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Case Report

Managing severe thrombocytopenia in co-infection of COVID-19 and dengue hemorrhagic fever: a case report

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ABSTRACT

COVID-19 pandemic in dengue endemic countries has becoming a concern due to its similarities in early clinical symptoms and laboratory features. The cases of co-infection between the two diseases are inevitable and associated with higher morbidity and mortality. Here we presented a case of a 28 years old female diagnosed with co-infection of COVID-19 and dengue hemorrhagic fever that complicated with severe thrombocytopenia and spontaneous bleeding. She came with fever that started 3 days prior to admission. Laboratory examination showed leucopenia, thrombocytopenia, elevated liver enzymes, and D-dimer. Patient tested positive for non-structural protein 1 (NS-1) dengue antigen. She had a pre-screening rapid test for COVID-19 as part of hospital protocol, and she tested positive. Followed by positive COVID-19 reverse transcriptase-polymerase chain reaction (RT-PCR) test confirming the diagnosis. During admission, patient started menstruating, resulting in active spontaneous bleeding while platelet counts dropped to below 10×10^9/l. Patient was given platelet transfusion, supportive therapy and put under close monitoring. The case of co-infection between COVID-19 and dengue is inevitable in tropical and sub-tropical countries. Both infections shared similar pathophysiology through different mechanism, such as plasma leakage, thrombocytopenia, and coagulopathy. Complications may arise and physician must aware of the therapeutical approach. Diagnostic testing must not be withheld when there was suspicion towards the infection. Prompt treatment and close monitoring can result in good prognosis.

Keywords: COVID-19, Dengue hemorrhagic fever, Co-infection, Thrombocytopenia

INTRODUCTION

The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) has spread around the world causing a worldwide pandemic. First confirmed case originated back in Wuhan, China in the year of 2019 and as per March 2022, over 433 million confirmed cases and over 5.9 million deaths have been reported globally.[1] In Indonesia, there were estimated 5.5 million cases reported in early March 2022 with 150.000 deaths. The SARS-COV-2 infection causes disease widely known as COVID-19.[2] COVID-19 pandemic in dengue endemic countries has becoming a concern due to its similarities in early clinical symptoms and laboratory features. It created a challenge for clinician to properly diagnosing, managing the diseases, and preventing the risk of transmission of the COVID-19 virus.[3-5]

Both diseases have similar early symptoms that overlap, such as fever, chills, myalgia, arthralgia, and flu-like symptoms. Complete blood count (CBC) may feature leukopenia and thrombocytopenia. But despite notable similarities, both diseases have different approach to management and therapy.[3,4] Particularly during the rainy season, cases of co-infection are non-avoidant. Co-infection of these diseases has been associated with higher morbidity.[3,6] The presence of both infections may affect the severities of the disease, prolong the infectious period,

and arising complication thus resulting in worse prognosis.[3,5]

Here we presented a case of co-infection between dengue hemorrhagic fever and COVID-19 in a 28 years old female patient in Indonesia. The case of co-infection was complicated by severe thrombocytopenia and spontaneous bleeding. In this literature, we aim to discuss about the important findings, shared pathophysiology of both of the disease, complication, approach to therapy and challenge upon encountering the complicated case of co-infection.

CASE REPORT

A 28-year-old female, living in Bali, Indonesia, came to the emergency room with fever that started 3 days prior to admission. Highest temperature recorded was 39.5˚C. She had chills, joint aches, headache, and general weakness. Patient also complained of some sore throat and dry coughs 2 days prior to admission. Patient lost her appetite and feeling nauseous. She felt dizzy when standing up. The morning prior to her visit to the emergency room, she had a nose bleeding after shower. It stopped after approximately 10 min. She had no history of traveling. She was vaccinated with two doses of Sinovac in August 2021 and September 2021.

She self-medicated at home with 500 mg paracetamol three times daily and 500 mg vitamin C once daily. The fever subsides temporarily, but after several hours, it returned. She had no known history of illness and not on any medications.

