Usefulness of Tumor Marker CA-125 Serum Levels for the Follow-Up of Therapeutic Responses in Tuberculosis Patients with and without Serositis

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SUMMARY: The aim of this study was to determine the usefulness of cancer antigen 125 (CA-125) serum levels in patients with tuberculosis (TB) with and without tuberculous serositis. A total of 64 TB patients with a mean age of 58.17 ± 19.05 years were enrolled in this observational case series study. All patients underwent blood sampling for the measurement of CA-125 serum levels before treatment. If the CA-125 serum levels were found to be elevated, the patients underwent blood sampling in the initial treatment phase, continuation treatment phase, and every 6 months thereafter for 2 years. The treatment outcomes of the pulmonary TB group were evaluated using chest radiography and sputum examinations, and those of the tuberculous serositis group were evaluated on the basis of the amounts of fluid determined by ultrasound. All patients in the tuberculous serositis group and 45% of the patients in the pulmonary TB group had elevated CA-125 serum levels before treatment. The pretreatment mean CA-125 serum level was significantly higher in the tuberculous serositis group than in the pulmonary TB group. CA-125 serum levels decreased along with improvement in anti-TB treatment outcomes in both the groups. In conclusion, the CA-125 serum levels in combination with clinical responses, chest radiography, and sputum examinations, can offer better monitoring of therapeutic responses in anti-TB treatment.

INTRODUCTION

Tuberculosis (TB) is 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 TB. In addition, early detection of treatment failure is very important because of increasing incidences of multidrug-resistant tuberculosis (MDR-TB) (1). Although novel diagnostic tools for serologic tests, including QuantiFERON-TB Gold In-Tube and T-spot. TB, have been developed for rapid and accurate diagnosis of TB, the results of these tests have not been correlated with disease activity or therapeutic responses. Standard methods such as chest radiography, sputum acid-fast staining, and mycobacterial cultures used for evaluating therapeutic responses of pulmonary TB patients are not effective for the evaluation of extrapulmonary TB and 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). Elevation in CA-125 serum levels occur in a number of diverse cancerous and non-cancerous conditions, particularly those with serosal involvement (3–6). Therefore, CA-125 cannot be considered a useful diagnostic tool, but it can be helpful in the therapeutic follow-up of tuberculous serositis patients with serosal involvement.

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

MATERIALS AND METHODS

Patients: We conducted an observational case series study involving 70 patients diagnosed with TB between January 2000 and January 2007 at the Taichung Veterans General Hospital. Female patients with cancerous and non-cancerous gynecologic conditions, such as ovarian cancer, endometriosis, and pregnancy were excluded by medical chart review. Among the diagnosed patients, 3 were with active pulmonary TB combined with lung diseases (2 with bronchiectasis and 1 with interstitial lung disease) and 3 with active pulmonary TB combined with tuberculous pleurisy were excluded. Thus, we enrolled 64 TB patients, including 40 having...
active pulmonary TB without serositis (pulmonary TB group; 23 men and 17 women; mean age, 59.6 ± 21.1 years) and 24 having extrapulmonary TB with tuberculous serositis and without any active pulmonary TB (tuberculous serositis group; 15 men and 9 women; mean age, 64.0 ± 16.0 years). The tuberculous serositis group included 13 patients with tuberculous pleurisy, 8 with tuberculous pericarditis, and 3 with tuberculous peritonitis.

Active pulmonary TB was diagnosed on the basis of chest radiographic findings and presence of Mycobacterium tuberculosis in sputum cultures. The diagnostic criteria for tuberculous pleurisy included the detection of M. tuberculosis in either the pleural fluid culture or biopsy samples, detection of acid-fast bacilli or a typical granuloma on histopathological examination, or adenosine deaminase (ADA) level of > 70 U/L in pleural effusion (7). The diagnosis of tuberculous pericarditis and peritonitis was on the basis of the detection of M. tuberculosis in either the pericardial/peritoneal fluid culture or biopsy samples, detection of acid-fast bacilli or a typical granuloma on histopathological examination, or ADA level of > 40 U/L in pericardial/peritoneal fluid (8,9). The patients received 6 months of anti-TB combination chemotherapy with isoniazid, rifampin, ethambutol, and pyrazinamide if they were aged < 65 years, or 9 months of anti-TB combination chemotherapy with isoniazid, rifampin, and ethambutol if they were aged ≥ 65 years. The patients were followed-up for 2 years after they completed the anti-TB combination chemotherapy. This study was approved by the Institutional Review Board and Ethics Committee of Taichung Veterans General Hospital.

Blood sampling: All patients underwent blood sampling before receiving the treatment (pretreatment phase). If the pretreatment CA-125 serum values were ≥ 35 U/mL, then the blood sampling was repeated in the second month of treatment (initial treatment phase), the sixth month (continuation treatment phase), and then every 6 months thereafter for 2 years.

