A study of CA-125 in patients with pleural effusion

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Background A significant concern of physicians treating patients with pleural effusion is to rule out a malignant etiology, which, in the majority of series, is the first cause of pleural exudates. Determination of tumor markers in serum and pleural fluid has been proposed as a nonaggressive means of establishing a diagnosis of pleural malignancy. Cancer antigen 125 (CA-125) is not a specific tumor marker and it is synthesized by normal and malignant cells of different origins. Recently, it has been shown that various diseases are associated with increased CA-125 levels, especially in the presence of serosal fluid.

Aim The aim of this study was to determine the level of serum and pleural fluid CA-125 to evaluate its value as a marker for differentiation between different types of pleural effusion.

Patients and methods The study was carried out on 30 patients with pleural effusion of different etiologies. They were further subdivided into two groups: exudates and transudates; the levels of both serum and pleural fluid CA-125 were evaluated.

Results In terms of pleural CA-125, there was a statistically significant increase in the exudative subgroup compared with transudative subgroup. Furthermore, it was found that malignant effusion was observed more frequently compared with benign effusion and tuberculosis was observed more frequently in comparison with other infections.

Conclusion The highest level of pleural fluid CA-125 was found in malignancy, followed by tuberculosis, and so pleural fluid CA-125 can be used as a marker for the diagnosis of pleural effusion. *Egypt J Broncho* 2015 9:283–286

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Introduction

Undiagnosed pleural effusions are a major clinical problem; thus, scientists spend considerable effort and time seeking a new parameter to aid the diagnosis of etiology of different types of pleural effusions [1]. In some pleural effusions, the cause might be obvious, such as pleural effusions associated with congestive heart failure or liver cell failure. In other cases, the cause of pleural effusions might not be obvious, necessitating extensive diagnostic procedures in an attempt to identify the cause of effusion [2].

CA-125 (cancer antigen 125 or carbohydrate antigen 125), also known as mucin 16 or MUC16, is a protein that is encoded by the *MUC16* gene in humans [3]. CA-125 is a 200 kDa glycoprotein that exists on the surface of ovarian and some inflammatory and noninflammatory cells. Proliferation of these cells causes this antigen to be released in the serum. CA-125 was first known to a specific tumor marker of the ovary, but gradually, it was found that inflammation even without polymorphism (the early stage of pregnancy, menstrual cycle, and endometriosis) causes this tumor marker to increase. Later, it was found that tuberculosis in various sites of body also causes an increase in serum antigen level [4].

The aim of the present study is to determine the level of serum and pleural fluid CA-125 to evaluate its value as a marker for differentiation between different types of pleural effusion.

Patients and methods

The present study was carried out on 30 patients admitted to Chest Department, Kasr El-Aini Hospital, during the period between August 2011 and October 2012 with pleural effusion of different etiologies. Written informed consent was obtained from all the participants before the study.

All patients were subjected basically to a full assessment of history, thorough clinical examination, routine laboratory investigations, plain chest radiography (posteroanterior and lateral views), and thoracentesis. Medical thoracoscopy was carried out for cases with undiagnosed exudative pleural effusion. The pleural fluid obtained was examined for the following: gross appearance and nature of the fluid, total protein (g/dl) was measured on a Synchron CX5 Autoanalyzer (Chemical analyzer, manufacturer: Beckman coulter), lactate dehydrogenase enzyme was measured in IU/l, adenosine deaminase enzyme was measured in IU/l, total and differential cell count of the pleural fluid, bacteriological examination by culture, sensitivity, and Ziehl–Neelsen stain for acid-fast bacilli, and cytological examination for malignant cells. Levels of CA-125 were measured in U/ml using the

commercially available ELISA kit (catalog number: EK-310-13; Phoenix Pharmaceuticals, Chemical analyzer, manufacturer: Beckman coulter) in pleural fluid. Venous blood samples were obtained simultaneously to measure protein, glucose, lactate dehydrogenase enzyme, adenosine deaminase enzyme, and CA-125. The CA-125 ELISA test is based on the principle of a solid-phase enzyme-linked immunosorbent assay. The assay system utilizes a monoclonal antibody directed against a distinct antigenic determinant on the intact CA-125 molecule that is used for solid-phase immobilization (on the microtiter wells).

Results

Table 1 shows that more than 63% of the studied cases were men, average age 51 years (Table 2).

Table 3 shows no statistically significant difference between the subgroups studied in serum CA-125 using the Kruskal–Wallis test.

Table 1 Distribution of the studied group in terms of general data

Variables	*N* (%)
Age	
<30	4 (13.3)
31–50	10 (33.3)
>51	16 (53.3)
Mean ± SD	51 ± 11 (25–67)
Sex	
Male	19 (63.3)
Female	11 (36.7)

Table 2 Distribution of the studied group in etiology

Variables	*N* (%)
Exudates	
Mesothelioma	6 (20)
Adenocarcinoma	1 (3.3)
Para pneumonic	5 (16.7)
Pleural metastasis	1 (3.3)
Empyema	3 (10)
TB	5 (16.7)
Transudate	
Chronic liver disease	7 (23.3)
Heart failure	2 (6.7)

TB, tuberculosis.

