

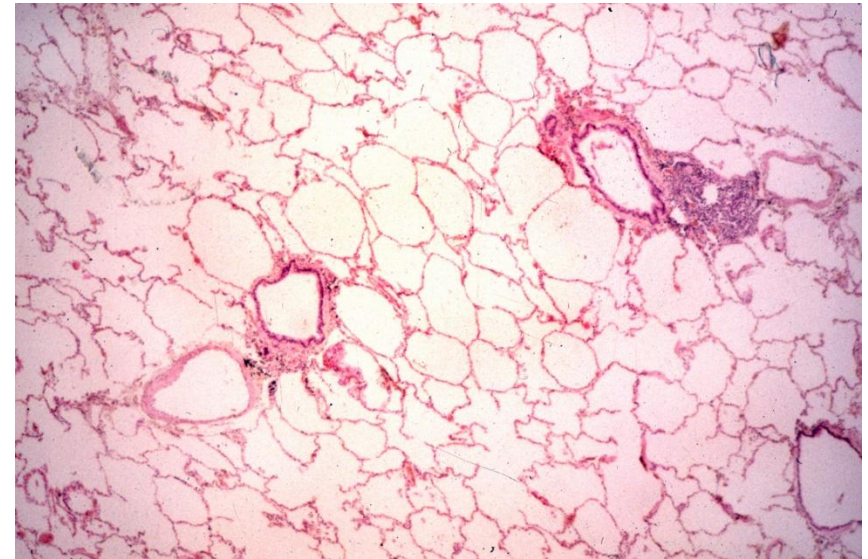
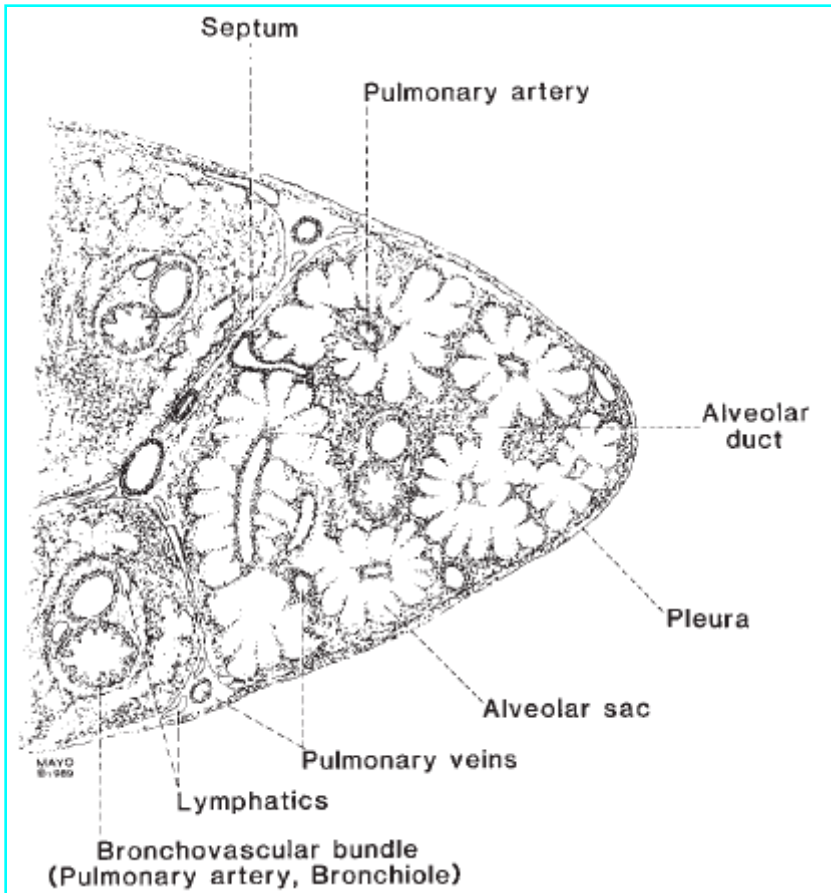
Comprehensive diagnosis of ILD: A multidimensional approach

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Interstitium



Interstitium

: space between the epithelial & endothelial basement membrane



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- Cases
- Clinical Evaluation
- Physical examination
- Laboratory Testing
 - Blood testing
 - PFT
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 - Bronchoscopy
 - Lung Biopsy
- Diagnostic Process



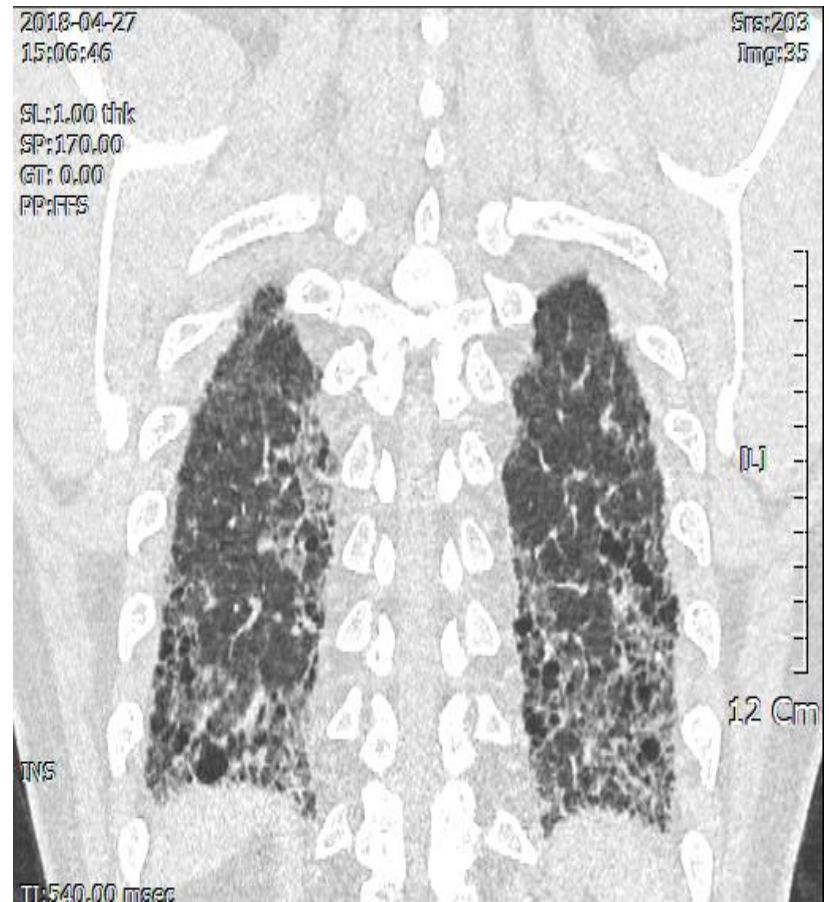
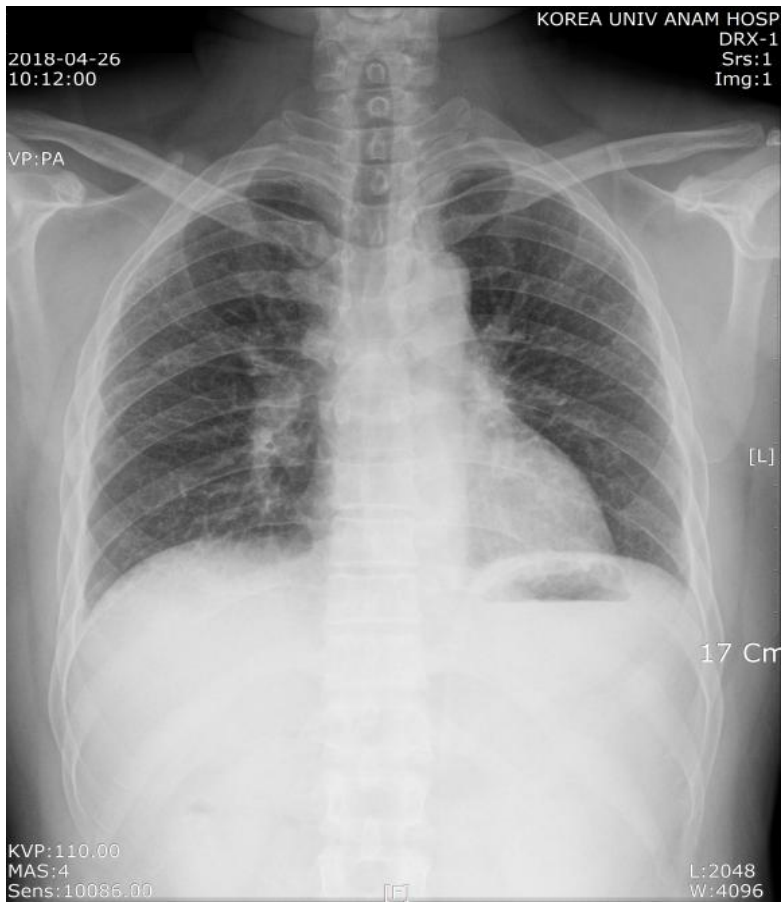
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Case 1

