CASE REPORT

Covid-19 with Methicillin-Resistant Staphylococcus Aureus: Based on Two Cases in Diponegoro National Hospital

Dwi Retnoningrum[✉*], Setyo Gundi Pramudo[**], Taufik Eko Nugroho[***], Qonita Nur Qolby[****]

[*]Department of Clinical Pathology, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
[**]Department of Internal Medicine, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
[***]Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
[****]Diponegoro National Hospital, Semarang, Indonesia

[✉]Korespondensi: dwiretno@fk.undip.ac.id

ABSTRACT

Background: Coronavirus disease 19 (COVID-19) has become pandemic in the world with a board spectrum of clinical presentation. Secondary infection of methicillin-resistant staphylococcus aureus (MRSA) affects morbidity and mortality in patients with COVID-19.

Case: We reported two COVID-19 patients with MRSA hospitalized in intensive care unit (ICU) of Diponegoro National Hospital. The first patient was 61-year-old woman that was referred from another hospital with confirmed COVID-19 infection and acute respiratory distress syndrome and had been intubated. Diabetes mellitus and hypertension were known as comorbid. On day 4 of treatment in ICU, blood culture results showed MRSA infection and antibiotic therapy was replaced with Vancomycin. The patient had clinical improvement and was discharge from the hospital on the 36th day of treatment. The second one was 51-year-old woman admitted with probable COVID-19, type II Diabetes Mellitus and hypertension. On day 9th the patient was transferred to ICU because of respiratory failure, blood culture on day 15th show a result of MRSA and antibiotic therapy was replaced with vancomycin. She declined intubation procedures and died on day 20.

Discussion: Antibiotic resistance has become one of the important things in infection management in the world. Multidrug-resistant bacteria (MDR) cause treatment failure which increases the risk of death and cost. MRSA has become one of the most important MDR bacteria during the last decade causing severe infections in health facilities. Complications of bacterial infection in COVID-19, especially bacteremia increases the severity and mortality of severe patients.

Conclusion: Coinfection of MRSA in COVID-19 patients can affect the clinical outcome. One of important risk factor is history or prolonged hospitalized. Other factors are comorbidity of the patient and appropriate therapy is needed to reduce mortality in Intensive Care Unit.

Keywords: COVID-19; diabetes mellitus; hypertension; infection; methicillin-resistant staphylococcus aureus

INTRODUCTION

Coronavirus disease-19 (COVID-19) is an infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The coronavirus, which becomes a COVID-19, belongs to the genus beta-coronavirus. The results of allogeneic analysis show that this virus is included in the same subgenus as the coronavirus that caused the severe acute respiratory illness (SARS) outbreak in 2002-2004. On this basis, the International Committee Taxonomy of Viruses (ICTV) proposed the name SARS-CoV-2 following a phylogeny-based line of reasoning for naming viruses. An assessment of the genetic linkage of the novel coronavirus was identified. Previously this virus was named 2019-nCoV, for known coronaviruses, and details (re) naming basis the virus is severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1]

By January 2021 COVID-19 has caused over 101 million cases and over 2 million deaths worldwide.[2] This infection is worldwide emergency, as it spread rapidly with high mortality rate and causes severe condition. Patients with COVID-19 infection have a board spectrum of clinical presentation, this disease can be mild such as the common cold, but can develop to pneumonia, acute respiratory distress syndrome (ARDS) and multiple organ failure.[3]

Bacterial and fungal coinfection in COVID-19 patients has been reported before. Systematic review and meta-analysis reported that 7% of hospitalized COVID-19 patients had a bacterial coinfection. A higher proportion of bacterial coinfection is in ICU patients. One of the bacterial pathogen that caused coinfection is methicillin-resistant Staphylococcus aureus (MRSA), the epidemiology of MRSA lung infection in patients with COVID-19, when considering all other bacteria ranging from 2% to 29%.[4,5]

Staphylococcus aureus is a gram-positive coccus that can cause pneumonia as a secondary infection from influenza virus infection. MRSA is a community and hospital acquired pathogen. MRSA infection can cause complications such as meningitis, osteomyelitis, necrotizing pneumonia, urinary tract infections and sepsis. MRSA is a problem in antimicrobial treatment in hospitals because vancomycin is one of antibiotic susceptible to these bacteria.

A study by Cusumano et al, reported 42 patients (1.57%) of all COVID-19 patients in hospital had secondary S. aureus infection, with 54.8% of patients death on day 14 and 66.7% on day 30.[6] Previous case reports have also reported secondary MRSA infections in COVID-19 patients.[7]

CASE

We reported 2 cases of COVID-19 patients who were admitted to the ICU of the Diponegoro National Hospital Semarang in October - December 2020. The patient was diagnosed positive for SARS-CoV-2 by RT PCR examination from nasopharyngeal and oropharyngeal swabs. During the course of the disease, the patient obtained a positive MRSA blood culture. Both patients had a history of type 2 diabetes mellitus and hypertension. Patient 1 recovered and was discharged from hospital after 36th days of treatment, while patient 2 deceased on the 20th days of treatment.

