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ИЗМЕНЕНИЕ МОРФОМЕТРИЧЕСКИХ И ОПТИЧЕСКИХ ПАРАМЕТРОВ ЛИМФОЦИТОВ КРЫС ПОД ВОЗДЕЙСТВИЕМ МЕДНО-ЦИНКОВОЙ КОЛЧЕДАННОЙ РУДЫ

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Резюме. ***Введение.*** Известно, что морфологические и оптические параметры отражают функциональную активность лимфоцитов, что позволяет использовать их для оценки состояния иммунной системы организма. Актуальность проблемы определяется тем, что при воздействии на человека неблагоприятных факторов среды, связанных с медно-цинковой колчеданной рудой, возникают отрицательные последствия для организма. Данные негативные эффекты могут наблюдаться у работников горнодобывающих предприятий при их контакте с рудой, так как в ее состав входят соли тяжелых металлов. ***Цель работы*** заключалась в исследовании площади поверхности лимфоцитов, площади и оптической плотности ядра и цитоплазмы лимфоцитов периферической крови крыс под воздействием медно-цинковой колчеданной руды. ***Материалы и методы.*** В работе с помощью компьютерной морфометрии в хроническом эксперименте изучены размерные показатели лимфоцитов и их структур, а также оптические свойства этих клеток у крыс, подвергнутых воздействию медно-цинковой колчеданной руды. В эксперименте использовали 70 нелинейных крыс-самцов 3-4-месячного возраста (средняя масса 210,5±10,5 г). В соответствии со сроками воздействия руды крысы были разделены на 5 групп. Морфометрические параметры лимфоцитов определяли методом компьютерной морфометрии, с помощью комплекса автоматической микроскопии «МЕКОС-Ц2» (Россия), установленного в составе функций для анализа мазков на микроскопе AXIO Lab.A1 (ZEISS, Германия). ***Результаты.*** Во все сроки эксперимента происходило увеличение площади ядра лимфоцитов на фоне снижения его оптической плотности. Наблюдалось уменьшение оптической плотности и площади цитоплазмы лимфоцитов. ***Обсуждение.*** Наблюдаемые изменения площади и оптической плотности ядра лимфоцитов периферической крови, возможно, были обусловлены превращением гетерохроматина в активный эухроматин, а цитоплазмы — снижением ее метаболической активности. ***Выводы.*** Выявленные перестройки морфометрических показателей и оптических свойств лимфоцитов были обусловлены адаптивными процессами иммунной системы крыс при действии на организм руды.

Ключевые слова: лимфоциты, гистограммы, медно-цинковая колчеданная руда, оптическая плотность, крысы

CHANGES IN MORPHOMETRIC AND OPTICAL PARAMETERS OF RAT'S LYMPHOCYTES UNDER THE INFLUENCE OF COPPER-ZINC PYRITE ORE

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Abstract. ***Introduction.*** It is well-established that morphological and optical characteristics of lymphocytes reflect their functionalactivity, making them suitable for assessing the status of the immune system. This is particularly significant as exposure to adverse environmental conditions, such as those associated with copper-zinc pyrite ore mining, can have negative effects on the body. The relevance of this issue is underscored by the potential risks faced by mining workers who come into contact with the ore, which contains heavy metal salts, and can lead to negative health outcomes. ***The aim of this study*** was to investigate the effects of copper-zinc pyrite ore on the surface area, nuclear area, and optical density of rat's lymphocytes of the peripheral blood. ***Materials and methods.*** The study utilized a sample of lymphocytes from the peripheral blood of rats, which were exposed to copper-zinc pyrite ore under controlled conditions. Measurements were taken of the aforementioned parameters, and statistical analysis was performed to determine any significant changes in these characteristics. In the study, we used computer morphometry to analyze the dimensional parameters and structural features of lymphocytes, as well as the optical properties of these cells, in rats that had been exposed to copper-zinc pyrite ore. In the study were used 70 male rats, aged three to four months and weighing an average of 210.5±10.5 grams. The rats were divided into 5 groups based on the timing of their exposure to copper-zinc pyrite ore. The morphometric parameters of the lymphocytes were determined using computer morphometry by "MEKOS-C2" automated microscopy system (Russia), which was integrated with the AXIO Lab A1 microscope (ZEISS, Germany) for smear analysis. ***Results.*** During the experiment, the nuclear area of lymphocytes was increased, while its optical density decreased, the cytoplasmic area and optical density were decreased. ***Discussion.*** The findings suggest that exposure to copper-zinc pyrite ore was leaded to changes of lymphocyte morphology, specifically an increase of nuclear area. Further research is needed to understand the implications of these changes and their potential impact on immune function. The observed changes of the size and optical density of the cell nucleus could be due to a conversion of heterochromatin to active euchromatin and a decrease in the metabolic activity of the cytoplasm. ***Conclusions.*** The rearrangements in the morphometric parameters and optical properties of lymphocytes that have been observed may be the result of adaptive processes of rat's immune system under the influence of copper-zinc pyrite ore.

