A naive human immunodeficiency virus (HIV) patient with extrapulmonary tuberculosis manifestation: diagnosis and management challenges

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ABSTRACT

Background: Co-infection of human immunodeficiency virus (HIV) and extrapulmonary tuberculosis (TB) is common tropical countries and could manifest with diverse clinical manifestations and mimic other diseases. This case report highlights the diagnosis and management challenges of a patient with HIV naive who had pleural and pericardial effusion manifestation due to extrapulmonary TB.

Case presentation: A male 48 years old was referred with shortness of breath, cough with phlegm, fever with night sweats. The patient complained of chest tightness and pain, decreased appetite, and weight loss approximately 10 kg in the last six months. The patient had several times having sexual intercourse with prostitutes. White patches were presented on the tongue. The patient was tested twice with three methods for HIV test and yielded inconclusive results. The chest X-ray examination suggested left pleural effusion and echocardiography with the results of pericardial effusion. The patient had thoracentesis with the adenosine deaminase (ADA) test 52 U/L and the culture resulted a positive for Mycobacterium tuberculosis sensitive to rifampicin, isoniazid, ethambutol, and pyrazamide. The patient was treated with anti-TB. Later, the viral load yielded a value of 1.43x10^9 IU/mL and the patient was treated with antiretroviral therapy.

Conclusion: Due to challenges of diagnose and manage of such co-infection with unusual clinical manifestations, multi-disciplinary approaches are required together with adequate healthcare facilities to support the diagnostics.

Keywords: HIV co-infection, tuberculosis, TB co-infection, extrapulmonary TB, naive HIV.

INTRODUCTION

Tuberculosis (TB) is a major health problem in Indonesia, especially during the coronavirus disease 2019 (COVID-19) pandemic. Extrapulmonary TB is one a case of TB that attacks organs other than the lungs, such as the pleura, lymph nodes (including the mediastinum and/or hilum), pericardium, bones, joints, skin, abdomen, genital tract, and the lining of the brain. Extrapulmonary TB occurs in 15-20% of TB cases in Bangladesh and India, affecting low-income communities (60%) and 55% of all cases occur in the age group of 16-45 years. Although multiple TB-specific diagnostic methods are available, extrapulmonary TB is harder to be diagnosed than pulmonary TB. Human immunodeficiency virus (HIV) and Mycobacterium tuberculosis are intracellular pathogens that interact with each other at the population and could be similar at clinical and cellular levels. The progression of TB to become active since the beginning of exposure is faster in people with HIV-AIDS (40%) compared to non-HIV infected individuals (5%) with a reactivation risk of 2.15% each year compared to non-HIV which is only less then 0.1% per year. The HIV-TB coinfection mortality rate is 20.35% or 4 times higher than the TB mortality rate without HIV.

Pleural TB is the second most common extrapulmonary TB after lymph node TB. With an incidence of 30% of all cases of tuberculosis. Pleural effusion, accumulation of excessive fluid in the pleural cavity, can be a manifestation of pleural TB either isolated or associated with pulmonary TB. Without treatment, pleural TB may resolve spontaneously but often progress to active TB. In addition, pericardial effusion, a condition where there is fluid in the space between the pericardium's visceral and parietal layers, could also present as the clinical manifestation of TB. In this case report, we report the challenges of diagnosing and managing a patient with HIV naive who had pleural effusion and pericardial effusion suspected to be associated with TB.

CASE PRESENTATION

A male 48 years old, married, Muslim, elementary school graduate, working as a factory worker was referred from a private hospital in Gresik, East Java, Indonesia with a suspected diagnosis of HIV with pleural effusion and pericardial effusion on March 24, 2021.

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The patient complained of shortness of breath for seven days before admission to the hospital which had been severe in the last three days. Shortness of breath occurred throughout the day that was not affected by changes in position and time. In addition, the patient also complained of cough with phlegm that was difficult to expel since the last month accompanied by fever and sometimes night sweats. The patient also complained of chest tightness and pain in the chest with a stabbing sensation in the last three days of before the admission. Chest pain like stabbing occurred suddenly in the center of the chest. The pain also felt heavy every time the patient takes a breath and felt less when the patient was sitting and bending forward.

The patient complained of nausea but no vomiting. The patient had decreased appetite in the last one week. There were no complaints about defecation or urination. Previously the patient was treated at a private hospital for five days but then the patient was referred. The patient also complained of white patches on the tongue and the mouth’s walls for the last month, making it difficult to eat. The patient also complained of weight loss in the last six months approximately 10 kg.

