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Deregulation and Shattering of Chromosomal Segments Containing Multiple Oncogenic Targets in the Pathogenesis of Diffuse Large B Cell Lymphoma, Not Otherwise Specified (DLBCL, NOS)

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Abstract: Diffuse large B cell lymphoma, not otherwise specified (DLBCL, NOS) is the most common type of non-Hodgkin lymphoma (NHL). Significant efforts have been focused on utilizing advanced genomic technologies to further subclassify DLBCL, NOS into clinically relevant subtypes. These efforts have led to the implementation of novel algorithms to support optimal risk-oriented therapy and improvement in the overall survival of DLBCL patients. The pathogenesis of DLBCL at the molecular level indicates copy number variation (CNV) as one of the major forms of genetic alterations in the somatic mutational landscape. Random deregulation that results in complex breaks of chromosomes and restructuring of shattered chromosomal segments is called chromothripsis. Gene expression changes influenced by chromothripsis have been reported in cancer and congenital diseases. This chaotic phenomenon results in complex CNV, gene fusions, and amplification and loss of tumor suppressor genes. We present herein a summary of the most clinically relevant genomic aberrations, with particular focus on copy number aberrations in a case that highlights DLBCL, NOS arising from relapsed Hodgkin lymphoma. The focus of our study was to understand the relationship between the clinical, morphological, and genomic abnormalities in DLBCL, NOS through multiple techniques for therapeutic considerations.

Keywords: diffuse large B cell lymphoma, not otherwise specified; DLBCL; DLBCL, NOS; amplification; chromothripsis; complex karyotype; SNP array; Hodgkin lymphoma; molecular genetics; mutations; diagnostics; GCB; ABC; clinical utility

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1. Introduction

Lymphomas are a heterogeneous group of neoplasms that are broadly classified as Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) due to biological, histological, and immunophenotypic differences and clinical behavior. HL makes up approximately 14%, and NHL approximately 86%, of all lymphomas [1,2].

Diffuse large B cell lymphoma, not otherwise specified (DLBCL, NOS) is the most common type of non-Hodgkin lymphoma (NHL) [3]. DLBCL, NOS is a diagnosis of exclusion and lacks the distinct features needed to be classified into one of the more specific diagnostic entities in the WHO classification scheme. The initial workup of large B cell lymphoma requires correlation of clinical, morphologic, immunophenotypic, and genetic findings to rule out specific categories of large B cell lymphomas [3], such as high-grade "double/triple-hit" lymphomas that show concurrent chromosome rearrangements of *MYC* and *BCL2* and/or *BCL6* (5% to 10% of cases), and double-expressor DLBCL lymphomas, which demonstrate overexpression of *MYC* and *BCL2* [3].

The 5th edition of World Health Organization (WHO-5) classification defines DLBCL, NOS and its subtypes based on clinical findings, morphology, immunophenotype, and genetics [4]. However, even within WHO subtypes, it is clear that additional clinical and genetic heterogeneity exists. Significant efforts have been focused on utilizing advanced genomic technologies to further subclassify DLBCL, NOS into clinically relevant subtypes. These efforts have led to the implementation of novel algorithms to support optimal risk-oriented therapy and improvement in the overall survival of DLBCL patients [3,5]. The pathogenesis of DLBCL at the molecular level indicates copy number variation (CNV) as one of the major types of genetic aberration in the somatic mutational landscape.

Recent genome sequencing projects for cancer, as well as congenital diseases, led to the identification of chaotic cellular events with gains and losses of chromosomal segments, which are recognized as chromothripsis, a phenomenon under study. Chromothripsis is defined as random restructuring of shattered chromosomal segments resulting in complex structural rearrangements, duplications, deletions, gene fusions, amplification, and loss of tumor suppressor genes. This phenomenon has been described as a potential macroevolution schema for cancer cells [6–8]. Copy number alteration mediated by chromosomal segmental deletions and duplications may affect gene expression patterns through dosage imbalances, disruption, fusion, and change in cis/trans-regulatory sequences [9].

A variety of technologies are available to detect CNVs, such as chromosome analysis, fluorescence in situ hybridization (FISH), array-comparative genomic hybridization (array CGH), single nucleotide polymorphism arrays (SNP arrays), optical genome mapping (OGM), droplet digital PCR (ddPCR), multiplex ligation-dependent probe amplification (MLPA), and high-throughput next generation sequencing (NGS) [3,10–15]. All of these techniques have unique advantages and limitations in cost, equipment, resolution, and sensitivity.

