^{99m}Tc-hexakis methoxy isobutyl isonitrile scintigraphy and bronchoalveolar fluid lactic dehydrogenase in pulmonary tuberculosis

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Abstract

In cases of chronic pulmonary tuberculosis (PTB) with negative sputum smears, particularly when they are symptomatic, physicians encounter problems in differentiating the active from the inactive stage of the disease. *This study was undertaken* to determine the usefulness of technetium-99m hexakis methoxy isobutyl isonitrile (^{99m}Tc-MIBI) pulmonary scintigraphy and lactic dehydrogenase (LDH) in bronchoalveolar lavage fluid (BALF), in differentiating active from inactive PTB. *According to the methods we used*, BALF LDH level was measured in 12 patients with documented active PTB (Group 1) before of treatment and in 7 patients with treated PTB (Group 2) after treatment. Lung scan with ^{99m} Tc-MIBI was performed in 7/12 patients of Group 1 (Group 1a) and in all of Group 2. Five patients of Group 1 refused the lung scan (Group 1b). Five adults who had a normal myocardial perfusion scan were considered as normal lung cases (Group 3). *Our results* showed that the mean LDH level in BALF was not statistically higher in Group 1 (252.42±189.06 mIU/ml) than in Group 2 (106.28±139.99 mIU/ml). Very low values, less than 24 mIU/ml, excluded active PTB. Of the 7 patients of Group 1a, 6 had a positive lung scan (85.7%). Of the 7 patients of Group 2, 6 had negative lung scan (85.7%). Both tests had a positive correlation in differentiating active and inactive PTB. In *conclusion,* although none of the tests were specific for PTB, low BALF LDH of less than 24 m IUL and negative ^{99m} Tc-MIBI pulmonary scintigraphy, seemed to indicate inactive PTB. If our findings are confirmed by others with more related cases, these tests can be shown useful in the follow-up of treated PTB patients.

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Introduction

The diagnosis of pulmonary tuberculosis (PTB) is usually based on clinical findings, chest X-rays (CXR) and sputum smears. However, sputum acid fast bacilli (AFB) smears are positive only in 40%-70% of the cases [1]. Clinical features may be atypical, especially in elderly and immunocompromised patients [2] and CXR may be unremarkable or difficult to be interpreted, particularly in those with chronic lung disease and a recrudescence. CXR is unable to differentiate a chronic PTB when inactive, healed or reactivated. Culturing respiratory tract secretions requires 2-8 weeks [1], biopsy needs invasive procedures and empirical treatment or wait and watch strategy, may be hazardous. Nucleic acid amplification techniques like polymerase change reaction may be used in some centers, however the technique is expensive, complex and not sensitive [1, 2]. The list of nuclear medicine techniques described as useful is large. When uptake of technetium-99m hexakis methoxy isobutyl isonitrile (^{99m}Tc-MIBI) by cultures of mycobacterium tuberculosis (MT) was compared with the uptake of cultures of two normal cells, fibroblasts and myocytes, MT showed higher ^{99m}Tc-MIBI uptake [3, 4] and also higher uptake when using ^{99r}Tc-tetrofosmin (^{99m}Tc-TF), especially 120 min after injection [5]. Nuclear medicine techniques may detect and evaluate the extent of the disease and differentiate the active from the inactive status of the disease [6]. Gallium-67 citrate (^{67}Ga-C) is a sensitive but not specific method: its tracer has poor physical and biological characteristics [7-14]. Other radiopharmaceuticals like ^{99m}Tc-citrate [7], pentavalent ^{99m}Tc-succinic acid [15], ^{99m}Tc-glucoheptonate [16] and ^{111}In-octreotide [11] are used with controversial results. Immunoscintigraphy is not widely used [12]. ^{99m}Tc-MIBI lung scan has been used diagnostically in PTB [13] and in a variety of other pulmonary diseases [14-22]. In active PTB quantitation of lactate dehydrogenase (LDH) level in bronchoalveolar lavage fluid (BALF) was increased [23, 24]. The present study was designed to investigate and confirm the potential role of the ^{99m}Tc-MIBI lung scan and LDH level of BALF, to determine the activity of PTB.

