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RESEARCH ARTICLE

State of lipid peroxidation and endogenous intoxication under non-small-cell lung cancer

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ABSTRACT

Background: The problems of optimizing the methods of diagnosis and predicting the course of lung cancer occupying a leading position in the structure of cancer are still relevant. **Aims and Objectives:** To establish the patterns of changes in the parameters of endogenous intoxication and lipid peroxidation processes in the saliva of patients with non-small-cell lung cancer (NSCLC) depending on the histological type of a tumor. **Materials and Methods:** A total of 505 people took part in the case–control study: The main group (NSCLC, n = 290) and the control one (healthy, n = 215). All participants were questioned and underwent the biochemical examination of saliva and histological verification of the diagnosis. The parameters of endogenous intoxication and lipid peroxidation were determined spectrophotometrically. **Results:** The results of the study support the hypothesis of association of endogenous intoxication and lipid peroxidation processes with the development of NSCLC. It was shown that against the background of NSCLC; the level of primary lipid peroxidation products decreases. Thereat, the content of triene conjugates and Schiff bases, as well as the MM 280/254 nm distribution coefficient, increases. The growth of these indicators with an increase in the size of the tumor was noted. The differences due to the histological type of NSCLC have been identified. **Conclusion:** Thus, with squamous cell NSCLC, a higher level of secondary lipid peroxidation products was noted. The presence of distant metastases in lungs significantly contributes to changes in indicators of endogenous intoxication and lipid peroxidation in case of adenocarcinoma.

KEY WORDS: Saliva; Medium Molecular Weight Toxins; Lipid Peroxidation; Lung Cancer; Oncology

INTRODUCTION

Nowadays, lung cancer holds a leading position in the structure of oncological diseases.[1,2] In connection with this, the problems of optimizing the methods of its diagnostics remain topical.[3] Lung cancer unites a group of tumors that differ in course, morphological structure, and prognosis.[4] In this regard, it is important to consider both the histological type of a tumor and the nature of its interaction with surrounding structures and in particular with the lympho-dynamic features of various regional zones.[5,6]

In recent years, the pathogenetic role of oxygen-free radicals and the initiated by them processes of lipid peroxidation in the development of diseases, including oncological, have been widely discussed.[7,8] In particular, in lungs, oxidative stress induces protein modification, macrophage activation and neutrophil recruitment in central and peripheral airways, accumulation of lipid peroxidation toxic products, hydrogen peroxide, nitrosothiols and nitrates in membranes of the lungs, blood and in inspired air.[9-11] Moreover,

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oxidative stress can provoke hyperplasia of mucous membranes of glands and apoptosis of bronchial epithelial cells.[12] The complex metabolic disorders and nonspecific clinical manifestations that accompany the development of malignant neoplasm are characterized as a syndrome of endogenous intoxication.[13] The endogenous toxins are the substances of low and medium molecular weight (1500-5000 D) and mainly are the fragments of endogenous proteins. Traditionally, there are 2 MM fractions with the wavelengths of 254 and 280 nm. The fraction of MM 254 nm is an integral indicator of the ultraviolet (UV)-absorbing substances content, which, in addition to the products of proteolysis, includes nonprotein substances of normal and abnormal metabolism. The intensity of the UV-absorption of saliva at 280 nm is determined mainly by the presence of aromatic chromophores and it increases mainly due to the accumulation of tyrosine and tryptophan-containing peptides. The reason for this can be the loss of proteins by aromatic amino acids as a result of oxidative modification and fragmentation of molecules. The more informative is the estimation of the MM 280/254 nm coefficient. The growth of this indicator may indicate the increase in catabolic processes, stimulation of lipid peroxidation, and immunogenesis.[14,15] The lipid peroxidation products are divided into primary (diene conjugates), secondary (triene conjugates and Schiff bases), and final (malondialdehyde [MDA]).