Keywords: lymphocytes, histograms, copper-zinc pyrite ore, optical density, rats

INTRODUCTION

Recent studies have shown that certain indicators of peripheral blood lymphocytes, such as diameter, perimeter, and area, reflect not only morphological features of the cells but also their functional activity [1]. Additionally, optical properties of these cells can provide insight into the state of their internal structures.

A change in the range of variations in the size parameters of lymphocytes can serve as an indicator of impaired immunoreactivity of the body and the development of pathological processes in response to adverse environmental factors [1, 2]. It is therefore of great practical importance to study the morphometric and optical characteristics of peripheral blood lymphocytes in laboratory animals under exposure to salts of heavy metals, which are part of the ores that mining workers come into contact with. There are three major deposits in Bashkortostan that produce copper-zinc pyrite ore, and their composition contains approximately 60 harmful impurities, including salts of heavy metals like arsenic, antimony, mercury, and fluorine [3].

AIM

The aim of the study was to investigate the morphometric and optical features of lymphocytes, such as cell surface area, nuclear and cytoplasmic size, and optical density, in the peripheral blood of rats exposed to copper-zinc pyrite ore.

MATERIALS AND METHODS

The effect of copper-zinc pyrite ore on hematological parameters was studied in 70 white non-linear male rats aged 3–4 months and weighing 210.5±10.5 grams. There were 5 experimental groups and one control group. Experimental rats received a water suspension of copper-zinc pyrite ore orally for 10, 20, 30, 45, and 60 days at a dose of 600 mg/kg body weight [4, 5]. During the experiment, we followed the principles outlined in the directives of the European Community (86/609/EEC), the Helsinki Declaration, and the "Rules for Carrying Out Work Using Experimental Animals" as well as the recommendations of the Bioethics Council of the Bashkir State Medical University. Standard cages (n=6), with free access to food and water, were used for the animal husbandry in the vivarium at an average temperature of 24±2 °C, in accordance with the guidelines of SP 2.2.1.3218 and Directive 2010/63/EU on the protection of animals used for scientific purposes. Blood was collected from the rat's tail vein. The animals were euthanized using decapitation and ether anesthesia [6]. A blood smear was stained by method Romanovsky–Giemsa. The morphometric parameters of lymphocytes were determined using computer morphometry of the "MEKOS-C2" automated microscopy system (Russia), which was installed as part of the smear analysis functions on the AXIO Lab A1 microscope (ZEISS, Germany). There were calculated all types of leukocytes, a database of their images was created, and after sorting, the data was transferred to MS Excel. Based on calculating the area of 200 cells in each sample, histograms were built to show the distribution of cells, which allowed for the average values and ratios of cell proportions to be taken into account of leukocyte formula. The sample of the ore was provided by the Uchalinsky Mining and Processing Plant.

