Technetium-99m-MIBI Scintigraphy in Pulmonary Tuberculosis

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We investigated the usefulness of ^{99m}Tc-methoxyisobutylisonitrile scintigraphy in patients with known or suspected pulmonary tuberculosis (PTB) in comparison with radiological and bacteriological findings. **Methods:** Thirty-six patients aged 13–59 yr were scanned 15 and 60 min after intravenous injection of 370 MBq (10 mCi) ^{99m}Tc-methoxyisobutylisonitrile. Twenty-four patients had active PTB proven by chest radiograph and sputum examinations, two had miliary tuberculosis and ten were suspected of having relapsed PTB with negative sputum examinations and indeterminate chest radiographs. In 12 patients ^{99m}Tc-MIBI imaging was repeated 1–3 mo after chemotherapy. **Results:** Of 24 patients with active localized PTB, 22 (92%) showed increased focal uptake of ^{99m}Tc-MIBI, but two patients with minimal infiltration on chest radiographs had no accumulation of ^{99m}Tc-MIBI. Both patients with miliary PTB showed diffuse ^{99m}Tc-MIBI uptake in the lungs. Among 10 patients with suspicion of relapse, ^{99m}Tc-MIBI scans were true-positive in 4 of 5 patients (80%) with culture-proven tuberculosis and false-positive in 2 of 5 (40%) patients with negative sputum cultures. For repeat imaging, 6 of 10 patients with active localized PTB showed reduced MIBI uptake, which correlated with chest radiograph findings, and one patient had increased MIBI uptake again concordant with clinical and radiological findings which were suggestive of resistance to first line chemotherapy of tuberculosis. The other three patients showed no significant scintigraphic changes despite clinical and partial radiological regression. **Conclusion:** Active PTB granulomas generally present considerable ^{99m}Tc-MIBI uptake that is most probably related to disease activity. Therefore, ^{99m}Tc-MIBI scanning could be used in the detection and follow-up of active PTB as a complement to routine techniques.

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

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The diagnosis of pulmonary tuberculosis (PTB) is fundamentally based upon a reaction to the tuberculin skin test, abnormal chest radiograph findings and the identification of mycobacteria in sputum smears in daily practice. Tuberculin skin testing and clinical features, however, are of little value in the diagnosis of active PTB, particularly in certain patient populations such as the elderly and immunocompromised individuals (*1,2*). Furthermore, direct identification of acid-fast bacilli by staining is not helpful in approximately 50% of patients (*3*), and radiographic findings may be atypical or unremarkable, particularly in elderly persons and in chronic cases with recrudescent infection because of superimposed chronic sequelae from previous PTB attacks (*4*). In addition, some patients with positive sputum smears may demonstrate a normal chest radiograph (*4*). Thus, chronic cases with suspicion of recrudescent PTB and patients with discordant results between sputum examination and chest roentgenogram present a difficult diagnostic and therapeutic problem. The definite diagnosis in such cases is possible by culturing of sputum (either spontaneous or induced) and bronchial washings or histological examination of specimens obtained by fiberoptic bronchoscopy (*5*). Transbronchial biopsy, however, is an invasive procedure and sputum culturing requires 2–8 wk, depending on the methodology used. To overcome these limitations, a variety of modern techniques based on molecular technology such as DNA hybridization probes and polymerize chain-reaction assay have been introduced, but these techniques have not been fully accepted in routine clinical practice due to their technical complexity and expense (*5,6*).

