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DIAGNOSTICS

The clinical significance of CA-125 in pulmonary tuberculosis

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SUMMARY

Cancer antigen 125 (CA-125) is usually elevated in ovarian cancer. However, there are several reports that serum CA-125 is elevated in tuberculosis. This study investigated the clinical significance of serum CA-125 measurements in patients with active pulmonary tuberculosis (TB).

Between September 2008 and March 2011, Serum CA-125 was measured in patients with active pulmonary TB before treatment (baseline), and 6 and 12 months after initiation of anti-TB treatment. Patients with pulmonary TB confirmed by culture or polymerase chain reaction for *Mycobacterium tuberculosis* (TB-PCR) were included.

The study enrolled 100 patients. The mean serum CA-125 was 38.9 ± 41.4 U/ml (reference value, <35 U/ml). Thirty-eight patients showed elevated CA-125. Significantly more of those with elevated CA-125 were female ($p < 0.001$), and had a positive sputum smear for acid-fast bacilli (AFB) ($p = 0.030$). They also significantly more showed extensive pulmonary lesions on chest X-ray ($p = 0.004$). Elevated CA-125 was independently associated with female gender (OR = 12.5, 95% CI: 3.4–45.2), positive acid-fast staining of sputum (OR = 6.0, 95% CI: 1.8–19.7), cavitary lung lesion (OR = 4.0, 95% CI: 1.2–12.9), and involvement of more than one lung on chest X-ray (OR = 9.4, 95% CI: 2.2–40.1). The CA-125 level decreased with anti-TB treatment ($p = 0.001$).

Serum CA-125 was related to the activity and severity of pulmonary TB, and it may be useful in the monitoring of therapeutic responses in certain cases of active pulmonary TB, especially in female patients of active pulmonary TB.

1. Introduction

Pulmonary tuberculosis (TB) is one of the leading causes of mortality worldwide and has become a global public health emergency.[1] Determination of pulmonary TB activity is as important as early diagnosis of pulmonary TB in optimal treatment strategy. Especially in patients with a previous history of cured TB, it is more difficult to discriminate between an old healed TB lesion and reactivation.[2,3] 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 *Mycobacterium tuberculosis* infection, the results of these tests have not been correlated with disease activity or therapeutic responses.[4,5] Usually chest radiography, sputum acid-fast staining, and mycobacterial cultures are used for evaluating therapeutic responses of pulmonary TB.[6–8] However, chest radiography improves slowly with treatment and does not accurately discriminate the activity of pulmonary TB.[6,9] Furthermore, sputum examination is impossible in some patients who do not expectorate sputum.

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.[10] CA-125 levels are elevated in a number of malignant diseases such as those involving the ovaries, lungs, breasts, colon, pancreas, and in some non-malignant conditions including endometriosis, hepatic cirrhosis or heart failure. Previously, it was reported that serum CA-125 levels were higher in patients with pulmonary and extra-pulmonary TB than healthy subjects.[11] However, there have been few reports on the relationship

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between the activity of pulmonary TB and CA-125 levels. The clinical usefulness of CA-125 in pulmonary TB is not fully understood.

The aim of this study was to investigate the clinical significance of serum CA-125 measurements in patients with active pulmonary TB.

2. Study population and methods

2.1. Patients and study design

A prospective study was performed. Patients diagnosed with active pulmonary TB between September 2008 and March 2011 at Seoul National University Bundang Hospital, a university-affiliated tertiary care hospital in Korea, were enrolled. Any patients with progressive malignancy and female patients with non-malignant gynecologic conditions, such as endometriosis, and pregnancy were excluded by medical history taking and interview.

The diagnosis of active pulmonary TB was based on positive respiratory specimen culture or polymerase chain reaction for *Mycobacterium tuberculosis* (TB-PCR). The patients were followed-up for at least 1 year after the initiation of the anti-TB treatment. Sputum staining for acid-fast bacilli (AFB), mycobacterial culture and chest radiography were examined every one or two months during the treatment. In patients who did not expectorate sputum, bronchoscopy was done for mycobacterial culture. TB PCR or interferon-gamma release assay was performed according to the physician's judgment. After written informed consent was obtained, patients underwent blood sampling for CA-125 before receiving the treatment and 6 months and 12 months after initiation of anti-TB treatment. This study was approved by the Institutional Review Board and Ethics Committee of Seoul National University Bundang Hospital, (IRB number: B-0807/059-003) and was conducted in compliance with the Declaration of Helsinki.

2.2. Measurement of serum CA-125

Serum CA-125 levels were measured using a commercial radioimmunoassay kit (Cis Biointernational, Gif sur Yvette, France), and the normal range was defined as <35 U/mL according to the manufacturer's instructions.

2.3. Statistical analysis

Statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed as mean ± SD or median and interquartile range. Student's *t*-test was used to compare continuous variables, and chi-square or Fisher's exact tests were used to compare categorical variables. Serial change of CA-125 level was analyzed by repeated measures generalized linear model. A two-tailed *p*-value of <0.05 was considered to indicate significant difference.

