Technetium-99m-Tetrofosmin Scintigraphy in Pulmonary Tuberculosis

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Technetium-99m-tetrofosmin, an agent that is widely used in myocardial imaging, has been reported to accumulate in several types of malignancies, including lung tumors. Yet, there is limited knowledge about its role in imaging infection or inflammatory lesions. The aim of this study was to investigate the role of ^{99m}Tc-tetrofosmin scintigraphy in pulmonary tuberculosis in cases with active and inactive tuberculosis in comparison with radiological and microbiological findings. **Methods:** Twenty-seven patients with active pulmonary tuberculosis (APTB) and 6 patients with inactive pulmonary tuberculosis (IPTB), proven by sputum smears and cultures, were included in this study. Mean age of the group was 42.6 ± 13 yr. Nine months after therapy, ^{99m}Tc-tetrofosmin scintigraphy was repeated in 6 patients with APTB to evaluate response to therapy. Ten-minute anterior and posterior chest images were acquired 20 and 60 min after the injection of 370 MBq (10 mCi) ^{99m}Tc-tetrofosmin. The images were evaluated both visually and semiquantitatively by two blinded nuclear medicine physicians. For semiquantitative evaluation, regions of interest (ROIs) were drawn over the lesion (L) and nonlesion areas (NL). The mean count values of ROIs were obtained and L/NL ratios were calculated. **Results:** According to the visual evaluations, ^{99m}Tc-tetrofosmin uptake was Grade (+) in 4 (15%) and Grade (++) in 23 (85%) patients with APTB. Technetium-99m-tetrofosmin uptake was negative in 5 patients with IPTB. Grade (+) ^{99m}Tc-tetrofosmin uptake was observed in only one inactive case. After therapy, there was no ^{99m}Tc-tetrofosmin uptake in 3 patients, which correlated well with chest radiography and clinical findings. In the other 2 patients, ^{99m}Tc-tetrofosmin uptake was slightly decreased when compared with a previous scan that correlated with radiological and clinical findings. In 1 patient with bilateral lung disease, ^{99m}Tc-tetrofosmin uptake decreased on the right lung lesions, whereas the left lung lesions persisted with no change. The mean early and delayed L/NL ratios of APTB were 1.53 ± 0.22 and 1.45 ± 0.21, respectively. Although ^{99m}Tc-tetrofosmin uptake in APTB lesions was more visually marked in early images than that in delayed images, there was no statistically significant difference between these two sets of images. **Conclusion:** Technetium-99m-tetrofosmin scintigraphy showed increased uptake in APTB lesions related to disease activity. After treatment, ^{99m}Tc-tetrofosmin uptake disappeared or decreased, correlating well with radiological and clinical findings. Technetium-99m-tetrofosmin scintigraphy may have a complementary role in the assessment of APTB as well as in follow-up treatment.

Key Words: technetium-99m-tetrofosmin; pulmonary tuberculosis, infection imaging

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Technetium-99m-tetrofosmin, an agent that is widely used for myocardial imaging, is a cationic and lipophilic radiopharmaceutical similar to ^{99m}Tc-hexakis-2-methoxyisobutyl isonitrile (MIBI). But it has certain advantages over MIBI, such as easy preparation and faster blood, liver and lung clearance (*1,2*). In several studies, it has been shown to accumulate in various neoplasms such as breast, thyroid and lung cancer, Hodgkin's disease, musculoskeletal tumors (*3–13*) and in parathyroid adenomas (*14*). The role of ^{99m}Tc-tetrofosmin scintigraphy in the infection or inflammatory lesions has not been well documented thus far. We observed ^{99m}Tc-tetrofosmin accumulation in active pulmonary tuberculosis (APTB) and investigated the role of ^{99m}Tc-tetrofosmin in the evaluation of pulmonary tuberculosis (PTB).

