Immunoglobulins and Complement Components in Patients with Lung Cancer

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SUMMARY

Based on data providing a correlation between immunoglobulin or complement components levels and malignancies and specific disease parameters, we examined the possible correlation between the immunoglobulins, complement component levels and the stage of disease and the survival of patients. Sera from 55 patients with lung cancer and 22 healthy donor were assayed in order to evaluate the concentration of IgG, IgA, IgM, IgE, C_3, C_4. No considerable differences were found between the levels of immunoglobulins in patients with carcinoma of the lung versus subjects in the control group. Complement components (C_3 and C_4) levels were elevated in cancer patients with different cell types compared with levels in the control group. No statistically significant differences were found between the levels of the studied parameters and the stage of the disease and the survival time of patients. Our study confirm the hypothesis that malignant tumours contribute to elevation of complement components levels but additional studies are needed for demonstrating the prognostic value of immunoglobulin and complement components levels in lung cancer patients.

Key Words: *Lung cancer, immunoglobulins, complement levels.*

ÖZET

Akciğer Kanserli Olgularda İmmünglobulin ve Kompleman Düzeyleri

Kanserli hastalarda immünglobulin ve kompleman düzeylerinde değişmeler olabileceğini savunan çalışmalardan yola çıkılarak; bu çalışma akciğer kanserli olgularda serum immünglobulin ve kompleman düzeylerindeki değişiklikleri ve bu değişikliklerin prognoz üzerine etkisini ortaya koymaya yönelik olarak planlanmıştır. Ellibeş akciğer kanserli olgunun ve 22 sağlıklı kontrol olgusunun serumlarında IgG, IgA, IgM, IgE, C_3, C_4 düzeyleri incelenmiştir. Kanser grupları ile kontrol grubu arasında immünglobulin düzeyleri açısından önemli bir farklılık tespit edilmemiştir. C_3, C_4 düzeyleri incelendiğinde ise, kanser grubunda kontrol grubuna göre yükseklik tespit edilmiştir. Bu çalışmada hastalık evresi ve prognoz ile kompleman ve immünglobulin düzeyleri arasında bir anlamlı korelasyon bulunamamıştır. Çalışmamız malign tümörlerde kompleman düzeylerinde artış olabileceği görüşünü desteklemekle birlikte, akciğer kanserli olgularda immünglobulin ve kompleman düzeylerinin prognoz ile ilişkisini otaya koymaya yönelik daha çok çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: *Akciğer kanseri, immünglobulin, kompleman düzeyleri.*

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Pulmonary carcinoma is the most frequently diagnosed "major" cancer in the world and the most common cause of cancer-related death in both men and women. In 1997, there were an estimated 170.000 deaths from pulmonary carcinoma in the United States, accounting for more than one third of all cancer deaths in men and close to one quarter in women. Because many of these individuals are between 50 and 70 years of age at the time of death, the neoplasm is responsible for the most years of life lost of any cancer (1).

Despite the constant development of diagnostic and therapeutic methods, there is no specific test for patients with lung cancer that can help in estimating prognosis of patients and monitoring follow-ups.

It is a well known fact that immunoglobulin and complement components levels in serum reflect acute or chronic phases of infectious disease; moreover, a considerable number of attempts have been made to establish a correlation between immunoglobulin or complement components levels and malignancies and specific disease parameters. Most of the studies showed that changes in the levels of immunoglobulins and complement might be found without specificity for malignancy (2-6).

Despite the demonstration of change of immunoglobulin and complement component levels in cancer patients, their clinical significance for prognosis has not been exactly verified. And also as far as we know there is only one article in the literature studied the levels of immunoglobulin and complement components in lung cancer (2).

The aim of the present study was to investigate serum levels of IgG, IgM, IgA, IgE, C_3, C_4 in a group of previously untreated patients with lung cancer, and to compare these values with those of patients age and sex-matched healthy donors and to gain information on the prognostic value of serum levels of immunoglobulins and C_3 and C_4 levels.

MATERIALS and METHODS

A group of 55 patients with newly diagnosed, untreated, histologically proven lung cancer and 22 healthy age and sex-matched donors were included in the study. The cancer group was classified according to histological type [small, squamous, adeno, nonsmall (undetermined)], and according to be metastatic or nonmetastatic.

The determination of IgA, IgG, IgM, C_3, C_4 was carried out by means of an auto-chemistry analyser (Auto-ICS, Beckman Co). The normal range proposed for IgG is 7.0-16.0 g/L, for IgA 0.7-4.0 g/L, for IgM 0.4-2.3 g/L, for C_3 0.9-2.0 g/L, and for C_4 0.1-0.4 g/L. For IgE level measurement an enzyme immunoassay method was used. Considering IgE's wide range of variation, serum concentrations of about 1.0 KU/mL to 100 KU/mL can be regarded as normal limits.

