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# Cytokines storm in COVID-19 with dengue co-infection in pregnancy: Fatal maternal and fetal outcome

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ABSTRACT

We report a 23-year-old pregnant woman who presented with acute high-grade fever, vomiting, and diarrhea for 5 days. She was first hospitalized in RSUD Tangerang—a secondary hospital based in Tangerang and were referred to Cipto Mangunkusumo General Hospital as a tertiary hospital. Initial laboratory results from previous hospital revealed leukopenia, low platelet, elevated aspartate transaminase, and alanine transaminase. Chest radiograph showed no pulmonary infiltration. Reverse transcriptase–PCR (RT-PCR) of the nasopharyngeal swab detected SARS-CoV-2, and NS1 antigen or IgM dengue-specific antibodies were positive. COVID-19 with dengue fever co-infection was diagnosed. Hemorrhagic manifestations were seen in both the mother (gum and gastrointestinal bleeding) and pregnancy (placental abruption). Patient was put on ventilator and was unfortunately lead to her death that were caused by multiorgan dysfunction failure due to co-infection of dengue and COVID-19. Both dengue and COVID-19 had similar manifestation, as it is a warning sign in pregnant patient experienced both that can lead to fatal result in mother and baby. Early diagnosis and management of co-infection is high clinical importance, especially in endemic area of dengue like Indonesia.



## Introduction

Coronavirus disease 2019 (COVID-19) has become a pandemic in throughout the world and specifically in Indonesia as of 2020. It has resulted 850,000 deaths worldwide within a period of 8 months [1]. Indonesia ranked as the one of the highest COVID-19 "*hot-spots*" in Asia. COVID-19 cases reached 4000 per day as in October 2020. Indonesia is also the fourth most populous country and also suffered the highest number of COVID-19 confirmed cases and deaths in Southeast Asia, second to India. Moreover, Indonesia is a country with many diseases related to its tropical region. Dengue is one of a great public health problems in tropical and sub-tropical region [2]. As of June 2020, 68,000 dengue cases have been reported as dengue outbreaks and resulted in 446 deaths [2,3]. In addition, COVID-19 pandemic might overlap with the dengue epidemics [4].

Similar signs and symptoms shared by both disease entities may have led to difficulties in diagnosis and treatment. Pre-existing DENV-antibodies might potentially affect COVID-19 through antibody-dependent enhancement [2]. Some studies reported involvement of high levels of cytokine that caused cytokine storm that can result in multiorgan failure and mortality in COVID-19 patients. Cytokine storm can also be found in patients with D=dengue that may contribute to the severity of the disease [2].

Most co-infection of dengue and COVID-19 were reported as case reports—stating that only a few that were reported. Overlapping clinical and laboratory features that are similar may be a challenge to distinguish dengue from COVID-19. Common diagnostic test for COVID-19 is reverse transcriptase PCR (RT-PCR) based detection of nasopharyngeal SARS CoV-2 RNA. While in dengue, laboratory diagnosis of dengue can be established by detection of virus expressed soluble non-structural protein 1 (NS1 antigen) or IgM dengue-specific antibodies by means of ELISA [4,5].

Dengue and COVID-19 during pregnancy carries a higher risk of maternal and fetal complications, such as preterm birth, intrauterine fetal death, and massive bleeding [6].

this study, we report the first case, in Indonesia, to the best of our knowledge of co-infection of Dengue and COVID-19 in pregnancy.

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## Case report

We report the case of a pregnant 23-year-old women, came to our hospital, referred from a secondary hospital due to her symptoms. Patient live in Tangerang, Banten, with no relevant past medical history and never traveled anywhere outside Indonesia.

Patient had first experienced fever, nausea, vomiting, and diarrhea on March 11, 2021. Patient came on March 14 to a primary hospital and were tested positive for SARS CoV-2 Rapid IgG antibodies, and were referred to secondary hospital in Tangerang.

On March 15, patient was tested COVID-19 positive by RT-PCR (*SD biosafer* reagen). Laboratory results showed leucopenia (4020 mL), thrombocytopenia (17,000 mL), and positive for NS1 antigen (*Rapidan* reagen). Ultrasound examination found 31 weeks of pregnancy — estimated fetal weight of 1798 g, fetal heart rate 150 bpm, anterior placenta, AFI normal. After 15 h of observation in the isolation room, patient experienced no fetal movement, on ultrasound evaluation no fetal heart rate was found. Patient experienced no contraction and no vaginal bleeding. Patient still had complained of diarrhea 4–5 times a day, blood pressure was 120/100 mmHg, heart rate 119 times per minute, fever reached 39 °C, and respiratory rate was 20 times per minute. Patient was then referred to our hospital, Cipto Mangunkusumo General Hospital.