The diagnosis of PTB is based on the tuberculin skin test, abnormal chest radiography findings and the identification of mycobacterium in sputum smears. However, these tools are sometimes of little value in the diagnosis of APTB, particularly in elderly and immunocompromised patient populations and in chronic cases with recrudescent infection owing to superimposed chronic sequelae from previous PTB attacks (*15–17*). A definite diagnosis in such cases is only possible by culturing sputum and bronchial washings or histological examination of specimens obtained by fiberoptic broncoscopy. Since bronchoscopy is invasive and sputum cultures require 2–8 wk, depending on the methodology used, there are limitations to this technique (*18*).

Several radiopharmaceuticals, including ^{67}Ga citrate, ^{99m}Tc-citrate, ^{99m}Tc-(V)-dimercaptosuccinic acid (DMSA), ^{201}TI, ^{99m}Tc-glucoheptonate, radiolabeled monoclonal antibodies, ^{111}In-octreotide and ^{99m}Tc-MIBI have been used in the evaluation of PTB (*19–26*) and treatment response.

The aim of this study was to assess the diagnostic potential of ^{99m}Tc-tetrofosmin scintigraphy in infection imaging and also in differentiating active from inactive PTB (IPTB).

MATERIALS AND METHODS

The study group included 33 patients (32 males and 1 female; age range 16–76 yr; mean age 42.6 ± 13 yr). Data from chest radiographs, erythrocyte sedimentation rates, sputum smears/culture and ^{99m}Tc-tetrofosmin imaging were available for the group. Informed consent for imaging studies was obtained from all patients.

The study group was divided into three subgroups. Group 1 included 27 patients with APTB proven by clinical, chest radiography, acid-fast staining of sputum smear and culture findings (Table 1). Group 2 contained 6 patients with IPTB confirmed by sputum smear or bronchial lavage and culture (Table 2). Group 3 included 6 patients who had been treated for 9 mo for tuberculosis (Table 3). Initial antituberculosis chemotherapy consisted of isoniazid (INH) 300 mg/day, rifampisin (RIF) 600 mg/day, morfozinamid (MPZ) 3 g/day, ethambutoal (EMB) 1 g/day for 2 mo, INH (300 mg/day) and RIF (600 mg/day) were continued for the following 7 mo.

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TABLE 1
Data for Patients with Active Pulmonary Tuberculosis

Patient no.	Sex	Age (yr)	ESR (mm/hr)	Sputum smear	Sputum culture	Chest radiograph	Technetium-99m-tetrofosmin RL V	RL Q	LL V	LL Q
1	M	16	64	Positive	Positive	RUL, LML	++	1.5	++	1.3
2	M	22	76	Positive	Positive	RUL, LML	++	1.5	++	1.3
3	M	29	75	Positive	Positive	RUL,LUL	+	1.3	+	1.3
4	M	27	85	Positive	Positive	LUL, LML	−		++	1.3
5	M	22	59	Positive	Positive	LUL, LML	−		+	1.3
6	M	45	57	Positive	Positive	RUL, RML, RLOL	++	1.5	−	
7	M	46	110	Positive	Positive	RUL, RML, RLOL	++	1.6	−	
8	M	55	85	Negative	Positive	RUL	++	1.8	−	
9	M	22	90	Positive	Positive	RUL, RML	++	1.4	−	
10	M	33	93	Positive	Positive	RUL, LUL, LML	++	1.5	++	1.7
11	M	68	123	Positive	Positive	RUL, RML, RLOL, LML	++	1.4	++	1.4
12	M	40	64	Positive	Positive	LUL, LML, LLOL	−		++	1.3
13	M	48	88	Positive	Positive	RUL, LUL	++	1.3	++	1.3
14	M	63	57	Positive	Positive	RUL, RML, LUL	+	1.4	++	1.4
15	M	61	110	Positive	Positive	RUL, LUL	+	1.4	++	1.4
16	M	43	134	Positive	Positive	RUL, RML	++	1.9	−	
17	M	37	123	Positive	Positive	RUL, RML, LUL, LML	++	1.8	++	1.5
18	M	24	28	Positive	Positive	LUL, LLOL	−		++	1.4
19	M	65	22	Negative	Positive	RML	+	1.6	−	
20	M	43	70	Negative	Positive	LUL, LML, LLOL	−		++	1.7
21	M	51	48	Positive	Positive	LUL, LML			++	1.5
22	M	30	60	Positive	Positive	LML, LLOL	−		++	1.9
23	M	34	90	Negative	Positive	RUL, RML, LUL, LML	++	2.0	++	1.9
24	M	46	85	Positive	Positive	LUL	−		++	1.6
25	M	31	105	Positive	Positive	RUL, RML, LUL, LML	++	1.5	+	1.3
26	M	43	97	Positive	Positive	LUL, LML, LLOL	−		++	1.4
27	M	41	105	Positive	Positive	RUL, LUL, LML, LLOL	++	1.2	++	2.5

