Case (AMC)

Chief complaint

61 / M

Fever for 1 day

Present illness

내원 7년전 (2004.12) 부터 MRC Grade 2 의 DOE 및 dry cough, general weakness있어, 내원 6년전 (2005.4) 외부병원에서 흉부 CT 시행하였고, ILD 의심되는 소견 있어 본원 호흡기내과 내원함. 당시 HRCT 와 PFT 및 Bronchoscopic BAL 소견 종합하여 Clinical IPF로 진단받았고 이후 안정적인 상태로 외래 경과 관찰하며 지내옴.

내원 3년 전(2008.10) HRCT 나 PFT 의 큰 변화 없이 호흡곤란 증가하여 N-acetylcysteine(NAC) 사용 시작하였으나 복부 불편감으로 인하여 중단하며 slow progression 상태로 경과 관찰함.

Present illness

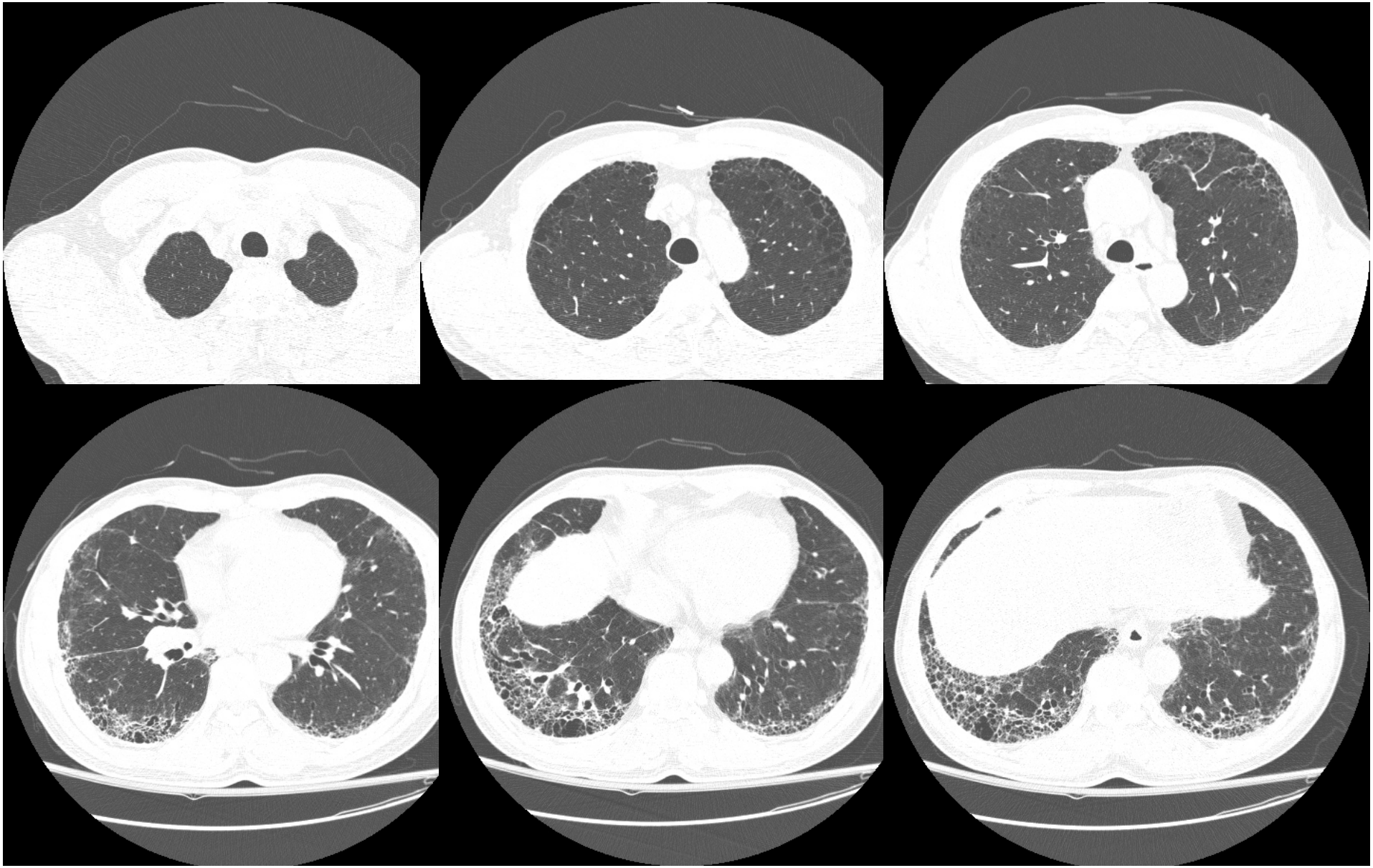
내원 2개월전 시행한 2-D Echo 에서 mild resting pulmonary HTN 발생 (TR Vmax=3.3m/s, PAP=49mmHg) 및 폐 병변의 slow progression 확인 되어 NAC 다시 시작하였고, 폐 이식 고려하기로 함.

내원 8일전 cough, sputum(white) 증가 및 DOE 악화(MRC 3->4), blood tinged sputum (scanty, redddish) 있으며, 산소요구량이 증가하고 (1L->6L), 내원 1일전 39도 이상의 fever 동반되어 ER 내원.

Past Admission(2005.6.2-6.7)

- HRCT: honey-comb/reticular and GGO with traction BE in both basal subpleural area
- PFT: FVC 4.99L(110%) FEV1 4.10L(126%) FEV1/FVC 82 TLC 6.66(103%) DL 14.9(65%)
- 6 min: 95% -> 92%(548m)
- Autoimmune marker
  - ANA titer (+,1:40,speckled) Jo-1 Ab : negative
  - Anti-SSA(Ro) : negative Anti-SSB(La) : negative
  - Scl-70 Ab : negative MPO-ANCA : negative
  - PR3-ANCA : negative Anti-ds-DNA : 6.2 IU/mL
  - RF : <10.6
  - Anti-U1RNP Ab : negative Anti-Sm Ab : negative
- BAL: WBC 70(N 7 L 7 Eo 24 AM 60): RML(100->70cc)
- Arthralgia(-), dry eye(-), dry mouth(+)

HRCT(2005.5.6)



PFT during OPD f/u

	FVC(%)	FEV1(%)	FEV1/FVC	TLC	DL	6MWT
05.06.02	110(4.99)	126(4.10)	82	103(6.66)	65(14.9)	548(95-92)
06.06.27	110(4.97)	125(4.03)	81	106(6.81)	87(19.9)	
07.07.24	114(5.15)	132(4.22)	82	106(6.84)	67(15.2)	606(97-90)
08.10.21	116(5.10)	134(4.19)	82	106(6.69)	64(14.4)	630(97-89)
09.12.01	119(5.26)	137(4.29)	82	104(6.63)	61(13.5)	640(96-84)
10.12.14	116(5.09)	136(4.20)	83	100(6.34)	51(11.2)	600(95-81)
11.09.06	112(4.91)	134(4.09)	83	94(5.96)	44(9.1)	575(95-81)
11.10.10	96(4.09)	119(3.58)	87			
11.11.01						435(94-77)

❖ Past medical history

- HTN/DM/pul.TB/Hepatitis(+/-/-/-)

❖ Social history

- Smoking: 8년 전 금연. 1pack X 45Yr
- Occupation: 과거 선반 제작(고무가루, 에폭시 노출, 20년 전 시작)
- 애완동물(-), 비둘기나 새 접촉(-), 화분(-)

❖ Family history

- none

Review of systems

- **General**
  - General weakness(-)
  - Easy fatigability(-)
  - Weight loss(-)
- **Cardiovascular**
  - Chest pain(-)
  - Palpitation(-)
  - Orthopnea(-)
  - Dyspnea on exertion(+)
- **HEENT**
  - Headache(-)
  - Dizziness(-)
  - Sore throat(-)
  - Hoarseness(-)

Review of systems

- **Gastrointestinal**
  - Anorexia(-)
  - Dyspepsia(-)
  - Nausea(-)
  - Vomitting(-)
  - Diarrhea(-)
  - Abdominal pain(-)
- **Neurologic**
  - Seizure(-)
  - Cognitive dysfunction(-)
  - Psychosis(-)
  - Motor/sensory change(-)
- **Genitourinary**
  - Flank pain(-)
  - Gross hematuria(-)
- **Skin**
  - Purpura(-)
  - Erythema (-)

Physical examination

- Height 175cm B.W. 71kg
- Vital sign
  - 113/77 mmHg – 83 회/min – 20 회/min – 38.0 ℃
- SpO_2 : 86% (room air)
- General appearance
  - Chronic ill-looking appearance
  - Mental status: alert
- HEENT
  - Visual field defect(-)
  - Pinkish conjunctiva
  - Icteric sclera(-)
  - Palpable lymph node(-)

