Report of Two COVID-19 ARDS (CARDS) Cases Who Survived without Intubation and Mechanical Ventilation

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ABSTRAK

Manifestasi klinis kritis COVID-19 adalah Acute Respiratory Distress Syndrome (ARDS) yang memerlukan intubasi dan ventilasi mekanik dan terjadi pada sekitar 2,3% kasus. Sekitar 94% kasus COVID-19 dengan ventilator ini berakhir dengan kematian. Serial kasus ini melaporkan dua pasien confirmed COVID-19 yang sudah memenuhi kriteria intubasi dan ventilasi mekanik namun tidak dilakukan. Pada perjalanan penyakitnya kedua pasien mengalami perbaikan klinis dan sembuh. Hal yang mungkin dapat menjelaskan adalah karena terdapat perbedaan antara COVID-19 ARDS (CARDS) dengan ARDS tipikal atau klasik. CARDS terbagi menjadi 2 fenotip tipe L (Low Elastance) dan tipe H (High Elastance). Perbedaan fenotip ini membedakan pula patofisiologi dan tatalaksana klinis, dan cara untuk membedakannya antara lain dengan CT scan thorax. Serial kasus ini menekankan pentingnya pemahaman terhadap fenotip COVID-19 agar klinisi dapat memberikan tatalaksana terapi dengan lebih tepat, sekaligus menekankan pentingnya ketersediaan CT scan pada fasilitas kesehatan yang menatalaksana COVID-19.

Kata kunci: *COVID-19, ARDS, CARDS, ventilasi mekanik, CT-scan thorax.*

ABSTRACT

The most severe clinical feature of COVID-19 is Acute Respiratory Distress Syndrome (ARDS) which requires intubation and mechanical ventilation and it occurs in approximately 2.3% of cases. About 94% of these cases end in death. This case series report two confirmed COVID-19 patients who had met criteria of intubation and mechanical ventilation, but not performed to them. Both patients experienced clinical improvement and recovery. This is probably due to differences of COVID-19 ARDS (CARDS) with typical or classic ARDS. CARDS is divided into two phenotypes of type L (Low Elastance) and type H (High Elastance). These different phenotypic also distinguish subsequent pathophysiology and clinical management. These phenotype can be differentiated by chest CT scan. This case series emphasizes the importance of understanding this phenotype so that clinicians can provide more appropriate treatment management and also availability of CT scans in health facilities that manage COVID -19.

Keywords: *COVID-19, ARDS, CARDS, mechanical ventilation, thorax CT-scan.*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a new coronavirus and was first reported in Wuhan, China, in December 2019. COVID-19 disease has clinical variations ranging from mild or even without symptoms to critical conditions require an intensive care unit. About 14% of COVID-19 cases develop severe cases and 5% may require intensive care units and developed Acute Respiratory Distress Syndrome (ARDS), sepsis, septic shock, multiorgan failure, Acute Kidney Injury and cardiac injury.[1] ARDS complicates in around 2.3%, and 94 of % of them ended in death.[2,3]

We describe two cases of COVID-19 that met the Kigali-Modified ARDS Berlin criteria. They also met indications of intubation and mechanical ventilation but they were not intubated, however both cases experienced clinical improvement and they were declared cured after two negative RT-PCR results.

CASE ILLUSTRATION

Case 1

A 46-year-old man came to hospital due to shortness of breath (SOB) for seven days which worsened in the previous two days. He also complained of cough, nasal congestion, and had a history of fever six days prior to the visit lasting for two days. He had a close contact with confirmed COVID-19 patient at a religious event. There was no history of hypertension, diabetes, heart disease or chronic lung disease.

Patient was alert, blood pressure 120/70 mmHg, pulse 84 beats per minute, respiratory rate 24 breaths per minute, temperature 36.7^{0}C. Body Mass Index (BMI) 24.7 kg/m^2. Crackles were present in both hemithorax. Other physical examination results were within normal limit.

