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Pleural Fluid CA-125 in Patients with Pleural Effusion

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ABSTRACT

Background: Primary and secondary infections and malignancies are inflammatory causes of fluid accumulation in the pleural space. TB is one of the infective causes of pleural effusion and is similar to malignancies because of its subacute and chronic process; although their management is extremely different.

CA-125 is a glycoprotein tumor marker with molecular weight of 200 KD, which is found on the surface of ovarian and some normal and inflammatory cells. In both malignancy and tuberculosis, this tumor marker increases in serum and consequently in pleural fluid. This study was conducted to evaluate and compare CA-125 tumor marker in pleural effusion resulting from malignancies and tuberculosis.

Materials and Methods: twenty-seven TB patients (18 men and 9 women), with the mean (\pm SD) age of 37.3 ± 13.9 yrs. and 23 patients affected by malignant tumors (16 men and 7 women) with the mean (\pm SD) age of 57.9 ± 17.7 yrs. were evaluated during 2004-2005. In malignant cases, diagnosis was made through microscopic inspection of the biopsy samples and cytology of pleural fluid. For recognition of tuberculosis, culture and smear of sputum or gastric lavage, biopsy of pleura and pleural fluid and PCR methods were used. Pleural fluid samples were collected and the amount of their CA-125 was measured by CLIA method. The cut-off value of CA-125 was obtained from a ROC curve.

Results: The mean (\pm SD) level of CA-125 in pleural fluid was 159.1 ± 214 , and 2149.2 ± 4513.6 U/ml in tuberculosis and malignancies, respectively; which showed a statistically significant difference between the two groups ($p < 0.01$).

Conclusion: CA-125 marker levels in pleural effusion may be used as a diagnostic index for differentiation of TB and malignancy induced pleural effusions. (*Tanaffos* 2005; 4(16):23-27)

Keywords: CA-125, Pleural effusion, Tuberculosis, Malignancy

Abbreviations: SD: Standard Deviation; ROC: Receiver Operating Characteristic; KD: Kilo Dalton

INTRODUCTION

Pleural effusion may occur through an inflammatory process a non-inflammatory process. In cases in which pleural effusion occurs without inflammation, increase in hydrostatic pressure,

decrease in oncotic pressure and changes in lymphatic drainage play an important role. In non-inflammatory cases, pleural space contains little transudate fluid with small amounts of protein, LDH and few cells, which are mainly lymphocytes, macrophages and endothelial cells (1). However, in pleura, the cross reaction between the infectious

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organisms and the defensive cells and the secretion of cytokine and chemokine, results in changes in the permeability of veins. However, recognition of the underlying cause is not simple in some cases. It is essential to keep this fact in mind for an appropriate treatment approach (1). Accumulation process of pleural fluid in tuberculosis is somewhat mild and chronic, just as in malignancy. This similarity, makes the cause of pleural effusion in TB or malignancy difficult to detect; whereas, knowing the underlying cause of pleural effusion (TB or malignancy) is important with regard to different treatments. Despite several parameters to distinguish these two from each other, none have a high sensitivity or specificity value. Therefore, distinguishing the reasons of pleural effusion in tuberculosis and malignant cases, plays an important role in patients' treatments (1).

CA-125 is a 200 KD glycoprotein, which exists on the surface of ovarian, and some inflammatory and non-inflammatory cells. Proliferation of these cells causes this antigen to be released in serum. CA-125 was first known as a specific tumor marker of the ovary but gradually it was found that inflammation even without polymorphism (the early stage of pregnancy, menstrual cycle, PID, and endometriosis) causes this tumor marker to increase. Later it was revealed that tuberculosis in various sites of body cause increase in serum Antigen level (2, 3, 4).

Increased serum CA-125 level in both malignancy and tuberculosis, caused some limitations in the use of this tumor marker in a way that the role of CA-125 was decreased as an acute phase reactor and a factor for observing the response to treatments (5, 6).

This study was performed in order to determine an appropriate range of CA-125 in pleural fluid of patients affected by pleural effusion, in tuberculosis and malignancies, so that this tumor marker could be used not only as an index of monitoring therapy but also as a diagnostic index.

