We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

5,800
Open access books available

142,000
International authors and editors

180M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter

Clinical and Laboratory Data Which Are Not Typical of De Novo Diffuse Large B-Cell Lymphoma

Aminat Magomedova, Anna Misyurina, Sergey Kravchenko, Fatima Babaeva and Andrey Vorobiev

Abstract

Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous group of diseases of the lymphatic system, which is represented by de novo and secondary tumors resulting from the transformation of indolent lymphomas. In the absence of a long history of the disease at the stage of histological transformation (HT), it is difficult to distinguish between de novo and secondary diffuse large B-cell lymphoma. According to the data of a randomized study, we obtained clinical and laboratory data that are not typical for de novo diffuse large B-cell lymphoma. These include exclusive, predominant retroperitoneal localization, compression of the ureters/kidneys with or without the development of acute renal failure (ARF), unilateral lymphostasis of the leg due to compression of the inguinal, iliac lymph nodes by the conglomerate, intratumor in the central nervous system (CNS) at the onset/relapse/progression of the disease, discordant bone marrow involvement, blood involvement, paraprotein secretion.

Keywords: DLBCL, ARF, retroperitoneal localization, asymmetric lymphostasis of the leg, CNS intratumor, paraprotein, discordant involvement of bone marrow, blood involvement, relapses

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) was isolated from the general group of lymphatic tumors by histological and immunotypic features—diffuse proliferation of large B-cells, which either can form a structure of diffuse growth or be diffusely scattered among nontumor cells of a specific organ [1, 2].

In the past, lymphomas were classified solely for histological features. The advent of immunophenotyping of tumor cells changed the situation, but it turned out that some lymphoproliferative diseases (LPD), including DLBCL, do not have an unambiguous specific immunophenotype. All markers (pan B-cell, CD10, Bcl-2, Bcl-6, CD5, MUM1, CD30, CD23, ALK, and CD138) occurring in DLBCL also found in other LPD [3–5]. Subsequently, cytogenetic disorders made it possible to distinguish a number of diseases of the lymphatic system into separate nosological forms. These include *c-MYC gene* rearrangement and 11q aberration, characteristic of Burkitt's lymphoma; rearrangement of gene *BCL-2*,

characteristic of follicular lymphoma (FL); the *CYCLIN D1* gene, characteristic of mantle cell lymphoma; t(2;5) (p23;p35); characteristic of anaplastic T-cell lymphoma, etc. The combination of rearrangement of the *c-MYC* gene with rearrangement of the *BCL2* and/or *BCL6 genes* in the recent past made it possible to isolate a separate form of high-grade B-cell lymphoma from DLBCL [6–11]. However, de novo DLBCL, unspecified, stands apart from all B-cell lymphomas, due to the absence of immunophenotype characteristic only of it, cytogenetic and molecular markers. Therefore, the diagnosis was made after excluding all other large B-cell lymphomas.

Although the "boundaries" of DLBCL are defined in the World Health Organization (WHO) classification, it is currently overdiagnosed. Moreover, the latter affects the tactics of choosing an induction course and therapy at the end of treatment.

The absence of clear clinical, morphological, immunophenotypic, cytogenetic, and molecular differential diagnostic signs puts the clinician in a difficult position, who needs to determine the polychemotherapy program, avoiding the appointment of the so-called R-CHOP to all patients, and in turn, without exposing patients unjustified risk, the appointment of high-dose therapy. Moreover, in cases of DLBCL because of the transformation of indolent lymphomas, patients remain without maintenance therapy with rituximab for 2 years, which is currently mandatory.

All of the above dictate the need to highlight the decisive differential diagnostic clinical and laboratory data of the disease; therefore, clinicians have to take into account all the details that are of key importance for differential diagnosis.

1.1 Medical history

Many mature cell LPDs transformed in DLBCL with varying frequency, in some cases. A carefully collected history helps to find out whether it is a de novo tumor or the result of the transformation of indolent lymphomas. Although the history of the disease is a purely subjective sign, and not all patients pay attention to some minor changes in the state of health or the results of the study, doctors must scrupulously find out all the details of the history. This is the time from the first manifestations of the disease to the diagnosis, independent reduction in the size of the tumor before starting treatment, multiple biopsies, and ambiguous data of histological, immunohistochemically studies; study medical documentation, correctly interpret the results of previous studies. Despite the absence of clear criteria regarding the duration of the history, it is known that de novo DLBCL does not proceed for years and has an aggressive course if this is not a local process. In the terminal stage, the histological picture of any indolent lymphomas may look like DLBCL, which leads to an error diagnosis by pathologists. Therefore, a carefully collected anamnesis, in some cases, helps to establish an accurate diagnosis, to identify cases of indolent lymphomas.

1.2 Clinical manifestations

In patients with DLBCL, there is no clinical picture typical only for it; it all depends on the localization of the tumor, the extent of the lesion, the presence of B-symptoms, etc. Therefore, the diagnosis is based on histological and immunohistochemically studies. However, at the same time, at present, some clinical manifestations give us a clue about de novo or the transformation of DLBCL. The experience of previous years allowed us to assume that an intratumor in the central

nervous system (CNS) at the time of diagnosis, progression, or recurrence does not occur with de novo DLBCL. In addition, the predominant retroperitoneal localization, asymmetric lymphostasis of the legs, compression of the ureters, kidneys by tumor and impaired urinary outflow, hydronephrosis, and acute renal failure (ARF) are not typical of de novo DLBCL. It turned out that intratumor in the central nervous system does not occur in patients with de novo DLBCL, and neuroleukemia is rare.

The most common extranodal form of de novo DLBCL is gastric DLBCL. Therefore, it was noticed that the pyloric stenosis, which persists after achieving complete remission (CR), due to the formation of fibrosis and requires bougienage or surgery, is not typical of de novo DLBCL of the stomach. Many of our assumptions were subsequently confirmed by the data of repeated biopsies and histological, immunohistochemical studies performed in progression and relapse within the framework of the DLBCL-2015 protocol. Further monitoring of patients is required to confirm some of the assumptions.

