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The diagnostic usefulness of tumour markers CEA and CA-125 in pleural effusion

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Abstract

Pleural effusion is a common diagnostic problem. The analysis of serum and pleural fluid for tumour markers is widely used as a diagnostic aid in clinical practice. The aim of the present study was to determine the usefulness of simultaneous quantification of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA-125) in distinction of malignant from benign effusion. Data from a total of 78 patients including 53 patients with benign and 25 patients with malignant effusion was evaluated. The cut-off values for differentiating benign from malignant effusions were determined using results obtained from patients with known benign effusions (mean + 2 SD, 95% confidence interval). The cut-off for CEA and CA-125 were 5.1ng/ml and 1707 IU/ml respectively. CEA assay in pleural fluid had an acceptable sensitivity and good specificity of 64% and 98% respectively. CA-125 had a sensitivity of 36% and specificity of 94%. The combination of the two tumour markers gave a sensitivity of 72% and specificity of 92.4%. We suggest a good clinical strategy may be to begin with CEA measurement (assay specificity 98%); if CEA is below the cut-off value (negative), CA-125 could then be measured to improve the sensitivity of detection of malignant effusions. However, measurement of these tumour markers is not cost effective from the point of view that it does not give information on the type of malignancy present. The latter has to be determined either by histological or cytological study.

Key words: Pleural effusion, tumour marker, carcinoembryonic antigen (CEA), carbohydrate antigen (CA-125)

INTRODUCTION

Pleural effusions may be the result of many pulmonary or systemic diseases. When a patient is diagnosed to have a pleural effusion, an effort should be made to determine the cause, and analysis of pleural fluid is an important step in the work-up of such patients. Transudative effusions are caused by a small, well-defined group of illnesses such as liver cirrhosis and congestive cardiac failure. Exudative effusions, on the other hand, are associated with a wide variety of causes, including pneumonia, tuberculosis, pulmonary embolism, viral infections, malignancy and many others.

Neoplastic processes cause approximately 20% of pleural effusions. Although cytology is the most specific routine diagnostic procedure, its sensitivity is only 50-60%. Hence more invasive techniques are carried out for diagnosis, like pleural biopsy or thoracoscopy.[1] Transudative and exudative pleural effusions are distinguished by measuring the lactate dehydrogenase (LDH), and protein level in the pleural fluid.[2] In all exudative pleural effusions, a description of the fluid, the glucose level, the amylase level, a differential cell count, microbiological and cytological studies are recommended. In some cases, however the conventional markers are not significant to differentiate malignant from benign pleural effusion. Measuring tumour-associated antigens in the pleural fluid, which the tumour cells express, could be possibly used for this distinction.[3]

The object of this study was to evaluate the use of the tumour markers, carbohydrate antigen-125 (CA-125) and carcinoembryonic antigen (CEA), in pleural fluid obtained by thoracocentesis for diagnosis of neoplastic pleural effusion and to determine the correlation between the level of CA-125 in the pleural fluid and serum. The aetiology of the underlying diseases were determined by cytologic, histologic and microbiological methods.

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METHODS AND MATERIALS

The study was done in the Department of Pathology, University of Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia. Pleural fluid samples from 78 consecutive patients, who were subjected to simple needle aspiration or tube drainage for diagnosis, were selected from the files of our institution, and included in this study.

In all pleural fluid samples routine laboratory tests like total protein, LDH, glucose, cytological examination, and microbiological tests were performed. The levels of tumour markers CEA and CA-125 in the pleural fluid and CA-125 level in the serum were measured by chemiluminescence method (ACS Chiron Diagnostics). The results of pleural biopsy to distinguish malignant from benign effusion were available in all the cases. Patients with pleural effusion were classified as benign or malignant. The benign group (n=53) included tuberculosis (n=17), congestive cardiac failure (CCF) (n=15), pneumonia (n=16), systemic lupus erythematosis (SLE) (n=2) and pancreatitis (n=1). The malignant group (n=25) included adenocarcinoma (n=14), non-Hodgkin's lymphoma (NHL) (n=5), mesothelioma (n=1), squamous cell carcinoma (SCC) (n=1), poorly differentiated carcinoma of lung (n=2) and metastatic adenocarcinoma (n=2).