There were studied an optical density of the cytoplasm and nucleus of lymphocytes was studied. To estimate optical density parameters, the brightness distribution over the object was used, using the specific optical density index. The specific optical density index was measured in three spectral ranges of the video camera — blue, green, red, determined by the color of the rays absorbed by the substance. The total spectral range reflected the functional activity of the cell. There were calculated the integral optical density of the cytoplasm, optical density indices and specific total optical densities of lymphocytes [7].

The number and volume of rat's lymphocytes were analyzed using a veterinary semi-automatic hematology analyzer, Vet Exigo 19 (Sweden).

The data obtained were processed using the statistical software STATISTICA 12 (StatSoft, USA). Nonparametric the Mann–Whitney and the Kruskal–Wallis tests, were used to determine the statistical significance of differences between samples. The median value (Me) and the interquartile range (Q1, Q3) of lymphocytes volume

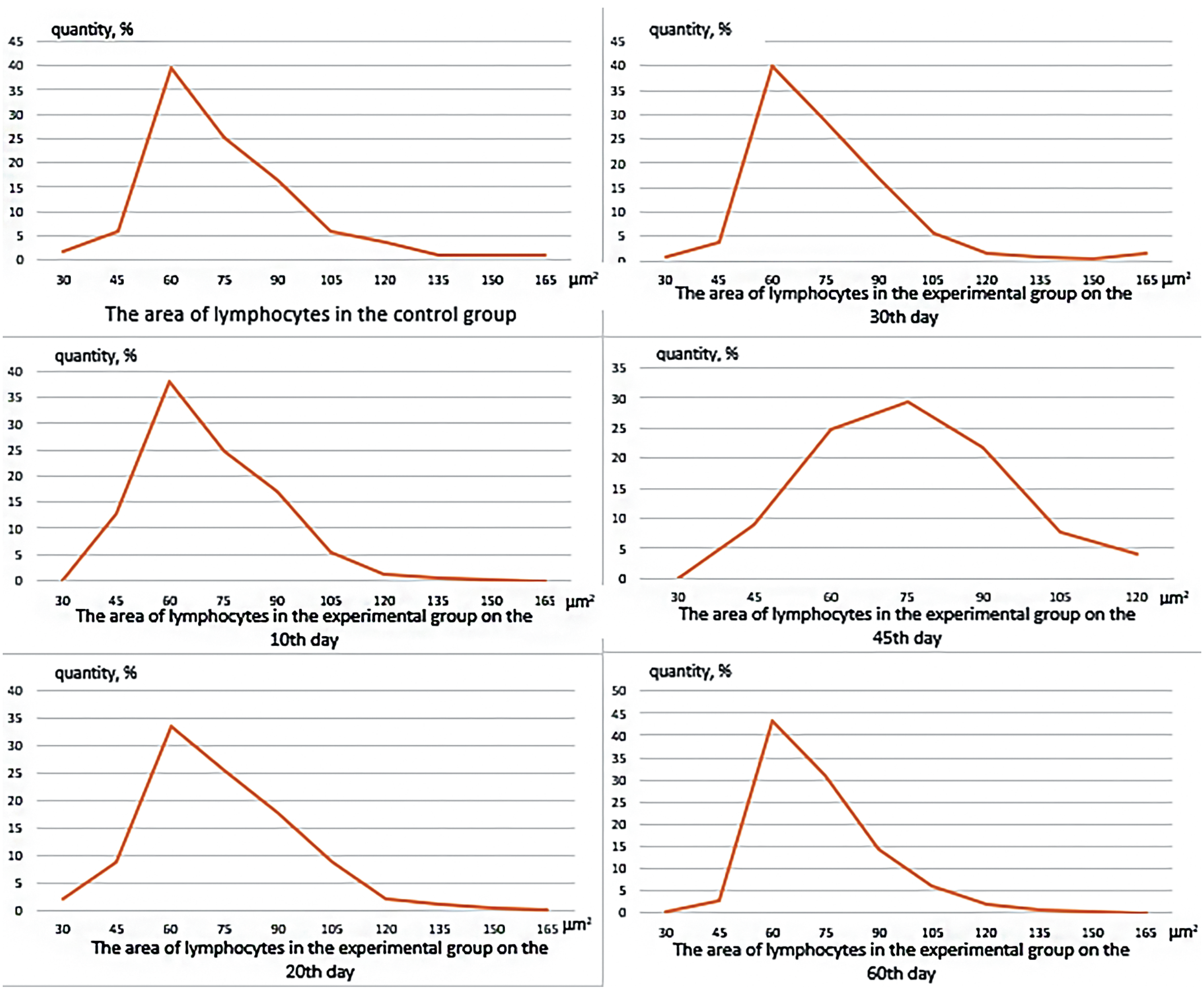

Fig. 1. Histograms of the distribution of the area of rat's lymphocytes exposed to copper-zinc pyrite ore

were calculated. Differences were considered statistically significant if $p < 0.05$. Correlations between variables were assessed using the Spearman correlation coefficient, a nonparametric measure of association.

RESULTS

There are presented histograms of the distribution of rat's lymphocytes across the area occupied by cells on the glass area in the initial state and at various experimental time points are presented in Figure 1.

The distribution of cells area during the experiment under the influence of copper-zinc pyrite ore was characterized by imperfections and asymmetry. This was manifested by a shift of the peak of the distribution curve to the left and the presence of a "tail" extending to large values of the indicator.

During all study periods, the histogram of the area showed a maximum value of 60 μm^2, except for 45 days. In control conditions, the proportion of small cells (less than or equal to 60 μm^2) accounted for 48% of the total, and medium cells (less than or equal to 90 μm^2), 43%. Together, these two groups accounted for more than 90% of circulating