Hypersensitivity pneumonitis: perspectives in diagnosis and management

2019. 03. 16

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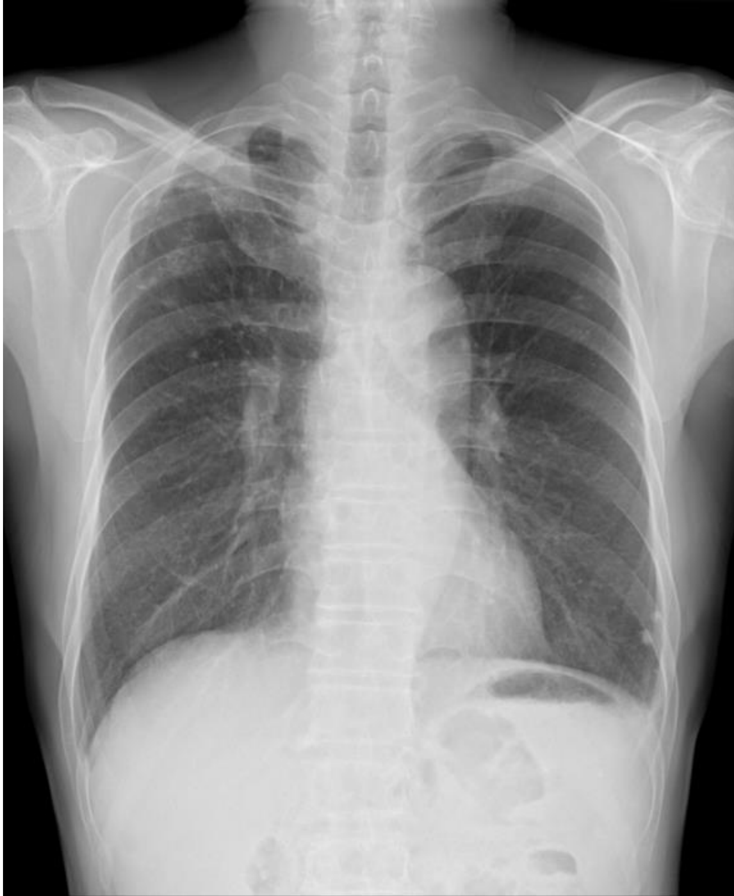
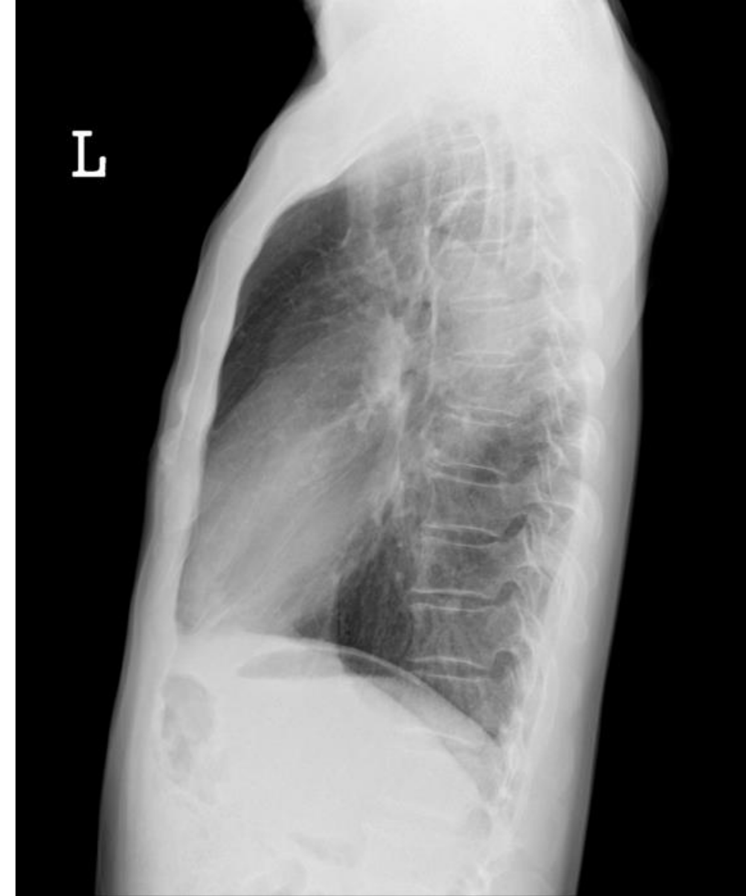
Case 1

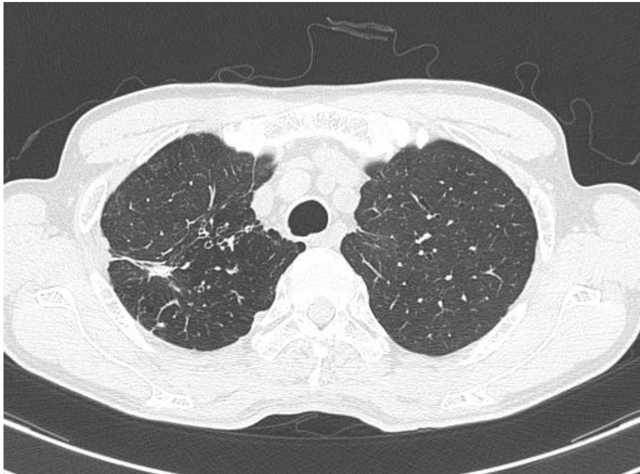
- M/ 66
- CC: Dyspnea, mMRC 2 (onset: 20 days ago)
- PI : gastric cancer로 본원 f/u 중인 분으로
  최근 20일 전부터 발생한
  호흡 곤란을 주소로 내원
- 애너멜 코팅 공장 (중국, 내원 2개월 전부터)
- smoker : 1* 40 PY
- 애완동물/가구(-/-)
  중국 거주, 2달 전에 최근 공장으로 이직

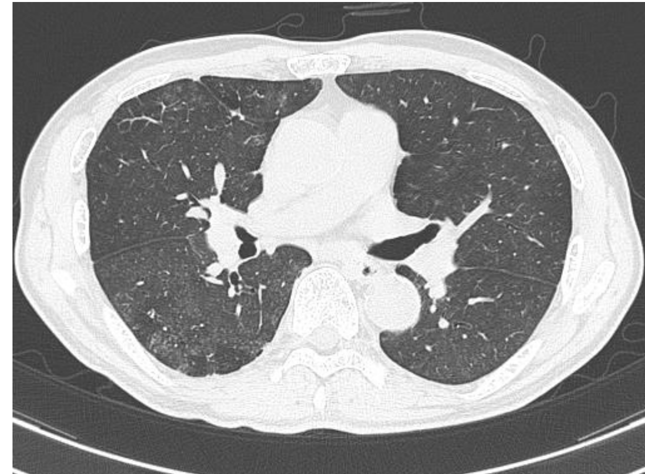
CXR (2014.2.9)

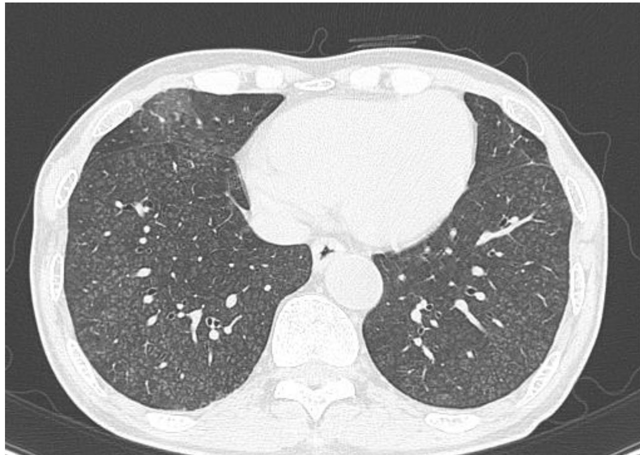


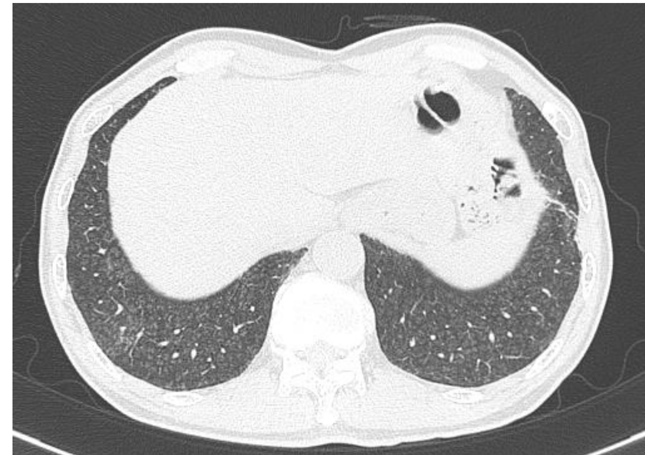


Chest CT (2014.1.28)









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Bronchoscopy

- BAL Fluid (RML, lateral segment)

  : clear

  WBC: 390 (/μL)

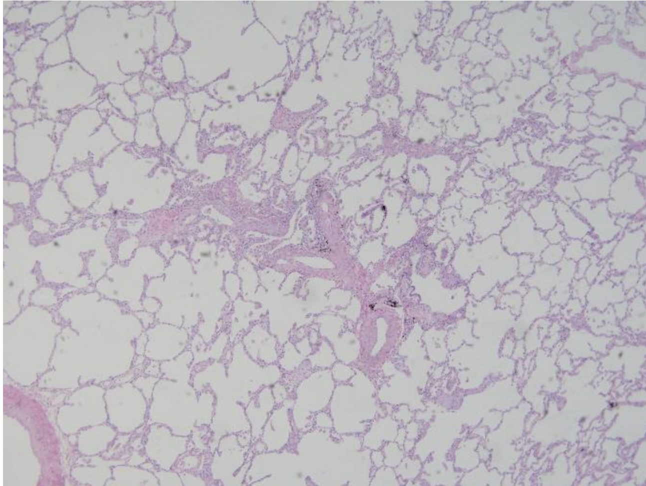
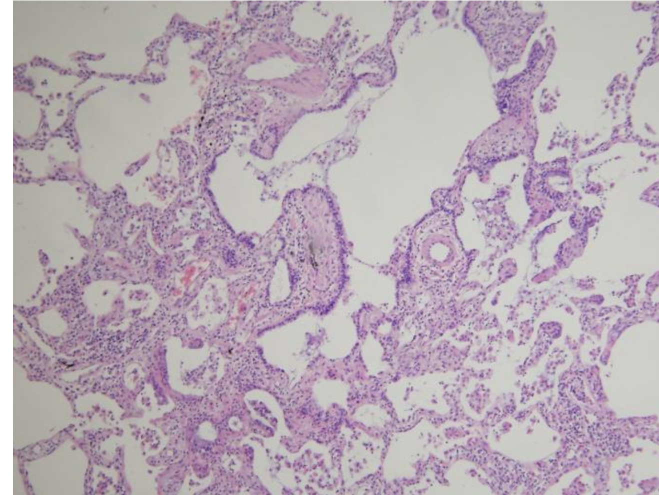
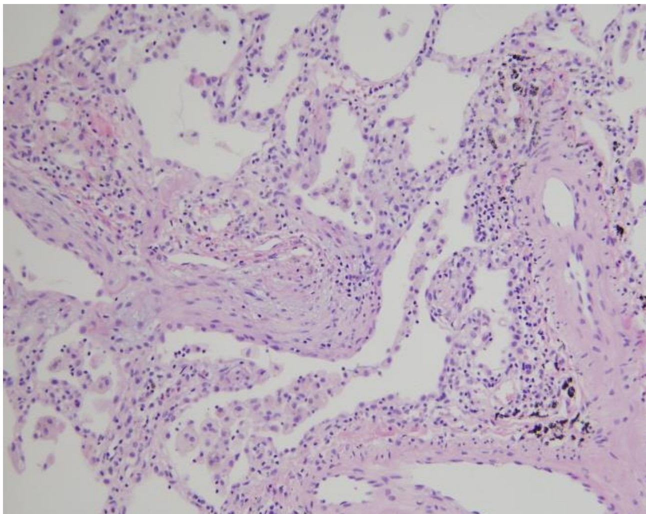
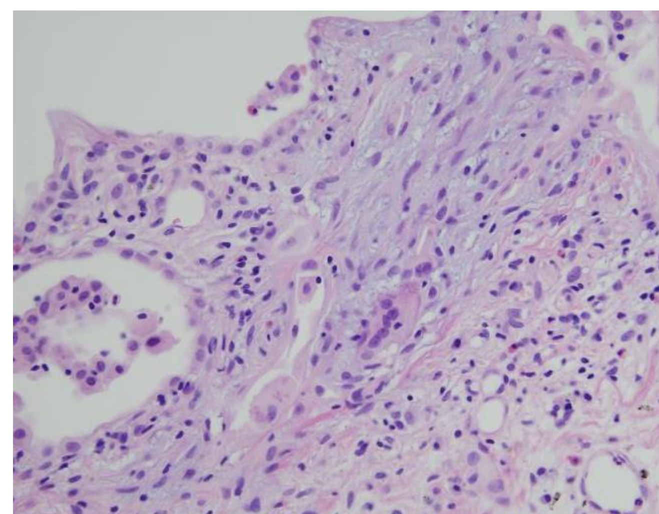
  (Neutro: 1%, Lympho: 82%, Eosino: 1%,

  Macrophage: 12%)