MATERIALS AND METHODS

A cross-sectional and diagnostic study was performed in Shaheed Beheshti University hospitals (Tehran, Iran) including Loghman Hakim, Labbafinejad and Masih Daneshvari, during 2004-2005.

In this regard, after getting permission from the authorities of the afore-mentioned hospitals, the study was performed on patients affected by pleural effusion, due to either tuberculosis or malignancy.

Non-tuberculosis infectious cases and benign causes of pleural effusion like heart failure were excluded from the study.

In malignant cases, diagnosis was made through microscopic inspection of biopsy samples and cytology of pleural fluid. For recognition of tuberculosis, culture and smear of sputum or gastric lavage, biopsy of pleura and pleural fluid and PCR methods were used. After getting consent from patients and recording their data, pleural fluid samples were collected to be evaluated. Then by CLIA method, the amount of CA-125 in pleural fluid samples was measured in Masoud laboratory (clinical lab in Tehran, Iran).

SPSS ver.11.5 software was used for statistical analysis. To compare the CA-125 variable in both groups, (as there was no normal distribution), Mann whitney U test was used and p-values<0.05 were considered to be statistically significant.

In order to determine an appropriate cut off point for recognizing tuberculosis cases from malignant ones, the ROC curve was used.

RESULTS

27 TB patients (18 men and 9 women), with the mean (\pm SD) age of 37.3 ± 13.9 yrs. and 23 patients with malignant tumor (16 men and 7 women) with the mean (\pm SD) age of 57.9 ± 17.7 yrs. were

enrolled in this study.

Among patients with malignancy, 18 cases had lung malignancy (%78.3), one case had an abdominal tumor (%4.3), one case had an ovarian tumor (%4.3), one case had lymphoma (%4.3) and one case had osteosarcoma that had metastasized to the pleura (%4.3).

The mean (\pm SD) level of CA-125 in TB patients was measured as 159.1 ± 214 and for malignant tumors was 2149.2 ± 4513.6 units per ml (table 1).

Table 1. Comparisons of sex, age and lab data of TB and malignant cases

	Tuberculosis cases	Malignant cases
	Male=18	Male=16
		Lung malignancy= 18 case (%78.3)
		Stomach malignancy= 1 case (%4.3)
Number of cases	27	23
		Ovarian tumor= 1 case (%4.3)
	Female=9	Female=7
		Lymphoma= 1 case (%4.3)
		Osteosarcoma= 1 case (%4.3)
Mean age (\pm SD)	37.3 \pm 13.9	57.9 \pm 17.7
Mean level of CA-125 (\pm SD)	159.1 \pm 214	2149.2 \pm 4513.6

By using Mann-Whitney U test, (as the distribution was not normal), a remarkable difference was found between the two groups ($P < 0.01$). The average rate of CA-125 in patients with tuberculosis and malignant tumors was 16.6 and 36 respectively and their sum was 47. Applying the ROC curve, the most appropriate cut off point for the amount of CA-125 for recognizing tuberculosis from malignant cases was calculated to be 221/5-253/5 units per ml (Fig-1).

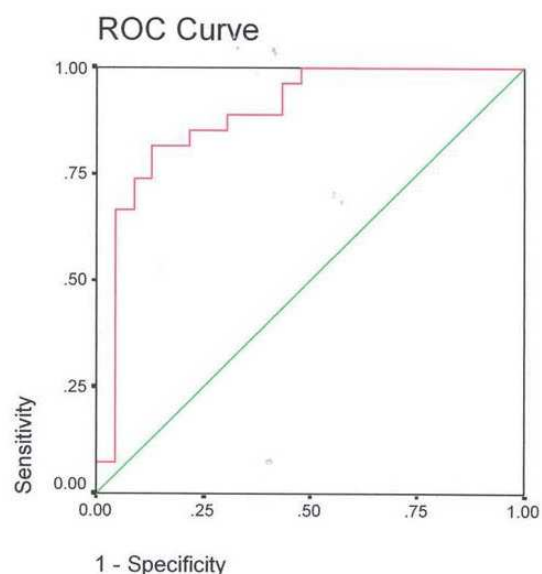


Figure 1. ROC curve related to the quantities of CA-125 in patients affected by malignant pleural effusion and tuberculosis (Shaheed Beheshti University –Tehran,Iran)

DISCUSSION

We found the amount of CA-125 in pleural fluid of patients affected by pleural effusion secondary to malignancy to be distinctly higher than the amount of this tumor marker in pleural fluid of those affected with tuberculosis.

