

Tuberculosis Peritonitis Patient with Septic Shock caused by Extended–Spectrum Beta Lactamases Producing *Pseudomonas Aeruginosa*

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ABSTRACT

According to World Health Organization (WHO), tuberculosis (TB) is a worldwide pandemic. Up to 5% of patients with TB may have abdominal disease and 25-60% may have peritoneal involvement. Diagnosis of TB peritonitis is still challenging, and symptoms are usually insidious. The sensitivity of acid fast bacilli (AFB) is very low, ranging from 0-6%. Conventional mycobacterial culture takes up to 8 weeks to achieve results. Laparoscopic or laparotomy biopsy is uncomfortable for patient. The consequence of these problems is missing and delays in diagnosing TB peritonitis. In the end, it can results in significant morbidity and mortality.

This case described a 20 year old female patient with TB peritonitis that suffered from septic shock caused by extended-spectrum beta lactamases (ESBL) producing *Pseudomonas aeruginosa*. In this case, TB peritonitis was diagnosed based on clinical features, high levels of adenosine deaminase (ADA) and a positive rapid DNA test with Xpert MTB/RIF.

Keywords: tuberculosis peritonitis, extended-spectrum beta lactamases producing bacilli, adenosine deaminase, XpertMTB/RIF assay

ABSTRAK

Menurut World Health Organization (WHO), penyakit tuberkulosis (TB) bersifat pandemik. Lebih dari 5% pasien TB menderita penyakit abdominal, dan dari jumlah tersebut 25–60% melibatkan peritoneum. Diagnosis peritonitis TB masih menjadi masalah karena keluhan biasanya tidak spesifik. Sensitivitas pemeriksaan bakteri tahan asam (BTA) sangat rendah berkisar 0–6%. Pemeriksaan kultur mycobakteri konvensional membutuhkan waktu 8 minggu. Prosedur laparoskopi atau laparotomi sering kali tidak menyenangkan pasien. Sebagai konsekuensi dari keadaan ini adalah sering terjadi kesalahan atau keterlambatan dalam menegakkan diagnosis peritonitis TB. Pada akhirnya hal ini menyebabkan morbiditas dan mortalitas yang signifikan.

Pada kasus ini dilaporkan seorang pasien perempuan berusia 20 tahun dengan penyakit peritonitis TB yang mengalami syok septic akibat terinfeksi bakteri *Pseudomonas aeruginosa* penghasil extended-spectrum beta lactamases (ESBL). Pada kasus ini diagnosis peritonitis TB ditegakkan berdasarkan gambaran klinis, peningkatan kadar adenosine deaminase dan pemeriksaan DNA cepat menggunakan Xpert MTB/RIF.

Kata kunci: peritonitis tuberkulosis, bakteri penghasil extended-spectrum beta lactamases, adenosine deaminase, pemeriksaan XpertMTB/RIF

INTRODUCTION

According to World Health Organization (WHO), tuberculosis (TB) is a worldwide pandemic. WHO fact sheet on TB stated that overall one third of the world's population (over 2 billion) is currently infected with the TB bacillus.¹ It has been reported that up to 5% of patients with tuberculosis (TB) may have abdominal disease. Of these, 25-60% may have peritoneal involvement.² Diagnosis of TB peritonitis is still challenging. Symptoms are usually insidious, with abdominal swelling, fever, night sweats, anorexia, weight loss, and abdominal pain. In this vague situation, clinician should maintain a high index suspicion for TB peritonitis, since missing the diagnosis can result in significant morbidity and mortality.³ If left untreated, the mortality rate with this disease is over 50%.⁴

This case report described about how to apply algorithm for evaluation of patient with suspected TB peritonitis that also suffered from septic shock caused by extended-spectrum beta lactamases (ESBL) producing *Pseudomonas aeruginosa*.

CASE ILLUSTRATION

A 20 year old female was admitted to Charitas hospital complaining of vomiting and fever 3 days before hospitalized. The patient said that in about two month latest she suffered from abdominal pain, tenderness and enlargement, anorexia and weight loss about 9 kg, but no bowel change habit. Two weeks before hospitalized in our hospital, she was cared as in patient for 5 days in other hospital. In the previously hospital she underwent ascitic fluid aspiration. The patient denied any history of TB, multiple sexual partners, or drug misused.

On physical examination the patient was fever, with temperature of 39.7 °C. There was no jaundice or pallor. Cardiac and lung examination were normal. Abdominal examination revealed abdominal tenderness and ascitic fluid collection. There were no lymph nodes, spleen or liver enlargement.

Blood investigations showed slight anemia (9.7 g/dL) and erythrocyte sedimentation rate was increase (47 mm/hour). Leukocyte, thrombocyte, liver and renal function were normal. A chest x-ray showed clear lung field. Ultrasound of the abdomen revealed liver, spleen, and gall bladder were normal. A small amount of loculated complex ascitic fluid was noted and ultrasound-guided ascitic aspiration was conducted to support the diagnosis. Ascitic fluid analysis was exudative and the serum ascitis albumin gradient

(SAAG) < 1.1 g/L, a total amount of leukocytes was 17,580 /uL with lymphocytes 52 %, and acid fast bacilli (AFB) was negative. A Mantoux intradermal reaction was negative, while an HIV test, CEA, CA-199 were also normal, except CA-125 was high 200 U/mL (normal < 38 U/mL).

