The Role of Gallium-67 Scintigraphy and High Resolution Computed Tomography as Predictors of Disease Activity in Sputum Smear Negative Pulmonary Tuberculosis

Pınar Ergün,MD[1]; Ülkü Yılmaz Turay, MD[1]; Hülya Ortapamuk, MD[2]; Çiğdem Biber, MD[1]; İhsan A. Keyf, MD[1]; Cihangir Çayan, MD[3]; Yurdanur Erdoğan, MD[1]

[1] *Atatürk Chest Disease and Chest Surgery Center, Ankara, Turkey*
[2] *Ankara Numune Hospital, Nucleer Medicine Department, Turkey*
[3] *Atatürk Chest Disease and Chest Surgery Center, Radiology Department, Ankara, Turkey*

Abstract

To determine the role of gallium-67 scintigraphy and high resolution computed tomography (HRCT) findings as predictors of disease activity in sputum smear negative patients with pulmonary tuberculosis, 30 hospitalised patients suspected of having active pulmonary tuberculosis on the basis of upper lobe infiltrates in the chest x-rays were studied prospectively. Ga-67 citrate scanning and HRCT were performed at the beginning of the study. Patchy unilateral or bilateral air-space consolidation, cavitation and a tree in bud appearance were accepted as activity criteria in HRCT. Gallium-67 uptake ratio (GR) and visual scoring were taken as the criteria in assessing gallium-67 imaging.

The sensitivity and specificity of Ga-67 scintigraphy in assessing the activity of pulmonary TB were 83.3% and 58.3%, while the sensitivity and specificity of HRCT in assessing the activity of pulmonary TB were 100% and 66.7%, respectively. Using these techniques together the sensitivity increased to 100% while specificity was 50%. Though the positive predictive value (PPV) of this assessment was 75%, a negative predictive value (NPV) of 100% was found.

The results indicate that the use of both GA-67 scintigraphy and HRCT scans will be helpful in determining disease activity in sputum smear negative pulmonary tuberculosis patients. When the two methods are used together, a negative predictive value of 100% is reached, a finding which suggests that both of these techniques must be used to rule out active disease.

Turkish Respiratory Journal, 2003;4:(3):123-126

Key words: *pulmonary aspergilloma, bronchial carcinoma, tuberculous cavity*

Introduction

Although the prevalence of pulmonary tuberculosis (PTB) has decreased, the number of patients with drug-resistant PTB and cancer or immunodeficiency complicated by PTB continues to increase. Prompt detection of PTB has become a public health priority in the effort to avert an epidemic. Therefore, it is useful to evaluate the role of various testing procedures in the detection of tuberculosis (1).

In recent years it has been suggested that gallium-67 (Ga-67) scan and high resolution computed tomography (HRCT) could be used to detect the existence of active pulmonary tuberculosis in patients with negative sputum smears. This would contribute to early detection of the disease and early initiation of therapy (2,3,4).

Correspondence: *Dr. Pınar Ergün*
Karapınar Mah. 46. Sok. 15-A/B Blok
Daire: 3 Özdoğu Kent Sitesi
Dikmen, Ankara, Türkiye
Tel: +90 (0) 312 475 28 18
GSM: +90 (0) 532 602 62 68
Fax: +90 (0) 312 355 21 35

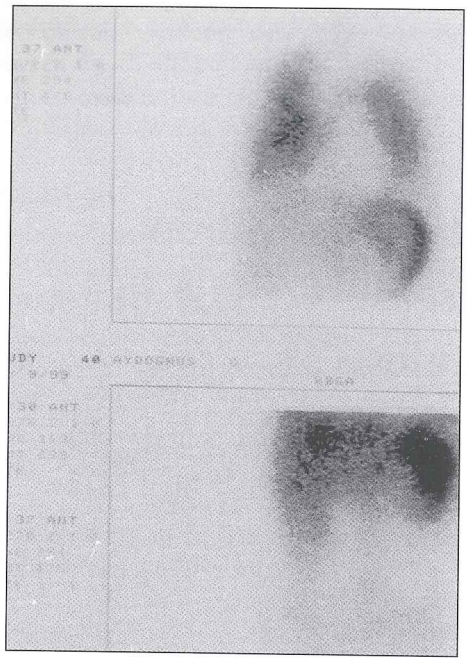

Figure 1. *Ga-67 scanning of a patient with a (-) sputum smear, diagnosed as PTB.*