Physical examination indicated normal vital signs. Oxygen saturation level was at 98-99% room air. Heart and lungs examinations were normal. There was some abdominal tenderness in the epigastric area upon palpation. There were none itchy red rashes on bilateral upper limbs of the body. Other examinations were unremarkable. Laboratory examination showed normal hemoglobin at 12.9 g/dl, leucopenia with total leucocyte counts at 2.36×10^9/l (lymphocyte count at 33.5%, neutrophil count at 58.5%, and neutrophil lymphocyte ratio (NLR) at 1.75%), thrombocytopenia with platelet count at 48×10^9/l, elevated liver enzymes, with alanine transaminase (ALT) at 115 U/l and ALT at 255 U/l. D-dimer was elevated at 4880.1 ng/ml. Markers of inflammation was not elevated, C-reactive protein (CRP) was at 7 mg/l. Rapid diagnostic tests (RDT) for dengue non-structural protein (NS1) antigen were requested, and it turned out to be positive. Other lab results were unremarkable. Chest X-ray was performed and pulmonary abnormal findings were absent. Patient was diagnosed with second degree dengue hemorrhagic fever. Before patient was transferred, she underwent RDT for COVID-19 antigen for hospital screening protocol. It resulted in positive. Patient was suspected for COVID-19 infection and second-degree dengue hemorrhagic fever. Specimens were taken for COVID-19 RT-PCR test. Patient was admitted into intensive care unit isolation ward for monitoring and further therapy. Patient was given symptomatic and supportive therapy. Antivirus was administered. Patient was given remdesivir 200 mg intravenous on the first day, continued with 100 mg intravenous daily for four days. Patient also was given enoxaparin sodium 0.6 cc twice daily.

In the isolation ward, patient was further investigated to trace contacts with COVID-19 positive patients or suspects. Patient denied any history of contacts. Complete blood count (CBC) was drawn every 24 hours to monitor the progression of the dengue infection (Table 1). On the second day of admission, the result for COVID-19 RT-PCR came out positive (FAM/ORF1AB 22.15), confirming the diagnosis. There were drop in platelet count to 17×10^9/l. Clinically, patient vital signs were stable, there are no remarkable complains. On the third day of admission, patient started menstruating. Patient complained that the amount of blood discharged was excessive than usual. Patient was bleeding approximately 200-250 cc daily. Platelet count was at 10×10^9/l. Enoxaparin injection was stopped. Fourth day of admission, patient was still bleeding profusely per vagina close to 300-400 cc. Other spontaneous hemorrhage was absent. CBC showed platelets count at 6×10^9/l, haemoglobin level was at 9.2 g/dl.

Table 1: Laboratory profile dynamic during hospital stays.

Laboratory profile	Day of admission							
	First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth
Leucocyte (10^9/l)	2.36	4.02	6.59	7.63	10.39	11.33	8.33	8.65
Hemoglobin (g/dl)	12.9	14.2	12.1	9.2	7.6	9.0	10.7	11.2
Hematocrit (%)	40.2	42.8	36.3	27.6	23	27.3	31.2	34.7
Platelet (10^9/l)	48	17	10	6	46	277	351	355
Ureum (mg/dl)	215							
S. creatinine (mg/dl)	1.0							
D dimer (ng/ml)	4880.1							
ALT (U/l)	115							
AST (U/l)	255							
Natrium (mmol/l)	136							
Potassium (mmol/l)	3.4							

Continued.

Laboratory profile	Day of admission							
	First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth
Chloride (mmol/l)	107							
CRP (mg/l)	7							
Dengue test (NS1)	Positive							
RT-PCR SARS-CoV-2		Positive					Negative	

Patient then was given 3 units of platelet concentration transfusion, and under close monitoring maintaining vital signs and adequate fluid administration. On fifth day of admission, haemoglobin level was dropped to 7.6 g/dl but platelet level increased to 46×10^9/l. Sixth day of admission, there were few dark brown discharges, but active bleeding was absent. Haemoglobin level and platelet level increased respectively to 9.0 g/dl and 277×10^9/l. On the succeeding days, increasing trends in haemoglobin and platelet counts were noted. On day seventh, patient COVID-19 RT-PCR resulted negative, patient was transferred to non-isolation ward. There are no significant respiratory symptoms noted throughout the stays in hospital. Patient was discharged on day eighth, with her symptoms improved. During follow up at out-patient clinic five days after discharged, she had complete resolution of her illness.

