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Tuberculous Pleural Effusion in Child with Acute Lymphoblastic Leukemia

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ABSTRACT

Tuberculosis (TB) is a world health problem, especially in developing countries. Extrapulmonary tuberculosis may occur in 25-30% of TB infected children. Immunocompromised patientsare in risk for developing TB disease, such as in malignancy. In this case, we will present pleural TB case in children with acute lymphoblastic leukemia with a history of previous pulmonary TB. This aims to highlight the diagnostic points of pleural effusion due to malignancies or reactivation of latent infection. A 16 years old boy had been known to have an acute L2 lymphoblastic leukemia and history of pulmonary TB at 6 years old and recovered. Patient has recurrent fever, weight loss, and shortness of breath. Chest pain and decrease of breath sound at left hemithorax were found in physical examination. Chest x-ray showed left pleural effusion. Pleural tapping was performed and showed mononuclear predominant, indicated TB or malignancy. Adenosine deaminade (ADA) test was performed, it confirmed the diagnosis of TB pleural effusion. Patient received anti tuberculosis therapy plus prednisone.n Diagnosing TB in malignancies is challeingchallenging due to similarity of clinical manifestation, and patient with malignancy are in high risk for developing TB infection. ADA pleural test has a higher specificity and sensitivity in diagnosing pleural TB.

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1. Introduction

In recent years there has been renewed interest in pediatric tuberculosis (TB) with growing awareness that more children have TB than was previously thought. The World Health Organization (WHO) estimates that in 2015, of the 10.4 million new TB cases, 10% (approximately 1 million cases) occurred in children.[1] Of the 9 million new TB cases worldwide, 1 million are children <15 years of age. Of all the cases of children with TB, 75% were found in twenty-two countries with high burden countries.Reported from various countries the percentage of all cases of TB in children ranges from 3% to >25%.[2]

Up to 25% of tuberculosis cases present extrapulmonary involvement. This is produced by hematogenous and lymphaticspread of the M. tuberculosis bacillus to other organs. The most common locations are the lymph nodes, pleura and theosteoarticular system.[3]Tuberculous pleural effusion (TPE) results from Mycobacterium tuberculosis infection of the pleura and is characterized by an intense chronic accumulation of fluid and inflammatory cells in pleural space.[4]

In immunocompromised children, risk factors for TB infection develop into TB disease, including malnutrition, HIV infection, malignancy, organ transplantation, immunosuppression, diabetes mellitus and chronic renal failure.[5]Patients with acute leukemia represent as an immunocompromised population with innate, humoral as well as cellular immune-paresis. These patients are therefore vulnerable for acquiring new infections and reactivation of latent infections including TB. Managing TB poses unique challenges in patients with acute leukemia on diagnostic and therapeutic fronts.[5] Presentation with long standing fever with constitutional symptoms and enlarged lymph nodes, as the important sign of TB, is often attributed to the hematological malignancy in patients of acute leukemia.

Despite the high prevalence of TB in general population in developing countries, tubercular re-activation is rarely suspected in patients with acute leukemia, and lesions found on imaging are frequently presumed to be of fungal etiology unless proven otherwise.[5]Furthermore, TB may present with atypical manifestations, leading to delay in diagnosis in these patients which may facilitate the transmission of TB to other immuno-compromised patients often being treated in the vicinity. The presence of cytopeniafurther precludes the use of invasive diagnostic modalities to obtain a definitive evidence for TB.[5]

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Treatment of tuberculous pleural effusioninvolve combination of many drugs.[6] The outcome is excellent if tuberculous pleural effusion is diagnosed early and treatment is begun quickly. Tuberculous pleural effusion can cause permanent lung damage if not treated properly.[7]

Here, we present pleural TB case in children with acute lymphoblastic leukemia with a history of previous pulmonary TB.