CA-125 serum levels were determined using an immunoradiometric assay kit (CIS Biointernational, Saclay, France) according to the manufacturer’s instructions, and a value of ≥ 35 U/mL was considered abnormal.

### Treatment outcomes

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

### Statistical analyses

CA-125 serum levels in the pulmonary TB group and tuberculous serositis group were compared using Fisher’s exact test. The Wilcoxon signed rank test was performed to evaluate the differences among the pretreatment, initial treatment, and continuation treatment phases. Data were 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 (version 12.0; SPSS, Chicago, Ill., USA).

### RESULTS

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

In the pretreatment phase, the mean CA-125 serum

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### Table 1. Demographic characteristics of the enrolled 64 tuberculosis patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pulmonary TB group</th>
<th>Tuberculous serositis group</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. (male/female)</td>
<td>40 (23/17)</td>
<td>13 (9/4)</td>
<td>8 (4/4)</td>
</tr>
<tr>
<td>Age</td>
<td>59.6 ± 21.1</td>
<td>69.2 ± 13.8</td>
<td>62.0 ± 18.1</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>5 (12.5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>H/T</td>
<td>7 (17.5%)</td>
<td>1 (7.7%)</td>
<td>0</td>
</tr>
<tr>
<td>COPD</td>
<td>10 (25%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CAD</td>
<td>2 (5%)</td>
<td>0</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>5 (12.5%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation (SD) or number (%). By Fisher’s exact test. 
\( P < 0.05 \) indicates statistical significance.

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DM, diabetes mellitus; H/T, hypertension; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; TB, tuberculosis.
levels of the tuberculous serositis group was 234.82 ± 279.25 U/mL, which was higher than that of the pulmonary TB group (48.26 ± 53.30 U/mL; \( P < 0.001 \)) (Fig. 1A). Subgroup analyses showed that the tuberculous peritonitis subgroup had the highest mean CA-125 serum levels (820.67 ± 419.22 U/mL). Moreover, the mean CA-125 serum levels in the tuberculous serositis group (151.13 ± 109.80 U/mL) was significantly higher than that of the pulmonary TB group (48.26 ± 53.30 U/mL, \( P < 0.001 \)) during the pretreatment phase, even after excluding the tuberculous peritonitis subgroup (Fig. 1B).

We observed that the CA-125 serum levels in the different treatment phases gradually reduced after the commencement of anti-TB treatment in both the pulmonary TB group and tuberculous serositis group (Fig. 2). In the pulmonary TB group, 18 patients (45%) had a CA-125 serum level >35 U/mL during the pretreatment phase, and all patients showed conversion of the sputum acid-fast stains and Mycobacterium cultures in the third month of treatment. However, after commencing the anti-TB treatment, we observed a serial decrease in the CA-125 serum levels along with a serial improvement in the follow-up chest radiographic findings in all 18 patients.

In the tuberculous serositis group, the CA-125 serum levels decreased along with a decrease in the amounts of pleural/pericardial/peritoneal effusion (determined by ultrasound) during anti-TB treatment (Fig. 3). In the tuberculous pleurisy subgroup (\( n = 13 \)), the thickness of the pleural lamella was ≥15 mm in all patients during the pretreatment phase. In the initial treatment phase, the thickness of the pleural 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 pleural 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 during the pretreatment 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 during 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 during the pretreatment phase. In the initial treatment phase, 2 patients (67%) had no visible ascites (grade 0), and 1 patient (33%) had grade 1 ascites. All 3 patients (100%) were found to have grade 0 ascites during the continuation treatment phase (Fig. 3C).

In the tuberculous pleurisy subgroup, 1 patient who initially responded to anti-TB treatment showed increased CA-125 serum levels at the 24th month of follow-up. The patient's chest radiograph showed a recurrent right-sided pleural effusion. This relapse of right-sided tuberculous pleurisy was diagnosed by an ADA level of >70 U/L in the pleural effusion. The increase in the CA-125 serum levels correlated with the clinical relapse of pleurisy (Fig. 4). All other patients were successfully treated without any clinical relapse or increase...
in 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 pretreatment phase. The mean CA-125 serum level was highest in the tuberculous peritonitis subgroup and lowest in the pulmonary TB group. The CA-125 serum levels had decreased along 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 tuber-
CA-125 serum levels have been used to evaluate the activity of pulmonary TB with a sensitivity ranging from 63.0% to 97.5% (13,14). However, only 45% of the patients having active pulmonary TB without serositis had elevated CA-125 serum levels in our study. Yatiraj et al. reported that pulmonary TB without the involvement of the pleural epithelium did not evoke a CA-125 release (15). Ozsahin et al. observed that several 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 pleural involvement or other pleuropulmonary diseases. This may explain why the sensitivity for the discrimination of pulmonary TB activity by CA-125 serum levels reported in our study was lower than that reported in the studies by Yilmaz et al. and Ozsahin et al. (13,14). We excluded patients with both active pulmonary TB and lung diseases, such as bronchiectasis and interstitial lung disease, and divided the enrolled TB patients into groups with active pulmonary TB without serositis and with tuberculous serositis without active pulmonary TB.

