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ORIGINAL ARTICLE

MORPHOLOGICAL AND IMMUNOPHENOTYPIC FEATURES OF THE MONOCLONAL POPULATION OF B-LYMPHOCYTES IN CHRONIC LYMPHOCYTIC LEUKEMIA

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ABSTRACT

Purpose of the study. To evaluate the features of morphological and immunophenotypic characteristics of the lymphoid population with different restriction of light chains of immunoglobulins in patients with chronic lymphocytic leukemia (CLL).

Materials and methods. The study included 30 CLL patients aged 47–79 years (20 men and 10 women). All patients underwent a General clinical blood test (SysmexXE 2100, Japan), morphological examination of the bone marrow (BioVision; Micros, Austria), immunophenotyping of bone marrow and peripheral blood by flow cytofluorometry (Navios10/3, Beckman Coulter, USA). B-cell clonality established by detection of restriction of light chains of surface immunoglobulins kappa or lambda. Morphological analysis of lymphocytes that differ in the expression of light chains of surface immunoglobulins: kappa (k) — group I (22 people — 73,3%), lambda (λ) — group II (8 people — 26,7%).

Results. Determination of cell types by values of direct (FSC) and lateral (SSC) light scattering during immunophenotyping of peripheral blood and bone marrow samples showed that in patients of group I (CD19k+/CD5+/CD23+) on the light scattering diagram, the lymphoid population had low parameters: on the FSC scale — from 200 to 400, on the SSC — from 10 to 160 units, which indicates morphological uniformity of cells. In group II (CD19λ+/CD5+/CD23+), on the contrary, on the light scattering sketogram, the lymphoid zone was heterogeneous and stretched: on the FSC scale — from 200 to 1000, on the SSC — from 10 to 400 units, which indicates morphological polymorphism of cells. There were also differences in the expression of the common leukocyte antigen CD45. In group I, the expression is higher: the population of B-lymphocytes in terms of fluorescence intensity is on the dot graph on the CD45 scale in the second half of the third decade and in the fourth decade — to the right, than in group II, in which B-lymphocytes lie in the third decade. The data indicate that the CD19k+/CD5+/CD23+ population is represented by Mature cells, while the Cd19k+/CD5+/CD23+ population is represented by less Mature and / or intermediate forms. Significant morphological differences in lymphocyte populations were also observed in microscopic studies of blood and bone marrow preparations.

Conclusion. The established immunophenotypic and morphological differences in lymphoid populations expressing either kappa — or lambda-light chains of immunoglobulins may be important for identifying risk groups among patients with biologically heterogeneous variants of chronic lymphocytic leukemia.

Keywords:
chronic lymphocytic leukemia, morphological and immunophenotypic features, kappa / lambda light chains of immunoglobulins, flow cytofluorimetry, general leukocyte antigen, CD antigens

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ОРИГИНАЛЬНАЯ СТАТЬЯ

МОРФОЛОГИЧЕСКИЕ И ИММУНОФЕНОТИПИЧЕСКИЕ ОСОБЕННОСТИ МОНОКЛОНАЛЬНОЙ ПОПУЛЯЦИИ В-ЛИМФОЦИТОВ ПРИ ХРОНИЧЕСКОМ ЛИМФОЛЕЙКОЗЕ

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РЕЗЮМЕ

Цель исследования. Оценить особенности морфологических и иммунофенотипических характеристик лимфоидной популяции с различной рестрикцией легких цепей иммуноглобулинов у пациентов с хроническим лимфолейкозом (ХЛЛ).

Материалы и методы. Обследованы 30 больных ХЛЛ (20 мужчин и 10 женщин) в возрасте 47–79 лет. Выполнены общеклинический анализ крови (SysmexXE 2100, Япония), морфологическое исследование костного мозга (BioVision; Micros, Австрия), иммунофенотипирование костного мозга и периферической крови методом проточной цитофлуориметрии (Navios10/3, Beckman Coulter, США). В-клеточная клональность устанавливалась обнаружением рестрикции легких цепей поверхностных иммуноглобулинов kappa или lambda. Проведен морфологический анализ лимфоцитов, различающихся по экспрессии легких цепей поверхностных иммуноглобулинов: kappa (k) — I группа (22 чел. — 73,3%), lambda (λ) — II группа (8 чел. — 26,7%).

