TUBERCULOSIS OF THE UROGENITAL AND CENTRAL NERVOUS SYSTEMS COMPLICATED WITH SEPTIC SHOCK: LESSONS LEARNED FROM A RESOURCE-LIMITED SETTING

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Abstract

The incidence of tuberculosis (TB) infection in multiple organs outside the lungs is of particular concern. We present the case of a 48-year-old woman with a history of pulmonary TB who had a gradual loss of consciousness in one day, worsening shortness of breath, and a cough with green phlegm two weeks before admission. She had been undergoing five days of TB treatment with the drug-sensitive TB treatment regimen. The genital examination revealed a whitish mass in the paraurethral area, which impaired her urination. Blood gas analysis showed respiratory acidosis, and a chest X-ray suggested pulmonary TB and concurrent community-acquired pneumonia. She was diagnosed with extrapulmonary tuberculosis (EPTB) in the central nervous systems and urogenital sites. To treat her life-threatening EPTB, she received crystalloid infusions, oxygen supplementation, ampicillin-sulbactam (converted to meropenem the next day), an oral fixed-dose combination antituberculosis therapy, pyridoxine, N-acetylcysteine, ursodeoxycholic acid, Curcuma, bisoprolol, proton pump inhibitor, and antiemetics. Additionally, she was inserted with a urethral catheter and a nasogastric tube to assist her urination and nutritional intake. Our facility was a sub-district hospital and had a limited capacity for diagnosing and treating EPTB due to a lack of advanced intensive care units, blood and sputum cultures, and laboratory panels. After her two-day hospital admission to ICU for stabilisation, she was referred to a higher-level hospital with more advanced pulmonary treatment overseen by a multidisciplinary team. Our resource limitations highlight the importance of being well-informed about evidence-based primary EPTB management strategies.

Keywords**:** Central Nervous System Tuberculosis, Extra-Pulmonary Tuberculosis, Granuloma of Urethra, Genitourinary Tuberculosis, Primary Care

Introduction

Extrapulmonary tuberculosis (EPTB) infection is a rare yet significant manifestation of tuberculosis, particularly in low and middle-income countries. For instance, in Indonesia, a middle-income country, the incidence rate of EPTB is estimated to be approximately 6% of the total 493,000 TB cases reported in 2022, according to World Health Organization (WHO) data (1, 2). It is worth noting that around 5 to 45% of TB cases may exhibit extrapulmonary manifestations, with the urogenital tract being the most commonly affected site (30 to 40% of EPTB cases) (3). Conversely, EPTB infection involving the central nervous system (CNS) is less common, accounting for only about 1% of all cases, but it can lead to significant morbidity and mortality (4, 5). In light of this data, raising awareness and understanding of EPTB in clinical management and its impact on public health is crucial.

Establishing a diagnosis of EPTB is still challenging, especially in low and middle-income countries. In conditions of limited resources, the diagnosis of EPTB is generally based only on clinical signs and symptoms. Bacteriological confirmation of EPTB often requires invasive specimen collection by biopsy or fine needle aspiration followed by adequate diagnostic tests. Here we present a rare case of TB infection in the CNS and genitourinary tract that we encountered at a limited-resource hospital in Jakarta, Indonesia (6, 7).

Case Presentation

A 48-year-old female patient came to the emergency department with decreased consciousness in one day, preceded by worsening shortness of breath and cough with green phlegm for two weeks before admission. She

had been diagnosed with pulmonary TB five days earlier at the community health centre and was currently on antituberculosis treatment. The patient's weight had decreased from 47 kg to 30 kg in the last three months. The patient reported that in the last two weeks, there had been a thicker, lumpy, fluid-like vaginal discharge upon urinating. When insertion of the urinary catheter was attempted for treatment, her urethral opening was not found because a mass covered it. The patient had been bed bound for the last three months due to generalised weakness and lack of appetite. However, she delayed seeking treatment due to feelings of anxiety and fear about the COVID-19 pandemic.

Physical examination

The patient came in an apathetic condition with a Glasgow Coma Scale (GCS) score of 12 (Eye 3; Verbal 4; Movement 5). Her respiratory rate (RR) was 40 per minute, pulse 133 beats/minute, and blood pressure (BP) 134/94 mmHg. Oxygen saturation was 69% on room air. When she arrived, her body mass index (BMI) was 13.3 kg/$m^{2,}$ and her upper arm circumference was 18 cm. Upon urethral examination, a 3 x 3 cm whitish mass was found in the paraurethral area, suspicious for urethral granulomas (Figure 1). The mass covered the urethral opening and impeded the catheter insertion.

