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EDN POWVSYОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
ORIGINAL RESEARCH

Elemental homeostasis in children and adolescents after completion of antitumor therapy for malignant neoplasms

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Abstract. Relevance. As medical research develops, more and more attention is being paid to the study of elemental changes in cancer patients not only as a marker of the disease, but also as a possible complication of the disease. The aim was to study changes in the level of essential and toxic trace elements in patients who have undergone antitumor therapy (AT) for malignant neoplasms (MN). **Materials and Methods.** As part of a retrospective monocenter study, a group of 214 patients from the Russian Field Medical and Rehabilitation Research Center aged 4 to 17 years was formed. All patients were in remission after the completion of antitumor treatment: 107 patients with hemoblastosis and 107 with solid tumors. The age of the participants ranged from 4.2 to 17.6 years, with an average age of 11.4 years. For a comprehensive assessment of the elemental status in children, hair and blood serum were used, measurements were carried out by mass spectrometry after mineralization of the samples. **Results and Discussion.** The results of the study of hair samples and blood serum showed that the elemental profile of patients after AT has both similar patterns and distinctive features depending on the histological type of tumor. **Conclusions.** Patients with solid tumors had a higher accumulation of toxic metals compared to samples taken from patients with tumors of the hematopoiesis organs. Nevertheless, no serious specific changes in elemental homeostasis were observed depending on the histological structure. The results obtained emphasize the importance of careful monitoring of homeostasis parameters to prevent the development of complications of antitumor therapy associated with elemental homeostasis.

Keywords: trace elements, macronutrients, essential elements, toxic elements, the element status, elemental imbalance, carcinogenesis, solid tumors, tumors of the hematopoiesis system, hair, the serum, late effects, inductively coupled plasma mass spectrometry

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Ethics approval. The study was developed and conducted in accordance with the approval of the Ethics Committee of Dmitry Rogachev National Medical Research Center for Pediatric Hematology, Oncology and Immunology, (Moscow, Russia) and complied with the requirements of the Helsinki Declaration.

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Consent for publication. The informed voluntary consent was obtained to take part in the investigation and to publish the results from the parents and guardians of children and adolescents.

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Introduction

The modern theory of carcinogenesis is attracting more and more attention to the role of elemental changes in the induction of tumor growth [1]. In particular, associations of essential and toxic chemical elements with several types of malignant neoplasms have been identified [2]. In studies devoted to the role of elemental changes in experimental or clinical models, toxic elements are most associated with carcinogenic activity [3, 4]. In addition, the imbalance of the main elements contributes either to the metabolic restructuring of proteins, providing activation or inhibition of enzymatic reactions, affecting the permeability of cell membranes [5, 6], or to changes in the cellular microenvironment and immune status [7], which can also modulate the progression of cancer. Some organic and inorganic compounds of essential elements, such as selenium (Se) or zinc (Zn), can affect the redox status of cells [8, 9], provoking the formation of reactive oxygen species (ROS), interfering with proapoptotic signaling pathways [10], an appropriate amount of ROS

can promote carcinogenesis and support transformation and proliferation of tumor cells [11].

Unfortunately, antitumor therapy (AT) has limited selectivity, and its components can cause various early and late metabolic complications. The direct cytotoxic effect of chemotherapeutic drugs and radiation therapy, along with potential iron overload as a result of repeated transfusions, can lead to adverse effects on the nervous, cardiovascular, and urinary systems. On the other hand, nutritional deficiency and metabolic homeostasis disorders are accompanied by clinical changes in the form of osteoporosis, nutritional deficiency, etc. Specific disorders of the elemental composition of tissues (Figure) are also observed in patients after AT [12, 13].

In particular, after treatment, there may be an excessive accumulation of toxic elements that can be considered as possible carcinogens, which directly leads to disruption of mitochondrial function, cell growth processes, and DNA damage [14]. It has also been shown that changes in the concentration of certain essential elements can affect oxidative stress



