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Does dengue infection lead to persistent thrombocytopenia in hiv patient? A report of two cases

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ABSTRACT

Dengue infection commonly results in fatal outcome. We compare two different dengue infection outcomes in HIV infected children and desribe other factors related to outcome.

First case: Dengue infection in 11-years-old HIV patient who has been with 1st line HAART for 3 years. On the 7th day, had persistent fever, low platelets, and neutropenia. To find out possible cause of this condition, we compared a similar case.

Second case: Dengue Shock Syndrome in 6-years-old boy with HIV infection, who has been with HAART for 2 years. The clinical and laboratory resolved in 7 days.

We investigated the old medical record of first patient and noticed prolonged pancytopenia with neutropenia. Macrocytic anemia began gradually since nine months after commencing ARV, hence working diagnosis was drug side effect either to zidovudine or cotrimoxazole. Cotrimoxazole was deceased and zidovudine was substituted with tenofovir. After one month follow up, the neutrophil, platelet, and hemogobin increased.

Keywords: *HIV, Dengue, thrombocytopenia, medical record*

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ABSTRAK

Infeksi dengue kerap menyebabkan luaran yang fatal. disini penulis membandingkan dua luaran infeksi dengue pada anak dengan HIV dan mengidentifikasi faktor-faktor yang berhubungan.

Kasus pertama : laki-laki usia 11 tahun dengan infeksi dengue dan HIV yang telah menjalani pengobatan ARV selama 3 tahun. Pada hari ke 7, pasien mengalami demam dan trombositopenia persisten serta neutropenia. Untuk mengetahui kemungkinan penyebab kondisi tersebut, dibandingkan dengan kasus kedua. Laki-laki usia 6 tahun dengan HIV dan *dengue shock syndrome* yang telah menjalani pengobatan ARV selama 2 tahun. Pada hari ke 7, klinis dan laboratorium pasien membaik.

Dilakukan pemeriksaan rekam medis pasien pertama, didapatkan pansitopenia dan neutropenia dalam jangka waktu yang lama. Terjadi anemia makrositer sejak 9 bulan dimulainya ARV. Pasien didiagnosis mengalami efek samping obat zidofudin atau kotrimoksasol. Dilakukan penghentian kotrimoksasol dan zidovudin diganti dengan tenofofir. Setelah 1 bulan, didapatkan netrofil, trombositopenia dan hemoglobin membaik.

Kata kunci *: HIV, Dengue, trombositopenia, rekam medis*

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INTRODUCTION

In tropical countries, numerous infectious diseases coexist, and therefore the possibilities of coinfections are common. In this context, infections with human immunodeficiency virus (HIV) and Dengue virus (DENV) are serious public health problems and represent major public health problems in several countries.[1] Indonesia is one of endemic of Dengue and at the same time prevalent for HIV infection. According to data from the Ministry of Health in 2012, the number of dengue fever case in Indonesia reached 90.245 cases with morbidity rate 0.88%.[2] Dengue infection in Bali reached 7.077 cases in 2013 from 2.649 cases in the previous year. Thus, the dengue incidence rate in 2013 amounted to 174.5 per 100.000 people with case fatality rate (CFR) 0.11%.[3]

In the other hand the cumulative number of children under 15 with HIV in Indonesia from 1987 to 2014 reported as many as 1,647 people with

1,206 reported under the age of five. Frequently the natural history of HIV infection includes a long period of latency followed by development of opportunistic complications.[4]

These situation make people to be in an encounter for HIV and the same time being at risk for dengue infection. As HIV patient has impaired immune system there is a question on how the immune system of HIV patient respond to Dengue infection. However, there is limited literature on the clinical presentations and outcomes of dengue infection in HIV infected person, and in especially children.[5]

We report two cases of HIV patient co-infected with Dengue virus with regard to clinical manifestation and outcome as well as comparison factors associated to outcome.

ILLUSTRATION CASE

First case: 11 years old boy came to emergency room on the forth day of fever. The fever rise with highest temperature reach 39°C, relieve with antipiretic then rise again. The patient also complain headache, retroorbital pain and joint pain. There was no other complaint such as cough, cold, nausea, vomit, cold extremities, and there was no active bleeding such as epistaxis and gum bleeding. Patient diagnosed with HIV infection at age seven years and starting Anti- Retroviral Therapy (ART) consist of zidovudine, lamivudine, and nevirapine since four years ago.