cells. The nature of the distribution curves changed slightly during the first period of the experiment. By the 30th day, based on the histograms of lymphocyte area, a shift in the apex was observed to the left, which was attributed to an increase in the proportion of larger cells within the overall population. The mean cell area did not statistically significantly change (Fig. 1).

On the 45th day, there was a slight modification to the shape of the histogram for the distribution. The curve for the lymphocyte region shifted towards larger values (73 μm^2), and the histogram became more symmetrical. This change in the proportion of cell fractions based on area led to an increase in the average size of lymphocytes. The proportion of medium-sized cells (between 75 and 90 μm^2) was greater than 50% at this time, compared to other periods where the proportion of these cells did not exceed 43%. It should be noted that during this time, the number of lymphocytes in circulation increased (Table 1).

The study of intracellular parameters throughout the experiment revealed that the cell's area occupied by the nucleus increased significantly compared to the control group (Table 1). Conversely, the dynamics of the cytoplasmic area showed a decreasing trend starting from the 10th day, and in subsequent stages, the average cytoplasmic area of lymphocytes was significantly lower than in the control group. On the 10th day, it decreased by 35%, on the 20th day by 50%, on the 30th day by 30%, and on the 45th day by 25%. At the 60-day mark, it was still lower by 35% compared to the initial value. This decrease in cytoplasmic area, as evidenced by a comparison of nuclear-cytoplasmic ratios, occurred against a background of increased nuclear proportion, with the overall cell area remaining unchanged. The exception to this pattern was on the 45th day, when a maximum value of total cell surface area was recorded. This was due to a significant increase in nuclear area, compared to both the control and earlier study periods. Specifically, on the 10th, 20th, and 30th days, there were increases in 9, 18, and 7%, respectively. However, on the 45th and 60th days, the increases were in 23 and 9%.

The particular interest was an analysis of parameters that characterize the optical properties of cytoplasm and nuclei (Table 2).

