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Total sialic acid level in lung cancer patients

Investigation of effective biomarkers for cancers is currently a popular area of study in clinical and cancer researches, because it can potentially lead to pre-cancer screening or pre-cancer diagnosis and may provide useful information about cancer type and the disease's stage of progression. More and more biochemical or chemical fluid components of the human body such as urine, blood, and cerebrospinal fluid have been considered to contain biomarkers.

Lung cancer is the most common cause of cancer death in the world for both men and women and it is generally held that there are no good screening tests available for lung cancer. The significance of tumor markers in lung cancer are not well established.

Previous studies have shown an important role in the measurement of serum sialic acid (SA) for the diagnosis of different types of cancer (2, 7, 9, 11). In the human body SA is synthesized from pyruvic acid and N-acetyl-D-mannosamine by the catalytic activity of N-acetylneuraminic aldolase, then sialytransferase catalyzes the transfer of SA moieties to the terminal glucose in the chains of the polysaccharides, glycoproteins or glycolipids (1). SA derivatives play an important role in stabilizing the conformation of glycoproteins of cellular membranes and in the function and survival of blood glycoproteins (14). Moreover, they contribute to membrane transport and are important in cell to cell recognition and cell to cell or cell to matrix interaction (10, 13). More than 40 naturally occurring SA derivatives of the three main forms: the N-acetylneuraminic, N-glycolylneuraminic and deaminoneuraminic acid have been identified (5). Approximately 98–99.5% of the SA is bound to glycoproteins but only a small amount is bound to lipids or occurs in the free state (15). SA containing glycoconjugates play a vital role in such processes as inflammation, embryogenesis, organogenesis, immune defence, infection by a variety of pathogens, and metastasis of neoplastic cell (3). Analysis of SA concentration in biologic material from patients is useful for a wider understanding of various pathophysiological processes and is valuable in disease diagnosis and monitoring (5).

The aim of this study was to examine serum total sialic acid (TSA) level and the relation of serum TSA to serum protein (TSA /serum protein index) in patients with lung cancer and to evaluate TSA concentration at different clinical stages of the disease.

MATERIAL AND METHODS

TSA level was determined in serum collected from 23 patients with histologically confirmed lung cancer treated in the Chair and Department of Pneumonology, Oncology and Allergology, Medical University of Lublin. We analyzed 17 men and 6 women aged from 49 to 75. The patients were divided into two groups according to the histological type of the tumor: non-small cell lung cancer

(NSCLC) and small cell lung cancer (SCLC), 16 and 7 patients, respectively, and into four groups according to the clinical stage of the disease. The clinical stage of the patients was assessed by means of the TNM classification system. The control group consisted of 20 healthy individuals (blood donors). The blood samples were collected from each patient before any treatment. Serum obtained by centrifugation at 4000 rpm for 20 min were stored at –20°C until analyzed. Serum TSA level was determined by modified thiobarbituric acid method according to Warren and Crook. Serum protein content was determined by the biuret reaction. TSA/ protein index expressed in μmol of sialic acid per gram of protein was calculated.

Data were analyzed using the STATISTICA for Windows software (Copyright Statsoft, Inc. 1993 release 5.1 G). The Mann-Withney U test and Spearman test were used to analyze the data. P values less than 0.05 were considered statistically significant. The results are expressed as mean ± SD.

RESULTS

The results are presented in Table 1. The mean serum level of the TSA in lung cancer patients (2.85± 0.60 mmol/l, range: 1.70–3.73) was significantly higher than in the control group (1.50± 0.18 mmol/l, range: 1.23–1.96). Serum TSA/serum protein index in lung cancer patients was significantly higher if compared to the control group as well (39.68 ± 11.75 μmol/g and 21.81 ± 4.62 μmol/g, respectively). Moreover, serum TSA level and serum TSA/ serum protein index was higher in non-small cell lung cancer patients in comparison with small cell lung cancer patients, however the differences were not significant (p>0.05).

Table 1. Serum total sialic acid level in lung cancer patients (mean ± SD)

	Number of cases	TSA (mmol/l)	P	TSA per gram of serum protein (μmol/g)	P
Control group	20	1.50 ± 0.18		21.81 ± 4.62	
Lung cancer patients	23	2.85 ± 0.60	p<0.001	39.68 ± 11.75	p<0.001
NSCLC patients	16	2.99 ± 0.55		42.21 ± 11.55	
SCLC patients	7	2.52 ± 0.62	p>0.05	33.90 ± 10.80	p>0.05

Figures 1 and 2 show that serum TSA level was increased in patients with various stages of lung cancer development. Serum TSA level (Fig. 1) and TSA / serum protein index (Fig. 2) were positively correlated with the clinical stage of the patients according to TNM classification system.

