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DEPENDENCE OF IMMUNE REACTIONS ON THE STAGE OF ONCOLOGICAL DISEASE

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Summary. 612 people with oncological diseases of various localization were examined. It has been established that immune responses in malignant neoplasms differ depending on the stage of the disease. At the initial stages (I-II), a cytokine reaction develops, antibody formation with the participation of IgE against the background of inhibition of phagocytic activity, which is associated with the reorientation of the phagocyte to exocytosis. At III-IV stages of cancer, the activity of cytokine and reagin reactions increases in parallel with autosensitization. This period of the disease is characterized by an increase in the phagocytic activity of neutrophils.

Keywords: immunity, oncology, cytokines, deficiency, natural killers, phagocytosis, autoantibodies, IgE.

The main protective role in the body in the fight against a tumor belongs to the immune system, a violation of its functioning leads to the failure of antitumor protection. Therefore, understanding the features of the immune response in the tumor process underlies the development of effective immunotherapy. The difficulty lies in the fact that the mechanisms that provide antitumor immunity are no different from those in anti-infective immunity, allergies, and autosensitization. It seems that it is the mixing, the formation of antigenic stress during the immune response to a tumor, the presence of a large number of qualitatively different autoantigens, the addition of a reagin defense mechanism and autoimmune damage that cause the ineffectiveness of immune responses in malignant neoplasms [33]. It is known that an immune response is formed to tumor cells both by cellular and humoral pathways, which is confirmed by their infiltration by lymphocytes, macrophages, dendritic cells, etc. [34]. At the same time, the formation of a specific tolerance of the immune system to a tumor in many people is beyond doubt [19, 31]. The specificity of tumor tolerance is also proved by the fact that cancer patients show a normal immune response to any other foreign antigens, infection, or transplant [7, 11, 26]. However, the positive effect of tumor regression upon vaccination with various tumor-specific vaccines is negligible and does not exceed 2.5% [28].

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Aim: to determine the characteristics of immune responses depending on the stage of oncological disease.

Materials and methods. 612 people with cancer of various localization who applied to the medical company "Biokor" (Arkhangelsk) were examined, 103 of them with stomach cancer, 105 with colon cancer, 112 with rectal cancer, 163 with breast cancer, 129 with cancer uterus. Cytogram and phagocytic activity of neutrophilic granulocytes were studied in smears of peripheral venous blood stained according to Romanovsky-Giemsa. Expression of markers of T-helper cells and natural killer cells was determined on lymphocytes by indirect immunoperoxidase reaction and flow cytometry (Epics XL, USA). In blood serum, the content of cytokines IL-6, TNFα (Bender MedSystems, Austria), anti-dsDNA, anti-RNP, IgE was determined by enzyme immunoassay using Multiscan MC (Finland) and Evolis (USA) analyzers. The results of the study were processed using the Statistica 6 software package (StatSoft, USA). To test the statistical hypothesis of the difference in values, the Shapiro-Wilk test was used. Significance of differences $p < 0.017$. Correlation analysis of the parameters was performed taking into account Spearman's rank correlation. The critical level of significance in testing statistical hypotheses was $p < 0.05$.

Results and discussion. Malignant neoplasms can form systemic immune responses; in all cases of accidental detection, not yet treated, and regardless of the location and type of tumor, patients quite often have an increase in the concentration of TNFα and IL-6, as well as autoantibodies to dsDNA and IgE (Table 1).

Attention is drawn to the most frequent increase in blood levels of interleukins and autoantibodies to double-stranded DNA in neoplasms of the large intestine and rectum. What this means is difficult to say now, but perhaps this is a reflection of the characteristics or advantages of immunocompetent intestinal tissue. Gut associated lymphoid tissue (GALT) is known to be one of the largest organs in the immune system, contains more than 1012 cells and produces the largest amount of cytokines and secretory IgA and IgE. In addition to diffusely located immunocompetent cells, phagocytes, T- and B-lymphocytes, plasma cells, the immune tissue of the intestine is represented by organized lymphoid structures in the form of an appendix, mesenteric lymph nodes and Peyer's patches. Peyer's patches are lymphoid follicles, the epithelium of which is represented mainly by M-cells, forming a cavity, called a package, in contact with lymphoid tissue. The bags contain polymorphonuclear leukocytes, macrophages, T- and B-lymphocytes, and plasma cells. Particularly rich in immunocompetent cells is the lamina propria mucosa, which consists of connective tissue located between the muscular layer of the mucosa and the epithelium. The lamina propria contains macrophages, mast cells, lymphocytes and plasma cells, as well as granulocytes, including eosinophils. Among the epithelium of lamina propria are intraepithelial lymphocytes. Statistically significant positive relationships were established between the concentrations of cytokines, autoantibodies, and reagins ($r = 0.75$, $p < 0.001$), from which it follows only that cell transformation and damage causes the appearance of autoantibodies, which requires an increase in the immune response from eosinophils and obese cells.