The informative value of studying optical properties lies in the fact that they reflect the peculiarities of the course of metabolism in the studied cells in normal and pathological processes. The revealed decrease of the optical density of the cytoplasm during the experiment compared with the control was indicate a decrease in viscosity of the cytoplasmic matrix (Table 2). At the same time, a direct correlation was established between total optical density and area of cytoplasm (r=0,57 in control, r=0,56

Table 1

Rat's lymphocyte counts under the influence of copper-zinc pyrite ore, Me (Q1; Q3)

Indicators	Control group	Experimental group 10 days	Experimental group 20 days	Experimental group 30 days	Experimental group 45 days	Experimental group 60 days
Number of lymphocytes ($\times 10^9$ cells/l)	10,35 (9,00;12,40)	14,45 (10,75;17,90)*	11,30 (10,40;14,10)	12,10 (10,70;14,50)	16,70 (9,70;18,70)*	13,40 (10,10;16,40) *
The average area of lymphocytes, μm^2	64,00 (51,00;78,00)	63,00 (50,00;75,00)	62,00 (48,00;78,00)	62,00 (50,00;77,00)	72,00 (59,00;85,00) * Δ	61,00 (53,00;73,00)
The average area of the cytoplasm, μm^2	19,00 (13,00;26,00)	12,00 (8,00;18,00)*	09,00 (4,00;17,00)* Δ	13,00 (9,00;24,00)* ■	14,00 (9,00;24,00)* ■	12,00 (6,00;19,00)* ■
Average core area, μm^2	43,00 (34,00;52,00)	47,00 (36,00;58,00)*	51,00 (39,00;64,00)* Δ	46,00 (37,00;54,00)* ■	53,00 (43,00;65,00)* Δ •	47,00 (41,00;57,00)*
The nuclear-cytoplasmic relationship, conventional units	2,12 (1,61;2,85)	3,53 (2,26;5,43)*	5,11 (2,81;10,32)* Δ	2,99 (1,80;4,32) * Δ ■	3,64 (2,07;6,26) * ■	3,71 (2,19;7,79) * ■ •

Note: * — statistically significant difference in the indicator of the experimental group in relation to the value of the control group of rats ($p < 0.05$); Δ — to the value of the 10-day experimental group of rats ($p < 0.05$); ■ — to the value of the 20-day experimental group of rats ($p < 0.05$); • — to the value of the 30-day experimental group of rats ($p < 0.05$); ▲ — to the value of the 45-day experimental group of rats ($p < 0.05$).

on 10th day, r=0,52 on 20th day, r=0,69 on 30th day, r=0,59 on 45th day, r=0,77 on 60th day). The value of the refractive index directly depends on the functional state of intracellular structures, it can be assumed that the decrease in area and optical density of cytoplasm observed during experiment compared to control was due to decrease in its functional activity under influence of ore [8]. On the 10th day, decrease in cytoplasmic area was 35% and specific total optical density decreased in 27.5%. On the 20th, 30th and 45th days, decrease was 50, 30 and 25%, respectively. On 60th day it was 35%.

Increase in nucleus size was combined with decrease in optical density in all spectral ranges during all periods of experiment (Table 2).

DISCUSSION

The study showed that intoxication of rats caused by exposure to copper-zinc pyrite ore was accompanied by an increase in the number of lymphocytes and changes in their morphometric and optical parameters. In the control group, the main proportion of circulating cells consisted of small and medium-sized lymphocytes, which corresponded to information from literature sources [9]. On days 30th and 45th of the experiment, the population of lymphocyte was redistributed with an increase in proportion of larger cells combined on the 45th day with an increase in their number and nucleus size. This allowed us to assume that lymphocytes entering circulation were replenished with cells with enlarged nuclei. According to Davydkin I.L. and Semenkov V.F., replenishment of population with larger cells could be due to immature thymocytes and natural killer cells [9, 10]. Intrapopulation rearrangement of lymphocytes and the appearance of groups of cells with different areas may indicate the development of an immune response to the effects of toxic substances in ore [1]. The study of intracellular components has made it possible to clarify information about the nature of these processes. Dynamic and objective indicators of cell state are size and optical density of nucleus [11]. It is known that size and shape of nucleus are determined not by amount of DNA but by modification of chromatin [11], and increase in area of nucleus is due to conversion of heterochromatin to euchromatin [12]. Therefore, increase in nuclear area and change in optical properties throughout study period can be considered as reflection of change in chromatin density due to transformation of inactive heterochromatin into active euchromatin. At the same time, the maximum activity of the nucleus occurred on the 45th day, manifested in the minimum optical density in the largest size of the nucleus and the cell as a whole.