Результаты. Определение типов клеток по значениям прямого (FSC) и бокового (SSC) светорассеяния при иммунофенотипировании образцов периферической крови и костного мозга показало, что у больных I группы (CD19k+/CD5+/CD23+) на диаграмме светорассеяния лимфоидная популяция имела низкие показатели параметров: по шкале FSC — от 200 до 400, по SSC — от 10 до 160 единиц, что указывает на морфологическую однородность клеток. Во II группе (CD19λ+/CD5+/CD23+), напротив, на скетограмме светорассеяния лимфоидная зона была неоднородна и растянута: по шкале FSC — от 200 до 1000, по SSC — от 10 до 400 единиц, что свидетельствует о морфологическом полиморфизме клеток. Отмечены различия и в экспрессии общелейкоцитарного антигена CD45. В I группе экспрессия выше: популяция В-лимфоцитов по интенсивности флуоресценции находится на точечном графике по шкале CD45 во второй половине третьей декады и в четвертой декаде — правее, чем во II-й группе, в которой В-лимфоциты лежат в третьей декаде. Данные свидетельствуют, что популяция CD19k+/CD5+/CD23+ представлена зрелыми клетками, а популяция CD19λ+/CD5+/CD23+ — менее зрелыми и/или промежуточными формами. Значительные морфологические различия популяций лимфоцитов отмечены и при микроскопическом исследовании препаратов крови и костного мозга.

Заключение. Установленные иммунофенотипические и морфологические различия лимфоидных популяций, экспрессирующих либо kappa-, либо lambda- легкие цепи иммуноглобулинов, важны для выделения групп риска среди больных с биологически разнородными вариантами хронического лимфолейкоза.

Ключевые слова:
хронический лимфолейкоз, морфологические и иммунофенотипические особенности, каппа/лямбда легкие цепи иммуноглобулинов, проточная цитофлуориметрия, общелейкоцитарный антиген, CD-антигены

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RELEVANCE

Chronic lymphocytic leukemia (CLL) belongs to a group of b-cell tumors from Mature (peripheral) cells and is a tumor of lymphoid tissue characterized by lesions of the bone marrow and lymph nodes [1]. CLL is a common type of B-lymphoproliferative diseases that mainly affects adults over 50 years of age, progresses slowly and often occurs without visible symptoms for a long time. The disease is detected, most often, by accident [2].

CLL patients are characterized by absolute peripheral blood lymphocytosis (more than 5, 0x10^9/l) and bone marrow lymphocytosis (more than 30%) [3]. Based on the cytological characteristics of lymphoid cells in the FAB classification (Bennet J.M., 1989), two morphological variants of B-CLL are distinguished: typical, represented by monotonous small lymphocytes, and mixed-cell, in which the tumor substrate is heterogeneous and consists of cells with different morphological characteristics — typical and atypical lymphocytes, prolymphocytes [4]. It is shown that in cases of mixed-cell variant B-CLL, the clinical condition, susceptibility to therapy and life expectancy of patients have significantly worse characteristics compared to the typical variant of the disease [5].

In modern diagnostics, detection of the immunophenotype of a tumor population is carried out by the method of flow cytofluorometry of blood/bone marrow. Tumor cells in CLL Express antigens-CD19, CD5, CD23, CD20 (weak), CD22(weak), CD43. B-cell clonality is determined by determining the ratio of expression of κ — and λ — (kappa-, lambda-) light chains of immunoglobulins [6, 7]. It is known from the literature that the concentration of free light chains (FLC) of immunoglobulins (Ig) in blood serum can be considered as a new biological marker that allows to divide CLL on this basis into FLC-positive and FLC-negative forms. In the course of a number of studies, the clonal nature of changes in FLC concentrations was noted and it was found that this criterion can be considered as an integral indicator of the mass of the tumor and a factor of the effectiveness of therapy. CLL patients with different forms may have different prognostic risks for the course of the disease [8]. The relationship of the detected changes in serum FLC Ig concentrations in CLL patients with the clinical picture of the disease is presented in a number of papers [9–12]. Interest in these studies remains high.