1.3 Bone marrow trephine biopsy data

Most often, 25–35%, FL transformed from indolent lymphomas in DLBCL [8]; therefore, cases with the presence of rearrangement of the *BCL2* gene are now referred to as FL. Previously, it was thought that rearrangements of the *BCL2* gene could also occur in de novo DLBCL. The assumption that such cases are a transformation of FL was made by us in 2004 and confirmed later [12]. Then, we noticed that the frequency of achieving complete remission (CR) is lower and the prognosis is worse in patients in whom the morphological picture of tumor foci and bone marrow biopsy at the same time differed from each other, that is, there was a discordant involvement of bone marrow. Therefore, we analyzed the morphological differences of tumor formations and the mitotic activity of tumor cells in different lesions. The proliferative activity of lymphoid cells of the lymph node, of the stomach, tonsil, spleen, and other foci and bone marrow was different—high in lymph node and other lesions and low in the bone marrow. The tumor in the bone marrow had signs of indolent LPD—morphologically, the cells corresponded to the structure of a normal lymphocyte, without polymorphism and atypism, and had low mitotic activity. In lymph nodes or other lesions, tumor cells had all signs of aggressiveness and high-proliferative activity. In such cases, we also noticed the retroperitoneal localization of the tumor and the complications caused by it, due to the compression of the urinary tract by the tumor, most likely due to fibrosis. Therefore, pathologists should take into account the severity of fibrosis during histological, immunohistochemically examination.

Currently, special attention paid to the transformation of lymphoma from cells of the marginal zone (LMZ) (splenic, nodal forms, and LMZ mucosa-associated lymphoid tissue (MALT-lymphoma), because it is one of the indolent lymphomas, with a similar histological picture with de novo DLBCL does not have a specific immunophenotype, cytogenetic, and molecular markers. In some cases, it is impossible to distinguish lymphoma transformation of the marginal zone from de novo DLBCL without information about the previous history. The frequency of transformation of lymphoma from cells of the marginal zone to DLBCL ranges from 8 to 10% [2, 13, 14]. According to a large retrospective study, which included 340 patients with LMZ, with a mean follow-up of 4.8 years, the mean overall survival and progression-free survival for the entire population was 14.5 and 5 years, respectively. Histological transformation (HT) observed in 13 (3.8%) cases—5% with splenic form, 4% with MALT—lymphoma, and 3% with nodal LMZ. The risk

of HT was 5% at 5 and 10 years after diagnosis and 10% at 12 years. With an average follow-up of 12 months after HT, four (31%) of 13 patients died, all because of disease progression. The two-year overall survival rate after transformation was 57% [15, 16]. In 1/3 of patients with LMZ, there is an involvement of bone marrow both discordant and concordant.

It noted that the prognosis of patients with the transformation of indolent lymphomas in DLBCL is similar to the prognosis of patients with blast crisis of chronic myeloid leukemia. Therefore, young patients with HT in DLBCL may now need to undergo intensive courses of induction chemotherapy with or without subsequent transplantation in order to increase relapse-free survival.

Thus, cases with the presence of focal, focal-interstitial, and diffuse mature cell involvement of bone marrow with the histological picture of DLBCL in lymph nodes or other tumor foci are considered as an outcome of indolent lymphomas.

1.4 Laboratory data

New generation sequencing made it possible to detect tumor messenger ribonucleic acid (mRNA) in the blood, because of which DLBCL is classified into three subgroups, differing from each other in pathogenesis [17]. However, leukocytosis with the presence of tumor cells in the blood is very rare in patients with DLBCL. Even with a concordant involvement of bone marrow, in no case did we confirm the presence of tumor cells according to the data of immunophenotyping of blood by flow cytometry, as well as B-cell clonally by polymerase chain reaction (PCR). On the contrary, in patients with indolent lymphomas, such as FL and LMZ, blood involvement is more common [4, 5, 8]. Therefore, this is taken into account in the differential diagnosis of de novo DLBCL from the transformation from indolent lymphomas.

1.5 Secretion of paraprotein

The next laboratory sign of the transformation of indolent lymphomas into DLBCL is the **secretion of paraprotein**, which occurs in 1/3 of patients with LMZ, in a smaller percentage of cases of FL [4, 5, 8]

In the latest WHO classification and many publications, it is noted that the secretion of paraprotein, including an increase in the concentration of light chains, as well as lesions of intramuscular tissue, including discordant ones, are signs of a poor prognosis in patients with de novo DLBCL [2].

It has now been proven that the secretion of paraprotein is a sign of a poor prognosis in patients with DLBCL with the presence of paraprotein [18, 19].

The fact that patients with de novo DLBCL cured can be, and secondary DLBCL – is not, despite the success achieved in the treatment of LPD. The secretion of paraprotein indicates the secondary nature of DLBCL. Indolent lymphomas transformed into DLBCL relapses after anytherapy. Allogenic hematopoietic cell transplantation is the only therapeutic option for complete recovery.

1.6 Relapses after adequate induction therapy

Some forms of DLBCL were isolated from the general group by the response to therapy; therefore, in all cases of relapses, as well as the progression of DLBCL with adequate induction therapy, morphologists should pay attention to this fact when establishing the form of the disease. Since de novo DLBCL is a curable disease, treatment outcomes, namely the incidence of PR, progression, and relapse, are independent predictors of prognosis.

Relapses in patients with DLBCL with discordant involvement of bone marrow, with the secretion of paraprotein, blood involvement, as well as all the clinical manifestations described above, should suggest that these cases are the result of the transformation of indolent lymphomas and, subsequently, should receive supportive therapy.