The working diagnosis was ascitic observation may be caused by infection process or malignancy. Antibiotic (ceftazidim 1 g per 8 hours) was given to eliminate the infection. Clinically response was poor although several days antibiotic injection was given. The patient has still fever. A second ultrasound - guided ascitic fluid aspiration was conducted to reconfirm ascitic characteristics and to examine adenosine deaminase (ADA), Xpert MTB/RIF, bacterial culture and sensitivity. Leukocyte was not decreasing, and adenosine deaminase was high (288 U/L; normal < 30 U/L), Xpert MTB/RIF was positive, and there was no drug resistance for rifampicin. Because of severe nausea and the patient refused to be inserted with nasogastric tube (NGT), anti TB was delayed.

After several days, ESBL producing *Pseudomonas aeruginosa* was identified from ascitic fluid culture. *Pseudomonas* was resistance to many antibiotics such as ceftriaxon, ceftazidime, cefotaxim, cefazolin, cefepime and aztreonam, but still sensitive to several antibiotics such as ertapenem, meropenem, amikacin, gentamicin, ciprofloxacin and tigecycline. Antibiotic was changed according to sensitivity test, with ciprofloxacin and gentamicin. Carbapenem was not used because of financial problem, which was patient using government's health insurance (BPJS).

On day 17 of hospitalization, the patient condition was deteriorate and suffered from septic shock. Antibiotics, antituberculosis drugs, fluid resuscitation, hemodynamic support and adjunctive therapy did not help the patient condition. The patient was died because of TB peritonitis with septic shock caused by ESBL producing *Pseudomonas aeruginosa*.

DISCUSSION

Culture growth of *Mycobacterium* of the ascitic fluid, detection of acid-fast bacilli (AFB) in the ascitic fluid or peritoneal biopsy is the gold standard test for diagnosis of TB peritonitis.^{2,3} Diagnosis of extrapulmonary TB (EPTB) is still challenging since the number of *Mycobacterium tuberculosis* (MTB) bacilli present in tissues at sites of disease is often low.¹ Conventional mycobacterial culture takes up to 8 weeks to achieve results, and its sensitivity is only 34.75 %.³ The acid fast bacilli is insensitive, with

reported sensitivity ranging from 0-6 %.² Zeneba et al reported their study that the prevalence of smear-positive extra pulmonary TB infection was 9.9%, which is higher than the prevalence reported in Nigeria (5%) and India (3.9%).⁵ Histology is timing consuming, tissue microscopy after special staining is often negative and when mycobacteria are seen, it is impossible to distinguish MTB from non-tuberculous mycobacterial disease.¹

Laparoscopy in combination with biopsy can clarify the causes of unexplained ascites in the majority of cases. The sensitivity of visual diagnosis and histology by laparoscopic is 92.7% and 93% respectively.³ The problems is not of each hospital have this facility. Tuberculous peritonitis can present in three different forms which are the wet ascites, fibrotic-fixed and the dry-plastic form. They have similar clinical manifestations except for abdominal distension which does not occur in the dry-palstic form. Ascites type is more present than the others.^{3,6}

The symptoms and signs of TB peritonitis are nonspecific, and the diagnosis still requires a high suspicion index. There are various diagnostic test and its sensitivity patterns. Sanai et al recommended to use the algorithm for evaluation of patients with suspected tuberculous peritonitis.³ While clinical features suggestive to TB peritonitis, ultrasound has role to differentiate whether there is ascites or not. If there is ascites absent, ultrasonography (USG) or computed tomography (CT) help to identify peritoneal disease. In ascetic type, ultrasound examination of the abdomen show the presence of interloop ascetic fluid with fibrotic, mesenteric and peritoneal thickening, enlarged lymph nodes with mesenteric thickening.⁷ Abdominal CT scan is better than ultrasound for detecting high density ascites, lymphadenopathy with caseation, bowel wall thickening and irregular soft tissue densities in the omental area.³ Laparotomy biopsy will be confirmed diagnosis of TB peritonitis in patients with ascites absent.

In patients with ascites, ascites fluid analysis (lymphocyte dominant, SAAG \leq 1,1, adenosine deaminase $>$ 30 U/mL, TB culture positive, acid fast bacilli or rapid DNA test positive) will help to establish the diagnosed of TB peritonitis.^{3,8} Ascitic fluid analysis should be done routinely in patients with suggestive of TB peritonitis. The sensitivity of predominant lymphocyte is 68.34%. The lymphocytic predominance is not a reliable marker for TB peritonitis, because it may also be seen in portal hypertensive ascites. Ascites fluid total protein levels $>$ 25 g/L and a low SAAG

(<1.1) are seen in almost 100% of patients with isolated TB peritonitis, although the specificity remains low.^{3,9}

