Clinical Evaluation of the Levels of CEA,CA15-3 and Alpha-Feto Protein in Malignant and Benign Pleural Effusion

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Abstract

Background: Pleural effusion is a common clinical problem.

Objective: The aim of the study was to evaluate the diagnostic utility of Carcino embryonic antigen (CEA), CA 15- 3, and alpha-feto protein (AFP) as a tumor markers in serum and pleural effusion and evaluate the value of combining them as a diagnostic tools that are complementary to cytology in the diagnosis of malignancies .

Methods: Forty patients (18 malignant and 22 benign pleural effusion) were included in this study .The serum and effusion levels of CEA, CA 15 – 3 and AFP were measured using immunoradiometric assay

Results: from the 40 effusions studied 26 were exudates and 14 were transudates. The level of pleural effusions of CEA, CA 15 – 3 and AFP were increased above the cutoffs in 72.5%, 94.4 % and 5.5 % of tested samples with malignancies respectively.

A direct strong significant correlation between serum and pleural fluid CEA, CA 15 – 3 and AFP was noted.

Conclusion: Pleural effusion CEA is the most accurate marker for the diagnostic separation of malignant and benign. The combination of both CEA, CA 15 – 3 improves the sensitivity by up to 11 %.

AFP has no role in the process.

Key words: malignant Pleural effusions, tumor markers, CEA, CA 15 – 3, AFP

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Introduction

Etiological diagnosis of pleural effusion is still a common problem in clinical practice [1]. Since pleural fluid presenting in a patients does not necessarily indicate malignancy, it is important to differentiate the nature of the effusion in order to decide appropriate treatment. The positive cytological analysis of malignant pleural fluid is reported to be about 50 - 66 % in most series [2].

The application of needle biopsy and thoracoscopy may enhance the diagnostic sensitivity [3],the disadvantages of the procedures are painful, costly and invasive, with some risk to the morbidly ill patients.

To increase the diagnostic sensitivity in the malignant pleural effusion, several tumor-associated markers have been studied as a non-invasive test [4, 5].

Carcinoembryonic antigen (CEA) is the most commonly studied and used, with an accuracy in pleural fluid higher than that of other tumor markers [6, 7, 8]

Likewise, there have been few studies of CA 15 – 3 and alpha - fetoprotein (AFP) in pleural fluid [9, 10]

To our knowledge, the diagnostic value of combinations of CEA, CA 15 – 3 and AFP assays in pleural fluid has not been reported in literature. We therefore undertook this study with the following objectives:

1. To determine the diagnostic utility of CEA, CA 15 – 3 and AFP assays as a tumor markers in pleural fluid.
2. To investigate the value of combining CEA, CA 15 – 3 and AFP assays as a diagnostic aid in malignant pleural effusion.

Methods

This is a prospective case study for 6 months period, 40 patients were admitted to the pulmonary units of two hospitals; Al-Yarmook Teaching Hospital and Ibn – Al Nafees Teaching Hospital in Baghdad with the diagnosis of pleural effusion of different origin or etiology. There were 25 males and 15 females with a mean age of59.5±6.5years (range,50–76 years).

Pleural effusion diagnosis was based on the case history, physical examination, chest x-ray film, thoracentesis and ultrasound. Many patients needed bronchoscopy and CT scan of the chest. Effusion required pleural biopsy and cytological study to confirm malignancy.

A matching group of 20 normal healthy subject, 12 males and 8 females' age 50 – 75 years were selected as controls for serum investigations.

All pleural effusion samples were centrifuged

immediately to discard the cell pellet and stored at – 20 ^{0} C until the day of analysis.
Biochemical analysis include measurement of protein, LDH,
Albumin, bilirubin and uric acid in pleural effusion and serum.
Complete blood count, WBC differentiation count, General Urine Exam and other investigations according to the requirements.

