

Acquired Immunodeficiency Syndrome Patient with A Dengue Hemorrhagic Fever Co-Infection

Dedy Hadi Prawono¹, Bramantono², Usman Hadi³

¹Senior Resident, ²Lecturer and Consultant, Division of Tropical and Infection, ³Professor, Division of Tropical and Infection, Departement of Internal Medicine Dr. Soetomo Hospital – Faculty of Medicine Airlangga University, Surabaya Indonesia

Abstract

Infection of human immunodeficiency virus (HIV) is the most infectious disease in tropic disease infection and co-infection of HIV is very large, one of which is DHF. Research on DENV-HIV is still limited. A patient 29-year-old, referred to Dr. Soetomo Hospital with chief complain nausea from yesterday. Accompanied epigastric pain, stomach feel full and decreased of appetite. Laboratory test finding Hb 18,6 g/dL, leukosit 2910/mm³, trombosit 9000/mm³, HCT 51,5 %, Anti dengue IgG 29,9 and IgM 10,5 on 2nd day admission, Anti dengue IgG 14,3 and IgM 13,1 on two weeks from out of admission. The most common symptom in HIV patients with co-infection DHF is fever and loss of appetite. Patients with DENV-HIV have plasma leakage. Patient with DENV-HIV found an increase in eosinophil and pulse but found a lower increase in serum hematocrit compared with DENV patients, but lower hematocrit levels in this patients can be caused in patients using zidovudine, which is associated with anemia caused by zidovudin side effects.

Keywords: HIV, AIDS, DHF, DENV

Introduction

Dengue fever is a viral infection that mostly occurs in tropical areas and its prevalence is quite high in Indonesia. This disease is transmitted by mosquitoes (*Aedes aegypti*). Patients with dengue fever come to health facilities with complaints of fever with or without bleeding.

The diagnosis of dengue fever is based on the patient's clinical history and hematological profile. Clinical manifestations of dengue fever are fever, muscle aches, and joint pain accompanied by leukopenia, rash, lymphadenopathy, thrombocytopenia, and hemorrhagic diathesis.^{3,14}

Dengue fever and HIV are the most common infectious diseases in Asia and have an impact on increasing the health burden in society. Dengue fever is caused by four strains of the virus (DENV 1-4). This virus is a group of RNA viruses that belong to the Flaviviridae family. Research on DENV-HIV and DENV infection is still very limited. Case reports of these infections are reported only four to six cases and these cases are common in Asia.^{3,8} Dengue fever patients can experience severe complications such as dengue shock syndrome (DSS), who have very low CD4 levels and opportunistic infections. This is due to the low immune system in patients with HIV.¹²

Case Description

A man, Mr. AR, 30 years old, who lives in Surabaya works as a private employee, he was hospitalized in Dr. Soetomo General Hospital and diagnosed with AIDS with co infection Dengue Hemorrhagic Fever (DHF).

Chief complain Nausea. Nausea has been felt from yesterday. Nausea constantly felt especially when eating. There is no vomiting, but the patient got indigestion

Corresponding author:

Bramantono,
Lecturer and Consultant, Division of Tropical and Infection, Departement of Internal Medicine Dr. Soetomo Hospital – Faculty of Medicine Airlangga University, Jl. Mayjen Prof. Dr. Moestopo 47, Surabaya, East Java, Indonesia, Phone: +6231-5020251. Email: ibambramantono@gmail.com

and he feels full. Then, he doesn't have any appetite. There is a history of fever. He got a fever three days ago. Initially, the fever was not high, then the fever becomes high until the patient shivering. The patient felt fever from the first day to the third day. On the fourth day, the fever was gone. There was no history of bleeding gums, no bruising, and no reddish spots appeared.

Past Medical History The patient had HIV two years ago. The patient has been taking Alluvia drugs regularly. The patient took alluvia because he was allergic to other anti-viral drugs. When he took other anti-viral drugs than Alluvia, suddenly a red rash appeared in his body. The patient is a homosexual.

Physical Examination General condition was sufficient; GCS 456; blood pressure was 110/75 mmHg; pulse rate was 103 beats/minute with a regular rhythm, good tone, normal amplitude; the respiratory rate was 22 times/minute; the axillary temperature was 37.0°C. Physical examination within normal limit. The Rumpel-Leed test was negative. The maculopapular rash was present on right and left upper extremities. Neurological examination within normal limit

Laboratory examination : HCV RNA was not detected, Hb 18.6 g/dL, Leukocytes 2910/mm³, Platelets 9000/mm³, HCT 51.5%, Lymph 17.3%, SGOT 191 U/L, SGPT 106 U/L. IgG and IgM tests (March 22, 2019): IgG Anti dengue 29.9 (positive > 11 NTU), IgM Anti dengue 10.5 (positive > 11 NTU). IgG and IgM tests (April 05, 2019): IgG Anti dengue 14.3 (positive > 11 NTU), IgM Anti dengue 13.1 (positive > 11 NTU).