However, to date, there is no data on comparing the immunophenotypic differences of the tumor pool expressing the κ — and λ-light chains of immunoglobulins with different morphological characteristics of the tumor substrate in B-CLL, which is of undoubted interest.

The purpose of the study: to evaluate the features of morphological and immunophenotypic characteristics of the lymphoid population with different restriction of light chains of immunoglobulins in patients with chronic lymphocytic leukemia (CLL).

MATERIALS AND METHODS

The study included 30 patients with chronic lymphocytic leukemia aged 47–79 years, median 64.9±8.6 l. among them, 20 men (66.7%) and 10 women (33.3%). All patients underwent a General clinical blood test with the calculation of the total leukocyte count (WBC), the parameters of the leukocyte profile — myelocytes, lymphocytes, neutrophils, monocytes, eosinophils, basophils (SysmexXE 2100, Japan), morphological examination of the bone marrow and peripheral blood using the Pappenheim-Kryukov method, which consists in painting smears with May-Grunwald fixative paint and Romanovsky paint and using the software and hardware complex (BioVision; Micros, Austria), immunophenotyping of bone marrow and peripheral blood by multicolored flow cytofluorometry (Navios 10/3, BeckmanCoulter, USA). The study used native bone marrow and peripheral blood cells in a solution of EDTA anticoagulant. The study panel included a combination of monoclonal antibodies: CD45 PB, CD19 ECD, CD20 PC7, CD22 PE, CD23 PE, CD43 APC, CD200 APC, CD5 PC7, CD5 ARS, CD3 PC7, CD4 FITC, CD8 ECD, CD56 PC5, CD38 FITC, kappa FITC, lambda PE, isotypic controls (Beckman Coulter, USA). Marker expression was taken into account if it was detected in 20% of cells

or more. Expressed expression was established when the antigen was detected on more than half of the cells. Expression of B-linearly associated antigens was evaluated in the gate of CD19-positive cells [7, 13]. B-cell clonality was established by detection of restriction of light chains of surface immunoglobulins (kappa or lambda). Monoclonal variants were considered when the ratio of κ: λ was more than 4:1 or less than 1: 2 [14, 15]. The immunophenotype of the B-CLL leukemic clone was characterized by the expression of CD5+ and CD23+ antigens in a population of CD 19-positive lymphoid cells. The number of cells expressing markers was determined as a percentage.

