The diagnostic values of serum and bronchoalveolar lavage carcinoembryonic antigen, tissue polypeptide antigen and ferritin levels in lung cancers*

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The diagnostic value of serum and bronchoalveolar lavage (BAL) levels of carcino embryonic antigen (CEA), tissue polypeptide antigen (TPA) and ferritin in pulmonary malignancies were evaluated. Serum CEA levels in malignancy cases were higher than the benign cases, regardless of the cell type ($p<0.05$). BAL CEA levels presented no difference among the group. Serum ferritin levels showed no difference among the groups. BAL ferritin levels either standardised or not, were significantly lower in SCLC cases, when compared with benign cases. Serum TPA levels were found to be significantly higher in NSCLC group than in benign cases ($p<0.05$). When the sensitivity and specificity values of tumor markers were in to considered separately or together, it was found that it showed no superiority to study these parameters together. [Turk J Med Res 1994; 12(6): 243-248]

Key Words: Lung cancer, Bronchoalveolar lavage, Tumor markers

The early diagnosis of the tumor in pulmonary malignancy has great importance in terms of radiotherapy, chemotherapy and the planning of the surgical aspect. In order to achieve an early diagnosis, to be informed about the disease and to observe how the disease responds to the treatment, measurable values are needed. It is known that important parameters are available in investigating the early diagnosis and disease activities of some biochemical substances which may arise from malignancies.

Studies have been increased in recent years to establish specific tumor markers and many tumor markers have been defined which are thought to be useful in the diagnosis of tumors of several types, in the staging procedure and in setting the treatment method.

In this study, CEA, TPA and ferritin levels in serum and bronchial secretions in pulmonary malignancy and benign cases were investigated and the results were discussed through comparison with the literature.

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MATERIALS AND METHODS

38 male and 4 female patients, a total of 42 patients who applied to the Atatiirk Chest Diseases and Surgery Centre for diagnosis and medical treatment through the dates January-May 1992 were included to the study. The diagnosis and numeric distribution of the patients is shown in Table 1.

The ages were between 17 and 76, (median=52.5).

The malignancy diagnosis was set by evaluating sitologically and pathologically the tissue sample obtained by bronchoscopic forceps biopsy, bronchoalveolar lavage, surgically or by a needle biopsy under computerized tomography of the 3 lung tuberculosis cases in the control group, 1 was miliary tuberculosis, the other patient was medically treated for lung tuberculosis. The miliary tuberculosis diagnosis was set by transbronchial biopsy and endobronchial tuberculosis diagnosis by bronchoscopic forceps biopsy.

We used an Olympus BF Type 1 TD20 D (Olympus Hyde Park New York) fiberoptic bronchoscope in our study.

In 24 patients with lung cancer, BAL was taken from the segment where lesion arose, and in 5 patients without an endobronchial lesion, from the seg-

Table 1. The diagnosis of patients and their numeric distribution

Diagnosis	Patient number
Malignancy	31
SCLC	12
NSCLC	19
Epidermoid carcinoma	10
Adenocarcinoma	7
Bronchioalveolar carcinoma	1
Large cell carcinoma	1
Control group	11
Pneumonia	5
Lung tuberculosis	3
Bronchiectasy	1
Condroma	1
Chronic obstructive lung disease	1

ment determined by conventional radiography or Computed Tomography (CT). Of the patients constituting the control group, BAL was taken from the involved segment, and in events with a spread lesion, from the middle lob or lingula. Before a BAL was taken, procedures like biopsy or brushing were not applied. The obtained hemoragical lavages were not included to the study. After the fiberoptic bronchoscope was set to the relevant segment, a total of 80 ml saline physiologic was intraduced at four times. Suction was applied after each instillation. The obtained BAL, after being centrifuged for 10 minutes at a speed of 3500 rpm, and taking 5 cc of its supernatant, was preserved to be worked on at 20°C.

10 cc of blood was taken from patients after bronchoscopy. The blood samples were left to room temperature for an hour, providing thus a clot. After centrifuge, the obtained serum sample was preserved at -20°C untill a work was held.

For a BAL standardization, the BAL tumor marker values were measured for a ratio with the total protein levels.

The CEA in the serum and BAL was measured with the ELISA method by using a "Eurogenetics CEA" kit.

