MDA-5 associated rapid progressive ILD with Clinically Amyopathic Dermatomyositis (CADM)

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PATIENT CASE: F/65

- **Chief Complaint**
  Dyspnea for 2 month, aggravating for last 1 month

- **Present Illness**

  특이 과거력 없는 65세 여환으로 **2021년 7월 mMRC 1**의 DOE 대해 타병원 내원하여 시행한 Chest CT 및 FOB BAL 검사상 r/o COP, r/o NSIP 의증 하 **methylprednisolone 40mg 투약**하였고, **내원 2주 전부터** mMRC 2로 **DOE 악화 및 발열** 있어 타병원 입원하여 **스테로이드 증량**하였고 BAL 상 PCP PCR positive 소견으로 SMX/TMP 투약 및 Sputum Cx 상 Klepsiella Pneumoniae 동정에 대해 항생제 치료하였던 환자임. 상기 치료에도 불구하고 호흡곤란 악화와 산소요구량 증가 보여 2021년 8월 본원 호흡기내과 외래 내원하여 r/o ILD, r/o AIP 의증 하 진단과 항생제, 스테로이드 치료 위해 입원함.

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- **Previous Medical History**

  None
  Never smoker
  Occupation: 음식점 운영 20년
  Place of Living: 16년 아파트
  Family Hx: none

- **V/S**

  BP 113/73 mmHg, PR 90/min, RR 24/min, BT 36.6℃, SpO2 90-94% at O2 6L/min

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- **ROS**

  DOE + : 2개월 전 mMRC I -> 1개월 전 mMRC II / Cough + / Sputum +

  Wrist joint pain + / skin rash at hand + : 1개월 전 발생

  Fever +: 2주 전 발생

  Dry mouth + / Dry Eye + / Oral Ulcer + / 속쓰림 + / 레이노 –

- **Physical Examination**

  Subungual Skin Rash (R/O Gottron papules) +

  Mechanic's hand +

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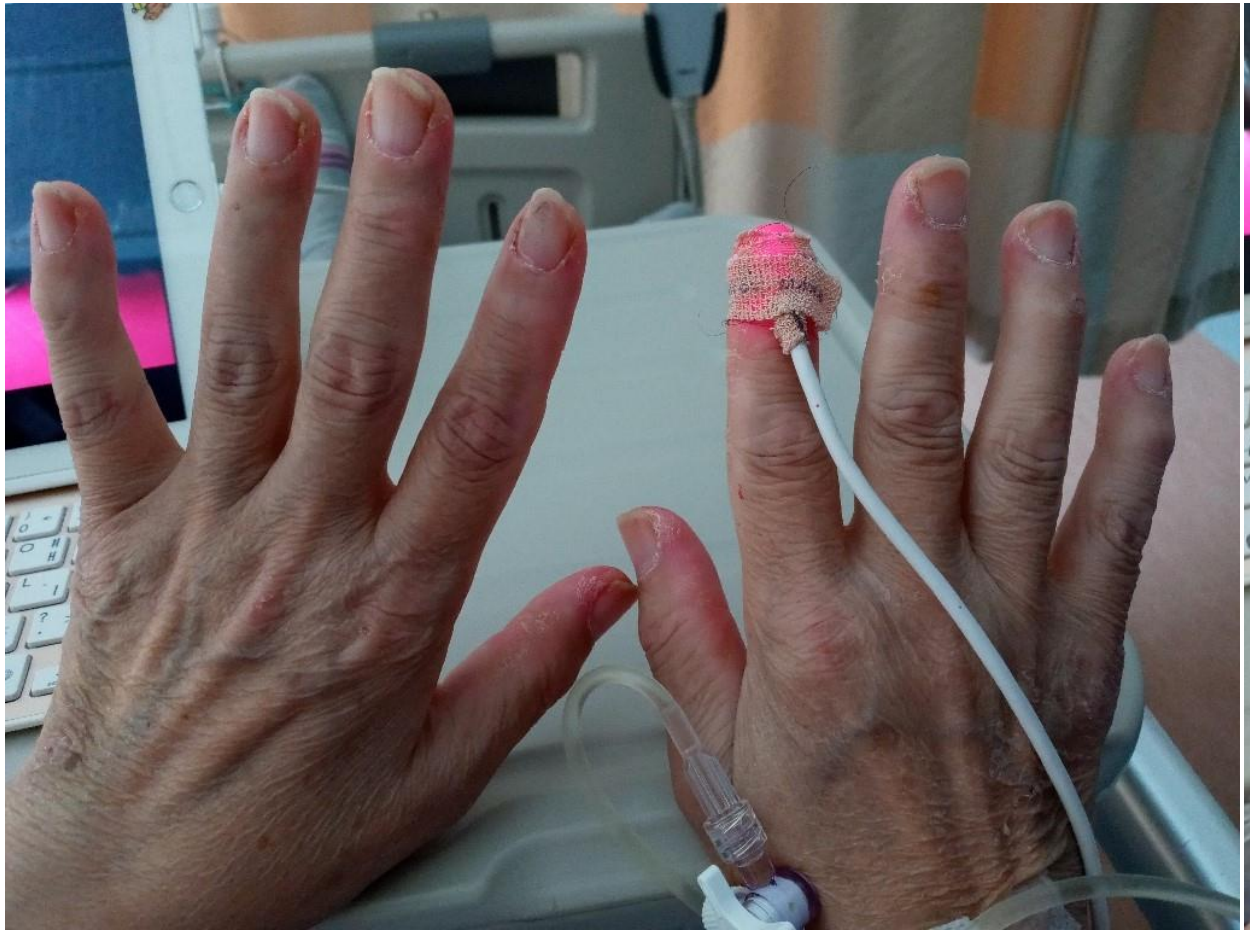
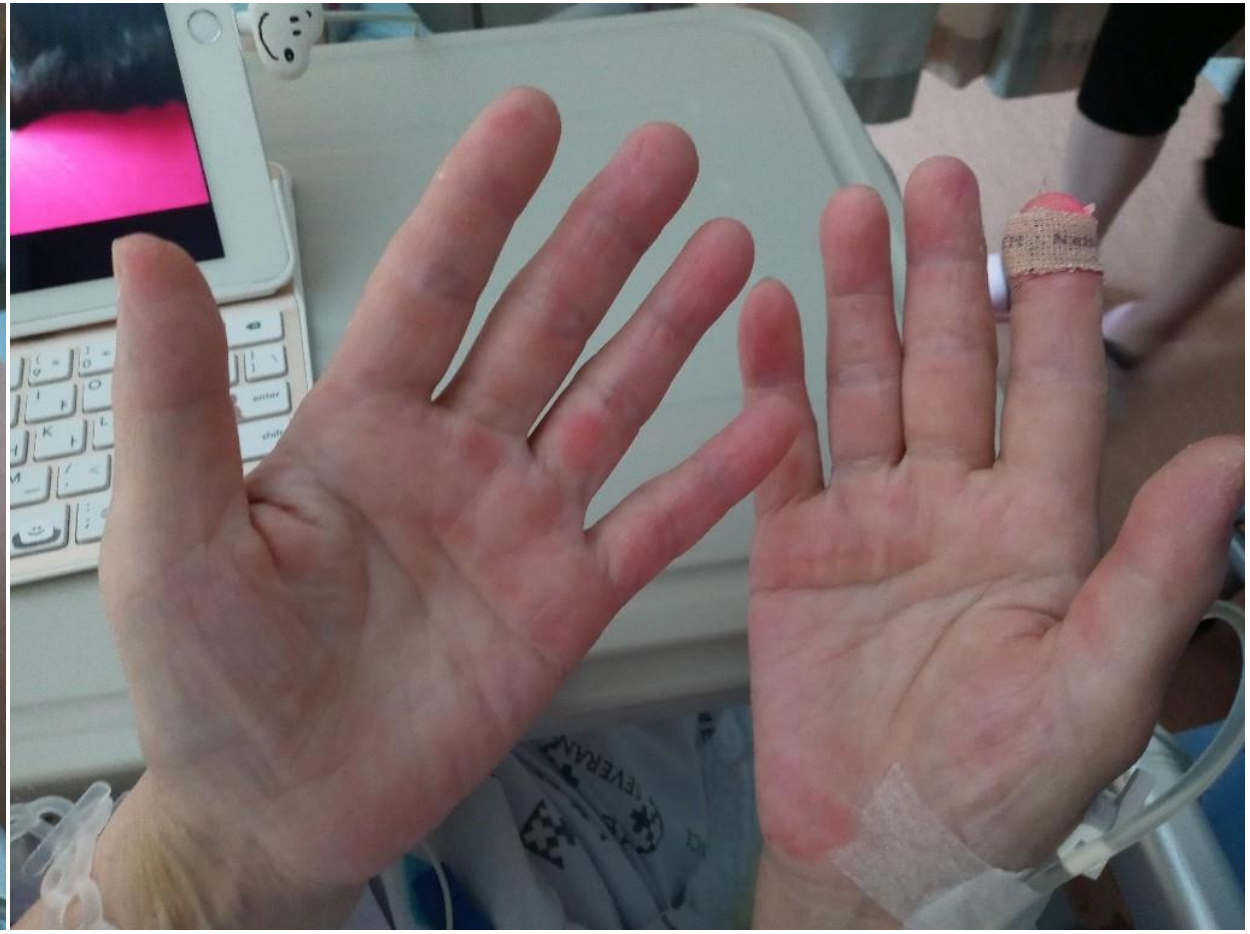
- **Physical Examination – Skin Rash (HOD #1)**





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- **2021/7/9 타병원 FOB** : no endobronchial lesion and mucosal change.
  BAL at LLL posterobasal- 의무기록사본상 Cytology negative, **PCP PCR positive (34.5)**만 확인 가능함

- **2021/7/24 타병원 검사**

CBC	7.66 (N 87.8%) / 12.3 / 345k
BUN/Cr (eGFR)	13.1 / 0.81 (eGFR >60)
E'	131 / 4.3 / 99 / -
AST/ALT/T.bil	**67 / 62** / 0.1
Troponin-T/NT-proBNP	0.008 / 129
LDH	**344**
CK / Aldolase	73 / -
CRP / Procalcitonin	2.91 (normal 0.5) / 0.06

Sputum Cx: alpha-hemolytic streptococcus (7/24), **K.pneumoniae (ESBL +, carbapenem S, 7/31)**
Atypical pathogen PCR / Urine Legionella Ag / Urine S.pneumoniae Ag / M.pneumoniae IgM - / - / - / -
TB Xpert PCR / AFB - / -
U/A WNL
Blood Cx: no growth