2. Case Report

A 16 years old boy was hospitalized in Dr. M. Djamil Hospital pediatric ward for 14 days with chief complain of fever since3 days before admission. The patient had been known to have high risk acute L2 lymphoblastic leukemia since 2015. He received chemotherapy regimenin maintanance phase. Patient had recurrent fever since two months before admission, not high, intermitten. But since three days before admission he got high fever, no sweating, no chills and no seizures. Cough since two months before admission, not productive, and no cold. Pain in the left chest since two months before admission, became worse since 1 week before admission. There was no shortness of breathing, no nausea and vomiting. There was no history of ear discharge. There was no bleeding on the skin, gums, nose and intestines. Weight loss in two months, from 63 kg to 61 kg. The appetite was still good. Void and defecation were within normal limits. He had been hospitalized twice for the same complaints. He received non-neutropenia fever therapy. Radiology of chest x-rays and other tests was normal. Patient had pulmonary tuberculosis at the age of 6 years, and was given anti-tuberculosis therapy for 9 months and had recovered. There was no family history who suffered from malignancy nor tuberculosis. His caregiver was diagnosed with tuberculosis based on chest x-rays.

Patient was first child from two siblings, patient was born by sectio caesarean delivery caused of prematurity rupture of membrane (PROM), preterm birth, with low birth body weight 1400 gram, hospitalized in neonatology for 1 ½ months. Basic immunization was completed, BCG scar was positive. Growth and developmental history were normal. Hygiene and sanitation were good.

Patient looked moderately ill. Alert. Blood pressure was 110/70 mmHg, heart rate 110 times per minute, respiratory rate 24 times per minute, body temperature 38,8^{o}C, body weight 61 kg, body height 172 cm, weight for age was 103%, height for age was 99,5%, weight for height was 106%, with impression normoweight. There were no anemic nor edema, no jaundice and no cyanotic. Skin was warm. Head was round. There was no regional lymph node enlargement, conjunctiva was not anemic, sclera was not icteric, pupil isochoric with diameter 2mm/2mm, light reflex was positive normal. Ears and nose were normal. Tonsil was T1-T1, not hyperemic and pharynx was not hyperemic. Mouthmucous was wet. On lungs examination, chest movement was asymmetric, movement of left hemithorax was lagged, left fremitus was lower, dim percussion from belowICS IV in left hemithorax, breath sound was vesicular, decreased from below ICS IV left hemithorax, and no rales nor wheezing were heard.On cardiac examination: ictuswas palpable at left midclavicularis line, intercostal space V, heart sound: regular rhythm, no murmur. There was no abdominal distension, liver and spleen was not palpable, peristaltic sound was normal. No abnormality found in genitalia, puberty state $A_2P_2G_2$. Extremities was warm with good perfusion, physiological reflexes were positive normal, pathological reflexes were negative.

On laboratory findings, haemoglobin was 13,0 g/dL, leukocyte 4.890/mm^3, differential count 0/0/0/86/11/3, hematocrite 41 vol%, platelet 341.000/mm^3, no blast cell. Total protein 6,1 g/dL, albumin 3,8 g/dL, globulin 2,3 g/dL. LDH 479 u/l. Routine urinalysis and stool analysis whithin normal limit.

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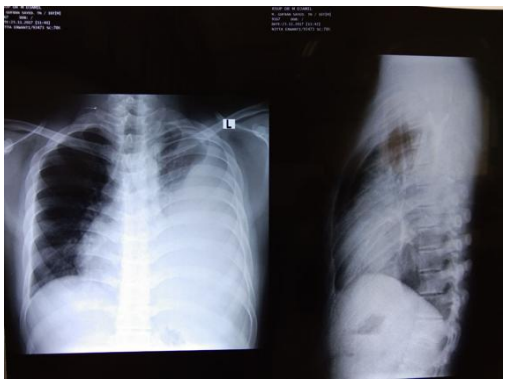

Fig 1. Cheat x-ray before pleural tapping

On chest x-ray we found homogenous semiopaq covered at base of left hemithorax. Trachea deviated to right side. Heart size and shape were not clear, impression no enlargement, aorta and superior mediastinum were not widening. Both of hillus not thickening, rbronchovascular shading in right lung within normal limits. No infiltrate or nodule on both hemithorax. Left costophrenicus sinus and diaphragma were covered, right costophrenicus and diaphragmaangle were sharp. Intact bone, no lytic/blastic lesions or destruction. Impression: Left pleural effusion

We diagnosed the patient as acute lymphoblastic leukemia on therapy and left pleural effusion due to malignancy differential diagnosed with tuberculosis.

