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COVID-19 Reinfection in 60-Year-Old Man with Diabetes Mellitus, East Nusa Tenggara, Indonesia: A Case Report

Albert William Hotomo*, Heri Sutrisno Prijopranoto

Department of Internal Medicine, St. Carolus Borromeus Hospital, Kupang, Indonesia

Email address:

albertwilliamhotomo@gmail.com (A. W. Hotomo), heri.sutrisno88@gmail.com (H. S. Prijopranoto)

*Corresponding author

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Abstract: Coronavirus Disease 2019 (COVID-19) is an infectious disease which is caused by a new strain of coronavirus. Older individuals and people with comorbidities have a higher risk to develop more severe illness. COVID-19 survivors will have active immunity in conjunction with increase of SARS-CoV-2 antibody (Ab) titer 2-weeks after the symptoms onset and will be lasted until 12-weeks. Therefore, it will give protection against reinfection of COVID-19. This study reports a case of COVID-19 rapid reinfection in sixty-year-old man with diabetes mellitus. *Case illustration*: a sixty-year-old man presented to the emergency department with fever accompanied by cough, runny nose, malaise, and metallic taste since one day before admission to hospital. There was a history of uncontrolled diabetes mellitus (DM) and COVID-19 infection 35-days before hospital admission without any symptoms. The current physical examinations demonstrated a mild dyspnea with oxygen saturation 97%, and diffuse rhonchi at the right area of chest auscultation. Chest X-ray discovered a multiple consolidation of the right lung, with suspicion of viral pneumonia. Fasting blood glucose (FBG) was 205 mg/dl, and 2-hour postprandial glucose was 508 mg/dl. The polymerase chain reaction (PCR) of SARS-CoV-2 via nasopharyngeal swab was taken and the result was positive. COVID-19 Ab titers IgM and IgG were 0.18 U/ml and 0.43 U/ml (<0.8 U/ml → non-reactive), respectively. The patient was diagnosed with COVID-19 reinfection and DM. The patient was treated with convalescent plasma, antivirus, antibiotics, insulin, steroid, anticoagulant, and other symptomatic medications. As the results, a well improvement of his clinical condition and the increase of Ab COVID-19 IgM and IgG evaluation test after convalescent plasma administration, 0.28 AU/ml and 17.67 AU/ml, respectively, were recorded. *Summary*: Researches revealed that DM might cause the specific immunity system dysfunction and the low production of antibody. This study found that poor blood-glucose control with a low Ab of SARS-CoV-2 production might induce this patient to have a COVID-19 reinfection. Advance immunological study about the correlation between DM and COVID-19 is very essential in the management of COVID-19 patients with DM.

Keywords: Coronavirus, COVID-19 Reinfection, Diabetes Mellitus, Antibody, Antibody Titer

1. Introduction

Coronavirus Disease 2019 (COVID-19) has developed into a serious novel public health issue leading to severe acute respiratory disease among individuals worldwide. [1] Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or 2019 novel coronavirus (2019-nCoV) is responsible as the etiologic agent of COVID-19 which came from bats; with unknown intermediary animals; and unknowingly transmitted into humans in Wuhan, Hubei province, China in December 2019. [2, 3] To date, according to the World Health Organization (WHO), COVID-19 has infected 426,624,859 people and caused 5,899,578 deaths. [4] COVID-19 has been proven to affect many life aspects among the people worldwide, such as global economic recession with extremely increased of poverty, decreased utilization of healthcare unit, and huge impact of social disruption (bereavement, social isolation, fear, etc.) which significantly may increase the mental health disorder. [5-8]

Diabetes mellitus (DM) has been discovered as one of the evident comorbidity which is associated with increased diseases severity and mortality in COVID-19. [9-11] The meta-analysis study by Kumar et al has proven that

COVID-19 patients who suffered diabetes have two-fold increase in mortality, as well as severity in COVID-19, in comparison with the non-diabetes patients. [12] A research at the New York City Area which involved 5,700 patients has determined that 1 out of 3 COVID-19 patients, suffered diabetes mellitus. [13] Poor glycemic controlled has been proven to be the cause of the declining of innate and adaptive immunity function by several mechanisms, including decreased interleukin production for infection response, declined chemotactic function and phagocytic activity, and immobilization of polymorphonuclear leukocyte. [14, 15] Study has discovered that antibody titers, such as IgM and IgG, were significantly lower among individual who suffer DM. As there are many ways for diabetes in disrupting the immune function, the susceptibility of COVID-19 reinfection might arise. [15, 16] This study presents a case report of COVID-19 reinfection in 60-year-old man with diabetes mellitus with highlight of diagnosing and treating issues which suffered by this patient.

