IMMUNE RESPONSES ASSOCIATED WITH HODGKIN LYMPHOMA

Patrakeeva VP ✉, Dobrodeeva LK

N. Laverov Federal Center for Integrated Arctic Research, Ural Branch of the Russian Academy of Sciences, Arkhangelsk, Russia

HL is characterized by significantly enlarged lymph nodes and the presence of rare Hodgkin and Reed-Sternberg cells. Pathogenesis is not fully understood. The increase in the disease risk can be associated with immunosuppression, HIV, parenchymal organ transplantation, autoimmune disorders, etc. The possibility of differentiating pathogenetic and protective immune responses associated with this disease will help understand the causes of the disease and the treatment prognosis. The study was aimed to determine the features of immune responses in HL depending on the disease duration and the circulating lymphocyte counts. A total of 134 patients with HL were assessed. The cytogram and phagocytosis were assessed in blood smears stained by the Wright-Giemsa procedure. The expression of lymphocyte markers in lymphocytes was determined using the indirect immunoperoxidase technique and flow cytometry. Serum levels of cytokines, immunoglobulins, autoantibodies and circulating immune complexes were assessed by enzyme immunoassay. Comparative analysis of the immune responses depending on peripheral blood leukocyte counts is provided. It has been found that prolonged HL course is associated with the decrease in the functionally active T cell counts, progressive neutropenia and monocytopenia, along with the increased activity of the reaginic reactions and autosensitization. In individuals with lymphocytopenia, mainly small lymphocytes die, the 3-fold decrease in the counts of such lymphocytes is observed; lymphocytopenia is associated with the deficiency of circulating T cells, both mature and immature, the concentrations of which decrease by 2.5–3 times, while B cell counts show no dramatic changes. The disease progression is associated with reduction of the lymphocyte homeostasis control by granulocytes and monocytes, along with progressive neutropenia and monocytopenia.

Keywords: Hodgkin disease, autosensitization, lymphopenia, lymphocytosis, reagins, antibody-dependent cytotoxicity

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✉ **Correspondence should be addressed:** Veronika P. Patrakeeva
Nikolsky prospect, 20, Arkhangelsk, 163020, Russia; patrakeewa.veronika@yandex.ru

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ИММУННЫЕ РЕАКЦИИ ПРИ ЛИМФОМЕ ХОДЖКИНА

В. П. Патракеева ✉, Л. К. Добродеева

Федеральный исследовательский центр комплексного изучения Арктики имени Н. П. Лавёрова Уральского отделения Российской академии наук, Архангельск, Россия

ЛХ характеризуется значительным увеличением лимфатических узлов и наличием редких клеток Ходжкина и Штернберга–Рид. Патогенез до конца не изучен. Риск развития может увеличиваться при иммуносупрессии, у пациентов с ВИЧ, трансплантацией паренхиматозных органов, аутоиммунными состояниями и т. д. Возможность дифференцировать патогенетические и защитные иммунные реакции при этой болезни позволит помочь разобраться в причинах заболевания и прогнозах лечения. Цель работы — определить особенности иммунных реакций при ЛХ в зависимости от длительности болезни и уровня циркулирующих лимфоцитов. Обследовано 134 пациента с ЛХ. Цитограмму и фагоцитоз изучали в мазках, окрашенных по Романовскому–Гимзе. На лимфоцитах методами непрямой иммунопероксидазной реакции и проточной цитометрии определяли экспрессию маркеров лимфоцитов. В сыворотке крови методом ИФА определяли содержание цитокинов, иммуноглобулинов, аутоантител и циркулирующих иммунных комплексов. Проведен сравнительный анализ иммунных реакций в зависимости от содержания лимфоцитов в периферической крови. Установлено, что длительное течение ЛХ сопряжено со снижением числа функционально активных Т-лимфоцитов, нарастанием нейтропении и моноцитопении, на фоне повышения активности реагиновых реакций и аутосенсибилизации. При лимфопении погибают преимущественно малые лимфоциты, их концентрация снижается в 3 раза; лимфопения ассоциирована с дефицитом циркулирующих Т-лимфоцитов и касается как зрелых, так и незрелых Т-клеток, концентрации которых в крови падают в 2,5–3 раза, при этом содержание В-лимфоцитов не претерпевает резких изменений. Прогрессирование болезни сопровождается сокращением резервов регуляции лимфоцитарного гомеостаза со стороны гранулоцитов и моноцитов с нарастанием нейтропении и моноцитопении.

Ключевые слова: лимфома Ходжкина, аутосенсибилизация, лимфопения, лимфоцитоз, реагины, антителозависимая цитотоксичность

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✉ **Для корреспонденции:** Вероника Павловна Патракеева
пр. Никольский, д. 20, г. Архангельск, 163020, Россия; patrakeewa.veronika@yandex.ru

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Lymphogranulomatosis (Hodgkin lymphoma, HL) is lymphoproliferative disease, the etiology of which is still being debated. First of all, the issue of the origin of cells affected by this disease is addressed. In fact, the lymph node is transformed into granuloma, in which the clusters of lymphoid, reticular, plasma cells, granulocyte neutrophils and eosinophil granulocytes are unevenly distributed. Mononuclear Hodgkin cells (cells with a strongly basophilic cytoplasm and large nucleoli that actively divide) are the main diagnostic feature. The Hodgkin cell is transformed into the multinucleate Reed–Sternberg cell, having cytoplasm with fewer basophils and low division rate, via endomitosis [1]. Such cells actively interact with their microenvironment, create optimal conditions for growth due to the cell proliferation autocrine and paracrine mediators, apoptosis inhibition and suppression of cytotoxic cells [2]. The Reed–Sternberg cells lose most of their B-cell identity, including B cell receptors, and do not undergo programmed cell death. It is well known that immunosuppression (HIV, infections caused by Epstein–Barr virus, autoimmune diseases, etc.) significantly increase the risk of lymphoma [3]. Infections caused by such viruses, as respiratory syncytial viruses, adenoviruses, parainfluenza viruses, coxsackievirus and echoviruses, herpes viruses and many other viruses, have a cytopathic effect, i.e. cause degenerative changes in the cellular structures affecting future cell proliferation, and have an anti-apoptotic effect. These infections equally affect cells of different origin having no lymphoid elements. Studying the features of the immune system function in individuals with proliferative disorders is necessary to understand the body's immune defenses against this disorder.