3. Results

3.1. Baseline characteristics of study patients

Among 280 patients with suspected pulmonary TB, 58 patients were excluded because they were not confirmed by mycobacterial culture or TB PCR. Finally, 100 patients with active pulmonary TB were enrolled (Figure 1). The demographic and clinical characteristics of the patients included in the study are presented in Table 1. Twenty seven (27.0%) patients had a previous history of TB. No participant suffered from any active or progressive malignancies. Approximately half of the patients (47 patients, 47%) had an initial sputum smear that showed acid-fast bacilli. Cavitation was present in 46% of patients, and 21 patients (21%) showed pulmonary lesions that involved more than one whole lung on chest X-ray (Table 1). The mean serum CA-125 level was 38.9 ± 41.4 U/ml (reference value, <35 U/ml). Female patients had significantly higher serum CA-125 levels ($p < 0.001$) and had more bronchiectatic lesions on chest X-ray ($p < 0.002$).

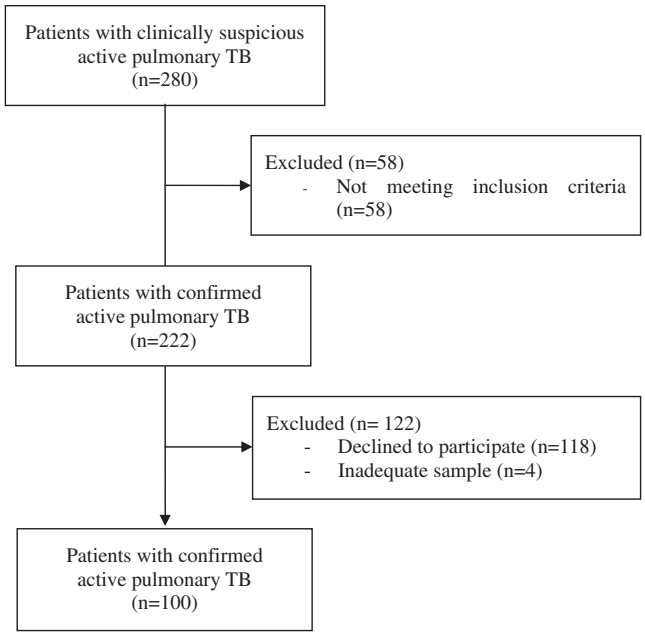

Figure 1. Flow chart of patient enrollment into the study.

3.2. Comparisons between patients with normal and elevated CA-125 levels

According to serum CA-125 levels, patients were subdivided into two groups: the normal CA-125 group and the elevated CA-125

Table 1
Baseline clinical characteristics of the study patients.

	Total ($n = 100$)	Male ($n = 54$)	Female ($n = 46$)	*p*-value
Age, yr (median, range)	46.5(15–89)	49.0(25–89)	43.0(15–87)	0.397
Body mass index, kg/m^2	20.2 ± 2.8	20.4 ± 2.7	20.0 ± 2.9	0.565
Smoking				<0.001
Never-smoker	53(53)	19(35.2)	34(73.9)	
Ever-smoker	32(32)	29(53.7)	3(6.5)	
Unknown	15(15)	6(11.1)	9(19.6)	
Diabetes mellitus	11(11)	8(14.8)	3(6.5)	0.187
Previous history of TB				0.522
Yes	27(27.0)	16(29.6)	11(23.9)	
No	73(73.0)	38(70.4)	35(76.1)	
AFB smear positivity	47(47.0)	28(51.8)	19(41.3)	0.296
M.TB culture positivity	90(90.0)	46(85.1)	44(95.6)	0.145
M.TB PCR positivity	39/63(61.9)	23/36(63.9)	16/27(59.3)	0.708
IGRA positivity	34/37(91.9)	18/20(90.0)	16/17(94.1)	0.651
Drug susceptibility test				0.383
Drug susceptible TB	66/83(79.5)	35/42(83.3)	31/41(75.6)	
Drug resistant TB*	17/83(20.5)	7/42(16.7)	10/41(24.4)	
Chest X-ray				
Cavitary lung lesion	47(47)	29(53.7)	18(39.1)	0.147
Extent, more than one whole lung	21(21)	11(20.4)	10(21.7)	0.867
Bronchiectasis	36(36)	12(22.2)	24(52.2)	0.002
Pleural effusion	13(13)	4(7.4)	9(19.6)	0.082
CA-125, U/ml	38.9 ± 41.4	27.6 ± 32.9	52.1 ± 46.6	0.008

Data are mean ± SD or number(%) patients.
TB, tuberculosis; AFB, acid-fast bacilli; IGRA, interferon-gamma release assay; CA-125, cancer antigen 125.
* Ten patients were multidrug resistant tuberculosis.