Physical examination revealed heart rate 100 beats/minute, regular; respiratory rate: 28 times/minute, regular; temperature: 38.3°C; blood pressure: 110/70 mmHg; body weight: 31 kg, height: 141 cm, ideal body weight 34 kg (well nourish). The capillary refill time was less than 2 second, the extremities were warm. Laboratory data at admission date: leukocyte: 0.94K/uL (neutrophil 0.25 K/µL (26.38%), lymphocytes0.51 K/µL (54.26%), hemoglobin: 8.16 g/dL, hematocrit: 22.73%, MCV: 100.4fl; MCH:36.05pg; MCHC: 35.89g/dL; thrombocyte:84.23 x10^3/µL. The IgM anti Dengue at six days fever was positive, IgG anti Dengue was negative. The patient was diagnosed dengue fever with HIV infection, given fluid therapy, paracetamol, continued ARV, and we did routine CBC check up every day. During the monitoring for dengue hospitalization, laboratory result were as we seen on table 1.

Table 1 Laboratory result of first case

	Variable				
Date/ time	WBC (K/µL)	Neu #(K/µL)	HB (g/dl)	HCT (%)	PLT (K/µL)
12/10/16 Fever day 4	0.94	0,25	8.16	22.7	84.23
12/11/16 Fever day 5	0.48	0,16	7.72	21.74	83.33
12/12/16 Fever day 6	0.55	0,16	7.31	20.83	68.43
12/13/16 Fever day 7	0.29	0,12	7.05	19.56	51.41

Table 2 Laboratory result of second case

	Variables				
Date/ time	WBC (K/µL)	Neu # (K/µL)	HB (g/dl)	HCT (%)	PLT (K/µL)
1/3/14, at 6.30 am	1.60	1.0	11.3	33.3	159
3/3/14, at 06.31 am	1.60	1.0	14.1	43.9	98
3/3/14, at 12.29 am	0.79	0.24	17.6	51.8	21
3/3/14, at 21.15 pm	1.81	0.18	135	39	25.9
4/3/14, at 03.19 am	2.52	0.3	11.5	33.3	17.4
4/3/14, at 01.12 pm	4.19	0.89	11.8	34.6	21
5/3/14, at 09.05 am	3.67	0.77	11.9	35	50

After seven days the fever still persist, there also was pancytopenia which consist of mild anemia, leukopenia, severe neutropenia, and thrombocytopenia. The CD4 level was 1, procalcitonin level was 1.53ng/mL, the urinalisis was normal. We suspected due to either expanded dengue syndrome, HIV treatment failure, ART side effect, and concomitant non-specific infection. The patient then consulted to hematology and oncology section, diagnosed with febril neutropenia and given antibiotic ceftazidim and amikacin.

On the 13 days of treatment the fever was resolved, but pancytopenia persisted. The viral load result was undetectable, procalcitonin level decrease into 0.25 ng/mL. Because there was improvement on clinical condition, we decided to stop antibiotics and planned to recheck the CBC and CD4 level which remain pancytopenia but the CD4 was increase to 80.

Noticing these laboratory results, we conclude there were no evidences for concomitant non-specific infection, treatment failure, and expanded dengue syndrome. As consequence, the possibility left for diagnose is medication side effect. We trace back all medical record since four years and found the patient was hospitalized twice in Sanglah Hospital. First hospitalization was on August 2015, he was diagnosed with febrile neutropenia,

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Table 3 Comparison between two cases

Patient	First case	Second case
Age	11 yo	6 yo
Gender	Male	Male
Laboratory DENV diagnosis	IgM positive IgG negative	IgM positive IgG positive
Dengue infection sign		
Fever	Yes	Yes
Hemorragic manifestation	No	No
Shock	No	Yes
Plasma leakage	No	Yes
Leukopenia	Yes	Yes
Thrombocytopenia	Yes	Yes
Months post-HIV diagnosis at first dengue presentation	48	49
HAART upon dengue diagnosis	Zidovudine, lamividine, nevirapine	Zidovudine, lamividine, nevirapine
Comorbidities	No	No
CD4		
Before dengue infection	205	287
On or after dengue infection	1 à 80	Not checked