Fig. The components of elemental homeostasis (elemental portrait) of a person

and suppress or enhance proliferative processes due to a violation of the redox balance [15]. Many elements show a correlation with oxidative stress in the blood of cancer patients [16, 17], therefore, excessive accumulation of individual elements affecting the redox status of tissues can be considered as a factor associated with oncogenesis. Based on this, the elemental imbalance after AT should be considered as a significant factor preventing or provoking cancer recurrence. The available data indicate a possible specificity of the elemental status in patients with tumors of various histological origin. For example, tumors of hematopoietic tissue differ from solid tumors not only in the variant of cell differentiation, but also in other related features: biochemical and tissue atypism, metastatic activity, signaling pathways, etc. [18], which can affect metabolism in different ways, contributing to the appearance of specific biomarkers of the disease [19]. Features of the microenvironment associated with the activation of matrix metalloproteinases [20], the distribution of metals in tissues due to their participation in ion transport [21], and their action as cofactors [22], changing the elemental composition of the malignant neoplasms MN bio substrate. In modern literature, the profile of microelements and macronutrients often appears as a possible application point for targeted diagnosis, treatment or prevention of MN [23], however, it is necessary to take into account the his-

tological affiliation of the tumor and the features of AT in this type of neoplasm. In this study, we sought to identify the specifics of the elemental changes after AT, depending on the histological structure of the tumor. Increased attention should be paid to the detection of carcinogenic elements: cadmium (Cd), nickel (Ni), arsenic (As), beryllium (Be), and chromium (Cr), which are already known and described in the literature [24]. The non-invasiveness and speed of the screening method using the analysis of chemical elements in blood serum and hair make it very promising in oncology.

Research objectives

To compare the elemental composition of biological substrates, such as hair and blood serum, depending on the histological types of tumors in children and adolescents who were in remission after completion of antitumor therapy (AT).

Materials and methods

Ethical standards

The study was developed and conducted in accordance with the requirements of the Helsinki Declaration and its later amendments. Before being included in the study, the informed consent of the parents of the examined children was obtained.

Research design

The one-cent cross-sectional retrospective study included patients of the Russian Field Clinical Research and Rehabilitation Center of the Dmitry Rogachev National Medical Research Center for Pediatric Hematology, Oncology and Immunology in 2019–2021 (Moscow, Russia), these were children and adolescents of both sexes aged 4 to 17 years.

The study group consisted of 214 children in remission of MN (malignant neoplasms), of which 107 were patients (group 1) who had completed treatment and were in remission according to the International Classification of Diseases version 10 (ICD) with disease codes C 91, C 92; C 81–84 and 107 patients (Group 2) who received AT according to regarding solid tumors with disease codes according to ICD C 22–C 76, with the exception of tumors of the central nervous system. The age of the children and adolescents included in the study ranged from 4.2 to 17.6 years. The average age was 11.4 years. The duration of MN remission ranged from 2.6 to 8.0 years, with an average of 3.9 ± 1.1 years. The treatment of hemoblastosis included BFM, MB, and DAL-HD protocols. Treatment of solid neoplasms was carried out in accordance with international protocols recommended in the clinical guidelines for the treatment of hypertension in children by the Russian Ministry of Health (SIOP, EURAMOS, etc.). The structure of the cytotoxic agents used excludes the use of the studied chemical elements in patients included in the study.

Criteria for inclusion in the study: (I) confirmed remission of malignant tumors in accordance with ICD 10: C 91; C 92, C 81–84, C 22–76; (II) patients under the age of 18; (III) signed informed consent by parents of children < 14 years old and adolescents ≥ 14 years old.

The exclusion criteria were: (I) the patient's somatic or psychological condition that prevents participation in the study, (II) eating habits (including a vegetarian diet), (III) metal implants (including dental fillings made of amalgam), (IV) surgical and traumatic diseases, (V) acute inflammatory and infectious diseases. The presence of any of these factors led to the exclusion of the patient from the study.

The control group was based at the Center for Bi-otic Medicine (Moscow, Russia). The study included

213 children aged 4 to 17 years without a history of cancer and other chronic somatic diseases. In addition, all participants in the control group reported that they had not consumed drugs containing macro- and microelements during the last year before the study. The appropriate exclusion criteria were applied to the participants of the control group.

Sample collection and preparation

Bio substrates were used for a comprehensive mass spectrometry assessment: hair and blood serum. Only the proximal sections of the strands, which are less susceptible to exogenous contamination, were used for the study. Sample preparation included washing and microwave treatment procedures to remove contaminants. Hair samples were degreased with acetone (Chimmed, Russia) for 10–15 minutes, washed three times with deionized water with a concentration of $18.2 \text{ M}\Omega \cdot \text{cm}$ (Labconco Corp., Kansas City, Missouri, USA) and dried at 60°C . Dry hair samples were kept in Teflon tubes with 5 ml of concentrated (65%) nitric acid (Sigma-Aldrich Co., St. Louis, Missouri, USA) for 20 minutes at a temperature of $170\text{--}180^\circ \text{C}$. Hair samples were also acid-treated using a microwave oven in the Berghof SpeedWave-4 DAP-40 system (Berghof Products + Instruments GmbH, 72800 Ehningen, Germany) at a frequency of 2.46 GHz with a power of 1450 watts. Distilled deionized water with a total volume of 15 ml was then added to the resulting solutions. The resulting solution was used for subsequent ICP-MS analysis.

