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Serum CA-125: biomarker of pulmonary tuberculosis activity and evaluation of response to treatment

Abstract

Purpose: CA-125 is a high molecular weight mucin-like glycoprotein and an ovarian cancer antigen. Elevated CA-125 levels are also seen with various other benign and malignant conditions. In this study, the ability of CA-125 to predict pulmonary tuberculosis activity was investigated.

Methods: This analytical study included 42 cases with active tuberculosis (Group 1), 35 cases with inactive tuberculosis (Group 2) and 20 healthy subjects (Group 3). CA-125 measurements were taken in all three groups. Measurements in Group 1 were repeated after completing a two month anti-tuberculosis treatment in 38 of the 42 patients.

Results: Mean serum CA-125 level for Group 1 was 76.48 ± 24.71 U/mL, which was significantly higher than levels in Group 2 (20.01 ± 7.89 U/mL) and Group 3 (18.32 ± 2.87 U/mL) ($p < 0.001$). Of the 38 patients in Group 1 who were studied both pre- and post-treatment, CA-125 levels decreased significantly: from 78.88 ± 24.72 U/mL before treatment to 22.78 ± 8.02 U/mL after treatment ($p < 0.001$). There was no statistically significant difference between the post-treatment values of Group 1 and either Group 2 and Group 3 values ($p > 0.05$). Group 2 and Group 3 levels were not significantly different ($p > 0.05$).

The cut-off level for accurate determination of activity was 36.35 U/mL. The sensitivity at this level was 97.6% and specificity was 100%.

Conclusion: Our findings suggest that CA-125 can be a beneficial parameter in determination of pulmonary tuberculosis activity and the evaluation of response to treatment.

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CA-125 is a high molecular weight mucin-like glycoprotein and an ovarian carcinoma antigen that is the basis for a widely used serum assay for the monitoring of patients with ovarian malignancies [1]. High serum levels are also found in benign conditions including thoracic and abdominal lining infections (peritonitis and pleuritis), during menstruation, pregnancy, endometriosis, liver diseases (like cirrhosis), uterine fibrinoids and adenomyosis, benign ovarian tumors, pancreatitis, renal and hepatic insufficiencies, pelvic irradiation, post-menopausal period, pelvic inflammatory disease and tuberculosis. CA-125 is primarily produced by amnion, fetal coelomic epithelium and its derivatives, but can also be produced by fallopian tube epithelium and in many adult tissues, including endometrium, endocervix, pleura or peritoneum [1]. In addition to its excretion that occurs with the synthesis of these epithelia, CA-125 may also be excreted in response to inflammation or to damage to these tissues [2]. Increased CA-125 levels in response to tuberculosis was first observed in 1980's in ascites from patients initially diagnosed with ovarian carcinoma; however, these patients were later diagnosed tuberculosis and not with malignancies [3,4]. Some studies investigated the ability of CA-125 levels to diagnosis tuberculous pleurisy and concluded that CA-125 could be a useful biomarker to evaluate the response to treatment [5,6]. CA-125 was also shown to be present in normal mesothelial cells and in normal epithelium of trachea and airway tissue [7] and both physiological and pathological stimulation of these tissues increased the levels of CA-125 in various body fluids, including serum. High levels have also been detected in cancers of endometrium, cervix, lung, breast, liver and in gastric, pancreatic, colorectal malignancies [8-15]. Bacteriological examination of sputum (AFB stain and culture) is the standard method in diagnosing pulmonary tuberculosis, but it sometimes gives false negative results. In such cases, anti-tuberculous treatment is given based on the clinical and radiological findings and the follow-up is performed radiologically. Studies with serum immunological tests (including IFN-gamma, TNF-alpha, IL-2, IL-12, IL-18) have been performed to determine if a more rapid diagnosis can be provide [16, 17, 18].

In the current study serum CA-125 levels were measured in pre-and post-treatment tuberculosis patients, in patients with inactive tuberculosis and in healthy controls, to determine if CA-125 levels showed promise as a biomarker for differential diagnosis of active from inactive tuberculosis and in post-treatment follow-up.