Patient arrived on our hospital on March 16, with fever day 4, diarrhea 5–6 times per day, vomiting >10x/day, had dark stool, gum and gastrointestinal bleeding. On arrival her blood pressure was 100/60 mmHg, heart rate 118 times/minute, respiratory rate of 22 times/minute, temperature 36.5 °C, and oxygen saturation of 99% with simple mask. Patient was diagnosed as dengue shock syndrome on dengue fever grade III, confirmed COVID-19 infection, with multiorgan failure, Gravida 1 32 weeks of gestational age, intrauterine fetal death. Upon arrival ultrasound examination showed no signs of placental abruption. Two packs of thrombocyte concentrate were given to the patient.

Unfortunately, patient experienced respiratory distress—blood pressure 100/60 mmHg, heart rate 119 times per minute, respiratory rate 28 times per minute, oxygen saturation 90% and severe respiratory acidosis on blood gas analysis—patient was put on ventilator on March 17. Patient had hypertonic uterine contraction, and retroplacental hematoma corresponds to placental abruption was found on ultrasound examination. Patient condition continues to deteriorate until March 18, and patient was eventually declared dead due to multiorgan failure due to dengue and COVID-19 coinfection.

**Table 2**
Cytokine level of the patient.

| | |
|---|---|
| Interleukin 6 | 18,812 pg/mL |
| Interleukin 10 | 1455 pg/mL |
| TNF-α | 181.1 pg/mL |
| IFN-γ | 5.5 pg/mL |

Detailed laboratory data on a day-to-day basis is provided in Table 1 (Table 2).

## Discussion

Similarities between COVID-19 and dengue were shown in their pathophysiology. They have spectrums of disease with overlap in clinical manifestations. Dengue has similar symptoms as COVID-19—it is both present with fever and headache, and also diarrhea—most common gastrointestinal symptoms of COVID-19 in pregnant women [7,8].

Capillary leakage, thrombocytopenia and coagulopathy were the main representation of both diseases [2,9]. Leucopenia at presentation is found in either dengue or COVID-19. In the present case, no abnormality was detected in chest x-ray, however we did not perform more sensitive CT of the chest because of the absence of respiratory symptoms (Picture 1.).

Mediated by the host immunological response, plasma leakage is crucial in dengue pathophysiology. Pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-6 (IL-6), interferon gamma (IFN-γ), and chemokines such as macrophage migratory factor are associated with plasma leakage [10,11]. In dengue, plasma leakage is related with the interaction between nonstructural protein 1 (NS1)-specific antibodies and protein expressed on endothelial cell surfaces that may pave the way for the elevated rate of viral replication and inflammatory cytokine secretion [12–14]. High CRP levels and altered platelet function are also attributed to plasma leakage [2].

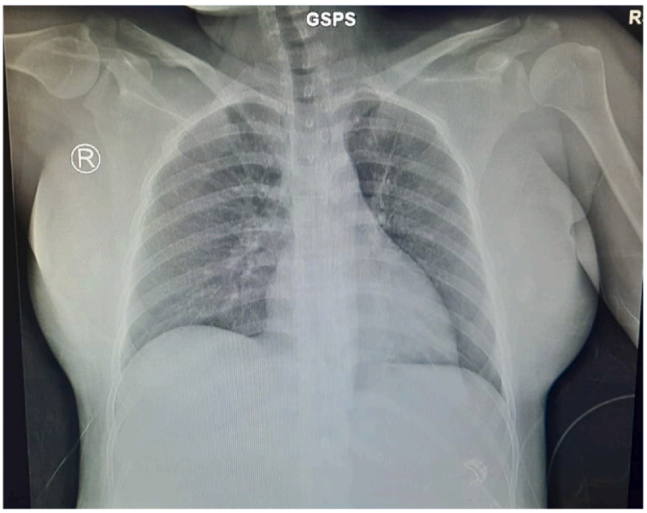
In COVID-19, there are over-activation of effector T-cell function and increased inflammatory cytokine production, especially IL-6 leading to a cytokine storm [15]. COVID-19 is also related with increased plasma CRP levels. IL-6 along with IL-1, TNF-α, and IFN-γ contributes to vascular permeability and disseminated intravascular coagulation (DIC) [2].

Rather than COVID-19, dengue has more acute course as plasma leakage last 24–48 h and enter the critical phase during 4–7 days of

**Table 1**
Laboratory findings during the course of disease.

| Laboratory Result | Day 1 – Primary hospital | Day 2 – Secondary hospital | Day 3 – at Cipto Mangunkusumo Hospital | Day 4 | Day 5 |
|---|---|---|---|---|---|
| Hemoglobin | 12.1 | 13.2 | 13.1 | 9.7 | 6.6. |
| Hematocrits | 36 | 38 | 41.5 | 30.2 | 20.4 |
| Leukocyte | 2908 | 4020 | 34,310[a] | 59,070 | 32,130 |
| Platelet | 50.000 | 17.000 | 120.000 | 112.000 | 55.000 |
| Neutrophil | | | 72.8% | 69.4% | 71.1% |
| Lymphocyte | | | 19.3% | 24.7% | 16.3% |
| Basophil | | | 1% | 0.6% | 0.8% |
| Monocyte | | | 6.5% | 4.9% | 11.7% |
| Eosinophile | | | 0.4 | 0.5% | 0.1% |
| AST | | | 15.084 | | 21.352 |
| ALT | | | 6190 | | 2174 |
| Prothrombin Time | | | 1.8x | 3x | 3.1x |
| Partial Thromboplastin Time | | | 2.4x | 3.8x | 3.4x |
| D- dimer | | 3466 | 6190 | | |
| Fibrinogen | | 255 | 151 | | |
| Urea | | | 30.2 | | |
| Creatinine | | | 1.7 | | |
| PCT | | | 0.78 | | 1.8 |
| CRP | | | 77.1 | | 35.1 |
| IgG/IgM Dengue | | | Positive | | |