Statistical analysis

The following calculations were made: sensitivity (S): true-positive / (true-positive + false-negative); specificity (s): true-negative / (true-negative + false-positive); positive predictive value (PPV): true-positive / (true-positive + false-positive); negative predictive value (NPV): true-negative / (true-negative + false-negative). The term 'positive' refers to histologically or cytologically proven malignant pleural effusion. While benign effusions are referred to as 'negative'; the latter category includes effusions with negative histology or cytology for malignancy [4].

The statistical evaluation was performed by computer analysis with SPSS software (SPSS Inc., USA). Results were compared according to the Mann-Whitney U test and student T-test. The cut-off values were defined as the benign group mean + 2 SD (95% confidence interval).

RESULTS

Distribution of the pleural effusions by aetiology is shown in Table 1. The levels of CEA and CA-125 in pleural fluid (median and range) are given in Table 2. The scattergram for CA-125 and CEA are shown in Figures 1, 2 and 3. The calculated cut-off values were 5.1 ng/ml and 1707 IU/ml for CEA and CA-125 respectively. Using these cut-off values, the sensitivity and specificity were found to be 64% and 98% respectively for CEA, and 36% and 94% for CA-125 (Table 3).

The sensitivity and specificity by combined use of both tumour markers ("combined markers") was also determined to evaluate the utility of this approach. A positive result, in this case, was defined as the elevation of at least one of the two tumour markers above the respective cut-off value. The calculated sensitivity and specificity of the "combined markers" were 72% and 92.4%. The sensitivity was higher than that of CEA but the specificity was lower than that of CEA.

CEA and CA-125 levels in malignant pleural fluid were significantly elevated compared with that of benign effusions (Table 2). Only one false positive was encountered for CEA (8 ng/ml) in the case of a patient with empyema. In malignant pleural effusion due to NHL and mesothelioma, CEA was not elevated. From Figure 2, it can be seen that while malignant effusion may have a lower CEA level, benign effusions very rarely show diagnostically high levels of CEA.

There is no correlation between serum CA-125 and pleural fluid CA-125 in benign or malignant conditions ($r = 0.5$ and 0.29 respectively). There was also no correlation between the CEA and CA 125 in malignant effusions ($r = 0.035$). There was statistical significance in the difference between the serum values in benign and malignant conditions.

DISCUSSION

Several authors have suggested using different tumour markers in pleural fluid to complement the cytological diagnosis of malignant pleural effusion. The purpose of this study was to determine the usefulness of the tumour markers CEA and CA-125 in diagnosing malignant pleural effusion that are routinely carried out in our laboratory.

CEA is an oncofoetal protein that is found to be elevated in the serum in colorectal, gastrointestinal, lung and breast carcinomas. In this study, the sensitivity of CEA (64%) was concordant with previous data that reported sensitivities around 50-60% in malignant

TABLE 1: Diagnosis in patients with pleural effusions

Diagnosis	n
Benign	**53**
Cardiac Failure	15
Pneumonia	16
Tuberculosis	17
SLE	2
Empyema	1
Pancreatitis	1
Cirrhosis of Liver	1
Malignant	**25**
Adenocarcinoma of Lung	14
Poorly differentated Carcinoma	2
Squamous cell carcinoma	1
Mesothelioma	1
Adenocarcinoma of other organ	2
Non-Hodgkin's Lymphoma	5
Total	78

TABLE 2: CA-125 and CEA levels expressed as median and ranges ( ) in malignant and benign pleural effusions

	n	CEA ng/ml	CA-125 IU/ml
Malignant	25	115 (0.5 –6921)	2420.3 (79-9820)
Benign	53	0.8 (0.2-8.8)	496 (62-2140)
Statistical significance (P)		<0.0001	<0.004

TABLE 3: Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CEA, CA-125, and CEA + CA-125

	Sensitivity	Specificity	PPV	NPV
CEA	64	98	94	85
CA125	48	85	60	78
CEA + CA-125	84	81	72	90