Materials and Methods

Patients and Procedures

This analytic study was performed in Yedikule Chest Disease and Surgery Training and Research Hospital between 2008-2009. The study was performed in accordance with the principles of the Declaration of Helsinki. Signed and informed consent was obtained from all the participants. Forty two cases with a mean age of 35.62 ± 9.48 years (Group 1; 26 male, 16 female) having active tuberculosis, 35 cases with a mean age of 38.23 ± 9.35 years (Group 2; 19 male, 16 female) having inactive tuberculosis and 20 healthy cases with a mean age of 35.80 ± 10.64 years (Group 3; 10 male, 10 female) were included in our study (Table 1). All patients in Group 1 had positive sputum of AFB (with Ziehl-Neelsen stain) and positive cultures (Löwenstein-Jensen medium) and were diagnosed with active pulmonary tuberculosis. Patients with new active tuberculosis cases, who had not previously been treated, were included in our study. Patients who had previously been treated for tuberculosis, or who had resistance to more than one anti-tuberculous drugs, were not included. A female patient, prediagnosed as having active tuberculosis was also diagnosed with uterine myoma and was excluded from the study. Group 2: All subjects who were diagnosed as having inactive tuberculosis, and who were given a six month standard anti-tuberculosis treatment at least 10 years ago with complete cure and who had no complaints, stable chest X-ray findings at least in the last six months, and negative findings in the three most recent consecutive sputum AFB and culture examinations, were included in the study. Group 3: Subjects included in the control group had no complaints, negative TST (Tuberculin Skin Test), normal chest X-rays and normal abdominal ultrasonographic and blood examinations. They were voluntary individuals attending the study from outside the hospital community. TST-positive individuals were excluded from the study. All participants had abdominal and pelvic ultrasonographs, chest X-rays and biochemical measurements. Subjects were excluded if there was a malignancy (such as ovarian, endometrium, cervix, lung, breast, liver, gastric, pancreatic, colorectal malignancies) and benign conditions (such as menstruation, pregnancy, endometriosis, cirrhosis, pancreatitis, renal and hepatic insufficiencies, uterine fibrinoids and adenomyosis, benign ovarian tumors, post-menopausal period, pelvic inflammatory disease, pelvic irradiation, peritonitis and pleuritis). HIV was not detected in any patients. No concomitant extrapulmonary tuberculosis was detected in any patients. Sputum culture was taken from all patients at the beginning and only two patients had primary INH resistance.

Patients were treated with a standard anti-tuberculosis treatment (two months INH/RIF/EMB/PZA and four months INH/RIF). Two patients with primary INH resistance, identified via culture-antibiograms, were treated based on the WHO tuberculosis consensus report according to the Health Ministry Tuberculosis Diagnosis and Treatment Guide-2011. Sputum AFB were negative in these patients after the two month treatment, so, these two patients were given the INH/RIF combination for four months to complete a six month standard treatment. A complete cure was observed in both patients.

All serum CA-125 measurements were performed by MEIA method (Microparticle Enzyme Immunoassay, Abbott-AxSYM System). Cut-off value was accepted to be <35 U/mL for this method. Levels >35 U/mL were considered abnormal. CA-125 measurements were taken in all three groups (Table 1). All 42 active tuberculosis patients had high serum CA-125 levels (>35 U/mL) prior to treatment. Measurements in Group 1 were repeated after completing two months anti-tuberculous treatment. Four patients did not return for serum CA-125 level evaluation after two month of treatment, so they were excluded from the section of the study pertaining to the evaluation of the treatment response; therefore, treatment responses for 38 of the 42 patients were evaluated (Table 1).

Statistical Analysis

All statistical analysis comparing Group 1, Group 2 and Group 3, and prior and post-treatment levels in Group 1, were performed using SPSS 11.5 statistical pocket program (SPSS Inc., Chicago, IL, USA). Correlations between the groups were analysed with Pearson Chi-Square method. Variants were equally distributed with Shapiro-Wilk and Kolmogorov-Smirnov normality tests. For this reason, One-way Anova Variant Analysing Test was used. Paired t-test was also used for comparison of results before and after treatment in Group 1. $p < 0.05$ was accepted as statistically significant. ROC Curve was used to

determine a meaningful serum CA-125 cut-off level for tuberculous activity.

