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A severe Covid-19 case in the early phase of the pandemic - Lessons learnt

***Abstract*— The management of severe Covid-19 cases has been changing throughout the past year. Lessons learnt on the progress of patients with severe disease in the early phase of the pandemic is important. We report a ventilated COVID-19 patient in a secondary hospital during the early phase of the pandemic which had resulted in a poor outcome. It also highlights the importance of adopting strategies and supportive care to conduct effective risk stratification and preparations such as adequate laboratory and intensive care support in treating patients with severe COVID-19.**

***Keywords* — Early phase, Severe COVID-19, supportive care, ventilated.**

1 INTRODUCTION

Starting from a cluster of atypical pneumonia cases in Wuhan, China, Coronavirus disease 2019 (COVID-19) has spread rapidly throughout the world. In January 2020, the World Health Organization (WHO) declared this as a pandemic and a global public health emergency. In Malaysia, confirmed COVID-19 cases started with imported cases in late January of 2020, and has since become widespread locally after October 2020.

We report one of the first ventilated COVID-19 patient in a secondary hospital in the early phase of this pandemic which had resulted in a poor outcome. This case report shares the experience before corticosteroid was recommended as a treatment for severe COVID-19. It also highlights the importance of adopting strategies and supportive care to conduct effective risk stratification and preparation in hospitals which are newly assigned to treat severe COVID-19 patients.

2 CASE REPORT

A 48-year-old gentleman with no underlying medical illness presented to the emergency department, with a one-week history of fever, dry cough, runny nose, nausea, lethargy and a reduced appetite. He had a history of international travelling and had just returned to the country 3 days prior to the onset of his symptoms.

Physical examinations revealed a low-grade fever of 37.5°C, blood pressure of 105/60mmHg, heart rate (HR) of 92 beats per minute (bpm), respiratory rate (RR) of 20 breath per minute, and oxygen saturation (SPO2) of 97% under room air. The patient had a coated tongue, and a capillary refill time of 2 seconds. He was not jaundiced and his lungs were clear on auscultation.

The initial blood investigations showed white cell count of 5.48 x109/L, platelet count of 182 5.48x109/L, urea of 4.6mmol/L and a raised CRP of 36.5mg/L. There was mild transaminitis and respiratory alkalosis with pH 7.52, pCO2 23.9mmHg, PO2 149mmHg and HCO3 of 19.5mmol/L. (Table I) Chest radiograph (CXR) showed heterogenous consolidation with air bronchogram at right middle zone and bilateral lower zone (Fig 1A).

