The Role of Trace Elements in the Malignant-Benign Differentation of Pleural Effusions

Plevral Efüzyonlarda Malign Benign Ayrımında Eser Elementlerin Rolü

Trace Elements in Pleural Effsions

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Özet

Amaç: Eser elementlerin bazı kanser türlerinde rol oynadığı öne sürülmektedir. Bu çalışmanın amacı plevral sıvıdaki eser elementlerin plevral efüzyonda tanısal yararını incelemektir. Gereç ve Yöntem: Bu çalışmaya, malign ve bening plevral efüzyon tanısı olan 38 hasta alındı. Krom, Nikel, Selenyum, Bakır, Kurşun ve Çinko konsantrasyonları örneklerde indüktif eşleşmiş plazma optik emisyon spektrometresi ile tespit edildi. Bulgular: Cr, Cu, Ni, Pb, Se ve Zn konsantrasyonları ile malign ve benign efüzyon arasında anlamlı ilişki bulunmadı. Tartışma: Eser elementler, birçok enzim bileşenidir ve bazı kimyasal reaksiyonlarda katalizör olarak işleve sahiptir. Kanserlerde değişik tip eser elementin eksiklik veya fazlasının ilişkisini gösteren çalışmalar olmuştur. Bizim çalışmamızda, efüzyon ayırıcı tanıda plevra sıvılarında ölçülen eser elementlerin rolü gösterilemedi.

Anahtar Kelimeler

Malign; Plevral Efüzyon; Eser Element

Abstract

Aim: It has been speculated that trace elements may play a role in some type of cancers. The aim of the present study was to examine the diagnostic utility of trace elements in pleural fluid with pleural effusions. Material and Method: This study consisted of 38 patients diagnosed with malignant and benign pleural effusions. Chrome, nickel, selenium, copper, lead and zinc concentrations in samples were determined by inductively coupled plasma optical emission spectrometry. Results: No significant difference was found between malignant and benign effusions with respect to Cr, Cu, Ni, Pb, Se and Zn concentrations in samples. Discussion: Trace elements have function as the component of many enzymes and the catalyst of some chemical reactions. There have been studies demonstrating the association of the deficiency or surplus of trace elements (TEs) with various type of cancers. In our study, the role of TEs measured in the pleural effusions in the differential diagnosis in the effusion etiology could not be demonstrated.

Keywords

Malignant; Pleural Effusion; Trace Element

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Introduction

Pleural fluid is originated from mainly the pleural capillaries of the parietal pleura, lymphatics, intrathoracic blood vessels, pulmonary space and the peritoneal cavity. It is reabsorbed through the lymphatic channels of the parietal pleura [1].

Physiologically, the amount of pulmonary fluid should be less than 10 mL in any of the pulmonary cavities. The pleural effusion can be associated with the increase in the production of pleural fluid or decrease in its removal, hydrostatic pressure changes, colloidal pressure changes or negative intrathoracic pressure. Because the pulmonary fluid accumulation at a clinically detectable level may be associated with pleural, pulmonary or non-pulmonary diseases, when the thickness of the pleural fluid in the decubitus graphy >10 mm or when the pleural effusion is shown by ultrasonography, thoracentesis should be considered for diagnosis. Although the reason of effusion may not be found in all of the pulmonary pathologies, it is determined in 70-80% of the cases. The differentiation of malignant and benign cases is important for deciding the treatment in pleural effusions [2].

The micro elements for which the daily need is less than 100 mg and which exist in the body fluids or tissues at very low concentrations (mg/dL and mg/kg) are defined as the trace elements (TE) and are categorized under micronutrients [3].

The TEs function as the essential cofactor in the physiological processes. At the same time, some trace elements can be toxic for human health. The TE deficiency or surplus, aside from some chronic diseases such as cardiovascular diseases and diabetes are also associated with the cancer pathogenesis [4,5]. The environmental exposure of some TEs such as cadmium (Cd), chrome (Cr), nickel C(Ni) and arsenic(As) is classified under Group 1 of the International Agency for Research on Cancer categories of carcinogen [6]. Again for human beings, lead (Pb, Group 2A) and mercury (Hg) (Group 2B) have been reported as probably suspicious carcinogens [7]. On the other hand, selenium (Se) is regarded as an anti-carcinogen TE [8].

In this study, the TE levels of the samples from pleural effusion patients with different clinical diagnosis were examined and it was investigated if these levels are different in the differentiation between malignant and benign ones.