Along with an increase in the size of the nucleus, a decrease in the optical density and area of the cytoplasm occurred under the action of the copper-zinc pyrite ore. At the same time, a positive correlation between these indicators was revealed. Considering that the value of the refractive index directly depends on the concentration of chemical components of the intracellular substance and the state of cellular organoids, it can be assumed that the functional state of cytoplasmic structures and metabolic processes decreases during ore intoxication.

CONCLUSIONS

Based on the assumption that morphometric parameters objectively reflect the functional state of lymphocytes, we can discuss the restructuring of the cellular components of the immune

Table 2

Optical parameters of rat's lymphocytes under the influence of copper-zinc pyrite ore, Me (Q1; Q3)

Indicators	Control group	Experimental group 10 days	Experimental group 20 days	Experimental group 30 days	Experimental group 45 days	Experimental group 60 days
Integral optical density of the cytoplasm, conventional units	0,38 (0,26;0,50)	0,17 (0,12;0,28)*	0,12 (0,05;0,20)* Δ	0,30 (0,16;0,48)* Δ■	0,22 (0,12;0,36)* ■ •	0,16 (0,07;0,25)* •▲
The specific total optical density of the cytoplasm, conventional units	1,19 (0,96;1,47)	0,86* (0,74;1,01)	0,81* (0,64;1,02)	1,06* Δ ■ (0,81;1,62)	1,03* Δ ■ (0,79;1.29)	0,77* Δ •▲ (0,61;0,97)
Specific optical density of the core according to the red component, conventional units	1,27 (1,06;1,51)	0,91* (0,76;1,14)	0,73* Δ (0,59;0,94)	1,04* Δ ■ (0,82;1,28)	0,70* Δ • (0,62;0,83)	0,73* Δ • (0,58;0,83)
Specific optical density of the core according to the green component, conventional units	1,73 (1,33;2,09)	0,81* (0,68; 0,99)	0,58* Δ (0,49;0,75)	1,33* Δ ■ (0,93;1,89)	0,55* Δ • (0,47;0,66)	0,70* Δ ■ •▲ (0,57;0,85)
Specific optical density of the core according to the blue component, conventional units	0,46 (0,32;0,60)	0,15* (0,12;0,20)	0,10* Δ (0,07;0,14)	0,37* Δ ■ (0,17;0,57)	0,09* Δ • (0,06;0,13)	0,14* ■ • ▲ (0,11;0,18)

Note: notation as in Table 1.

system under the influence of copper-zinc pyrite ore. Upon activation of a cell, the structural organization of chromatin undergoes conformational changes, resulting in changes to its optical properties [13, 14]. As a result, the experimentally observed increase in nuclear size, combined with a decrease in optical density, may indicate changes in the degree of chromatin condensation due to copper-zinc pyrite ore, and, consequently, an increase in DNA activity [11, 15].

The observed changes in the size and optical characteristics of the nucleus are accompanied by a decrease in metabolic activity in the cytoplasm. As a result, structural and functional alterations in the lymphocyte population, aimed at the body's adaptation to the effects of copper-zinc pyrite ore, impact the nuclear apparatus but do not occur at the level of cytoplasmic processes.

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ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that there is no conflict of interest.

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Ethics approval. The study was conducted in compliance with the "Rules of work using experimental animals". The study was approved by the local Ethics Committee of the Bashkir State University of the Ministry of Health of the Russian Federation, Protocol No. 5 dated 09/13/2017.

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