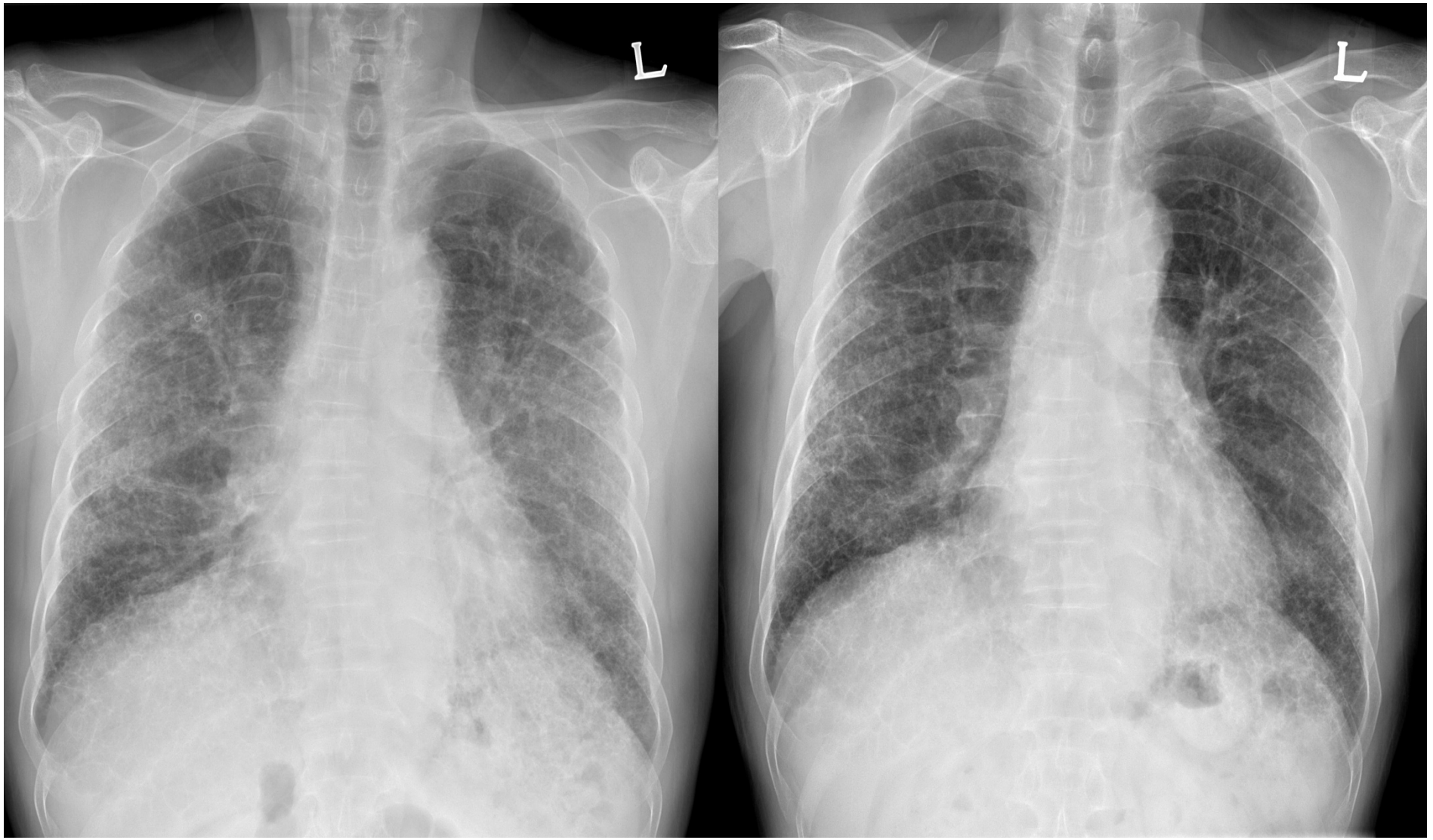
Physical examination

- Thorax
  - Symmetric expansion without retraction
  - Coarse breathing sound with crackle (inspiratory, BLL), wheezing(-)
  - Regualr heart beat without murmur
- Abdomen
  - soft & flat abdomen,
  - normoactive bowel sound, tenderness (-), rebound tenderness (-/-)
- Skin
  - skin turgor: normal, ecchymosis (-), rash (-), purpura (-)
- Back and extremity
  - CVA tenderness(-/-), Pretibial pitting edema (-/-)
- Neurology
  - Motor weakness (-), Sensory disturbance (-)

Initial laboratory data (2011.11.09)

- CBC
  - WBC 2.1x10^3/mm^3(N14L43.9M40.2,ANC 300) > Hb 13.9g/dL < platelet 200x10^3/uL
- Coagulation battery: PT(INR) 83.9%(1.10)/aPTT 28.1sec
- Chemical battery
  - BUN/Cr 9/0.7 mg/dL
  - T.bili/AST(SGOT)/ALT(SGPT)/ALP 0.9/32/18/73 IU/L
  - Calcium/phosphorus 7.4/3.7 mg/dL
  - Glucose 115 mg/dL
  - Protein/albumin 7.5/2.7 g/dL
  - Electrolyte battery(Na/K/Cl/T.CO_2) 124/3.3/93/23.5 mmol/L
  - LD 264 IU/L
  - CRP 7.66 mg/dL, Procalcitonin 0.06 ng/mL
  - BNP 20 pg/mL
- Initial ABGA
  - pH 7.49 – PCO_2 35.0 – PO_2 37.0 – HCO_3^- 27.0 – 76.0 % (Room air)

Chest radiography



2011.11.09

2011.10.10

Initial problem list

#1 Clinical IPF

#2 Fever

#3 Increased cough, sputum

#4 Blood tinged sputum

#5 Aggravation of DOE

#6 Increased GGO at both lung fields in chest X-ray

#7 Hypoxemia

#8 Leukopenia

#9 Elevation of CRP

Initial assessment

#1 Clinical IPF

#2 Fever

#3 Increased cough, sputum

#4 Blood tinged sputum

#5 Aggravation of DOE

#6 Increased GGO at both lung fields in chest X-ray

#7 Hypoxemia

#8 Leukopenia

#9 Elevation of CRP

#1,#2,#3,#4,#5,#6,#7,#8,#9

Atypical or viral pneumonia

#1,#3,#5,#6,#7

Acute exacerbation of underlying clinical IPF

#4,#5,#6,#7

Alveolar hemorrhage

Plan

#1,#2,#3,#4,#5,#6,#7,#8,#9

Atypical or viral pneumonia

#1,#3,#5,#6,#7

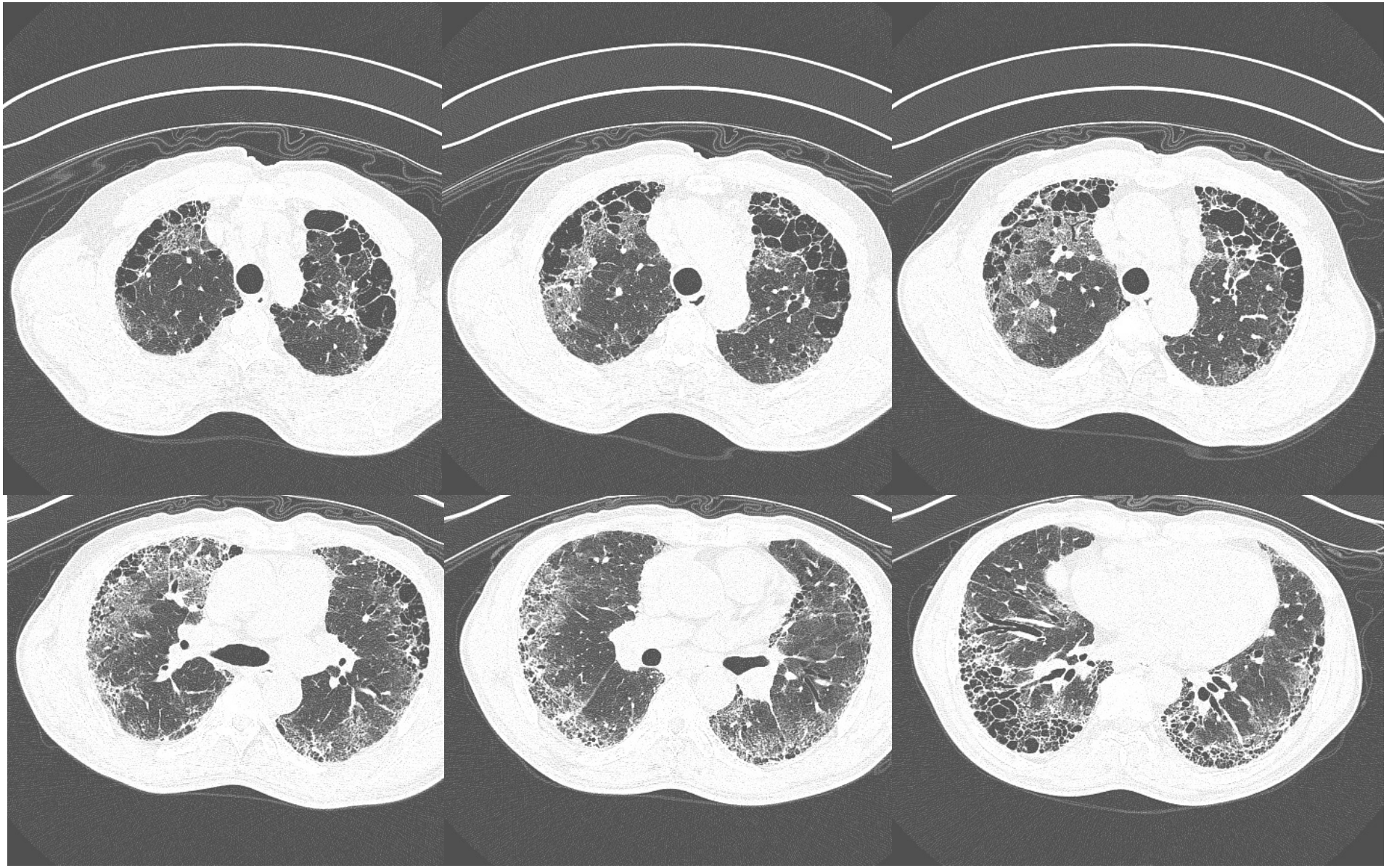
Acute exacerbation of underlying clinical IPF