Blood samples were taken from the ulnar vein using Vacutest tubes (Greiner Bio-One International AG, Austria) with blood clotting activator. The serum was obtained by centrifugation of blood for 10 min at 1800 rpm. The analysis was performed only on blood serum samples, in which no signs of hemolysis were found. All samples were diluted 1:15 with an acidified ($\text{pH} = 2.0$) diluent containing (by volume) 1-butanol 1% (Merck KGaA, Darmstadt, Germany), Triton X-100 0.1% (Sigma-Aldrich, Co., St. Louis, Missouri, USA) and HNO_3 0.07% (Sigma-Aldrich, Co., St. Louis, Missouri, USA) in distilled deionized water.

ICP-MS analysis (inductively coupled plasma mass spectrometry)

The content of macro- and microelements in hair and blood serum, including Na, P, K, Mg, Ca, Al, As, Be, Co, Cr, Cu, Fe, Hg, I, Mn, Ni, Pb, Se, Sn, V, Zn, Li, Mo, Rb, Tl, Cd, Bi, B were determined using inductively coupled plasma mass spectrometry (ICP-MS) on a NexION 300D device (PerkinElmer Inc., Shelton, CT 06484, USA) equipped with an ESI SC-2 DX4 autosampler (Elemental Scientific Inc., Omaha, NE 68122, USA). The use of Dynamic Reaction Cell (DRC) technology has eliminated most of the polyatomic interference in the system. The system was calibrated using a universal set of data collection standards (PerkinElmer Inc., Shelton, CT 06484, USA), diluted with distilled deionized water (acidified with 1% HNO₃) to final concentrations of 0.5, 5, 10 and 50 micrograms/l. 10 micrograms/l of yttrium solution prepared from a single-element standard of pure yttrium (Y) (PerkinElmer Inc., Shelton, CT 06484, USA) was used as an internal online standard prepared on a matrix containing 8% 1-butanol (Merck KGaA, Darmstadt, Germany), 0.8% Triton X-100 (Sigma-Aldrich, Co.), 0.02% tetramethylammonium hydroxide (Alfa-Aesar, Ward Hill, Massachusetts 01835 USA) and 0.02% ethylenediaminetetraacetic acid (Sigma-Aldrich, St. Louis, Missouri, USA).

Laboratory quality control

Laboratory quality control was carried out using a control analysis of GBW09101 certified human hair reference material (Shanghai Institute of Nuclear Research, Shanghai, China) and ClinCheck plasma control (batch 129, levels 1 and 2, RECIPE Chemicals + Instruments GmbH, Germany). The recovery rates of all analyzed trace elements were in the range of 90–110%. In addition, the values obtained for all metals and metalloids were within the limits that, according to the estimates of the manufacturer of the reference samples, were acceptable. The laboratory also participates in the External quality assessment system in the field of occupational medicine and the environment (EMAS OELM).

Statistical analysis

The search and calculations of statistically significant deviations in the elemental status of patients were carried out using the Jupyter Notebook software development environment in Python 3.9. The algorithm was based on open source libraries: Pandas, NumPy and Pingouin.

The nature of the data distribution was assessed using the Shapiro-Wilk criterion. The significance of the intergroup differences was assessed using the nonparametric Mann-Whitney test for data with an abnormal distribution. The boundaries of the median (Me) and interquartile range (IQR) were also calculated to compare the statistical significance of the observations. The difference between the values in the groups was considered significant at $p < 0.05$.

Results and discussion

The trace element composition in patients with tumors of the hematopoietic system was characterized by a significant decrease in the content of Co, Mn, I, Fe, Al, Ni, Pb (p -value < 0.05). It is noteworthy that an elemental imbalance with a predominantly reduced concentration in the hair was detected significantly more often in the cohort of patients with tumors of the hematopoiesis system than in the group of solid tumors.

In patients with solid tumors, the spectrum of manifestations of the elemental composition in the hair is different: reduced values of Na, P, Mg at unchanged concentrations of Ca and K. As for trace elements, the Mn level decreased significantly (p -value < 0.05), and the concentration of V, Cr, I, Sn, Se, Co, on the contrary, increased (Table 1).