ESR = erythrocyte sedimentation rate; RL = right lung; LL = left lung; R = right; L = left; U = upper; M = middle; LO = lower; V = visual grading; Q = semiquantitative evaluations (lesion-to-normal lung mean counts ratio).

Imaging Procedures

Ten-minute anterior and posterior chest images were acquired 20 and 60 min after the injection of 370 MBq (10 mCi) ^{99m}Tc-tetrofosmin. Acquisition was performed using a large-field gamma camera fitted with a low-energy, all-purpose collimator. Images were recorded in a 256 × 256 matrix. To reduce the superimposed scapular and pectoral muscular activities from the field of the lungs, acquisition was performed with the hands extended over the head. All patients were off therapy at the time of imaging. Technetium-99m-tetrofosmin scintigraphy was repeated 9 mo after initiation of chemotherapy in 6 patients. Commercially available tetrofosmin kits (Myoview™; Amersham Medical Ltd., Buckingamshire, United Kingdom) were prepared using freshly eluted ^{99m}Tc with quality control performed before injection according to manufacturers' recommendations. The labeling efficiency was higher than 95%. Images were evaluated visually and semiquantitatively by two blinded nuclear medicine physicians to assess activity of PTB. The interobserver variability was resolved by consensus. Visual grading was made as follows: (−) no uptake; (+) radiotracer uptake (RTU) equal to that in the sternocleidomastoid muscle (SMU); (++) RTU greater than SMU; (+++) RTU equal to that in the cardiac muscle. For semiquantitative evaluation, regions of interest (ROIs) were drawn over the lesion (L) and nonlesion areas (NL). The mean count values of ROIs were obtained and L/NL ratios were calculated. Technetium-99m-tetrofosmin scan data were compared to the corresponding chest radiograph. The Wilcoxon test was applied for the control of differences in L/NL ratios of the images obtained at 20 and 60 min.

RESULTS

Group 1 and Group 2

Features of active and inactive cases are shown in Tables 1 and 2. Table 4 summarizes visual grading of patients with IPTB and APTB.

According to the visual evaluations, ^{99m}Tc-tetrofosmin uptake in patients with APTB was Grade (+) in 4 (15%) and Grade (++) in 23 (85%) patients. There was no patient with Grade (+++) uptake.

Technetium-99m-tetrofosmin scintigraphy was negative in 5 (85%) patients who had radiologically and clinically suspected APTB. Imaging findings were confirmed by sputum or bronchial lavage cultures and clinical follow-up, all of which revealed IPTB. In one inactive case (Patient 28), Grade (+) uptake was observed. In this particular patient, the infiltration on the chest radiograph disappeared after treatment for pneumonia. Technetium-99m-tetrofosmin scintigraphy could not be repeated after treatment of pneumonia because the patient

