The current classification of lymphoid tumors (LT), presented by WHO in 2017, continues to be based on the concept of the development of tumor cells from normal progenitor cells, which stopped at various stages of their differentiation as a result of malignant transformation.\(^1\) Differences in morphology, immunophenotype, somatic hypermutation of immunoglobulin heavy chain genes, and specific genetic abnormalities determine individual nosological entity of lymphoproliferative diseases.

**Objectives:** Composite lymphomas (CL), which are a combination of different types of lymphomas in a single patient can occur simultaneously or sequentially. Diagnosis and treatment of CL require a full range of modern approaches.

**Methods:** The study included 37 cases of CL (M:F=2:1), the median age of patients was 64 (38-83 years). All patients underwent a full range of diagnostic procedures, including histopathological, immunohistochemical/immunophenotypic (flow cytometry), cytogenetic/FISH, and molecular tests at the National Research Centre for Hematology, Moscow.

**Results:** Metachronous CL were observed in 17 cases and the most common type of the second lymphoma was diffuse large B-cell lymphoma (DLBCL) or Hodgkin’s lymphoma (HL). In 30% of cases, DLBCL developed after HL therapy, and in 30% - after therapy of angioimmunoblastic T-cell lymphoma (AITL). In 20 cases of synchronous CL the most common was B-cell chronic lymphocytic leukemia (B-CLL) combined with hairy cell leukemia (HCL) - 54.5%, large granular lymphocytic leukemia, marginal zone lymphoma (MZL), follicular lymphoma, multiple myeloma, or mycosis fungoides. A combination of HL with other lymphoma was observed in 25% of cases (HL+MZL represent 60% of cases).

**Conclusion:** CL are excellent models for studying the complex process of tumor cells evolution during the course of the disease. Treatment of CL is a non-trivial task and aims to control both diseases.

**Keywords:** Composite lymphomas

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ship and vice versa. In most cases, tumor substrates of CL develop simultaneously in one organ or one anatomical region, with one tumor component prevailing over the other. The most common development of high-grade lymphoma is against the background of long-term indolent lymphoma, but such cases must be strictly differentiated from cases of tumor transformation. The term “composite lymphoma” was introduced in 1954 by Custer, and later in 1977 improved by Kim.

Diagnosis of CL is often difficult and requires a comprehensive approach using the full range of modern laboratory methods: histopathological, immunohistochemical, and molecular genetics. The study of clonal rearrangements of T-cell receptor (TCR) genes and immunoglobulin (Ig) genes is important for the differential diagnosis of tumor and reactive conditions in hematology. Normally, each T-lymphocyte has an unique TCR, as well as a B-lymphocyte – a unique Ig. High diversity is provided by the complex rearrangement of the gene segments encoding the formation of these receptors. Thus, the identification of multiple clonal rearrangements of TCR or Ig genes in the study material, or the presence of both T- and B-cell clonality, is particularly important in the diagnosis of CL. Determination of the nucleotide sequence and belonging of the V-genes of the heavy chain of immunoglobulins to one or different families allows us to determine whether the substrates of CL are products of one or different tumor clones.

Treatment of CL is a non-trivial and complex task, not yet standardized.

In this article, we present an analysis of 37 CL cases observed in the National Research Center for Hematology, Moscow, Russia from 2012 to 2019. Histological, molecular-genetic, and therapeutic features of three clinical cases are presented in detail.

**Methods**

The study included 37 cases of CL (M:F=2:1), the median age of patients was 64 (38-83 years). All patients underwent a full range of diagnostic tests, including histopathological, immunohistochemical/immunophenotypic, cytogenetic/FISH, and molecular methods.

**Results and Discussion**

Among 37 patients diagnosed with CL, 54% (n=20) of cases had synchronous and 46% (n=17) cases had metachronous tumor development.

As it shown in figure 1, among 20 cases of synchronous diseases, the most common were combinations of B-CLL with various LT in 55% (n=11) cases, and a combination of HL with other LT (25% of cases, n=5).

