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by Muhammad Vitanata Arfijanto

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An expanded dengue syndrome patient with manifestation myocarditis: case report

M V Arifijanto[1*], H P Luqmana[2], M Rusli[1] and Bramantono[1]

[1]Tropical Medicine and Infectious Disease Division, Department of Internal Medicine Faculty of Medicine, University of Airlangga-RSUD Dr. Soetomo, Surabaya, Indonesia
[2]Department of Internal Medicine Faculty of Medicine, University of Airlangga-RSUD Dr. Soetomo, Surabaya, Indonesia

*Corresponding author: divtropin@yahoo.com

Abstract. Dengue infection may manifest asymptomatic, dengue fever, dengue hemorrhagic fever, dengue shock syndrome. However, atypical manifestations in other organs have been increasingly reported and called expanded dengue syndrome. One of the cardiac complications in dengue is myocarditis. An 18-year-old woman complains of high fever since 3 days, epistaxis, chest pain, dyspnea, and vomiting. Laboratory examination obtained thrombocytopenia, hemoconcentration, NS1, IgG-IgM dengue positive, CKMB and Troponin-I increase. Electrocardiogram result ischemic anterior-posterior. Echocardiography results hyperechogenic on myocardial suspicious a myocarditis. The patient was diagnosed with acute myocarditis and dengue hemorrhagic fever. Condition improved after five days of treatment. Cardiac complications in dengue are now increasingly observed with the most common case is myocarditis. The main mechanism of dengue myocarditis is still unknown though both direct viral infection and immune mediated damage have been suggested to be the cause of myocardial damage. The low incidence of dengue myocarditis is because it's asymptomatic and diagnosis is easily missed. Almost all cases of dengue myocarditis are self-limiting and severe myocarditis leading to dilated cardiomyopathy is extremely rare. There have been reported a patient with dengue hemorrhagic fever with manifestation myocarditis. Condition improve with supportive management.

1. Introduction

Dengue Hemorrhagic Fever (DHF) is a disease with the main symptoms of fever, muscle and joint pain that usually worsens after the third day. This disease manifests bleeding, causing shock and can cause death.[1] During January 2015 in East Java Province, the outbreak occurred in 37 districts / cities, with a total of 3,136 cases and 52 deaths(*Case Fatality Rate* = 1.65%).[2]

World Health Organization (WHO) classification of symptomatic dengue infection, continuously evolved, first in 1997 it divided into dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). In 2009 it improved into dengue with or without warning signs and severe dengue.[3] However, in 2011, WHO Regional Office for South East Asia (SEARO) revised and further improving the classification, divided into DF, DHF without shock or with shock (DSS) and expanded dengue syndrome.[4]

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Expanded dengue syndrome is a new entity added to the classification system to incorporate a wide spectrum of unusual manifestations of dengue infection affecting various organ systems that had been reported including gastrointestinal, hepatic, neurological, cardiac, pulmonary and renal systems.[4]

Cardiac complications in patients with dengue illness are not uncommon and might have been under-diagnosed because most of the cases are clinically mild and self-limited. The most common complication is myocarditis. However, the study of myocarditis in dengue is still very lacking. The pathogenesis of myocarditis in dengue is still not clear. Clinical manifestation of myocarditis dengue is varied. Endomyocardial biopsy (EMB) is a deterministic diagnostic method but difficult to popularize. According to the ESC (European Society of Cardiologist) New Criteria, the combination of symptoms, electrocardiography, cardiac enzyme marker and cardiac imaging can use to diagnose the dengue hemorrhagic fever patient with myocarditis. The fatal complication of myocarditis dengue are arrhythmias, heart failure, cardiogenic shock until death.[5]

Here we will discuss a case of a female sufferer experiencing myocarditis triggered by a dengue virus infection. This case was raised because it is a rare case in the community, with a high mortality rate.

2. Findings

Ms. E, female, 18 year's old, unmarried, lives in Surabaya, came to emergency department. Soetomo Teaching Hospital on August 12, 2017, with a chief complaint of fever.

From anamnesis, fever complaint since 3 days prior to admission. High fever is accompanied by complaints of a headache and joint pain. Patients also complain of heartburn, nausea, and vomiting. Vomiting occurs every meal, 2-3x/day with an amount of approximately ½ glass of aqua every time vomiting, containing food, no blood. No complaints a cough, congested. There are spontaneous bleeding complaints in the form of nosebleeds 1-day prior admission to hospital, no complaints of gum bleeding or reddish spots on the skin. Patients also complained of dyspnea, palpitation and left chest pain, such as heavy objects struck and spread to the back left rear and worsen 1 hours prior to admission.