The ineffectiveness of the mechanisms of antitumor protection of innate immunity can be due to several reasons. Before decay, the tumor actually contains nothing foreign, it is not noticed by natural killers and phagocytes [13, 14, 24]. In any case, in malignant neoplasms,

Table1

The frequency of registration of signs of a systemic immune response in patients

Diagnosis	Increased blood levels, %			
	TNFα > 20 pg/ml	IL-6 > 20 pg/ml	Anti-dsDNA> 50 IU/ml	IgE> 100 ME/ml
Stomach cancer	31.57	26.32	55.26	44.74
Colon cancer	**47.37**	**57.89**	**73.68**	63.16
Rectal cancer	**81.82**	**68.18**	**77.27**	59.09
Mammary cancer	31.43	22.86	37.14	25.71
Uterine cancer	36.36	27.27	45.45	54.55

a deficiency of phagocytic protection (<50% active) on the part of neutrophilic granulocytes was recorded almost always (93.95%), except for a few cases (Table 2). It seems that everything begins with a lack of phagocytosis. However, the deficiency of phagocytic protection cannot be used as a risk criterion due to the wide distribution (up to 33%) of this defect among practically healthy people at the time of examination [1, 2]. In more than half of the cases, low levels of natural killers (CD3-CD16+CD56+; NK) and T-helpers were recorded in the peripheral blood (Table 2).

Thus, in malignant neoplasms, a high frequency of a deficiency in phagocyte activity, the content of natural killers and T-helpers in the blood, as well as elevated levels of IL-6, TNFα, with activation of the reagin defense mechanism and an increase in the concentration of autoantibodies, is recorded. Phagocytes, especially macrophages, damage the tumor cell by antibody-dependent cytolysis and subsequent utilization of cell debris. The decrease in the importance of phagocytic protection during tumor transformation may be due to a deficiency in phagocytic activity, inhibition of chemotaxis factors or phagocyte secretion products. The activity of natural killers ensures the body's natural resistance to a tumor, protects against metastasis, and participates in the formation of an adaptive level of IFNγ. IL-6 is known to be the most sensitive marker of tissue damage. Fever, leukocytosis, the content of acute phase proteins, increased vascular permeability are comparable with the release of IL-6 [27, 30]. An increase in the expression of the IL-6 gene by cells occurs under the influence of IL-1β, tryptase, histamine, or upon direct stimulation by mast cells [8]. IL-6 induces the transcription of acute phase protein genes and enhances the production of cortisol, which inhibits the expression of proinflammatory cytokine genes [18, 21]. An increase in the content of activated T-lymphocytes by increasing the energy resource of the cell against the background of elevated concentrations of IL-6 is explained by its stimulating effect on glycogen production, lipolysis and fat oxidation, and ATP synthesis. According to our studies, an increase in the content of IL-6 in the blood is associated with the activation of lymphocyte recirculation and with an increase in the concentration of T-lymphocytes with the transferrin receptor [3]; this is understandable, because IL-6 is the main inducer of the key regulator of iron levels – hepcidin.

The question of the possible role of the protective action of reagins has not been studied. The reaginic reaction is the fastest and appears almost instantly. Due to the release of a large number of chemoattractants, eosinophils, neutrophils, macrophages, and lymphocytes are attracted, which prolongs the reaction of antibody-dependent cytotoxicity. IgE are involved in antigen presentation; in addition, they can directly participate in the maturation of dendritic cells and activate the specific proliferation of T-lymphocytes [4]. Binding of reagins to receptors on basophils and eosinophils contributes to the release of large amounts of histamine and IL-4, IL-5, IL-13 [22]. It seems that an increase in the activity of antibody-dependent reactions is an informative criterion for prolonging the course of almost any pathological process and has a prognostic value. It can be considered that an increase in the content of IgE in the blood of patients with malignant neoplasms enhances various protective reactions, including hemodynamic reactions, and can be used in a complex of diagnostic signs.

