CASE REPORT

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A patient with CD4+ T cells deficiency and HIV negative with pulmonary tuberculosis, tuberculous pleuritis and meningitis tuberculosis

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ABSTRACT

Background: CD4+ T cells deficiency generally occurs in human immunodeficiency virus (HIV) patients, leading to some infections such as pulmonary and extrapulmonary tuberculosis. A rare case of decreased CD4+T cells is idiopathic CD4+ T cell lymphocytopenia, a rare and unexplained immunodeficiency syndrome with no evidence of HIV infection. In this case report, we are reporting a patient with CD4+ T cells deficiency, pulmonary tuberculosis, pleuritis tuberculosis, and meningitis with HIV test negative.

Case Presentation: A 58-year-old male was referred to the Emergency Department of Dr. Soetomo General Hospital with a gradual decrease of consciousness following six days of hospitalization at a private hospital. During hospitalization, one liter of fluid was evacuated from the right lung and analyzed, revealing tuberculosis infection. History of diabetes, hypertension, stroke, hepatitis, and cardiovascular disease was denied. The patient also never had chemotherapy or radiation treatment. Based on history taking, physical examination, and laboratory results, this patient has been diagnosed new case of pulmonary tuberculosis with deficiency CD4+ T cells and altered consciousness et causes meningitis tuberculosis with pleurisy tuberculosis. After 32 days of hospitalization with anti-mycobacterium therapy, the patient was improved and was discharged.

Conclusion: This case highlights the challenges of having the definitive cause of CD4+ T cells deficiency either active tuberculosis infection or idiopathic CD4+ lymphocytopenia. Therefore, serial analyses of CD4+ T cells are advised on the patient during the treatment with anti-tuberculosis drug.

Keywords: CD4+ T cells deficiency, pulmonary tuberculosis, pleurisy tuberculosis, meningitis tuberculosis, ICL.
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INTRODUCTION

The CD4+ T cells have an essential role in the human immune system by providing help to B cells. CD4+ T cells also contribute to the antiviral responses by producing cytokines and enhancing the response of CD8+ T cells.[1] The deficiency of CD4+ T cells in blood, airways, and lymph nodes can occur due to anti-CD4 antibodies.[2] Human immunodeficiency virus (HIV) infection is the most common cause of CD4+ T cells deficiency by binding to CD4+ T cells molecules on the surface of T helper cells and replicating inside them. Destroying CD4+ T cells cause a decrease in the stable T cell population and leading to risk of infections caused by bacteria, mycobacteria, viruses, fungi, and parasites.[3] However, several cases of CD4+ T cells deficiency cannot be identified. Idiopathic CD4+ lymphocytopenia (ICL) is a rare immune defect with an unexplained CD4+ T cells deficit. In addition, individuals suffering from severe opportunistic infections are also associated with low CD4+ T cell counts. If the patient has no evidence of HIV infection, then ICL became an alternative explanation for CD4+ T cells deficiency.[4]

Another disease associated with CD4+ cells deficiency is tuberculosis. Tuberculosis is the most common leading cause of death among people infected with HIV worldwide.[5] In 2014, 1.2 million people living with HIV were infected with tuberculosis and over 32% died.[6] Several cases have shown that ICL is also involved in the immune responses to *Mycobacterium tuberculosis* infection. A study found that among 259 reviewed cases of ICL, 19 patients were infected with *M. tuberculosis*.[7]

M. tuberculosis can infect other organs except lung causing extrapulmonary tuberculosis. Common manifestations of extrapulmonary tuberculosis include pleurisy tuberculosis and meningitis tuberculosis.[8] Pleurisy tuberculosis is the most common form of extrapulmonary tuberculosis and it is the commonest cause of unilateral pleural effusion in countries with a high tuberculosis burden.[9] Meningitis tuberculosis is associated with high morbidity and mortality and when meningitis tuberculosis is suspected, treatment should be commenced immediately without waiting for bacteriological proof of diagnosis. The incidence of pleurisy and meningitis

tuberculosis is higher in people living with HIV than in uninfected patients.[9,10] Here, we report the case of a patient with no history of HIV with a CD4+ T cells reduction with pulmonary and extrapulmonary tuberculosis.

