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The value of Ca 125 in the evaluation of tuberculosis activity

A. YILMAZ, F. ECE, B. BAYRAMGÜRLER, E. AKKAYA AND, R. BARAN

SSK Süreyyapaşa Center For Chest Disease and Thoracic Surgery, Istanbul, Turkey

Abstract The aim of the present study was to investigate the value of Ca 125, a tumour marker, in evaluation of pulmonary tuber culosis activity. This study included 96 subjects who were divided into three groups. Group 1 consisted of 40 patients with active pulmonary tuberculosis. Group 2 included 20 patients with inactive pulmonary tuberculosis. There were 36 healthy subjects in group 3. While measurement of serum Ca 125 level was performed only once in groups 2 and 3, Ca 125 levels were measured five times in group 1. The measurements were performed before the treatment, at the second, fourth and sixth months and the third year following the end of the treatment. Mean $\pm$ SD serum Ca 125 concentrations were 109·7 $\pm$ 86·9 U ml^{-1} in group 1, 14·5 $\pm$ 7·8 U ml^{-1} in group 2 and 10·5 $\pm$ 7·3 U ml^{-1} in group 3. Serum Ca 125 levels were significantly higher in group 1 than in the other groups ($P < 0{\cdot}0001$), but there was no significant statistical difference between the values of groups 2 and 3 ($P > 0{\cdot}05$). Ca 125 levels in group 1 showed a significant decrease after treatment ($P < 0{\cdot}0001$). For estimation of the activity of tuberculosis, the sensitivity and specificity of Ca 125 were found 97·5% and 100%, respectively, at a 31 U ml^{-1} cut-off point. Our results suggest that Ca 125 is beneficial in the determination of tuberculosis activity and in differentiation between active and inactive pulmonary tuberculosis.

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INTRODUCTION

Pulmonary tuberculosis is the most prevalent clinical manifestation of tuberculosis (1). Determination of disease activity is important for treatment in pulmonary tuberculosis (2) but the clinical and laboratory determination, follow-up of the infection activity and response to therapy is not always easy to evaluate (2,3). Although bacteriological examination of sputum is the gold standard in diagnosis and follow-up of disease, it is sometimes hard to obtain. The most important determinant of treatment success is sputum culture conversion from positive to negative state, but it takes several weeks to know whether the patient is undergoing successful therapy. A rapid serological test for follow-up of the tuberculosis activity and response to therapy would be very useful to clinicians (1–3). Several parameters such as cell activation markers, acute phase reactants, enzymes and tumour markers have been proposed as indicators of disease activity in pulmonary and extrapulmonary tuberculosis (2,4–8).

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Correspondence should be addressed to: Dr A. Yilmaz, Zümrütevler Atatürk Cad. Abant Apt, No: 30 Daire:1, 81530 Maltepe, Istanbul, Turkey. E-mail: elifim @ rt.net.tr

Ca 125 is a tumour marker of which concentration is increased in benign conditions and in malignant diseases (9–11). It has been reported that Ca 125 levels are elevated in patients with pulmonary and extrapulmonary tuberculosis, including pleural, peritoneal, pelvic, miliary and abdominal tuberculosis (5,10–19). Most of these reports include case reports with pelvic–peritoneal tuberculosis and they are incidental findings in suspected ovarian carcinoma patients (12,13,15,17). To our knowledge, there are few case-series or case-control studies including the cases with pulmonary tuberculosis and elevated Ca 125 levels in the literature.

In this study, we aimed to investigate the value of Ca 125 in the evaluation of pulmonary tuberculosis activity.

METHODS

Subjects

The study was performed in SSK Süreyyapaşa Center for Chest Diseases and Thoracic Surgery between 1993 and 1998. The 96 subjects included in the study were divided into three groups. Group 1 consisted of 40 newly diagnosed [female/male: 6/34, mean age 29·1 (range 16–60) years] active pulmonary tuberculosis patients. None of the patients had extrapulmonary tuberculosis in addi-

tion to pulmonary tuberculosis. The diagnosis was based on positive sputum smear for acid-fast bacilli in all of the patients. All the patients also had positive sputum culture for *Mycobacterium tuberculosis*. Group 2 included 20 patients [female/male: 1/19, mean age 38·8 (range 28–56) years] with inactive pulmonary tuberculosis. These patients had a history of previous episode of tuberculosis with documentation of a positive culture at the time of diagnosis. There were abnormal stable radiographical findings and no change in last 6 months. Three sputum culture for *Mycobacterium tuberculosis* were negative in all patients (1). Thirty-six healthy subjects were non-medical personnel [female/male: 1/35, mean age 36·3 (range 27–66) years] in group 3. They had no tuberculosis history or other underlying disease and their roentgenograms were normal. Acid-fast bacilli stains were performed according to the Ziehl–Neelsen method. Cultures for *Mycobacterium tuberculosis* were performed in Löwenstein–Jensen solid media.

