Original Article

The role of Technetium-99m-Ethambutol scintigraphy in the management of spinal tuberculosis

ABSTRACT

Spines is a common site of extrapulmonary *Mycobacterium tuberculosis* infection (MTI). Spine destruction due to MTI can mimic other etiologies. Treatment of choice for spinal tuberculosis (STB) is anti-TB drugs while surgery could be needed in other causes. The gold standard for STB diagnosis is histopathology examination from biopsy tissue. Technetium-99m-ethambutol (^{99m}Tc-EMB) scintigraphy can be used to detect and localize of TB. The aim of this study was to evaluate the role of ^{99m}Tc-EMB scintigraphy in STB management. Retrospective study was carried out from 2006 to 2014. Subject STB were patient STB with suspected of STB and underwent ^{99m}Tc-EMB scintigraphy. The histopathologic result was used as gold standard. Whole body planar acquisition was taken at 1 and 3 h postinjection of 370 MBq. Single-photon emission computed tomography/computed tomography acquisition was performed on suspected area. ^{99m}Tc-EMB image were analyzed by two nuclear medicine specialis. The 93 subject STB were included in this study. Histopathologic data were available in 40/93 subject STB. Positive and negative ^{99m}Tc-EMB scintigraphy were 32 and 8 subject STB. ^{99m}Tc-EMB scintigraphy result STB was concordance with the histopathologic finding in 37 subject STB. Sensitivity, specivicity, positive- and negative-predictive value, and accuracy of ^{99m}Tc-EMB scintigraphy 90.91%, 71.43%, 93.75%, 62.5%, and 87.5%, respectively. This study showed that patient STB with suspected ^{99m}Tc-EMB scintigraphy result could be directly treated with anti-TB. ^{99m}Tc-EMB scintigraphy has significant role in the management of STB.

Keywords: Imaging, technetium-99m-ethambutol, spinal tuberculosis

INTRODUCTION

Tuberculosis (TB) infection remains a global health problem. It can involve not only lung but also any other organs in the body known as extrapulmonary TB (EPTB).[1-3] Spinal TB (STB) is a common EPTB and remain a major health problem, particularly in the developing countries. The diagnosis of EPTB sometimes is very difficult since the symptoms of EPTB are not specific. It may manifest as fever, anorexia, weight loss, malaise, and fatigue. Sometimes, EPTB patient complain of only mild localized pain. Most of patients with EPTB came in advanced stage with neurological defisits or cold abscess (swelling without inflammation). Rapid and accurate diagnosis of STB is a cornerstone of the global TB control strategies.[4] Many modalities can be used to diagnose STB, but every modality has its advantages, and limitations as well in diagnosis of TB. The final diagnosis of TB depends on *Mycobacterium tuberculosis* finding on either histopathological test and/or culture.[5] Nevertheless, these histopathological test and culture may need between 10 and 14 days to get the results, and sometimes, it is difficult to get adequate specimen tissues.

Nuclear medicine modality is a noninvasive technique, which is a quick, sensitive, and specific method to detect as well as localize the site of infection and inflammation at an early stage of the disease. A wide variety of radiopharmaceuticals

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are used, such as Ga-67 citrate,[6] technetium-99m (^{99m}Tc)- ethylene cysteine dimer, ^{99m}Tc-tetrofosmin,[7] fluorodeoxyglucose-positron emission tomography,[8] ^{99m}Tc-methoxyisobutylisonitrile,[9] and ^{99m}Tc-ciprofloxacin[10] not specific for TB. Ethambutol (EMB)[11] is a specific anti-TB drug can be labeled with ^{99m}Tc. The aim of this study was to evaluate the role of ^{99m}Tc-EMB scintigraphy in the management of STB.

MATERIALS AND METHODS

This retrospective study was carried out in the Department of Nuclear Medicine and Molecular Imaging, Dr. Hasan Sadikin Hospital, Bandung. Subjects were patient with clinical diagnosis of suspected STB who referred for ^{99m}Tc-EMB scintigraphy were included in this study.

