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Serum Total Sialic Acid Levels in Lung Cancer Patients of Different Histological Types with and No Extrapulmonary Metastases

[Ekstrapulmoner Metastazı Olan ve Olmayan Farklı Histolojik Tipteki Akciğer Kanserli Hastalarda Serum Total Sialik Asid Düzeyleri]

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ABSTRACT

It has been reported that sialic acid containing oligosaccharides play an important role in the adhesion between cancer cells and endothelial cells and also demonstrated that metastatic potential of tumor cells is proportional to cell surface sialylation. In the present study, we investigated serum total sialic acid levels in lung cancer patients with different histological types and evaluated its role for diagnosis of extrapulmonary metastases. Untreated lung cancer patients of different histological types with metastases (60.78±10.55 years, all men, n=77) and those with no metastases (61.77±10.43 years, all men, n=82) and 35 healthy volunteers (59.08±10.46 years, all men) were included in the study. Patients with metastases consisted of 45 subjects with nonsmall cell lung carcinoma (29 of which were squamous cell carcinoma and 16 of which were adenocarcinoma) and 32 subjects with small cell lung carcinoma. Patients with no metastases consisted of 57 subjects with nonsmall cell lung carcinoma (35 of which were squamous cell carcinoma and 22 of which were adenocarcinoma) and 25 subjects with small cell lung carcinoma. Serum total sialic acid levels in lung cancer patients of different histological types with metastases and those with no metastases were significantly elevated as compared to control ($p<0.001$ for all). The levels of serum total sialic acid in total lung carcinoma ($p<0.001$), nonsmall cell lung carcinoma ($p<0.01$) and squamous cell lung carcinoma ($p<0.01$) patients with metastases were significantly higher than those with no metastases. There was also a significant difference between the levels of serum total sialic acid of small cell lung carcinoma patients with extended disease and those with limited disease ($p<0.01$). Using the metastases values as positive and the no metastases values as negative controls, the sensitivity, specificity and cutoff point of total sialic acid were found to be 63.6%, 68.3% and 93.67 mg/dl, respectively. As a result, we conclude that, (a) serum total sialic acid is elevated in lung cancer patients of different histological types with metastases and those with no metastases, (b) serum total sialic acid in lung cancer patients with metastases is significantly higher than those with no metastases, and, (c) however, total sialic acid does not appear as a suitable marker for distinguishing lung cancer patients with extrapulmonary metastases from those with no extrapulmonary metastases

Key Words: Total sialic acid, lung cancer, extrapulmonary metastases

ÖZET

Sialik asid içeren oligosakkaridlerin kanser hücreleri ve endotelyal hücreler arasındaki adhezyonda önemli bir rol oynadığı ve tümör hücrelerinin metastaz yeteneğinin hücre yüzeyinin sialilasyonu ile ilişkili olduğu bildirilmiştir. Bu çalışmada farklı histolojik tipteki akciğer kanserli hastalarda serum total sialik asid düzeylerini inceleyerek, ekstrapulmoner metastazın teşhisinde rolünü değerlendirdik. Çalışmaya hiç tedavi görmemiş, metastazı olan 77 erkek (yaş ortalaması 60.78±10.55 yıl) ve metastazı olmayan 82 erkek (yaş ortalaması 61.77±10.43 yıl) akciğer kanserli hasta ve 35 sağlıklı erkek gönüllü (yaş ortalaması 59.08±10.46 yıl) dahil edildi. Metastazı olan hastaların 45'i küçük hücreli dışı akciğer kanserli (29'u skuamöz hücreli, 16'sı adenokarsinomlu) ve 32'si küçük hücreli akciğer kanserli hastadan oluşmaktaydı. Metastazı olmayan hastaların 57'si küçük hücreli dışı akciğer kanserli (35'i skuamöz hücreli, 22'si adenokarsinomlu) ve 25'i küçük hücreli akciğer kanserli hastadan oluşmaktaydı. Metastazı olan ve olmayan akciğer kanserli hastalarda serum total sialik asid düzeyleri kontrol grubuna göre daha yüksekti (tümü için $p<0.001$). Metastazı olan total akciğer kanserli grupta ($p<0.001$), küçük hücreli dışı akciğer kanserli grupta ($p<0.01$) ve skuamöz hücreli akciğer kanserli grupta ($p<0.01$), serum total sialik asid düzeyleri metastazı olmayan hastalara göre daha yüksekti. Yaygın ve sınırlı hastalığı olan küçük hücreli akciğer kanserli hastaların serum total sialik asid düzeyleri arasında da anlamlı bir fark vardı ($p<0.01$). Total sialik asid için metastazı olan ve olmayan hastalar arasında cut-off noktası 93.67 mg/dl, duyarlılık %63.6 ve spesifiklik %68.3 olarak bulundu. Sonuç olarak, (a) serum total sialik asidin metastazı olan ve olmayan akciğer kanserli hastalarda arttığını, (b) metastazı olan akciğer kanserli hastaların serum total sialik asid düzeylerinin metastazı olmayan hastalardan daha yüksek olduğunu, (c) ancak total sialik asidin metastazı olan ve olmayan akciğer kanserli hastaları birbirinden ayırmada uygun bir marker olamayacağını söyleyebiliriz.