Blood serum, as a biochemical active substrate, is represented by a wide variety of elements. In the samples of patients with MN of the hematopoietic system, an increase in the content of trace elements Al, Mn, Ni, V, Tl, Cu, Zn, Fe, B, Bi and a decrease in the content of Co, Rb, Mo (p -value < 0.05) was observed. Deviations from the control values were observed for metals of the toxic and essential groups: increased levels of P, Al, Mn, Ni, V, Tl, Cd, Be, Bi (p -value < 0.05) and decreased values of Co, Cr, Rb, Mo in solid tumors (Table 2).

Table 1

Hair elemental status according to the main diagnosis

Trace elements, µg/g	Me(Q1-Q3) Tumors of the hematopoietic tissues (n=107)	P-value	Me(Q1-Q3) Solid tumors (n=107)	P-value	Me(Q1-Q3) Control group (n=213)
Al	3,632(2,303–5,398)	0.0291	4,51(3,05–7,57)	0.524	4,202(2,839–6,882)
As	0,029(0,020–0,044)	0.846	0,029(0,018–0,041)	0.582	0,029(0,019–0,046)
Be	0,00048(0,0001–0,001)	0.146	0,0003(0,0002–0,0009)	0.161	0,00039 (0,0001–0,0007)
Co	0,0089(0,004–0,014)	0.039	0,015(0,007–0,027)	0.0102	0,0105 (0,006–0,016)
Cr	0,123(0,059–0,241)	0.553	0,835(0,469–0,90)	0.000	0,1291 (0,082–0,269)
Cu	11,007(8,69–14,47)	0.805	11,98(9,38–15,51)	0.064	10,76(8,74–13,76)
Fe	12,86(9,01–18,21)	0.0008	16,73(12,62–26,04)	0.372	17,038 (11,28–24,02)
Hg	0,089(0,03–0,15)	0.083	0,108(0,05–0,18)	0.668	0,1145(0,05–0,18)
I	0,341(0,21–0,55)	0.029	0,793(0,33–1,64)	0.004	0,4776(0,26–0,94)
Mn	0,241(0,15–0,43)	0.000	0,343(0,19–0,68)	0.041	0,4702(0,22–1,52)
Ni	0,148(0,101–0,239)	0.015	0,173(0,118–0,407)	0.959	0,173(0,132–0,282)
Pb	0,293(0,155–0,651)	0.0001	0,533(0,235–1,12)	0.325	0,566(0,268–1,33)
Se	0,4704(0,382–0,56)	0.003	0,441(0,381–0,572)	0.044	0,409(0,369–0,491)
Si	23,3(14,2–36,66)	0.152	23,13(12,99–34,86)	0.099	25,45(17,94–36,35)
Sn	0,092(0,054–0,238)	0.104	0,167(0,087–0,472)	0.030	0,1208(0,07–0,282)
V	0,025(0,015–0,047)	0.111	0,045(0,026–0,08)	0.000	0,021(0,013–0,035)
Zn	175,84(128,94–216,16)	0.217	179 (127–227)	0.373	189,63 (153,1–225,61)

Table 2

Serum elemental status according to the main diagnosis

Trace elements, µg/g	Me(Q1-Q3) Tumors of the hematopoietic tissues (n=38)	P-value	Me(Q1-Q3) Solid tumors (n=38)	P-value	Control group (n=213)
Al	0,0338(0,024–0,095)	0.0003	0,0336(0,027–0,036)	0.0003	0,0151(0,008–0,024)
As	0,0018(0,001–0,001)	0.98	0,0016(0,001–0,002)	0.66	0,0018(0,001–0,006)
Be	0,00004(0,000–0,00007)	0.052	0,0001 (0,00007–0,0001)	0.0000	0,00001 (0,000–0,00002)
Co	0,00069(0,0005–0,0009)	0.0000	0,00062 (0,0004–0,0008)	0.0000	0,0054(0,001–0,011)
Cr	0,0026(0,001–0,002)	0.1	0,0025(0,001–0,002)	0.01	0,0351(0,001–0,13)
Cu	1,196(1,093–1,386)	0.0002	1,079(0,99–1,24)	0.11	0,991(0,9–1,082)
Fe	2,59(1,78–3,574)	0.0000	1,69(1,44–1,845)	0.06	1,37(1,153–1,699)
Hg	0,00018(0,0001–0,0001)	0.72	0,00018 (0,0001–0,0001)	0.29	0,00018 (0,0001–0,0001)
I	0,059(0,051–0,069)	0.78	0,058(0,053–0,067)	0.47	0,05(0,052–0,066)
Mn	0,0024(0,001–0,003)	0.0000	0,0018(0,001–0,002)	0.02	0,0014(0,001–0,001)
Ni	0,0054(0,003–0,006)	0.0000	0,0051(0,003–0,006)	0.0000	0,0019(0,001–0,002)
Pb	0,0005(0,0002–0,001)	0.57	0,0004 (0,0002–0,001)	0.46	0,0005 (0,0004–0,0007)
Se	0,084(0,072–0,098)	0.57	0,091(0,073–0,099)	0.68	0,087(0,08–0,095)
Sn	0,0001(0,00006–0,0004)	0.46	0,0001 (0,00003–0,0001)	0.07	0,00017 (0,0001–0,0002)
V	0,0029(0,0004–0,004)	0.0000	0,00525 (0,0005–0,006)	0.0000	0,00008 (0,0000–0,0004)