2. Case Illustration

A 60-year-old man admitted to the emergency department at St. Carolus Borromeus Hospital, Kupang with fever since one day before admission to hospital. The fever was accompanied by cough, runny nose, malaise, and metallic taste. There was a history of uncontrolled diabetes mellitus (DM) and COVID-19 infection 35-days before hospital admission. The previous COVID-19 was asymptomatic without any significant symptoms. It was confirmed by a positive result of SARS-CoV-2 PCR test via nasopharyngeal swab. The period between the previous and the current positive SARS-CoV-2 PCR test was 40 days.

On admission, vital sign showed the patient was alert, along with Glasgow Coma Scale (GCS) was 15, pulse rate was 82 beats per minute, respiratory rate was 22 times per minute, temperature was 38°C, blood pressure (BP) was 130/90 mmHg, and oxygen saturation 97%. The physical examination represented a mild dyspnea and diffuse rhonchi at the right area of chest auscultation. Chest X-ray revealed a multiple consolidation of the right lung, with suspicion of viral pneumonia. Fasting blood glucose (FBG) was 205 mg/dl, and 2-hour postprandial glucose was 508 mg/dl. D-dimer test was 460 ng/ml, hs-CRP test was 2.1 mg/L, procalcitonin test was <0.05 ng/ml, and erythrocyte sedimentation rate (ESR) was 35 mm/hour. The PCR test of SARS-CoV-2 via nasopharyngeal swab result was positive with CT-value 5.35. The quantitative serum antibody analysis of COVID-19 IgM and IgG were 0.18 AU/ml and 0.43 AU/ml, respectively. The patient was diagnosed with COVID-19 reinfection and DM. The management plan for this patient was convalescent plasma, antivirus, antibiotics, insulin, steroid, anticoagulant, and other symptomatic medications. The convalescent plasma therapy was administered one unit per day, in total for two days. Ceftriaxone 2 gram intravenously once daily and azithromycin 500 mg orally once daily, both were used as the antibiotics for this patient. For the antiviral drugs, this patient was given Favipiravir 1,600 mg orally bid for the first day of admission, then 600 mg orally bid for the next 5 days. Aspart, as the rapid-acting insulin, was used with a dosage 8 units tid subcutaneously. Dexamethasone, as the anti-inflammation was given intravenously with a dosage 5 mg once a day. Heparin was used as the anticoagulant with a dosage 5,000 unit subcutaneously bid. Simvastatin was given to this patient with a dosage 20 mg orally once a day. The oral antioxidant drugs used for this patient was N-acetyl cysteine 200 mg tid, vitamin C 500 mg tid, and vitamin D 1,000 IU bid.

As the results, there was a significant improvement of his clinical condition, altogether with the increase of Ab titer COVID-19 IgM and IgG after convalescent plasma administration, 0.28 AU/ml and 17.67 AU/ml, respectively.

3. Discussion

COVID-19 reinfection has been identified as one of the major health problem worldwide. It was firstly emerged in April 2020 among geriatrics population. [18, 19] Furthermore, a follow up study which has been done from March- November 2020 in Iran has proven that all the patients who suffer COVID-19 reinfection were elderly, along with one or more comorbidities, including diabetes mellitus. [20]. A nationwide analysis in China has been revealed that almost 10% in-hospital COVID-19 patients were people who suffer diabetes mellitus. [9] In our cases, we report 60-year-old man who suffers COVID-19 reinfection, along with history of uncontrolled diabetes mellitus.

Diabetes mellitus has been discovered as the substantial aggravating factors that contribute to a poor outcome among COVID-19 patients. Studies have demonstrated that hyperglycemia considerably interfere the immunity function, which significantly might lead into a poor outcomes among hospitalized patients. [15, 21, 22] Guan et al stated that DM was the major determinant factor which increase the probability for COVID-19 patients to be admitted in intensive care unit (ICU) with a high mortality rate. [9] Higher inflammation biomarkers, such as high-sensitive C-reactive protein (hs-CRP) and procalcitonin (PCT), has been recorded in diabetic COVID-19 subjects rather than non-diabetic subjects. [11, 23, 24] A hypercoagulability state, such as D-dimer, was also discovered higher in diabetic COVID-19 patients compared to non-diabetic patients. [11, 25, 26] These phenomenon would cause COVID-19 patients who suffer diabetes mellitus are more prone to an inflammatory storm that eventually lead into a prompt deterioration of COVID-19 disease severity. However, this patient's inflammation biomarker, such as hs-CRP and PCT did not elevate significantly. Moreover, the hypercoagulability state also did not found in this patient.