The results of our pilot prospective study on the treatment of DLBCL patients with the modified mNHL-BFM-90 program demonstrated that all relapse cases, including late ones (two cases after 13 years) turned out to be other forms, that is, there was an overdiagnosis of de novo DLBCL.

Since 2002, we have been using a modified mNHL-BFM-90 program as an induction program for the treatment of patients with de novo DLBCL with signs of poor prognosis, which has demonstrated high efficiency, including those from the high-risk group [20]. From that moment, all our observations allowed us to identify clinical and laboratory data that are not characteristic of de novo DLBCL. These include all of the above data—a long history of the disease an independent decrease in the size of the tumor from the moment the first symptoms appear and the diagnosis is made to the start of therapy; multiple and uninformative biopsies; secretion of paraprotein; intratumor in the central nervous system initially, in relapse, in progression. Moreover, the exclusive or predominant retroperitoneal localization of the tumor with data of tumor compression of the urinary tract, as a result of which ARF, asymmetric lymphostasis of the limbs of the lower leg due to compression of the conglomerate of the inguinal and iliac lymph nodes, discordant involvement of bone marrow, blood, and relapses after adequate therapy do not occur in patients de novo DLBCL. Our pilot, prospective, and randomized studies allowed us to assume that all of the listed signs indicate the transformation of mature cell lymphomas into DLBCL, these cases are not de novo DLBCL and in such cases, patients should receive maintenance therapy with Rituximab. This is very important, especially for elderly patients.

Thus, de novo DLBCL is currently the diagnosis of exclusion among large B-cell lymphomas.

The aim of our work is to determine additional clinical and laboratory signs of differential diagnosis of de novo and transformation of indolent lymphomas into DLBCL within the framework of the DLBCL-2015 protocol.

2. Materials and methods

We are conducting a prospective multicenter randomized study on the treatment of primary patients with DLBCL with ≥2 signs of poor prognosis—the DLBCL protocol—2015 (ClinicalTrials.gov. R-DA-EPOCH-21 versus R-mNHL-BFM-90 and auto-SCT in Poor Prognosis DLBCL NCT02842931). From January 2015 to April 30, 2021, 140 patients were randomized from 13 hematology clinics in Russia. The analysis included 130 patients. Treatment was completed in 127 patients. The diagnosis of DLBCL was established according to the WHO criteria of 2008 and 2017 [2, 3].

At the diagnostic stage, all patients underwent examination according to the LPD protocol—all routine tests, positron emission tomography combined with computed tomography (PET-CT), CT scan of the brain. In the absence of time according to the severity of the patient's condition or the possibility of performing it—CT or magnetic resonance imaging (MRI) of the neck (if indicated), chest, abdominal cavity, retroperitoneal space, and small pelvis, trepan biopsy of the ilium, as well as diagnostic lumbar puncture. A Fluorescence in situ Hybridization (FISH) cytogenetic study was performed in 70 patients to determine rearrangement involving the *c-MYC, BCL2,* and *BCL6* gene loci to exclude high-grade B-cell lymphoma; in 11 patients, next generation sequencity was performed in order to

determine the mutation of the *TP53* gene (4-9 exons). Analyzed separately, both the intent to treat group (**Table 1**) and the de novo DLBCL patient group (**Table 2**). This work analyzes the above described clinical and laboratory signs of differential diagnosis of de novo and a secondary result of the transformation of indolent lymphomas of DLBCL.

Characteristics of patients included by intent to treat are presented in **Table 1**.

The characteristics of patients with primary DLBCL are presented in **Table 2**.

The groups are compared with each other in all parameters.

Variable	R-DA-EPOCH ± autoSCT n = 62 (48%)	R-mNHL-BFM-90 ± autoSCT n = 68 (52%)	Total n = 130 (100%)
Age, median of years (range):			
<40	15 (24.2%)	20 (29.4%)	35 (26.9%)
40–60	39 (62.9%)	45 (66.2%)	84 (64.2%)
>=60	8 (12.9%)	3 (4.4%)	11 (8.5%)
Gender:			
M	30 (48.4%)	41 (60.3%)	71 (54.6%)
F	32 (51.6%)	27 (39.7%)	59 (45.4%)
Nodal	53 (85.5%)	58 (85.3%)	111 (85.4%)
Extranodal	9 (14.5%)	10 (14.7%)	19 (14.6%)
Stage:			
II (bulky diseases)	2 (3.2%)	5 (7.3%)	7 (5.4%)
III	12 (19.4%)	18 (26.5%)	30 (23.1%)
IV	48 (77.4%)	45 (66.2%)	93 (71.5%)
Exclusive/predominant retroperitoneal localization with compression of the ureters /kidneys/ hydronephrosis/ARF	3 (4.8%) 2 (3.2%)	2 (2.9%) 1 (1.5%)	5 (3.8%) 3 (2.3%)
Retroperitoneal localization in stage III–IV: Compression of the ureters/kidneys/ hydronephrosis/acute renal failure	22 (46.8%) 0	25 (53.2%) 0	47 (36%) 0
Asymmetric lymphostasis of the leg	1 (1.6%)	1 (1.5%)	2 (1.5%)
Involvement bone morrow:			
Histological (n = 120):	7 (5.8%)	5 (4.2%)	12 (10%)
Discordant	2 (1.7%)	1 (0.83%)	3 (25%)
Concordant	5 (4.2%)	4 (3.3%)	9 (75%)
Immunophenotyping (n = 11) Blood involvement	2 (18.2%)	0	2 (18.2%)
Mutation gene *TP53* (n = 11)	1 (9%)	2 (18.2%)	3 (27.3%)
Neuroleukemia	1 (1.6%)	0	1 (0.76%)
Intratumor	0	0	0
Paraprotein (n = 103): n = 50, R-DA-EPOCH n = 53, R-m-NHL-BFM-90	7 (14%)	5 (9.43%)	12 (11.65%)
Aa IPI:			
1	0	1 (1.5%)	1 (0.8%)
2	21 (33.9%)	19 (27.9%)	40 (30.8%)
3	41 (66.2%)	48 (70.6%)	89 (68.4)
PR	36 (58.06%)	63 (92.65%)	99 (76.15%)
Relapse	5 (14%)	6 (9.5%)	11 (11.1%)

