Original Article

Diagnostic Accuracy of Cancer in Pleural Effusion: A Combination Serum Tumor Markers and Cytology

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Abstract

Background: Cytological examination of body effusion has an essential role in different tumor staging and research of malignancy. **Objectives:** It is to study the diagnostic effect of serum tumor markers in differentiation between benign and malignant pleural effusion. **Materials and Methods:** A retrospective research was done on 39 patients (28 male and 11 female with an age range of 50–77 years old). All samples undergo diagnostic thoracocentesis. The cutoff values of serum tumor markers (CEA < 5 ng/mL; CA125 <35 U/mL; CA19-9 < 37 U/mL; and CA15-3 < 31 U/mL). **Results:** Thirty-nine cases, resulting in 26 (67%) benign pleural effusions and 13 (33%) malignant pleural effusions, mean ± SD of age was higher malignant pleural effusion than benign type. The sensitivity of cytology was 33%. Malignant pleural effusion tended to have higher serum marker tumor concentrations. A comparison association between benign and malignant pleural effusion revealed statistically significant only in CEA. Most areas under the curve had moderate values that ranged between 0.6 for CA125, CA15.3, and other combined tumor markers, except for CEA, which had a good AUC (0.799). The best efficacy of a single tumor marker is CEA with a cutoff value of 2.05 ng/mL; at this cutoff value, the sensitivity, specificity, and accuracy were 69.2%, 88.5%, and 82.1%, respectively. **Conclusion:** Single serum tumor markers showed moderate sensitivity and low specificity; their combination does not result in to increase level of sensitivity and specificity to a good and dependent level for diagnosis of the malignant pleural effusion. Cytology and serum tumor markers have aided role in diagnosis. Thoracoscopy and pleural biopsy remain dependent diagnostic tools for malignant pleural effusion.

Keywords: Benign and malignant pleural effusion, cytology, serum tumor makers

Introduction

Malignant pleural effusion affected more than 125,000 hospitalized patients in 2012 in the United States of America,[1] and about 90% are due to metastasize lung and breast malignancies, [2] and it is associated with distressing symptoms and many manipulations in a chest that due to recurrence.[3]

Histologically, the whole body cavities are coated by a single layer of epithelial cells with the smallest amount of fluid between them that has lubrication and protection functions for the adjacent organs, but when there is a disproportion between the synthesis of fluid and its elimination, that consequently results in effusion formation.[4]

Cytological examination of body effusion has an essential role in different tumor staging and research of malignancy,[5] and it may give an indication of inflammation of underlying organs or serous membranes.[4] The positive cytological result, particularly for cancer cells, is regarded as a final diagnosis and consequently, it aided to more additional directed investigations and patient's management.[6] Also, it gives data regarding malignant cell features, for example, morphological and molecular characteristics of cancer cells.[7]

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The sensitivity level of cytology is correlated with the amount of good morphological cancer cells and cytopathologist skills, and that is specifically for pleural effusion because of problems in differentiation between normal (or reactive) mesothelial cells from malignant mesothelioma cells.[8]

The cytological examination of pleural effusion has 100% specificity and 43%–83% sensitivity, but in negative cases, there are additional invasive methods, for example, thoracoscopy with its sensitivity of 90%, and noninvasive methods, such as tumor marker concentration measurement in pleural effusion, that aided in differentiating between benign and malignant pleural effusion.[9-11]

Also, multiple studies are attempted to investigate the tumor marker to become a probable replacement of invasive methods in order to know the type of pleural effusion etiology.[12] A possible tumor markers that give a good chance for better diagnosis of malignant effusion are discussed by many authors, but at the same time, those authors show a big difference in their sensitivity and specificity.[13]

There are three possible indications for taking tumor marker level in pleural effusion, firstly, as an additional tool for diagnosis, earlier diagnosis of cancer metastasis to pleural, and as a supporting method to diagnose the location of primary neoplasia.[13-19]

Only one tumor maker for diagnosis may not be sufficient,[20] but a group of tumor marker are better; for example, total four tumor markers [carcino embryonic antigen (CEA), CA125, carbohydrate antigen 15-3 (CA15-3), and cytokeratin 21-1] have sensitivity 54% in compare with sensitivity below 30% for alone tumor marker.[16] This is supported by several tumor marker combinations that give similar end results.[13]

CEA, CA125, CA15-3, and CA19-9 can help to make a distinction between malignant pleural effusion from benign type.[21,22]

The objectives of the research are to study the diagnostic effect of serum tumor markers and cytology and to compare combined tumor markers in differentiation between benign and malignant pleural effusion.

