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Original Research Article

The Role of Bronchial Wash Carcino-Embryonic Antigen Assay In The Diagnosis of Non-Small Cell Lung Cancer

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Abstract

The bronchogenic cancer is one of the most common cancers in human kind & it represents a diagnostic challenge because of the most available tests are either yielding in the late stages or it is some of invasive nature ,so the need for diagnostic test in the early stages is mandatory, aim of the study is to assess the significance of bronchial carcino-embryonic antigen (CEA) as a tumour marker for aiding the diagnosis of non-small cell lung cancer (NSCLC) and to see if there is any difference between the serum & bronchial CEA and between tumour and non-tumour sides

Thirty patients were involved in this study ,divided into 3 groups according to their diagnosis as cancer ,airway disease & Tuberculosis groups, assessment of their socio-demographic features ,clinical features chest X ray ,computerized tomography (CT) scan , fibro-optic bronchoscopy were done & the carcino-embryonic antigen (CEA) level were tested in the samples taken from serum, tumour& non-tumoursides.

There was a statistically significant difference in the level of the carcino-embryonic antigen in the bronchial wash of cancer patients group comparing to the serum of the same group & to the bronchial wash level in the other groups in favor of the cancer group patients, but no difference between the tumour& non tumour sides in the cancer group patients.

The carcino-embryonic antigen assay in the bronchial wash may be helpful in the diagnosis of non-small cell lung cancer& may be take into consideration in the future work up

Key words: Tumor markers, serum carcino-embryonic antigen, bronchial carcino-embryonic antigen, bronchial wash ,non-small cell lung cancer.

الخلاصة

السرطان الرئة القصبي المنشأ واحدة من أكثر أنواع السرطان شيوعا في النوع البشر وتمثل تحديا في التشخيص بسبب ان الاختبارات المتاحة إما تكون ذات شأن تشخيصي في المراحل المتأخرة أوتداخلية بعض الشيء، وبالتالي فإن الحاجة إلى اختبار تشخيصي في مراحل مبكرة صار امرا إلزامية, الهدف من الدراسة هو لتقييم أهمية CEA في السائل القصبي كعلامة للورم لمساعدة في تشخيصNSCLC و لنرى هل هناك أي فرق بين المصل و CEA الشعب الهوائية وبين جانبي الورم وغير الورم.شارك 30 مريضا في الدراسة، وتنقسم الى 3 مجموعات وفق لتشخيصهم: السرطان وأمراض الشعب الهوائية ومجموعات السل، تم دراسة الخصائص الاجتماعية والديموغرافية، وميزات السريري ,اشعة الصدر ، والاشعة المقطعية وناظور القصبات الليفي البصري. مستوى CEA تم قياسه في العينات المأخوذة من مصل الدم ومن سائل الشعب القصبية من جانب الورم ومن الجانب الاخر . كان هناك فروق ذات دلالة إحصائية في مستوى CEA في السائل القصبي في مجموعة مرضى السرطان مقارنة مع المصل من نفس المجموعة وعلى مستوى السائل القصبي في المجموعات الأخرى لصالح مرضى مجموعة السرطان، ولكن لافرق بين المستوى من جانب الورم والجانب الاخر في مرضى مجموعة السرطان

فحص مادة (CEA) في السائل القصبي يمكن أن تكون مفيدة في تشخيص NSCLC ويمكن أن تأخذ بعين الاعتبار في العمل في المستقبل.

الكلمات المفتاحية: علامات الاورام، المستضد السرطاني الجنيني في مصل الدم ،المستضد السرطاني الجنيني في السائل القصبي , الغسل القصبي،سرطان الرئة ذو الخلايا غير الصغيرة.

Introduction

Lung cancers have the highest incidence and mortality of all cancer worldwide [1].

In contrast to the reducing mortality rate in men, lung cancer mortality rates in women have been increasing over the recent years [2].

There are two main variants of the disease:

- SCLC
- Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers. Histologically, NSCLC is divided into types as adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma [3].

There are many methods of confirming the diagnosis which include the following:

- Sputum cytology
- Endoscopy of the bronchus
- Transthoracic needle biopsy (CT- or fluoroscopy-guided)
- Mediastinoscopy
- Pleural fluid aspiration & analysis
- Thoracoscopy [2,4]

Do we need new diagnostic tools for NSCLC ?

