

Evaluation of Tumor Markers in Asthma Patients

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Background: Although tumor markers have been used as biomarkers for monitoring response to therapy and detecting early relapse in malignancies, it is well known that most tumor marker increases are not specific enough to be used for diagnosis of cancer.

Aim: The aim of this study was to investigate the serum concentrations of α -fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen (CA) 19-9, CA 125, CA 15-3 and IgE in asthma patients.

Materials and Methods: Thirty-five newly diagnosed asthmatic patients and 14 healthy subjects were included into the study. Blood samples were drawn from antecubital vein of asthma patients and control subjects. Serum AFP, CEA, CA 125, CA 15-3 and CA 19-9 levels were determined by chemiluminescent and IgE levels by electrochemiluminescent immunometric method on automatic hormone analyzers.

Results: Serum levels of AFP, CEA, CA 19-9, CA 125, and CA 15-3 of asthma patients were not significantly different when compared with the control group. In asthma patients, there was a significant negative correlation between serum IgE and CA 125 ($r = -0.401$; $p = 0.017$) and a positive correlation between CA 125 and CA 15-3 ($r = 0.368$; $p = 0.029$).

Conclusions: We concluded that in asthma patients' sera, AFP, CEA, CA 125, CA 19-9 and CA 15-3 levels were not different from control subjects. Elevation in any of these tumor markers in asthma patients should be a sign for clinicians to evaluate patients for additional diseases.

Key Words: Asthma, AFP, CA 125, CA 15-3, CA 19-9, CEA

Astım Hastalarında Tümör Belirteçlerinin Değerlendirilmesi

Amaç: Tümör belirteçleri malignitelerin relapsının erken tespitinde ve tedaviye cevabın izlenmesinde biyobelirteçler olarak kullanılmasına rağmen, çoğu tümör belirtecinin kanser tanısında kullanmak için yeterince spesifik olmadığı bilinmektedir. Biz bu çalışmada astımlı hastalarda serum AFP, CEA, CA 19-9, CA 125, CA 15-3 ve IgE düzeylerini araştırmayı amaçladık.

Yöntem ve Gereç: Bu çalışmaya 35 yeni tanı konulmuş astım hastası ve 14 sağlıklı birey dahil edildi. Astımlı ve kontrol bireylerinin antekübital venlerinden kan örnekleri alındı. Otomatik hormon analizöründe, serum AFP, CEA, CA 125, CA 15-3 ve CA 19-9 düzeyleri kemiluminesans, IgE düzeyleri de elektrokemilüminesans immünometrik metotla ölçüldü.

Bulgular: Astım hastalarının serum AFP, CEA, CA 125, CA 15-3 ve CA 19-9 düzeyleri kontrol grubundan istatistiksel olarak farklı değildi. Astım hastaları grubunda IgE ile CA 125 arasında negatif ($r = -0,401$; $p = 0,017$) ve CA 125 ile CA 15-3 arasında ise anlamlı pozitif korelasyon olduğu gözlemlendi ($r = 0,368$; $p = 0,029$).

Sonuç: Astım hastalarının serumlarında AFP, CEA, CA 125, CA 19-9 ve CA 15-3 düzeyleri kontrol grubundan farklı olmadığı sonucuna vardık. Astımlı hastalarda bu tümör belirteçlerindeki herhangi bir yüksekliğin tespit edilmesi durumunda klinisyenlerin, astımdan başka ilave hastalıklarında göz önünde bulundurmaları gerektiğini düşünmekteyiz.

Anahtar Sözcükler: Astım, AFP, CA 125, CA 15-3, CA 19-9, CEA

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Introduction

Although tumor markers have been introduced to clinical use as biomarkers for monitoring response to therapy and detecting early relapse in malignancies, it has been observed that most tumor marker increases in normal or benign conditions are not specific enough to be used for diagnosis of cancer (1).