Preparation of technetium-99m-ethambutol

EMB kit for ^{99m}Tc-EMB was obtained from Indonesion National Atomic Agency/BATAN, which consists of two vials. Vial A contains 0.7 mg of $SnCl_2$. H_2O and 35 mg Na - pyrophosphate and vial B contains 3.5 mg EMB and 5 mg of mannitol. A volume of 0.5 ml of vial A solution, previously mixed with 1 ml aquabidest, was added to vial B. Shaken until completely mixed. Then, 1 ml Na $^{99m}TcO_4$ added to vial B, allow the solution for 5–10 min at room temperature with occasional shaking.[12]

Purity of technetium-99m-ethambutol

The ^{99m}Tc-EMB purity was determined by instant thin layer chromatography examination using acetone solvent. The only radiopharmaceutical with purity >85% was used in ^{99m}Tc-EMB imaging procedures.[12]

Scintigraphy procedure

There was no particular preparation for scintigraphy procedure. Whole body and single-photon emission computed tomography/computed tomography (SPECT-CT) images were taken at 1 and 3 h after intravenous injection of 370 MBq ^{99m}Tc-EMB. A dual-head SPECT-CT Gamma Camera was used with Low Energy High Resolution Collimator, energy peak 140 keV and window wide 20%. SPECT-CT was done in the suspected area of STB.

Interpretation

^{99m}Tc-EMB scintigraphy was interpreted visually by two nuclear medicine specialists. The image interpretation is as follow: (1) Normal scan, if there is no pathological increase uptake of ^{99m}Tc-EMB. Normal high uptake was seen in kidney and urinary bladder, liver, and spleen. There is the uptake of ^{99m}Tc-EMB in bone, bone marrow, and soft tissue. (2) Positive scan, if pathologic uptake of ^{99m}Tc-EMB were seen in the spine and gradually increased with time. (3) Negative scan, if pathologic uptake of ^{99m}Tc-EMB were seen which was increased at 1 h and gradually decreased (washed out) at 3 h images.

Statistical analysis

Statistical analysis was performed to determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of ^{99m}Tc-EMB scintigraphy with histopathologic finding postsurgery as gold standard.

RESULTS

Table 1 showed the clinical characteristic of patients. From March 2006 and March 2014, there were 93 subjects who clinically suspected of having STB underwent ^{99m}Tc-EMB scintigraphy. Histopathologic data were available only in 40 subjects who included in this study. Positive and negative ^{99m}Tc-EMB scintigraphies were found in 32 and 8 subjects, respectively.

Table 2 showed characteristic of patients according to histopatologic result and ^{99m}Tc-EMB scintigraphy. 99mTc-EMB scintigraphy was positive and negative concordance with the histopathologic finding in 30 and 7 subjects, respectively. Only 2/32 (6.25%) subjects with positive ^{99m}Tc-EMB scintigraphy were negative histopathologic finding (false positive). While 3/8 (37.5%) subjects with negative ^{99m}Tc-EMB scintigraphy were positive histopathologic finding (false negative).

True positive finding in 27-year-old, female, with suspected of having STB underwent ^{99m}Tc-EMB scintigraphy and histopathologic procedure postsurgery [Figure 1].

Sensitivity, specificity, PPV, NPV, and accuracy of ^{99m}Tc-EMB scintigraphy was 90.91%, 71.43%, 93.75%, 62.5%, and 87.5%, respectively.

