

Disseminated Tuberkulosis in a 4-Year Old HIV Infected Boy with Multiple Comorbidities

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Abstract

HIV infection is a major health problem for pediatric population and often accompanied with several comorbidities which make the case even more difficult to manage. It was need interdisciplinary collaboration to manage HIV infection successfully. We present a case of a 4 year-old boy with clinical stage IV of HIV and disseminated tuberculosis, HCV infection, severe malnutrition, hypercalcemia, anemia and their clinical consequences. The patient was treated with antiretroviral therapy, anti-tuberculosis therapy, cotrimoxazole prophylaxis, nutritional support, and surgical interventions. During inpatient and outpatient care, the patient was assessed and treated by a multidisciplinary team consisted of pediatricians (infection, immunology, nutrition and respirology divisions), surgeons (pediatric and orthopedic divisions), and a physiotherapist. The patient was discharged after 27 days of inpatient care. HIV infection in children is very complicated due to its comorbidities. HIV-TB co-infection leads to poorer prognosis and requires regiment modification. HCV and HIV have a shared transmission mode so as co-infection of both viruses often occur. Compared with their contrary, HIV-infected patients have higher HCV viral loads, lower rate of spontaneous HCV clearance and accelerated liver disease. HIV infection and malnutrition often come together in children. Malnutrition also increases the frequency and severity of infection and hinders recovery process. These conditions need to be treated comprehensively for successful treatment. HIV infected boy with disseminated tuberculosis, severe malnutrition, abscess and hepatitis C infection was successfully treated comprehensively by giving ART, anti-tuberculosis drug, adequate nutrition, and infection eradication.

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INTRODUCTION

HIV infection is a major health problem for pediatric population. The global death from HIV-AIDS peaked in 2005 at 2.3 million and decreased to 1.6 million in 2012.¹ Many children with HIV infection has tuberculosis infection as initial presentation.^{2, 3} Although the exact incidence of disseminated tuberculosis is unclear, HIV infection is a risk factor for children to develop disseminated tuberculosis.⁴ Disseminated tuberculosis (TB) is defined if the infection of *Mycobacterium tuberculosis* have spread to at least two non-continuous locations through lymphohematogenous.⁵ Mortality of patient with disseminated TB reached 31.1%.⁶ This report presents a successful treatment case of a children with clinical stage IV HIV infection with disseminated TB with the emphasis of the importance of multi-disciplinary approach in treating patient with HIV and its comorbidities.

CASE REPORT

On April 2018, a 4 year and 10 months old boy hospitalized in dr. Kariadi Hospital Semarang because of prolonged fever. He was diagnosed of HIV infection 11 months before admission. The patient had prolonged fever, severe malnutrition unresponsive to nutrition therapy (body weight was 6.2 kilograms; body length was 70 cm), multiple lymphadenopathies, severe anemia, and a reddish, tender, swollen and suppurative left knee. He was HIV infected and was severely immunodeficient (CD4+ count 167 cells/ μ L). The viral load count was 9,060,457 copies/ μ L. Microscopic examination from swab of wound on his left knee yielded positive result for acid fast bacilli and *Mycobacterium tuberculosis* was also detected by GeneXpert MTB-RIF assay from tissue specimen. The boy then was diagnosed with HIV clinical stage IV, TB arthritis, disseminated TB, stomatitis, and severe chronic malnutrition. The patient was initially treated with anti-retroviral fixed dose combination (zidovudine, lamivudine, and nevirapine), but because complicated by anemia and tuberculosis, the regimen was later changed to tenofovir, lamivudine, and efavirenz.

For disseminated TB, the patient was treated with 2HRZE/10HR regimen.



Figure 1. Knee X- ray showed periostitis at distal metaphysis of femur with arthritis of left genu

After 10 and half months of treatment, fever arose and lump appeared on the left side of the neck and left inguinal fold. The initial diameter size was 1 cm and got bigger. The patient was examined at local hospital and referred to Kariadi Hospital for further treatment.