The patients were placed into the following diagnostic groups after careful evaluation of all data and results at the end of hospitalization. Light's Criteria [11] used to establish the classification.
1- Transudates 14 patients
2- Exudates 26 patients

Table (1)
Diagnostic Categories of Patients with Transudative and Exudative Pleural Effusion.

	Diagnosis	**No. of patients**	**%**
Transudate	Congestive heart failure	10	25
	Chronic renal failure (with nephrotic syndrome)	4	10
	Malignancy (lung cancer)	18	
Exudate	Squamous cell carcinoma	14	45
	Small cell lung carcinoma	2	
	Adenocarcinoma	2	
	Tuberculosis	5	12.5
	Trauma	1	2.5
	Pneumonia	2	5

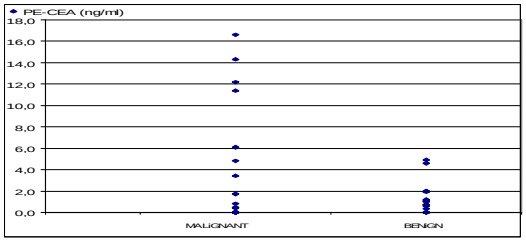
Marker Assessments
All markers were assayed in serum and pleural effusion using commercial immunoradiometric kits (Immunotech Kit ; Immunotech SA – 130 av, latter de- tassigny–B.P.177– 13276 marseille Cedex 9 France)
Assays were performed in duplicate according to the procedure recommended by the manufacturer.
Statistical Analysis:
All Statistical Analysis were using SPSS version 11.5 computer software (statistical packages for social Sciences) . The level of significance was determined by student's t-test between two groups. A probability of $p < 0.05$ was considered significant.
To obtain our own standard of judgments, we estimate the cut-off levels for each biochemical parameters as Mean + 1 SD of all values found in serum obtained from controls. For the effusion, we took mean + 1 SD of all values found in transudate [12] . Simple linear correlation and regression was used to measure the relationship between serum and pleural level of different carcinoma markers with regression equation ($y = a + bx$) and significant using t – test .

Results

From the 40 pleural effusion, 18 (45%) were due to malignancy and 22 (55 %) were due to benign causes. The mean pleural fluid CEA levels of the patients with lung cancer and other benign causes were 339.3 ± 70.1 and 4.1 ± 6.2 ng/ml respectively.
There were statistically significant differences in pleural fluid CEA levels between the groups of patients ($P < 0.03$) with the cut-off level of 3.0 ng/ ml pleural effusion, determination of pleural effusion CEA was diagnostic in 73% of patients with pleural malignant effusion

(Figure-1).

Levels of Pleural Effusion CEA in Malignant and Benign Groups.



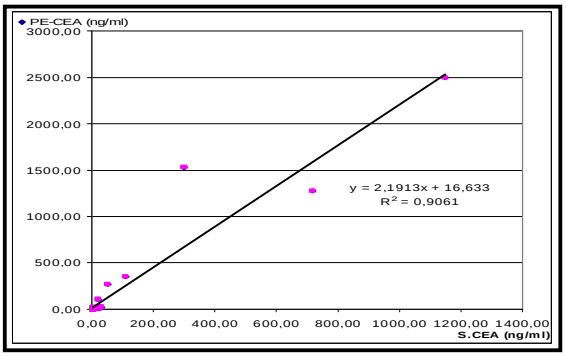
In this study, a recorded elevated level of pleural effusion CEA reach 2500 ng/ml was noted in a patient with lung cancer (sequamous cell carcinoma) who underwent radiotherapy.

There was a strong correlation between the elevated level of pleural effusion CEA and the staging of lung cancer in this patient.

In ***(Figure-2),*** there was a direct strong significant correlation between serum and pleural effusion CEA (r = + 0.9, P < 0.05).

(Figure-2)

Correlation between Serum and Pleural Effusion CEA.