Pleural effusion puncture was performed, in sterile condition with 18 Fr needlebelow the 5th rib on posterior axillary line. We evacuated approximately of 600 ml yellowish clear pleural fluid, no blood, no pus. Then, needle was exerted and close with sterile gauze. Pleural fluid and cytology analysis, pleural fluid culture, pleural fluid gene expert, pleural fluid *Adenosine Deaminase Analysis* (ADA) were performed

Pleural fluid analyze result: macroscopic were clear yellow, ±10 cc. Microscopic: cell 925/mm^2, PMN 5 %, MN 95%, no blast cell was found, Protein 4,5 gr/dl, glucose 82 mg/dl, LDH 549 u/L, albumin 2,3 gr/dl, rivalta was positive, no group of cells with various size, nucleus and cytoplasmic membrane not clear, no sign of malignancy. Pleural effusion was suggested tuberculosis. Cytology of pleural fluid: no malignancy cell and specific prosess. Sputum induction was performed to check gene x-pert of pleural fluid.

Patient lrecieved FDC (RHZE) 1x4 tablets, Prednison 3x20 mg (4 tablets), Paracetamol 500 mg, continue antibiotic for neutropenia fever.Sputum gene X-pert was negative.

On 14^{th} day of hospitalization, there were no fever, no cough, no breathlessness. Pain on left hemithorax was decrease. Chest movement was asymmethric, movement of left hemithorax was left, left phremitus was decrease than right, dim percussion below ICS VII in left hemithorax, breath sound was vesicular, decreased from below ICS VII in left hemithorax, and no rales nor wheezing were heard. We did pleural puncture, pleural ADA test. Patient then discharged, planned to tappering off prednison until 2 weeks and control at ambulatory clinic.Adenosine Deaminase (ADA) level was 47 U/l (>40 U/l) suggestes TB pleural effusion.

On 2 weeks after hospitalization, patient in good condition, no fever, no cough, pain in left hemithorax intermittent, decrease, no breathlessness. Patient should get chemotherapy based on the chemotherapy protocol. He was alert, normal vital signs, chest movement was asymmethric, movement of left hemithorax was lagged, left phremitus was decreased, dim percussion below CS VII in left hemithorax, breath sound was vesicular, decreased from below of ICS VII left hemithorax, and no rales nor wheezing were heard. We performed chest x ray for evaluation.

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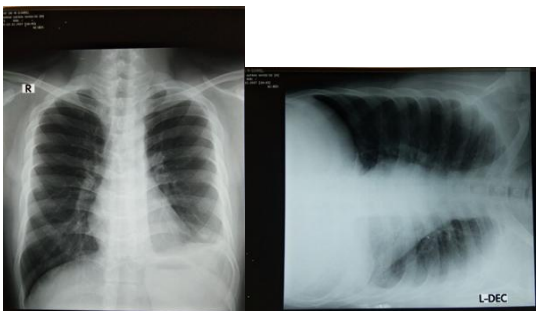

Fig 2. Chest x-ray on evaluation

Chest X-ray examination on PA and lateral decubitus view: Normal heart size and shape, thickening hillus, infiltrate at right and left perihiler, left costophrenicus sinus were covered, normal diaphragma. Impression was minimal left pleural effusion. Chest x-ray image showed resolution

Patient recieved chemotherapy, continue anti tuberculosis therapy, and prednisone was stopped.

