The Contribution of Serum Ferritin, Iron, Iron Binding Capacity and Bronchoalveolar Lavage Ferritin Levels in Differential Diagnosis of Lung Cancer from Benign Pulmonary Diseases

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ABSTRACT

The aim of this study is to investigate if serum iron, iron-binding capacity, ferritin and bronchoalveolar lavage (BAL) ferritin levels are useful to differentiate lung cancer from benign pulmonary diseases, and also to test the accuracy of hypothesis of "ferritin accumulation in the tumor area".

Patients prospectively scheduled for diagnostic bronchoscopy were included and divided into three diagnosis groups: lung cancer, pulmonary tuberculosis and other benign pulmonary diseases.

Sixty six men and 7 women, 73 patients were included. Statistically significant difference was not found among three groups for serum iron, iron binding capacity and ferritin levels (p=0.151, p=0.972, p=0.278). The difference was statistically insignificant for BAL ferritin levels between three groups (p=0.584). Mean BAL ferritin level was 73.56 ng/ml in central and 31.54 ng/ml in peripheric lung cancer (p=0.087). The mean serum iron level was lower in stage IV and III compared to Stage II and I patients (p=0.004). None of other measurements differed according to tumor stages. In lung cancer group, the type of tumor had no effect on serum iron, iron binding capacity, and serum and BAL ferritin levels.

In conclusion; serum ferritin, serum iron, serum iron binding capacity and BAL ferritin measures do not help in differantiating lung cancer from benign pulmonary diseases. The histological types, stages and localization of lung cancer do not effect BAL ferritin levels. The results of the study did not support the hypothesis of ferritin accumulation in the tumor area.

Key Words: Ferritin, Iron, Bronchoalveolar lavage, Lung cancer, Pulmonary tuberculosis

ÖZET

Akciğer Kanserinin Benign Akciğer Hastalıklarından Tanısal Ayırımında Serum Ferritin, Demir, Demir Bağlama kapasitesi ve Bronkoalveolar Lavaj Sıvısı Ferritin Düzeyinin Katkısı

Bu çalışmanın amacı serum demir, demir bağlama kapasitesi, ferritin ve bronkoalveoler lavaj (BAL) ferritin düzeylerinin akciğer kanserini benign pulmoner hastalıklardan ayırmada yardımcı olup olmadıklarını ortaya koymak ve "tümör alanında ferritin birikimi hipotezinin" doğruluğunu araştırmaktır.

Prospektif olarak tanısal amaçlı bronkoskopi yapılan hastalar alındı ve akciğer kanseri, pulmoner tüberküloz ve diğer benign akciğer hastalıkları olarak üç tanı grubuna ayrıldılar.

Altmışaltı erkek ve yedi kadın, toplam 73 hasta dahil edildi. Üç grup arasında serum demir, demir bağlama kapasitesi ve ferritin düzeyleri açısından istatistiksel olarak anlamlı fark bulunmadı (p=0.151, p=0.972, p=0.278). Üç grup arasında BAL ferritin düzeyleri anlamlı farklılık göstermedi (p=0.584). Ortalama BAL ferritin düzeyi santral akciğer kanserinde 73.56 ng/ml ve periferik akciğer kanserinde 31.54 ng/ml idi (p=0.087). Evre I ve II ile karşılaştırıldığında, serum demir düzeyi ortalaması Evre III ve IV'de daha düşüktü (p=0.004). Diğer ölçümlerin hiçbiri tümör evresine göre farklılık göstermedi. Akciğer kanseri grubunda tümör tipinin serum demir, demir bağlama kapasitesi ve serum ve BAL ferritin düzeyine etkisi saptanmadı.

Sonuç olarak; serum ferritin, serum demir, serum demir bağlama kapasitesi ve BAL ferritin ölçümleri akciğer kanserini benign akciğer hastalıklarından ayırt etmede yardımcı olmamaktadır. Akciğer kanserinin histolojik tipleri, evreleri ve yerleşimi BAL ferritin düzeylerini etkilememektedir. Çalışmanın sonuçları tümör alanında ferritin birikimi hipotezini desteklememektedir.

Anahtar Kelimeler: Ferritin , Demir, Bronkoalveoler lavaj, Akciğer kanseri, Pulmoner tüberküloz

INTRODUCTION

Lung cancer is the most frequent cancer type around the world and a continuously growing health problem (1).