In general, the cut-off value of the serum CEA level in the literature is taken to be 5 ng/ml. However, there is no standard value in terms of the cut-off value of the CEA in bronchus lavage, and different values are submitted about this. While Goldstein (1) marks this value to be 35 ng/ml total protein, the same value is accepted to be as 1 ng/ml albumin, too (1,2). The cut-off value of the nonstandardized BAL is taken to be 100 ng/ml (13).

In our study, we took this value to be 5 ng/ml for serum CEA, standardized 5 ng/ml for CEA in BAL and as 20 ng/ml without the presence of protein.

The ferritin in serum and BAL was measured by the EIA method by using the "bio Merieux Ferritine EIA" kit. The normal boundaries of the serum ferritin level at men is accepted to be 17-200 ng/ml, and 14-150 ng/ml at women. The cut-off value for BAL is taken to be 30 ng/ml, and 100 ng/ml for standardized BAL

The TPA in serum and BAL is measured by the IRMA method using a "BEKI Diagnostic A.B. TPS-irma" kit. The molality values are 1000 U/L for serum, 1000 U/L for BAL and 3 U/ml for standardized BAL.

The BAL total protein levels were determined by the "Lowry" method.

The results were evaluated by the "student t" test among groups.

RESULTS

The serum CEA levels were found to be above the cut-off value in 45% of the events with SCLC. The serum CEA level was in 47.5% of the patient with NSCLC high. In this group, the highest value 100 ng/ml was determined in two patients with adenocarcinoma (Figure 1).

When benign and SCLC cases were compared in terms of serum CEA levels, it was found that in the group with SCLC this value appears to be statistically significant ($p<0.05$). The serum CEA level in NSCLC cases showed a higher significance with respect to the benign group ($p<0.05$) (Table 2).

In pulmonary malignancy cases, a statistically significant difference among the groups in terms of the nonstandardized BAL CEA levels was not determined.

There was no statistically significant difference between the malign groups and benign cases.

The standardized BAL CEA levels were found to be high in 89.47% of the NSCLC event and in 72.7% of the benign events. Standardized BAL CEA levels were hight in each three group. The percentage of the CEA hight in pulmonary malignancy cases was more than the others', and a statistically significant difference among the groups was not determined ($p>0.05$).

The serum ferritin levels were found to be high in 54.5% of the patients undergoing a SCLC, in 21% of patients with a NSCLC and in 31% of benign cases. When BAL and BAL ferritin levels were compared with the groups, the result in SCLC patients was determined tube significantly low with respect to the benign group ($p<0.05$).

The serum TPA levels were found to be above the cut-off value in 66% of the SCLC events, in 68.42% of the NSCLC events and in 54.5% of the benign events. The TPA levels in NSCLC events were presenting a statistically significant hight with respect to the benign control group ($p<0.05$).

With the method of our study, by evaluating the BAL TPA levels, values above the 2400 U/L limit could have ftot been determined. The averages were