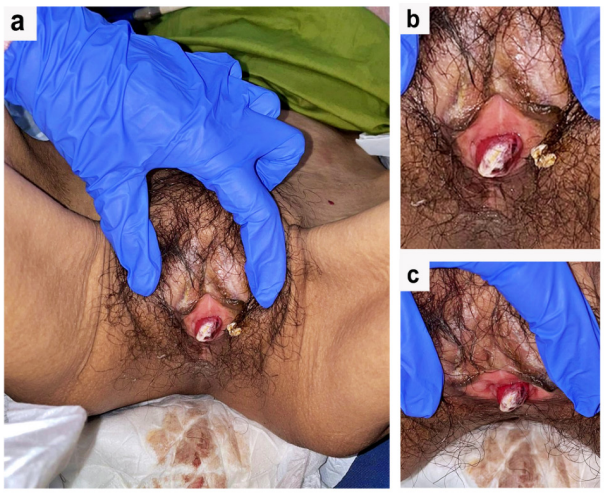

Figure 1: Physical examination. On the paraurethral region, a pedunculated solitary white mass of 3 cm x 3 cm out of the urethral opening resembling granulation tissue with pus suggestive of pyogenic granuloma was found.

Investigations

The patient's electrocardiogram (ECG) showed infrequent ventricular extrasystoles (Figure 2). Blood investigations found an increase in platelets (647,000/mL), erythrocyte sedimentation rate (ESR, 67 mm/h) and neutrophils (87%), even though the leukocyte count was normal (8,900 cells/mm^3). There was an increase in the patient's liver enzymes (aspartate transaminase, AST, 102 U/L, and alanine aminotransferase, ALT, 94 U/L). Blood gas analysis showed that the patient had respiratory acidosis. GeneXpert Mycobacterium tuberculosis (MTB)/rifampicin (RIF) test results revealed low MTB detection, and rifampicin resistance was not detected.

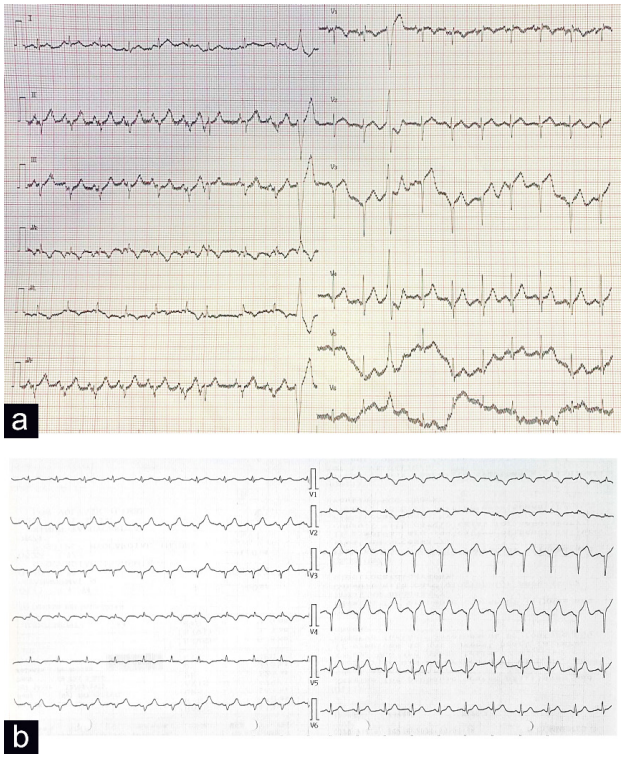

Figure 2: Electrocardiography (ECG) assessment. (a) at admission, ECG showed infrequent ventricular extra-systole (VES). (b) after an 8-hour follow-up, there was a change in the shape of the ECG, showing non-specific ST-segment elevation in leads V3 and V4 with suspicion of anterior ST-elevation myocardial infarction (STEMI)

Table 1: Blood gas analysis results in 18 hours after admission to the intensive care unit

Components	Results	Reference values
PCO_2	**114 mmHg**	**35–45 mmHg**
PO_2	**130 mmHg**	**80–105 mmHg**
pH	**7.24**	**7.35–7.45**
SaO_2	98%	92–99%
HCO_3^-	**48 mmol/L**	**22–27 mmol/L**
Total CO_2	**52 mmol/L**	**24–29 mmol/L**
Base excess (BE)	**21 mmol/L**	**(–2) to 3 mmol/L**

PCO_2: partial pressure of carbon dioxide
PO_2: partial pressure of oxygen
SaO_2: oxygen saturation
The parameter written in bold indicates an abnormality.

