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Keywords: innate immunity. breast cancer, tcrγδ cells, b1-lymphocytes, nk cells, hematopoiesis.

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Bone Marrow Lymphocyte Populations of Innate Immunity in Breast Cancer Patients

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Abstract- The innate immunity system plays an important role in antitumor protection, and more and more attention has been paid to its study recent years. However, the interrelation of the effect or subpopulations of the cells of the innate immunity in bone marrow with clinical parameters is poorly studied. The paper presents data on the composition of innate immune cells in the bone marrow of 64 patients with operable breast cancer, as well as 10 women with benign processes in the mammary gland. As result a significant correlation between the molecular subtype of cancer and the level of B1-lymphocytes was identified. Breast cancer patients levels of NK cells (CD56 + CD3- and CD16 + CD3-) in the bone marrow were significantly higher in patients with low proliferative activity (Ki-67 less than 20%), compared to patients having a high tumor proliferation index. Populations of NK cells were interrelated with erythropoiesis in patients with breast cancer and were significantly higher in cases of reduced basophilic and polychromatophilicnormoblasts. A relationship was also found between bone marrow populations of plasma cells and B1-lymphocytes.

Keywords: innate immunity. breast cancer, tcrγδ cells, b1-lymphocytes, nk cells, hematopoiesis.

I. Introduction

The innate immunity system plays an important role in antitumor immunity, and more and more attention has been paid to its study in recent years. However, the interrelation of the effect or subpopulations of the cells of the innate immunity in bone marrow with flow and prognosis of oncologic diseases is poorly studied. The significance of innate immunity has been proven in sarcomas [1,2], gastric cancer [3], melanoma and other tumors. At present, innate immunity has the leading importance in oncology[4].

A significant number of works have been devoted to studying the characteristics of immunity in breast cancer. The role of tumor-infiltrating lymphocytes and, in particular, CD8 + cells in the prognosis of the disease at early stages (N0) has been proven [5]. Number of antitumor immunity effectors was increased in the bone marrow of patients [6].

Cellular lymphoid effectors of innate immunity are NK cells, B1-(CD5 +) lymphocytes, TCRγδ lymphocytes.

B1-lymphocytes in normal bone marrow can make up 5% of lymphocytes or less. They produce pentameric (IgM) antibodies which recognize tumor cells when interacting with their tumor-associated glycans, transport lipids into the tumor cells, and thus play the role of antibody effectors of innate immunity leading to lipoapoptosis [7,8].

TCRγδ - lymphocytes are considered to be one of the most "mysterious" subpopulations in immunology. They participate in many processes during the immune response, both innate and acquired, but further studies are still needed to uniquely determine their mechanism of action and clinical role. It has been shown that they produce many cytokines, chemokines, are capable of both presenting antigen and cytotoxicity. It is known that a change in the number of TCRγδ-lymphocytes has diagnostic and prognostic significance in some stages of rhabdomyosarcoma in children. [2] The works of the last ten years have shown that antiresorptive drugs (bisphosphonates) lead to an increase in the concentration of TCRγδ-lymphocytes, thereby causing an additional antitumor effect. [9,10]

Specific recognition of tumor cells by antibodies-effectors of innate immunity produced by B1-lymphocytes occurs when these antibodies interact with tumor-associated glycans of malignant cells [7]. Immunodeficiencies based on a deficiency in the blood serum of patients with breast cancer antibodies to tumor-associated Le^c glycan are described [11]. An important role in the mechanism of action of NK cells is played in cases of loss of HLA-I class molecules on cancer cells during tumor progression [5].

The bone marrow is the organ in which the generation and maturation of cells of innate and acquired immunity occurs. Some of them accumulate in the bone marrow, and the levels, as well as the subpopulation of these cells in malignant tumors, differ from the norm. According to our data, both the

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subpopulation of innate immune cells in the bone marrow and erythropoiesis in patients with malignant tumors have a number of peculiarities [12.13]. However, innate immunity in the bone marrow of patients with breast cancer has not been studied. That study is undoubtedly an urgent task, as it will allow a deeper understanding of the immune mechanisms of controlling the prolonged persistence of disseminated tumor cells in the bone marrow of these patients. This, in turn, can serve as the basis for the development of methods for influencing the immune system of the bone marrow in order to eradicate disseminated tumor cells.