Results

Mean serum CA-125 levels of Group 1 (42 cases; pre-treatment) were 76.48 ± 24.71 U/mL. All serum CA-125 levels were higher than normal (range 55.3-125.1 U/mL). After treatment, mean serum values decreased to 22.78 ± 8.02 U/mL ($p < 0.001$). Only three patients still had high serum CA-125 levels (i.e., >35 U/mL) and all of these patients had lower serum CA-125 than pre-treatment levels (decreases from 63.2 to 45.3 U/mL; from 77.8 to 38.7 U/mL and from 60.1 to 35.6 U/mL). In all other patients, serum CA-125 levels decreased to normal levels after treatment. Sputum AFB were negative in all patients after two months of four drug therapy (INH/RIF/EMB/PZA). Even in three patients with CA-125 levels higher than normal after treatment, sputum AFB and cultures were negative after treatment and X-ray examinations showed distinct recovery in all patients. CA-125 serum levels of these INH-resistant patients before and after treatment were as follows: 88.4 - 32.3 U/mL and 55.3 - 23.9 U/mL. Serum levels returned to normal after treatment. After a six month of standard anti-tuberculous treatment, sputum AFB and cultures were negative, X-ray findings and serum tests (e.g., erythrocyte sedimentation rates) showed distinct recovery in all patients. X-ray chest examination showed cavitory lesions in 18 patients of the 42 patients; and these patients recovered after treatment (partially after two months of treatment and totally after six months of treatment). Pre-treatment CA-125 serum levels of patients with cavitory lesions were compared to serum CA-125 levels of patients with non-cavitory lesions, but no statistically significant difference was shown ($p > 0.05$). No relapses or unsuccessful treatments were observed. These patients were followed up every three months for the year after this six month treatment and all cases were found to be stable.

TABLE 1. Features and serum CA-125 levels of the groups.

	# of subjects	Age (Mean $\pm$ SD)	Serum CA-125 Level; U/mL (Mean $\pm$ SD)	Serum CA-125 (Range)
Group 1	42	35.62 $\pm$ 9.48	76.48 $\pm$ 24.71	55.3-125.1
Pre-treatment	38	36.46 $\pm$ 11.31	78.88 $\pm$ 24.72*	56.8-125.1
Post-treatment	38	36.46 $\pm$ 11.31	22.78 $\pm$ 8.02*	15.3-45.3
Group 2	35	38.23 $\pm$ 9.35	20.01 $\pm$ 7.89	8.6-29.8
Group 3	20	35.80 $\pm$ 10.64	18.32 $\pm$ 2.87	6.3-25.6

* $p < 0.001$ Post-treatment vs Pre-treatment in Group 1; $p < 0.001$ Pre-treatment Group 1 vs Group 2 and Group 3.

FIGURE 1. ROC curve for using Ca-125 in determination of pulmonary tuberculosis activity. (Red lines are data in our study).

Pre-treatment levels in Group 1 were significantly higher than levels in Group 2 (20.01 ± 7.89 U/mL) and Group 3 (18.32 ± 2.87 U/mL). ($p < 0.001$). There was no significant statistical difference among Group 1 (post-treatment), Group 2 and Group 3 values ($p > 0.05$).

The evaluation of sensitivity and specificity of CA-125 was evaluated by comparing active tuberculosis patients with healthy volunteers and with patients with inactive tuberculosis. The cut-off level for accurate determination of activity was found to be 36.35 U/mL (Fig.1 and Fig.2). The sensitivity of this level was 97.6%, the specificity was 100%, the negative predictive value was 98.2% and the positive predictive value was 100% (Table 2).

TABLE 2. Sensitivity and specificity in different levels of serum CA-125.

Serum CA-125 Levels (U/mL)	Sensitivity (%)	Specificity (%)
31.45	100	94.5
32.95	97.6	98.2
36.35	97.6	100
40.10	95	100
42.95	90.5	100

FIGURE 2. Comparison of groups at the best cut-off point (36.35 U/mL).

Discussion

CA-125 has been found to be increased in 80% of women with epithelial ovarian carcinoma [19]. In 1996, a corrected version of the test was introduced [20,21]. Usually blood CA-125 is measured, but pleural or peritoneal fluid levels can also be measured. Tests are based on an anticore technique involving the binding against CA-125 proteins (Monoclonal Anticor Technique). Normal levels were determined to be < 35 U/mL; consistent with previously published reports [20]. Increased CA-125 levels are not specific for ovarian carcinoma but are also seen in some benign and malignant conditions. In all of these conditions, the affected organs were derived from coelomic epithelia (pleura, pericardium, peritoneum) [22,23]; therefore serosal content appears to be a required factor for CA-125 production.

