

# Non-GCB Diffuse Large B-Cell Lymphoma With an Atypical Disease Course: A Case Report and Clinical Exome Analysis

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## Abstract

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid tumor among other non-Hodgkin lymphomas (30-40% of all cases). This type of lymphoma is characterized by significant differences in treatment response and the heterogeneity of clinical traits. Approximately 60% of patients are cured using standard chemotherapy (CT), while in 10-15% of cases, the tumor is characterized by an extremely aggressive course and resistance to even the most high-dose programs with autologous stem cell transplantation (auto-SCT). The activated B-cell (ABC) subtype of DLBCL is characterized by poor prognosis. Here, we describe a clinical case of diffuse ABC-DLBCL with an atypical disease course. Complete remission was achieved after four courses of CT, followed by autologous hematopoietic stem cell transplantation (auto-HSCT). However, early relapse occurred 2 months after the completion of treatment. According to the results of cytogenetic studies, significant chromosome breakdowns were observed. Exome sequencing allowed for the detection of several novel mutations that affect components of the NOTCH2 and NF- $\kappa$ B signaling pathways, a number of epigenetic regulators (*KMT2D*, *CREBBP*, *EP300*, *ARID1A*, *MEF2B*), as well as members of the immunoglobulin superfamily (*CD58* and *CD70*). Whether these mutations were the result of therapy or were originally present in the lymphoid tumor remains unclear. Nevertheless, the introduction of genomic technologies into clinical practice is important for making a diagnosis and developing a DLBCL treatment regimen with the use of targeted drugs.

**Keywords:** Lymphoma; Diffuse large B-cell lymphoma; ABC type;

Manuscript submitted November 17, 2021, accepted December 31, 2021  
Published online February 8, 2022

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doi: <https://doi.org/10.14740/wjon1436>

Exome; Sequencing; NOTCH2 pathway; NF- $\kappa$ B pathway; R-mNHL-BFM-90 protocol

## Introduction

Diffuse large B-cell lymphoma (DLBCL) is a lymphoid tumor that represents one of the most complex therapeutic problems in hematology due to the heterogeneity in both clinical characteristics and the response to therapy. The combination of cyclophosphamide, hydroxydaunorubicin, hydrochloride, vincristine, prednisone (CHOP) with rituximab (R-CHOP), the first anti-cluster of differentiation (CD)20 monoclonal antibody, has changed the outcome of DLBCL, becoming the new standard of care. While about 60% of patients are cured by standard chemotherapy (CT), in 10-15% of cases, the tumor is characterized by an extremely aggressive course and resistance to even the most high-dose programs involving autologous hematopoietic stem cell transplantation (auto-HSCT) [1-4].

Recent studies of gene expression, mutational status, and chromosomal abnormalities have clearly demonstrated the biological diversity of DLBCL and provide a basis for revising existing classifications and developing new differentiated treatment protocols. For example, the wider implementation of fluorescence *in situ* hybridization (FISH) led to double-hit lymphoma (DHL) being singled out from the general group of DLBCL as a separate entity, and it is characterized by the combined rearrangement of the *MYC*, *BCL2*, and/or *BCL6* genes [5]. There are currently no effective CT programs for this group of patients. Gene expression profiling of activated B-cell (ABC)-DLBCL cells in the postgerminal stage of differentiation, conducted by Alizadeh et al, allowed for a prognostically unfavorable molecular variant of DLBCL to be identified [6]. This subtype is characterized by constitutional activation of the B-cell receptor signaling pathway and the transcription factor NF- $\kappa$ B (nuclear factor kappa-light chain-enhancer of activated B cells). According to the International Prognostic Index (IPI), the 5-year non-progressive survival (NPS) of ABC-DLBCL patients in the high-risk group was only 28%

following standard CT [2, 7]. The high expression of multiple myeloma 1 (MUM1) protein, characteristic of this DLBCL subtype, became the basis for the introduction of lenalidomide into the treatment regimen [8-11]. It is also known that lenalidomide as an immunomodulatory drug, increases the T-cell immune response against B-cell tumors [12].

Until recently, most molecular genetic studies focused on the study of single gene abnormalities, such as in *c-MYC*, *MYD88*, *EZH2*, *CREBBP*, *FOXP1*, and *TP53* [13-18]. Mutations of some of these genes are a powerful negative prognostic factor, regardless of other clinical and laboratory factors.