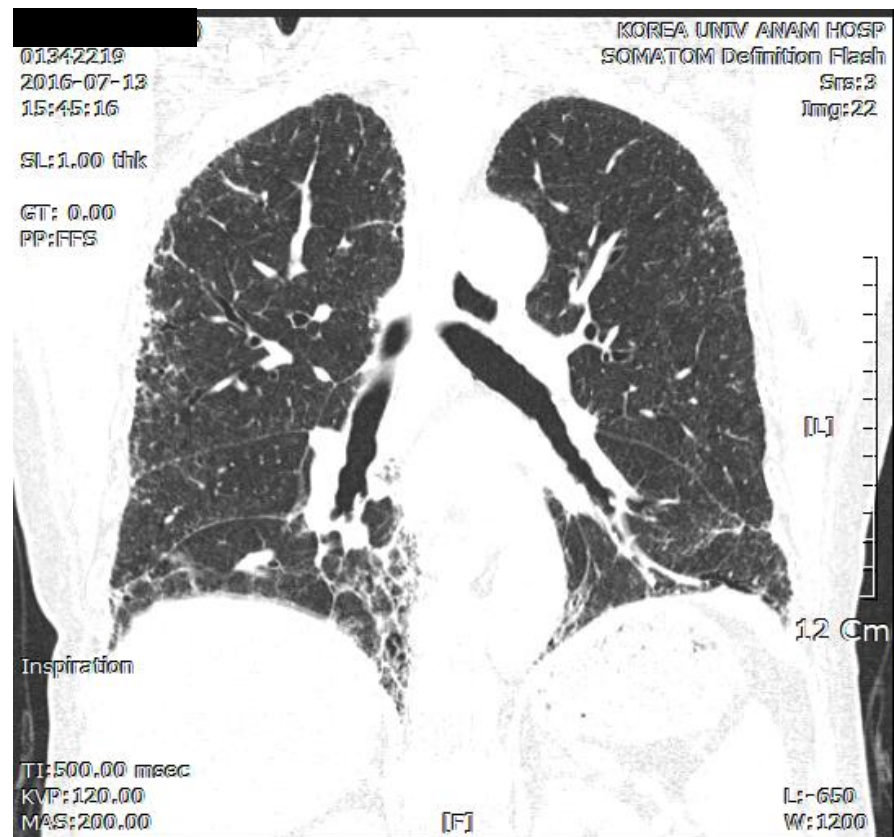
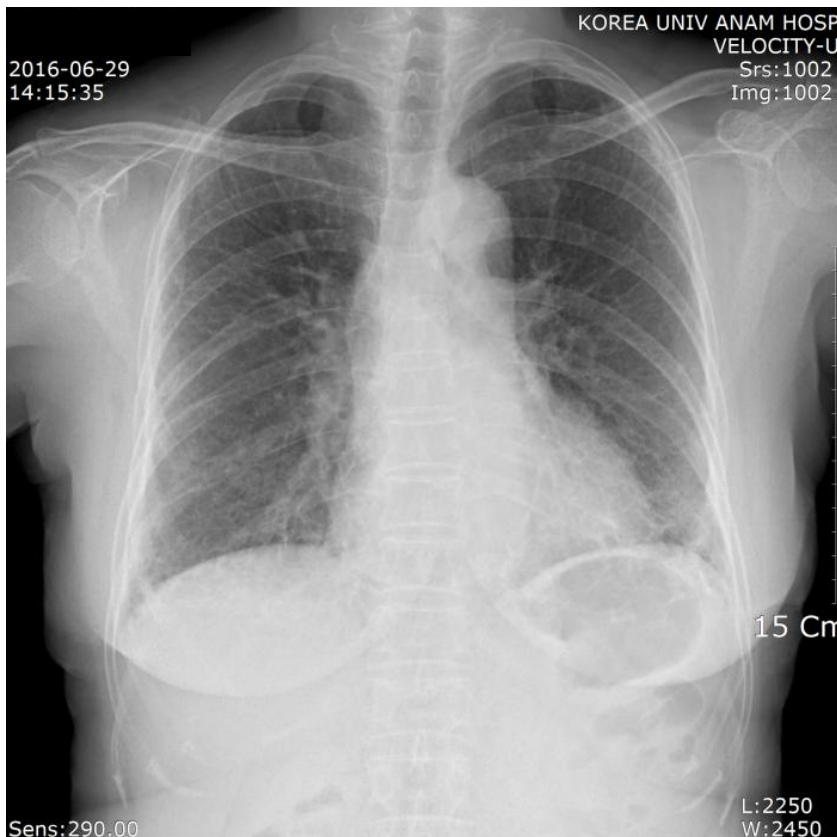
- M/ 62
- CC: cough, sputum, dyspnea
- 한약방
- ex smoker : 10년 전 중단
- PHx : DM/HTN/TBc/hepatitis(-/+/-/-), 협심증(+)
- ROS : C/S(+/+), dyspnea, mMRC 2
arthralgia(-), dry mouth/eye(±/-), Raynaud phenomenon(-)
skin rash(-), photosensitivity(-)
- P/Ex : whole lung inspiratory crackles(+)
- Lab : FANA: 1: 160 → ENA profile: negative
ANCA, C3,C4, Anti-ds DNA, Ig A/M/G : negative





Case 2

- F/ 71
- CC: cough, sputum, dyspnea
- PI : 2006년 exertional dyspnea로 내원하여 VATS lung Bx 시행,
UIP pattern 소견으로 IPF 진단 후 특별한 치료 없이 local f/u 중
호흡기 증상 악화되어 내원
- 식당
- Never smoker
- PHx : DM/HTN/TBc/hepatitis(-/-/-/-)
- ROS : C/S(+/+), dyspnea, mMRC II
arthralgia(-), dry mouth/eye(-/-),
Raynaud phenomenon(-)
skin rash(-), photosensitivity(-)
- Lab : FANA, ANCA, C3,C4, Anti-ds DNA, Ig A/M/G
RF/anti CCP
: All negative