We present herein a summary of the most clinically relevant genomic aberrations using a few of the techniques described above, with particular focus on complex copy number aberrations in a case that highlights DLBCL, NOS arising from relapsed Hodgkin lymphoma.

1.1. Clinical History

A 26-year-old male with a prior history of relapsed Hodgkin lymphoma, initially diagnosed in 2010, with relapses occurring in 2011 and 2012, was treated with chemoradiotherapy and autologous stem cell transplant at an outside institution. He was seen by the clinical hematology–oncology team of our institution in 2021. He had daily fever, weight loss, back pain, and worsening fatigue. Multiple lytic skeletal lesions and soft tissue densities were observed on imaging, and laboratory studies revealed anemia, thrombocytopenia, hypercalcemia, and renal dysfunction.

1.2. Bone Marrow (BM) Evaluation

Peripheral blood counts showed WBC 4.2 K/μL; hemoglobin 7.5 g/dL; and platelets 26 K/μL. Evaluation of the bilateral core biopsies showed a markedly hypercellular marrow (>95% cellular) with numerous large atypical lymphoid cells and large nuclei, moderate condensed chromatin, prominent nucleoli, and scant basophilic cytoplasm with occasional cytoplasmic vacuoles. Normal hematopoietic cells were markedly decreased. The hypercellular marrow was diffusely involved by atypical medium-sized to large lymphocytes with an immunophenotype consistent with diffuse large B cell lymphoma (DLBCL, NOS), germinal center type (GCB), which was found to involve bone, bone marrow, lymph nodes, nasopharynx, kidney, and spleen. Cell of origin (COO) subtyping of diffuse large B cell lymphoma (DLBCL, NOS), germinal center type (GCB), was based on immunohistochemical (IHC) classification using Hans' algorithm [16].

2. Materials and Methods

2.1. Sample Collection and Preparation

Cytogenetic and molecular studies of concurrent bone marrow specimens of the above case were ordered by the clinician as a part of the diagnostic testing and/or for follow-up studies for therapeutic considerations.

2.2. Cytogenetics, FISH, SNP Array, and NGS Analyses

Cytogenetic analysis was performed on metaphase cells prepared from bone marrow aspirates cultured for 24 h without mitogens, using standard laboratory techniques. Giemsa-banded metaphases were analyzed, and results were reported using the International System for Human Cytogenetic Nomenclature, 2020 (ISCN, 2020).

Fluorescence in situ hybridization (FISH) analysis was performed on interphase nuclei obtained from cultures of bone marrow aspirates using probes for a *IGH*/*BCL2* dual-color dual-fusion translocation probe, *BCL6* and *MYC* break-apart probes (Abbott Molecular, Downers Grove, IL, USA), respectively, using standard techniques.

Genomic DNA extracted from bone marrow aspirates was PCR amplified and processed for an SNP (Thermo Fisher Scientific, Waltham, MA, USA) array and NGS.

DNA copy number detection analysis was performed using the SNP array Cytoscan High Density platform (Thermo Fisher Scientific, Chelmsford, MA, USA), which has 2.6 million oligonucleotide markers, 1.9 million non-polymorphic copy number probes for copy number detection, and 750,000 SNP probes for heterozygosity/homozygosity detection. An SNP array can detect subtle copy number variants (CNVs), submicroscopic deletions and duplications, unbalanced translocation products, and copy-neutral loss of heterozygosity (cnLOH) with precise genomic coordinates. Single nucleotide polymorphism (SNP), a variation at a single site in DNA, is the most frequent type of variation in the genome. SNP array technology is based on the discrimination between the two possible SNP alleles (A- or B-polymorphism) for a specific position in the genome. By comparing the differential amount of hybridization of the target DNA to each of these probes, it was possible to determine homozygous and heterozygous alleles. Results of the testing were assessed based on cut-off values established in the laboratory.

The custom NGS assay was designed by the VUMC Molecular Diagnostics Laboratory to assess the presence of myeloid disease-associated variants in a set of 50 genes, with potential diagnostic, prognostic, and/or therapeutic significance in myeloid neoplasms. Of note, the entire list of 50 genes included in the myeloid NGS is not included here, as it is beyond the scope of this paper.

3. Results

Cytogenetic and Molecular Testing and Analysis

Polymerase chain reaction (PCR) analysis showed a clonal population of cells immunoglobulin heavy chain (*IGH*) in the chromosome 14q32 region.