pancytopenia, suspected sepsis, HIV infection and well nourish. Patient was treated for one month and got antibiotics. The physical condition was improved but white blood cell count remains low. Second hospitalization was on May 2016 with diagnosis of febrile neutropenia and HIV infection. Patient was treated with antibiotics for 19 days. Patient discharged with good condition but pancytopenia not improve. This history of chronic and recurent pancytopenia supported diagnosis for medication side effect with regard to zidovudine or cotrimoxazole. There is no diagnostic tool to determine these drug cause of pancytopenia. Hence, we did risk benefit analysis, decided to stop cotrimoxazole and substitute zidovudine into tenovovir. At the time he discharged from hospital, the lab results were leukocyte: 0.58 K/uL (neutrophil 0.17 K/µL (29.35%), hemoglobin: 10.34 g/dL, hematocrite: 29.36%, thrombocyte: 42.22 K/µL, procalcitonin 0.22 ng/mL.

During one month follow up on polyclinic, the CBC revealed better result, leukocyte: 2.27 K/uL (neutrophil 1.22 K/µL (53%), hemoglobin: 8.91 g/dL, hematocrite: 28%, thrombocyte: 196.6 K/µL.

Second case: A six years old boy referred to Sanglah Hospital with a chief complaint of fever since 5 days before admission. The fever with a sudden onset, continued for 5 days with remitten pattern, the highest temperature was not measured, and there was no nose/ gum bleeding or black stool. Parents also complained that their child had vomiting since 3 days before admission, with a frequency of 2-3 times per day, every after eating or drinking, volume of approximately ¼ glass of mineral water, contain food and drink. Patient also complained of right upper abdominal pain since three days before admission to the hospital. Pain is like being stabbed and did not spread. When arrived at Sanglah Hospital, the parents also complained of the cold hands-feet's. Eating and drinking only a little. The last urinary was 6 hours prior admission and the color was yellow.

On physical examination, patient was compos mentis, blood pressure was 90/60 mmHg, pulse 120 beat per minute, regular but weak pulse quality, respiratory rate 24 rate per minute, axillary temperature was 36.5°C and 96% oxygen saturation in room air. Nutritional status according to Water low is a well- nourished (95%). The extremities were cold, with positive rumple leede test. Capillary refill time was 3 seconds. The complete blood count revealed leucocyte 1.6 K/µL, hemoglobin 14.1 g/dl, hematocrit 43.9 % and platelet 98 K/µL. The IgM and IgG anti dengue serology were positive. The serial blood count were showed increase hematocrit until 20% and platelet was decrease until 17.4 K/µL. On lateral decubitus position X-ray showed air fluid level from anterior to superior, conclusion right pleural effusion.

Based on history taking, physical examination and laboratory results, patient was diagnosed with Dengue Shock Syndrome, HIV infection with well- nourished and given fluid therapy, the ARV was continued. At the sixth day of fever, he gained a better condition, and the platelet slowly increased. During the monitoring for dengue hospitalization, laboratory result was as follow.

From the previous disease history, he never suffered from a similar illness. HIV infection was dignosed at the age of 2 years (19-2-2010) based on PCR results of 541.000 HIV - 1 RNA copies/ml and absolute CD4 of 1379 cells/ml or 30 %. The absolute CD4 was 962 cells/ml or 23 % on 06-10-2011 and was on Duviral and Nevirapine treatment since October 2012.

DISCUSSION

Several studies and case reports about HIV and dengue, suggest different results about outcomes. Some said that HIV-dengue coinfected patient will have milder clinical symptom but some also state they will had more severe clinical symptom than Dengue monoinfected patient. All of these study are from adult patient, lack of study report about case in children.