However, aberration variants and combinations of different genes make it difficult to accurately assess their clinical significance and identify the group of patients with the highest risk of developing resistance/relapse. With the introduction of next-generation sequencing (NGS) technology, it became possible to comprehensively analyze a much larger amount of data and create a “molecular portrait” of the tumor. As a result of whole exome sequencing (WES) of tumor samples from 304 patients with DLBCL, five molecular clusters were identified, each of which was determined by considering the spectrum of the most frequent genetic breakdowns, commonly used signaling pathways, and prognosis [19, 20]. Of these, clusters C2 (cases with biallelic inactivation of the *TP53* gene) and C5 (cases of ABC-DLBCL in combination with 18q/*BCL2* amplification and mutations of the *CD79B*, *MYD88*, *PIM1*, *ETV6* genes) were associated with the worst prognosis.

However, it is not always possible to accurately determine the particular molecular subtype of a tumor. Tumor cells can simultaneously engage several signaling pathways and acquire additional mutations during their evolution. Therefore, research clarifying the molecular subtypes and their number is ongoing. Given that most of these studies are conducted on groups of patients who received standard CT, the results vary significantly [21]. It seems rational to determine the most significant driver mutations in tumors of DLBCL patients from the high-risk group, which are resistant to the most intensive treatment programs.

In our clinic, the use of the intensive block program R-mNHL-BFM-90 resulted in the improved treatment of a group of DLBCL patients with unfavorable prognosis factors [22]. A retrospective evaluation of the results showed that in most cases of treatment failure, the tumor belonged to the postgerminal immunohistochemical variant of DLBCL (non-germinal center B-cell (non-GCB)-DLBCL), a molecular analog of the ABC-DLBCL subtype [23].

In this article, we present a clinical case description and full-exome sequencing analysis of tumor material from a high-risk patient with non-GCB-DLBCL, who relapsed after first remission following intensive therapy in combination with lenalidomide and high-dose consolidation.

## Case Report

The male patient, 55 years old, presented with enlargement of the cervical nodes, left palatine tonsil, difficulty swallowing, night sweats, and fever. Positron emission tomography combined

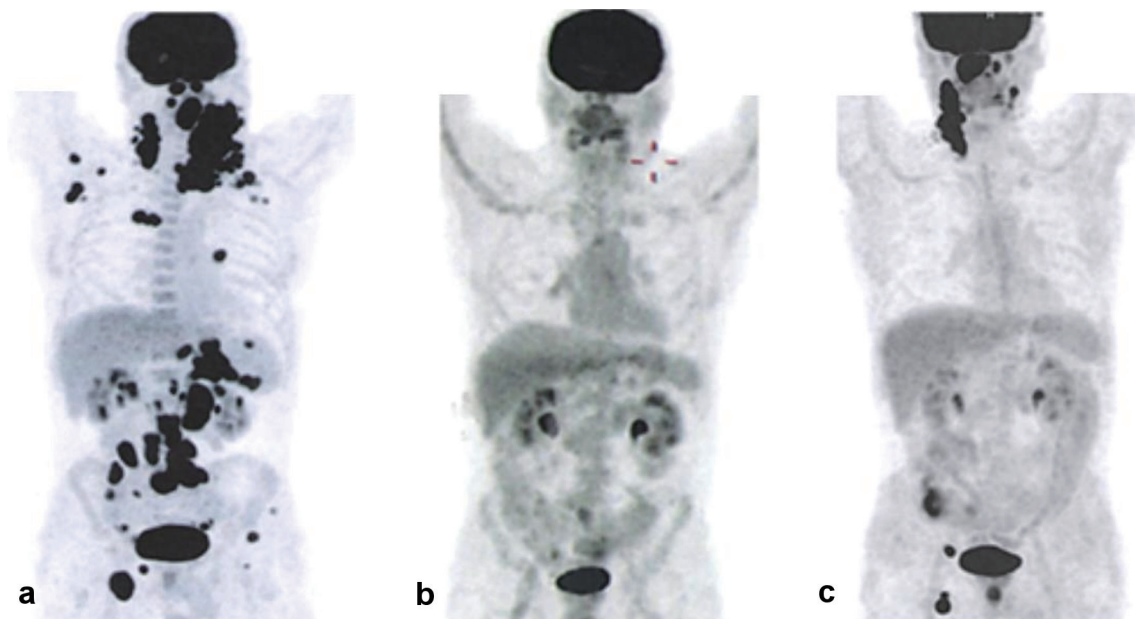
with computed tomography (PET/CT) examination revealed an increase in the size of the left palatine tonsil, cervical, intra-abdominal, inguinal, and femoral lymph nodes up to 5 cm in diameter, and a paratracheal conglomerate of lymph nodes up to 9 cm (SUVmax up to 21.2). The activity of lactate dehydrogenase (LDH) was 557 U/L. No data were obtained for bone marrow damage. Immunomorphological examination of the lymph node biopsy revealed diffuse proliferation of medium- and large-sized cells with round-oval, multi-lobed nuclei each containing 2 - 3 nucleoli. The tumor cells expressed CD20, BCL-2, and MUM1 and were negative for CD10, BCL, and Ki67 in 80-90% of the population. Standard cytogenetic examination (SCE) of lymph node cells did not reveal chromosomal aberrations. Translocation involving the *BCL6/3q27* gene locus and an additional signal from the *BCL2/18q21* gene locus were observed in 30% of the nuclei using FISH. The deletion of 17p13 and monosomy of chromosome 17 were not detected. Thus, the diagnosis was established as non-GCB type DLBCL, BCL-2 positive.

