/DIP

- RB-ILD
  - usually do not need any specific treatment other than smoking cessation if considering a good survival
  - In case of progression → steroid

- DIP
  - No better prognosis than expected in the past
  - smoking cessation + corticosteroid + ?
  - In case of progression → Consider lung transplantation