Usefulness of Tumor Marker CA-125 Serum Levels in the Follow-up of Therapeutic Responses of Tuberculous Patients with and without Serositis

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Summary

The aim of this study was to determine the usefulness of CA-125 serum levels in patients with tuberculosis (TB) with and without tuberculous serositis. A total of 64 tuberculosis patients with a mean age of 58.17 ± 19.05 years were enrolled in this observational clinical series study. All patients underwent blood sampling for CA-125 serum levels before treatment. If elevated, the patients underwent blood sampling in the initial treatment phase, continuation treatment phase, and then every six months for two years. The treatment outcomes of the pulmonary TB group were evaluated with chest radiography and sputum examinations, and based on fluid amounts determined by ultrasound in the tuberculous serositis group. All of the patients in the tuberculous serositis group and only 45% of patients in the pulmonary TB group had elevated CA-125 serum levels before treatment. The pre-treatment mean CA-125 serum level was significantly higher in the tuberculous serositis group than in the pulmonary TB group. CA-125 serum levels dropped in parallel with treatment outcomes in both groups. In conclusion, CA-125 serum levels in combination with clinical responses, chest radiography, and sputum examinations, can offer better monitoring in the therapeutic responses of tuberculosis treatment.

Introduction

Tuberculosis (TB) remains one of the leading causes of mortality worldwide and has become a global public health emergency. Early diagnosis and treatment are the most important strategies to control this disease. In addition, early detection of treatment failure is also very important because the incidence of multi-drug-resistant tuberculosis (MDRTB) is rising.[1] Although novel diagnostic serologic tools such as QuantiFERON-TB Gold In-Tube and T-spot tests have been developed for rapid and accurate diagnosis of tuberculosis, these tests have no correlation with disease activity or therapeutic responses. Chest radiography, sputum acid-fast stains, and mycobacterial cultures are the standard methods used to evaluate the therapeutic responses of patients with pulmonary TB, but are not effective for extrapulmonary tuberculous serositis, including pleurisy, pericarditis and peritonitis.

Cancer antigen 125 (CA-125) is a high molecular weight glycoprotein that is expressed on the epithelial cells of the fallopian tube, endometrium, and mesothelial cells lining the pleura, pericardium and peritoneum.[2] CA-125 serum levels are elevated in a number of diverse cancerous and noncancerous conditions, particularly in those with serosal involvement.[3-6] As a result, CA-125 is not a useful diagnostic tool but might be useful in the therapeutic follow-up of patients with tuberculous serositis with serosal involvement.

The aim of this study was to determine the usefulness of CA-125 serum levels in monitoring the therapeutic responses of patients with TB with and without tuberculous

serositis.

Materials and Methods

Patients

This study, an observational clinical series study design, recruited 70 TB patients diagnosed between January 2000 and January 2007 at Taichung Veterans General Hospital after excluding cancerous and non-cancerous gynecologic conditions, such as ovary cancer, endometriosis, and pregnancy in female patients. Three patients with active pulmonary TB combined with lung structure diseases (2 with bronchiectasis and 1 with interstitial lung disease), and 3 patients with active pulmonary TB combined with tuberculous pleurisy were excluded. Thus, 64 TB patients including 40 with pure active pulmonary TB without serositis (pulmonary TB group) (23 men and 17 women, mean age 59.6 ± 21.1 years), and 24 with pure extrapulmonary tuberculous serositis without active pulmonary TB (tuberculous serositis group) (15 men and 9 women, mean age 64.0 ± 16.0 years), including 13 patients with tuberculous pleurisy, 8 patients with tuberculous pericarditis, and 3 patients with tuberculous peritonitis were enrolled.

Active pulmonary TB was diagnosed by chest radiography and sputum culture positive for *Mycobacterium tuberculosis*. The diagnostic criteria for TB pleurisy included either a positive TB culture from the pleural fluid or biopsy, detection of acid-fast bacilli or a typical granuloma on histopathological examination, or an adenosine deaminase (ADA) level of the

pleural effusion > 70 U/L.[7] The diagnosis of tuberculous pericarditis and peritonitis was based on either a positive TB culture from the pericardial/peritoneal fluid or biopsy, detection of acid-fast bacilli or a typical granuloma on histopathological examination, or an ADA level of pericardial fluid/peritoneal fluid > 40 U/L.[8,9] Patients received six months of anti-tuberculosis chemotherapy with isoniazid + rifampin + ethambutol + pyrazinamide if they were < 65 years old, or nine months of anti-tuberculosis chemotherapy with isoniazid + rifampin + ethambutol if they were ≥ 65 years old. The enrolled patients were followed-up for two years after they completed the anti-tuberculosis treatment. The Institutional Review Board and Ethics Committee of Taichung Veterans General Hospital approved this study, and we obtained informed consent from all patients.

