

Case Report

The role of ^{99m}Tc-ethambutol scintigraphy to diagnose pulmonary tuberculosis

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Abstract

Tuberculosis is a significant health problem in many parts of the world. According to the Global Tuberculosis Report 2020, 10 million new tuberculosis cases were reported worldwide in 2019, with only 57% of these cases being bacteriologically confirmed. Current tuberculosis diagnostic tests depend on the quality of the sputum, leaving many diagnostic uncertainties. Diagnostic delays result in ongoing transmission and more severe, progressive disease in the affected person. This shows that current diagnostic tests are not sufficient to establish all tuberculosis cases accurately, and there is a need for a new diagnostic technique. ^{99m}Tc-ethambutol scintigraphy was recently reported as a new diagnostic test for tuberculosis, with a sensitivity and specificity of 93.9% and 85.7%, respectively. Here, we report a case of the importance of this new technique for diagnosing tuberculosis when the existing bacteriological and molecular tests failed to confirm the diagnosis.

Key words: Tuberculosis; diagnostic test; ^{99m}Tc-ethambutol scintigraphy.

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Introduction

Tuberculosis (TB) is a significant health problem worldwide. In 2019, 10 million new cases and relapses have been reported globally. Of these, only 57% were confirmed bacteriologically [1]. Microscopic examination of sputum for *Mycobacterium tuberculosis*, molecular diagnostic tests, and culture methods are specimen-dependent. Diagnostic delays result in continuous transmission and more severe, progressive disease in the affected person. This shows that current diagnostic tests are insufficient to establish all TB cases accurately, and there is a need for a new diagnostic technique [2,3].

Tuberculosis (TB) is a great imitator disease, and pulmonary tuberculosis (PTB) can imitate various other pulmonary disease processes [4]. Lung cancer (LC) is one of the most important diseases that can be differentiated from PTB. Several symptoms, such as fever, cough, haemoptysis, weight loss, and anorexia are common in both diseases. It is difficult to clinically

differentiate them, especially in TB-endemic countries such as Indonesia. Failure to recognise them could lead to treatment delays and be associated with a dismal prognosis [1,5]. We report ^{99m}Tc-Ethambutol scintigraphy in diagnosing TB when the other examinations could not confirm the diagnosis.

Case presentation

A 41-year-old Indonesian HIV-negative man was referred to our hospital with progressive dyspnoea of one-week duration. It was associated with productive cough, continuous fever, and right pleuritic chest pain. Further history revealed that he had clinical symptoms of exertional dyspnoea, intermittent cough, light evening fever, night sweats, and unintentional weight loss (6 kg) in the last two months. His medical history was significant for PTB in 2007 when he did not finish the treatment. He reported no alcohol abuse, and he was a smoker (5 pack-years).