  CD4/CD 8 ratio : 0.07

  G/S, AFB, Fungus, Virus: negative

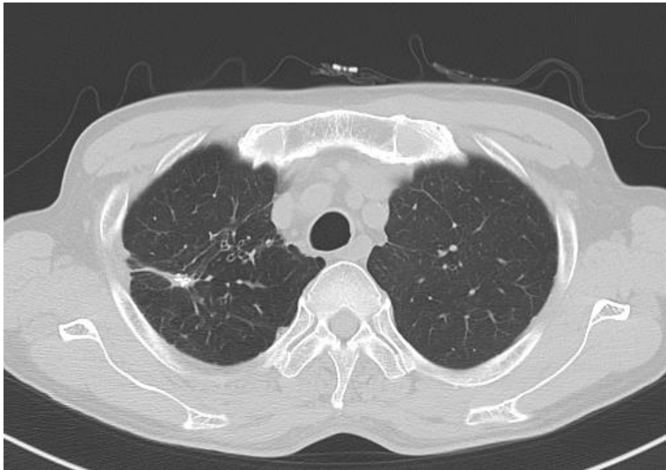
VATS lung Bx(2014.02.12)

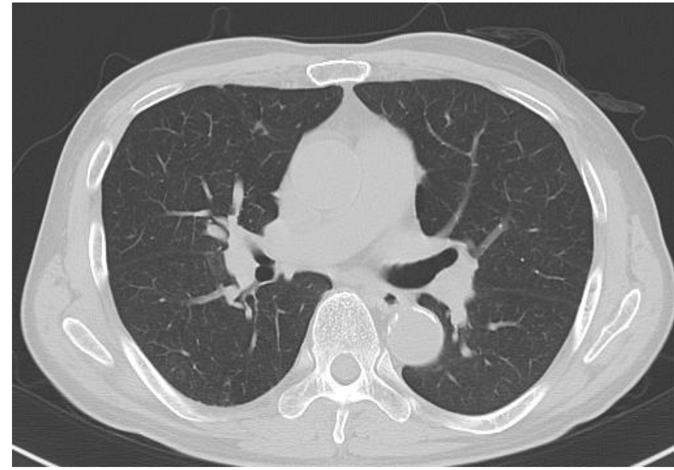





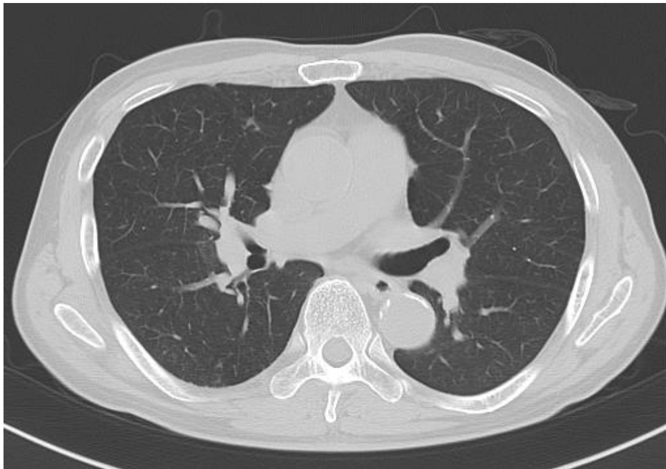
Progress

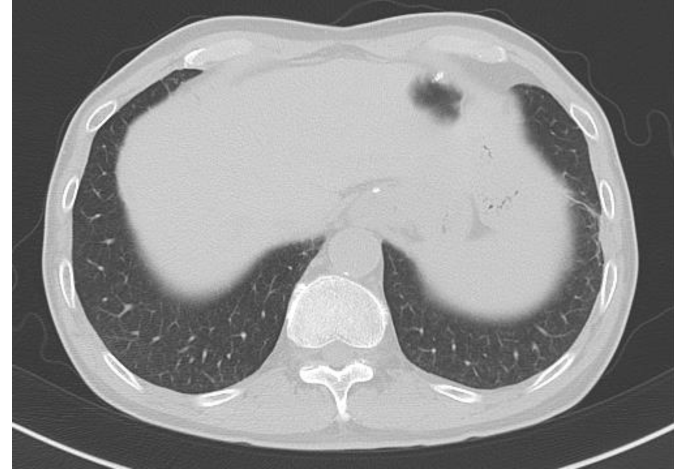
- Dx : HP, acute(subacute)
- Tx: 이직 고려
  solondo 0.5mg/kg start

F/U Chest CT (2014.5.13)









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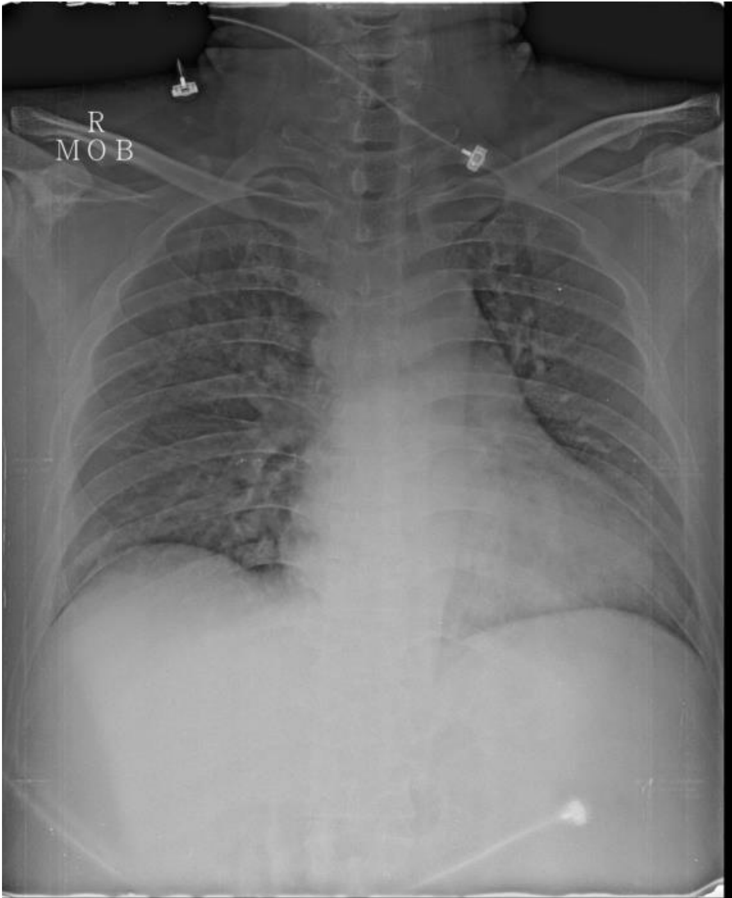
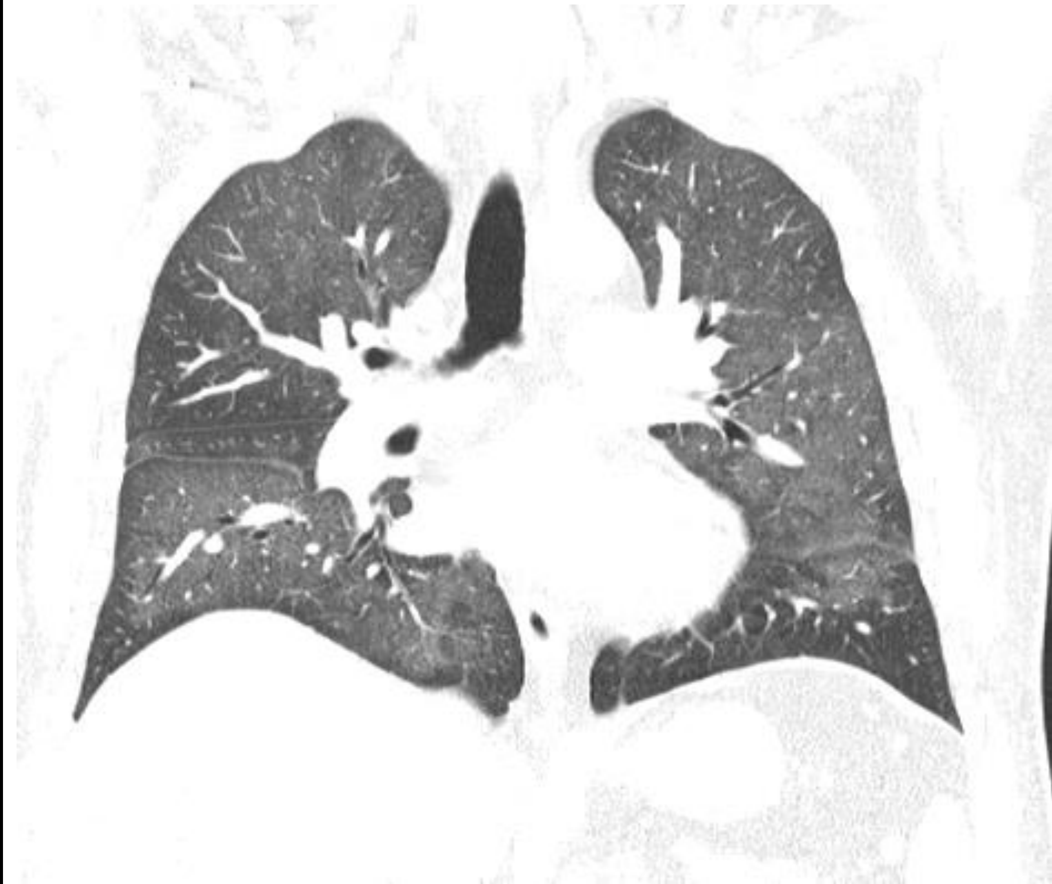
Case 2

- M/ 48
- CC: Dyspnea, mMRC 4 (onset: 1 hr ago)
- PI : 내원 전일 보트 밑바닥에 spry type의 water-proof coating paint로 30분간 작업 후 내원 1시간 전부터 발생한 호흡 곤란으로 내원
- Ex smoker : 4년 전 중단 ← 1* 20 PY
- Stomach ca로 4년 전 수술
  Bipolar, panic disorder로 본원 정신과 f/u 중
- ABGA(R/A): 7.453-30.9-57.9-21.8-91.4

CXR & CT (2018.6.4)





Bronchoscopy (2018.6.5)

- BAL Fluid (RML, medial segment)

  : clear

  WBC: 550 (/μL)

  (Neutro: 62%, Lympho: 7%, Eosino: 1%,

  Macrophage: 30%)

  G/S, AFB, Fungus, Virus: negative

Bronchoscopy (2018.6.7)

- BAL Fluid (RML, medial segment)

  : clear

  WBC: 40 (/μL)

  (Neutro: 5%, Lympho: 42%, Eosino: 1%,

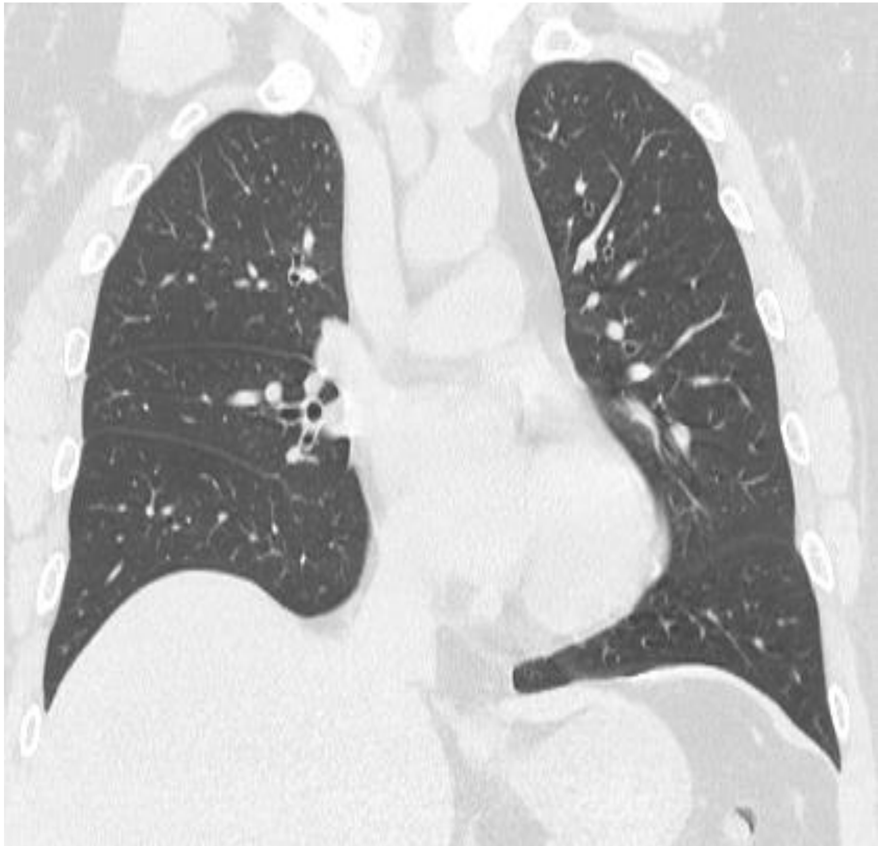
  Macrophage: 51%)