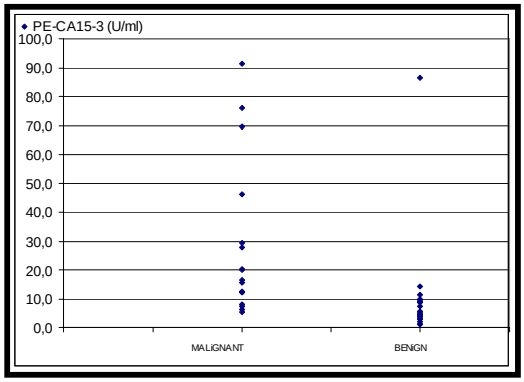


Simultaneous elevation in both serum and pleural CEA in 12/18 (66.6%) lung cancer patients, while there was a decline levels in both serum and pleural CEA in the other group. Overlap was noted.

The mean pleural fluid CA 15 – 3 levels of the patients with lung cancer and other benign causes were 27.1 ± 26.1 and 9.3 ± 17.5 U/ ml respectively. Significant difference was noted between malignant and benign levels of CA 15 – 3 (P<0.014) (***Figure-3)***.

(Figure 3:)

Levels of Pleural Effusion CA15-3 in Malignant and Benign Groups.

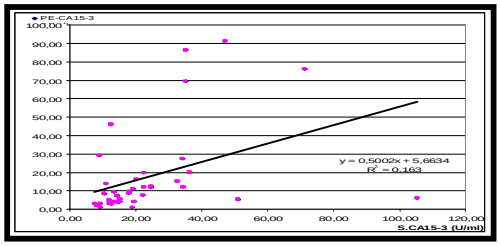


Using the cut –off value of 6.0.U/ml, pleural CA 13-5 was diagnostic in 94.4 % of patient with lung cancer. In ***(Figure-4),*** a direct weak significant correlation between serum and

pleural effusion CA 15 – 3 (r=+0.4, P <0.05) was noted. Simultaneous elevation in the level of serum and pleural CA 15-3 in 15/18 lung cut – off value showed no significant difference between malignant and benign (1.02 ± 1.1 and (0.76 ± 1.05 U/ml) respectively. cancer patients and overlap was noted. The Third tumor marker AFP, with 3.0 U/ml as a

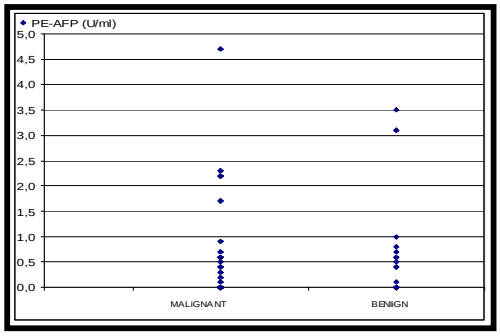
(Figure 4)

Correlation between Serum and Pleural Effusion CA15-3.



(Figure- 5)

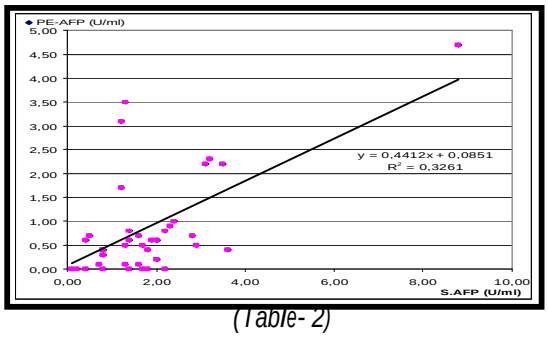
Levels of Pleural Effusion AFP in Malignant and Benign Groups



In ***(Figure- 6)*** a direct strong significant correlation between serum and pleural AFP (r = + 0.56 , P <0.05) and overlap was noted .

Figure 6

Correlation between serum and pleural effusion AFP



(Table- 2)

Number of cases misclassified in malignant and benign pleural effusion for tumor marker studied.