Patient 1 was a 61 years old woman with a history of type 2 diabetes mellitus and hypertension. The patient was referred from another hospital with a confirmed COVID-19 diagnosis, previous cough

and shortness of breath. The patient had been intubated and referred because of the need for mechanical ventilation. On the physical examination of the patient, patient in delirium, blood pressure 122/60 mmHg, heart rate 113 x/minute, respiratory rate 40 x/minute, with 97% oxygen saturation with 100% FiO2. Initial laboratory tests showed hemoglobin 11.3 g/dl, leukocyte count 7,760/µL, platelet count 178,000/µL, Eosinophil count 0%, Basophil 0%, Neutrophil Band 1%, Neutrophil segment 75%, Lymphocyte 14%, Monocyte 10 %, with neutrophil to lymphocyte ratio (NLR) 5.42, random blood glucose 139 mg/dl, Urea 52 mg/dl, creatinine 1.8 mg/dl, D-dimer 3060 ng/mL, Fibrinogen 1452 mg/dL and C-reactive protein level 170 mg / L. The result of anti-SARS-CoV-2 IgM/IgG test was still non-reactive. (Table 1.) The results of blood gas analysis showed metabolic acidosis with severe ARDS (pH 7.34, PCO2 33 mmHg, HCO3 18 mmol/L, with PaO2/FiO2 71.1). Chest X-rays showed cardiomegaly and bilateral pneumonia. The patient had received therapy from the previous hospital, namely: favipiravir, hydroxychloroquine, N-acetylcysteine, azithromycin and vitamin C. While in ICU the patient was given ventilator management oxygen PEEP 10 cmH2O, respiratory rate 16, head up 30^{o}, heparin, midazolam, morphine, meropenem, N-acetylcysteine, zinc, vitamin C, omeprazole, dexamethasone, short acting insulin continuous pump dose according to blood glucose.

On day 5 of treatment, the patient had sepsis, the complete blood count results showed leukocytosis (20,600/µL), 90% neutrophil (NLR "31"). Blood culture results for the left arm showed the growth of MRSA, which is only susceptible to vancomycin. (Table 2) The patient was treated with vancomycin. The diet was administered through a nasogastric tube as much as 600 kcal and given supplemental vitamin D treatment. On day 13 the patient had increased aminotransferase and dyslipidemia, so the patient was given ursodeoxycholic acid (UDCA) and fenofibrate. The patient had improvement in ARDS (pH 7.4, PCO2 34.5 mmHg, HCO3 21.4 mmol/L, with PaO2/FiO2 ratio 267.27) and was carried out by extubation followed by oxygen therapy with non-rebreathing mask (NRM) 15 lpm, the patient was planned to move to regular isolation ward. The patient had improvement and was discharged from the hospital on the 36th day of treatment.

Patient 2, a 51-year-old woman, came to the emergency department with fifth day of fever and cough without sputum. The patient had a history of diabetes mellitus and hypertension. On physical examination, blood pressure 140/90 mmHg, pulse 95x/minute, temperature 37.8 ^{o}C, respiratory rate 22x/minute, with oxygen saturation of 53%, with 15 lpm NRM oxygen supplementation the saturation improved to 91%. Chest examination obtained crackles in both lungs. Initial laboratory tests obtained hemoglobin 9.7 g/dl, leukocyte count 17,200/µL, platelet count 658,000/µL, eosinophil count 0%, basophil 0%, neutrophil Band 3%, neutrophil segment 73%, lymphocyte 18%, monocyte 6 %, with NLR 4.2, random blood glucose 357 mg/dl, Urea 126 mg/dl, creatinine 1.9 mg/dl, D-dimer 1157.36 ng/mL, fibrinogen 988 mg/dL and c-reactive protein (CRP) level 111 mg/L. (Table 1.) The results of blood gas analysis showed respiratory alkalosis (pH 7,45, PCO2 30 mmHg, HCO3 21 mmol/L) with severe ARDS (PaO2 / FiO2 83.75). Chest X-rays showed bilateral pneumonia and duplex pleural effusions. Patient was diagnosed probable COVID-19

pneumonia, type 2 diabetes, azotemia and moderate anemia. Patient was treated with oxygen 15 lpm NRM, levofloxacin, oseltamivir, heparin, N-acetylcysteine, omeprazole, vitamin C, zinc, paracetamol, dexamethasone and insulin according to blood glucose.