Four courses of the R-mNHL-BFM-90 program with lenalidomide were conducted. After three courses,  $19 \times 10^6$ /kg CD34<sup>+</sup> cells were harvested. When staging after the fourth course, residual tumor tissue with low metabolic activity (SUVmax 2.4, DS3) remained in the jugular lymph node, according to PET/CT data. For the purpose of consolidation, auto-HSCT was performed.

When the patient was examined 2 months after the end of therapy, he had subfebrile temperature, increased LDH activity (to 670 U/L), and lymph nodes that were enlarged on the right. The metabolically active cervical, iliac, inguinal and femoral lymph nodes, and left tonsil (SUVmax 30.74) were characterized according to the results of PET/CT (Fig. 1). Disease relapse was confirmed based on histological examination of the cervical lymph node sample. Karyotype analysis revealed a clone with multiple subclones, complex karyotype disorders (> 20) including derivatives of chromosomes 3, 14, and 17 (with translocations of *BCL6*, *IGH* gene loci, and deletion of *TP53*), and dicentric marker chromosomes (Fig. 2). Using FISH, translocations involving loci in the *BCL6/3q27* and *IGH/14q32* genes were detected, along with two additional signals from loci in the *IGH/14q32* gene, an additional signal from a locus in the *BCL2/18q21* gene, and a *TP53/17p13* deletion (Fig. 3).

In the course of further research, exome sequencing of the patient's DNA was carried out on recurrent tumor and normal tissue (blood) samples. The data were then filtered according to the list of genes associated with oncological diseases of the lymphoproliferative system. As a result, 299 variations were identified, mostly single-nucleotide substitutions. A feature of this patient was the large number of mutations related to a single gene, five to eight mutations were observed in almost all analyzed genes.

The samples were then examined for the presence of pathogenic mutations. Thus, 141 mutations were identified, of all these mutations, only six are included in the dbSNP database, one of which is also in the ClinVar database, and the remaining 135 variants have not previously been discovered. Details of the mutations that were found are listed along with their predicted damaging effect here (Supplementary Material 1, www.wjon.org).



**Figure 1.** PET/CT results showing disease progression. (a) Before the start of therapy. (b) After the end of therapy. (c) Following disease relapse. PET/CT: positron emission tomography combined with computed tomography.

## Discussion

According to the literature, mutations leading to DLBCL are found in a number of functionally significant genes. Among these genes are those whose functional role in the pathogenesis of DLBCL has been studied for many years, including *CD79B*, *TP53*, *CARD11*, *MyD88*, *CREBBP*, and *EZH2* [8, 24-26]. To date, there are a number of other genes for which mutations were confirmed to have pathological significance for the development of DLBCL: *MEF2B*, *MLL*, *BTG1*, *GNA13*, *ACTB*, *P2RY8*, *PCLO*, *TNFRSF14*, *KRAS*, *BRAF*, *BCL2*, *BCL6*, *MYC*, *TNFAP3*, *TCF4*, and *NOTCH1*, and *NOTCH2* [27-29].