There are important points:

1- In patients with NSCLC, some genetic and regulatory abnormalities have been considered vital for the cancer survival advantage. In this way, some researcher focus on the evaluation of a variety of tumor associated antigens (TAAs) for a better & early diagnosis[5]

2- Lung cancer patients often do not exhibit specific symptoms, particularly in early stages. Therefore, the majority of lung cancer patients are diagnosed at late stage, which limit their beneficial treatment. recently, conventional diagnostic tests such as chest radiographs, computed tomography (CT) scans, and fiber optic bronchoscopy (FOB) are not sensitive enough for effective early diagnosis. Meanwhile, the benign pulmonary nodules and malignant cancer cannot be distinguished by imaging methods currently . Whereas, the pathological and cytological detections needed to obtain tissue samples are invasive and difficult to be done again[6]

3- Endemic infectious lung disease may reduce accuracy of PET scanning for lung cancer

In a meta-analysis of 70 studies, it had been seen a high levels of heterogeneity in the accuracy of FDG-PET scanning for diagnosing lung nodules. Screening with FDG-PET with computed tomography was less specific in diagnosing malignancies in areas with endemic infectious lung disease compared with areas with non-endemic disease. A 16% lower average adjusted specificity was observed in endemic regions compared with non-endemic regions[7]

The New Era diagnostic tools:

- **Advance Bronchoscopy:** as basic bronchoscopy with some technical advances that increase the diagnostic yield as:
  - autofluorescence bronchoscopy (AFB)
  - the narrow-band imaging bronchoscope (NBI)
- Optical coherence tomography (OCT)
- Confocal fluorescence microscopy
- Molecular Screening of blood,sputum or bronchial wash[5,8,9,10].

Tumour markers & bronchogenic carcinoma

Tumour markers are products found in tumour cells or body fluids. They are made by the tumour, or the host in response to the presence of the tumour and can be beneficial in differentiating tumour from normal tissue or determine the presence of a tumour[2,10].

Carcino-embryonic antigen (CEA):

It was first described in 1965 by Gold and Freedman, was characterized as a glycoprotein of 200 KD.[11,12]
It is normally produced in fetal life, but the production of CEA stops before birth. Therefore, it is not usually seen in the blood of healthy adults, although levels may increase in heavy smokers.[13,14]
The aims of this study was to:
1- assess the significance of bronchial CEA as a tumour marker for the diagnosis of NSCLC
2- seeif there any difference between the serum & bronchial CEA in patients with NSCLC
3- correlate the bronchial CEA level in tumour& non-tumour sides with the diagnostic significance
4- correlate the serum & bronchial CEA with multiple patients variables

Materials and Methods

A case control study include30 patients 15 male & 15 femaleage ranging from 41-70 years,from Dec. 2013 to Sept. 2014, conducted in AL-Immamam Al-Kademmain medical city, Baghdad.

Inclusion criteria

1- Any patients who were refer to our unit for donning fibro-optic bronchoscopy for solid reasons(mention below) & he accept to participate in the study
2- Patients found to have endo-bronchial lesion macroscopically in the FOB & the results return to be NSCLC by 2 pathologists
3- Patients have normal FOB (macro- & microscopically) with evidences of COPD by HRCT & PFT
4- Patients have lung parenchymal lesions on radiological tests & fail to produce sputum with +ve TB tests

Exclusion criteria:

1- Any patients with uncertain diagnosis
2- Any patients with mixed diagnosis as cancer with COPD or TB with COPD
3- Any patients with any cancers rather than NSCLC
4- Any patients with liver or GI diseases
5- Any patients with hemolytic ,icteric or lipemic serum as it interfere with the test result
6- Any patients enrolled in other studies
7- Any patients with unstable personality or psychiatric disease

For all included patients:
- written consents were taken from patient to participate in the study
- concentrated history& physical exam were done to them.
-Chest X Ray were done for all patients
-for all patients chest CT(16 chest CT with contrast & 14 HRCT of chest) were done .
-3 ml of blood were collected from a peripheral vein & were sent to CEA assay
-Fibro-optic bronchoscopy (storz type)were done to all patients.