Anahtar Kelimeler: Total sialik asid, akciğer kanseri, ekstrapulmoner metastaz

INTRODUCTION

Lung cancer is one of the common health problems of the 20th century (1). The use of tumor markers as prognostic factors or risk factors has gained popularity in recent years. Measurement of the level of risk factors has been found to be valuable in the assessment of the aggressiveness of a tumor and is helpful in the selection of treatment strategies (2).

In recent years, several biochemical markers associated with lung tumors including hormones, regulatory peptides, fetal proteins and enzymes, have been suggested for diagnosis and prognosis of lung cancer patients (3).

It has been proposed that sialic acid may be a useful tumor marker for lung cancer (4-9). The sialic acids, a group of acylated neuraminic acid are widely distributed in nature as terminal sugars on oligosaccharides attached to protein or lipid moieties (10, 11).

Since sialic acids possess relatively strong carboxyl groups (pKa 2,6 for N-acetyl neuraminic acid), their presence in glycoproteins or at the cell periphery makes a significant contribution to the negative surface charge (11, 12), they are responsible for the electrostatic repulsion as seen with platelets, erythrocytes and carcinoma cells. Sialic acids serve a number of major biological functions; sialic acid at the terminal position is involved in cellular adhesion (10, 13), they are components of many cell surface receptors and have an ability to mask specific cellular recognition sites which is of particular importance in the reaction of the environment to foreign cells including cancer cells (11).

It has been suggested that tumor cells have ability to change their surface properties and alter the sialo-glycoconjugates expressed on their plasma membranes which affect their behaviour and ability to invade (14, 15).

The aim of the present study is to investigate serum total sialic acid levels in lung cancer patients of different histological types with metastases and those with no metastases and to assess the usefulness of the method in distinguishing lung cancer patients with metastases from those with no metastases.

MATERIALS AND METHODS

Untreated lung cancer patients of different histological types with metastases (or extended disease) (60.78±10.55 years, all men, n=77) and those with no metastases (or limited disease) (61.77±10.43 years, all men, n=82) as evidenced by histopathological, radiological and cytological findings, and 35 healthy volunteers (59.08±10.46 years, all men) were included in the study. Patients with metastases consisted of 45 subjects with nonsmall cell lung carcinoma (29 of which were squamous cell carcinoma and 16 of which were adenocarcinoma) and 32 subjects with small cell lung carcinoma. Patients with no metastases consisted of 57 subjects with nonsmall cell lung carcinoma (35 of which were squamous cell carcinoma and 22 of which were adenocarcinoma) and 25 subjects with small cell lung carcinoma. Limited disease was defined as primary lung cancer without the spread of the disease to other organs. Lung cancer patients with metastases to the liver, lymph nodes, ribs, neck, etc., were classified as having extended disease.

The chemicals used for total sialic acid determination were purchased from Merck (Darmstadt, Germany) and Sigma Aldrich Chemie (Steinheim, Germany) and were of analytical grade.

For total sialic acid determination, serum samples were obtained from venous blood after a 12h fast by centrifugation of clotted specimen within 30 min. Serum specimens were divided into multiple fractions that were frozen at -70°C until used.

Serum total sialic acid determination was performed by the thiobarbituric acid method described by Warren (16). Prior to the determination of sialic acid levels, serum was incubated at 80°C for 1h in 0.1 N sulphuric acid in order to liberate the bound sialic acid. A calibration curve was obtained using 25, 50, 75 and 100 μg/ml standard N-acetylneuraminic acid solutions.