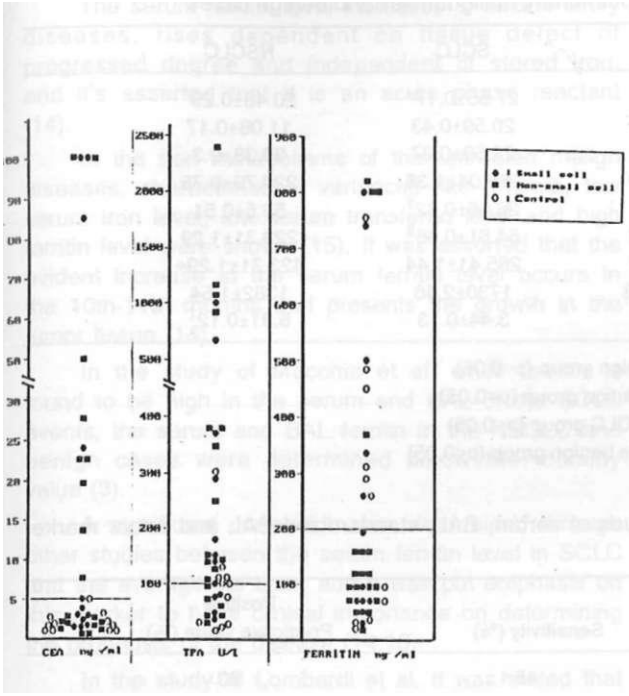

Figure 1. The serum CEA, TPA ferritin levels distribution among the groups

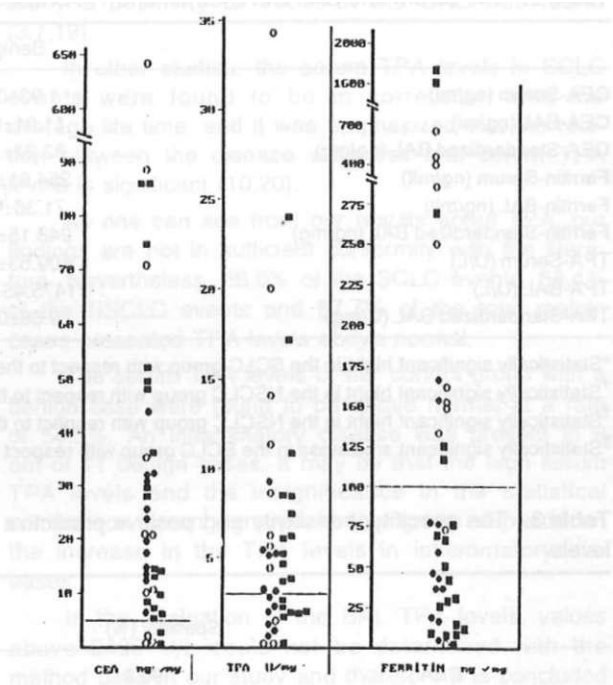

Figure 2. Standardized BAL, CEA, TPA, ferritin levels distribution among the groups

counted by accepting 2400 U/L for values above 2400 U/L. For that reason, statistical studies concerned with the BAL TPA levels could have not been established trustworthy.

In 81.8% of the SCLC events, the BAL TPA levels were above the cut-off value mentioned in the literature. In 7 out of 12 (58.3%) SCLC events, the BAL TPA level was found to be above 2400 U/L. In 68.42% of the NSCLC events, the BAL TPA level was above the cut-off value, and in 42.1% of them the values were above 2400 U/L.

In 63.6% of the benign cases, values were above the cut-off value, and in 36.3, above 2400 U/L.

The specifity, sensitivity and positive predictive values of serum, BAL, standardized BAL CEA, TPA and ferritin levels in the groups are shown in Table 3.

DISCUSSION

At present days, the tumor markers are widely used as assisting parameters for a diagnosis rather than being diagnostic, by patients suspicious of having malignity, and for that reason it is suggested to use more than one tumor marker analysis at tumors including also pulmonary malignancies (3).

Among various tissue markers which are proved to be specific to fetal and malign tissues, the CEA, also present at normal tissues, is the most experienced cell surface glycoprotein (4,5). It was emphasized in early studies that the CEA measurement

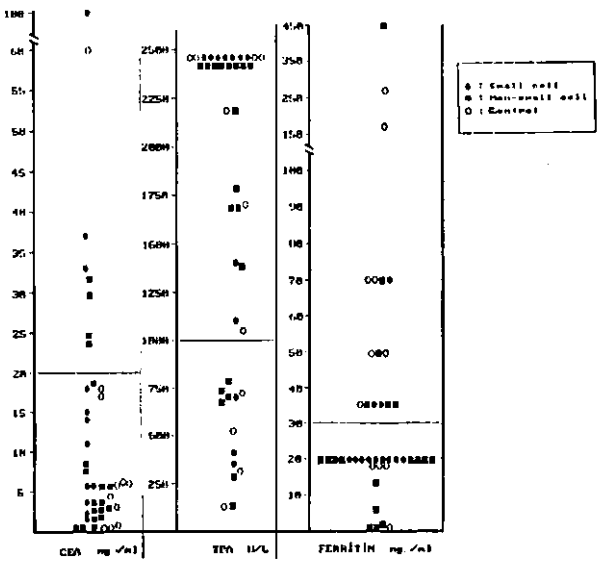

Figure 3. BAL, CEA, TPA ferritin levels distribution among the groups

in peripheral blood is not a specific test for the diagnosis of cancer (4).