α -Fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen 125 (CA 125), cancer antigen 19-9 (CA 19-9) and cancer antigen 15-3 (CA 15-3) are commonly used tumor markers in monitoring and screening of various tumors of liver, pancreas, gastrointestinal system, ovary and breast. However, these tumor markers are not

specific for these malignancies. Serum AFP levels are elevated in patients with benign liver conditions such as cirrhosis and hepatitis (1). CEA has been found to be elevated in some patients having benign conditions, such as cirrhosis, pulmonary emphysema, rectal polyps, benign breast diseases, and ulcerative colitis (1). CA 125 levels are increased in endometriosis, adenomyosis, uterine fibroids, ovarian cysts, salpingitis, peritonitis, pleuritis, pericarditis, alcoholic hepatitis, and the first trimester of normal pregnancy (2). CA 19-9 is an intracellular adhesion molecule, and elevated levels have been reported in patients with benign conditions such as cirrhosis, cholestasis, cholangitis, and pancreatitis (3). Elevated levels of CA 15-3 have been reported in benign breast and liver diseases (1).

The relation between various tumor markers and non-neoplastic diseases of the lung, such as asthma, warrants investigation since high levels of serum tumor markers might indicate a tumoral formation in a patient with benign pulmonary disease and can alert the pulmonary specialist to evaluate the patient. On the other hand, a benign lung disease with an increased serum tumor marker can lead the clinician to the sophisticated and unnecessary diagnostic procedures.

In the asthmatic airway, shedding of the bronchial epithelium with selective loss of columnar epithelial cells from their attachment to basal cells is a characteristic feature (4). Airway epithelium is an important source of cytokines, growth factors, and chemokines and exhibits an altered profile of adhesion molecules expression (5). Thus, it is not surprising to determine elevated levels of different tumor markers in asthmatic patients. The aim of this study was to investigate the serum levels of AFP, CEA, CA 19-9, CA 125, and CA 15-3 in patients with different stages of asthma.

Materials and Methods

Patient population

Thirty-five newly diagnosed asthmatic patients (17 women) aged 10–66 years (mean: 38.4 years) and 14 healthy subjects of similar age as a control group were included into the study. None of the patients had received inhaled or orally administered corticosteroids or any other anti-inflammatory drugs such as sodium cromoglycate or nedocromil sodium in the previous four months. The patients used inhaled beta-2 stimulants only

when necessary. Patients had shown no signs of upper or lower respiratory disease for at least two weeks before entering the study.

Study design

At the initial visit a full history was obtained. Skin prick tests to common aeroallergens were performed and blood was drawn for measurement of total IgE. Asthmatic subjects measured their peak expiratory flow (PEF) in the morning and evening using a Peak Flowmeter (Vitalograph Alpha, USA) and recorded results on a diary card.

Definition of asthma patients

Asthma is a chronic inflammatory disorder associated with an increase in airway hyperresponsiveness that leads to recurrent and often reversible episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. All patients satisfied the Global Initiative for Asthma (GINA) criteria for asthma (6).

Classification of Asthma Severity by Clinical Features before Treatment (GINA)

The severity of a patient's asthma may be classified into one of these four steps based on the clinical features present before treatment is begun. No step 4 patients were present in our study.

Step 1: Intermittent

- Symptoms less than once a week
- Brief exacerbations
- Nocturnal symptoms not more than twice a month
- Forced expiratory volume in 1 second (FEV1) or (PEF) \geq 80% predicted, PEF or FEV1 variability < 20%

Step 2: Mild Persistent

- Symptoms more than once a week but less than once a day
- Exacerbations may affect activity and sleep
- Nocturnal symptoms more than twice a month
- FEV1 or PEF \geq 80% predicted, PEF or FEV1 variability 20-30%

Step 3: Moderate Persistent

- Symptoms daily
- Exacerbations may affect activity and sleep
- Nocturnal symptoms more than once a week

- Daily use of inhaled short-acting beta-2-agonist
- FEV1 or PEF 60-80% predicted, PEF or FEV1 variability > 30%

Step 4: Severe Persistent

- Symptoms daily
- Frequent exacerbations
- Frequent nocturnal asthma symptoms
- Limitation of physical activities
- FEV1 or PEF \leq 60% predicted, PEF or FEV1 variability > 30%

Methods

Blood samples were drawn from antecubital vein of asthma patients and control subjects. All blood samples were centrifuged for 10 min at 1500 g and sera were stored at -40°C until analysis. All samples were processed within one month.

Biochemical assay

Serum AFP, CEA, CA 125, CA 19-9 and CA 15-3 levels were determined by chemiluminescent immunometric methods in each group on an automatic hormone analyzer (Immulite, DPC, Los Angeles, USA).

Serum IgE level was determined by electrochemiluminescence immunoassay in each group on an automatic hormone analyzer (Roche Modular Analytics Hitachi E 170, Japan).