TABLE 2
Data for Patients with Inactive Pulmonary Tuberculosis

Patient no.	Sex	Age (yr)	ESR (mm/hr)	Sputum smear	Sputum culture	Chest radiograph	Technetium-99m-tetrofosmin RL V	RL Q	LL V	LL Q
28	M	66	35	Negative	Negative	LUL, RUL	+	1.4	+	1.4
29	M	31	32	Negative	Negative	LUL	−		−	
30	M	43	60	Negative	Negative	LUL, LML, LLOL, RUL, RML	−		−	
31	M	65	22	Negative	Negative	RUL, LUL	−		−	
32	F	30	45	Negative	Negative	LUL	−		−	
33	M	76	52	Negative	Negative	LUL, LLOL, RUL	−		−	

See Table 1 for definitions.

refused the test. Technetium-99m-tetrofosmin uptake was positive in 4 patients who had negative sputum smears but positive cultures.

Semiquantitative evaluations are presented in Table 1. On semiquantitative evaluation, the early and delayed average L/NL ratio of APTB lesions was 1.53 ± 0.22 and 1.45 ± 0.21. The L/NL ratio was higher than 1.5 in 17 of 27 patients with active APTB. The lowest L/NL ratio was 1.2 for APTB lesions.

Technetium-99m-tetrofosmin uptake was more marked in the early images (20 min) than that in the delayed images (60 min) visually. But, in semiquantitative evaluations, the difference between early and delayed L/NL ratios was not statistically significant.

Figure 1 shows ^{99m}Tc-tetrofosmin scintigraphy and planar chest radiograph findings of a 34-yr-old man with APTB in both lungs. Marked ^{99m}Tc-tetrofosmin uptake was observed at the APTB lesions bilaterally, which correlated well with chest radiograph findings.

Figure 2 also shows ^{99m}Tc-tetrofosmin scintigraphy and planar chest radiograph findings of a 31-yr-old man with APTB in both lungs. Cavitary disease in the right middle and fibronodular infiltrations in the bilateral upper and middle zone were observed on chest radiography. There was marked ^{99m}Tc-tetrofosmin uptake surrounding the cavity and at the infiltrative area. There was also focal ^{99m}Tc-tetrofosmin uptake in the right axilla, and on physical examination, palpable lymph nodes were found there. Regression was seen in these lymph nodes by treatment of PTB.

Group 3

Data of follow-up patients are summarized in Table 3.

After 9 mo of treatment, ^{99m}Tc-tetrofosmin uptake disappeared in 3 patients, which correlated well with radiological and clinical findings (Fig. 3). In 2 follow-up patients, ^{99m}Tc-tetrofosmin uptake slightly decreased when compared with the previous scan. In another patient, ^{99m}Tc-tetrofosmin uptake decreased in the right lung lesion, whereas left lung lesions persisted (Fig. 4).

DISCUSSION

Technetium-99m-tetrofosmin, an agent that has ideal physical properties for gamma cameras, is a cationic and lipophilic radiopharmaceutical that is easily prepared and has fast blood, liver and lung clearance (*1,2*). This radiopharmaceutical is widely used in myocardial perfusion imaging and has also been reported to accumulate in various types of cancer (*3–13*). After we had fortuitously observed marked ^{99m}Tc-tetrofosmin uptake in active PTB lesions, we planned to further investigate its potential diagnostic role in infection imaging and in assessing the activity of PTB.

There may be difficulties in the detection of reactivation and in the evaluation of treatment response based on the clinical, laboratory and radiological findings in patients with PTB. Early studies for detection of PTB activity were performed with ^{67}Ga. Siemsen et al. (*19*) found that 95% of active or bacteriologically positive patients had abnormal ^{67}Ga scans and all of the remaining inactive or bacteriologically negative patients had normal scans. Utsunomiya et al. (*23*), compared ^{67}Ga and ^{201}TI in detection of the activity of PTB and found sensitivity, specificity and accuracy of 83.1%, 60.7% and 74.1%, respectively for ^{67}Ga; the same ratios for ^{201}TI were 88%, 82% and 85.6%, respectively. However, the fact that ^{67}Ga imaging can be performed 24–48 hr after injection and the suboptimal physical characteristics of both radionuclides limit the avail-