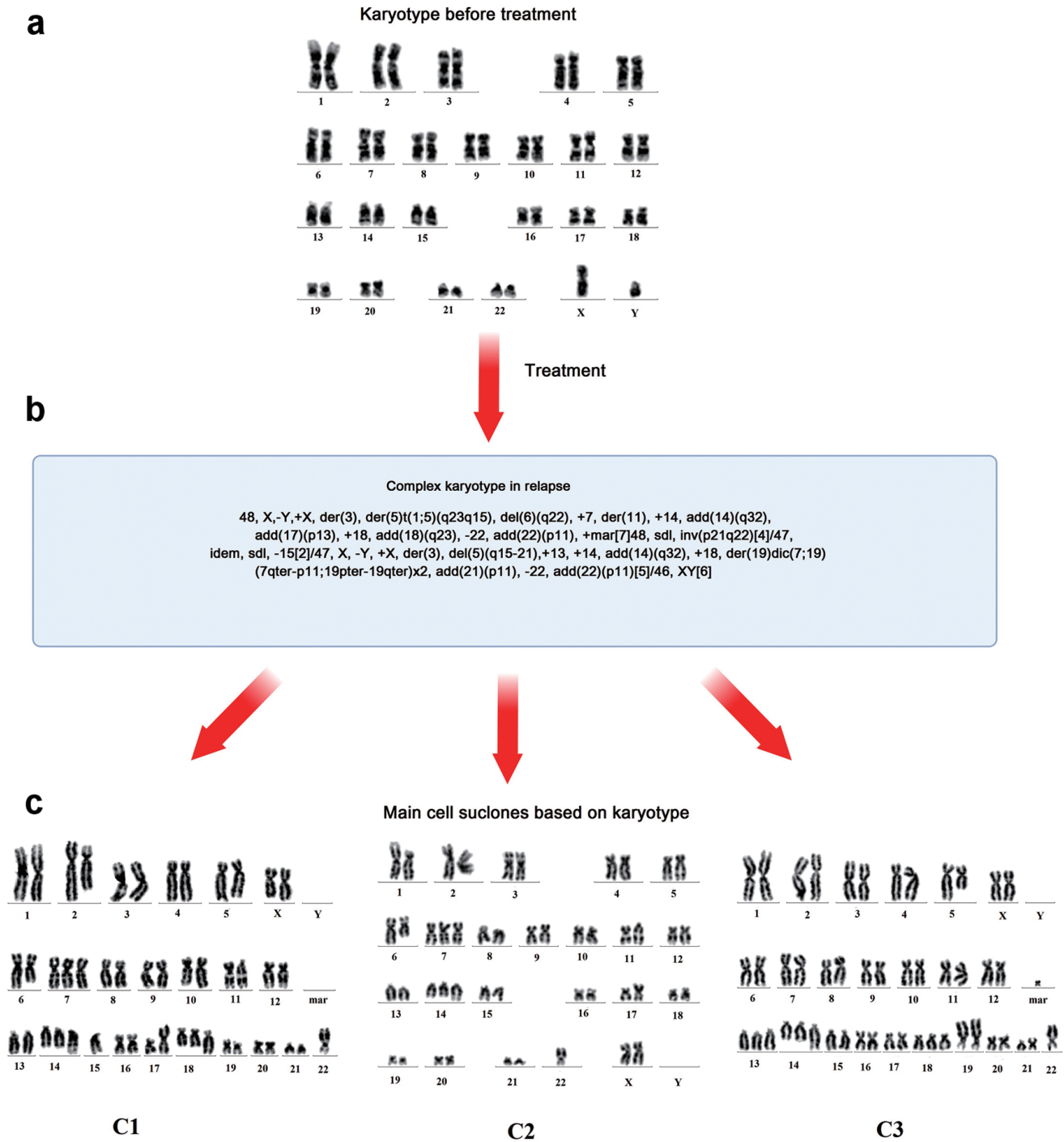
The *TP53* gene is an anti-oncogene, since the encoded p53 protein functions in preventing the formation of malignant tumors. Disruption of *TP53* gene function is one of the most universal indicators of functional changes in the cells of various neoplasms. Activation of *TP53* leads to changes in the expression level of more than 500 other genes. Deficiency in its function manifests as a loss of control over the cell cycle, apoptosis, aging processes, chromosomal stability, and excisional DNA repair. *TP53* gene loss is accompanied by an uncontrolled accumulation of genetic damage that leads to malignant cell growth, and as a result, to the death of the body. Our patient had a *TP53/17p13* deletion, which is associated with a particularly poor prognosis of the disease course and extremely low survival. Together with the 17p deletion, pathogenic mutations are often found in the second allele of the *TP53* gene, leading to its inactivation. In the case studied here, no such mutations were found.