An unfavorable prognosis for the course of the disease is associated with tumor metastasis. There is evidence that an unfavorable course is associated with an increase in the content of activated CD3+CD4+CD25+, CD3-CD4+CD25+, and CD4+CD25+Foxp3+ T cells in the peripheral blood [10, 12, 29, 32]. Perhaps these associations arise, but do they reflect the further development of the immune response to the tumor? The opinion that activated cells in the immune response to a tumor have nothing to do with tumor cytotoxicity reactions is rather doubtful. On the contrary, activated cells are able to block cytotoxic T cells [23, 26]. After all, the immune response, accompanied by lymphoproliferation, significantly exceeds the level that is necessary for an adequate immune response. And not all activated lymphocytes will be included in the number of cells for subsequent differentiation; most of them undergo apoptosis. But the main question in this situation is the question of the specific weight of suppressors in the composition of differentiated T cells. Does the degree of activating and suppressing activity remain proportional in this case as well? If this proportionality is preserved, as in an adequate immune response, then the inductor cells responsible for the activation of differentiation themselves become the target of the suppressor action. In this case, the degree of suppressor activity increases in proportion to the number of activated cells. Cytotoxic T-lymphocytes

Table2

The frequency of registration of defects in immune defense in patients, %

Diagnosis	Active phagocytes < 50 %	NK content in blood < 0,25×109cell/l	CD3+CD4+ content in blood < 0,40×109 cell/l
Stomach cancer	59.22	56.31	65.52
Colon cancer	51.43	55.34	61.05
Rectal cancer	61.61	60.71	74.29
Mammary cancer	57.03	52.15	51.53
Uterine cancer	54.21	61.24	55.81

(CD3+CD8+) of immune donors cause lysis of tumor cells under in vitro conditions, and spontaneous tumor disintegration under in vivo conditions in the experiment. At the same time, CD3+CD8+ retain their specific activity in cell culture for up to 6-12 months. However, it is interesting that even with the most unfavorable outcome, the CD3+CD8+ content always remains very high, often significantly exceeding the concentration of CD3+CD4+ [5, 6, 25].

We found that, regardless of localization, in stages III-IV of cancer, the frequency of registration of deficiency of actively phagocytic neutrophils is lower (average 38.54±0.43%) compared with stages I-II - 59.68±0.56% ($p < 0.001$) and higher frequency of detection of elevated IgE concentrations (respectively 79.33±1.29% in stages III-IV and 65.38±0.92% in stages I-II, $p < 0.01$). The assessment of the significance of this reaction is probably ambiguous; maybe this is a signal that an alternative risky defense mechanism is being used, or maybe this is a sign of using the last reserve to fight the tumor. But, at least, there is every reason to believe that such a reaction is necessary and useful for enhanced clearance of tumor decay products from the body. The relationship between the content of serum IgE and pro-inflammatory cytokines in the blood is quite constant in adults. It is usually positive and stronger in various pathological processes associated with inflammation and destruction. The relationship between the content of pro-inflammatory cytokines and autoantibodies is largely stable and strong.

Deficiency of phagocytic protection at the level of blood neutrophils active in phagocytosis <50% among all those examined with malignant neoplasms is detected on average in 49.48±1.62%. At stages III and IV of the disease, the concentrations of cytotoxic lymphocytes, % of active phagocytes, and the concentration of autoantibodies are significantly higher than at the initial stages of the disease (Table 3).

In inflammatory processes, the facts of an increase in the content of autoantibodies to a wide range of cytokines and nuclear proteins are known [9, 20, 35]. As can be seen from the presented data, the frequency of registration of elevated concentrations of autoantibodies to double-stranded DNA and the ribonucleotide complex is noticeably higher in III and IV stages of the disease. The average concentrations of anti dsDNA were not high and, depending on the stage of the disease, ranged from 41.87 ± 0.38 - 57.29 ± 0.42 IU / ml at stages I-II and 48.15 ± 0.31 - 86, 29±0.34 IU/ml at III and IV stages. Thus, autosensitization during tumor decay is confirmed not only by an increase in the frequency of registration of elevated levels of autoantibodies, but also by an increase in their concentrations.