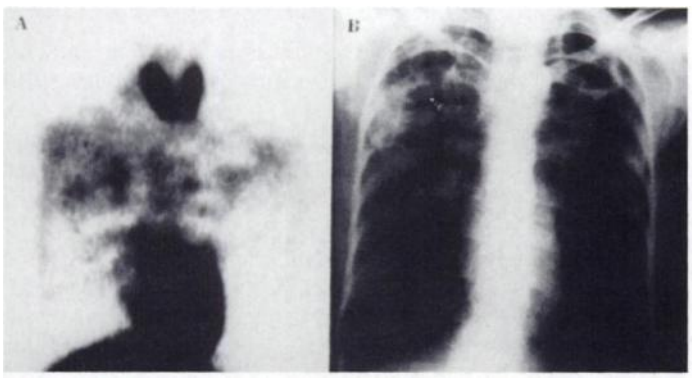

FIGURE 1. (A) Technetium-99m-tetrofosmin scintigraphy and (B) planar chest radiograph of patient with APTB (Patient 23). Cavitary disease together with fibronodular infiltrations in left upper and middle zones and in right upper and middle zones are seen on chest radiograph. There is marked ^{99m}Tc-tetrofosmin uptake surrounding cavity and at infiltrative area.

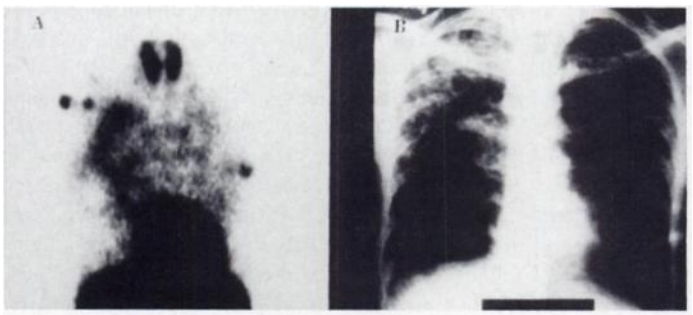

FIGURE 2. (A) Technetium-99m-tetrofosmin scintigraphy and (B) planar chest radiograph of patient with APTB (Patient 25). Cavitary disease in right middle and fibronodular infiltrations in bilateral upper and middle zones are seen on radiograph. There is marked ^{99m}Tc-tetrofosmin uptake surrounding cavity and at infiltrative area and also focal ^{99m}Tc-tetrofosmin uptake in right axilla. On physical examination, palpable lymph nodes were found in right axilla. Regression was seen in these lymph nodes by treatment of PTB.

TABLE 3
Data for Follow-up Patients

Patient no.	ESR (mm/hr)		Technetium-99m-tetrofosmin					
			Visual		L/NL			
	Initial value	Follow-up value	Initial scan	Follow-up scan	Initial scan		Follow-up scan	
					RL	LL	RL	LL
1	64	17	++	–	1.5	1.3	–	–
2	123	26	++	++	1.4	1.4	1.4	1.4
3	110	45	++	+	1.4	1.4	1.2	1.1
4	105	12	++	+	1.2	2.5	1.2	1.2
5	85	32	++	–	–	1.6	–	–
6	60	7	++	–	–	1.9	–	–

ESR = erythrocyte sedimentation rate; L = lesion; NL = nonlesion; RL = right lung; LL = left lung.

ability of these techniques. Indium-111-octreotide, which has limitations similar to ^{67}Ga, was also used in the evaluation of PTB. Vanhagen et al. (*25*) reported marked ^{111}In-octreotide uptake in APTB lesions. Although radiolabeled monoclonal antibodies seem specific for PTB, their high cost, the development of HAMA response and the lack of experience in studies limit their routine application (*24*).