Blood sampling

All patients underwent blood sampling before treatment (pre-treatment phase). If the pre-treatment CA-125 serum value was above 35 U/mL, the patients underwent blood sampling at the second month of treatment (initial treatment phase), the sixth month of treatment (continuation treatment phase), and then every six months for two years. In the menstrual period in female patients, the timing of blood sampling will be delayed for one week after menstruation conclusion.

CA-125 concentration was determined in the serum by an immunoradiometric assay kit (CIS Biointernational, Saclay, France) according to the manufacturer's instructions. A value >

35 U/mL was considered abnormal.

Treatment outcomes

The treatment outcomes of active pulmonary TB were evaluated every 3 months with chest radiography, sputum acid fast stains, and *Mycobacterium* cultures according to the World Health Organization/International Union against Tuberculosis and Lung Disease (WHO/IUTLD) guidelines.[10] Ultrasonography was performed when patients with tuberculous serositis visited the hospital for CA-125 blood sampling. The amount of pericardial effusion was recorded as large, moderate, or mild according to the method described by Eisenberg and colleagues.[11] The amount of ascites was divided into four grades: grade 0, not visible on ultrasound; grade 1, mild, only visible on ultrasound; grade 2, detectable with flank bulging and shifting dullness; and grade 3, directly visible, confirmed with fluid thrill. Quantification of the pleural effusion was recorded by the measurement of the thickness of effusion lamella.[12]

Statistical analyses

Comparisons of CA-125 serum levels between the pulmonary TB group and tuberculous serositis group were performed using Fisher's exact test. The Wilcoxon signed ranks test was performed to evaluate the differences between the pre-treatment phase, initial treatment phase, and continuation treatment phase. Data are expressed as frequency (n), percentage (%), and mean ± standard deviation (SD). A value of $P < 0.05$ was considered statistically significant.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 12.0, Chicago, IL, USA).

Results

The demographic and clinical characteristics of patients are reported in Table 1. The pulmonary TB group had significantly more chronic obstructive pulmonary disease (COPD) comorbidity compared to the tuberculous serositis group. There were no differences between these two groups in other comorbidities. The sensitivity of an elevated CA-125 serum level for the diagnosis of disease activity in the tuberculous serositis group was 100%, which was higher than that for the pulmonary TB group (45%), using a cut-off value of 35 U/mL.

In the pre-treatment phase, the mean CA-125 serum level of the tuberculous serositis group was 234.82 ± 279.25 U/mL, which was higher than that of pulmonary TB group (48.26 ± 53.30 U/mL; $P < 0.001$) (Fig. 1A). Subgroup analysis showed that the tuberculous peritonitis subgroup had the highest mean CA-125 serum level (820.67 ± 419.22 U/mL). After excluding the tuberculous peritonitis patients, the mean CA-125 serum level in the tuberculous serositis group (151.13 ± 109.80 U/mL) was found to be higher than that of pulmonary TB group (48.26 ± 53.30 U/mL, $P < 0.001$) with statistical significance in the pre-treatment phase (Fig. 1B).

When we monitored CA-125 serum levels in the different treatment phases, we found that CA-125 serum levels dropped gradually after beginning anti-tuberculosis treatment both

in the pulmonary TB group and tuberculous serositis group (Fig. 2).

In the pulmonary TB group, a total of 18 patients (45%) had a CA-125 serum level > 35 U/mL in the pre-treatment phase. Conversion of the sputum acid-fast stains and *Mycobacterium* cultures occurred in all of these 18 patients at the third month of treatment. After beginning anti-tuberculosis treatment, serial CA-125 serum levels dropped in parallel with an improvement in serial follow-up chest radiographs in all of these 18 patients.

In the tuberculous serositis group, CA-125 serum levels dropped as the amount of fluid (determined by ultrasonography) decreased during anti-tuberculosis treatment (Fig. 3). In the tuberculous pleurisy subgroup (n = 13), the thickness of the effusion lamella was ≥ 15 mm in all patients in the pre-treatment phase. In the initial treatment phase, the thickness of the effusion lamella was < 15 mm in all patients (10 mm in 3 patients (23%), 5 mm in 4 patients (31%), and no detectable pleural effusion in 6 patients (46%)). In the continuation treatment phase, the thickness of the effusion lamella was < 10 mm in all patients (5 mm in 3 patients (23%), and no detectable pleural effusion in 10 patients (77%)) (Fig. 3A).