From the previous history of disease did not get the history of dengue fever, diabetes mellitus, hypertension and heart disease. Patients do not smoke and do not consume alcohol. From the family illness history also did not get the same disease with the patient.

From physical examination, the general condition appears weak, sufficient nutritional status (body weight 55 kg, height 165 cm, BMI 20,20 kg/m2), conscious alert, GCS 456. Blood pressure 100/60 mmHg, pulse 100 x/minute, regular, strong pulsation, breathing 24x/minute, axillary temperature 39.0ºC. On examination of the head and neck, there is no anemia in the conjunctiva, jaundice or cyanosis. No enlargement of lymph nodes nor increased jugular venous pressure. On the heart examination S1, S2 normal, no murmur and gallop. Pulmonary examination obtained vesicular breath sounds in all lung fields, neither ronchi nor wheezing. On abdominal examination, no distended, normal bowel sounds, liver and lien are not palpable. On examination of the extremity was not obtained yellow skin, edema, and purpura on the skin and obtained positive *Rumple Leede* examination results.

From laboratory examination when the patient was admitted to hospital (12th of August 2017), Hb 12.0 g/dL, leukocyte 4500/µL, platelet 84,000/µL, HCT 34.6%, SGOT 78U/L, SGPT 59U/L, GDA 104mg/dL, Alb 4.8g/dL, BUN 11.0mg/dL, creatinine serum 0.75mg/L, sodium 142mmol/L, potassium 3.6mmol/L, chloride 107mmol/L, HbsAg (non-reactive), CKMB 87U/L (normal 7.0-25.0U/L) and Troponin I 0.14ng/mL (normal <0.02 ng/mL). The results of the NS-1 examination showed positive results. From the radiological examination of thorax photographs, no abnormalities were found. From the ECG results is the sinus rhythm 96x/minute with normal axis and ischemic anterior-inferior (ST depressed in V1-V4 and II, III, avF).

From the anamnesis, physical examination, laboratory examination and radiological examination, the patient was diagnosed with Dengue Hemorrhagic Fever grade II (3rd day) + Chest Pain Observation. Patients are given high-calorie high-protein diet therapy 2100 kcal/day, infusion of

Ringer Acetate 2000cc/day, injection Omeprazole 40 mg/12 hours, Paracetamol tablet 3 x 500mg. Patients planned Complet Blood Count serial inspection every morning,

The 2nd day of admission, the patient complains of persistent nausea, but the vomiting begins to decrease, the fever begins to decrease, chest pain is reduced. General condition was appeared weak, GCS 456, blood pressure 100/70mmHg, pulse 94x/min, regular, strong pulsation, breathing 18x /minute, more axile temperature 38.4ºC. The result of a laboratory test is Hb 13.2g/dL, leukocyte 4,100/µL, platelet 76,000/µL, HCT 39.6%, Patient diagnosed with Dengue Hemorrhagic II (4th day) + Chest Pain Observation. Previous therapy given to the patient is continued. Patients are planned for IgG, and IgM Dengue, Complet Blood Countserial and are scheduled for an Echo-cardiography examination the next day.

The 3rd day of admission, clinical sufferers begin to improve, reduced fever complaints, nausea reduced, no vomiting, reduced chest pain. General condition was appeared weak, GCS 456, blood pressure 110/70 mmHg, pulse 94 x/minute, regular, strong pulsation, breathing 16x/minute, more axile temperature 37.6ºC. Results of laboratory examination were obtained Hb 13.7g/dL, leukocyte 3800/µL, platelet 56,000/µL, HCT 41.6%, IgG dengue positive, IgM dengue positive. Examination Echocardiography obtained normal results echo with a hyperechogenic picture on microcard suspicious a myocarditis with normal Ejection Fraction 74%. Patients were diagnosed with Dengue Hemorrhagic grade II (5th day) + Myocarditis Dengue. Patients planned Complet Blood Count serial examination. Previous therapy given to the patient is continued.

The 4th day of admission, the patient's condition improved, no complaints of fever, nausea, vomiting, and chest pain. General condition was appeared weak, GCS 456, blood pressure 110/70mmHg, 88x/minute, regular, strong pulsation, breathing 16x/minute, 37.2ºC more axile temperature. The results of laboratory examination obtained result Hb 12.8g/dL, leukocyte 4800/µL, platelet 84,000/µL, HCT 38.4%. Patients diagnosed with dengue hemorrhagic grade II (6th day) + Dengue myocarditis improved. Patients planned Complete Blood Count serial inspection, Serum Electrolytes, SGOT, SGPT, BUN, SC, Alb. Patients given Ringer Answering therapy 1500cc/day, previous therapy continued.

