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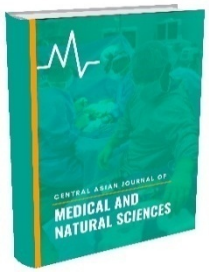

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ASSESSMENT OF THE STATE OF IMMUNITY IN PATIENTS WITH TUMORS

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ABSTRACT: *Cellular immune status provides information on the relative and absolute numbers of cell populations (monocytes, granulocytes and lymphocytes) and subpopulations of lymphocytes in the blood. The human body is equipped with a complex defence mechanism whose primary function is to distinguish foreign antigens from the body's own antigens and initiate an appropriate immune response. Historically, innate immunity differs from adaptive immunity, and these systems work closely together. The immune response is mediated by both cellular components (B- and T-lymphocytes, NK cells, macrophages/monocytes, granulocytes and antigen-presenting cells) and humoral components (antibodies, complement factors, cytokines and other soluble effector molecules). [12,13].*

Keywords: immunity, orbital tumors, leukocyte formula

Both external factors (climatic, physical, mechanical, etc.) and the state of the organism itself (inflammatory processes, metabolic disorders, regulatory nervous influences, changes in connective tissue) play a role in the emergence and development of neoplasms [1].

Tumor transformation of one or several cells causes the body to respond to the elimination of foreign information. The body's response to a developing tumor is carried out using humoral and cellular mechanisms, which can be determined by counting the number of peripheral blood leukocytes [2,3].

The leukocyte blood count is an indicator of the body's nonspecific response, which quite fully reflects the typical processes in the immunity system in health and disease. Leukocytogram outside the expanded immunogram can serve as an immunologically informative component and guideline for determining the functional state of immunity in general and in some diseases: toxic infection, sepsis, hypo- and avitaminosis, rheumatism, alimentary exhaustion, etc. [4].

Changes in the leukocyte formula in the dynamics of the pathological process, the level of leukocytes, lymphocytogram contribute to assessing the severity of the patient's condition, determining the amount of therapy, assessing the patient's response to surgery, predicting the effectiveness of therapy and the course of the rehabilitation period [5].

The choice of the ratio of certain cellular elements is due to their closest functional relationship in the system of cellular cooperation [6,7,8]

From the point of view of various authors, the most significant of the many integral hematological indicators are: leukocyte index (LI), leukocyte intoxication index (LII), leukocyte shift index (LSI), leukocyte to ESR ratio, lymphocyte-granulocyte index (LGI), general index (GI), the index of the ratio of neutrophils and lymphocytes (IRNL), the index of the ratio of neutrophils to monocytes (IRNM), the index of the ratio of lymphocytes to monocytes (IRLM), the index of the ratio of lymphocytes and eosinophils (IRLE), the coefficient of redundancy (CR) [9, 10,11]

Objective: to study changes in hematological indices in patients with various types of orbital tumors.

Materials and methods:
Integral hematological parameters were determined in 179 patients with primary orbital tumors.

Men were 42.5%, women - 57.5%, mainly (42.9%) of the most working age: from 40 to 60 years. Benign tumors accounted for 69.2%, malignant - 30.8% of cases.Among the primary benign tumors of the orbit, tumors of neurogenic origin predominated - 19.5%. Vascular tumors accounted for 15.4%, epithelial tumors (mainly of the lacrimal gland) - 9.4%. Less common were fibrous histiocytoma - 3.4%, fibroma - 1.5%, osteoma and lipoma - 1.2% each, etc. Congenital cysts and false tumors considered in the group of primary tumors were observed in 16.5% and 32, 2% of cases (Diagram 1).

Table 1 Patient characteristics

Parameter	Numbers of patients	Percentage (%)
Age		
mean	50 year	-
Range	25–85 year	-
Gender		
male	76	42,5
female	103	57,5
Tumortype		
malignant	56	31,2
benigntumors	123	68,8