In the studied sample, B-CLL was combined with HCL in more than half (n=6, 54.5%) of cases. At the same time, in all cases, patients required therapy for HCL, but not for B-CLL. The remaining cases included a combination of B-CLL with large granular lymphocytic leukemia (n=1), MZL (n=1), follicular lymphoma (n=1), multiple myeloma (n=1), and fungal mycosis (n=1).

It was previously reported, that combinations of two B-cell non-Hodgkin lymphomas can cover almost all possible combinations, and in 61% of cases they consist of two clonally unrelated B-cell tumors, which was proved by the study of IgH gene rearrangements and translocations – t(14;18) for follicular lymphoma and t(11;14) for mantle cell lymphoma.

In our sample, synchronous development of HL with other LT was rare, and in 60% (n=3) of these cases, a combination of HL with MZL was noted. Moreover, it is unclear whether HL in this combination is a clonal transformation from MZL cells or is a second tumor developing de novo. As often in both cell types we have found the same types of IGHV rearrangement. This may indicate that B-cells have passed germinal center of the follicle and acquired some mutations subsequently gave rise to the 2 clones, responsible for the development of MZL and HL respectively. Combinations of HL with follicular lymphoma (n=1), and mantle cell lymphoma (n=1) were also observed.

Among metachronous CL, the development of DLBCL after treatment of other LT – 10 out of 17 cases (59%) and HL after treatment of other LT – 5 out of 17 cases (29%) were most often noted (Fig. 2).

In 30% of cases (n=3), DLBCL developed after treatment of HL, in 30% of cases (n=3) – after treatment of AITL. The median time to development of the 2nd LT in this group of
patients was 6 years (from 7 months to 40 years). HL as a second LT developed after treatment of AITL in two cases, and after treatment of HCL, B-CLL, and T-cell lymphoma in one case, respectively.

Treatment of CL is a complex task, with no clear consensus recommendations for the management of patients so far. Presumably aggressive lymphoma (for example, HL or DLBCL) in combination with long-term indolent (for example, follicular lymphoma or B-CLL) should be treated, while "watch and wait" tactics should adhere to indolent lymphoma. The most difficult cases are simultaneous manifestation of both substrates of CL (clinical case 2, presented below). In such situations, it is difficult to stage each of the lymphomas, while the volume of tumor lesion with one or another substrate of CL affects the choice of intensity and type of therapy. In cases of combination of classical HL with indolent B-cell lymphoma, we treated HL with standard courses with the addition of rituximab, which helped reduce the substrate of indolent lymphoma and achieve long-term remissions.

According to our observations, the course of disease and the response to therapy in patients with HCL, indolent B-cell lymphomas, and DLBCL, are similar whether they are part of CL or presented separately. Therefore, each disease could be treated according to the regimens prescribed for this disease. The exception, in our experience, were patients with classical HL, which in combination with indolent lymphomas manifested at an older age than HL, presented separately, and this is probably why we faced a large number of complications due to polychemotherapy courses.

Here we present the most interesting clinical cases in detail.

**Clinical case 1** (synchronous development of classical HL and MZL with subsequent transformation into DLBCL). Patient V, born in 1953, was diagnosed with HL, NS type I, stage IVB with lesions of the peripheral, intrathoracic, retroperitoneal lymph nodes (LN), spleen, and bone marrow (BM) in 2011 (at the age of 58) based on histological and immunohistochemical (IHC) studies of a biopsy of the peripheral LN and BM. At diagnosis, the morphological and IHC picture of HL lesions revealed some laboratory features that attracted attention:

1. histological study of LN biopsy showed HL substrate.
2. B-cell clonality (rearrangements of IGHV genes) was revealed in LN (Fig. 3).

It is known that in HL tumor cells are represented by a small population (from 0.1 to 10%) and IGHV gene rearrangements in LN biopsies are detected in 16 - 24% cases only. Furthermore, B-cell clonality is low and detected against significant polyclonal background (Fig. 3). Therefore B-cell clonality in HL should always alert clinicians to the presence of B-cell lymphoma as a second disease.

The patient underwent 8 courses of BEACOPP-14 program chemotherapy (X/2011-III/2012). According to PET-CT data, complete metabolic remission was confirmed after treatment, which persisted for 2 years.