The 5th day of admission, the patient has no complaints. General condition was appeared enough good, GCS 456, blood pressure 110/70mmHg, pulse 80x/minute, regular, strong pulsation, breathing 16x/minute, more axile temperature 36.8ºC. The result of laboratory examination was obtained by Hb 12.3g/dL, 5200/µL leukocyte, 124,000/µL platelet, 36.9% HCT, SGOT 58U/L, SGPT 41U/L, albumin 3.7g/dL, sodium 131mmol/L, potassium 4.6mmol/L, chloride 100mmol/L, BUN 9.0mg/dL, creatinine serum 0.6mg/L. From the Electrocardiography, sinus rhythm 90x/m with the normal axis. Patients were diagnosed with Dengue Hemorrhagic grade II (7th day) + Dengue myocarditis improved. Patients discharged and given medicine home that is Paracetamol tablet 3 x 500mg. Patients were asked to return control to the policlinic 3 days after leaving the hospital.

3. Discussion

Dengue virus infection is a disease that found in children and adults with the main symptoms of fever, muscle and joint pain that usually worsens after the first three days. This disease is an acute febrile illness accompanied by bleeding manifestations with potential shocking and can lead to death in children <15 years, but not likely to attack adults.[1] Signs of this disease are sudden high fever 2 to 7 days with no obvious cause, weakness, lethargy, anxiety, heartburn, accompanied by signs of bleeding in the skin (petechiae), bruising (ecchymosis) or rash (purpura). Sometimes there are other spontaneous bleeding manifestations such as nosebleeds, bleeding gums to dysentery. Severe symptoms can lead to decreased awareness or shock.[2]

Laboratory results in dengue fever are found in thrombocytopenia (<100,000/µL), While the increase of hematocrit >20% of the baseline on dengue hemorrhagic fever is a sign of plasma. Serological tests results in dengue are influenced by the type of dengue infection, whether it is the primary/first, or secondary/reinfection. IgM antibodies are detectable by days 3–5 after the onset of illness, rise quickly in two weeks and decline to undetectable levels after 2–3 months, because this late

appearance, the first five days of clinical illness are usually negative of IgM. In dengue secondary infection, the rise of IgM are not as high as primary infection, and sometimes absent / undetectable completely.[6]

IgG antibodies in primary infection, evolves relatively slow, with low titres 8-10 days after fever onset, increase subsequently and remain for many years, whereas in secondary infection it evolves rapidly, with high titres soon after fever onset and persist to a lifelong period. Hence, a ratio of IgM/IgG is commonly used to differentiate between primary and secondary dengue infections. Ratio of IgM/IgG titre less than 1.2 is considered a secondary dengue infection. But to be noted, titre ratio only could be validly use as a data if the IgG/IgM serological test is using pure quantitative means, not by qualitative or semi-quantitative.[7]

NS1 antigen detection is widely used and cost-effective, NS1 could be detected from day 1-8 of fever onset, unaffected by a primary or secondary dengue infection. In conclusion, by combining the serological (IgG and IgM) and NS1 tests, clinicians could rapidly assess the dengue diagnosis with its types (primary or secondary infection) and applies the best treatment.[8]

In 2011, based on many reports of cases with dengue-related unusual manifestations and organ complications, WHO-SEARO further improved and revised 2009 WHO guidelines by adding a new entity, that is expanded dengue syndrome (unusual/atypical manifestation of dengue), these include neurological, hepatic, renal, cardiac and other isolated organ involvement, that could be explained as complications of severe, profound shock or associated with underlying host conditions/diseases or coinfections.[4]

Myocarditis is an uncommon complication of dengue infection. Data about prevalence and characterization of myocarditis in dengue still lacking. In China from August to October 2014, from 1782 diagnosed dengue patients, there are about 201 cases patient were diagnosed with myocarditis and the prevalence of myocarditis in hospitalized dengue was 11.28%. Clinical presentation in myocarditis is varied. The sign and symptoms are chest pain, dyspnea at rest or exercise, palpitation, syncope, cardiac shock and sudden cardiac death.[5]