Ending table 2

Trace elements, $\mu\text{g/g}$	Me(Q1-Q3) Tumors of the hematopoietic tissues (n=38)	P-value	Me(Q1-Q3) Solid tumors (n=38)	P-value	Control group (n=213)
Zn	1,809(1,636–1,981)	0.0000	1,12(0,967–1,54)	0.25	1,09(1,013–1,21)
Li	0,0014(0,0009–0,001)	0.8	0,0014 (0,0008–0,002)	0.46	0,0014 (0,0009–0,001)
Mo	0,0009(0,0006–0,001)	0.0005	0,00095 (0,0007–0,001)	0.0002	0,0015(0,001–0,001)
Rb	0,169 (0,134–0,22)	0.0088	0,187(0,161–0,227)	0.03	0,251(0,191–0,35)
Tl	0,00002(0,000–0,00003)	0.03	0,00002 (0,000–0,00002)	0.003	0,00001 (0,000–0,00001)
Cd	0,00002(0,000–0,00007)	0.21	0,00008 (0,000–0,0001)	0.0066	0,00002 (0,000–0,00003)
Bi	0,00002(0,000–0,00002)	0.004	0,00001 (0,000–0,00002)	0.018	0,000006 (0,00–0,0000)
B	0,0531(0,023–0,082)	0.018	0,0202(0,011–0,037)	0.53	0,0242(0,012–0,033)

In addition, we presented a table that more clearly shows a statistically significant change in concentration in all three analyzed biosubstrates depending on the histological nature of the tumor (Table 3).

Table 3

Changes of elemental status depending on substrate and tumor nature ($p < 0.05$)

Significant change in the concentration of elements	Tumors of the hematopoietic tissues		Solid tumors	
	Hair	Serum	Hair	Serum
↑	Se	Al, Mn, Ni, V, Tl, Cu, Zn, Fe, B, Bi	V, Cr, I, Sn, Se, Co	Al, Mn, Ni, V, Tl, Cd, Be, Bi
↓	Al, Co, Fe, I, Mn, Ni, Pb	Co, Rb, Mo	Mn	Co, Cr, Rb, Mo

Note: signs '↓' and '↑' denote elements with statistically significant ($p < 0.05$) change in concentration.

In this study, the levels of 23 trace elements in blood serum and hair were compared in 107 patients after chemotherapy with tumors of hematopoietic tissues and 213 healthy individuals in the control group, as well as in 107 patients after AT with solid tumors and 213 healthy individuals in the control group. The results showed that significant changes in the concentration of trace elements were observed in both groups of patients. Thus, in the cohort of patients who completed treatment of hematopoietic tumors, higher concentrations of Al, Mn, Ni, V, Tl, Cu, Zn, Fe, B, Bi ($p < 0.05$) in the blood serum were found, but lower concentrations of Co, Rb, Mo ($p < 0.05$) in blood serum. In addition, in the same patients, a higher content of Se ($p < 0.05$) and a lower content of Al, Co, Fe, I, Mn, Ni, Pb ($p < 0.05$) were found in the hair. In addition, patients treated for solid tumors had higher serum levels of Al, Mn, Ni, V, Tl, Cd, Be, Bi ($p < 0.05$) and lower serum levels of Co, Cr, Rb, Mo ($p < 0.05$). However, higher levels of V, Cr, I, Sn, Se,

Co ($p < 0.05$) and lower levels of Mn ($p < 0.05$) were found in the hair.

The results obtained confirm the presence of an imbalance of trace elements in patients with cancer, including in the period after the end of the sweat. The elemental imbalance was slightly different depending on the type of neoplasm, although the trends were similar. The trends in the concentration of chemical elements in the blood serum of patients in both groups partially coincided: an increase in the content of manganese (Mn), aluminum (Al), vanadium (V), nickel (Ni), thallium (Tl) and a decrease in the content of magnesium (Mg), cobalt (Co), rubidium (Rb) and molybdenum (Mo). The concentration of Mn in hair decreased in both solid and hematopoietic tumors; the concentration of Se increased similarly (Table 3).