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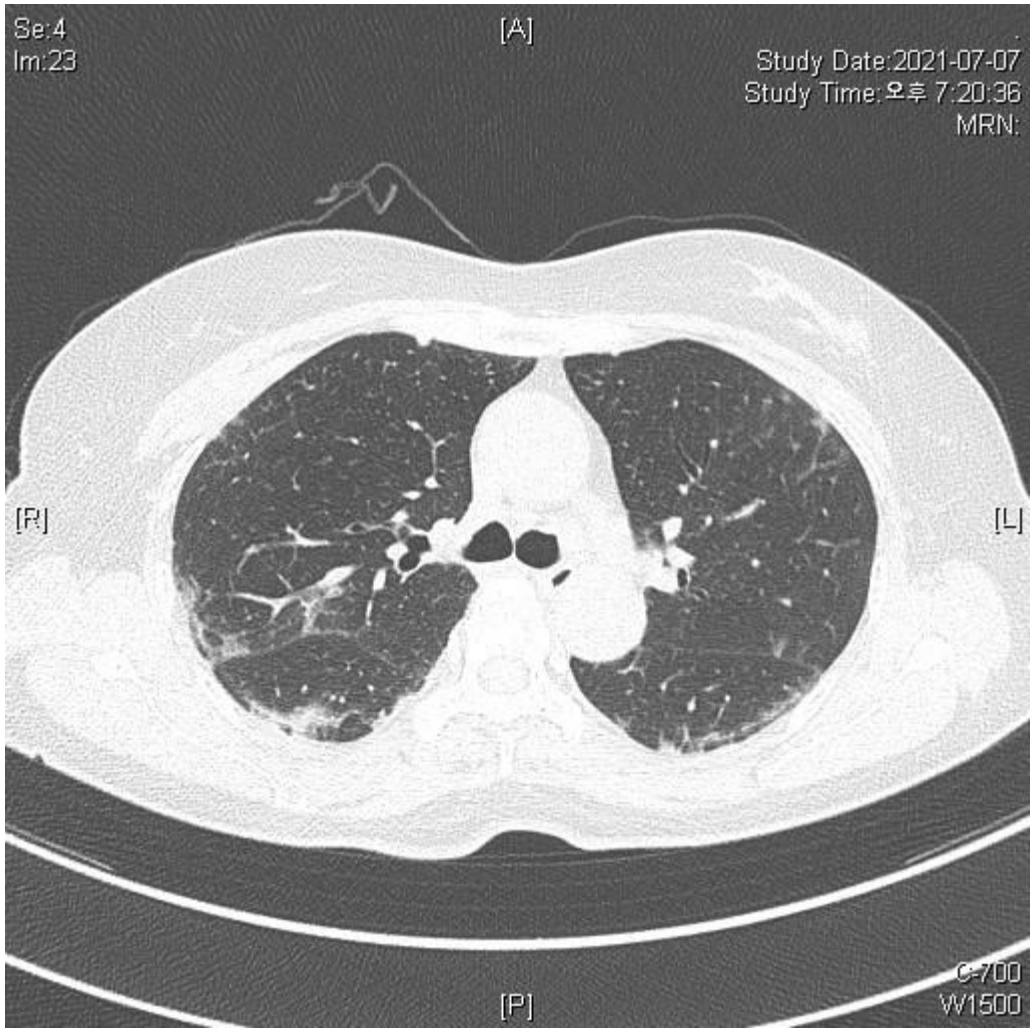
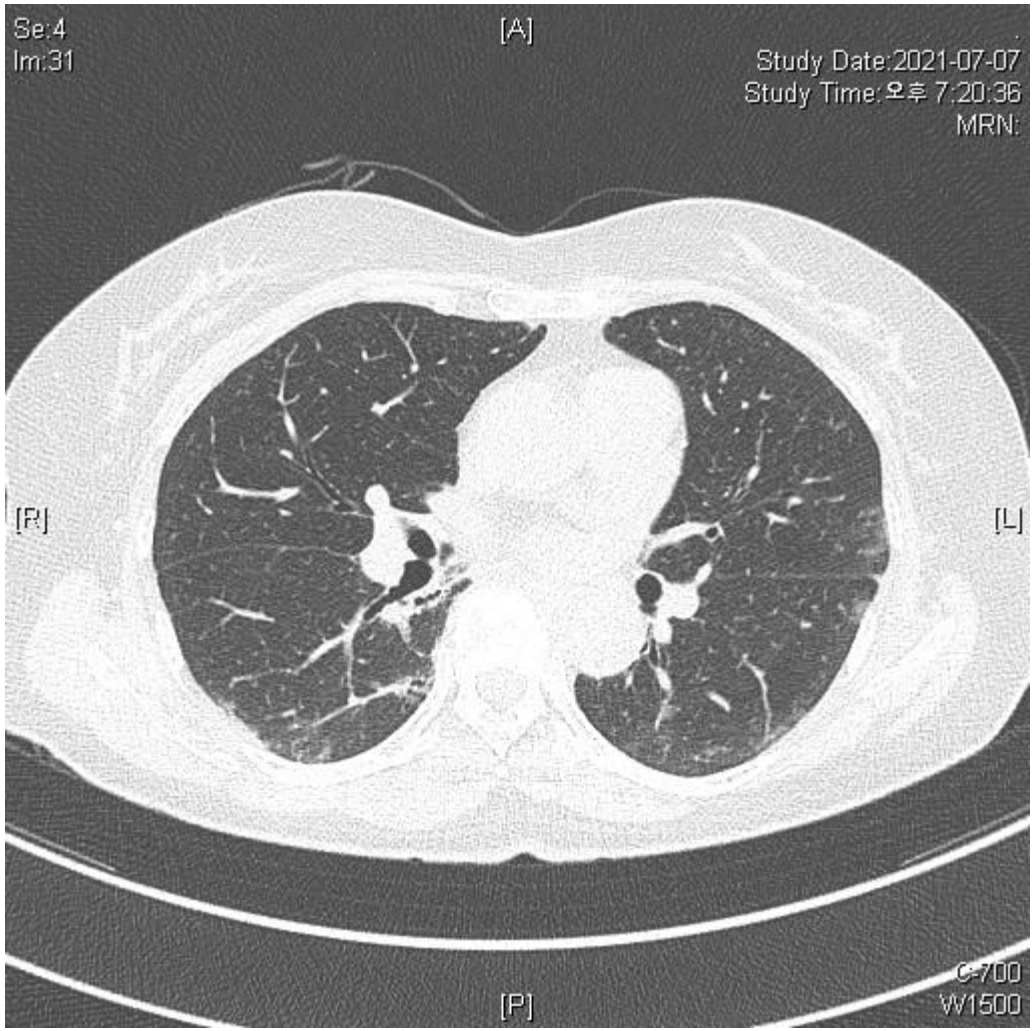
- **Chest CT Scan (2021/7/7, 내원 1개월 전)**





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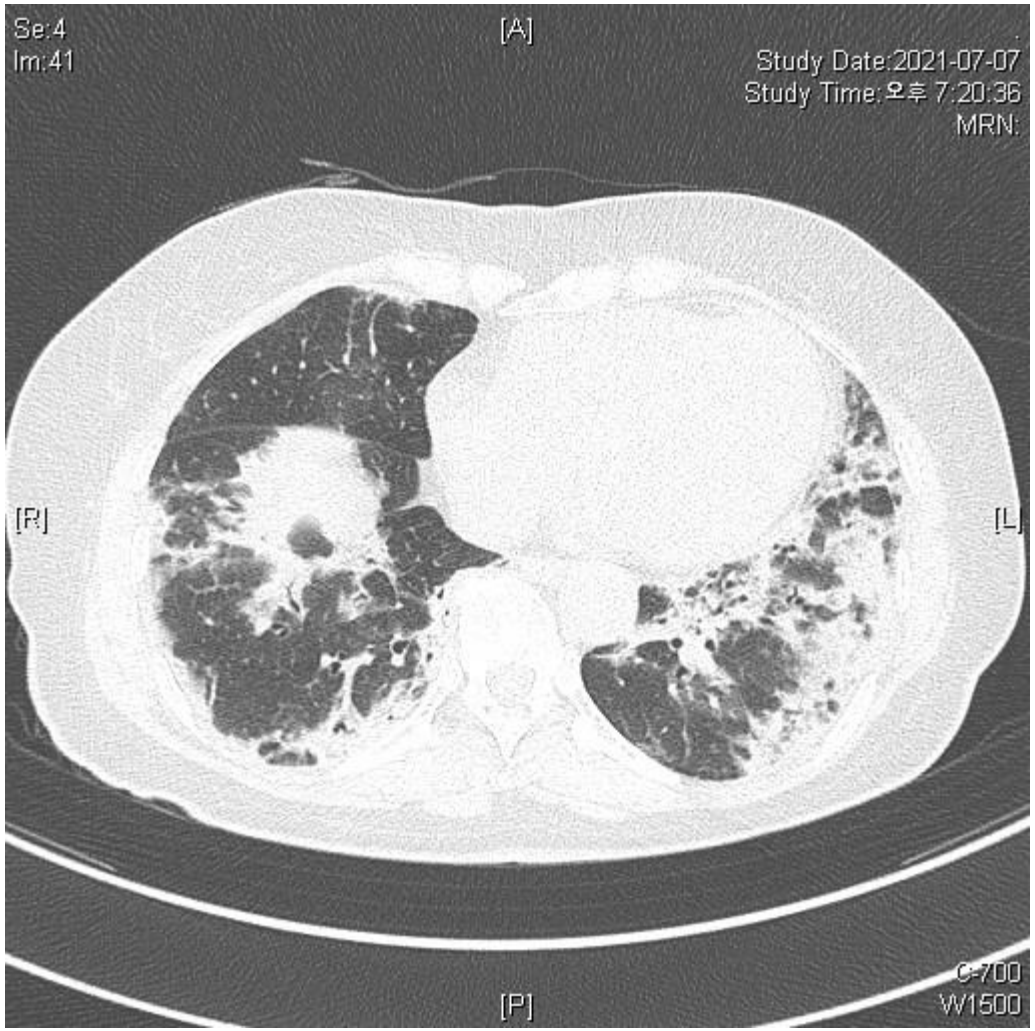
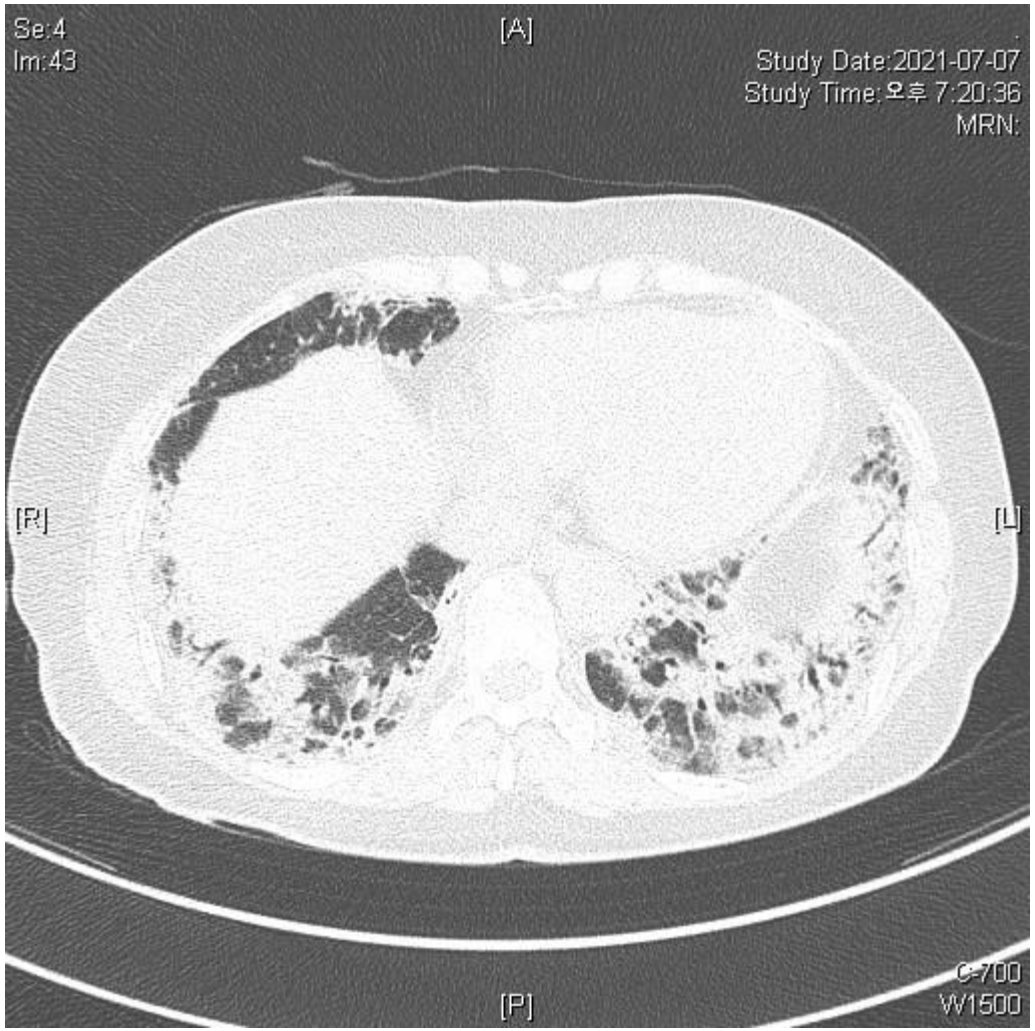
- **Chest CT Scan (2021/7/7, 내원 1개월 전)**