In many of the studies, the levels of this marker in the serum and BAL fluids of patients with malignancy were found to be obviously high with respect to the normal controls, to nonmalign diseases and to metastatic lung cancers (1,3,4,6,8).

Table 2. The serum and BAL CEA, ferritin and TPA values in pulmonary malignancies and benign cases

	Benign	SCLC	NSCLC
CEA-Serum (ng/ml)	1.93±0.09	27.55±0.17*	20.43±0.29^
CEA-BAL (ng/ml)	11.01 ±0.37	20.59±0.43	11.08±0.17
CEA-Standardized BAL (ng/mg)	82.32+1.22	22.59+0.27	30.38±0.3
Ferritin-Serum (ng/mlf)	254.81 ±1.39	268.04±1.36	224.73+0.78
Ferritin-BAL (ng/mlt)	71.36±0.78	26.66±0.32§	53.5±0.51
Ferritin-Standardized BAL (ng/mg)	248.15±1.43	64.61 ±0.66§	223.31+1.29
TPA-Serum (U/L)	109.63±0.91	265.41+1.44	423.31+1.29+
TPA-BAL (U/L)	1475.45+2.78	1730±2.46	1382+1.54
TPA-Standardized BAL (U/mg)	9.68±0.28	3.44±0.13	6.31 ±0.12'

•Statistically significant hight in the SCLC group with respect to the benign group (p<0.05)
^Statistically significant hight in the NSCLC group with respect to the benign group (p<0.05)
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Table 3. The specifity, sensitivity and positive predictive values of serum, BAL, standardized BAL and tumor marker levels

		Spesifity (%)	Sensitivity (%)	Positive Predictive value (%)
Serum	CEA	90.9	45.1	93
	Ferritin	45	29	6
	TPA	45	67.74	77
	CEA+TPA	83	53	92
	CEA+Ferritin	90	32	90
	TPA+Ferritin	63	29	69
	TPA+Ferritin+CEA	100	22	100
BAL	CEA	45.4	48.3	71
	Ferritin	29	27	56
	CEA+Ferritin	80	10	60
Standardize BAL	CEA	27	93	78
	Ferritin	18	22	40
	CEA+Ferritin	12	100	58

In another study, again the CEA levels in the BAL liquid in events with peripheral lung cancer were found to be higher than that of the control group (2). Wasselius and his colleagues have found the serum and BAL CEA levels in chronic bronchitis and pulmonary malignancy events to be high. There was no significant difference between the two groups, but these groups showed a significant high level with respect to normal controls (5). While Diego found the serum CEA levels in bronchus carcinoma insignificant with respect to the normal controls, he found the BAL CEA levels significantly high (9).

In limited and widespread SCLC patients, the serum CEA levels were found to be high (10,11), and in another study it is stated that this level is high in widespread disease (12). There are also studies present which emphasize that with the widespread and limited disease in SCLC, the serum CEA levels are not significant (13).

As a result of these evaluations in our study, we determined that the specifities and sensitivities of CEA serum levels in malignancy cases were confirming with the literature. In our study, the BAL CEA levels were presenting disagreement with the literature and the specifity and sensitivity levels were low. Although the BAL CEA levels in the benign and malign groups were found to be high in our benign and malign studies, we could not determine a statistical significance. Similarly, in the studies of Wasselius et al (5) although the BAL CEA level in the benign and malign group was definitely found to be high, a statistical significance was not determined, too. It may occur that the CEA levels in BAL are found to be high due to permeability increasing in cases with a respiratory inflammation (5). It may be for the same reason that the CEA levels in the benign group were determined to be high, too, and a statistical significance between the benign-malign group was not found in our study.

The serum ferritin level increases in inflammatory diseases, rises dependent on tissue defect of progressed degree and independent of stored iron, and it's asserted that it is an acute phase reactant (14).

In the iron metabolisms of the untreated malign diseases, characteristical variances like anemia, low serum iron level, low serum transferrin level and high ferritin level were shown (15). It was asserted that the evident increase in the serum ferritin level occurs in the 10th-11 th months and presents the growth in the tumor tissue (14).

In the study of Macchia et al, while ferritin is found to be high in the serum and BAL of the SCLC events, the serum and BAL ferritin in the NSCLC and benign cases were determined below the molality value (3).