The student's t test, Oneway Anova test and ROC analysis were used to analyze the results. $p<0.05$ was taken as statistically significant.

Table I. Serum total sialic acid (TSA) levels in study groups (1).

Group	Range	Means±SD	Median
With metastases (total) (n=77)	56.37-148.02	99.83±19.44*	100.94
Nonsmall cell (n=45)	56.37-148.02	99.03±19.50*	98.40
squamous cell carcinoma (n=29)	56.37-148.02	98.19±20.10*	97.46
adenocarcinoma (n=16)	70.47-144.17	100.54±18.90*	102.48
Small cell (n=32)	60.62-146.11	100.96±19.62*	105.57
No metastases (total) (=82)	46.15-118.04	87.05±16.19*	86.27
Nonsmall cell (n=57)	46.15-115.44	87.33±15.52*	86.74
squamous cell carcinoma (n=35)	46.15-115.44	85.35±15.97*	84.68
adenocarcinoma (n=22)	59.90-109.26	90.48±14.59*	88.91
Small cell (n=25)	56.58-118.04	86.41±17.96*	82.90
Control (n=35)	41.76-61.87	53.75±5.57	54.40

*p<0.001

(1) Compared to control

RESULTS

The mean serum total sialic acid levels of study groups are shown in Table 1. Serum total sialic acid levels in patients with metastases (total) and those with no metastases (total) were significantly elevated when compared with control group ($p<0.001$ for all).

Total sialic acid levels in nonsmall cell, small cell and squamous cell carcinoma and adenocarcinoma patients with metastases and those with no metastases were also significantly elevated as compared to control ($p<0.001$ for all).

There was a significant difference between the levels of serum total sialic acid of lung cancer patients with metastases and those with no metastases ($p<0.001$) (Figure 1).

Similarly the levels of serum total sialic acid in nonsmall cell lung carcinoma ($p<0.01$) and squamous cell carcinoma ($p<0.01$) patients with metastases were significantly higher than those with no metastases (Figure 2 and 3).

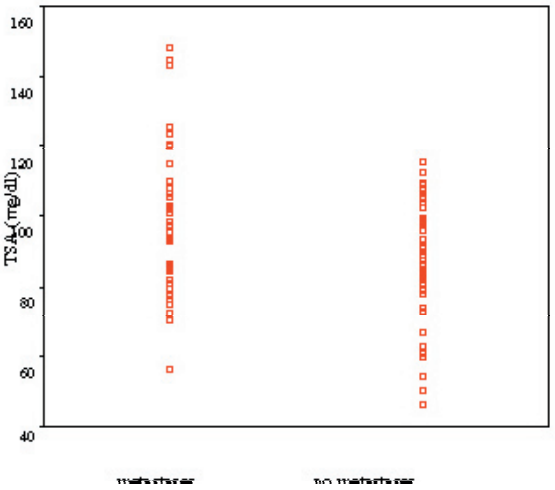
There was no significant difference between serum total sialic acid levels of adenocarcinoma patients with metastases and of adenocarcinoma patients with no metastases. We also found a significant difference between serum total sialic acid levels of small cell lung carcinoma patients with extended and those with limited progresses of the disease ($p<0.01$) (Figure 4).

Using the metastase values as positive and the ones as negative controls, we found that the sensitivity, specificity and cutoff points of total sialic acid measurements are 63.6%, 68.3% and 93.67 mg/dl, respectively.

DISCUSSION

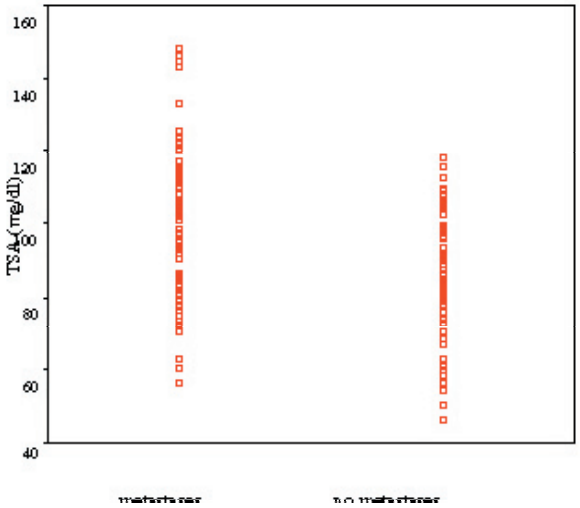
Tumorigenesis is a multistep process involving several mutations each of which results in discrete changes in the cellular metabolism (18).