We undertook the present study to evaluate the role of these two techniques separately and to examine whether the diagnostic accuracy of sputum smear-negative active pulmonary tuberculosis improves when they were used together.

Methods

Thirty hospitalised patients suspected of having active pulmonary tuberculosis on the basis of upper lobe infiltrations on chest radiography with or without positive sputum smears for acid-fast bacilli underwent Ga-67 citrate scanning and HRCT at the beginning of the study. All patients had undergone routine clinical and laboratory evaluation including at least six sputum specimens stained with auramine-rhodomine and cultured on Lowenstein Jensen medium. There were no patients in the series who were positive for human immunodeficiency virus (HIV). Ten with positive sputum smears were on antituberculous therapy during the evaluation with gallium-67 scanning and HRCT. In patients with (-) sputum smears other diagnostic procedures such as bronchoscopy were done.

For Ga-67 scintigraphy, 8 mci Ga-67 citrate was injected intravenously. Planar images were then acquired in both anterior and posterior views at 48 and 72 h after injection using medium-energy collimator at 13%, 10% and 20% windows using 93, 184, 300 keV energy peaks respectively. Data were collected using a gamma camera (Elscint SPX-6). For anterior and posterior planar thorax images, 750 000 calculations were summed up. Whole body scans were not done routinely. Every patient underwent a SPECT evaluation during which 64x64 matrices were used. Tomographic images were taken at 72 hours.

Radioisotope uptake was mapped and regions of interest (ROIs) were designated as areas where uptake exceeded the mean by visual inspection. Total radioactivity in the ROIs was then calculated and ratio of radioactivity in the ROI to that in an identically sized sample of the normal lung field on the contralateral side at the same level was obtained. These ratios for Ga-67 scintigraphy were recorded as gallium uptake ratio (GR). Also visual scoring was made as follows;

Grade	Radiogallium uptake
0	less in the lung than in soft tissue
1+	equal in the lung to soft tissue
2+	greater in the lung than soft tissue but less than liver
3+	equal in the lung to liver
4+	greater in the lung than liver

Results showing GR>1 in Ga-67 scintigraphy and 2+ in visual scoring were accepted as Ga-67 scintigraphy positive (5). For HRCT, HRCT scans were obtained with a CT scanner (Hitachi-Practico spinal CT, Japan). Scanning was performed with 15mm collimation, 120 kvp-200mA, 1 second Sean time, venous contrast medium was not administered. The terms used to interpret HRCT findings in the active cases were: (i) Patchy unilateral or bilateral air-space consolidation, frequently peribronchial in distribution, (ii) Cavitation, and (iii) Scattered air-space (acinar) nodules, centrilobular branching structures 'Tree-in Bud'(6).

Accordingly, HRCT scans showing one of these findings were regarded as HRCT positive for active pulmonary tuberculosis.

The data were analysed on a personal computer using commercial software (Sytat for Windows, version 6.0, SPSS) and comparisons between mean GR in each group were analysed using Mann-Whitney U tests. Probability values less than 0.05 were considered significant ($p< 0.05$) .

Results

Eighteen patients were diagnosed as active PTB cases, based on (i) detection of acid fast bacilli in sputum smears and in cultures of sputum or bronchial washings, (ii) radiographic and clinical improvement following antituberculosis chemotherapy (iii) positive histopathological findings for tuberculosis. Twelve patients were eventually diagnosed as having at least one of the following: destroyed lung, post tuberculous bronchiectasis, sarcoidosis, pneumonia, malignancy. Smears and cultures were all negative for acid fast bacilli in these patients.