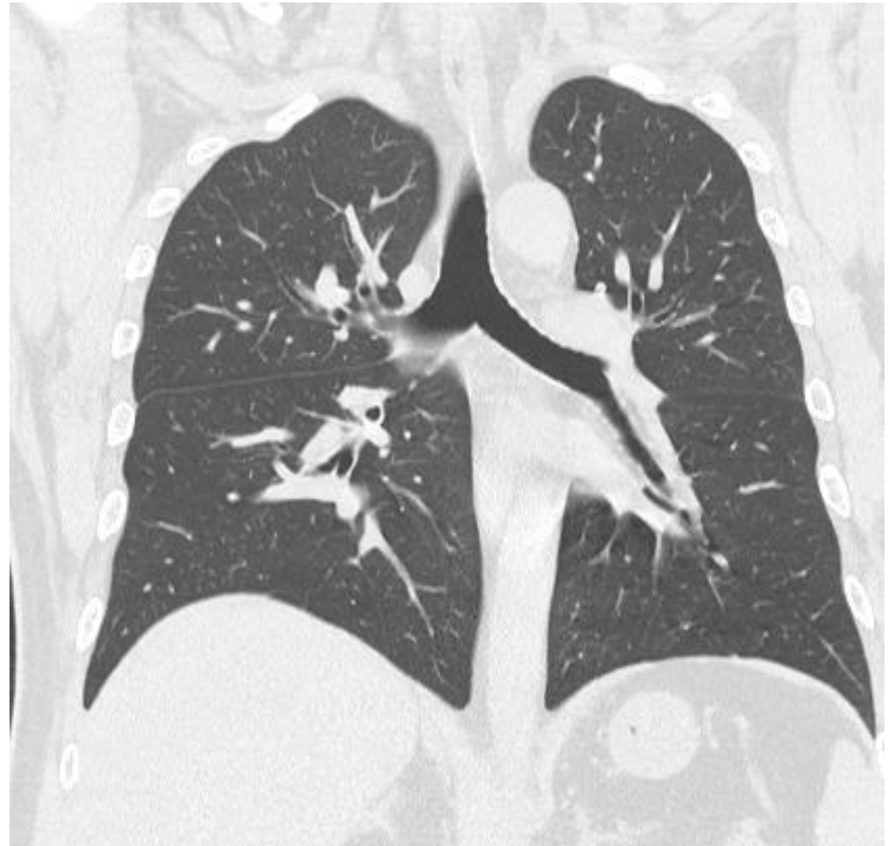
  CD4/CD 8 ratio : 2.6

Progress

- Dx : HP, acute
- Tx: 보트 페인팅 작업 중단

F/U Chest CT (2018.8.10)





Case 3

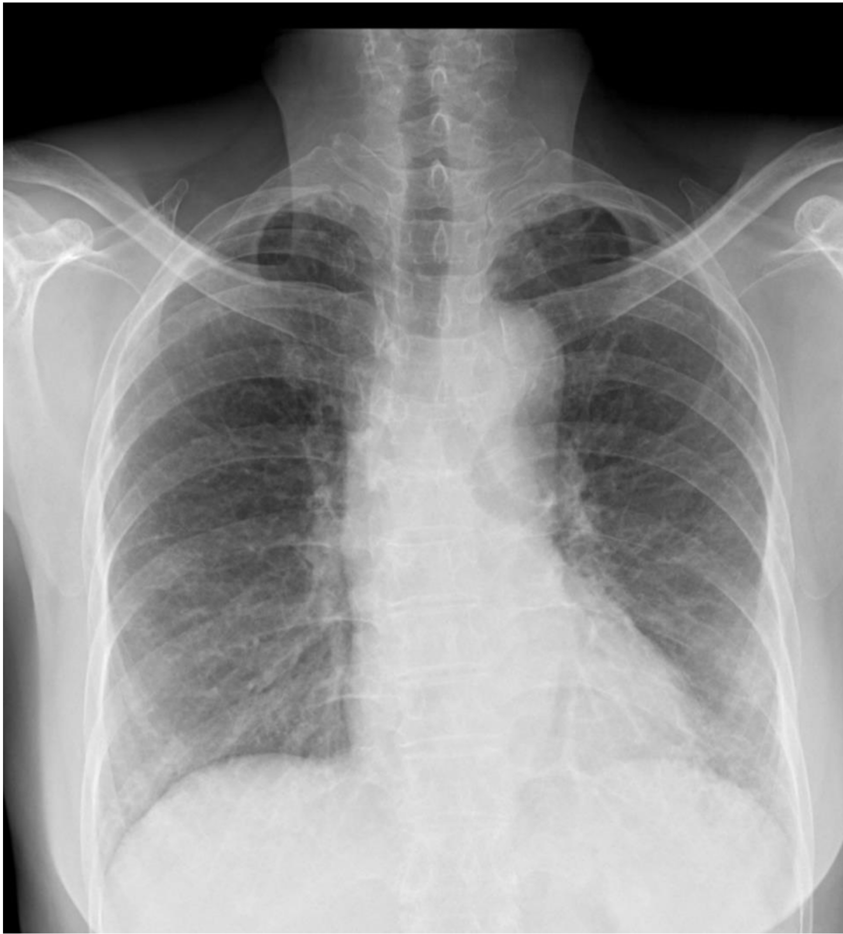
- F/ 64
- CC: Abnormal CXR
- PI : 한달 전 시행한 검진 CXR 이상으로 refer
- 주부
- Alcohol/ smoking (-/-)
- PHx : DM/HTN/TBc/hepatitis(-/+, 20년 전 진단/-/+, CHB carrier)

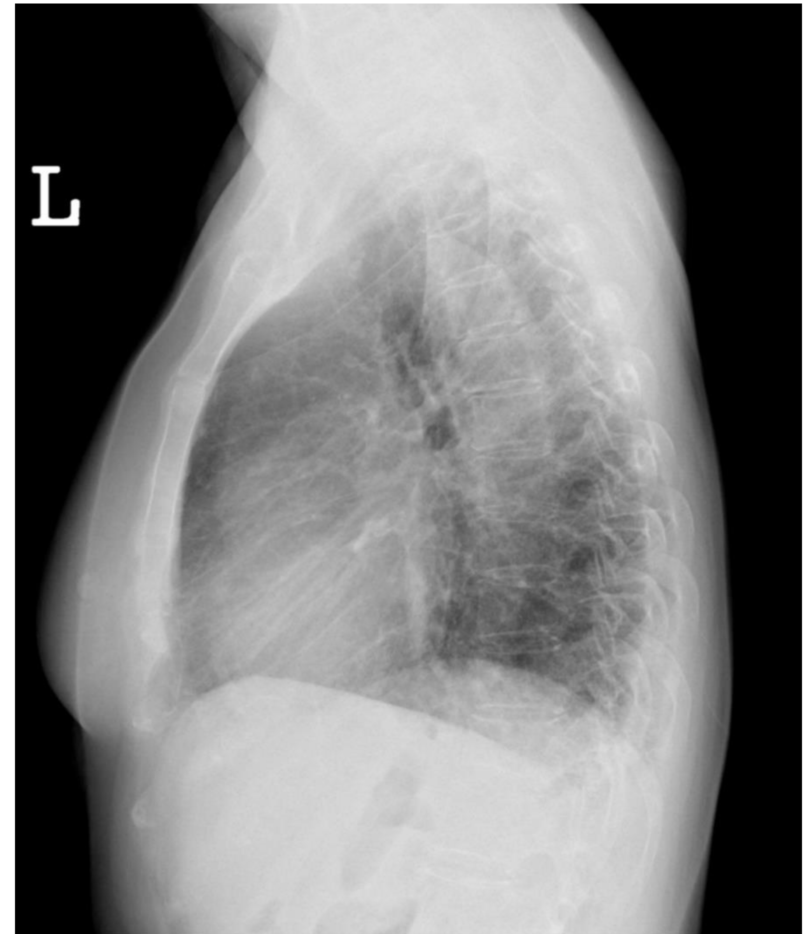
- ROS : C/S(-/-), dyspnea (-)
  rhinorrhea (+): clear
  arthralgia(-), dry mouth/eye(-/-),
  Raynaud phenomenon(-)
  peripheral cold feeling (+)
  skin rash(-), photosensitivity(-)

- P/Ex : V/S 130/90-110/min-20/min-36.8C
  coarse breathing sound with crackle on BLLF
  clubbing (-)

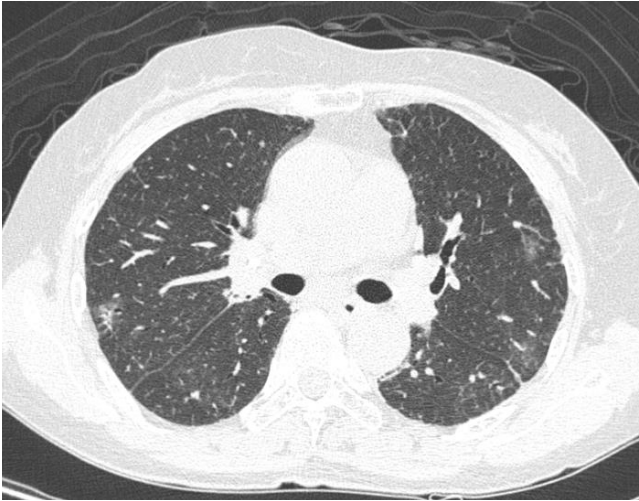
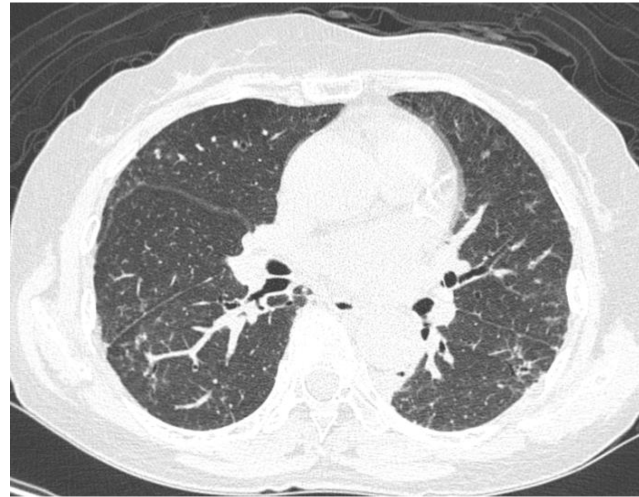
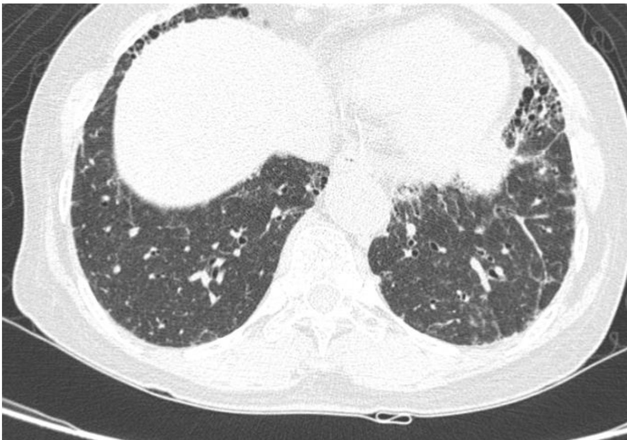
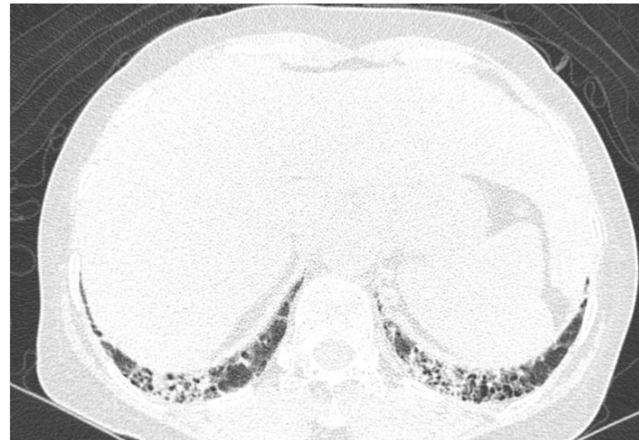
- Lab : Hb 12.5 g/dL – WBC 4400/μL - Plt 80k/ μL
  ESR 66 mm/hr, CRP 1.4 mg/L
  LFT, BUN/Cr, e : WNL
  FANA, ANCA, C3,C4, Anti-ds DNA, Ig A/M/G : negative

CXR (2010.1.21)

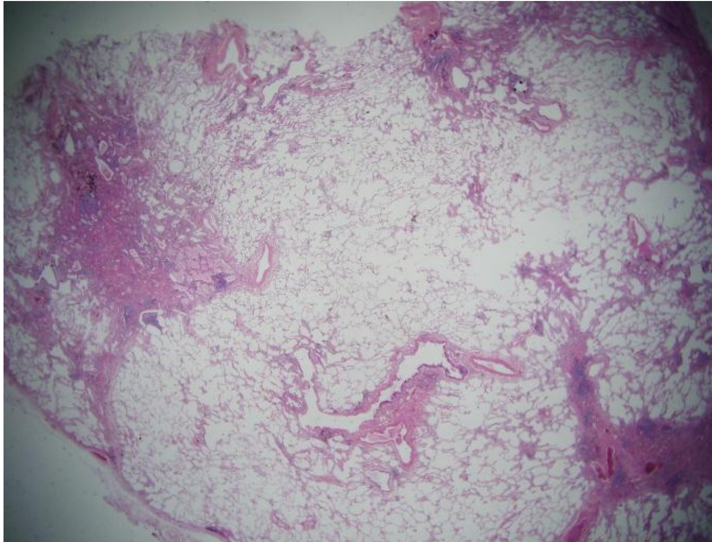


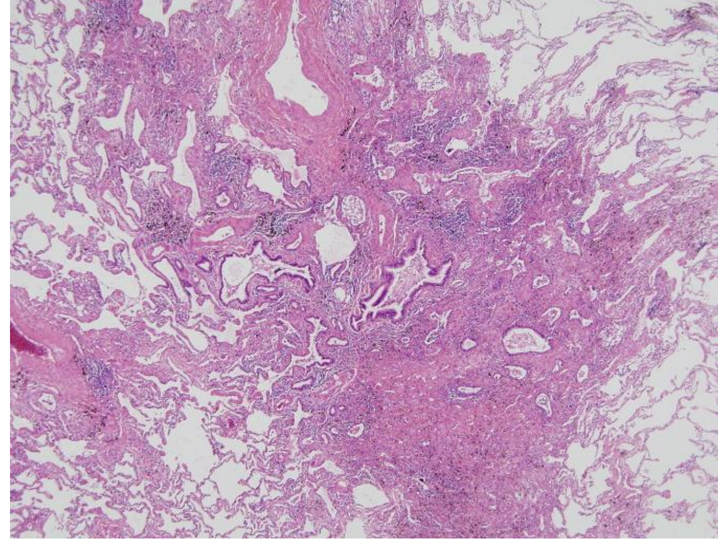


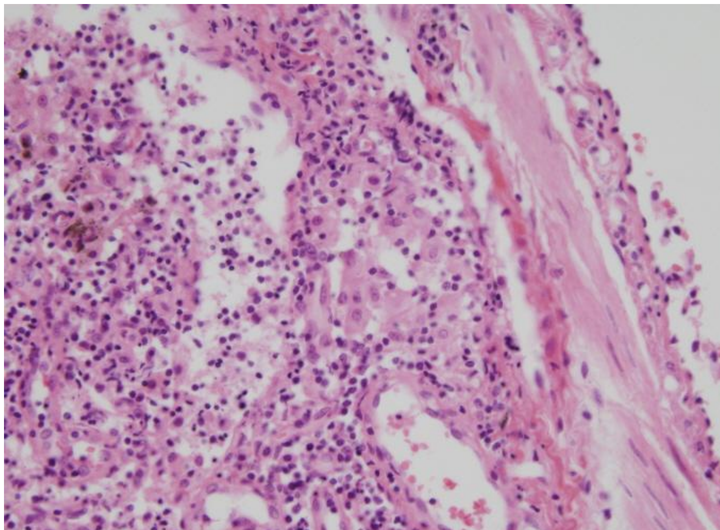
HR CT (2010. 02.04)