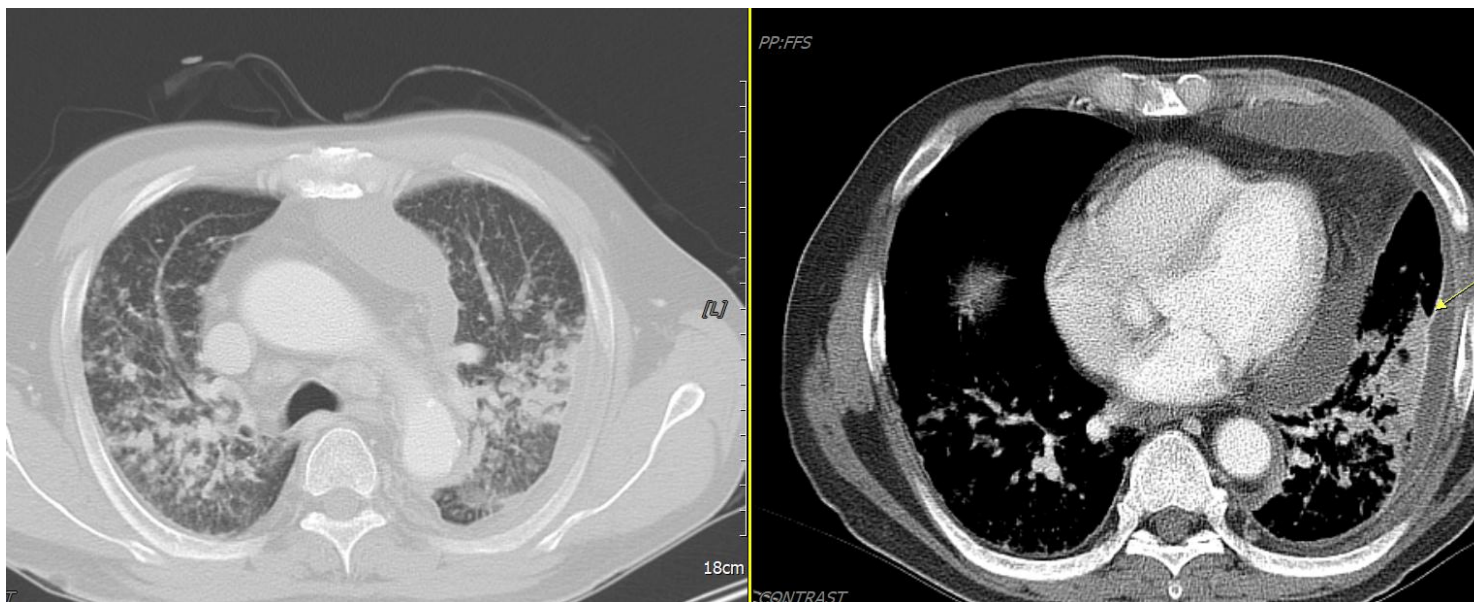


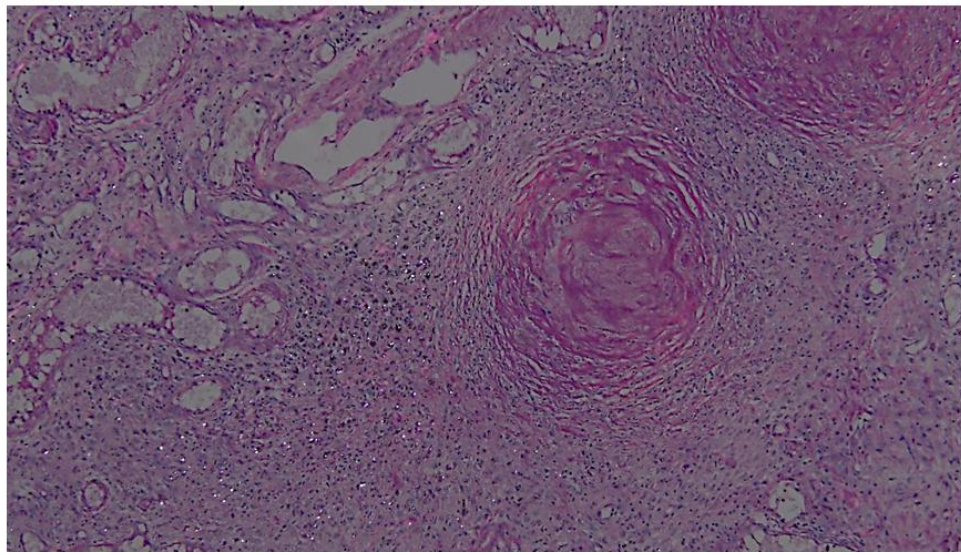
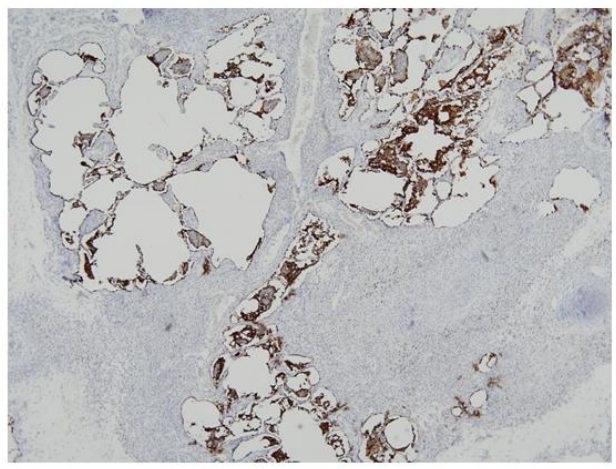
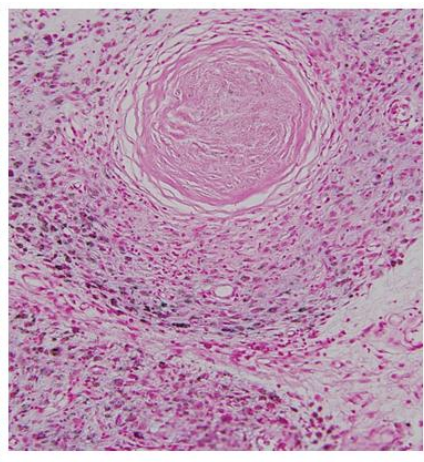
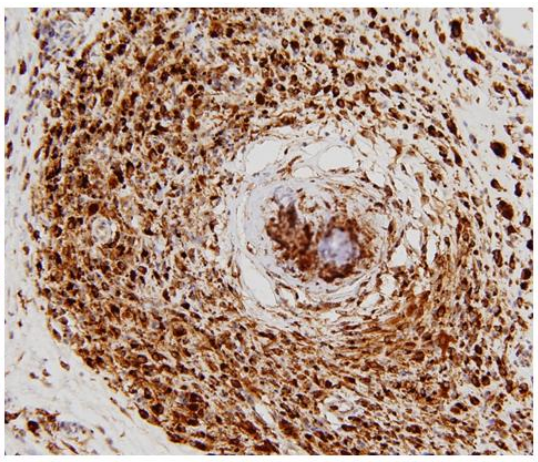
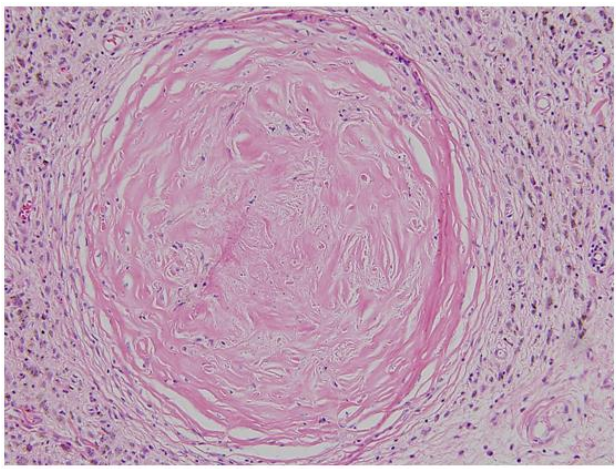