#4,#5,#6,#7

Alveolar hemorrhage

- Diagnostic plan
  - ✓ HRCT
  - ✓ Consider BFS with BAL
  - ✓ Blood culture, Sputum Gram stain/culture
  - ✓ Sputum atypical pneumonia PCR
  - ✓ Respiratory virus multiplex PCR
- Therapeutic plan
  - ✓ O2 supply
  - ✓ Start Antibiotics covering atypical pathogens and antiviral agent
  - ✓ Systemic Steroid

Chest CT (2011.11.09)



BFS c BAL (2011.11.09)

- Blood streaks in Lt main to LUL bronchus
- No evidence of active bleeding
- BAL at RUL anterior seg.(100->72cc)
  - Aggravating redness in recruited BAL fluid
  - Bloody turbid color
  - S.G. 1.025
  - RBC 23,000
  - WBC 110
    - N 1% **L 24%** Eo 3% AM 72%
    - CD4/CD8 3.71(505/136)
- **A> diffuse alveolar hemorrhage**
- **PD 60mg start**

BFS c BAL

(2011.11.09)

HD #1 (2011.11.10)

- Lab
  - 호흡기바이러스 PCR(BAL,Nasopharyngeal swab) : Parainfluenza virus 2
- Assessment
  - Parainfluenza viral pneumonia
  - Diffuse alveolar hemorrhage due to viral infection
  - Underlying clinical IPF
- Treatment plan
  - Antiviral agent (ribavirin) + IVIG
  - PD stop
  - O2 supply via Heated humidified high flow nasal cannula
  - Close monitoring in MICU

HD #3

❖ Vital sign

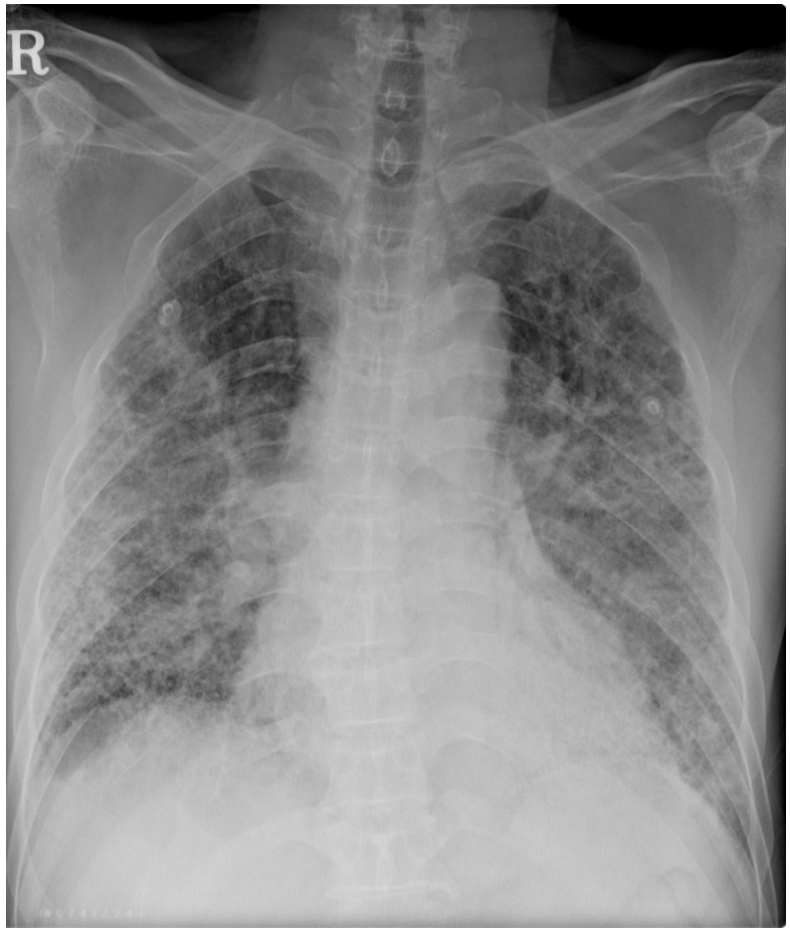
- 105/57 mmHg – 65 회/min – 17 회/min – 36.4 ℃
- 94% (FiO2 80%)
- Blood tinged sputum(+): decreased amount

❖ Lab

- WBC 10.4x10^3/mm^3 (N 80.6%)
- Hb 13.4g/dl
- Platelet 181x10^3/uL
- CRP 21.97 mg/dL
- Procalcitonin 4.44 ng/mL
- ABGA 7.440 – 46.0 – 84.0 – 31.0 – 97.0%
- BAL virus culture: PIV2(+)

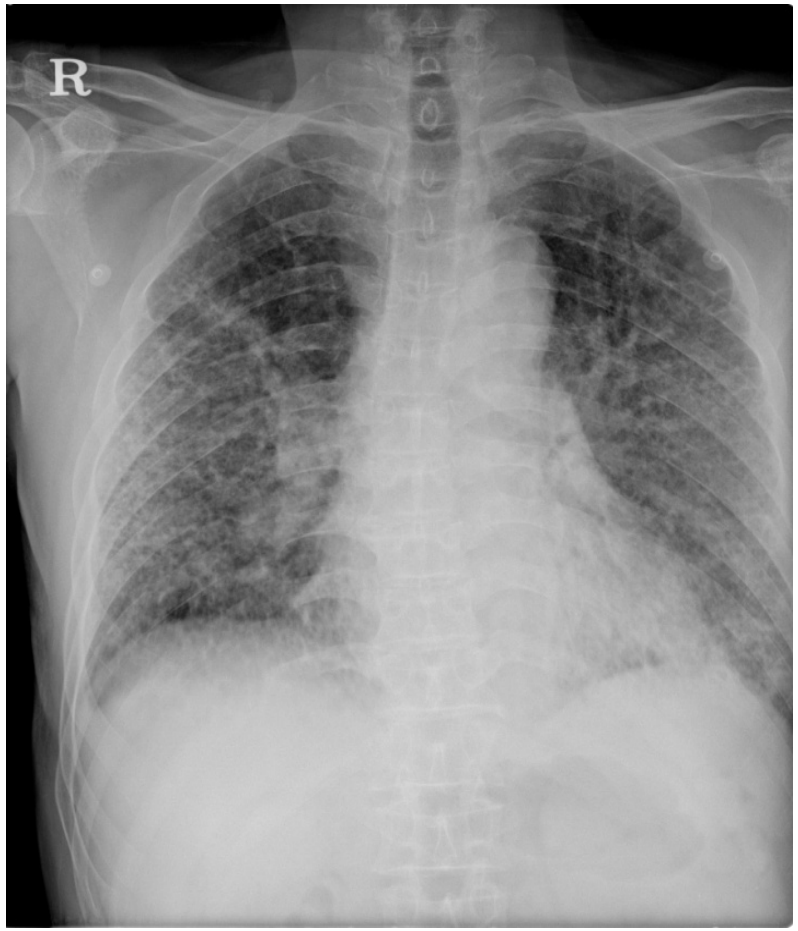
❖ CXR

- Increased extent of multifocal patch GGO in peripheral portion of both lungs.