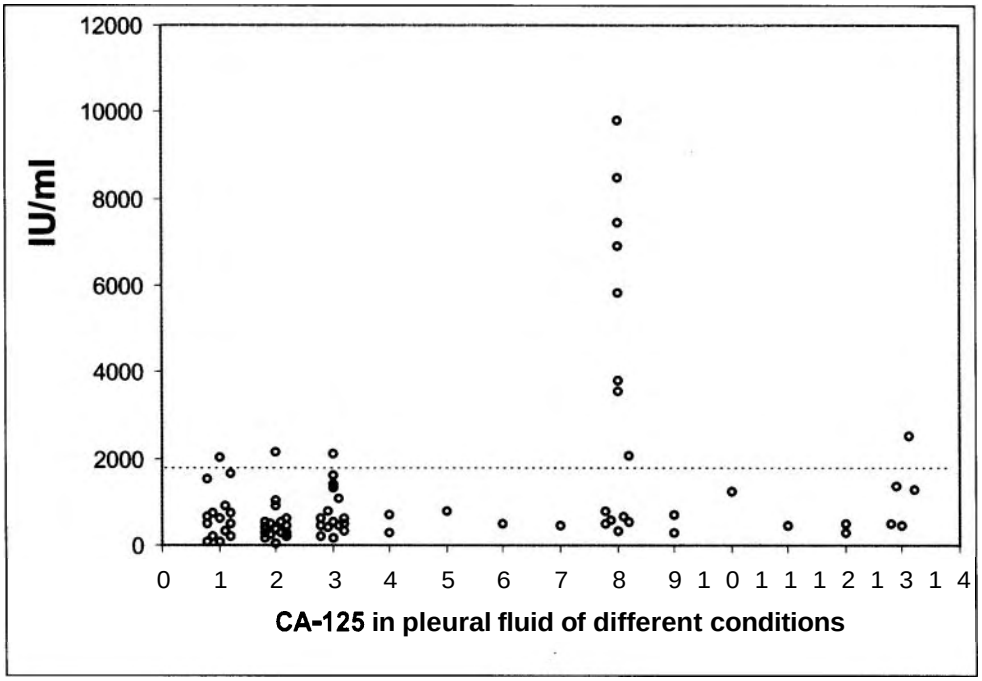

FIG. 1: CA-125 levels in benign and malignant pleural effusion. Benign: 1 = CCF, 2 = Tuberculosis, 3 = Pneumonia, 4 = SLE, 5 = Empyema, 6 = Cirrhosis, 7 = Pancreatitis. Malignant: 8 = Adenocarcinoma, 9 = Poorly differentiatedcarcinoma, 10 = Mesothelioma, 11 = Squamous cell carcinoma, 12 = Secondaries, 13 = NHL