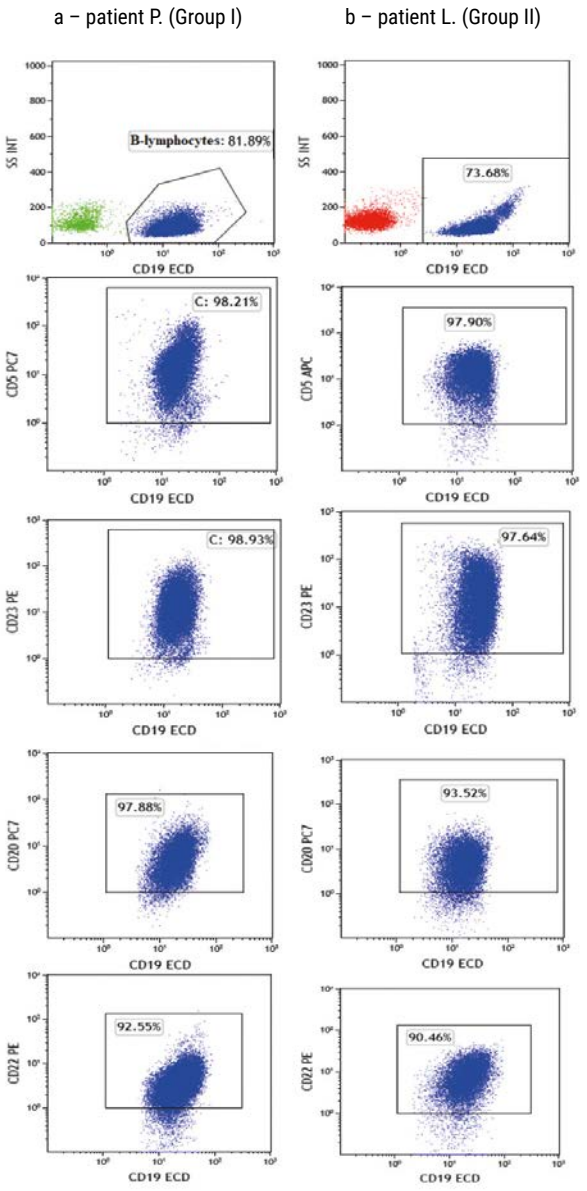

Fig. 1. Results of immunophenotyping of peripheral blood of CLL patients by flow cytometry. Dot graphs of the expression of the main markers analyzed, the blue color indicates the population of pathological B-lymphocytes: a – patient P. (group I), b – patient L. (group II).

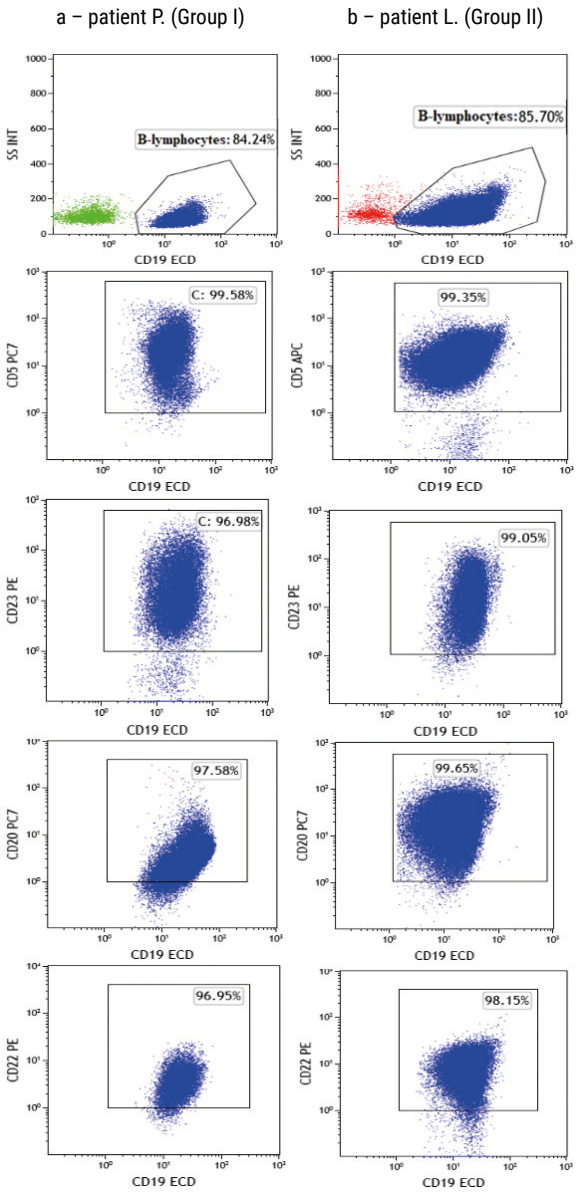

Fig. 2. Results of immunophenotyping of the bone marrow of CLL patients by flow cytometry. Dot graphs of the expression of the main markers analyzed, the blue color indicates the population of pathological B-lymphocytes: a – patient P. (group I), b – patient L. (group II).

RESEARCH RESULTS AND DISCUSSION

The immunophenotype of bone marrow and peripheral blood lymphocytes was studied in all patients with CLL. Monoclonal B-cell proliferation of lymphocytes with an immunophenotype characteristic of B-CLL/lymphoma from small lymphocytes — CD19+/CD5+/CD23+/CD20+ (weak expression)/CD22+ (weak expression) was detected. When determining clonality by restriction of light chains of surface immunoglobulins-kappa or lambda, it was found that in 22 patients (73.3%), tumor cells Express k-light chains of immunoglobulins — from 87.5% to 100% (group I), in 8 (26.7%) — λ — from 95.9% to 100% (group II) (fig. 1, 2, 3).