Ferritin, the major component of stored iron, is a hydrosoluble protein. It is mainly concentrated in the liver, spleen and bone marrow in humans. Ferritin is present in all body cells including erythrocytes, leukocytes and thrombocytes. Ferritin concentration of the lower respiratory tract is increased in smokers, patients with chronic obstructive lung disease, cystic fybrosis, Pneumocystis carinii pneumonia patients and after lung transplantation. High intracellular ferritin concentrations are thought to be a response to the increased iron load observed in these pathologies and can effectively suppress the intracellular iron and iron-mediated cell injury. The high concentrations of ferritin in these patients can lead to oxygenative cell injury. The mechanism underlying the high alveolar concentrations of ferritin are still not understood well. Ferritin synthesis in cells may be regulated with stimulations like hypoxia, nitrous oxide, oxydative stres and cytokines rather than the intracellular iron content. In many respiratory diseases alveolar cells can be exposed to hypoxia or nitrous oxide and this exposure can lead to increased sensitivity against iron mediated oxidative injury in alveolar cells (2-5).

In acute infection and inflammation, a prompt decrease in serum iron levels is observed while serum ferritin increases. Hepatoma, lung cancer, pancreas cancer and metastatic breast cancer are the solid tumors in which serum ferritin concentrations rise most. The sensitivity and specificity of ferritin in early cancer diagnosis are low, because of the great number of pathologies effecting iron metabolism (for example liver diseases, chronic infections). Factors leading to high ferritin levels in malignancies can be classified as:

1. Like inflammation, malignancy leads to anemia and iron accumulation in the reticuloendotelial system.
2. Tissue necrosis can cause direct release of cytosolic ferritin and can increase ferritin levels.
3. Experimental data revealed that ferritin is cleared from the circulation by liver parenchimal cells. Dysfunction due to liver disease can lead to prompt decrease in clearence and serum ferritin levels will rise.
4. Ferritin synthesis in malignant cells can show qualitative and quantitative abnormalities (4,6-9).

Bronchoalveolar lavage is widely used to obtain and investigate cells and other system components reflecting the inflammatory and immune system of the lower respiratory tract epithelium. Although BAL is not enough alone for absolute diagnosis in many situations, the combination of BAL cell profiles with clinical data can give important information. Fourty to sixty mililiter volume including cells and 1-10 mg protein can be obtained when BAL with 100 ml serum physiologic is performed on an average adult patient (10).

In this study, the aim was to investigate if serum iron, serum iron binding capacity, serum ferritin and BAL ferritin levels help us in differentiating lung cancer from benign pulmonary diseases; and to investigate the hypothesis of ferritin accumulation in the tumor area.

PATIENTS AND METHODS

Patients groups

Patients scheduled for diagnostic bronchoscopy, except existing contraindications, were included in the study. Patients with forced expiratory volume per one second under 1000 ml, or noncooperative, or had moderate and serious asthma, oxygen resistance hypoxemia, hypercarbia, persistent hemorrhagic diathesis, serious cardiac arytmias, myocardial infarction in the last six weeks or endobronchial hemorrhagia were excluded (10). After diagnosis, patients were classified in three groups by the definite diagnosis:

Lung Cancer Group: Patients with histopathologically and radiologically diagnosed lung cancer.

Lung Tuberculosis Group: Patients diagnosed tuberculosis using microbiology and/or histopathology and radiology.

Other Disease Group: Patients with any diagnosis except lung cancer and tuberculosis.

Bronchoscopy and BAL

Premedication with 10 mg diazepam was performed to patients before 45 minutes of bronchoscopy procedure. Then, local anesthesia was performed to the upper respiratory tract with 5 ml of 2% Lidokain. Bronchoscopy was performed trans-orally with Olympus BF1T-30 type fiber optic bronchoscope in the supine position. Chest x-ray and thorax computed tomography were evaluated for patients with preliminary diagnosis of lung cancer. So BAL was performed through the relevant segment if mass lesion was peripheral and endobronchial lesion in bronchoscopy was not detected. If mass lesion was central and endobronchial lesion was detected in bronchoscopy, BAL was performed, upon not affected from disease, through firstly the same party middle lob bronchus/lingula or lower lob segments. Chest x-ray and thorax computed tomography were evaluated for patients whom bronchoscopy operations were performed because of other pre-diagnosis; so BAL was performed through relevant bronchus in patients with radiological lesion, and performed through middle lob bronchus/lingula in patients with no radiological lesion. For BAL, bronchoscope was fixed by wedging to a segmental bronchus. Serum warmed to 37^{o}C with physiological injector was given at flow rate of 5 ml/sec through catheter in aspiration canal of bronchoscope. Back aspiration was performed with injector. One hundred – one hundred sixty mililiter serum physiologic were given for BAL and at least 60% was obtained back. Materials were reached to laboratory in injectors.