The results of GR and visual scoring are summarised in Table 1. Mean GR was 1.22±0.15 in active PTB while it was 1.06±0.17 in pulmonary disease other than PTB (p: 0.023). The sensitivity and specificity of Ga-67 scintigraphy in assessing the activity of pulmonary tuberculosis were 83.3% and 58.3% respectively. Figure 1 shows the Ga-67 scan of a patient with a (-) sputum smear and diagnosed as PTB .

Table 1. Results of GR and visual scoring					
Active pulmonary TB				Disease other than active pulmonary TB	
AARB (-)		AARB (+)			
GR	Visual scoring	GR	Visual scoring	GR	Visual scoring
1.20	++	1.13	+++	1.00	0
1.32	+++	1.26	+++	1.28	++
1.38	+++	1.31	+++	1.14	++
1.09	+++	1.51	++++	1.00	+
1.06	++	1.00	0	1.38	+++
1.00	+	1.19	+++	1.16	++
1.02	++	1.06	+++	0.9	0
1.00	+	1.25	++	1.00	+
1.36	+++	1.38	+++	1.26	++
				1.00	+
				0.82	0
				1.00	+

Table 2. HRCT findings of patients		
	Active tuberculosis findings n=18 (%)	**Pulmonary disease other than TB n=12 (%)**
Air-space consolidation	16 (80)	4 (33)
Cavity	8 (44)	2 (16)
Tree-in-bud	2 (11)	0 (0)

According to the activity criteria, HRCT findings in patients with active pulmonary tuberculosis and those with diseases other than active pulmonary tuberculosis are summarised in Table 2. Air-space consolidation was the most common finding, seen in 16 (80%) of 18 patients with PTB. The sensitivity and specificity of HRCT in assessing the activity of pulmonary tuberculosis were 100%, and 66.7% respectively. When these techniques were employed together the sensitivity was 100% while specificity was 50%. Though the positive predictive value (PPV) was 75%, the negative predictive value (NPV) was found to be 100%.

Discussion

Diagnosis and treatment will become a big problem in cases where radiologically suspected active PTB, *Mycobacterium tuberculosis* can not be identified in smears. For this reason, various testing procedures are often necessary to decide whether to start treatment before the results of cultures become available (7). Although chest radiographs are extremely useful in the diagnosis of active pulmonary tuberculosis, minimal exudative lesions can be overlooked and sometimes it is difficult to distinguish active lesions from old fibrotic lesions (3). Ga-67 citrate scintigraphy and HRCT are frequently employed as diagnostic methods to overcome these difficulties (2-7). Ga-67 is useful in determining the degree of activity of a disease process, in monitoring treatment response and in detecting unsuspected disease foci located in the mediastinum, behind the heart or in pleural or parenchymal scars (8,9).

Siemsen and associates have suggested that scarred and fibrotic processes such as interstitial fibrosis and successfully treated tuberculosis do not concentrate gallium (9). In the present study; 12 of 21 patients with negative sputum smears were rated as Ga-67 (+) while 8 of 9 patients with positive sputum smears were rated as Ga-67(+). Nine of 21 sputum smear negative patients were diagnosed as active PTB cases. According to GR, a positive Ga-67 scan had a sensitivity of 83.3% and specificity of 58.3% for active PTB. In the study of Lai and colleagues these ratios are given as 100% and 83% respectively (4).

In a recent study by Goldforb and colleagues, Ga-67 scintigraphy was reported to be useful in early diagnosis of PTB; it detected adenopathy missed on physical examination and was more sensitive than chest x-rays for the detection of pulmonary lesions (8). In our study in two patients with parenchymal lesions but with negative sputum smears, Ga-67 citrate uptake was detected in the region of the cervical lymph nodes that were nonpalpable on physical examination. Histopathological examination of the lymph nodes showed tuberculous lymphadenitis. Both chest x-ray and HRCT findings of the two patients showed regression after anti-tuberculosis therapy.