Multiple mutations of the *KMT2A* (*MLL1*)/*KMT2D* (*MLL2*) genes were also detected. The proteins encoded by these genes are lysine methyltransferases responsible for the methylation of lysine residues on histones, particularly his-

tones H3 and H4 during oogenesis and early development [30]. Dysregulation of this methylation is crucial in the development of cancer. In the literature, numerous inactivating mutations have been described in medulloblastoma [31] and multiple myeloma [32], and chromosomal translocations involving a member of the *MLL1* family are described in detail in acute leukemia [33]. In the tumor sample from our patient, we found seven mutations in the *KMT2D* gene and five mutations in the *KMT2A* gene that have not previously been described, and according to the results of predictor programs, have an inactivating effect.

The *MEF2B* gene encodes a transcription activator, and according to the literature, mutates in about 11% of cases of DLBCL, and about 12% of cases of follicular lymphomas. Ying et al in one of his papers showed that *MEF2B* can directly activate the transcription of the *BCL6* protooncogene in normal B cells of the germinal center and is necessary for the proliferation of DLBCL [34]. Mutations enhance the transcriptional activity of *MEF2B*, either by disrupting its interaction with the co-repressor *CABIN1*, or by rendering it insensitive to mediated phosphorylation and sumoylation, which inhibit signal transmission. Consequently, the transcriptional activity of *BCL6* is deregulated in DLBCL, with *MEF2B* mutations. Somatic mutations of *MEF2B* can lead to unregulated expression of the *BCL6* oncogene in diffuse B-large cell lymphoma [34]. In our study, we found a non-synonymous substitution of p. L245M and a nonsense mutation of p. Q14\*.

The *CREBBP* gene encodes a highly conserved and ubiquitously expressed nuclear phosphoprotein, which, together with the closely related EP300 protein, belongs to the KAT3 family of histone/protein lysine acetyltransferases. By modifying lysine residues on both histone and non-histone nuclear proteins, *CREBBP* and *EP300* function as transcriptional co-activators for a large number of DNA-binding transcription



**Figure 2.** Results of cytogenetic examination of the cervical lymph node biopsy during disease onset and relapse. (a) Karyotype before treatment. (b) Karyotype after treatment. (c) Three main cell subclones after treatment and their karyotypes. c1: 48, X,-Y,+X,der(3),der(5)t(1;5)(q23q15), del(6)(q22),+7,der(11),+14,add(14)(q32), add(17)(p13), +18,add(18)(q23),-22,add(22)(p11),+mar[7]48; c2: sdi,inv(p21q22)[4]/47, idem,sdi,-15[2]/47; c3: X,-Y,+X,der(3),del(5)(q15-21),+13,+14,add(14)(q32),+18,der(19) dic(7;19) (7qter→p11::19pter→19qter)×2,add(21)(p11),-22,add(22)(p11)[5]/46,XY[6]. der: derivative chromosome; del: deletion; add: additional; +mar: marker chromosome; sdi: sidelines; inv: inversion.

factors involved in multiple signaling and developmental pathways [35, 36]. About 39% of cases of DLBCL and 41% of cases of follicular lymphoma show genomic deletions and/or

somatic mutations that remove or inactivate the HAT coding domain of these two genes. In addition, it was demonstrated that the mutant CREBBP and EP300 proteins are deficient in



**Figure 3.** FISH of the 17p13 deletion in cervical lymph node biopsy following disease relapse. FISH: fluorescence *in situ* hybridization.

the acetylation of *BCL6* and *p53*, which leads to constitutive activation of the oncoprotein and a decrease in the activity of the tumor suppressor *p53* [37]. In our study, the inactivating mutation p.M1385I in the HAT domain of the *CREBBP* gene and the nonsense mutation p.C380\* were detected, but no mutations were found in the *EP300* gene.