HD #7

- **Vital sign**
  - 108/66 mmHg – 78 회/min – 22 회/min – 36.3 ℃
  - 93% (FiO2 100%)
  - Blood tinges sputum(-)
- **Lab**
  - WBC 7.6x10^3/mm^3(seg 74.7%)
  - Hb 13.8g/dl
  - Platelet 245x10^3/uL
  - CRP 9.16 mg/dL
  - ABGA 7.480 – 35.0 – 77.0 – 26.0 – 96.0%
- **Planning for lung transplantation**



HD #9

❖ Vital sign

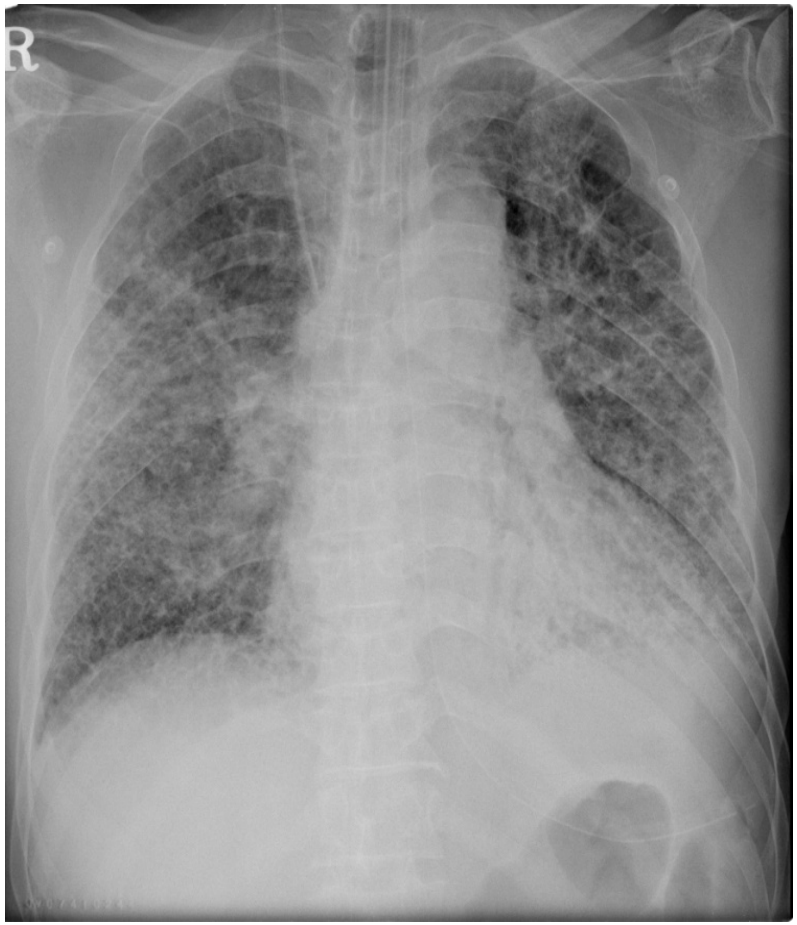
- Intubated

  refractory hypoxia(83%) and hypercapnea
- 94/58 mmHg – 122 회/min – 34 회/min – 37.1 ℃
- 91% (MV: FiO2 55%, Pr 16-10mmHg + NO)
- NE 0.36ug/kg/min, dobutamine 10ug/kg/min

❖ Lab

- WBC 10.6x10^3/mm^3(seg 76.8%)
- Hb 12.9g/dl
- Platelet 264x10^3/uL
- CRP 13.58 mg/dL
- ABGA 7.310 – 51.0 – 96.0 – 26.0 – 97.0%

  7.190 – 70.0 – 79.0 – 27.0 – 92.0%



HD #11

❖ Vital sign

- 106/67 mmHg – 113 회/min – 28 회/min – 38.5℃
- 96% (MV, NO) : FiO2 50%, Pr 20-5mmHg
- NE 0.32ug/kg/min, dobutamine 3ug/kg/min

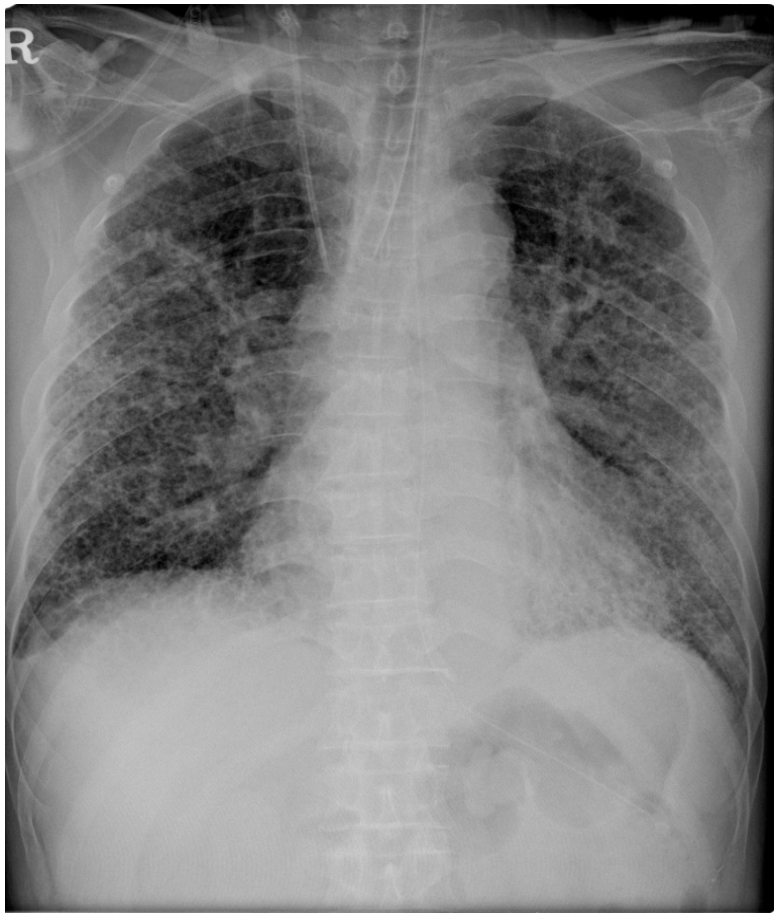
❖ Lab

- WBC 12.7x10^3/mm^3(seg 82.9%)
- Hb 11.7g/dl, Platelet 199x10^3/uL
- BNP 1186pg/mL
- CRP 15.57 mg/dL
- ABGA 7.350 – 48.0 – 77.0 – 27.0 – 95.0%

❖ Echo

- RV dysfunction: LV sys D-shape: TR(2-3)
  - TR Vmax 4.3m/s, PGsys 74mmHg
  - severe pul.HTN
- LV contractility 저하

❖ Sildenafil try



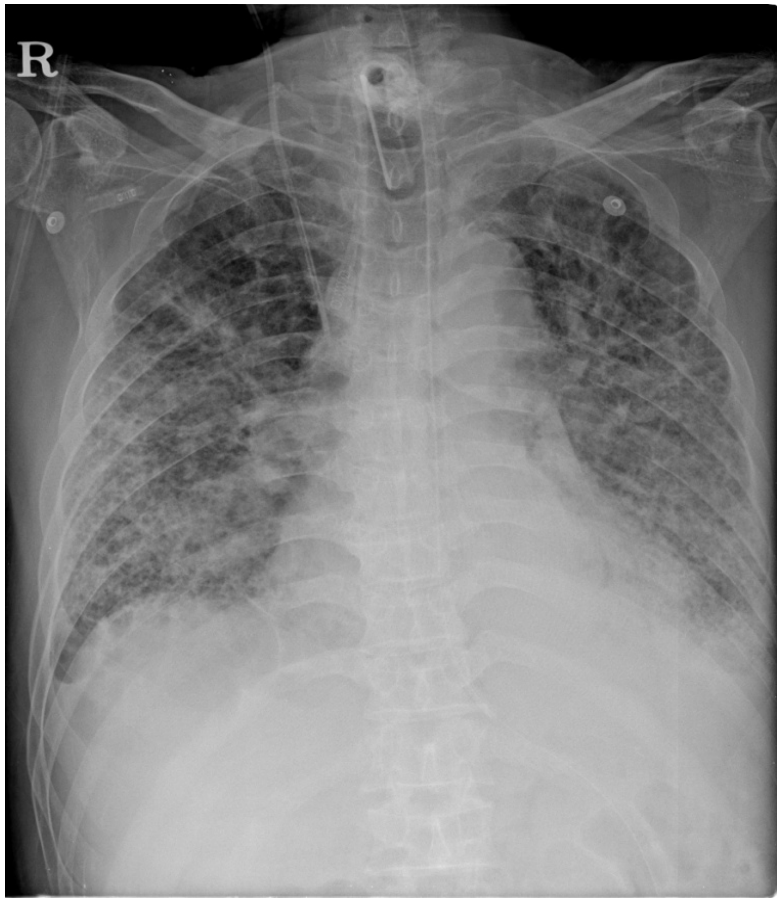
HD #22

❖ Vital sign

- 117/64 mmHg – 87 회/min – 25 회/min – 38.0 ℃
- 99% (MV, NO): FiO2 65%, Pr 14-5mmHg
- NE tapered, dobutamine 3μg/kg/min