Based on the history, physical examination, and supporting examination, the patient was diagnosed with HIV on ARV with dengue hemorrhagic fever (DHF) co-infection daily serial complete blood count, CD4 check, and viral load. Initial Therapy: a high-calorie and high-protein diet 2100 kcal/day, NaCl infusion of 0.9% 18 drips per minute, if there is bleeding. Transfusion of 10 bags of platelets concentrated per day up to more than 20,000 platelets, ranitidine injection 2 times a day intravenously, metoclopramide injection 3 times a day intravenously, Aluvia 1 time a day per oral, observe vital sign and the signs of bleeding. 4th day of treatment: no complaints, with GCS 456. Complete blood count showed Hb was 14.1 g/dL, leukocytes was 4820/mm³, platelets 60,000/mm³, HCT 41.6%, MCV 92.3%, MCH

35.2%, MCHC 30.0%, Lymph 56.3%. Therapy: hospital discharge and take 1 tablet Aluvia a day per oral.

Discussion

Thrombocytopenia in DHF was first reported in 1982, based on the literature the prevalence is less than 40%. HIV virus attaches to megakaryocyte and platelets so that the megakaryocyte and platelets are damaged. Thrombocytopenia in HIV is caused by several causes including HIV infection causes megakaryocyte apoptosis, then dysmegakaryosis occurs. It's causing platelets to not form and excessive platelet breakdown due to HIV infection. The causes of thrombocytopenia are divided into 3 causes such as decreased production vitamin B12 deficiency, dysmegakaryoposis (HIV infection, drugs, pro-inflammatory or malignant cytokines), bone marrow infection, malignancies that infiltrate bone, congenital disorders, drugs], peripheral consumption (ITP, diffuse intravascular coagulopathy, thrombotic purpura thrombocytopenia), and peripheral sequestration / hypersplenism (infection, hemophagocytosis, cirrhosis).¹³

Dengue fever diagnosis is based on the clinical history and hematological examination. Clinical history with a history of fever with or without bleeding. The hematological examination is characterized by hemoconcentration with marked increases in hemoglobin levels and an increase in hematocrit level. On the other, there was also a decrease in platelet levels.¹⁴

HIV-infected patients with other co-infections can have a bad impact. The most common symptom in HIV patients with DHF co-infection is fever accompanied by loss of appetite. Other symptoms that can be found in this case are headache, fever, diarrhea, rash, and vomiting. Most patients come to the hospital complaining of fever. Patients usually come to the hospital on the day two to six after the fever first appeared. Decreased appetite appears until day 7.⁴ There are studies that report no significant difference in symptoms and clinical signs between patients with DENV-HIV and DENV unless there is an increase in pulse rate in patients with DENV-HIV. During hospitalization, DENV-HIV experienced fewer bleeding manifestations than DENV. In contrast, patients with DENV with co-infection with chikungunya were more likely to experience joint pain, rash, and diarrhea, but less likely to experience nausea, vomiting,

and myalgia.⁸

In primary dengue infection, the patient has a mild to severe fever and it is often difficult to distinguish it from other viral infections. A maculopapular rash can appear during fever or during the critical phase. Fluid accumulation, hepatomegaly, and severe organ involvement can be associated in patients with DENV-HIV. However, it was reported to be statistically insignificant. Close monitoring of the vital organ involvement is needed. Most of the patients with DENV-HIV develop plasma leakage. Only a few DENV-HIV patients meet the WHO criteria for diagnosis with DHF. This is due to the lack of bleeding manifestations. Most of the patients with DENV-HIV are classified as severe dengue fever based on the 2009 WHO classification of dengue fever. This is because the patient has met the requirements for heavy plasma leakage, heavy bleeding, or severe organ involvement.⁸ During DENV infection, there isn't fever in the second to the seventh day and at this duration manifested plasma leakage (pleural effusion or ascites) or hemoconcentration. This condition appears for 48 hours and will get better on its own. In severe conditions, plasma leakage can cause hemodynamic disturbances due to bleeding and decreased intravascular volume.^{6, 11}

Patients with DENV-HIV had increased eosinophil and pulse rates, but had a lower increase in serum hematocrit compared with DENV-HIV. Lower hematocrit levels in DENV-HIV may be associated with anemia due to zidovudine side effects.⁹ Eosinophilia is common in patients with HIV and is associated with parasitic infections, pruritic conditions, drug allergy and Sarcoma Kaposi. However, a higher number of eosinophils did not significantly correlate with immunity, changing HIV viral load, or thrombocytopenia and granulocytopenia in dengue hemorrhagic fever.⁹ Laboratory examination of HIV patients with DHF co-infection showed thrombocytopenia (less than 100,000/l) and leukopenia (less than 4000/l). Thrombocytopenia can occur from day three to day six of a fever.