A SARSC-CoV-2 infection induces the production of neutralizing antibodies in order to prevent reinfection. [27, 28] Neutralizing antibodies will be generated and aimed against two types of SARS-CoV-2 proteins, spike (S) and nucleocapsid

(N). Studies have found that IgM antibodies would be presented within 5 days after initial symptoms and IgG around 5-7 days. Ultimately, the peak seroconversion for IgM appears at 2-3 weeks and for IgG 3-6 weeks. [27, 29] However, the neutralizing antibody availability in individuals is still ambiguous. [17] Tan et al discovered that 10-20% of COVID-19 subjects have low level or even no detectable antibody titer after COVID-19 infection and the reason still unknown. [30] Moreover, Rimesh et al. have revealed that people who suffer DM were more presumably to have non-detectable SARS-CoV-2 Ab than people without DM. [31] Similarly, our patient's antibody titer were very low even after suffer the prior COVID-19 infection. By using the electro-chemiluminescence immunoassay analyzer (ECLIA) was used for detecting the total quantitative Ab which targeted the S-receptor binding domain (S-RBD) proteins of SARS-CoV-2.

Diabetes mellitus impaired immunity function, including both innate and adaptive. High blood glucose weakened innate immunity function by disrupting the establishment of interferon which has antiviral activities and reduced the transmigration of polymorphonuclear (PMN), phagocytosis, cytokine secretion, and superoxide production. [17, 32, 33] Adaptive immunity function also impaired by hyperglycemia by diminishing the pathogen-specific memory CD4+ and T-helper 17 (Th17) responses to infection. [34, 35] Besides, studies have proven that diabetes mellitus independently decreased the production of IgM and IgG, and also blunt the humoral innate immunity response. [16, 36] Moutschen et al have stated that there is a decrease of memory CD4+ T-cells, abnormal natural killer response against infection, and hypocomplementemia. [37] Moreover, studies have revealed compromised antibody response among diabetic subjects, especially with poor blood glucose control, following hepatitis B and influenza vaccinations. [38, 39] Ultimately, antibody response among diabetic patients are impaired which cause negative COVID-19 seroconversion. Correspondingly, in this case report, we discovered that our patient who suffered uncontrolled diabetes mellitus did not achieve seroconversion after the first COVID-19 infection at January 2021.

To the best of our knowledge, the significant definitive treatment for COVID-19 remains in study. The drug of choice against SARS-CoV-2 infection is still unknown. There are many therapeutic regimens currently being given for COVID-19 infection. The plasma convalescent transfusion was given to our patient and the Ab titers were significantly higher after the administration of plasma convalescent, in simultaneous with the clinical improvement. These finding was similar with the study by Simonovich et al. which have proven that the total SARS-CoV-2 antibody titers were higher in the convalescent plasma group at day 2 after intervention, although on day 30 both groups Ab titers have no significant difference. In addition, they also discovered there was no significant difference in clinical status or overall mortality between patients who were administered with convalescent plasma than those who received placebo [40] Moreover, the PLACID Trial among moderate COVID-19 adults in India have proven that there was no association between convalescent plasma administration and COVID-19 disease progression or all causes mortality. [41] However, Libster et al. have reported that the early administration of convalescent plasma in older adult patients (<72 hours after the symptom onset) would reduce the risk of progression to severe respiratory distress. [42] Furthermore, Joyner et al. also have stated that the higher levels of SARS-CoV-2 antibody in plasma convalescent transfusion in hospitalized patients who did not take mechanical ventilation was correlated with a lower risk of death in comparison with lower antibody levels plasma transfusion. [43] Ultimately, the COVID-19 Treatment Guidelines Panel has declared that plasma convalescent administration is recommended particularly for patients who suffer immunodeficiency. [44] In this case report, our patient was given plasma convalescent on the second day of the diseases. As the result, the patient achieved a considerable increase of Ab titers, along with the recovery of his clinical status.

Currently, Favipiravir is one of the most common antiviral drugs for SARS-CoV-2 infection. It has been proven in several countries as an effective antiviral therapy in the treatment of COVID-19, especially in mild to moderate disease. It has been convinced as a promising regimen because of its role in order to make a quick viral clearance, greater clinical improvement, and its availability as an oral medication. [45] This finding also supported by a systematic review and meta-anaysis of clinical trials which have demonstrated a substantial clinical recovery among Favipiravir group in comparison with control group during a week after hospitalization. Nonetheless, the mortality rate among Favipiravir group was 30% lower than the control group, although this finding was not statistically significant. [46] In this case report, our patient was given Favipiravir with a dosage 1,600 mg orally bid as the loading dose for the first day of admission, then 600 mg orally bid as the maintenance dose for the next 5 days. The clinical improvement was recorded.