Based on the formula for calculating blood gas analysis (BGA) (8), the results, as given in Table 1, were interpreted as respiratory acidosis considering the value of pH, PCO_2, and base excess. The value of HCO_3^- in this patient rose

proportionally to the calculation of the compensatory acidosis formula ($0.1 \times \Delta PCO_2$), suggesting fully compensated acidosis. The calculation of the anion gap using the value of electrolytes and bicarbonate [$(Na^+ + K^+) – (Cl^- + HCO3^-)$] indicated a normal gap, making the diagnosis a fully compensated respiratory acidosis with a normal anion gap. The chest X-ray, in Figure 3, showed bilateral pulmonary infiltrates suggestive of TB with concurrent community-acquired pneumonia (CAP).

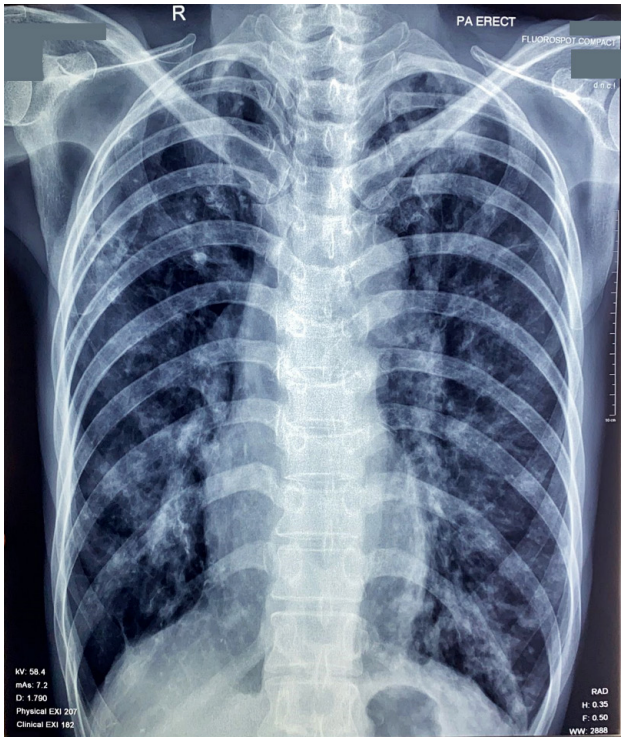

Figure 3: Chest X-ray radiograph giving the impression of TB with concurrent community-acquired pneumonia. An increase in broncho-vascular markings was found with inhomogeneous consolidation in the upper-right lung fields and infiltration in both lung fields without nodules, calcifications, cavities, and fibrosis. Pleural thickening and abnormalities of the hilum, costophrenic angle, diaphragm, trachea, and mediastinum were not seen. There was the aortic elongation of the heart without calcification.

Preliminary Diagnosis

The patient came in a state of shortness of breath and reduced consciousness. The initial preliminary diagnosis of the patient was CNS TB infection with a differential diagnosis of septic shock in the presence of CAP and pulmonary TB with a score of confusion, uraemia, respiratory rate, BP, age > 65 years (CURB-65): 2 (confusion and tachypnoea). Based on the International Guidelines for Management of Sepsis (9-11) the patient was diagnosed with possible sepsis (quick score of sequential organ failure assessment/qSOFA: 2; and sepsis-related organ failure assessment/SOFA: 5). The qSOFA score was based on increased RR >22 bpm (score 1), altered mental status <15 (score 1), but no hypotension (score 0). The detailed measurements of the SOFA components were: PaO_2/FiO_2 = 130 or SpO_2/FiO_2 = 105 (score 3); platelet 647,000/mL (score 0); bilirubin (n/a); Mean Arterial Pressure (MAP) 107 (score 0); GCS 12 (score 2); creatinine 0.6 mg/dL (score 0); with a total score of 5. The mass in the urethra was assessed as suspected genitourinary tract TB with a differential diagnosis of malignancy. The diagnosis of septic shock was not completely established as there was no lactate test available to diagnose multiorgan dysfunction, and at first admission, the patient's BP and MAP were within normal limits. COVID-19 had been excluded through antigen and PCR tests. The additional diagnosis was respiratory acidosis fully compensated with a normal anion gap, arrhythmia, and malnutrition.