Differences among five groups for IgA, IgG, IgM, IgE, C_3, C_4 were evaluated by Kruskal-Wallis variance analysis. When the p-value from the Kruskal-Wallis test statistics is statistically significant, multiple comparison test was used to know which groups differ from which other (7). For the survival estimates we used the method of Kaplan Meier and Log rank test was used to compare survival in the examined group.

RESULTS

There were no differences between the control and the study groups in age, sex, smoking habits. The distribution of cancer patients according to the histological type of lung cancer and the stage of disease are presented in Table 1.

In IgM and IgE, the mean values of all groups were in the normal range (Table 2). There were no significant differences between any of groups statistically.

In IgA, too, the mean values of all groups were in the normal range (Table 2). The serum IgA concentrations showed statistically significant decreases in patients with nonsmall cell carcinoma compared with the squamous cell carcinoma, small cell carcinoma, adenocarcinoma and the control group. But no differences were found between the metastatic and non-metastatic groups.

Considering IgG; the mean values of all groups were in the normal range (Table 2). The serum IgG concentrations showed statistically signifi-

Table 1. The distribution of cancer patients according to the histological type of lung cancer and the stage of disease.

	Stage of the disease				
Histologic type	II	IIIA	IIIB	IV	Total
Squamous cell carcinoma	6	5	7	6	24
Adenocarcinoma		1	3	6	10
Nonsmall cell carcinoma		2	3	6	11
	Limited-disease		Extensive disease		
Small cell carcinoma	6		4		10

Table 2. Serum immunoglobulins (IgM, IgE, IgA, IgG) levels (mean ± SD and median) in patients with lung cancer and control group.

		IgM (g/L)		IgE (KU/L)		IgA (g/L)		IgG (g/L)	
	n	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Control	22	1.03 ± 0.59	0.88	55.20 ± 49.70	44.42	2.79 ± 1.43	2.79	12.90 ± 1.93	12.70
Lung cancer	55	1.02 ± 0.60	0.90	239.39 ± 500.60	68.00	2.94 ± 1.32	2.70	17.00 ± 18.48	13.90
Cancer type									
SCC	10	1.10 ± 0.87	0.85	414.69 ± 922.91	70.50	2.75 ± 0.92	2.50	12.75 ± 3.39	13.50
Adeno	10	1.14 ± 0.66	0.95	448.20 ± 1033.07	110.00	3.12 ± 1.65	2.77	13.88 ± 4.16	13.35
Squamous	24	1.07 ± 0.55	0.98	167.27 ± 198.96	74.50	3.43 ± 1.34	3.60	21.90 ± 27.10	15.30
NSCC	11	0.73 ± 0.23	0.70	47.54 ± 49.67	18.00	1.87 ± 0.50	1.70	12.86 ± 4.93	11.20
Stage									
Nonmetastatic	33	0.98 ± 0.52	0.90	237.83 ± 530.84	74.00	3.14 ± 1.40	2.79	19.30 ± 23.42	13.90
Metastatic	22	1.09 ± 0.70	0.90	241.72 ± 705.82	62.50	2.63 ± 1.17	2.50	13.52 ± 4.66	13.25

SCC: Small cell carcinoma, NSCC: Nonsmall cell carcinoma.

cant increases in patients with squamous cell carcinoma compared with the small cell carcinoma, nonsmall cell carcinoma and the control group.

Analysis of the serum C_3 concentration showed statistically significant increases in patients with different tumour cell types, although the mean values were all in normal range (Table 3).

When we studied the C_4 concentration in serum, we saw that, although a statistically significant correlation was not presented, C_4 levels seemed to have a tendency to be higher in cancer patients compared with the healthy control (Table 3).

In this study we couldn't find a correlation between the levels of studied parameters and the stage of disease and survival time of patients.

DISCUSSION

Levels of serum protein, especially of acute-phase proteins and immunoglobulins and also complement components, have been studied in patients with carcinoma of different histology and localisation. Previous studies show that, the presence of a malignant tumour may alter the levels of immunoglobulins and complement levels without a specificity for the type of cancer. But there are contradictory results establishing the correlation between either immunoglobulin or complement component levels, and clinical stage, activity of malignant disease or prognosis in cancer patients (2-6).