*EZH2* is a catalytic subunit of polycomb repressive complex 2 (PRC2), which along with other components of PRC2, suppresses gene expression by methylation of histone H3 in lysine 27. *EZH2* aberration is observed in a wide range of cancers, including several categories of B-cell and T-cell malignancies, and is associated with a poor clinical prognosis and outcomes. *EZH2* plays a significant role in the development of the lymphoid system, so its deregulation, due to genetic or non-genetic causes, contributes to the development of lymphoma or leukemia associated with B-cells as well as T-cells [38, 39]. We identified two non-synonymous mutations in the *EZH2* gene, p. Q730H and p.K492N, as well as four mutations with a reading frame shift. The effect of these mutations on protein function is unknown.

The protooncogene *BCL6* has been shown to be deregulated due to t(3; 14) (q27; q32) translocation in 5-10% of DLBCL cases [40]. In addition, somatic mutations in *BCL6* that disrupt the negative autoregulation of its expression have been reported in cases of DLBCL [41]. In our case, we observed not only a translocation involving loci of the *BCL6/3q27* gene, but also three mutations in this gene with pathogenic significance: p. P483T, p.P286S, and p.C475\*.

Translocation of *BCL2* t(14;18), detected in 20% of DLBCL cases [40], leads to an increase in the activity of the *BCL2* oncogene, and as a result, an increase in the survival of tumor cells. We detected this rearrangement in our patient, but there were no point mutations of pathogenic value in the *BCL2* gene.

*MYC* is a protooncogene encoding the Myc protein, a transcription factor of great importance for proliferation, metabolism, differentiation, apoptosis, microenvironment remodeling, and immune responses. *MYC* deregulation has oncogenic potential, which leads to increased cell proliferation, angiogenesis, apoptosis, genome instability, and inhibition of cell differentiation [42]. In addition to Burkitt's lymphoma, *MYC* gene rear-

rangements were detected in 5-15% of patients with DLBCL as well as in other types of lymphomas [43, 44]. In patients with DLBCL, *MYC* rearrangement has been shown to be associated with worse survival prognosis [45]. According to various literature data, it is known that mutations in the *MYC* gene in DLBCL are not as well studied as translocations. Xu-Monette et al found a wide range of single-nucleotide variations of *MYC* gene in DLBCL that have different functional and clinical effects [46]. In this study, we did not detect any rearrangements of the *MYC* gene in the patient, but we found four single-nucleotide variations with pathogenic significance, namely p. E400\*, p.E399\*, p.E385\*, and p.P43L, although the clinical effect these mutations is unknown.

According to the conducted studies, more than 50% of ABC-DLBCL and a small proportion of GCB-DLBCL cases involve somatic mutations in several genes of the NF- $\kappa$ B signaling pathway that regulates signal transmission. The *TNFAIP3* gene, which encodes the ubiquitin-modifying enzyme (A20) involved in terminating NF- $\kappa$ B responses, is frequently affected. At the same time, missense mutations of *CARD11* produce molecules with a significantly increased ability to activate NF- $\kappa$ B pathway. Thus, the regulation of the NF- $\kappa$ B pathway in DLBCL caused by genetic changes in these genes that lead to their loss or activation may contribute to lymphomagenesis [24, 47]. In our analysis, we found mutations in both the *CARD11* and *TNFAIP3* genes.

*ATM* encodes a serine/threonine kinase belonging to the phosphatidylinositol-3-kinase (PI3-K) family and plays a central role in signaling pathways activated by DNA damage. ATM kinase normally plays a key role in the response to DNA damage, being a tumor suppressor gene and part of the ATM-p53 pathway. DNA damage induces activation of ATM and ATR kinases, which, together with the p53 and p14/ARF proteins, can induce cell cycle arrest, DNA repair, or apoptosis. In patients with DLBCL, *ATM* mutations were shown to be associated with inactivation of the *ARF* tumor suppressor gene and the P53 tumor protein (TP53) [48]. It has been suggested that mutations in ATM and inactivation of the ARF-TP53 pathway may contribute to the development of DLBCL. Several studies have shown that ATM may be involved in the development of certain subtypes of sporadic

lymphoma and leukemia: missense mutations and loss of function in the *ATM* gene have been demonstrated in T-cell prolymphocytic leukemia [49], mantle cell lymphoma [50], B-cell chronic lymphocytic leukemia [51], diffuse B-large cell lymphoma, and follicular lymphoma [48]. The protein kinase encoded by the *ATM* gene is involved in regulation of the activity of the p53 protein encoded by the *TP53* gene. P53 activity may decrease when the function of the *ATM* gene is lost. In our case, nine mutations with a poor prognosis were detected in the *ATM* gene.