On the other hand, several radiopharmaceuticals, including ^{67}Ga-citrate (*7–10*), ^{99m}Tc-glucoheptonate (*11,12*), radiolabeled monoclonal antibodies (*13*) and ^{111}In-octreotide (*14*), have been used in the evaluation of tuberculosis, but they all have limitations in clinical settings. Technetium-99m-methoxyisobutylisonitrile (MIBI), which is widely used for myocardial perfusion imaging, has been shown to accumulate in some neoplasms, including thyroid (*15–17*), lung (*18–20*), brain (*21*), bone (*22*) and breast tumors (*23,24*), as well as in some inflammations such as fibrosing alveolitis (*19*), pulmonary actinomycosis (*25*), active pulmonary sarcoidosis (*26*) and acute osteomyelitis (*27*). We have also observed ^{99m}Tc-MIBI accumulation in PTB during thyroid tumor imaging.

After this incidental observation, we conducted a prospective study to determine the efficacy of ^{99m}Tc-MIBI imaging in the detection and follow-up of PTB.

MATERIALS AND METHODS

Patients

The study group included 36 patients (31 men, 5 women, aged 13–59 yr, mean age 35 yr) with either proven PTB or suspected PTB reactivation. The study was approved by the Hospital Ethics Committee and informed consent was obtained from all patients.

The patients had standard radiological (chest radiograph and/or CT) and bacterial (sputum smears and culturing) examinations. Nine patients who were not able to produce sputum underwent fiberoptic bronchoscopy to collect bronchial lavage and biopsy specimens. On the basis of chest radiographs and acid-fast staining of sputum smear findings, the patients were classified into three groups:

- Group 1 consisted of 24 patients with active localized PTB. Of these, 20 patients had extensive advanced disease showing distinct lesions on chest radiographs (bilateral in 11 and unilateral in 9) and heavily positive sputum smears (Table 1). The other four patients with minimal infiltration on the chest roentgenogram were classified as minimal PTB (Table 2).
- Group 2 included two patients with miliary PTB showing the typical (miliary) nodular pattern on their chest roentgenograms (Table 3).
- Group 3 contained 10 patients who had been previously treated for PTB but currently showed some suggestive symptoms for recrudescence together with equivocal chest radio-

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graphic changes but negative sputum smears or bronchial lavage (Table 4).

Imaging

Commercially available MIBI kits were prepared using freshly eluted ^{99m}Tc. The labeling efficiency of MIBI was always higher than 95%.

Technetium-99m-MIBI imaging was performed using a large field of view gamma camera fitted with a low-energy, all-purpose collimator. Anterior and posterior images of the chest were obtained 15 and 60 min following intravenous injection of 370 MBq (10 mCi) ^{99m}Tc-MIBI. Images were recorded in a 128 × 128 word matrix on a nuclear medicine computer. To reduce the superimposed scapular and pectoral muscular activities from the field of the lungs, acquisition was performed in the hands-overhead position. In instances of no abnormality on the early images, either additional oblique-lateral views or SPECT images (in two patients) were taken following late planar imaging to enhance lesion detectability. None of the patients were undergoing chemotherapy at the time of imaging. Technetium-99m-MIBI scintigraphy was repeated 1–3 mo after initiation of chemotherapy in 12 patients.

We also obtained ^{99m}Tc-human polyclonal immunoglobulin G (HIG) planar labeled in four patients and with ^{99m}Tc-nanocolloid in four other patients 1 wk after MIBI imaging.

Image Analysis

The scintigrams were visually evaluated by two nuclear medicine physicians. Any focally or diffuse increased ^{99m}Tc-MIBI uptake within the lung fields was considered positive. A basic visual scoring system was used for grading MIBI lesion uptake on the 1-hr image as follows: −= not detectable; += detectable; ++= prominent.