Treatment

In the emergency room, the patient was immediately given oxygen at 10 litres/minute on a non-rebreather mask, and the SaO_2 improved to 99%. Sepsis care bundles were activated: she was fluid resuscitated with 30 ml/kgBW NaCl 0.9% within 3 hours. Broad-spectrum antibiotic ampicillin/sulbactam 1.5 grams per 8 hours was administered, and on the next day, the antibiotic was switched to meropenem 1 gram per 8 hours as her condition worsened. Oral fixed-dose combination antituberculosis therapy (Rifampicin 150 mg/ Isoniazid 75 mg/ Pyrazinamide 400 mg/ Ethambutol 275 mg) for 30 kg weight was given 1 × 2 tablets during the intensive phase. Regarding the sepsis bundle, although blood culture sampling was taken before she was transferred to another hospital, a lactate measurement was unavailable. The anti-TB drug treatment was continued according to national TB guidelines. Additional therapy included intravenous proton pump inhibitors (omeprazole 2 × 40 mg), intravenous antiemetics (ondansetron 4 mg if needed), oral N-acetylcysteine (3 × 200 mg), oral pyridoxine (2 × 10 mg), oral ursodeoxycholic acid (2 × 250 mg), Curcuma supplementation (3 × 1 tablet), and oral bisoprolol (1 × 2.5 mg). The patient was also inserted with a urine catheter and a nasogastric tube with a diet of 1600 kcal/day. The patient was planned for admission to the intensive care unit (ICU) for hemodynamic stabilisation.

Follow-up and outcome

On day one, after admission to the ICU, the patient was still experiencing shortness of breath, delirium, and difficulty in communication. Her respiratory rate was 36 breaths/minute, and her oxygen saturation was 99%, with oxygen at 10 litres/minute on the non-rebreather mask. Her BP needed norepinephrine support of 0.05 mcg/kg/h. Serial ECG examination showed ST segment elevation in leads V3 and V4, which led to a diagnosis of anterior ST Elevation Myocardial Infarction (STEMI) with right bundle branch block (RBBB). Since there was no anatomical pathology facility to work up a mass biopsy of the genitourinary tract, no available microbiological culture for monitoring, no lumbal puncture diagnostic modality, and no available septic markers (i.e., procalcitonin and C-reactive protein)

in our setting, the patient was eventually referred to a secondary hospital for further treatment after being stable for 10 hours since admission. The summary of the clinical course of this patient in our hospital is depicted in Figure 4.

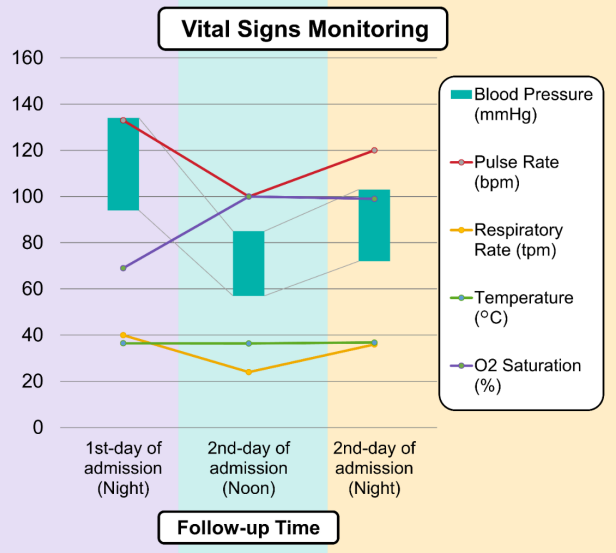

Figure 4: Patient's vital signs monitoring during hospitalization.

In the referral hospital, the histopathological results from the biopsy specimen of the urethral mass revealed an epithelioid cell granuloma and caseous necrosis with Langhans-type giant cells. Based on the brief report from the referral hospital, the patient responded well to treatment, and her condition improved steadily during her hospitalisation. She was discharged in stable condition with instructions for follow-up care, including ongoing medication management and regular check-ups. However, due to confidentiality reasons and limited access to information from the referral hospital, we could not follow up with the patient during her treatment course and after her discharge. The doctor at the referral hospital has been handling further care and follow-up for the patient since her discharge.