Trace elements with significant changes can be divided into 2 categories: essential trace elements and toxic trace elements [25]. It is known that exposure to certain toxic elements contributes to the development of

MN, affects the processes associated with mutagenesis (apoptosis, proliferation, neoplastic transformation) [26], therefore, their increased content can be considered as a factor of unfavorable prognosis of the disease [27].

In our study of patients with tumors of the hematopoietic system, we observed changes in the content of toxic elements in the levels of Al, Be, Cd, Tl, Bi, and Pb. Changes in the levels of Al, Tl, Cd, Be, and Bi in the hair and blood serum of patients with solid tumors were also detected.

A number of publications have shown that high serum levels of aluminum (Al) are also characteristic of patients with breast tumor tissue, but there is no evidence that this is directly related to carcinogenic effects [28]. No information was found on an increase in Al levels in the hair and blood serum of patients with tumors of the hematopoiesis system.

It cannot be excluded that the increase in thallium (Tl) content is a consequence of previously realized mechanisms of carcinogenesis. Tl can carry out carcinogenic activity by interfering with important processes, replacing potassium, in particular, in the (Na⁺/K⁺)-AT-Pase. However, the antitumor role of thallium salts has been described and shown in individual cell cultures [29]. Participation in oncogenesis is confirmed by the effectiveness of Tl-scintigraphy for detecting malignant tumors such as breast cancer and lymphoma [30].

It was also reported that bismuth-Bi (BisBAL NPs) nanoparticles obtained from the bis (p-aminophenyl) compound lumazine can inhibit the growth of TNF cells, and the effectiveness directly depends on the dose used [31]. This is an important discovery because it suggests that BisBAL nanoparticles may have potential as a targeted therapy for breast cancer, specifically targeting tumor cells without affecting healthy tissues. Interestingly, our data showed a decrease in serum Bi levels after completion of the AT. Lead (Pb) exposure is also associated with various health risks, including harmful effects on the nervous system, reproductive system, and kidneys [32]. However, the relationship between lead exposure and the development of AT is less obvious. It should be noted that our data indicate a low level of Pb in the hair of patients with tumors of the hematopoiesis system.

In addition, a group of patients with solid tumors had elevated concentrations of cadmium (Cd) and beryllium (Be), which the International Agency for Research on Cancer (IARC) has recognized as carcinogens for humans or animals. Numerous studies have shown that chronic exposure to these metals is associated with the development of solid tumors [33, 34]. This may be due to their ability to disrupt the repair of nucleotide fragments, which leads to genome instability [35] and subsequent tumor growth. Notably, high levels of Cd and Be were found only in the blood serum of patients with solid tumors. Patients from the group of tumors of the hematopoiesis system were characterized by the absence of changes in the content of these toxic metals in the blood serum.

It has been reported that significant deviations from the norm in the content of essential elements may be the cause of toxicity due to homeostasis disorders. Among the essential trace elements in the group with tumors of the hematopoietic system, changes in the levels of Se, Mn, Ni, V, Cu, Zn, Fe, B, Co, I, Rb, Mo, as well as V, Cr, I, Sn, Se, Co, Mn, Ni, V, Co, Rb, Mo was found in the group with solid tumors. The described significant elemental imbalance in the blood serum in the group with tumors of hematopoietic tissues largely coincides with the data obtained by other authors.

Thus, we found similar patterns of increased serum levels of Fe, Cu, and Ni, known from previous studies [36, 37]. It has been found that nickel (Ni) can stimulate the proliferation of cancer stem cells through the NADPH oxidase/ROS-dependent mechanism [38]. It has also been reported that high Ni levels have been associated with breast cancer, and this may be a risk factor for carcinogenesis [39]. Some authors note the predominance of epigenetic modulation in nickel carcinogenesis, which may include changes in histone acetylation, methylation, ubiquitination, and changes in DNA methylation affecting gene expression [40]. In addition, Ni may be involved in the hypoxic signaling pathway leading to nickel-induced carcinogenesis, since Ni has been found to be a strong inducer of HIF-1 α protein and an activator of HIF-dependent transcription [41], which may provide conditions for resistance to apoptosis. Although nickel (Ni) and iron (Fe) are very

similar and can alter each other's metabolism [42], the effects of Fe are more based on the regulation of oxidative stress and subsequent carcinogenesis [43]. Excess Fe, which is a cofactor of hematopoietic cell proliferation, can also stimulate the growth of tumor cells [44]. Caroline L. et al. It has been shown that in patients with acute leukemia, the level of iron in the blood serum is increased [45].