To compare pre- and post-therapy images, the corresponding frames of two separate studies were displayed on the same screen and optimally normalized to each other after excluding the liver and salivary gland activities from the frames. In addition to visual evaluation, regions of interest were manually drawn over the lesion and nonlesion area, after which, the lesion-to-background average count ratios were calculated on the corresponding frames from both

TABLE 1
Data for Patients with Active Localized Pulmonary Tuberculosis

Patient no.	Sex	Age (yr)	ESR (mm/hr)	PPD (mm)	Sputum smears	Sputum culture	Chest radiograph	^{99m}Tc-MIBI
1	F	56	95	13	Positive	Positive	BUZ	++
2	M	31	60	18	Positive	Positive	BUZ(R>L)	++ (R > L)
3	M	59	65	16	Negative	Positive	RUMZ	++
4	M	21	90	10	Negative	Positive	LUMZ	++
5	M	21	140	30	Positive	Positive	LUMZ	++
6	M	21	50	12	Negative*	Positive*	LUZ	++
7	M	57	116	15	Positive	Positive	RUMZ	++
8	M	26	105	15	Positive	Positive	BUZ	++
9	M	23	45	16	Positive	Positive	RUMZ	++
10	M	22	35	22	Positive	Positive	RUZ+LUZ†	++
11	M	37	150	24	Positive	Positive	BUMZ(L>R)	++ (L>R)
12	M	36	88	21	Positive	Positive	BUZ	++
13	M	33	40	20	Positive	Positive	BUZ	++
14	M	37	110	16	Positive*	Positive*	BUZ (R>L)	++ (R>L)
15	M	35	105	14	Positive	Positive	RUZ+LUZ†	++ (R>L)
16	M	19	55	21	Positive	Positive	BUZ	++
17	F	28	120	11	Negative*	Positive*	RUZ	++
18	M	38	55	16	Positive	Positive	RUZ	++
19	M	25	90	15	Positive*	Positive*	BUZ (R>L)	++
20	M	45	40	17	Negative	Positive	RUZ	++

*Specimens from bronchial lavage.
†Lesion uptake was minimal.
ESR = erythrocyte sedimentation rate; PPD = tuberculin skin test; B = bilateral; R = right; L = left; U = upper; M = mid; Z = lung zone; ++ = prominent uptake.

TABLE 2
Data for Patients with Minimal Infiltration on Chest Radiographs

Patient no.	Sex	Age (yr)	ESR (mm/hr)	PPD mm	Sputum smears	Sputum culture	Chest radiograph	^{99m}Tc-MIBI
21	M	41	25	16	Positive	Positive	RUZ†	−
22	M	17	100	16	Negative*	Positive*	RUZ†	+
23	M	29	30	12	Negative	Positive	LUZ†	−
24	F	17	120	13	Positive	Positive	RUZ†	+

*Specimens from bronchial lavage.
†Lesion uptake was minimal.
ESR = erythrocyte sedimentation rate; PPD = tuberculin skin test; R = right; L = left; U = upper; Z = lung zone; − = not detectable; + = detectable uptake.

initial and follow-up studies. To evaluate the change in the lesion activity from the initial to follow-up studies more objectively, we also computed a percentage of difference (DF %) as follows:

$$DF\% = (\text{Initial ratio}) - (\text{Follow-up ratio})/(\text{Initial ratio}) \times 100.$$

Any change of more than 1 s.d. (8.4) in the DF% value was significant (Table 5).

The MIBI scan data were compared to the corresponding chest roentgenograms and to the bacteriological findings from the same patients, as well as to the ^{99m}Tc-HIG or ^{99m}Tc-nanocolloid scans if available.

RESULTS

Group 1

Of 20 patients with extensive, advanced disease, sputum culturing or bronchial washing was positive in all, whereas acid-fast staining of sputum smears was positive in only 15 (75%) (Table 1). Technetium-99m-MIBI images were positive in all 20 patients, which correlates with chest radiograph findings (Fig. 1). In contrast to positive MIBI scans, ^{99m}Tc-HIG scans of two patients (Nos. 2, 16) and ^{99m}Tc-nanocolloid images of two other patients (Nos. 7, 8) were negative (Fig. 2). Of four patients with minimal infiltration on chest radiographs and positive cultures, two had evident uptake on planar ^{99m}Tc-MIBI scans and the other two showed no abnormal ^{99m}Tc-MIBI uptake (Table 2).