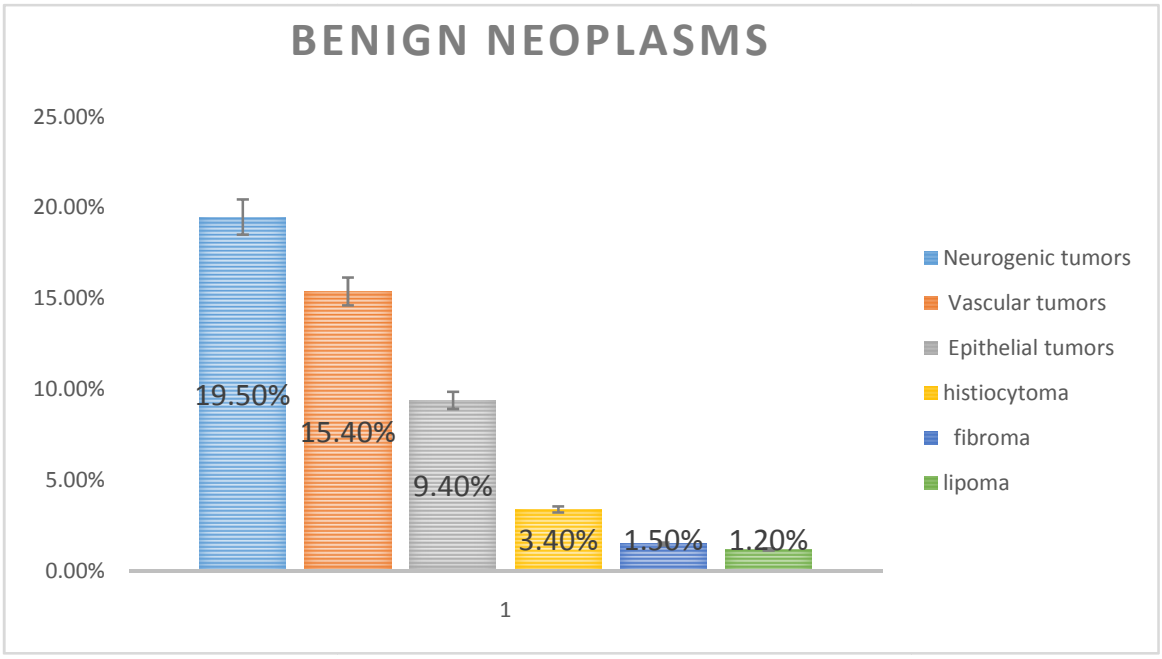

Diagram 1 distribution of patients with benign tumors

Among malignant neoplasms, lymphomas prevailed - 39.50%, undifferentiated sarcomas - 11.20%, rhabdo-myosarcomas - 4.80% are much less common. Malignant tumors of the lacrimal gland (adenocarcinoma, adenocarcinoma in pleomorphic adenoma) were observed in 22.80%, malignant paraganglioma - 4.70%, malignant histiocytoma - 3.8%, etc. (Diagram 2).

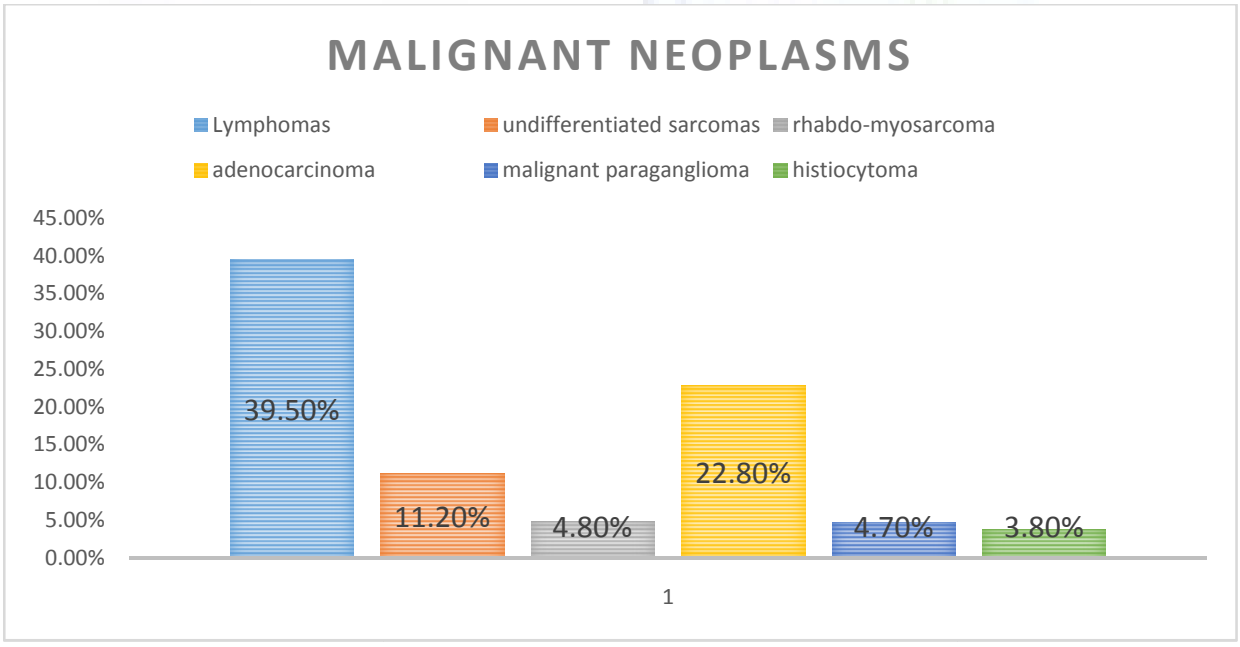

Diagram 2 distribution of patients with malignant tumors

All patients underwent standard clinical and instrumental studies, including visometry, biomicroscopy, ophthalmoscopy, exophthalmometry, perimetry. Removed neoplasms were examined by morphological methods.