Study design

For measurement of serum Ca 125 levels, 10 ml venous blood was drawn from each subject. Blood samples were left to coagulate for 20–30 min at room temperature. Then they were centrifuged for 10 min and serum samples were obtained. The serum samples were stored at − 18°C until the date of analysis. Packard Gamma Counter RIA instrument and IRMA mat Ca 125 II kit were used to measure Ca 125 levels. While measurement of serum Ca 125 level was performed only once in the group 2 and group 3, Ca 125 levels were measured five times in group 1. The measurements were performed before the treatment, at the second, fourth and sixth months and the third year following the end of the treatment.

Analysis

Ca 125 levels were compared using the Mann–Whitney *U*-test between the groups and Wilcoxon test within group 1. The performance of Ca 125 for determination of tuberculosis activity was measured by the receiver operating characteristic curve.

Table 1. Serum Ca 125 levels of the groups (U ml^{-1})

	Mean ± SD	Median	95% CI
Group 1	109·7 ± 86·9	77·5	81·8–137·5
Group 2	14·5 ± 7·8	13·5	10·8–18·2
Group 3	10·5 ± 7·3	10·0	8·1–13·9

Table 2. Pretreatment and post-treatment serum Ca 125 levels of the group 1 (U ml^{-1})

	Mean ± SD	Median	95% CI
Pretreatment	109·7 ± 86·9	77·5	81·8–137·5
Post-treatment			
Second month	38·4 ± 30·5	28	27·4–48·1
Fourth month	16·4 ± 13·2	12	12·0–20·8
Sixth month	11·0 ± 7·7	8·8	8·5–13·5
Third year	10·5 ± 7·3	9·0	8·5–12·2

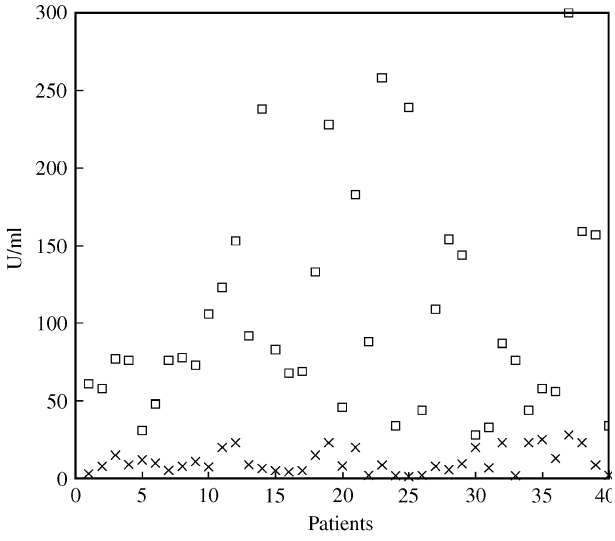

Fig. 1. Serum Ca 125 concentration of patients with active pulmonary tuberculosis before the treatment (□) and at the sixth month of the treatment (×).

Results

Serum Ca 125 concentrations of the groups are shown in Table 1. Serum Ca 125 levels were significantly higher in group 1 compared to the other groups ($P < 0.0001$), but no statistical significant difference between the values of groups 2 and 3 were found ($P > 0.05$).

Serum Ca 125 values of the patients with active pulmonary tuberculosis are summarized in Table 2. Mean (SD) serum Ca 125 concentration was found as 38·4 ± 30·5 U ml^{-1}, 16·4 ± 13·2 U ml^{-1}, 11·0 ± 7·7 U ml^{-1} and 10·5 ± 7·3 U ml^{-1} on the second, fourth and sixth months of treatment and after 3 years following the end of treatment, respectively. Serum Ca 125 levels of the patients showed significant decrease after treatment ($P < 0.0001$). Figure 1 demonstrated the decrease of serum Ca 125 levels with the treatment. Smear examination for tuberculosis bacilli was negative in 32 of 35 patients in whom sputum could be obtained at the end of the second month of treatment. Three smear positive patients