In the tuberculous pericarditis subgroup (n = 8), 4 patients (50%) had large amounts of pericardial effusion, and 4 patients (50%) had moderate amounts of pericardial effusion in the pre-treatment phase. In the initial treatment phase, 2 patients (25%) had mild amounts of pericardial effusion and 6 patients (75%) had no detectable pericardial effusion. No pericardial effusion was detected in any patient in the continuation treatment phase (Fig. 3B).

In the tuberculous peritonitis subgroup (n = 3), 2 patients (67%) had grade 2 ascites and 1 patient (33%) had grade 1 ascites in the pre-treatment phase. In the initial treatment phase, no visible ascites (grade 0) was seen in 2 patients (67%), and one (33%) had grade 1 ascites. All 3 tuberculous peritonitis patients (100%) were found to have grade 0 ascites in the continuation treatment phase (Fig. 3C).

One tuberculous pleurisy patient who initially responded to anti-tuberculosis treatment had a rebound of CA-125 serum levels at the 24th month follow-up. The patient's chest radiograph showed a recurrent right-sided pleural effusion. The relapse of right-sided tuberculous pleurisy was diagnosed by an ADA level in the pleural effusion > 70 U/L. The rebound of CA-125 serum levels correlated well with the clinical relapse (Fig. 4). All other patients were successfully treated without clinical relapse or rebound of CA-125 serum levels during the 2-year follow-up.

Discussion

In this study, all of the patients in the tuberculous serositis group and only 45% of the patients in the pulmonary TB group had elevated CA-125 serum levels in the pre-treatment phase. The mean CA-125 serum level was highest in the tuberculous peritonitis group and lowest in the pulmonary TB group. CA-125 serum levels dropped in parallel with improvements in follow-up chest radiographs, conversion of sputum acid-fast stains and *Mycobacterium* cultures in the pulmonary TB group, and decreased amounts of effusion in

the tuberculous serositis group.

CA-125 serum levels have been used to evaluate the activity of pulmonary TB with a sensitivity ranging from 63% to 97.5%.[13-14] However, only 45% of the patients with pure active pulmonary TB without serositis had elevated CA-125 serum levels in our study. Yatiraj *et al*. reported that pure pulmonary TB without involvement of the pleural epithelium did not evoke CA-125 release.[15] Ozsahin *et al*. found that diseases often mistaken for active pulmonary TB, such as pneumonia, bronchiectasis, and interstitial lung diseases were associated with increased CA-125 serum levels.[14] However, neither of the aforementioned authors reported whether the active pulmonary TB patients in their studies had involvement of the pleura or other pleuro-pulmonary diseases. This may explain why the sensitivity for the discrimination of pulmonary TB activity by CA-125 serum levels in our study was lower than in those of Yilmaz *et al*. and Ozsahin *et al*.[13-14] We excluded patients with both active pulmonary TB and lung structure diseases, such as bronchiectasis and interstitial lung disease, and divided the enrolled tuberculosis patients into those with pure active pulmonary TB without serositis and those with pure tuberculous serositis without active pulmonary tuberculosis.

In our study, CA-125 serum levels were elevated in all 13 patients with tuberculous pleurisy, and dropped in parallel with pleural fluid amounts rapidly after anti-tuberculosis treatment. The rapid decrease after treatment is a result of the short half-life (4-8 days) of

serum CA-125. Chest radiography is a good tool to follow up the therapeutic responses of tuberculous pleurisy. However, half of tuberculous pleurisy patients will develop pleural thickening after anti-tuberculosis treatment,[16] which makes it difficult for clinicians to monitor the therapeutic responses. In our study, 3 tuberculous pleurisy patients (23%) had a residual 5 mm in thickness of the effusion lamella in the continuation treatment phase. However, no color signs were found under color Doppler ultrasound in these 3 patients, indicating that the residual effusion lamella was pleural thickening. According to our observations, CA-125 serum levels combined with chest radiography might offer better monitoring efficacy, especially in patients with tuberculous pleurisy complicated with pleural thickening after anti-tuberculosis treatment.

Tuberculous peritonitis is the most well-known type of serositis associated with CA-125 serum levels, which return to normal after anti-tuberculous therapy in tuberculous peritonitis patients.[6,17-19] A positive correlation between the amount of ascites and CA-125 serum levels was found in patients with ovarian cancer.[20] In our study, the CA-125 serum levels of the tuberculous serositis group in the pre-treatment phase were significantly higher than in the pulmonary TB group, indicating that serosal involvement may be associated with higher CA-125 serum levels. The CA-125 serum level in the tuberculous peritonitis subgroup was higher than that in the tuberculous pleurisy or pericarditis subgroups; however, the result was not statistically significant, possibly because there were only 3 tuberculous peritonitis patients.