CD38 activation antigen is represented variably: in group I from 0.1% to 94.5%, in group II from 0.5% to 69.2%. There were no differences in the expression of other markers. However, immunophenotyping of peripheral blood and bone marrow samples revealed certain differences between these groups of patients. The combination of lateral and direct light scattering allows us to judge the morphology of the cell as a whole and identify different cell populations for further analysis. Direct FSC light scattering gives the researcher information about the cell size. Lateral SSC light scattering allows us to judge the presence of granules in the cell, the nucleus/cytoplasm ratio, and other parameters. For example, using only the two detectors listed above allows for primary analysis of white blood cell populations. Lymphocytes are the smallest cells with a round nucleus, located lower on the SSC axis and to the left on the FSC axis, whereas neutrophils are characterized not only by a larger size, but also by polymorphonuclearity, and therefore they are located higher and to the right in the diagram. Thus, in patients of group I (CD19k+/CD5+/CD23+), the distribution of tumor cells showed morphological uniformity, which was reflected in the low values of light scattering parameters in the diagram: the location to the left on the FSC axis — from 200 to 400 units / lower on the SSC axis — from 10 to 160 units. In group II (CD19λ+/CD5+/CD23+), on the contrary, on the light scattering sketogram, the lymphoid zone is heterogeneous and stretched: the location to the right on the FSC axis is from 200 to 1000 units /higher on the SSC axis is from 10 to 400 units, closer to the monocyte zone, which indicates morphological polymorphism of tumor cells. It was noted that this pattern was typical for both peripheral blood and bone marrow (fig. 4).

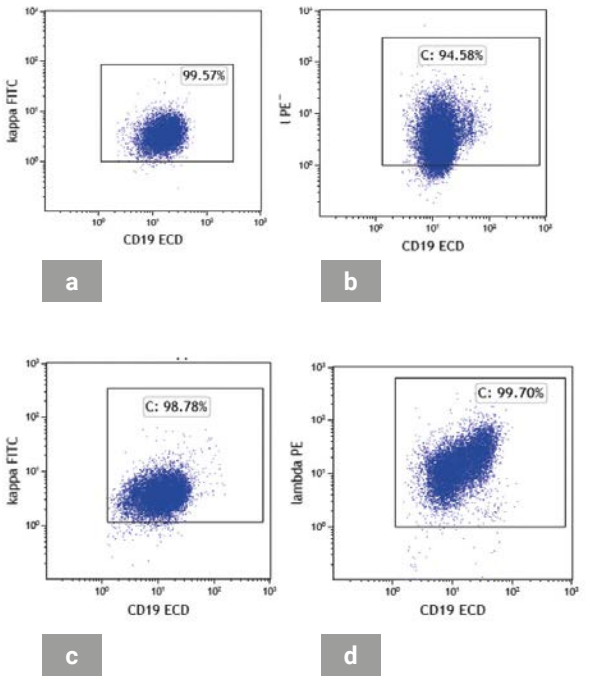

Fig. 3. Histograms of expression of light chains of surface immunoglobulins (kappa/lambda). The population of pathological B-lymphocytes is highlighted in blue: a – peripheral blood of patient P. (group I), b – peripheral blood of patient L. (group II), c – bone marrow of patient P. (group I), d – bone marrow of patient L. (group II).

Also were noted the differences in expression of general leukocyte antigen CD45 in the blood and bone marrow: in the I group, the expression of higher — intensity fluorescence monoclonal population of b-lymphocytes is in a scatter chart on a scale of CD45 in the second half of the third decade and fourth decade — more than in the second. In this group, aberrant B-lymphocytes in terms of fluorescence intensity on the dot graph on the CD45 scale lie in the third decade — to the left than in the I-th (fig. 5).

