CASE REPORT

CONCURRENT TUBERCULOUS PLEURAL EFFUSION AND PERITONITIS:

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ABSTRACT

Introduction: Extrapulmonary tuberculosis accounted for about 16% of 7.5 million tuberculosis cases worldwide in 2019 with lymph nodes, pleura, and gastrointestinal system as its most common sites of infection.
Case description: A 36 year-old female patient presented with dyspnea and abdominal distention due to unilateral pleural effusion and ascites. She had accompanying symptoms of weight loss and night sweat since 6 months prior to her presentation. The patient's medical history was unremarkable, but she had positive contact with tuberculosis patients. Diagnostic approach was taken. Both pleural fluid and ascitic fluid were analysed, revealing exudative fluid with lymphocyte predominance. ADA for both pleural and ascitic fluid was elevated. Abdominal CT scan showed para-aortic lymphadenopathy, omental thickening, and complex ascites. Pleural fluid culture for Mycobacterium was positive for M. tuberculosis. Diagnosis of tuberculous pleural effusion and peritonitis was made and anti-tuberculous treatment was initiated.
Conclusion: The variable manifestation of extrapulmonary TB can make diagnosis difficult, but this diagnosis should always be considered especially in the setting of high TB prevalence. Confirmatory diagnosis with microbiological examination should always be attempted, but clinical feature highly suspicious of TB supported with biological marker can aid in the diagnosis of extrapulmonary TB.
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INTRODUCTION

Tuberculosis (TB) is a communicable disease caused by *Mycobacterium tuberculosis*. It is spread through inhalation of droplet nuclei containing tuberculous bacilli which can cause infection in the lungs or spread to other organs.[1] TB causes a major burden to global health. In 2020, about 10 million people globally contracted the disease and about 1.5 million deaths were attributed to tuberculosis, making TB the 13th leading cause of death worldwide. Despite its high burden, TB is treatable and prompt treatment with anti-tuberculous drugs may lead to cure.[2]

Extrapulmonary tuberculosis accounted for about 16% of 7.5 million tuberculosis cases worldwide in 2019.[3] The most commonly involved organs are the lymph nodes (50%), followed by pleura (18%), genitourinary system (13%), and gastrointestinal system (6%).[4] Indonesia, being the second highest burden country for TB, contributes to 9.2% of global TB cases in 2021.[2] With TB prevalence of 759 cases per 100,000 persons in Indonesia[5], extrapulmonary TB is not uncommon.

The manifestation of extrapulmonary tuberculosis is variable and can often mimics other diseases. Therefore, awareness of the possibility of such diagnosis is needed for early diagnosis and prompt treatment.[4]

This case report presents a patient with unilateral pleural effusion and ascites which turned out to be tuberculous pleuritis and peritonitis. Diagnostic approach taken to diagnose extrapulmonary TB in this patient will be discussed.

CASE ILLUSTRATION

A 36 year-old female patient was admitted to the emergency department due to increased sensation of dyspnea since three days prior. The symptom was worsened while lying down, walking, and prostrating, but alleviated by sitting upright or lying on her left side. She denied having any chest pain. She had been experiencing such symptoms for 2 months but had not seek any medical advice until the dyspnea became unbearable to her. She also had a complain of non-productive cough, but she denied having any fever. She also experienced night sweats and had lost 19 kg of weight within the past two months.

Six months before presentation, the patient noticed that her stomach was getting bigger. There was no palpable lump or mass in her stomach, but she felt that it was increasing in circumference. She experienced abdominal fullness and early satiety, thus decreasing her appetite. However, she did not notice any change in bowel movement and did not have any abdominal pain. She had consulted her symptoms to an obstetric-gynaecologist, at first thinking that she was pregnant. However, no abnormality was found on the gynaecological ultrasound aside from fluid accumulation in the peritoneum. She had been referred to our specialist clinic for further evaluation and a contrast abdominal CT scan had been ordered to rule out intra-abdominal malignancy as a cause of her ascites. When she presented at the emergency department, the result of her CT scan was not yet available.

The patient had hypertension which was diagnosed 2 years prior. She was prescribed with amlodipine which she rarely took. Her systolic blood pressure ranged between 140-160 mmHg. History of heart condition, diabetes, liver, kidney, and autoimmune disease was denied. She also denied taking any over the counter medication or herbal medicine. She had no history of prior tuberculosis infection or treatment.