Copper (Cu) is a trace element that plays an important role in the functioning of the cellular substrate. Elevated serum Cu levels may increase oxidative stress associated with the PI3K/Akt metabolic pathway, which may be a beneficial factor for the development of oncogenic processes [46], and this is consistent with our results, since serum Cu levels were elevated in patients with hematopoietic tumors. Numerous studies have unequivocally confirmed a significant increase in Cu levels both in tumors and in the blood serum of cancer patients, which is significantly higher than in healthy people [47]. So, Li Y. et al. It has been shown that an increased level of copper in the blood serum increases the risk of colorectal cancer, therefore, a high level of copper in the blood serum can be considered as an indicator of a risk factor for the development of the disease [48].

We can also note a higher concentration of vanadium (V) in the blood serum compared to the control. V can affect many enzyme systems, such as phosphatases, ATPases, peroxidases, ribonucleases, protein kinases, and oxidoreductases, and a number of animal cancer models have shown that vanadium provides protection against all stages of carcinogenesis [49]. V promotes cellular instability, in some cells, induces tyrosine kinase phosphorylation and, thus, can affect oncogenesis [50]. Due to its physiological duality, V becomes toxic in excessive amounts and probably has procancerogenic properties [51].

Numerous studies have shown that a number of boron (B) derivatives have proven effective in fighting cancer [52]. Various types of compounds and structures in B have the ability to inhibit the progression of MN and are associated with a decrease in the incidence of various types of cancer. B exhibits its antitumor effects by participating in the regulation of specific molecular

mechanisms, such as induction of apoptosis and cell cycle arrest [53]. However, many aspects of this effect remain unclear. We found an increase in serum B levels in patients with hematopoietic tumors.

In addition, in patients with solid tumors, the concentration of chromium (Cr) in the blood serum was lower than in patients with hematopoietic tumors. Carcinogenesis associated with Cr(VI) is described in the literature and includes mutational inactivation of p53, base substitutions in A/T pairs, and double missense mutations [54]. Cr(VI) belongs to the first group of carcinogens. In patients with solid tumors, changes in the Cr content were observed in the hair and blood serum, while the Cr content in the serum decreased and in the hair increased. Zekavat et al. It was shown that serum Cr levels decreased after completion of combined chemotherapy [55], which is consistent with our results. In the same study, a decrease in the concentration of manganese (Mn) in the blood serum was recorded. On the other hand, Diez et al. Higher Mn levels have been found in patients with lung cancer [56]. Our results indicate a decrease in Mn levels in the hair, but the level of Mn in the blood serum is increased compared to the control group. Mn^{2+} induces apoptosis in cells and participates in the antitumor immune response through the cGAS-STING signaling pathway, which means it is usually characterized by antitumor action [57].

Iodine (I) is one of the main antioxidants. Antitumor, antiproliferative, and cytotoxic effects of I in cancer have been described [58]. We found a decrease in the level of I in the hair in the group of patients with tumors of the hematopoiesis organs and an increase in the level of I in the blood serum in the group of solid tumors.

Tin (Sn) compounds also have the described antitumor properties. Sn-DBPTF-1 has been reported to be effective against cancer or oncogenic cell lines because Sn-DBPTF-1 (dibenzylphosphinoyl dithioformate) It can induce apoptosis and double-stranded DNA breaks [59]. It is noteworthy that we found an increased level of Sn in the hair of patients with solid tumors.

Also pay attention to the general patterns of decreasing levels of Co, Rb, Mo in blood serum in patients with both solid and hematopoietic tumors.

Cao G.H. et al. It was reported that the cobalt (Co) content in hair and blood serum in patients with stomach cancer was lower than in healthy people in the control group [60]. The introduction of Mo compounds promotes apoptosis and the formation of reactive oxygen species, which demonstrates their potential use for the treatment of metastatic cancer cells [61]. The case-control study conducted by Yetişgin F. and co-authors. Studies have shown that Co levels were elevated in the group of patients with myeloproliferative neoplasms [62]. Several studies have shown that Co(II) ions are genotoxic due to the formation of reactive oxygen species and inhibition of DNA repair [63]. It is also worth noting the discovery of Wang X. and co-authors. that Rb levels correlate with a lifetime risk of cancer, which may be related to possible involvement in the etiology of MN [64].