Sialic acids widely distributed in nature as terminal sugars in glycoproteins or glycolipids, impart a net negative charge to cell surface and are reported to be important in cell-to-cell and cell-to-matrix interactions (10, 11). It was previously demonstrated that neoplastic transformation leads to elevated plasma sialic acid concentration (19-24) through the shedding or secreting of sialic acid from the tumor cell surfaces (25, 26). Increased concen-



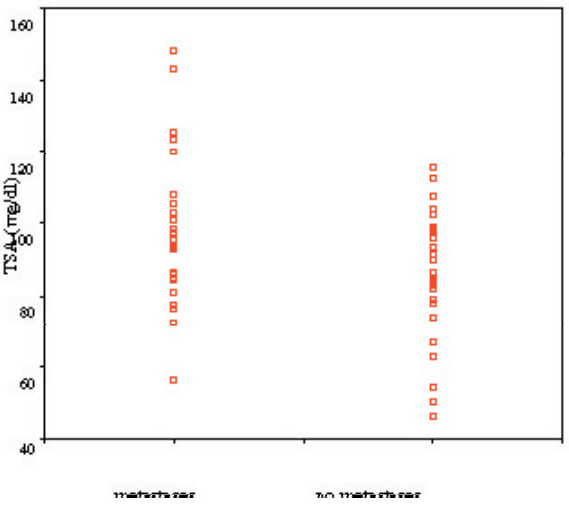
(n=45) (n=57)

Figure 2. Comparison of serum total sialic acid (TSA) levels in nonsmall cell lung carcinoma patients with metastases and those with no metastases.



(n=77) (n=82)

Figure 1. Comparison of serum total sialic acid (TSA) levels of patients with metastases and those with no metastases.



(n=29) (n=35)

Figure 3. Comparison of serum total sialic acid (TSA) levels in squamous cell carcinoma patients with metastases and those with no metastases.

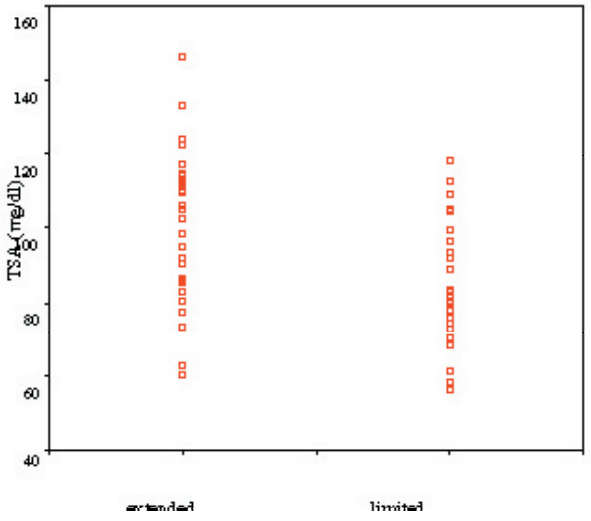


Figure 4. Comparison of serum total sialic acid (TSA) levels in small cell lung carcinoma patients with extended and limited disease stages.

trations of serum sialic acid have been reported in lung cancer patients (4, 5, 7, 9, 27-29).

Of the nonsmall cell lung carcinomas, 35% to 71% are squamous cell, 9% to 29% are adenocarcinomas and 3% to 16% are large cell carcinomas. Small cell carcinomas represent 12% to 25% of cases and these tumors metastasize early to hilar and mediastinal lymph nodes, and readily invade blood vessels. In squamous cell carcinoma, the tumor usually develops as a polypoid or sessile mass in major bronchi, which often obstructs the lumen of the airway. Adenocarcinomas of the lung are developed most commonly as a peripheral parenchymall mass and invade blood and lymph vessels early in their development and frequently give rise to metastases before the primary lesion causes any symptomps (28).

Serum total sialic acid levels in total lung cancer patients with metastases and those with no metastases were found to be significantly elevated as compared to controls in the present study ($p<0.001$ for both). These results are in agreement with the previous studies (4, 29).