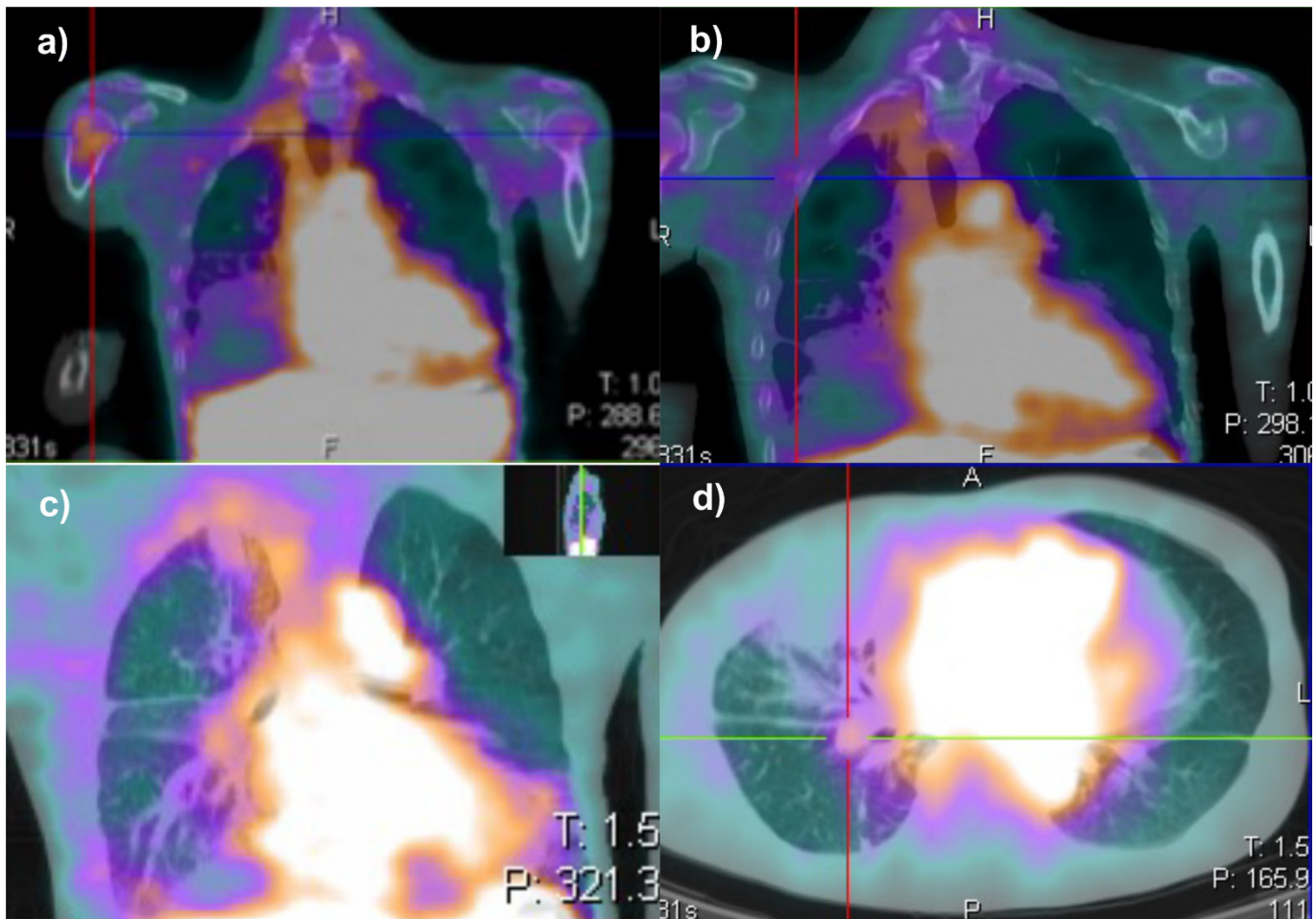
He was conscious and oriented toward physical examination. His blood pressure was 140/80 mmHg, pulse was 92 beats·min⁻¹, respiratory rate was 26 breaths·min⁻¹, and temperature was 36.5°C. The patient was thin and pale, and lymphadenopathy was not observed. Chest examination revealed bilateral suprasternal-intercostal retractions, dull sound on percussion, reduced breath sounds in the right lower lobe, and scattered crackles on both lungs from auscultation. The remaining systemic examination was unremarkable.

Blood investigations revealed a haemoglobin level of 6.7 g·dL⁻¹ and a total leukocyte count of 12,850 cells·mm⁻³ with a differential count of 83% neutrophils, 10% lymphocytes, 7% monocytes, and 0% for both eosinophils and basophils. The platelet count was 381,000 cells·mm⁻³. The MCV was 76 fl, MCH was 23.3 pg, and MCHC was 30.6%. Albumin levels were below the normal values (2.9 g/dl). Blood urea nitrogen, creatinine, electrolytes, and blood glucose

levels were within the normal limits. Human immunodeficiency virus was excluded. The ECG findings were unremarkable.