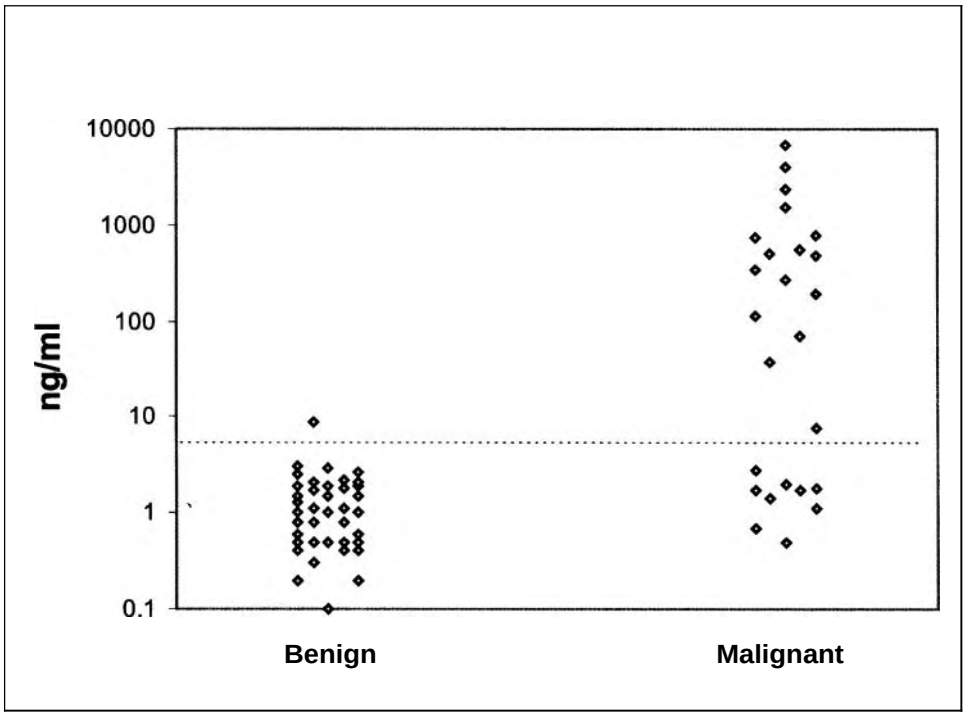

FIG. 2: CEA levels in benign and malignant pleural effusion.

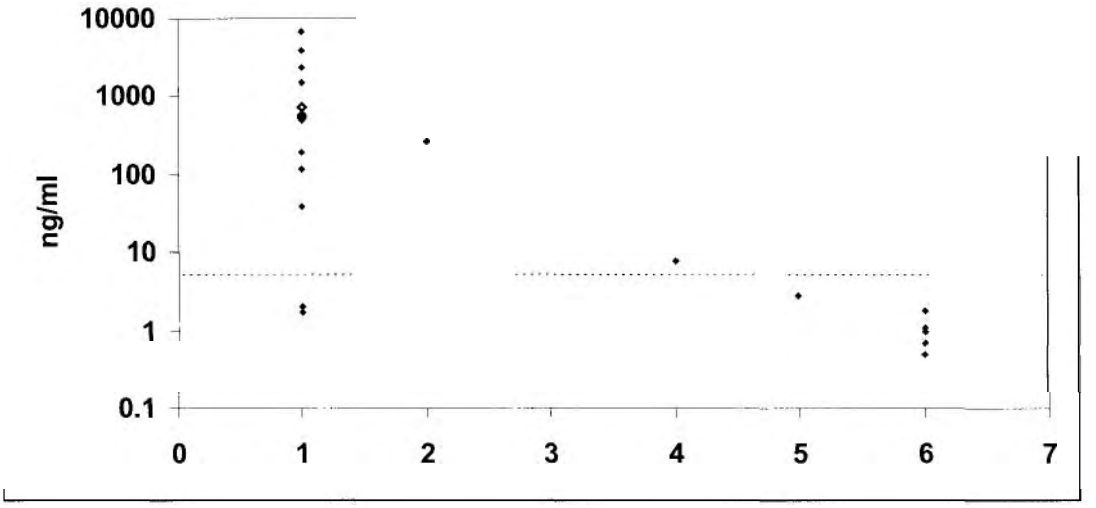

FIG. 3: CEA levels in different malignancies. 1 = Adenocarcinoma. 2 = Poorly differentiated carcinoma. 3 = Mesothelioma, 4 = Squamous cell carcinoma. 5 = Secondaries. 6 = NHL

effusions.' The highest level of CEA was logically observed in carcinomas, while much lower values were observed in NHL and mesothelioma; this finding is also in agreement with previous studies.[6]

It is well known from immunohistochemical studies, that the mesothelial cells of the pleura and peritoneum[7,8] express CA-125. It has also been reported that the CA-125 levels in pleural fluid from lung adenocarcinoma and mesotheliomas were significantly higher than those in benign effusion.[8] In our series, the observed values of CA-125 in pleural tluid appeared to be significantly higher compared with the corresponding values observed in the serum of benign and malignant effusions. Indeed the determined cut-off value in pleural fluid of benign effusions was 1707 IU/ml; in contrast, the serum cut-off value is only 35 IU/ml. The large amounts of CA-125 in pleural fluid originate from mesothelial cells [7]. Mezer et al [9] reported that the mean CA-125 values in effusion fluid were 512 U/L in benign and 812 U/L in malignant effusion. Since there was no significant difference between both the groups either for serum or for effusion fluid, they did not recommend CA-125 as a useful diagnostic tool. Kandylis et al [10] found in their study that CA-125 in pleural fluid had a sensitivity of 93%; however, the specificity was very low at 29%. They concluded that CA-125 on its own was insufficient to discriminate malignant from benign effusion.