DISCUSSION

Most of investigators have reported increased values of TSA in various diseases and disorders: inflammatory processes, alcohol abuse, diabetes, chronic renal failure and chronic glomerulonephritis. An association between increased SA levels and elevated stroke and cardiovascular mortality risk has also been reported (10,13,14) as well as an increased serum TSA level in the case of patients with various types of cancer: prostate, colon, breast, bladder cancer, gynecological cancer and in patients with leukemia and malignant melanoma (2, 4, 6, 11, 12). Some researches suggest that SA level may be elevated in patients with cancer before the occurrence of clinical symptoms that could be useful in disease screening or pre-cancer diagnosis (5, 6).

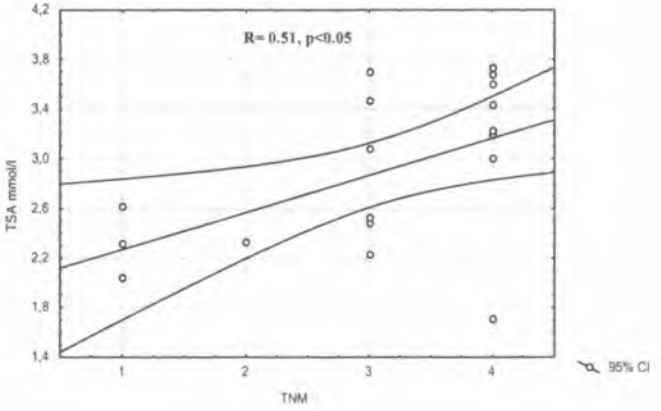

Fig. 1. Serum TSA (mmol/l) in patients with various stages of lung cancer

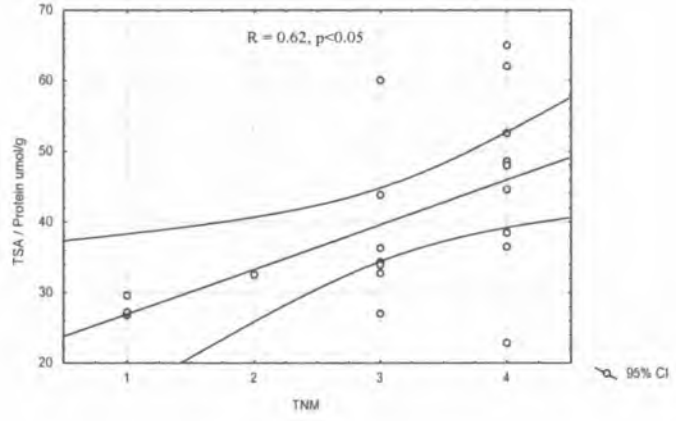

Fig. 2. TSA/ serum protein index (μmol/g) in patients with various stages of lung cancer

SA level has also been taken into account as a marker for lung cancer (4, 6, 11). Several investigators have found elevated serum and pleural fluid SA levels in malignant pleural effusions if compared with benign pulmonary disease (2, 4). Rokicki et al. (11) showed that there is a significant difference in the serum levels of SA in patient with lung cancer if compared with normal controls. Narayanan (6) reported significantly higher mean concentration of serum TSA and lipid-bound SA in lung cancer in comparison with benign pulmonary disease.

In our study we demonstrated that serum SA level in lung cancer patients is significantly higher than in the control group. Moreover, serum TSA level and TSA/serum protein index were associated with the clinical stage of the patients assessed by means of the TNM classification system. It was previously shown that serum SA content increases with the severity of neoplasia and it positively correlates with the tumor growth and degree of metastasis (7, 8, 13). In this study TSA level was also analyzed in the context of the histological type of lung cancer. We observed higher TSA level in cases of non-small cell carcinoma in comparison to small cell carcinoma, which is generally consistent with the data presented by Rokicki et al. (11).

