A case of endocarditis and spondylodiscitis associated with *Mycobacterium tuberculosis*

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**Abstract**

Tuberculosis (TB) is a global health problem, in which the majority of cases occur in population-dense developing countries. Despite advances in various diagnostic TB modalities, extrapulmonary TB remains a challenge due to complexities related to its diagnostic approach. Hereby, we present a rare case of endocarditis and spondylodiscitis associated with *Mycobacterium tuberculosis* (MTB). This case report highlighted the challenges faced in diagnosing blood culture-negative infective endocarditis (BCNIE). We also emphasized the importance of considering MTB as etiology of BCNIE, particularly in endemic TB areas.

**Introduction**

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB). Today, TB remains one of the leading causes of death globally. Indonesia is one of the most TB prevalent countries globally, second only to India [1].

Extrapulmonary tuberculosis (EPTB) occurs in approximately 15–20% of TB cases. The most common sites of EPTB are lymph nodes, pleura, and the osteoarticular system; although rare, EPTB may involve the endocardial layer of the heart [2]. Hereby, we presented a case of EPTB manifesting as endocarditis and spondylodiscitis. Furthermore, we highlighted the diagnostic challenges in identifying MTB.

**Case report**

A fifty-seven-year-old male patient without previous history of heart disease presented to the hospital with worsening shortness of breath since one week before admission. He also complained of fever and weight loss for three months. Additionally, he also experienced back pain along with lower limb weakness for a month. The patient was diagnosed with pneumonia and was treated with moxifloxacin.
His sputum examinations were sterile and negative for acid-fast bacilli staining and GeneXpert MTB/RIF. After one week of antibiotic therapy, at the day of illness (DOI=14), there is no noticeably clinical improvement. The patient was then referred to the cardiology department and underwent transthoracic echocardiography (TTE), in which a large oscillating mass at the posterior mitral leaflet (PML) was detected. The patient was diagnosed with infective endocarditis (IE) and given Ampicillin/Sulbactam and Gentamicin. Three consecutive blood cultures were negative. On the third week of hospitalization (DOI-28), the patient’s condition did not improve, and he was referred to our hospital.

Upon our hospital admission (DOI-30), the patient looked lethargic; the blood pressure was 100/60 mmHg, with a heart rate of 88 bpm, respiratory rate of 30 times per minute, and the temperature was 36.8 °C. Physical examination showed an enlarged heart with a 3/6 pansystolic murmur at the apex with paraparesis and paresthesia of the lower limb at the level of L3. However, no gibbous was observed on spine examination.

The laboratory results showed a hemoglobin of 9.2 gr/dl, leukocytes of 15,230/mm³ with increased C-reactive protein (CRP) (6.01 mg/dL), and procalcitonin (10.20 ng/ml) level, and positive rheumatoid factor. The electrocardiogram showed left ventricular hypertrophy with first-degree AV block. The echocardiography evaluation revealed mitral regurgitation (MR) with ruptured chordae tendineae, perforated leaflet, and multiple vegetation attached to both leaflets (Fig. 1). Magnetic resonance imaging (MRI) for the spine revealed multiple small abscesses at L2-3, L5-S1 (Fig. 2). The patient was diagnosed with blood culture-negative infective endocarditis (BCNIE) and spondylodiscitis due to pyogenic infections. We resumed the antibiotic, performed blood culture assessments, and planned for early surgery. However, the subsequent five consecutive blood cultures were negative for aerobic, anaerobic, and fungal blood cultures. A multidisciplinary clinical meeting was performed, and it was decided that the patient would undergo discectomy first, followed by cardiac surgery afterward.

An open discectomy was performed three weeks after admission to our hospital (DOI-48). Granuloma tissue was found without purulent or abscess tissue. Debridement and irrigation were conducted. The pathologic examination of the spinal tissue showed proliferation of epithelioid cells with multinucleated data of Langhans (Fig. 3a and b). Although these findings suggest tuberculous infection, the GeneXpert MTB/RIF test was negative.

Cardiac surgery was performed one week later (DOI-57). The surgery was performed with the left atrial approach. Multiple vegetation in the anterior mitral leaflet (AML) and PML (Fig. 4) were detected. The mitral valve was replaced with a mechanical prosstatic valve. During the postoperative period, rebleeding occurred in the intensive care unit. We planned to perform a redo surgery; however, the patient’s family refused, and the patient passed away.

