Original Article

^{99m}Tc-Ethambutol Scintigraphy with Single-Photon Emission Computed Tomography/Computed Tomography in Lymph Node Tuberculosis: An Initial Experience

Abstract

Purpose of the Study: The purpose of the study is to evaluate ^{99m}Tc-labeled ethambutol (^{99m}Tc-EMB) as a potential diagnostic agent in lymph node tuberculosis (LNTB). **Materials and Methods:** A prospective pilot study was done at All India Institute of Medical Sciences, New Delhi. We included adult consenting patients who were diagnosed with LNTB and were either treatment naïve or had just started treatment. Patients were injected with 10–15 mCi of ^{99m}Tc-EMB. Whole-body anteroposterior planar imaging was done from 15 min after injection at serial intervals till 4–6 h along with one single-photon emission computed tomography–computed tomography (SPECT-CT) imaging with the help of a dual-head SPECT-CT gamma camera. The uptake of ^{99m}Tc-EMB was analyzed and corroborated with clinicoradiological findings. **Results:** Between January 2019 and November 2020, we recruited 23 patients who underwent ^{99m}Tc-EMB, and 19 scans were interpretable and considered for analysis. Cervical lymphadenopathy was the most common presentation (13, 68.42%), followed by mediastinal (9, 47.36%) and abdominal (4, 21.05%) nodes. Other involvement included pulmonary (8, 42.1%), gastrointestinal (3, 15.78%), and chest wall abscess and bone marrow deposits in 1 patient each. A positive scan was noted in 7 (53.84%) patients with cervical lymphadenopathy, whereas uptake in abdominal and mediastinal lymph nodes was seen in 1 (25%) and 2 (22.22%) cases, respectively. Uptake in pulmonary lesions was noted in 3 (37.5%), but uptake in hepatic and splenic lesions was not seen. **Conclusion:** ^{99m}Tc-EMB scan can demonstrate drug penetrance *in vivo* in some patients with LNTB and should be explored further with a larger sample size.

Keywords: *^{99m}Tc-ethambutol, radiolabeled antibiotics, scintigraphy, tuberculosis*

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Introduction

Tuberculosis (TB) caused by Mycobacterium tuberculosis (MTB) persists to be a major public health problem around the globe. Approximately 10 million people were reportedly affected worldwide in 2019, with India being one of the countries with the highest burden of TB.[1] TB is classified as pulmonary and extrapulmonary types. Although pulmonary TB is still the most common form, extrapulmonary involvement has been increasing lately, boosted by the rising number of human immunodeficiency virus (HIV) infection and organ transplantation.[2] Lymph node TB (LNTB) is the most frequently encountered form of extrapulmonary TB (EPTB), which can be either an isolated peripheral LNTB or a part of disseminated disease with widespread lymph node involvement. Due to its varied clinical facets and often overlapping features with lymph node malignancies, LNTB frequently poses diagnostic challenges to clinicians. Confirmation of the diagnosis requires the detection of MTB in the clinical samples, which can be a drawback in EPTB owing to the paucity of bacteria in extrapulmonary lesions.[3] Radiologic techniques such as computed tomography (CT) and magnetic resonance imaging as well as functional imaging such as positron emission tomography (PET) scan have become critical components of TB diagnostics. Although PET-CT can identify more tubercular lesions than a CT and differentiate active and inactive states, it cannot set TB apart from other infections or malignancies.[4] The use of radiopharmaceuticals has augmented infection imaging as they can detect changes in infection earlier than conventional imaging techniques. Radiolabeled antibiotics can be taken up by living bacteria, thus discriminating between

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infection and inflammation. Some of them have been used either only scarcely in clinical studies or only in animal studies, whereas ethambutol, a specific antitubercular agent, labeled with technetium-99m (Tc-99m) has been used successfully in some studies, albeit with limitations.[5-7] The encouraging results obtained previously demand further prospective studies, particularly in EPTB. We conducted this prospective study in patients with LNTB to further evaluate its potential as an additional tool in the diagnosis of TB in this group of patients.