A significant correlation was determined through other studies between the serum ferritin level in SCLC and the average life time, and it was put emphasis on this marker to have clinical importance on determining the prognosis of the disease (14,16).

In the study of Lombardi et al, it was stated that serum ferritin is insignificant by distinguishing benign and malign diseases from each other (8). But Shultex on the contrary, in the results of his comparative study including patients with chronic bronchitis and lung cancer, stated that the BAL ferritin level was in none of the groups high, and that in malignity cases lower values were determined (17). The BAL ferritin levels in our study are confirming with the study of Shultex et al.

Of the events in the NSCLC group in 5 out of 8 (62%) events with adenocarcinoma, the serum and BAL ferritin level was much above the normal values. Whether ferritin in the diagnosis of events with NSCLC is one of the best tumor markers is stated in the literature, too (8). Moreover, as we mentioned before, a statistically significant result with a diagnostic aim among the groups in terms of serum and BAL ferritin level, could not be established. Therefore, it is impossible for us to conclude that ferritin alone has no diagnostic value in lung cancer, for that reason our study is negative.

The TPA, a tumor marker in the structure of polypeptide, is a structural component of the cytokeratin and the high serum TPA level shows an Increase in the proliferative activity of the cell (18). A rising in the serum TPA level has been observed in many malignity cases including also pulmonary malignancy. Having alone a high diagnostic sensitivity, the major problem Is that this tumor marker increases in benign cases like hyperplasy or infection, too (7,18).

The serum TPA level in the studies of Spinnazzi, Buccheri and Macchia showed a high level in lung cancer regardless of the cell type, and in Macchias' study a positivity of 100% in the BAL was found (3,7,19).

In other studies, the serum TPA levels in SCLC events were found to be in correlation with the average life time, and it was emphasized that the relation between the disease wideness and serum TPA levels is significant (10,20).

As one can see from our results about TPA, our findings are not in sufficient conformity with the literature. Nevertheless, 66.6% of the SCLC events, 68.4% of the NSCLC events and 67.7% of the total malign cases presented TPA levels above normal.

The serum TPA levels of our control group with a benign case were found to be above normal at a rate of 54.5%. An inflammatory disease was present in 9 out of 11 benign cases. It may be that the high serum TPA levels and the insignificance in the statistical comparison among groups in this group depends on the increase in the TPA levels in inflammatory diseases.

In the evaluation of the BAL TPA levels, values above 2400 U/L could not be determined with the method used in our study and therefore it is concluded that our results are not trustworthy. But in spite of this, it was established that the levels were high.

When the specificity and sensitivities of the serum tumor markers were jointly evaluated, it was remarked that the specifities were increasing and the sensitivity values on the other hand were decreasing (Table 3). It was observed that when the standardized BAL tumor marker levels were jointly evaluated, the sensitivities increased and the specifities decreased dependent on false positive results. These observations were conforming with the literature (8).

As a result, the belief that the stabilization of tumor markers in only serum and BAL would be insufficient in the diagnosis of malignancy cases is widespread. The specification of the conventional bronhoscopy applied events is low. At events, whose bronchoscopic results are negative, additional examinations may be needed, and at this step, bronchoscopic findings and lavage tumor marker levels could be helpful for the diagnosis.

Akciğer kanserlerinde karsinoembriyonik antijen (CEA), doku polipeptid antijen (TPA) ve ferritin serum ve bronkoalveoler lavaj düzeylerinin tanı değeri

Akciğer kanserli olgularda serum ve bronkoalveoler lavaj (BAL) da karsinoembriyojenik antijen (CEA), doku polipeptid antijen (TPA) ve ferritinin tek tek ve birlikte tanı değerleri araştırıldı. Serum CEA düzeyi, primer akciğer kanserli 31 olguda, hücre türüne bağımlı olmaksızın, benign akciğer hastalığı bulunan 11 olguya göre yüksek bulundu

