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ORIGINAL RESEARCH ARTICLE

ROLE OF PLEURAL FLUID CEA LEVEL IN PLEURAL FLUID ANALYSIS

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ABSTRACT

Pleural fluid cytology is usually the initial diagnostic tool in pleural fluid analysis. However, the conventional cytological evaluation of pleural effusion in detecting malignancy has a sensitivity wide range – from 22 to 81%. Measurement of carcinoembryogenic antigen (CEA) level in pleural fluid may be valuable in the diagnosis of malignant pleural effusion. The study was performed on 70 different patient samples at the Department of Pathology and Serology Section, Department of Microbiology of TUTH from March 14, 2004 to March 13, 2005. CEA levels in pleural effusions were above cut off value (10ng/ml) in 19 out of 70 samples. Out of 19 cases, 14 (73.7%) were malignant pleural effusion. CEA level was elevated in 3 benign condition (15.8%) and 2 suspicious cases (10.5%). At cut off value of 10ng/ml, pleural fluid CEA had sensitivity of 58.3%, specificity of 92.7%, and positive and negative predictive values of 82.3% and 79.1% respectively. CEA level was above the cut off value in 55.6% of cytology negative malignant pleural effusions. The pleural fluid CEA level assay in patient with malignant effusions is a valuable adjunct to pleural cytology, especially with negative cytology when the clinical presentation cannot clearly exclude an underlying malignancy.

Keywords: *CEA, malignant pleural effusion, pleural fluid cytology, tumor marker.*

INTRODUCTION

Pleural effusion is a common finding and occasionally creates a diagnostic problem that remains unsolved despite clinical and laboratory evaluation. Pleural fluid cytology is usually the initial diagnostic tool. However conventional cytological evaluation of pleural effusion often yields borderline result. Apart from malignant or benign diagnosis, a relatively large part of the findings are 'suspicious for malignancy' with sensitivity ranging from 22 to 81% in detecting malignancy.[1,2-5,6,7] Accurate diagnosis of the cause of pleural effusion is essential because treatment and prognosis vary accordingly. Therefore, further additional test are required to rule out the malignant causes of effusion in those with high index of suspicion. Tumor markers offer a putative clinical use in cancer diagnoses. Carcinoembryogenic antigen (CEA) level in pleural fluid, as a tumor marker, is more extensively studied and shown to have diagnostic utility in diagnosing malignancy when used in combination with pleural fluid cytology.[5,8-13] The objective of this study was to assess the role of pleural fluid CEA level in the diagnosis of malignant pleural effusion.

MATERIALS AND METHOD

This was a hospital based prospective study conducted in the Department of Pathology and Department of Microbiology (Serology Section), Tribhuwan University Teaching Hospital, Institute of Medicine, Maharajgunj during the time period of 1 year from 14 March 2004 to 13 March 2005. Samples of pleural fluid sent to the Department of Pathology for routine cytological examination were collected. CEA level was estimated in the pleural fluid samples by using enzyme immunoassay method in the serology section of Microbiology Department.

Most studies have taken 5ng/ml or 10ng/ml as cut level of CEA in pleural fluid. Comparing the ROC curves of the two values indicated 10ng/ml as a better cut off level for this study. Data were analysed by software programme SPSS 10 for windows. Chi-square test was applied and a p value of less than 0.005 was considered to be statistically significant.

RESULTS

Total samples from 70 different patients were evaluated, which comprised of 35 males and 35 females. The patients' age ranged from 16 to 91 years. Out of 70 patients, 41 (58.5%) had benign diseases, 24 (34.5%) had malignancy and remaining 5 (7%) patients were labeled as suspicious for malignancy. Malignancy was proven by different diagnostic

approaches including biopsy (6 cases), fine needle aspiration cytology (5 cases), bronchial brush cytology (1 case), sputum cytology (2 cases), CT findings (1 case), and pleural fluid cytology (9 cases).

Lung cancer (66.9%, n=16) was the most common cause of malignant pleural effusion and lung adenocarcinoma (41.8%, n=10) was the commonest type of tumor leading to pleural effusion. Other causes of malignant pleural effusion and the detection rate in pleural fluid cytology are depicted in Table 1.