Discussion

Tuberculosis continues to pose a significant threat to public health globally. Mortality rates ranging from 33 to 67% have been reported for patients with active TB or respiratory failure (12). Among the various forms of TB, tuberculous leptomeningitis, affecting the CNS is the most common. This type of TB is particularly concerning because patients often experience neurologic deterioration. In fact, in the case of our patient progressive loss of consciousness was the main reason for ICU admission, providing a strong indication of tuberculosis meningitis (TBM) (12, 13).

Tuberculosis is a disease that can affect various organs, including the genitourinary tract (7). When the immune system does not control the primary lung infection, extrapulmonary TB can occur, spreading through the bloodstream or lymphatic system. Rare modes of transmission include sexual transmission and accidental inoculation (14, 15). Urogenital tuberculosis can present in many ways, from asymptomatic to severe obstruction and renal failure. While isolated urethral TB in a female patient is uncommon and has not been reported in the literature, male patients with EPTB in the urogenital area often show prostate or kidney involvement. Urogenital TB may also present with other symptoms such as back pain, flank and suprapubic pain, hematuria, increased frequency of urination, and nocturia. Patients often report frequent urination in small amounts, initially at night and later during the day. Renal colic is uncommon and occurs in only 10% of patients (15, 16). Constitutional symptoms such as fever, weight loss, and night sweats are rare. Symptoms tend to be intermittent and persist until patients seek medical attention (15, 16). In our case, an asymptomatic urethral mass presented as a diagnostic challenge, with various potential differential diagnoses, including urothelial papilloma, fibroepithelial polyp, xanthogranulomatous inflammation, and urothelial carcinoma (15, 16). However, the subsequent histological examination of the biopsy specimen revealed that the mass was, in fact, urethral EPTB with evidence of well-formed granuloma and caseous necrosis, along with multi-nucleated giant cells.

Tuberculosis is a pathogenic disease that can result in severe complications, especially in immunocompromised individuals, and can ultimately lead to sepsis. To facilitate the identification of patients at risk of sepsis, physicians in emergency departments may rely on various validated scoring systems. These include the qSOFA scoring system, which enables a rapid initial assessment of the patient, and the Sequential Organ Failure Assessment (SOFA) score, which utilises laboratory indicators to assess the degree of organ dysfunction. Additionally, the CURB-65 score is a widely used scoring system that aids in determining whether patients with suspected community-acquired pneumonia CAP should be hospitalised (17). Studies have shown that patients with a CURB-65 score of 2 have a 30-day death rate of 9.2% (17, 18). However, in more complex cases, such as those involving TB, the estimated probability of death is higher than 9.2% (17, 18). Although TB rarely causes acute respiratory distress syndrome (ARDS), when it occurs secondary to TB, admission to the ICU is necessary, and the mortality rate increases significantly to 50% (19, 20). In our patient's case, the CURB-65 score suggested that her condition could be considered for either hospitalisation or outpatient therapy. However, the physicians decided to admit her to the ICU due to the SOFA score indicating sepsis. By incorporating the aforementioned scoring systems into their clinical practice, physicians can deliver appropriate and timely interventions to patients with tuberculosis, including those at risk of developing sepsis.

Patients with TB who require ICU care are prone to high rates of comorbidities and ICU-related complications. A considerable proportion of these patients, up to 65.5%, exhibit impaired liver function. Moreover, ICU-requiring

TB-related complications include ARDS at 12.1%, acute kidney failure also at 12.1%, and multiorgan failure (MOF) at 3.4% (12). EPTB is common in ICU patients with immunocompromised pulmonary TB (13, 21). CNS TB is a particular concern among the complications, accounting for about 6 to 18%. This complication, which encompasses tuberculous meningitis (TBM) and cerebral tuberculoma, can lead to impaired consciousness, requiring mechanical ventilation (observed in 75% of cases), and neurosurgical procedures in 33% of cases (13, 21). The 1-year mortality rate among TBM cases admitted to the ICU is reported to be as high as 65% (13, 21, 22).