Statistical analysis

Data were expressed as the mean \pm SD. The un-paired Student's t test was used to evaluate the significance of difference between asthma (all patients) and control groups. The significance of difference among all steps of asthma and control groups was analyzed using analysis of variance (ANOVA), and if the F value was found to be significant, differences between means was then analyzed using the post-ANOVA (Tukey) test. Correlations between parametric and non-parametric variables were assessed using Pearson and Spearman's correlation analysis respectively. Values of $p < 0.05$ were considered as statistically significant.

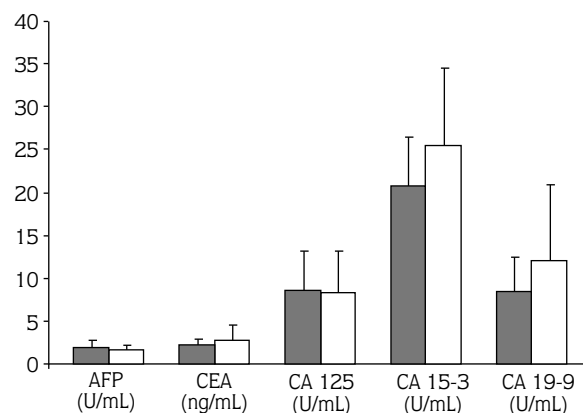


Figure 1. Serum levels of AFP, CEA, CA 125, CA 15-3 and CA 19-9 in control subjects (first column) and asthma patients (second column).

Results

Serum levels of AFP, CEA, CA 125, CA 15-3 and CA 19-9 of all asthma patients and control subjects are shown in Figure 1. The differences between serum levels of CEA (2.7 ± 1.8 ng/ml), CA 19-9 (12.0 ± 8.9 U/ml), CA 125 (8.3 ± 4.8 U/ml), AFP (1.6 ± 0.6 U/ml), and CA 15-3 (25.4 ± 9.0 U/ml) in asthma patients and in those of control subjects (CEA = 2.2 ± 0.7 ng/ml; CA 19-9 = 8.5 ± 3.9 U/ml; CA 125 = 8.6 ± 4.5 U/ml; AFP = 2.0 ± 0.8 ; CA 15-3 = 20.7 ± 5.7) were not statistically significant ($P > 0.05$).

As shown in Table 1, we also evaluated serum levels of AFP, CA 15-3, CEA, CA 19-9 and CA 125 in patients based on asthma severity. Serum levels of AFP, CA 15-3, CEA, CA 125 and CA 19-9 in step 1, 2, 3 asthma patients and control subjects were not significantly different ($P > 0.05$).

In asthma patients, serum total IgE levels ranged from 1 to 1450 U/mL (median 131 U/mL). Reference range for IgE was 0-200 U/mL. In asthma patients, there was a significant negative correlation between serum IgE and CA 125 levels ($r = -0.401$; $p = 0.017$) and a positive correlation between serum CA125 and CA 15-3 levels ($r = 0.368$; $p = 0.029$) (Figure 2).

Discussion

Biological and technical advances have led to greatly increased research and development in the area of tumor biomarkers. Despite intensive studies, there is not yet a specific tumor marker for known tumors.

Table 1. Serum levels of tumor markers in control subjects and asthma patients.

Tumor markers	Control (n=14)	Serum levels in asthma patients				Reference range
		All Patients (n = 35)	Step 1 (n = 7)	Step 2 (n =14)	Step 3 (n =14)	
AFP (U/mL)	2.5 ± 1.1	1.6 ± 0.6	1.8 ± 0.7	1.4 ± 0.3	1.6 ± 0.7	0.56 – 2.6
CEA (ng/mL)	2.2 ± 0.7	2.7 ± 1.8	2.8 ± 0.3	2.5 ± 2.3	2.7 ± 1.8	0.21 – 6.3
CA 125 (U/mL)	8.6 ± 4.5	8.3 ± 4.8	7.0 ± 5.1	8.2 ± 4.5	9.1 ± 5.2	2.6 – 18.0
CA 15-3 (U/mL)	16.8 ± 5.7	25.4 ± 9.0	25.6 ± 10.8	28.4 ± 8.1	22.4 ± 8.5	9.0 – 51.0
CA 19-9 (U/mL)	8.5 ± 3.9	12.0 ± 8.9	8.6 ± 5.6	12.7 ± 8.9	13 ± 10.3	0.0 – 33.0

Values are given as mean ± SD.