On day 3 of treatment patient was confirmed positive for SARS-Cov-2. On the 8th day, a complete urine examination showed increase leukocytes with bacteriuria and nitrite (+) which indicates the urinary tract infection. On day 11 the patient had impending respiratory failure with oxygen saturation of 72%, PaO2 / FiO2 ratio of 72.37, The patient was oxygenated using HFNC with 100% FiO2 and flow at 60 lpm, head up 30^{o}, antibiotics switched to meropenem, and aminofusin infusion. The treatment plan will be intubation but the family refused to intubate the patient. On the 15th day, the blood culture result was Methicillin-resistant Staphylococcus aureus bacteria, susceptible to the antibiotics clindamycin, fosfomycin and vancomycin. (Table 2) Antibiotic was escalated according to culture result using vancomycin. Antibiotic response with Vancomycin was not as expected and patient die on day 20.

Table 1. Laboratory examination results

Parameters	Unit	Reference range	Patient-1				Patient-2	
			Day-1	Day-5	Day-13	Day-17	Day-1	Day-16
Hemoglobin	(g/dL)	11.7-15.5	11.3	10.3	7.8	11.1	9.7	10
Leukocytes	10^3(/uL)	3.6-11.0	7,760	20,600	25,490	11,730	17,200	29,100
Platelet	10^3(/uL)	150-440	178,000	434,000	406,000	383,000	658,000	313,000
Hematocrit	(%)	35-45	33	30.9	23.5	33.9	28	30
Erythrocytes	(/uL)	3.8-5.2		4.2	3.11	4.39	3.4	3.49
MCV	fl	80-100		74.1	75.6	77.2	82.8	86
MCH	pg	26-34		24.7	25.1	25.3	28.7	28.7
MCHC	(g/dl)	32-36		33.3	33.2	32.7	34.6	33.3
RDW-CV	(%)	11.5-14.5		14.1	14.9	17.4	11.6	12.7
Eosinophil	(%)	1-3	0	0	0	2	0	0
Basophil	(%)	0-1	0	0	0	0	0	0
Neutrophil band	(%)	2-5	1	3	3	2	3	3
Neutrophil segment	(%)	50-70	75	90	84	70	73	82
Lymphocyte	(%)	20-40	14	3	8	18	18	5
Monocyte	(%)	1-6	10	4	5	8	6	4
NLR			**5.4**	**31**	**10.9**	**4**	**4.2**	**17**
ESR	mm/hour	0-15		123	112	53		
Blood glucose	mg/dl		139	130	143		357	205
Urea	(mg/dL)	10-50	52		80		126	102
Creatinine	(mg/dL)	0.6-1.3	1.8		0,8		1.9	1.1
Cholesterol	(mg/dL)	<200			169			140
Triglycerides	(mg/dL)	<200			323			151
HDL	(mg/dL)	≥ 35			35			40
LDL	(mg/dL)	≤130			69			70
D-dimer	ng/mL	<500	3060		5136		1157.36	1514
Fibrinogen	mg/dL	180-384	1452				988	
CRP	mg/L	<10	170				111	
SGOT	U/L	<31	37	56	81			
SGPT	U/L	<32	20	55	46			
Sodium	mmol/L	135-150	130		137		133	
Potassium	mmol/L	3.5-5.5	4.7		3.78		4.2	
Chloride	mmol/L	96-110	103		89		92	
Anti SARS CoV-2 IgM			Non-reactive				Reactive	
Anti SARS CoV-2 IgG			Non-reactive				Reactive	

Table 2. Antibiotic susceptibility test

Antibiotic	Patient-1	Patient-2
Cefoxitin	Resistant	Resistant
Ceftriaxone	Resistant	Resistant
Clindamycin	Resistant	Sensitive
Meropenem	Resistant	Resistant
Amoxycillin/Clavulanic acid	Resistant	Resistant
Ampicillin/Sulbactam	Resistant	Resistant
Sulfamethoxazole/Trimethoprim	Resistant	Resistant
Fosfomycin	Resistant	Sensitive
Vancomycin	Sensitive	Sensitive
Levofloxacin	Resistant	Resistant

DISCUSSION

We reported 2 cases of COVID-19 infection in the presence of MRSA bacterial coinfection. Until now, COVID-19 is a newly emerging life-threatening infectious disease whose cases are still increasing, and the mortality in critical patients has reached 50%.[8] On the examination of patient-1, complete blood count showed neutrophilia and decreased lymphocyte count resulting in an increase in NLR even though the leukocyte count was within normal limits. After several day leukocyte was high with an increase in NLR, whereas patient 2 since entering the ER, the patient had leukocytosis with neutrophilia and increased NLR. A study by Yang et al, reported that the mean leukocyte count was higher in severe patients, NLR of more than 3.3 increased the risk of disease severity[9], whereas the study by Liu et al, stated that NLR was used for early identification of risk factors for the severity of COVID19, especially in patients aged ≥ 50 years and NLR ≥ 3.13, which is reference predictors that clinicians can use to access ICU if necessary with the incidence of severe infection 50%.[10]