CASE PRESENTATION

A 58-year-old male was referred to the Emergency Department of Dr. Soetomo General Hospital with a gradual decrease of consciousness following six days of hospitalization at a private hospital. At the private hospital, the level of consciousness started to decrease; the patient spoke confusingly, communicated barely, and closed his eyes often. Two weeks before the admission the patient had headaches, nausea, and vomiting that had gradually worsened. The local community health center has prescribed the patient anti-pain and anti-emetic. The patient also had progressive dyspnea, which was not relieved by rest but by sitting and sleeping sideways. The patient was reported to have a dry cough with fever for three weeks and lost eight kilograms in one month. During the hospitalization, approximately one liter of fluid was evacuated from the right lung, and the patient diagnoses with tuberculosis infection. History of diabetes, hypertension, stroke, hepatitis, and cardiovascular disease were denied and no history of prior swelling, bleeding, or transfusion. The patient also never had chemotherapy or radiation treatment.

Physical examination showed a Glasgow Coma Score (GCS) of 11 (E3V2M5); blood pressure 140/90 mmHg with a regular heart rate of 114x/min (strong pulsation); oxygen saturation of 97% while wearing a three liters per minute (lpm) nasal cannula; regular respiratory rate of 25 x/min and axillary temperature of 37.9°C. The patient had a normal body mass index, 20.7 kg/m^2.

Head and neck examination revealed no anemic conjunctiva, icteric sclera, lymph enlargement, or thyroid gland enlargement. Chest examination revealed symmetrical breath movement without chest wall retraction. Chest percussion revealed dullness and decreasing tactile fremitus in the third half of the right lung. There was decreased vesicular sound in the third half of the right lung. The bronchovesicular sound was heard in the left parahillar region. Heart, adnominal, and extremities examinations were all within normal limits. Laboratory tests revealed low count of lymphocyte count (Table 1). Adenosine deaminase (ADA) test of pleural fluid was 79IU/L, Rivalta test positive with protein 251 mg/dL (Table 1).

Table 1. Laboratory test results of the patient.

Laboratory test	Lab parameter	Result
Blood analysis	Hemoglobin	14.0 g/dL
	Lymphocytes	7960/mm^3
	Platelet	229000 /mm^3
	Albumin	3.86 mm/h
	Blood urea nitrogen	18 mg/dL
	Creatine	0.73 mg/dL
	Sodium	136 mmol/L
	Potassium	3.7 mmol/L
	Chloride	106 mmol/L
	Blood glucose	116 mg/dL
	Lymphocyte	6.9%
	HIV rapid test	Negative
	HBsAg	Negative
	Aspartate transaminase (AST)	22 U/L
	Alanine transaminase (ALT)	21 U/L
	pH	7.48
	pCO_2	40
	pO_2	121
	HCO_3	24.8
	BE	3.3
Urinalysis	Urinalysis	Within normal limit
Pleural fluid analysis	Adenosine deaminase (ADA) test	79IU/L
	Glucose	9 mg/dL
	Mononuclear	79%
	Polymorphonuclear	21%
	Protein	251 mg/dL
	Rivalta	Positive
	Cytology	Negative

The chest radiograph (CXR) showed homogenous opacity in the right laterobasal hemithorax shadowing the right costophrenic sinus and fibroinfiltrate in the left and right suprahilar (Figures 1A and B). Neurologic diagnosed with suspected cerebrovascular accident (CVA) with differential diagnostics of tuberculous meningitis and bacterial meningitis. However, a head CT scan with contrast revealed no infection process, infarct, bleeding, or mass on brain parenchyma (Figure 1C-F).

Based on history taking, physical examination, and laboratory results, the patient was diagnosed with altered consciousness due to meningitis tuberculosis with differential diagnosis of bacterial meningitis with suspected new pulmonary tuberculosis and pleurisy tuberculosis. After five days of hospitalization, cerebrospinal fluid was analyzed for Gram stain and the acid-fast stain. Cerebrospinal fluids analysis demonstrated cell counts of 112 cell/mm^3, mononuclear 98%, polymorphonuclear 2%, protein 225 mg/dL, glucose 9 mg/dL, cerebrospinal glucose: serum ratio of 0.075, positive result of acid-fast staining and CD4+ T cells counts 154 cells/mm^3. The patient was diagnosed with a new case of pulmonary tuberculosis with ICL and altered consciousness due to meningitis tuberculosis and pleurisy tuberculosis.