Variable	R-DA-EPOCH ± autoSCT n = 62 (48%)	R-mNHL-BFM-90 ± autoSCT n = 68 (52%)	Total n = 130 (100%)
Progression	6 (9.7%)	0	6 (8.4%)
Death	3 (4.84%)	1 (1.47%)	4 (3.08%)
The therapy continues	3 (4.84%)	1 (1.47%)	4 (4.6%)
The diagnosis is in relapse, progression:			
DLBCL	4 (6.5%)	1 (1.47%)	5 (3.8%)
FL grade 1–2	1 (1.6%)	0	1 (0.76%)
FL grade 3 (A/B)	3 (4.8%)	1 (1.47%)	4 (3.1%)
NLPHL	1 (1.6%)	1 (1.47%)	2 (1.53%)
PMBL	0	1 (1.47%)	1 (0.76%)
AITL	1 (1.6%)	0	1 (0.76%)
NMZL	2 (3.2%)	0	2 (1.53%)
HGBL: with *c-MYC* and *BCL2*	1 (1.6%)	0	1 (0.76%)
NOS	1 (1.6%)	0	1 (0.76%)

FL-follicular lymphoma, NLPHL-nodular lymphocyte-predominant Hodgkin lymphoma, PMBL-primary mediastinal (thymic) large B-cell lymphoma, AITL-angioimmunoblastic T-cell lymphoma, NMZL-nodal marginal zone lymphoma.

Table 1.
Characteristics of patients in the intention-to-treat included in the DLBCL-2015 trial.

Variable	R-DA-EPOCH ± autoSCT n = 55 (47%)	R-mNHL-BFM-90 ± autoSCT C n = 62 (53%)	Total n = 117 (100%)
Age, median of years (range):			
<40	14 (25%)	18 (29%)	32 (27%)
40–60	35 (64%)	41 (66%)	76 (65%)
>=60	6 (11%)	3 (5%)	9 (8%)
Gender:			
M	22 (47%)	39 (63%)	65 (56%)
F	29 (53%)	23 (37%)	52 (44%)
Nodal	46 (84%)	52 (84%)	98 (84%)
Extranodal	9 (16%)	10 (16%)	19 (16%)
Stage:			
II (bulky diseases)	2 (4%)	5 (8%)	7 (6%)
III	11 (20%)	16 (26%)	27 (23%)
IV	42 (76%)	41 (66%)	83 (71%)
Exclusive/predominant retroperitoneal localization with compression of the ureters/kidneys/hydronephrosis/ARF	0	0	0
Retroperitoneal localization in stage III–IV:	22 (46.8%)	25 (53.2%)	47 (36%)
Compression of the ureters/kidneys/hydronephrosis/acute renal failure	1 (4.5%)	0	1 (2.12%)
Asymmetric lymphostasis of the leg	0	0	0
Involvement bone marrow:			
Histological (n = 120):	5 (5.6%)	4 (3.7%)	9 (10%)
Discordant	0	0	0
Concordant	5 (5.6%)	4 (3.7%)	9 (10%)
Mutation gene *TP53* (n = 8)	1 (9%)	2 (18.2%)	3 (27.3%)
Neuroleukemia	1 (1.81%)	0	1 (0.85)
Intratumor	0	0	0

Variable	R-DA-EPOCH ± autoSCT n = 55 (47%)	R-mNHL-BFM-90 ± autoSCT C n = 62 (53%)	Total n = 117 (100%)
Paraprotein (n = 97): R-DA-EPOCH (n = 48) R-m-NHL-BFM-90 (n = 49)	2 (4.2%)	5 (10.2%)	7 (7.2%)
Aa IPI:			
1	0	1 (2%)	1 (1%)
2	19 (35%)	18 (29%)	37 (32%)
3	36 (65%)	43 (69%)	79 (67%)
CR	36 (65.45%)	59 (95.16%)	95 (81.20%)
Relapse	3 (5.45%)	2 (3.23%)	5 (4.27%)
Progression	5 (14%)	6 (9.5%)	11 (11.1%)
Death	3 (5.45%)	2 (3.23%)	5 (4.27%)
The therapy continues	3 (4.84%)	1 (1.47%)	4 (4.6%)

Table 2.
Characteristics of patients with de novo DLBCL.

3. Results

This section will discuss the clinical and laboratory signs that have differential diagnostic value, obtained in the course of a prospective study.

3.1 An intent to treat the group

As indicated in **Table 1**, generalized lesion of peripheral, intrathoracic, intra-abdominal lymph nodes with or without extranodal foci and with massive retro-peritoneal conglomerate >7 cm, bulky diseases (stage III–IV), was observed in 47 (37%) patients and not in one case, ARF was not observed due to compression of the urinary tract by tumor bulky. However, five patients had preferential/exclusive retroperitoneal localization, and three of them had data of renal/ureteral compression—ARF and hydronephrosis. In two of these three cases, it combined with the presence of Mk paraprotein secretion, as well as with discordant lesion of the bone marrow. All this allows us to assume the transformation of indolent lymphomas into DLBCL. In two of 47 patients, asymmetric lymphostasis of the lower extremity was noted, due to squeezing of the iliac and/or inguinal lymph nodes by the conglomerate. Neuroleukemia was diagnosed in one patient, no one initially had intratumor, and one patient had a relapse, and this patient was diagnosed with primary mediastinal large B-cell lymphoma (PMBL). Peripheral blood immuno-phenotyping was performed in 11 patients with leukocytosis, and in two of them, a monoclonal population of lymphoid cells with a tumor-like immunophenotype was found. The *TP53* gene mutation was detected in three out of 11 patients studied. Paraproteinemia/paraproteinuria was found in 12 (11.65%) patients. Complete remission was achieved in 99 (76.15%)—in 36 (58.06) on R-DA-EPOCH therapy, in 63 (92.65%) on R-mNHL-BFM-90; progression was observed in six (9.65%), and all patients received R-DA-EPOCH therapy, relapse developed in 11 (11.1%) patients. At the time of progression and relapse, the patients underwent repeated tumor biopsy, histological and immunohistochemically studies. Of the 16 cases, 11 turned out to be different diagnoses (**Table 1**)—five patients diagnosed with de novo DLBCL, three of these five patients found to have a *TP53* mutation and two patients were on R-DA-EPOCH therapy. Involvement of bone marrow was observed in 12