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Previous Treatment

- **2021/7/6: DOE로 타병원 첫 내원, 7/9 FOB BAL**
  MPD 40mg, septrin 1T 시작

- **2021/7/24: DOE악화로 타병원 입원, BAL PCP positive, ESBL+ KPn 대해**
  IV SMX/TMP (21/7/20-8/2) -> 2nd line Clindamycin+primaquine (8/3)
  MPD 60mg (7/20-30) ->80mg (7/28-8/1) -> 60mg (8/2-3)
  Meropenem (8/3)

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- **Laboratories (2021/8/4, HOD #1)**

CBC	8.85 (N 78.5%) / 14.9 / 345k
Ca/P	9.1 / 4.0
BUN/Cr (eGFR)	18.3 / 0.68 (eGFR 92)
E'	137 / 5.2 / 100 / -
T.pro/Alb	6.5 / 4.0
AST/ALT/T.bil	**326 / 360** / 0.5
PT(INR)/aPTT	1 / 30.7
Troponin-T/NT-proBNP	9 / 52
LDH	**670**
CK / Aldolase	68 / **24.2**
KL-6	**2048.6**
CRP / ESR	18 / 11
Hepatitis viral marker	negative

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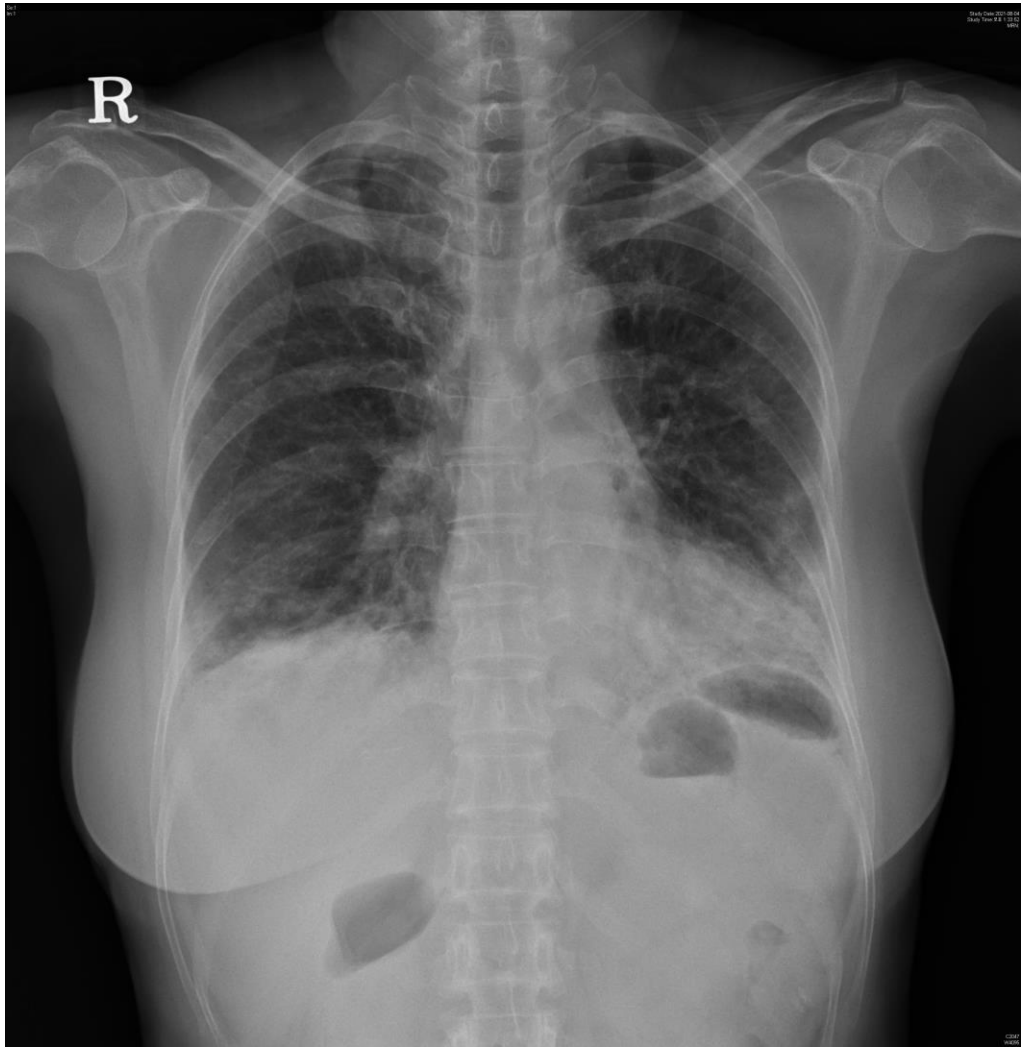
- **Chest X-ray (2021/8/4, HOD #1)**



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- **Further Studies**
- **Autoimmune**

ANA	Negative
Anti-SS-A/Ro	Negative
Anti-SS-B/La	Negative
Anti-cyclic citrullinated peptide antibody	Negative
P-ANCA, IFA	Negative
C-ANCA, IFA	Negative
MPO(P-ANCA)	Negative
PR3(C-ANCA)	Negative
Anti-Jo 1	Negative
Anti-RNP	Negative
Anti-Sm	Negative
Anti-Scl 70	Negative
Anti-Centromere Ab	Negative
Rheumatoid factor (RF)	10.0

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- **Further Studies**
- **신경과 협의진료:**

  PI: 1년 전부터 손끝 피부가 갈라지고 피가 나는 증상 있었음. 5-6월부터 손목에 열감있고 통증 있었으며 피부 여기저기에 빨갛게 피부병변이 있었는데 타병원 입원하여 치료받은 뒤 현재는 손끝만 발진이 남아 있음. 6월말부터 숨이 찼으며 전반적으로 호흡곤란으로 힘이 없는 것 외에는 본인이 느끼기에 weakness는 없음.

  Plan: NCV, EMG

  21/8/27 NCV, EMG: 상하지에서 neuromuscular disease를 시사하는 소견은 관찰되지 않음

- **심초음파 (21/8/25) : no RWMA, LVEF 70%, E/e' 9 타병원**
- **상복부초음파 (21/8/25) : liver, GB, Bile ducts grossly normal**

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- **Further Laboratories**
- **Myositis Specific 11 Antibodies Panel (21/8/10시행, 보고 21/8/27)**

DOB: 11/14/1955 Age: 65
SEX: F

CLIENT INFORMATION
54512
SCL
A-DONG 26F
13 HEUNGDEOK 1-ro, GIHEUNGU
YoungInSi KyeongGiDo S Korea 4,

SPECIMEN INFORMATION
SPECIMEN: 27720970
REQUISITION: 545120012675
LAB REF NO:

ID: 0810-110229

COLLECTED: 08/13/2021 00:00
RECEIVED: 08/19/2021 19:29
REPORTED: 08/24/2021 23:42

Test Name	In Range	Out of Range	Reference Range	Lab
MYOSITIS SPECIFIC 11 ABS PNL				*VAL
Jo-1 Ab	<11		<11 SI	
PL-7 Ab	<11		<11 SI	
PL-12 Ab	<11		<11 SI	
EJ Ab	<11		<11 SI	
OJ Ab	<11		<11 SI	
SRP Ab	<11		<11 SI	
Mi-2 Alpha Ab	<11		<11 SI	
Mi-2 Beta Ab	<11		<11 SI	
MDA-5 Ab		**>100 H**	<11 SI	
TIF-1y Ab	<11		<11 SI	
NXP-2 Ab	<11		<11 SI	

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- **Further Studies**
- **PET-CT (21/9/17)**

  Subpleural consolidation/GGOs with increased uptake in both lungs, probably inflammatory process.

  Mildly increased uptake in the left adrenal gland, probably adrenal hyperplasia.

  Probably physiologic bowel uptake in the pelvis. Otherwise, unremarkable.