The presence of inflammation in both patients was indicated by elevated levels of CRP. The increase in CRP at the onset of the disease is related to the lung parenchymal lesions and disease severity.[11] Herold et al, reported CRP more than 32.5 mg/L was found to offer 80% predictive power for a person needing mechanical ventilation.[12] Sharifpour et al, reported higher CRP levels in patients with a poor prognosis.[13] CRP more than 40 mg/L on admission to hospital should be seen as a reliable indicator of disease severity and increased risk of death.[14] The results of anti-SARS Cov-2 IgM and IgG in patient 1 were non-reactive, while in patient 2, reactive IgM and IgG were obtained. Guo et al demonstrated the longitudinal change of anti-SARS-CoV-2 IgG/IgM in patients with COVID19. IgM antibody detection was 5 (IQR, 3–6) days, while IgG was detected 14 (IQR, 10–18) days after symptom onset.[15]

Both patients had elevated serum D-dimer and fibrinogen levels. In COVID-19 patients with ARDS and sepsis, it is associated with disseminated intravascular coagulation (DIC), which is one of the causes of multi-organ failure and an increased risk of death. Fibrinogen is an acute phase protein that is synthesized by the liver in response to an increase in IL-1 and IL-6. Fibrinogen should be evaluated with D-dimers. D-dimer is a soluble plasmin-mediated degradation product of fibrin, which is produced after activation of coagulation and fibrinolysis. Research reports that high D-dimer levels increase the mortality of COVID-19 patients.[16]

Antibiotic resistance has become one of the important things in infection management in the world. Multidrug-resistant bacteria (MDR) cause treatment failure which increases the risk of death and cost. MRSA has become one of the most important MDR bacteria during the last decade causing severe infections in health facilities.[17] Risk factors for MRSA are a history of previous treatment, prolonged hospitalization, use of invasive equipment (catheters, endotracheal tube) and the presence of comorbidities.[18]

Both patients had MRSA blood culture results at the hospital admission. The history of diabetes mellitus in both patients is one of the risk factors for colonization of MRSA.[19] Complications of bacterial infection in COVID-19, especially bacteremia have been previously reported. The study by Sepulveda et al, reported that bacteremia occurred in 1.6% -3.8% and the incidence of S. aureus infection was 13.3%.[20] Patients with COVID-19 are given respiratory fluoroquinolone antibiotics, levofloxacin or moxifloxacin, in cases of suspicion of bacterial infection and severe-critical disease, which are first-line therapeutic agents for the management of severe community pneumonia.[21]

Secondary infection by S. aureus has been reported as a complication of previous viral infections, such as in the H1N1 pandemic and influenza viruses which are associated with high rates of patient severity and mortality. The mechanism that occurs is thought to be bacterial coinfection in viral infections caused by viruses contributing to dysfunction and death of epithelial cells in the respiratory tract, increasing the susceptibility to opportunistic bacterial pathogen. Viral neuraminidase cleaves respiratory epithelial cell, sialic acids, contributing to increased bacterial adhesion and dissemination.[22] In addition, in the previous report on bacterial coinfection in influenza virus infection, there was depletion of alveolar macrophages, thereby facilitating bacterial invasion of the respiratory tract.[23]

In this report, both patients had COVID-19 with MRSA that showed severe symptoms and need to use ventilator. Patient-1 had clinical improvement after administration and antibiotic therapy, in addition to bacterial infection factors, oxygenation and nutritional factors in COVID-19 patients were very important. Patient-2 had a worse outcome because the patient had severe ARDS and refused intubation, and oral food intake was also not as expected. The second patient had poorer glycemic control which may have contributed to the worse outcome.[24] People with diabetes mellitus have a possible low-grade chronic inflammation that facilitates cytokine storms, and cause of severe cases of Covid-19.[25] There were social problems such as refusal to intubate, because of the assumption that intubation had a bad prognosis.

CONCLUSION

Coronavirus disease (COVID)-19 is a systemic infection caused by the SARS-Cov-2 virus which can cause disruption of organ systems, sepsis, and multi-organ failure. Coinfection by MRSA bacteria increases the severity and mortality of severe patients. In order to prevent antibiotic resistance, comprehensive management needs to be done apart from oxygenation, proper nutrition, and the use of rational antibiotics.

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