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Case Report

Co-infection of COVID-19 and dengue: a case report

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ABSTRACT

COVID-19 has now spread to most countries, causing a global pandemic. As the COVID-19 pandemic is still ongoing, some part of the world region with tropical climate is facing a dual burden of infection with the presence of concurrent endemic infectious disease. This endemic dengue infection and the COVID-19 pandemic may turn out into a fatal and hazardous combination. In addition, dengue and COVID-19 possess clinical and laboratory features that are sometimes difficult to differentiate. The possibility of COVID-19 and dengue co-infection has also been a noticeable issue. We present a case of 19-year-old male with COVID-19 and dengue co-infection admitted at Wangaya Regional Hospital Denpasar, Bali. Co-infection of COVID-19 and dengue requires special attention from all health care workers in dengue-endemic countries in order to avoid diagnostic delays and improve clinical outcome. It is also necessary to conduct further research which explores the potential of co-infection between coronavirus and arbovirus.

Keywords: COVID-19, Dengue, Co-infection

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] This disease firstly emerged as an outbreak in Wuhan, China and has now spread to most countries, causing a global pandemic.[2] The first confirmed COVID-19 case in Indonesia was reported in March 2020.[3] The number of cases has increased significantly ever since. The number of confirmed cases in Indonesia is reaching 1.736.670, with 47.967 deaths by May 2021.[4] Human to human transmission of COVID-19 infection occurs via close contact with an infected person by exposure to infectious respiratory droplets or aerosols. Penetration to human body happens primarily by inhalation.[1,5] Symptoms may range from fever, upper respiratory and flu-like symptom, gastrointestinal manifestation such as nausea and vomiting to severe illness including pneumonia, acute respiratory distress syndrome (ARDS), septic shock, and multi-organ failure.[2]

Certain condition that should not be overlooked during the COVID-19 pandemic is the presence of concurrent endemic infectious disease. As the COVID-19 pandemic is still ongoing, some part of the world region with tropical climate such as Indonesia is facing a dual burden of infection. Dengue infection which caused by dengue virus (DENV) of arbovirus class and transmitted by *Aedes aegypti* and *Aedes albopictus* occurs year-round in Indonesia and has been endemic for decades. This endemic dengue infection and the COVID-19 pandemic co-existence may turn out into a potentially fatal combination.[2,5] In addition, dengue and COVID-19 possess clinical features and laboratory characteristic that are sometimes difficult to differentiate. COVID-19 has been previously misdiagnosed as dengue infection, and the other way around in several cases.[6] The possibility of COVID-19 and dengue co-infection within an individual should also be considered as this also has been previously reported.[2,5-7] Similarity in clinical features and the potential of co-infection raise the concern of inaccurate

diagnosis and delayed recognition that may hinder the management plan directed for each infection.

We present a case of COVID-19 and dengue co-infected patient, admitted at Wangaya Regional Hospital Denpasar, Bali. Transmission rate of COVID-19 in Bali is concerning as a cumulative total of 46.290 cases and 1.439 deaths were reported in Bali per May 2021. This case presentation is noteworthy as COVID-19 and dengue co-infection diagnosis might be challenging, and may pose greater burden. Thus, physician should be aware of these circumstances, especially in tropical areas.

CASE REPORT

A 19-year-old male presented with complaint of fever since five days prior to hospital admission. He also experienced nausea, vomiting, muscle and joint pain. The patient did not notice any specific pattern of fever. Patient had no symptom of spontaneous bleeding and denied any upper and lower respiratory symptom. Previous medical illnesses were denied.

Physical examination revealed body temperature of 39 °C, respiratory rate of 20/min, pulse rate of 98/min, and blood pressure of 120/80 mmHg. Oxygen saturation was 98% on room air. Other physical examinations were unremarkable. No sign of plasma leakage and bleeding were found.

Laboratory result at initial presentation showed normal leukocyte count (5.02×10^3/µl), normal lymphocyte count (1.76×10^3/µl), normal hematocrit level (44.5%) and low platelet count (60×10^3/µl). Follow-up blood work-up showed progressive decreased of platelet which improved at seventh day of fever. Marked elevation of liver enzymes was found - serum glutamic-oxaloacetic transaminase (SGOT)=947 U/l, and serum glutamic-pyruvic transaminase (SGPT)=416 U/l. Hepatitis B and C virus serology were negative. Electrolyte levels showed mild hiponatremia (128 mmol/l) and hipokalemia (3.2 mmol/l). Laboratory results also showed elevated D-dimer (7246 ng/ml) and slightly prolonged prothrombin time (13.4 seconds). C-reactive protein (35 mg/l) was found to be high. Plain chest X-ray showed no pulmonary infiltration (Figure 1). Reverse transcriptase–polymerase chain reaction (PCR) for SARS-CoV-2 from specimens of nasopharyngeal and throat swabs was positive. Anti-dengue IgM and IgG were tested 7 days after initial presentation of fever and were found to be positive. The patient was diagnosed as confirmed mild COVID-19 infection and dengue fever, accompanied by reactive transaminitis, electrolyte imbalance (hiponatremia and hipokalemia) and coagulopathy.