DISCUSSION

Dengue virus is the most common cause of acute febrile illness in South East Asian countries. Dengue is an endemic disease in Asia, with ongoing outbreak annually. The emergence of COVID-19 pandemic raises a concern, especially among these countries, due to the risk of overlapping features between the diseases.[4,5] The similarities between symptoms and laboratory examination of both diseases pose as a diagnostic challenge for physician at current time. Fever is the most common early manifestation in both diseases, followed with flu-like symptoms.[4-6] Laboratory examinations share the presence of leukopenia and thrombocytopenia.[5-7] Diagnosis for dengue is established with serology test, finding the presence of NS1 antigen, IgM antibody, and IgG antibody. Rapid NS1 antigen test is promising, because it seems to have no cross-reaction with other virus infection and providing sensitivity and specificity rate at 55.5% and 92%. However, after three days, the accuracy for NS1 antigen decreased to 39.4% on day 4-6th, and further to 13.1% on day 7-9th. The combination of NS1 antigen and IgM antibody specifically confirming the acute phase of dengue infection, and it is proven to be more accurate than one single test.[3,8,9] Meanwhile, the diagnosis of COVID-19 is confirmed by detecting the virus RNA using RT-PCR method. Although the COVID-19 rapid antigen tests are available. In Indonesia it used mostly as a mass screening tool.[10,11]

Our patient came in with acute fever and flu-like symptoms. She had history of mild nose bleeding prior coming to the hospital. She had completed her second dose of COVID-19 vaccination. Laboratory examination shown the result of leukopenia, thrombocytopenia, transaminitis, and elevated D-dimer levels. Patient was tested positive for NS1 dengue antigen. Aside from elevated D-dimer level, patients complain, history, and laboratory result was leaning towards the diagnosis of grade II dengue hemorrhagic fever. COVID-19 initially was not suspected in this patient, as respiratory symptoms were not predominant and chest X-ray was clear. However, we did not perform chest CT-scan due to absent of concerning respiratory symptoms. COVID-19 was found incidentally as a result of hospital protocols of rapid antigen testing patients prior to admission. The rapid antigen test then followed with RT-PCR that turned out to be positive as well confirming the diagnosis of COVID-19. Our patient then diagnosed with co-infection and transferred into isolation ward. We were fortunate to caught this early prior to admission, thus manage to lower the risk of transmission and took precaution among healthcare staffs and other patients.

The co-infection between dengue and COVID-19 has higher morbidity compare to single infection.[3,5,6] The critical phase may be more severe due to interaction between two infections. COVID-19 and Dengue exhibit similarities in pathophysiology such as plasma capillary leakage, thrombocytopenia, and coagulopathy.[5] Plasma leakage is one of the pathophysiology hallmarks of dengue infection. Plasma leakage is associated with the host immunological response towards the virus' NS1 antigen and proteins expressed on host's endothelial cell surfaces. It is mediated by various pro-inflammatory cytokines, such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and interferon gamma (IFN-γ), and as result increasing the vascular permeability in peripheral blood vessels.[5,12] Although it is not yet well understood, COVID-19 also manifested plasma leakage. It is hypothesized as a result of cytokine storm. Cytokine storm is a phenomenon in COVID-19 infection caused by overproduction of inflammatory cytokines, mainly IL-6 and over activation of host's T-cell function when the virus entered the body.[5,13,14]

Following plasma leakage, thrombocytopenia is the major hallmark that has become the main characteristic of dengue infection. It is widely used as a "telltale" sign of the disease and have a significant diagnostic prediction value. Thrombocytopenia happened through several processes that occur in both central and peripheral. Initially, it is due to bone marrow suppression during the early febrile viremia phase of the illness. Then it followed with immune mediated platelet destruction in the peripheral vessels.[12] The virus antibody complexed

attached on the platelet surfaces induced the destruction. However, thrombocytopenia in Dengue is rarely correlates with spontaneous bleeding even when the platelet counts dropped below 10×10^9/l, instead it is more strongly associated with vascular leakage. The platelet counts of 10×10^9/l or lower associated with a more severe form of the disease.[5,12,15] COVID-19 patients also shown to have thromboyctopenia. A meta-analysis study hypothesized that cytokine storm damages the haematopoietic progenitor cells in bone marrow, leading to declining of platelet production. It also aggravated with consumptive damages on the endothelial cells and aggregation of the platelet in the lung.[13,16]