Different from the previous studies, serum total sialic acids in lung cancer patients of each different histological type with metastases were also investigated and compared with control in the present study. Total sialic acid levels in nonsmall cell lung, squamous cell, small cell carcinoma, and adenocarcinoma patients with metastases were significantly elevated as compared to control ($p<0.001$ for all).

Similar to the results of Patel (29), total sialic acid levels in nonsmall cell, squamous cell, small cell carcinoma and adenocarcinoma patients with no metastases were also found to be significantly elevated as compared to those of controls ($p<0.001$ for all).

The assessments of tumor aggressiveness and prognosis for the outcome of a cancer patient have gained increasing popularity in recent years. The clinical value of any given tumor marker will depend on the intended clinical use and the specificity and sensitivity of the tumor marker (2). Several biochemical markers associated with lung cancer including hormones, regulatory peptides, fetal proteins and enzymes have been suggested for diagnosis and prognosis of lung cancer patients [3]. Serum sialic acid has also been reported to be a highly sensitive marker in lung cancer (4, 5, 7, 8, 27, 30, 31).

Despite advances in the management of solid tumors, the development of metastases continues to be the most significant problem and cause of death for cancer patients. There is great interest in the role of cell surface glycoconjugates as recognition molecules for adhesion between both matrix and other cells because interactions of the tumor cell surface with the extracellular matrix and with cells of the target organ are important for invasion and the development of distant metastases (32-34). One characteristic feature of cancer cells is increased sialylation in cell surface glycoproteins. The amount of sialic acid present on the surface of malignant cells has been found to be correlated directly with the ability to metastasize (14, 15, 23). Expression of lysosomal-type sialidase has been shown to be inversely associated with metastatic potential and tumor growth in cancer cells (35, 36). Inhibitors of sialyltransferase, the enzyme that is responsible for the synthesis of sialoglycoconjugates (37) have also been reported to have potential roles in tumor growth and metastases (38). It has also been reported that membrane-bound sialic acid plays a role in invasiveness of human lung carcinoma cells (39).

Contradictory results have been reported in the levels of serum total sialic acid between lung cancer patients with metastases and those with no metastases. Patel et al (29) reported that no significant difference was observed in the levels of total sialic acid of primary and metastatic lung cancer patients. In a previous study it has been shown that elevations in total sialic acid values were more frequently associated with extended lung disease compared to limited disease (4). Kakari et al (7) reported that total sialic acid concentrations were significantly higher in extensive than limited disease stages in small cell lung carcinoma patients.

In the present study, we found that serum total sialic acid levels in patients with metastases were significantly elevated as compared to those with no metastases ($p<0.001$).

As different from the previous studies, we also compared total sialic acid levels between different histological types of nonsmall cell lung carcinoma patients with metastases and those with no metastases. Serum total sialic acid levels in nonsmall cell lung carcinoma ($p<0.001$) and squamous cell carcinoma ($p<0.01$)

patients with metastases were significantly higher than those with no metastases. There was no significant difference between serum total sialic acid levels of adenocarcinoma patients with metastases and of adenocarcinoma patients with no metastases. Serum total sialic acid levels of small cell lung carcinoma patients with extended disease were also higher than those of small cell lung carcinoma patients with limited disease progress ($p<0.01$). It has been previously reported that serum total sialic acid concentrations were significantly higher in extensive than limited disease stages in small cell lung carcinoma patients (7).

We could not encounter any studies investigating sialic acids as tumor markers for distinguishing lung cancer patients of different histological types with metastases from those with no metastases. Using the metastases values as positive and the no metastases values as negative controls, we found that the sensitivity, specificity and cutoff point of total sialic acid is 63.6%, 68.3% and 93.67 mg/dl, respectively. According to these results, we could say that serum total sialic acid is not a suitable marker for distinguishing lung cancer patients with metastases from those with no metastases.

In conclusion, we report that (a) serum total sialic acid levels in lung cancer patients of different histological types with metastases and those with no metastases are significantly elevated, (b), serum total sialic acid in nonsmall cell lung carcinoma, squamous cell carcinoma and small cell carcinoma patients with metastases is significantly higher than those with no metastases, and, (c) however, total sialic acid is not a suitable marker for distinguishing lung cancer patients with extrapulmonary metastases from those with no extrapulmonary metastases.

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