A Study of Cancer Antigen-125 as a Diagnostic Marker in Tuberculous and Malignant Pleural Effusion

Abstract

Background: Cancer Antigen-125 (CA-125) was first identified as an ovary-specific tumor indicator but subsequently shown that inflammation exists even in the absence of polymorphism leads to this marker to rise. Multiple locations of tuberculosis (TB) produce an increase in serum antigen levels. This research objects to estimate the diagnostic value of CA-125 and to establish the cut-off value, distinguishing tuberculous from malignant pleural effusion.

Methods: This prospective analytic case control study involved 90 subjects above 18 years old and with a confirmed diagnosis of tuberculous pleural effusion (TPE), malignant pleural effusion (MPE) and parapneumonic effusion (PPE). Subjects were equally allocated into 3 groups: group I "Tuberculous": subjects with a confirmed diagnosis of TPE, group II "Malignant": subjects with a confirmed diagnosis of MPE and group III " Control": subjects with a confirmed diagnosis of PPE.

Results: There was positive significant correlation among CA-125 in serum and pleural fluid in tuberculous effusion group (group I) and in malignant effusion group (group II).

Conclusions: For reliable detection of pleural effusion cause, serum and pleural fluid CA-125 might be included to the pleural fluid diagnostic workup.

Keywords: Cancer antigen-125, Tuberculous, MPE

Introduction:

Pleural effusion is the buildup of fluid inside the pleural cavity as a consequence of a systemic or intrathoracic method. This pathological entity is a common issue in pulmonology, and the occurrence differs depending on the patient's clinical history. Congestive heart failure, pneumonia and malignant processes account for 90% of all pleural effusions. [1].

The primary concerns involving pleural effusions are the distinction between exudates and transudates and the correct diagnosis of effusion cause. To distinguish between exudates and transudates, many biochemical characteristics must be evaluated and compared in pleural fluid and serum. As distinguishing transudates from exudates utilizing traditional Light's characteristic, it is advantageous to identify the pathogenic process causing the pleural effusion. Identifying the proper pathogenic process is as well helpful for differential assessment [2].

Cancer Antigen-125 (CA-125) is a glycoprotein of 200 KD which resides on ovary surface, inflammatory and non-inflammatory cells. The cells proliferation results in the release of this antigen into the blood. CA-125 was identified firstly as an ovary-specific tumor indicator but subsequently shown that inflammation exists even in the absence of polymorphism leads to this tumor indicator to rise. Eventually, it was shown that tuberculosis (TB) at different body locations causes a rise in serum antigen concentration [3-5]. Raised blood CA-125 levels in malignancy and TB led to some limits utilizing this tumour biomarker, since CA-125's significance as an acute stage reactor and a factor for monitoring therapy efficacy was diminished [6, 7].

This research objects to evaluate the diagnostic value of CA-125 and to determine the cut-off value, distinguishing tuberculous from malignant pleural effusion.

Patients and Methods:

This prospective analytic case control research involved 90 subjects above 18 years old with a confirmed diagnosis of tuberculous pleural effusion (TPE), malignant pleural effusion (MPE) and parapneumonic effusion (PPE) in Chest Department, Tanta University Hospitals and Tanta Chest Hospital.

Exclusion criteria were subjects with hepatic cirrhosis, heart failure, or any other non-infectious diseases, female patients with endometriosis and pregnancy and age less than 18 years.

Subjects were equally allocated into 3 groups: group I "Tuberculous": subjects with a confirmed diagnosis of TPE, group II "Malignant": subjects with a confirmed diagnosis of MPE and group III " Control": subjects with a confirmed diagnosis of PPE.

All subjects underwent CA-125 measured in both serum and pleural fluid using ELISA kit.

CA 125 ELISA

The CA-125 ELISA-kit is a sandwich-based, solid-phase ELISA. Coating the microtiter wells with a monoclonal [mouse] antibody directed against a particular antigenic location of the CA-125 molecule. An enzyme conjugate consisting of a monoclonal anti-CA-125 antibody coupled with horseradish peroxidase was treated with a patient sample containing endogenous CA-125.

Statistical analysis

SPSS v26 was applied to do statistical analysis (IBM Inc., Chicago, IL, USA). Quantitative variables were described as mean and standard deviation (SD) and compared between the two groups by ANOVA (F) test. When applicable, qualitative variables were described as frequency and percentage (%) and analysed by Chi-square test or Fisher's exact test. Linear Correlation and ROC-curve (study of the receiver operating characteristic curve) were applied. A two-tailed P value ≤ 0.05 was described as a statistically significant.