Study design

This was a prospective study undertaken at the All India Institute of Medical Sciences, New Delhi, from January 2019 to November 2020. Since this was a pilot study using a novel potential diagnostic technique rarely used before in India, it was decided to keep a sample size of 20. Adult patients were recruited from the inpatient wards and outpatient clinics under or affiliated with the department of medicine after proper written consent.

Inclusion criteria

1. Age ≥18 years
2. Patients diagnosed with TB having lymph node involvement
3. Treatment naïve for antitubercular therapy or within 14 days of treatment initiation.

Exclusion criteria

1. Pregnancy and lactating mothers
2. Patients with impaired renal and liver function
3. Nonconsenting patients
4. Patients with severe acute or chronic illness with end-organ damage
5. Multidrug-resistant and central nervous system TB.

Scanning procedure

^{99m}Tc-labeled ethambutol scintigraphy (^{99m}Tc-EMB) was done in the Department of Nuclear Medicine, AIIMS, New Delhi. Patients were injected with radiolabeled ethambutol (10–15 mCi). Dynamic phase imaging was done immediately after injection of the radiotracer for 10 min. Planar whole-body imaging with anterior and posterior views was done hourly starting 15 min after injection of the radiotracer till 4–6 h. At least three images were taken in total for each patient.

Single-photon emission CT/CT (SPECT/CT) imaging was done once between 1 and 2 h.

For whole-body and SPECT/CT acquisition, a dual-head SPECT/CT gamma camera (Symbia T6 Siemens Inc., Germany, and Discovery NM CT 670, GE, USA) equipped with low-energy high-resolution collimator was used. SPECT/CT images were acquired with a time per acquisition of 20 s with a matrix size of 128 × 128 and 60 views.

Interpretation of results

The images were interpreted by an experienced nuclear medicine physician with 15 years of experience in reporting scintigraphy images.

Acquired images were interpreted as follows:

i. Presence of free Tc-99m was evidenced by visualization of thyroid and stomach activity
ii. Presence of colloid formation was evidenced by visualization of liver, spleen, and bone marrow activity together
iii. If both of the above were not found and gallbladder activity was visualized, the scan was considered to be interpretable
iv. Any focal uptake of the tracer outside the expected normal biodistribution and corresponding to the site of a disease known on clinical examination or prior imaging was considered positive. Any focal uptake of the tracer outside the expected normal biodistribution with no prior corroboration on clinical examination or prior clinical imaging was evaluated with single-photon emission computed tomography (SPECT-CT) or other imaging on follow-up
v. Pulmonary uptake was considered positive if it corresponded to the structural lesion on chest X-ray or CT scan
vi. Lack of any abnormal focal or patchy uptake on scan outside the expected normal biodistribution was interpreted as a negative scan.

Uptake of ^{99m}Tc-ethambutol during initiation of antitubercular therapy was analyzed and corroborated with clinicoradiological presentation.

Results

We included 23 patients in the study. Thirteen (56.5%) patients were male and 10 (43.5%) were female. The median age of our study population was 30 years (interquartile range [IQR]: 26–39.5). Eleven (47.82%) patients were antitubercular drug (ATD) naive and 12 (52.18%) patients were within 14 days of initiation at the time of antibiotic scintigraphy. Nineteen scans were interpretable and were considered for analysis and four scans were noninterpretable due to altered biodistribution of the radiotracer.

Baseline characteristics

Thirteen (68.42%) patients had cervical lymphadenopathy and mediastinal lymph node involvement was present in 8 (42.1%). Four (21.05%) and 1 (5.26%) patients had abdominal and paratracheal lymphadenopathy, respectively.

Other organ system involvement was also present in some patients. Eight (42.1%) patients had involvement of the respiratory system in the form of nodular opacities, centrilobular nodules, consolidation, and pleural thickening. Gastrointestinal involvement was found in 3 (15.78%) patients (splenic granulomas and subcapsular hepatic

nodules). One patient (5.26%) had a chest wall abscess and 1 (5.26%) patient had bone marrow deposits.