In Walsh's study, the false negative rate of Ga-67 scanning in active tuberculosis was thought to be related to severe malnutrition (2). In one of our sputum smear negative patients, Ga-67 scanning was found to be normal while HRCT findings revealed active PTB. This patient was a diabetic and was also malnourished. So, the negative result obtained by Ga-67 scanning in this patient may be due to malnutrition, as suggested by Walsh (1,2).

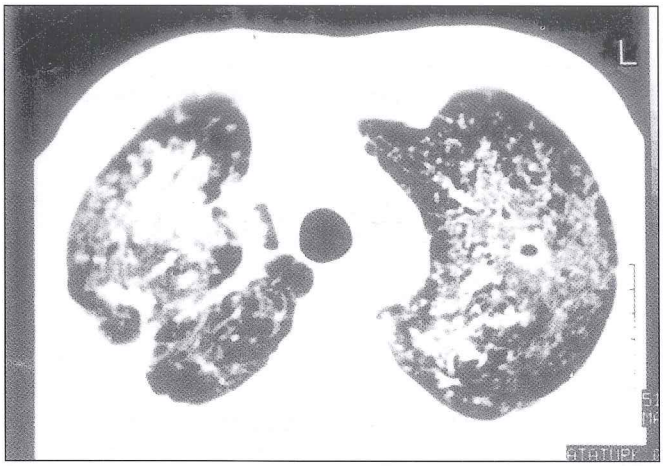

Figure 2. *HRCT of a patient with a (-) sputum smear and a (+) culture for acid-fast bacilli.*

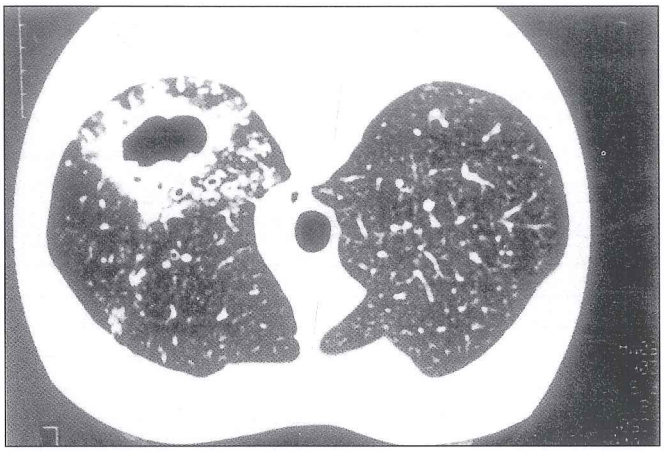

Figure 3. *HRCT of a patient with (-) sputum smear and (-) cultures for acid-fast bacilli. PTB was proven histopathologically.*

Gallium deposition is proportional to cellular metabolism and protein and DNA synthesis as well as to vascularity and phagocytic activity. One of our patients whose HRCT findings were evaluated as tuberculoma, showed normal results in the Ga-67 scan. This result was consistent with reports which suggest that Ga-67 scanning would be normal in tuberculoma (9,10).

HRCT was the other procedure which we used in detecting active pulmonary tuberculosis. HRCT scanning was suggested as useful in differentiating old fibrotic lesions from new active lesions and demonstrating early bronchogenic spread (3,7). HRCT scanning may also be of value in deciding on treatment in cases with negative sputum smears who are suspected of having active pulmonary tuberculosis on chest radiograms.