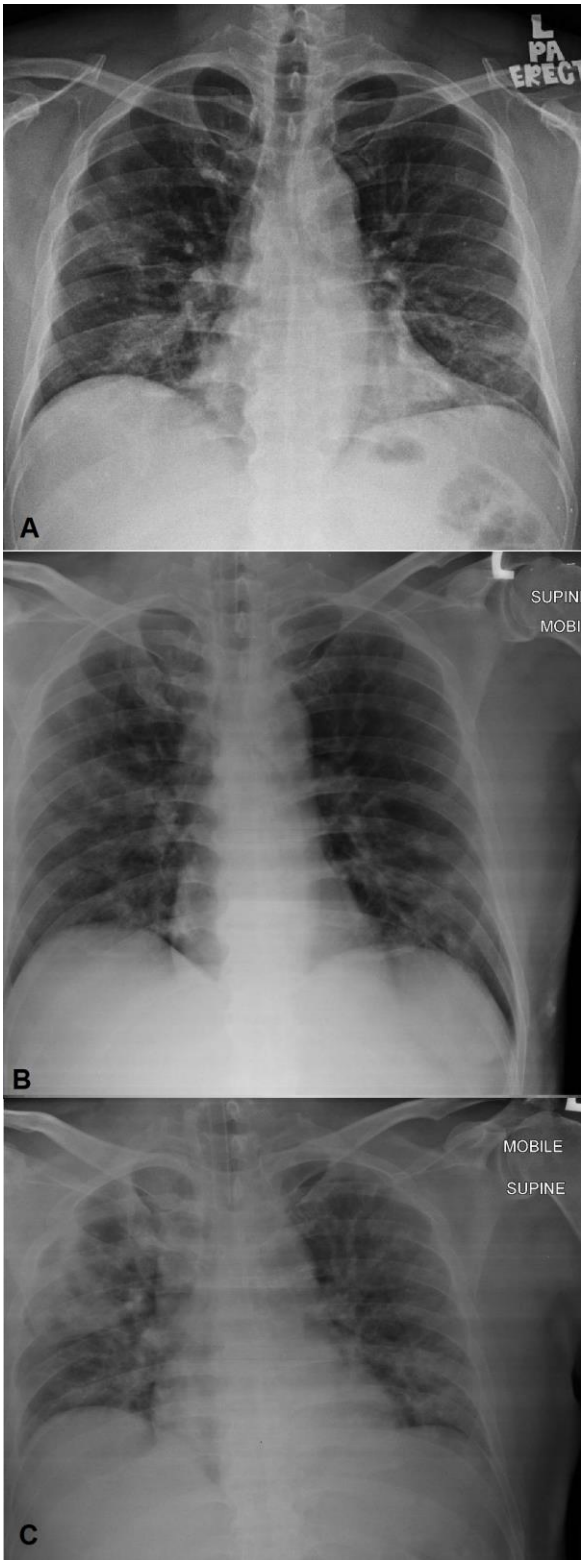

Figure 1: Serial chest radiograph at (A) Day-8, (B) Day-12 and (C) Day-14 of illness showed worsening bilateral lung heterogenous opacity.

The patient was initially treated as pneumonia and dehydration. He was given supportive care and started on oral Azithromycin 500mg daily and intravenous (IV) Ceftriaxone 2g daily. Due to his traveling history, the patient was transferred to a negative pressure isolation room, nasopharyngeal and oropharyngeal swab was tested for COVID-19 using real-time reverse transcription polymerase chain reaction (rRT-PCR) assay.

On day-3 of admission (day 10 of illness), rRT-PCR result was confirmed to be positive. He was started on tab Lopinavir/Ritonavir (Kaletra) 400mg/100mg BD, tab Ribavirin 1.2g BD, tab Hydroxychloroquine 200mg BD. IV Rocephine was discontinued.

On day-11 of illness, the patient developed a high-grade fever accompanied by tachycardia and tachypnea. There was coarse crepitation over the right lower zone and ABG under room air showed mild hypoxemia with hypocapnia. (Table II) Due to the hospital isolation unit policy during the early phase of the pandemic, only initial point-of-care laboratory testing were permitted. Full investigations and serum chemical studies were only approved after a few days of hospitalization. The patient was given IV fluid replacement and oxygen supplement via nasal prongs.

On day-12 of illness, the patient became more lethargic, dehydrated, tachypnic and feverish despite treatments. This was also accompanied by a worsening diarrhoea. Due to the worsening respiratory failure, after a multidisciplinary discussion and consensus, an elective intubation was performed with strict universal precautions.

After mechanical ventilation was started, the patient developed hypotension requiring inotropic support with 0.1mcg/kg/min IV noradrenaline. SPO2 was kept more than 98%, HR ranged 88-94bpm. He was ventilated according to lung protective strategy. [1] Good tidal volume was generated and airway pressure was not high, ranged 14-18cmH_2O. CXR showed worsening heterogeneous opacities over both lungs. (Fig 1B) The patient was treated as pneumonia and moderate ARDS secondary to COVID-19. IV meropenem 2g TDS was added to cover for hospital acquired pneumonia.

On day-13 of illness, the fever persisted, with sinus tachycardia and raised creatinine kinase. The patient developed gastrointestinal bleeding, hyperglycemia and coagulopathy. (Table I) Infusion of proton pump inhibitor was administered, as well as correction of

coagulopathy. Regular doses of IV frusemide was started to keep a slight negative fluid balance. He was started on subcutaneous interferon 1b 250mcg EOD and tocilizumab.

On day-14 of illness, the spiking temperature, tachycardia and hyperglycemia still persisted. Repeated cultures were all negative. Repeated CXR showed bilateral ground-glass opacities with heterogenous consolidation over the right middle and upper zones. (Fig. 1C) In view of the unresolved clinical septic parameters, IV vancomycin was added. The ventilator setting was able to be weaned to FiO_2 0.4 with PEEP 10 and IV noradrenaline was able to be tapered down to 0.02mcg/kg/min (MAP maintained > 70mmHg). Regular tepid sponging was performed on top of an antipyretic agent to control the fever.

On day-15 of illness, the patient deteriorated dramatically. He was septic looking, gasping despite deep sedation with cold peripheries. The inotropic support requirement increased sharply, accompanied by a persistent temperature spike (Table III), tachycardia and hyperglycemia. SPO2 dropped to 92% despite on 100% FiO2, and ABG showed hypoxemia. Urgent CXR showed similar changes with no pneumothorax.