(p<0.05). BAL, CEA düzeyleri gruplar arasında farklılık göstermedi. Serum ferritin düzeyi gruplar arasında anlamlı farklılık göstermedi. BAL ferritin düzeyleri küçük hücreli akciğer kanserli (SCLC) olgularda benign hastalıklı olgulara göre anlamlı düşüklük gösterdi (p<0.05). Serum TPA düzeyi ise küçük hücre dışı akciğer kanserli (NSCLC) grupta benign akciğer hastalıklı gruba göre anlamlı derecede yüksek bulundu (p<0.05). Değerlendirilen tümör belirleyicilerinin tek tek ve birlikte spesifite, sensitivite değerleri göz önüne alındığında çalışılan parametrelerin birlikte değerlendirilmesinin, tek tek değerlendirilmesine üstünlüğü olmadığı kanısına varıldı. [TurkJMedRes 1994, 12(6): 243-248]

REFERENCES

1. Goldstein N, Lippmann ML, Goldberg SK et al. Usefulness of tumor markers in serum and bronchoalveolar lavage of patients undergoing fiberoptic bronchoscopy. Am Rev Respir Dis 1985; 132:60-4.
2. Diego A, Compte L, Sanchis J et al. Diagnostic value of CEA in bronchoalveolar lavage fluid of peripheral lung cancer. Chest 1990; 97:767-8.
3. Macchia V, Mariano A, Cavalcantii M et al. Tumor markers and lung cancer: Correlation between serum and bronchial secretion levels of CEA, TPA, Can Ag CA-50, NSE anu ferritin. The international Journal of Biological Markers 1987; 2:151-6.
4. Sementato G, Spatofora M, Ferugloio C. Bronchoalveolar lavage and the immunology of lung cancer. Lung 1990(Suppl):1041-9.
5. Wesselius U, Dark DS, Papasian CJ. Airway CEA concentration in patients with central lung cancer or chronic bronchitis. Chest 1990; 98:393-7.
6. Berthiot G, Marechal F, Cattan A et al. Serum levels of CA-50, CA-19, 9, CA-125, NSE and CEA in lung cancer and benign diseases of the lung. Biomed Pharmacother 1989; 43:613-20.
7. Buccheri GF, Ferringo D, Sartoris AM et al. Tumor markers in bronchogenic carcinoma. Cancer 1987; 60:42-50.
8. Lombardi C, Tassi GF, Pizzocolo G et al. Clinical significance of a multipl biomarker assay in patients with lung cancer. Chest 1990; 97:639-44.
9. Diego A, Compte L, Sanchis J et al. Usefulness of CEA determination in bronchoalveolar lavage fluid. Chest 1991; 100:1060-3.
10. Gronowitz JS, Bergstrom R, Nou E et al. Clinical and serologic markers of stage and prognosis in small cell lung cancer. Cancer 1990; 66:722-32.
11. Laberge F, Fritsche HA, Umsawasdi T et al. Use of CEA in small cell lung cancer. Cancer 1987; 59:2047-52.
12. Granz PA, Ma PY, Wang HJ et al. Evaluation of three biochemical markers for serialy monitoring the therapy of small cell lung cancer. Journal of Clinical Oncology 1987; 5:472-9.
13. Jorgensen LGM, Hansen HH, Cooper EH. NSE, CEA and LDH as indicators of disease activity in small cell lung cancer. Eur J Cancer. Clin Oncol 1989; 25:123-8.
14. Milman N, Sengelov H, Dombernowsky P. Iron status markers in patients with small cell carcinoma of the lung. Br J Cancer 1991; 64:895-8.
15. Groop C, Havemann K, Lehmznn FG. CEA and ferritin in patients with lung cancer before and during therapy. Cancer 1978; 42:2802.
16. Cox R, Gyde O, Leyland MJ. Serum ferritin levels in small cell lung cancer. Eur J Cancer Clin Oncol 1986; 22:831-5.
17. Schultex T, Braun J et al. Bronchoalveolar lavage. Dtsch-Med Wschr1986; 111:333.
18. Jotti GS, Bombardieri E. Circulating tumor markers in breast cancer. Anticancer Research 1990; 10:253-8.
19. Spinazzi A, Soresi E, Borghini U et al. Clinical value of NSE and TPA for the management of patients with lung cancer. The Journal of Nuclear Medicine and Allied Sciences 1990; 34:141-5.
20. Gaast A, Putten WU, Oosterom R et al. Prognostic value of serum thymidine kinase, TPA NSE in patients with small cell lung cancer. Br J Cancer 1991; 64:369-72.