Lastly, coagulopathy has been observed in both infections, presenting prolonged prothrombin time and partial prothrombin time. Although, the hypercoagulable state is more prominent in COVID-19, where there is notably increasing incidence of venous and arterial thromboembolism, myocardial infarction, stroke, and microvascular thrombosis. D-dimer has been noted as the disease severity marker in both of the disease, but it is recorded more often in COVID-19. The raised D-dimer levels in COVID-19 marks the need of initiating thrombolytic therapy, instead in dengue, it is indication for blood component initiation, hence creating a dilemma in the case of co-infection.[12,13]

Our patient did not develop significant plasma leakage during the course of the disease, but she developed severe thrombocytopenia with spontaneous active bleeding. Patient started bleeding on fifth day of illness until the seventh. Patient's platelet level dropped below 10×10^9/l on day fifth and continuously drop to the lowest, which is 6×10^9/l. As result of the profuse bleeding, haemoglobin levels subsequently dropped as well to 7.6 g/dl on the seventh day of illness. Platelet transfusion in the case of dengue hemorrhagic fever is advised when the platelet count drop below 10×10^9/l with active hemorrhagic manifestations.[12,15] Prophylactic transfusion is still remains debatable.[15] We gave our patient platelet concentrate on the fifth day of illness, when the bleeding started and platelet count was at 10×10^9/l. The total of three bags of platelet concentrate was given to our patient, within three days. Platelet transfusions was given to raise the platelet therefore stop the bleeding. Platelet count raised as the critical phase elapse and bleeding significantly reduced by the second bag of transfusion. Although there was reduced in haemoglobin levels in our patient due to the bleeding, we did not give packed red cells (PRC) transfusions for we decided it shall recover as the platelet bounce back to normal levels and adequate fluid was given to maintain normal haemodynamic in our patient.

Our patient initially had a high D-dimer levels, indicating a coagulopathy. We initiated low molecular weight heparin as anti-coagulant. Patient was given enoxaparin 0.6 cc twice daily to prevent thromboembolism incident. Despite clinically patient was still at the critical phase, and platelet level trend was dropping, we decided that administering anti-coagulant will be more beneficiary for the patient. Patient was put under intensive care with close monitoring at this moment. Upon entering the fifth day of the illness, when patient started bleeding, we immediately stop the administration of anti-coagulant. After a week at the hospital, the patient was responding and recovering well towards the treatment, tested negative for COVID-19 and discharged from the hospital.

CONCLUSION

The case of co-infection between COVID-19 and dengue will be inevitable especially in tropical and sub-tropical countries. Physician must be aware of the presence of the co-infection, due to overlapping symptoms and laboratory similarities. Both infections shared similar pathophysiology although through different mechanism, such as plasma leakage, thrombocytopenia, and coagulopathy. Interaction during co-infection may enhanced the severity, as both infections aggravating the clinical course of the disease. Our case of co-infection was complicated by severe thrombocytopenia and spontaneous bleeding. Platelet transfusions were given to manage both the complication. Anti-coagulation therapy may be given under close monitoring. It is recommended to be ceased upon encountering active bleeding and based on physician's clinical judgement. Sharp clinical diagnosis from physician is necessary, because delayed diagnosis may lead to significant losses, such as exposure of medical staffs and other patient's to COVID-19, delayed contract tracing, incorrect measures of therapy, and poor prognosis. Complications may arise and physician must aware of the therapeutical approach. Diagnostic testing must not be withheld when there was suspicion towards the infection. Notably, not all healthcare facility has the access of rapid antigen test as screening protocol, whilst the similarities are pitfalls for risking the exposure of the virus. Although the case of co-infection is associated with higher morbidity and mortality, with close monitoring and prompt treatment shown to have good prognosis. Larger studies are needed to further study about the various form of complication and the morbidity of the case of co-infection.

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