Preparation and Measurements

Blood was collected to 10 mililiter empty tubes from patients for measurements of serum iron, serum ferritin, serum iron-binding capacity on the day of bronchoscopy. Collected bloods were studied after 10 minutes of centrifugation. Serum ferritin was studied in Advia Centavur (Bayer) hormone catalyst via direct chemiluminometric technology (two-side sandwich immunoassay). Iron and iron-binding capacity were studied with colorimetric method with Olympus AU-640 authoanalyzer.

Bronchoalveolar lavage fluid ferritin level was studied with Advia Centavur (Bayer) hormone catalyst via direct chemiluminometric technology (two-side sandwich immunoassay).

Statistical Analysis

Comparisons of serum iron, serum iron-binding capacity, serum ferritin and BAL ferritin levels between three patients groups were studied with One-way ANOVA test; tumor types in patients with lung

Table 1. Distributions of patients' diagnoses.

GROUPS	DIAGNOSIS	N	%
GROUP – I	Lung Cancer	41	56.2
GROUP – II	Pulmonary Tuberculosis	12	16.4
GROUP - III	Other Diseases	20	27.4
	Antracose	1	
	Plasmositoma	1	
	Extra Plevral Adipose Tissue	1	
	Sarcoidosis	2	
	Solitary Pulmonary Nodule	2	
	Sequaeale Pulmonary Tuberculosis	1	
	Pneumonia	4	
	Mediastinal/Cervical Lenfadenitis	2	
	Hemoptysis	1	
	Interstitial Lung Disease	2	
	Silicosis	1	
	Congestive Heart Failure	1	
	Chronic Obstructive Pulmonary Disease	1	
	Total	73	100

cancer and analysis according to stages were studied with One-way ANOVA and t-Test. This study was approved by the Hospital Ethics Committee.

RESULTS

The mean age of the 73 patients (66 men (90.4%), 7 women (9.6%), included into the study was 57.26 13.5 (28-81) years. Thirteen (17.8%) patients were non-smokers while the mean package/year value among the other 60 (82.2%) patients was 41.17 (7-200) packages/years. Fever after BAL was recorded in 5 (6.8%) of patients. According to obtained diagnosis, distribution of patients is shown in Table 1.

The lowest serum iron levels and iron binding capacity were measured in the tuberculosis group, but significant statistical difference was not found among the three groups (p=0.151, p=0.972).

Serum ferritin levels were higher in lung cancer and tuberculosis patients compared to the other disease group but the difference was statistically insignificant (p=0.278)

While the lowest BAL ferritin level was measured in the lung cancer group, the highest BAL ferritin level was in the lung tuberculosis group, but the difference was statistically insignificant (p=0.584).

Serum iron, serum iron binding capacity, serum ferritin and BAL ferritin levels in three groups are presented in Table 2.

Tumor location was central in 26 (63.4%) and peripheral in 15 (36.6%) of total 46 patients in the lung cancer group. Mean BAL ferritin level was 73.6 ± 112.6 ng/ml in central and 31.5 ± 34.3 ng/ml in peripheric tumors. Because the central tumor

Table 2. Serum iron, serum iron binding capacity, serum ferritin and bal ferritin levels in three patients groups.

Patients Group	Lung Cancer Group	Pulmonary TB Group	Other Disease Group	Mean	Normal Level	P
(N) - Serum Iron (n=72)	(40) – 49.58 ± 30.8	(12) – 31.25 ± 25.9	(20) – 54.75 ± 41.7	47.96 ± 33.9	49-167	0.151
(N) - Serum Iron Binding Capacity (n=71)	(39) – 225.46 ± 48.7	(12) – 222.58 ± 30.7	(20) – 226.45 ± 44.0	225.25 ± 44.3	155-300	0.972
(N) Serum Ferritin (n=72)	(41) – 324.53 ± 408.8	(11) – 357.48 ± 427.8	(20) – 178.09 ± 195.2	288.89 ± 367.5	Male: 22-322 Female: 10-291	0.278
(N) BAL Ferritin (n=73)	(41) – 58.19 ± 93.6	(12) – 90.06 ± 167.9	(20) – 84.52 ± 123.7	70.64 ± 115.8		0.584

group was not homogeneous, statistical analysis showed no significance between the two groups (p=0.087).

