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Carcinoembryonic Antigen Level as Potential Tumor Biomarker in Patients with Effusion; Khartoum, Sudan 2020

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Abstract

Background: *Effusions are fluids that accumulate within one or more serous cavities, (Pleural, Pericardial or peritoneal) resulting in a true fluid-filled cavity. They can be classified as Transudates or Exudative. A malignant effusion forms when cells from either a lung cancer or another type of cancer spread to the serous space. These cancer cells increase the production of effusion fluid and thus decreasing the absorption of the fluid. Certain tumor markers are used in screening for malignancies, such as, Carcinoembryonic antigen (CEA). Effusion fluid concentrations of CEA may be elevated in patients with certain malignancies that secrete CEA into circulation, including breast, gastrointestinal tract, colorectal, liver, lung and ovarian cancer.*

Methods: *The study aimed to estimate the value of Carcinoembryonic Antigen as a potential tumor biomarker in Sudanese patients with effusions a descriptive analytical (cross sectional) prospective laboratory-based study was done during the period from September to November 2020. The study was conducted in Al-Mubark Cytology Laboratory and Al Ribat University Hospital which are located in Khartoum state. A total of 50 consecutive patients with effusion were enrolled in the study after their approval has been acquired.*

Results: *At the cut-off value of 3.41 ng/ml, CEA showed a specificity of 100 % and sensitivity of 100%. There was a significant*

association with cytological diagnosis and CEA levels (0.00001) p value less than 0.05, CEA level in Negative samples (1.01 ± 0.028), Inflammation (1.12 ±0.475) and Malignancy (120.05± 137.278). Moreover, there was another significant relationship between heart disease and CEA levels (0.00001) p value less than 0.05. On the other hand, Gender showed insignificant difference with CEA level (0.743) p value more than 0.05.

Conclusions: *The quantitative measurement of CEA is a useful tool in predicting malignant effusions. Cytology-negative patients with high CEA levels should lead to further investigations, such as repeated cytological examination or thoracoscopy.*

Keywords: carcinoembryonic antigen, serous effusions, Body effusion cytology and tumor markers

BACKGROUND

Malignant effusions are a common clinical problem in patients with neoplastic disease. In one postmortem series, malignant effusions were found in 15% of patients who died with malignancies[1]. Advanced malignancies are frequently complicated by malignant pleural effusions (MPEs). They present either synchronously or as recurrence after the completion of treatment of the primary malignancy[1]. The pathogenesis of MPE is by hematogenous or lymphatic implantation of tumor cells or by direct extension of tumor cells from adjacent organs such as lung, breast, chest wall, or pleura[1].

Neoplasms of lung, breast, ovary, and lymphomas constitute more than 75% of cases of MPE less commonly, ovarian carcinoma, stomach cancer, sarcomas, melanoma[2].Metastatic adenocarcinoma is the most common cause. In male patients, lung cancer is the most common cause and in females, breast cancer is the most common cause[3].

Some of the greatest diagnostic dilemmas in cytopathology are in the field of effusion cytology. Hyperplastic mesothelial cells observed in various benign conditions can undergo cytologic alterations mimicking malignant cells. Extensive morphologic overlap

also exists between malignant mesothelial cells and metastatic carcinoma cells[4,5].

Nowadays, with the wide spread of cancer and malignancies, Effusions have become the primary or contributory causes of death in 86% of cancer patients worldwide [6] In Sudan, the prevalence of mortality caused by Cancer complication rate per year is 5,000 to 7,000 among Adults [6]. Despite the growing burden of cancer worldwide, it continues to receive low priority in Africa and specifically in Sudan. Therefore, diagnosing the cause of an effusion can be difficult and often require multiple types of analyses, which might be Complicated, expensive and Time consuming.

All that necessitate the use ofbiochemical examination of various tumor markers in patients with serous effusions is simple, cost effective and requires minimal invasive methods. Moreover, it can differentiate between effusions caused by non-malignant and malignant conditions and can enhance cytology and imaging findings. However, studies conducted in Sudan are very rare regarding biochemical analysis of effusions. Therefore, CEA results should be used in conjunction with cytological analysis of effusion fluid, imaging studies, and other clinical findings to obtain maximum beneficence and accuracy especially in negative cytological examination.