Materials and methods

During an 18 months period, we have studied in Nemazee and Shahid Faghihi Hospitals, affiliated to Shiraz University of Medical Sciences, 19 cases of TBC patients and 5 cases with suspected coronary artery disease (CAD). Studied subjects were divided into 3 Groups. Group 1 consisted of 12 patients with active PTB as diagnosed by a positive AFB sputum smear (9 cases), a BALF AFB smear (2 cases) or an endobronchial biopsy histopathology (1 case). These patients were divided in Group 1a: 7/12 patients who had undergone a lung scan (6 men, 1 woman, aged 17-71 years, mean age 37 years) and in Group 1b: 5/12 patients without a lung scan (3 men, 2 women, aged 18-79 years, mean age 39.5 years). Group 2 consisted of 7 cases (5 male, 2 women, aged 24-67, years, mean age 42.5 years) with treated and healed PTB, based on: clinical examination, CXR and sputum studies. These patients underwent investigation, 1-2 weeks after the end of their drug treatment. Group 3 consisted of 5 persons (3 male, 2 female, aged 41-67 years, mean age 49 years) with healthy lungs (based on history, physical examination and CXR) suspected to have CAD, who underwent myocardial perfusion scan and lung scan simultaneously.

This study was approved by the Ethics Committee of the University and informed consent was obtained from each patient. Groups 1 and 2 underwent bronchoscopy and bronchoalveolar lavage (BAL) during the weeks following the start and the end of their drug treatment. Lung scan with ^{99m}Tc-MIBI was performed 1-3 days after bronchoscopy and BAL, in Groups 1a and 2. Five patients of Group 1 (Group 1b) refused to be submitted to lung scan.

After BAL of the involved lobe, a small amount of fluid was tested for AFB positive smears and cultured in Lowenstein-Jensen media. The remaining fluid was used for the measurement of total LDH activity, utilizing the reduction rate of NAD to NADH in the presence of L-lactate expressed in mIU/ml [25].

A ^{99m}Tc-MIBI radiotracer with labeling efficiency of more than 95% was used and a dose of 370 MBq was intravenously administered to each patient. A planar scan was done 10 and 60 min later (early and delayed images, respectively) in anterior and posterior views. Acquisition was done using a large field of view of a single head Diacam Siemens, Germany, gamma camera fitted with a low energy, all purpose collimator. Images were recorded in a 256×256 matrix, with 10^6 counts. Scans were qualitatively evaluated via direct visual observation by one of us (M.A.). Any focal or diffusely increased uptake of ^{99m}Tc-MIBI was considered a positive finding (Fig.1).

In Group 3, we performed a myocardial perfusion scan. Planar anterior and posterior views of the lungs were obtained at rest before acquisition. Radiologists interpreted CXR and one of us (M.A.) compared CXR with the lung scan. If the lesions in the CXR and in the scan matched, we diagnosed a positive correlation.

Analysis of Variance, the Fisher Exact, the Wilcoxon Pairs method and the Mann-Whitney tests, were used for statistical analysis. P values ≤0.05 were considered significant.

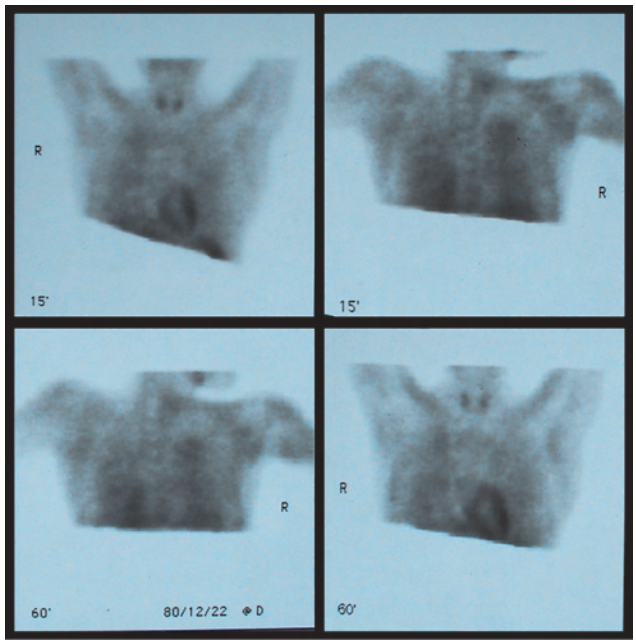

Figure 1. Non uniformly diffuse bilateral abnormal accumulation of ^{99m}Tc-MIBI on the 15 and 60 min lung scan in the anterior and posterior views of the lung, especially in the lower lobes bilaterally (Case 6).