Chromosome analysis of the BM revealed a complex karyotype with poor morphology, and multiple numerical and structural rearrangements (Figure 1): karyotype 43~46,XY,-2,add(3)(p25),add(8)(p21),add(11)(q23),add(13)(q34),add(18)(q23)[cp14]/46,XY [6].

Fluorescence in situ hybridization (FISH) of the same bone marrow sample analysis showed no rearrangement of the *BCL6*, *MYC*, and *IGH/BCL2*. However, amplification with approximately 10 copies of the *BCL2* at 18q21 in 47% of cells and 3 intact copies of the *MYC* at 8q24.1 in 8.5% of cells were observed (Figure 2A–C).

SNP microarray analysis of BM detected several genomic aberrations: amplification of *BCL2* that was consistent with FISH (Figure 2A and Figure 6); amplification of *KMT2A* gene at 11q23 with 10 copies, 3p, 8p, 13q, and copy-neutral loss of heterozygosity (cn-LOH) of 16 Mb chromosome 17p13 region containing *TP53* (Figures 3–6). Complex CNVs included losses adjacent to gains of several chromosomes, including 2, 3, 8, 11, 13, and 18. In addition, regions of losses and gains of different chromosome regions included several genes, many of those with unclear clinical significance. Additional genes *ZMAT4*, *GPC5*, and *GPC6* with

amplifications of five, four, and seven copies, respectively, were also noted; however, the clinical significance of these genes in DLBCL, NOS is unclear (Figures 7 and 8). Of note, the type and clinical significance of large segmental aberrations containing many genes were beyond the scope of this study.

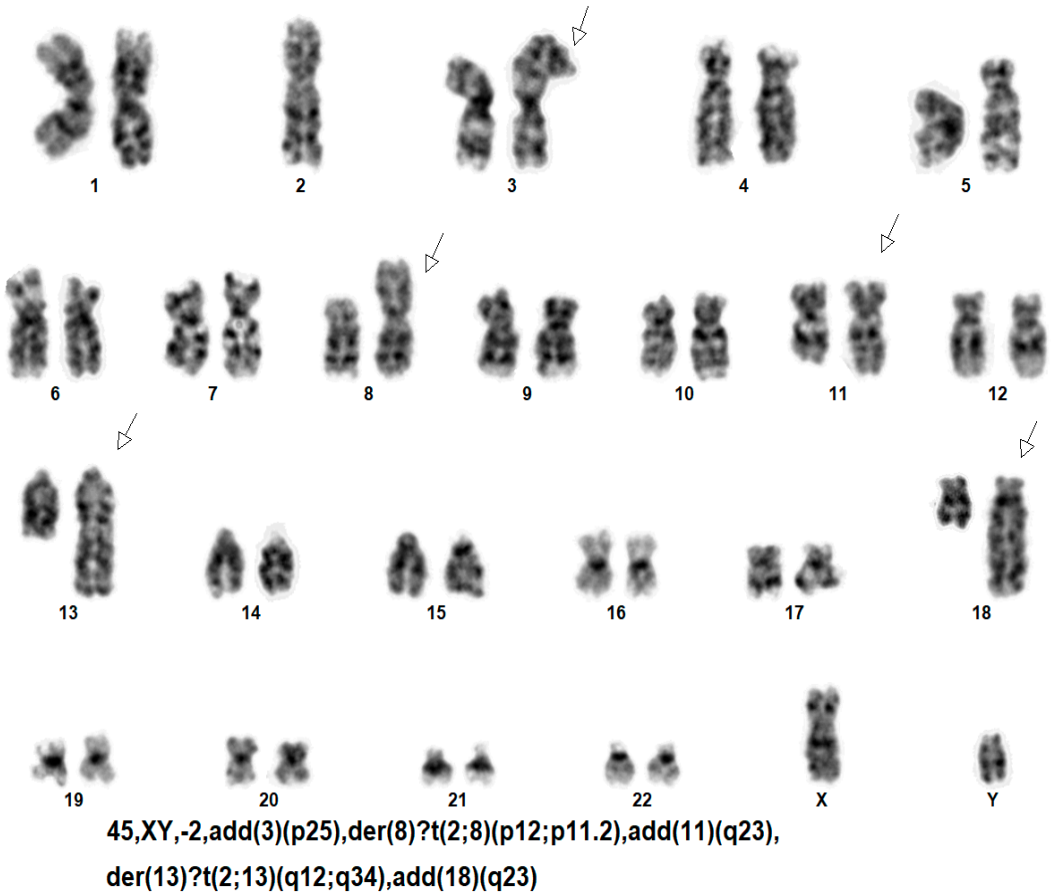

Figure 1. Abnormal male karyotype.