Laboratory results showed Hb 14.5 g/dL, Ht 42.5%, white blood cell count 11,810/mm^3, platelet count 302,000/mm^3, basophil 0%, eosinophils 0%, stab neutrophils 0%, segmented neutrophils 91%, lymphocytes 5%, monocytes 4%, Total Lymphocytes Count (TLC) 590/mm^3, blood sugar 134 mg/dL, serum ureum 68 mg/dL, serum creatinine 1.19 mg/dL, potassium 4.2 mEg/L, blood gas analysis pH 7.424, pCO2 27.8 mmHg, pO2 127.9 mmHg, HCO3 18.4 mmol/liter, BE -3.9 mmol/liter, SaO2 98.5%, partial pressure of oxygen/ fraction of inspired oxygen (P/F) ratio 426, with oxygen 3 liters/minute. Chest X Ray (CXR) showed peripheral infiltrate sugestive for pnemonia and slight cardiomegaly.

The diagnosis of Community Acquired Pneumoniae (CAP) was made and the patient was under investigation for COVID 19.

The patient was treated in isolation ward with supplementary oxygen 3 l/min (lpm), empirical antibiotics ceftriaxone 2x1 grams and azithromycin 1x500 mg, N-Acetylcystein 3x400 mg and oseltamivir 2x150 mg to cover

Table 1. Clinical course of case 1.

Day	Symptoms	BP	Pulse	RR	Temp	SpO2/ FiO2
01	Cough	116/73	96	24	37.0	342
07	Dyspnea	123/80	78	24	36.8	156
08	Dyspnea	130/90	96	28	36.4	160
09	Dyspnea, cough	130/80	96	26	36.3	156
10	Dyspnea, cough	120/80	80	28	36.4	101
11	Dyspnea, cough	125/70	84	32	36.8	101
12	Dyspnea, cough	117/75	88	30	36.2	97
23	None	110/70	86	20	36.4	350
48	None	126/76	80	20	36.4	490

Table 2. Laboratory data during hospitalization.

Day	Leucocyte	TLC	CRP	PC	Ferritin	RT-PCR
01	11.810	590				POS
07	9.170	730				
08	10.550	950	6.27			POS
12	7.060	1060				
13	7.020	1470				
14	6.240	1310				
18			0.22	0.3		
19			0.26			
21	7.200	1944				POS
24	5.000	2200				
27			0.11		797	
33			0.19		833	
44	6.650	2261				NEG

TLC (Total Lymphocyte Count), CRP (C Reactive Protein), PC (Procalcitonin)

the influenza empirically. Chloroquine 2x500 mg and paracetamol 3x500 mg orally. Three days later antibiotic was changed to 3x1 gram meropenem and 2x400 mg ciprofloxacin intravenously. Then, on the 6th day of treatment the patient received 2x1 grams of vancomycin and UFH 3x5000 U was also given.

On day 7 SOB was worsening, oxygen saturation dropped to 94% with Simple Mask 10 lpm (**Table 1**). CXR showed progressive infiltrate (**Figure 1**). RT-PCR result was positive For SARS-CoV-2 infection. Care plans included transferring the patient to the isolation ICU and considering to be intubated. At that time, the patient could communicate appropriately and refused intubation. Subsequently, patient's condition continued to worsen for six days with lowest SpO2 92% with Non-Rebreathing Mask (NRM) 12 lpm and lowest SpO2/FiO2 97.

On the 14th day, the patient clinical condition began to improved. Decreased SOB, still in NRM 7 lpm oxygen, SpO2 92% and P/F ratio increases to 245. From the 14th day onwards until 45th day of treatment improvement continue and RT-PCR was negative twice, the P/F ratio 381 without oxygen supplementation, CXR obtained improved infiltrate. Because of limited resources, CT Scan examination could only be done once immediately before discharge and a ground glass opacity was still obtained (**Figure 2**).