In present study, we showed that C_3 levels were significantly elevated in the cancer patients compared with the control group. Although a

Table 3. Serum complement components (C_3 and C_4) levels (mean ± SD and median) in patients with lung cancer and control group.

		C_3 (g/L)		C_4 (g/L)	
	n	Mean	Median	Mean	Median
Control	22	1.03 ± 0.59	0.88	5.20 ± 49.70	44.42
Lung cancer	55	1.02 ± 0.60	0.90	239.39 ± 500.60	68.00
Cancer type					
SCC	10	1.10 ± 0.87	0.85	414.69 ± 922.91	70.50
Adeno	10	1.14 ± 0.66	0.95	448.20 ± 1033.07	110.00
Squamous	24	1.07 ± 0.55	0.98	167.27 ± 198.96	74.50
NSCC	11	0.73 ± 0.23	0.70	47.54 ± 49.67	18.00
Stage					
Nonmetastatic	33	0.98 ± 0.52	0.90	237.83 ± 530.84	74.00
Metastatic	22	1.09 ± 0.70	0.90	241.72 ± 705.82	62.50

SCC: Small cell carcinoma, NSCC: Nonsmall cell carcinoma.

statistically significant correlation was not presented, C_4 levels seemed to have a tendency to be higher in cancer patients compared with the healthy control. When we studied the each cancer type separately, we saw that in all types of cancer C_3 and C_4 levels were higher than the control group. So we can say that our study confirm the hypothesis that malignant tumours contribute to elevation of complement components and the complement activity as mentioned in previous studies (2,4,8).

What contributes to such an increase is not clear. However, as a major defence mechanism against cancer, the effector mechanisms of both cell mediated immunity and humoral immunity including antibody and complement system have shown to kill tumour cells in vitro. But the question "which of these mechanisms may contribute to protective immune responses against tumour" remains to be answered.

Matsuomi et al, in glioma patients, showed that the complement titres rise in accordance with the degree of progress of the tumour and a negative tendency in the tuberculin reaction runs parallel to this. So they suggest the concept that complement activity rises to compensate for depressed cell mediated immunity in order to preserve the activity of biophylaxis mechanism against cancer (8).

However, in this study, there were no statistically significant differences of levels of the two parameters mentioned between the patients in nonmetastatic group with metastatic group.

Immunoglobulins, the other component of the humoral immunity were also evaluated in this study. As we all know immunoglobulins IgG and IgM play a dominant role in humoral immunity in peripheral blood, where as IgE and IgA do so in local immune reactions. In previous studies the alteration in serum immunoglobulin levels are mainly observed in the locally effective immunoglobulins IgA and IgE levels.

In recent studies an elevation in serum IgA level has been shown in nasopharyngeal cancer suggesting that local immune response to cancer is reflected by increased levels of IgA. Vinzenz and et al showed, in a group of patient with head and neck cancer, that in cancer patients pretherapeutically serum immunoglobulin levels were elevated compared with the control group and also the group of patients with relapses in follow up were found to have pretherapeutically higher levels of both IgE and IgA compared with those without evidence of disease for more than six months. Based up on these study they suggest that serum IgA and IgE levels in patients with head and neck cancer may be used as parameters for monitoring malignant disease and may be a prognostic factor (6).

As we mentioned before there is only one clinical trial about immunoglobulin levels and lung cancer. In this article Gminski and et al show that serum IgA levels were elevated in patients with different tumour cell types, as well as in all stages of disease and stage IIIB patients had significantly elevated levels of IgG as compared with the control group. They suggested that as histologic studies of lung tumours had demonstrated the presence of IgA, IgM, IgG secreting plasma cells and the increase in serum IgA and IgG levels were an effect of the local antibody producing mechanism in the lung (2).

In this study we didn't find a correlation between the levels of immunoglobulins (IgA, IgE, IgM, IgG) and stage of disease and survival time of patients. The only statistically significant correlation was found in IgG levels. The patients with squamous cell lung cancer had significantly elevated levels of IgG as compared with small cell, nonsmall cell (not identified) and control group. Like Gminski we believe that the presence of IgG positive plasma cells at the site of the tumour may contribute to an increase in serum IgG levels but we can not exclude the fact that cancer patients have predisposition for infection. So the rise in IgG may be the result of both situation.

In conclusion, we believe that our study, given the limited number of patients in each group, cannot be a precious data about the relation between immunoglobulin or complement components levels, and clinical stage or prognosis in lung cancer patients. However, we believe that, additional studies involving a larger patient population can be helpful for demonstrating the prognostic value of immunoglobulin and complement levels in lung cancer patients.

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