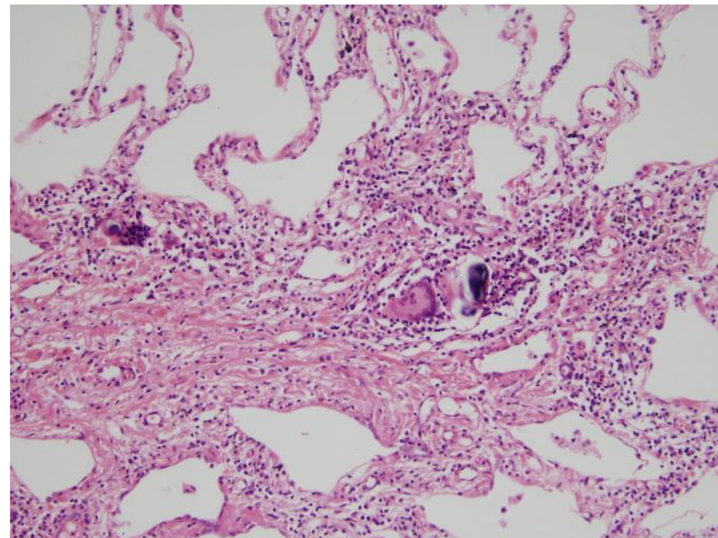





VATS lung Bx(2010.03.21)









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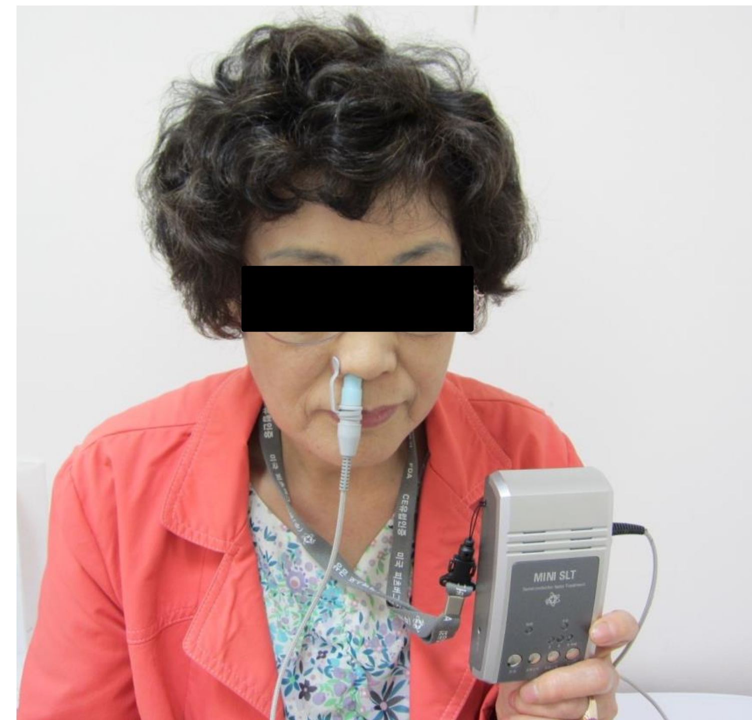
History

- 월곡동 햇볕 잘 드는 2층 양옥에서 10여년 넘게 거주
- 새로운 가구/ 애완 동물 /취미 생활 (-/-/-)

- 수개월 전부터 중국산 코에 넣는 레이저 기계 사용

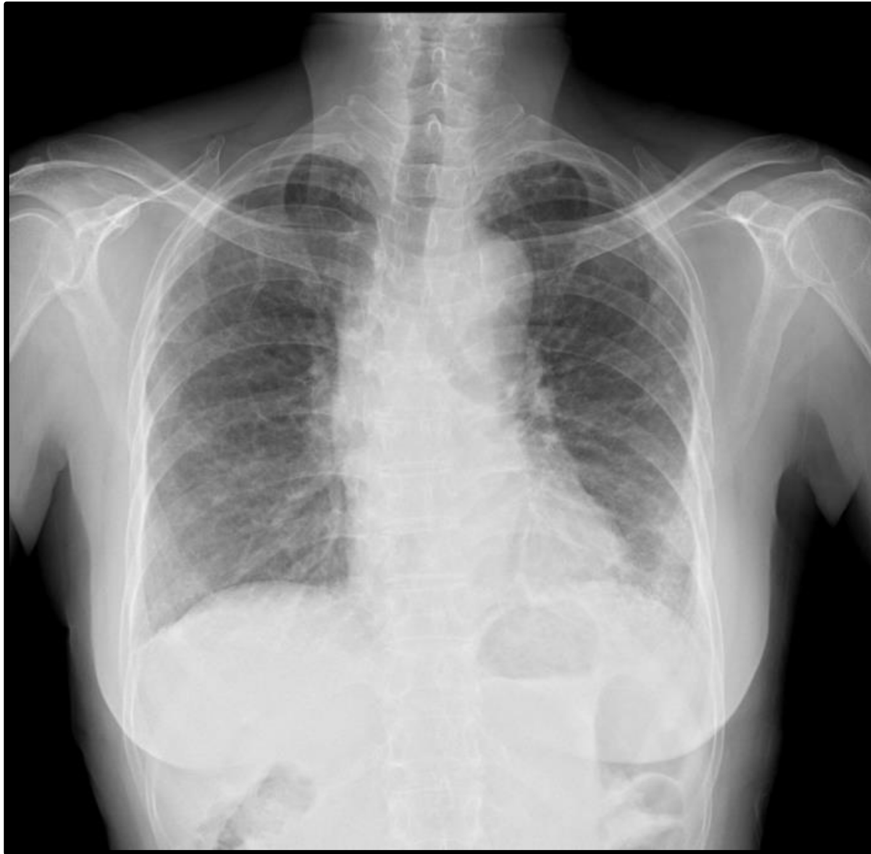


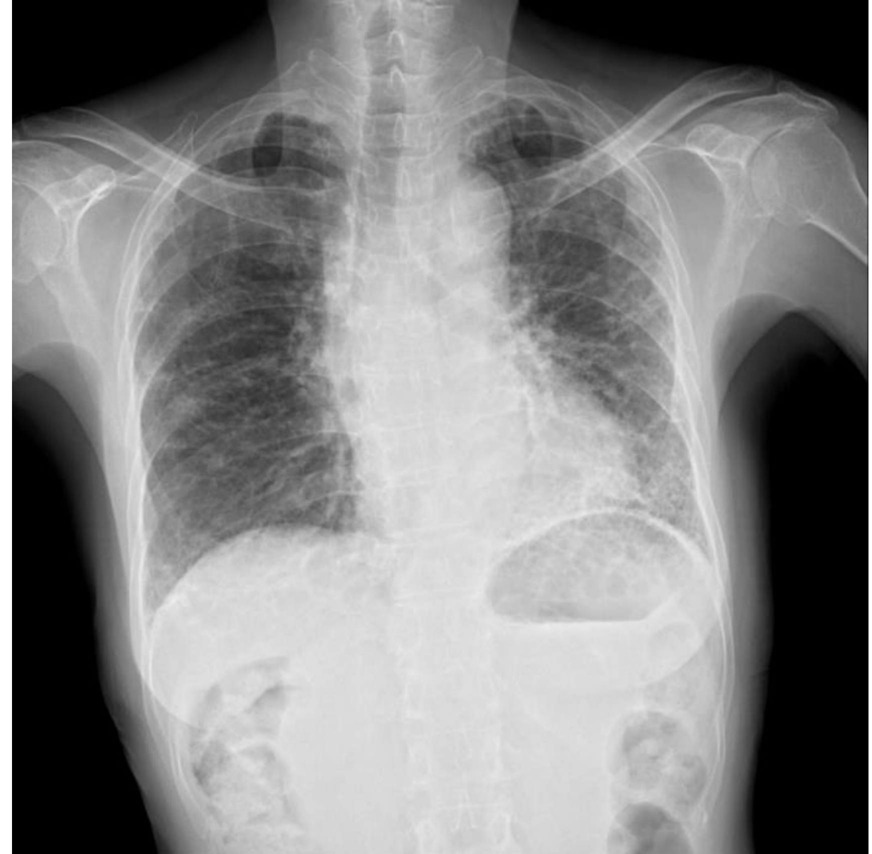
Progress

- 중국산 기계 사용하지 않도록 하고 외래 추적 관찰 하기로 하던 중 2010년 5월 이후 f/u loss 됨
- 2011년 4월 new onset cough/dyspnea 로 외래 다시 방문

(이전에 사용하였던 중국산 레이저 기계는 지속적으로 사용하였다 함)

CXR (2011.4& 2015.3)





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Introduction

- Formerly called Extrinsic allergic alveolitis

- An immune-mediated disease that occurs after inhalation of fine particulate organic or inorganic material by a sensitized subject.

- First descriptions similar to HP appeared in 1713.
  (pt who worked with cereals)
  Farmer's lung: 1932
  Mushroom worker: 1959
  Bird-breeder's lung: 1960

Pulmonol 2019, Epub ahead of print

Semin Roentgenol 2019; 54: 37-43

Epidemiology

- Incidence : 0.3-0.9 / 100,000 (Europe)
  <1/100,000 (Denmark)
  ≈ 30 /100,000 (New Mexico, USA)
  4-170 /1,000 farmers (farmer's lung)
  1-100/1,000 breeders (pigeon breeder's lung)

- Nearly half of pts with new-onset ILD (after MDD, India)
  18~30% of ILD

- Less frequent in cigarette smoker
  (Nicotine is thought to inhibit MΦ activation,
  LΦ proliferation and function)

Pulmonol 2019, Epub ahead of print

Semin Roentgenol 2019; 54: 37-43

Am J Respir Crit Care Med 2017;196:680-689

Etiology-1

- Exposure can occur at home, in the workplace, related to hobbies
- A mixture of Ags rather than a single Ag
- Occult HP inducer is reported as unsuccessful in up to 60%
  - "Cryptogenic HP"

- More than 300 substances
  → 3 groups (microbials/ animal & plant proteins / chemical)
  Trombone/Saxophone player's lung
  HP associated green tea

Semin Roentgenol 2019; 54: 37-43

Am J Respir Crit Care Med 2017;196:680-689

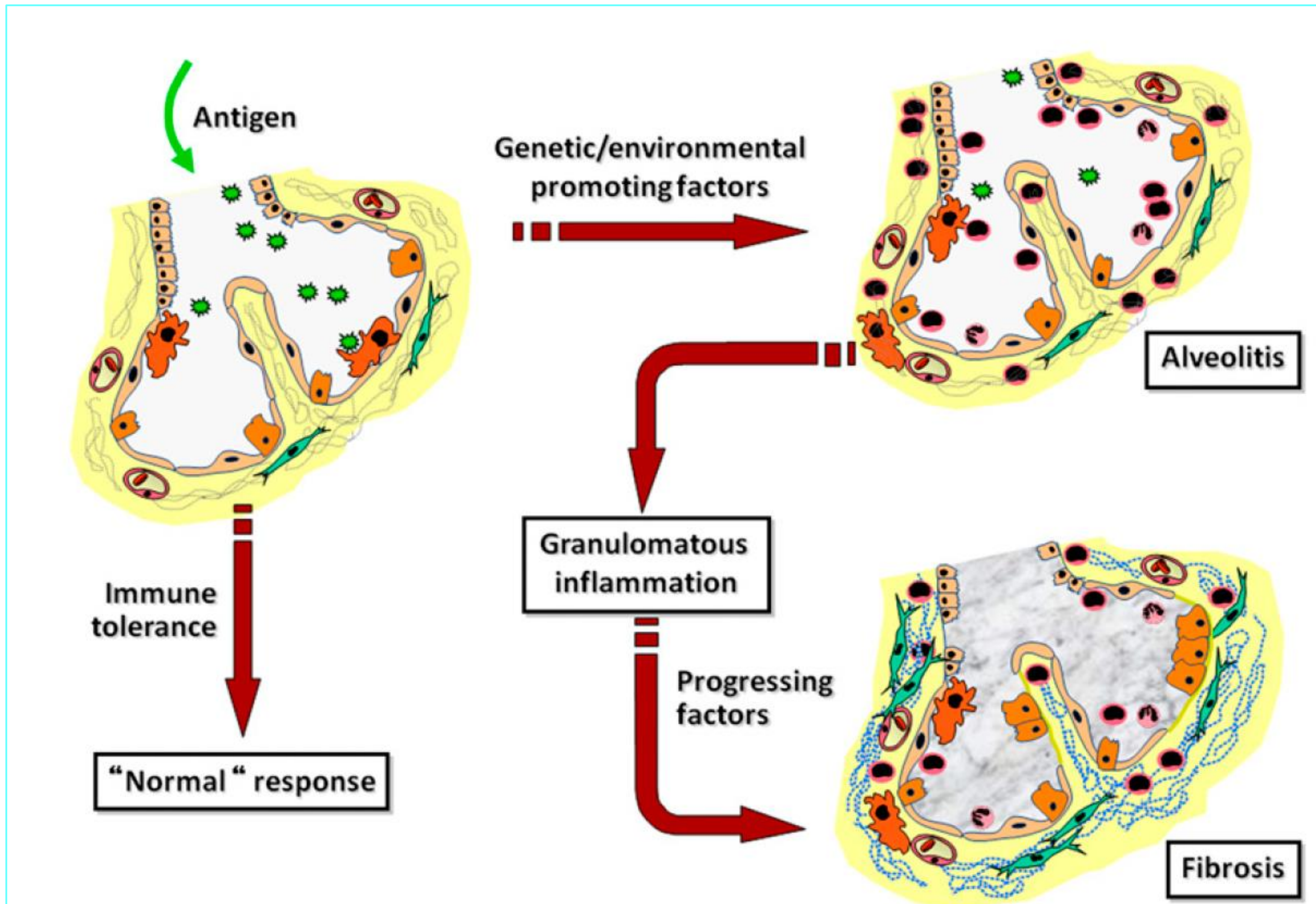
Etiology-2

Table Causes of Hypersensitivity Pneumonitis (HP)