Group 2

Acid-fast staining of sputum and bronchial washing were negative in both patients, whereas culturing was positive in one (Table 3). These patients showed diffusely increased uptake of ^{99m}Tc-MIBI throughout both lung fields (Fig. 3).

Group 3

All 10 patients had unremarkable chest roentgenograms and clinical findings as well as repeatedly negative sputum smears (Table 4). Finally, recrudescence of PTB was confirmed in only five by sputum or bronchial aspirate culturing. Of these culture-proven patients, four had positive ^{99m}Tc-MIBI scans and one had a negative scan (even on SPECT images). Conversely, ^{99m}Tc-MIBI scans were positive in two of five patients with negative culturing (Patients 30, 36). These two patients were finally diagnosed as atypical pneumonia, and the other one as bronchial carcinoma.

In this group, ^{99m}Tc-HIG imaging, which was performed in two patients (Nos. 28, 29), and ^{99m}Tc-nanocolloid imaging in two other patients (Nos. 31, 34), were negative, which are similar to ^{99m}Tc-MIBI results.

Abnormal ^{99m}Tc-MIBI uptake was seen in 28 (90%) of 31 patients with proven active PTB (Table 5). On the other hand, ^{99m}Tc-MIBI scans yielded false-positive results in 2 (40%) of 5 patients with inactive PTB who were suffering from other pulmonary disorders.

The extent of ^{99m}Tc-MIBI uptake, when the images were positive, generally exceeded the extent of radiographic abnormalities. The density of MIBI uptake in the lesions was always lower than that of myocardial uptake.

Post-therapy Follow-up Scans

Of ten patients with abnormal uptake on the initial scans, six patients showed reduced uptake in follow-up scans obtained within 1–2 mo after initiation of chemotherapy (Fig. 1), one patient had prominently increased uptake consistent with clinical and radiological findings, which implied primary resistance to first line chemotherapy (Fig. 4), and the remaining three patients showed no significant scintigraphic changes within 2–3 mo, despite clinical and partial radiological regression (Table 6). None of these lesions was completely resolved scintigraphically during the limited follow-up periods.

Two patients with negative initial ^{99m}Tc-MIBI scans (Patients 23, 34) also had negative repeat scans.

TABLE 3
Characteristics of Patients with Miliary PTB

Patient no.	Sex	Age (yr)	ESR (mm/hr)	PPD (mm)	Sputum smears	Sputum culture	Chest radiograph	^{99m}Tc-MIBI
25	F	13	40	12	Negative*	Positive*	BN	+ (Diffuse)
26	M	38	80	16	Negative	Negative	BN	+ (Diffuse)

*Specimens from bronchial lavage.
ESR = erythrocyte sedimentation rate; PPD = tuberculin skin test; BN = bilateral nodular pattern; + = detectable uptake.

TABLE 4
Data of Patients with Suspected PTB Recurrence

Patient no.	Sex	Age (yr)	ESR (mm/hr)	PPD (mm)	Sputum smears	Sputum culture	Chest radiograph	^{99m}Tc-MIBI
27	M	45	45	21	Negative	Positive	RUZ?	+
28	M	50	38	11	Negative	Negative	BUZ?	−
29	M	54	23	17	Negative	Negative	LUZ?	−
30	M	49	96	21	Negative	Negative	LMZ?	+
31	M	49	28	18	Negative*	Positive*	BUZ?	−
32	M	18	50	13	Negative*	Positive*	RUZ?	++
33	F	56	20	15	Negative	Positive	RUZ?	+
34	M	44	65	11	Negative	Negative	RUZ?	−
35	M	19	82	13	Negative	Positive	LUZ?	++
36	M	50	57	16	Negative*	Negative*	LUMZ?	++

*Specimens from bronchial lavage.
ESR = erythrocyte sedimentation rate; PPD = tuberculin skin test; B = bilateral; R = right; L = left; U = upper; M = mid; Z = lung zone; ? = indefinite findings; − = not detectable; + = detectable; ++ = prominent.