[a] After patient was given two packs of thrombocyte concentrate.




**Picture 1.** Chest radiograph shows no signs of pneumonia.

illness [1,16]. In a study comparing cytokines and chemokines in both COVID-19 and dengue, IL-10 are significantly higher in patient with severe dengue (DHF) compared to COVID-19. In contrast, IL-6 levels are higher in patient with severe pneumonia compared to DHF. IL-10 levels of more than 34.3 pg/mL, the sensitivity and specificity of developing DHF was 71.9% and 70% [1].

IL-6 was significantly higher in early illness and critical phase in patient with severe dengue, but it is also higher in patient who developed severe pneumonia in COVID-19 [1,17,18]. In our patient, IL-6 and IL-10 were both very high but the patient did not develop severe pneumonia yet. Dengue pathogenesis indicates a hyperactivation of immune cells that leads to production of mediators which is mainly cytokines. Cytokines in dengue infection can be a result from the infection or the interaction of immune system components with infected cells or byproducts of the viral replication [19].

CRP is an acute phase inflammatory protein produced by hepatocytes that maybe elevated in conditions related to inflammation and also infection [20]. CRP is also an important marker for dengue progression and may be potentially be used as a prognostic biomarker [21–24]. Elevated serum of CRP was associated with an increased composite poor outcome (RR 1.84) and also showed increased risk of severe COVID-19. Majority of the studies used a > 10 mg/L CRP level cutoff for a composite poor outcome in COVID-19 [20,25,26].

Thrombocytopenia is one of the main characteristics of DENV infection, and it also observed in patient with COVID-19. A meta-analysis found that thrombocytopenia is associated with the severity of COVID-19 thus it is a clinical indicator of worsening illness during a course of hospitalization [27]. Thrombocytopenia also increases higher risk of mortality in patient with COVID-19 (OR 6.23, 1.031–37.67) [28].

Coagulopathy are both presented in DENV and COVID-19 infection. Both exhibit prolonged prothrombin time and partial thromboplastin time, as our patient in the case report. Currently, no therapy is available beyond supportive care for COVID-19 or dengue. As both entities present with coagulopathy, thrombotic prophylaxis and anticoagulant therapy is often used. Intravenous immunoglobin and steroids are commonly used also in treating COVID-19 [4]. In our patient, neither heparin anticoagulant therapy nor steroids were given, since it is feared to increase bleeding risk in our patient.

NS1 antigen positivity in the first week can be a diagnostic criteria for dengue infection and/or detection of IgM antibody 7–10 days after the infection [4]. However, since rapid test accuracy vary and influenced by the disease progression, confirmatory testing for both COVID-19 and dengue is through RT-PCR test [29,30]. Some studies provided evidence of cross-reactivity between DENV and COVID-19 which can lead to false-positive COVID-19 serology in dengue patients [29]. Two cases from Singapore were reported to have COVID and dengue co-infection, but further RT-PCR test for both cases were negative [31].

We identified similar cases although previous case reports were non-pregnant patients, but also a covid case of co-infection with dengue. Verduyn et al. presented a case of dengue and COVID co-infection diagnosed by RT-PCR for COVID-19 and positive NS-1 rapid antigen test and were late confirmed of serotype 1 dengue with RT-PCR [31]. Patient also had trombocytopenia, leucopenia, lymphopenia and neutropenia. Elevated liver function was found but CRP was normal. Fever lasted 10 days and patient's symptoms gradually improved and returned home [31]. Whether it is a false-positive dengue infection or it is a true co-infection with COVID-19, both situation is complicated by the course of the diseases [31,32].

Dengue in pregnancy can cause maternal and fetal mortality. Early diagnosis and management of co-infections is high clinical importance. The patients presented in late condition that leads to fatal result in both mother and baby. Furthermore, a larger study is needed to evaluate the conditions and morbidity of this co-infection.

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## Ethical approval

This study has been approved by Ethical Committee for Research in Human from the Faculty of Medicine, Universitas Indonesia.

## Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

## Author contribution

R.I conceived the presented topic and case report of the co-infection of COVID and dengue. R.I,N.W, N.P searched the data and findings. R.I and N.P took lead writing the manuscript. All author contributes and the analysis, and discussed the result altogether.

## Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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