II. Materials and Methods

The study was conducted in 64 patients with operable breast cancer. The age of women is from 28 to 77 years, the median is 56 years. 2 women with tumors in situ participated, 20 – with stage IA, 21 – with stage IIA, 10 – with stage IIB, 6 – with stage IIIA, 2 – with stage IIIC, and three patients had their stage which was not determined (treatment to the Oncology Research Center after non-radical operations in other institutions; when the histological preparations were reviewed, the diagnosis was confirmed, but there was no reliable information about the primary

All patients underwent morphological examination of the bone marrow (myelogram).

An immunological study of bone marrow subpopulations was performed by multicolor flow cytometry, the antibody panel for the study is presented in table 1.(Table1)

Table 1: Panel of monoclonal antibodies

Sample No.	Fluorochromes and antibody specificity							
	FITC	PE	PerCP-Cy5	PerCP-Cy7	APC	APC-H7	V450	V500
1.	CD20	CD95	CD27	CD5	CD3	CD19	CD4	CD45
2.	CD22	CD38	CD27	CD5	CD3	CD19	-	CD45
3.	CD4	CD25	CD3	TCRγδ	CD5	CD8	CD2	CD45
4.	CD16	CD45RO	CD3	CD56	CD94	CD8	CD2	CD45
5.	CD16	HLA-DR	CD3	CD56	CD94	CD8	CD2	CD45
6.	CD16	CD7	CD3	CD56	CD94	CD8	CD2	CD45
7.	Perforin	Granzyme	CD3	CD56	CD94	-	-	CD45
8.	CD57	CD26	CD3	CD56	CD94	-	-	CD45

Studies of subpopulations of bone marrow lymphocytes were performed in the gate of CD45 ++ cells with low side light scattering characteristics of the laser beam (SSC low). Samples 1 and 2 are destined to study the innate link of B-cell immunity (B1-cells). Sample 3 is a characteristic of TCR γδ-lymphocytes. Samples 4-6 are a characteristic of NK and NKT lymphocytes. Sample 7 is an assessment of the cytotoxic potential of T cells and NK cells. Sample 8 is additional markers of the characteristics of the subpopulations of T and NK cells.

Cell collection and recording of the corresponding files was performed on a FACSCANTO II flow cytometer. Data analysis was performed using the FCS 3 program.

Statistical data processing was performed using the SPSS program.

III. Results

One of the main tasks of the work was to study the indicators of innate immunity based on the levels of lymphoid cell subpopulations in bone marrow in breast cancer compared with benign processes, as well as to study these subpopulations in breast cancer, depending on the clinical and biological characteristics of the tumor.

From the number of B-cells of innate immunity, we studied mature (CD45 ++) B1-lymphocytes (CD19 +, CD20 +) of bone marrow expressing the CD5 molecule on the membrane. The natural killer cells (NK cells) studied in the work, included 2 subpopulations (CD56 + CD3 - and CD16 + CD3-), of course, mature T-cells (CD3 +) expressing these receptors (CD16, CD56) were studied along with it. In addition, TCRγδ-lymphocytes were studied from the number of T-cells of innate immunity.

Comparison of indicators for breast cancer and benign processes did not reveal significant differences. As a comparison, we evaluated the levels of mature T and B bone marrow lymphocytes in patients with breast cancer, which also did not differ. Only T-cells, of the studied subpopulations, expressing CD16 were slightly higher (differences are close to authentic, $p=0.055$) in patients with breast cancer compared with benign processes in the mammary gland: $3.4\pm0.89\%$ ($n=49$) and $1.45\pm0.4\%$ ($n=9$), $p=0.055$. For the remaining subpopulations, no differences were found.