In the study reported by Poey et al. ground glass opacity, peribronchovascular centrilobular nodules, acinar opacities and multiple apical cavities were accepted as the HRCT features of active pulmonary tuberculosis (7). According to Hatipoğlu et al. centrilobular nodules or linear structures, 'tree-in-bud' appearance and macronodules were the most common HRCT findings detected in active PTB (3). In the present study, in accordance with a previous study, patchy unilateral or bilateral air-space consolidation which was frequently peribronchial in distribution, cavitation and 'tree-in-bud' appearance were found as the most common indicative features for active pulmonary tuberculosis (Fig. 2) (6). In our study, air-space consolidation was found in 80% of patients with PTB. According to Poey and colleagues, this is a finding which can be taken as evidence for endobronchial spread and is an important sign of tuberculous activity. Cavities were found in 44% of our patients with PTB. They were multiple in 60% of the cases and were usually located in the upper lobes or in the upper segment of the lower lobes. Cavitation was present in 2 of the patients with pulmonary diseases other than active PTB. One of these patients was diagnosed as inactive PTB while the other was diagnosed as obstructive pneumonia due to malignancy. Scattered air-space nodules (acinar nodules) and centrilobular branching structures (tree-in- bud structures) are accepted as the earliest HRCT findings of tuberculosis (3,11). In our study 'tree-in-bud' appearance was visualized in 2 patients with active PTB (Figure 3). According to these findings, the sensitivity and specificity of HRCT in assessing the activity of PTB were 100% and 66.7%, respectively.

In conclusion, it can be stated that if there is a clinical suspicion of PTB, both Ga-67 scintigraphy and HRCT scans will be helpful in determining disease activity in sputum smear negative patients. When the two methods are used together the NPV increases to 100%, a finding which suggests that both of these two techniques can be used to rule out active disease.

References

1. Utsunomiya K, Narabayashi I, Nishigaki H, Tsujimoto K, Kariyone SW. Clinical significance of thallium-201 and gallium–67 scintigraphy in pulmonary tuberculosis. Eur J Nucl Med 1997; 24: 252-257.
2. Walsh HJ, Bekerman C, Chausow A, Szidon P. The value of gallium-67 scanning in pulmonary tuberculosis. Am Rev Respir Dis 1985; 132: 746-747.
3. Hatipoğlu ON, Osma E, Manisalı M, Uçan ES, Balcı P, Akkoçlu A, Akpınar O, Karlıkaya C, Yüksel C. High resolution computed tomographic findings in pulmonary tuberculosis. Thorax 1996; 51: 397-402.
4. Lai FM, Liam CK, Paramsothy M, George J. The role of 67 gallium scintigraphy and high resolution computed tomography as predictors of disease activity in sputum smear-negative pulmonary tuberculosis. Int J Tuberc Lung Dis 1997; 1(6): 563-569.
5. Alavi A, Worsley D. Scintigraphic evaluation of pulmonary disease. In: Fishman A, eds. Fishman's Pulmonary Diseases and Disorders. 3rd edition. NewYork: McGraw Hill Comp. 1998; 517-31
6. Webb WR, Müller NL, Naidich DP. High Resolution CT of the Lung. 2nd ed. New York: Lippincott-Raven, 1996; 173-80
7. Poey C, Verhaegen F, Giron J, Lavayssiere J, Fajadet P, Duparc B. High resolution chest CT in tuberculosis: Evolutive patterns and signs of activity. J Comput Assist Tomogr 1997; 21(4): 601-607.
8. Goldfarb CR, Colp C, Ongseng F, Finestone H, Havas J. Gallium scanning in the new tuberculosis. Clin Nucl Med 1997; 22(7): 470-474.
9. Siemsen JK, Grebe SF, Sargent EN, Wentz D. Gallium-67 scintigraphy of pulmonary diseases as a complement to radiography. Radiology 1976; 118: 371-375.
10. Siemsen JK, Grebe SF, Waxman AD. The use of gallium-67 in pulmonary disorders. Seminars Nucl Med 1978; 8(39): 235-249.
11. Laissy JP, Cadi M, Cinqualbre A, Boudiaf ZE, Lariven S, Casalino E, Wolff M, Schouman-Claeys E. Mycobacterium tuberculosis versus nontuberculous mycobacterial infection of the lung in AIDS patients: CT and HRCT patterns. J Comput Assist Tomogr 1997;21(2):312-317.