METHODS

A total of 134 patients with the final diagnosis of HL, who contacted the Biocor Medical Center (Arkhangelsk, Russia), were studied. The immune status and blood counts of patients were assessed during remission. Inclusion criteria: patients of both genders; duration of the disease of 2–18 years; duration of remission of 5 months to 2.5 years. The diagnosis was confirmed by histological examination: the Hodgkin cells were found in all cases, and the Reed-Sternberg cells were found in 78 patients (58.21%). When making a diagnosis, the mixed cell lymph node involvement was detected in 98 patients (73.13%), while in other cases nodular sclerosis prevailed. Localization of the lymph nodes involved was as follows: mostly axillary (125 cases; 93.28%), mediastinal (65 cases; 48.51%) or inguinal (52 cases; 38.81%); the cases of submandibular lymph node involvement were rare (21 patients, 15.67%). The cytogram and phagocytosis were assessed in blood smears stained by the Wright-Giemsa procedure, the numbers per 100 cells were counted. The expression of lymphocyte markers in lymphocytes was determined using the indirect immunoperoxidase technique and flow cytometry (Epics XL; USA). Serum levels of cytokines IL1β, IL2, IL4, IL10, IFNγ, TNFα (Bender MedSystems; Austria), anti-dsDNA, IgG, IgA, IgM (ORGenTec Diagnostika; Germany), IgE (Monobind; USA), circulating immune complexes were assessed by enzyme immunoassay using the Multiskan FSC system (ThermoFisher Scientific Inc., Finland) and the Evolis automated analyzer (Bio-Rad; USA). The study results were processed using the Statistica 6 software package (StatSoft; USA). The Shapiro–Wilk test was used to test the statistical hypothesis of differences between the values. The data obtained were described using the mean values and standards deviations, as well as the rate of elevated concentrations. Significant differences between groups were identified using the parametric Student's t-test for independent samples and the nonparametric Mann–Whitney U test. The differences were considered significant when p did not exceed 0.05.

RESULTS

Comparative analysis of the mean indicators of immune status depending from the lymphocyte counts in peripheral venous blood was conducted (Table 1).

The increase in lymphocyte counts is accompanied by activation of the granulocyte neutrophils and monocytes. Activation of neutropils is observed in 62% of HL cases with normal or elevated lymphocyte counts in peripheral venous blood. The increase in neutrophil counts is associated with the left shift; the stab neutrophil counts are markedly higher in patients having no lymphocytopenia. It is well known that activation of the neutrophilic leukocyte proliferation is accompanied by the increase in CD10 expression associated with the increased cell's ability to respond to numerous inflammatory peptides [4–8]. In cases of lymphocytopenia, there is no response of granulocyte neutrophils. The increase in neutrophil counts in HL patients with normal or elevated lymphocyte counts is associated with the increase in monocyte counts, signs of monocyte proliferation activation, and elevated promonocyte counts. Hence, HL in patients with normal blood lymphocyte counts was associated with neutrophilia and monocytosis, while patients with severe lymphocytopenia had a 4 times lower rate of elevated monocyte and neutrophil counts. Such a response is quite similar to the body's response to glucocorticoids. Glucocorticoids, that have long been used for treatment of neutropenia [9–12], affect migration of progenitor cells, granulocyte-monocyte progenitors in blood flow from bone marrow with the 2–4-fold increase in the number of colony forming cells. Glucocorticoids stimulate production of colony-stimulating factors by monocytes, the release of mature granulocytes from the bone marrow into the blood, granulocyte rearrangement in bloodstream and migration [13–16]. The following question remains open: what is observed in HL patients with lymphocytopenia, no response of glucocorticoids or no significant effect of hormones on all the above processes? It was found that the disease duration was a significant factor that affected lymphocytopenia associated with HL: no lymphocytopenia was observed in almost all patients (61 individuals; 89.71%) with the disease duration of up to two years (68 patients); in contrast, the decrease in absolute lymphocytes counts was found in 46 cases (88.46%) with the disease duration of four years or more (52 patients). Lymphocytopenia developing in patients with the long-term disease results in the increasing circulating mature T cell ($CD3^+$) deficiency and is correlated to the decrease in the levels of circulating neutrophils and monocytes ($p < 0.001$).

Neutropenia ($< 2 \times 10^9$ c/L) was found in 19 cases (31.14%), and monocytopenia ($< 0.2 \times 10^9$ c/L) was revealed in 6 patients (9.84%). Given the fact that granulocyte neutrophils and monocytes secrete a wide variety of interleukins capable of changing the cells' receptor activity together with the cell adhesive and migratory abilities, chemotaxis, as well as the activating, colony-stimulating and mitogenic products, it can be assumed that the changes in their counts are the criteria of poor disease outcome. Neutrophils are not only important effector cells, but also regulate and shape the lymphocyte responses. Neutrophils are actively engaged in shaping the paracrine cytokine profile, since these cells, secreting all known cytokines, are involved in apoptosis, contribute to antibody-dependent cellular cytotoxicity and form extracellular traps

Table 1. Содержание лейкоцитов в венозной периферической крови больных при ЛХ (M ± *m*)