Table 1: Causes of malignant pleural effusion, the detection rate in pleural fluid cytology and the mean pleural fluid CEA level

Primary site of tumor	Cause of malignant pleural effusion	Frequency (%)	Cytology – positive or suspicious (%)	Cytology– negative (%)	Mean CEA† level (ng/ml)
Mediastinum	Adenocarcinoma	10 (41.8)	9 (90)	1 (10)	86.7
	SQCC‡	5 (21)	1 (20)	4 (80)	61.0
	Ca. Lung	1 (4.1)	0 (0)	1 (100)	54.7
Breast	IDC‡‡	1 (4.1)	1 (100)	0 (0)	59.0
Kidney	RCC‡‡‡	1 (4.1)	1 (100)	0 (0)	2.1
Ovary		1 (4.1)	1 (100)	0 (0)	13.8
GIT *	NHL**	2 (8.5)	1 (50)	1 (50)	1.4
Gall bladder	Adenocarcinoma	1 (4.1)	1 (100)	0 (0)	0.1
Mediastinum	#M. melanoma	1 (4.1)	0 (0)	1 (100)	2.7
Pleura	##M. mesothelioma	1 (4.1)	0 (0)	1 (100)	3.2
Total			24 (100)	15 (62.5)	9 (37.5)

†Carcinoembyogenic antigen, ‡ Squamous cell carcinoma. ‡‡Infiltrating ductal carcinoma of breast, ‡‡‡Renal cell carcinoma,* gastrointestinal tract- small intestine & tonsisl, **Non-Hodgkin's lymphoma, #malignant melanoma, ##malignant mesothelioma

Mean CEA value for benign diseases was 5.8ng/ml (range 0.0-85.3). In malignant cases, it was significantly higher with mean value of 58.2ng/ml, with a range between 0.1 and 172.7ng/ml. Maximum pleural fluid CEA level was found in lung adenocarcinoma (172.7ng/ml, p value 0.0001). The mean values of pleural fluid CEA level in malignant effusion are shown in Table 1 with respect to the site of primary malignancy and different histolologic types.

According to the histopathological types, highest CEA level was found in adenocarcinoma of lung; it was followed by squamous cell carcinoma lung, metastatic adenocarcinoma from breast, and metastasis from ovary. But pleural fluid CEA level was low (<10ng/ml) in metastatic adenocarcinoma from gallbladder and renal cell carcinoma and in non-carcinomamatous malignant conditions such as non-Hodgkin's lymphoma (NHL), malignant melanoma, malignant mesothelioma.

In benign pleural effusions, pleural fluid CEA level was found to be below 5ng/ml except in tuberculous effusion and traumatic hemothorax with maximum values up to 85.3ng/ml and 25.5ng/ml, respectively. Mean pleural fluid CEA level in benign pleural effusions of various causes are shown in table 2. In malignancy-suspected cases, mean value was 11.7ng/ml with maximum value of 25.8ng/ml.

Table 2: Pleural fluid CEA level in benign pleural effusion (n=41).

Benign pleural effusion	Mean (ng/ml)	Frequency	Minimum (ng/ml)	Maximum (ng/ml)
Empyema	5.9	1	5.9	5.9
Filariasis	1.9	1	1.9	1.9
Pulmonary TB	7.5	24	0.0	85.3
Traumatic haemothorax	13.4	2	1.3	25.5
Cardiac disease	2.3	1	2.3	2.3
Chronic renal failure	1.2	4	0.0	2.9
Pneumonia	1.3	7	0.0	4.2
Cirrhosis	1.5	2	1.2	1.9

CEA level in pleural effusions was above cut off value (>10ng/ml) in 19 out of 70 cases. Out of the 19 cases, 14 (73.7%) were malignant pleural effusions and it was also elevated in 3 benign condition (15.8%) and malignancy-suspected cases (10.5%). The benign conditions included 2 cases of pulmonary tuberculosis and 1 case of traumatic hemothorax.

CEA level was higher than 10ng/ml cut off value in 5 out of 9 cytologically negative malignant pleural effusions. In cytology negative cases, CEA could detect 55.6% of false cytology-negative cases. Combined cytology and CEA level assessment identified 83.3% of total malignant cases. This was an increase in detection rate by 20.8%. Statistical analysis showing sensitivity, specificity, positive predictive value and negative predictive value for pleural fluid cytology alone, CEA level and combined CEA and pleural fluid cytology is depicted in Table 3.

Table3: Statistical analysis for cytology, CEA alone and combined

Assay	False Positive %	False Negative %	Sensitivity %	Specificity %	PPV %	NPV %	P Value
Cytology	0	37.5	62.5	100	100	82	0.001
CEA	7.3	41.7	58.3	92.7	82.3	79.1	0.001
Combined cytology + CEA	0	16.7	83.3	100	100	90.4	0.0004

DISCUSSION

The differential diagnoses of benign and malignant pleural effusions represent a critical clinical problem. Several ancillary tests may be performed on the pleural fluid, in addition to cytologic examination, to aid the diagnosis of malignant pleural effusions. The quantification of tumor markers in pleural fluid has also been reported to be useful in establishing the diagnosis of malignant effusions. The tumor marker most commonly measured in pleural fluid is CEA. Several studies using panel of tumor markers had been undertaken including CEA, CA125, CA 15-3, CYFRA 21-1, NSECA72-4, and squamous cell carcinoma antigen which could detect malignancy of different histopathologic type to increase sensitivity of the tests.[11-15] In present study, CEA assessment alone was undertaken.