- **PFT (21/10/17)**

			Ref	Pre	% Ref
Spirometry					
	FVC	Liters	2.92	0.95	32
	FEV1	Liters	2.29	0.85	37
	FEV1/FVC	%	77	90	
	FEV3	Liters		0.93	
	FEV6	Liters		0.94	
	FEF25-75%	L/sec	2.26	2.65	117
	IsoFEF25-75	L/sec	2.26	2.65	117
	FEF50%	L/sec	2.98	4.48	151
	PEF	L/sec	5.23	4.78	91
	FET100%	Sec		7.34	
	FIF50%	L/sec		1.75	
Diffusing Capacity					
	DLCO	mL/min/mmHg	17.0	8.0	47
	DL Adj	mL/min/mmHg	17.0	8.0	47
	DLCO/VA	mL/min/mHg/L	4.18	2.83	68
	DL/VA Adj	mL/min/mHg/L		2.83	
	VA	Liters		2.83	
	IVC	Liters		1.29	

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Final Diagnosis and Treatment

- Diagnosis
  MDA-5 associated rapid progressive ILD with Clinically Amyopathic Dermatomyositis (CADM)

- Treatment
  본원 PCP 음전 확인되어 Clinda+primaquine 중단 (-8/6), septrin 2T 유지
  Meropenem (8/3-16) -> Maxipime+Metronidazole (8/17-) > Banan (10/25-31)

  MPL 62.5 (8/4-) >감량시도 > 62.5(8/19-) >125 (9/3-) > 감량시도 >62.5 (10/5-)> 감량하여 **현재 PL 20mg (22/3/16-)**

  Azathioprine 25mg (8/16-24) hold d/t OT/PT elevation

  Cyclophosphamide #1-2 750mg (8/26, 9/23) > #3-5 750mg/BSA (10/14, 11/4, 11/25) > UTI sepsis, CMV pneumonia 로 hold > #6 CYC 1g (22/2/18) > #8 cycle 까지 고려하였으나 2022.3 UTI sepsis와 neutropenia 발생하여 6차에서 종료하기로 하였음

  Cyclosporine : 200mg (10/6-) < 150mg (9/16-) < 100mg (9/10-) < 50mg (9/7-9)

  IVIG (10/7,8)

  #1-6 Plasma exchange (10/18, 20, 22, 25, 27, 29)

  CMV pneumonia 로 12/22-29 Ganciclovir, 12/30-21/1/25 Valganciclovir

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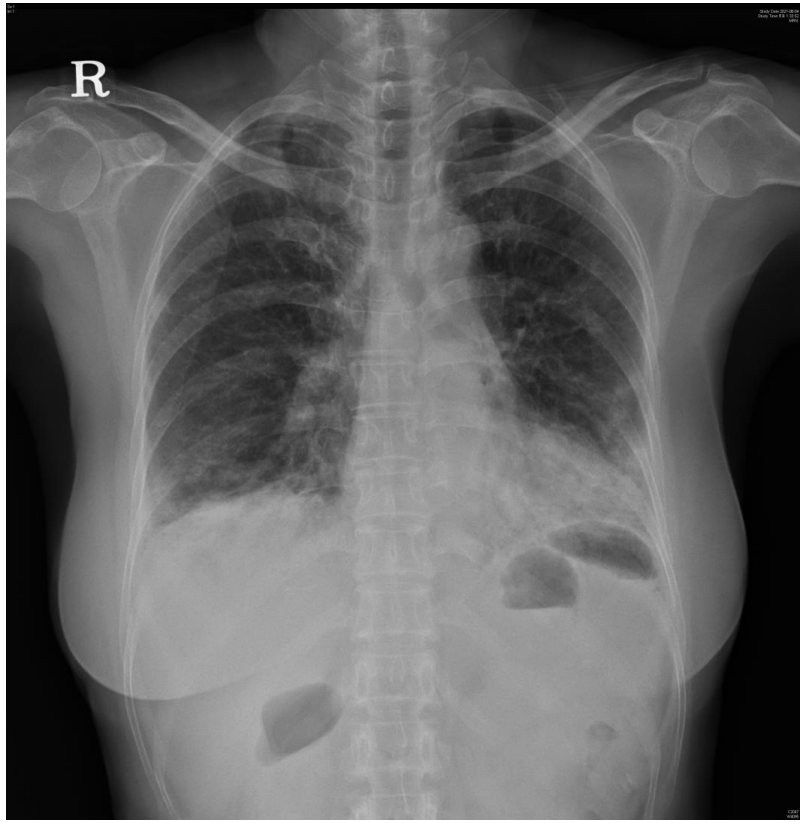
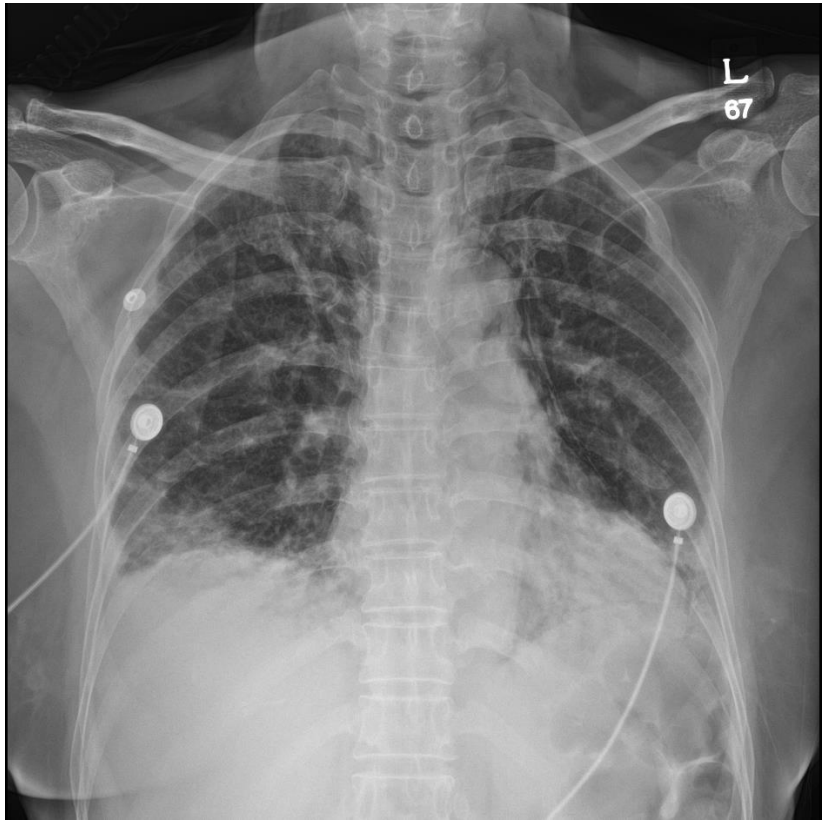
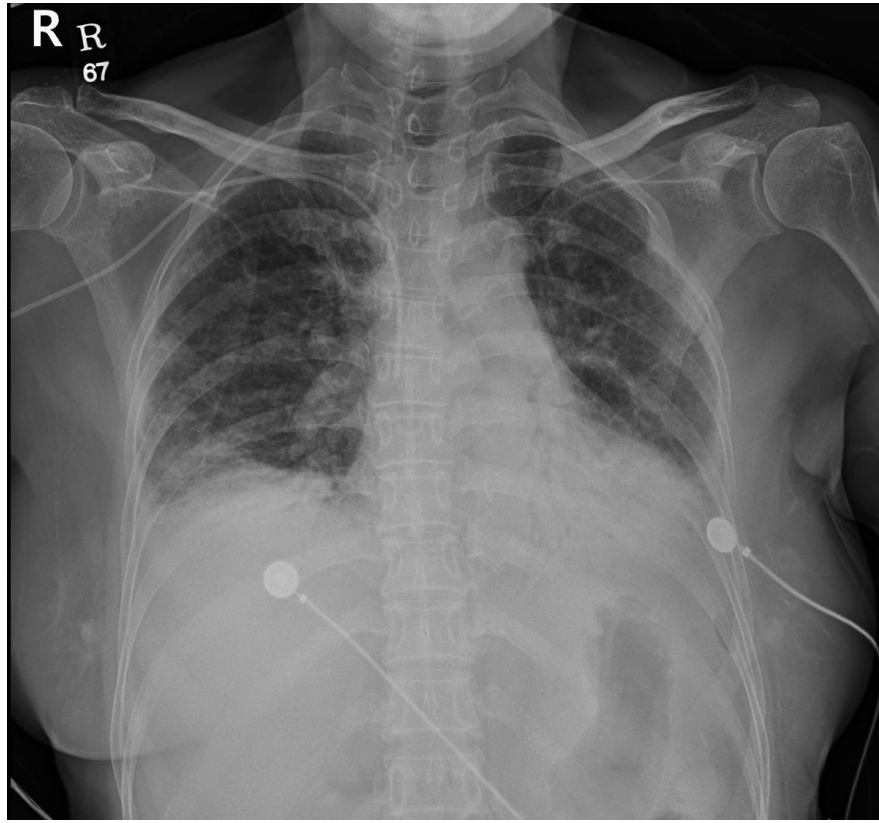
- **Chest X-ray**



2021/8/4, HOD #1
O2 6L/min



2021/8/23, HOD #20
Fever spiking (38.7℃), O2 HFNC 0.5/35
> 8/26 #1 CYC 750mg 후 O2 6L/min 감량



2021/9/3, HOD #31
Fever spiking (38.7℃), O2 HFNC 0.8/50
> Cipol start (9/7) 후 O2 2L/min감량

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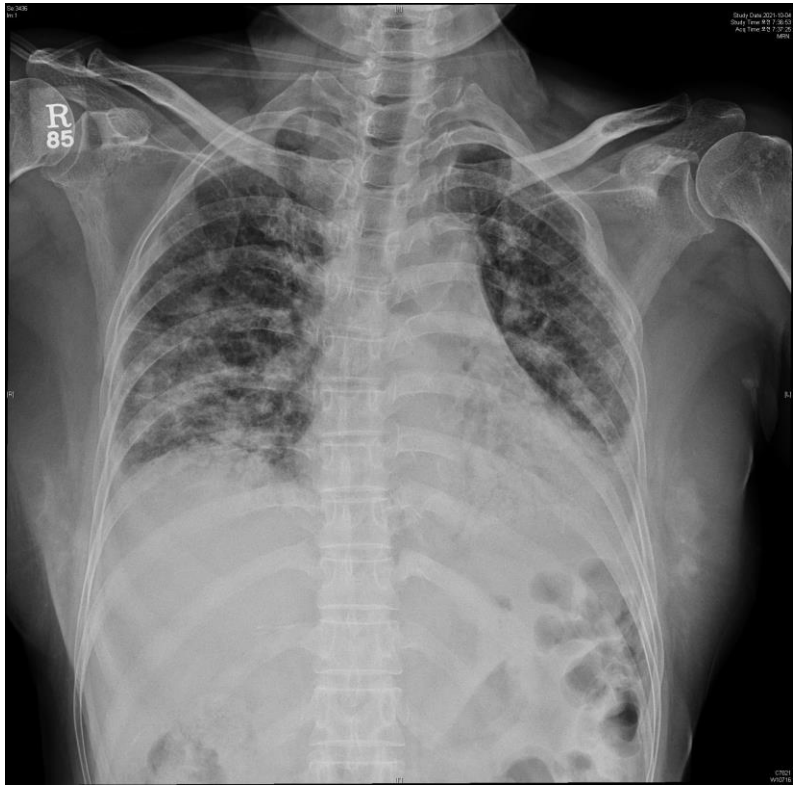
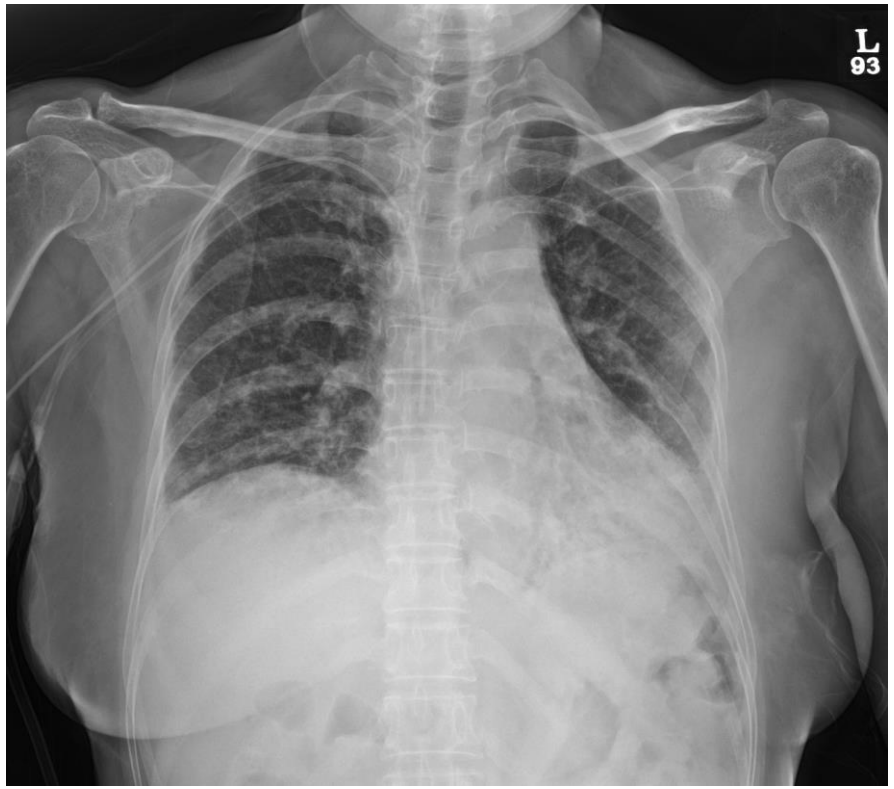
- **Chest X-ray**