The patient denied history of HIV, TB, diabetes mellitus (DM), hypertension, liver and kidney disease. The patient was married once in 20 years to the current wife. The patient admitted that more than seven years ago he had several times having sexual intercourse with prostitutes. The patient denied same-sex relationships. The patient denied that he had ever had sexual intercourse with prostitutes. The patient also denied the use of any narcotics.

At the previous hospital, the patient had HIV testing with three methods which were repeated with inconclusive results, the patient also had a chest X-ray examination with the results of left pleural effusion and echocardiography with the results of pericardial effusion.

General condition was weak, composites, with blood pressure of 100/80 mmHg, pulse 85 times per min, respiration 26 times per min, blood temperature 36.9°C, SpO₂ 89% which became 97% with support O₂ 7 liter per min (lpm) with simple mask, and Wong-Baker 3 Pain Scale were 3. The body weight 60 kg, height 160 cm, and body mass index (BMI) 23.4 kg/m². On physical examination, the conjunctiva was non-anemic, non-icteric and non-cyanotic. The jugular vein pressure (JVP) did not increase, chest had symmetrical movements but had decreased lung fremitus, dullness and decreased vesicular breath sounds in 1/2 of the left lung. Auscultation of single S1 and S2 heart with no murmur and gallop. On abdominal examination, the abdomen was soft, bowel sounds were normal, the liver and spleen were not palpable, no shifting dullness, no muscular defans and no erythema. Extremities examinations found warm acral, capillary refill time <2 s and no edema.

Laboratory examination showed hemoglobin 9.1 g/dL, hematocrit 28%, MCV 101.1 fl, MCH 30.4 pg, MCHC 28.7 g/dL, leukocytes 9.94x10⁹/µL, platelets 287x10¹²/µL, neutrophils 71%, lymphocytes 17%, blood urea nitrogen (BUN) 22 mg/dL, serum creatinine 1.2 mg/dL, albumin 3.8 g/dL, sodium 129 mmol/L, potassium 3.9 mmol/L, chloride 98 mmol/L, HbSAg negative, HIV test with three methods, CD4 count, rapid test was negative, SGOT 48 U/L, SGPT 22 U/L, PPT 12.7 s, APTT 28.8 s, CRP 23 mg/L, CKMB 26.2 U/L and troponin T 12 pg/mL. Blood gas analysis found pH 7.41, pO₂ 98% and P/F ratio 330.

Immunological examination found HIV reactive.

Electrocardiography (ECG) examination showed sinus rhythm, 100 bpm and low voltage QRS. AP chest X-ray re-examination found the cast the left heart border was partially covered with suffocation, pulmonary infiltrates did not appear, the trachea was in the middle; there was an inhomogeneous opacity in the lower to upper left hemithorax that covered the left phrenicocostal sinus and left hemidiaphragm that suggested an impression of cardiomegaly with pericardial effusion (Figure 1A). The echocardiography was performed with the results of left ventricular (LV) dilatation, no intracardiac thrombus/vegetation, decreased LV systolic function, abnormal relaxation of LV diastolic function, normal right ventricular (RV) systolic function, pulmonary capillary wedge pressure (PCWP) 2.48 and ejection fraction (EF) 53%, LV segmental analysis. There was eccentric LV hypertrophy (LVH), moderate pericardial effusion was seen at the base, no LV collapse was seen. The cardiologist advised that there was no need for pericardiocentesis. The pulmonologist has performed a proven puncture examination on the patient.

The initial assessment of this patient was suspected HIV with serositis (massive left pleural effusion and moderate pericardial effusion), suspected TB with oral candidiasis, hypoalbumin and hyponatremia. The patient then was planned for having serial tests including a complete blood count test, albumin test, post-corrected serum electrolyte test, HIV test with three methods, CD4 count, viral load count and procalcitonin test. The patient was treated with diet high calory and high protein 2100 kcal/day extra egg white, O₂ 6-8 lpm with simple mask, albumin infusion, albumin transfusion of 20% 100 mL in 4 h, PRC transfusion 1 bag/day up to Hb>10g/l.
sensitive to rifampicin, M. tuberculosis

The patient was given anti TB drugs with suspected pericarditis and suspected patient has diagnosed with TB pleurisy.