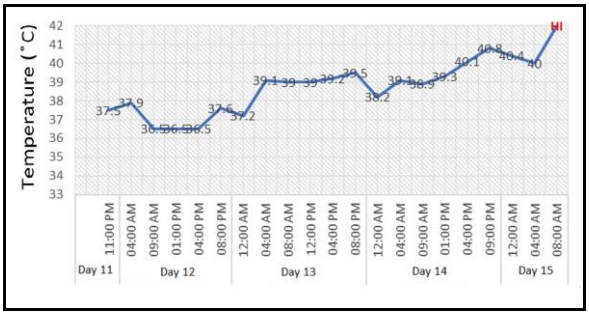

Table III: Temperature chart

Despite maximal resuscitation effort, the patient deteriorated and died. His cause of death was septic shock secondary to cytokine storm and fulminant myocarditis. Investigation results which was released subsequently supported the diagnosis of fulminant cytokine release syndrome with raised serum ferritin, triglyceride and fibrinogen levels. (Table I)

Table I: Laboratory results

Day of illness	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15
White-cell count ($x10^3/\mu L$)	5.5	7.1	6.84	8.03	5.17	10.14
Hemoglobin (g/dL)	13.5	12.6	12.3	11.7	12.1	12.9
Hematocrit (%)	36	34	33	31	32	36
Platelet Count ($x10^3/\mu L$)	182	190	221	247	269	299
Sodium (mmol/L)	135		133	136	141	146
Potassium (mmol/L)	3.9		3.8	4	4.1	4.2
Urea (mmol/L)	4.6		2.7	2.7	6.3	9
Creatitine (µmol/L)	80		71	85	105	128
Protein (g/L)	72		64	60	66	
Albumin (g/L)	39		34	31	32	
Total Bilirubin (µmol/L)	16		21	30	62	
Indirect Bilirubin (µmol/L)	12.3		15.5			
Alkaline phosphatase (U/L)	64		56	51	68	
Alanine aminotransferase (U/L)	52		66	55	57	
Aspartate aminotransferase (U/L)	65		83	50	37	
Uric Acid (mmol/L)						278.9
Calcium (mmol/L)			1.88	1.73	1.98	1.88
Magnesium (mmol/L)			0.88	0.92	1.6	1.05
Phosphate (mmol/L)			0.63	0.51	0.41	0.33
C-Reactive Protein (mg/L)	36.5		5.8		128.4	
ESR	8					
Creatinine kinase (U/L)			>2000	1302	508	
CKMB (U/L)			29	20		
Protrombin Time (s)					16.3	12.4
INR					1.7	1.2
APTT (s)					69.2	50.4
Lactate			1.36		1.63	
Triglycerides (mmol/L)					1.74	
Ferritin (ng/mL)					>1500	
Cortisol (nmol/L)					962.2	
Fibrinogen (mg/dL)					343.1	

Abbreviation: APTT, activated partial thromboplastin time; CKMB, creatine kinase myocardial band; ESR, erythrocyte sedimentation rate; INR, international normalized ratio.

Table II: Serial arterial blood gas and culture results.

Day of illness	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15
pH	7.52	7.46	7.39	7.50	7.40	7.39
PCO_2	23.9	25.8	41.2	22.5	47.5	45.5
PO_2	149	75	156	156	175	76
HCO_3	19.5	18.4	25.4	17.4	29.5	27.6
BE	-3	-5	1	1	5	3
SPO_2	100	96	99	100	100	95
Blood C&S	No growth	-	No growth	-	-	-
TAS C&S	-	-	-	-	-	No growth

Abbreviation: BE, base excess; C&S, culture and sensitivity; HCO3, bicarbonate; pCO2, partial pressure of carbon dioxide; pO2, partial pressure of oxygen; SPO2, oxygen saturation; TAS, tracheal aspirates.

3 DICUSSION

Studies have shown that among COVID-19 patients, elderly adults with co-morbidities are at higher risk of morbidity and mortality. Other risk factors for poorer outcomes include secondary infection, higher SOFA score at presentation, high neutrophil to lymphocyte ratio and elevated d-dimer. [2] This case report describes a clinical scenario in a relatively young patient with no known medical illness during the early stage of the pandemic before dexamethasone and methylprednisolone was recommended and the description of cytokine release syndrome (CRS) which was drastic and refractory to resuscitation. [3]

For early detection of CRS, all COVID-19 patients should be risk stratified according to risk factors, comorbidities, clinical features such as Modified early warning score (MEWS) and laboratory predictors such as serial neutrophil count, lymphocyte count, C-reactive protein (CRP), ferritin, troponin, procalcitonin, d-dimer as well as cardiac myoglobin. However, during the early phase of the COVID-19 outbreak, the diagnosis and management of the disease was complicated by the lack of understanding of its diverse clinical presentation, limitation in supportive care, unclear pathophysiology and management.