When analyzing the clinical characteristics of the tumor and bone marrow subpopulations of TCRγδ-lymphocytes and B1-lymphocytes (CD19 or CD20) + CD5 +, we did not establish any correlation between the innate cellular immunity indices and tumor size, N index, histological type of tumor, the fact of lymph nodes damage, and localization metastases (axillary, subclavian, parasternal).

No significant differences were found in the level of bone marrow subpopulations of innate immunity cells in patients with breast cancer depending on the

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receptor status of tumor cells (estrogen, progesterone receptors, Her2 /neu).

Interesting and reliable interrelations between the subpopulation composition of bone marrow lymphocytes were found depending on the levels of proliferative activity of cancer cells (Ki-67), these data are presented in table 2. (Table 2).

Table 2: Subpopulations of cells of innate immunity in the bone marrow, interrelated with the level of proliferative activity (Ki-67) of cancer cells

Subpopulation of lymphocytes	KI67, %	N	Average	Std average error	p
CD56+CD16+ (%% among NK-cells)	>= 20,00	6	77,4500	4,20894	0,021
	< 20,00	4	91,8000	2,59551	
CD16+CD3-	>= 20,00	29	11,0890	1,20889	0,028
	< 20,00	17	15,8312	1,79148	
CD16+CD3+	>= 20,00	18	2,4067	,37303	0,045
	< 20,00	6	6,4883	3,27183	
CD56+CD3-	>= 20,00	30	9,4407	1,10127	0,009
	< 20,00	18	14,5806	1,60064	
CD3+	>= 20,00	32	62,9394	2,04285	NS
	< 20,00	19	62,0311	1,59818	
CD20+	>= 20,00	32	16,7394	1,54649	NS*
	< 20,00	21	13,1729	1,92918	

NS – differences are not statistically significant.

As it can be seen from the table, both studied subpopulations of NK cells (CD16 + CD3-, CD56 + CD3-) were reliably higher in patients with a low proliferative index (less than 20% Ki-67 + of tumor cells). Particularly significant differences were noted in CD56 + CD3-lymphocytes: 9.4% and 14.6%, p = 0.009.

It is interesting to note that the population of bone marrow NK-cells expressing both markers (CD16 + CD56 + CD3-) in all cases of breast cancer was dominant among NK-cells, but significantly prevailed in cancer with low proliferative activity (92% and 77 %, p = 0.021). This is a new feature that has not been previously described. Of course, the number of observations here is small (6 and 4), and it is necessary to continue the collection of material for more reliable information.

It is important to emphasize that the levels of T-lymphocytes expressing the CD16-receptor were significantly higher in patients with low proliferative activity of breast cancer cells. As a comparison, the table shows the levels of mature T and B bone marrow lymphocytes in patients with breast cancer, which did not differ depending on the proliferative index.

Molecular subtypes of breast cancer varied in levels of innate immune cells in the bone marrow. Significant differences were obtained when comparing the levels of B1-lymphocytes with luminal B Her2-negative and luminal B Her2-positive types, p = 0.032. The maximum levels of B1-cells were noted in these cases in the presence of the Her2 receptor (table 3).

Table 3: Levels of the cells of innate immunity in molecular subtypes of luminal B mammary tumors

	Molecular sub type	N	Average	Std average error	p
CD5+B-cells	luminal B (Her2-negative)	20	4,0030	0,79890	0,032
	luminal B (Her2-positive)	10	10,2170	3,60638	
TCRγδ-cells	luminal B (Her2-negative)	17	4,0147	0,52155	0,57
	luminal B (Her2-positive)	12	4,6567	1,11408	

When comparing the luminal B Her2-positive subtype to Her2-positive subtype lacking expression of estrogen and progesterone receptors, the same tendency for B1-lymphocytes remains, however, the data are unreliable (p = 0.066) due to the small number of observations in Her2 + receptor-negative group (n = 2).

Thus, there is a clear selectivity in the bone marrow indices of innate immunity depending on the molecular subtype of breast cancer. The percentage of B1-lymphocytes is the highest with the luminal B Her2-positive subtype.