The patient was given hypotonic saline, intravenous antiviral agent (favipiravir), intravenous corticosteroid, macrolide antibiotic (azithromycin), vitamin C and vitamin D supplementation and symptomatic therapy according to Indonesian national protocol for COVID-19 management. The patient also received intravenous anticoagulant (lovenox) as thromboprophylaxis. The patient was discharged on eleventh day after onset of illness.

Table 1: Laboratory profile of patient during hospitalization.

Laboratory parameter	Day of admission			
	1st	2nd	3rd	4th
Hemoglobin (g/dl)	15.0	15.2	14.8	14.7
Hematocrit (%)	44.5	45.1	45	43.8
White blood cell (10^3/µl)	5.02	4.79	10.6	11.7
Neutrophil (%)	56.3	42	56	67.8
Lymphocyte (%)	35.1	47.2	38.9	25.5
Total lymphocyte count (10^3/µl)	1.76	2.26	4.14	3.0
Monocyte (%)	8.2	10.2	4.7	6.5
Eosinophil (%)	0.0	0.0	0.1	0.0
Basophil (%)	0.4	0.6	0.3	0.2
Platelet (10^3/µl)	60	59	71	134
SGOT (U/l)	947	-	-	256
SGPT (U/l)	416	-	-	192
Natrium (mmol/l)	128	-	-	144
Kalium (mmol/l)	3.2	-	-	3.5
Chloride (mmol/l)	92	-	-	99
CRP (mg/l)	35	-	-	16

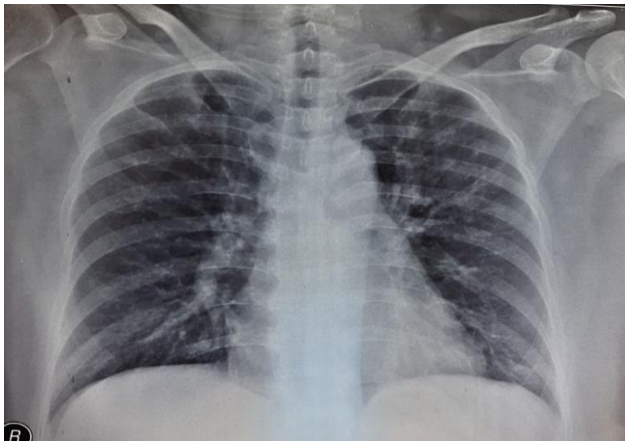

Figure 1: Chest X-ray of the patient revealed no abnormality.

DISCUSSION

This case report presents a case of confirmed COVID-19 accompanied by dengue infection. Dengue is one of the most common tropical infectious diseases in Indonesia.[9] As the COVID-19 pandemic has not been resolved, it is notable to consider the possibility COVID-19 and dengue co-infection occurrence. In dengue-endemic countries, physician faced difficulty in COVID-19 and dengue distinguishment as they both exhibit non-specific presentations. Both diseases have some overlapping clinical spectrums and laboratory features which make each disease differentiation challenging.

The reported patient presented with fever, nausea, vomiting, muscle and joint pain. Fever is a common initial manifestation for both COVID-19 and dengue. In the case of dengue, it causes a development of abrupt onset high fever with saddleback characteristic of two temperature peak. Meanwhile, COVID-19 patient usually showed up with mild fever with no distinct temperature pattern, accompanied by respiratory symptoms including cough or shortness of breath.[7,8] The patient in this case report had no specific pattern of fever and denied any upper and lower respiratory symptom. Respiratory symptom initially considered as the clinical point of distinction for COVID-19 and dengue. However some studies reported that 20% of patients with confirmed dengue present with upper respiratory tract symptoms associated with ARDS, pulmonary hemorrhage, bilateral pneumonitis, and pleural effusion.[8,10] Respiratory distress may also be found in severe dengue cases.[7] Similarly, COVID-19 may manifest itself without respiratory symptoms.[10]

Headache, nausea, vomiting, abdominal pain, muscle and joint pain, rash and malaise are some of the overlapping symptoms in both of these illnesses.[2,7] Skin manifestations such as rash or petechiae, which are commonly encountered in dengue infection, have also been reported in COVID-19. Both diseases may also progress to multi-organ involvement and shock at the later stage.[7] These similarities happen because approximately 80% of COVID-19 cases are mild to moderate in severity, thus the symptom was unspecific and may mimic dengue.[5] Therefore, most patients with unspecific presentation must be explored clinically for both diseases.