- 2016.7월부터 Pirfenidone 투여하면서 stable 하게 지내던 중 2017년 겨울 arthralgia 발생하고, RF/ anti CCP (+) 로 conversion 되어 본원 류마티스 내과에서 RA 진단 됨
- Final Dx: RA-ILD (UIP pattern)
- Plan : pirfenidone 중단 후 추적 관찰

Case 3

- M/ 62
- CC: dyspnea, pleuritic chest pain
- PI : 3주 전부터 dyspnea 발생, 내원 10일 전부터 Lt pleuritic chest 발생하여 내원
- 벼루 공예 장인

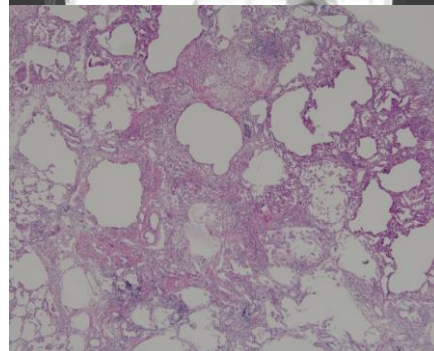
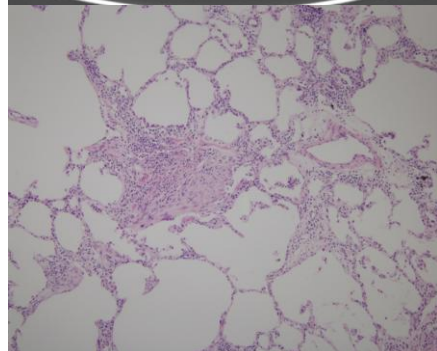




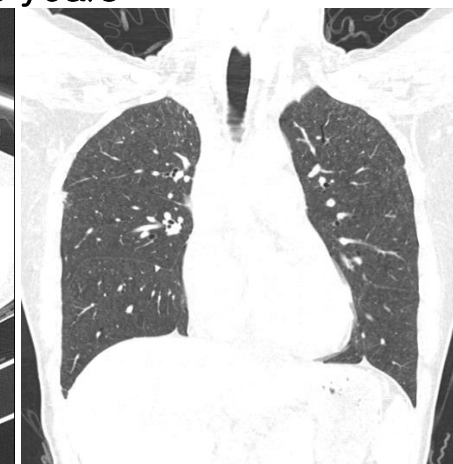
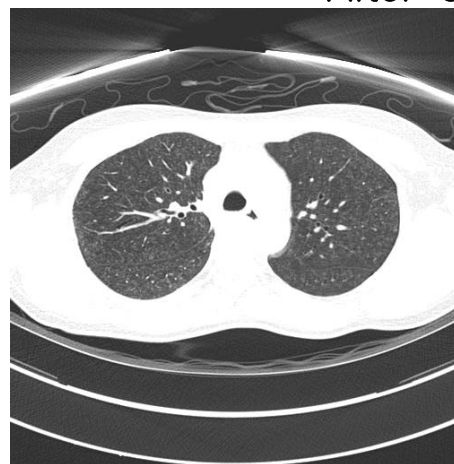


Case 4

- F/ 35, pregnant
- CC: Cough, dyspnea, mMRC 3 (onset: 3 weeks ago)



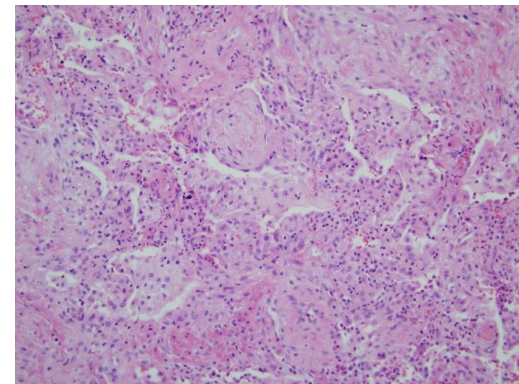
After 3 years





Case 5

- M/ 57
- CC: Fever
- PI : 3년 전 Colon ca로 수술 후 f/u 중 recur 소견으로 FOLFOX(oxali, 5-FU, LV)으로 항암제 시작
4C, #1 oxaliplatin 투여 중 fever 발생하여 항암제 중단 후 fever 호전되면 나머지 항암제 (5-FU, LV)을 투여하는 과정을 8C 시행 후 F/U CT에서 이상 소견으로 의뢰





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Clinical Evaluation

Symptoms

- Dyspnea
- Cough, hemoptysis, wheezing
- Associated symptoms

Medical history

- medications/ comorbidity (CTD)

Smoking history

- ever vs. never / how much


Exposure history

- home / work / avocational/infectious

Family history

- pulmonary disease/ autoimmune disease/ other

Duration of ILD
Acute (days to weeks)
AIP, AEP, Nonfibrotic HP, COP
Subacute (weeks to months)
Sarcoidosis, drug induced ILD, COP, CTD-ILD, alveolar hemorrhage
Chronic (months to years)
IPF, sarcoidosis, fibrotic HP



CHEST FOUNDATION | **Boehringer Ingelheim**

CHEST Interstitial and Diffuse Lung Disease Patient Questionnaire

- How often do you cough? (Do not include clearing your throat)
 - Not at all, or only rarely
 - Occasionally, but not bothersome
 - Most days
 - Often or in severe attacks that interfere with activity
- How long have you been coughing? ___ Months ___ Years ___ Not applicable
- Do you cough at night? Yes No

3a. If you cough at night, does it awaken you? Yes No
- The cough produces: (Check all that apply)
 - No phlegm Phlegm Blood Don't cough
- Check the single number that describes the point at which you became short of breath:
 - ___ 1. I am not troubled with breathlessness except with strenuous exercise.
 - ___ 2. I get short of breath when hurrying on level ground or walking up a slight hill.
 - ___ 3. I walk slower than people of my age because of breathlessness or I have to stop from breath when walking on my own pace.
 - ___ 4. I stop for breath after walking about 100 yards (90 meters) (or after a few minutes).
 - ___ 5. I am too breathless to leave the house or breathless on dressing or undressing.
- When did your shortness of breath begin? _____
- Has a doctor ever told you that you have:

	YES	NO	Mononucleosis	YES	NO	Pneumonia	YES	NO
Heart disease	<input type="checkbox"/>	<input type="checkbox"/>	Hepatitis B or C	<input type="checkbox"/>	<input type="checkbox"/>	Asthma	<input type="checkbox"/>	<input type="checkbox"/>
Thyroid disease	<input type="checkbox"/>	<input type="checkbox"/>	Tuberculosis	<input type="checkbox"/>	<input type="checkbox"/>	Blood clots	<input type="checkbox"/>	<input type="checkbox"/>
Diabetes	<input type="checkbox"/>	<input type="checkbox"/>	Kidney disease	<input type="checkbox"/>	<input type="checkbox"/>	Pulmonary hypertension	<input type="checkbox"/>	<input type="checkbox"/>
Sinus disease	<input type="checkbox"/>	<input type="checkbox"/>	Kidney stones	<input type="checkbox"/>	<input type="checkbox"/>	Heart failure	<input type="checkbox"/>	<input type="checkbox"/>
Stroke	<input type="checkbox"/>	<input type="checkbox"/>	Blood in urine	<input type="checkbox"/>	<input type="checkbox"/>	Fluid on the lungs	<input type="checkbox"/>	<input type="checkbox"/>
Seizure	<input type="checkbox"/>	<input type="checkbox"/>	Pleurisy	<input type="checkbox"/>	<input type="checkbox"/>			
Eye inflammation	<input type="checkbox"/>	<input type="checkbox"/>						
- Have you noticed any:

	YES	NO	YES	NO	YES	NO
Weight loss	<input type="checkbox"/>	<input type="checkbox"/>	Rash or change in skin	<input type="checkbox"/>	Hand ulcers	<input type="checkbox"/>
Difficulty swallowing	<input type="checkbox"/>	<input type="checkbox"/>	Foot or leg swelling	<input type="checkbox"/>	Mouth ulcers	<input type="checkbox"/>
Hearburn or reflux	<input type="checkbox"/>	<input type="checkbox"/>	Sensitivity to light	<input type="checkbox"/>	Chest pain	<input type="checkbox"/>
Dry eyes or dry mouth	<input type="checkbox"/>	<input type="checkbox"/>	Brusings	<input type="checkbox"/>	Joint pain or swelling	<input type="checkbox"/>
- Have you ever smoked, inhaled, or injected "recreational" drugs? (Include "street drugs" or crushed pills. Do not include prescription inhalers.) Yes No
- Have you smoked 100 cigarettes (5 packs) or more in your life? Yes No

If yes, Do you smoke now? Yes No

How old were you when you started? _____ years old

Average number of cigarettes per day _____ cigarettes

If you quit, How old were you when you quit? _____ years old
- Do any of your grandparents, parents, brothers, sisters, aunts, uncles, cousins, or children have any of the following lung diseases?

YES	NO	
<input type="checkbox"/>	<input type="checkbox"/>	Emphysema, Chronic Obstructive Pulmonary Disease (COPD)
<input type="checkbox"/>	<input type="checkbox"/>	Asthma
<input type="checkbox"/>	<input type="checkbox"/>	Sarcoidosis
<input type="checkbox"/>	<input type="checkbox"/>	Cystic fibrosis
<input type="checkbox"/>	<input type="checkbox"/>	Pulmonary fibrosis
<input type="checkbox"/>	<input type="checkbox"/>	Hypersensitivity pneumonitis
- Have you lived in an old house within the past 10 years? Yes No
- Does your current or past home or work place have any of the following?

YES	NO	YES	NO
<input type="checkbox"/>	<input type="checkbox"/>	Humidifier	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	Severe Asthma	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	Hot tub (jacuzzi)	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	Water damage	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	Mold	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	Animals	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	Birds (include pigeons, doves, parakeets, cockatiels, chickens, ducks, geese, pheasants)	<input type="checkbox"/>
- Have you ever had a chest X-ray or CT scan of the chest? Yes No

If yes, please indicate the earliest and most recent you can remember:

Earliest X-ray: Year ____ Where? _____

Most recent X-ray: Year ____ Where? _____

Earliest CT scan: Year ____ Where? _____

Most recent CT scan: Year ____ Where? _____
- Where have you previously lived? (Please list all locations where you lived for at least 6 months.) _____

Outside this country? (Please indicate which countries) _____



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Physical examination





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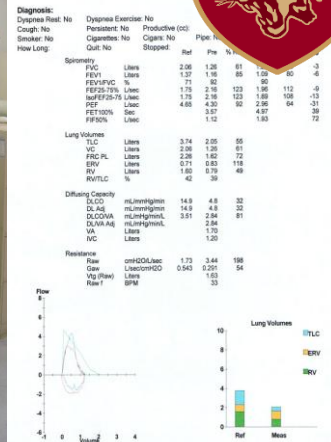
Laboratory Testing – Blood testing

- Biochemical tests to evaluate hepatic & renal function
- Hematologic test to check for evidence of anemia, polycythemia, leukocytosis, or eosinophilia
- Urinalysis
- ±hepatitis serology, HIV
- Rheumatology lab: ANA, RF, CCP, anti-synthetase Ab(Jo -1), anti-dsDNA, anti-Sm, anti-RNP, Sjogren's Ab (SS-A/B) Scleroderma Ab(Scl -70, centromere) CPK, aldolase, anti-MDA-5, overlap Abs
- Pulmonary hemorrhage lab: Anti GBM Ab, ANCA, ANA, Antiphospholipid Ab
- Serologic test for HP Ab based on potential Ag