Table 3 Comparison between etiology in serum CA-125 among the group studied

Variables	Serum CA-125		*P*
	Mean	SD	
Exudates			
Malignancy	159	29	>0.0 (NS)
Parapneumonic and empyema	63	40	
TB	51.6	20	
Transudate			
Chronic liver disease	45.7	21	
HF	48.6	20	

HF, heart failure; TB, tuberculosis.

Table 4 shows that the malignancy group had higher pleural fluid CA-125 compared with the other subgroups, with a statistically significant difference between the subgroups studied using the Kruskal–Wallis test.

Table 5 shows no statistically significant difference between the subgroups studied using the Mann–Whitney test.

Table 6 shows that CA-125 is considered more sensitive than specific in detection of exudates due to malignant lesions.

Table 7 shows that pleural CA-125 is considered better positive than negative in detection of exudates due to TB, while serum better negative than positive.

Figure 1 shows that CA-125 is considered more sensitive than specific in the detection of exudates because of malignant lesions.

Figure 2 shows that pleural CA-125 is considered better positive than negative (more specific) in the detection

Table 4 Comparison between etiology in pleural fluid CA-125 among the studied group

Variables	Pleural fluid CA-125		*P*
	Mean	SD	
Exudates			
Malignancy	1482	540	<0.001 (HS)
Parapneumonic and empyema	59.5	30	
TB	597	320	
Transudate			
Chronic liver disease	70	39	
HF	73	20	

HF, heart failure; HS, highly significant; TB, tuberculosis.

Table 5 Comparison between transudate and exudate in serum CA-125

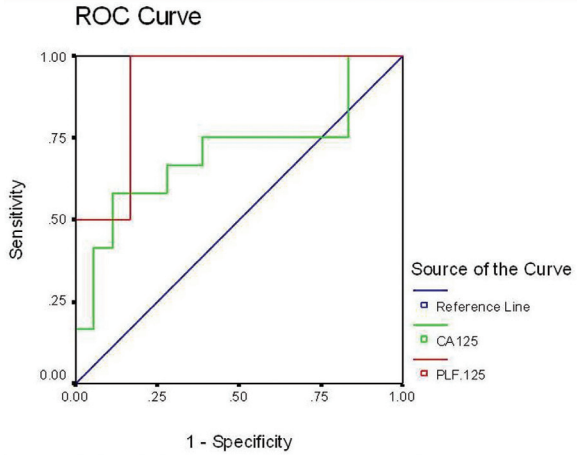
Variables	Serum CA-125		*Z*	*P*
	Mean	SD		
Exudate	111	60	1	<0.05 (NS)
Transudate	44.4	20		

Table 6 Validity of CA-125 in the prediction of pathology of pleural fluid (benign or malignant)

Variables	Serum CA-125	Pleural CA-125
Best cut-off	150	700
AUC (%)	75	90
Sensitivity (%)	79	94
Specificity (%)	68	87
PPV (%)	73	95
NPV (%)	77	93

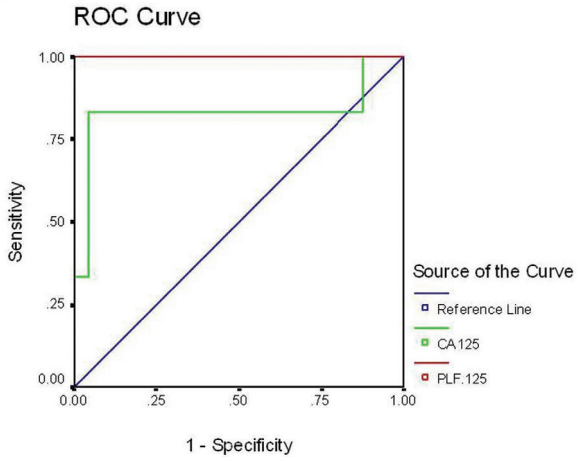
AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

Fig. 1



ROC curve of CA-125 in exudates due to malignant lesions.

Fig. 2



ROC curve of CA-125 (pleural and serum) in exudates due to tuberculosis.

Table 7 Validity of CA-125 in the prediction of pathology of pleural fluid tuberculosis versus other

Variables	Serum CA-125	Pleural CA-125
Best cut-off	100	600
AUC (%)	0.83	0.99
Sensitivity (%)	84	99
Specificity (%)	96	78
PPV (%)	78	99
NPV (%)	97	89

AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

of exudates because of tuberculosis, whereas serum CA-125 is better negative than positive (more sensitive).