Studied parameters	Lymphocytosis (*n* = 73)	Lymphocytopenia (*n* = 61)
Leukocytes, 10^9 c/L	11.54 ± 0.29	5.86 ± 0.28
Neutrophils, %	49.05 ± 0.19	36.69 ± 0.21
Neutrophils, 10^9 c/L	5.66 ± 0.19	2.15 ± 0.21***
Neutrophilia rate, number/%	62 / 84.93	8 / 13.11
Neutropenia rate, number/%	1 / 1.37	27 / 44.26
Monocytes, 10^9 c/L	1.98 ± 0.06	0.67 ± 0.05***
Monocytosis rate, number/%	59 / 80.82	12 /19.67
Lymphocytes, %	31.46 ± 0.18	36.69 ± 0.21
Lymphocytes, 10^9 c/L	3.63 ± 0.15	1.24 ± 0.06***
Lymphocyte subset panel:		
small, 10^9 c/L	1.93 ± 0.12	0.92 ± 0.04***
medium, 10^9 c/L	1.51 ± 0.05	0.29 ± 0.01***
large, 10^9 c/L	0.19 ± 0.03	0.15 ± 0.02
Mature $CD3^+$ T cells, 10^9 c/L	1.66 ± 0.09	0.55 ± 0.09***
Immmature T cells, 10^9 c/L	1.39 ± 0.07	0.06 ± 0.01***
$CD3^+$ deficiency, number/%	22 / 30.14	61 / 100
B cells, $CD19–20^+$, %	15.55 ± 0.32	50.81 ± 0.19***
B cells, CD19–20+, 10^9 c/L	0.57 ± 0.06	0.63 ± 0.05
Elevated $CD19^+$, number/%	62 / 84.93	53 / 86.88
$CD16^+$, 10^9 c/L	0.43 ± 0.06	021 ± 0.04**
$CD10^+$, 10^9 c/L	0.47 ± 0.04	0.34 ± 0.05*
$CD71^+$, 10^9 c/L	0.63 ± 0.05	0.31 ± 0.06**
$CD25^+$, 10^9 c/L	0.51 ± 0.04	0.42 ± 0.03*
$HLADRII^+$, 10^9 c/L	0.55 ± 0.05	0.47 ± 0.07
$CD8^+$, 10^9 c/L	0.76 ± 0.05	0.21 ± 0.06***
$CD4^+$, 10^9 c/L	0.52 ± 0.02	0.58 ± 0.06
$CD95^+$, 10^9 c/L	0.45 ± 0.05	0.28 ± 0.05**
Cortisol, nmol/L	218.32 ± 10.34	129.48 ± 9.67**
Norepinephrine, nmol/L (lying down)	1.59 ± 0.27	9.22 ± 0.51**

Note: *** — $p < 0.001$; ** — $p < 0.01$; * — $p < 0.05$.

[17–22]. The activated neutrophils influenced by IFNγ express high-affinity CD64 (FcγRI) that determines antibody-dependent cytotoxicity [23–29]. It can be assumed that the decrease in the neutrophil response activity indicates depletion of the the lymphoproliferative process reserve capacity, lymphocyte migration and recirculation control. The same pattern underlies the monocyte response. Like neutrophilic leukocytes, monocytes shape the cytokine profile, serete colony-stimulating factors, enable phagocytosis and antibody-dependent cytotoxicity [30–37]. Perhaps, the effects of monocytes are more prolonged, since the tissue-resident monocyte counts are several times higher than the tissue-resident neutrophil counts, and lifespan of tissue-resident monocytes can be several years. Thus, the neutrophil and monocyte activation responses associated with HL can compensate for functional impairment of lymphocytes and perform regulatory functions of maintaining the portion of lymphocytes that retains the capability of performing functional duties.

When there are relatively high neutrophil and monocyte counts, some favorable features of the leukocyte cellular compositions are revealed: on average, normal mature T cell counts, while $CD3^+$ deficiency is found in individuals with lymphocytopenia, and the $CD3^+$ deficiency detection rate is 2.5 times higher; predominance of cell-mediated cytotoxicity over the helper effects of T cells; finally, the relative large pool of lymphocytes capable of further differentiation. Small lymphocytes that belong to inactive cells carrying genetic information hold the largest share of the patients' circulating lymphocytes. It is believed that small (usually dark-colored, "naked") lymphocytes sized 6–8 μm account for 10–15% of the whole lymphocyte population circulating in the venous blood of generally healthy people [38–41]. The significant increase in the blood small lymphocyte counts (up to 53.17 and 74.19% of total lymphocyte counts) in patients with the diagnosis of Hodgkin disease suggests activation of lymphocyte recirculation in individuals with this disorder. It is well known that lymphocyte recirculation gives lymphocytes access to all parts of the body, enables cell–cell interaction and interaction of lymphoid masses with the lymph nodes, as well as preservation of adaptive counts of lymphocytes circulating in blood.

The most striking differences revealed were represented by mature $CD3^+$ T cell counts against severe deficiency of such cells in individuals with lymphocytopenia. Insufficient amounts of mature circulating T cells were revealed in all patients with lymphocytopenia, while in individuals with no lymphocytopenia the deficiency of mature T cells was revealed only in 30% of cases. However, in fact this significant difference had almost no effect on the activated T cell counts and helper T cell counts. By contrast, individuals with lymphocytopenia had 3 times lower concentrations of cytotoxic T cells. It should be borne in mind

Table 2. Levels of cytokines, immunoglobulins and autoantibodies in peripheral venous blood of patients with LH (M ± *m*)

Studied parameters	Lymphocytosis (*n* = 73)	Lymphocytopenia (*n* = 61)
IL1β, pg/mL	4.37 ± 0.06	1.57 ± 0.05 ***
IL2, pg/mL	8.34 ± 0.15	6.32 ± 0.19 **
IL4, pg/mL	15.29 ± 0.22	12.36 ± 0.23
IL10, pg/mL	1.57 ± 0.07	1.79 ± 0.05
IFNγ, pg/mL	21.58 ± 0.12	10.94 ± 0.09 **
TNFα, pg/mL	24.43 ± 0.23	11.67 ± 0.13 **
IgM, g/L	1.62 ± 0.19	1.98 ± 0.22
IgG, g/L	21.34 ± 0.59	19.85 ± 0.41 *
IgA, g/L	0.92 ± 0.08	1.52 ± 0.11 ***
IgE, IU/mL	108.13 ± 2.35	194.45 ± 3.89 ***
Elevated IgE rate, number/%	25 / 34.25	49 / 80.32
Anti-dsDNA, U/mL	73.29 ± 1.51	116.52 ± 3.58***
Elevated anti-dsDNA rate, number/%	32 / 50.68	48 / 96.72
Elevated CICs (circulating immune complexes), number/%	51 / 69.86	55 / 78.68

Note: *** — $p < 0.001$; ** — $p < 0.01$; * — $p < 0.05$.