Tumor Markers	Malignant		Benign	
	n=18	%	n=22	%
Pleural CEA	5	27.7	7	31.8
Pleural CA15-3	1	5.5	8	36.3
Pleural AFP	17	94.4	3	13.6

Table (2) presented number of cases misclassified in malignant and benign pleural effusion for tumor markers studied combined assay of CEA, CA 15 – 3 and AFP improved sensitivity for detecting carcinomatous effusion.
Bilirubin and uric acid assays can serve to distinguish exudates from transudates, and considered as a desirable tests due to their reliability, cost and availability [13].

Discussion

Several workers have focused their attention on the diagnostic usefulness of the determination of pleural fluid tumor markers as a discriminating assay between benign and malignant pleural effusions [14].
Measurement of the effusion level of several tumor – associated markers has been proposed as a non-invasive method to increase the diagnostic sensitivity in malignant pleural effusion. [15] Unfortunately, considerable overlap was observed between benign and malignant pleural effusion in these assays. CEA was one of the first markers measured in patients with cancer [16].
It is known as a marker of choice for lung adenocarcinoma [17]. In the present study, in lung cancer, the diagnostic sensitivity of CEA was 72.2% and close to the values given by other workers [18, 19].who reported that CEA could be a valuable tool in the detecting of pleural malignancy and diagnostic value for differentiating malignant from benign effusion.
We found a possible correlation between increased pleural effusion CEA level and the extent of the disease. If an abnormal CEA is confirmed, additional evidence of metastatic disease should always be sought before initiating therapy.
In our lung cancer patients (18 cases), 27.7% of cases were misclassified and showed decrease in pleural fluid CEA. Using the cut-off values for pleural fluid CEA, the sensitivity, (72.2%) and specificity (68.2%) as well as the positive predictive value (65.0%) indicate the significance of the determination of CEA in the sera and pleural effusion in the differentiation of malignant from benign pleural effusion.
Using the cut – off value of 6.0 U/ml pleural CA 15-3 was diagnostic in 94.4 % of patients with pleural malignant effusion and significant difference ($P < 0.014$) between malignant and benign was noted.
The sensitivity, specificity and positive predictive values were 94.4%, 63.6% and 68.0 % respectively. This was in consistent with other workers [20, 21].
From 18 patients with lung cancer only (5.5%) cases where it's level was below the cutoff value, misclassified as a malignant pleural effusion. The combined use of CEA and CA 15-3 in our study led to more improved sensitivity (94.4%) in malignant effusion than CEA or CA 15-3 alone. This was in agreement with other workers [22].
In this study, pleural effusion AFP showed little value in differentiating malignant from benign serious effusion.
It recorded low sensitivity (5.6 %), high specificity(84.4%) with no significant difference between malignant and benign$P> 0.05$.
This was in agreement with other studies [23] which found that measurement of AFP concentration in pleural effusion is of no clinical value in malignant pleural effusion.
The number of cases misclassified in 18 patients with lung cancer was 17 (94. 4 %).
Combination of CEA + AFP did not improve the discriminative value for differentiating malignant from benign effusion, which was in agreement with previous study [24].
Combination of the tumors markers CEA + CA15-3 + AFP decreased specificity to 50 % while sensitivity was 94.4 % , However this combination did not improved the diagnosis of malignant effusion which was in agreement with previous study [20]
We conclude that a good clinical strategy for diagnosing malignant pleural effusion may begin with CEA assay and then if it is negative, to add CA 15-3 assay to improve sensitivity. These two combinations are highly specific and have acceptable sensitivity.
The use of these combinations may enhance the prediction of probability of malignancy. However, our data need to be confirmed by larger series of patients.