The patient was administered with anti-mycobacterium therapy for three days with isoniazid, rifampin, ethambutol, and pyrazinamide. After five days of treatment, additional therapy was given in which the patient was treated with dexamethasone

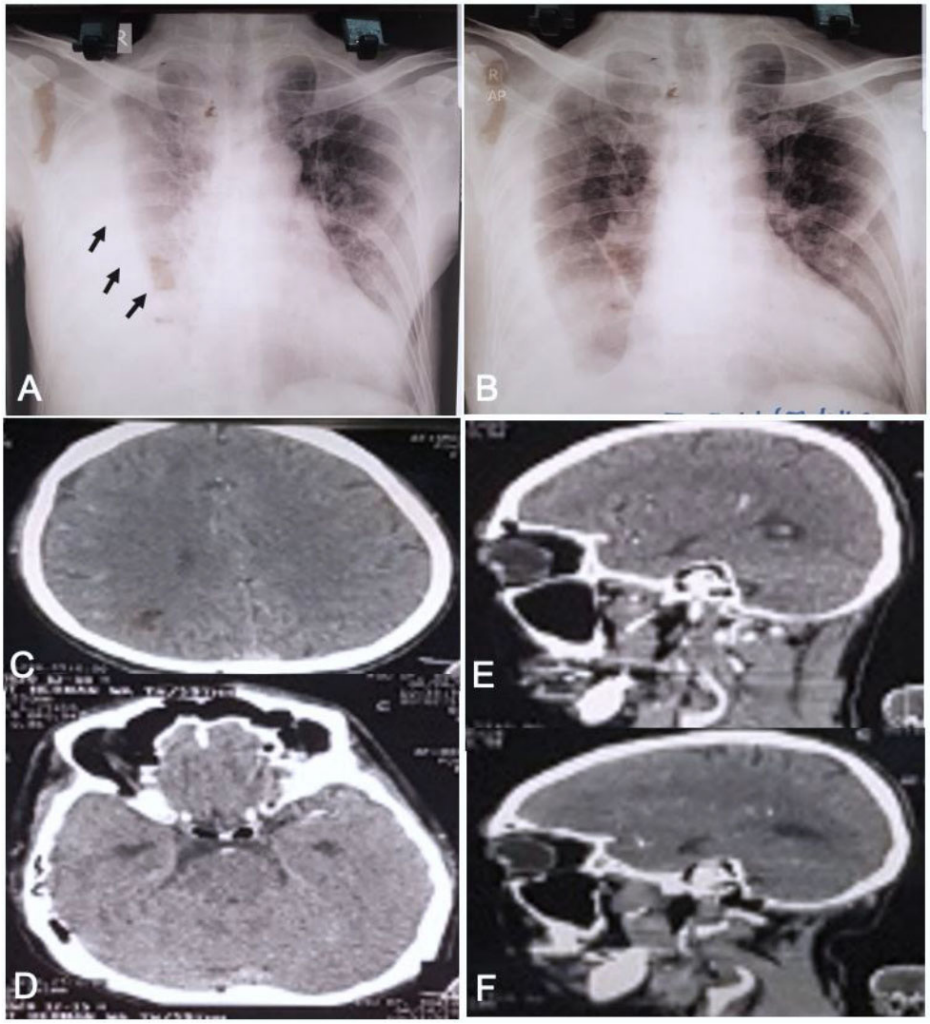

Figure 1. Chest radiograph and head CT-scan of the patient. (**A**) Chest radiograph showing homogenous opacity in right laterobasal hemithorax prior to fluid evacuation suggesting pleural effusion (black arrows). (**B**) Chest radiograph showing homogenous opacity in right laterobasal hemithorax shadowing the right costophrenic sinus, fibroinfiltrate in the left and right suprahilar post-evacuation of 1000 ml. (**C-F**) showing the normal head CT-scan.

and streptomycin until day 11 after which the streptomycin was discontinued. The patient showed improvement after 11 days of treatment with a restored sign of consciousness with GCS of 15 (E4V5M6), orientation to time, place, and person was good, dyspnea had improved, the speech had improved. Day 25 of hospitalization, the swallowing had improved and on day 32, the patient had no complaint and was discharged and was advised to have regular outpatient appointments on Department of Pulmonology, Neurology and Physiotherapy.