It is known that the level of CD45 expression increases with the differentiation of hematopoietic cells from immature precursors to Mature forms: on point graphs, cells with minimal ex-

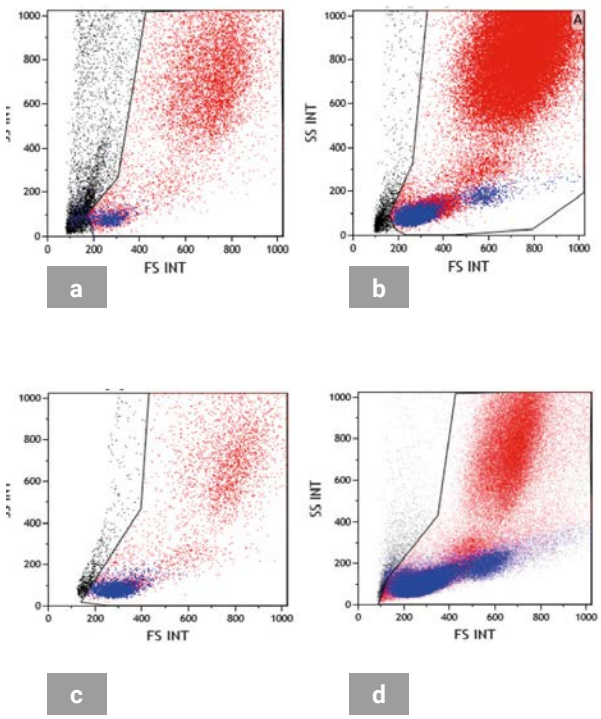

Fig. 4. Results of immunophenotyping of biological material of CLL patients by flow cytometry. Allocation of a lymphocytic gate by parameters of light scattering channels. The population of pathological B-lymphocytes is highlighted in blue: a – peripheral blood of patient P. (group I), b – peripheral blood of patient L. (group II), c – bone marrow of patient P. (group I), d – bone marrow of patient L. (group II).

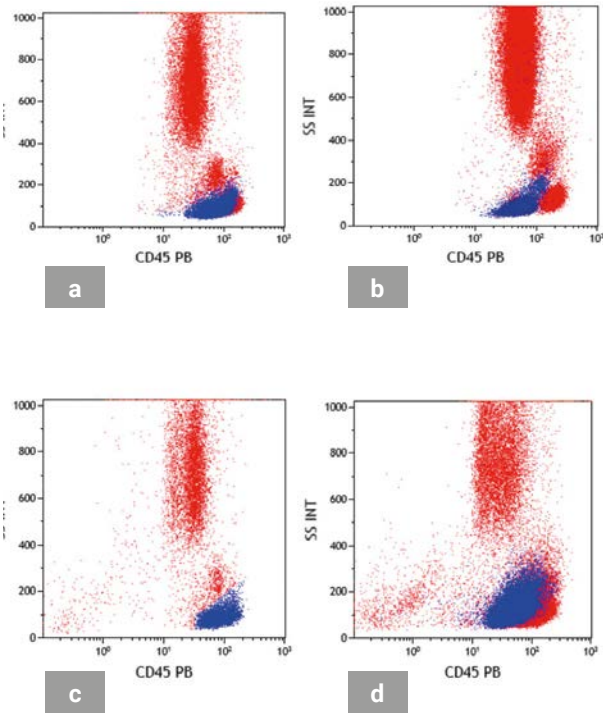

Fig. 5. Results of immunophenotyping of biological material of CLL patients by flow cytometry. Isolation of aberrant b-lymphocyte gate (in blue) by CD45 expression and lateral light scattering (SSC): a – peripheral blood of patient P. (group I), b – peripheral blood of patient L. (group II), c – bone marrow of patient P. (group I), d – bone marrow of patient L. (group II).