The indicators of endogenous intoxication, as well as the products of lipid peroxidation, are traditionally determined in blood plasma; however, there is a possibility of using saliva as a substrate.[16,17] It should be noted that the study of saliva has advantages over the use of venous or capillary blood, which is due to noninvasive collection and the absence of a risk of infection when producing the biomaterial.[18] Thereat, the saliva adequately reflects the biochemical status and physiological state of a person, which allows using it in clinical laboratory diagnostics.[19,20]

There is a number of scientific works[21-23] dedicated to the study of indicators of endogenous intoxication and lipid peroxidation in saliva; however, the overwhelming majority of studies are limited to an evaluation of the MDA content.[22,24,25] The changes in the lipid peroxidation processes in the saliva of patients with oral cavity precancer and cancer are described by the example of MDA.[26,27] Yet, despite the numerous literature data that show an increase in the level of MDA in saliva in case of malignant tumors,[28,29] we have noted that the character of MDA concentration change in case of lung cancer is nonlinearly connected with the tumor progression.[30] In this connection, for the complex assessment of the level of endogenous intoxication and lipid peroxidation processes, the determination of MDA is not that much informative.[30,31]

The object of this study is to establish the patterns of changes in the parameters of endogenous intoxication and lipid peroxidation processes in the saliva of patients with lung cancer depending on the histological type of a tumor.

MATERIALS AND METHODS

Study Design

For the case–control study, we have selected the volunteers and divided them into two groups: The main group (with the diagnosis of lung cancer) and the control group (conditionally healthy). Inclusion into both groups was made in parallel. The inclusion criteria included: Age of patients (30-75 years old), the absence of any treatment at the time of the study, including surgical, chemotherapeutic or radiation, the absence of signs of active infection (including purulent processes), and conduction of oral cavity sanitation. The exclusion criterion was the absence of histological verification of the diagnosis.

Patient Recruitment and Sampling

The patients of the main group were examined at the Clinical Oncology Dispensary (Omsk, the Russian Federation). The patients for the control group were recruited under the routine check-ups from the city ambulatory-care clinic No. 4 database (Omsk, the Russian Federation). The biochemical studies were carried out in the laboratory of KhimServis LLC (Omsk, the Russian Federation).

All participants had a saliva intake of 2 ml before treatment. Samples of saliva were collected in the morning on an empty stomach by spitting into sterile tubes and centrifuged at 7000 rpm. The patients of the control group underwent photofluorographic examination. The patients of the main group were hospitalized for radical surgery in the volume of lobectomy, bilobectomy, pneumonectomy, combined treatment, or video-assisted thoracoscopic surgery for tumor biopsy. In each case, a histological verification of the diagnosis was made.

The main group included patients with a histologically confirmed diagnosis of lung cancer. The main group was additionally divided into subgroups according to the following characteristics: Histological type of a tumor (adenocarcinoma [AC] and squamous cell carcinoma [SCC] of the lung), tumor, node and metastasis staging and presence/absence of distant and regional metastasis. The control group included conditionally healthy patients who had no pulmonary pathology during routine clinical examination. The evaluation of the biochemical parameters of saliva of the patients from the control group was performed without additional subdivision into subgroups.

Test Methods

All participants had a saliva intake of 2 ml before treatment. Samples of saliva were collected in the morning on an empty

stomach by spitting into sterile tubes, centrifuged at 7000 rpm. By spectrophotometric methods, we determined the content of substrates for lipid peroxidation processes – diene conjugates, triene conjugates, and Schiff bases by Volchegorskiy et al. method,[32] and albumin - by reaction with green bromocresol.[33] The content of the final lipid peroxidation product (MDA in μmol/l) was determined in the reaction with thiobarbituric acid by Gavrilov et al. method.[34] The MM level was determined by UV spectophotometery at wavelengths of 254 and 280 nm.[35] The results were expressed in units that are quantitatively equal to the extinction indicators. In additional, the value of the distribution coefficient (MM 280/254 nm) was estimated as the ratio of extinctions at wavelengths of 280 and 254 nm, respectively.

Ethical Review

The study was carried out in accordance with the Helsinki Declaration (adopted in June 1964 in Helsinki, Finland and revised in October 2000 in Edinburgh, Scotland) and approved at a meeting of the Ethics Committee of the Omsk Regional Clinical Hospital "Clinical Oncology Center" on July 21, 2016 (Protocol No. 15).