The onset of symptoms in TB is usually subacute to chronic, with an average onset of 7–30 days, and around one-third of patients have symptoms lasting less than a week. The most commonly reported symptoms include headache (80-90%), fever (60-95%), weight loss (60-80%), decreased consciousness (30-60%), vomiting (30-60%), and seizures (50%). These symptoms may be accompanied by neurologic deficits such as neck stiffness (40-80%), cranial nerve paresis (30-50%), and hemiparesis (10-20%) (13, 23). Therefore, when patients present with symptoms of headache and fever lasting over five days, it is essential to consider the possibility of TBM (22). Generally, when diagnosing TB, confirmation of TB bacteria is typically obtained from at least two sputum specimens for microscopic examination and drug sensitivity testing, one of which is the rapid molecular test. Diagnosing EPTB can be challenging, and a biopsy of targeted tissue is often required. TBM diagnosis relies on characteristic cerebrospinal fluid (CSF) findings, such as high protein, low glucose with a CSF-to-serum glucose ratio below 50%, and lymphocyte dominance (13, 21).

Principally, treatment of TBM follows the guidelines for treating EPTB with a minimum recommended duration of 12 months. The selection of effective drugs is based on their bactericidal ability and the ability to penetrate the blood-brain barrier and reach optimal concentrations in the cerebrospinal fluid (22). Standard antituberculosis drugs penetrate the CSF in the order of isoniazid > pyrazinamide > rifampicin, while ethambutol and streptomycin have a low ability to penetrate the blood-brain barrier. Research is currently being conducted to maximise drug effectiveness in TBM cases, such as increasing the dose of oral rifampicin to 20-30 mg/kg BW to a maximum of 1200 mg/day or using intravenous rifampin (24). Adjuvant corticosteroid therapy is still recommended in patients with suspected TBM with negative HIV results, according to the severity of the disease. Prednisone is typically given at 1-2 mg/kg/day, up to 4 mg/kg/day in severely ill cases, with a maximum dose of 60 mg/day for four weeks, followed by gradual tapering off over 12 weeks before being released (25). Corticosteroids inhibit the release of inflammatory cytokines, which may help reduce tissue damage and constitutional symptoms.

Our patient was also suspected of having EPTB in the form of urogenital TB. The duration of treatment for TB of the urogenital tract is typically six months for uncomplicated cases, and 9-12 months for cases with complications, such as relapse cases, immunosuppression, and HIV/AIDS. While in the hospital, our patient was given a fixed-dose combination antituberculosis therapy regimen of 2(HRZE)/4(HR) while waiting for a definite diagnosis from the referral hospital to determine the duration of treatment. Once a diagnosis of TBM was confirmed, the patient was given a regimen of 2(HRZE/S)/10(HR) for 12 months, along with additional corticosteroids for four weeks and then tapering off.

Challenges

Handling TB in Indonesia during the COVID-19 pandemic has become increasingly complex and challenging, as noted in recent reports (26). The fear of visiting health services for TB treatment, combined with the reduction of active or passive TB case-finding activities due to a shift in focus toward COVID-19 contract tracing, has led to a decline in reported TB cases (24, 25).

In the European Union, studies have shown that diagnosing EPTB is challenging due to the rarity of cases (21). However, this is not the case in Indonesia, which carries a high burden of TB. The most significant challenge faced by the authors was the limited capacity of our setting to obtain specimens for EPTB diagnosis via CSF and histopathological examinations. The patient was immediately referred to a higher level of care after she became stable in our primary-level hospital.

Another drawback of this case study was the limited access to the complete clinical records of the patient since we did not have access to the referral hospital's medical records, and only received a brief report after the patient was discharged. Nevertheless, we assume that this report has adequately presented the case from the perspective of initial management and highlights the rare case of EPTB manifestation in the CNS and urogenital tract.

Conclusion

The diagnosis and management of EPTB are difficult in health institutions with limited resources and often rely only on clinical signs and symptoms. EPTB should be suspected in patients with active TB that presents with reduced consciousness. Despite aggressive treatment, EPTB with CAP and sepsis has a poor prognosis. To optimise patient outcomes, the physician should be well-informed on fundamental EPTB care strategies, including the medicine, rationale, and safety profile, using evidence-based guidelines.

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Competing interests

The authors declare that they have no competing interests.

Ethical Clearance

The patient and the patient's family acknowledge and agree that the clinical data will be published as a case report, with the investigator trying to maintain the patient's confidentiality and identity as best as possible.

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Availability of data and materials

The additional information or data generated and/or analysed during the study are available from the corresponding author upon reasonable request.

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