Material and Method

Patient Selection

The patients who were followed for pleural effusion in the Thoracic Diseases and Thoracic Surgery Clinic of Ministry of Health Batman District Hospital between 2011-2012 were involved in the study. Exclusion criteria were renal or hepatic insufficiency, vascular disease (i.e., peripheral vascular disease, cerebrovascular disease), alcohol usage, and intake of supplements containing with antioxidants (Cu, Se, Zn or vitamin supplements) or aspirin within 1 week. Subjects taking oral contraceptives, or hormone replacement therapy were also excluded from the study. The patients without sufficient samples for analysis were excluded from the study. The TE levels of the samples obtained were measured in the Chemistry Department of Dicle University Faculty of Science and Letters. The patient files were scanned and the data such as the age, sex, pleural effusion obtainment method were obtained retrospectively.

Obtaining the Samples

The samples to be examined for pleural effusion of the cases were obtained by either thoracentesis, videothoracoscopy or closed thorax drainage methods. The samples remaining after biochemical and cytological examination were put into 6-mL royal blue top (containing K2EDTA) trace element vacutainer tubes (Becton Dickinson, U.S) and centrifuged at 3000 rpm for 10 minutes. Then, the centrifuged effusion material was put into trace element-free transport tube and the samples were stored at -80 C0. The TE levels were measured from these samples.

TE Measurement

Approximately, 3.0 g of lung liquid were weighted in a beaker and 4.0 mL mixture of HN03:H202 was added and transferred to microwave vessel. It was waited for 20.0 min before microwave irridation. The following program was applied to vessel for digestion (Table 1).

Table 1. According to cytology patients characteristics

	Bening N (%)	Malign N (%)	P value
Gender			
Female	5 (16.7)	5 (62.5)	
Male	25 (83.3)	3 (37.5)	0,742
Age	62.1±23.3	55.6±22.6	0,443
Cu	0.81±0.32	0.99±0.38	0,205
Ni	67±21.7	58.1±25.4	0,328
Cr	34.9±14.7	43±24.1	0,281
Pb	74.9±34.2	107.3±80.1	0,281
Se	68.2±35	73.7±38.4	0,739
Zn	615.5±123.7	657.8±205.3	0,720

Samples were digested in temperature and pressure controlled microwave oven (Berghof MWS-3). Cr, Cu, Ni, Pb, Se and Zn concentrations in samples were determined by Perkin Elmer Optima 2000 DV inductively coupled plasma optical emission spectrometry (ICP-OES) at wavelengths of 267.716, 327.393, 231.604, 220.353, 192.026 and 343.823 nm, respectively. The entire optical system is enclosed and purged with nitrogen.

Statistical Analysis

The SPSS statistical software system for Windows (SPSS version 15.0) was used for the statistical analysis. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Because the Cu and Ni levels were normally distributed, their averages in the benign and malignant patients were evaluated using student t test. Whereas, Cr, Pb, Se, and Zn levels were not normally distributed, they were evaluated via Mann-Whitney U test. A significance level of 0.05 ($p < 0.05$) was used in all tests.

Results

Total 38 patients, of which 28 (73.7%) were male and 10 were female, were involved in the study. The average age of the patients was determined as 61±23 (range 15-92). 23 (60.5%) of the patients with pleural effusion was displaying right-side localisation, 14 (36.8%) of patients left-side and in 1 patient

bilateral localisation. In 33 (86.8%) patients, pleural effusions were obtained by thoracentesis, in 4 (10.5%) patients by closed thorax drainage and in 1 (3.2%) patient by videothoracoscopy.
The cytology of 30 (78.9%) patients was evaluated as benign and of 8 (21.1%) patients as malignant. A statistically significant relation was determined between the sexes and cytological diagnosis of the patients (P= 0.009). The cytology of 3 (10.7%) male patients was rated as malignant while it was 5 for the female patients. When the patients were grouped by cytology, the average ages of the malignant and benign patients were not different (P= 0,443).
In the patients, Cr was determined as 36.6±17 (range 19-99) ng/mL (nanogram /mL) , Cu as 0.85±0.34 (range 0.17-1.63) microgram/mL, Ni as 65.1±22.4 (range 19-101) ng/mL, Pb as 81.7±17 (range 19-99) ng/mL, Se as 64.9±35.2 (range 13-131) ng/mL, and Zn as 624,4±142.3 (range 341-1114) ng/mL .
In the patients diagnosed as benign and malignant, the difference with respect to the Cu and Ni levels was analyzed using student t test and no statistically significant difference was determined (P= 0.205, P= 0.328, respectively). In the patients diagnosed as benign and malignant, Cr, Pb, Se and Zn levels were analyzed using Mann-Whitney U test and no statistically significant inter-group difference was determined (P= 0.281, P= 0.281, P= 0.739, P= 0.720, respectively) (Table 2).