(9.23%) patients—in three patients, the lesion was discordant and in all patients in relapse, the diagnosis was changed in favor of FL in 2 cases and indolent lymphoma, unspecified in 1 case.

3.2 De novo DLBCL

Table 2 presents the data of the group of primary DLBCL. As seen in none of the cases was there an exclusive/predominant retroperitoneal localization, as well as out of 47 cases lesions of peripheral, intrathoracic, intra-abdominal lymph nodes with or without extranodal foci and with a massive retroperitoneal conglomerate >7 cm, bulky diseases, III–IV stage, no one had data of compression by the tumor conglomerate of the kidneys/ureters, ARF. In addition, in this group, no one had asymmetric lymph stasis of the leg, intratumor in the central nervous system; one patient had neuroleukemia at the time of diagnosis. None of the patients had mature cell lesions bone marrow; large cell lesions were observed in nine (97.7%) patients. In this group, there were no cases of blood involvement. All three patients with the *TP53* mutation were in the de novo DLBCL group. Paraproteinemia/paraproteinuria was observed in only seven (7.2%) patients, five of whom received intensive induction therapy with R-mNHL-BFM-90, the effectiveness of which exceeds 90%. Complete remission was achieved in 95 (82.20%) patients—36 (65.45%) after R-DA-EPOCH therapy, in 59 (95.16%) patients after R-mNHL-BFM-90. Progression was observed in five (4.27%) patients and all of them underwent R-DA-EPOCH therapy and belonged to a high-risk group. Relapses developed only in two patients, and both had a *TP53* mutation.

4. Discussion

Thus, the obtained data indicate that currently there is an over diagnostics of de novo DLBCL. Most often, the reason for this is either a lack of some data or an incorrect interpretation of the available research results. However, the main reason remains the lack of clear diagnostic criteria.

As a rule, a carefully collected anamnesis of the disease allows you to find out the duration of the disease, whether the tumor size decreased without any treatment or not, how long they were observed or treated by doctors of other specialties. Multiple and uninformative biopsies performed by different specialists also indicate the transformation of indolent lymphomas into DLBCL. However, there are cases when both do not allow for an accurate diagnosis.

4.1 Clinical manifestations

4.1.1 Exclusive/predominant retroperitoneal localization

Even in the REAL 1994 classification, some forms of DLBCL distinguished into separate nosological forms according to the localization of the tumor. These include primary mediastinal large B-cell lymphoma, serous cavity lymphoma, and intravascular DLBCL and CNS lymphoma [1]. Therefore, there is reason to think that exclusive/predominant retroperitoneal localization with compression of the ureters/kidneys, with or without ARF in morphological diagnosis, is a separate form of B-cell lymphomas. Compression is most likely due to the development of fibrosis in the tumor tissue, as in PMBL and Hodgkin's lymphoma (HL). In the development of fibrosis, various cytokines produced by tumor cells can participate, among other mechanisms. Back in the early 90s of the last century, it was known

which important role cytokines play in the pathogenesis of lymphomas. Some of the clinical and morphological features of aggressive lymphomas are partially explained by the action of cytokines, the level of which is increased in serum or tissues of patients with lymphomas. In particular, it proved that Hodgkin's lymphoma cells express IL-1, IL-5, IL-9, TNFα, M-CSF, etc., which are responsible for the enhancement of the cellular response and fibrosis observed in HL tissues [21]. In addition, the effect of blood plasma of a patient with DLBCL on the properties of mesenchymal hematopoietic stem cells through cytokines and proteins secreted by tumor cells is proven [22]. Therefore, it assumed that tumor cells of de novo and secondary DLBCL secrete "their" cytokines, and it causes different clinical manifestations. Recently, for the first time, large changes were obtained in mesenchymal stem cells in patients with DLBCL without the involvement of bone marrow. It assumed that tumor cells that do not populate the bone marrow have a humoral, pathological effect on the stromal progenitor cells of the bone marrow. The tumor process in one way or another affects the entire body. Recently, for the first time, it has been shown that the precursors of the stromal microenvironment—multipotent mesenchymal stromal cells—change in DLBCL patients without involvement of bone marrow due to the humoral effect of the tumor and the body's response to it. A comprehensive analysis of the results showed that when remission is achieved in patients with DLBCL, the composition of plasma cytokines normalizes, but does not reach the level observed in healthy donors [23].

As it can be seen from the results of the study, in almost 40% of patients, the dimensions of the retroperitoneal conglomerate with generalized lesions are larger than 7 cm and, in only one case, was hydronephrosis. The same patient had paraproteinemia Mκ. In this case, too, we assume the transformation of indolent lymphoma. The patient is under our supervision.

4.1.2 Asymmetric lymphostasis

Asymmetric lymphostasis of the leg was observed in two patients from the intent to treat group, and when the diagnosis was revised at the reference center, the diagnosis changed in favor of type 3 FL. The pathogenesis of lymphostasis due to compression of the inguinal and/or iliac lymph nodes by a tumor conglomerate is most likely to be the same as in retroperitoneal localization.