that a sharp decrease in total lymphocyte counts is due to not only cytotoxic T cells, but also to the equal extent lymphocytes having no CD3 on the membrane, and the share of these cells is relatively large (38.57%). Hence, the disease progression and long disease duration are associated with the decrease in total lymphocyte counts, mostly due to $CD3^+CD8^+$ cytotoxic T cells and unidentified lymphocytes. The almost 2-fold decrease in the counts of lymphocytes labeled for apoptosis indirectly indicates that the levels of lymphoproliferative activity in patients with lymphocytopenia are significantly lower. Indeed, HL is associated with reduced lymphocyte functional activity: lower levels of blast transformation induced by phytohemagglutinin (22.56 ± 1.13 и 43.24 ± 1.89%, respectively); individuals with lymphocytopenia have lower counts of activated T cells, especially cells having IL2 receptors. The proliferating part of lymphocytes ($CD10^+$) is probably represented mostly by B cells: both types are more abundant in individuals with lymphocytopenia; patients with lymphocytopenia have higher concentrations of autoantibodies against dsDNA and reagins (IgE), as well as T cells having FcIg $CD23^+$ receptor. B cell counts were significantly higher than normal in 85–87% of cases against the background of moderate increase in total lymphocyte counts and lymphocytopenia; patients of both groups had almost the same absolute B cell counts (Table 2).

The decrease in effector cell activity also affects phagocytes. Among the surveyed individuals with normal lymphocyte counts and lymphocytopenia, phagocytic deficiency was found in 65 (89.04%) and 60 (98.36%) patients, respectively. However, the most significant differences were related to phagocytic activity of monocytes: the percentage of actively phagocytic monocytes was very low, in individuals with normal lymphocyte counts is was 21.35 ± 1.33%, while in individuals with lymphocytopenia the phagocytic cell counts were 9.57 ± 0.27%. Reduced functional activity of the effector cells, especially monocytes, is probably one of the key factors having a pathogenetic significance for the HL development. High concentrations of circulating immune complexes in 69 and 78% of surveyed patients confirm failure of the phagocytic ability of macrophages in this situation. Perhaps, autoantibodies are of some importance, the secretion of which is obviously enhanced in affected individuals, of IgE synthesis intensification. It is well known that synthesis of this class of antibodies (reagins) is associated with low doses of antigen and the duration of antigen exposure. Reagins, having the highest sensitivity, recognize even the conformational antigen alterations and realize one of the most strong and effective antibody-dependent cytotoxicity responses.

DISCUSSION

HL is characterized by alterations in the lymph node structure and formation of inflammatory tumor microenvironment due to crosstalk between the Hodgkin Reed-Sternberg cells and the immune infiltrate [42, 43]. The study results have made it possible to develop various HL treatment options, including targeted small molecule therapy, treatment with antibody-drug conjugates and checkpoint inhibitors [44, 45]. However, there is not enough information about the functional activity of immunocompetent cells associated with the impact of inflammatory microenvironment depending on the disease duration. We have found that HL is associated with the immune response involving activation of cell-mediated and antibody-dependent responses of isolation and clearance of the pathogen in the lymphocyte or of the transformed lymphocyte itself. Perhaps, all the options, including the backup and rather risky protective mechanisms, such as intensification of the synthesis of autoantibodies and immunoglobulins of specific class (IgE) enabling the increased responses, are used in this case. It is likely that nodular sclerosis in the lymph nodes also represents the form of pathogen isolation that is considered to be enforced in this situation. The intense or long-term struggle may be followed by the phase of the immune defense reserve reduction and the period of lymphocyte depletion. The latter is characterized by mature T cell deficiency with all the consequences. There is a question about the Hodgkin cells and the ensuing Reed-Sternberg cells. The presence of immunoglobulins, receptors of the Fc portion of immunoglobulin (FcIgR), immune complexes on the membranes of these cells, and, most importantly, the phagocytic ability of these cells testify in favor of their macrophagal origin. This issue is still being debated. However, if we assume that initiation of immune response by phagocytic and presenting cells predetermines its further intensity, we can accept all the difficulties related to pathogen isolation in case the pathogen is preserved and even reproduced in the phagocyte. Anyway, our findings show that monocytes of the surveyed patients are characterized by extremely low activity;

accumulation of extremely high concentrations of circulating immune complexes actually utilized only by monocytes is reported. This view is also supported by the fact of reduced blood $CD16^+$ mononuclear cell counts in case of the disease progression in individuals with lymphocytopenia. It is well known that expression of the gene encoding the CD16 protein is not associated with the phagocytosis rate and is inherent to the cells actively secreting cytokines. Thus, lymphocytopenia observed in affected individuals actually represents a phase of the immune homeostasis maintenance reserve depletion due to impaired function of phagocytes and cells showing antibody-dependent cytotoxicity. This phase of depletion results from imbalance of the catecholamine and cortisol responses. However, in contrast to cortisol, catecholamine levels do not decrease, even when stress becomes habitual [46–48]. From this perspective, lymphocytopenia associated with HL is likely to be a criterion of adverse outcome. Such lymphocytopenia is associated with both the decrease in activated T cell counts and the deficiency of differentiated immunocompetent cells.

CONCLUSIONS

The major events in lymphoid organs of individuals with HL are represented by the lymphocyte death. Perhaps, lymphocytes die due to severe antibody-dependent cytotoxicity involving granulocyte neutrophils, and later eosinophils and macrophages. Antibodies that ensure such responses belong mainly to IgA and IgE. This response is supported by IL1β and TNFα; it is well known that TNFα induces the IL1β and IL5 synthesis, thereby preventing apoptosis [49]. Predominantly small lymphocytes die, their concentrations decrease by 3 times in individuals with lymphocytopenia; lymphocytopenia is associated with the circulating T cell deficiency and involves both mature and immature T cells, the 2.5–3-fold decrease in blood counts of which is observed in lymphocytopenia, however, there are no dramatic changes in B cell counts. Increasing lymphocytopenia, i.e. the disease progression, is accompanied by reduction of the lymphocyte homeostasis control reserve by granulocytes and monocytes with increasing neutropenia and monocytopenia.