In this study, considerable ^{99m}Tc-tetrofosmin uptake was observed in all 27 patients with APTB, most probably related to disease activity. On the other hand, in 5 of the 6 patients with IPTB, no uptake was detected. Only in 1 of 6 patients with IPTB, was there Grade (+) tetrofosmin uptake. The uptake in this patient was considered to be due to pneumonia because clinical and radiological improvement was observed after treatment for pneumonia. Technetium-99m-tetrofosmin uptake was observed in 4 patients with negative sputum smear but positive sputum culture for acid-fast bacilli. This finding suggests that this 1-day method may be more sensitive than sputum smear tests and gives clinically useful information until results of sputum cultures are available (2–8 wk).

TABLE 4
Visual Grading and Numbers of Patients with Active (APTB) and Inactive (IPTB) Pulmonary Tuberculosis

Visual Grading	APTB	IPTB
(–)	0 (0%)	5 (83%)
(+)	4 (15%)	1 (17%)
(++)	23 (85%)	0 (0%)
(+++)	0 (0%)	0 (0%)

Technetium-99m-tetrofosmin scintigraphy may also play a role in follow-up of patients with APTB after therapy. In this study, the APTB lesions completely resolved in 3 patients. Technetium-99m-tetrofosmin scintigraphy became normal in these patients—reflecting the recovery of the disease—and correlated well with radiological findings. In the other 3

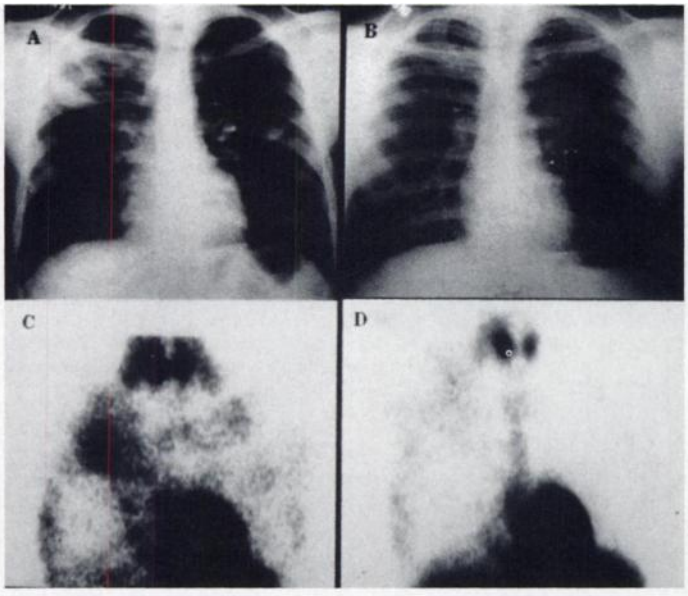

FIGURE 3. Technetium-99m-tetrofosmin scintigraphy and planar chest radiographs of 16-yr-old boy before and after chemotherapy treatment. (A) Before therapy, there was cavitary lesion with fibronodular infiltration on right upper lung and fibronodular infiltrations on left upper-middle lung zones on chest radiograph. (B) After therapy, lesions disappeared on chest radiograph. (C) Before therapy, ^{99m}Tc-tetrofosmin scintigraphy shows increased radiopharmaceutical uptake on right upper lung extending to medial part of right middle lobe and left upper-middle lung zone. (D) After treatment, there was no pathological radiopharmaceutical uptake in the lung, which may be related to APTB.