On the second day of treatment, the patient still complained of shortness of breath, nausea and fever. General condition was weak, compos mentis, with blood pressure 100/80 mmHg, pulse 85 times per min, respiration 26 times per min, body temperature 36.9°C, SpO₂ 97% with O₂ 6-8 lpm (simple mask). The pleural fluid analysis found pH 7.2, glucose 86 mg/dL, cell count 1,367, lactate dehydrogenase (LDH) 581 IU/L, MN 72.6%, PMN 27.4%, protein 48 g/L, WBC 1.153x10⁹/µL, and RBC 0.019x10⁹/µL. The patient received additional oral therapy of colchicine 0.5 mg per 24. Other therapies were the same.

On fourth day of treatment, the complaint of shortness of breath has decreased, the nausea and vomiting were gone, no fever, the white patches on the tongue were reduced. The patient agreed and had a 1.5 liters thoracentesis (Figure 1B). The lungs were then examined for the adenosine deaminase (ADA) test, culture, and aerobic/anaerobic/M. tuberculosis. General condition was weak, compos mentis, with blood pressure 110/90 mmHg, pulse 95 times per min, respiration 24 times per min, body temperature 36.9°C and SpO₂ 98% with O₂ 6 lpm simple mask. The results of HIV investigations with three methods were inconclusive, CD4 119 cell/mm³, hemoglobin 10.8 g/dL, hematocrit 30.4%, MCV 103.1 fl, MCH 29.4 pg, MCHC 28.7 g/dL, leukocytes 7.94x10⁹/µL, platelets 178 x 10⁹/µL, neutrophils 71%, lymphocytes 17%, albumin 2.3 grams/dL, blood glucose 103 mg/dL, sodium 134 mmol/L, potassium 3.6 mmol/L, chloride 100 mmol/L, and serum LDH 540. The patient was then tested for HIV viral load.

On sixth day of treatment, the patient had no complaints. General condition was still weak, compos mentis, with blood pressure 120/72 mmHg, pulse 85 times per min, respiration 21 times per min, body temperature 36.8°C, SpO₂ 96% with free air. The results of the ADA test 52 U/L. The patient has diagnosed with TB pleurisy with suspected pericarditis and suspected HIV. The patient was given anti TB drugs rifampicin 450 mg, isoniazid 300 mg, pyrazinamide 1500 mg, and ethambutol 1000 mg. The patient was discharged and scheduled for follow-up.

Two months later, the patient had no complaints and the TB therapy was continued. The HIV viral load yielded a value of 1.43x10⁹ IU/ml. The PA chest x-ray evaluation suggested the cardiac appeared enlarged, pulmonary infiltrates did not appear, the trachea was in the middle, the right and left phrenicocostal sinuses were sharp, the right and left hemidiaphragm within normal limit, the impression was cardiomegaly (Figure 1C). Pleural fluid culture resulted with M. tuberculosis sensitive to rifampicin, isoniazid, ethambutol, and pyrazinamide. The patient then received additional ARV therapy with a regimen of tenofovir 300 mg, lamivudine 150 mg, and efavirenz 600 mg plus cotrimoxazole 960 mg.

**DISCUSSION**

HIV diagnosis was made based on WHO clinical criteria with a positive HIV test and at least two major and minor symptoms, including major symptoms (weight loss of more than 10% in one month, chronic diarrhea lasting more than one month, prolonged fever for more than one month, decreased consciousness or neurological disorders, dementia/HIV encephalopathy) and minor symptoms (persistent long cough, generalized dermatitis, recurrent multisegmental lymph nodes. The second stage is an advanced stage with weight loss, recurrent bacterial infections of the respiratory tract and mouth and decreased quality of life. The fourth is an advanced stage with weight loss of more than 10%, oral candidiasis, pulmonary and extra-pulmonary TB, bacterial pneumonia, cerebral toxoplasmosis, herpes virus infection, diarrhea due to cryptosporidiosis, Kaposis sarcoma, cytomegalovirus infection and other findings. AIDS is established if there is an opportunistic infection or CD4+ lymphocytes are less than 200 cells/mm³. The patient was diagnosed with AIDS (HIV stage four) because the patient met the criteria of HIV infection with CD4 <200 cells/mm³ accompanied by opportunistic infections in the form of extrapulmonary TB.

ARV therapy should be given to all TB patients with HIV regardless of CD4 cell count. In TB-HIV co-infection, TB treatment should be started first, followed by ARV treatment for at least two weeks and no later than eight weeks after starting anti-TB therapy to reduce mortality or AIDS conditions. First-line ARV combinations should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or protease inhibitor (PI). CD4 counts below 200 cells/mm³ are recommended to receive preventive therapy of cotrimoxazole 960 mg/day. The recommended tests are CD4 assessment, serum creatinine, liver function every six months, and HIV RNA within six months after therapy and every 12 months thereafter. Evaluation of drug compliance needs to be carried out as well as an assessment of whether toxicity occurs. Our patient received ARV therapy with a regimen of tenofovir 300 mg, lamivudine 150 mg, and efavirenz 600 mg. In addition, the patient also received cotrimoxazole 960 mg per day prophylaxis for CD4 count <200 cells/mm³. The patient was educated on the importance of taking medication regularly. ARV therapy needs to be changed if it causes severe or grade 3 reactions and discontinued if there is life-threatening toxicity.