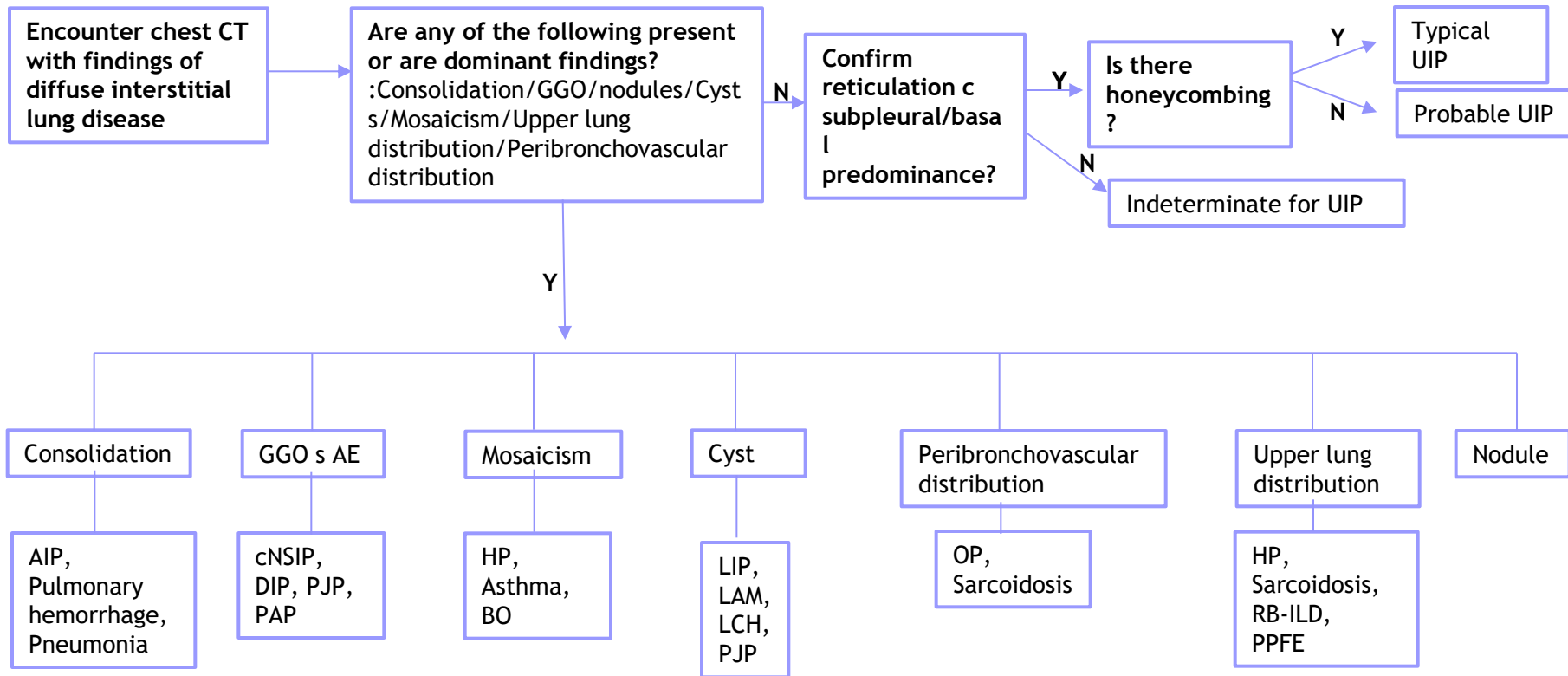


Laboratory Testing - PFT

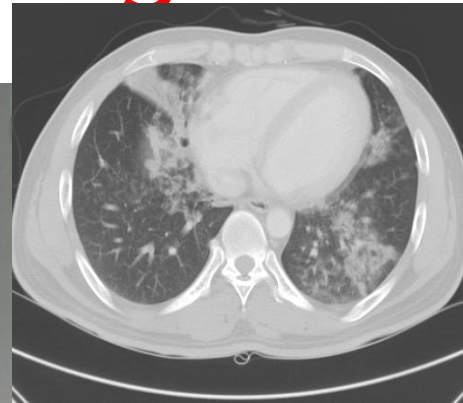
- Assessment of the severity and pattern
- Restrictive defect
 - : M/C, reductions in lung volumes \propto dz progression
- Obstructive defect
 - : Sarcoidosis, LAM/PLCH, HP, CPFE, constrictive bronchiolitis
- DL_{CO}
 - : Reduction is common, but nonspecific
 - not correlate well with dz Px, unless $DL_{CO} < 35\%$
 - Longitudinal changes to assess dz progression or regression



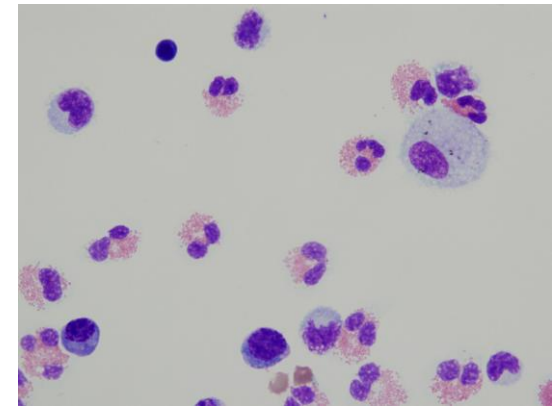
Laboratory Testing – Radiology assessment



Laboratory Testing - Bronchoscopy 1



- Acute: acute EP, DAH, malignancy, infection
- Subacute/chronic
 - : sarcoidosis, HP, PLCH, infection
- No established role in the assessment of progression/response to Tx



Laboratory Testing – Bronchoscopy 2

I. Normal Adults (Nonsmokers)		BAL Differential Cell Counts
Alveolar macrophages		>85%
Lymphocytes (CD4+/CD8+ = 0.9–2.5)		10–15%
Neutrophils		≤3%
Eosinophils		≤1%
Squamous epithelial*/ciliated columnar epithelial cells [†]		≤5%
Lymphocytic cellular pattern	Eosinophilic cellular pattern	Neutrophilic cellular pattern
>15% lymphocytes	>1% eosinophils	>3% neutrophils
Sarcoidosis	Eosinophilic pneumonias	Collagen vascular diseases
Nonspecific interstitial pneumonia (NSIP)	Drug-induced pneumonitis	Idiopathic pulmonary fibrosis
Hypersensitivity pneumonitis	Bone marrow transplant	Aspiration pneumonia
Drug-induced pneumonitis	Asthma, bronchitis	Infection: bacterial, fungal
Collagen vascular diseases	Churg-Strauss syndrome	Bronchitis
Radiation pneumonitis	Allergic bronchopulmonary aspergillosis	Asbestosis
Cryptogenic organizing pneumonia (COP)	Bacterial, fungal, helminthic, <i>Pneumocystis</i> infection	Acute respiratory distress syndrome (ARDS)
Lymphoproliferative disorders	Hodgkin's disease	Diffuse alveolar damage (DAD)

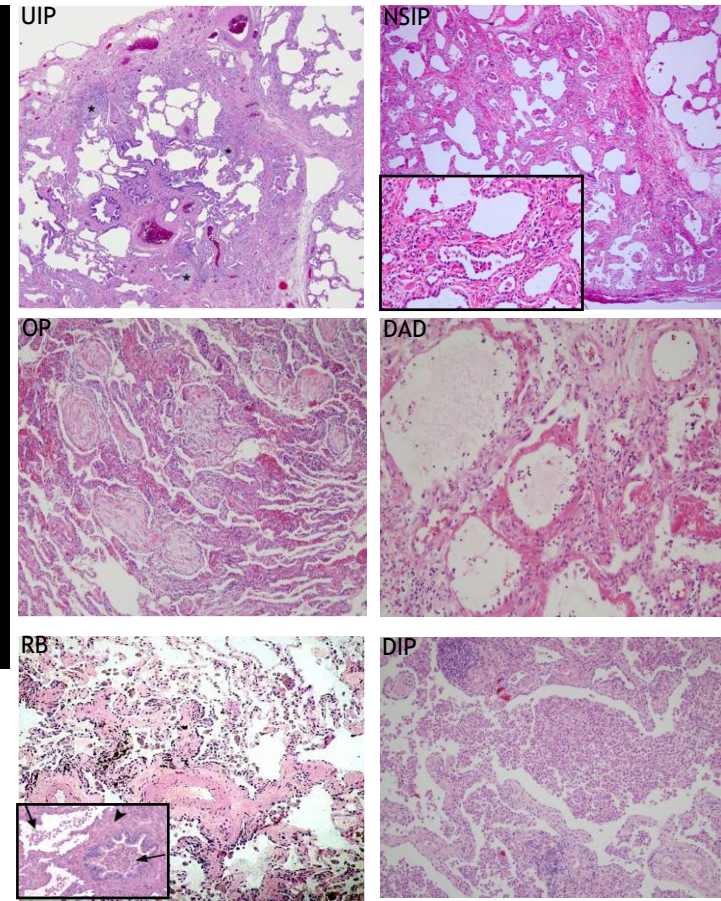
Laboratory Testing - Bronchoscopy 3

Condition	Bronchoalveolar lavage (BAL) finding
Acute interstitial pneumonia(AIP)	Neut ↑↑
Idiopathic pulmonary fibrosis(IPF)	AM ↑ Neut ↑
Desquamative interstitial pneumonia(DIP) / Respiratory bronchiolitis-ILD	AM (heavily pigmented) ↑↑
Organizing pneumonia	AM ↑, lymph ↑, Neut ↑
Eosinophilic pneumonia	Eosino > 25%
Sarcoidosis	Lymph ↑↑, CD4:CD8 ratio > 3.5
Hypersensitivity pneumonitis	Lymph ↑↑
Diffuse alveolar hemorrhage	Hemosiderin-laden macrophages, red blood cells
Diffuse-induced pneumonitis	Variable Lymph/ Neut
Pulmonary infections	Neut (suppurative, bacterial) ↑↑, Lymph (viral) ↑↑, Eosino (parasitic) ↑↑
Lymphangitic car, avelolar cell car, pul. lymphoma	Malignant cells
Pulmonary alveolar proteinosis	Cloudy BAL fluid c milky to light brown appearance, PAS+ amorphous debris
Lipoid pneumonia	Oily layer on surface of BAL fluid, lipid-laden macrophages
Pulmonary Langerhans' cell histiocytosis	Increased CD1+ Langerhans' cells > 5%
Asbestosis-related pulmonary dz	Dust particles, ferruginous bodies