2021/10/4, HOD #61
호흡곤란 악화, 운동시 6L/min 유지안됨
> 폐이식 준비, 10/14 #3 CYC에도 증상 지속되어 6회 Plasma exchange (10/18-)



2021/11/11, HOD #99
O2 3L/min 유지하며 퇴원

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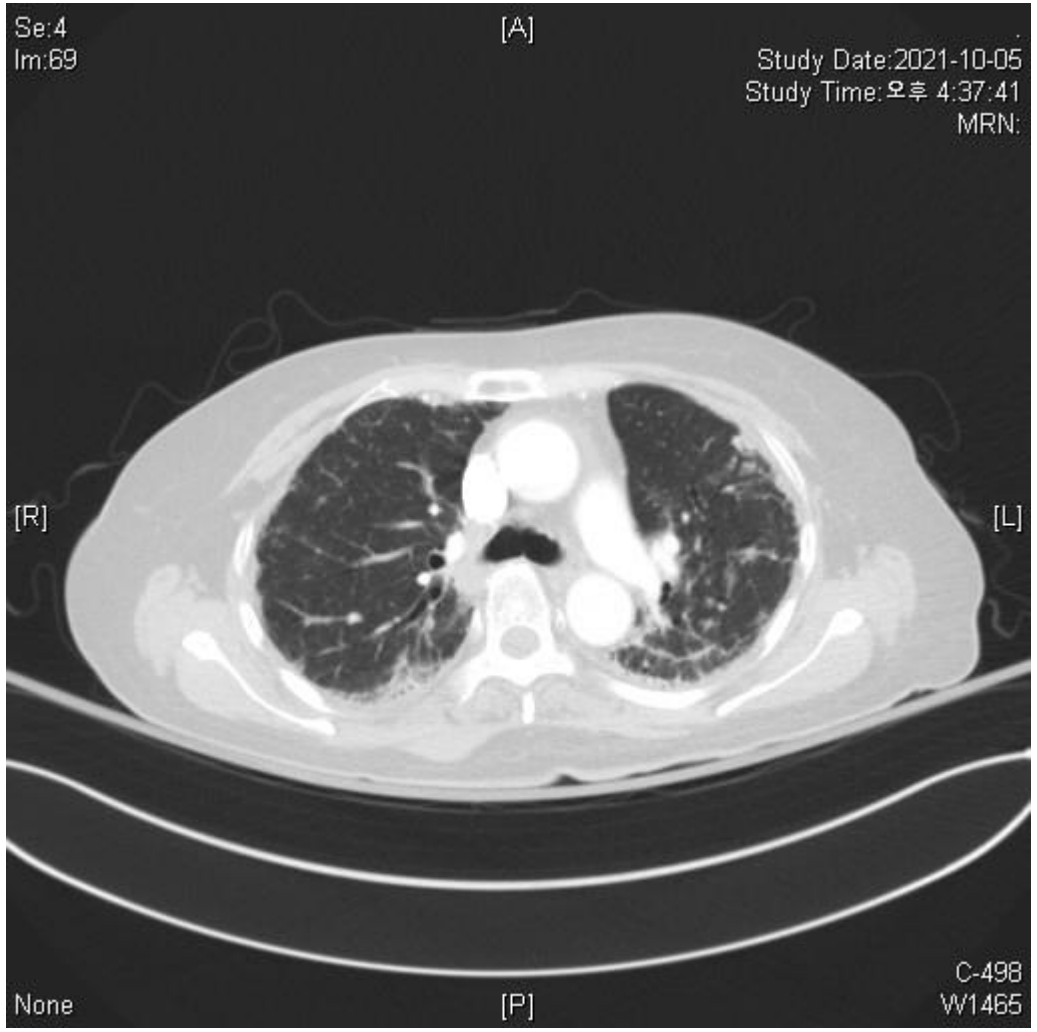
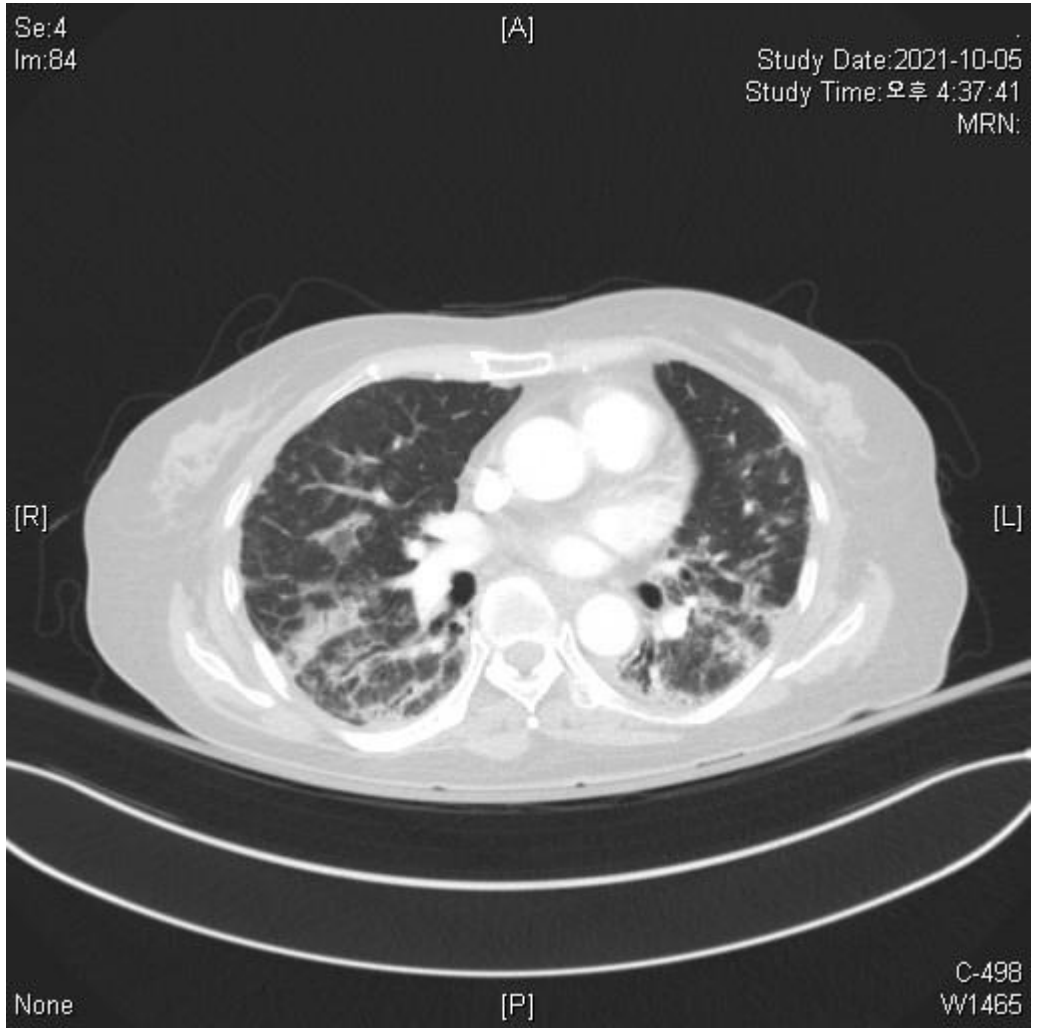
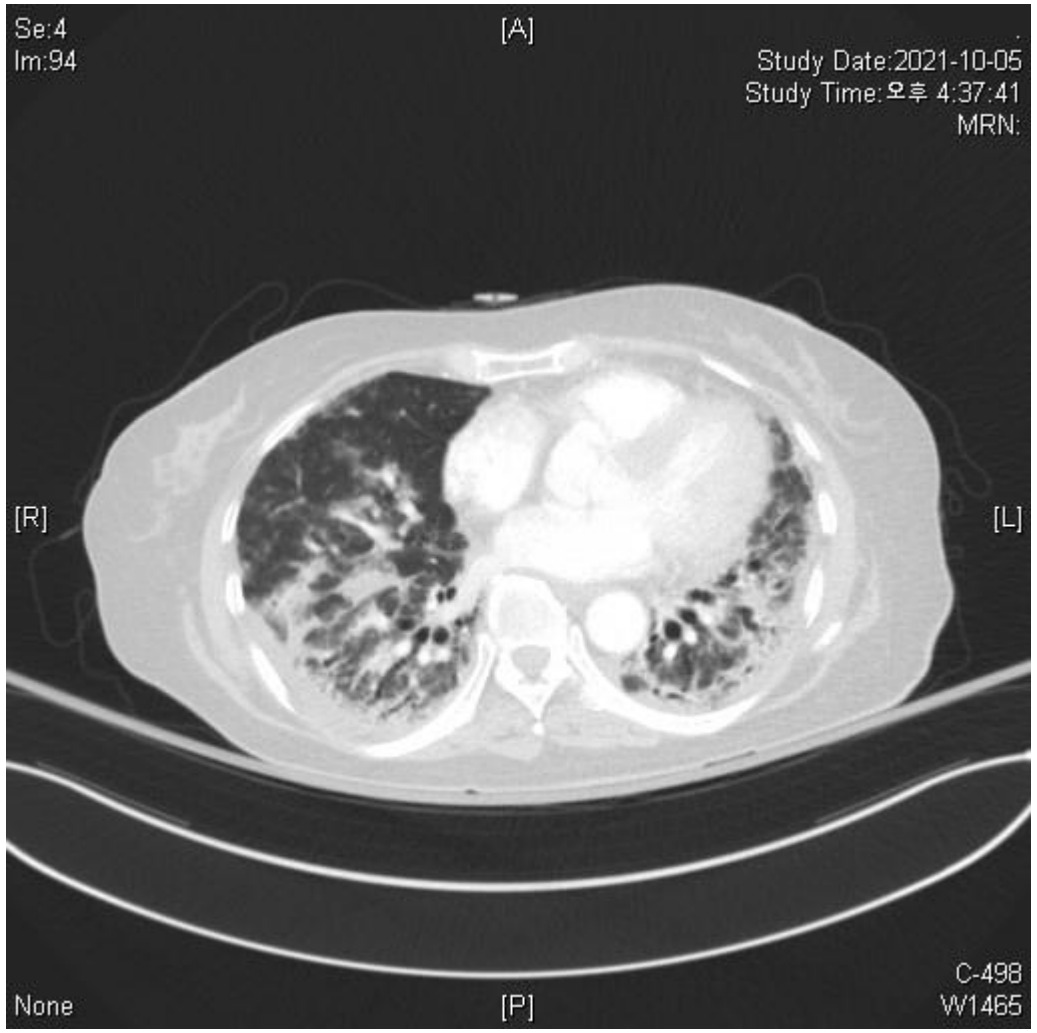
- **Chest CT Scan (2021/10/5, HOD #62)**