Overall, 11 (57.89%) patients had isolated lymphadenopathy and 8 (42.11%) patients had additional involvement, which includes three patients with disseminated TB.

Xpert MTB/rifampicin (RIF) assay for the detection of MTB was done in various samples such as lymph node aspirate, sputum, bronchoalveolar lavage, and pus, which was positive in 18 out of 19 patients. Smear positivity for acid-fast bacilli was seen in 3 (15.78%) patients. Mycobacterial growth indicator tube (MGIT) culture grew MTB in 3 (15.78%) cases and histopathological evidence was present in 9 (47.36%) patients [Table 1].

^{99m}Tc-labeled ethambutol scintigraphy results

^{99m}Tc-EMB scintigraphy was done in 23 patients and 19 scans were interpretable. Xpert MTB/RIF results were positive in 18 patients. MGIT culture was positive in 3 patients and histopathological examination evidence of TB was present in 9 samples. Serial planar imaging was done in all the patients and SPECT-CT was done in 16 patients. Out of the 13 patients having cervical lymphadenopathy, an increased uptake was noted in 7 (53.84%) patients [Figure 1].

Mediastinal lymphadenopathy was present in 9 patients. Commenting on the uptake results in planar images was not possible in cases of mediastinal lymph node involvement due to the overlying cardiac blood pool uptake. SPECT-CT showed increased lymph node uptake in two patients. Increased radiotracer uptake was evident in both the planar and SPECT-CT images in one patient having paratracheal lymph node involvement. Since SPECT-CT was not available in all patients, the actual percentage of uptake in mediastinal lymph nodes could not be commented.

In cases with pulmonary involvement, increased uptake was noted in planar imaging in one (50%) patient with lung consolidation, which was confirmed by SPECT-CT finding, while SPECT-CT image was not available for the other case. Nodular opacities were present in two patients which did not show any increased tracer uptake in planar or SPECT-CT images. Centrilobular nodules were seen in three patients, of which 2 (66.6%) patients had an increased tracer uptake in the lungs in both planar and SPECT-CT images. Pleural thickening was present in one patient which did not show any increased uptake in either planar or SPECT-CT images.

Among the gastrointestinal organ involvement, one patient had subcapsular nodules in the liver and two patients had splenic granulomas. Increased uptake was not noted in the scintigraphy images in these patients.

Increased radiotracer uptake was detected in planar and SPECT-CT imaging in one patient having a chest wall abscess.

Bone marrow deposits were present in one patient with disseminated TB, which did not show any increased uptake [Table 2].

Four out of 11 (36.36%) patients within the ATD-naïve cohort have positive uptake studies and 8 out of 12 (66.6%) patients in the ATD-initiated group had positive findings, whereas two patients from each cohort had noninterpretable results.

Table 1: Baseline characteristics of patients who underwent ^{99m}Tc-labeled ethambutol scintigraphy (*n*=19)

Median age	30 years (IQR: 26-39.5)
Male sex, *n* (%)	13 (56.5)
Lymph node involvement, *n* (%)	
Cervical	13 (68.42)
Mediastinal	9 (47.36)
Abdominal	4 (21.05)
Organ involvement, *n* (%)	
Pulmonary	8 (42.1)
Gastrointestinal	3 (15.78)
Chest wall abscess	1 (5.26)
Bone marrow deposits	1 (5.26)
Diagnosis, *n* (%)	
Isolated TB lymphadenitis	11 (57.89)
TB lymphadenitis with additional organ/site involvement	8 (42.11)
Diagnostic evidence, *n* (%)	
Xpert MTB/RIF positive	18 (94.73)
AFB smear positive	3 (15.78)
MGIT culture positive	3 (15.78)
Histopathological evidence	9 (47.36)
ATD naïve	9 (47.36)
Within 2 weeks of ATD initiation	10 (52.63)