Special attention should be paid to the effects of trace elements such as selenium (Se) and zinc (Zn), since they are considered to have the maximum anti-tumor effect among trace elements. The Zn level was assessed as a marker for predicting the response to perspiration. It has also been reported that zinc deficiency is common in hematopoietic and solid tumors [65]. Apparently, this relationship can be explained by the properties of zinc to inhibit MT expression and additionally induce an increase in ROS content [66]. Some studies show that impaired redox activity can lead to the progression of tumor growth by affecting signal transduction pathways that cause the expression of anti-apoptotic genes regulating cell death [67, 68]. However, redox-active trace elements can be useful in AT. Thus, Se-based compounds are considered as chemotherapeutic agents that mediate the activation of apoptosis receptors expressed on the cell surface and the production of ROS, which leads to necrosis [69]. Increased Se levels in hair contradict the data of other studies on decreased Se levels in patients with leukemia and lymphoma [70].

Since our study considered the delayed effects of AT, an increase in Se levels can be interpreted as a violation of the elimination process. In addition, essential trace elements may have therapeutic applications when used synergistically with AT, especially

due to their ability to modulate the toxicity of therapy and promote the restoration of healthy tissues [71, 72]. It is important to take this into account, since an imbalance of essential trace elements can lead to impaired immune function, an increased risk of side effects of AT, and a deterioration in the quality of life of patients [72–74].

Our study has some limitations, such as the number of participants, the lack of measurement of the elemental profile before the start of treatment, and the lack of follow-up after measuring the elemental status after the start of the AT, which makes it impossible to accurately determine whether the apparent violations of the elemental status are caused by the disease or treatment. Our goal was not to study the relationship between the elemental imbalance caused by AT and metabolic disorders associated with the tumor process. This should be evaluated in subsequent studies.

Conclusions

Thus, we found a statistically significant difference between the content of elements in blood serum and hair in patients with different histological structures of the tumor and in the control group. As clinical data accumulate, it is advisable to take into account metabolic changes in the levels of essential and toxic elements.

Our data indicate that neoplasms of the hematopoiesis system are characterized by more pronounced changes in the composition of essential elements in hair and blood serum, and solid tumors exhibit a more pronounced accumulation of certain toxic metals compared to tumors of the hematopoiesis system. However, no significant or specific differences were found between the groups. Depending on the type of tumor and treatment, a more differentiated approach to nutritional support may be required.

Further research is needed to assess the causes of the elemental imbalance, the associated toxic effects, and the possible role of nutritional support as supportive therapy. It is necessary to study the long-term effects of AT on changes in the homeostasis of trace elements and the associated deterioration of general health, the effects of treatment and the risk of tumor recurrence.

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Элементный гомеостаз у детей и подростков после завершения противоопухолевой терапии злокачественных новообразований

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Аннотация. *Актуальность.* По мере развития медицинских исследований все больше внимания уделяется изучению элементных изменений у онкологических больных не только как маркера заболевания, но и как возможного осложнения заболевания. Целью данного исследования является изучение изменений уровня эссенциальных и токсичных микроэлементов у пациентов, прошедших противоопухолевую терапию (ПОТ) по поводу злокачественных новообразований (ЗНО). *Материалы и методы.* В рамках проведения ретроспективного моноцентрового исследования была сформирована группа из 214 пациентов лечебно-реабилитационного научного центра «Русское поле» в возрасте от 4 до 17 лет. Все пациенты находились в состоянии ремиссии после завершения противоопухолевого лечения: 107 человек — по поводу гемобластозов и 107 — солидных опухолей. Возраст участников составлял от 4,2 до 17,6 лет, средний возраст — 11,4 года. Для комплексной оценки элементного статуса у детей использованы биосубстраты (волосы и сыворотка крови), измерения проводили методом масс-спектрометрии после минерализации образцов. *Результаты и обсуждение.* Результаты исследования образцов волос и сыворотки крови показали, что элементный профиль пациентов после ПОТ имеет как сходные закономерности, так и отличительные особенности в зависимости от гистологического типа опухоли. *Выводы.* Наши данные показывают, что у пациентов с солидными опухолями наблюдалось более высокое

накопление токсичных металлов по сравнению с образцами, взятыми у пациентов с опухолями органов кроветворения. Тем не менее, серьезных специфических изменений элементного гомеостаза в зависимости от гистологической структуры не наблюдалось. Полученные результаты подчеркивают важность тщательного мониторинга параметров гомеостаза для предотвращения развития осложнений противоопухолевой терапии, связанных с элементным гомеостазом.

Ключевые слова: микроэлементы, макроэлементы, эссенциальные элементы, токсичные элементы, элементный статус, элементный дисбаланс, канцерогенез, солидные опухоли, опухоли системы кроветворения, волосы, сыворотка, поздние эффекты, масс-спектрометрия с индуктивно связанной плазмой

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