SIGNIFICANCE OF TUMOR MARKERS IN LUNG CANCER

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ABSTRACT

The objective was to test the utility of the cytokeratins CYFRA 21-1, tissue polypeptide specific antigen (TPS), Neuron specific enolase (NSE) and Carcino Embryonic antigen (CEA) in patients with lung cancer and in the pleural fluid of the patients with lung cancer and also the predicting ability of these tumor markers with respect to the histological types [including non small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)] and pathological stages. 40 normal subjects and 222 cases of histological proven lung cancer were studied. The findings suggest that TPS and CYFRA 21-1, are useful serum markers for the diagnosis of NSCLC and NSE seems to be useful tumor marker for monitoring course of patients especially SCLC. The combined use of these cytokeratin markers TPS and CYFRA 21-1 may provide additional information for prognosis.

INTRODUCTION

Tumor markers are not only of significance to the researcher in understanding tumor biology, but also to the clinician in treating patients with cancer (1). In oncology practice, the use of tumor markers may be helpful in the diagnosis and pathologic classification of tumors. Tumor markers may reflect both, stage of the disease and prognosis. Serial estimation after diagnosis may aid in assessing the response to treatment, in monitoring the spontaneous course of illness, and in keeping surveillance for tumor recurrences (2).

Markers originating from the cytoskeleton, are of practical interest(3). Tissue polypeptide antigen (TPA) has been defined as the degradation product of the cytoskeleton formed by the cytokeratin (CK) 8,18 and 19 (4). CK19 fragments (CYFRA 21-1) is a new cytoskeleton marker that measures only the level of CK19 (5). TPA and CYFRA 21-1 are helpful in the clinical management of non small cell lung cancer (6-8).

AIM OF STUDY

In the last few years, several prognostic factors have been investigated in order to identify the patients with completely resected lung cancer subsets at high risk of recurrence. In this context, the actual role of serum tumor markers is still unclear. The diagnostic value

of tumor markers in pleural effusion is also not yet clearly defined. Therefore, the aim of this study was to evaluate the clinical significance of the tumor markers TPS, CYFRA 21-1, NSE and CEA in pleural fluid and sera of group of patients with lung cancer and to study the diagnostic utility and the predicting ability of these tumor markers with respect to histological types and pathological stages was also assessed. Histological classification was done according to the Veterans administration lung group (VALG) and pathological staging according to the International Union Against Cancer (UICC) staging system.

PATIENTS AND METHODS

Two hundred and eighty three subjects which comprised of 222 cases of lung cancer, 21 pleural fluids of patients with lung cancer and pleural effusion and 40 normal healthy ambulant controls were included in this retrospective study. Fasting blood samples collected, were allowed to clot and the serum separated after centrifugation at 4000 rpm for 10 minutes was used for analysis. Pleural fluid tapping were also centrifuged at 4000 rpm for 10 minutes and analyzed.

MARKER EVALUATION

TPS was measured by means of enzyme-immunological assay with a commercial kit from BEKI Diagnostics AB, Bromma, Sweden; CYFRA 21-1 was measured by means of enzyme-immunological assay with a commercial kit supplied by Boehringer Mannheim immunodiagnostics and that of NSE were determined by assay kit supplied by Can-Ag Diagnostics. CEA was estimated by using Abbot's AxSYM System which is based on Microparticle Enzyme Immunoassay (MEIA) technology.

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TPS, CYFRA 21-1, NSE and CEA levels were evaluated in all the 222 lung cancer patients and 40 normal controls as well as in pleural effusion of 21 patients with lung cancer. The serum samples and pleural fluids were stored at -20°C until analysis was performed.

RESULTS

The cut-off levels for serum were 80 U/L for TPS, 3.3 ng/ml for CYFRA 21-1, 13 g/l for NSE and 5 ng/ml for CEA level.

STATISTICAL ANALYSIS

The results were evaluated statistically using ANOVA.

Tumor Markers in Total cases of lung cancer

When the normal were compared with the total cases of lung cancer, except CYFRA 21-1 all the other parameters were significantly elevated ($p < 0.001$).

Tumor Markers in lung cancer stage wise

Table 1 gives the serum levels of TPS, CYFRA 21-1, NSE and CEA in normal, total number of patients with lung cancer and also the levels in patients with lung cancer stage wise (stage II, stage III and stage IV).

On comparing lung cancer cases stage wise with the normal, a significant elevation in the values of TPS, ($p < 0.001$) was observed in stages II, whereas CYFRA 21-1, NSE levels were found to be elevated in

stage II, III and IV ($p < 0.001$). The CEA values were significantly elevated in stage II ($p < 0.001$) but did not differ significantly with stage III & IV of disease.

Tumor Markers in Lung cancer classified on the basis of their Histology

Table 2 gives the levels of TPS, CYFRA 21-1, NSE and CEA in patients on the basis of their histology.