The bronchial samples were centrifuged & the precipitate was taken for cytology & the supernatant was divided into plain test tubes & sent for :
- Fluid for AFB smear
- Fluid for gene X-pert
- Fluid for TB culture
- Fluid for CEA

After we receive the results, the patients were divided into 3 groups:
1- Patient with NSCLC :10 patients all were diagnosed as NSCLC by 2 pathologists, 5 the diagnosis based on +ve cytology in bronchial wash,3 +ve brush & 2 by percutaneous CT guided FNA
2- Patients with airway diseases: 11 patients with COPD & bronchiectasis diagnosed by PFT & HRCT
3- Patients with inflammatory parenchymal respiratory diseases namely pulmonary TB: 9 patients diagnosed as TB by +ve AFB smear in bronchial wash in 6 patients,2 patients +ve gene X-pert in wash & 1 +ve culture of the wash

Results

There were no differences between the types of diseases groups regarding the age & gender with P values 0.26 & 0.89 respectively. Meaning the 3 study groups are matched

Table 1: The Distribution of Cancer Patients group by Socio-Demographic Characteristics

Variable		No. of pat.	% of pat.	total
gender	Male	4	40	10
	Female	6	60	
Clinical presentation	SOB	2	20	10
	Hemoptysis	1	10	
	Cough	7	70	
smoking	smoker	6	60	10
	Non-smoker	4	40	
Duration of symptoms	Duration <6 months	9	90	10
	Duration >6months	I	10	
Lesion site	Rt. Side	6	60	10
	Lt. side	4	40	

Table 2 :CEA values in the serum of the 3 patients groups

Variable	Type of disease	N	Mean ± SD	F-test	P-value
	CA	10	2.95 ± 1.95		
Serum (CEA)	**TB**	9	3.38 ± 1.96	0.994	0.383
	Airway dis.	11	2.26± 1.51		

The CEA values analysis

There were no statistically significant differences in between CEA values between the three study groups regarding the serum (table 2)&the bronchial wash levels regarding side vs. side levels (Table 3) with P value 0383 & 0.596 respectively.

Table 3: CEA values of the bronchial wash of tumour non tumour sides

Variable	Categories	N	Mean	Paired ttest	df	P value
CEA (Ng/ml)	Tumor side	10	15.77	-0.549	9	0.596
	Non-tumor side	10	21.56			

as there is no difference in between the tumour & non tumour sites in all diseases groups so the mean of the both sides were measured & taken as bronchial CEA level as the normal level of the CEA in the bronchial fluid is not equal to that of the serum & no accurate cut for the normal limit is set so trials for the cut level were conducted on 5,10,15 & 20 Ng/ml & show the significant differences stared from 15 Ng/ml .

There was significant association between bronchial CEA and type of disease (table 4) & between the bronchial wash & serum levels (table 5) with P-value 0.016& 0.007 respectively.

Table 4 : the CEA bronchial wash levels in the 3 study groups

Characteristic	Type of disease			P-value
	CA (%)	TB (%)	COPD (%)	
Bronchial CEA (Ng/ml)	6 (60.0)	0 (0.0)	5 (45.5)	
≥15	4 (40.0)	9 (100.0)	6 (54.5)	0.016*
< 15				

Table 5: the CEA levels between the bronchial wash & the serum					
Variable	**Categories**	**N**	**Median**	**Z**	**P value**
CEA (Ng/ml)	bronchial wash	10	15.67	-2.701	0.007*
	Serum	10	2.05		

By analyzing the differences of serum (CEA) by study variables among CA patients. There were significant differences between means of serum (CEA) by smoking habit, while there were no significant differences between means of serum (CEA) for other study variables while there were no differences between the study variables & the bronchial wash CEA level as shown in tables 6 & 7 respectively.

Table 6: the relationship of serum (CEA) by study variables among CA patients

Variable	**Categories**	**N**	**Mean ± S.D**	**t-test**	**P value**
Gender	Male	4	2.64 ± 1.86	-0.395	0.704
	Female	6	3.15 ± 2.10		
Smoking habit	Smoker	6	3.93 ± 1.84	2.489	**0.038***
	Non smoker	4	1.48 ± 0.73		
Mode of presentation	Cough	7	2.79 ± 2.22	- 0.391	0.706
	Other presentation	3	3.33 ± 1.17		
Duration of disease	< 3 month	5	2.92 ± 2.29	-0.048	0.963
	≥ 3 months	5	2.98 ± 1.73		
Side of lesion	Right	6	3.31 ± 2.3	0.717	0.494
	Left	4	2.40 ± 1.24		
Co-morbidity	Present	2	2.05 ± 0.07	-1.511	0.174
	Absent	8	3.17 ± 2.10		