	Allergens	**Source(s) of Exposure**
Microbial agents		
Bacterial	Thermophilicactinomycetes	Decomposing hay, humidifiers and water-based heating/cooling systems
	Nontuberculous mycobacteria	Hot tubs, warm water, metal-cutting fluid
	Klebsiella	
Fungal	Aspergillus	Moldy malt, cork dust
	Penicillium	Moldy cheese
Protozoan	Naegleriagruberi	Humidifier/air conditioners
Plant/Animal Proteins		
Animal	Birds	Avian proteins, including stool and feathers
	Mollusk shells	Button manufacturing
	Proteins in animal fur	Pet grooming, veterinary care
Plant	Soy bean	Food processing
	Coffee	Food processing
Low-molecular weight chemicals		
Chemical	Isocyanates	Polyurethane foam, varnish, lacquer
	Copper sulfate	Copper sulfate use

Semin Roentgenol 2019; 54: 37-43

Pathogenesis



Am J Respir Crit Care Med 2012; 186: 314- 324

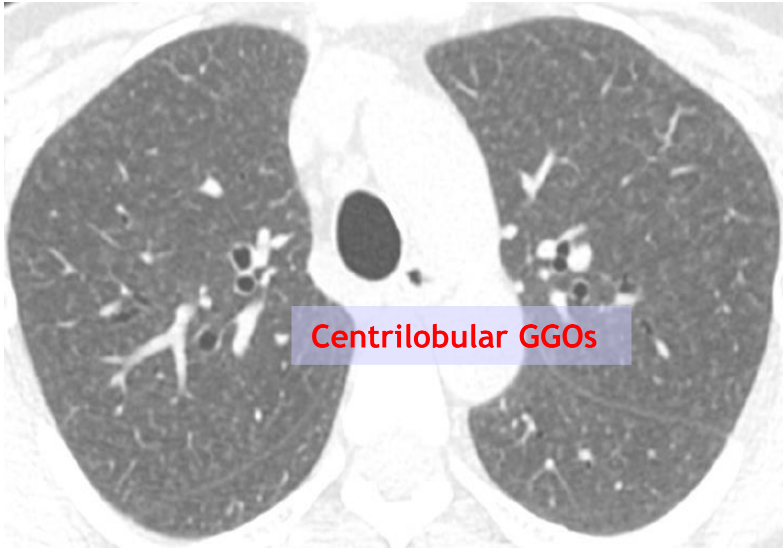
Clinical Findings

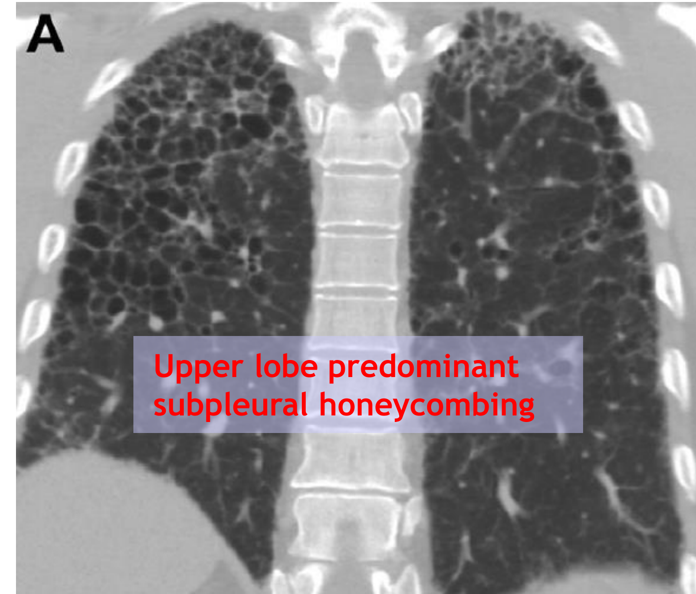
- P/Ex : normal ~ crackle, inspiratory squeaks
- PFT : to assess severity of lung function impairment
  monitor disease course
  Δ FVC – strong predictor of mortality
- BAL : more than 80% of pts c CHP have more than 20% lymphocytosis
  lymphocyte counts may be normal, or even lower than normal
  OP/ cellular NSIP like pattern >> UIP like pattern
  CD 4/CD 8<1 (39% of CHP) - nonspecific & insensitive
  neutrophilia within 48 after exposure & acute episode

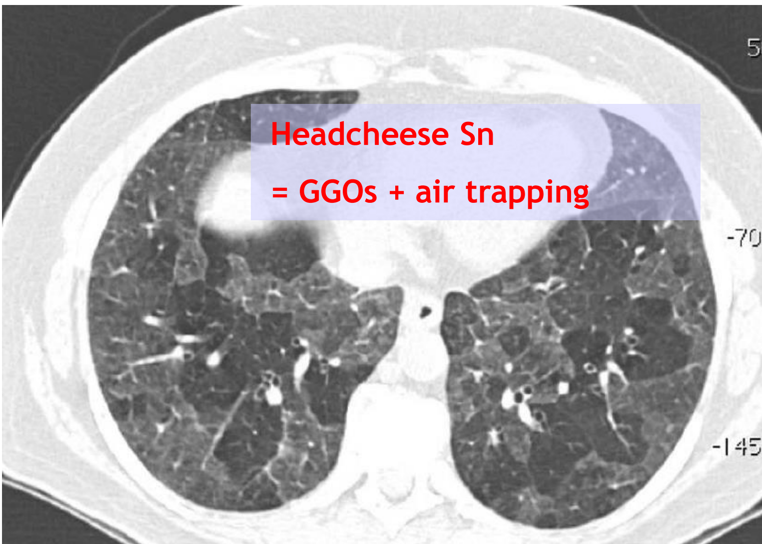
Expert Rev Respir Med 2018; 12: 496-507

Am J Respir Crit Care Med 2017;196:680-689

Radiology-1



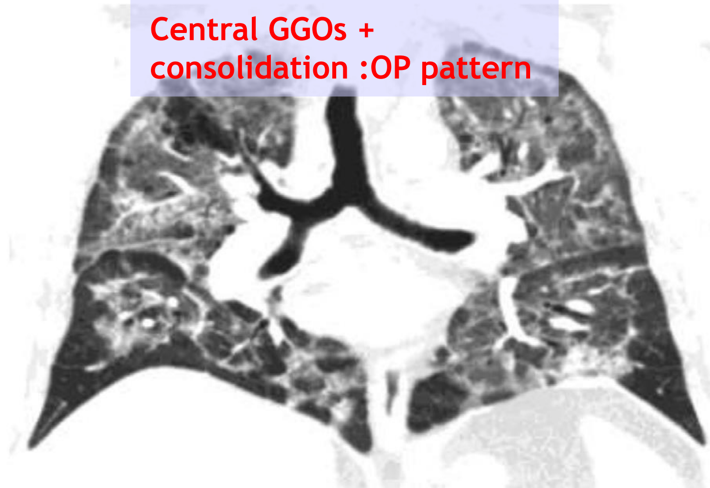


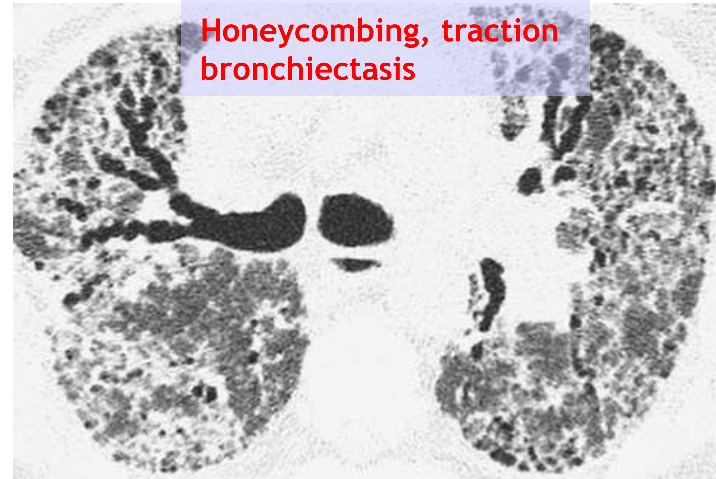


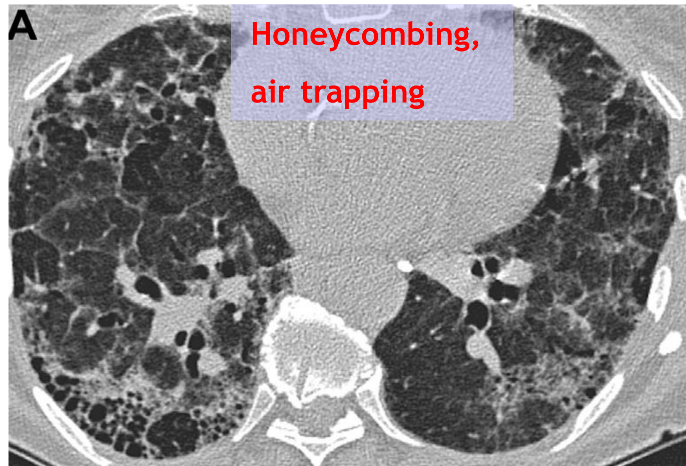
Expert Rev Respir Med 2018; 12: 5-13

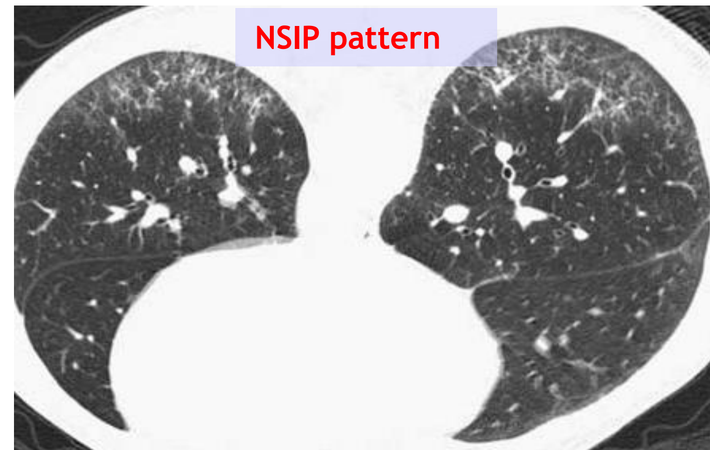
Radiol Clin N Am 2016;54: 1033-1046

Radiology-2









J Thorac Imaging 2016; 31: 92-103

Radiol Clin N Am 2016;54: 1033-1046

Radiology-3

- Retrospective cohort
- 2009.2-2014.8, Deviation cohort, Michigan
  (total = 356, HP = 121)
  ➔ validation cohort, multicenter
  (total= 424, HP = 66)
- Honeycombing, reticulation, GGO, mosaic attenuation, air trapping, centrilobular nodules, traction bronchiectasis, craniocaudal distribution, axial distribution
  : 1) Mosaic attenuation/air trapping >> reticulation
  &
  2) diffuse axial distribution
  ➔ False HP Dx risk < 10%