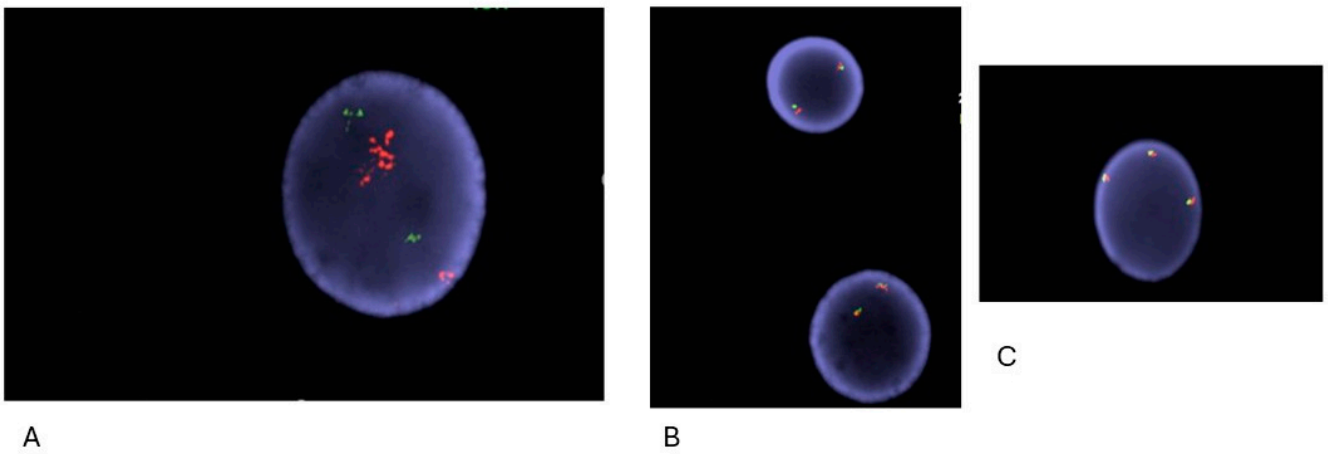

Figure 2. FISH with *IGH* (14q32)/*BCL2* (18q21), *MYC* (8q24.1), and *BCL6* (3q27) probes. (**A**) Green color—*IGH* Red color—*BCL2*, no rearrangement of *IGH/BCL2*, note amplification with approximately 10 copies in 47% of cells. (**B**) *BCL6* breakpart probe—No rearrangement. (**C**) *MYC*—breakpart probe, no rearrangement, note three intact copies in 8% of cells.