The patient's family history was positive for diabetes. There was no family history for heart attack and hypertension. Her brother and his wife had a history of lung tuberculosis which had been treated and cured half a year before the patient's symptoms appeared. The patient denied any history of smoking or taking alcohol. She had no history of promiscuity and intravenous drug usage. The patient was obese with body mass index of 26.5 kg/m^2.

Upon arrival at the emergency room, the patient appeared dyspnoeic with

respiratory rate of 28 times per minute, peripheral oxygen saturation of 99% with oxygen supplementation of 3 litre/minute via nasal canula. Physical examination revealed decreased vesicular breathing sound on the left lung beneath the second intercostal space. No rales, crackles, or wheezing was heard. Chest x-ray showed massive left pleural effusion with no visible pulmonary infiltrate, mandating thoracentesis. About 1500 ml of serous fluid was aspirated from the left pleura in two sequential thoracentesis. The pleural fluid was sent for fluid analysis. The patient who had been stabilized was then transferred to the regular ward.

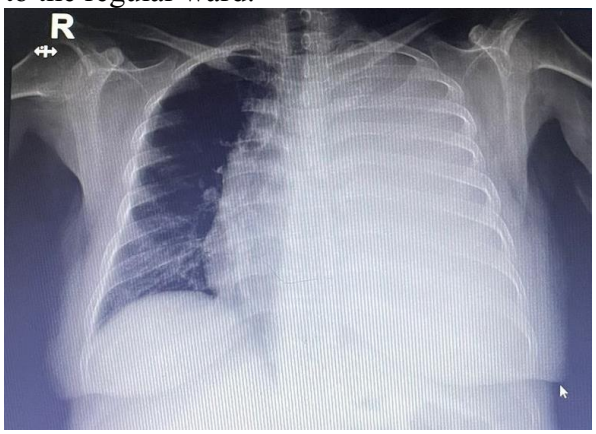

Figure 1. Chest X-ray
The patient's chest x-ray at presentation, revealing massive left pleural effusion.

Physical examination revealed normal jugular vein pressure. There were no palpable lymph nodes on the neck and axillae. The chest was symmetrical with no intercostal retraction, but there was reduced expansion of the left lung side. Percussion on the left hemithorax was dull from beneath the third intercostal space and sixth thoracic vertebrae. Vesicular lung sound was diminished on the left lower lobe, but there was no rales, crackles, and wheezing. The abdomen was inflated with the circumference of 90 cm. The examination was negative for chess board phenomenon, but the test for shifting dullness was positive. There was no tenderness upon palpation. The liver and spleen were not enlarged and there was no palpable mass in the abdomen. There was no ankle edema.

Basic laboratory examination showed elevated erythrocyte sedimentation rate of 97. Liver enzyme and renal function were within normal value. Her fasting blood sugar level was normal. Tumor marker Ca-125 which was evaluated during her previous outpatient visit was elevated at the level of 99.1 U/mL (normal value 0-35 U/mL) .

The analysis of pleural fluid revealed exudative fluid with increased number of cells and mononuclear cell predominance (1,189/L). The fluid pH was 7.9 with fluid glucose level of 92 and fluid LDH level of 273. Most common differential diagnosis for exudative pleural effusions are malignancy and tuberculosis.

Sputum specimen was attempted to be collected for microbiological examination and acid fast bacilli staining. However there was no expectorated sputum even after sputum induction.

The patient's follow up chest x-ray showed residual pleural effusion on the left side without any visible infiltrate on the lungs. She went through the third thoracentesis and 600 ml of pleural fluid was evacuated which was sent for cytology, microbiological analysis, and ADA testing. Since there is a suspicion towards tuberculous pleural effusion, the pleural fluid was also sent for *Mycobacterium* culture and PCR. The patient also underwent paracentesis to alleviate her abdominal fullness. About 1.5 litre of ascitic fluid was aspirated and sent for analysis, culture, and cytological examination.

The patient also underwent thoracoscopy procedure which showed fibrin covered visceral pleura and multiple miliary nodules on the surface of the parietal pleura. Biopsy specimen was taken from both the parietal and visceral pleura. A chest tube was inserted after the thoracoscopy procedure and serous production was observed from the chest tube.

Her abdominal CT scan showed loculated ascites with thickened peritoneum and para-aortic lymphadenopathy. There was no intra-abdominal and gynaecological mass which ruled out intra-abdominal malignancy.