The chest CT revealed a right peribronchial mass sized 1.0 cm × 1.5 cm × 1.5 cm (with contrast enhancement), tree-in-bud appearance in the superior lobe of the right lung, right pleural effusion, and multiple adenopathy. The CT finding was suggested for an LC stage T1b N1 M1, yet an active post-primary PTB was an important differential diagnosis. Transthoracic needle biopsy or endobronchial ultrasound could not be performed because of the difficult mass location and limited hospital facilities. Three specimens were sent for sputum smear microscopy and two sputum specimens for the Xpert MTB-RIF assay (sensitivity of 68% and specificity of 99% for negative smear microscopy) [3], all of which yielded negative results. We tried to perform the pleural fluid analysis; unfortunately, we obtained a dry tap from the trial of ultrasonography-guiding thoracentesis.

Figure 1. SPECT/CT ^{99m}Tc-ethambutol scintigraphy results showed an increasing uptake of radioactivity by time in the: a) bilateral humeri; b) multiple ribs; c) right lobe apex area, right basal lobe, and peribronchial right lobe; and d) the right peribronchial mass. SPECT/CT: Single-photon emission computed tomography/Computed tomography.



The sputum culture test also showed unsatisfactory results, which revealed a cluster of commensal oral bacteria.

The various examinations above did not provide a conclusive diagnosis; therefore, we performed additional ^{99m}Tc-ethambutol scintigraphy to help localise TB foci (Figure 1). The visual analysis of the whole-body image for one and 4 hours after injection of ^{99m}Tc-ethambutol showed increased uptake of radioactivity over time in the right pulmonary apex and basal area, right peribronchial tree, the mass previously suspected as an LC (probably peribronchial adenopathy), bilateral axillary lymph nodes, bilateral humeri, and multiple ribs. Based on the ^{99m}Tc-ethambutol SPECT/CT scanning results, LC was excluded, and disseminated TB was the final diagnosis.

Discussion

The patient's clinical symptoms and chest imaging results were suggestive of LC. However, since he lived in a TB endemic area (Indonesia is listed as the world's second-largest TB burdened country in 2019) [1] and had been lost to follow-up in the last PTB treatment, PTB was considered as the underlying disease. Moreover, the patient fulfilled five out of six International Standard for Tuberculosis Care (ISTC) criteria (age <65 years, night sweat, weight loss, exposure to TB history, and upper lobe opacities on chest radiograph to suggest PTB infection [3]. However, LC has a high incidence rate in Indonesia (ranked third after cervical cancer), with 30.023 cases (8.6%) reported in 2018 [6]. Indeed, there are many similarities between LC and PTB; both share the same clinical signs and symptoms, high prevalence, and equally affect the lung parenchyma [5]. The negative results from sputum smear and Xpert MTB/RIF examination and a mass in the right peri-bronchial from the chest CT scan made both PTB and LC possible as a diagnosis. Here, we discuss several modalities for diagnosing PTB.

Sputum examination

Sputum smear microscopy is the most widely available test to establish a microbiological diagnosis of PTB. The World Health Organization reported that same-day sputum sample collection is as accurate as a standard smear test; both had comparable sensitivity (63% for same-day sputum collection vs. 64% for standard approach) and specificity (98%). Two other methods of bacteriological examination are rapid molecular testing and TB culture. The ISTC recommends rapid molecular testing as an initial

diagnostic test to detect TB when possible. Two sputum specimens were sent for rapid molecular tests with negative results. When used as a preliminary test, the sensitivity and specificity of rapid molecular tests were 89% and 99%, respectively. However, when used in smear-negative patients, the sensitivity decreased to 68% [1,3,7].

Chest radiography

According to the ISTC, chest radiography could be used as an entry point to evaluate patients presumptive to have PTB who need further diagnostic evaluation. Furthermore, chest radiography is useful to evaluate presumptive PTB patients who have negative sputum smear and Xpert MTB/Rif results. The ISTC reported that chest radiography as a diagnostic test for PTB had a high sensitivity (98%) but lower specificity (75%). Hence, diagnosis of PTB based on chest radiography alone is not recommended [3,8]. In our case, the chest radiograph revealed an active PTB lesion in the upper lobe of the right lung, along with pneumonia and right pleural effusion.