Discussion

In our study, not any correlation between the Cr, Cu, Ni, Pb, Se and Zn levels we measured in the pleural effusions of the patients and the state of being malignant or benign was determined.
Cr exists in all organs of the adults and newborns. The concentration of Cr is typically high in the lung tissue and has a tendency to increase with age. The increase is associated with the likely inhalation and retention of the water-soluble compounds. Cr compounds have been shown to stimulate chromosomal anomalies and mutations. Cr compounds may cause genetic damages such as DNA damage as single-chain fractures, damage in the DNA-protein and DNA-DNA ligaments [9]. In our study, no difference was determined in the Cr levels measured in the pleural effusions of the patients diagnosed as benign and malignant.
In the human body, Cu is the third abundant TE after Zn and iron (Fe). The normal serum Cu level is 0.6–1.6 microgram/mL [10]. It exists in the structure of many enzymes which take place in many biochemical processes such as antioxidant-prooxidant balance, energy production, metabolism, heme synthesis, iron use and neurotransmitter production [11]. As the cofactor of some antioxidant enzymes eliminating free radicals, Cu is a TE that helps to maintain the cell membrane integrity, slows down the aging process and decreases the cancer risk [12]. Kosova et.al. in their study with benign and malignant thyroid patients have found out that serum Cu level increases in the malignant group and decreases in the benign group [13].
In highly Ni-contaminated environments, exposure causes several pathological effects. Among these pathologies, skin allergies, lung fibrosis and respiratory tract cancers are included. Ni compounds have shown to be carcinogenic for human and animals in many epidemiological studies [14,15]. On the other hand, in our study it could not be demonstrated that the Ni level is higher in malignant pleural effusions.
The Pb related oxidative stress disturbs the delicate oxidant/antioxidant balance in the mammals' cells contributing to Pb intoxication pathogenesis. In in vivo studies, Pb exposure leads to ROS production and changes the antioxidant defense systems in occupationally exposed workers and in animals [16].
Pb-related oxidative stress has influences on the cell membrane, DNA and the antioxidant defense systems of the cell. In both animal studies and epidemiological studies, Pb exposure has shown to cause oxidative stress in lungs, blood vessels, testicle, sperm, liver, and brain. Oxidative stress also is another mechanism associated with carcinogenesis [17].
Se is a TE that presents at the active center of selenoprotein which has many important duties including the preservation of redox balance [18]. For example, glutathione peroxidase, which protects the body from oxidative damage and from free radical damage, is a selenoenzyme [19]. Se is an essential TE with growth-modulating capacity. Also, in several empirical model systems it was shown to inhibit the growth of the malignant cells [20;21].
In a study from Iran, although not any significant difference has been found between the heavy metal accumulation in the samples taken from different sites of cancerous tissues of the patients with breast cancer, Se concentration in the tissue has been found maximum as compared to the other elements [22].
Zn takes place in approximately 100 enzyme activities such as polymerase, carbonic anhydrase, superoxide Cu-Zn dismutase. In the genome there exists DNA associated Zn-finger structure. In the human body there is 2-3 g of Zn. Zn deficiency is a common phenomenon in underdeveloped countries. In its deficiency, the immune system, wound healing, the senses of taste and smell and DNA synthesis may be negatively affected [3]. The superoxide dismutase enzyme, of which Zn is the cofactor, plays a key role in the protection of body against free radicals thus inhibiting the initiation and progression of neoplastic phenomena [23].
In the study by Martin-Lagos et.al. serum Zn levels in gynecologic cancers have been found significantly lower than the control group whereas serum Cu levels of cancerous patients were not statistically significantly different than the control group [24]. There was not a statistically significant difference between serum Cu, Zn concentrations of male and female patients and they couldn't demonstrate any statistically significant effect of the patient age on serum Cu and Zn levels. On the other hand in our study, a statistically significant relation was determined between the sex and cytological diagnosis of patients.
Pirincci et. al. in their study on the patients with renal cell carcinoma, have found that serum Pb level is higher in the patient group than the control group whereas Zn level is lower [25].
The role of TEs in various types of cancers has been investigated in several studies. Tekşen et.al. have compared the Se, Cu, Zn, and magnesium levels in serum and pleural effusions of malignant patients and non-malignant control group [26]. They have not determined any difference in the result data of malignant patients and control group, similar to our study.
In the study of Domej et.al. results similar to our study have been obtained. In that study, no statistically significant differ-

ence has been determined in the serum or pleural fluids of the patients with pleural effusion who were diagnosed as benign and malignant [27].

Other than pleural effusion, in a study on the serum and cancerous tissues of patients, Zn, Cu, Se, and Fe concentrations have been shown to be high in the malignant tissues. In this study also Cu levels and Cu / Fe and Cu / Zn (in serum and tissue) have been determined at high levels in the advanced malignant tumors [28].

TEs have function as the component of many enzymes and the catalyst of chemical reactions. There have been studies demonstrating the association of the deficiency or surplus of TEs with many type of cancers. In our study, the role of TEs measured in the pleural effusions in the differential diagnosis in the effusion etiology could not be demonstrated. In order to achieve a definite judgment, we suggest that further studies with greater number of patients should be conducted.

Competing interests

The authors declare that they have no competing interests.

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