Tuberculous peritonitis is among the diseases with high CA-125 levels. Previous studies showed that serum CA-125 levels increased in patients with tuberculous peritonitis accompanied by ascites, then decreased by 30% with a three week anti-tuberculous treatment and eventually returned to normal by the end of a six month treatment [24,25]. Immunohistochemical staining showed that CA-125 formed a sharply defined line surrounding tuberculous granuloma in patients with peritoneal tuberculosis. This was thought to be related to an inflammatory increase in mesothelial cell proliferation, causing an increased production and secretion of CA-125 [25]. High CA-125 level were seen in an elderly woman with ascites and miliary tuberculosis, and these levels returned to normal after an eight week treatment [26]. In another report, in which a

patient with positive ARB in sputum, feces and ascitic fluid was diagnosed with active pulmonary, intestinal and peritoneal tuberculosis, ADA was not found to be increased in the ascitic fluid, but serum CA-125 was high and returned to normal after treatment [27]. In a case report from Iran, a patient had ascites, an abdominal mass and high serum CA-125 levels; laparoscopy was performed with a prediagnosis of ovarian carcinoma, but pathology revealed peritoneal tuberculosis [28]. In a case from India, a patient had a cystic lesion of the right ovary, ascites and high serum CA-125 levels; pathological examination after laparotomy revealed tuberculosis [29]. These cases show that a number of conditions, especially peritoneal tuberculosis, may mimic advanced ovarian carcinoma and, thus, may cause misdiagnosis, and that high CA-125 levels are not specific to ovarian carcinoma. Tuberculosis bacilli sometimes cannot be detected in ascitic fluid formed during tuberculous peritonitis or in pleural fluid formed in tuberculous pleuritis. Thus, there are cases of tuberculous pleurisy that cannot be diagnosed, even when biopsies are taken. These difficulties in diagnosis gave rise to a necessity of using various immunological tests and tumor markers [30,31]. A study investigating the value of CA-125 levels in tuberculous pleurisy in our country showed that CA-125 levels were elevated in serum and pleural fluid and returned to normal levels with treatment, suggesting that CA-125 could be a useful parameter to evaluate the response to treatment [32].

In a study conducted in Japan, high serum levels of CA-125 were detected in 45% of the 40 patients with active pulmonary tuberculosis and in all of the 24 patients with tuberculous serositis (pleurisy, pericarditis, peritonitis). Serum levels of the serositis group were much higher than the levels in the pulmonary tuberculosis group and a distinct decrease was reported in both groups after anti-tuberculosis treatment [33]. There are limited number of studies investigating the ability of serum CA-125 levels to determine activity of pulmonary tuberculosis. In a study conducted in Singapore, a 26 year old patient had high serum CA-125 levels although she had no gynecological pathology. Her complaint was cough and fever, she was diagnosed as having pulmonary tuberculosis, and her serum CA-125 levels returned to normal after anti-tuberculous treatment [12]. In a study conducted in Japan, a number of serum tumor markers (CA-125, CEA, SL) were studied in 123 active pulmonary tuberculosis patients: CA-125 was found to be the most frequently elevated marker, with high levels found in 44% of the patients And CA-125 levels decreased to normal levels after anti-tuberculous treatment [34]. In another study including 35 pulmonary tuberculosis and 54 other respiratory infection cases, serum CA-125 levels were measured and found

to be higher in tuberculosis cases. In 10 of the patients with pulmonary tuberculosis, measurements were repeated after two to four months of treatment and serum levels decreased. The cut-off level for pulmonary tuberculosis cases was determined to be 32.5 IU/mL [35], comparable to that found in our study (36.35 IU/mL).

Conclusions

A significant increase in serum CA-125 levels was found in active pulmonary tuberculosis patients as compared with inactive pulmonary tuberculosis cases. For the most part (92% of patients), these elevated CA-125 levels returned to normal after anti-tuberculosis treatment. High serum CA-125 levels may be useful for detecting tuberculous activity in uncertain cases, in cases with negative sputum for ARB or in cases for which a sputum examination cannot be performed. Additionally, decreasing serum levels during treatment are an indicator of response to the treatment, especially when taken together with clinical, radiological and other laboratory findings. Our results show a strong correlation between sputum AFB becoming negative and a decrease in the level of serum CA-125.

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