Results

Mean BALF LDH in Groups 1 and 2 was 252.41±187.06 and 106.28 ±139.99, respectively. BALF LDH in Group 3 was not measured. Comparison of the mean BALF LDH level in Groups 1 and 2 showed that the BALF LDH level in Group 1 was greater than that in Group 2 (P=0.05). There was not any difference between BALF LDH level in Groups 1a and 1b. One Group 2 patient with negative sputum, negative AFB smears and culture and negative BALF AFB smears, also had, persistent chest pain, weakness and inadequately resolved lesions in the CXR: a positive lung scan and elevated BALF LDH. This patient had presumably relapsed. One month later, the sputum AFB smear and the BALF culture, became positive and the patient was treated again.

Positive and negative lung scans in Groups 1 and 2 are shown in Tables 1 and 2. Early and late images were well correlated although the magnitude of uptake was less in the late images. Positive lung scans was significantly more in Group 1a than in Group 2 (P=0.02), or in Group 3 (P=0.01) while the difference between Groups 2 and 3 was not significant.

To evaluate the correlation between BALF LDH level and the lung scan in detecting active PTB, BALF LDH levels of those with positive scans (6 patients from Group 1 and 1 from Group 2) were compared with those who had negative scan, (6 patients of Group 2 and 1 of Group 1). Patients with positive scans had BALF LDH levels (310±198.30mIU/ml), well higher than patients with negative lung scans: (100.14±142.91mIU/ml), (P=0.03).

Table 1. *BALF LDH and pulmonary scan pattern of Groups 1 and 2.*

GP	No	BALF LDH (mlu/ml)	Early scan uptake	Delayed scan uptake
1a	1	281	+	+
1a	2	556	+	+
1a	3	170	+	+
1a	4	206	+	+
1a	5	24	-	-
1a	6	289	+	+
1a	7	601	+	+
1b	8	33	Not performed	
1b	9	145		
1b	10	394		
1b	11	92		
1b	12	268		
2	13	67	+	+
2	14	22	-	-
2	15	7	-	-
2	16	378	-	-
2	17	38	-	-
2	18	15	-	-
2	19	217	-	-

Discussion

There may be difficulties in the detection of recurrence and of treatment response in patients with PTB. It has been reported that 95% of active or bacteriologically positive patients had abnormal ^{67}Ga-C scans and all the others, inactive or bacteriologically negative patients had normal scans [26]. In another study ^{67}Ga-C and ^{201}Tl scans were compared for the detection of active PTB and found that the sensitivity, specificity and accuracy of these scans were 83.1%, 60.7% and 74.1% for ^{67}Ga-C and 88%, 82% and 85.6% for ^{201}Tl-Cl [27]. Others reported marked ^{111}In-octreotide uptake in APTB lesions [28].

Our statistics are based on a small number of patients but for the importance of ^{99m}Tc-MIBI scan to drag more active PTB they show a sensitivity of 85.7% and a false positive and negative rate of 14.3%. Others found a sensitivity of 92% [13] or greater, 96% [29]. One case with false negative lung scan in our Group 1a had minimal infiltration in CXR with a low BALF LDH level, which could be due to a low level of inflammation. The ^{99m}Tc-MIBI scan should be interpreted cautiously in cases with minimal CXR infiltration even in miliary TB as reported by others [30] and as found in one of our false negative cases.

In some cases, CXR had more abnormal findings than the lung scan, which may be attributed to an inactive lesion of a chronic disease, and pointing to the affinity of ^{99m}Tc-MIBI to indicate active lesions [31]. Normal value of the BALF LDH is 14.1±8.69 miu/ml [23]. The BALF LDH level of <24 mIU/ml seems to be suggestive of a non- active PTB [23].

In conclusion, although our cases are few, our results suggest that positive ^{99m}Tc-MIBI lung scan and elevated BALF LDH can support the differential diagnosis of active from inactive PTB and also characterize the disease during the follow up in selected patients under treatment. Negative uptake of ^{99m}Tc-MIBI and very low values of BALF LDH (<24 mIU/mL) may exclude active PTB.

Table 2. *Correlation of sputum smears and ^{99m}Tc-MIBI scans.*

	Sputum Smears		^{99m}Tc-MIBI	
	Positive	Negative	Positive	Negative
Active disease (Group1a) n=7	4 59%	3 41%	6 85.7%	1 14.3%
Inactive disease (Group 2) n=7	-	7	1 14.3%	6 85.7%

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