The pathologic examination of mitral valve tissue showed proliferation of epithelioid cells with caseous necrosis area and multinucleated data of Langhans (Fig. 3c and d). The vegetation was cultured and showed no bacterial, MTB, or fungal growth. The smear for Acid Fast Bacilli and GeneXpert MTB/RIF were also negative. The real-time polymerase chain reaction (RT-PCR) consisted of IS6110, an insertion gene corresponding to the detection of MTB complex, which was performed on the vegetation tissue. The RT-PCR result showed amplification for IS6110 and was confirmed with the pyrosequencing method. The summary of patient history can be seen in Fig. 5.

Discussion

Blood culture-negative infective endocarditis (BCNIE) poses challenges for physicians despite the advancement of cardiac imaging diagnostic and therapeutic fields. It is associated with higher morbidity and mortality than blood culture-positive endocarditis [3]. Previous studies also described that BCNIE was associated with a higher frequency of heart failure and valve perforation; furthermore, even surgically treated BCNIE is associated with a higher incidence of multiorgan failure, postoperative heart failure, and in-hospital mortality [4,5].

In all cases of culture-negative endocarditis, an evaluation of epidemiological factors, history of prior infections, cardiovascular disease, antimicrobial exposure, and extracardiac sites of infection should be performed. Typically, BCNIE can be found in three
Fig. 2. The vertebrae magnetic resonance imaging. The coronal view with (a) T1 weighted (b) T2 post-contrast showed mild scoliosis with multiple small abscesses indicates spondylodiscitis L2-3, L5-S1 (white arrow) caused spinal canal compression at the level of L2-3. The axial view at the level of L2-3 with (c) T1 weighted (d) T2 post-contrast and at the level L5-S1 with (e) T1 weighted (f) T2 post-contrast also showed abscess (white arrow).
conditions: previous antibiotic use, fastidious microorganisms that need a more extended growth period or particular culture media, and non-infectious endocarditis [6]. The microorganism which has been known related to BCNIE including Coxiella burnetii, Bartonella spp., Aspergillus spp., Mycoplasma pneumonia, Brucella spp. and Legionella pneumophila, Tropheryma whippelii, Bartonella spp., and fungi (Candida spp., Aspergillus spp.) [7].

There is still no universal guideline that is uniformly applicable with regards to BCNIE. According to the European Society of Cardiology guidelines, several modalities are needed to identify the causative microorganism in BCNIE, including serology and PCR [7]. The incidence of MTB as a cause of endocarditis is unknown and could be underestimated due to its diagnostic complexities. Furthermore, no consensus nor guideline has included MTB as a cause of BCNIE [7–9]; hence, it might be missed in TB’s endemic country, such as our country. Detecting MTB from the blood is difficult due to its paucibacillary nature with slow-growing - fastidious characteristics [10].

The pathogenesis for tuberculous endocarditis is not well understood. The mechanism which likely could explain is similar to EPTB pathogenesis. The process begins when MTB is inhaled into the lungs as the primary site of infection. They multiply and induce macrophages and neutrophils to migrate to the infected area. Accumulated macrophages at sites of bacterial implantation further differentiate into epithelioid cells that form tuberculoid granuloma. MTB is maintained and persists within the center of the granuloma in a low active and anaerobic state to avoid an encounter with the host’s immune defense. Reactivation happens once the balance between bacillary persistence and the immune response gets disturbed due to aging, malnutrition, steroids, or Human Immunodeficiency Virus (HIV) infection. The infection then leads the epithelial layer of alveolar cells to erode and spread through the bloodstream to other organs. Another way for MTB to infect other organs is by using phagocytes as vehicles to approach other organs through lymph nodes and blood [11].