Table 1. Indicators of general clinical blood analysis in CLL patients (M±m)

Parameters of the leukocyte profile, %	Groups	
	I *n*=22	II *n*=8
The total number of leukocytes, ×10^9/l	39.96±26.42	35.16±29.30
Myelocytes, %	0.18±0.01	0.50±0.044*
Neutrophils, %	22.05±3.46	15.00±1.41
Eosinophils, %	0.86±0.049	0.42±0.038*
Basophils, %	0.15±0.07	0.67±0.047*
Monocytes, %	2.92±0.31	4.92±0.12*
Prolymphocytes, %	-	8.05±1.73
Lymphocytes, %	72.98±5.76	70.50±7.87

Note: * – differences are statistically significant at p<0.05-0.001

pression (blasts) lie to the left on the scale, myeloid cells occupy an intermediate position, and Mature lymphocytes with the maximum level of expression are located to the right on the scale. [16]. In this regard, it is obvious that in the population of CD19k+/CD5+/CD23+ the tumor clone is represented by Mature cells, and in the population of Cd19k+/CD5+/CD23+ — by less Mature and/or intermediate forms.

The data of the General clinical blood analysis indicate that there are no statistically significant differences in the level of the total number of white blood cells and lymphocytes in patients of CLL groups I and II (table 1). In group I, the WBC was-39.96±26.42×109/l, in group II -- 35.16±29.3 ×109/l and ranged from 10.4 to 113.6 × 109/l and from 14.51 to 85.84 × 109/l, respectively. There is marked lymphocytosis in peripheral blood up to 72.98±5.76% in group I and 70.50±7.87% in group II. However, in group II, in contrast to the I-th, prolymphocytes are determined, making an average of 8.05±1.73% of the total level of white blood cells.

In the bone marrow of CLL patients, pronounced lymphocytosis is observed against the background of suppression of granulocytic and erythroid sprouts of hematopoiesis. The observed changes are more pronounced in group II (table 2). the content of lymphocytes in group I was 62.15±7.47%, in group II — 76.10±8.76% of the total number of myelocaryocytes.

Microscopic examination of blood and bone marrow smears confirmed the differences in the pathological population of lymphoid cells in terms of light scattering parameters established during immunophenotyping. In group I patients (restriction of Kappa light chains of immunoglobulins), lymphoid cells are represented by small cells of the same type with a sparse, often non-visualized cytoplasm. The nuclei have a lumpy chromatin structure, without distinct nucleoli (fig. 6).

In group II patients (restriction of lambda light chains of immunoglobulins) in blood and bone marrow preparations, the size of cells in the lymphoid population varies from small to large, with rounded or folded nuclei, smoothed chromatin structure, 1–2 nuclei, abundant cytoplasm (fig. 7).

So, the degree of severity of lymphoid infiltration of the bone marrow and, as a result, the suppression of granulocytic and erythroid sprouts of hematopoiesis are more pronounced in patients of group II. Attention was drawn to the difference in morphological characteristics of lymphocyte

Table 2. Myelogram indicators in CLL patients (M±m)

Indicators	Groups	
	I *n*=22	II *n*=8
Myelocaryocytes, In 1mcl ×10^9/l	100.68±42.98	104.76±58.82
NBK, %	2.21±0.72	2.98±0.42
Granulocyte germ cells, %	27.63±3.36	14.76±3.92*
Monocytes, %	1.09±0.98	1.00±0.60*
Lymphocytes, %	62.15±7.47	76.10±8.76*
Megakaryocytes, %	0.20±0.06	0.20±0.05
Erythroid germ cells, %	6.87±1.38	4.84±2.88