Materials and Methods

A retrospective research was done on 39 patients (28 male and 11 female with an age range of 50–77 years old) who were admitted to Marjan Medical City Hospital and duration period between June, 2020 and December, 2022. Demographic data of patients are age, sex, symptoms, and all samples are fluid aspirations (diagnostic thoracocentesis) are done with aseptic circumstances in Marjan Medical City Hospital for cytology. The biochemical analysis, bacteriological, and serum tumor markers analysis (CA125, CA15-3, CA19-9, CEA) were done. The serum tumor markers had cutoff values according to Roche Diagnostics GmbH kits (CEA < 5 ng/mL; CA125 < 35 U/mL; CA19-9 < 37 U/mL; and CA15-3 < 31 U/mL). Serum tumor marker assays are done in a private laboratory which is provided with a cobase 411 analyzer (serial no. is 18P8-03). Cytology samples are done in a hospital laboratory; the fluid is firstly centrifuged for 3000 rpm/15 min, then supernatant is eliminated, and half of the cells sediment is stained with Papanicolaou stain (after fixation by 95% ethanol). Other cells' sediment was stained with Giemsa (after fixation by air dried) was done. Malignant pleural fluid was diagnosed by either positive cytology or was confirmed by histopathology.

Statistical analysis

The statistical calculation was performed by means of SPSS software version 22 (SPSS, IBM Company, Chicago, IL, USA). Data were presented as number, percentage, median, mean, and standard deviation. Mann–Whitney *U* test indicated an association between continuous data after using Kolmogorov–Smirnov test for determining not normal distribution of data. ROC (receiver operating characteristic) curve was used to determine the best serum cutoff values of interesting parameters to diagnose the malignant effusion. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated using a cross table. *P* value <0.05 was a statistically significant difference.

Ethical approval

The study was conducted in accordance with the ethical principles. It was carried out with patients' verbal and analytical approval before a sample was taken. The study protocol and subject information, and consent form were reviewed and approved by Babylon University College of Dentistry, a local ethics committee, according to document number 616, on May 14, 2020, to get this approval.

Results

The cytopathology of 39 pleural fluids was examined, resulting in 26 (67%) benign pleural effusions and 13 (33%) malignant pleural effusions, mean ± SD of age was higher malignant pleural effusion than benign type (68.23 ± 3.92 and 65.77 ± 8.26, respectively). The sensitivity of cytology was 33% [Table 1].

The clinical diagnosis, cytological and histopathological analysis of studies of patients that showed congestive heart failure lung cancer are common causes of benign and malignant pleural effusion [Table 2].

In this study, patients with malignant pleural effusion tended to have higher serum marker tumor concentrations; comparison 25–75th interquartile range in malignant type showed 1.4–73.1 for CEA, 7.25–600.35 for CA125,

Table 1: Clinical data characteristics of study group

Parameters		Benign pleural effusion	Malignant pleural effusion
Subjects number (%)		26 (67%)	13 (33%)
Age	Mean ± SD	65.77 ± 8.26	68.23 ± 3.92
Sex	Male, *N* (%)	18 (64.3%)	10 (35.7%)
	Female, *N* (%)	8 (72.7%)	3 (27.3%)

Table 2: The most common etiologies of pleural effusions studied

Etiology of benign pleural effusions	Etiology of malignant pleural effusions
Congestive heart failure	Lung cancer
Parapeumonic effusion	Breast cancer
Tuberculosis	Ovary cancer
Cirrhosis	

9.9–59.5 for CA19.9, 18–120.3 for CA15.3. A comparison association between benign and malignant pleural effusion revealed statistically significant only in CEA [Table 3].

Table 4 shows AUC, cutoff values, sensitivity, specificity, PPV, NPV, and accuracy were analyzed for CEA, CA125, CA19.9, and CA15.3 tumor markers. Most AUCs had moderate values that ranged between 0.6 for CA125, CA15.3, and other combined tumor markers, except for CEA, which had a good AUC (0.799).

The best efficacy of a single tumor marker is CEA with a cutoff value of 2.05 ng/mL; at this cutoff value, the sensitivity, specificity, and accuracy were 69.2%, 88.5%, and 82.1%, respectively. Where The best efficacy of combined tumor markers is CA15.3 + CA125, which showed the sensitivity, specificity, and accuracy were 50.0%, 86.5%, and 74.4%, respectively, as illustrated in Table 4.

Discussion

Unilateral pleural effusion is mainly investigated by analysis of pleural effusion and cytology to diagnose the malignancy, whether primary or secondary cancer;[23] perhaps, the cytological diagnosis for malignant pleural effusion can be enough for malignant staging and avoiding other invasive diagnostic tools, at the same time, there are cytological limitations such undefined low sensitivity and a long period of cytological preparation (5–7 days).[24] Also, it may aid in defining the selection of patient groups who need intervention by thoracoscopy.[25]

In other studies,[25,26] cytological sensitivity is 46.4% and 57.5%, while our result of low cytological percentage (33%) may be related to retrospective findings,[27-30] selective cases study,[31,32] the experience of the pathologist and different preparation methods of cytology. Also, the sensitivity of cytology is affected by the original cancer location and type of cancer; the cytological sensitivity reaches about 80% for adenocarcinoma of the breast, respiratory or gastrointestinal systems, and 95% for ovarian neoplasm.[33]