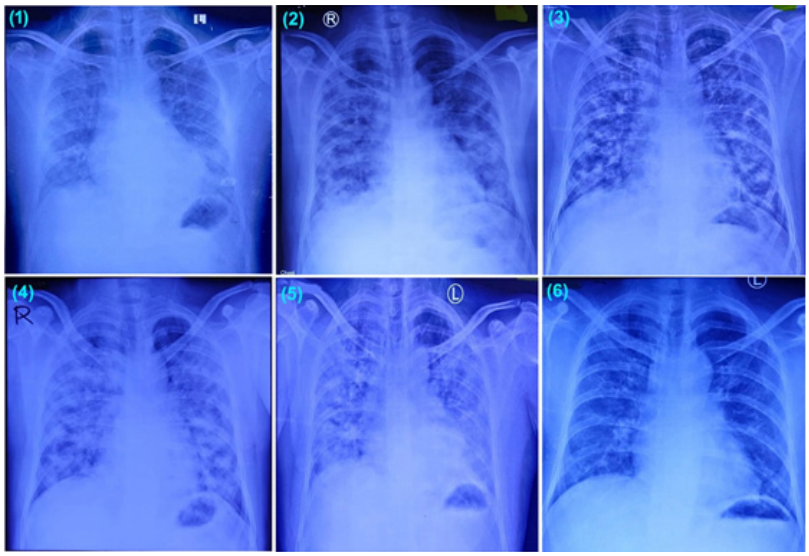

Figure 1. Serial chest X ray of case 1 from day 1 until before hospital discharge.

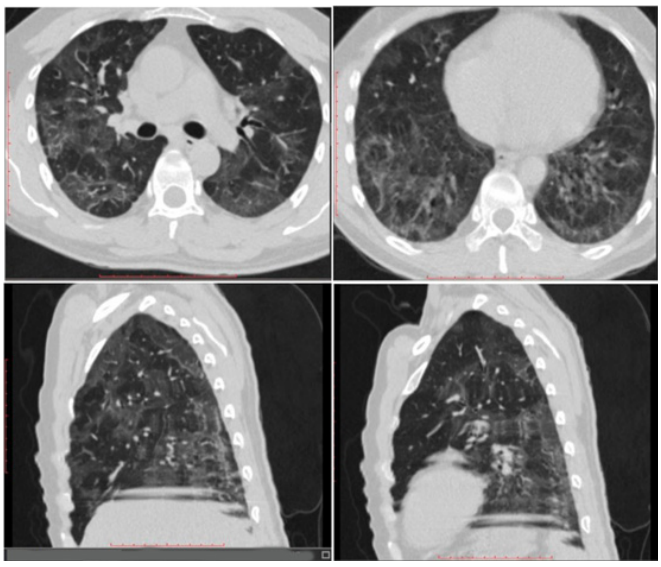

Figure 2. CT scan thorax case 1 on 57th day of illness.

Case 2

A 64-year-old man came to hospital due to shortness of breath for seven days and worsening in the last three days, cough with yellowish phlegm and cold. There was no fever, sore throat and diarrhea. He already had a history of dyspnea on exertion since 3 months ago. Three months earlier he underwent cardiac catheterization and stent placement.

Routine medications are aspirin, bisoprolol, furosemide and atorvastatin. He had Diabetes Mellitus (DM) for 14 years and treated with metformin. He is an active smoker and had a history of high cholesterol. He had no history of traveling outside city. There was no history of contact with COVID 19 cases.

The patient appeared seriously ill but fully awake, BP 130/80 mmHg, pulse 118 beats per minute, respiratory rate 32 breaths per minute, temperature 36.7^{o}C, ratio SpO2/FiO2 was 98 and BMI 28.6 kg/m^{2}. Coarse crackle was heard at right hemithorax. He had slight cardiomegaly and other findings were within normal limit.

The laboratory data were Hb 12.1 g/dL, Ht 33.7%, white cell count 9.170/mm^{3}, platelet count 274,000/mm^{3}, basophils 0%, eosinophils 0%, band neutrophils 2%, segmented neutrophils 73%, lymphocytes 16%, monocytes 9%, TLC 1470/mm^{3}, RBS 240 mg/dL, serum ureum 38 mg/dL, serum creatinine 1.19 mg/dL, sodium 132 mEq/L, potassium 4.7 mEq/L, pH 7.551, pCO2 27.1 mmHg, pO2 103.2 mmHg, HCO3 21.9 mmol/l, BE 0.5 mmol/L, SaO2 97.7% and P/F ratio 149, Electrocardiography suggested sinus rhythm, and CXR showed bilateral peripheral opacity with slight cardiomegaly.