DISCUSSION

This study showed the diagnostic performance of ^{99m}Tc-EMB scintigraphy in clinically suspected STB, with sensitivity, specificity, PPV, NPV and accuracy 90.91%, 71.43%, 93.75%, 62.5%, and 87.5%, respectively. Only 2/32 (6.25%) subjects with positive ^{99m}Tc-EMB scintigraphy were has no STB based on histopathologic results (false positive or nondiagnostic). False positive ^{99m}Tc-EMB scintigraphy could be caused by: (1) Hypervascularization in nonspecific spine infection will lead to accumulation of ^{99m}Tc-EMB either in 1 h and 3 h postinjection.[11] (2) There is some difficulties to get the adequate specimen biopsy from tissues postsurgery.[5,13] (3) Culture can identify acid-fast bacilli reliably require the

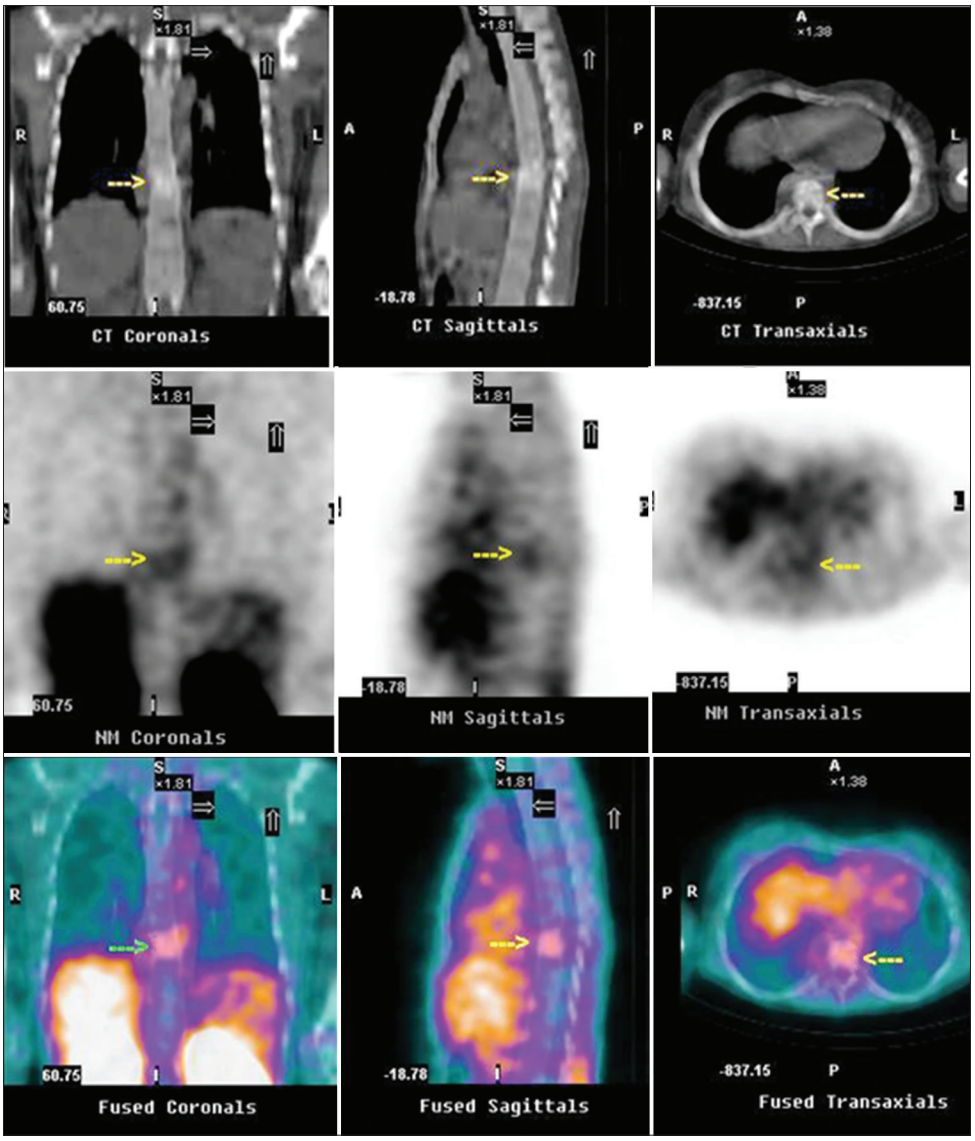

Figure 1: Technetium-99m-ethambutol scintigraphy diagnostic image of 27-year-old female with suspected spinal tuberculosis. Image single-photon emission computed tomography/computed tomography in os vertebra thoracolumbal produced at 3 h pasca-injection technetium-99m-ethambutol. Image show pathologic uptake of technetium-99m-ethambutol in os vertebra T7 that gradually increased with time. Positive technetium-99m-ethambutol scintigraphy was concordance with histopathologic finding postsurgery of paravertebral abscess (true positive)

presence of at least 10^4 acid-fast bacilli per milliliter of the specimen.[14,15]