RIF: Rifampicin, TB: Tuberculosis, MTB: *Mycobacterium tuberculosis*, IQR: Interquartile range, AFB: Acid-fast bacilli, MGIT: Mycobacterial growth indicator tube, IQR: Interquartile range, ATD: Antitubercular drug

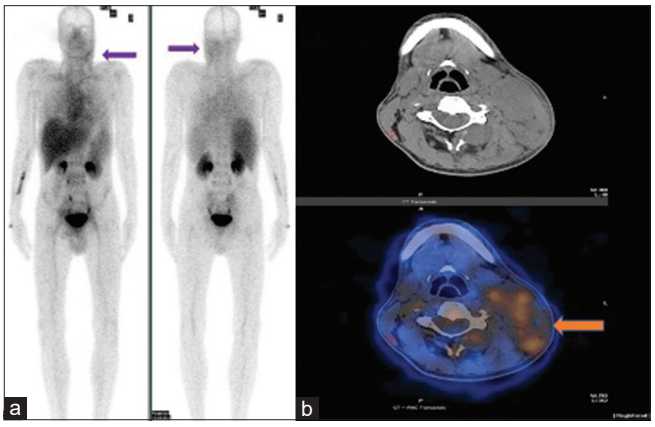

Figure 1: Whole-body anteroposterior planar imaging (a) and SPECT-CT imaging of neck (b) showing increased pathological uptake of ^{99m}Tc-EMB in left-sided cervical lymph nodes (indicated by arrows). SPECT-CT: Single-photon emission computed tomography, ^{99m}Tc-EMB: ^{99m}Tc-labeled ethambutol

Table 2: ^{99m}Tc-labeled ethambutol scintigraphy results (*n*=19)

Structural involvement	Number of patients (*n*=19)	Positive-uptake noted	
		Planar images	SPECT-CT
Lymph node involvement			
Cervical	13	7/13 (53.84)	7/11*
Abdominal/ retroperitoneal	4	1 (25)	0/3*
Mediastinal	9	Cannot comment	2/7*
Pulmonary involvement			
Consolidation	2	1 (50)	1/1*
Nodular opacities	2	0	0
Centrilobular nodules	3	2 (66.6)	2/2
Pleural thickening	1	0	0
Gastrointestinal involvement			
Subcapsular nodules in liver	1	0	NA
Splenic granulomas	2	0	0
Soft tissue involvement			
Chest wall abscess	1	1 (100)	1
Hematological involvement			
Bone marrow deposits	1	0	0

*SPECT-CT imaging was not available in all patients.
SPECT-CT: Single-photon emission computed tomography, NA: Not available

We followed up all the patients till the end of treatment or the end of the study period, whichever was earlier. A total of 14 patients had completed their treatment at the end of our study period. Two patients expired during the period from disseminated disease, two patients had ongoing treatment at the conclusion of our study, and one patient experienced treatment failure on first-line ATD. The median treatment duration of patients with a positive scan was 7.75 (IQR: 6.25–8.25) months, whereas that of patients with a negative scan was 6.25 (IQR: 6.25–10) months.

A total of 13 patients had palpable cervical lymphadenopathy and 10 of them had completed treatment at the time of analysis. Six of them had a positive uptake on scan. Out of the six patients with positive ^{99m}Tc-EMB scintigraphy, 1 (16.66%) had persistent palpable lymph node enlargement, and among the four patients with negative scan, 2 (50%) had persistent palpable lymphadenopathy after 6 months of treatment.

Discussion

Although significant advances have been made in the diagnosis of TB, noninvasive techniques that can reliably differentiate it from other diseases are still elusive.

Radiolabeled antibiotics, owing to their ability to bind specifically to bacteria, theoretically have an edge over conventional radiopharmaceuticals which target only the inflammatory response of the host.[8] When a gamma emitter like Tc-99m is used as a radionuclide, the binding of the radiopharmaceutical with the bacteria can be visualized by a gamma camera.