Initial diagnosis were patient under investigation (PDP) COVID-19 with respiratory insufficiency, DM type 2 with diabetic neuropathy, diabetic kidney disease, coronary arterial disease one vessel disease post primary coronary (one vessel disease post primary coronary intervention on left anterior descending artery), heart failure, hypertension and overweight.

Patient received care in isolation ward, oxygen 10 lpm NRM, NaCl 0.9% 1000 cc/24 hours, ceftriaxone 2x1 gram and levofloxacin 1x750 mg intravenously, oseltamivir 2x150 mg, chloroquine 2x500 mg, ISDN 1x5 mg sublingual, aspilets 1x81 mg, bisoprolol 1x5 mg, ramipril 1x1.25 mg, atorvastatin 1x40 mg, N-acetylcysteine 3x200 mg and furosemide 1x40 mg orally.

Since the first day of hospitalization until day 8, the patient experienced clinical deterioration (**Table 3**), worsening SOB, respiratory rate 32 breaths per minute, lowest P/F ratio 149, and CXR suggested increased infiltrates (**Figure 3**).

Table 3. Clinical course of case 2.

Day	Symptoms	BP	Pulse	RR	Temp	SpO2/ FiO2
01	Dyspnea, cough	130/80	112	32	36.7	98
02	Dyspnea, cough	129/80	100	30	36.4	98
03	Dyspnea, cough	114/72	94	28	36.6	100
04	Dyspnea, cough	130/80	84	24	36.3	103
05	Dyspnea	127/82	93	26	36.0	123
06	Dyspnea	120/70	100	24	36.9	124
07	Dyspnea	123/85	100	26	36.2	104
08	Dyspnea	130/90	96	24	36.4	192
09	Dyspnea, cough	130/80	96	26	36.3	161
17	Dyspnea	125/83	82	22	36.2	269
21	Cough	128/76	87	20	36.2	400
22	None	127/75	86	20	36.4	346
32	None	110/70	80	20	36.2	490

Table 4. Laboratory data of case 2 during hospitalization.

Day	Leucocyte	TLC	CRP	PC	Ferritin	RT-PCR
01	9.170	1470				
02	8.670	1210				POS
05	10.001	1400				
07	10.730	1610				
08	8.580	1460	6.75			
09	8.810	1321			1378.5	
12						NEG
13			7.31			
14			5.68		1628	
16	6.970	1742				
18	11.580	1968	13.09		1692.2	
19	9.430	1980				NEG
20	9.310	2606				
23	5.980	1973				
31	6.800	1900	0.53			
35	7.280	2402				

TLC (Total Lymphocyte Count), CRP (C Reactive Protein), PC (Procalcitonin)

RT-PCR result which obtained later was positive.

Since hospital admission, the patient was planned to be treated in isolation ICU, for intubation and mechanical ventilation but he refused. Fortunately from ninth day of treatment, clinical condition was improved, on the thirty fifth day of care the patient was declared cured after two negative RT-PCR results. Before discharged, the patient underwent CT scan of the thorax without contrast, and the result suggested persistence of ground glass opacity (**Figure 4**).