Since III/2014, there has been a slow gradual increase in the size of the spleen and intra-abdominal LNs with a satis-

![Figure 2. Distribution of metachronous composite lymphomas (described in the text). DLBCL - diffuse large B-cell lymphoma; HL - Hodgkin’s lymphoma; HCL - hairy cell leukemia; B-CLL - B-cell chronic lymphocytic leukemia; MALT – MALT-lymphoma; LT - lymphoproliferative diseases.](image-url)

Figure 2. Distribution of metachronous composite lymphomas (described in the text). DLBCL - diffuse large B-cell lymphoma; HL - Hodgkin’s lymphoma; HCL - hairy cell leukemia; B-CLL - B-cell chronic lymphocytic leukemia; MALT – MALT-lymphoma; LT - lymphoproliferative diseases.

![Figure 3. Fragment analysis of B-cell clonality (IGH) in patient B., 1953: clonal rearrangement (280bp) was detected in the material of the peripheral lymph node biopsy (LN) in 2011 (a), retroperitoneal LN in 2015 (c), spleen in 2016 (d), retroperitoneal LN in 2017 (e), and in bone marrow (BM) in 2017 (f).](image-url)

Figure 3. Fragment analysis of B-cell clonality (IGH) in patient B., 1953: clonal rearrangement (280bp) was detected in the material of the peripheral lymph node biopsy (LN) in 2011 (a), retroperitoneal LN in 2015 (c), spleen in 2016 (d), retroperitoneal LN in 2017 (e), and in bone marrow (BM) in 2017 (f).
factory general condition of the patient. No treatment was performed.

In XI/2015, histological examination of BM revealed small-cell lymphoid infiltrates expressing CD20 and PAX-5 according to IHC data and not expressing cyclin D1, CD5, CD23. There were no signs of damage specific for HL. Immunophenotyping of BM show that about 20% of all lymphocytes were represented by a monoclonal population of B-lymphocytes with the CD19k+CD20++CD5+CD23-CD10-CD200-CD38-CD43- immunophenotype. No chromosomal aberrations were found in the standard cytogenetic study of BM.

In XII/2015, a laparoscopic biopsy of the retroperitoneal LN and liver was performed. There was a disruption of LN tissue architectonics due to a dense diffuse – nodular proliferation of small lymphoid cells with round-oval, angular, centrocyte-like nuclei; with an admixture of scattered large cells with the morphology of centroblasts. In some areas, subcapsular preexisting follicles with signs of colonization by small cell proliferation with CD20+, PAX-5+, BCL2+, CD10-, cyclin D1-, and BCL6- phenotype. Ki-67 index of proliferative activity was 10-15%. At the same time, large cells with sharply hypertrophied eosinophilic nucleioli with broad light or dense eosinophilic cytoplasm with Hodgkin cell morphology, binuclear forms with Reed-Sternberg cell morphology expressing CD15, CD30, and weakly PAX-5, and large atypical cells were scattered among the small cell proliferation.

Liver tissue showed minimal signs of involvement in small-cell B-cell lymphoma.

Thus, at this stage, based on the results of histological examination of the biopsy material of retroperitoneal LN, liver, and BM, the patient was diagnosed with CL represented by HL (retroperitoneal LN) and MZL (retroperitoneal LN, liver, BM). B-cell clone detected in histological samples did not differ in the length of rearranged IGHV gene from the one found at the onset of HL (Fig. 3).

In V/2016, a splenectomy was performed. IHC revealed small cell lymphoid proliferation with CD20 expression, a significant part of them were IgD+, CD11c+, DBA44+, TRAP+, with a pronounced extracellular component. Large tumor cells scattered along the periphery of follicle-like structures expressed CD15, CD30, PAX-5, and fascin; they did not express BoB1, CD79a, or CD20 under the corresponding "internal" controls. Immunohistochemistry of splenic LNs were similar and represented by both substrate of HL, NS type I (large tumor cells with reactive T-cell microenvironment and rosette formation), and substrate of MZL.