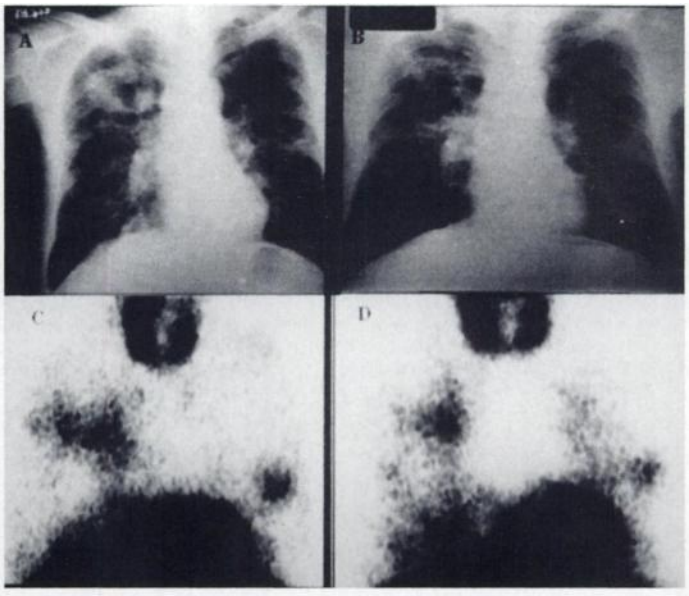

FIGURE 4. Technetium-99m-tetrofosmin scintigraphy and planar chest radiographs of 68-yr-old man with bilateral APTB. (A) Before therapy, there is cavitary disease with fibronodular infiltrations on upper right lung and left upper-middle lung zones on chest radiograph. (B) After therapy, cavitary lesion on right upper lung disappeared, but there are still fibronodular infiltrations on same regions compared to previous chest radiograph. (C) Marked increased of ^{99m}Tc-tetrofosmin uptake is present at the APTB lesions, which correlated well with chest radiograph findings before therapy. (D) After therapy, there is some improvement of right upper lung, but no significant change on left middle zone.

patients, ^{99m}Tc-tetrofosmin uptake either decreased or remained.

The uptake mechanism of ^{99m}Tc-tetrofosmin in APTB is not well understood. Uptake in cells is deemed to be related to blood flow, membrane permeability, negative plasma and mitochondrial potentials, rich mitochondrial content and metabolic activity (*27,28*). Alterations in cell metabolism that affect membrane potentials might be held accountable for ^{99m}Tc-tetrofosmin uptake in inflammatory lung lesions. Furthermore, rich mitochondrial content of the epitheloid cells in granulomas and increased blood flow in the inflammatory lesions might be other responsible factors for ^{99m}Tc-tetrofosmin uptake in APTB. Onsel et al. (*26*), reported that 92% of patients with APTB showed increased focal uptake of ^{99m}Tc-MIBI. They proposed a similar uptake mechanism for ^{99m}Tc-MIBI in APTB lesions.

Based on the findings in the present study, differential diagnosis between pulmonary tumors and tuberculosis seems to be difficult because of marked ^{99m}Tc-tetrofosmin uptake in APTB. Prospective studies are also needed for the evaluation of the difference or similarities in ^{99m}Tc-tetrofosmin uptake patterns in PTB and other lung infections because of the uptake of ^{99m}Tc-tetrofosmin in pneumonia.

Technetium-99m-tetrofosmin imaging of PTB is limited by relatively high cost, which is significantly diminished in laboratories using the agent for routine myocardial perfusion. Because a dose of ^{99m}Tc-tetrofosmin can be easily saved, the study can be performed without any additional cost and be completed in less than 1 hr.

CONCLUSION

Technetium-99m-tetrofosmin scintigraphy may play a complementary role in assessing APTB and in follow-up of patients after therapy. It is a simple, noninvasive and rapid method, especially in patients with chronic PTB and those in whom recurrent disease is suspected but direct radiological and bacteriological evidence of activity is not yet available. Technetium-99m-tetrofosmin uptake can be seen in APTB but other lung infections may also show ^{99m}Tc-tetrofosmin uptake. This observation may cause potential limited sensitivity and specificity of ^{99m}Tc-tetrofosmin scintigraphy in the evaluation of activity of PTB.

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