Laboratory Testing – Lung Biopsy

- TBLB/C, VATS Bx, thoracotomy

**VATS wedge resection
(RUL)**



Laboratory Testing – Lung Biopsy (TBLC)

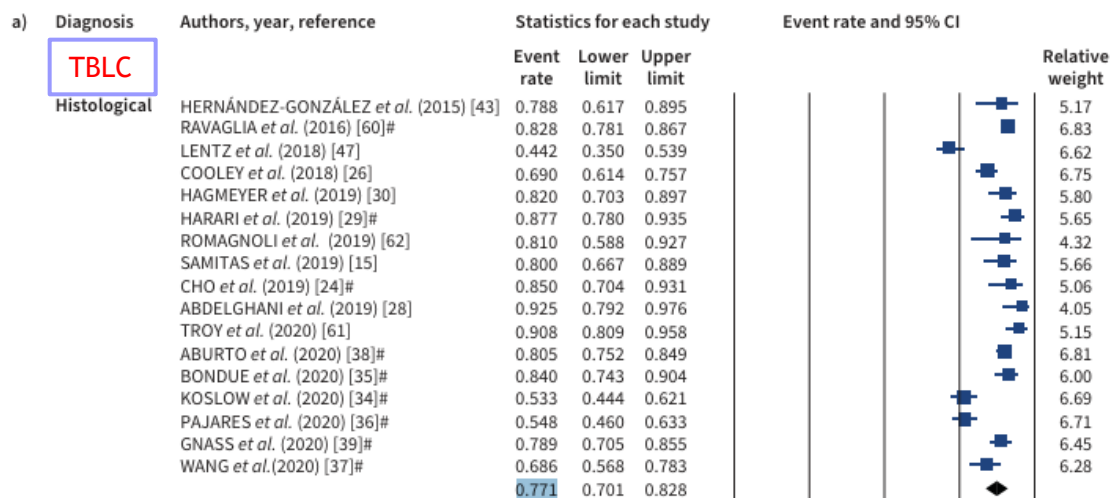
- Observational, retrospective cohort study
 2011.3 -2017. 9, Single center(Italy), 699 ILD pt
 Deeply sedated, Intubated c a rigid tracheoscope
 under fluoroscopic guidance + Fogarty balloon for bleeding
 → 3.3 Bx/pt, 4.57mm (shortest axis)
 Diagnostic yield: 87.8(pathological) ~90.1% (MDD)
 ↑ different sites(than 1 site)
 ↓ FVC <50%, DLCO <35%
- Cx: PNx(19.2%, 134) → chest tube (70%, 94)
 bleeding(12.4%, 87) (mild 29/moderate 53/severe 5)
 death (0.4%, 3)

Laboratory Testing – Lung Biopsy (TBLC)

- CHEST Guideline and Expert Panel Report
 - TBC can be used to provide Bx for MDD Dx (weak, very low quality)
Diagnostic yield: 80% for TBC vs 95% for SLB
 - At least 2 different sites (weak, low quality)
 - Bx with the tip of the cryoprobe located 1cm from the pleura
(consensus-based statement)
 - Use of fluoroscopy (consensus-based statement)
 - Bronchial blocker either through an endobronchial tube
or rigid bronchoscope(consensus-based statement)
 - Small cryoprobe(1.9mm) rather than a large cryoprobe(2.4mm)
(consensus-based statement)

Laboratory Testing - Lung Biopsy (TBLC)

- 2010.10~2020.10, 43 Studies(n=4550), TBLC(n=2824), SLB(n=1814)



TBLC

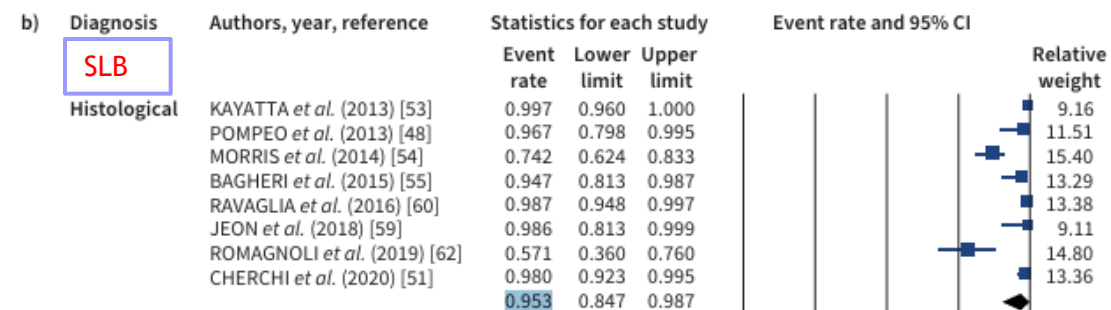
- Bleeding
 - mild (29.9%)
 - moderate (9.1%)
 - severe (1.6%)
- PNX 9.2%
 - (chest drainage 5.6%)

SLB

- recurrent/persistent PNX 5.5%
- pneumonia/empyema 2.1%

30-day mortality

TLBC 0.6% vs SLB 1.7%





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Diagnostic Process

Perform Hx & P/Ex, including assessment of:

- Sx onset (acute/subacute/chronic)
- Occupational & Environmental exposure Hx including smoking hx
- Hx of CTD
- Family Hx
- Medication Hx
- Hx of RTx/Cancer
- Signs of systemic inflammation & other extrapulmonary dz

Imaging: CXR, CT, compare results with any prior imaging to assess evolution or progression

PFT: compare results with any prior PFT to assess evolution or progression

Lab test:

- CBC, basic metabolic panel, LFT, U/A
- ANA, RF, CCP,
- appropriate other serologies (ANCA, CPK, Aldolase, myositis/antisynthetase Ab Panel, ds DNA, SSA/SSB, anti SLC 70/anti centromere)



Are there any likely environmental or iatrogenic etiologies?

(drug toxicities (bleomycin, immune checkpoint inhibitors..), RTx,
Inhaled organics (hay, grains, humidifiers, indoor pool, feathers, molds),
Inhaled inorganics(silica, asbestos, beryllium, coal)

Y

N

- Remove identified cause
- Temporary systemic glucocorticoid Tx may be appropriate, depending on Dz severity & etiology
- Is there clinical recovery?