According to the diagnostic criteria from European Society of Cardiology 2013, dengue patients were subjected to electrocardiogram (ECG), echocardiography and cardiac enzyme test (CET) to make the diagnosis of myocarditis. Myocarditis was diagnosed if 1 or more clinical presentation and 1 or more auxiliary diagnosis method; 2 or more auxiliary diagnosis method should be met if the patient is asymptomatic. 12 leads ECG was considered abnormal with any of following, such as sinus arrest, AV-block, bundle branch block, atrial fibrillation, ST wave change (ST elevation, ST depression, T inversion), abnormal Q waves. Based on echocardiography usually found functional and structural abnormalities such as ventricular dilatation, increased wall thickness, diastolic function abnormality, pericardial effusion, left ventricular ejection fraction less than 55%, valvular regurgitation or vegetation. The cardiac enzyme was considered to be elevated and abnormal if CK-MB more than 25U/L and/or cTnI more than 0.02ng/m and/or NT-proBNP more than 450ng/L (age <50 years), 900ng/L (age 50–75 years), and 1800ng/L (age >75 years). The gold standard to diagnose myocarditis is EMB (Endomyocardial Biopsy), but it is not performed regularly.[5]

The pathogenesis myocarditis in dengue patient is still unclear. The mechanism of myocardial damage in dengue could be the release of inflammatory mediators and the direct action of the virus on cardiomyocytes, as seen in acute myocarditis caused by other viruses. Using immunofluorescence confocal microscopy in heart tissue, reported that myotubes were infected by dengue virus in one child with fatal DHF, although the myocardium sections appeared morphologically normal, with minimal cellular, infiltrates. Moreover, clinical characterization of myocarditis, in this case, was not complete.[9]

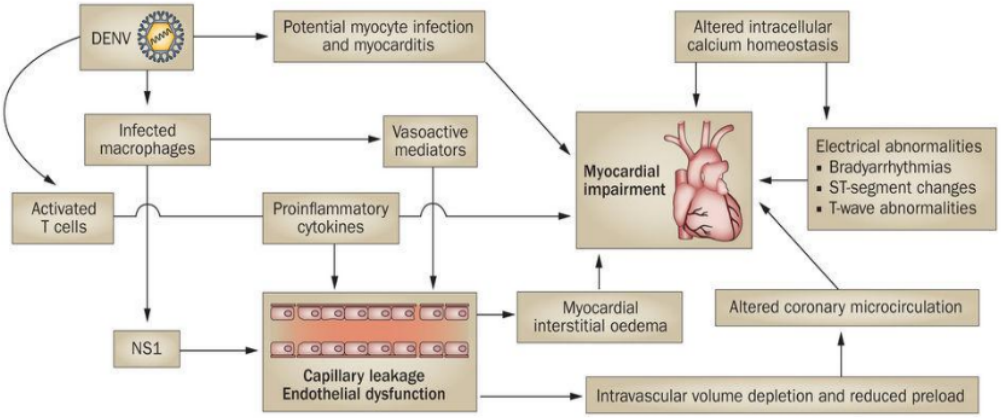

Figure 1. Pathogenesis myocarditis in dengue infection virus [10].

The gold standard of myocarditis in dengue patient is Endomyocardial Biopsy, the fulminant course of clinical dengue myocarditis was associated with intense interstitial edema, several multifocal areas of necrosis, and diffuse inflammatory infiltration. Interestingly, the myocytolitic necrotic areas were replete with virus particles; therefore providing detailed histological evidence of a possible dengue direct action in cardiomyocytes. Further clinical and experimental studies are necessary to better understand the molecular mechanism of dengue virus-induced lesions on the myocardium.[11]

Patients with dengue hemorrhagic fever should be treated according to the existing protocol based on the degree of dengue itself. For DHF grade I-II without any signs of shock the patient was treated with crystalloid maintenance fluid with the formula 1500 + (20x (BB-20)) cc/24 hours. While the other therapy is symptomatic therapy.[12]

4. Conclusion

It has been reported a female patient, 18 years old with dengue hemorrhagic fever grade II + myocarditis dengue. A patient comes with fever for 3 days, headache, joint pain, heartburn, nausea, vomiting epistaxis, dyspnea, palpitation, left chest pain like heavy objects and spread to the left back. From the previous history of disease did not get the history of diabetes mellitus, hypertension, and heart disease.From physical examination positive *Rumple Leede* examination results. In laboratory tests, the results of thrombocytopenia, increased HCT >20%, NS-1 positive, IgG and IgM dengue positive, higher titter of CKMB and Troponin-I. From the ECG results obtained the results of sinus rhythm, with ischemic anterior-inferior whereas echocardiography examination obtained with a hyperechogenic picture on my card suspicious of myocarditis with Ejection Fraction 74%. The patient recovers with adequate intravenous fluid rehydration and symptomatic therapy. In the course of admission, patient experienced a better condition The patient finally discharged on the 5th day of admission, with general condition improved, platelet count >100,000/mm3, and the improvement of cardiac condition based on electrocardiography evaluation.

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