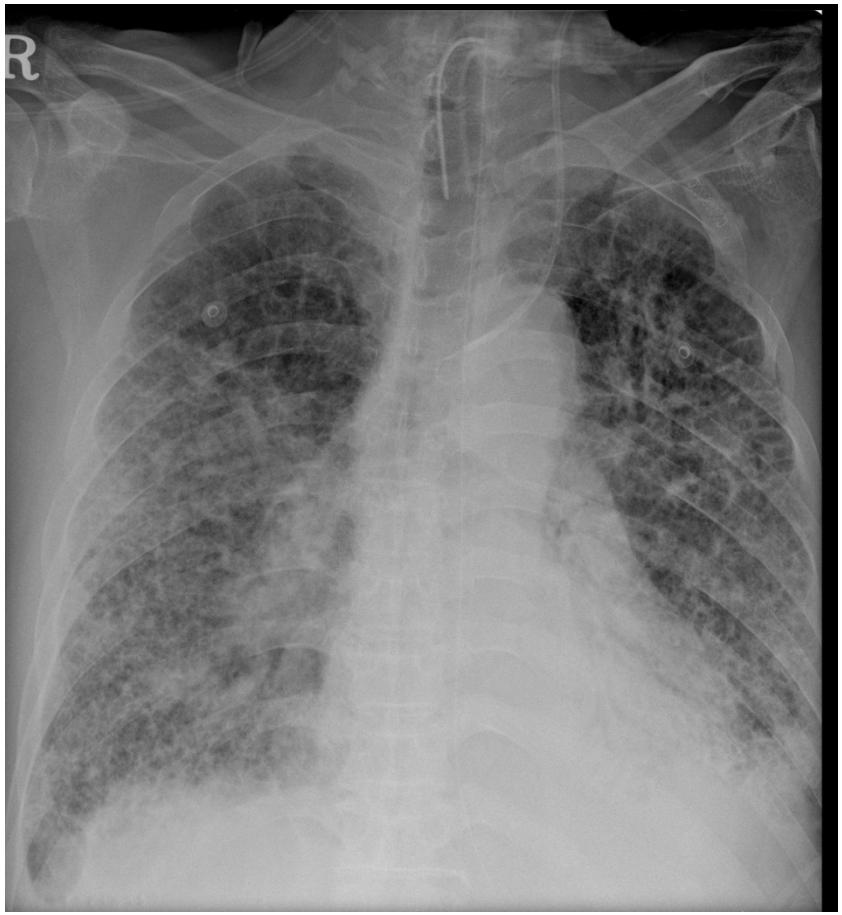
❖ Lab

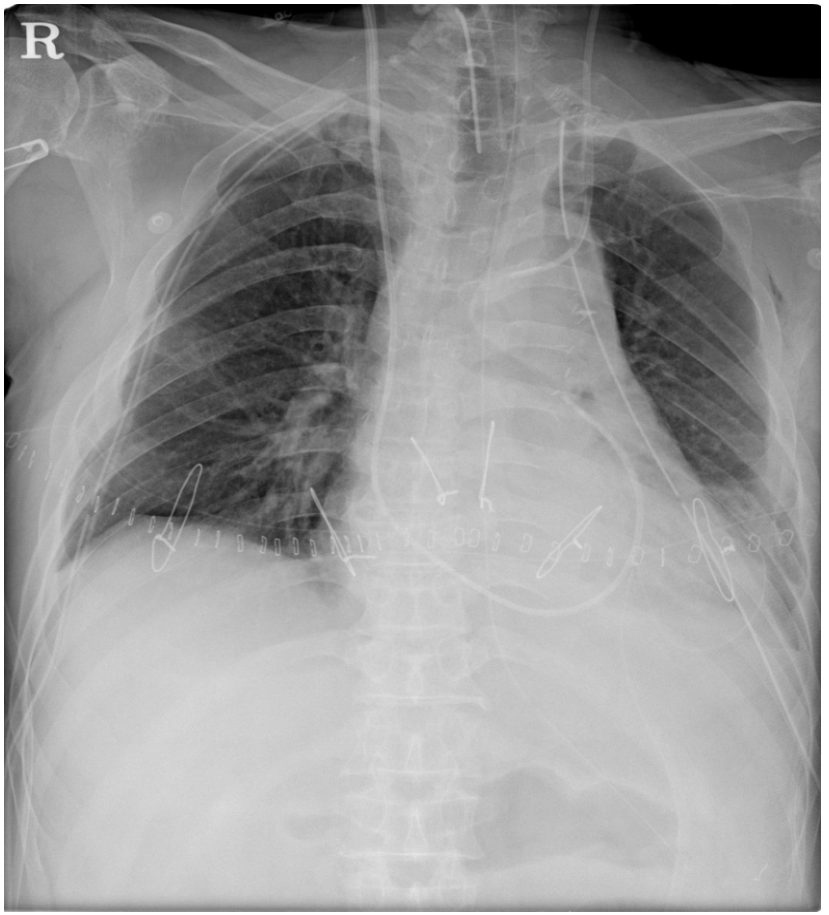
- WBC 7.9x10^3/mm^3(seg 77.2%)
- Hb 9.4g/dl
- Platelet 133x10^3/uL
- CRP 7.97 mg/dL
- ABGA 7.430 – 65.0 – 70.0 – 43.0 – 94.0%