Thus, a histological picture of CL was seen in the spleen and peripheral LN, as well as in retroperitoneal LN. Subsequently, the patient had disease progression with the increase in the size of retroperitoneal LN. Taking into account the indolent course of the disease, the patient underwent 5 courses of immunochemotherapy under the RB program (rituximab-bendamustine). Partial response was received. However, later in VI/2017, a rapid increase in the size of visceral LNs max to 38-40 mm was again observed. PET/CT was not performed. Based on histological examination of repeated biopsy of retroperitoneal LN, the transformation of MZL to DLBCL, CD20-non-GCB-type, Ki-67 to 80% was confirmed. B-cell clonality remained unchanged (Fig. 3). The patient underwent 1 course of chemotherapy under the DHAP program, 1 course of EPOCH, with a temporary positive effect. Chemotherapy courses were complicated by severe infectious complications, from which the patient died in a state of progression of the underlying disease.

According to the literature, almost half of the CL represented by classical HL and B-cell non-Hodgkin’s lymphoma were clonally related, while the other half were clonally unrelated. In these cases, the development of the second lymphoma may have been an accidental event or may have been the result of chemotherapy or radiation therapy that the patient received to treat the first lymphoma.

In the case presented B-cell clone originally identified in the LN material at the onset of HL, persisted unchanged throughout the observation period. Therefore it could be concluded, that same B-cell clone gave rise to the second HL and to MZL, which was indolent for about 5 years, and lately transformed into DLBCL (Fig. 3).

**Clinical case 2** (synchronous development of classical HL and MZL). Patient C, born in 1958. The onset of the disease since 2014 (at the age of 56 years) in the form of B-symptoms appearance. Since 2015, a gradual increase in the size of the spleen, isolated retroperitoneal LNs (20*12 mm) and hepatic nodes (21*10 mm) is noted. Immunophenotyping of BM cells revealed a monoclonal population of B-lymphocytes with an immunophenotype corresponding to the MZL. Histological and IHC studies of BM also characterized MZL. Taking into account the increasing splenomegaly up to 370*131mm, anemia up to 82 g/l, progression of B-symptoms, the patient underwent splenectomy with liver biopsy. Removed spleen 340*230*100mm weighing 5500 g. Examination of the spleen showed a disruption of its histological structure due to diffuse-nodular lymphoid infiltrate from small and medium-sized cells with round-oval nuclei, some of them with blastoid morphology, with increased mitotic activity (6-8 mitoses in the X400 field of view). At the same time, within large nodule-like structures, among small and medium-sized lymphoid cells with atyp-
ical nuclei, large tumor cells with the morphology of Hodgkin and Reed-Sternberg cells are located separately.

The IHC study confirmed the presence of CL, represented by MZL with signs of blast transformation (in the spleen, liver, regional LN, BM) and classical EBV-positive HL (in the spleen and regional LN). Ki-67 expression from 40% to 60% in tumor cells.

The patient underwent 6 courses of R-BEACOPP-14 pro-gram chemotherapy with the introduction of rituximab 1 time in 2 courses. Entecavir was also delivered constantly, taking into account the concomitant chronic viral hepatitis B. Complete PET-negative remission was achieved, BM was sanitized. He is in remission for 26 months.

**Clinical case 3** (synchronous development of two B-cell LT). Patient G., born in 1960. The disease diagnosed in April 2017 (at the age of 57) with fever, joint syndrome, cytopenia (thrombocytopenia 78*10^9/l and leukopenia 1.4*10^9/l), pronounced splenomegaly (226*196 mm). After further examination, the diagnosis of HCL was verified based on the presence in the blood of a monoclonal population of B-lymphocytes with the characteristic immunophenotype CD19k+CD20+ br+CD22+ CD79b+ CD25-C- D81+ROR-1+CD11c+CD200+ CD10-CD5- with additional CD23+ expression, and a mutation of the B-RAF gene leading to the amino acid substitution of V600E.

From IX/2016 to II/2017, the patient underwent the first stage alpha-interferon therapy –3 million ME subcutaneously every other day with positive dynamics in the form of spleen reduction to 176*63 mm, blood counts improvement.

In II/2017, a course of therapy with cladribine (0.14 mg/kg/day 5 days) was performed, after which the spleen remained the same size, and single small intra-abdominal LNs were located in the abdominal cavity. Taking into account splenomegaly and lymphadenopathy, the patient was recommended quarterly administration of rituximab at a dose of 375 mg/m^2 for a year, but the patient did not receive this therapy.