TABLE 5
Correlation of Sputum Smears, Chest Radiograph and Technetium-99m-MIBI Scans

	Sputum smears		Radiologic findings		^{99m}Tc-MIBI	
	Positive	Negative	Diagnostic	Indefinite	Positive	Negative
Active disease (n = 31)	17 (55%)*	14 (45%)*	26 (84%)*	5 (16%)*	28 (90%)*	3 (10%)*
Inactive disease (n = 5)	—	5	—	5	2 (40%)*	3 (60%)*

*See the Results section, Group 3 for significance of the percentages.

DISCUSSION

Early studies showed that ^{67}Ga scanning is a sensitive indicator of the presence of active tuberculosis (*7,8*). Siemsen et al. (*8*) studied 144 patients with PTB, and found that 95% of the 110 active or bacteriologically positive patients had abnormal ^{67}Ga scans and all of the remaining 34 inactive or bacteriologically negative patients had normal scans. This study indicated that ^{67}Ga scans may be useful in determining the degree of activity of a disease process as a complement to chest radiographs. Nevertheless, ^{67}Ga-citrate, which has relatively poor physical characteristics, is not readily available and requires a delay of 24–48 hr between injection and scanning.

In contrast to the Siemsen study, however, Ito et al. (*28*) observed ^{67}Ga uptake in only 1 of 11 patients with positive smears and sputum cultures. Technetium-99m-glucoheptonate has also been proposed as a useful agent for detection of active tuberculosis, but the results obtained were controversial (*11,12*). Experimental immunoscintigraphic studies with radiolabeled polyclonal BCG-specific intact antibody and BCG-specific $F(ab')_2$ appear to be promising for the future for specific localization of PTB, but no human trials have been made thus far (*13*). Vanhagen et al. (*14*) used ^{111}In-octreotide in granulomatous disease, including tuberculosis, and reported that granuloma localization could be visualized in all patients studied. Their study, however, comprised only four patients with PTB. Additionally, somatostatin receptor imaging with ^{111}In-octreotide has limitations such as late imaging times, no shelf-use availability and high cost.

In our preliminary study, we observed abnormal ^{99m}Tc-MIBI uptake in 28 of 31 (90%) patients with proven PTB. Technetium-99m-MIBI scans did not reveal active granulomas in two patients with minimal infiltration on chest roentgenograms and in one patient with recrudescent disease probably due to poor spatial resolution. Furthermore, MIBI scans were false-positive in two of five patients with inactive disease who were suffering from a different pulmonary pathology. Our results imply that ^{99m}Tc-MIBI scan also may be of value in the follow-up of PTB.