Eur Respir J 2018; 52: 1800443

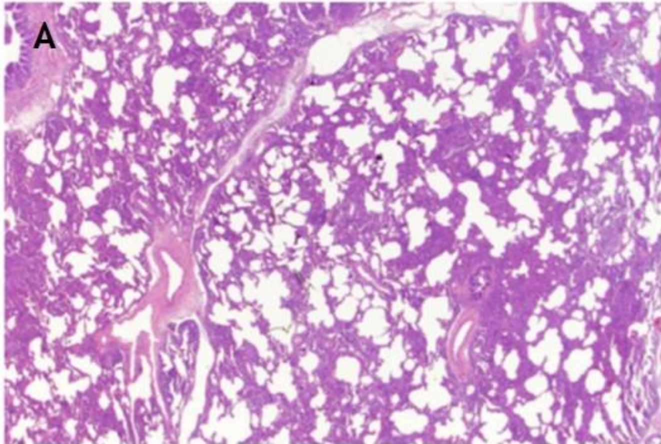
Histopathology-1

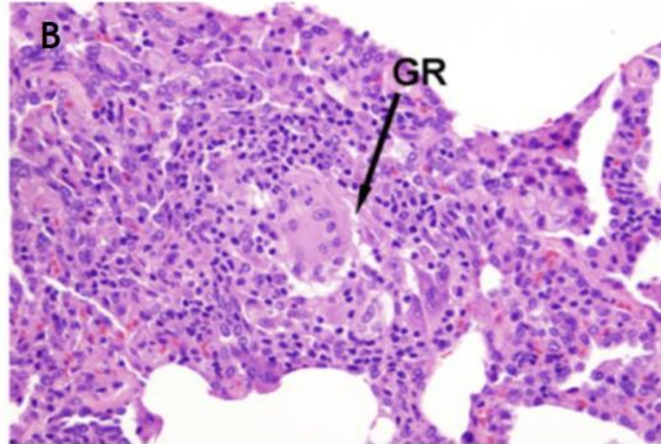
- Surgical lung biopsy (SLB)
  : gold standard
  HP is excluded if Bx reveals features inconsistent with HP

- Transbronchial lung biopsy/cryobiopsy (TBLB/TBLC)
  : less invasive than SLB
  TBLC – diagnostic accuracy is comparable with SLB
  acceptable safety profile
  only in a few experienced centers
  HP is not excluded based on non-diagnostic Bx
  in TBLB/C specimens

Am J Respir Crit Care Med 2017;196:680-689

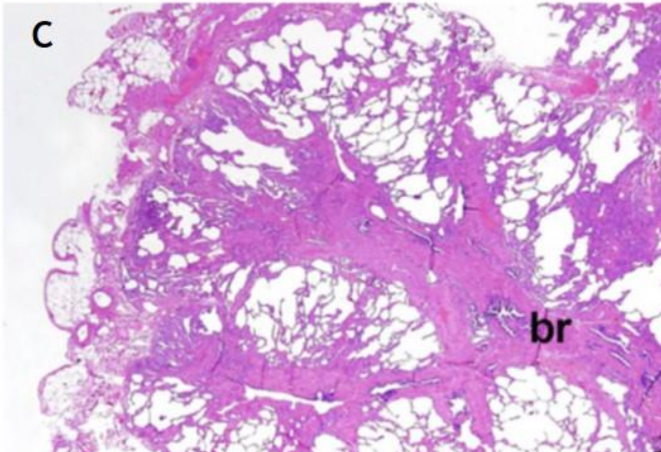
Histopathology-2

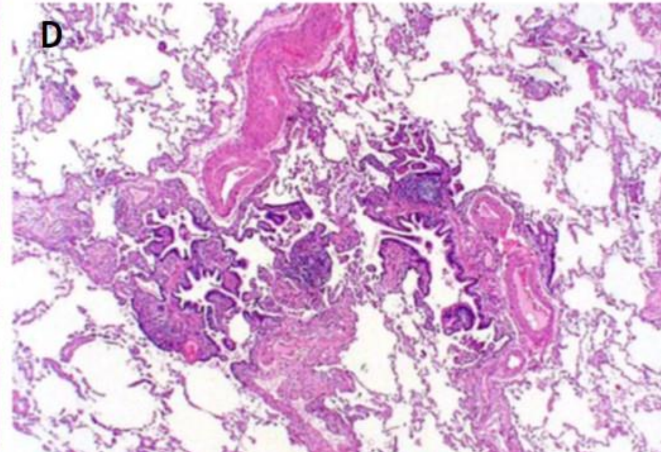




A) Diffuse lymphohistiocytic infiltrate ≈ cellular NSIP

B) Poorly formed, interstitial grauloma





C) Branching pattern on fibrosis following the bronchovascular bundles

D) Peribronchiolar metaplasia commonly present in CHP

Am J Respir Crit Care Med 2017;196:680-689

Antigen Detection

- The use of a standardized questionnaire as an aide may be very useful. But it should be validated before using in routine clinical practice.

- Check the presence of serum specific IgG

- Specific inhalation challenge
  : direct challenge with inhalation → to confirm an etiology
  not standardized/validated
  requires experienced personnel and laboratories

- Environmental sampling (ledge, fluid tank, carpet, wall board..)

Respiratory Medicine 2016; 112: 97-105

Am J Respir Crit Care Med 2017;196:680-689

Biomarkers & Genetic testing

- Serum KL-6/SP-D were higher in HP(A/C) than IPF, CTD-ILD and sarcoidosis.
- Human intelectin-1(Hitln-1) in BALF of pt with ICEP/HP were higher than drug-induced EP, sarcoidosis, COP, and IPF

- HLA? SNP?

  MUC5B minor alleles & risk of CHP

  short telomere length
- Several cases, mainly avian & summer type HP, within the same family have been published

- Genetic testing are not currently recommended

Intern Med 2018; 57: 3507-3514

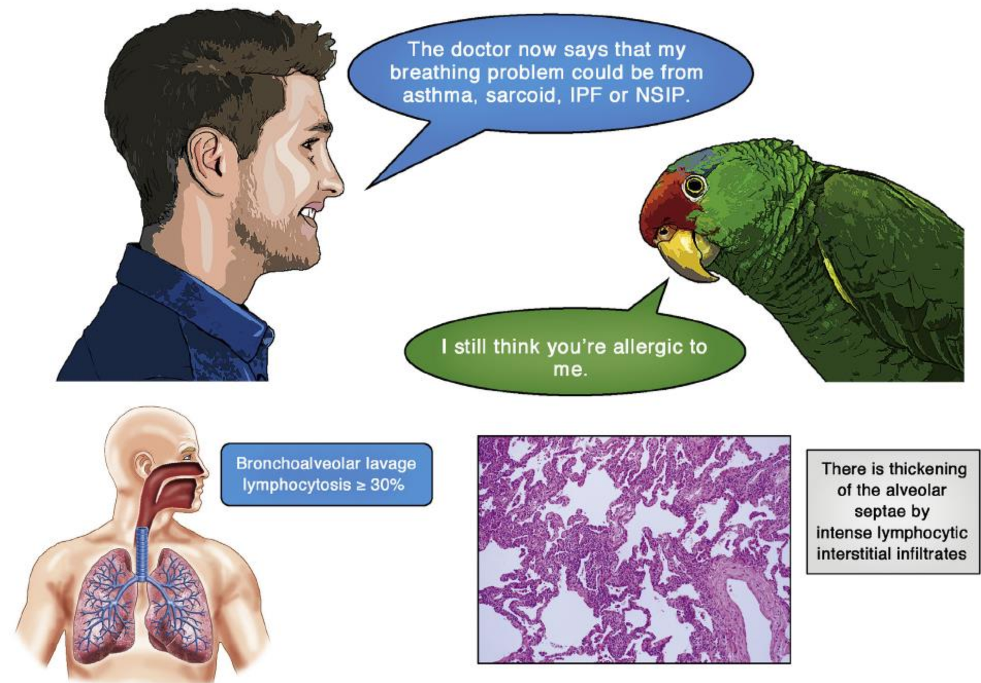
Respir Med 2015; 109: 1576-1581

Expert Rev Respir Med 2018; 12: 496-507

Diagnosis-1

- Agreement across MDD on HP Dx : k=0.24
  (IPF, k=0.6,   CTD-ILD, k=0.64)

- based on
  1) compatible clinical Sx
  2) inducing Ag
  3) abnormal HR CT
  4) PFT
  5) evidence of IgG
  6) for some pt, lung Bx



Lancet Respir Med 2016; 4: 557-565

J Allergy Clin Immunol 2019, Epub ahead of print

Diagnosis-2

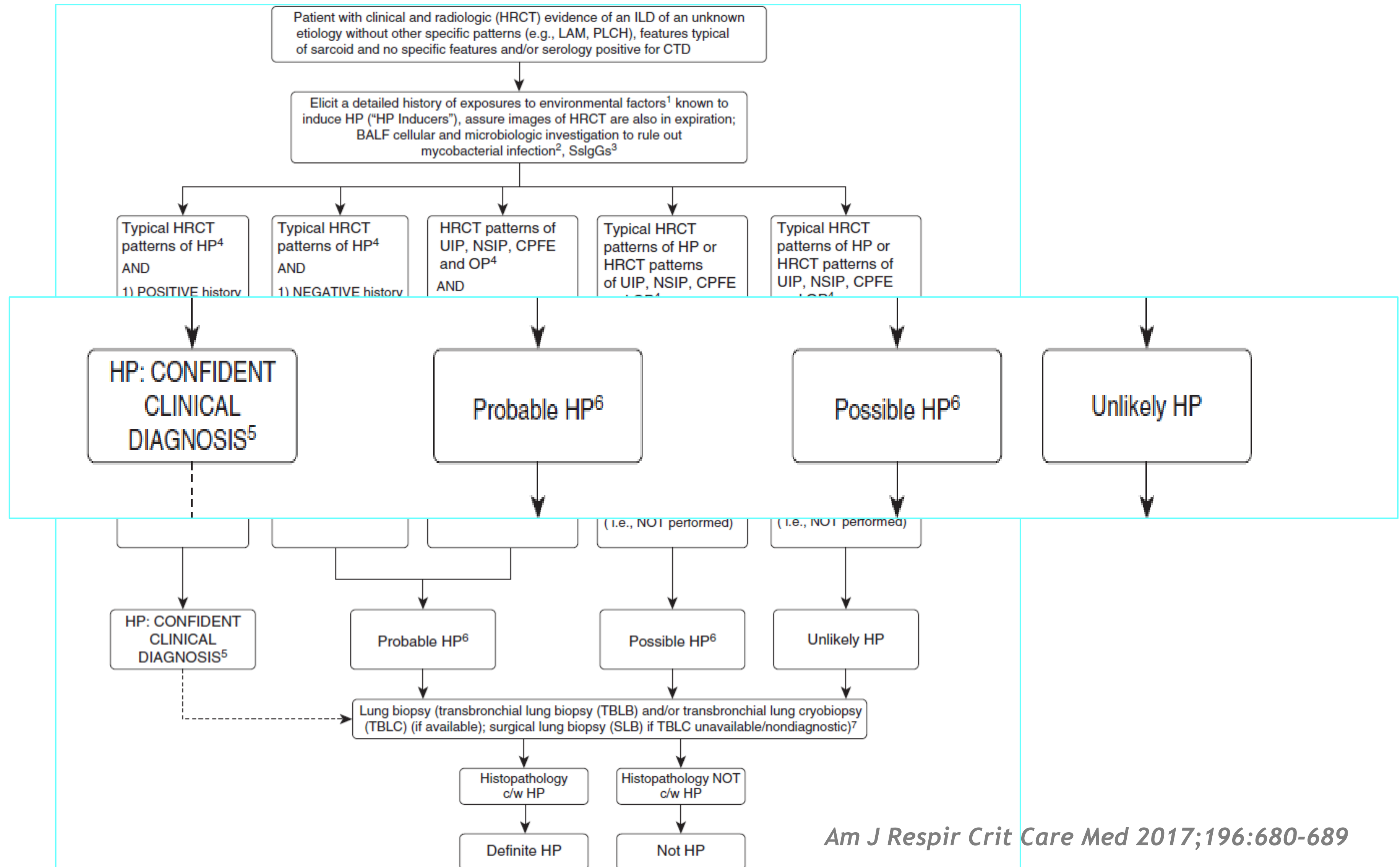
Table 2 Proposed Diagnostic Criteria for Hypersensitivity Pneumonitis for Clinical Purposes

Author	Major Criteria	Minor Criteria
Terho[2]	1. Exposure to offending antigens (revealed by history, aerobiological or microbiological investigations of the environment, or measurements of antigen-specific IgG antibodies) 2. Symptoms compatible with HP present and appearing or worsening some hours after antigen exposure 3. Lung infiltrations compatible with	1. Basal crepitant rales 2. Impairment of the diffusing capacity 3. Oxygen tension (or saturation) of the
…	…	or appropriate treatment
Schuyler, Cormier[5]	1. Symptoms compatible with HP 2. Evidence of exposure to appropriate antigen by history or detection in serum and/or BAL fluid antibody 3. Findings compatible with HP on chest radiograph or HRCT 4. BAL fluid lymphocytosis 5. Pulmonary histological changes compatible with HP 6. Positive natural challenge	1. Bibasilar rales 2. Decreased DLCO 3. Arterial hypoxemia, either at rest or during exercise

Richerson et al[3]	
	1. The history and physical findings and pulmonary function tests indicate an interstitial lung disease 2. The x-ray film is consistent 3. There is exposure to a recognized cause 4. There is antibody to that antigen

