

CASE REPORT

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Fulminant myocarditis-associated expanded dengue syndrome in pregnant woman: a case report

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Abstract

Background: Dengue fever is a mosquito-borne viral disease whose incidence has increased globally, with Indonesia as hyperendemic. In Indonesia, around 17.4% of febrile cases were due to dengue. Expanded dengue syndrome is a term for dengue fever with atypical manifestations in other organs such as renal, respiratory, and cardiac. Dengue myocarditis remains underdiagnosed and usually has a low risk of heart failure. However, pregnancy increases the risk of expanded dengue syndrome, with the incidence six times higher in pregnant women. Due to limited studies about myocarditis treatment during pregnancy, it is critical to understand the effects of heart drugs and the importance of treatment choices with limited selection during fulminant myocarditis.

Case presentation: We reported a case of an adult pregnant woman in her second trimester with fulminant myocarditis-associated expanded dengue syndrome based on criteria. The patient suddenly worsened with progressive cardiomegaly and lung edema accompanied by cardiogenic shock. Multidisciplinary treatment management has been given to improve cardiac function and other organs due to dengue by considering the risk and family consent. The patient recovered from myocarditis, and the cardiac size has reduced.

Conclusions: Fulminant myocarditis is a serious complication of expanded dengue syndrome, and aggressive therapy is required to prevent it. Further investigations and a multidisciplinary system are required to reduce or minimize fetal abnormalities.

Keywords: Fulminant myocarditis, Dengue fever, Pregnant, Heart failure

Background

Dengue fever (DF) is a mosquito-borne viral disease whose incidence has increased globally. Indonesia and other subtropical countries are hyperendemic; in Indonesia itself, there has been a 700-fold increase in incidence over the past 45 years. In Indonesia, around 17.4% of febrile cases were due to DF, with Bali having the highest incidence of DF (52%). Due to the wide range of clinical presentations, from fever, hemorrhagic presentation,

shock, and also the atypical presentations in expanded dengue syndrome (EDS), dengue has become a common etiology for hospitalization in Indonesia (Made Susila Utama et al. 2019).

Expanded dengue syndrome is a term from the World Health Organization (WHO) for DF with atypical manifestations in other organs such as gastrointestinal, nervous system, renal, respiratory, and cardiac. Despite a self-limited disease, EDS can lead to organ damage, complex management, and deterioration (Umakanth and Suganthan 2020). Pregnancy increases the risk of EDS, as seen in one study, with the incidence in non-pregnant women and pregnant women, 4.59% and 27.19%, respectively. Among all those participants, only one out of 370 non-pregnant women was found with myocarditis (John

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2021). Due to limited study about heart failure in dengue myocarditis, especially during pregnancy, we highlight the importance of treatment choices with limited selection during fulminant myocarditis (FM), as we described in our case.

Case presentation

A 29-year-old pregnant woman came to the emergency department with fever for three days, dizziness, abdominal pain, and nausea, without a history of spontaneous bleeding, hypertension, cardiovascular problem, or significant family history. She was taking Paracetamol without improvements. This was her second pregnancy with a gestation of 21–22 weeks, without prior medical problems in her first or second pregnancy. She was febrile with normal vital signs, normal heart, and lung sounds without any sign of bleeding. The hematology test showed hemoglobin (Hb) 11.2 g/dL with a hematocrit level of 31%, thrombocytopenia (145,000/ μ L) and normal leukocyte level, hypokalemia (3.1 mmol/L) and hyponatremia (131 mmol/L), normal liver and renal function tests. Prior to our hospital, the patient carried a positive NS1 test. Our working diagnosis was dengue fever with warning signs and electrolyte imbalance. Fluid management and symptomatic medications were given, a hematology test was repeated each day, and the patient was admitted to internal medicine.

During the third day of hospitalization, the patient's condition deteriorated with multiple petechiae in the lower extremities, blood pressure 88/67 mmHg, constant

Hb level, thrombocytopenia (85,000/ μ L), leukopenia, and hypoalbuminemia (2.5 g/dL). The patient was transferred to the intensive care unit and consulted to a cardiologist. We corrected the albumin and performed a chest X-ray with consent, showing a normal cardiac ratio with increased bronchovascular pattern also normal central venous catheter placement (Fig. 1a). The fetal heart rate was 150 times per minute. On the seventh day of hospitalization, the patient showed dyspnea and hemoptysis, blood pressure 116/73 mmHg, and a heart rate 138 times per minute on dobutamine and norepinephrine. The thrombocyte level 68,000/ μ L, leukocytosis (20,000/ μ L), elevated liver function test, troponin T 275 ng/L (reference range <14 ng/L), NT-proBNP >9000 pg/mL with D-dimer and procalcitonin increased. Another chest X-ray was performed, finding cardiomegaly with increased lung infiltrate (Fig. 1b). The electrocardiograph was sinus tachycardia. Levofloxacin combined with meropenem was added, and continuous furosemide infusion was added. Ivabradine 2.5 mg twice daily, sildenafil 3.125 mg once daily, and spironolactone 25 mg twice daily were given after receiving family consent.