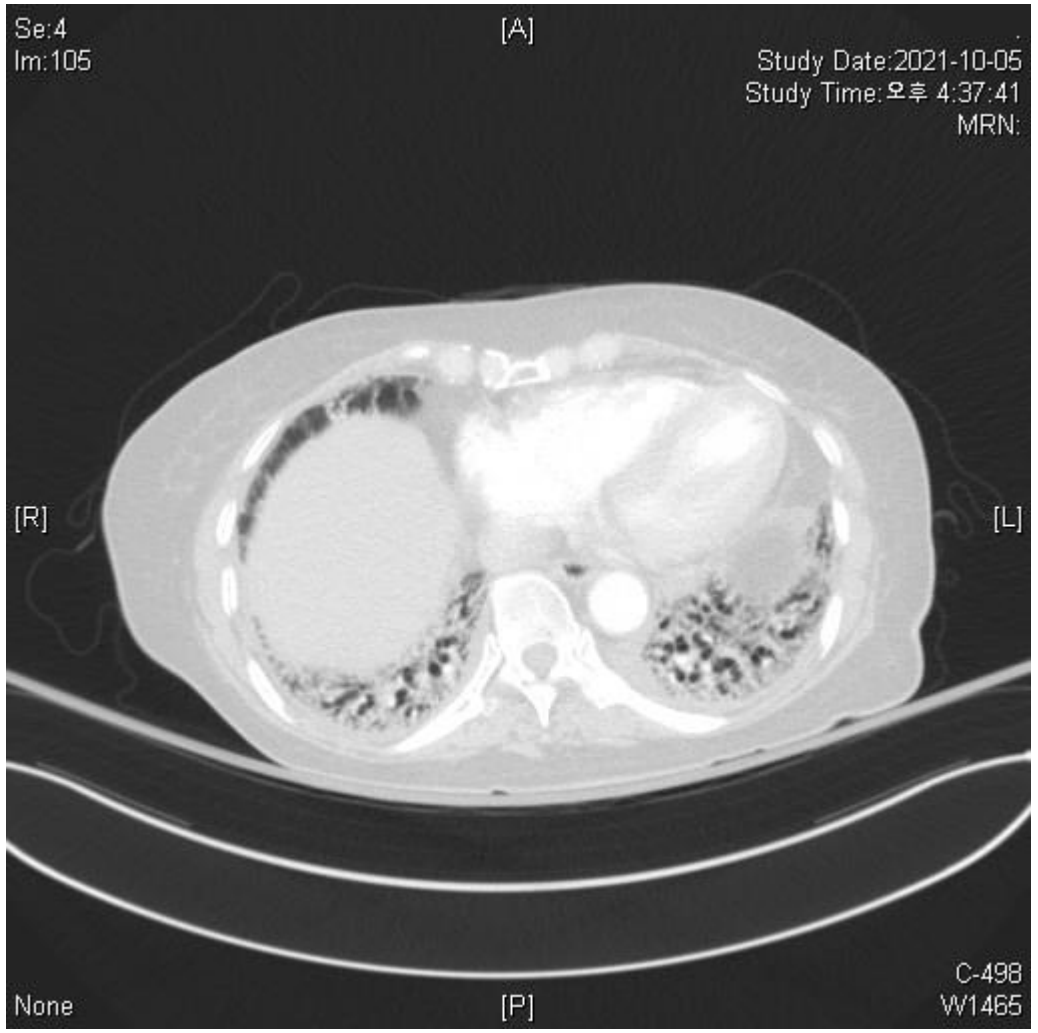




PATIENT CASE: F/65

- **Chest CT Scan (2021/10/5, HOD #62)**





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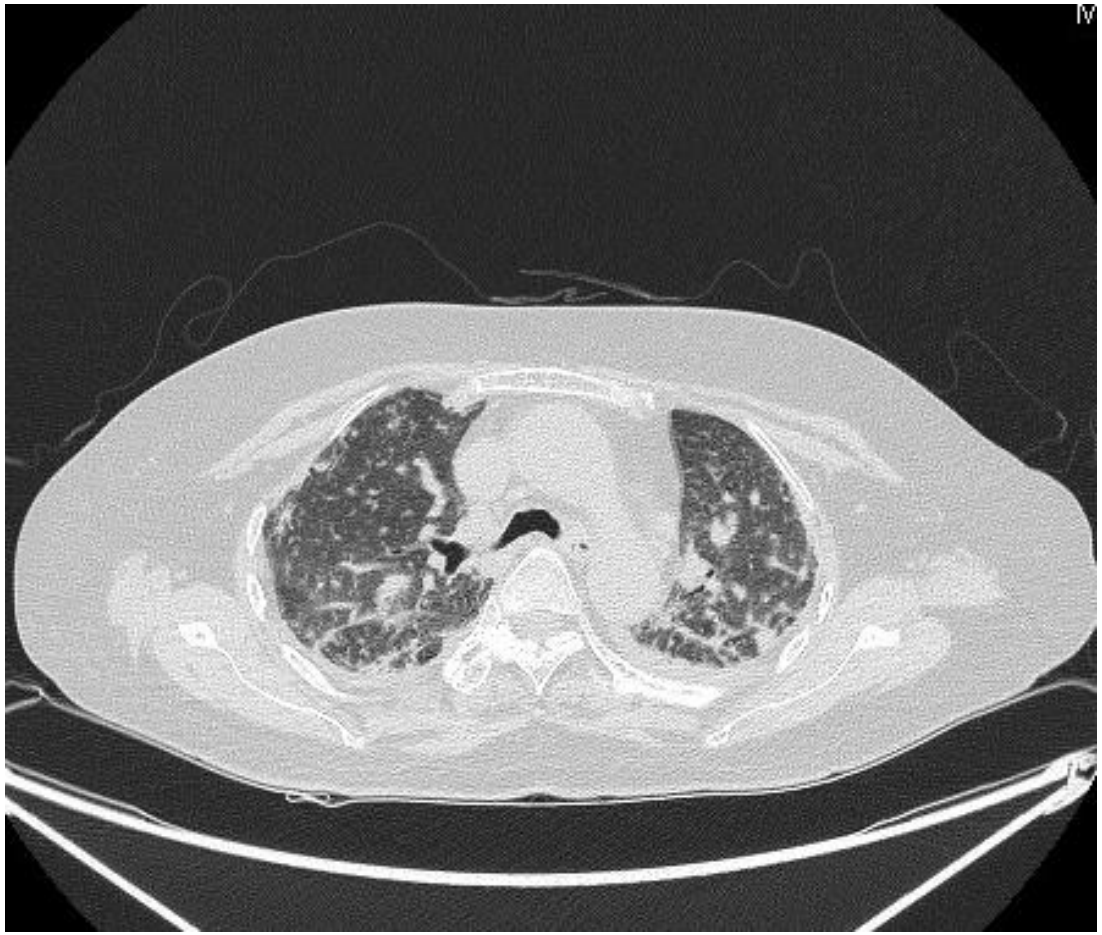
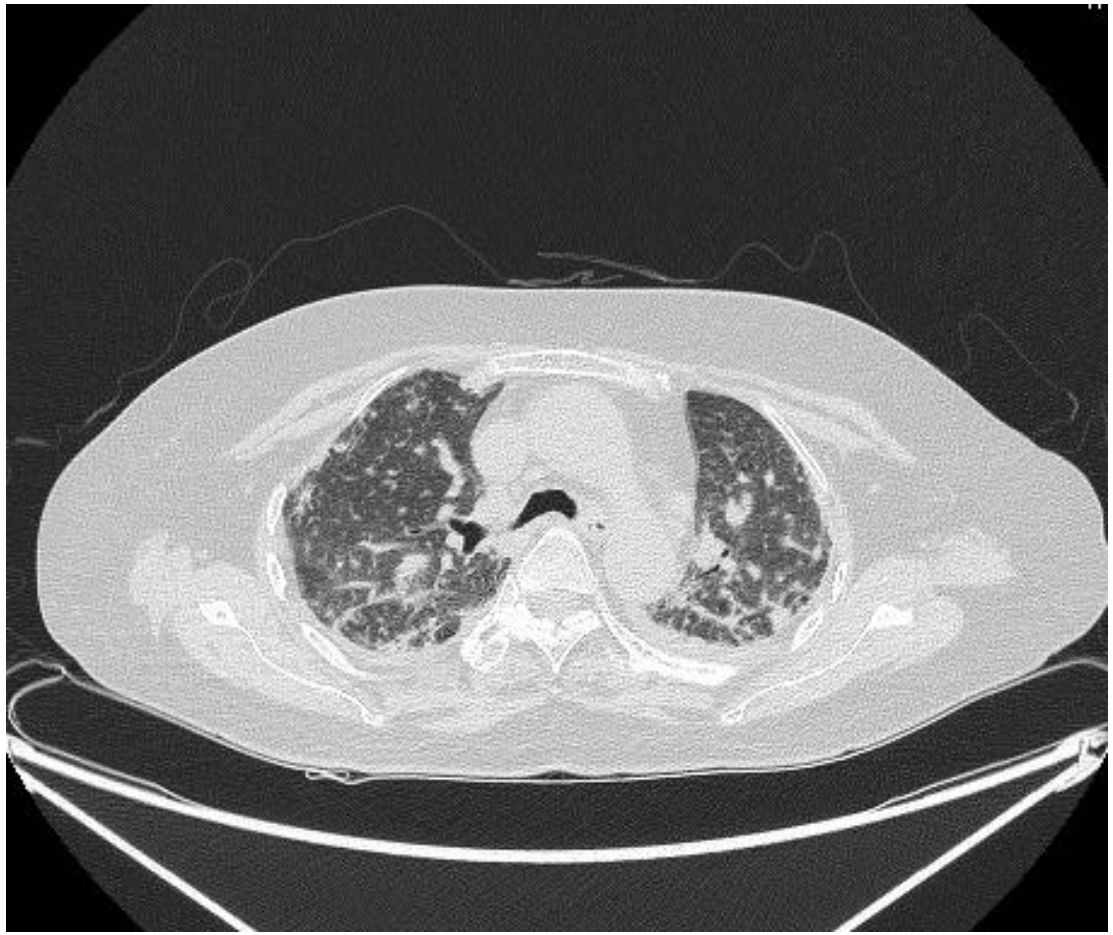
- **Chest CT Scan (2021/12/18, opd)**