There was no difference in serum iron, serum iron binding capacity, and serum ferritin and BAL ferritin levels between patients with lung cancer (Table 3). There was no difference in serum iron, serum iron binding capacity, and serum ferritin and BAL ferritin levels between small cell lung cancer and non-small cell lung cancer (Table 4).

Five patients (12.2%) were in Stage-I, two (4.9%) were in Stage-II, 15 (36.6%) in Stage-III and 19 (46.3%) in Stage-IV disease. Serum iron levels were lower in stage-IV (49.8 ± 26.1) and III (34.6 ± 25.8) compared to Stage-II (98.5 ± 28.9) and I (74.2 ± 31.5) patients (p=0,004). Serum iron binding capacity, serum ferritin and BAL ferritin levels showed no difference according to tumor stage (Table 5).

DISCUSSION

Both ferritin levels in BAL fluid and peripheral blood had no value in differentiating lung cancer from benign pulmonary diseases and did not differ according to the stage, localization or histopathologic type of lung cancer.

Fiberoptic bronchoscopy and BAL are the most useful methods in cancer diagnosis because they give the opportunity to obtain biological neoplastic markers from the tumor area. Although there are many studies investigating serum concentrations of ferritin, the possible diagnostic value and biological role as a tumor marker of ferritin levels in tumoral tissue and BAL is rarely discussed in literature. The relation between iron accumulation and cancer risk has been recently introduced as a hypothesis. Also it was proposed that low iron levels could play a role in the prevention of infection and cancer (11,12).

In patients with malignancy, serum ferritin levels are affected from the large storage of iron and the increase due to tumor. In normal patients, levels over 300 mg/L are defined as mild while levels over 700-800 mg/L are defined as extreme increases (13,14).

It has been reported that there is a statistically significant increase in serum ferritin levels in patients with lung cancer compared with benign inflamma-

Table 3. Serum iron, serum iron binding capacity, serum ferritin and bal ferritin levels in lung cancer type.

Lung Cancer Type	(N) - Serum Iron (n=40)	(N) - Serum Iron Binding Capacity (n=39)	(N) - Serum Ferritin (n=41)	(N) - BAL Ferritin (n=41)
Small Cell	(4)-71.25 ± 17.5	(4)-216.25 ± 67.0	(5)486.08 ± 667.5	(5)-119.48 ± 127.4
Squamous Cell	(5)-41.4 ± 26.5	(5)-261.4 ± 24.7	(5)-279.5 ± 274.0	(5)-33.0 ± 19.5
Undefined Type	(7)-33.0 ± 20.4	(7)-218.0 ± 70.0	(7)-492.64 ± 484.8	(7)-87.39 ± 178.1
Adenocarsinom	(8)-49.63 ± 28.7	(7)-235.86 ± 34.7	(8)-167.38 ± 102.0	(8)-21.65 ± 13.7
Non-Small Cell	(16)-53.94 ± 36.9	(16)-215.25 ± 43.3	(16)-293.16 ± 413.7	(16)-52.4 ± 59.5
Mean	49.58 ± 30.8	225.46 ± 48.7	324.53 ± 408.8	58.19 ± 93.6
P	0.331	0.415	0.527	0.357

Table 4. Serum iron, serum iron binding capacity, serum ferritin and bal ferritin levels for small cell lung cancer and non-small cell lung cancer.

Lung Cancer Type	Small Cell	Non-Small Cell	P
(N) - Serum Iron	(4)-71.25 ± 17.5	(36)-47.17 ± 31.1	0.190
(N) - Serum Iron Binding Capacity	(4)-216.25 ± 67.0	(35)-226.51 ± 47.4	0.534
(N) - Serum Ferritin	(5)-486.08 ± 667.5	(36)-302.1 ± 368.5	0.137
(N) - BAL Ferritin	(5)-119.48 ± 127.4	(36)-49.68 ± 86.8	0.167

tory lung disease (15). In another study the diagnostic sensitivity of serum ferritin levels in 66 lung cancer patients was found to be 36.3% while the specificity in benign lung disease was 95% (16).

Kakari et al, who measured serum ferritin levels in 152 patients with primary lung cancer, 107 patients with benign lung disease and 207 control patients, found a statistically significant increase in serum ferritin levels in lung cancer patients compared with control group, but found no similar difference compared with patients with benign lung disease. When 300 micg/L was accepted as threshold and benign lung disease patients as negative controls, the sensitivity was 36% and specificity 72% (17). In our study, patients were analyzed by dividing into three groups. Although serum ferritin levels were higher in lung cancer and the tuberculosis groups compared other disease group, the difference was not statistically significant (p=0.278).