Table3

The frequency of registration of elevated concentrations in the blood of CD8+, active phagocytes and autoantibodies in patients, %

Cancer, localization, stage	CD8+ > 0,4×109 cell/l	Active phagocytes > 65 %	Anti-dsDNA> 50 IU/ml	Anti-RNP >1,0 IU/ml
Stomach cancer I-II stage (n=41)	43.90	31.71	29.26	36.58
Stomach cancer III-IV stage (n=62)	**90.32**	**88.71**	**90.32**	**93.55**
Colon cancer I-II stage (n=48)	47.92	43.75	39.58	35.42
Colon cancer III-IV stage (n=57)	**89.47**	**85.96**	**82.46**	**71.93**

Conclusion. Deficiency in the content of actively phagocytic neutrophilic granulocytes in malignant neoplasms is a known fact. An increase in the activity of phagocytes in an unfavorable course of the disease with metastases and tumor decay requires an explanation. Neutrophil granulocytes perform an important effector function in the immune response. Neutrophils, through the generation of cytokines, chemokines, expression of receptors, etc., modulate cell functions, regulating the formation of the immune response, as well as the development of apoptosis. The literature today is rapidly replenished with facts about the regulatory role of neutrophils. Neutrophilic granulocytes secrete various proteolytic enzymes, reactive oxygen species, as well as acid hydrolases, cathepsins and collagenases that destroy cells and intercellular structures. The literature contains numerous data on the function of vesicular structures in inflammation, angiogenesis, and oncopathology [15, 16]. It is known that neutrophils differentiate into phagocytes and cells with predominantly secretory functions. Functionally, different neutrophilic granulocytes differ in the set of membrane receptor structures. The low phagocytic ability of neutrophilic leukocytes coincides with low extracellular activity and high superoxide-anion-forming ability (NST-test), which is most often detected in chronic inflammatory processes.It seems that in malignant neoplasms, neutrophilic granulocytes are oriented towards extracellular activity, and therefore a sharp decrease in the percentage of active phagocytes and a high frequency of its deficiency are recorded. Activation of the reagin defense mechanism during this period is probably necessary to stimulate the migration, chemotaxis of neutrophils and their phagocytic capacity. A feature of reagins is their ability to bind conformational epitopes, while other immunoglobulins recognize linear protein epitopes [17]. This ensures the formation of an antibody-dependent cytotoxicity reaction even at a very low antigen concentration. The activity of the reagin reaction is significantly enhanced by the activation of cells that express the high-affinity IgE receptor (FcεRI) on their surface - eosinophils, basophils and mast cells. These cells have a wide range of secreted cytokines, vasomotor amines and other biologically active substances, thus modulating the intensity of the immune response, leading to a more severe reaction of antibody-dependent cytotoxicity. The concentration of IgE and inflammatory mediators affects the severity of the protective reaction. At the same time, too hyperreaction of antibody-dependent cytotoxicity can cause the formation of a pathological process associated with damage to the body's own tissues.

High concentrations of autoantibodies damage through activation of the complement system and are associated with very extensive damage [7]. In turn, cell damage causes, through Toll-like receptors, the launch of a cascade of reactions leading to the synthesis of inflammatory mediators - chemokines, adhesion molecules, acute phase proteins, cytokines, etc. The production of cytokines - interleukins, neurotransmitters, vasomotor amines, neuropeptides and hormones that provide migration, cooperation, proliferation, differentiation and suppression of the activity of cells involved in the reactions of preventive and pathological inflammation. A local increase in the concentration of cytokines is necessary to cope with the local problems that have arisen; an increase in the content of cytokines in the blood indicates the need for systemic regulation. Damage to the cellular structure induces the release of

the most significant concentrations of cytokines and the expansion of their spectrum of activity.

So, immune responses in malignant neoplasms differ depending on the stage of the disease. At the initial stages of the disease, a cytokine reaction develops, antibody formation with the participation of IgE against the background of inhibition of phagocytic activity, which is associated with the reorientation of the phagocyte to exocytosis. With the disintegration of the tumor and metastasis, the activity of cytokine and reagin reactions increases in parallel with autosensitization. During this period of the disease, the activity of phagocytes increases. The main question in this situation is to find out what provides the deficiency of phagocytic protection during the period of tumor formation? Elucidation of this problem will provide new knowledge about the pathogenesis of malignant neoplasms.

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