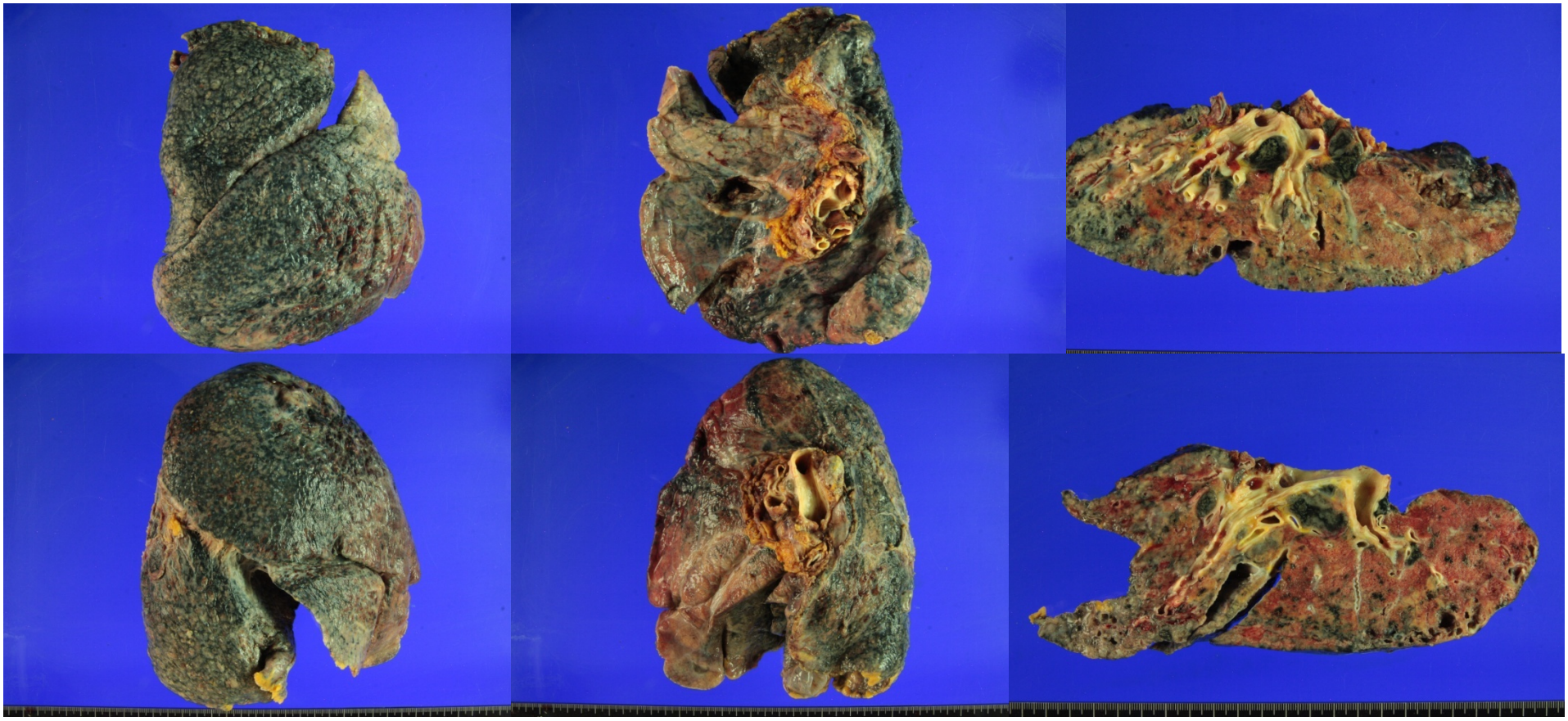
HD #26

❖ **Bilateral lung tranplantation was done.**





Explantated lung

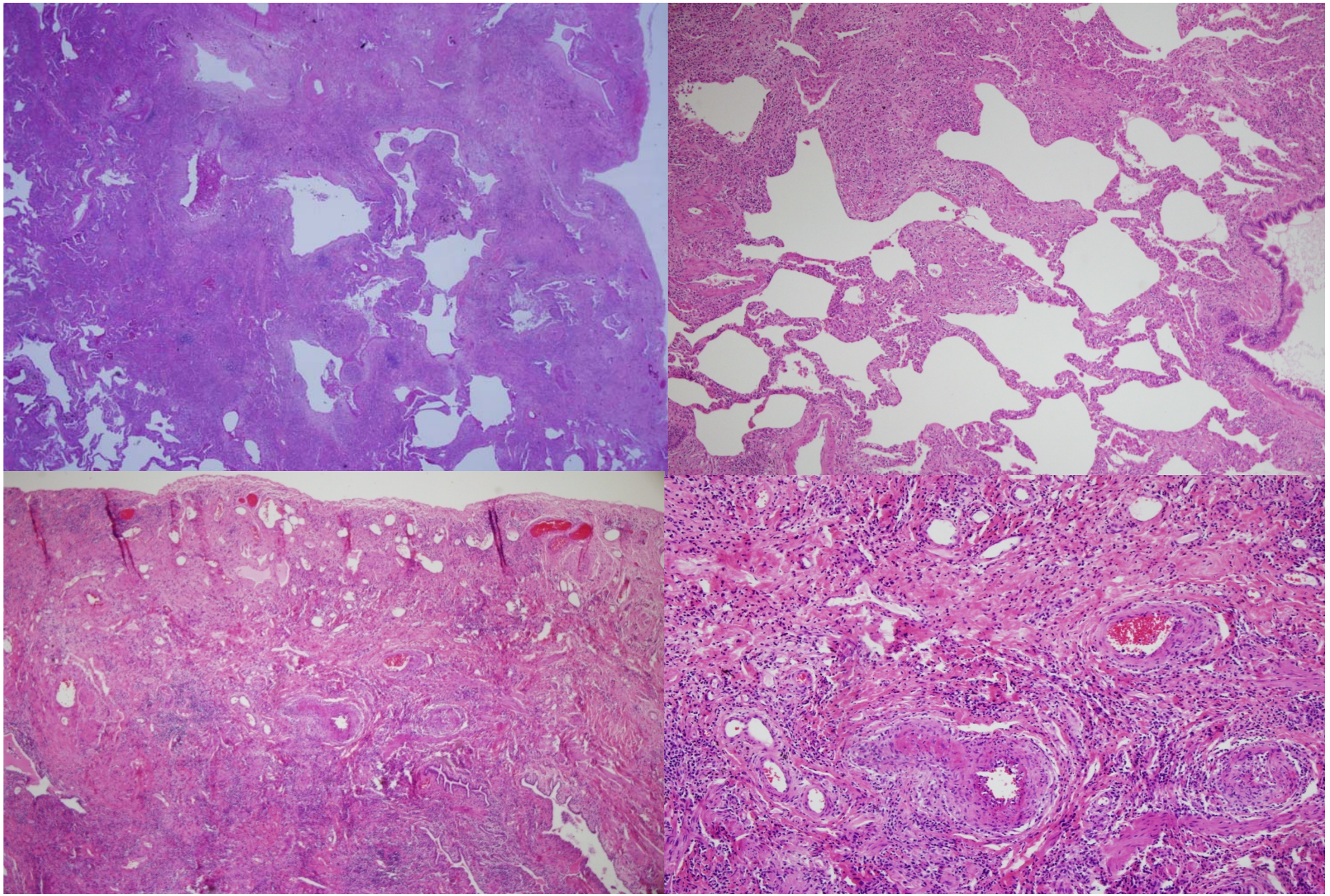


Tissue culture: no growth of RSV,influenza,parainfluenza,adenovirus,CMV

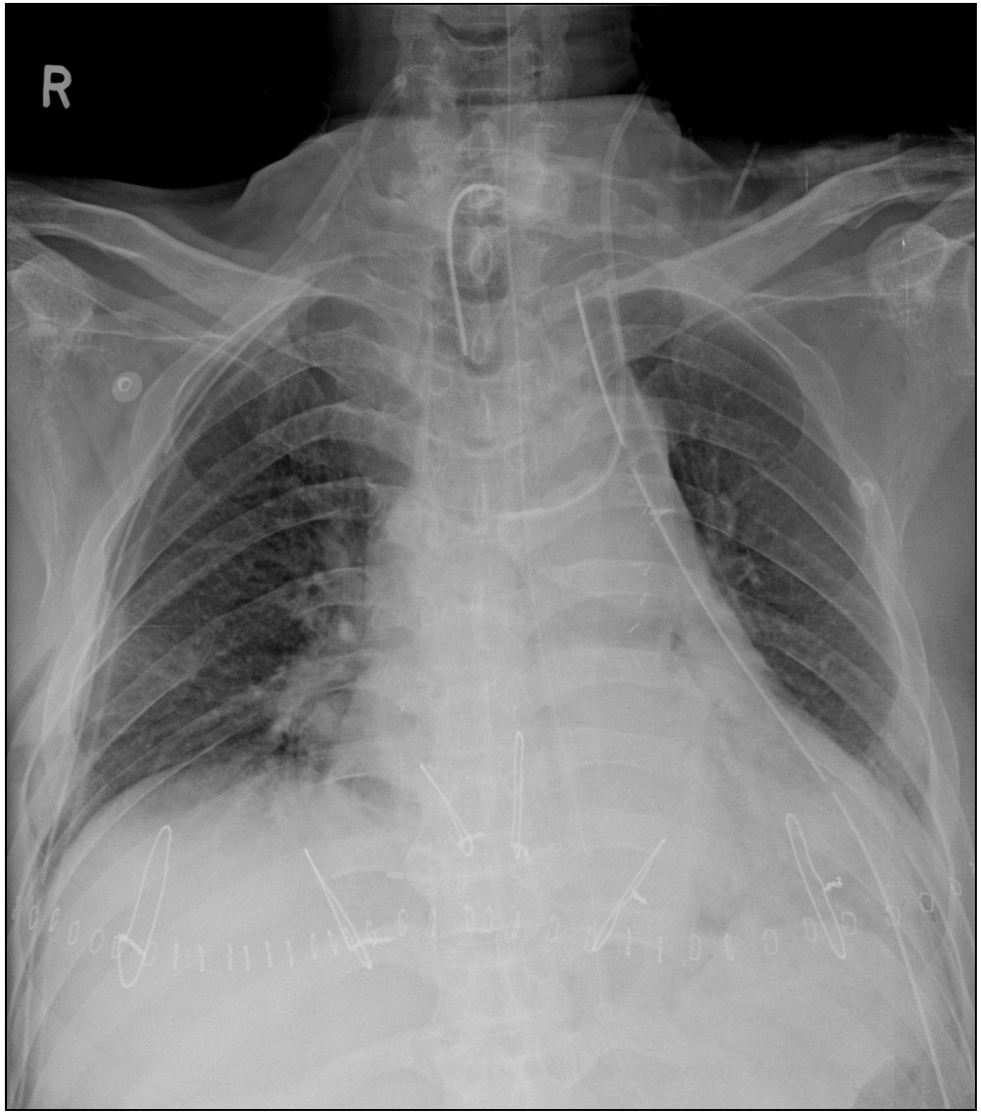
Pathology of explantated lung

- End stage lung disease,
  - 1) areas of mature fibrosis and honeycomb change, suggesting underlying idiopathic pulmonary fibrosis.
  - 2) diffuse organizing acute lung injury pattern and extensive interstitial inflammation.
  - 3) multifocal granulomas.
  - 4) diffuse necrotizing pulmonary vasculitis.