To rule out possible intra-thoracic malignancy, contrast CT scan of the thorax was also ordered. It showed complex hydropneumothorax of the left pleura with fibrosis of the right lung, mediastinal lymphadenopathy and paraaortic lymphadenopathy. There was no intra-thoracic mass and no pulmonary nodules.

Ascitic fluid was exudative with serum ascites albumin gradient (SAAG) of 0.1 and elevated number of mononuclear cells. The Gram stain and culture for both the pleural and ascitic fluid were negative for any microorganism. Acid fast stain for pleural fluid was negative. Cytological analysis for both fluids turned out negative for any malignant cells. However, adenosine deaminase (ADA) was elevated for both the pleural (46 IU/L) and ascitic fluid (102 IU/L). Her pleural fluid sample was also sent for *Mycobacterium* culture. The result was positive for *Mycobacterium tuberculosis.*

Table 1. Results of pleural fluid and ascitic fluid analysis in this patient

	Pleural Fluid	**Ascitic Fluid**
Appearance	Yellowish, slightly turbid	Yellowish, slightly turbid
Rivalta	Positive	Positive
Cells	1200	840
PMN	11	168
MN	1189	672
Fluid albumin	N/A	3.4
Serum albumin	N/A	3.5
Fluid LDH	273	669
Serum LDH	263	185
Fluid protein	6.4	8.7
Serum protein	8.5	8.6
Fluid glucose	92	41
Serum glucose	103	95
Conclusion	Exudate	Exudate
Gram stain	No bacteria was found	No bacteria was found
Culture	No organism was grown	No organism was grown
Cytology	Negative for malignant cells	Negative for malignant cells
ADA	46	102

Results of the pleural biopsy showed multiple tubercles consisted of caseous necrosis surrounded by cells, Langhans giant cells and lymphocytes-a typical presentation of granulomatous inflammation that can be seen in *M. tuberculosis* infection. The PCR of the pleural tissue was also positive for *M. tuberculosis*.

The diagnosis of tuberculous pleural effusion and tuberculous peritonitis was made. Anti-tuberculous drug was initiated with first line regiment consisting of rifampicin, isoniazid, ethambutol, and pyrazinamide. The patient was tested for HIV to rule out coinfection and the result turned out negative. The patient was finally discharged from the hospital after the chest tube removal.

During her follow up visit, two months after the initiation of anti-tuberculous drugs, she appeared well with improved clinical condition. She no longer complained of dyspnea and there was no longer any abdominal fullness. She then continued taking anti-tuberculous drugs and being under observation for adherence, clinical improvement, and drug intolerance.

DISCUSSION

Extrapulmonary tuberculosis accounted for 16% of TB cases in 2019. The manifestation of extrapulmonary TB varies according to its site of infection, but may be accompanied by systemic symptoms such as fever, night sweat, and weight loss.[6] Tuberculous pleural effusion is the second most common form of extrapulmonary tuberculosis, followed by tuberculosis of the genitourinary system and abdominal tuberculosis.[4]

Extrapulmonary tuberculosis can be caused by primary infection at the extrapulmonary site, such as by ingestion of tuberculous bacilli in abdominal TB, or caused by secondary spread from the primary infection at the lungs. The bacilli can spread via hematogenous or lymphogenous route.[4] About 10-50% of extrapulmonary tuberculosis is accompanied with pulmonary tuberculosis. Definitive diagnosis of extrapulmonary TB requires positive culture for *Mycobacterium tuberculosis* from the infected tissue, but it is not sometimes possible since the method of specimen procurement can be invasive. [7]

TB pleuritis, which accounted for 18% of extrapulmonary TB, was thought to be caused by mycobacterial infection within the pleural space, originating from adjacent parenchymal lesions. The infection within the pleural space resulted in inflammatory response which disrupts the pleural fluid balance. Initial inflammatory response may induce neutrophil activation, followed by lymphocyte driven immune reaction that causes granuloma formation and release of ADA. Therefore lymphocyte predominant pleural effusion can be observed in TB pleuritis. Containment of TB infection in pleural space involves activation of T-helper type 1 lymphocytes. These Th1 cells release IFN-γ which can be found elevated in TB disease.[8]