Kakari et al found serum ferritin levels higher in patients with advanced stage small cell cancer compared with limited stage (17). There are also evi-

Table 5. Serum Iron, Serum Iron Binding Capacity, Serum Ferritin and BAL Ferritin Levels For Lung Cancer Stages

Stage of lung cancer	Stage-I	Stage-II	Stage-III	Stage-IV	P
(N) - Serum Iron	(5)-74.2 ± 31.5	(2)-98.5 ± 28.9	(15)-34.6 ± 25.8	(18)-49.78 ± 26.1	0.004
(N) - Serum Iron Binding Capacity	(5)-234.8 ± 43.1	(2)-205.5 ± 72.8	(15)-232.73 ±52.9	(17)-218.65 ±47.1	0.772
(N) - Serum Ferritin	(5)-64.6 ± 54.7	(2)-105.35±102.7	(15)-256.67 ±355.9	(19)-469.59 ±470.6	0.142
(N) - BAL Ferritin	(5)-52.8 ± 51.7	(2)-76 ± 94.7	(15)-28.23 ± 25.4	(19)-81.38 ±128.5	0.438

dences that the increase of serum ferritin levels is parallel to tumor mass (18). When analysis was made according to cancer stage in our lung cancer patients, serum iron levels were lower in Stage-IV and III compared to stage-II and I (p=0.004). Serum iron binding capacity, serum ferritin and BAL ferritin levels showed no difference among stages.

Linder et al, investigated ferritin levels in normal lung tissue and lung tumors and found total iron and ferritin levels high in these two tissues. There was no relation between cancer histopathology and the iron or ferritin contents (19). Franchia et al determined that serum or BAL ferritin levels did not show any difference according to histopathologic type (20). In our study, there was no difference in serum iron, iron binding capacity, serum and BAL ferritin levels between different types of tumors in lung cancer patients. When small cell lung cancer and non-small lung cancer were compared, there was also no difference between serum iron, iron binding capacity, serum and BAL ferritin levels.

Milman et al determined an inverse relation between serum ferritin levels and prognosis in their serial including 197 lung cancer patients (21).

Macchia et al found an increase in BAL ferritin levels in lung cancer patients compared with a healthy control group although the difference showed no marked sensitivity and specificity (22).

Fracchia et al measured serum and BAL ferritin levels in 22 peripheric lung cancer patients and compared these values to levels from 20 healthy and 10 chronic obstructive pulmonary disease patients. Ferritin was measured in BAL of the tumor bronchus in 9 patients with peripheric lung cancer, and from the tumor bronchus plus the unaffected lung (middle lobe or lingula) in 13 patients. It was interesting that the BAL ferritin levels were different in the tumor bronchus and the unaffected lung in the 13 patients who underwent bilateral BAL. Bronchoalveolar lavage ferritin levels from the tumoral bronchus samples were found to be higher (603 548 ng/ml) compared to chronic obstructive pulmonary disease patients (186 225ng/ml). The authors thought BAL ferritin level in lung cancer patients as a partially good local tumor marker and could differentiate benign lung diseases and lung cancer with a sensitivity of 54% and specificity of 93%. In the same study, serum ferritin levels did not show significant difference between lung cancer patients and control group and small cell lung cancer, and it was stated that serum ferritin levels had no diagnosis value (20). We found that BAL ferritin levels were not different between lung cancer, infection and other diseases groups, and it was considered that it could not be used in differential diagnosis of these diseases. The localization of lung cancer did not have any effect on BAL ferritin levels.

Ferritin levels in body fluids show difference in wide range and as seen in our study, high standard deviations in both serum and BAL ferritin levels oc-

cur (20,22,23).

In conclusion, serum ferritin, iron, iron-binding capacity and BAL ferritin levels do not assist to differentiate lung cancer from benign pulmonary diseases. The histological types, stages and localization of lung cancer do not effect BAL ferritin levels. The results of the study did not support the hypothesis of ferritin accumulation in the tumor area. Because serum and BAL ferritin levels detected in this study had a wide range and there were significant difference between the lowest and the highest levels, statistical analysis was not performed in homogeny group. Despite significant difference between groups and according to location of lung cancer, observing statistically insignificant results was considered as conclusion of this situation.

Relation of lung cancer and BAL ferritin levels is still unclear. New study plans are needed especially in three ways:

1. To research serum and BAL ferritin in combination with carcinoembryonic antigen or other markers to differentiate benign and malignant lung diseases,
2. To validate compartmentalization and to research roles of cigarettes and inflammation.
3. To research effectiveness of new biological markers and complex techniques.

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