In VII/2017, the patient noted an increase in the size of the abdomen, loss of appetite and weight. In VIII/2017, there was a sharp pain in the left abdomen after physical exertion. During the examination – splenomegaly 301*250*91 mm with an infarction zone up to 51*72*38 mm; an increase the hepatic LNs up to 50 mm and the splenic LNs up to 30 mm, in the projection of the small omentum LNs up to 40 mm; pancytopenia (leukopenia 2.2*10^9/l, thrombocytopenia 68*10^9/l, anemia 66 g/l); febrile fever.

Splenectomy with liver biopsy was performed. Spleen immunophenotyping revealed 2 monoclonal populations (Fig. 4): 99% with the immunophenotype of mantle cell lymphoma (CD19k+ CD20+ CD5+ CD22+ CD79b+ CD25+C- D81+ROR-1+CD10-CD103-),

• 0.9% with HCL immunophenotype (CD19k+ CD20bright+ CD22brightCD103+ LAIR-1+ CD11c+ CD25+ CD81+ ROR-1+ CD200+ CD10-CD5-).

Morphological studies of the spleen (with IHC), regional LN, and liver tissue corresponded to MCL. Histological, IHC, and immunophenotypic studies of BM also revealed MCL involvement (Fig. 5). Cytogenetic examination of the BM and spleen revealed translocation t(11;14)(q13;q32.3) in 50% of the nuclei; deletions 17p13/TR53, and monosomy 17 were not detected. Populations with the HCL immunophenotype were not detected in BM.

A molecular study of B-cell clonality in spleen tissue, BM, and peripheral blood revealed a clonal rearranged IGH gene product of 267 nucleotide pairs length. At the same time, in peripheral blood from 2016 (at the time of on diagnosis), a clonal product was also detected by IGH gene rearrangements, but its size differed from the clone that characterizes the MCL substrate. Data from the fragment analysis is shown in figure 6. Changes in the clonal rearrangements of the Ig and TCR genes during the course of the disease are typical for patients with acute lymphoblastic leukemia,[22] which is explained by the increased activity of the recombinant complex in immature tumor cells. However, this situation is not typical for mature cell lymphoproliferative diseases[23, 24] and rather characterizes the development of a new disease.

![Figure 4. Flow cytometry of spleen biopsy. Red color – the population of tumor cells of the mantle cell lymphoma (99%), dark blue color – the population of tumor cells of hairy cell leukemia (0.9%). Blue – normal T-and NK-lymphocytes.](image_url)
To date, we have not found any descriptions of cases of synchronous development of HCL and MCL in the literature. In this case, the two tumors were clonally unrelated, which was confirmed by sequencing of IGH genes, as well as immunomagnetic selection of CD103+ and CD5+ lymphocytes, followed by analysis of B-cell clonality in each of the populations.

Given the lack of minimal volume of HCL and no signs of progression, HCL therapy was not delivered. The patient was treated for MCL – 6 courses of immunochemotherapy under the R-BAC program. Complete remission of the disease was achieved, confirmed by PET-CT, histological, molecular, and cytogenetic studies of BM, and maintenance therapy with rituximab is being performed. Remission of both diseases persists for 24 months (flow cytometry does not detect tumor cell populations).

**Conclusion**

Primary multiple LT with localization in one or more areas can be presented in one patient. Diagnosis of such conditions is possible only through a comprehensive assessment of the clinical picture and data from the entire range of modern histological, immunohistochemical, and molecular genetic methods. If there is an atypical clinical course of the disease or there are laboratory signs that do not fit into the classic picture, a full examination is necessary to exclude the second disease. Clonally related CL are excellent models for studying the complex process of transformation of tumor cells during the course of the disease. Treatment of CL is a non-trivial task and is aimed at controlling both diseases.

**Disclosures**

**Statement of Ethics:** The study was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 2008. Written informed consent was given by all participants.

**Ethics Committee Approval:** Approved by the Ethics Committee of National Research Center for Hematology (protocol #01/2012).

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