During hospitalisation, the patient still had fever and multiple lymph node enlargement on the left side of his neck and on left inguinal fold. The patient looked sick and very thin. Beside fever, other vital signs were normal. Physical examination revealed anemia, muscle wasting, hepatomegaly with visible dilated vein on his abdomen, suppurative lymphadenitis on his neck and left inguinal fold. Initial blood test showed normocytic normochromic anemia, leukocytosis and thrombocytosis. Peripheral blood smear showed loose spread erythrocytes, anisocytosis, poikilocytosis, neutrophilia, neutrophil vacuolization and neutrophil hyper-granulation. Other



Figure 2. Physical conditions of the patient and the chest x-ray results

results showed hypoalbuminemia, mild hyponatremia, and hypercalcemia. Chest x-ray revealed soft tissue mass at left neck region. The patient was diagnosed as HIV clinical stage IV with severe malnutrition, disseminated TB (arthritis TB and lymphadenitis TB), normocytic normochromic anemia, hypoalbuminemia, hypercalcemia and severe immunodeficiency state. He was treated with paracetamol, folic acid, zinc, vitamin B6, pediatric FDC for anti-TB treatment at continuation phase, cotrimoxazole, tenofovir, efavirenz and lamivudine. He was treated comprehensively involving pediatricians from nutrition, gastroenterohepatology, respiratory, immunology and infection divisions, surgeons (pediatric and orthopedic divisions) and a physiotherapist.

The patient was hospitalized for 27 days. During treatment, the patient was given blood transfusion and albumin correction. For suppurative lymphadenitis, debridement was performed and tissue biopsy was sent for microscopy examination and microbial culture. The microbiology result showed *Staphylococcus haemolyticus*. His biopsy result showed lymphadenitis and gene X-pert result was negative. The patient was also screened for hepatitis virus and found that the patient was infected by hepatitis C virus. HCV RNA examination was not requested because of limited resources. His nutritional status improved during hospitalization and after discharge. The anti-TB medications were stopped after 12 months of treatment. Eight months after discharge, the patient

gained normal nutrition status, improved movement of his left knee and the patient started to walk again.

DISCUSSION

This case highlights the complexity of the problem and management of HIV infection in children with several comorbidities such as disseminated TB,



Figure 3. The patient condition at 8 months after discharge

lymphadenitis suspected for paradoxical upgrading reaction (PUR) with secondary infection, anemia, severe malnutrition, hepatitis C infection and hypercalcemia.

Most HIV infection in children occur through Mother-to-Child Transmission (MTCT) at three different time points: in utero (5-10%), intrapartum (10-20%) or through breast milk (5-15%).⁷ The progression of HIV is different between children and adults. Younger children have a greater risk of death or progression to AIDS compared to those who are older.⁸ The reason for the differences is associated with immunological immaturity and rapid expansion of CD4 + T cells that accompany somatic growth.⁹ Clinical manifestations of HIV infection in children include oral candidiasis, pulmonary tuberculosis, recurrent respiratory infections, bacterial skin infections, papule-pruritus

dermatitis, hepatosplenomegaly, lymphadenopathy, and chronic diarrhea.^{2,3} HIV clinically can be divided into 4 stages.¹⁰ The patient was assessed as clinical stage IV because he had severe malnourished and had extrapulmonary TB.

Disseminated TB is defined if there is a spread of TB to two or more non-continuous locations that is via lymphohematogenous spread of *Mycobacterium tuberculosis*.⁵ Exact incidence of disseminated TB is unclear. However, disseminated TB is common in infants and children.⁴ Disseminated tuberculosis develop in patients who have underlying comorbid conditions such as AIDS, diabetes mellitus, malignancy, end-stage renal disease, liver cirrhosis, post-transplantation and autoimmune disease. The most common involved organs are lung (87.2%) and musculoskeletal (19.5%). HIV/AIDS patients have higher incidence of to develop mycobacteremia (30.4%) and bone marrow involvement (39.1%).⁶ The patient was diagnosed with disseminated TB 11 months before admission because the manifestation of TB lymphadenopathy and osteoarticular tuberculosis at the same time.

Tuberculous arthritis most commonly involved hips, knees, and ribs. Typical symptoms consist of slowly progressive joint pain, swelling, and loss of function that progress over weeks to months. Constitutional symptoms, fever and weight loss occur in about 30% of cases. A single joint or multiple lesions can occur.¹¹ This patient was diagnosed with TB arthritis based on clinical signs and confirmed by biopsy and PCR results.