Results:

Age was significantly increased in group II than group III (P3 = 0.009) with no significant variance among groups I and II or groups I and III. Sex was insignificantly variance among the three studied groups. Table 1

Table 1: Age and sex in the three studied groups

		Group I	Group II	Group III	P. value		
Age		54.60 ± 14.79	60.80 ± 15.84	51.13 ± 11.17	0.031*	**P1**	0.092
						P2	0.343
						P3	0.009*
Sex	**Male (%)**	22 (73.3%)	16 (53.3%)	20 (66.7%)	0.257	**P1**	0.107
	Female (%)	8 (26.7%)	14 (46.7%)	10 (33.3%)		**P2**	0.573
						P3	0.292

Data are presented as mean ± SD or frequency (%). P1: Group I & Group II; P2: Group I & Group III; P3: Group II & Group III, *: statistically significant as P value ≤ 0.05

X ray findings were significantly different in the three studied groups (P value= 0.001). TLC and CRP were significantly increased in group III than groups I and II (P2=0.024, P3=0.011, P2 = 0.001, P3 = 0.001 respectively) with no significant variance among groups I and II. ESR was significantly increased in group I than group II and III (P1=0.001 and P2=0.001 respectively) with no significant variance among groups II and III. Table 2

Table 2: X ray and routine laboratory findings in the three studied groups

		Group I (N=30)	Group II (N=30)	Group III (N=30)	P-value
X ray findings	**Unilateral obliteration of costophrenic angle rising to axilla**	9 (30%)	9 (30%)	19 (63.3%)	0.001*
	Unilateral upper lobe infiltration + unilateral obliteration of costophrenic angle rising to axilla	17 (56.7%)	0 (0%)	0 (0%)	
	Unilateral upper lobe cavitary lesion + unilateral obliteration of costophrenic angle rising to axilla	4 (13.3%)	0 (0)	0 (0%)	

	Unilateral well defined opacity + unilateral obliteration of costophrenic angle rising to axilla	0 (0%)	10 (33.3%)	0 (0%)	
	Bilateral multiple opacities + unilateral obliteration of costophrenic angle rising to axilla	0 (0%)	11 (36.7%)	0 (0%)	
	Unilateral consolidation with air bronchogram + unilateral obliteration of costophrenic angle rising to axilla	0 (0%)	0 (0%)	11 (36.7%)	
Laboratory findings	**TLC (mm^3)**	8386.67 ± 2081.73	8153.33 ± 3656.05	10160.00 ± 3020.57	0.021* P1= 0.763 P2= 0.024* P3= 0.011*
	ESR (mm/h)	108.67 ± 21.29	17.07 ± 18.23	42.33 ± 17.99	0.001* P1= 0.001* P2= 0.001* P3= 0.372*
	CRP (mg/L)	15.33 ± 11.86	11.67 ± 14.35	112.93 ± 70.81	0.001* P1= 0.738 P2= 0.001* P3= 0.001*

Data are presented as mean ± SD or frequency (%). P1: Group I & Group II; P2: Group I & Group III; P3: Group II & Group III, TLC: total leucocytic count, ESR: Erythrocyte Sedimentation Rate, CRP: C-reactive protein, *: statistically significant as P value ≤ 0.05

Positive tuberculin test and turbid yellow appearance were significantly increased in group I than group II and group III (P value <0.05). Cloudy appearance, growth of culture and sensitivity of pleural fluid were significantly increased in group III than group I and group II (P value= 0.001). Bloody turbid appearance, serum CA-125 and pleural CA-125 were significantly increased in group II than group I and group III (P value <0.05). Serum CA-125 and pleural CA-125 were significantly increased in group I than group III (P2 <0.05). Table 3

Table 3: Comparison between the three studied groups as regard to Tuberculin test, gross appearance, culture and sensitivity of pleural fluid, serum levels of CA125 and Pleural CA-125 U/ml

		Group I	**Group II**	**Group III**	**P-value**
Tuberculin test	**+ve**	18 (60.0%)	10 (33.3%)	8 (26.7%)	**0.020***

	-ve	12 (40.0%)	20 (66.7%)	22 (73.3%)	
Gross appearance	**Cloudy**	0 (0%)	0 (0%)	6 (20.0%)	**0.001***
	Turbid yellow	22 (73.3%)	8 (26.7%)	18 (60.0%)	
	Bloody turbid	8 (26.7%)	22 (73.3%)	6 (20.0%)	
Culture and sensitivity of pleural fluid	**Growth**	0 (0%)	0 (0%)	26 (86.7%)	**0.001***
	No growth	30 (100%)	30 (100%)	4 (13.3%)	
Serum CA-125 U/ml		120.07 ± 112.77	363.67 ± 221.40	29.40± 19.32	0.001* P1= 0.001* P2= 0.017* P3= 0.001*
Pleural CA-125 U/ml		138.83 ± 149.43	780.87 ± 427.27	44.83 ± 29.02	0.001* P1= 0.001* P2= 0.034* P3= 0.001*