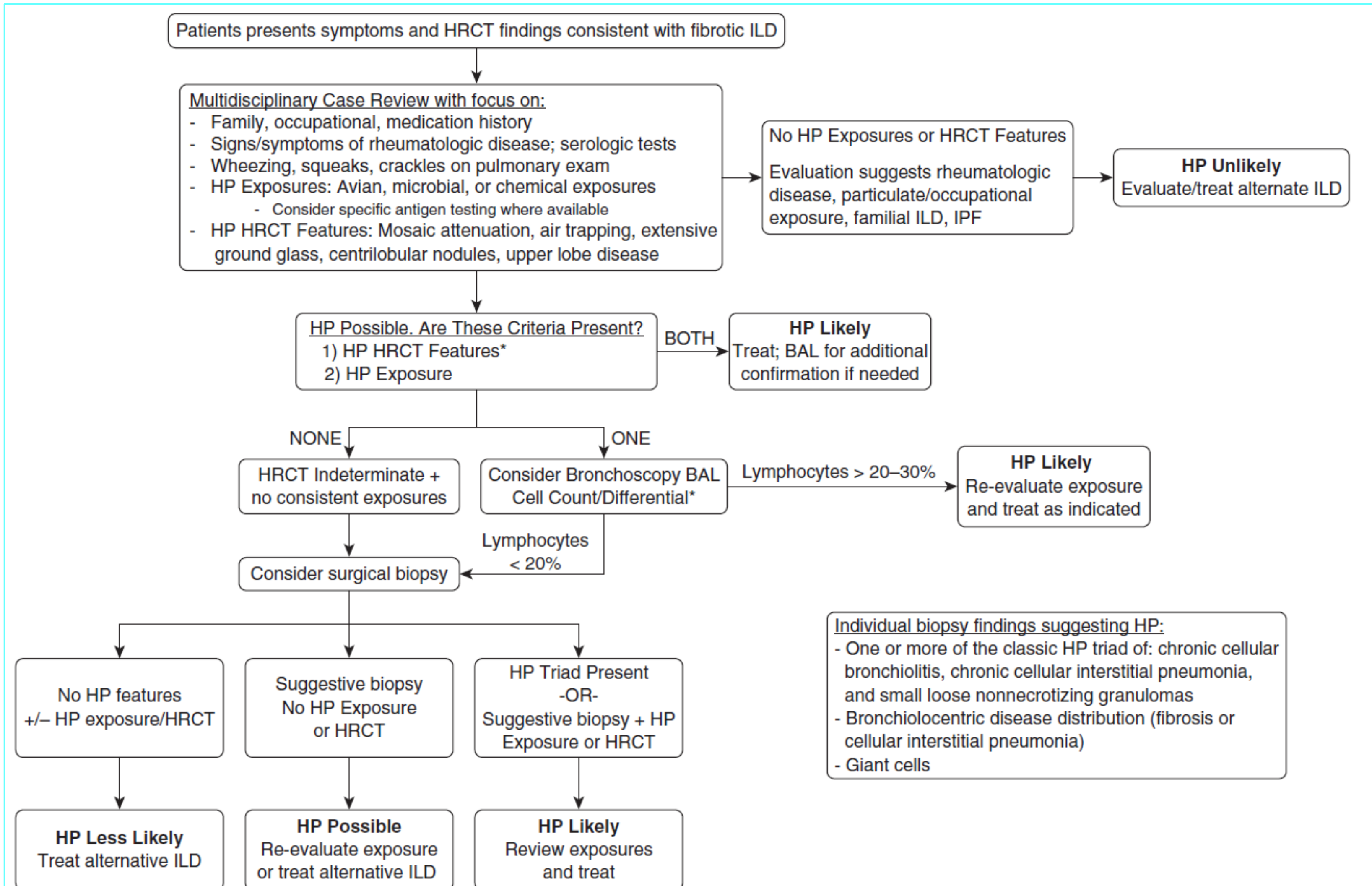
Semin Respir Crit Care Med 2008;29:631-642

Diagnosis-3



Am J Respir Crit Care Med 2017;196:680-689

Diagnosis-4



Am J Respir Crit Care Med 2017;196:690-699

Diagnosis-5

Exposure

Yes

HRCT

Combination of mosaic attenuation, ground-glass and normal lung
or
Combination of mosaic attenuation and HRCT signs of fibrosis

Diagnosis confidence >70%

Consider BAL

BAL lymphocytosis > 40%

Confident diagnosis of cHP

Possible UIP
or
Definite UIP

*

BAL

BAL lymphocytosis > 40%

Diagnosis confidence >50%

Lung biopsy

Pathological features of cHP
- Chronic bronchiolocentric inflammation
- Poorly formed non-necrotizing granulomas
- Giant cells
- Airway-centered interstitial fibrosis
- Absence of alternative diagnosis

Confident diagnosis of cHP

No

HRCT

Combination of mosaic attenuation, ground-glass and normal lung
or
Combination of mosaic attenuation and HRCT signs of fibrosis

*

BAL Lymphocytosis >40%

Diagnosis confidence >50%

Consider

Lung biopsy

Pathological features of cHP
- Chronic bronchiolocentric inflammation
- Poorly formed non-necrotizing granulomas
- Giant cells
- Airway-centered interstitial fibrosis
- Absence of alternative diagnosis

Diagnosis confidence >70%

Possible UIP
or
Definite UIP

Consider other diagnosis

Am J Respir Crit Care Med 2018;197:1036-1044

Classification-1

Classification	Clinical description
Acute	Sx begin 2-9 hr after exposure, peak typically between 6-24hr, and last from hrs to days Influenza-like Sx: chill, fever, sweating, myalgia, lassitude, headache, nausea Respiratory Sx(C/D) are common but not universal
Subacute	May appear gradually over several days to wks Marked by C/D, and may progress to severe D c cyanosis, leading to hospitalization
Chronic	Insidious onset over a period of months Increasing C and exertional D Fatigue & wt loss may be prominent Sx

J Allergy Clin Immunol 1989; 84: 839-844

Classification-2

- A large prospective multicenter cohort study
- Cluster analysis (clinical Sx, Sn, PFT, CXR, CT, BAL, Blood)

Cluster	Richerson's classification			Total
	Acute	Subacute	Chronic	
1	21	7	13	41
2	7	18	102	127
Total	28	25	115	168

- Cluster 1 : more recurrent Sx (chill, body aches), normal X-ray
  Cluster 2 : more clubbing, hypoxemia, restrictive PFT, fibrosis

- Subacute HP is difficult to define

Int Arch Allergy Immunol 2009; 149: 161-166

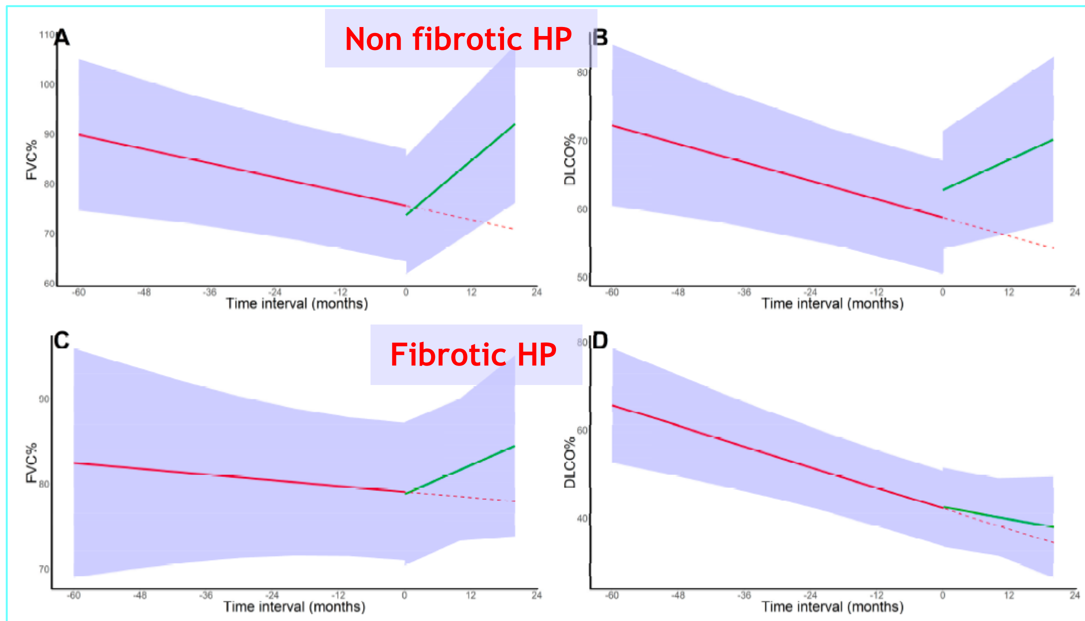
Classification-3

	Clinical Behavior	Typical HRCT pattern	Histopathology pattern
Acute HP **:Sx duration < 6 m**	- Most reversible - Complete resolution possible - Sx related to exposures to the HP induced, which can resolved completely after further avoidance	Upper- & middle-lobe predominant GGO, poorly defined centrilobular nodules; mosaic attenuation, air trapping or, rarely, consolidation	Inflammatory (cellular) HP **lymphoplasmocytic/mononuclear (MΦ) infiltrates** **Airway-centric lymphocytic infiltrates/peribronchiolar** **Poorly/loosely formed granulomas** **Multinucleated giant cells** **NSIP cellular-like**
Chronic HP **:Sx duration > 6m**	- Potentially reversible to some extent - Risk of progression	Upper- & middle-lobe predominant fibrosis, peribronchovascular fibrosis, honeycombing, mosaic attenuation, and centrilobular nodules, relative sparing of the bases	Fibrotic HP **UIP-like** **NSIP fibrotic-like** **Airway-centered fibrosis, NOS** **Unclassifiable** **Histopathologic Sn of inflammatory HP can be present on the background of fibrosis**

Am J Respir Crit Care Med 2017;196:680-689

Treatment-1

- Exposure avoidance



2005.1-2016.12

A single center cohort study (Belgium)

Non-fibrotic (n=93) vs. fibrotic (n=109)

Fibrosis on CT

: extensive reticulation,

traction bronchiectasis,

honeycombing

Red line: before terminating exposure

Green line: after terminating exposure

J Clin Med 2019; 8: 14

Treatment-2

- Steroid
  : varying doses & duration
    (0.5 mg/kg for a few days
    → slow tapering over several months to a year of longer)

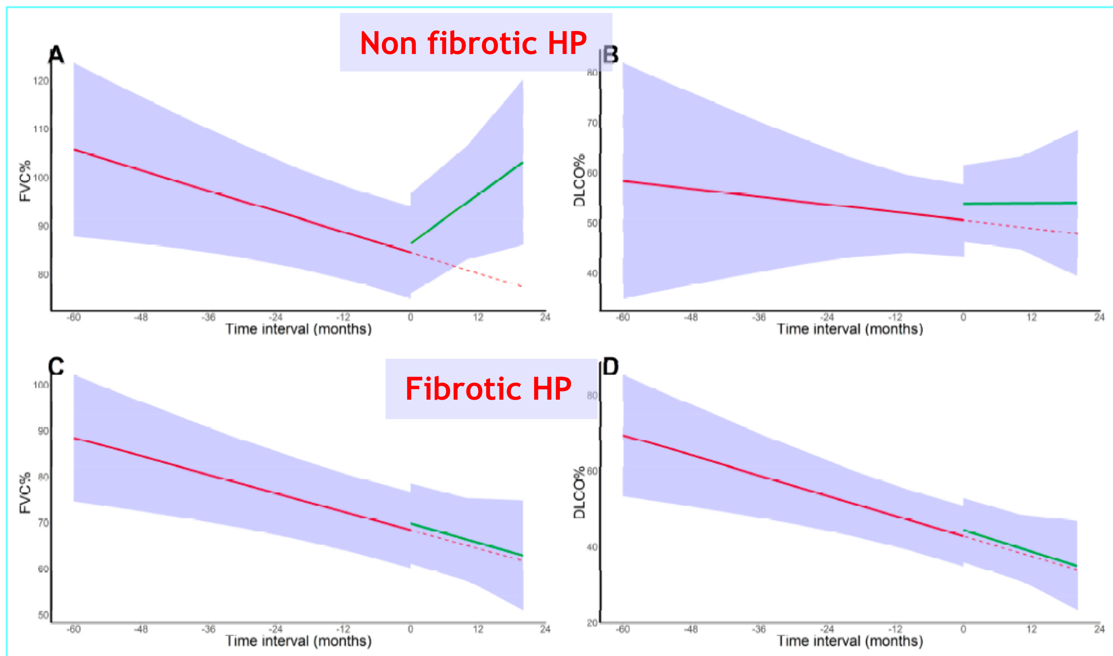
- 1 RCT
  acute farmer's lung
  steroid (n=20) vs placebo (n=16) for 8 wk
  → steroid improved lung function more rapid
  but no influence on the lung term result (5 yrs)

Am J Respir Crit Care Med 2017;196:680-689

Am Rev Respr Dis 1992; 145: 305

Treatment-3

- Steroid



2005.1-2016.12

A single center cohort study (Belgium)

Non-fibrotic (n=93) vs. fibrotic (n=109)