Ciprofloxacin was the earliest ATD to be used as a radiolabeled antibiotic in clinical studies.[9] Being a broad-spectrum antibiotic makes it less specific for TB. Other radiolabeled ATDs that have been used only scarcely include ^{99m}Tc-isoniazid (^{99m}Tc-INH), ^{99m}Tc-rifabutin, and ^{99m}Tc-RIF.[6,10,11]

Ethambutol being a specific drug against TB would be an ideal agent to combine with Tc-99m and used for the detection and localization of tubercular lesions. Ethambutol is a bacteriostatic agent, which is used for the treatment of MTB infection and nontuberculous mycobacteria. ^{99m}Tc-ethambutol has recently been studied by some investigators for the diagnosis of TB, although only in retrospective designs and mostly in bone TB.[5,12] Only the study by Kartamihardja *et al*. included multiple forms of TB, including LNTB (33 patients).[5]

In our patients, we found an increased uptake in 53.4% of cervical lymph nodes both in planar and SPECT-CT images. However, a lesser percentage of abdominal (25%) and mediastinal lymph nodes (14.28%) showed positive ^{99m}Tc-EMB uptake. SPECT-CT imaging is essential to localize the radiotracer uptake to mediastinal and abdominal lymph nodes, as planar images will have overlapping mediastinal blood pool and gut activity.

Pulmonary involvement in our patients was detected in 42.85% of patients, despite the radiotracer being uniformly distributed in the lung parenchyma in all cases. However, other organ involvement such as hepatic, splenic, and bone marrow involvement was not detected. Two patients were coinfected with HIV and, therefore, could have been harboring other infections apart from TB. Chest wall abscess in one patient was demonstrated well by both planar and SPECT-CT imaging.

Most of the absorbed ethambutol (around 80%) is excreted renally as an unchanged drug over 24 h of administration. The Tc-99m-labeled antibiotic has a short effective half-life, which necessitates imaging within the first 6 h to get good-quality images. At these time points, there is a persistent activity of tracer in the mediastinal blood pool, which may lead to underestimation of uptake in mediastinal lymph nodes leading to false-negative scans (masking). Similarly, there

is a possibility of masking by the hepatic/renal/gut activity in the abdomen. The initial biodistribution study by Singh and Bhatnagar found that ^{99m}Tc-EMB was well distributed in the various body compartments with a slightly higher concentration in blood. The radiotracer did not cross the blood–brain barrier and was excreted mainly through the renal route. Gallbladder visualization in scintigraphy was an indicator of proper biodistribution.[13] Some amount of colloid formation is seen at times, which will result in activity in bone marrow and spleen, which we also found in our study.

An interesting finding was the lower percentage of patients with a persistent palpable cervical lymphadenopathy after 6 months of treatment in the patients who had a positive uptake compared to those patients who had a negative scan. However, this finding cannot be extrapolated to other forms of lymphadenopathy in our cohort because we did not have the follow-up microbiological or imaging results in all patients. Further, because of our small sample size, a significant conclusion cannot be derived.

A negative ^{99m}Tc-EMB scan probably indicates a lack of antibiotic penetration in the affected site, which at times may be due to necrosis of the affected lymph nodes and reduced vascular supply. Lower bacterial loads in extrapulmonary lesions such as lymph nodes further contribute to the lower sensitivity. Liver is a site of physiological uptake of the labeled antibiotic; hence, lesions get underreported as they do not get noticed against the physiological uptake. This is commonly referred to as the "Sun and Star" effect or the masking effect in nuclear medicine imaging.

Therapeutic drug monitoring which ensures adequate serum concentrations of the antibiotic concerned is an integral part of the treatment of TB.[14] It is, however, not routinely performed due to logistic challenges. Not much is known about the actual concentration of the drug at the site of infection, which can help immensely in the optimization of treatment.[15,16] Failure of an ATD to concentrate at the active site of disease leads to treatment failure. Currently available imaging techniques cannot estimate the accumulation of an ATD at the site of infection, which is a possible advantage of radiolabeled antibiotic scintigraphy.