The patient had lymphadenitis suspected as PUR with secondary infection. PUR is a unique feature that might interfere the success treatment of drug-susceptible tuberculosis lymphadenitis that the patient had been experienced. There were the worsening of symptoms during treatment such of the development of new enlarged glands, nodes, or new draining sinuses in patients who have received at least 10 days of treatment.¹² PUR manifestations include enlargement of existing or new lymphadenopathy, pain and draining sinuses.¹² Biopsies or gland cultures involved in PUR showed granuloma formation with negative culture results as well as negative acid-fast bacilli staining. These characteristics are consistent

with a strong immune response to *M. tuberculosis* with the initiation of antibiotic therapy and the release of mycobacterial antigens.¹²

Anemia is one of the most common hematological disorders in patients with HIV.¹³ Opportunistic infections, malignancies, micronutrient deficiencies, and ART can cause anemia in HIV patients.¹⁴ In this case, the patient had normocytic normochromic anemia that might be caused by anemia of chronic disease, drug adverse effect, micronutrient deficiency or because of HIV infection itself. Examination of serum iron level was not done so the exact cause of anemia in this case was undetermined.

The patient also had hepatitis C virus (HCV) infection, severe malnutrition and hypercalcemia. The majority (65% -80%) of HCV infected individuals remain chronically infected and are at risk of severe liver disease (cirrhosis, end-stage liver disease and liver cancer). The remaining 15-40 % might spontaneously resolves their infection.¹⁵ HCV and HIV have the same transmission route and therefore, co-infection with both viruses often occurs. The transmission of this virus can occur through blood, sexual intercourse, and MTCT. Co-infection with HIV increases transmission rates 4-5 times.^{16, 17} In this case, HCV infection was diagnosed definitively based on positive anti HCV serological result. The abdominal ultrasound showed hepatomegaly with a homogeneous parenchymal structure. HCV RNA and fibro scan were not done due to limited facilities. The patient was not given treatment for HCV. His infection might come from blood transfusions or transmission from mother to child. His mother had never been screened for HCV infection. Because of co-infection with HIV, the progression toward liver fibrosis is accelerated.¹⁸

The risk of malnutrition is higher in children infected with HIV.¹⁹ The weight-loss mechanism in HIV-infected patients is complex and multifactorial. Various contributing factors include low nutritional intake, increased nutritional requirements, absorption disorders in the gastrointestinal tract due to infection or enteropathy as well as metabolic disorders of amino acids and proteins. Clinical manifestations of HIV infection are characterized by metabolic

disorders followed by decreased immune system function, progressive decrease of T-CD4 lymphocytes, increasing energy demand, anorexia, and increasing proteolytic muscle activity. If metabolic failure occurs for a long time and accompanied by failure of the neurochemical system, it will go into severe anorexia and cachexia and will end up as wasting syndrome.²⁰

This patient had also hypercalcemia. This condition can be caused by hyperparathyroidism, hypervitaminosis D (tuberculosis and chronic inflammatory disorders), immobilization, malignancy associated with hypercalcemia (primary bone tumors, metastatic tumors with osteolysis) and Williams syndrome.⁶ In this case, the etiology of hypercalcemia was unknown but might be related to immobilization, HIV infection, and TB infection. Investigations were needed to identify the cause.

This patient was treated comprehensively by collaboration of pediatricians of nutrition, respiratory, immunology, and gastroenterohepatology divisions, surgeons, and a physiotherapist. The patient was treated with ART initially with zidovudine, lamivudine, and nevirapine. Zidovudine was changed to tenofovir because of severe anemia. Nevirapine was changed to efavirenz because of drug interactions with rifampicin. Rifampicin can reduce blood nevirapine levels by up to 31%.²¹ Finally, the patient was treated with lamivudine, tenofovir, and efavirenz. He was given cotrimoxazole prophylaxis as indicated by clinical stage IV of HIV infection and planned to be given for a lifetime. Cotrimoxazole prophylaxis effectively prevents *pneumocystis jiroveci* pneumonia which is the leading cause of death in HIV infants.²² For osteoarticular TB, the patient had had surgery 11 months before admission and was treated with 2HRZE/10HR regiment of anti-TB drug.²³ Suppurative lymphadenitis was treated by surgical debridement and antibiotics in accordance to culture result. Transfusion was given to correct anemia. For hepatitis C infection, no treatment was given because no confirmation of active infection. If the patient had active infection, pegylated-interferon (PEG-IFN) plus ribavirin can clear HCV infection by 50-90%.¹⁷ Without therapy, 90 - 95% of HIV and HCV co-

infected patients will develop chronic HCV infection.²⁴ Malnutrition was treated using pediatric nutrition care approach. Nutritional requirements were calculated in accordance with the Recommended Daily Allowance.

CONCLUSION

A 4 year-old HIV infected boy with disseminated TB, severe malnutrition, abscess, and hepatitis C infection was successfully treated multidisciplinary by giving ART, anti-tuberculosis drug, adequate nutritional provision and therapy for infection eradication.

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