OBJECTIVES

The main objective of this study was to assess the quantity of Carcinoembryonic Antigen levels in Sudanese patients with effusion. Specifically, the study focused on estimating CEA level in fluid of patients with pleural, pericardial and peritoneal effusion, measure CEA level in benign and malignant serous effusions, analyze the association between serous effusion and demographic variables (age and gender), investigate significance of CEA levels with cytological examination, and analyze the correlation between heart disease and CEA level.

METHODS

A descriptive analytical (cross sectional) prospective laboratory-based study was done during the period from September to November 2020.

The study was conducted in a private laboratory which is located in Khartoum state. The study aimed to estimate the value of CEA in patients with serous effusions. A total of 50 consecutive patients with effusion were included in the study after their approval has been acquired. After samples centrifugation done at 3000 two drops of effusions were poured off on CEA Kit. Then were left for 10 monutes for incubation. And then read by Ichroma II and according to leaflet of the test . For the quality of work control sera were used with low , moderate and high concentration of CEA.

The test uses a sandwich immunodetection method; Dried antibodies in the detector tube, once diluted with the diluent, bind with antigens in the sample to form antigen-antibody complexes. These complexes then migrate through the nitrocellulose matrix and are captured by another sets of immobilized antibodies on the test line. The more antigens in the sample, the more antigen-antibody complexes, which leads to a stronger fluorescence signal. This signal then is interpreted by the reader to display the CEA concentration in the sample.

Plan for Data analysis: Data was entered and organized into Microsoft Office Excel 2010 data sheet, then for the analysis, Statistical Package for Social Sciences software, version 23.0 (IBM SPSS Inc.) was used. Initially, all information gathered via questionnaire were coded into variables. Normality of data was tested using Kolmogorov- Smirnov test. Both descriptive and inferential statistics involving Independent T- test, One way ANOVA test, Fisher's exact test, ROC curve to determine sensitivity and specificity of CEA cut off value were used to present results. For each test, a *p*-value of less than 0.05 was considered statistically significant.

RESULTS:

At the cut-off value of 3.41 ng/ml, CEA showed a specificity of 100 % and sensitivity of 100%. According to the the cytological examination - which is the golden technique for diagnosing effusions- with significant association P value with cytological diagnosis and CEA levels (0.00001) which p value is less than 0.05, CEA level in Negative samples (1.01 ± 0.028), Inflammation (1.12 ±0.475) and Malignancy

(120.05± 137.278). Moreover, there was another significant relationship between heart disease and CEA levels (0.00001) p value less than 0.05. On the other hand, Gender showed insignificant difference with CEA level (0.743) p value more than 0.05.

Table [1] shows cross tabulation between CEA level with Gender, Cytological diagnosis and heart disease.

Variables		CEA		Fisher's Exact Test P value
		Normal	Elevated	
Gender	Female	16	6	0.743*
		72.70%	27.30%	
	Male	22	6	
		78.60%	21.40%	
Cytological diagnosis	Malignant	1	14	0.00001**
		6.67%	93.33%	
	Benign	35	0	
		100.00%	0.00%	
Heart diseases	Yes	1	11	0.00001**
		8.3%	91.7%	
	No	31	7	
		81.6%	18.4%	

Table [2] shows cross tabulation of CEA level in cytomorphological findings (Negative, inflammation and malignancy)

One Way ANOVA-Test						
Variables		Number	CEA level			P value
			Mean	S.D	Std. Error	
Cytomorphological findings	Negative	19	1.01	0.028	0.006	0.00001**
	Inflammation	16	1.12	0.475	0.119	
	Malignancy	15	120.05	137.278	35.445	
	Total	50	36.76	91.754	12.976	

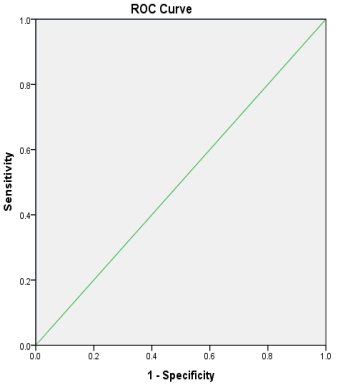

Figure [1] ROC curve that shows sensitivity and specificity of CEA cut off value.