One of the interesting and promising areas of bone marrow research in recent years has been the

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study of hematopoiesis and, in particular, erythropoiesis in tumors.

Levels of basophilic normoblasts were increased in comparison with the norm in only one patient (1.6%), in most cases (50 out of 62, 80.7%), this indicator was decreased, the normal range of oxyphilicnormoblasts was noted in 11 patients (17,7%). Polychromatophilicnormoblasts were increased in 4 patients (6.5%), decreased in 53.2% of cases and were within normal limits in 25 patients (40.3%). A completely different picture was observed regarding oxyphilicnormoblasts. These cells were increased in most patients (67.7%; 42 patients), and in the remaining cases were within normal limits - 20 patients, 32.3%. In general, the sum of erythroid cells was increased in 8.1% of cases (5 patients), was within normal limits in 36 patients (58.1%) and was reduced in 20 patients (32.3%).

We evaluated how the changes in erythropoiesis are related to the levels of cells of innate immunity, primarily NK-cells in the bone marrow of patients with breast cancer.

It is interesting to note that among the evaluated markers, only subpopulations of NK cells were associated with basophilic normoblast levels. Higher values of NK cells for both indicators were canceled in patients with a decrease in basophilic normoblasts. For the population of CD16 + CD3-, the indices in cases of a decrease in basophilic normoblasts amounted to 13.6 ± 1.2% (n = 36), in cases with a normal content of these cells – 7.9 ± 1.6% (n = 8), p = 0.013. For the population of CD56 + CD3-: 12.2 ± 1.2% (n = 38) and 7.5 ± 1.2% (n = 8), p = 0.012.

Similarly, polychromatophilicnormoblast levels were associated only with these two populations of NK cells. Higher levels of CD16 + CD3-cells were marked with a decrease in polychromatophilicnormoblasts in comparison with those at normal levels of these cells: 15.4 ± 1.3% (n = 26) and 9.1 ± 1.6% (n = 16), p = 0.004. Similar figures for the population of CD56 + CD3-cells: 13.7 ± 1.3% (n=27) and 8.5 ± 1.4% (n=17), p = 0.013.

No significant differences in NK cells were obtained for oxyphilicnormoblasts. A population with coexpression of CD16 and CD56 on NK cells predominated in patients with normal levels of oxyphilicnormoblasts compared with a group of patients with elevated levels of these cells, however, the number of observations was small: 89.7 ± 2.9% (n = 4) and 75 , 4 ± 4.3 (n = 5), p = 0.036.

Thus, our data indicate that NK cells of both subpopulations (CD56 + CD3- and CD16 + CD3-), as well as T / NK lymphocytes with the CD16 + CD3 + phenotype, prevail in patients with breast cancer with low proliferative activity, as the levels of proliferative activity rise, the content of these subpopulations in the bone marrow of patients reduces.

There is an interesting fact of the interrelation of nucleated cells of the erythroid series with the levels of NK cells of the bone marrow of patients with breast cancer. At reduced levels of basophilic and polychromatophilicnormoblasts, the content of NK cells was significantly higher.

When assessing the correlation of TCRγδ-lymphocytes with other subpopulations of bone marrow lymphocytes, reliable interconnections were established only with CD5 + B cells: R = 0.28; p = 0.044; n = 52. It is interesting to note that this subpopulation, as well as TCRγδ lymphocytes, belongs to innate immunity, which is of undoubted interest. These data were obtained by analyzing the entire patient population - breast cancer patients and patients with benign changes in breast tissue. Therefore, it was of interest to evaluate the presence of correlations in these 2 groups separately.

Indeed, there was no correlation between CD5 + B lymphocytes and TCRγδ lymphocytes (p> 0.05) in patients with breast cancer. On the contrary, the correlation between these two subpopulations was very high in patients with benign diseases: R = 0.757; p = 0.03; n = 8. Thus, a kind of “imbalance” occurs between the cells of innate immunity in the bone marrow in breast cancer, and the high correlation of TCRγδ-lymphocytes with CD5 + B-lymphocytes is lost.