COVID-19 and dengue also share some similar laboratory findings such as leukopenia and thrombocytopenia.[2,11] Leukopenia with lymphopenia at presentation are found in both early stage of dengue and COVID-19. A study found that 29% of COVID-19 and 20% of dengue patients had leukopenia. This study stated that most of hospitalized COVID-19 patients were predominantly lymphopenic, and lymphopenia was also more prevalent in severe dengue.[8] Thrombocytopenia was reported in 36.2% of the patients with COVID-19.[11] On the contrary, thrombocytopenia in dengue patient was observed in a higher proportion (69.5%).[8] In the present case, complete blood count of the patient revealed normal leukocyte and lymphocyte count, normal hematocrit, and decreased platelet count. Hemoconcentration and plasma leakage syndrome are thought to be the distinct manifestations of dengue, which can help discriminate dengue from COVID-19.[6] However, another literature stated that COVID-19 and dengue may exhibit some pathophysiological similarities including capillary leakage.[9] Signs of plasma leakage were not found in the reported case.

Marked elevation of liver enzymes was found in the reported patient. This elevation was likely attributed to COVID-19 and/or dengue infection as the patient denied any history of systemic medical illness, negative hepatitis virus serology and no other factor or pathomechanism that may underlie the occurrence of transaminitis. Elevated liver enzymes are reported in both COVID-19 and dengue. Hepatic injury in COVID-19, as in dengue fever may be related to immune-mediated damage or direct cytotoxicity due to active viral replication in hepatic cells. It could be also be associated with hypoxic hepatitis due to anoxia, reactivation of pre-existing liver disease, or drug-induced liver injury due to paracetamol, antiviral agents, or other medication used in the management of COVID-19 and dengue.[11]

Coagulopathy is one of the main pathologies associated with DENV infection and is also present in COVID-19. Both COVID-19 and dengue infection may exhibit prolonged prothrombin time and partial thromboplastin time.[9] Increased D-dimer may also be observed in COVID-19 and dengue patients.[8] This correlates with the findings of elevated D-dimer and prolong prothrombin time of the reported case. The patient was given thromboprophylaxis agent despite presented with thrombocytopenia as there were no sign of spontaneous bleeding. Majority of patients with COVID-19 also presented with elevated inflammatory biomarker such as CRP which corresponds with the elevated CRP level of the reported patient.[12]

An early COVID-19 infection may initially presents as acute undifferentiated febrile illness, however the disease in partial cases will eventually progress to pneumonia which usually showed up as chest radiology abnormality.[6] Plain chest X-ray may evidence sparse bilateral consolidations and ground glass opacities.[13] No abnormality was detected in plain chest X-ray examination of the reported case. This might be due to asymptomatic or mild COVID-19. We did not perform a more sensitive chest computed tomography scan (CT) as no respiratory symptom was found in the patient. COVID-19 pneumonia in chest CT scan typically initiated with small, subpleural, unilateral, or bilateral ground glass opacities in the lower lobes, which subsequently developed into a crazy-paving pattern and consolidation.[12]

Laboratory diagnosis of dengue in the setting of COVID-19 pandemic is a great challenge. Serological cross-reactivity between dengue and COVID-19 has been reported, especially in DENV endemic areas. False positive result may occur for serology of COVID-19 among dengue patients and reciprocally, serology of dengue among COVID-19 patients.[5,14] Therefore, relying upon serology test for COVID-19 and dengue co-infection is not always applicable. The preferable confirmatory test for COVID-19 is through nucleic acid amplification tests using PCR. However, this modality depends upon more advanced facilities and requires longer duration to obtain results as referral is sometimes needed in low-resources area.[5]

Additionally, several studies have previously found COVID-19 and dengue co-infection cases.[2,5,6,11] Fortunately, in Indonesia, it is a preliminary measure to rule out the possibility of COVID-19 infection in patient

who showed symptom of fever. The patient in this case showed positive reverse transcriptase–PCR for SARS-CoV-2 from specimens of nasopharyngeal and throat swabs as well as positive anti dengue IgM and IgG. Either dengue NS1Ag or dengue RT-PCR should be performed to confirm the diagnosis if co-infection is suspected.[6] NS1Ag was not done in the patient as it was not the appropriate time according to dengue infection course at the time of hospital presentation. Meanwhile, RT-PCR for dengue infection is not commonly done in Indonesia. Recommendation to test for both dengue and COVID-19 in patient with fever and unspecific manifestation in this COVID-19 pandemic era with accurate methods, together with isolation of suspected cases were done on the reported patient.[6]

The possibility of co-infection and limitation in diagnosis modality could lead to delayed molecular diagnosis of COVID-19 and dengue, resulting in poor clinical outcomes.[14] COVID-19 and dengue co-infection may lead to unfavourable outcome as it is associated with more complex and unpredictable disease severity.[10,14] Literature reported a mortality rate as high as 60% in COVID-19 and dengue co-infected patients (p=0.001).[15] Comprehensive preparation and prevention should be considered to address this issue and to mitigate the potential burden of healthcare system and provide efficient clinical management in this COVID-19 pandemic era.

CONCLUSION

Dual infection of dengue and COVID-19 requires special attention from all health care workers in dengue-endemic countries. Physician should always consider the probability of either dengue and/or COVID-19 in patient with non-specific manifestation as they may share some clinical and laboratory features similarity, in order to avoid diagnostic delays and improve clinical outcome. This case report also highlights the necessity of further research which explores the potential of co-infection between coronavirus and arbovirus.

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