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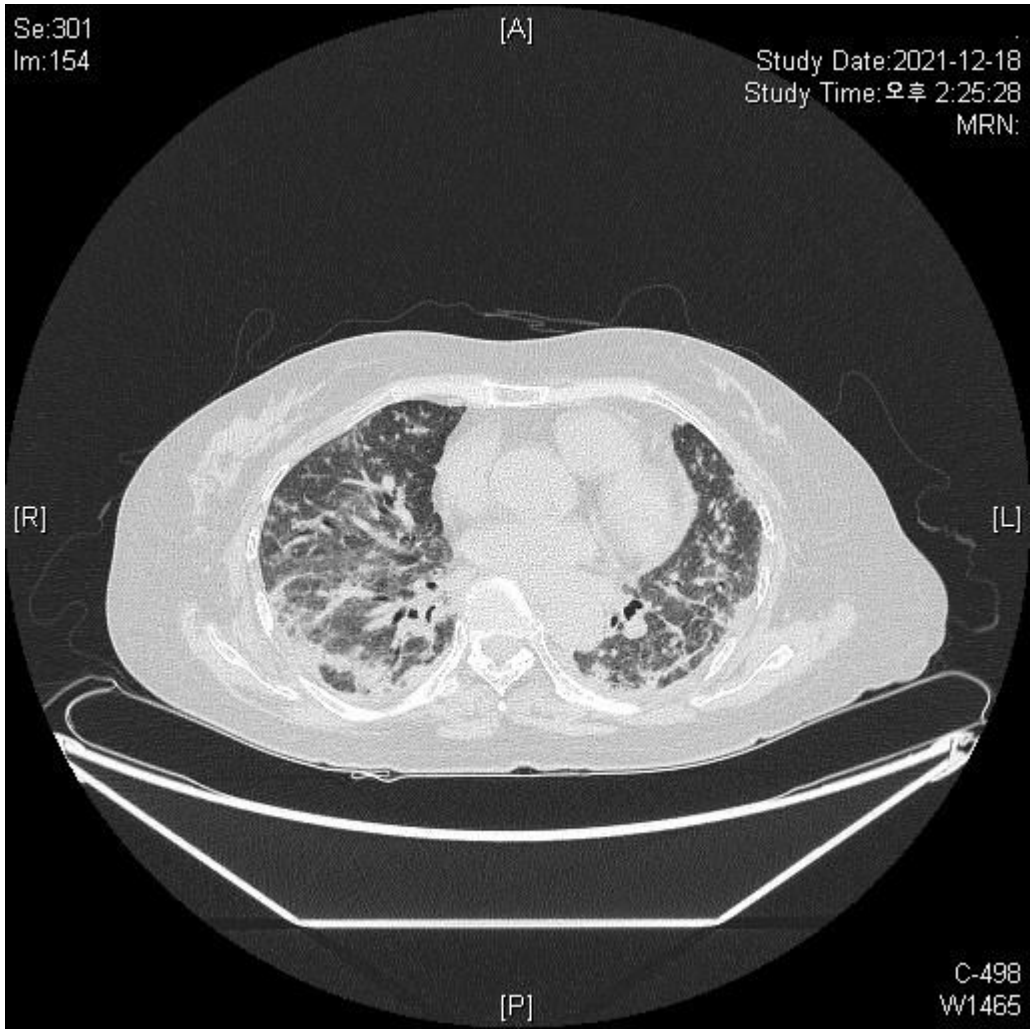
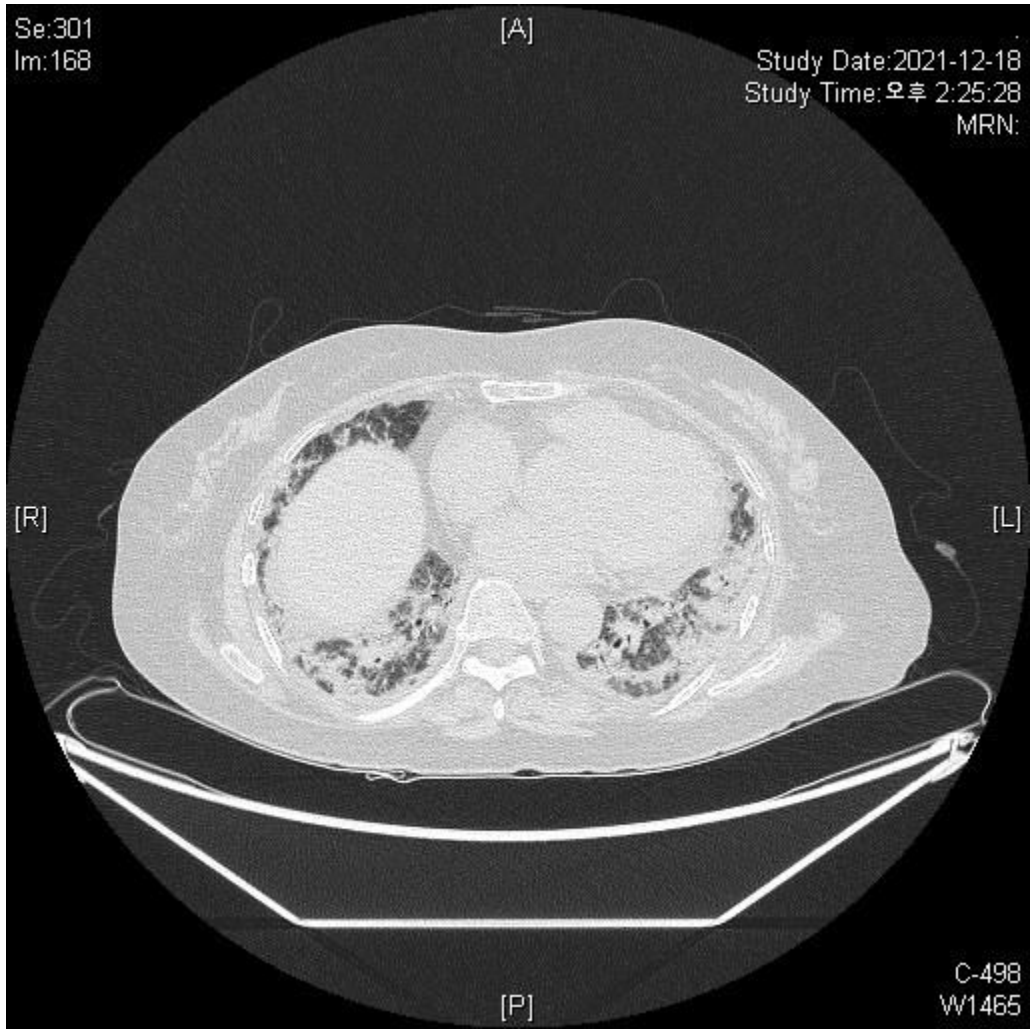
- **Chest CT Scan (2021/12/18, HOD #137)**





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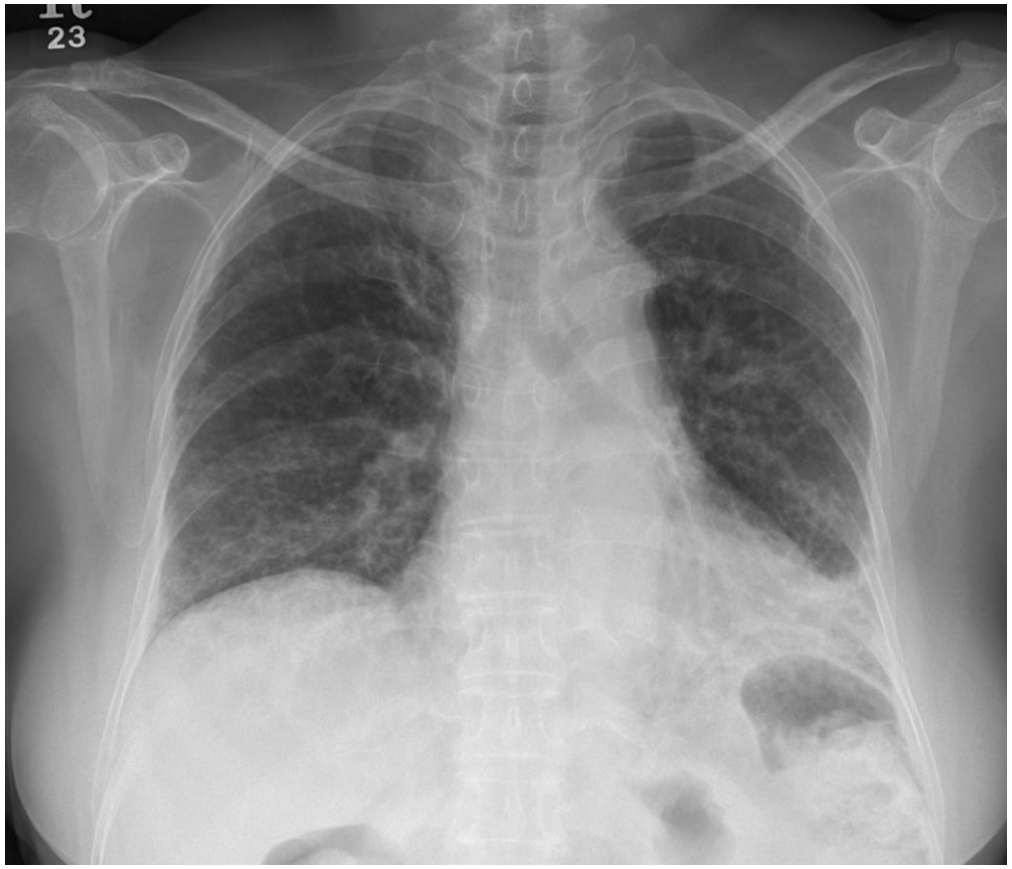
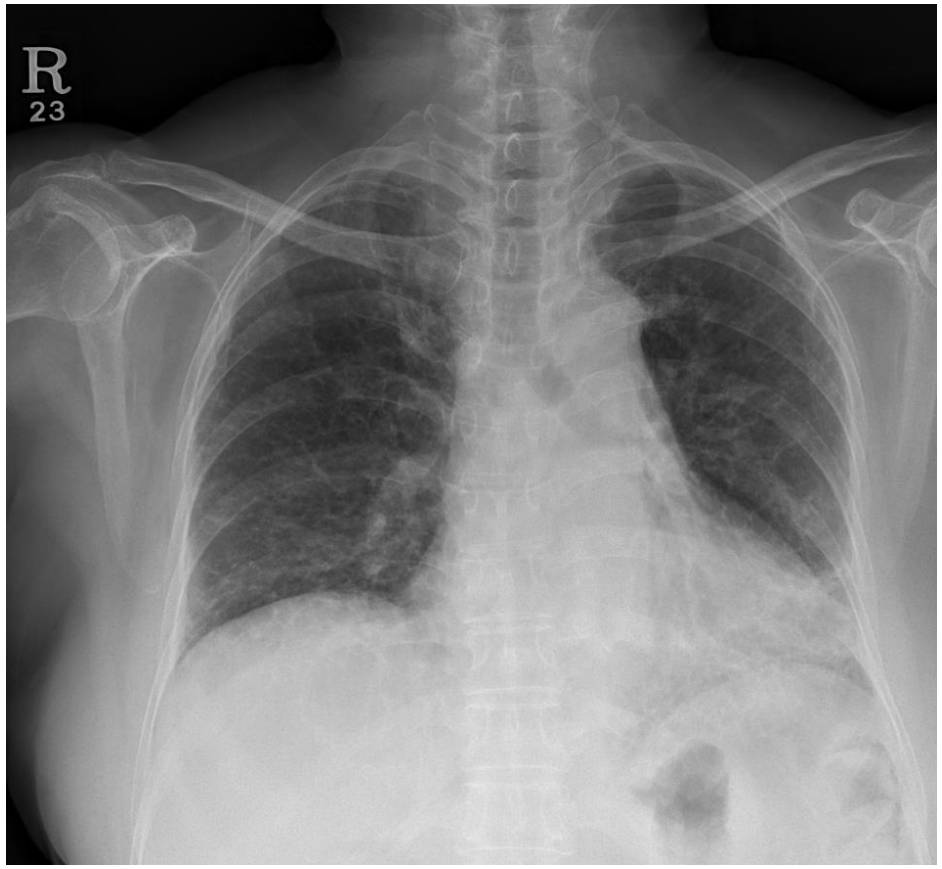
- **Chest X-ray**