We have cases of gastric DLBCL with pyloric stenosis. As a rule, in such cases, they need to bougienage or surgery. I think that these cases are similar and represent the transformation of indolent lymphomas in DLBCL.

4.1.3 Intratumor and neuroleukemia

No cases of intratumor in CNS at the time of diagnosis/relapse/progression was observed in de novo DLBCL. All patients underwent a CT scan of the brain. In one case, an intratumor was detected in a relapse, and when the diagnosis was revised at the reference center, the patient was found to have PMBL [24]. Therefore, when conducting a differential diagnosis of primary DLBCL with other lymphomas, it is necessary to consider this. Neuroleukemia was diagnosed at the time of diagnosis in one patient.

The US National Multidisciplinary Cancer Network (NCCN) recommends the use of IPI-CNS to determine the likelihood of a relapse involving the CNS. This predictive model is based on data from the German non-Hodgkin lymphoma research group [25]. It assumed that the IPI-CNS would allow stratification of patients into groups with a low, medium, and high risk of recurrence with involvement of the CNS. The same German research group for the study of non-Hodgkin

lymphomas published the updated results in 2016, which showed that the rate of recurrence in the central nervous system during the first 2 years in the high-risk group was 10%, in the moderate-risk group—2.9%, and low risk—0.8% [26]. Based on these data, it is recommended to prevent the development of relapse with the involvement of the central nervous system in patients with high-risk DLBCL. At the same time, the pathogenesis mechanism of the development of relapses with the involvement of the central nervous system is unknown.

The registry of DLBCL patients of the German research group for the study of non-Hodgkin's lymphomas began long before the change in the diagnostic criteria for DLBCL and before the isolation of new forms of aggressive B-cell lymphomas. In 2008 WHO classification, an unclassified B-cell lymphoma was isolated from the heterogeneous group of DLBCL, which occupies an intermediate position between DLBCL and Burkitt's lymphoma, based on the determination of the gene expression profile, characterized by an aggressive clinical course and poor prognosis [3]. In the 2017 revised WHO classification, based on the detection of molecular breakdowns—translocations involving the *c-MYC, BCL2,* and/or *BCL-6* gene loci, it was given a new name—high-grade B-cell lymphoma—double-/triple-hit lymphoma (HGBL, DHL/THL), and without these translocations—high-grade B-cell lymphoma, unspecified (HGBL, NOS) [2]. It is known from the literature that it is in these two groups that the intratumor of the central nervous system is more common. The likelihood of developing relapses with involvement of the central nervous system exceeds 10–20% in the medium and high-risk groups, respectively [27, 28]. Relapses with isolated involvement of the brain substance also occur in patients with primary mediastinal B-cell large cell and follicular lymphoma [29].

4.2 Bone marrow trephine biopsy data

Discordant involvement of the bone marrow in patients with DLBCL in 2017 WHO classification remains as a manifestation of DLBCL and indicated as a sign of a poor prognosis. Everyone understands that the signs of prognosis are considered within the framework of a specific program, and adverse signs on R-CHOP leveled out on intensive care. Since de novo DLBCL is an aggressive and curable disease, and indolent lymphomas constantly recur and cannot be cured, discordant involvement of bone marrow indicates the transformation of indolent lymphomas into DLBCL.

According to the concept of tumor progression, hemoblastoses, including lymphomas, usually go through two stages—monoclonal (indolent) and polyclonal (malignant); a tumor can sequentially go through different stages of progression, but it can also start directly from the malignant stage [16, 30].

4.3 Laboratory data

4.3.1 Paraprotein secretion

Paraprotein secretion is characteristic of indolent lymphomas. However, like discordant involvement of bone marrow in the WHO classification in 2017, indicated that patients with de novo DLBCL can occur and is a sign of a poor prognosis. Therefore, all that said regarding discordant involvement bone marrow applies to the secretion of paraprotein. Paraprotein M is usually secreted. However, there are isolated cases of secretion of paraprotein G and, it is a laboratory sign indicating the secondary nature of DLBCL. However, we must not forget that some of these cases may be a manifestation of Monoclonal gammopathy of undetermined significance (MGUS), especially in elderly patients.

According to a large retrospective study, which included 599 patients with de novo DLBCL, an immunochemical study was performed in 245 patients, of whom the secretion of paraprotein M was detected in 12.5%, and the latter turned out to be an independent sign of a poor prognosis, the reason for which the authors could not explain. In another retrospective study, which included 245 patients, the predominant paraprotein isotype was immunoglobulin G and this was explained either by the different methodology used to determine the paraprotein isotype or by racial differences. The authors of both studies indicated that the presence of paraprotein, regardless of isotype, was an independent sign of lower overall and event-free survival [19]. The authors of one of these works attributed the reason for the poor results to the presence of the *MYD88 L265p* mutation.

In another large retrospective study involving 382 patients who underwent an immunochemical analysis of blood and urine, of which 225 (59%), patients had M paraprotein secretion and Waldenstrom's macroglobulinemia was diagnosed. Of the remaining 157 (41%) cases, 77 (49%) had Chronic lymphocytic leukemia (CLL)/small lymphocyte lymphoma, 27 (17.2%) LMZ, 18 (11.5%) FL, 11 (7%)—lymphoma from cells of the mantle zone, in 5 (3.2%)—DLBCL as a result of transformation of mature cell lymphomas, in 7 (4.5%)—de novo DLBCL, in 4 (2.5%)—angioimmunoblastic T-cell lymphoma, in another 8 (5%) people—unspecified B-cell lymphoma [31]. Thus, the percentage of paraproteinemia, paraproteinuria in patients with DLBCL is small, but when examining patients, an immunochemical study of blood and urine is mandatory.

According to Gavrilina OA, significant differences in survival were obtained in the group with involvement of the bone marrow. Monoclonal paraprotein secretion was typical for DLBCL with involvement of the bone marrow (p < 0.0001) [32].