Several different mechanisms may lead to an increase in SA concentration in inflammatory and cancer disorders. An important role in the elevation of serum TSA plays the activity of sialidase (N-acetylneuraminidase), which cleaves the terminal SA residues from oligosaccharides, glycoproteins and gangliosides (1, 13). According to Achyuthan et al. (1) sialidase activity level in various tissues and body fluids is a helpful biomarker for several diseases, including cancer. On the other hand, malignant cells are characterized by an increase binding of SA with glycoproteins of the cell surface and membranes. One of the mechanisms by which glycoconjugate SA content is elevated in tumor cells, is increase in the activity of sialyltransferases (3). It has been hypothesized that tumor cells use their heavily sialylised surface as a mask to avoid recognition by the immune surveillance system and thus facilitate metastatic spreading (7). The high turnover of tumor cells and the consequently increased release of SA supposedly cause the high TSA concentration in the serum (16). The increased TSA level in tumor patients has been also explained by a spontaneous release (shedding) of abberant SA-containing cell surface glycoconiugates (14, 15).

It has been reported that the determination of serum SA is helpful for monitoring of patients suffering from various types of neoplasm after treatment (6, 7). Painbeni et al.(7) used serum TSA level in predicting the efficacy of the treatment in patients with colon and rectum adenocarcinoma metastasis after three months' treatment. They compared TSA with two common markers, i.e. carcinoembryonic antigen (CEA) and the carbohydrate antigen 19-9 (CA 19-9). Changes in CEA and CA 19-9 did not correlate as well as SA with the treatment efficacy. TSA determination could provide useful information about the spreading and metastatic properties of the tumor. The researchers concluded that SA concentration normalization within treatment is an indicator of tumor growth arrest and SA elevation could be a marker of relapse (7).

CONCLUSIONS

Various investigators have suggested that TSA may by a valuable biochemical marker in detecting metastases, staging of disease, indicating the risk for recurrence and evaluating therapeutic response. In this study serum TSA level demonstrated in lung cancer patients was found to be significantly elevated when compared to the control group. Our experiments show that there is a correlation between serum TSA concentration and the clinical stage of lung cancer.

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SUMMARY

A number of biochemical parameters and tumor markers in the blood have been intensively evaluated to distinguish malignant diseases from benign. Among these parameters SA has been found to have a diagnostic significance. The aim of this study was to evaluate diagnostic utility of SA as a tumor marker in lung cancer patients and to assess the relationship between serum SA concentration and severity of disease in these patients. Serum TSA levels expressed in mmol/l and μmol/g of serum protein were significantly higher in lung cancer patients in comparison with the control group of healthy individuals. The mean serum level of the TSA in lung cancer patients was 2.85± 0.60 mmol/l, and TSA/ protein index was 39.68± 11.75 μmol/g. Moreover, serum TSA level and TSA/ serum protein index were significantly correlated with the severity of lung cancer. In this study SA level was also analyzed in the context of the histological type of lung cancer. Serum SA level was higher in non-small cell lung cancer group (2.99± 0.55 mmol/l) in comparison with small cell lung cancer group (2.52± 0.62 mmol/l), however, the results were not significant ($p>0.05$).

Poziom kwasu sialowego u pacjentów z rakiem płuc

W celu zróżnicowania chorób nowotworowych od innych chorób badanych jest wiele biochemicznych parametrów i markerów nowotworowych. Jednym z takich związków jest kwas sialowy, który jak się uważa ma znaczenie diagnostyczne. Celem przeprowadzonych badań była ocena przydatności oznaczania poziomu kwasu sialowego w surowicy krwi jako markera w nowotworach płuc i ocena związku pomiędzy jego stężeniem we krwi a zaawansowaniem choroby. Kwas sialowy, wyrażony zarówno w milimolach na litr surowicy, jak i w mikromolach na gram białka surowicy krwi, był znacząco wyższy u pacjentów z rakiem płuc w porównaniu z grupą kontrolną. Średni poziom

kwasu sialowego w raku płuc wynosił 2,85± 0,60 mmol/l, a indeks kwas sialowy/ białko 39,68 ± 11,75 μmol/g. Ponadto poziom kwasu sialowego i indeks kwas sialowy/ białko znacząco korelował ze stopniem zaawansowania klinicznego choroby. W naszych badaniach poziom kwasu sialowego był porównywany u pacjentów z rakiem drobnobnokomórkowym i niedrobnokomórkowym. W drugim przypadku poziom kwasu sialowego był wyższy, odpowiednio 2,99± 0,55 mmol/l i 2,52± 0,62 mmol/l, ale różnica ta nie była istotna.