However, it is important to keep in mind that despite the high correlation coefficients and the reliability of the relationship, the number of patients in the comparison group with benign processes is small (10 patients), and therefore further accumulation of material is necessary.

The correlation of TCRγδ-lymphocytes with the cell types and indices allocated in the myelogram, as a whole, was absent for the studied group of patients. Similarly, there were no corresponding associations in patients with breast cancer. It is interesting to note that in benign breast diseases, an inverse reliable correlation was established between TCRγδ-lymphocytes and the erythroid cell maturation index: R = -0.688; p = 0.04; n = 9.

In general, a significant correlation between B1-(CD5 +) lymphocytes and eosinophilicmyelocytes (R = 0.331; p = 0.012; n = 57), as well as with plasma cells (R = 0.399; p = 0.002; n = 57) was observed in the examined group. Patients with a reduced or normal content of segmented neutrophils showed significantly higher levels of these cells (CD5 + B-lymphocytes) compared with cases of increased segmented neutrophils: 8.1 ± 1.8% (n = 39) and 2.0 ± 0, 5% (n = 19); p = 0.002. In patients with breast cancer, the same interdependence was noticed: for eosinophilicmyelo-cytes, R = 0.365; p = 0.011; n is 48; for plasma cells, R = 0.409; p = 0.004; n = 48. The average levels of CD5-positive B-lymphocytes were also significantly higher in patients with normal or reduced values of segmented neutrophils in comparison to

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cases of increase in these cells: 8.5 ± 2.0% (n = 33) and 1.7 ± 0.47% (n = 16), p = 0.003. The indicated correlations were not observed in patients with benign processes: the only inverse correlation between the population of CD5 + B-lymphocytes was established with the number of monocytes: R = -0.953; p = 0.002, n = 9.

IV. Discussion

In recent years, innate immunity has attracted a lot of attention from oncologists. The discovery of a specific mechanism for the destruction of tumor cells - lipoapoptosis - marked a new stage in the development of immuno-oncology (8). This can be called a turn to the humoral immunity, or rather - to the innate component of this link of immunity - B1-lymphocytes. It is natural pentamerIg M-antibodies that are able to specifically bind to tumor-associated glycans of cancer cells and transport lipids in them, leading to the death of malignant cells.

Deficiencies of antibodies to tumor-associated glycans in breast cancer have been proven in approximately 35% of cases (14). Breast cancer with the expression of some tumor-associated carbohydrates on the membrane (e.g., Le^C) is characterized by poor prognosis in the early stages (15,16).

Natural IgM antibodies are produced by B1(CD5+)-lymphocytes, for this reason we have paid considerable attention in the work to this particular population of bone lymphocytes.

The role of NK-cells in tumors has been the subject of a large number of publications. In the context of immunophenotypic characteristics, some differences in the subpopulations of NK cells in cancer patients are described. In general, pronounced NK cell tumor infiltration is usually associated with a better prognosis. This has been demonstrated for lung and stomach tumors, colorectal cancer, and head and neck tumors. However, there is evidence that there is no correlation between NK cell levels and prognosis, or even, on the contrary, the association of NK cell infiltration with a more aggressive, advanced stage of the tumor process, in particular with breast cancer [17-20]. Obviously, these contradictions may well be explained by differences in the receptor repertoire of tumor-infiltrating NK cells, which drastically affects their functions. The functional inferiority of NK cell subpopulations revealed in cancer patients is naturally reflected in the change in the immunophenotypic characteristics of NK cell subpopulations. Thus, tumor-infiltrating NK cells of non-small cell lung cancer show a particular immunophenotype and were characterized by weak expression or complete absence of CD57, DHAM, NKp30 NKG2A antigens. While the expression of CD127 was distinct, and an increase in the proportion of these cells was associated with tumor progression [21]. Certain features of the immunophenotype of NK cells isolated from pleural effusion in cancer patients were also identified [22,23]. There is no unified concept regarding tumor-infiltrating NK cells, and their biological features, as well as prognostic significance, require detailed study.