Statistical Analysis

The statistical analysis was performed using Statistica 10.0 (StatSoft, the USA) and R (version 3.2.3) software by a nonparametric method with implementation of the Wilcoxon test in dependent groups, and with implementation of Mann-Whitney U-test in independent groups. The sample was described by calculating the median (Me) and interquartile range in the form of the 25th and 75th percentile (lower quartile; upper quartile). The differences were considered to be statistically significant at $P < 0.05$. The statistical interrelations were studied using the nonparametric correlation analysis by performing the calculation of Spearman's correlation coefficients (R).

RESULTS

The study included 290 patients from the Omsk Clinical Oncology Dispensary and 215 practically healthy people selected as a control group. The average age of the patients was 58.9 ± 1.1 years old for the main group and 57.4 ± 1.5 years old for the control group. The main group included 290 patients with lung cancer of different histological types. A detailed description of the group is presented in Table 1.

Table 1: Description of the study group

Characteristics	Adenocarcinomas, *n* (%), *n*=174	Squamous cell carcinomas, *n* (%), *n*=116
Age (years)	61.00 [56.00; 65.00]	59.00 [55.00; 66.50]
Sex		
Male	120 (52)	110 (48)
Female	54 (90)	6 (10)
pT		
T_1	17 (81)	4 (19)
T_2	80 (70)	34 (30)
T_3	15 (29)	36 (71)
T_4	12 (39)	19 (61)
pN		
N_0	76 (63)	44 (37)
N_1	30 (52)	28 (48)
N_2	49 (55)	40 (45)
N_3	19 (83)	4 (17)
pM		
M_0	123 (57)	93 (43)
M_1	51 (69)	23 (31)

It was determined that against the background of non-small-cell lung cancer (NSCLC); there is a decrease in the MM level (Table 2); thereat, the revealed regularity is typical for both aromatic and nonaromatic chromophores. At the same time, we observed a statistically significant increase in MM 280/254 nm distribution coefficient and decrease of the content of primary lipid peroxidation products, while the level of triene conjugates and Schiff bases, vice a versa, increased. In addition, we have noted an increase in albumin concentration in NSCLC (+13.1% for AC, +5.7% for SCC) (Table 2).

With the presence of metastatic lesions, a decrease in the level of diene conjugates for SCC (−20.5%, $P = 0.0341$) is observed; thereat, the albumin concentration stays practically unchanged (+1.3%). For AC, we observe the reverse tendency: At a constant level of diene conjugates (−1.0%), the decrease in albumin concentration was 17.1% (Table 3). However, the level of secondary lipid peroxidation products increases for both histological types, while the increase in the level of triene conjugates is more pronounced for SCC only, whereas the level of Schiff bases is more typical and pronounced for AC. The MDA content decreases in both cases (−4.7 and 13.5% for AC and SCC, respectively). The similar thing is observed for products of endogenous intoxication under metastasis: Both the content of individual fractions of medium molecular toxins (MM 254 and 280 nm) and the distribution coefficient decrease.

With an increase in the tumor size (T), the character of the changes in the studied parameters is ambiguous (Table 4). It was found out that under the transition from $T_1N_{0-3}M_0$ to $T_4N_{0-3}M_0$; a decrease in the level of diene conjugates is observed with a simultaneous increase in the level of triene conjugates and Schiff bases. The decrease in the level of diene conjugates is mostly pronounced in the AC case (−27.2%), while the increase in the content of Schiff bases is typical and mostly pronounced for SCC (+27.7%). In both cases, with the

Table 2: The indicators of lipid peroxidation and endogenous intoxication depending on the histological type of lung cancer