References

1. Hoffman R, Benz EJ, Silberstein LE, Heslop HE, Weitz JI, Anastasi J, et al, editors. Hematology: basic principles and practice. Elsevier, Philadelphia, 2017; p. 130.
2. Liu Y, Abdul Razak FR, Terpstra M, et al. The mutational landscape of Hodgkin lymphoma cell lines determined by whole-exome sequencing. Leukemia. 2014; 28: 2248–51.
3. Ramazanova RD, Ratobolskix AV. Rol' virusa Ehpshtejna–Barr v patogeneze limfomy xodzhkina u detej. Universitetskaya medicina Urala. 2021; 7–3 (26): 34–35. Russian.
4. Ship MA, Stefano GB, Switzer SN, Griffin JD, Reinherz EL. CD10(CALLA)/neutral endopeptidase modulates inflammatory peptide-induced changes in neutrophil morphology, migration, and adhesion proteins and is itself regulated by neutrophil activation. Blood. 1991; 78: 1834–41.
5. Hirashima M, Higuchi S, Sakamoto K, Nishiyama T, Okada H. The ratio of neutrophils to lymphocytes and the phenotypes of neutrophils in patient with early gastric cancer. Journal of Cancer Research and Clinical Oncology. 1997; 124 (6): 329–34. DOI: 10.1007/s004320050178.
6. Marini O, Costa S, Bevilacqua D. Mature CD10+ and immature CD10– neutrophils present in G-CSF–treated donors display opposite effects on T cells. Blood. 2017; 129 (10): 1343–56. DOI: 10.1182/blood-2016-04-713206.
7. Ding L, Vezzani B, Khan N, Su J, Xu L, Yan G, et al. CD10 expression identifies a subset of human perivascular progenitor cells with high proliferation and calcification potentials. Stem Cells. 2020; 38 (2): 261–75. DOI: 10.1002/stem.3112.
8. Huang X, He C, Lin G, Lu L, Xing K, Hua X, et al. Induced CD10 expression during monocyte-to-macrophage differentiation identifies a unique subset of macrophages in pancreatic ductal denocarcinoma. Biochemical and Biophysical Research Communications. 2020; 524 (4): 1064–71. DOI: 10.1016/j.bbrc.2020.02.042.
9. Kassirskij IA, Alekseev GA. Klinicheskaya gematologiya. M.: Medicina, 1970; 328 s. Russian.
10. Fajnshejn FEh. Aplasticheskie i gipoplasticheskie anemii. M.: Medicina,1965; 215 s. Russian.
11. Juutilainen A, Hämäläinen S, Niemenpää J, Kuittinen T, Pulkki K, Koivula I, et al. Serum cortisol and inflammatory response in neutropenic fever. Annals of Hematology. 2011; 90 (12): 1467–75. DOI: 10.1007/s00277-011-1211-6.
12. Zierath D, Tanzi P, Shibata D, Becker KJ. Cortisol is More Important than Metanephrines in Driving Changes in Leukocyte Counts after Stroke. Journal of Stroke & Cerebrovascular Diseases. 2018; 27 (3): 555–62. DOI: 10.1016/j.jstrokecerebrovasdis.2017.09.048.
13. Bagby GC, Gabourel JD, Linman JW. Glucocorticoid therapy in the preleukemic syndrome. Annals of Internal Medicine. 1980; 92: 241–248.
14. Golde D, Cline M. Hormonal interactions with hemopoietin cells in vitro. Transplantation Proceedings. 1978; 10: 95–97.
15. Wright DG, Fanci AS, Dale DC. Correction of human cyclic neutropenia with prednisolone. The New England Journal of Medicine. 1978; 298: 295–300.
16. Lightman SL, Birnie MT, Conway-Campbell BL. Dynamics of ACTH and cortisol secretion and implications for disease. Endocrine Reviews. 2021; 41: 470–490. DOI: 10.1210/ENDREV/BNAA002.
17. Nexaev SG, Grigorev SG. Polimorfnoyadernye lejkocity kak sistema antiehndotoksikacionnoj zashhity organizma. Immunologiya. 2010; 31 (3): 116–8. Russian.
18. Cascao R, Rosario HS, Fonseca JE. Neutrophils: Warriors and commanders in immune mediated inflammatory diseases. Acta reumatologica portuguesa. 2009; 34 (2B): 313–26.
19. Hen Y, Wu H, Winnall WR, Loveland KL. Tumor necrosis factor-a stimulates human neutrophyls to release preformed activin. Immunology and Cell Biology. 2011; 89 (8): 889–96.
20. Hedrick CC, Malanchi I. Neutrophils in cancer: heterogeneous and multifaceted. Nature Reviews Immunology. 2021; 22 (3): 1–15. DOI: 10.1038/s41577-021-00571-6.
21. Kenny EF, Herzig A, Krüger R, Muth A, Mondal S, Thompson PR, et al. Diverse stimuli engage different neutrophil extracellular trap pathways. Elife. 2017; 6: e24437. DOI: 10.7554/eLife.24437.
22. Jorch SK, Kubes P. An emerging role for neutrophil extracellular traps in noninfectious disease. Nature Medicine. 2017; 23: 279–87. DOI: 10.1038/nm.4294.
23. Huizinga TW, van der Schoot CE, Roos D, Weening RS. Induction of neutrophil Fc-gamma receptor I expression can be used as a marker for biological activity of recombinant interferon-gamma in vivo. Blood. 1991; 77: 2088–90.
24. Kakinoki Y, Kubota H, Yamamoto Y. CD64 surface expression on neutrophils and monocytes is significantly up-regulated after stimulation with granulocyte colony-stimulating factor during CHOP chemotherapy for patients with non-Hodgkins lymphoma. International Journal of Hematology. 2004; 79 (1): 55–62.
25. Kerst JM, van der Winkel JG, Evanse AH. Granulocyte colony-stimulating factor induces FcγRI(CD64) positive geutrophils via an effect on myeloidprecursor cells. Blood. 1993; 81: 1457–64.
26. Gasparoto TH, Dalboni TM, Amôr NG, Abe AE, Perri G, Lara VS, et al. Fcγ receptors on aging neutrophils. Journal of Applied Oral Science. 2021; 29: e20200770. DOI: 10.1590/1678-7757-