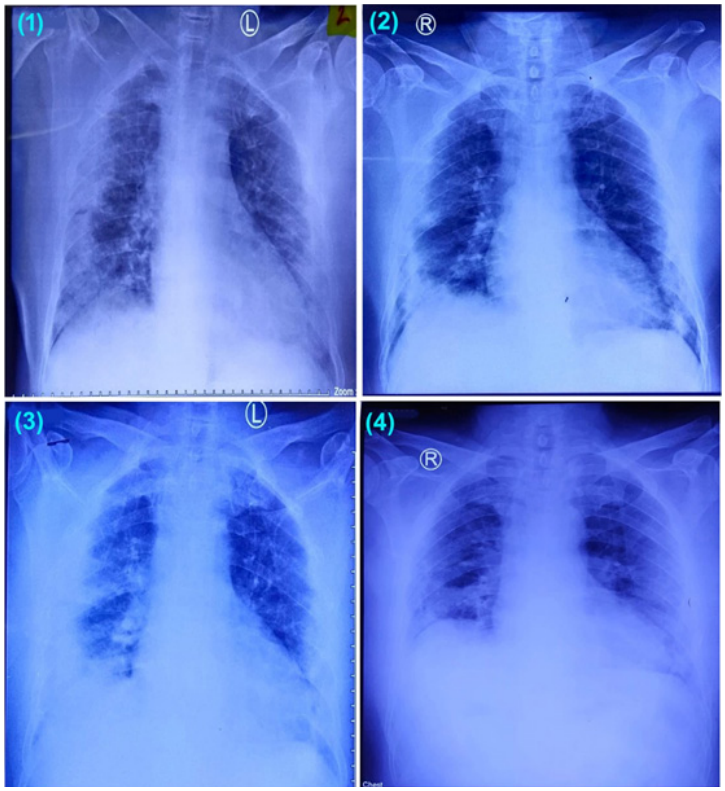

Figure 3. Serial chest X ray of case 2.

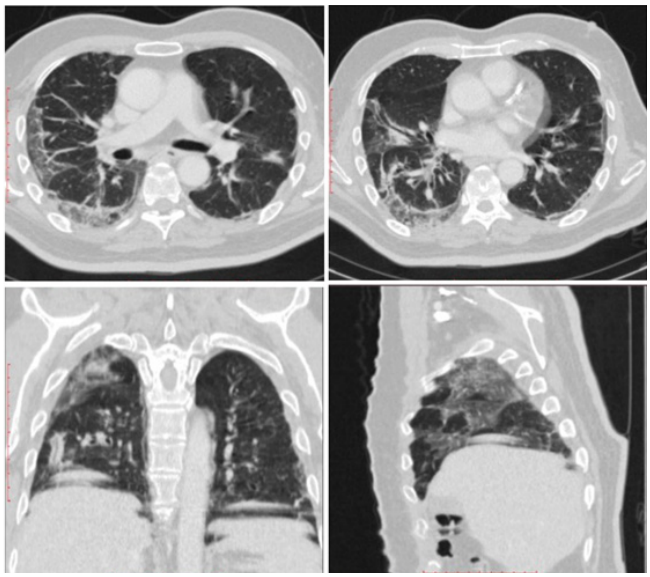

Figure 4. CT scan thorax case 2 on 46th day of illness.

DISCUSSION

In case 1, clinical deterioration occurred between 7th to 13th day hospitalization (day 14th to 20th from onset), SOB worsen, RR 30/ min, lowest SpO2 92% with NRM 12 lpm, lowest SpO2/FiO2 ratio 97. CXR showed progressive infiltrates (**Figure 1**). While in case 2 clinical deterioration occurred from the first to eighth day of hospitalization (day 7th to 15th from onset), highest RR 32 times/min with the lowest SpO2/FiO2 ratio 98. CXR series showed increase infiltrate (**Figure 3**).

Based on Kigali modification of the Berlin criteria in 20174 cases 1 and 2 fall in ARDS conditions. In Kigali modification ARDS was defined without the need of positive end-expiratory pressure, with the presence of bilateral opacities of chest radiograph or lung ultrasound and hypoxia was defined with a cutoff of SpO2/ FiO2 ratio $\leq$ 315.[1,4]

According to the criteria established by Meng et al.[5] on the seventh day of hospitlization in case 1 and the first day in case 2 already met the criteria for intubation. But intubation were not performed. If these patients were not mechanically ventilated, according to pathway proposed by Vincent et al.[6] both cases are in the death path. In fact, both cases were improved and survived without intubation and mechanical ventilation.

There is an assumption that ARDS in COVID-19 (CARDS) is different with classic ARDS.[7,8] Gattinoni et al.[7] suggested that COVID-19 ARDS had two different phenotypes, namely type L and type H.