Indicator	Control, *n*=215	AC, *n*=174	SCC, *n*=116
Albumin, mmol/l	0.298 [0.199; 0.484]	0.337 [0.183; 0.535]	0.315 [0.178; 0.495]
Diene conjugates	3.90 [3.79; 4.07]	3.87 [2.99; 4.10]	3.81 [2.82; 4.05]
	-	P_1=0.0036	P_1=0.0001
Triene conjugates	0.894 [0.828; 0.973]	0.946[0.836; 1.188]	0.985 [0.827; 1.231]
	-	P_1=0.0003	P_1<0.0001
Shiff bases	0.543 [0.508; 0.575]	0.556 [0.503; 0.671]	0.579 [0.513; 0.681]
	-	P_1=0.0420	P_1=0.0005
MDA, nmol/ml	6.75 [5.90; 8.38]	7.18 [5.81; 9.32]	7.52 [5.64; 9.49]
MM 254 nm	0.287 [0.200; 0.407]	0.267 [0.185; 0.400]	0.244 [0.155; 0.379]
	-	-	P_1=0.0052
MM 280 nm	0.248 [0.176; 0.356]	0.242 [0.168; 0.365]	0.216 [0.149; 0.333]
	-	-	P_1=0.0460
MM 280/254 nm	0.852 [0.773; 0.957]	0.913 [0.817; 1.002]	0.907 [0.804; 1.058]
	-	P_1=0.0012	P_1=0.0009

P - Statistically significant differences are compared with the control group values, AC: Adenocarcinoma, SCC: Squamous cell carcinoma, MDA: Malondialdehyde

Table 3: The indicators of lipid peroxidation and endogenous intoxication depending on the presence/absence of distant metastasis

Indicator	HT	$T_{1-4}N_{0-3}M_0$	$T_{1-4}N_{0-3}M_1$	*P*-value
Albumin, mmol/l	AC	0.356 [0.184; 0.553]	0.295 [0.178; 0.455]	-
	SCC	0.313 [0.166; 0.500]	0.317 [0.178; 0.490]	-
Diene conjugates	AC	3.87 [3.16; 4.10]	3.83 [2.66; 4.13]	-
	SCC	3.84 [2.93; 4.09]	3.05 [2.41; 3.90]	0.0341
Triene conjugates	AC	0.940 [0.83; 1.15]	0.991 [0.85; 1.24]	-
	SCC	0.962 [0.831; 1.179]	1.121 [0.808; 1.290]	-
Shiff bases	AC	0.551 [0.50; 0.66]	0.562 [0.51; 0.71]	-
	SCC	0.579 [0.514; 0.681]	0.580 [0.499; 0.677]	-
MDA, nmol/ml	AC	7.18 [5.90; 9.57]	6.84 [5.81; 8.72]	-
	SCC	7.61 [5.56; 9.49]	6.58 [5.81; 9.57]	-
MM 254 nm	AC	0.274 [0.198; 0.424]	0.241 [0.136; 0.364]	0.0467
	SCC	0.254 [0.155; 0.373]	0.189 [0.141; 0.387]	-
MM 280 nm	AC	0.260 [0.192; 0.370]	0.226 [0.111; 0.319]	0.0401
	SCC	0.225 [0.154; 0.331]	0.167 [0.127; 0.362]	-
MM 280/254 nm	AC	0.926 [0.821; 1.002]	0.896 [0.801; 1.004]	-
	SCC	0.908 [0.804; 1.046]	0.906 [0.792; 1.108]	-

HT: Histological type, AC: Adenocarcinoma, SCC: Squamous cell carcinoma, MDA: Malondialdehyde

progression of the tumor the increase in MDA concentration is observed, and the maximum corresponds to $T_4N_{0-3}M_0$ stage. The level of endotoxins (MM 254 and 280 nm) remains practically constant in AC case, but for SCC the increase of both indicators (+55.4 and +84.4% for 254 and 280 nm fractions, respectively) are observed. Despite the revealed differences in the dynamics of endotoxicosis indicators, the values of MM 280/254 nm distribution coefficient uniformly increase during the transition from $T_1N_{0-3}M_0$ to $T_4N_{0-3}M_0$, except $T_1N_{0-3}M_0$ stage for AC. The maximum value of the distribution coefficient for the first stage of AC corresponds the high concentration of albumin, which then sharply decreases (−25.5%) and reaches the initial values only at $T_4N_{0-3}M_0$. For SCC, an insignificant decrease in albumin concentration is observed in the studied direction.