In 2009, WHO issued the recommendations to help clinicians diagnose DHF, namely probable dengue with or without a warning sign and severe dengue. The criteria for probable dengue are obtained in patients who live or have a history of traveling to dengue endemic

areas accompanied by fever and are followed by two criteria (nausea, vomiting, rash, pain, positive tourniquet test, leukopenia and / or warning sign). The warning sign shows abdominal pain or abdominal stiffness, repeated vomiting, fluid excess, mucosal bleeding, weakness, an enlarged liver more than 2 cm, and laboratory tests show an increase in hematocrit and a decrease in platelets. In severe dengue, it is said to be severe plasma leakage if there is shock (DSS) and fluid accumulation accompanied by hemodynamic disturbances. Severe bleeding is obtained when clinical bleeding has been evaluated by the clinician. Severe organ involvement is obtained when there is impaired liver function (SGOT and SGPT more than 1000), central nervous system disorders (decreased consciousness), heart and other organ disorders. In dengue infection, there is a "sign of alarm" which is an early indicator of shock, these indicators are abdominal pain, vomiting, drowsiness, and a sudden drop in body temperature that causes hypothermia. This sign indicates that extravasation of body fluids is starting to occur, which can lead to shock.⁵

Based on the severity of dengue infection, in 2011 the WHO issued a recommendation regarding the severity of dengue infection. There are four degrees of severity of dengue infection, such as DHF grade I (criteria for dengue fever plus a positive tourniquet test and evidence of plasma leakage, thrombocytopenia $<100,000/\text{mm}^3$, and an increase in hematocrit $> 20\%$), DHF grade II (there is evidence of spontaneous bleeding in the skin or other organs (black stool, nosebleeds, and bleeding gums) and abdominal pain, thrombocytopenia $<100,000 / \text{mm}^3$, and increased hematocrit $> 20\%$), DHF grade III / DSS / Dengue shock syndrome [circulatory disorders (rapid pulse, systolic blood pressure with narrowed diastole $<20\text{mmHg}$, hypotension, cold, weakness, thrombocytopenia $<100.000 / \text{mm}^3$, and increased hematocrit $> 20\%$], and DHF grade IV / DSS / Dengue shock syndrome (shock patients who cannot feel the pulse or blood pressure, thrombocytopenia $<100.000 / \text{mm}^3$, and an increase in hematocrit $> 20\%$).¹²

Dengue virus isolation and culture tests performed during the fever phase are the gold standard of diagnosis. There are tests that can help make a diagnosis and find out the viral genome, namely PCR. The indirect diagnosis of dengue fever uses serologic methods to detect DENV IgM and IgG. These IgG and IgM tests are called

ELISA tests and they have a very high sensitivity for the diagnosis of dengue. ELISA test is useful for seeing acute infection (IgM) and in the recovery phase or the chronic phase we can see it in (IgG). This examination is best done on the second to the fourth day after the complaint appears. This IgM test will remain positive or remain high until the eighth day of symptoms begin to appear. In patients with anti-retroviral therapy, it is very important to make a diagnosis of dengue infection, including by doing ELISA tests (IgG and IgM) on the first day of illness.²

In the last decade, the emergence of anti-viral combination therapy can reduce the mortality rate and opportunistic infections of HIV patients. Long-term complications in patients with HIV can be associated with the suppression of immune function. This causes a non-opportunistic infection, such as dengue fever. Dengue infection causes fatal consequences such as hemodynamic disturbances. The mechanisms underlying the severity of dengue fever are not fully understood, but excessive immune activation in the presence of increased production of proinflammatory cytokines and chemokines is thought to support the pathology and severity of DENV infection. Interestingly, HIV-infected patients with DENV co-infection who were given ARV (anti-retroviral) therapy had a very low frequency of DENV severity.