CARDS type L phenotype characteristics: (1) typical viral pneumonitis at initial presentation; (2) increase infiltrate but only in limited area, at first usually characterized by a pattern of ground glass on CT and more likely as interstitial edema rather than alveolar. Many patients do not complain SOB despite poor oxygenation conditions; (3) hypoxemia with good CO2 clearance (type 1 respiratory failure); (4) low in: (a) elastance (high compliance), (b) ventilation to perfusion ratio V/Q due to hypoxic induced vasoconstriction abnormalities (vasoplegia), (c) recruitability (poor response to PEEP and proning), (5) implications of these: (a) can avoid the use of mechanical ventilation with more conservative oxygen supplementation; (b) responsive to pulmonary vasodilators (for example inhalation of nitric oxide); (c) many experience clinical improvement at this stage, however some are deteriorating and transitioning to type H.

Type H CARDS has the following characteristics: (1) continuation of the worsening of COVID-19 with a classic picture of ARDS; (2) hypoxemia that occurs with impaired CO2 clearance (type 1 and/ or type 2 respiratory failure); (3) widespread consolidation of the chest CT scan (extensive CT consolidations), increased lung mass; (4) high in: (a) elastance (low compliance), (b) V/Q matching, (d) recruitability (responsive to PEEP and proning); (5) implications: It is better to use mechanical ventilation and ARDS therapy as usual. CT scan be used to distinguish COVID-19 ARDS phenotype type L and type H. Where Type H present as typical picture of ARDS.[7]

Both cases appeared to have type L CARDS, which means that their lungs were still in high compliance state and type L patients could experience improvement without mechanical ventilation. But this assumption could not be confirmed, because when both cases experienced clinical deterioration, CT scan could not be ordered. This was due inavailability of CT scan machine intended specially for infectious cases of COVID-19 in our hospital.[7]

There are several possible explanations for why these two cases recovered from type L instead progress to type H which is a typical picture of ARDS.

Siddiqi et al.[9] divided the course of COVID-19 into three stages: (1) Stage I or the initial phase of infection. This stage can be asymptomatic or non specific mild symptoms, such as malaise, fever and dry cough. During this period the virus replicates in the host, especially in the respiratory system. The virus binds to ACE 2 receptors in human cells, these receptors are found in the human lung, small intestinal epithelium and blood vessel endothelium; (2) Stage II or pulmonary phase. At this stage patients developed respiratory symptoms due to local inflammation of the lungs. Viral pneumonia occurs with symptoms of cough,

fever and possible hypoxia, PaO2/FiO2<300. CXR or CT scan shows the presence of bilateral infiltrate or ground glass opacity; (3) Stage III or hyperinflammatory phase in this stage, markers of systemic inflammation appear to be elevated. Inflammatory cytokines and biomarkers such as interleukin (IL)-2, IL-6, IL-7, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-α, tumor necrosis factor-α, C reactive protein, ferritin, and D-dimer are significantly elevated in those patients with more severe disease.[9] This condition is also known as cytokine storm.[10,11] At this stage, shock, vasoplegia, respiratory failure and even cardiopulmonary collapse are discernable.[9]

In COVID-19, cytokine storm is a key factor in the process of ARDS. Serum cytokines increase significantly in patients with ARDS, and high serum cytokine levels correlate with high mortality.[12]

Cytokine Release Syndrome (CRS) had characteristic signs and symptoms: (1) continuous high fever; (2) tissue and organ damage caused by immune reactions related to cytokines and coagulation disorders; (3) significant increase in IL-6 cytokines in the blood; (4) decreased circulation of CD4, CD8 and NK cells in the blood. CRS conditions on COVID-19 often occur between day 7 to day 16. The best marker to evaluate progress and decline of this CRS is IL-6 level. Several other markers including CRP, LDH and ferritin can also be used, their kinetic almost similar with IL-6.[13-15]

A cohort study conducted by Liu, et al.[15] provides a description of the kinetic changes in cytokine levels such as IL-2, IL-4, IL-6, IL-10, IFN-g and TNF-a. In mild and severe COVID-19 patients, Cytokine levels reached their peak levels on the sixth day after the onset of illness except IL-6. IL-6 and IL-10 could continuously increase in severe COVID-19, IL-6 levels would begin to decrease on the sixteenth day after the onset of the disease, while IL-10 had reached its lowest thirteen days after onset disease. Increased serum IL-2 and IFN-g levels in severe COVID-19 only appeared 4-6 days after disease onset. All cytokines decreased both in severe and mild patients on the 16th day after disease onset.[16,17]