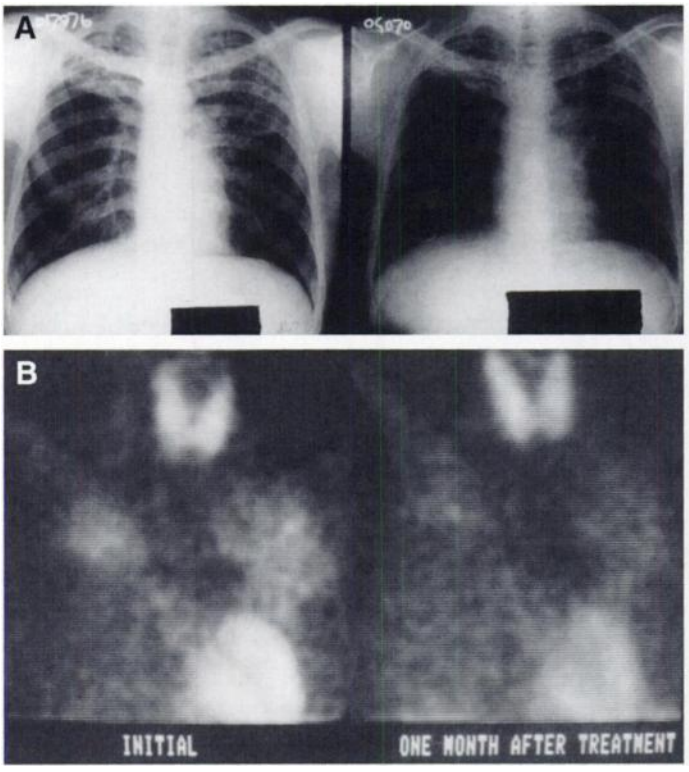

FIGURE 1. Patient 8, a 26-yr-old man with active localized PTB in both lungs. (A) Postero-anterior chest roentgenogram on the left side demonstrates focal infiltration with some cavitation in both upper lung fields being more prominent on the left side. Despite exposure differences, partial regression of the lesions is seen on the right radiograph obtained 1 mo after chemotherapy. (B) Abnormal focal accumulations of ^{99m}Tc-MIBI on 1-hr scan in both upper lungs and partial diminution after chemotherapy can be easily seen in the corresponding scintigraphs.

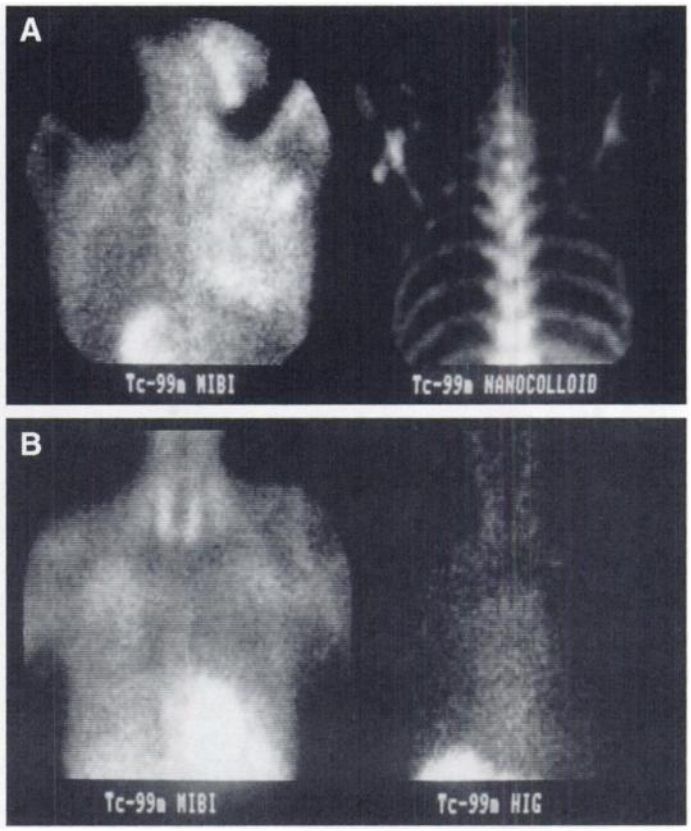

FIGURE 2. (A) Apparent abnormal accumulations of MIBI on the 1-hr scan (left) in the right lung were not present on the 2-hr nanocolloid scan (Patient 3). (B) Despite the clearly positive MIBI scan on the left, the ^{99m}Tc-HIG scan is negative (right image) (Patient 16).