It is possible, however, that as the area of involved serosa increases, the CA-125 serum level will increase.

To the best of our knowledge, the correlation of CA-125 serum levels and the therapeutic responses in tuberculous pericarditis has not been reported in the literature. In our study, pericardial fluid amounts decreased in parallel with a drop of CA-125 serum levels in tuberculous pericarditis patients during treatment. Although clinical response was the main method used to evaluate the therapeutic effects, CA-125 serum levels could ~~be used~~ assist in the follow-up of therapeutic responses in tuberculous pericarditis patients.

Besides CA-125 serum levels, serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were elevated in patients with pulmonary tuberculosis (72%-87% and 75-87% respectively) and dropped to a mean level close to that of the control group after anti-tuberculous treatment parallel with sputum smear conversion.[21-23] As a result, serum CRP concentrations, like CA-125 serum levels in the present study, could assist in the evaluation of pulmonary tuberculosis treatment. The change in ESR was slower and had a controversy to be a timely indicator of clinical improvement or deterioration.[24]

In patients with lymphocytic pleural effusion, pleural fluid and serum CRP levels were significantly higher in the tuberculous pleurisy group than in the malignant pleural effusion group. The cut-off value for serum CRP level of $\geq$ 60 mg/L had a sensitivity of 71% with 80% specificity. A CRP pleural fluid level < 30 mg/L virtually ruled out the possibility

of tuberculosis as the cause of a lymphocytic pleural effusion (72%-95% sensitivity, >90% specificity).[25-27]

CA-125 serum and pleural effusion levels were higher in malignant pleural effusion than in benign pleural effusion. For the discrimination between malignant and benign effusions, CA-125 serum and pleural effusion levels had a low sensitivity (43.8%-50% and 48.0%-56.3% respectively) and high specificity (45.5%-70% and 70%-85.0% respectively).[28-31] CA-125 on its own is insufficient to discriminate malignant from benign pleural effusion including tuberculous pleurisy.

From the point of view, measurements of CA-125 serum levels are not cost effective and less sensitive (45% in the pulmonary TB group in the present study) but offer an alternative follow-up tool when rising before anti-tuberculosis treatment, especially in patients with tuberculous serositis because of its high sensitivity (100%) in the tuberculous serositis group in the present study.

There are some weaknesses to this study. This study was an observational clinical series study design and lacked patients with serositis other than tuberculosis and extrapulmonary TB other than serositis as the control groups. Although there were only 3 tuberculous peritonitis patients in our study, our observational results were similar with the results reported by Mas MR, *et al.* and Kuno Y, *et al.*.[6,17] Comparing with the patient number of tuberculous peritonitis, larger numbers of patients with tuberculous pleurisy and pericarditis

were enrolled in the present study, but the small number of patients with tuberculous serositis were noted. Neither drug resistances nor poor compliances encountered in the present study. So whether CA-125 serum levels rebounded or not when encountering drug resistances or poor compliances could not be defined. However, we detected clinical relapse in 1 tuberculous pleurisy patient presented with recurrent right-sided pleural effusion by CA-125 serum level rebound. The role of CA-125 serum levels in patients with drug resistances or poor compliances and long-term follow-up of tuberculosis should be studied further.

In conclusion, CA-125 serum levels combined with clinical responses, chest radiography, and sputum examinations, can offer better monitoring of the therapeutic responses of tuberculosis treatment.

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Conflict of interest: The authors disclose no conflicts

Table legends

Table 1. Demographic characteristics of the enrolled 64 tuberculous patients

Figure legends

Figure 1A. Distribution of CA-125 serum levels in the pulmonary tuberculosis group and tuberculous serositis group, including tuberculous pleurisy, tuberculous pericarditis, and tuberculous peritonitis.

Figure 1B. Distribution of CA-125 serum levels in the pulmonary tuberculosis group and tuberculous serositis group after exclusion of the tuberculous peritonitis subgroup.

Figure 2. The change of CA-125 serum levels in different treatment phases in pulmonary tuberculosis group and tuberculous serositis group.

Figure 3. The relationship of CA-125 serum levels and sonographic findings in different treatment phases in (A) tuberculous pleurisy, (B) tuberculous pericarditis, and (C) tuberculous peritonitis subgroups.

Figure 4.The rebound of CA-125 serum levels in one tuberculous pleurisy patient during the 2-year follow-up