Pleural fluid analysis

It is difficult to differentiate malignant or tuberculous pleural effusions from pleural fluid analysis. *Mycobacterium tuberculosis* is rarely found in pleural fluid smears. On the contrary, pleural biopsy is difficult to perform, and the culture procedure takes time, leading to a delay in proper patient management. The presence of malignant cells in the cytology examination of pleural fluid favours malignant effusion diagnosis [9,10], and adenosine deaminase (ADA) measurement with a cutoff value >35 U/L has consistently demonstrated high accuracy for diagnosing pleural TB. Unfortunately, both examinations could not be performed in our case due to district hospital facility limitations and a dry tap result when we attempted to perform thoracentesis in our hospital. The ADA test has a sensitivity of 92% and specificity of 90% for detecting pleural TB [11].

Chest CT-scan With Contrast

Tree in bud appearance is a pattern on thorax CT, which revealed centrilobular nodules with linear branching dispersion. This pattern is commonly seen in cases of infection, with pathogenesis as follows [12]:

- The bronchioles are filled with pus or exudate, as seen in pulmonary tuberculosis, aspiration, and bronchopneumonia.
- Bronchiolitis, thickening of bronchioles, and bronchovascular walls, as seen in

cytomegalovirus pneumonitis or obliterative bronchiolitis.

- Bronchiectasis with mucous plug (cystic fibrosis).
- Centrilobular artery emboli caused by a tumour (carcinomatous endarteritis) are commonly seen in breast cancer or stomach cancer.
- Interstitial bronchovascular infiltration is seen in sarcoidosis, lymphoma, and leukemia.

^{99m}Tc-Ethambutol Scanning

The greatest advantage of using nuclear medicine imaging is that it is easy to perform whole-body imaging. In this procedure, radiopharmaceutical ^{99m}Tc-ethambutol is taken by *Mycobacterium tuberculosis* bacilli; therefore, ^{99m}Tc-ethambutol scintigraphy using a gamma camera can visualise or localise the tuberculosis lesions. The SPECT/CT images were analysed visually for qualitative analysis with white to red colour, showing increased uptake of ^{99m}Tc-ethambutol. The normal distribution of ^{99m}Tc-ethambutol is seen as high uptake in the kidney, urinary bladder, liver, and spleen. Any increased pathological uptake of ^{99m}Tc-ethambutol seen in the location outside the normal distribution was considered positive [13-15].

This examination had a sensitivity and specificity of 93.9% and 85.7%, respectively, for the diagnosis of PTB. Furthermore, when used to detect extrapulmonary TB lesions, the sensitivity and specificity were 95.5% and 77.8%, respectively. Perhaps due to the low number of *Mycobacterium tuberculosis* bacilli colonies in the case of pleural or pericardial effusion, the accumulation of ^{99m}Tc-ethambutol under these conditions could be faint or difficult to see. ^{99m}Tc-ethambutol scintigraphy is known for its safety profile. Adverse effects of this method are rare and dose-dependent. To the best of our knowledge, this method has no side effects. This method is also considered safe, even in paediatric patients. The disadvantage of this method lies in its image acquisition time, which is performed at one and four hours post-injection. The U.S. Food and Drug Administration classifies technetium-99m as category C in pregnancy; hence, pregnancy and lactation are contraindicated for the procedure. However, patients are informed about pumping and discarding breast milk up to 60-hours post technetium-99m administration when the procedure had to be performed. Moreover, a previously documented hypersensitivity reaction to technetium-99m would be a precaution for its use [13,14,16].

Conclusions

^{99m}Tc-ethambutol scintigraphy is a useful and reliable procedure to diagnose TB, even though it has not yet been included in the international or national tuberculosis diagnostic guidelines. It has an important role in establishing and localising TB foci, especially when other studies cannot conclude the diagnosis. ^{99m}Tc-ethambutol scintigraphy in this patient showed disseminated TB as the diagnosis. Retreatment of anti-TB regimens was the best treatment in this case.

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