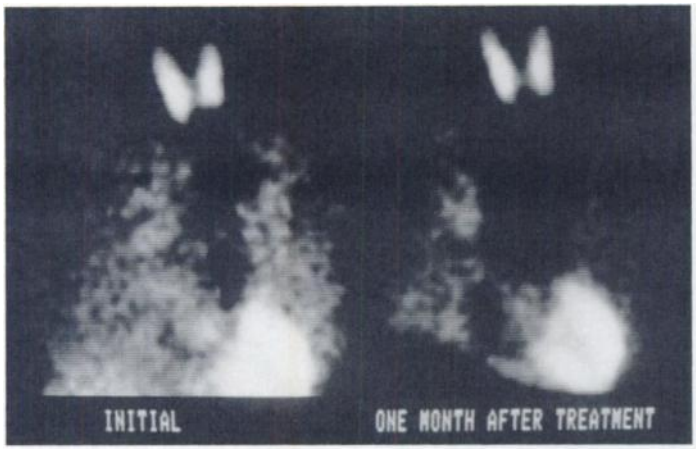

FIGURE 3. Patient 26, a 38-yr-old man with miliary tuberculosis. Diffusely increased uptake of MIBI is seen throughout both lung fields where partial regression takes place, particularly in the left lung and both upper lung zones after chemotherapy.

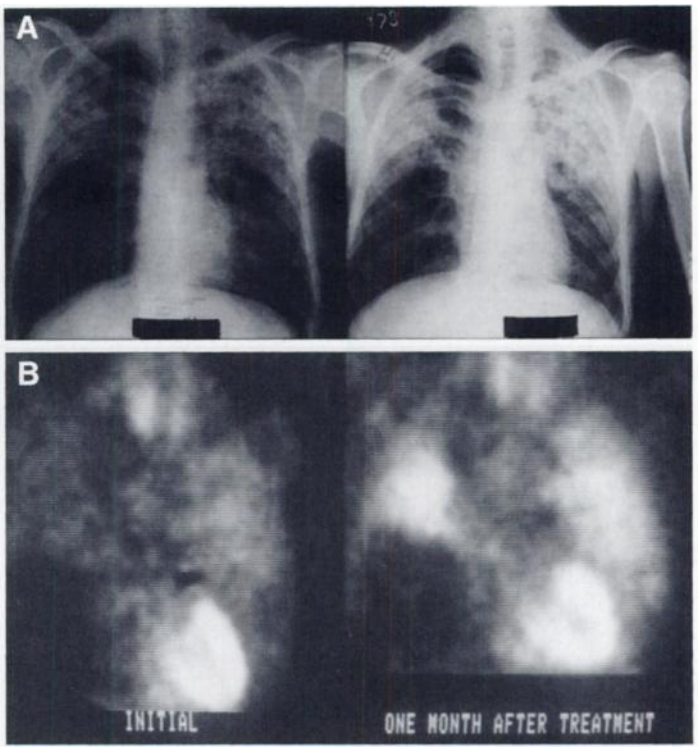

FIGURE 4. Patient 11, a 37-yr-old man with bilateral PTB. Cavitary disease together with fibronoduler infiltrations are present in the right upper and also in the left upper-mid lung zones on the chest roentgenograms; they are more prominent on the post-therapy radiograph, indicating disease progression. The corresponding MIBI scans demonstrate similar changes more apparently.

In this study, no lesions were completely resolved on the repeat scans, probably due to the limited follow-up periods. There was, however, clear regression in six of ten patients, but remarkable aggravation was observed in one patient. This finding agrees with the clinical and radiological findings (Table 6). The three patients who had repeat scanning after 2–3 mo of chemotherapy showed no significant quantitative differences, despite diminished erythrocyte sedimentation rates and partial radiological regression.

Limitations

Technetium-99m-MIBI imaging of PTB is limited by relatively high cost and lack of specificity. Cost is not necessarily a factor for laboratories using ^{99m}Tc-MIBI for routine myocardial perfusion studies because at least 740 MBq (20 mCi) can be easily saved from each vial for other applications without any additional cost. Because some benign and malignant disease processes in the lungs show ^{99m}Tc-MIBI uptake, the value of this agent in the differential diagnosis of PTB from other lung diseases is expected to be low. Another difficulty with ^{99m}Tc-MIBI scintigraphy is the wide range of physiological distribution of this agent in the body that may prohibit its use in the extrapulmonary localization of tuberculosis. Skeletal muscle uptake of the thorax and lower neck can interfere with pulmonary lesions detected in the apical regions and minimal lesions, in particular, could be missed. We were able to reduce this muscle effect by positioning the patients' arms over the head. Additional oblique and lateral views or SPECT studies may also be useful to increase sensitivity.