The patient remained dyspnea after the ninth day of hospitalization. Electrical cardiometry revealed decreased stroke volume (47 mL) and cardiac contractility (27.6), with chest X-ray revealing increased cardiomegaly without worsening lung infiltrate (Fig. 2a). Trimetazidine 35 mg twice daily, coenzyme Q10 100 mg twice daily, amiodarone 200 mg once daily, and ramipril 2.5 mg once daily were added. During the twelfth day,

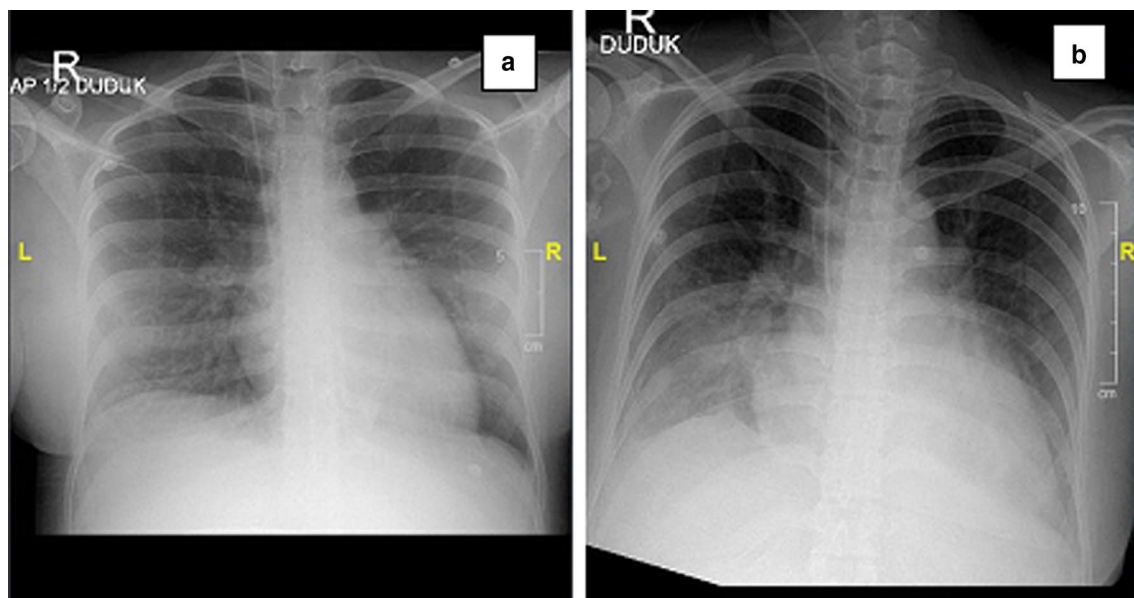


Fig. 1 Thorax X-ray during the third day **a** compared to the seventh day **b** showed progression from pulmonary hypertension to cardiomegaly and pulmonary edema