DISCUSSION

The patterns of changes in autotoxemia parameters and lipid peroxidation processes in the saliva of lung cancer patients

Table 4: The indicators of lipid peroxidation and endogenous intoxication depending on the size of the tumor

Indicator	HT	$T_1N_{0-3}M_0$	$T_2N_{0-3}M_0$	$T_3N_{0-3}M_0$	$T_4N_{0-3}M_0$
Albumin, mmol/l	AC	0.411 [0.228; 0.519]	0.306 [0.179; 0.546]	0.382 [0.163; 0.553]	0.465 [0.282; 0.903]
	SCC	0.342 [0.219; 0.390]	0.387 [0.232; 0.500]	0.302 [0.148; 0.409]	0.313 [0.157; 0.624]
Diene conjugates	AC	3.82 [3.62; 4.05]	3.92 [3.35; 4.13]	3.93 [3.39; 4.00]	2.78 [2.00; 3.70]
	SCC	3.95 [3.69; 4.21]	3.87 [2.91; 4.07]	3.83 [2.89; 4.05]	3.86 [2.14; 4.14]
Triene conjugates	AC	0.881 [0.83; 0.98]	0.940 [0.82; 1.17]	0.984 [0.88; 1.10]	1.052 [0.85; 1.27]
	SCC	0.836 [0.763; 0.893]	0.941 [0.827; 1.163]	1.018 [0.840; 1.317]	1.029 [0.843; 1.336]
Shiff bases	AC	0.513 [0.49; 0.57]	0.561 [0.50; 0.67]	0.564 [0.49; 0.67]	0.601 [0.52; 0.65]
	SCC	0.495 [0.483; 0.522]	0.566 [0.513; 0.657]	0.565 [0.514; 0.654]	0.632 [0.548; 0.781]
MDA, nmol/ml	AC	6.97 [5.77; 9.44]	7.26 [5.98; 9.32]	7.18 [5.38; 9.40]	9.57 [5.90; 10.38]
	SCC	6.07 [4.87; 9.44]	7.44 [5.56; 8.85]	7.78 [5.47; 9.49]	7.95 [6.41; 12.14]
MM 254 nm	AC	0.315 [0.205; 0.417]	0.273 [0.188; 0.435]	0.273 [0.208; 0.396]	0.301 [0.200; 0.535]
	SCC	0.202 [0.143; 0.240]	0.211 [0.154; 0.385]	0.258 [0.174; 0.352]	0.314 [0.169; 0.519]
MM 280 nm	AC	0.265 [0.217; 0.351]	0.256 [0.190; 0.409]	0.254 [0.186; 0.327]	0.274 [0.192; 0.417]
	SCC	0.167 [0.125; 0.192]	0.211 [0.147; 0.289]	0.238 [0.165; 0.319]	0.308 [0.195; 0.471]
MM 280/254 nm	AC	0.957 [0.884; 0.997]	0.907 [0.816; 1.018]	0.924 [0.821; 0.961]	0.940 [0.872; 1.012]
	SCC	0.833 [0.800; 0.877]	0.860 [0.746; 1.024]	0.942 [0.817; 1.042]	0.981 [0.903; 1.157]

HT: Histological type, AC: Adenocarcinoma, SCC: Squamous cell carcinoma, MDA: Malondialdehyde

have been established. It is shown that the accumulation of medium molecular toxins and the degree of damage to cell membranes vary depending on the histological type of tumor; the presence and/or absence of distant metastasis. Features of the disease progression parameters change are noted for NSCLC (squamous cell lung cancer and AC).

MDA is a final product and a marker of lipid peroxidation, but the nature of its change is nonlinearly associated with the tumor progression.[31] It should be noted that the MDA content increases in case of lung cancer, but we found no statistically significant increase in this indicator even despite the numerous confirmations of this fact in the literature.[22-30]

During the performed studies, we have elicited the fact of an increase in the level of MM, which is an indirect evidence of excessive generation of active oxygen metabolites: Superoxide radicals and hydrogen peroxide.[36] Hydroxyl radicals are capable to damage the phosphoglyceride membrane structures of cell membranes and its organelles. The object of active oxygen metabolites effect is the arachidonic acid that contains four double bonds separated by CH_2-groups. When exposed to hydroxyl radicals, these double bonds become conjugated and form diene conjugates which a later transformation into lipid hydroperoxides.