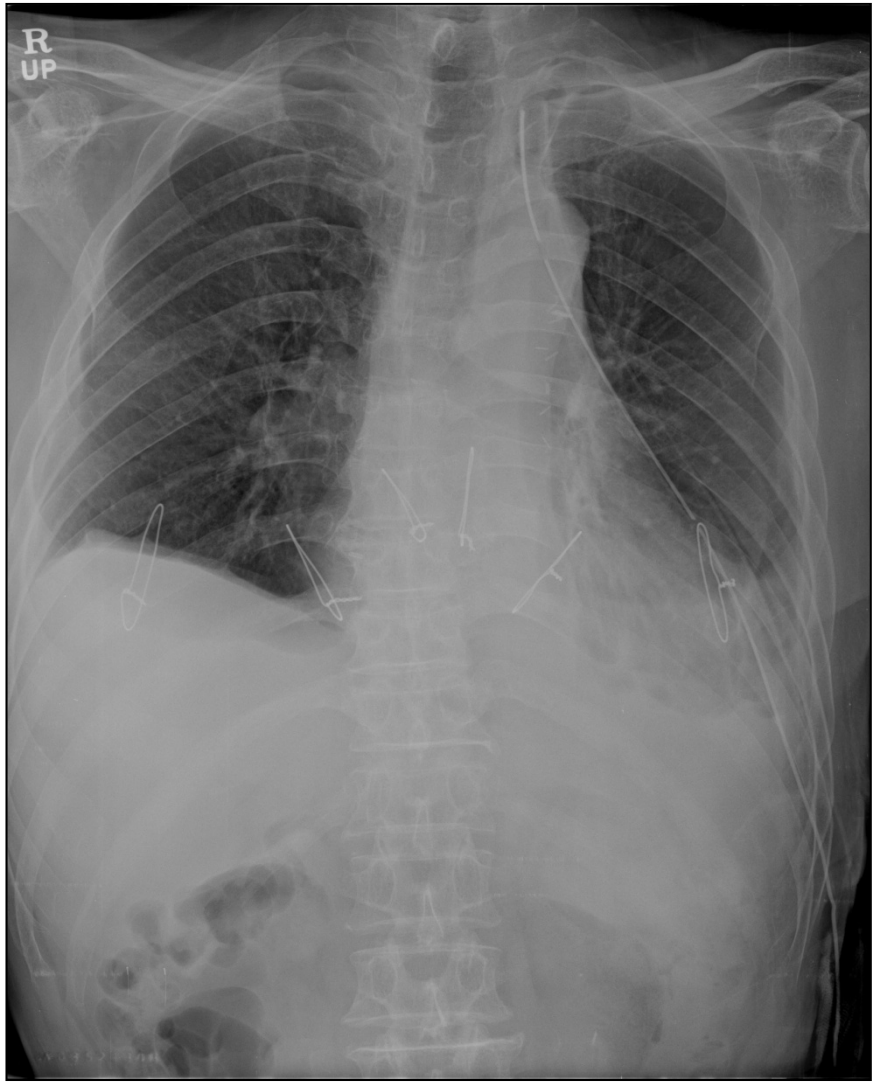
Pathology of explantated lung

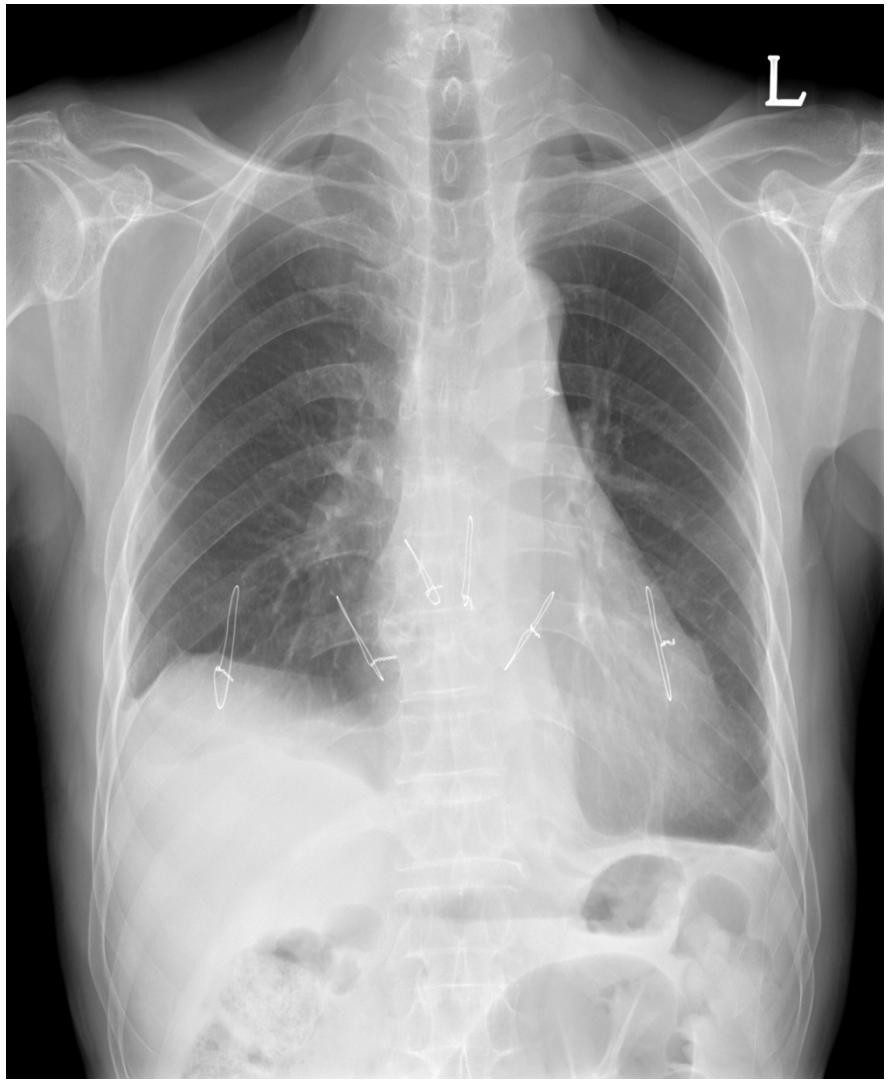


HD #34, POD#8 (2011.12.12) : GW 전동



HD #70, POD #44 (2012.1.17) : T-can removal
HD #123, POD # 97 (2012.3.10) : discharge





Review : Vascultitis and PIV

Clinical scenarios suggestive of vasculitis

- Destructive upper airway lesions
- Chest imaging findings of cavitary or nodular disease
- Diffuse alveolar hemorrhage
- Acute glomerulonephritis
- Pulmonary-renal syndrome
- Palpable purpura
- Mononeuritis multiplex
- Multisystem disease

DAH(diffuse alveolar hemorrhage)

- **Clinical features**
  - Hemoptysis
  - Anemia
  - Diffuse radiographic pulmonary infiltrates
  - Hypoxemic respiratory failure
- **Histopathology**
  - intraalveolar RBCs and fibrin
  - eventual accumulation of hemosiderin-laden macrophages
- **histologies that are associated with DAH**
  - pulmonary capillaritis
  - bland pulmonary hemorrhage
  - diffuse alveolar damage
  - Miscellaneous histology

Vasculitis: specific testing

- Antinuclear Cytoplasmic Antibodies immunofluorescent testing
  - c-ANCA, p-ANCA
- PR3 and MPO ELISA testing
- **c-ANCA**
  - highly sensitive (90% to 95%) in active, systemic NGV
  - but slightly less so (65% to 85% sensitive) in organ-limited disease.
  - Specificity is approximately 90%
- **positive c-ANCA/anti-PR3**
  - sufficient positive predictive value
- **positive p-ANCA and anti-MPO**
  - lack sufficient sensitivity
  - may provide no more than suggestive evidence of CSS, MPA, or pauci-immune rapidly progressive glomerulonephritis
  - Because, they can be found in rheumatoid arthritis, Goodpasture's syndrome, and a wide variety of other clinical circumstances.