Adenosine deaminase (ADA) is an enzyme that increases in TB peritonitis because of the stimulation of T-cell lymphocytes by mycobacterial antigens. In addition, price is inexpensive and it has good sensitivity. ADA may be used for early diagnosis of TB, especially in case of negative acid-fast bacterium (AFB) smear from the body specimens.¹⁰ Anil et al reported that in the receiver operating characteristic (ROC) curve for ascites, ADA cut off level of 45.5 U/L was found to yield the best results of differential diagnosis. The sensitivity and specificity, positive predictive value, negative predictive value, and accuracy of the test in TB peritonitis cases were 80.0%, 97.2%, 96.6%, 82.9% and 88.6% respectively.¹¹

Nucleid acid amplification test (the Xpert MTB / RIF assay) for rapid TB diagnosis are increasingly being used.⁸ This new DNA tests for TB was rapidly endorsed by the WHO as a replacement for sputum smear microscopy, particularly in settings with high rates of HIV-associated TB and multidrug-resistant TB.¹² This assay are simultaneously detects TB and rifampicin drug resistance that provides accurate results in 100 minutes so that patients can be offered proper treatment immediately. A single Xpert MTB/RIF test detected 90.4% of cultured-confirmed pulmonary TB patients (98.7% of smear-positive specimens and 75.0% of smear-negative specimens). The sensitivity and specificity ranged between 77% and 95% for biopsy, urine and pus, while it was lower than 50% for cavitory fluids.¹

In this case, our patient was diagnosed as TB peritonitis based on clinical feature, high level of adenosine deaminase and rapid DNA test (Xpert MTB/RIF). In this case, ovarian cancer was excluded although the level of CA-125 was high (200 U/ml; normal $<$ 38 U/ml) because CA-125 is not specific for ovarian cancer. Malignant and benign lesions causes of raised Ca-125.¹³ One study showed that CA-125 titers higher than 1,000 U/ml correlated with malignancy, but there was a reported case of peritoneal TB with a CA-125 level of 909 U/ml.¹⁴

Intra-abdomen infection is classified as primary. For example, primary bacterial peritonitis in cirrhosis patient) secondary and tertiary. Secondary peritonitis refers to infection that arises from microbes in the alimentary tract that contaminate the otherwise sterile peritoneal cavity.¹⁵ Intra-abdomen infection can be further classified as community acquired or health care associated (HCA).¹⁶ There are three clinical

outcomes that can occur when peritoneal space has been contaminated by microbes such as clearance of the bacteria by the host, abscess formation and peritonitis.¹⁵ In this case, our patient was classified as intra-abdominal infection. The defences of the patient could not eradicate microbes. In the end, she was suffered from peritonitis and septic shock caused by ESBL *Pseudomonas aeruginosa*.

According to the Surgical Infection Society and the Infectious Diseases Society of America, recommendation for empiric antimicrobial therapy for complicated HCA intra-abdominal infection are carbapenem (imipenem-cilastatin, meropenem or doripenem), piperacillin-tazobactam, ceftazidime or cefepime and metronidazole.¹⁷ In this case, our patient suffered from septic shock caused by ESBL producing *Pseudomonas aeruginosa*. According to our opinion *Pseudomonas aeruginosa* contaminated peritoneal cavity may be through ascitic fluid aspiration that conducted during in our hospital (twice) or in previous hospital. In our case, the risk factor for infection with pseudomonas were antibiotic use (ceftazidime), prolonged stay in hospital, comorbid disease and use instrumentation (ascitic fluid aspiration), as noted by Kulkarni et al.¹⁸

ESBL are beta-lactamases conferring resistance to oxy-imino-cephalosporins (3rd generation cephalosporin) and aztreonam, but not carbapenems.¹⁸ Umadevi et al reported the prevalence and antimicrobial susceptibility pattern of ESBL producing Gram Negative Bacilli. A total of 213 isolates were tested for ESBL production. Among the 132 *Escherichia coli*, 54 *Klebsiella pneumoniae* and 27 pseudomonas isolates which tested, 81%, 74% and 14%, respectively were found to be ESBL producers.¹⁹ *Pseudomonas aeruginosa* is an opportunistic pathogen with innate resistance to many antibiotics and disinfectants. Infection due to *Pseudomonas aeruginosa* are seldom encountered in healthy adults, the organism has become increasingly recognized as the etiological agent in hospitalized patients. Aggarwal et al reported that *Pseudomonas aeruginosa* were multidrug resistant and isolates were 100% sensitive to imipenem.²⁰

There were at least two reasons on why the patient was failed to manage. First, the diagnosing and treating of TB peritonitis were delayed. Chow et al reported that more than 80% of the patients, the condition deteriorated and/or the patient died within 6 weeks after initial presentation.² Patients who died of TB peritonitis had a significantly longer time lag from symptom onset to initiation of treatment than did the survivors.

Second, in spite of ciprofloxacin and gentamicin were still sensitive, it may be inadequate. Umadevi et al reported that ESBL producing bacilli showed maximum susceptibility to imipenem (100%), piperacillin-tazobactam (84%), amikacin (68%), gentamicin (9%) and ciprofloxacin (9%).¹⁹ In this case, carbapenem was the drug of choice. Financial handicap and government policy were the source of problems, because the patient was government's health insurance or BPJS member.

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