Table 7:the relationship of bronchial (CEA) by study variables among CA patients

Study variables	Bronchial CEA		P-value
	≥15 (%)	< 15 (%)	
Gender			
Male	2 (33.3)	2 (50.0)	1.000
Female	4 (66.7)	2 (50.0)	
Smoking habit			
Smoker	5 (83.3)	1 (25.0)	0.19
Non smoker	1 (16.7)	3 (75.0)	
Mode of presentation			
Cough	5 (83.3)	2 (50.0)	0.5
Other presentation	1 (16.7)	2 (50.0)	
Duration of disease			
< 3 months	3 (50.0)	2 (50.0)	1.000
≥ 3 months	3 (50.0)	2 (50.0)	
Side of lesion			
Right	5 (83.3)	1 (25.0)	0.19
Left	1 (16.7)	3 (75.0)	
Co-morbidity			
Present	1 (16.7)	1 (25.0)	1.000
Absent	5 (83.3)	3 (75.0)	

Discussion

I- Regarding the demographical features of the cancer group:

the age is above 50 years as the disease commoner in elderly due to prolonged exposure time to the risk factors as smoking.

Regarding the gender in the study is more in female 60% which is against the expected male predominance but this can be explained on the base of small sample size & the study include only the non-small cell bronchogenic cancer not all the types of bronchogenic cancer.

The commonest mode of presentation is cough while the hemoptysis is the least common & the duration of the symptoms in the cancer group is shorter in relation to the airway diseases as the symptoms in the latter group is usually slowly progressive.

The site of the cancer is more common on the right side & that can be explain by the larger size of the right lung.

II- regarding the carcino-embryonic antigen values:

1- There are no difference in between the bronchial wash level in tumour& non tumour sites which may indicate no benefit for the CEA level in the localization or there is some sort of contamination between the both side fluid in the lungs or can indicate micro-metastasis between the two sides make the CEA level about the same

2- There is a statistically significant difference between the bronchial & serum CEA in the cancer group which mean the use of bronchial CEA may aid in diagnosis even when the serum level is normal which can be explain on the base of earlier stage, direct excretion of the antigen from the endobronchial growth or poor serum CEA reaction to endobronchial NSCLC.

The failure of finding a significant role of serum CEA assay in the diagnosis of bronchogenic cancer is consistent with most of the study that state a weak

diagnostic benefits as comparing with the follow up,response to treatment & disease recurrence.

3- The level of statistical differences is increased with increasing the cut value of the CEA test as in 5ng/l with no significant difference to 20 ng/l as a very significant finding with the 15 ng /l (taken as the standard in this test) is the 1st level with statistical significance, this finding is against most of the paper that state the level of CEA in the serum is equal to that of the body fluid (except CSF) as pleural fluid or pancreatic cyst aspirate.

In JinHuretal study they use the cytological fluid from a transthoracic pulmonary nodules aspirate to measure the CEA level they face the same problem of no defined normal valve for CE in the cytological fluid so they use 0.6 ng/ml which is much lower than our cut level of 15 ng/ml or even that of the pleural fluid =5 ng/ml,but really there is no published study about the use of such test in the bronchial wash as in our study.

III- Regarding the correlation of the CEA level with study variables:

There are no statistical differences among all the variables with the bronchial level while only the smoking affect the serum level meaning the effect of the smoking on the serum level (increase the serum level by the smoking without an accompanied diseases) is not seen in the bronchial CEA level which mean more specific for the diseases.

The finding of higher serum level of CEA in smoker is go with all the papers that where mention in the introduction

Conclusions

1- The bronchial CAE assay may be useful diagnostic test for NSCLC & can add weight to the other diagnostic tools

2- The serum CEA is not useful as bronchial level in diagnosis

3- There is no similar effect of smoking on the bronchial level of CEA as the serum level which can be affected by smoking without other pulmonary diseases

4- There is no difference in the diagnostic significance of localization of the bronchial CEA test as both the tumour& non tumour sides show non-significant different results

5- Thereare no affection of the serum & bronchial CEA level with many socio-demographic variable for the patients which mean it can be a specific test.

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