Discussion

In practice, the cause of pleural effusions might not be obvious, necessitating extensive diagnostic procedures in an attempt to identify the cause of effusion [2]. Pleural fluid cytology and blind pleural biopsy are the methods used most commonly, but are inadequate procedures for the diagnosis. In some studies, blind pleural biopsy has been reported to be inadequate in up to 40% of the patients [5].

This situation indicates the need for a different method with a focus on pleural fluid. Certain molecular markers, if proven to be sensitive and specific enough, can help the physician decide whether the patient should undergo further investigation or not to diagnose a suspected malignancy; that is, open pleural biopsy (VATS, minithoracotomy) or not. Among these biomarkers, insulin growth factor, hepatocyte growth factor, and Simian virus-40 have been proven to play an important role in the development and progression of malignant mesothelioma [6].

The present study was carried out on 30 patients with pleural effusion of different etiologies, admitted to Chest Department, Kasr El-Aini Hospital, during the period from August 2011 to October 2012. There were 19 men and 11 women ranging in age from 29 to 67 years.

The etiology of pleural effusion was established. The effusions were classified as transudates and exudates considering the underlying etiology. The patients were classified into two groups according to the type of effusion, whether transudate (30%) or exudates (70%).

For pleural CA-125, there was a statistically significant difference between the subgroups studied (transudates and exudates) in its value. Also, it was found that in malignant effusion, the value was higher than that in benign effusion; in addition, it was also higher in tuberculosis in comparison with other infections.

In our study, patients with transudative effusions had a mean serum CA-125 level of 44.4 U/dl as shown in Table 5, whereas in the study carried out by How *et al.* [7], 76.9% of patients with transudative effusions had elevated serum CA-125 reaching 291 U/dl, suggesting that the insult to the pleural mesothelial cells is probably not related to inflammation.

Tables 3 and 4 shows that the level of pleural CA-125 in different etiologies is higher than the serum level, except in pneumonia and parapneumonic effusion, and this is also the same as the result of the study carried out by How *et al.* [7] and Kalantri *et al.* [8]; this means that there is some sort of CA-125 reabsorption from the pleural fluid into the serum.

Shokouhi *et al.* [4] showed that the amount of CA-125 in the pleural fluid of patients affected by pleural

effusion secondary to malignancy was higher than the number of tumor markers in the pleural fluid of those affected with tuberculosis; that is, in malignancy, the mean ± SD CA-125 was 2149 ± 4513.6 U/ml, whereas in tuberculosis, the mean ± SD CA-125 was 159.1 ± 214, and this was the same in our study as shown in Table 4 as the mean ± SD CA-125 in malignancy was 1482 ± 540 compared with a mean ± SD of CA-125 of 597 ± 320 in tuberculosis.

Aoki *et al*. [9] compared the amounts of CA-125 in the serum of 11 cases of tuberculous pleurisy and 28 nontuberculosis cases and reported that the average in tuberculous pleuritis cases was higher than that of other infections. In contrast, our study showed that serum CA-125 was lower in tuberculosis than that in other nontuberculous infections as shown in Table 3.

Also, Tomita [10] 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 markedly higher than benign cases; this means that CA-125 in pleural effusion is produced by both malignant cells and active mesothelial cells. Our study also showed that both serum and pleural fluid CA-125 are higher in patients with malignant effusion than those with benign effusion as shown in Tables 3 and 4.

Ferrer *et al*. [11] showed in their study that in the group proved to have malignant effusion, pleural fluid CA-125 was higher than serum CA-125, and the same result was fund in our study as shown in Tables 3 and 4, suggesting pleural production of the tumor marker than passive diffusion from serum. This is in agreement with previous studies that mesothelial cells express CA-125.

Table 6 shows that serum and pleural CA-125 were more sensitive than specific in the detection of malignant pleural effusion. Also, in Table 7, pleural CA-125 was more sensitive than specific in the detection of tuberculous pleural effusion. To our knowledge, there have been no comparable studies in terms of these results.

The exact origin of CA-125 in patients with ascites and pleural effusion has not been defined as yet, but there are three theories: Kabawat *et al*. [12] detected CA-125 in all kinds of celomic epithelium derived from the same origin as pericardium, pleura, and mesothelial cells lining the peritoneum. Mezger *et al*. [13] defined CA-125 as a strong immunohistochemical marker in mesothelial cell proliferation. Mezger *et al*. [14] and Molina *et al*. [15] suggested that CA-125 may be synthesized from peritoneal epithelial cells as a response to mechanic distress because of ascites and then diffuse to serum.

In conclusion, the highest level of pleural fluid CA-125 was found in malignancy, followed by tuberculosis. The differential diagnosis of effusions might be further improved by including CA-125 concentrations in the diagnostic armamentarium available to the clinician.

Acknowledgements

Conflicts of interest

None declared.

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