2020-0770.
27. Dang Y, Lou J, Yan Y. The role of the neutrophil Fcγ receptor I (CD64) index in diagnosing spontaneous bacterial peritonitis in cirrhotic patients. International Journal of Infectious Diseases. 2016; 49: 154–60.
28. Ambruso DR, Ellison M, Briones N. Effects of Interferon-Gamma 1-b (IFN-Î³) on Neutrophil Function and Biochemistry in Patients with Chronic Granulomatous Disease. Blood. 2018; 132 (Supp. 1): 2400. DOI: 10.1182/blood-2018-99-115683.
29. Nesterova IV, Chudidova GA, Lomtatidze LV, Kovaleva LV, Sapun OI. Fenotipicheskie xarakteristiki subpopulyacij monocitov CD64+CD16–CD32+CD11B+, CD64+CD16+CD32+CD11B+, CD64–CD16+ CD11B+ pri vrozhdennoj pnevmonii u gluboko nedonoshennyx novorozhdennyx. Immunologiya. 2014; 35 (1): 33–37. Russian.
30. Aguilar-Ruiz SR, Torres-Aguilar H, Gonzalez-Dominguez E, Narvaez J, Gonzalez-Perez G, Vargas-Avala G, et al. Human CD16+ and CD16- monocyte subsets display unique effector properties in inflammatory conditions in vivo. Journal of Leukocyte Biology. 2011; 90 (6): 1119–31. DOI: 10.1189/jlb.0111022.
31. Barclay AN, Brown MH, Law SK. The leukocyte antigen facts-book. Academic Press. 1997; p. 192–193.
32. Belg KU, Dayyani E, Horelt A, Siedlar M, Frankenberger M, Frankenberger B, et al. The protein-flammatory -CD14+CD16+DR- monocytes are a major source of TNF. Journal of Immunology. 2002; 168 (7): 3536–42. DOI: 10.4049/jimmunol.168.7.3536.
33. Kapellos TS, Bonaguro L, Gemünd I, Reusch N, Saglam A, Hinkley ER, et al. Human Monocyte Subsets and Phenotypes in Major Chronic Inflammatory Diseases. Frontiers of Immunology. 2019; 10: 2035. DOI: 10.3389/fimmu.2019.02035.
34. Sanchez-Torres C, Garcia-Roto GS, Cornejo-Cortes MA, Rivas-Carvalho A, Sanchez-schmitz G. CD16+ and CD16+- human blood monocyte subsets differentiate in vitro to dendritic cells with different abilities to stimulate CD4T-cells. International Immunology. 2001; 13: 1571–81. DOI: 10.1093/intimm/13.12.1571.
35. De Maeyer RPH, Chambers ES. The impact of ageing on monocytes and macrophages. Immunology Letters. 2021; 230: 1–10. DOI: 10.1016/j.imlet.2020.12.003.
36. Ziegler-Heitbrock L, Ancuta P, Crow S, Dalod M, Grau V, Hart DN. Nomenclature of monocytes and dendritic cells in blood. Blood. 2010; 116 (16): 74–80.
37. Gasparoto TH, Dalboni TM, Amôr NG, Abe AE, Perri G, Lara VS, et al. Fcγ receptors on aging neutrophils. Journal of Applied Oral Science. 2021; 29: e20200770. DOI: 10.1590/1678-7757-2020-0770.
38. Kozinec GI, Terenteva GI, Fajnshtejn FEh, Shishkonov EhG, Lulcina SM, Yarustovskaya LEh, Lipac AA. Morfologicheskaya i funkcional'naya xarakteristika kletok kostnogo mozga i krovi. V kn.: Normal'noe krovetvorenie i ego regulyaciya. M.: Medicina, 1976; s. 98–155. Russian.
39. Chelovek: mediko-biologicheskie dannye: doklad rabochej gruppy Komiteta II MKRZ po uslovnomu cheloveku. Per. s angl. M.: Medicina, 1977; 496 s. Russian.
40. Miller JFAP. The function of the thymus and its impact on modern medicine. Science. 2020; 31: 369 (6503): eaba2429. DOI: 10.1126/science.aba2429.
41. Egorov ES, Merzlyak EM, Shelenkov AA, Britanova OV, Sharonov GV, Staroverov DB, et al. Quantitative profiling of immune repertoires for minor lymphocyte counts using unique molecular identifiers. Journal of Immunology. 2015; 194 (12): 6155–63. DOI: 10.4049/jimmunol.1500215.
42. Aldinucci D, Gloghini A, Pinto A, De Filippi R, Carbone A. The classical Hodgkin's lymphoma microenvironment and its role in promoting tumour growth and immune escape. J Pathol. 2010; 221 (3): 248–63.
43. Carbone A, Gloghini A, Castagna L, Santoro A, Carlo-Stella C. Primary refractory and early-relapsed Hodgkin's lymphoma: strategies for therapeutic targeting based on the tumour microenvironment. J Pathol. 2015; 237 (1); 4–13.
44. Bachanova V, Hegerova L, Cao Q, Janakiram M, Maakaron J, Ayyappan S, et al. Ruxolitinib plus nivolumab in patients with R/R Hodgkin lymphoma after failure of check-point inhibitors: Preliminary Report on Safety and Efficacy. Blood. 2021; 138 (1): 230.
45. Zhao P, Xie L, Yu L, Wang P. Targeting CD47-SIRPα axis for Hodgkin and non-Hodgkin lymphoma immunotherapy. Genes & Diseases. 2023; 100070.
46. Elenkov IJ, Chrousos GP. Stress-system — organization, physiology and immunoregulation. Neuroimmunomodulation. 2006; 13 (5–6): 257–67. DOI: 10.1159/000104853.
47. Antoni MH, Dhabhar FS. The impact of psychosocial stress and stress management on immune responses in patients with cancer. Cancer. 2019; 125 (9): 1417–31. DOI: 10.1002/cncr.31943.
48. Pulopulos MM, Baeken C, De Raedt R. Cortisol response to stress: The role of expectancy and anticipatory stress regulation. Hormones and Behavior. 2020; 117: 104587. DOI: 10.1016/j.yhbeh.2019.104587.
49. Balkwill F. TNF-alpha in promotion and progression of cancer. Cancer and Metastasis Reviews. 2006; 25 (3): 409–16. DOI: 10.1007/s10555-006-9005-3.