3. Discussion

A 16 years old boy was hospitalized with tuberculous pleural effusion, acute lymphoblastic leukemia. Diagnosis was established based on history of prolonged fever for 2 months, pain at left hemithoraxduring deep breath. There was history of recieveing anti tuberculosis therapy when he was 6 years old for 9 months from pediatrician, transmitted from his careguver. Basic immunization was completed, BCG scar was positive. Patient suffered from malignancy, high risk acute lymphoblastic leukemia L2, recieved chemotherapy regimen in maintanance phase. Pleural effusions may be asymptomatic until there is an increase in fluid volume in the pleural space causing cardiorespiratory disorders (dyspnea, and orthopnea). In older children, symptoms of pleuritic chest pain that usually arise during inspiration or cough caused by parietal pleural stretching. When fluid increases and separates the two pleural membranes, chest pain becomes blunt and may disappear.[8]TB effusions typically present as acute to subacute illnesses, characterized by unilateral pleuritic chest pain (~75%), cough (~70%), fever (~85%), night sweats (~50%), dyspnoea (~50%) and weight loss (25–85%). A small proportion of patients have only mild symptoms.[9]

On physical examination, chest movement was asymmetric, movement of left hemithorax was lagged, left phremitus was decreased, dim percussion below ICS IV in left hemithorax, breath sound was vesicular, decreased from below ICS IV left hemithorax, and no rales nor wheezing were heard.Apleural rub may be the only initial manifestation during theearly stage of pleurisy. The rub disappears as fluidaccumulates between the pleural surfaces. A large fluidcollection causes fullness of the intercostal spaces anddiminished chest excursion on the affected side. Excessiveunilateral fluid accumulation shifts the mediastinum anddisplaces the trachea and cardiac apex to the contralateralside.[10]

On chest X-Ray examination – PA and lateral projection, both hilluswere not thickening, no infiltrate or nodule on both hemithorax, left costophrenicus sinus and diaphragmawere covered, right costophrenicus and diaphragmaangle were sharp. Chest radiology examination is a routine examination in patients with pleural effusion. An anteroposterior radiological image showed dull angle between the diaphragm and costae.[11] Decubitus lateral projection are important for the presence of subpulmonary pleural effusions. This examination is very sensitive to detect the presence of ±5 ml fluid in the pleural cavity.[12]Additionally, CT scans may detect abnormalities suggestive of intrathoracic TB in a child suspected of having complicated intrathoracic lymph node or pleural disease, endobronchial lesions, bronchiectasis, or cavities that are not well revealed on plain radiography.[13]

Pleural tapping was performed on the patient based on clinical, physical and radiological examination. The goal is for diagnostic and therapeutic. Shortness of breath and chest pain improved after pleural tapping. Estenne et al suggested that relief of dyspnea after thoracocentesis

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results primarily from reduction in size of the thoracic cage, which allows the inspiratory muscles to operate on a more advantageous portion of their length-tension curve. Another study showed improvement of gas exchange as a result of an improved ventilation-perfusion ratio due to increased ventilation in previously poorly ventilated but perfused lung.[8]

Pleural fluid with tuberculosis is invariably an exudate. Usually, the pleural fluid protein level exceeds 5 g/dL, which suggests TB pleuritis. The majority of patients has greater than 50% of small lymphocytes in their pleural fluid, and some have more than 90%. However, a patient who presents with symptoms for less than 2 weeks in duration is more likely to have predominantly neutrophils in his pleural fluid.[14] Pleural fluid glucose levels with TB pleuritis may be reduced but are usually similar to serum levels. The pleural fluid pH is usually >7.30 but may be lower. Pleural fluid lactic acid dehydrogenase (LDH) levels are usually higher than serum LDH levels.[15]Fluid analysisin this patient showed exudate, with LDH 549 u/L (>200 u/L). Cell count was 925/mm^2 with monoluclear predominant 95%, indicated tuberculosis or malignancy. No blast cell was found and no grouping cells with varied size and not clear edge of nucleus-cytoplasmic that features of malignany. No paracyte was found in pleural fluid. Cytology of pleural fluid: no malignancy cell and no specific prosess was found.Other diagnostic tests available to help establish the diagnosis pleural TB disease including adenosine deaminase (ADA), interferon-γ, and polymerase chain reaction (PCR). ADA has high sensitivity and specificity and is used routinely in various endemic TB countries.[15] There is no doubt that pleuroscopy-guided biopsy is of great value for TPE diagnosis; however, sensitivity and specificity of noninvasive tests, especially ADA, can help to distinguish between TB and malignancy.[5] ADA level of pleural fluid in this patient was 47 U/L (>40 UL). It confirmed the diagnosis of tuberculosis pleural effusion and exclude malignancy etiology.