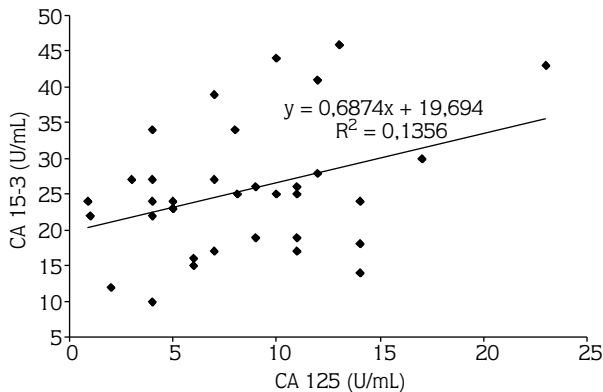


Figure 2. Correlation between CA 125 and CA 15-3 in asthma patients.

Biological features of a tumor are different from normal tissues. In neoplasia, progressive biological heterogeneity with transient characteristics of expression is a characteristic of a tumor cell (7). Biological heterogeneity is present both among cells within a tumor at a given time point and in cells during the development of tumors from earlier to later time points (8).

Cytokines, metalloproteinases, some growth factors and other molecules may play important roles in remodeling of asthmatic patients' airway tissues, many different tumors, and inflammatory processes. Airway smooth muscle hyperplasia is an important pathologic feature of chronic asthma that contributes to airway obstruction and exaggerated bronchoconstriction. In asthmatic patients, chronic inflammation causes marked remodelling of the structure of the bronchi. Bronchial biopsy specimens from asthmatic patients have indicated

that remodeling of the airways is caused by thickening of the subepithelial layer and this is associated with an increase of myofibroblasts (9). In light of the literature about the pathophysiology of asthma and tumors, it is not surprising to measure elevated serum concentrations of some bioactive molecules like growth factors, cytokines and metalloproteinases. The tumor markers that we have measured in our study were not related to asthma significantly. This point is important, especially for clinicians, when evaluating asthma patients with elevated tumor markers.

CEA, an oncofetal glycoprotein, is a marker for colorectal, gastrointestinal, lung and breast carcinoma (10-13). Maeda and co-workers (14) have reported that CEA concentration is elevated in asthma patients with mucoid impaction in comparison with patients without mucoid impaction and healthy volunteers. In the present study, there were no asthma patients with mucoid impaction in our study groups, and serum CEA levels in asthma patients were not different from the control group and were within reference range for the normal population.

Elevated levels of CA 19-9, an intracellular adhesion molecule, occur primarily in patients with pancreatic and biliary tract cancers (3). Takayama and co-workers (15) studied CA 19-9 in 156 patients with benign pulmonary disease (11 with bronchial asthma) and found elevated levels of CA 19-9 in 27.3% of patients with asthma. However, in our study, serum CA 19-9 levels in asthma patients were not different than those of control subjects and were within reference range of the normal population.

AFP, an oncofetal glycoprotein, is a marker of hepatocellular and germ cell carcinoma; CA 125 is a marker of ovarian and endometrial carcinoma; and CA 15-3 is a marker of breast carcinoma (1). In our study, serum AFP, CA 125 and CA 15-3 levels in asthma patients also did not differ from those of the control group. There was no statistical difference between steps in AFP, CA 125 and CA 15-3 levels. No step 4 patients were present in our study. To the best of our knowledge, this study is the first to investigate CA 125, CA 15-3 and AFP levels in asthma patients since a literature search at the time of manuscript preparation (using asthma and CA 125; asthma and CA 15-3; asthma and AFP as key words

in PubMed) produced no study measuring and discussing CA 125, CA 15-3 and AFP in asthma cases. In the present study, we found that there was a significant negative correlation between serum IgE and CA 125 and a positive correlation between CA 125 and CA 15-3 in asthma patients. Further studies are needed to establish the interaction between these tumor markers in asthma patients.

We conclude that in asthma patients' sera, AFP, CEA, CA 125, CA 19-9, and CA 15-3 are not elevated significantly. Thus, elevation in any of these tumor markers in asthma patients should be a sign for clinicians to evaluate patients for additional diseases.

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