The low severity of DENV infection with HIV treated with ARV can be proven in a study. The results showed that HIV patients coinfecting with dengue had better clinical presentation outcomes. These clinical presentations included: postural hypotension of HIV patients was lower than that of non-HIV patients (OR [95% CI] = 0.225 [0.063–0.779], $p = 0.0245$). In the others, HIV patients with dengue co-infection compared to non-HIV patients with dengue co-infection showed HIV patients with dengue co-infection were more likely to avoid liver function damage (hepatomegaly or steatosis as evidenced by ultrasonography, elevated liver enzymes > 200 U / L). (OR [95% CI]= 0.1396 [0.0171-1.1421], $p=0.0491$), spontaneous bleeding (gastrointestinal, vaginal bleeding and hematuria) (OR [95% CI] = 0.1429 [0.0175-1.1681], $p = 0.0501$), Hematocrit levels and plasma glutamic-pyruvic transaminase (TGP) levels were significantly lower in patients with HIV than dengue infection without HIV

co-infection.⁷

Management of HIV patients with DHF co-infection must be carried out with care. This is because patients are very prone to developing DSS conditions. Patients with dengue fever infection have a poor outcome if the patient has HIV with a low CD4 cell count (<250) and has an opportunistic infection. Management of HIV patients with DHF co-infection, especially management of adequate fluids, should be adjusted to the DHF degree.¹²

Conclusion

DENV-HIV infection presents with atypical symptoms. If the CD4 count is low (<250) and there is an opportunistic infection it will be very easy to develop dengue shock syndrome. Diagnosis of DENV-HIV is based on clinical manifestations, laboratory examinations and immunological examinations. Based on clinical manifestations, a history of fever, signs of bleeding, abdominal pain, nausea and vomiting were obtained. Laboratory examination showed a hemoconcentration which was marked by an increase in hematocrit levels $> 20\%$ and a decrease in platelets. Immunological examinations are carried out using anti-dengue IgG and IgM tests and immunological examinations can be performed on day 5 of fever.

Conflict of Interest: The authors report no conflict of interest.

Funding: None.

Ethical Clearance: Not required for a case report.

Acknowledgment: The authors would like to thank to Faculty of Medicine Airlangga University, Surabaya, Indonesia.

References

1. Anema A, Ritmeijer K. *Treating HIV/AIDS and leishmaniasis coinfection in Ethiopia*. CMAJ. 2005. **172** : 1434-1435.
2. Cogan JE. *Dengue and Severe Dengue*. 2009, WHO. <http://www.who.int/news-room/fact-sheets/detail/dengueand-severe-dengue>.
3. Coker RJ, Hunter BM, Rudge JW, Liverani M, Hanvoravongchai P. *Emerging infectious diseases in southeast Asia: regional challenges to control*.

- Lancet. 2011 **377**: 599–609.
4. Cutter JL, Lim WY, Ang LW, Tun Y, James L, Chew SK. *HIV in Singapore – past, present and future*. AIDS Educ Prev. 2004. **16** (3 suppl A): 110-118.
 5. *Dengue*. 2009. Geneva: TDR.
 6. Erni JN. *Early Detection of Plasma Leakage in Dengue Hemorrhagic Fever*. Acta Med Indones-Indones J Intern Med. 2018 Vol **50(3)**, pp: 183-184.
 7. Hottz, E., Quirino-Teixeira, A., Valls-de-Souza, R., Zimmerman, G., Bozza, F. and Bozza, P. *Platelet function in HIV plus dengue coinfection associates with reduced inflammation and milder dengue illness*. Scientific Reports. 2019. **9(1)**.
 8. Pang J, Thein T, Lye D and Leo Y. *Differential Clinical Outcome of Dengue Infection Among Patients With and Without HIV Infection: A Matched Case–Control Study*. The American Journal of Tropical Medicine and Hygiene. 2015. **92(6)**, pp.1156-1162.
 9. Pang J, Thein TL, Leo YS, Lye DC. *Early clinical and laboratory risk factors of intensive care unit requirement during 2004–2008 dengue epidemics in Singapore: a matched case–control study*. BMC Infect Dis. 2014. **14**:649.
 10. Phe T, Thai S, Veng C, Sok S, Lynen L, van Griensven J. *Risk factors of treatment-limiting anemia after substitution of zidovudine for stavudine in HIV-infected adult patients on antiretroviral treatment*. PLoS ONE. 2014. **8**:e60206.
 11. Rajapakse S. *Dengue shock*. J Emerg Trauma Shock. 2011. **4(1)** : 120-127.
 12. Ustafa, M. *Dengue Fever: Clinical Spectrum, And Management*. IOSR Journal of Dental and Medical Sciences. 2017. **16(02)**, pp.53-59.
 13. Volberding PA, Baker KR, Levine AM. *Human immunodeficiency virus hematology*. American Society of Haematology Annual Meeting. 2003. 294-312
 14. Wiwanitkit V. *Dengue fever : diagnosis and treatment*. Expert rev Anti Infect. 2010. **8(7)** : 841-845
 15. *World Health Organization. Dengue Haemorrhagic Fever. Diagnosis, treatment, prevention and control*. Geneva. 1997. P:1-84.