Extrapulmonary TB can also involve the peritoneum, which is the sixth most common site of infection.[9] Tuberculous peritonitis is thought to be caused by reactivation of latent foci of infection in the peritoneal lymph nodes, preceded by previous pulmonary infection. Other mechanism is thought to be direct spread via mesenteric lymph node after infection of ingested bacilli at the Peyer's patches of the intestinal mucosa.[10] Ascites is found in 73% of cases while abdominal tenderness only presents in 47,7%.[10] Diagnosis of peritoneal TB can be confirmed by laparoscopy and peritoneal biopsy which should show histopathological characteristics of tuberculous infection. However, laparoscopic procedure is invasive and usually done only when the diagnosis cannot be concluded from other examinations. Non-invasive testing such as ascitic fluid analysis is the preferred method of diagnosis. Ascitic fluid examination usually shows straw colored fluid. AFB staining usually yields negative result as the sensitivity of such examination is only 3%.[10] On the other hand, ADA of peritoneal fluid has 100% sensitivity, 96% specificity, 53,3% positive predictive value, and 100% negative predictive value to diagnose peritoneal TB.[11]

In this case, the patient presented with worsening dyspnea that was caused by massive left pleural effusion. Dyspnea is a common manifestation in patients with pleural effusion although in some patients, such symptom only appears after there is sufficient amount of effusion that causes respiratory disturbance.[12] Pleuritic chest pain can also be found, but was not apparent in this patient. This patient's posteroanterior chest x-ray showed unilateral opacity of the left lung. She also had accompanying symptoms of abdominal distention, night sweats, cough, and weight loss. No history of heart, renal, and hepatic disease was found.

Unilateral pleural effusion with no clear etiology mandated diagnostic pleural aspiration.[13–15] Macroscopically, the pleural fluid was yellowish and slightly turbid. The pleural fluid was classified as exudate according to Light's criteria with fluid protein to serum protein ratio of 0.7 and pleural lactate dehydrogenase (LDH) to serum LDH ratio of 1.03. Light's criteria has 99,5% sensitivity to classify a pleural effusion as exudate.[13,14] Differential diagnosis for exudative pleural effusion consisted of malignancy, parapneumonic pleural effusions, tuberculosis, autoimmune pleuritis, and pancreatitis.

The pleural fluid showed increased cellularity with mononuclear (MN) predominance (99% cells are lymphocytes). Elevated mononuclear cells is usually observed in long standing pleural effusion caused by malignancy, cardiac failure, or

chronic infection such as TB. Very high lymphocyte count (80%) occurs most frequently in TB, lymphoma, chronic rheumatoid pleurisy, or sarcoidosis.[13,14] On the other hand, neutrophil-predominant pleural effusions are associated with acute processes such as parapneumonic effusions and pulmonary embolism.[14]

No signs of acute bacterial infection was found in this patient with no visible infiltrate on her chest radiograph. Therefore, the diagnosis of parapneumonic effusion is less likely. Malignancy is a possible diagnosis, thus cytological examination of the pleural fluid was done and the result was negative. The sensitivity of pleural fluid cytology is 60%.[14] A contrast CT scan of the chest revealed no mass in the thoracic cavity, ruling out pulmonary malignancy.

Since her accompanying symptoms were highly suggestive of TB, the pleural fluid was also tested for Adenosine Deaminase (ADA). ADA is an enzyme produced by lymphocytes which is found to be elevated in malignancy, tuberculous pleural effusion, empyema, or rheumatoid pleurisy. A meta-analysis and systematic review has evaluated the diagnostic value of ADA in diagnosing tuberculous pleural effusion. With a cut off of 40 IU/L, ADA has the sensitivity of 93% and specificity of 90% to diagnose tuberculous pleural effusion.[17] The pleural ADA level in this patient was elevated at 42 U/L, making tuberculous pleuritis a plausible diagnosis. Sputum examination should also be ordered to rule out pulmonary TB in patients suspected to have extrapulmonary TB.[18] However, in this case, sputum specimen was not able to be collected even after sputum induction. Acid fast bacilli (AFB) staining for pleural fluid was also ordered but it turned out negative. Positive results of AFB staining only occurs in about 10% of cases which requires the presence of more than 10,000 AFB/ml pleural fluid.[16]

Lymphocytic effusion with elevated level of ADA can be used to make a presumptive diagnosis of tuberculous pleuritis and give the consideration to start anti-tuberculous treatment.[8,18] However, in this case, we managed to retrieve microbiological confirmation with positive culture of *M. tuberculosis* in the pleural fluid. Pleural fluid culture using liquid media has sensitivity of 70% to diagnose tuberculous pleuritis.[8] The pleural tissue taken during biopsy was also tested for *M. tuberculosis* PCR which showed positive result. A meta-analysis showed that PCR for TB from pleural fluid has a pooled sensitivity of 58% and specificity of 87%.[16]