Watt and others reported that HIV and dengue interaction was associated with a reduced HIV viral load.[7] In regard to this finding, there are some reports on HIV and DENV interaction in humans. The first study refers to study by Mendes et al, describes an HIV patient with dengue hemorrhagic fever without arterial hypotension, serious hemorrhage, or other life-threatening complications and CD4 cell count did not show significant alterations in the two periods evaluated.[8] The second report is a case series by Siong et al, that includes five HIV patients infected with dengue in Singapore who showed mild clinical symptom and recovery was uneventful.[7] The third case report from Cuba, two men with HIV coinfected with Dengue showed no hemorrhagic manifestations, abdominal pain, or shock signs. There were also no accelerated progression of HIV and the CD4+ cells remained within normal levels after Dengue infection.[6] There is a match case control study by Pang et al, observed differential clinical outcome of Dengue among HIV and non HIV patient. The conclusion is Dengue-HIV patient more likely to have more severe dengue, because they had higher pulse rate, eosinophils proportion, and lower hematocrit level. There were no significant differences in presentation of clinical warning signs and symptoms.[5]

In vitro studies have reported that NS_5 protein expression in certain flaviviruses, including DEN-2, west nile virus, hepatitis C virus, yellow fever virus, and GB virus type C(GBV-C), are associated with HIV replication suppression in CD4+ T cells. This replication supression is attributed to an increase in the stromal cell-derived factor-1 (SDF-1) cytokine level expression. SDF-1 is the principle ligand for the CXCR4 co-receptor, and it blocks HIV fusion and entry into the CD4+ T lymphocytes.[10] However the participation of the NS5 polyprotein during HIV suppression is not clear. So it need to do additional studies may be able to explain the possible interactions between the dengue virus with HIV immunopathological.[11] In this case, on first patient we found mild simptom of dengue which no bleeding or shock happen to this patient. We also found decline on CD4 level reach 1 and slowly increase in one week into 80, and the viral load on twice examinations was undetectable. This finding empower the statement that HIV and dengue interaction was associated with a reduced HIV viral load and milder clinical status of the patient. But in the second case, which had Dengue Shock Syndrome, this condition could be due to secondary Dengue infection confirmed by positive IgM and IgG anti Dengue.

Thrombocytopenia is the most common hematologic manifestation observed during acute phase of Dengue infection but also characteristic of HIV individuals.12 A kinetic description of platelet count in DHF/DF showed a significant decrease on the 4th until the 7th day of illness and reached normal levels on the 8th or 9th day. The mechanism of thrombocytopenia on dengue is bone marrow suppression. The precise mechanisms underlying DENV-induced bone marrow suppression during the acute phase remain unclear. However, three main factors have been suggested: (1) direct lesion of progenitor cells by DENV; (2) infected stromal cells; (3) changes in bone marrow regulation.[13]

Otherwise, the low circulating platelet counts in HIV patients are the result of two mechanisms : a) increased immune-mediated peripheral platelet destruction, and impaired platelet production by the infected megakaryocytes of the bone marrow.14 Thrombocytopenia also occur as a secondary phenomenon in HIV patient, due to hypersplenism, bone mareow infiltration from infection or lymphoma, and myelosuppressive effects of medications.15 In this case, both patient suffer from thrombocytopenia. The platelet level of first patient remain low after acute dengue infection. Dengue could be the cause of thrombocytopenia in this patient, but it supposed to increase after 7th day of dengue infection. So, we should analyze other cause of this condition. Meanwhile, platelet level of second patient gradually increase on the 7th day of dengue infection concordant to the natural history of dengue infection.

Dengue also characterized by leocopenia. Neutropenia in dengue infection has also been reported, although it less frequently.[16] Thein et al reported severe neutropenia, define as absolute neutrophil count (ANC) ≤ 0,5x109/L, was found in 11,8% with a median duration of one day. ANC nadir occurred on illness day 5. Severe neutropenia was not predictive of more severe disease and not associated with secondary bacterial infections, prolonged hospital stay, prolonged fever, or fatal outcome.[17] Neutropenia and myelosuppression also frequently occur in individuals infected with HIV. The etiology of neutropenia during HIV infection is multi-factorial, which may include HIV cytotoxicity, complications of secondary infection and malignancy, and the effects of myelosuppresive agents used for treatment.18 In this case, the first patients had leukopenia and neutropenia that continued until day 7 of dengue fever. The second patient also had neutropenia, but increased slowly along with the clinical improvement of dengue fever.

From the description above, the first patient had dengue fever but clinical and laboratory did not improve after day 7. Patients still had fever and

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pancytopenia. Compared with the second case, resolved normally clinical and laboratory after seven days. We analized the possible causes of this condition and found several differential diagnosis such as expanded dengue syndrome, failure of anti retroviral therapy, and anti retroviral side effect.