Y

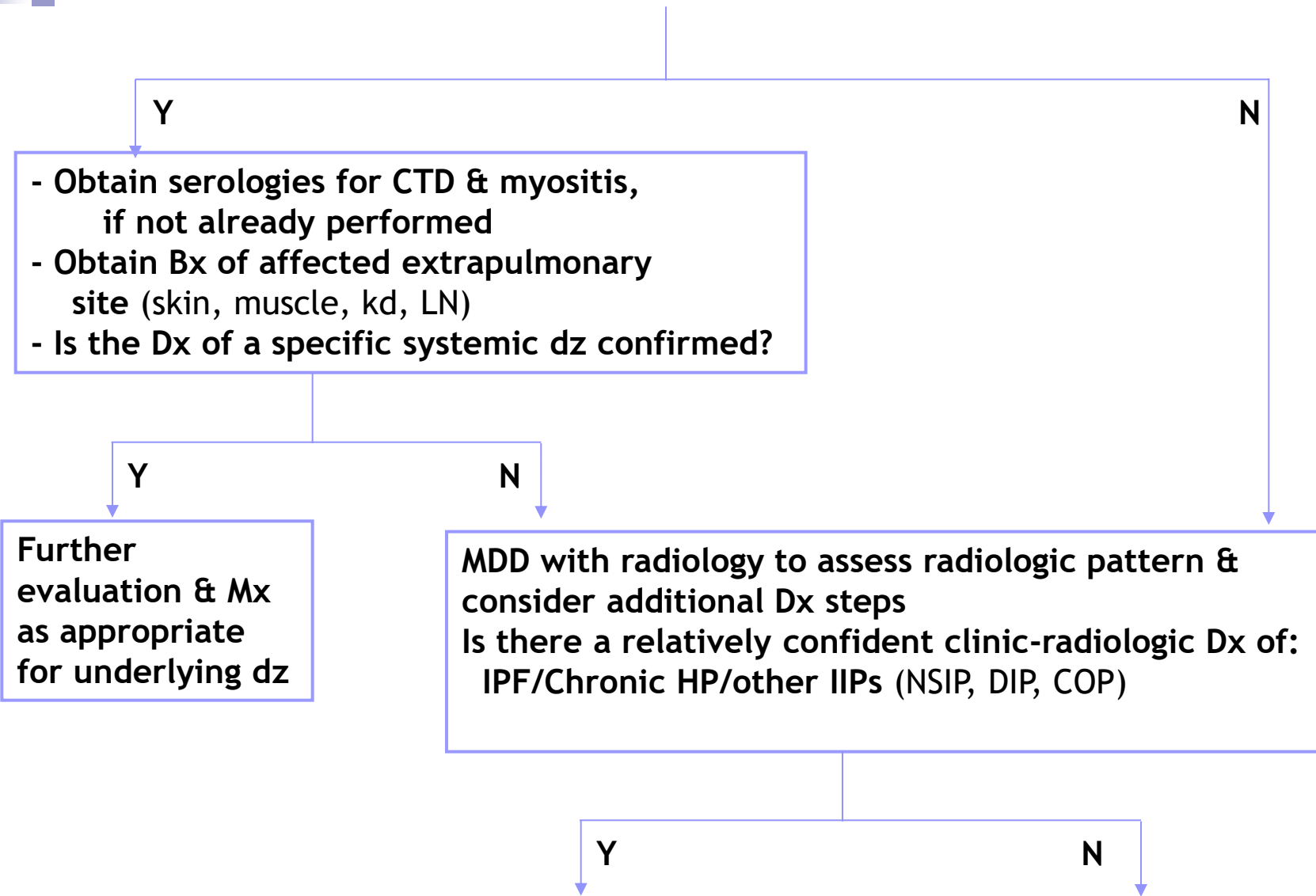
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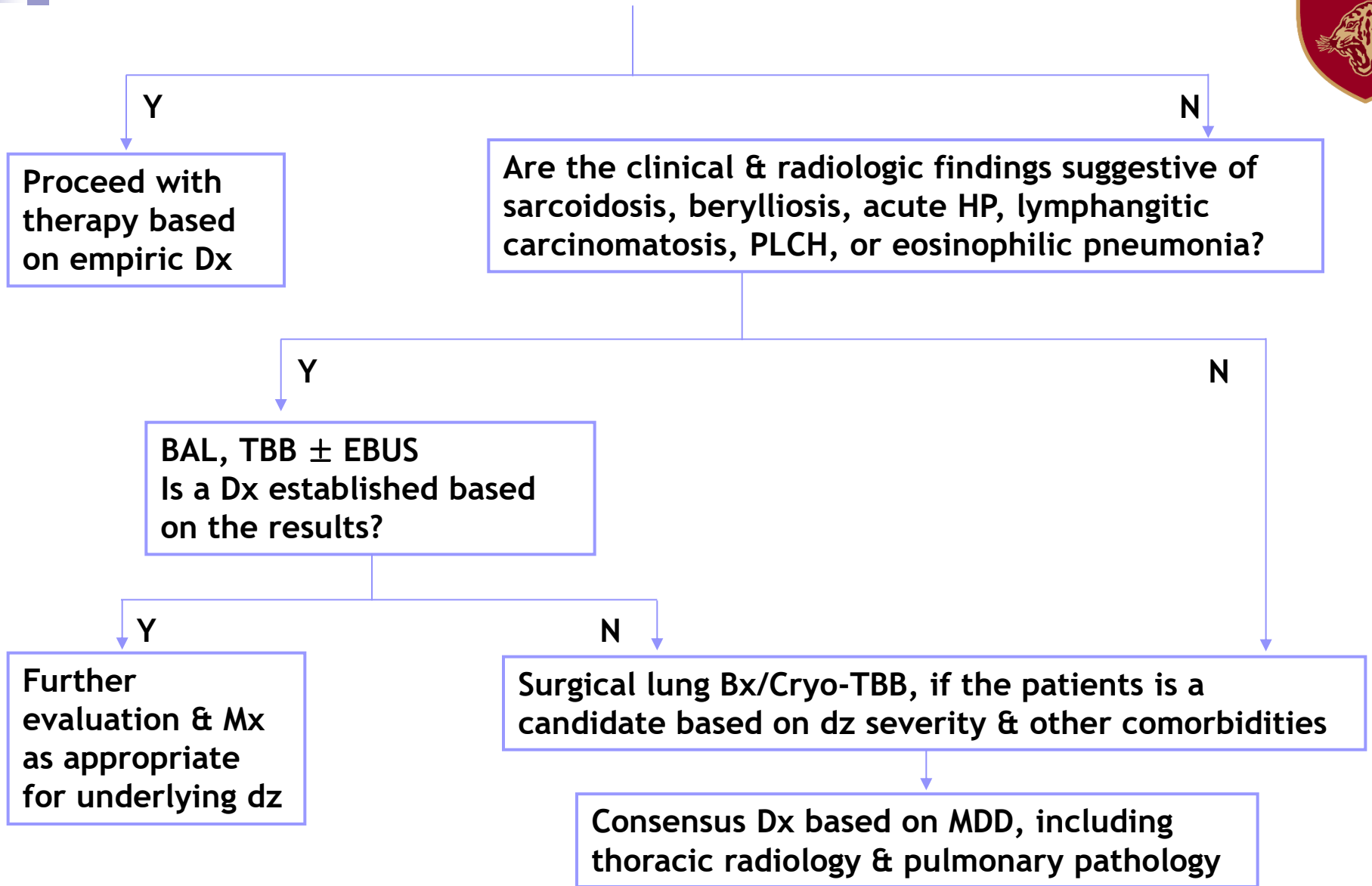
No further
Diagnostic steps
are necessary

Does the patient have suspected extrapulmonary dz?
(CTD, vasculitis, extrapulmonary sarcoidosis)

Y

N





Summary

- A history, physical examination, autoimmune serologies, and Chest CT are essential components of evaluation that should be performed in all pts presenting with a new ILD.
- BAL cellular analysis has a role in specific situations.
- The most important distinction in ILD classification is between IPF and non-IPF ILDs.

Summary

- All available data should be considered within a multidisciplinary discussion, which is considered the gold standard for ILD Dx and can provide additional information on the anticipated disease behavior and expected response to therapy.



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