Among the panel of serum CEA, CA125, CA19.9, and CA15.3 study in the present study. Only CEA show significantly more concentration level association with malignant effusion type (mean = 29.29 ng/mL and *P* value = 0.003) but serum CA125, CA19.9, and CA15.3 have no significant association with malignant and benign pleural effusion (*P* value = 0.071, 0.766, and 0.233, respectively) but also with high concentration level in malignant effusion (mean = 237 U/mL, 33.22 U/mL, and 63.77 U/mL, respectively, this results may related of low advantage of using of tumor markers in patients older than 50 years old[34] due to the cancer is 1st etiology of pleural effusion between age 40 and 50 years old.[35]

In comparison to Paşaoğlu *et al.*[36] research that all panels of serum CEA, CA125, CA19.9, and CA15.3 tumor markers have been significantly associated highly with malignant pleural effusion, except CA125 is associated significantly with a high concentration in benign effusion than malignant effusion.

In using ROC, the best serum cutoff values of CEA, CA125, CA19.9, and CA15.3 are 2.05 ng/mL, 43.5 U/mL, 19.05 U/mL, and 23 U/mL, respectively.

By comparing single tumor markers in the current study, serum CEA give a high level of specificity (88.5%) and accuracy (82.1%), while serum CA15.3 display more sensitivity level (76.9%). Paşaoğlu *et al.*[36] exhibit serum CEA has higher specificity and accuracy (100% and 73%, respectively), while CA125 exhibits higher sensitivity (80%).

However, this study showed that combined CEA + CA125 lead increased sensitivity to 84.6%, also specificity increase in combined CA19.9 + CA125 and CA15.3 + CA125 to 82.7% and 86.5%, respectively. In Paşaoğlu *et al.*[36] study, a combination of CEA + CA125 and CA15.3 + CA125 lead to an increase specificity to 100%. In Yang *et al.*[37] study, CEA + CA125 combination is resulting a sensitivity of 65% and a specificity of 98%.

The conclusion, the elderly age groups and advanced tumor stage showed low cytological sensitivity, and the difference in serum concentration of most tumor markers (CA125, CA19.9, and CA15.3) between benign and malignant pleural effusion are not reached to significant level to differentiate between them. Single serum tumor

Table 3: Association of serum tumor markers between benign pleural effusion and malignant pleural effusion

Serum tumor markers		Benign pleural effusion ($N = 26$)	Malignant pleural effusion ($N = 13$)	*P value
CEA (ng/mL)	Mean ± SD	1.42 ± 0.785	29.28 ± 44.9	0.003
	Median (25–75th IQR)	1.4 (0.85–1.905)	2.4 (1.4–73.1)	
CA125 (U/mL)	Mean ± SD	29.21 ± 25.344	237.18 ± 326.162	0.071
	Median (25–75th IQR)	23.5 (4.742–54.25)	52 (7.25–600.35)	
CA19.9 (U/mL)	Mean ± SD	22.76 ± 13.21	33.22 ± 31.086	0.766
	Median (25–75th IQR)	24.5 (7.67–34.95)	22 (9.9–59.5)	
CA15.3 (U/mL)	Mean ± SD	24.43 ± 13.473	63.77 ± 67	0.233
	Median (25–75th IQR)	21.5 (10.5–37.67)	35 (18–120.3)	

*Mann–Whitney *U* test

IQR = interqaurtile range

CEA, carcino embryonic antigen

Table 4: Receiver operating characteristic analysis for diagnosis of malignant pleural effusion

Serum tumor markers	Optimal cutoff value	*P* value	Area under the curve (AUC) (95% CI)	Sensitivity (%)	Specificity (%)	Positive predictive value (PPV) (%)	Negative predictive value (NPV) (%)	Accuracy (%)
CEA (ng/mL)	2.05	0.003	0.799 (0.647–0.951)	69.20%	88.50%	75.00%	85.20%	82.10%
CA125 (U/mL)	43.5	0.071	0.679 (0.479–0.879)	69.20%	73.10%	56.30%	82.60%	71.80%
CA19.9 (U/mL)	19.05	0.766	0.53 (0.316–0.743)	69.20%	46.20%	39.10%	75.00%	53.80%
CA15.3 (U/mL)	23	0.233	0.618 (0.413–0.824)	76.90%	53.80%	45.50%	82.40%	61.50%
CEA + CA125		0.006	0.69 (0.563–0.818)	84.60%	44.20%	43.10%	85.20%	57.70%
CA19.9 + CA125		0.088	0.619 (0.471–0.767)	50.00%	82.70%	59.10%	76.80%	71.80%
CA15.3 + CA125		0.022	0.66 (0.516–0.804)	50.00%	86.50%	65.00%	77.60%	74.40%

markers showed moderate sensitivity and low specificity; their combination does not result to increase level of sensitivity and specificity to a good and dependent level for the diagnosis of malignant pleural effusion. So, cytology and serum tumor markers have aided role in diagnosis. Invasive clinical instruments such as thoracoscopy and pleural biopsy remain the final dependent diagnostic tools for malignant pleural effusion.

Data availability

All the data utilized to support the outcomes of this current study is available in the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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