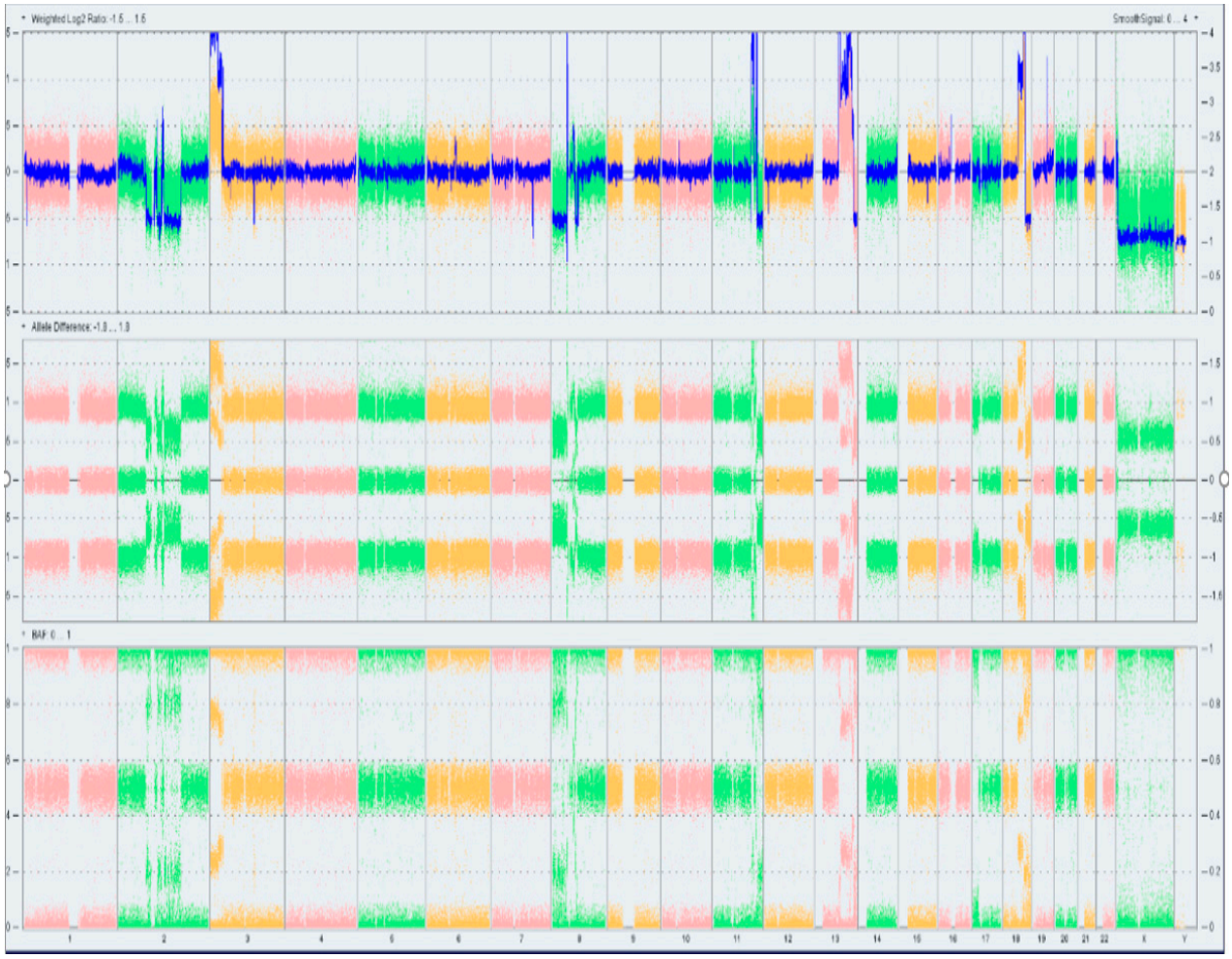

Figure 3. Whole genome view—losses and gains of copy numbers 2, 3, 8, 11, 13, and 18.