Data are presented as mean ± SD or frequency (%). P1: Group I & Group II; P2: Group I & Group III; P3: Group II & Group III, CA: cancer antigen, *: statistically significant as P value ≤ 0.05

Specific gravity and pleural fluid protein / serum protein ratio were insignificantly different in the three studied groups. PH was significantly decreased in group I than group II (P1=0.001), and in group III than groups I and II (P <0.05). Protein and LDH were significantly increased in groups II and III than group I (P <0.05) with no significant difference among groups II and III. Glucose was significantly increased in groups I and II than group III (P <0.05) with no significant variance among groups I and II. Pleural fluid LDH /serum LDH ratio was significantly increased in group II than groups I and III (P1 <0.05) and in group III than group I (P2=0.001). ADA was significantly increased in group I than groups II and III (P <0.05) with no significant difference among group II and III. Table 4

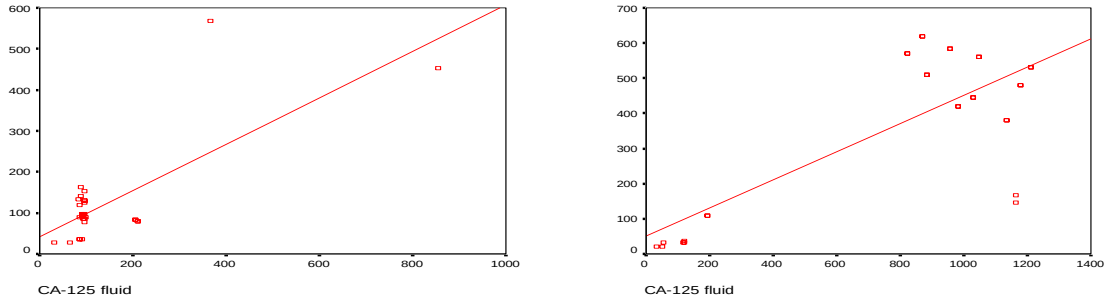
Table 4: Thoracentesis parameters in the three studied groups

		Mean ± S. D	**P. value**		
Specific gravity	**Group I**	1026.80 ± 7.68	0.909	P1	0.706
	Group II	1027.53 ± 7.18		P2	0.708
	Group III	1027.53 ± 7.64		P3	0.999
PH	**Group I**	7.17 ± 0.06	0.001*	P1	0.001*
	Group II	7.39 ± 0.06		P2	0.001*
	Group III	7.02 ± 0.14		P3	0.001*
Protein (mg/dl)	**Group I**	4.06 ± 0.63	0.018*	P1	0.022*
	Group II	4.62 ± 1.08		P2	0.009*

	Group III	4.70 ± 1.02		P3	0.753
Glucose (mg/dl)	**Group I**	44.00 ± 10.09	0.001*	P1	0.129
	Group II	40.80 ± 6.83		P2	0.001*
	Group III	27.27 ± 6.92		P3	0.001*
LDH (U/L)	**Group I**	510.07 ± 100.11	0.001*	P1	0.001*
	Group II	1251.13 ± 548.35		P2	0.001*
	Group III	1475.40 ± 639.01		P3	0.080
Pleural Ptn./S. Ptn.	**Group I**	0.71 ± 0.09	0.910	P1	0.776
	Group II	0.70 ± 0.09		P2	0.670
	Group III	0.70 ± 0.09		P3	0.887
Pleural LDH/S. LDH	**Group I**	0.95 ± 0.21	0.001*	P1	0.001*
	Group II	1.91 ± 0.49		P2	0.001*
	Group III	1.60 ± 0.57		P3	0.009*
ADA (U/L)	**Group I**	60.80 ± 9.66	0.001*	P1	0.001*
	Group II	17.37 ± 9.77		P2	0.001*
	Group III	21.57 ± 13.91		P3	0.1543

Data are presented as mean ± SD or frequency (%). P1: Group I & Group II; P2: Group I & Group III; P3: Group II & Group III, LDH: lactate dehydrogenase; Ptn: protein; S: serum, ADA: adenosine deaminase, *: statistically significant as P value ≤ 0.05