The role of blood culture in TB has its limitations, especially in an immunocompetent patient, such as our patient. Blood cultures for MTB detection require mycobacteria-specific, radioisotope-labeled systems with specific nutrient growth requirements that are not met by routine culture systems. In studies among HIV patients, MTB can
Identification of tuberculosis as a cause of endocarditis could be made by detecting mycobacteria from extrapulmonary sites, using (1) direct method, through detecting the mycobacterium and its product which is difficult due to its nature, inadequate clinical sample sizes, nonuniform bacteria distribution, and difficulty to access the site and (2) indirect method, which depends on the measurement of the host’s humoral and cellular response against mycobacterium. Despite the negative results of acid-fast bacilli staining and GeneXpert MTB/RIF tests, due to the high suspicion of TB infection, we examined the RT-PCR with the pyrosequencing method, which revealed MTB deoxyribonucleic acid (DNA) on vegetation tissue. This method has a higher sensitivity than Gene Expert MTB/RIF, which makes the etiology successfully shown in our case [2].

The percentages of the association between IE and spondylodiscitis vary from 5% to 13%. The spondylodiscitis in IE occurred predominantly through the hematogenous arterial route, allowing the seeding of infection from a distant site into the vertebral column. It is suggested that spondylodiscitis is due to microemboli of immune complexes, with or without bacteria [14]. The locations of infection metastatic typically occur in the lumbar vertebrae site due to the highest density of vascular followed by the thoracic vertebrae [15]. It was almost impossible to determine whether the endocarditis or spondylodiscitis occurred first or whether both occurred simultaneously. Both tuberculosis infection and infective endocarditis are systemic diseases with various systemic manifestations and could mask symptoms of each entity. From the literature, only two old cases of tuberculous endocarditis were reported to have a complication with vertebrae involvement, which are similar to our patient’s [16, 17].

The treatment of tuberculous endocarditis consists of damaged valve replacement, mass evacuation, and aggressive disease eradication with anti-TB chemotherapy. In most reported cases, the anti-TB treatment has a minimum duration of six months and up to twelve months [18]. In this report, the patient underwent surgery due to uncontrolled infection and a high risk of embolization, which was planned to be followed by a minimum of 9 months of anti-tuberculosis drugs per TB treatment guidelines for patients with bone involvement [19].

Before the 1980s, most of the patients who reported having tuberculous endocarditis cases died and were diagnosed through an autopsy study [16,20]. The prognosis of patients with tuberculous endocarditis began to improve since the 1980s with the improvement and advancement of cardiac imaging and appropriate treatment [21]. To date, a limited study has described the prognosis among particularly tuberculous endocarditis patients. A study of mycobacterium endocarditis conducted by Yuan SM showed that approximately 50% of the patients with endocarditis were event-free. In contrast, many patients experienced relapses or complications, and 34% died during the follow-up. The cause of death in these patients include multiorgan failure, hospital-acquired pneumonia, stroke, progressive heart failure, and respiratory distress [22].
Conclusion

Physicians should consider Mycobacterium tuberculosis as a cause of BCNIE, particularly in tuberculosis endemic areas and in cases with concomitant spondylodiscitis. The PCR method should be used in highly suspicious tuberculosis cases, regardless of the culture results.

Limitation

In this case, the patient didn’t go through any autopsy due to no obligation for the procedure at our center when the cause of death was inevitable. However, we believe that the data from the autopsy may shed light on the patient’s illness. Secondly, we did not perform the pulmonary computed tomography scan, which could more precisely recognize pulmonary tuberculosis. Finally, MTB strain and complete drug sensitivity examination were also not conducted due to limited specimens.

Ethics approval and consent to participate

Informed consent was obtained from the participant in this study.

Statement of human rights: This study was conducted following the 1964 Declaration of Helsinki and its subsequent amendments.

Statement of animal welfare: We do not involve animals in our study.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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CRediT authorship contribution statement

Aninka Saboe: Conceptualization, Investigation, Supervision, Writing – review & editing. Sylvie Sakasasmita: Data curation, Investigation, Writing – original draft, Writing – review & editing. Yovita Hartantri, Euis Maryani, Abdul Kadir Hadar, Aftati, Lidya Chaidir, Harry Galuh Nulraga, Melawati Hasan: Data curation, Investigation, Writing – review & editing. Bachtli Alisjahbana: Data curation, Investigation, Writing – review & editing, Supervision. Reza Widianto Sudjod, Charlotte Johanna Cool, Mohammad Rizki Akbar: Writing – review & editing.

Competing interests

The authors have no conflicts of interest to declare.

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