Immature NK cells arise from a precursor in the bone marrow and are characterized by the expression of CD56 + CD94 +/- NKG2A / C-KIR-. Further differentiation consists in increasing expression levels of CD56 ++. At this stage, the cells do not yet express CD16, are characterized as NKG2A +, NKG2C +/-, KIR-. Further, the expression levels of CD56 become weak, CD16 appears; NKG2A + NKG2C +/- KIR +/-. The next stage of differentiation is the occurrence of KIR diversity: cells still express CD16, NKG2A is lost; NKG2C +/-, KIR receptors are stably expressed (KIR +). At the terminal stage of NK cell differentiation, adaptive NKG2C ++ cells similar to memory cells arise. They retain the expression of CD16, NKG2A are absent, the cells are iKIR +. This is the stage of clonal expansion and survival of NK cells [24].

Bone marrow NK cells, which we described in this study in patients with breast cancer, were mainly quite mature cells coexpressing CD56 and CD16, and this fraction was in all cases prevailing among NK cells and significantly more pronounced in patients with a low index of proliferation of tumor cells. It is not entirely clear today whether this means that as breast cancer progresses, levels of effector (CD16-positive) NK cells decrease.

In general, NK cells of both subpopulations (CD56 + CD3- and CD16 + CD3-) decreased as the proliferative activity of breast cancer cells increased, and this parallelism is probably due to coexpression of these molecules on the patient's bone marrow NK cells.

Other patterns are noted for T / NK lymphocytes. Here, a decrease was noted only for cells with the CD16 + CD3 + phenotype (but not CD56 + CD3 +), which prevailed in patients with breast cancer with low proliferative activity, and decreased as the levels of proliferative activity increased.

According to B. Fisher [25], about 35% of breast cancer patients have clinically detectable metastases during the detection of the primary tumor, in addition, another 30–35% of patients have micrometastases, which subsequently manifest clinically. Therefore, the number of studies and publications on macro- and micrometastases of cancer is growing: the detection and study of their correlations with clinical parameters. For this, new methods are used which are much more sensitive than the examinations included in the "gold standard": from PET-CT and MRI studies [26-28] to the study of bone marrow aspirates using multicolor flow cytometry, immunocytochemical [29] and other cytological methods [30,31]. Bone marrow is one of those organs where single tumor cells

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and micrometastases are most often found, both in an active and in a "dormant" state. This is due to the intensity of blood supply to the bone marrow and its components - immune, stromal, hematopoietic cells of different degrees of maturity, to many different growth factors and other cytokines [32]. Therefore, it seems necessary to study the populations of bone marrow cells in cancer patients in the presence and absence of micrometastases.

The study of hematopoiesis in patients with breast cancer revealed a number of patterns that we had noted in earlier studies with squamous cell carcinoma of the head and neck, melanoma, and also with lymphomas [12,13]. A decrease in the populations of basophilic and polychromatophilicnormoblasts and an increase in oxyphilic forms have been established. It is important to note that such observations often occurred in cases of bone marrow involvement in the tumor process, for example, with melanoma [13]. In this study, we did not provide data on the presence of breast cancer micrometastases in the bone marrow; there was no lesion in all cases at the morphological level. A completely new fact described in this work was the establishment of the interrelation of altered erythropoiesis with levels of NK cells in the bone marrow.

In this work, a reliable inversely proportional relation of CD5 + B lymphocytes with myeloid cells — eosinophilicmyelocytes and segmented neutrophils — was shown for breast cancer.

According to the myelogram an increase in the level of plasma cells was significantly more often detected with an increased level of B1-lymphocytes in the bone marrow. It was previously established that the presence of accumulations of plasma cells can be attributed to the earliest manifestation of the presence of tumor cells in the bone marrow: bone marrow micrometastases were immunocytologically determined in 100% of patients in whose punctures accumulations of plasma cells were registered [33]. Thus, it can be assumed that an increase in the level of B1-lymphocytes is associated with a higher probability of micrometastatic damage to the bone marrow by a tumor.

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