2022/1/5, opd
O2 2L/min



2022/4/15, opd
O2 2L/min, 폐이식 준비하다가 호전되어 현재 외래 추적 관찰 중

Discussion

Review and Discussions

Review

- There are 3 subsets of dermatomyositis positive for anti-melanoma differentiation-associated gene 5 (MDA5) antibodies :

  1) a cutaneous form without muscle or lung involvement

  2) a chronic form of cutaneous features with interstitial lung disease resembling the antisynthetase syndrome

  3) the most severe form of cutaneous manifestations with rapidly progressive ILD (RPILD)

  > up to 80% of these patients do not survive even after an early diagnosis or intensive immunosuppressive therapy.

Review and Discussions

Review

Vuillard et al. Ann. Intensive Care (2018) 8:87
https://doi.org/10.1186/s13613-018-0433-3

Annals of Intensive Care

RESEARCH Open Access

Clinical features and outcome of patients with acute respiratory failure revealing anti-synthetase or anti-MDA-5 dermato-pulmonary syndrome: a French multicenter retrospective study

Constance Vuillard[1], Marc Pineton de Chambrun[2], Nicolas de Prost[3], Claude Guérin[4,5], Matthieu Schmidt[2], Auguste Dargent[6], Jean-Pierre Quenot[6], Sébastien Préau[7], Geoffrey Ledoux[7], Mathilde Neuville[8], Guillaume Voiriot[9], Muriel Fartoukh[9], Rémi Coudroy[10], Guillaume Dumas[11], Eric Maury[11], Nicolas Terzi[12], Yacine Tandjaoui-Lambiotte[13], Francis Schneider[14], Maximilien Grall[15], Emmanuel Guérot[16], Romaric Larcher[17], Sylvie Ricome[18], Raphaël Le Mao[19], Gwenhaël Colin[20], Christophe Guitton[21], Lara Zafrani[22], Elise Morawiec[23], Marie Dubert[24], Olivier Pajot[1], Hervé Mentec[1], Gaëtan Plantefève[1] and Damien Contou[1*]

- A 13-year multicenter retrospective study in 35 ICUs in France from 2005, to 2017.
- 47 patients with anti-synthetase syndrome (*n* = 28, 60%) or MDA-5 dermatopulmonary syndrome(*n* = 19, 40%)
- Muscular, articular and cutaneous manifestations occurred in 11 patients (23%), 14 (30%) and 20 (43%) patients, respectively.
- **42 patients (89%) had ARDS**, which was severe in 86%, with a rate of 17% (*n* = 8/47) of VV-ECMO
- **Patients with aMDA-5 dermatopulmonary syndrome had a higher hospital mortality** than those with AS syndrome (*n* = 16/19, **84%** vs. *n* = 8/28, 29%;*p* = 0.001).

Review and Discussions

Review

Rheumatology International
https://doi.org/10.1007/s00296-021-04897-1

Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH

Disease characteristics and clinical outcomes of adults and children with anti-MDA-5 antibody-associated myositis: a prospective observational bicentric study

Sai Kumar Dunga[1] · Chengappa Kavadichanda[1] · Latika Gupta[2] · R. Naveen[2] · Vikas Agarwal[2] · Vir Singh Negi[1]

- Individuals with anti-MDA5 antibody-positive DM diagnosed between 2017 and 2020 from two centres in India
- Anti-MDA5 antibody was positive in 25 (7.5%) out of the 330 individuals with myositis. These 25 (21 adults, 4 juvenile) patients were followed up for a median duration of 14 months.
- Among adults, a majority had **cutaneous manifestations 21 (84%)** followed by, **arthritis 17 (80%)**, and **interstitial lung disease 12 (ILD, 57.1%)**. **Four (19%) had rapidly progressive ILD (RP-ILD). Eight (38%) presented as clinically amyopathic DM.**
- Among cutaneous manifestations, majority (62%) had classic features (**gottron's papules/sign**, heliotrope rash) while 8 (38%) had cutaneous ulceration and 2 each had periorbital edema and tendon rupture
- Out of 21 adults, **8 (38%) succumbed to the diseases**. **RP-ILD (*n* = 4; 19%), ulcerative gottron's (*n* = 5) and anti-Ro-52 (*n* = 8) were significantly associated with mortality (*p* < 0.05).**

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Review and Discussions

Review

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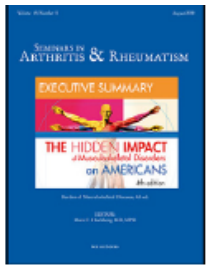

Recommendations for the treatment of anti-melanoma differentiation-associated gene 5-positive dermatomyositis-associated rapidly progressive interstitial lung disease

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Seminars in Arthritis and Rheumatism 50 (2020) 776-790

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- Patients with DM-associated RPILD anti-MDA5 (+) should be treated with combination therapy as a first option: **glucocorticoids plus a calcineurin antagonist (cyclosporine A or tacrolimus)**, or triple therapy adding **intravenous cyclophosphamide** to the previous schedule, are both considered good initial alternatives.
- In patients with DM-associated RPILD anti-MDA5 (+) who do not respond to combination, clinicians have to consider the following alternatives: Adding one of these immunosuppressive drugs (cyclophosphamide, mycophenolate mofetil, rituximab, basiliximab or tofacitinib) to the current therapy
- Rescue therapies: Polymyxin B hemoperfusion, **Plasmapheresis, Intravenous immunoglobulins**
- VV-ECMO and lung transplantation should be considered as a therapeutic option in patients with refractory RPILD associated with anti-MDA5.

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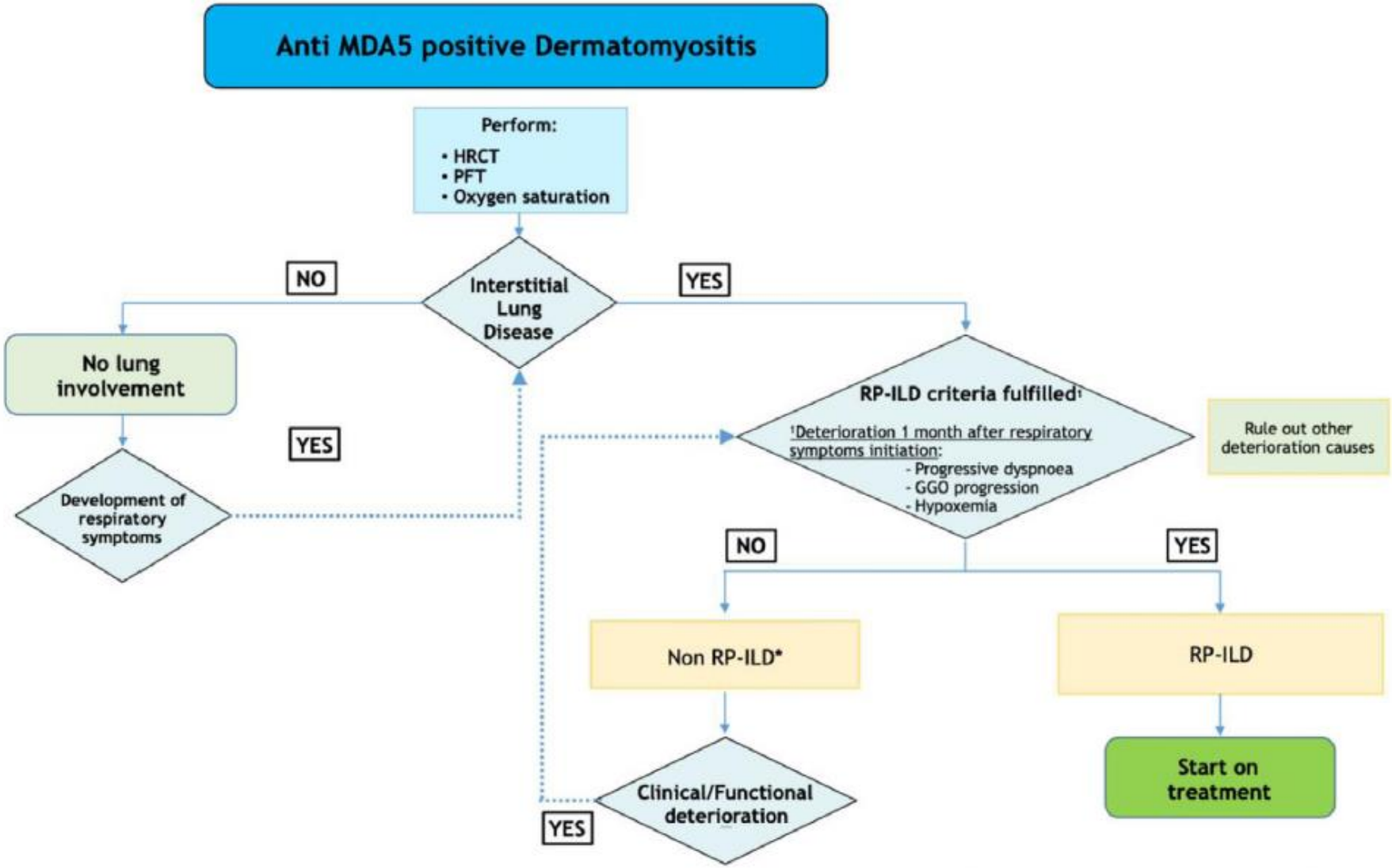

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- In CADM or anti-MDA-5 antibody-positive DM patients with ILD, who are **refractory to combination therapy** of high-dose glucocorticoids, calcineurin inhibitors, and cyclophosphamide, **the survival rate for treatment with PE was higher** than for treatment without PE (**91%** and 50%, respectively, $p < 0.05$).
- Among PE-treated patients, **anti-MDA-5 antibody titer, ferritin, and KL-6 were sustainably reduced only after initiating PE**.

Scand J Rheumatol (2021);00:1–7

- In a prospective study, anti-MDA5–CADM patients who received **a glucocorticoid combined with tofacitinib (at a dose of 5 mg twice daily), survival 6 months after the onset of ILD was significantly higher** among the patients in the prospective group (18 of 18, 100%) than among the patients in the control group (25 of 32, 78%) ($P = 0.04$)

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