In the present study we found that, although there was a significant difference in pleural fluid CA-125 levels in benign and malignant effusions ($p<0.004$), the sensitivity and specificity were 36% and 94% respectively, which were lower than that of CEA. The low sensitivity could be explained by the high cut-off value. CA-125 was elevated in three cases of benign effusion. These cases included patients with tuberculosis, pneumonia and end stage renal failure patient who was on peritoneal dialysis. Filiz Kuralay et al[11] also observed high CA-125 in tuberculous effusions.

CEA appears to have a better sensitivity (64%) and specificity (98%) than CA-125 in the diagnosis of malignant effusions, with a positive predictive value of 94%. We conclude that a good clinical strategy for diagnosing malignant pleural effusion would be to begin with the CEA assay. If it is negative, CA-125 assay can be added to improve the sensitivity of detection. The combination of the tumour markers CEA and CA-125 gives a specificity of 72% and increases the sensitivity to 92.4%. The use of combinations may therefore enhance the prediction of probability of malignancy.

In our case of mesothelioma and NHL, both CEA and CA-125 levels in pleural fluid were below the cut-off value except in one case of NHL. The combination of tumour markers did not increase the probability of diagnosing

malignant pleural effusion. Moreover, in view of the fact that the prevalence of neoplastic pleural effusion is higher among patients older than 50,[12] routine assay of these tumour markers may be limited to patients older than the age of 50 with pleural exudate. This would enhance the positive predictive value, reduce false positive results and be more cost effective.

It must be stressed that the high levels of CEA and CA-125 in pleural fluids can only positively predict the presence of malignancy and the latter needs cytological or histological confirmation. Besides, increased CEA and CA-125 levels do not allow for typing of the tumour. This must be made again histologically or cytologically. Whatever the aetiology of malignant effusion, the ultimate diagnosis still relies on cytological or histological study. In clinical practice therefore the cost effectiveness of measurement of these tumour markers remains questionable and should be verified by further studies.

REFERENCES

1. Johnston WW. The malignant pleural effusion: a review of the cytopathologic diagnoses of 584 specimens from 472 consecutive patients. Cancer 1985; 56: 905-9.
2. Heffner JE, Brown LK, Barbieri C. Diagnostic value of tests that discriminate exudative and transudative pleural effusions. Primary Study Investigators. Chest 1997; 111:970-80.
3. Wardman AG, Bowen M, Struthers LP. The diagnosis of pleural effusions: are cancer markers clinically helpful? Med Paediatr Oncol 1984; 12:68-72.
4. Griner PF, Mayewski RJ, Mushlin AI, Greenland P. Selection and interpretation of diagnostic tests and procedures. Principles and application. Ann Intern Med 1981; 94:557-92.
5. Villena V, Lopez-Encuentra A, Echave-Sustaeta J. Diagnostic value of CA 72-4, carcinembryonic antigen, CA 15-3 and CA19-9 assay in pleural fluid. Cancer 1996; 78:736-40.
6. Salama G, Miedouge G et al. Evaluation of pleural CYFRA 21-1 and CEA in the diagnosis of malignant pleural effusion. Br J cancer 1998; 77:472-6.
7. Vergote I, Onsrud M, Bormer OP. CA-125 in peritonea1 fluid of ovarian cancer patients. Gynecol Oncol 1992; 44:161-5.
8. Lindgren J, Kuusela P, Hellstrom PE. Ovarian cancer antigen CA-125 in patients with pleural effusions. Eur J Cancer Clin Oncol 1988; 24:737-9.
9. Merger J, Permanetter W, Gerbes AL et al. Tumour associated antigens in diagnosis of serous effusion. J Clin Pathol 1988; 41:633-43.
10. Kandylis K, Vassilomanolakis M, Baziotis N. Diagnostic significance of the tumour markers CEA, CA15-3 and CA-125 in malignant effusion in breast cancer. Ann Oncol 1990: 1:435-8.
11. Filiz Kuralay, Zeynep Togoz, Abdurrahaman Comlekci. Diagnostic usefulness of tumour marker levels in pleural effusion. Clin Chem Acta 2000; 300:43-55.
12. Chretien J, Pleural response in malignat metastatic tumours. In: Chretien J, Bignos J, Hirsch A, ditors. The pleura in health and diseases. New York: Marcel Dekker, 1985:489-505.