The protein encoded by the *ATR* gene is a serine/threonine protein kinase, a key activator of cellular responses to DNA damage caused by ultraviolet light, ionizing radiation, and halting of DNA replication. In response to these events, ATR phosphorylates key proteins in various branches of the DNA damage response pathways, such as p53, BRCA1, CHK1, and Rad17, thereby activating DNA repair, cell cycle checkpoints, or apoptosis [52]. An important role of *ATR* mutations in hereditary predisposition to breast and ovarian cancer has been demonstrated [53]. One paper shows the significance of *ATM* and *ATR* mutations for the initiation and progression of pyothorax-related lymphoma [54]. Using exome sequencing, seven mutations with pathogenic significance were detected in the *ATR* gene.

Phosphatidylinositol-3-kinases (PI3Ks) are lipid kinases that regulate signaling pathways important for neoplasia, including cell proliferation, adhesion, survival, and motility. We found pathogenic mutations in the *PIK3CA* and *PIK3CD* genes of our patient. The large number of mutations observed in these genes indicates their functional importance, and the dysregulation of the PI3 kinase pathway is a common feature of many cancers [55, 56]. In addition, mutations have been identified in the *MTOR* gene, one of the known oncogenes in the PI3 kinase pathway, which also indicates deregulation of the PI3 kinase pathway [57]. In our work, we found three non-synonymous substitutions that probably lead to damage to the protein encoded by the *MTOR* gene.

We identified five protein-damaging mutations in the *ALK* gene encoding anaplastic lymphoma kinase. This kinase was first detected in anaplastic large cell lymphoma as a result of translocation between chromosomes (2; 5) (p23: q35). Changes in the *ALK* gene are implicated in neuroblastoma, lung cancer, and other malignancies [58, 59].

GTPases of the RHO family are guanine-nucleotide-binding enzymes that bind guanosine triphosphate (GTP) and catalyze its hydrolysis to guanosine diphosphate (GDP). RHO GTPases are active in the GTP-bound state and inactive in the GDP-bound state, and the relationship between GTP/GDP-bound conformations (active/inactive) is critical for proper intracellular signaling [60]. The RHO GTPase family consists of 18 to 22 members. They can be classified according to their homology and structure into the following subfamilies: typical and atypical. Both typical and atypical RHO GTPases are critical transducers of intracellular signaling and are associated with human cancers. Moreover, both gain of function and loss of function mutations have been described in various tumors [61]. Studies using whole exome sequencing technology have identified repeated *RHOA* mutations in various human lymphomas of both B-cell and T-cell origin, including diffuse

B-large cell lymphoma [62]. Further studies of the biological significance of these mutations suggested a leading role for *RHOA* in the pathogenesis of these lymphomas. In our patient, three non-synonymous substitutions with a pathogenic value in the *RHOA* gene were identified: p. P101T, p.A177D, and p.W99C.

Proteins of the NOTCH family are integral receptor proteins, represented in humans by four types (NOTCH 1 - 4). These proteins control the proliferation, differentiation, and development of cells and tissues, as well as activate the transcription of genes involved in regulating the balance between these processes [63]. In adult tissues, NOTCH-mediated signals are important regulators in maintaining self-renewal, promoting, for example, myogenesis, neurogenesis, and lymphocyte development [64]. Given the important role of NOTCH proteins in a wide range of processes and tissues, aberrations leading to an increase or loss of NOTCH signaling components and functions are associated with a variety of disorders, including solid cancer and hematological malignancies, where NOTCH can act as an oncogene or as a tumor suppressor. Currently, there are many examples that clearly show the relationship of mutations in the *Notch1* and *Notch2* genes with lymphoproliferative disorders, including chronic lymphocytic leukemia, mantle lymphoma, marginal spleen lymphoma, diffuse B-large cell lymphoma, follicular lymphoma, and Burkitt and Hodgkin lymphomas [65-68]. According to our data, the patient has an inactivating nonsense mutation p.Y1508\* in their *NOTCH2* gene as well as a non-synonymous replacement of p.G736V with a pathogenic value.