Expanded dengue syndrome is a rare or unusual manifestation of dengue fever which is usually caused by prolonged shock conditions and progresses to organ failure or patients with comorbidity and co-infection. Clinical manifestations include dengue encephalopathy or encephalitis, severe bleeding, multiple infections, kidney disorders, myocarditis.[7] In this first case, the patient had HIV co-infected with dengue. This could be one of the risk factors for expanded dengue syndrome. However, clinical manifestations of patients are incompatible with expanded denge syndrome because patients have no dengue encephalopathy or encephalitis, severe bleeding, multiple infections, kidney disorders, and myocarditis.

The second differential diagnosis is failure of therapy. Failure of antiretroviral therapy is assessed from clinical, immunologic and virologic. The earlier parameters appear is virological failure (when the viral load returns to 5000 copies RNA / ml, examined in 2 different different times), followed by immunological failure (when the CD4 count falls in the second examination done at least 3-month intervals) and the last is clinical failure appear in the form of new diseases classified in stage 3 or 4.[19] In the first case, patients had decreased levels of CD4 into 1, but a week later after rechecking, CD4 began to rise to 80. Patients had prolonged febrile and pancytopenia but there was no new disease classified as stage 3 or 4. The viral load was undetectable, so the possibility of treatment failure can be excluded.

After expanded dengue syndrome and treatment failure can be excluded, the most likely cause of pansitopenia prolongation in these patients is the side effects of ARVs. Combination antiretroviral (ARV) therapy is the current standard of care for treating patients with HIV/AIDS. In resource-limited settings, combination ART consisting of two nucleoside analogues (reverse transcriptase inhibitors) [either zidovudine (AZT) or stavudine (d4T) along with lamivudine (3TC)] and non-nucleoside reverse transcriptase inhibitor (NNRTI) [either nevirapine (NVP) or efavirenz (EFV)] are frequently used. AZT is used in the first-line drug combination as stavudine is more frequently associated with mitochondrial toxicity.[20] AZT, however, is associated with haematological toxicity particularly bone marrow aplasia leading to varying degrees of cytopenias especially anaemia in some patients. The mechanism of this anaemia is attributed to 50-70 percent inhibition of proliferation of blood cell progenitor cells in a time-and dose-dependent fashion.[21] Zidovudine exhibits cytotoxicity to the myeloid and erythroid precursors in the bone marrow at drug concentrations. This haematological toxicity is observed in most of the patients within 3-6 months and is reversible.[20] Agarwal et al, reported a high incidence of zidovudine induced anaemia in HIV infected patients in India. After reguler hemoglobin measurement it found 94,4% ZDV induce anemia occur within six months of therapy initiation. The peripheral smear showed normocytic, normochromic anaemia in almost half of the patients and in the remaining it showed macrocytic changes.[22] In the first case, patients took first-line antiretroviral drugs such as nevirapin, zidovudine and lamifudin since 3 years ago. After checking the medical record, the patient begins to experience bone marrow suppression in the form of anemia, neutropenia and thrombocytopenia after nine months of ARV use. This disorder is exacerbated by the use of cotrimoxasole which it is known that cotrimoxazole can also cause bone marrow suppression.

Anemia experienced by patients can be caused by two drugs consumed; zidovudine and cotrimoxazole. Cotrimoxazole use has been reportedly associated with the development of megaloblastic anaemia and pancytopenia.[23] First patients taking cotrimoxazole as a Pneumocystis pneumonia (PCP) prophylaxis from the beginning of HIV diagnosed. It takes careful consideration to determine which drugs are more influential to the state of pancytopenia. In the first case, after a risk benefit analysis was decided to stop cotrimoxazole and replace zidovudine into tenofofir. After one month of evaluation we got improvement from pancytopenia.

CONCLUSION

In conclusion, some studies reported that co-infection of HIV with acute infection can lead to cellular activation, resulting in a significantly increased viral replication of HIV or reducing the viral load of HIV. But other studies reported HIV patients infected with dengue may run a mild course and no significant severe complication, no DHF/DSS or accelerated progression of HIV. In this case also shows that dengue fever infection in child with HIV infection who are taking antiretroviral drugs can run into dengue shock syndrome. However, the interaction between the lines dengue pathogenesis of HIV infection, and between antiretroviral treatment with dengue infection still can not be explained, but would require further research.

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