In our study, the CA-125 serum levels were elevated in all 13 tuberculous pleurisy patients, and the serum levels of CA-125 had rapidly decreased along with a decrease in the amounts of pleural fluid rapidly after anti-TB treatment. The rapid decrease after anti-TB treatment is a result of the short CA-125 half-life (4–8 days). Chest radiography is a useful tool in the follow-up of the therapeutic responses of tuberculous pleurisy patients. However, 50% of the tuberculous pleurisy patients will develop pleural thickening after anti-TB treatment (16), which makes it difficult for clinicians to monitor their therapeutic responses. In our study, 3 tuberculous pleurisy patients (23%) had a residual 5-mm thick pleural lamella in the continuation treatment phase. However, no color signs were found in color Doppler ultrasound analysis in these 3 patients; this indicated that the residual pleural lamella showed thickening. On the basis of our observations, the measurement of CA-125 serum levels combined with chest radiography may offer better monitoring efficacy, particularly in patients with tuberculous pleurisy complicat-
ed with pleural thickening after anti-TB treatment.

Tuberculous peritonitis, the most well-known type of serositis associated with CA-125 serum levels, becomes normal after anti-TB 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 pretreatment phase were significantly higher than those of the pulmonary TB group, indicating that the 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. However, it is possible that the CA-125 serum levels may increase with an increase in the area of serosal involvement in tuberculous peritonitis.

To the best of our knowledge, the correlation of CA-125 serum levels and the therapeutic responses in tuberculous pericarditis patients have not been reported in the literature. In our study, the CA-125 serum levels decreased along with a decrease in the amounts of pericardial fluid during anti-TB treatment. Although the clinical response was the main method used for the evaluation of the therapeutic effects, CA-125 serum levels could assist in the follow-up of therapeutic responses in tuberculous pericarditis patients.

In addition to the CA-125 serum levels, the C-reactive protein (CRP) serum levels, and erythrocyte sedimentation rate (ESR) were elevated in pulmonary TB patients (72–87% and 75–87%, respectively) and had decreased to a mean level close to that of the control group after anti-TB treatment along with the sputum smear conversion (21–23). Therefore, the serum CRP levels, similar to the CA-125 serum levels in the present study, could assist in the evaluation of therapeutic responses of pulmonary TB. The changes in ESR were slower and hence could not be a timely indicator of clinical improvement or deterioration of pulmonary TB (24).

Among patients with lymphocytic pleural effusion, pleural fluid and serum CRP levels were significantly higher in patients in the tuberculous pleurisy group than in patients with malignant lymphocytic pleural effusion. The cut-off value for a serum CRP level of ≥60 mg/L had a sensitivity of 71% and a specificity of 80%. A pleural fluid CRP level of <30 mg/L can practically rule out the possibility of TB as the cause of lymphocytic pleural effusion (72–95% sensitivity; >90% specificity) (25–27).

The CA-125 levels in serum and pleural effusion were higher in malignant pleural effusion than in benign pleural effusion. For differentiating malignant and benign pleural effusions, the CA-125 levels of the serum and pleural effusion 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). Measuring only the CA-125 level is insufficient to differentiate malignant from benign pleural effusion including tuberculous pleurisy.

To the best of our knowledge, serum CRP concentrations and ESR have never been used as the treatment indicators in tuberculous serositis patients. From our per-
spective, measurement of CA-125 serum levels has less sensitivity (45% in the pulmonary TB group in the present study). However, the measurement of CA-125 serum levels offers an alternative follow-up tool for the pretreatment evaluation in anti-TB treatment, particularly in tuberculous serositis patients because of its high sensitivity (100%), as observed in the tuberculous serositis group in the present study.

Our study has some limitations. We conducted an observational study, and we had not included patients with serositis other than TB and those with extrapulmonary TB with diseases other than serositis in the control groups. Although there were only 3 tuberculous peritonitis patients in our study, our observational results were similar to the results reported by Mas et al. (17) and Kuno et al. (6). We enrolled a larger numbers of patients with tuberculous pleurisy and pericarditis than patients with tuberculous peritonitis and a small number of patients with tuberculous serositis was noted. We did not encounter drug resistances or poor drug compliances in the present study. Therefore, we could not conclude whether CA-125 serum levels increased because of probable drug resistances or poor compliances. Because we detected a clinical relapse in 1 patient with tuberculous pleurisy who presented with recurrent right-sided pleural effusion by measuring the increase in CA-125 serum levels, we assume that CA-125 serum levels play a role in patients with drug resistances or poor compliances, however, further studies on the long-term follow-up of TB are required.

In conclusion, measurement of CA-125 serum levels in combination with analysis of clinical responses on the basis of chest radiography and sputum staining and culturing offer a better monitoring of the therapeutic responses of patients undergoing anti-TB treatment.

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Conflict of interest None to declare.

REFERENCES