Several studies have supported the value of pleural fluid CEA level as an adjunct to cytology to distinguish benign from malignant condition. Also pleural fluid CEA level is seen to be significantly raised than in serum. Choosing cut off value for malignancy, different studies proposed variable cut off level ranging from 3 to 40ng/ml. Adopting high cut off levels that are not exceeded by any of the benign pleural effusion makes tumor marker assays very insensitive.

Approximately 30-40% of patients with malignant pleural effusions have positive pleural fluid CEA levels that exceed 10ng/ml and only rarely a benign effusion has levels that exceeded this value. Most studies had used 5ng/ml as cut off point with sensitivity between 41% and 60% and specificity between 98% and 100%.[5, 7, 13] Therefore, using ROC curve, the validity of both 5 and 10ng/ml cut off level were evaluated. The cut off value 10ng/ml had a larger area of coverage for sensitivity and specificity than the 5ng/ml level (0.776 vs. 0.736). Thus, 10ng/ml was taken as cut off value.

At this cut off value in the present study, CEA level in malignant effusions were significantly higher than those in benign effusions (p value 0.001) with sensitivity of 58.3%, specificity of 92.7%, positive predictive value of 82.3%, and negative predictive value of 79.1%. Supervia et al[16] reported high diagnostic sensitivity of 87.5% and Riantawan et al[17] had a sensitivity of 77%, while Marel et a[17]showed only 34% of sensitivity at 10ng/ml cut off value. Specificity was comparable in all these studies, ranging between 91.5% and 94%. Variation in sensitivity might be due to different histological type causing malignant pleural effusion in different studies.

In this study, most common primary site of malignancy leading to pleural effusion was lung, accounting to 66.7%. Other studies show similar findings, studies, such as Marel et al[7] and Antony et al[18] that reported 60% and 57% respectively. Most common histopathological type seen was adenocarcinoma 58.3%, mainly lung adenocarcinoma (41.6%). Ong et al[3] and Hsu et al[19] also reported lung adenocarcinoma as the most frequent cause of malignant pleural effusion (40% and 51.5%, respectively).

Among the conditions of CEA level above the 10ng/ml cut off, lung adenocarcinoma caused highest elevation followed by squamous cell carcinoma of lung, breast carcinoma, and ovarian carcinoma. Klech et al[9] also reported highest CEA values in adenocarcinoma of the lung and metastasing breast cancer.

CEA level was significantly low in malignant mesothelioma, malignant melanoma, and NHL. The lower CEA level in malignant mesothelioma is unhelpful to detect malignant pleural effusion but it would useful to differentiate it from adenocarcinoma. Most of the time, these two malignancies are difficult to differentiate by cytology alone. In the present study, the CEA level in malignant mesothelioma was only 3.2ng/ml. According to Ogushi et al,[20] the CEA level is helpful to rule out the diagnosis of mesothelioma above 3ng/ml with the sensitivity and specificity of 100% and 77%, respectively. Several other studies also showed low level of CEA in malignant mesothelioma.[16, 17]

Benign effusions had below cut off CEA levels. However, exudates in benign effusion, especially due to tuberculosis and traumatic haemothorax showed higher CEA level, with 7% rate of false positivity towards malignancy. However, as pulmonary tuberculosis cases had average 7ng/ml CEA level, the 10ng/ml cut off level could be useful in differentiating the

conditions. Empyema and pneumonia could be distinguished as benign at cut off value of 10ng/ml. Similar findings were obtained from studies performed by Ryu et al,[21] and Trape et al.[8] In the study of Ryu et al,[21] false positive results were observed showing pleural fluid CEA level elevated above 5ng/ml in 14.7% of parapneumonic effusion, 38.6% for empyema, 14.3% of exudates of other origin, and 7.3% of tuberculosis cases.

In this study, CEA level was above the cut off level in 5 (56%) of false negative cases (by pleural fluid cytology). Similar findings were found in study done by Jose et al showing detection rate of 37% in cytology negative effusions.[22] Therefore, this finding suggests that even with cytology negative effusion if CEA level is significantly high, keeping in mind the possibility of malignancy further investigation should be considered wherever possible. With combined cytology and CEA approach, detection rate was increased by 20.8% when compared to cytology alone. Jose et al[22] also showed similar finding with increase in detection rate by 18%.

CONCLUSION

Pleural fluid CEA level has high specificity but low sensitivity, therefore, is not the tool of choice when used alone to distinguish malignancy from benign disease. However, the combined cytology and pleural fluid CEA level gives better sensitivity and specificity than either of these parameters used alone. Therefore, quantitative determination of CEA level can be a useful addition to pleural cytology in the diagnosis of malignant pleural effusions, especially in suspicious cytology for malignancy and cytology negative malignant effusions. In addition, it can be of great help in differentiating metastatic adenocarcinoma from malignant mesothelioma, which at times is difficult to decide by cytology alone.

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