Based on our results, an appropriate range that may help distinguish tuberculosis from malignant cases, was determined to be 221.5-253.5. Pleural fluid CA-125 higher than this range would be malignancy, and with the lower amounts, TB.

This type of approach to patients affected by pleural effusion with an unidentified and unclassical history is very useful because the chronic nature of this disease, whether malignant cases or tuberculosis makes it very difficult to distinguish these two from each other requiring costly tests which may be avoided by using this method (7).

Another point is that these findings have caused a change in the validity of this index, because regarding the various causes that lead to increase in

the amount of CA-125, the usage of this tumor marker is restricted to apply it just as a monitoring therapy index (5, 6). Thakur and his colleagues mentioned that abdominal and peritoneum tuberculosis can result in an increase in the amount of serum CA-125, which can be reduced by using the right treatment approach. Therefore, the rate of response to treatment can be defined according to this index (8).

Study results suggest that serum CA-125 levels in patients with tuberculous peritonitis are as high as ovarian cancers associated with peritoneal infiltration (3, 9, 10, 11).

They also suggest that serum CA-125 can be used to evaluate the efficacy of therapy in tuberculous peritonitis (3, 12).

However, Hirose and his colleagues reported a case of tuberculous pleuritis in which the level of serum CA-125 was 1150 units per ml (13). They showed that pleural cells were covered with antibodies against CA-125 and it was revealed that CA-125 originated from pleural cells and for secretion of CA-125 malignant morphologic changes in the cells are not necessary. The amount of CA-125 in both infection (TB) and malignant cases increases and can be a useful diagnostic guide.

Although CA-125 was mentioned as the most available tumor marker in our study, Hamamoto and his colleagues revealed that CA-125 is the only marker that increases remarkably in tuberculosis and the increase in the amounts of NSE, SLX, TPA, and CEA is not significant (14).

Aoki and his colleagues compared the amounts of ADA in pleural fluid, CA-125 in serum, and pleural fluid gamma interferon in 11 cases of TB pleurisy and 28 non-tuberculosis cases and stated that the amounts of pleural fluid ADA and serum CA-125 in two groups have a considerable overlap. However, the average in tuberculous pleuritis cases was higher compared with other infections (15).

Also, we insist that our study doesn't include patients with benign causes of pleural effusion such as infections or heart failure and is only inclusive of tuberculosis and malignant cases.

In studying the amounts of SLX, CA-125 and CEA in serum, Ichiki and his colleagues determined that in patients affected by pulmonary tuberculosis, these indices are as follows respectively: 16.9%, 39.5% and 44.4%. After treatment by anti-tuberculosis drugs, the mean amounts of CA-125 and SLX in serum decreased considerably (3, 12, 16).

In two patients who died due to respiratory failure, the amount of CA-125 did not change in serum after the treatment. Based on this result, the prognostic role of CA-125 was revealed (16).

Also, Tomita clinically studied the histological distribution of CA-125 in patients affected by pleural effusion. In examining 51 patients affected by pleural effusion secondary to malignancy and 38 patients affected by benign effusion, they determined that the amount of CA-125 in malignant effusion is remarkably higher than the other cases. Also, CA-125 in pleural effusion is produced by both malignant cells and active mesothelial cells (17). In fact, it can be mentioned that our study is a supplementary to theirs, because our study also revealed that the amount of CA-125 in malignant cases is higher than tuberculosis and an appropriate range for CA-125 in order to distinguish malignant cases from tuberculosis was defined.

In most of the previous studies, the amount of CA-125 was considered only in serum, whereas in this study we measured the amount of this tumor marker in pleural effusion. The other advantage of this study was to determine the cut off point for the amount of CA-125 by drawing the ROC curve. Based on this, the recognition ability of CA-125 in pleural fluid for distinction between tuberculosis and malignant cases was remarkably increased but beside these advantages the study contains a few samples

and this is revealed through the high variation of CA-125 results in malignant cases. Also in this study patients affected by different types of malignancy were evaluated (Primary or Secondary). Another limitation of this study was absence of a gold standard for recognizing tuberculosis and its various recognition methods.

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