All of the above allows us to assume that cases with the secretion of paraprotein are also the transformation of indolent lymphomas in DLBCL.

4.4 Relapses

Response to therapy should be considered an independent predictor of the prognosis within any protocol. All patients with de novo DLBCL who received R-mNHL-BFM-90 at the Federal State Budgetary Institution of the National Medical Research Center of Hematology are under our supervision. Of 86 patients from the high- and intermediate-risk group included in the pilot study from 2002 to 2010 with a diagnosis of de novo nodal DLBCL, unspecified, relapses within 3 years developed in 11 people, 2 more patients developed relapses after 13 years. Only two cases out of the 11 indicated that there was de novo DLBCL. When reviewing histological preparations in nine patients, the diagnoses were revised in favor of FL, LMZ, nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), and high-grade B-cell lymphoma. The five-year disease-free survival rate was 86%.

The histological results of relapses of patients in a randomized trial are presented above. As it can be seen from **Table 2**, relapses for primary DLBCL are not typical, including on R-CHOP therapy, even in high-risk patients if CR is achieved and there is no *TP53* gene mutation. However, there is an assumption that cases with the presence of a mutation in the *TP53* gene are also the result of the transformation of indolent lymphomas. This assumption arose from the theoretical concepts of tumor progression that the changing signs of a tumor during its growth, the emergence of resistance to previously effective antitumor drugs are explained by repeated mutations of tumor cells, the appearance of subclones, and the selection of more resistant forms among them. Therefore, given the aggressiveness of de novo DLBCL, there is no time for changes in tumor signs during its growth, as well as for the selection of the most resistant forms. In our two patients with de novo

DLBCL with relapse and the presence of a *TP53 gene* mutation, in one case, paraprotein secretion took place, indirectly indicating the transformation of indolent lymphoma. In the second case, it has an exceptional lesion of extranodal organs—at the onset of the mammary gland, in the first relapse - of the pleura involvement. The second relapse was represented by mammary gland involvement.

In the case of achieving CR, with the exception of cases with a mutation in the *TP53* gene, in patients with primary DLBCL, including extranodal, including DLBCL of the testes and mammary gland, relapses are casuistic.

It is currently difficult to distinguish de novo DLBCL from nodular LMZ, as well as MALT - lymphoma in the case of histological transformation if there is no long history of the disease.

Finally, in recent years, there are fewer and fewer cases of de novo DLBCL with Germinal center (GC) molecular type, which indicates that all cases from B-cells of the germinal center are either FL or high-grade B-cell lymphoma.

Conflict of interest

The authors declare no conflict of interest.

Dedication

The work is dedicated to the memory of my deceased Teacher, Academician Andrei Vorobyov.

Author details

Aminat Magomedova*, Anna Misyurina, Sergey Kravchenko, Fatima Babaeva and Andrey Vorobiev[†]
Federal State Institution "National Research Center for Hematology", Ministry of Health, Moscow, Russian Federation

*Address all correspondence to: maminat@mail.ru

† Deceased author

IntechOpen

References

[1] Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasm's: A proposal from the international lymphoma study group. Blood. 1994;**84**(5):1301-1392. DOI: 10.1182/84.5.1361.1361

[2] Gascoyne RD, Campo E, Jaffe ES, Chan WC, et al. Diffuse large B-cell lymphoma, NOS. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4nd ed. Lyon: International Agency for Research on Cancer; 2017. pp. 291-3253

[3] Stein H, Warnke RA, Chan WC, Jaffe ES. Diffuse large B-cell Lymphoma. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: International Agency for Research on Cancer; 2008. pp. 233-257

[4] Campo E, Pileri SA, Jaffe ES, Nathwani BN, Stein H, Muller-Hermelink HK. Nodal marginal zone lymphoma. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: International Agency for Research on Cancer; 2017. pp. 263-266

[5] Cook JR, Isaacson PG, Chott A, Nakamura S, Muller-Hermelink HK, Harris NL, et al. Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: International Agency for Research on Cancer; 2017. pp. 259-263

[6] Leoncini L, Campo E, Stein H, Harris NL, Jaffe ES, Kluin PM. Burkitt lymphoma. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4nd ed. Lyon: International Agency for Research on Cancer; 2017. pp. 330-334

[7] Leoncini L, Campo E, Stein H, Harris NL, Jaffe ES, Kluin PM. Burkitt-like lymphoma with 11q aberration. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4nd ed. Lyon: International Agency for Research on Cancer; 2017. pp. 334-335

[8] Jaffe ES Harris NL Swerdlow SH. H Ott G. Nathwani BN. de Jong D. Yoshino T. Spagnolo D. Gascoyne RD. Follicular lymphoma. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues,International Agency for Research on Cancer, Lyon 2017. 266-282

[9] Swerdlow SH, Campo E, Seto M, Muller-Hermelink HK. Mantle cell lymphoma. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4nd ed. Lyon: International Agency for Research on Cancer; 2017. pp. 285-344

[10] Falini B, Lamant-Rochaix L, Campo E, Jaffe ES, Gascoyne RD, Stein H, et al. Anaplastic large cell lymphoma, ALK-positive. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4nd ed. Lyon: International Agency for Research on Cancer; 2017. pp. 413-418

[11] Kluin PM, Harris NL, Stein H, Leoncini L, Campo E, Jaffe ES, et al. High-grade B-cell lymphoma. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: International Agency for Research on Cancer; 2017. pp. 335-341

[12] Magomedova A, Kremenetskay A, Kravchenko S, et al. Prognostic value of focal bone marrow lesions in diffuse large B-cell lymphosarcoma. Therapeutic Archives. 2004;7:60-63

[13] Maeshima AM, Taniguchi H, Toyoda K, Yamauchi N, et al. Clinicopathological features of histological transformation from extranodal marginal zone B-cell

lymphoma of mucosa-associated lymphoid tissue to diffuse large B-cell lymphoma: An analysis of 467 patients. British Journal of Haematology. 2016;**174**:923-931. DOI: 10.1111/bjh.14153, Epub 2016 Jul 27