Research results .Based on the calculation of the leukocyte formula, it was found that LII significantly (P <0.05) increases in all patients with orbital tumors, regardless of genesis, indicating the development of endogenous intoxication of a nonspecific nature.

Table 2 Comparative characteristics of leukoformula indicators for various orbital tumors

	Malignant tumor	**Benign tumor**
Parameter	**HR (95% CI)**	**HR (95% CI)**
Leukocyte index (LI)	1,088 (0,745 - 1,589)	0,895 (0.77-1,02)
Leukocyte intoxication index (LII)	1,244 (0,928 - 1,669)	1,18 (0,86-1,5)
Leukocyte shift index (LSI)	1,921 (1,19 3– 3,092)	3,155 (2,168 - 4,591)
Lymphocyte – granulocyte index (LGI)	2,492 (1,876 - 3,310)	1,715 (1.200 - 2.451)
Lymphocyte to eosinophil ratio (LTER)	1,558 (1,190 - 2,040)	1,385 (1,049 - 1,829)
Lymphocyte to Monocyte Ratio Index (LTMR)	0,81 (0,70-0,92)	1,352 (1,037 - 1,764)*
Index of the ratio of neutrophils and lymphocytes (IRNL)	1,676 (1,271 - 2,209)	1,392 (1,045 - 1,855)
Neutrophil to monocyte ratio (NTMR)	0,5 (0,34-0,7)	1,348 (0,954 - 1,904)*
General index (GI)	0,924 (0,712– 1.200)	0,67 (0,51-0,83)
Index of the ratio of leukocytes and ESR (erythrocyte sedimentation rate, sed rate)	3,54 (2,85 – 4,22)	2,93 (2,56-3,3)

Abbreviations: CI, confidence interval; Heart rate, hazard coefficient.

** Significantly (p <0.05).*

An increase in LII in pseudotumor by 1.5 times is associated with an inflammatory reaction in the tissues. A significant 1.8-fold increase in this indicator in individual patients (16%) with malignant tumors of the orbit (malignant lymphoma-lymphoma-lymphocytic type and rhabdomyosarcomas) is, in our opinion, a sign of an increase in the process of tissue decay of tumors.

An increase in LIESR in malignant ones up to - 3.54 ± 0.45 compared with benign neoplasms - 2.93 ± 0.32 - indicates an increase in the concentration of antibodies and autointoxication associated with the autoimmune process. This is also confirmed by an increase in GI by 1.4 times in patients with malignant tumors (malignant lymphomas, adenocarcinomas).

The simultaneous increase in LII and LIESR, revealed by us, speaks of the depletion of the T-lymphocytic link of immunity. The absence of changes in the indicators of LI and IRNL (the ratio of lymphocytes and segmental-nuclear neurophils), indicating a positive correlation of their content in the peripheral blood, may be associated with damage to the specific and nonspecific defense of the body, regardless of the type of tumor. The data of changes in the integral hematological parameters in patients with orbital tumors are presented in Table 2.

A significant 2-2.5-fold increase in NTMR in all types of tumors is considered by us as an increase in the activity of the microphage system against the background of a pronounced effector response. A

1.2-fold increase in LTER, which is more typical for patients with benign orbital tumors, is considered by us as a manifestation of delayed-type hypersensitivity.

An increase in LSI (by 2.2-2.6 times), also more pronounced in benign tumors, indicates, as we believe, the predominance of the affector link in the immunological process. CI is a generalizing indicator of the quantitative composition of peripheral blood leukocytes increased by 1.2-1.1 times compared to the norm, which, in our opinion, speaks of the adaptation of the body to the tumor process in the orbit. As our studies have shown, in the leukocytogram of patients who applied in the initial period of development of malignant tumors (1-3 months) and in the period from 2 to 4 years, the highest LIESR is noted, and with a long-term illness - more than 10 years - these indicators decrease to normal level, which may be associated with the chronization of the process and adaptation of the organism, or with the characteristics of a long-existing tumor.

With pseudo tumor, the indicators of LIESR, LSI, GI reach the norm in patients who are sick for more than a year, with benign tumors - more than 2-4 years, that is, during this period, according to these indicators, pseudotumor and benign tumors differ from malignant neoplasms, which also indicates, in our opinion, on the adaptation of the body, but at an earlier date.