Other study showed that on the third day of hospitalization, severe COVID-19 patients had high levels of IL-6, CRP, and LDH. Then the levels began to fall on days seven to nine in patients with moderate and severe COVID-19.[18] So it could be assumed that CRS could be occurred between day three of hospitalization to sixteen days after symptom onset.16 Higher levels of IL-6 also associated with increased ground glass opacity in the CT scan of the thorax of severe COVID-19 patients.[13]

When their clinical manifestation deteriorate, both cases were between day 7-16 after onset of illness and it was likely that they were at stage III COVID-19 (hyperinflammation stage) which was characterized by severe symptoms and ARDS. So CRS was currently underway. Although it could not be proven with IL-6 levels but there were CRP and ferritin data were available even though the test was not precisely done at the same time as the disease course when CRS occurred.

In case 1, at day seventh of hospitalization, CRP level was high 6.27 mg/dL (normal CRP<0.03 mg/dL). Serial CXR of the patient also showed an increase in infiltrate (**Figure 1**). Then on fourteenth day CRP levels decreased by 0.57 mg/dL, in line with the patient's clinical condition which showed improvement (**Table 1**). In case 2, CRP and ferritin levels on the 8th day were high, i.e. 6.75 mg/dL and 1378.5 ng/ml (normal ferritin 22-232 ng/ml). In serial CXR, infiltrates were also increase (**Figure 3**). On the fourteenth day, the CRP and ferritin levels of the patient were still high at 13.09 mg/dL and 1692 ng/ml. On day twenty eighth when clinical condition already improved, CRP levels fell to 0.53 mg/dL. These data suggested that CRS occurred when both cases experienced worsening clinical condition.

Ventilation management of type L and H CARDS is quite different. In the type L phenotype, the initial steps to restore hypoxemia are: (1) increase FiO2; noninvasive options such as High Flow Nasal Cannula (HFNC), Continuous Positive Airway Pressure (CPAP) or with Non-Invasive Ventilation (NIV); (2) estimate work of breathing; (3) increase PEEP wisely because it has the potential to reduce

pleural pressure swings so that the phenotype may be altered; (4) conditioning patient in prone position; (5) if respiratory distress present intubation may be able to avoid/ limit progression to the H type phenotype.[7]

Treatment to both cases that probably gave positive impact include ventilation with adequate FiO2 even though it was given with conventional masks (SM and NRM). This adequate administration of oxygenation did not make intrathoracic pressure became more negative and increasing in tidal volume while in spontaneous breathing. The combination of intrathoracic negative pressure and increased lung permeability due to inflammation was thought to be the cause of interstitial pulmonary edema. This phenomenon was referred to as Patient-Self Inflicted Lung Injury (P-SILI).[17]

Although still controversial, but there were probability benefit of medication given to both cases. Several studies have shown chloroquine and hydroxy chloroquine could reduce the production of various proinflammatory cytokines, such as IL-1, IL-6, interferon-α and tumor necrosis factor, which are involved in cytokine storm, reduce the occurrence of exacerbation of pneumonia, and increase the possibility of negative conversion to COVID virus.[12,18]

The course of the disease of this two cases we presented supports the different pathophysiological concepts between ARDS that occur in COVID-19 (CARDS) and classic ARDS. It is crucial to understand the concept of the pathophysiology of L and H phenotype and to apply it in the management of patients with COVID-19 ARDS

CONCLUSION

Understanding the pathophysiology is very important for appropriate and adequate management. The underlying mechanism of CARDS phenomenon is Cytokine Relase Syndrome (CRS) which occurs around seven to sixteen days from the onset of symptoms. CARDS is quite different from classical ARDS. Type L CARDS does not exactly the same as ARDS although it meets the ARDS criteria according to the Kigali modification of the Berlin criteria, whereas the H COVID-19 phenotype may be the clasic ARDS. Type L and H CARDS patients can be identified using CT scan. This emphasizes the importance of the availability of CT scan examinations in health facilities that manage COVID-19.

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