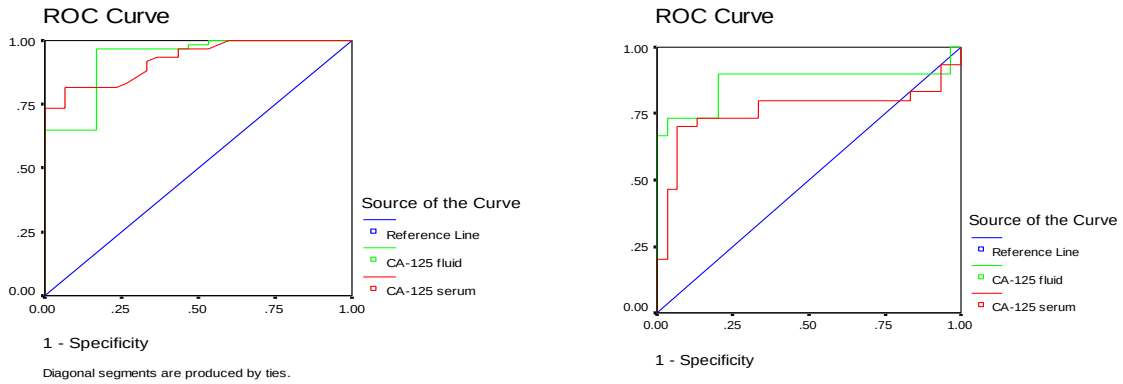
There was a significant positive correlation among CA-125 in serum and pleural fluid in group I and in group II. Figure 1



(A) **(B)**

Figure 1: Positive significant correlation between CA-125 in serum and pleural fluid in (A) tuberculous effusion group (group I) and (B) malignant effusion group (group II)

Regarding (group I and group II) and group III, CA125 in pleural fluid, at the cut off value of 45 the sensitivity was 93% and the specificity was 83%. While CA125 in serum, at the cut off value of 40 the sensitivity was 82% and the specificity was 77%. Regarding group I and group II, CA125 in pleural fluid, at the cut off value of 110 the sensitivity was 90% and the specificity was 80%. While CA125 in serum, at the cut off value of 100 the sensitivity was 73% and the specificity was 67%. Figure 2



(A) **(B)**

Figure 2: Roc curve show sensitivity and specificity of CA125 in pleural fluid and serum between cases of (A)[Group I & Group II] and Group III and (B) [Group I & Group II]

Discussion

In our work, ADA (U/L) was significantly increased in group I than group II and III, with no significant variance among group II and III.

In the same way, in Lee et al. [10], pleural fluid ADA concentrations were significantly different among TPE and PPE groups.

In our study, serum levels of CA-125 (U/ml) was significantly increased in group II than groups I and III, and in group I than group III.

In contrast, Zhai et al. [11] found that, the concentration of serum CA-125 in MPE cases was not significantly higher than those in benign pleural effusion (BPE) ones.

Similarly, Mohammad et al. [12] reported that, there was a significant variance in CA-125 serum level among the studied groups. The serum level of CA-125 was significantly increased in group I.

In our research regarding CA-125 between cases of (group I and group II) and group III in serum at the cut off value of 40; the sensitivity, specificity, positive and negative predictive values and diagnostic accuracy were 82%, 77%, 88%, 68%, 80%.

While regarding CA-125 between cases of (group I and group II) in serum at the cut off value of 100; the sensitivity, specificity, positive and negative predictive values and diagnostic accuracy were 73%, 67%, 69%, 71%, 70% respectively.

According to sensitivity of CA-125, in Mohammad et al. [12], at a CA-125 serum level of 21.05 U/ml as a cut-off value, CA-125 had sensitivity, specificity, positive and negative predictive values and diagnostic accuracy of 82.5%, 72.5%, 77.3%,83.3% and 80.0% respectively.

Our data showed that pleural fluid levels of CA-125 (U/ml) was significantly increased in group II than groups I and III, and in group I than group III.

Also, in our study regarding CA-125 between cases of (group I and group II) and group III in pleural fluid at the cut off value of 45; the sensitivity, specificity, positive and negative predictive values and diagnostic accuracy were 93%, 83%, 92%, 86% and 90%.

While regarding CA-125 among cases of (group I and group II) in pleural fluid at the cut off value of 110; the sensitivity, specificity, positive and negative predictive values and diagnostic accuracy were 90%, 80%, 82%, 89% and 85% respectively.

Similarly, Santotoribio et al. [13], revealed that the pleural fluid concentrations of CA125 were significantly increased in MPE cases than in BPE ones.

Our data showed that correlations between CA-125 in serum and pleural fluid levels was highly positive significant in group II and in group I.

Only a handful of the studies addressing the level of tumour markers in serum and pleural fluid addressed the P/S ratio. In Gu et al. [14] study, they found that the pleural fluid/serum ratio of CA-125 was lower in TPE than in MPE.

Limitations: First, we obtained single center participants in our study. In addition, the sensitivity and specificity of CA-125 was not assessed in combination with other biomarkers.

Conclusions:

CA-125 concentrations in serum and pleural fluid might be utilized to differentiate between TB and malignancy-induced effusions. Additionally, CA-125 might be included to the diagnostic workup of pleural fluid in order to accurately diagnose malignant pleural effusion.

Ethical Approval and consent :

An informed written consent was obtained from all participants. The research was done after approval from the Ethical Committee Tanta University Hospitals.

Financial support and sponsorship: Nil

Conflict of Interest: Nil

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