Among the routinely performed biochemical tests for investigating pleural effusion, serum lactate dehydrogenase (LDH), pleural ADA, and pleural lymphocyte count change in reciprocal manner in patients with MPE and TPE. Serum LDH is raised in MPE whereas pleural ADA and pleural fluid lymphocyte count remain comparatively low. Conversely, serum LDH is low in TPE whereas pleural ADA and pleural fluid lymphocyte count are raised. Previous report form Verma et al, a retrospective analysis demonstrated that a “cancer ratio” (serum LDH: pleural ADA ratio) yielded sensitivity and specificity of 0.98 and 0.94, respectively, at the cut-off level of >20 for identifying MPE. In this patient, cancer ratio was 10.2 therefore not appropriate to MPE.[16]

Direct smear examination is the easiest, quickest, and cheaper diagnostic procedure, but it can only confirm the possibility of TB because it has not been able to distinguish TB or non-TB.[12] The paucibacillary nature of pleural TB reduces the yield of positive stain and culture for acid-fast bacillus. Usually, the AFB positivity in the fluid is < 20% and fluid culture grows AFB in 18-38% of samples, which takes 6-12 weeks. Comparing for adults, the sensitivity of AFB and culture was lower in detection of TPE for pediatrics.[9] Sputum AFB in this patient was negative. Gene expert sputum patient was negative. In this patient there was no sign of pulmonary tuberculosis, and no productive sputum. Tuberculous pleural effusion in this patientmight be due to reactivation of post primary tuberculosis.

For a patient suspected of having TB pleuritis, the tuberculin skin test is being utilized less and less. This is because a negative test does not rule out the diagnosis of TB pleuritis. In a recent study of 66 patients, 22 were diagnosed with pulmonary TB via the presence of sputum cultures that were positive for TB or via bronchoscopy. Among the 22 patients with pulmonary TB, 9 patients had a negative TB skin test, indicating a positive response rate of only 59.1%.[17]However, the skin test may remain a negative result if the patient is immunosuppressed with HIV infection or is severely malnourished.[15]In this patient, tuberculin skin test was not performed because no PPDRT 23. Patient was suffered pulmonary TB when he was 6 years old, tuberculin skin test might be not a beneficial test in this case.

Patients received anti tuberculosis therapy plus prednisone. Steroids can accelerate the clinical improvement and absorption of pleural fluid. Wyser et al found that corticosteroids may contribute to complete resolution of effusion in the lung cavity, but no clinical improvement is accelerated and does not affect pulmonary thickening. Corticosteroids are useful for patients with high fever, impaired immunity, and patients with severe pleurisy chest pain who do not respond well to anti-tuberculosis drugs alone.[18]

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This patient received oral prednisone at a dose of 2 mg/kgBW/day divided in 3 doses, administered for 4 weeks, then the chestx-ray was reevaluated. Chest x-ray evaluation was performed 2 weeks after therapy, there was improvement and tappering off prednisone was performed.

Chest tube drainage maybe indicated in patients withenlarged effusions. In various studies, the main indicationsfor acquiring chest tube placement have been pointed asfrank pus on thoracentesis, a positive pleural fluid Gramstain and culture finding, a pleural fluid pH level of less than7, a glucose concentration of less than 40 mg/dL, or an LDHlevel of more than 1000 IU.[10]Therapeutic thoracentesis can be considered in patients with larger pleural effusions or significant dyspnea, as it has been shown to more quickly resolve dyspnea, though there is no effect on long-term outcomes.[19]

The prognosis for children with TB pleural effusion is better than other forms of extrapulmonary TB, although it has not been treated. Permanent damage to lung function in patients with TB pleural effusion rarely occur.[14]A prompt diagnosis will lead to early treatment to control the disease, improve patient outcomes and reduce ongoing spread in the community.[20]

4. Conclusion

Diagnosing TB in malignancies is stillchallenging due to similarity of clinical manifestation, and patient with malignancy are in high risk for developing TB infection. *Adenosine deaminase* (ADA) pleural test has a higher specificity and sensitivity in diagnosing pleural TB.

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