Classification of vasculitis

1. Primary idiopathic	
Small vessel	Necrotizing granulomatous vasculitis(NGV)
	Churg-Strauss syndrome(CSS)
	Microscopic polyangiitis(MPA)
	Idiopathic pauci-immune glomerulonephritis
	Idiopathic capillaritis
Medium vessel	Polyarteritis-nodosa(PAN)
	Kawasaki's disease
Large vessel	Takayasu's arteritis(TA)
	Giant cell arteritis
2. Primary immune complex mediated	
	Goodpasture's syndrome
	Henoch-Schonlein purpura
	Immunoglobulin A nephropathy
	Behcet's disease
	Essential cryoglobulinemia

Classification of vasculitis

3. Secondary vasculitis	
Classic autoimmune disease	Systemic lupus erythematosus(SLE)
	Rheumatoid arthritis(RA)
	Antiphspholipid antibody syndrome(APAS)
Infection	
Paraneoplastic	
Drug-induced	e.g., propylthiouracil
Inflammatory bowel disease	
Hypocomplementemic urticarial vasculitis	

Infection and Vasculitis

- **Experimental animal models of vasculitis which suggest that infection could be a trigger in vasculitis.**
  - parvovirus infection in Aleutian mink leading to vasculitis similar to human PAN
  - epidemic equine coronavirus infection which is followed by endothelial infection with local inflammation and fibrinoid necrosis
  - streptococcal toxins injected into the ear arteries of rabbits
  - Chlamydia pneumoniae was shown to induce aortic vasculitis
  - RNA virus and/or herpes virus produced aortitis
  - Infection of golden hamsters with eastern equine encephalitis virus
    - vasculitis with cerebral micro-haemorrhages

Rheumatology 2009;48:475–482

Infection and Vasculitis

TABLE 1. Infectious agents and PAN

Infectious agent	Frequency of association (references)	Supporting data
HBV	Strong [27–30]	Prevalence studies, virol
Streptococcus β-haemolyticus	Possible [33–35]	Anecdotal case reports
Klebsiella	Weak [36]	Anecdotal case reports
Pseudomonas	Weak [36]	Anecdotal case reports
Yersinia	Weak [37]	Anecdotal case reports
HIV	Weak [38–40]	Anecdotal case reports
Parvovirus B19	Weak [41, 42]	Anecdotal case reports
VZV	Weak [43]	Anecdotal case reports
Echinococcus	Weak [44, 45]	Anecdotal case reports
Trichinella	Weak [44, 46]	Anecdotal case reports
Ascaris	Weak [44, 45]	Anecdotal case reports

TABLE 3. Infectious agents and WG

Infectious agent	Frequency of association	Supporting da
Staphylococcus aureus	Possible [69–71]	Serological, virolc
Parvovirus B19	Weak [76, 77]	Anecdotal cases
Nocardia	Weak [78]	Anecdotal cases

TABLE 6. Infectious agents and GCA

Infectious agent	Frequency of association	Supporting
Chlamydia pneumoniae	Possible [9, 119–121]	Serological
Parvovirus B19	Possible [9, 119–121]	Serological
Parainfluenza virus	Possible [9, 119–121]	Serological

TABLE 4. Infectious agents and KD

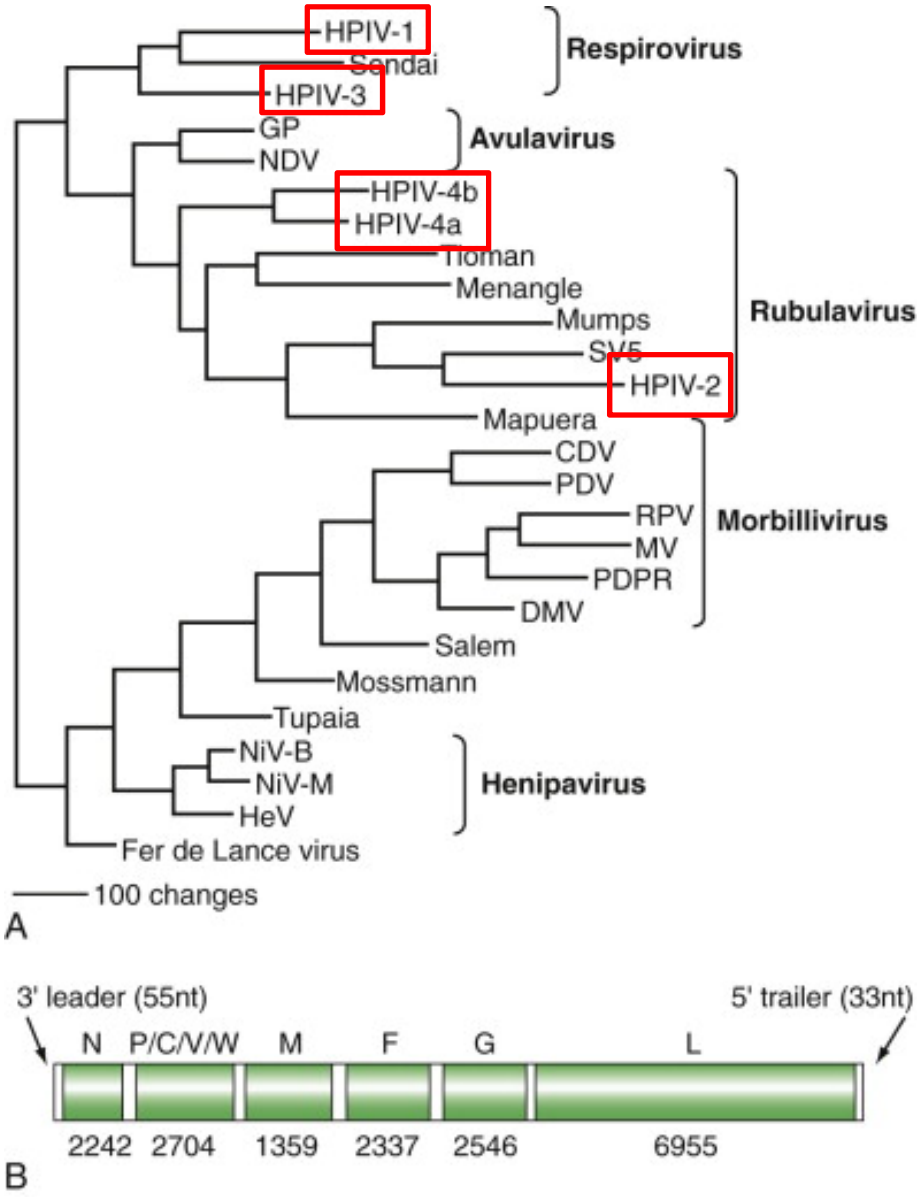
Putative aetiological agent	Frequency of association	Supporting data
Adenovirus	Weak [79]	Anecdotal
Herpes virus	Weak [80]	Anecdotal
Mycoplasma species	Weak [81]	Anecdotal
Toxigenic streptococci	Weak [82, 83]	Anecdotal
Toxigenic staphylococci	Weak [83–85]	Anecdotal
Propionibacterium acnes	Weak [86]	Anecdotal
Ehrlichia chaffeensis	Weak [87, 88]	Anecdotal
Rickettsia species	Weak [89, 90]	Anecdotal
EBV	Weak [91, 92]	Anecdotal
Retrovirus	Weak [93, 94]	Anecdotal
Human coronavirus New Haven	Weak [95]	Anecdotal
Measles virus	Weak [96, 97]	Anecdotal
Chlamydia pneumoniae	Weak [98, 99]	Anecdotal
Bartonella henselae	Weak [100]	Anecdotal
Coxiella burnetii	Weak [101, 102]	Anecdotal
Lactobacillus	Possible [103]	Experimental
Candida	Possible [104]	Experimental

TABLE 5. Infectious agents and TA

Infectious agent	Frequency of association	Supporting data
Mycobacterium tuberculosis	Possible [110]	Laboratory tests and anecdotal cases
Chlamydia pneumoniae	Possible [111, 112]	Experimental
RNA virus	Possible [113, 114]	Experimental
Herpes virus	Possible [113, 114]	Experimental
CMV	Possible [115, 116]	Experimental

Rheumatology 2009;48:475–482

Paramyxoviridae family



❖ Phylogenetic tree of the subfamily Paramyxovirinae based on the nucleocapsid gene sequence (A) and schematic of the Nipah virus genome (B).

(Reprinted from Lo MK, Rota PA. The emergence of Nipah virus, a highly pathogenic paramyxovirus. J Clin Virol. 2008;43:396-400.)

Parainfluenza viruses

worldwide distribution, and almost **all persons are infected initially during childhood**.

Type 1, 2, 3, 4A/4B (on the basis of natigenic differences)

Infections by type 3 : infancy

Infections by type 1 and 2 : prevented by maternal antibody and usually occur later

seasonality for type 1 : biennial outbreaks in the fall of odd-numbered years

yearly outbreaks of type 3 : annually in the spring, smaller fall outbreaks(no type 1 OB)

type 2 : much less frequently, but appeared to be more prevalent in the fall

type 4 does not exhibit notable seasonality

Transmission :

from person to person:

direct contact with infectious respiratory secretions or by large-particle aerosols

incubation period is approximately 3 to 6 days

high attack rates (40% to 80%)

Parainfluenza viruses

- Croup, pneumonia, and exacerbations of COPD in adults and the elderly
- Upper respiratory illness may be absent and nasopharyngeal cultures negative, **bronchoalveolar lavage is often required for diagnosis**.
- Treatment

  currently no available antiviral agents of proven effectiveness against PIV

  Ribavirin: active in vitro, aerosolized ribavirin(not delayed treatment)

  IV or aerosolized ribavirin or both

    in immunosuppressed patients with severe parainfluenza virus infection

    inconsistent clinical benefits

  Aerosolized ribavirin

    in solid organ transplant recipients

    seems ineffective in parainfluenza virus pneumonia in HSCT recipients