DISCUSSION

CD4+ T cell is essential component in white blood cells that plays a central role in activating, coordinating, modulation, and regulating adaptive immune responses.[11] The deficiency of CD4+ T cells causes several problems, one of which is an infection caused by pathogens.[12] Several factors causes the deficiency of CD4+ T cells including HIV infection. CD4+ T cells deficiency in HIV patients is common in which HIV is attached to the CD4+ protein on the T cells surfaces and destroys CD4+ T cells, leading to a weakened immune system.[13] If CD4+ T cells become depleted to less than 200 cells/UL, the body becomes more susceptible to opportunistic infections, particularly intracellular pathogens such as herpes simplex virus, *Mycobacterium*, *Listeria*, and intracellular fungal infection.[14] Our patient showed a CD4+ T cells deficiency to 154 cells/mm^3 and was diagnosed as having tuberculosis and CD4+ T cells deficiency pro evaluation with negative HIV test. This confirms that decreased CD4+ T cells are not associated with HIV.

Other factors contributing to the decline of CD4+ T cells are active tuberculosis and ICL.[15] The possibility of CD4+ T cell deficiency in tuberculosis may be caused by excessive and persistent stimulation during active tuberculosis infection. During developing immunity to M tuberculosis infection, CD4+ T cells act as antibodies to send signals to other effector cells. However, *M tuberculosis* dissemination causes CD4+ T cells to overuse functionally and inhibits the proliferation of CD4+ T cells.[16]

The CD4+ T cells deficiency in ICL patients is a rare case and ICL is a rare disease. Clinically, ICL manifests from asymptomatically to the possibility of severe infections such as caused by *Candida*, cytomegalovirus, and *M. tuberculosis*. Some researchers hypothesize that apoptosis is the cause of CD4+ T cells deficiency ICL patients by T cell receptor cross-linking.[17] The most common infection in ICL patients is caused by *Cryptococcus neoformans* followed by *M.* tuberculosis.[18] In the present case report, the patient was positive for *M. tuberculosis* that infected multiple organs causing pulmonary tuberculosis, meningitis tuberculosis, and pleurisy tuberculosis. Pulmonary tuberculosis is the infectious and the most common form of tuberculosis, occurring in over 80% of cases.[19] A study found that patients who had recently been infected with *M tuberculosis* caused functional fatigue and reduced CD4+ T cells. This correlation between *M. tuberculosis* infection and CD4+ T cells which underlies that tuberculosis treatment will correlate with an increase in CD4+ T cells counts.[20] Meningitis tuberculosis also could cause

a decreased in CD4+ T cell levels.[10] The patient with pleural tuberculosis with CD4+ T cells deficiency with HIV was never reported. Pleural tuberculosis generally occurs at a young age with acute or subacute syndromes. Diagnosis of this disease uses pleural fluid biomarkers such as adenosine deaminase (ADA). Patients with ADA values >70 U/L are positive for pleural tuberculosis.[21,22]

Treatment of CD4+ T cells deficiency can be done by treating the infectious pathogens. In our case, the patient began to improve when anti-tuberculosis drugs were provided clinically. On day 32 of anti-tuberculosis treatment, the patient had no complaints and was advised to discharge. Anti-tuberculosis provided was isoniazid, rifampicin, and pyrazinamide. Since this anti-tuberculosis could cause the hepatitis, monitoring the side effects during treatment is essential and ethambutol is the only safe drug for people with liver disease.[23,24] Besides side effect monitoring, the risk drug interaction between anti-tuberculosis drugs and other drugs must be evaluated.

CONCLUSION

We reported a case of a fifty-eight-year-old male suspected of CD4+ T cells deficiency with pulmonary and extra pulmonary tuberculosis (meningeal and pleural). The suspected etiology of CD4+ T cells deficiency, in this case, was either active tuberculosis infection or idiopathic CD4+ T cells lymphocytopenia. Therefore, CD4+ T cells recount was advised after tuberculosis treatment to ensure the patient's causative of CD4+ T cells deficiency. This patient highlights the difficulty of have definitive cause of the CD4+ T cells deficiency.

PATIENT CONSENT

The patient's written informed consent was obtained to publish the case in an academic journal.

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DISCLOSURE OF CONFLICTS OF INTEREST

All authors declare that there is no conflict of interest.

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AUTHOR CONTRIBUTION

All authors contributed equally to the study.

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