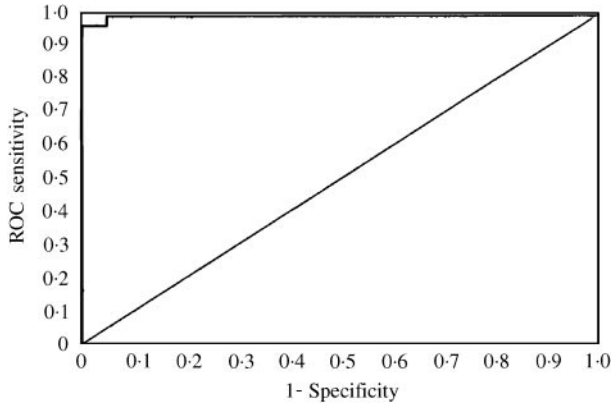

FIG. 2. Receiver operating characteristic curve for using Ca 125 for determination of pulmonary tuberculosis activity.

had high serum Ca 125 levels (53, 71 and 104 U ml^{-1}). Following the end of 6 months of treatment, there was no significant difference between patients with active pulmonary tuberculosis and patients with inactive pulmonary tuberculosis with respect to Ca 125 levels. Treatment failures or relapses were not observed in group I. All the patients were cured with the treatment.

For activation of tuberculosis, the sensitivity and specificity of Ca 125 were found to be 97·5% and 100%, respectively, at a 31 U ml^{-1} cut-off point. An ROC curve based on this data was constructed as shown in Fig. 2.

Discussion

We found that serum Ca 125 concentration increased in pulmonary tuberculosis. This increase was only obtained in patients with active tuberculosis. Serum Ca 125 levels were not elevated in patients with inactive pulmonary tuberculosis and in healthy subjects. Diez *et al*. (10) reported that serum Ca 125 concentration were higher in some patients with benign pulmonary diseases including pulmonary tuberculosis than in healthy subjects. O'Riordan *et al*. (15) determined very high serum Ca 125 level in patients with tuberculosis peritonitis. Similar results have been reported in many other studies (12,13,16,20). High levels of Ca 125 were found in patients with peritoneal and pleural tuberculosis in which bacteriological studies of the pleural effusions and ascites were negative (16,20). Ca 125 is expressed by cells of coelemic epithelium. It was determined in normal mesothelial lining cells by immunohistochemical methods and in normal bronchial epithelial cells by immunoperoxidase staining technique (21). If these cells are activated by physiological or pathological reactions such as menstruation, inflammation or tumoral involvement, they secrete Ca 125. Therefore, the concentration of Ca 125 levels increase in serum and other body fluids (9,10,14,22,23). Ronay *et al*. (22) determined that Ca 125 was immunohistochemically localized and sharply demarcated around tuberculous granuloma in two patients with peritoneal tuberculosis. They concluded that a possible explanation for this finding was the inflammatory mesothelial cell proliferation. The other study demonstrated that epithelioid and giant cells in both pleural effusion and ascites were stained with antibodies to Ca 125 in a patient with pleural and peritoneal tuberculosis (20).

We also found that serum Ca 125 levels decreased into normal values following treatment. Gurgan *et al*. (17) reported that in two cases with pelvic–peritoneal tuberculosis, serum and pleural fluid Ca 125 levels were high and decreased after treatment. The other study indicated that specific tuberculostatic treatment normalized serum Ca 125 levels in patients with pelvic–peritoneal tuberculosis (16). In our study, following the end of 6 months of therapy, no statistically significant difference was present between patients with active pulmonary tuberculosis and patients with inactive pulmonary tuberculosis according to Ca 125 levels. We repeated Ca 125 measurements after 3 years and obtained low Ca 125 levels in group I patients. There was no significant difference with respect to Ca 125 levels between other groups and results of group I after 3 years. In our study the best cut-off point was 31 U ml^{-1}. This yields a sensitivity of 97·5% and a specificity of 100%. According to these results, Ca 125 has high sensitivity and specificity for estimation of the activity of tuberculosis. Most of the activation markers have shown limited sensitivity and specificity (2). These results indicate that Ca 125 is a valuable parameter in determination of disease activity. Because tumour marker levels increase in benign and malign conditions, they are more applicable in monitoring therapy than in screening or diagnosis (24).

In conclusion, Ca 125 concentration increases in patients with active tuberculosis and its level decrease into normal values following treatment. According to our findings, high serum Ca 125 levels depend on the secretion of Ca 125 from immunologically active tissue rather than bacillus itself. It is beneficial in the determination of tuberculosis activity and in the differentiation between active and inactive pulmonary tuberculosis.

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