There were 3 out of 8 (37.5%) subjects with negative ^{99m}Tc-EMB scintigraphy showed positive histopathologic for STB (false negative). False negative ^{99m}Tc-EMB scintigraphy could be due to: (1) Competition between ^{99m}Tc-EMB and anti-TB drugs (EMB) given before ^{99m}Tc-EMB scan.[16] (2) The dose of EMB labeled with ^{99m}Tc was only 2 mg much less than the dose of EMB as anti-TB drugs (15–25 mg/kg body weight).[17,18] (3) Small numbers of bacteria at the site of the lesion at the time of imaging. The number of bacteria should be at least 10^4 to be able to imaged.[19,20] (4) Necrotic tissues in patients with STB will not uptake ^{99m}Tc-EMB.[11] (5) At the early stage of the disease, most of *M. tuberculosis* were in macrophage with the result low uptake of ^{99m}Tc-EMB.[21,22]

This study showed the high PPV of ^{99m}Tc-EMB scintigraphy (71.43%). Based on high PPV, we could conclude that if a patient with clinically suspected STB had positive ^{99m}Tc-EMB scintigraphy, it mean that patient could directly treated with anti-TB drugs without cytologic diagnostic. Whereas if patient with suspected STB showed negative ^{99m}Tc-EMB scintigraphy, it mean others causes of STB should be considered.

Others advantages of ^{99m}Tc-EMB scintigraphy are: (1) Noninvasive procedure. (2) Result will be faster than cytologic diagnostic. (3) Minimal or no side effects of

Table 1: Clinical and ^{99m}Tc-ethambutol scintigraphy characteristic of patient spinal tuberculosis ($n=40$)

Characteristic	Total
Sex	
Male	20
Female	20
Age	
Range (years)	8-79
	2-61
Mean	35.7
	24.5
Histopathologic result from specimen tissue postsurgery	
Positive	32
Negative	8
^{99m}Tc-EMB skintigrafi	
Positive	33
Negative	7
Lesion site of ^{99m}Tc-EMB uptake	
Cervical	2
Thoracal	16
Lumbal	9
Thoracolumbal	6

^{99m}Tc-EMB: Technetium-99m-ethambutol

Table 2: 2×2 of histopathologic finding and ^{99m}Tc-ethambutol skintigrafi ($n=40$)

^{99m}Tc-EMB scintigraphy	Histopathologic finding		Total
	Positive	Negative	
Positive	30	2	32
Negative	3	5	8
Total	33	7	40

^{99m}Tc-EMB: Technetium-99m-ethambutol

radiotracer since dosage of radiotracer given to patients is only 2 mg dan excreted through the physiological process.[22]

This study showed that patients with clinically suspected STB and ^{99m}Tc-EMB scintigraphy result support the evidence of STB, could be directly treated with anti-TB regimen without underwent to the histopathologic procedure.

This study has several limitations. First, we conducted the retrospective study, and therefore, selection bias should be considered in the interpretation of our results. Second, mostly patients included in this study had treated with anti-TB drugs <1 month before the time of ^{99m}Tc-EMB scintigraphy. Third, we did not consider the amount of calculated numbers of bacteria at the site of tuberculose infection at the time of imaging.

CONCLUSION

^{99m}Tc-EMB scintigraphy is a promising diagnosis modality for detection and localization of spine TB.

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Conflicts of interest

There are no conflicts of interest.

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