In addition, pathogenic mutations with a damaging effect were detected in a number of other genes, namely *BCL10*, *BCL9*, *CD58*, *XPO1*, *DTX3L*, *PARP14*, *TP63*, *MAP3K1*, *IRF4*, *CCND3*, *RAD54B*, *NFKB2*, *STAT6*, *DDX3X*, *MLLT10*, *DNTT*, and *BCR*, which are associated with different types of lymphomas. Recently, genomic studies have focused on the identification of genetic subtypes of DLBCL, which are dictated by the genetic, phenotypic and clinical heterogeneity of this type of lymphoma, and as a result, a different response to generally accepted treatment regimens [21].

## Conclusions

Our clinical case is characterized by an atypical picture of the disease course, where the primary chemotherapy regimen gave satisfactory results. However, after 2 months, the patient experienced rapid relapse, and as a result, their clinical outlook deteriorated significantly. In cytogenetic studies, multiple focal formations and significant chromosome breakdowns were observed. We found, in our patient, mutations that affect components of signaling pathways such as NOTCH2 and NF- $\kappa$ B, a number of epigenetic regulators (*KMT2D*, *CREBBP*, *EP300*, *ARID1A*, *MEF2B*), as well as members of the immunoglobulin receptor superfamily (*CD58* and *CD70*). Without data on the primary tumor, it is impossible to say with certainty whether these mutations were the result of therapy or were originally present in the tumor. Possibly, if similar data had been available when making the diagnosis and developing the treatment regimen, a different tactic would have been chosen. The im-

portance of research and development in the field of molecular therapy for DLBCL cannot be overemphasized. We believe that future research should focus on an in-depth search for predictive biomarkers based on genomic, transcriptomic and epigenetic data and on the development of molecular tools and delivery systems to target tissues and organs. In addition, pharmacogenetic studies that anticipate the effects of specific therapy and studies related to the effects on the molecular pathways of anticancer drugs (such as lenalidomide during remission and relapse) are promising.

## Supplementary Material

**Suppl 1.** Somatic mutations detected in tumor biopsies.

## Acknowledgments

None to declare.

## Financial Disclosure

This research was funded by an internal grant of the National Research Center Kurchatov Institute #1360 of 25.06.2019 (development of markers to identify different types of diffuse large B-cell lymphoma (DLBCL)). The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

## Conflict of Interest

The authors declare no conflict of interest.

## Informed Consent

Informed consent was obtained from the patient. All patient information was deidentified.

## Author Contributions

Conceptualization: EZ, S. Tsygankova, MGA and NG; methodology: D. Komova., EB, NS, S. Tsygankova; software: FS and SR; validation: D. Komova., EB, NS, AS, TO and S. Tsygankova; formal analysis: FS and SR; investigation: D. Komova, D. Koroleva, NG, EB, NS, AS, S. Tatarnikova, TO and S. Tsygankova; resources: S. Tsygankova and EZ; data curation: FS; writing-original draft preparation: NG, S. Tsygankova, and AN; writing-review and editing: MGA, NG, S. Tsygankova, EZ, and AN; visualization: D. Koroleva, NG, and SR; supervision: S. Tsygankova and EZ; project administration: S. Tsygankova and EZ; funding acquisition: S. Tsygankova. All authors have read and agreed to the published version of the manuscript.

## Data Availability

All DNA sequences were uploaded to the NCBI Sequence Read Archive (BioProject ID PRJNA752256).

## Abbreviations

DLBCL: diffuse large B-cell lymphoma; CHOP: cyclophosphamide, hydroxydaunorubicin, hydrochloride, vincristine, prednisone; R-CHOP: rituximab, cyclophosphamide, hydroxydaunorubicin, hydrochloride, vincristine, prednisone; auto-SCT: autologous stem cell transplantation; ABC-DLBCL: activated B-cell subtype of diffuse large B-cell lymphoma; auto-HSCT: autologous hematopoietic stem cell transplantation; CT: chemotherapy; FISH: fluorescent *in situ* hybridization; DHL: double-hit lymphoma; IPI: international Prognostic Index; NPS: non-progressive survival; NGS: next-generation sequencing; WES: whole exome sequencing; non-GCB: non-germinal center B-cell; PET/CT: positron emission tomography combined with computed tomography; LDH: lactate dehydrogenase; SCE: standard cytogenetic examination

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