References

1. Beckett WS. Occupational respiratory disease. *N Engl. J. Med.*,2000;342:406– 413.
2. Cohen M. and Sahn S.A. Resolution of pleural effusion. Chest,2001.119: 1547 – 62.
3. Nkere, U.U., Griffin, S.C.and Foundation S.W. Pleural abrasion: a new method of pleurodesis. Thorax, 1991; 46 : 596 – 8.
4. Bates S.E.Clinical application of serum tumor markers. Ann Int. Med., 1991; 155:623-38.
5. Bast R.C., Ravdin P.,and Hayes D.F. update of recommendation for the use of tumor markers in cancer. J.Clin Oncol., 2001; 19 (6): 1865 – 78.
6. Bronick A., Rojinska E. and Kwiek S. Usfulness of examining levels of CEA in pleural fluid for establishing the cause of plural effusion. Pneumnol Alergol., 1994 ; 62 : 239 – 45
7. Garcio – pachon E., Padilla N.I and Miralles – Lipos A. Elevated levels of CEA in non malignant pleural effusion. Chest, 1997; 111: 643 –7.
8. Kulpa J., Wojcik E., and Koodzieski L. CEA, CYFRA 21 and NSE in squanous cell lung cancer. *Clin chem*..,2002;48:1931–7.
9. Romero S., Fernandez C., and Espasa A. CEA, CA 15-3 and CYFRA 21-1 in serum and pleural fluid of patients with pleural effusions. Eur. Resp. J., 1996; 9 (1): 17- 23.
10. Johnson P.G. The role of serum AFP estimation in the diagnosis and management of hepatocellular carcinoma. Clin Liver. Dis., 2001; 5 (1): 145 – 59.
11. Light R.W.Disorder of the pleura, modiastinum and diaphragm. Principles of Internal Medicine. Harrison 16th Ed., 2005; 1: 506 – 16.
12. Porcel –Perez J.M., Vives S., and Esqerda S.A. Cut –off values of biochemical tests on pleural fluid. An Med. Intrna., 2004; 21(3): 113 – 7.
13. Gupta KB., Ghalaut V., Arora P., Tandon S. Evaluation of pleural fluid bilirubin, creatine kinase, uric acid, alkaline phosphatase and their ratio to respective serum levels to distinguish pleural transudates and exudates. Ind. J. Tuberculosis, 2004; 51:136-67.
14. lai R.S., Chen C.C., and Lee P.C. Evaluation of cytokeratin 19 as a tumor marker in malignant pleural effusion. Jpn. J Clin. Oncol., 1999 ; 18:421 – 4.
15. Colice G.L., Curtis A. and Deslauriers J. Medical and surgical treatment of paraphenumonic effusion. Chest, 2000; 118: 1158 – 71.
16. Thomson N.C., and Rana B. CEA assay in pleural effusion. Ann Intern. Med., 1979; 90: 721 – 25.
17. Garcia – Pachon E. Tumor markers for diagnosing pleural effusion .Chest, 2002; 121: 302-3.
18. Toumbis M., Chondros K., Ferderigos A.S., Daganon M.*et.al*. Clinical evaluation of tumor markers in malignant and benign pleural effusion. Anti. cancer Res., 1992; 12 (4):1267 –70.
19. Ryu J.S., Lee H.J and Hans H.S. The implication of elevated CEA level in pleural fluid. Respirology, 2003; 8 (4): 487 – 91.
20. Klapdor R Effusion – diagnosis and therapy. Tumor markers in clinical oncology, 1994; 191 -8.
21. Alatas F., Metintas M., Clolak O.et.al … Diagnosis value of CEA, CA 15 -3, CA 19-9 and NSE assay in pleural effusion. Lung cancer 2001. 31 (1): 9 -19.
22. Mezger J., Permantter w., Gerbes A.L., and Wilmanns w. Tumor markers in diagnosis of serous effusion.*JClin.Path*.,1998;41:633-43.
23. Fuhraman C., Duche J.C. Chouaid C. Abd – Al – Samad *et.al*. Use of tumor markers for differential diagnosis of mesothelioma and secondary pleural malignancies. Clin.Biochem.,2000;33(5):405–10 .
24. Martinez V.A., gahell J.M.Sergura F., Heiman C. *et.al*. Diognostic value of tumor markers in serous effusion cancer, 1982; 50 (9): 1783 –8.

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