Table [3] CEA cut off value

Positive if Greater than or Equal To[a]	Sensitivity	1 - Specificity
.00	1.000	1.000
1.06	1.000	.081
1.28	1.000	.054
1.67	1.000	.027
3.41	1.000	.000
4.76	.923	.000
8.22	.846	.000
9.91	.769	.000
36.81	.692	.000
66.61	.615	.000
77.43	.538	.000
105.02	.462	.000
126.10	.385	.000
200.61	.308	.000
275.59	.231	.000
323.85	.154	.000
374.09	.077	.000
378.87	.000	.000

DISCUSSION:

The sample size of the study was 50 patients with effusion, 28 (65%) were males and22 (44%). Females. The mean age of the participants was (54±17). 17 (34%) were between the age of 20-49 years old while most of the study group 33 (66%) were 50 years and older which was slightly lower than the median age 69 (31–95) found by Klaus Hackner[7].

As for Smoking in this study, there was no apparent effect on CEA level or the occurrence of effusion. Both smokers, who were 19 (38%) participants and nonsmokers, 31(62%) had variable CEA levels. This study contradicts the findings of the study done by Khan Mohammad Sajid, et al [8]. which concluded that smoking plays an important role in raising CEA level.

On the other hand, Heart disease showed a significant association with effusion and higher CEA levels with a p value of (0.00001**). These findings were in line with the study done by VasanthiPerumal[9]. which stated that CEA levels are higher among stroke patients.

Moreover, there was another significant association with Cytological diagnosis and CEA levels (0.00001) p value less than 0.05. Malignant effusions presented with much higher levels of CEA

(120.05± 137.278) while benign conditions, such as negative samples (1.01 ± 0.028) and inflammation (1.12 ±0.475) had lower CEA levels respectively. This property is what makes CEA a potential marker for differentiating malignant from benign effusions. These observations were on the same line with the studies made by Renato Tozzoli[10], K Karatolios[11].

Furthermore,The CEA cut off value of 3.41 ng/ ml showed high sensitivity and specificity of 100%. This result was higher than cut-off of 1.0, the CEA ratio showed a specificity of 92% and sensitivity of 85%, with a positive predictive value of 91% and a negative predictive value of 87% originated by Klaus Hackner[7].

CONCLUSIONS:

From the results of this study the following conclusions were conducted:

- The most common type of effusion was pleural effusion followed by peritoneal effusion.
- Both sexes have an equal chance to get diseased with effusion.
- Malignant Effusions were more common in the elderly group (50 years and older).
- Malignant effusions had higher CEA levels than Benign effusions. thus, confirming its efficiency in differentiating malignant from benign effusions.
- Heart disease is associated with high level of CEA.
- The cut off value of CEA level for malignancy is 3.41 ng/ml with specificity and sensitivity of 100% compared with cytopathological examination, which is the golden standard of diagnosing effusion.

RECOMMENDATIONS:

Based on the results and conclusions drawn from the study, the following recommendations are suggested:

- Applying of CEA level measurement for differentiating benign from malignant effusion.
- Any effusion sample with 3.41 ng/ml and above should be examined along with cytopathological diagnosis for suspicious malignancy.

- In case of suspicious or negative cytology with high CEA level and in absence of visible tumor, Cytopathological examination should be repeated. Furthermore, Other investigations should be done such as thoroscopy and other imaging techniques.
- Follow up for monitoring of patients after treatment by measurement of CEA.
- Further study with larger samples with more tumor markers and more advanced techniques should be done.

LIMITATIONS:

Due to the occurrence of Covid-19 pandemic, the collection of the effusion samples was very challenging. Time for specimen collection was also very challenging, not so many patients with effusion attended both Al-Mubark Cytology laboratory and Alribat University Hospital.

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