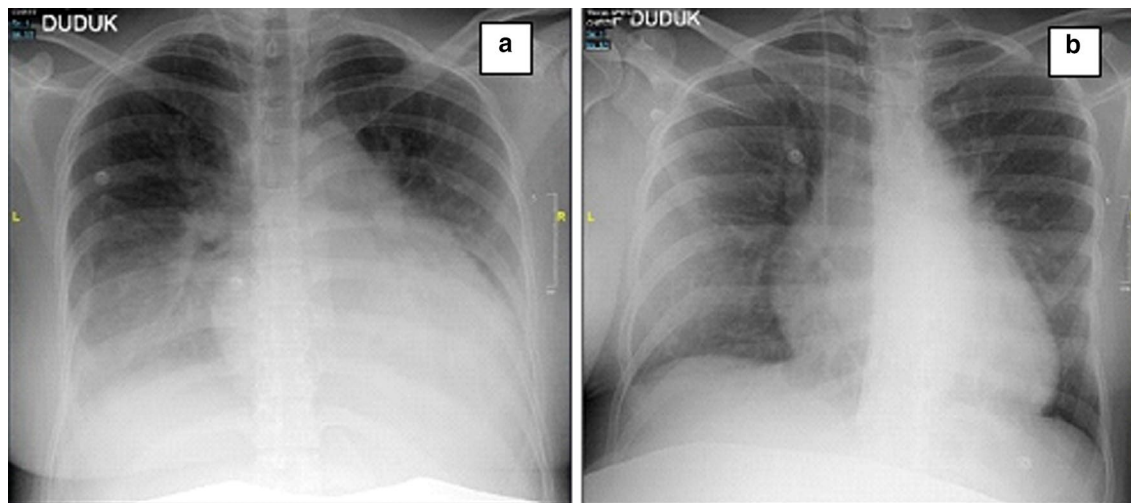


Fig. 2 Thorax X-ray during the ninth day **a** showed worsening cardiomegaly. But compared to the twelfth day **(b)**, cardiac size declined with lesser lung infiltrates as the symptoms subsided

dyspnea decreased, vital signs, all laboratory tests, and chest X-ray showed improvement (Fig. 2b). The fetal heart rate was 141 times per minute. Echocardiography showed normal ejection fraction/EF (66.8%), as shown in Fig. 3. All heart medications were tapered down and

stopped. The patient was discharged without symptoms after the 22nd-day hospitalization. The next week, the patient did a medical checkup with a cardiologist without any symptoms and was encouraged to routine checkups with an obstetrician considering potential side effects.

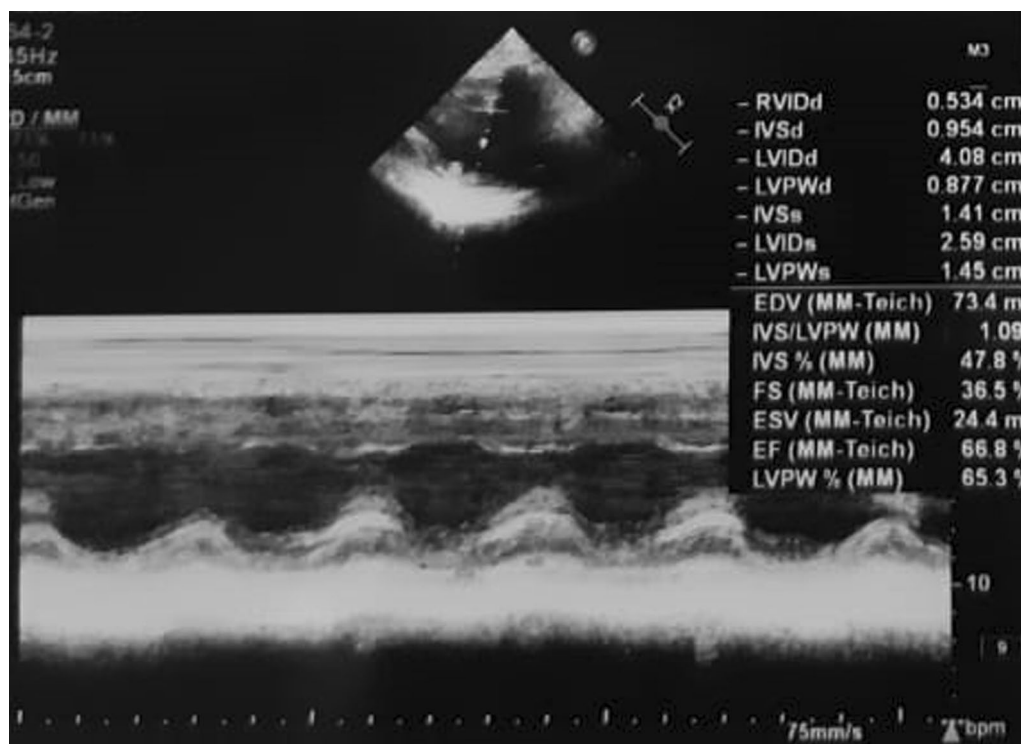


Fig. 3 Echocardiograph before outpatient showed no hypokinetic with normal EF (66.8%)

Unfortunately, the patient did not return for obstetric checkups.