Литература

1. Hoffman R, Benz EJ, Silberstein LE, Heslop HE, Weitz JI, Anastasi J, et al, editors. Hematology: basic principles and practice. Elsevier, Philadelphia, 2017; p. 130.
2. Liu Y, Abdul Razak FR, Terpstra M, et al. The mutational landscape of Hodgkin lymphoma cell lines determined by whole-exome sequencing. Leukemia. 2014; 28: 2248–51.
3. Рамазанова Р. Д., Ратобольских А. В. Роль вируса Эпштейна–Барр в патогенезе лимфомы ходжкина у детей. Университетская медицина Урала. 2021; 7-3 (26): 34–35.
4. Ship MA, Stefano GB, Switzer SN, Griffin JD, Reinherz EL. CD10(CALLA)/neutral endopeptidase modulates inflammatory peptide-induced changes in neutrophil morphology, migration, and adhesion proteins and is itself regulated by neutrophil activation. Blood. 1991; 78: 1834–41.
5. Hirashima M, Higuchi S, Sakamoto K, Nishiyama T, Okada H. The ratio of neutrophils to lymphocytes and the phenotypes of neutrophils in patient with early gastric cancer. Journal of Cancer Research and Clinical Oncology. 1997; 124 (6): 329–34. DOI: 10.1007/s004320050178.
6. Marini O, Costa S, Bevilacqua D. Mature CD10+ and immature CD10– neutrophils present in G-CSF–treated donors display opposite effects on T cells. Blood. 2017; 129 (10): 1343–56. DOI: 10.1182/blood-2016-04-713206.
7. Ding L, Vezzani B, Khan N, Su J, Xu L, Yan G, et al. CD10 expression identifies a subset of human perivascular progenitor cells with high proliferation and calcification potentials. Stem Cells. 2020; 38 (2): 261–75. DOI: 10.1002/stem.3112.
8. Huang X, He C, Lin G, Lu L, Xing K, Hua X, et al. Induced CD10 expression during monocyte-to-macrophage differentiation identifies a unique subset of macrophages in pancreatic ductal denocarcinoma. Biochemical and Biophysical Research Communications. 2020; 524 (4): 1064–71. DOI: 10.1016/j.bbrc.2020.02.042.
9. Кассирский И. А., Алексеев Г. А. Клиническая гематология. М.: Медицина, 1970; 328 с.
10. Файншейн Ф. Э. Апластические и гипопластические анемии. М.: Медицина,1965; 215 с.
11. Juutilainen A, Hämäläinen S, Niemenpää J, Kuittinen T, Pulkki K, Koivula I, et al. Serum cortisol and inflammatory response in neutropenic fever. Annals of Hematology. 2011; 90 (12): 1467–75. DOI: 10.1007/s00277-011-1211-6.
12. Zierath D, Tanzi P, Shibata D, Becker KJ. Cortisol is More Important than Metanephrines in Driving Changes in Leukocyte Counts after Stroke. Journal of Stroke & Cerebrovascular Diseases. 2018; 27 (3): 555–62. DOI: 10.1016/j.jstrokecerebrovasdis.2017.09.048.
13. Bagby GC, Gabourel JD, Linman JW. Glucocorticoid therapy in