A noteable finding in this study is the lack of ^{99m}Tc-HIG and ^{99m}Tc-nanocolloid uptake in lesions with positive MIBI uptake. In the study of Hovi et al. (*29*), one patient with spondylitis and a paravertebral abscess caused by *Mycobacterium tuberculosis* showed neither increased uptake of the tracer nor cold lesions on ^{99m}Tc-HIG images. Of course, these limited observations do

TABLE 6
Characteristics of Patients with Follow-up Scans

			^{99m}Tc-MIBI				
	ESR (mm/hr)		Visual		Lesion/Background		
Patient no.	Initial value	Follow-up value	Initial scan	Follow-up scan	Initial scan	Follow-up scan	DF%
4	90	48	++	++	1.31	1.35	3.1
8	105	50	++	+	1.42	1.15	19
10	35	15	++	+	1.49	1.29	13.4
11	150	120	++	++	1.51	1.96	23
12	88	55	++	+	1.51	1.37	8.6
13	40	15	++	+	1.41	1.20	14.9
15	105	80	++	+	1.28	1.15	12.1
20	40	18	++	++	1.32	1.31	0.76
23	30	17	–	–	ND	ND	ND
24	120	34	+	++	1.24	1.32	6.1
26	80	30	++	+	ND	ND	ND
34	65	35	–	–	ND	ND	ND

ESR = erythrocyte sedimentation rate; DF % = percentage of difference; ++ = prominent; + = detectable; – = not detectable; ND = not done.

not indicate that ^{99m}Tc-HIG and ^{99m}Tc-nanocolloid images are useless in PTB. Further work-up is needed to clarify this matter.

Mechanism of MIBI Uptake

The uptake mechanism of ^{99m}Tc-MIBI in inflammatory lesions is still unclear. The uptake mechanism generally involves passive diffusion across the plasma and mitochondrial membrane (*30*). At equilibrium, strong negative transmembrane potentials promote concentration of the agent within the mitochondrial inner matrix. The normal biodistribution of ^{99m}Tc-MIBI supports this concept, since all tissues accumulating MIBI maintain negative plasma membrane potentials or are rich in mitochondrial content. MIBI uptake is a cell metabolism dependent, not a tissue-specific process because metabolically induced hyperpolarization of mitochondrial and plasma membrane potentials increases MIBI uptake and retention, as seen in some malignant cells (*30*). Therefore, alterations in cell metabolism that affect membrane potential, as might be the case in inflammatory lung lesions, could influence accumulation of ^{99m}Tc-MIBI. Furthermore, rich mitochondrial content of the epitheloid cells in granulomas might be a key point for ^{99m}Tc-MIBI uptake in tuberculosis (*31*).

CONCLUSION

The favorable imaging characteristics (140 keV peak energy, 6 hr half-life) and shelf availability make ^{99m}Tc-MIBI superior to other radionuclide techniques in investigations of PTB. Nuclear medicine practitioners should be aware of ^{99m}Tc-MIBI uptake in PTB, as a nonspecific event. Also, ^{99m}Tc-MIBI scintigraphy with its high sensitivity can be helpful for diagnosis of patients with chronic PTB, particularly those in whom recurrent disease is suspected but direct radiological and bacteriological evidence is lacking. Screening of patients with positive tuberculin skin testing but indeterminant chest radiograph findings might be another potential application of ^{99m}Tc-MIBI imaging in PTB. In such situations, the scintigraphic results may help the clinician in determining whether to initiate antibiotic therapy.

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