Discussion

Fulminant myocarditis (FM) defines as inflammation of the heart muscle, commonly due to viral infection, characterized by severe symptoms and sudden onset (≤ 2 weeks from the onset of precursor symptoms) that requires hemodynamic support. Comparing the outcomes, FM has higher mortality (over 50%) than non-fulminant. Despite the comprehensive treatment regimen in this study, 1-year follow-up results in 19.6% of patients showed decreasing EF or arrhythmias, while the others have recovered (Hang et al. 2020). We exclude peripartum cardiomyopathy since the gestation age is below the criteria. Cardiac involvement in dengue fever is still uncommon. In another study, myocarditis was found in 201 of 1782 patients, with 25.4% being diagnosed with heart failure using indexes such as cardiac shock (in 7 cases), bilateral rales, pulmonary congestion, and other markers without decreased EF. Only two mortal cases were found in the study (Li et al. 2016). There are a few cases that show dengue with FM similar to our case, but the patients are in third trimester and very limited discussion in treatment (Koshy and John 2012; Neki et al. 2015). So far, the dengue virus is not considered one of the main viral myocarditis etiologies, and we cannot conclude if a particular serotype predominates to FM.

There are many hypotheses about dengue myocarditis; the most common is its involvement in vascular and cardiac through immune mechanisms. The dengue virus potentially infects myocytes and activates T cells and macrophages, leading to pro-inflammatory cytokines (especially tumor necrosis factor/TNF), endothelial dysfunction, and vasculopathy contributes to reduced preload for coronary microcirculation and myocardial edema (Yacoub et al. 2014). Increased activity in monocytes (especially CD14⁺ in the heart), complement system, and pro-inflammatory cytokines with decreased number of CD4⁺CD25 for immune regulation during < 24 weeks gestation probably contributes to this patient's rapid progression to cardiac failure, possibly evolving to dilated cardiomyopathy (Abu-Raya et al. 2020; Schultheiss et al. 2021).

The main treatment for FM is a life support-based regimen, which is immunomodulators, antivirals, inotropic and vasopressor, heart failure therapy, and mechanical circulatory support (Hang et al. 2020; Schultheiss et al. 2021). Hence, a limited selection of therapeutics and no access to mechanical support prove to be a challenge. Despite continuous diuretics, the dyspnea worsens due to increasing cardiomegaly with poor ejection. Ivabradine is given better tolerance and heart rate control in

inappropriate sinus tachycardia than bisoprolol (Martino et al. 2021). Ivabradine has been known as teratogenic in some animal studies, and future studies are required to refute other findings by Hoeltzenbein M et al., which have shown a low teratogen risk (Hoeltzenbein et al. 2021). Trimetazidine has shown no significant reduction in blood pressure compared to nitrates, with the additional benefit of improved left ventricular systolic performance (Meiszterics et al. 2017). While coenzyme Q10 reduces the severity of myocarditis, superior effect in combination with trimetazidine improves ejection fraction (Zozina et al. 2018). We add low-dose amiodarone to improve rate control since beta-blocker should be held until stabilization despite the risk of fetal hypothyroidism (Halpern et al. 2019).

Short-term spironolactone and ramipril were added to prevent worsened heart failure symptoms and cardiac remodeling despite the contraindication. While spironolactone is mainly contraindicated during the first trimester due to the risk of feminization, angiotensin-converting enzyme inhibitor (ACE-I) leads to renin-angiotensin system blocker fetopathy (Halpern et al. 2019). One case from Saar et al. (2016) shows the possibility of reversible fetal renal impairment after discontinuation of the drug. Due to a lack of research on complications in short-term use of spironolactone and ACE-I in pregnancy, further investigation and observation are required for the patient. With the symptoms and the cardiac function improvements, the family chooses to continue the pregnancy despite the risks. The side effect of the drugs remains to be seen; hence, multidisciplinary with an obstetrician is a must. Unfortunately, the patient did not return for further medical checkups, and this limited our study.

Conclusions

This case report highlights rare FM as a part of EDS. Despite being known for self-limiting with low mortality cases, dengue myocarditis in high-risk patients such as pregnancy may lead to severe consequences, and aggressive therapy may be required to reduce the complications. With limited therapies and choices, further investigations are required to prevent or minimize fetal abnormalities. A multidisciplinary system between cardiologists, obstetricians, and pediatrics can improve the outcome for the mother and the child.

Abbreviations

ACE-I: Angiotensin-converting enzyme inhibitor; DF: Dengue fever; EDS: Expanded dengue syndrome; EF: Ejection fraction; FM: Fulminant myocarditis; TNF: Tumor necrosis factor; WHO: World Health Organization.

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Author contributions

WSW was responsible for the design and drafting the manuscript. IK was involved in revision and content approval. All authors read and approved the final manuscript.

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Declarations**Ethics approval and consent to participate**

The patient consented to participate in the study. Informed written consent was obtained and signed.

Consent for publication

Written informed consent for publication was obtained from the patient to publish this case report and any accompanying images.

Competing interests

All authors have no conflict of interest to declare.

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