Azithromycin is macrolide antibiotic which are routinely being used to treat bacterial co-infection in SARS-CoV-2 infection. Studies have stated about its capability to decrease replication of some classes of virus through the expression increase of anti-viral pattern recognition receptors, initiation reaction of anti-viral type I and III interferon, decrease cytokine production, and preserve the integrity of epithelial cell. [47, 48] Nevertheless, the PRINCIPLE study has demonstrated that azithromycin should not be taken as a routine medication for SARS-CoV-2 infection among the elderly in community. They recommended that in spite of the anti-inflammatory and anti-viral ability, azithromycin was not effective in curing COVID-19, in the absence of additional indication. [49] Furthermore, azithromycin and ceftriaxone are prevalently applied for community-acquired pneumonia, thus Nestler et al. considered that these antibiotics might empirically protect against bacterial superinfection among COVID-19 patients. [50] In this patient, he was given ceftriaxone 2 gram intravenously once daily and azithromycin 500 mg orally once daily as the prophylaxis antibiotics.

The venous thromboembolism (VTE) has been found as the essential cause of death among COVID-19 patients. Studies have revealed that SARS-CoV-2 infection might increase the risk of VTE as high as 31% among severely ill patients, which may be seen also form the elevated D-dimer levels (>1,000 mg/L). [51-53] Several guidelines have declared that hospitalized COVID-19 patients should be treated with prophylactic dose anticoagulation for VTE. [54-59] In our patient, heparin was administered as the prophylaxis anticoagulant with a dosage 5,000 unit subcutaneously bid.

SARS-CoV-2 infection might induce systemic inflammatory response which may cause lung damage, along with multiple organ dysfunctions. The role of corticosteroid as an effective anti-inflammatory medication could diminish the detrimental effect of COVID-19. However, there is still lack of evidence which revealed the administration of corticosteroid among non-hospitalized COVID-19 patients. [44] In addition, the RECOVERY Trial had elaborated a well breakthrough study for the anti-inflammatory treatment among hospitalized COVID-19 patients. They have revealed that the administration of dexamethasone 6 mg daily for up to 10 days decreased mortality at 28 days, especially among mechanically ventilated patients. [60] Furthermore, similar findings have also been studied by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group which has done a prospective meta-analysis of clinical trials among severely ill COVID-19 patients. [61] Moreover, Tomazini et al. have established that the administration of intravenous dexamethasone with standard care among moderate to severe Acute Respiratory Distress Syndrome (ARDS) in COVID-19 patients, in comparison with standard care alone lead into the increase number of ventilator-free days. [62] In this case report, as the patient suffered moderate COVID-19, along with multiple consolidation of the right lung which might lead to severe inflammation, dexamethasone with a dosage 5 mg intravenously daily was given to our patient.

Simvastatin shows ability to protect COVID-19 patients to severely inflammatory response induced by SARS-CoV-2 infection. It has been discovered about its pleiotropic impact for oxidative stress and inflammation, by reducing reactive oxygen species (ROS), repairing endothelial function and integrity, and regulating cytokine production, along with the evidence about the anti-viral action by blocking the infectivity of enveloped virus and inhibiting the protease enzyme which act as an important enzyme for SARS-CoV-2. [63-65] Furthermore, studies have stated that statins might decrease the mortality risk among COVID-19 patients, but it was not significant among COVID-19 patients who were admitted in the ICU. [66, 67] In this patient, 20 mg of simvastatin was given orally once a day which was administered in-hospital and be continued after recovery.

Ascorbic acid (vitamin C) is a water-soluble vitamin which is believed to have valuable impact among severely ill patients. It has been proven to protect lung architecture and barrier function, together with weaken the pro-inflammatory chemokine response and thrombosis. [68] Studies have discovered inconsistent findings about the ascorbic acid potential role in treating COVID-19. [69-71] Wei et al. have done a meta-analysis including 6 retrospective studies and 4 randomized controlled trials (RCTs). They stated that the administration of ascorbic acid did not reduce the risk of patient's mortality and the length of stay in-hospital. However, from the subgroup analysis of two RCTs, they represented that ascorbic acid administration demonstrated reduced 28-day mortality. [69] Whereas, a RCTs from Thomas et al. has been proven that the treatment of high-dose vitamin C did not significantly reduce the duration of COVID-19 symptoms among ambulatory patients compared with the standard of care. [70] Nevertheless, studies showed that the administration of high-dose ascorbic acid was safe, feasible and cost-effective choice for COVID-19 treatment. [71, 72] Accordingly, in this patient, the 500 mg ascorbic acid was given orally three-times-a-day after meal.