It was shown that the level of diene conjugates decreases in case of lung cancer in comparison with the control group. The insufficient level of primary lipid peroxidation products can result from the stability of tumor tissue to initiators of peroxide stress and modification of functioning of enzymatic systems that regulate the lipid peroxidation.[37,38] The level of secondary products against the background of lung cancer increases; the growth of these indicators in the dynamics of the disease was noted. The calculation of the Spearman's correlation coefficient has shown that there is a negative correlation between the level of diene and triene conjugates ($R = -0.3665$; $R = -0.5532$, $P = 0.001$) and a positive correlation between the content of triene conjugates and Schiff bases ($R = 0.7283$; $R = 0.7555$ for AC and SCC, respectively, $P = 0.001$). The increase of Schiff bases level is an adaptive process aimed at removing more toxic metabolites (diene conjugates and MDA) from the cells. Basing on the assumption that the primary products of MM formation are the acyl hydroperoxides and fragments of damaged cell membranes, we can observe a shift in equilibrium toward the accumulation of lipid peroxidation products, while the processes of endogenous proteolysis against the lung cancer slow down.

It was proved that the histological type largely determines the tumor growth rate and the transition to the stage of metastasis.[39] In this regard, both the features of tumor cells metabolism and the reactivity of the immune system, and in particular, the disorders in the cellular and humoral immunity system,[37] are taken into account. It was found out and established that a similar decrease in the concentration of T-lymphocytes and T-helpers with an increase in the B-lymphocyte content[40] is observed among patients with SCC and AC. However, the content of natural killer cells in peripheral blood increases only among patients with SCC, which allows us to speak about the less pronounced intensity of immune processes in the lymph nodes.

The obtained information allows us to draw a parallel between the more pronounced processes of endogenous intoxication

and the formation of final lipid peroxidation products MDA in case of AC with activation of aerobic reactions, and the higher growth rate and metastatic potential. At the same time, more active formation of secondary lipid peroxidation products and a smaller increase in endogenous toxins against the background of SCC may indicate the higher tumor aggressiveness but lower growth rate and lower metastatic potential.

It is known that the active oxygen forms and products of their reactions with other biomolecules, and in particular lipid peroxides, affect the conformation of albumin, and consequently, its binding properties.[41,42] An increase in albumin concentration may be due to changes in the volume of transport of various metabolites and, primarily, fatty acids which are an important link in the restructuring of energy metabolism with the growth of a malignant tumor.[13,43]

In general, against the background of SCC, we have noted a higher level of triene conjugates and Schiff bases, and higher values of MM 280/254 nm distribution coefficient. When analyzing the indicators of proliferative activity among patients with different morphological types of the tumor, it was found out that the percentage of dividing cells among patients with AC is much lower than among patients with SCC.[44,45] This may indicate a high aggressiveness of the tumor. This fact is confirmed by the higher level of secondary lipid peroxidation products in case of SCC.

The limitations of performed study are related to the coverage of only two histological types of a lung cancer, whereas it is promising to carry out similar studies for other types as well (small cell and large cell lung cancer, carcinoid, etc.) including mixed groups, and in particular, the combinations of SCC and AC. It should be noted that the grounding for applying the obtained results to monitor and supervise the course of the disease requires the study of the dynamics of the examined parameters against a background of various types of treatment, including chemotherapeutic and radiotherapy.

CONCLUSIONS

Thus, against the background of lung cancer, we observe the development of oxidative stress, which are manifested in the increase in the level of lipid peroxidation and endogenous intoxication products. The nature of changes in the study parameters is ambiguous and depends on both the histological type of the tumor and the stage of the disease. In this regard, it is required to perform a comprehensive assessment of parameters of endotoxicosis and lipid peroxidation, including individual fractions of medium molecular toxins, the MM 280/254 nm distribution coefficient and the levels of diene/triene conjugates and Schiff bases. A promising direction may be the study of the antioxidant protection component in addition to the parameters listed above. The obtained results can be used to optimize traditional diagnostic methods, to predict the course of the disease, to monitor the treatment process, etc.

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