In patients with multisite involvement, increased ^{99m}Tc-EMB uptake in all the active sites of infection was noted in 28.57% of cases. This indicates that despite adequate distribution throughout the body, there is restricted antibiotic uptake in some areas which might affect the response to treatment.

Overall, ^{99m}Tc-EMB scintigraphy yielded a diagnostic positivity of 63.16%, which is less than that observed in previous studies, although they were performed mostly in musculoskeletal TB patients. Although we did not find any direct comparative studies between ethambutol scintigraphy and 18-fluorodeoxyglucose (FDG-PET), the potential of ^{99m}Tc-EMB to map the extent of tubercular involvement, provide objective evidence of penetration of antitubercular agents inside the lesion, and thus differentiate it from malignant or other nontubercular lesions is an advantage over the latter.

Potential interference of the radiolabeled antibiotic with oral ATD intake is another issue that needs to be addressed. In accordance with previous studies, we included patients within 2 weeks of ATD initiation. We did not find any significant difference between ATD-naive and experienced patients, but repeat testing late in the course or at the end of therapy would be more helpful to answer this question.

Our study has certain limitations. This was a single-center study, and being a pilot study, we had a small sample size. This investigation is operator dependent and needs preparation of the radiotracer with adequate radiochemical purity before the scan. Serial images need to be taken over a period of 5–6 h, which makes it time-consuming compared to other imaging techniques. Ethambutol scintigraphy for nodal TB does not yield visually appealing images like FDG PET/CT since the tracer targets the viable mycobacteria rather than the leukocytic response to it. However, uptake more than background levels is easily seen. Moreover, the slow clearance of the antibiotic from the blood results in persistent blood pool activity at even delayed time points. This can also mask lesions on planar images, as seen in Figure 2.

We could not assess the specificity of this diagnostic technique because we did not include healthy individuals or healed lesions of TB or patients with other pathologies. Finally, follow-up scans were not performed, which can assess the treatment response by comparing with initial scans.

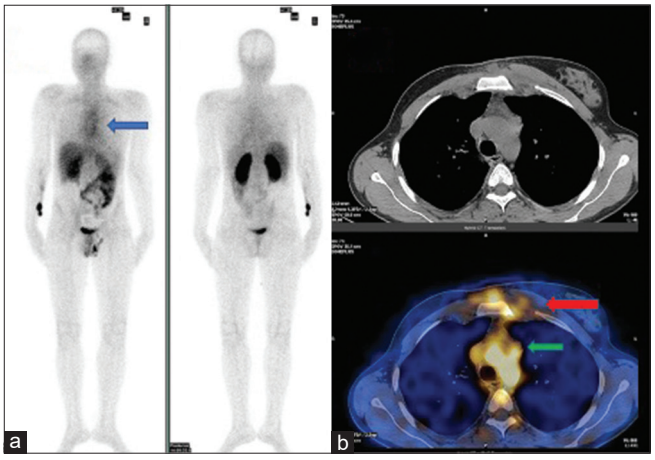

Figure 2: Whole-body anteroposterior planar imaging of a patient with chest wall abscess and mediastinal lymphadenopathy showing physiological mediastinal blood pool activity masking the pathological uptake (blue arrow) (a) and SPECT-CT imaging of the same patient showing the increased pathological uptake in the chest wall abscess (red arrow) and in the mediastinal lymph node along with the mediastinal blood pool (green arrow) (b). SPECT-CT: Single-photon emission computed tomography

Conclusion

Our study provides a good platform for further studies with this rarely used diagnostic technique. Although the false positives in this modality are yet to be established, the favorable property of ^{99m}Tc-EMB uptake and retention by the tubercular lesions can be utilized for various indications such as mapping of lesions, demonstration of drug penetrance, and possibly determining response to therapy on follow-up scans.

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Conflicts of interest

There are no conflicts of interest.

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