N-acetyl cysteine presents a beneficial role as an adjuvant treatment for SARS-CoV-2 infection. Beside it acts as a robust mucolytic, it also performs as a counterbalance in viral infections. [73] Several studies have thoroughly elaborated about its ability to modulate immune response, produce antioxidant, and prevent cytokine storm. [73-77] However, de Alencar et al. have done a double-blind, randomized, placebo-controlled trial which demonstrated that the usage of high-dose NAC did not affect the progression of COVID-19. [78] Moreover, the interventional study in order to investigate the beneficial impact of NAC among COVID-19 patient is still lacking. Based on the substantial protective mechanism of NAC, our patient was given 200 mg of NAC orally three times-a-day as a mucolytic, along with the consideration of its possible antioxidant, antiviral, and anti-inflammatory impact.

Vitamin D is an essential nutrient which is needed in mineral and bone metabolism. Studies have discovered that poor vitamin D levels were significantly correlated with higher inflammatory cytokines, increased thrombotic events, and greater risk of SARS-CoV-2 infection and pneumonia. [79, 80] Increased hospitalization and disease severity were recorded among COVID-19 patients who suffer vitamin D deficiency. [81] Furthermore, vitamin D has been established as an important factor in immune regulation, especially the expression of T regulatory (Treg) lymphocytes. In addition, vitamin D administration might increase Treg function which is needed in order to regulate the uncontrolled COVID-19 inflammation. [79, 81] Nonetheless, Murai et al. have done a multicenter, double-blind, RCT in Brazil which revealed that a single high dose of vitamin D did not considerably reduce the length of stay among hospitalized COVID-19 patients. [82] In addition, Bassatne et al. have demonstrated the protecting role of vitamin D supplementation among COVID-19 related ICU admissions. [83] In spite of the variety findings of vitamin D impact on COVID-19, as it might have a beneficial role in treating COVID-19 patient, thus our patient was given vitamin D with a dosage 1,000 IU orally twice daily.

4. Summary

In conclusion, the absence of seroconversion after initial SARS-CoV-2 infection has been recorded in our patients who suffer uncontrolled DM. The complex pathogenesis has been hypothesized by studies which reported how poor glycemic control lead into immunity dysfunction, especially the abnormal production of neutralizing antibodies against SARS-CoV-2 pathogens. Moreover, these phenomena hypothetically imply a high probability of recurrent infection with SARS-CoV-2 pathogens. To the best of our knowledge, the drug of choice for COVID-19 remains unknown and the current treatment options are considered to relieve symptoms of COVID-19. Reinfection might become a crucial challenge for both public health sector and worldwide. By increasing the concern about good glycemic control among patient who suffers diabetes mellitus, we believe the SARS-CoV-2 reinfection risk could be decreased.

Table 1. *Comparison between the previous and current COVID-19 infection.*

Comorbidities	**Previous**	**Current**
	DM type 2	**DM type 2**
Presenting Symptoms	Asymptomatic	Cough, runny nose, malaise, metallic taste.
Vital signs	Within normal range	Respiratory rate was 22 breaths per minute, temperature was 38°C.
Physical examination	Within normal range	Diffuse rhonchi at the right area of chest auscultation.
Hospital admission	No	Yes
Nasopharyngeal swab	Positive	Positive
Investigations		
Chest radiography	Not done.	Multiple consolidation of the right lung, with suspicion of viral pneumonia
Blood test:		
Hemogloblin (11.0-17.0 gm/dL)	-	15.5
Erythrocyte count (4.0-5.5×10^6/UL)	-	4.52
Leukocyte count (4.0-12.0×10^3/UL)	-	8.2
Platelet count (150-450×10^3/UL)	-	164
Fasting plasma glucose (70-100 mg/dL)	-	205
2-hr post prandial glucose (<140 mg/dL)	-	508
Procalcitonin (<0.05 ng/mL)	-	<0.05
Hs-CRP (<=10.0 mg/L)	-	2.1
D-dimer (<500 ng/mL)	-	460
Erythrocyte Sedimentation Rate (0-20 mm/h)	-	45
ALT (<45 U/L)	-	42.5
AST (<35 U/L)	-	38.5
Ureum (16.8-43.4 U/L)	-	23.8
Creatinine (0.81-1.44 U/L)	-	0.66
Ab C-19 IgM (<0.8 U/mL)	-	0.18
Ab C-19 IgG (<0.8 U/mL)	-	0.43

* The example for this table.

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