The patient also had ascites as confirmed by physical examination that showed abdominal distention with positive shifting dullness. No signs of liver disease was found during examination. The ascites had been present since 6 months prior to her current admission which had been evaluated for gynecological malignancy. Her abdominal CT scan showed no abnormality in the gynecological organs, but there were multiple lymph nodes enlargement and complex ascites accompanied with omental thickening, a radiological finding typical of peritoneal TB.[19] Elevated level of Ca-125 observed in this patient, which is usually associated with ovarian tumor can also be elevated in tuberculous infection, including peritoneal tuberculosis.[19]

Diagnostic paracentesis was done and revealed serous ascitic fluid with serum ascites albumin gradient (SAAG) of 0.1. SAAG value of 1.1 g/dL or higher has 97% accuracy for diagnosis of ascites due to portal hypertension,[20] while lower level indicates non-portal hypertension cause of ascites.[21] The fluid glucose level was lower than that of the serum, a condition which can be observed in infection and malignancy.[21] Meanwhile, the fluid's level of LDH was highly elevated with fluid/ serum ratio of LDH of 3.6. Ascitic fluid/ serum ratio of LDH of more than 1.0 can be found in infection, bowel perforation, or malignancy.[22] The ascitic fluid showed elevated number of cells with mononuclear predominance. However, the neutrophil count was less than 250 cells/L, ruling out spontaneous bacterial peritonitis. The ascitic

fluid culture was negative for microorganism growth. Cytology of the ascitic fluid was also negative for any malignant cells. With the suspicion of tuberculous pleuritis, the ascitic fluid was also tested for ADA which showed elevated level of 102. Elevated ascitic ADA with cut off value of 40 IU/L has 100% sensitivity, 96% specificity for tuberculous peritonitis.[11,21]

Complex ascites, omental thickening, and intra-abdominal lymphadenopathy with no visible mass as showed in the abdominal CT scan alongside with elevated ascitic fluid ADA support the diagnosis of TB peritonitis in this patient.

Concurrence of multiple sites of extrapulmonary TB has been reported in a few case reports.[23,24] An observational study from China showed that about 14% of patients with extrapulmonary TB had multiple sites of involvement. According to this study, the most common concurrent extrapulmonary TB are TB peritonitis and pleuritis which occurred in 1.8% of cases. Female gender is associated with higher risk to develop concurrent extrapulmonary TB.[25,26] This gender associated risk is observed in patients 45 years old or older.[26] HIV infection and end stage renal disease are also found as a risk factor for concurrent extrapulmonary TB.[27] The patient in this case was tested negative for HIV. No additional risk factor was discovered. The possibility of autoimmune disease has not been evaluated, but there was no apparent clinical symptoms and signs of autoimmune disease in this patient.

Standard regimen of anti-tuberculous drugs was initiated according to the national guideline with 4 drugs combination for 2 months of intensive phase (rifampicin, isoniazid, ethambutol, and pyrazinamide) and then continued with 2 drug combination of rifampicin and isoniazid for 4 months. The duration of treatment that is recommended is 6 months in total.[28] Treatment evaluation after two months showed clinical improvement with alleviation of dyspnea and abdominal fullness. Even though the pleural involvement in this case was confirmed bacteriologically, there was no recommendation regarding microbiological evaluation of extrapulmonary TB.[28] A cohort study showed that weight gain, symptoms improvement, and physical signs correlated with treatment response in extrapulmonary TB. About 93% patients with tuberculous pleuritis showed regression of effusion in routine chest x-ray after 2 months of treatment. Regression of ascites in abdominal TB was also observed after patients completing the course of treatment.[29]

CONCLUSION

Extrapulmonary tuberculosis comprises of 16% of TB cases worldwide. The manifestation of extrapulmonary TB is highly variable and depends on its specific site of involvement. TB is highly prevalent in Indonesia, thus extrapulmonary TB should always be considered as a possible diagnosis in patients presenting with TB symptoms and extrapulmonary manifestation. The challenge in diagnosing extrapulmonary TB is the retrieval of specimen for microbiological confirmation. However, other parameter can be used to diagnose extrapulmonary TB especially in the setting of high suspicion for TB. Prompt treatment with anti-tuberculous drugs can be given after the diagnosis is made and clinical improvement should be evaluated as the parameter of treatment response.

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