Steroid: 약 80% 사용

Fibrotic HP에서는 Steroid 용량, 기간에 무관하게 효과 없음

Median survival for fHP: 9.2 yrs

Red line: before steroid

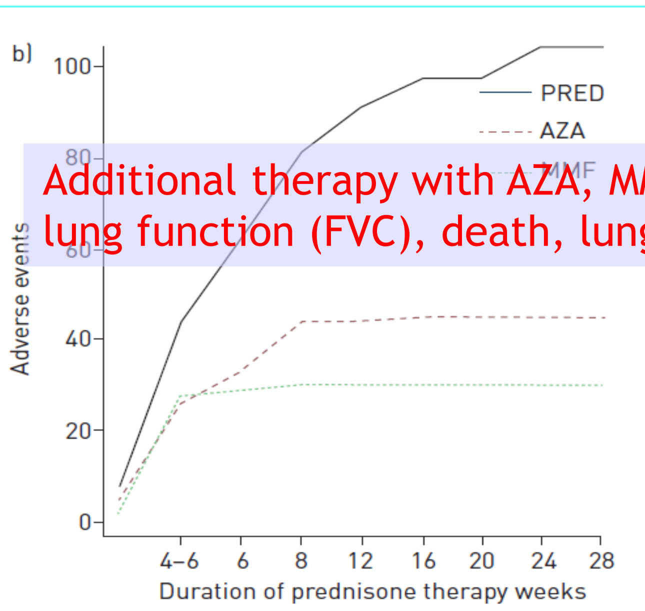
Green line: after steroid

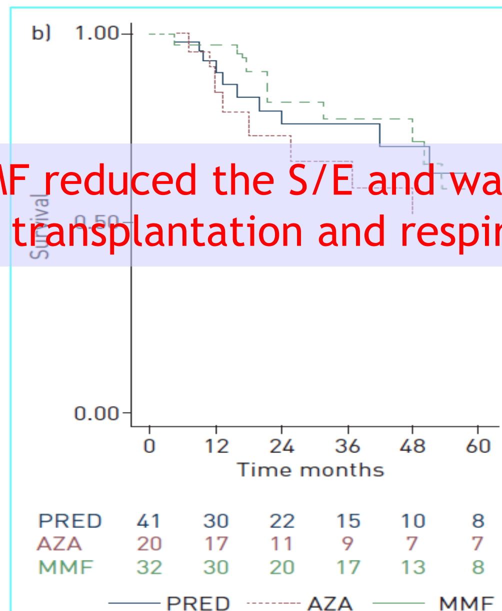
J Clin Med 2019; 8: 14

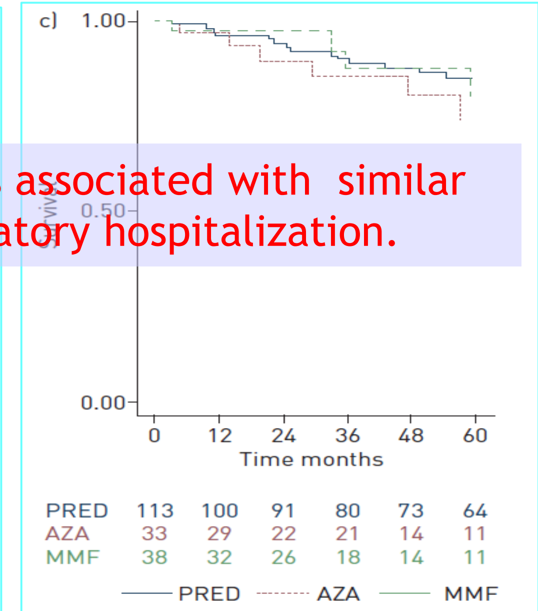
Treatment-4

- Immune-modulating agents

  steroid only vs. steroid + azathioprine/mycophenolate mofetil







Additional therapy with AZA, MMF reduced the S/E and was associated with similar lung function (FVC), death, lung transplantation and respiratory hospitalization.

2006-2015, Chicago (131 HP 중 93명 치료받음)

Pred only (n=41), 40mg/d x 11 wk

Pred + AZA(n=20), 40mg/d+ 125mg/d x 8 wk

Pred + MMF(n=32), 20mg/d + 2000mg/d 9 wk

External validation(4 center,184 HP)

Pred only (n=113)

Pred+AZA (n=33)

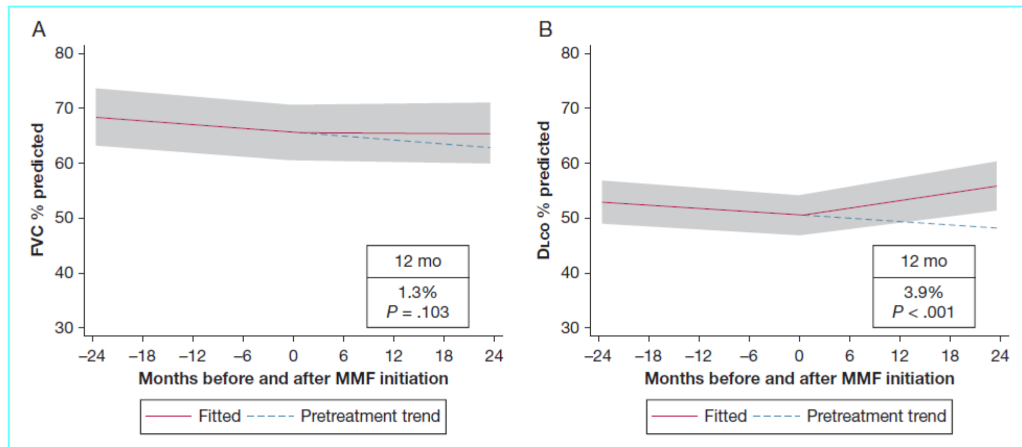
Pred+MMF (n=38)

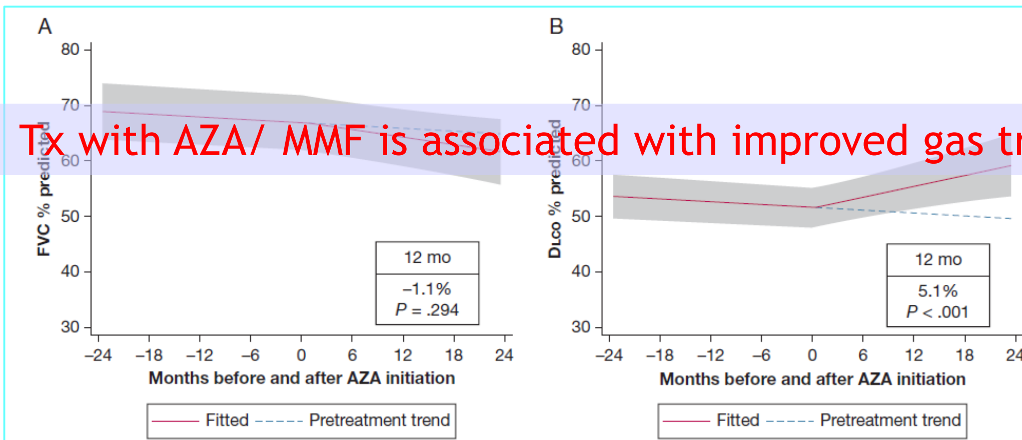
ERJ Open Res 2017; 3: 00016-2017

Treatment-5

- Immune-modulating agents

  Retrospective, multicenter(4)





70 cHP

MMF (n=51)

AZA (n=19)

Pred (n=59)

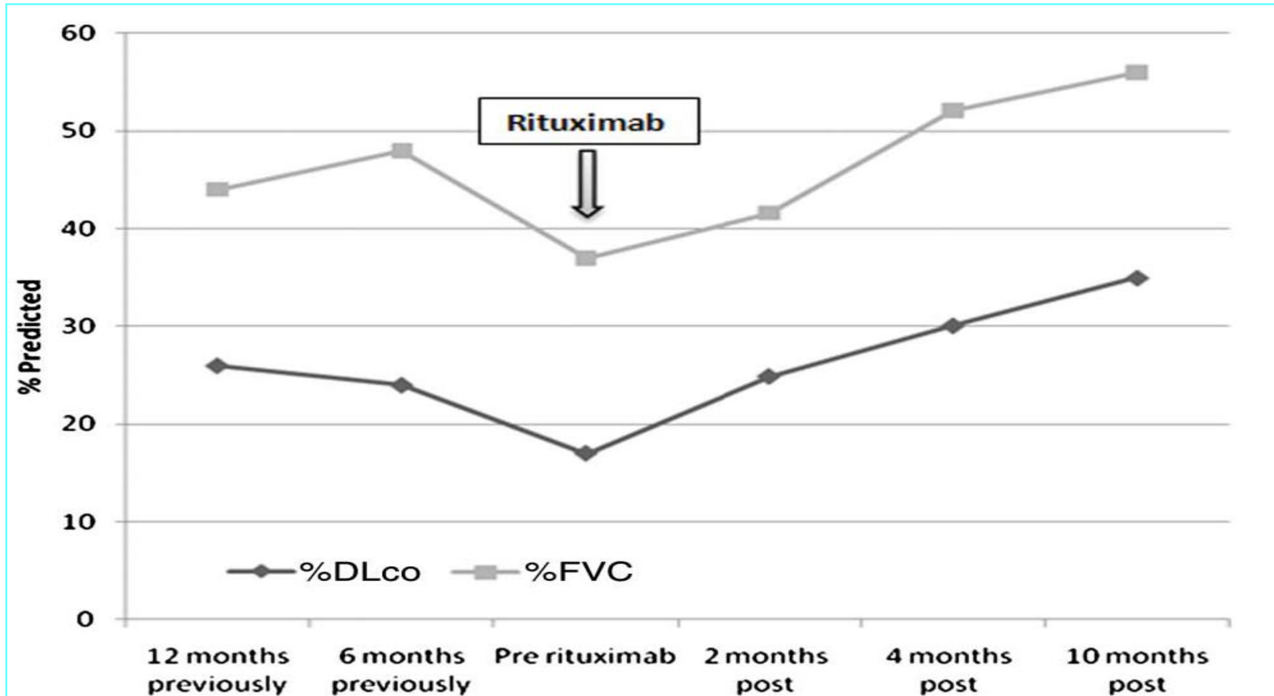
- Tx with Pred before AZA/MMF (n=14)
- Pred dose at AZA/MMF initiation : 12mg
- Pred dose at 6 m after AZA/MMF: 3.75mg

Tx with AZA/ MMF is associated with improved gas transfer in cHP pt.

Chest 2017; 151: 619-625

Treatment-6

- Rituximab



F/ 57,

never smoker

6- month course dyspnea & cough

Oral pred: 40→20

IV methylpred: 500 q wk x 3

IV cyclophosphamide : 600 q 3wks x6

IV methylpred: 500→750 →750

Rituximab 1000 q 2wk x2

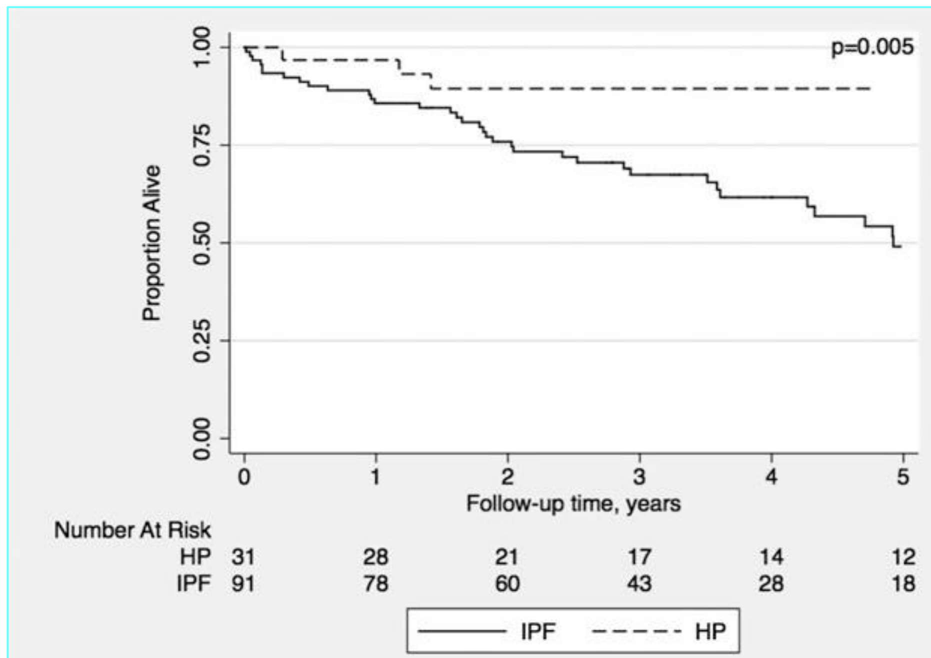
Oral pred: 30→10

AZA: 50

Thorax 2013; 68: 780-781

Treatment-7

- Lung transplantation
  2000.1~2013. 7, Retrospective cohort study, UCSF (USA)
  31 HP vs. 91 IPF (among 183 lung transplantation for ILD)
  excellent survival after LT relative to IPF
  2 (among 31) developed recurrent HP in their allografts



Chest 2015;147:1558-1565

Treatment-8

Row	Saved	Status	Study Title	Interventions	Locations
1	☑	Unknown †	Pirfenidone in the Chronic **Hypersensitivity Pneumonitis** Treatment	• **Drug**: Placebo • **Drug**: Pirfenidone	• Instituto Nacional de Enfermedades Respiratorias Mexico city, Distrito Federal, Mexico
2	☑	Recruiting	Study of Efficacy and Safety of Pirfenidone in Patients With Fibrotic **Hypersensitivity Pneumonitis**	• **Drug**: Pirfenidone • Other: Placebo controlled	• National Jewish Health Denver, Colorado, United States
3	☑	Suspended	Stop Exogenous **Allergic Alveolitis** (EAA) in Childhood	• **Drug**: Placebo • **Drug**: Prednisolone	• Klinikum der Universität München, Haunersches Kinderspital München, Bayern, Germany • Universitätsklinikum Frankfurt, Pneumologie, Allergologie, Mukoviszidose Frankfurt, Hessen, Germany • Justus-Liebig-Universität, Allgemeine Pädiatrie u. Neonatologie Gießen, Hessen, Germany • (and 4 more...)
4	☑	Completed	Small Airway Involvement in Patients With Chronic **Hypersensitivity Pneumonitis**	• **Drug**: Salbutamol	• Olívia Meira Dias São Paulo, Brazil

Clinicaltrials.gov on March 2nd, 2019

Prognosis

- Median survival for chronic progressive HP: 7 yrs

- Poor prognosis
  : greater age,
  history of cigarette smoking,
  crackles on P/Ex,
  baseline low FVC/DL_{CO},
  absence of lymphocytosis in BAL,
  presence of fibrotic changes in radiology/pathology,
  increased pulmonary artery/arota ratio
  unidentified source of exposure

Eur Rdiol 2017; 27: 5127-5135

Am J Respir Crit Care Med 2017;196:680-689

Summary

- No consensus in the diagnosis of HP
- Diagnostic criteria/algorithms include detailed Hx about environment + Ag exposure, clinical Sx, BAL analysis, HR CT pattern, histopathological pattern and sIgG
- Separate acute from a chronic clinical course
- Ag avoidance is crucial in the management of HP, corticosteroids and other immunomodulatory drugs are possible
- More consensus/evidence is necessary for Dx & Tx of HP