Note: * – differences are statistically significant at p<0.05-0.001

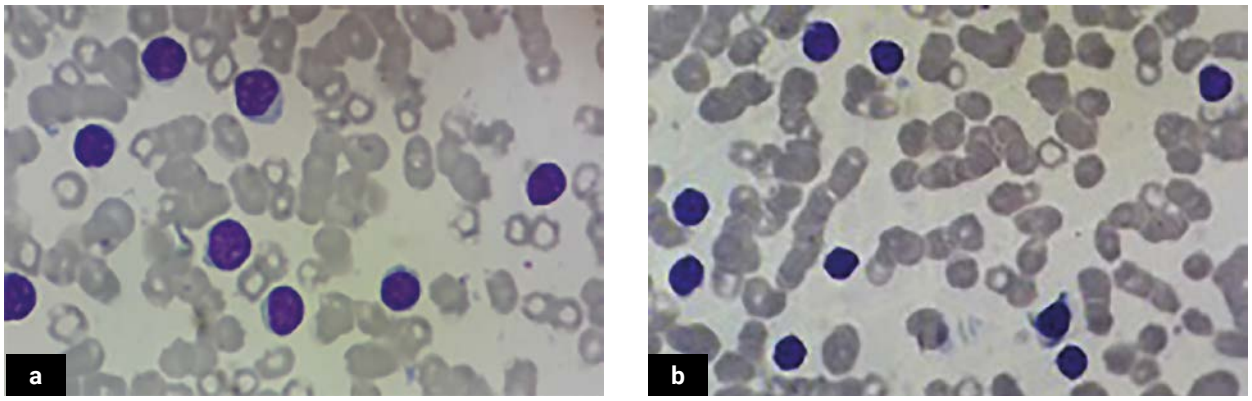

Fig. 6: a – peripheral blood, b – bone marrow. Mature monomorphic lymphocytes with dense nuclei. Painting on Pappenheim-Kryukov ×1000

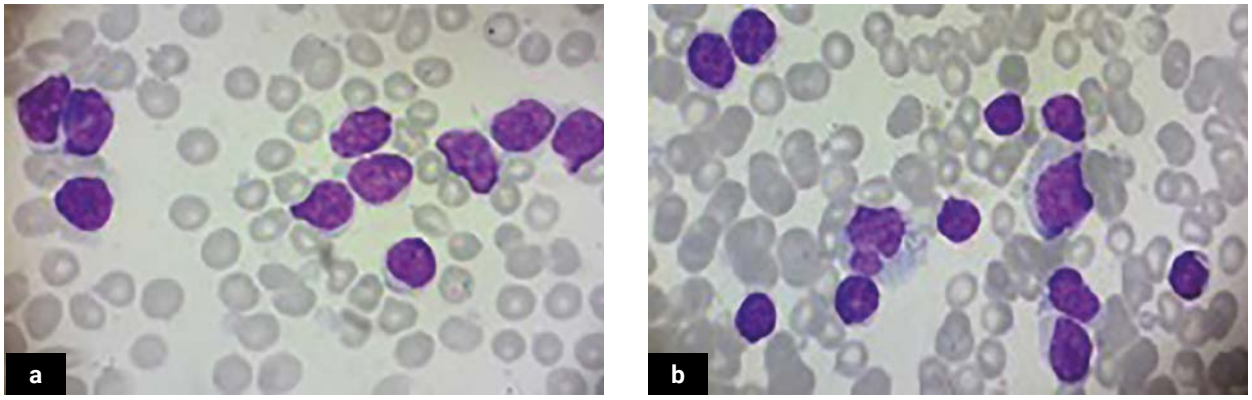

Fig. 7. a – peripheral blood, b – bone marrow. Atypical lymphocytes with a broad rim of cytoplasm, with the nuclei round or folded shape. Painting on Pappenheim-Kryukov ×1000

populations in the blood and bone marrow of the analyzed groups of patients.

Thus, the combination of results of immunophenotyping and microscopic examination of the lymphoid population demonstrated obvious morphological differences between tumor clones with different restriction of light chains of immunoglobulins (kappa or lambda) in patients with CLL, which undoubtedly requires further study.

CONCLUSIONS

The study established immunophenotypic and morphological differences in lymphoid populations expressing either kappa — or lambda-light chains of immunoglobulins. The obtained data are extremely important for identifying risk groups among patients with biologically heterogeneous variants of chronic lymphocytic leukemia (typical and mixed-cell).

Authors contribution:

Guskova N.K. – research design development, morphological research, systematization and analysis of the obtained data, writing the text of the manuscript, consultation.

Selyutina O.N. – performing cytofluorimetric studies, collecting clinical material, systematization and analysis of the obtained data, reviewing publications on the topic of the article, writing the text of the manuscript.

Novikova I.A. – analysis of the received data, consultation.

Maksimov A.I. – analysis of the obtained data, consultation.

Nozdricheva A.S. – collection of clinical material.

Abakumova S.V. – collection of clinical material.

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