the preleukemic syndrome. Annals of Internal Medicine. 1980; 92: 241–248.
14. Golde D, Cline M. Hormonal interactions with hemopoietin cells in vitro. Transplantation Proceedings. 1978; 10: 95–97.
15. Wright DG, Fanci AS, Dale DC. Correction of human cyclic neutropenia with prednisolone. The New England Journal of Medicine. 1978; 298: 295–300.
16. Lightman SL, Birnie MT, Conway-Campbell BL. Dynamics of ACTH and cortisol secretion and implications for disease. Endocrine Reviews. 2021; 41: 470–490. DOI: 10.1210/ENDREV/BNAA002.
17. Нехаев С. Г., Григорьев С. Г. Полиморфноядерные лейкоциты как система антиэндотоксикационной защиты организма. Иммунология. 2010; 31 (3): 116–8.
18. Cascao R, Rosario HS, Fonseca JE. Neutrophils: Warriors and commanders in immune mediated inflammatory diseases. Acta reumatologica portuguesa. 2009; 34 (2B): 313–26.
19. Hen Y, Wu H, Winnall WR, Loveland KL. Tumor necrosis factor-a stimulates human neutrophyls to release preformed activin. Immunology and Cell Biology. 2011; 89 (8): 889–96.
20. Hedrick CC, Malanchi I. Neutrophils in cancer: heterogeneous and multifaceted. Nature Reviews Immunology. 2021; 22 (3): 1–15. DOI: 10.1038/s41577-021-00571-6.
21. Kenny EF, Herzig A, Krüger R, Muth A, Mondal S, Thompson PR, et al. Diverse stimuli engage different neutrophil extracellular trap pathways. Elife. 2017; 6: e24437. DOI: 10.7554/eLife.24437.
22. Jorch SK, Kubes P. An emerging role for neutrophil extracellular traps in noninfectious disease. Nature Medicine. 2017; 23: 279–87. DOI: 10.1038/nm.4294.
23. Huizinga TW, van der Schoot CE, Roos D, Weening RS. Induction of neutrophil Fc-gamma receptor I expression can be used as a marker for biological activity of recombinant interferon-gamma in vivo. Blood. 1991; 77: 2088–90.
24. Kakinoki Y, Kubota H, Yamamoto Y. CD64 surface expression on neutrophils and monocytes is significantly up-regulated after stimulation with granulocyte colony-stimulating factor during CHOP chemotherapy for patients with non-Hodgkins lymphoma. International Journal of Hematology. 2004; 79 (1): 55–62.
25. Kerst JM, van der Winkel JG, Evanse AH. Granulocyte colony-stimulating factor induces FcγRI(CD64) positive geutrophils via an effect on myeloidprecursor cells. Blood. 1993; 81: 1457–64.
26. Gasparoto TH, Dalboni TM, Amôr NG, Abe AE, Perri G, Lara VS, et al. Fcγ receptors on aging neutrophils. Journal of Applied Oral Science. 2021; 29: e20200770. DOI: 10.1590/1678-7757-2020-0770.
27. Dang Y, Lou J, Yan Y. The role of the neutrophil Fcγ receptor I (CD64) index in diagnosing spontaneous bacterial peritonitis in cirrhotic patients. International Journal of Infectious Diseases. 2016; 49: 154–60.
28. Ambruso DR, Ellison M, Briones N. Effects of Interferon-Gamma 1-b (IFN-Î³) on Neutrophil Function and Biochemistry in Patients with Chronic Granulomatous Disease. Blood. 2018; 132 (Supp. 1): 2400. DOI: 10.1182/blood-2018-99-115683.
29. Нестерова И. В., Чудидова Г. А., Ломтатидзе Л. В., Ковалева Л. В., Сапун О. И. Фенотипические характеристики субпопуляций моноцитов CD64+CD16–CD32+CD11B+, CD64+CD16+CD32+CD11B+, CD64–CD16+ CD11B+ при врожденной пневмонии у глубоко недоношенных новорожденных. Иммунология. 2014; 35 (1): 33–37.
30. Aguilar-Ruiz SR, Torres-Aguilar H, Gonzalez-Dominguez E, Narvaez J, Gonzalez-Perez G, Vargas-Avala G, et al. Human CD16+ and CD16- monocyte subsets display unique effector properties in inflammatory conditions in vivo. Journal of Leukocyte Biology. 2011; 90 (6): 1119–31. DOI: 10.1189/jlb.0111022.
31. Barclay AN, Brown MH, Law SK. The leukocyte antigen facts-book. Academic Press. 1997; p. 192–193.
32. Belg KU, Dayyani E, Horelt A, Siedlar M, Frankenberger M, Frankenberger B, et al. The protein-flammatory -CD14+CD16+DR- monocytes are a major source of TNF. Journal of Immunology. 2002; 168 (7): 3536–42. DOI: 10.4049/jimmunol.168.7.3536.
33. Kapellos TS, Bonaguro L, Gemünd I, Reusch N, Saglam A, Hinkley ER, et al. Human Monocyte Subsets and Phenotypes in Major Chronic Inflammatory Diseases. Frontiers of Immunology. 2019; 10: 2035. DOI: 10.3389/fimmu.2019.02035.
34. Sanchez-Torres C, Garcia-Roto GS, Cornejo-Cortes MA, Rivas-Carvalho A, Sanchez-schmitz G. CD16+ and CD16+- human blood monocyte subsets differentiate in vitro to dendritic cells with different abilities to stimulate CD4T-cells. International Immunology. 2001; 13: 1571–81. DOI: 10.1093/intimm/13.12.1571.
35. De Maeyer RPH, Chambers ES. The impact of ageing on monocytes and macrophages. Immunology Letters. 2021; 230: 1–10. DOI: 10.1016/j.imlet.2020.12.003.
36. Ziegler-Heitbrock L, Ancuta P, Crow S, Dalod M, Grau V, Hart DN. Nomenclature of monocytes and dendritic cells in blood. Blood. 2010; 116 (16): 74–80.
37. Gasparoto TH, Dalboni TM, Amôr NG, Abe AE, Perri G, Lara VS, et al. Fcγ receptors on aging neutrophils. Journal of Applied Oral Science. 2021; 29: e20200770. DOI: 10.1590/1678-7757-2020-0770.
38. Козинец Г. И., Терентьева Г. И., Файнштейн Ф. Э., Шишконов Э. Г., Лульцина С. М., Ярустовская Л. Э., Липац А. А. Морфологическая и функциональная характеристика клеток костного мозга и крови. В кн.: Нормальное кроветворение и его регуляция. М.: Медицина, 1976; с. 98–155.
39. Человек: медико-биологические данные: доклад рабочей группы Комитета II МКРЗ по условному человеку. Пер. с англ. М.: Медицина, 1977; 496 с.
40. Miller JFAP. The function of the thymus and its impact on modern medicine. Science. 2020; 31: 369 (6503): eaba2429. DOI: 10.1126/science.aba2429.
41. Egorov ES, Merzlyak EM, Shelenkov AA, Britanova OV, Sharonov GV, Staroverov DB, et al. Quantitative profiling of immune repertoires for minor lymphocyte counts using unique molecular identifiers. Journal of Immunology. 2015; 194 (12): 6155–63. DOI: 10.4049/jimmunol.1500215.
42. Aldinucci D, Gloghini A, Pinto A, De Filippi R, Carbone A. The classical Hodgkin's lymphoma microenvironment and its role in promoting tumour growth and immune escape. J Pathol. 2010; 221 (3): 248–63.
43. Carbone A, Gloghini A, Castagna L, Santoro A, Carlo-Stella C. Primary refractory and early-relapsed Hodgkin's lymphoma: strategies for therapeutic targeting based on the tumour microenvironment. J Pathol. 2015; 237 (1); 4–13.
44. Bachanova V, Hegerova L, Cao Q, Janakiram M, Maakaron J, Ayyappan S, et al. Ruxolitinib plus nivolumab in patients with R/R Hodgkin lymphoma after failure of check-point inhibitors: Preliminary Report on Safety and Efficacy. Blood. 2021; 138 (1): 230.
45. Zhao P, Xie L, Yu L, Wang P. Targeting CD47-SIRPα axis for Hodgkin and non-Hodgkin lymphoma immunotherapy. Genes & Diseases. 2023; 100070.
46. Elenkov IJ, Chrousos GP. Stress-system — organization, physiology and immunoregulation. Neuroimmunomodulation. 2006; 13 (5–6): 257–67. DOI: 10.1159/000104853.
47. Antoni MH, Dhabhar FS. The impact of psychosocial stress and stress management on immune responses in patients with cancer. Cancer. 2019; 125 (9): 1417–31. DOI: 10.1002/cncr.31943.
48. Pulopulos MM, Baeken C, De Raedt R. Cortisol response to stress: The role of expectancy and anticipatory stress regulation. Hormones and Behavior. 2020; 117: 104587. DOI: 10.1016/j.yhbeh.2019.104587.
49. Balkwill F. TNF-alpha in promotion and progression of cancer. Cancer and Metastasis Reviews. 2006; 25 (3): 409–16. DOI: 10.1007/s10555-006-9005-3.