Patients with COVID-19 infection generally undergo 3 chronology phases: viral response phase (around Day 1-5), pulmonary phase (around Day 6 - 9), hyperinflammatory phase (Day 10–20) before recovery. [4] At the hyperinflammatory phase, there will be a drastic increase in inflammatory cytokines which cause tissue damage and clinical deterioration. This progression explains the clinical phenomenon in our patient. A persistent fever despite adequate antibiotic coverage, antipyretics, and negative cultures are warning signs for COVID-19 patients entering the hyperinflammatory phase.

Approximately 8-15 % of Covid-19 patients develop severe infection with dyspnea, hypoxia, and pulmonary involvement. [5] ARDS is one of the major complications in patients with severe disease and can manifest shortly after the onset of dyspnea. 2.9% of severe cases and 17.9% of non-severe cases had normal CXR on initial presentation. [6] Other complications of COVID-19 include thromboembolic events, acute cardiac injury, acute kidney injury, and CRS. CRS has features similar to bacterial sepsis or hemophagocytic lymphohistiocytosis HLH. Clinical markers of CRS include elevations of C-reactive protein (CRP), LDH, ferritin and IL-6. Dropping in absolute lymphocyte count (ALC), increasing neutrophil to lymphocyte ratio (NLR), elevated d-dimer and fibrinogen levels may correspond to disease severity and mortality. [7-9]

Thus, for a centre to treat COVID-19 patients, apart from the nursing, medical and critical care support, laboratory support is also extremely crucial for close monitoring of these blood parameters, prompt detection and early management of cytokine release syndrome. In our patient, there was a limitation on running unconventional blood tests due to a limited understanding of the virus and guidelines in processing blood samples of COVID-19 patients at that point of time.

Treatment guidelines of COVID-19 infection is constantly changing with input on how patients respond to various treatments. The latest COVID-19 management is based on the patient's severity which can be categorised into 5 stages. Stage 1: asymptomatic, stage 2: symptomatic but no pulmonary changes, stage 3: symptomatic with pulmonary changes, stage 4: requiring oxygen supplementation, stage 5: intubation or end-organ damage. [10] The current treatment for COVID-19 infection is generally divided into antiviral, immunomodulatory therapy and anticoagulants. Antivirals are best given at the viral response phase when the patient has warning signs or comorbidities at stage 3 and beyond. When the patient enters the hyperinflammatory phase, immunomodulating

agents such dexamethasone, methylprednisolone, tocilizumab are currently being used. [11, 12] However, these medications should be given with caution and guided by inflammatory markers and septic parameters. Sepsis and CRS shares nearly similar clinical features and might be hard to differentiate. Giving high dose corticosteroid to a patient with sepsis could be detrimental. Patients with severe COVID-19 should be managed meticulously in prevention, precaution and empirical treatment for any secondary infections. Antibiotic should be given when secondary bacterial infection is suspected in these vulnerable patients because they are on immunomodulatory therapy. Serial procalcitonin and CRP measurements may be useful in guiding management for CRS and bacteria sepsis.

Anticoagulants are given to those on oxygen therapy, as they will be less ambulating and thus at a higher risk of thromboembolism. A hypercoagulable state tends to happen after the hyperinflammatory phase and may present as myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism.

The current situation of COVID-19 had overburdened the healthcare system in many countries. Many patients are on home quarantine and do not receive hospital treatments. The disease progress can deteriorate rapidly from a condition that looks like a common cold, just like our encounter. Thus, efficient risk stratification is of utmost importance, eg daily follow-up assessment of symptoms such as persistent fever, objective assessment of worsening dyspnea, exertional dyspnea, and other warning signs.

4 CONCLUSION

In conclusion, there are multiple limitations and learning points in treating severe COVID-19 patients during the early phase of the pandemic. Treatment of severe COVID-19 has improved much since then. However, it still requires the full support of a comprehensive laboratory service, primary care screening, good nursing and a dedicated critical care service.

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