We did not reveal a significant difference in indicators in the groups of patients with various types of orbital tumors depending on age, only in patients over 60 years old with malignant tumors we noted a decrease in LI and an increase in CI, which apparently characterizes a decrease in the activity of polynuclears and the development of breakdown in the peripheral blood cell system. In benign tumors, we found an increase in ISLM, with pseudotumor, an increase in addition to ISLM, and ISNM, which is associated with inhibition of the macrophogenic and effector links of immunity.We did not reveal any gender dependence in patients with malignant tumors in comparison with the initial data, but in women LIESR and GI were higher in benign tumors, LII and LSI in pseudotumor, which, in our opinion, indicates a decrease in the cellular component of immunity in these types tumors in female patients.

Integral hematological indices of benign tumors were significantly higher than normal ($P < 0.05$), with the exception of LI, ILH, IRNL; in patients with false and malignant do not differ from the norm LI, ILH, LTER; the rest of the indices were significantly higher than the norm.

Significant differences ($P < 0.05$) between benign and false tumors are noted in the LII and LTER indicators, between benign and malignant there are differences in the NTMR and ISLM indicators ($P < 0.05$). There were no statistically significant differences ($P > 0.05$) in hematological parameters between false and malignant tumors. The correlation coefficient between LII, LTER, NTMR and ISLM and the diagnosis “benign tumor” is 0.291, 0.265, 0.238 and 0.197, respectively; between the indicated indices and the diagnosis “false tumor” - 0.114, 0.276, 0.192 and 0.278, respectively, and between the listed indices and the diagnosis “malignant tumor” the correlation coefficient was 0.363, 0, 273, 0.269 and 0.283, that is, between the indicated indices and the diagnosis, according to our data, mainly a weak correlation.

Discussion. To predict a marker of infection and inflammation, the indicators of total and differential leukocyte count are historically considered. Despite this, its role has gone beyond the assessment of infectious processes, and today it is used as a prognostic marker to measure the results of the course and treatment of a tumor. The association between inflammation and tumors has long been known, compelling recent evidence suggesting a strong association between peripheral inflammatory cells before treatment and prognosis in different types of tumors [12,13,14,15].

Inflammatory processes lead to a chronic oxidative process and generate oxygen free radicals that stimulate the emergence, development and progression of tumors [16]. Here, we retrospectively

studied orbital tumors, based on medical records, to assess the prognostic values of the total number of leukocytes, neutrophils, lymphocytes, monocytes in a comparative aspect with other clinical factors. Our results confirmed the conclusions that factors such as the lymphocyte-to-monocyte ratio (ISRM and the neutrophil-to-monocyte ratio (ISNR)) were associated with benign tumors, while the leukocyte intoxication index (LII) was an unfavorable prognosis for patients with orbital tumors. More importantly, we found that an increased ratio of neutrophil lymphocytes and monocyte counts were significantly associated in benign tumors, while at the same time in malignant processes had a poor prognosis, which is confirmed by SaurabhBobdey (2017) with lower overall survival and did not depend on other variables to predict prognosis for patients with oral cancer [11].

These results are consistent with other published studies that indicate a role for monocyte counting (Tsai et al, n = 213) [12] and Perisanidis et al, n = 97 in predicting oral cancer patients [17].

There is evidence that in advanced cancer, the systemic host immune response is an important independent predictor of outcome, and measurements of the systemic inflammatory immune response before treatment can be used to independently predict cancer survival [17].

Sasaki A (2007) and colleagues studied the preoperative absolute monocyte count in patients who underwent liver resection for hepatocellular carcinoma and in patients who underwent liver surgery for colorectal metastasis and found that the absolute monocyte count before treatment was independent a prognostic indicator of tumor recurrence and survival [18].The monocyte index as an independent prognostic indicator has been obtained in breast cancer [19], Hodgkin's lymphoma [20], rectal cancer [18], and ovarian cancer [21].

Some authors have reported that neutrophils and other cells such as macrophages secrete factors that promote tumor growth, including vascular endothelial growth factor [22], IL-8 [23], matrix metalloproteinases and elastaseare likely to contribute to stimulation of the tumor microenvironment.

Conclusion

Thus, on the basis of calculating the ratios of the elements of the general blood test in patients with orbital tumors, it was revealed that, regardless of the origin of the neoplasm in the patient's body, against the background of suppression of the functions of effector cells, complex disorders of the microphage-macrophage system, endogenous intoxication develops, accompanied by delayed-type hypersensitivity. The duration of the tumor process, the age and gender of the patients have no significant effect on the level of integral hematological indices. A correlation has been established between some indices and a tumor diagnosis (benign, false, malignant), which allows us to recommend the determination of integral hematological indices as additional diagnostic tests for various types of orbital tumors, especially benign and malignant ones.

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