[14] Camacho FI, Mollejo M, Mateo MS, et al. Progression to large B-cell lymphoma in splenic marginal zone lymphoma: A description of a series of 12 cases. The American Journal of Surgical Pathology. 2001;**25**:1268-1276. DOI: 10.1097/00000478-200110000-00007

[15] Conconi A, Franceschetti S, Aprile von Hohenstaufen K, Margiotta-Casaluci G, et al. Histologic transformation in marginal zone lymphomas. Annals of Oncology. 2015;**26**:2329-2335. DOI: 10.1093/annonc/mdv368, Epub 2015 Sep 23

[16] Parry-Jones N, Matutes E, Gruszka-Westwood AM, et al. Prognostic features of splenic lymphoma with villous lymphocytes: A report on 129 patients. British Journal of Haematology. 2003;**120**:759-764. DOI: 10.1046/j.1365-2141.2003.04165.x

[17] Dubois S, Viailly P-J, Mareschal S, Bohers E, et al. Next-generation sequencing in diffuse large B-cell lymphoma highlights molecular divergence and therapeutic opportunities: A LYSA study. Clinical Cancer Research. 2016;**22**(12):2919-2928. DOI: 10.1158/1078-0432.CCR-15-2305

[18] Christina Cox M, Di Napoli A, Fabbri A, Ruco ECL. The significance of serum immunoglobulin paraprotein in diffuse large B-cell lymphoma. British Journal of Haematology. 2018;**182**(5):741-742. DOI: 10.1111/bjh.14873, Epub 2017 Aug 17

[19] Li Y, Wang L, Zhu H-Y, Liang J-H, Wu W, et al. Prognostic significance of serum immunoglobulin paraprotein in patients with diffuse large B cell lymphoma. British Journal of Haematology. 2018;**182**(1):131-134. DOI: 10.1111/bjh.14735, Epub 2017 May 11

[20] Magomedova A, Kravchenko S, Kremenetskay A, Zvonkov E, et al. Nine years of experience in the treatment of patients with diffuse large B-cell lymphosarcoma. Therapeutic Archives. 2011;**7**:5-10

[21] Hsu SM, Hsu PL. Autocrine and paracrine functions of cytokines in malignant lymphomas. Biomedicine & Pharmacotherapy. 1994;**48**(10):433-444. DOI: 10.1016/0753-3322(94)90004-3

[22] Petinati N, Bigildeev A, Karpenko D, Sats N, et al. Humoral effect of a B-cell tumor on the bone marrow multipotent mesenchymal stromal cells. Biochemistry. 2021;**86**(2):207-216. DOI: 10.1134/S0006297921020097

[23] Fastova A, Magomedova A, Petinati N, Sats N, et al. Multipotent mesenchymal bone marrow stromal cells in patients with diffuse large B-cell lymphoma. Cell Technologies in Biology and Medicine. 2019;**1**:33-36. DOI: 10.1007/s10517-019-04480-6, Epub 2019 Jun 10

[24] Magomedova A, Misiurina A, Mangasarova J, Gorenkova L, et al. Involvement of the central nervous system and the feasibility of preventing recurrence in the central nervous system in patients with nodal diffuse large B-cell lymphoma, NOS. Prospective study data. Therapeutic Archives. 2019;**91**(7):35-40. DOI: 10.26442/00403660.2019.07.000323

[25] Boehme V, Zeynalova S, Kloess M, Loeffler M, et al. Incidence and risk factors of central nervous system recurrence in aggressive lymphoma: a survey of 1693 patients treated in protocols of the German high-grade non-Hodgkin's lymphoma study group

(DSHNHL). Annals of Oncology. 2007;**18**(1):149-157. DOI: 10.1093/annonc/mdl327

[26] Schmitz N, Zeynalova S, Nickelsen M, Kansara R, et al. CNS international prognostic index: A risk model for CNS relapse in patients with diffuse large B-cell lymphoma treated with RCHOP. Journal of Clinical Oncology. 2016;**34**(26):3150-3156. DOI: 10.1200/JCO.2015.65.6520

[27] Savage KJ, Slack GW, Mottok A, Sehn LH, et al. Impact of dual expression of MYC and BCL2 by immunohistochemistry on the risk of CNS relapse in DLBCL. Blood. 2016;**127**(18):2182-2188. DOI: 10.1182/blood-2015-10-676700, Epub 2016 Feb 1

[28] Horn H, Ziepert M, Becher C, Barth TF, et al. MYC status in concert with BCL2 and BCL6 expression predicts outcome in diffuse large B-cell lymphoma. Blood. 2013;**121**(12): 2253-2263. DOI: 10.1182/blood-2012-06-435842

[29] Papageorgiou SG, Diamantopoulos P, Levidou G, Angelopoulou MK, et al. Isolated central nervous system relapses in primary mediastinal large B-cell lymphoma after CHOP-like chemotherapy with or without rituximab. Hematological Oncology. 2013;**31**(1):10-17. DOI: 10.1002/hon.2012

[30] Vorobiev AI. Guidelines for Hematology. 3rd ed. Vol. 3. Moscow: Newdiamed; 2003. pp. 40-69

[31] Gavrilina OA, Parovichnikova EN, Zvonkov EE, Troitskaya VV, et al. Diffuse large B-cell lymphoma with monoclonal immunoglobulin secretion. Therapeutic Archives. 2016;**88**(7):56-61. DOI: 10.17116/terarkh201688756-61

[32] Dorokhina EI, Magomedova AU, Kulikov SM, Kremenetskaya AM, et al. Long-term results of high-dose chemotherapy in patients with diffuse large B-cell lymphoma according to the modified NHL-BFM-90 program. Hematology and Transfusiology. 2016;**61**(1):44