Acute pericarditis is a group of symptoms of pericardial inflammation...
that may or may not be accompanied by pericardial effusion. Based on European Society of Cardiology (ESC) acute pericarditis is diagnosed if there are 2 of 4 criteria, namely the presence of chest pain, pericardial friction rub, ST elevation concave upwards or saddle-shaped on the ECG, and the presence of pericardial effusion.18,19 The patient was diagnosed with acute pericarditis because it met 2 of the 4 criteria according to the ESC: chest pain and pericardial effusion. ECG showed LV dilatation, decreased LV systolic function, PCWP 2.48 and EF 53%, eccentric LVH and moderate pericardial effusion was seen at the basal level. The patient received 0.5 mg colchicine therapy every 24 h and showed improvement.

Pericardial effusion caused by TB in AIDS patients occurs in more than 85% of cases. To diagnose TB pericarditis, a scoring system is used for patients living in TB endemic areas of which a score 6 is suggestive of TB pericarditis. The scoring includes fever >38°C (score 1), night sweats (score 1), weight loss >10% (score 2), globulins >40 g/L (score 3), and peripheral leukocytes <10,000/L (score 3).18,20,21 The patient had fever (1), night sweats (1), weight loss (2) with a total score of 4. The possibility of TB as the cause of pericarditis still requires further evaluation.

Other causes of inflammation due to systemic inflammatory conditions such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) and malignancies which are usually caused by malignant metastases in the lung or even primary cardiac tumors and trauma that injures the aortic or coronary vessels or myocardium can cause blood accumulation in the pericardial space causing a pericardial effusion.22,23 Our patient is male and there was no suspicion of autoimmune diseases such as hair loss, oral ulcers and no complaints related to joints. In our case, the possible rheumatological causes can be ruled out because there were no symptoms and did not meet the criteria for SLE or RA. In addition, suspicion of malignancy can be ruled out because no mass abnormality was found on chest X-ray or echocardiography. The patient did not complain of any other specific symptoms indicating malignancy or nonspecific symptoms such as weight loss or subfebrile fever. The patient also did not complain of a history of previous trauma.

TB pleurisy can occur in patients with pleural effusions with epidemiological risk factors, exposure or family history of TB, or in patients who have traveled to an area where TB is endemic. Definitive diagnosis was with the discovery of M. tuberculosis in sputum, pleural fluid or pleural biopsy. A chest X-ray shows a dulling of the costophrenic angle. Thoracentesis and analysis of pleural fluid with characteristic exudate with pH <7.40, leukocytes 100-5000 cells/μL, predominant lymphocytes, protein >3.0g/dL and more than 50% of serum protein, normal/low glucose, LDH may be elevated in 75% of the cases. ADA is a biomarker that can be used and shows significant results with the sensitivity and specificity of the diagnosis of TB pleurisy more than 90% at value above 40 U/L.24,25 Our patient complained of shortness of breath, fever, and weight loss. Pleural fluid analysis performed showed exudate results and led to suspicion of TB with a pH below 7.4, LDH>500, predominantly mononuclear, effusion protein >5 g/dL then confirmed by the results of the ADA test 52 U/L. The results of effusion fluid culture showed M. tuberculosis sensitive to rifampicin, isoniazid, ethambutol, and pyrazinamide and showed improvement after treatment.

CONCLUSION
Serositis patient been reported with pleuritic manifestations in the form of pleural effusion with ADA test positive and pleural fluid culture positive with M. tuberculosis that was sensitive to rifampicin, isoniazid, pyrazinamide and ethambutol. The patient also had a suspected pericardial effusion associated with M. tuberculosis. The pericardial fluid culture was not performed because there was no indication for pericardiocentesis. The serositis condition improved with first-line anti-TB drugs. The patient was also diagnosed with HIV and received first-line ARVs.

PATIENT CONSENT
The patient signed informed consent prior to the study and agreed that the case will be published in an academic journal without revealing the patient identity.

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DISCLOSURE OF CONFLICTS OF INTEREST
The authors declare no conflict of interest.

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