Significantly elevated levels of TPS ($p < 0.001$) was found in squamous cell carcinoma, CYFRA 21-1 ($p < 0.001$) was found in adenocarcinoma, squamous carcinoma and non-small cell lung cancer (NSCLC), NSE was elevated significantly ($p < 0.001$) in small cell lung cancer (SCLC) whereas CEA levels were elevated in adenocarcinoma and squamous carcinoma ($p < 0.001$).

Tumor Markers in Pleural effusion of patients with lung cancer

In the pleural effusion of patients with lung cancer, the levels of TPS, CYFRA 21-1, NSE was found to be elevated whereas the CEA levels did not show any rise. These findings are in agreement with the findings of Lai (9).

Our study showed that TPS, CYFRA 21-1 and NSE markers had 94% sensitivity, where as sensitivity of CEA marker was 54%, while specificity of TPS, CYFRA 21-1 and NSE markers was 95% and that of CEA marker was 56%.

Table 1. Serum levels of TPS, CYFRA 21-1, NSE and CEA in normal, total patients with lung cancer and also the levels in patients with lung cancer stage wise (stage II, stage III and stage IV)

Group		TPS U/L	CYFRA 21-1 ng /ml	NSE g/l	CEA ng/ml
Normal (n = 40)	Range	0 - 80	0.0 - 3.3	0 - 13	0 - 2
	Mean±S.E.	34.9±4.1	0.5±0.2	6.2±0.6	0.9±0.6
Lung cancer total cases (n = 222)	Range	0 - 3842	0 - 90	0 - 170	0.6 - 588
	Mean±S.E.	242.7±27.5*	81.7±38.4*	38.7±2.9*	78.5±8.5*
Lung cancer Stage II (n = 56)	Range	10 - 3842	0 - 90	0 - 170	2.5 - 576
	Mean±S.E.	351.6±90	24.5±6.9*	47±6*	121±21.8*
Lung cancer Stage III (n = 123)	Range	0 - 1271.5	0 - 80	0 - 160	0.6 - 588
	Mean±S.E.	239.7±22.5*	125.4±8.5*	33.2±8.2*	71.7±10.6
Lung cancer Stage IV (n = 43)	Range	15.2 - 1364	0 - 90	0 - 170	0.8 - 500
	Mean±S.E.	194.1±42.9*	32.3±4.3*	41.4±6.9*	59.8±13.0
Cut Off Level		80.0	3.3	13.0	5.0

* $p < 0.001$

Table 2. Levels of TPS, CYFRA 21-1, NSE and CEA in serum of patients with lung cancer depending on their histology and also in the pleural effusion of patients with lung cancer

Group		TPS U/L	CYFRA 21-1 ng /ml	NSE g/l	CEA ng/ml
Adeno carcinoma (n = 133)	Range	10-3842	0-90	0-170	0.6-588
	Mean±S.E.	223.4±4.602*	36.8±0.353*	27.9±0.386	81.8±1.348*
Squamous carcinoma (n = 55)	Range	0-3000	0-90	0-145	0.8-587
	Mean±S.E.	348.4±13.34*	31.7±0.78*	33.75±1.06*	103.34±3.79*
NSCLC (n = 56)	Range	24.2-2000	0-90	0-140	1-573
	Mean±S.E.	297.33±15.82	38.9±1.38*	31.39±1.76	90.7±5.53
SCLC (n = 34)	Range	12.5-773	0-80	15.173	0.9-284.8
	Mean±S.E.	175.51±3.15	16.96±0.38	66.78±7.7	52.34±1.5
Pleural effusion (n = 21)	Range	640-3000	53-140	130-190	0.4-600
	Mean±S.E.	1419.5±122.7	57.3±3.3	158.6±110.32	30.8±28.5

* p < 0.001

Note : The levels of TPS, CYFRA 21-1, NSE and CEA were studied in serum of 133 patients of NSCLC, 55 patients SCLC and 34 patients with other histological type. These parameters were also studied in pleural effusion of 0.21 lung cancer patients.

DISCUSSION

The current study is the attempt to compare the two known cytokeratin TPS and CYFRA 21-1 and also to study the combined use of these two cytokeratin markers TPS and CYFRA 21-1 (6). Our study showed elevated levels of TPS which is in agreement with the findings of Buccheri *et al.* who evaluated a panel of different tumor markers and found TPA to be more useful than CEA (10). Combining the two cytokeratin markers - TPS and CYFRA 21-1, 88% elevation was seen in lung cancer patients and 100% in lung cancer patients with pleural effusion. Raised levels of NSE were also seen in lung cancer patients as well as in pleural effusion with lung cancer patients.

CEA did not seem to be specific for this disease, when combined with TPS, CYFRA 21-1 and NSE markers. To assess the levels of CYFRA 21-1, CEA and NSE, Barlesi (11) reported that the combination of the three markers remained a prognostic determinant.

CONCLUSION

In conclusion, findings suggest that TPS and CYFRA 21-1 are useful serum markers for the diagnosis of NSCLC and NSE seems to be useful tumor marker for monitoring course of patients especially SCLC. The combined use of these cytokeratin markers TPS and CYFRA 21-1 may provide additional information for prognosis.

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