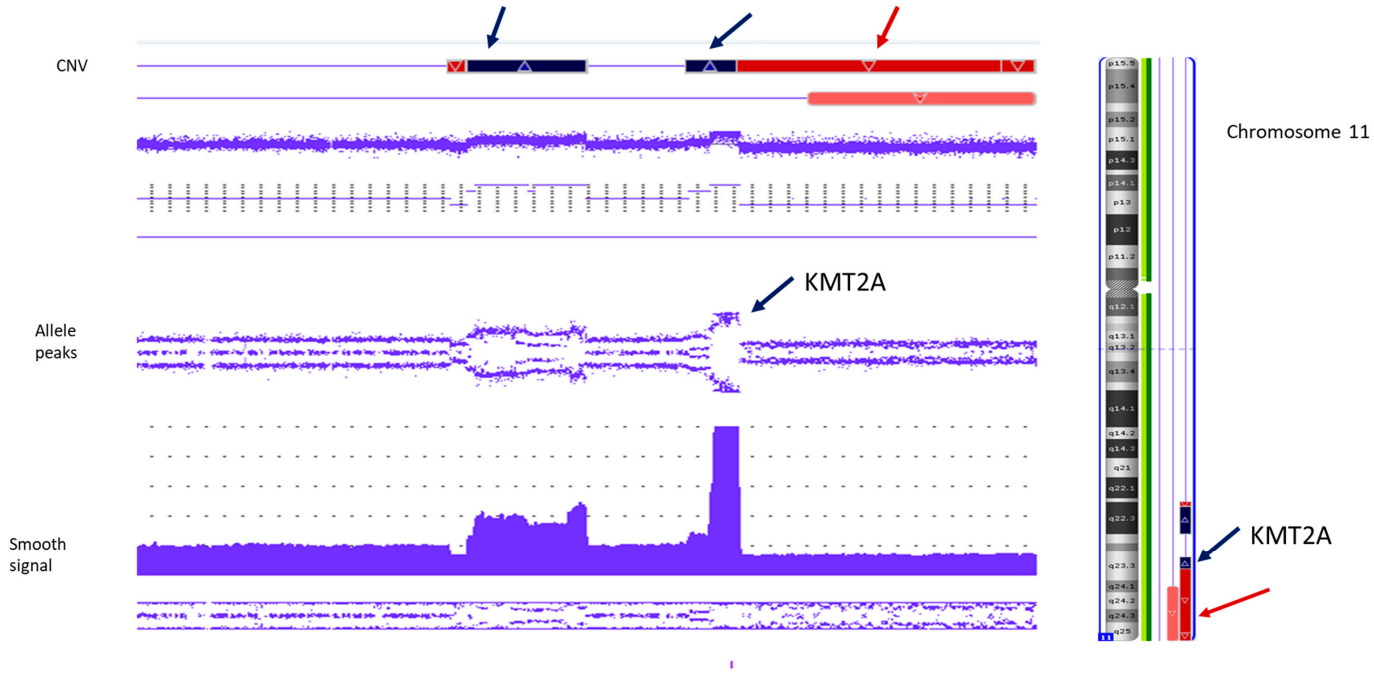

Figure 4. Amplification of *KMT2A* (11q23) (~10 copies) adjacent gains (blue arrow) and mosaic loss (red arrow).

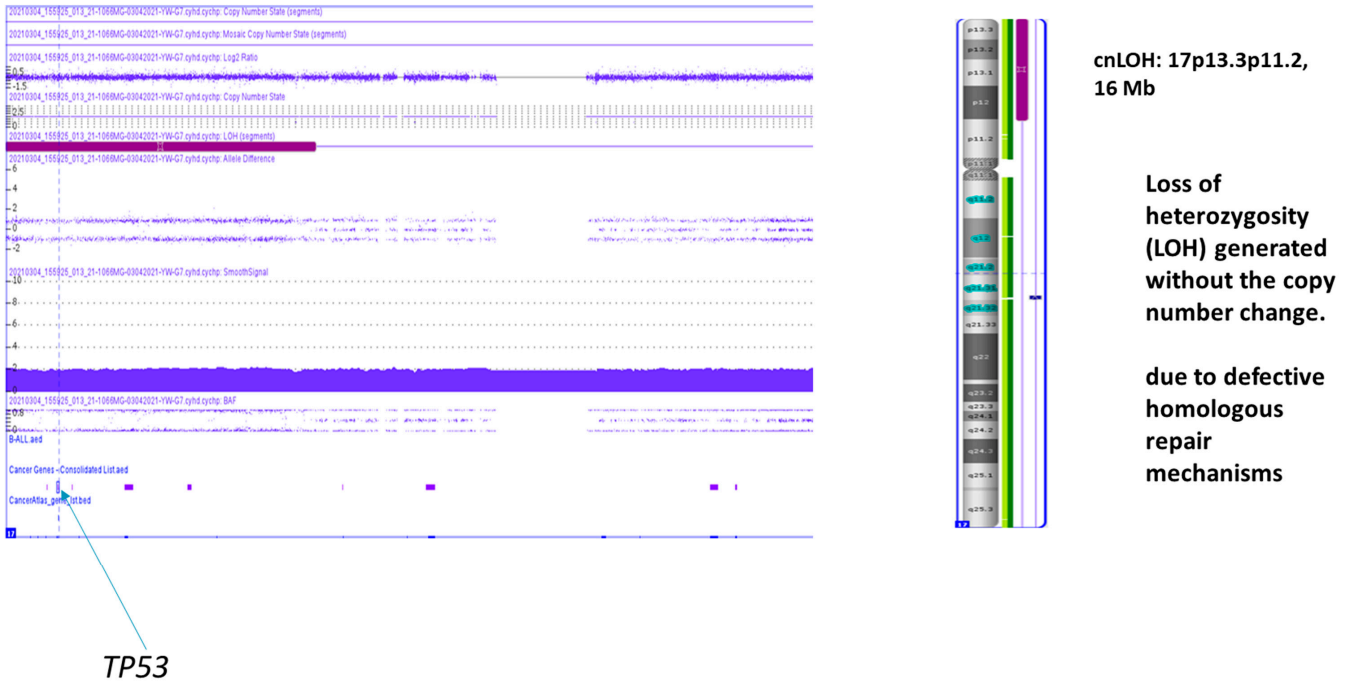

Figure 5. cnLOH of chromosome 17p (*TP53*).

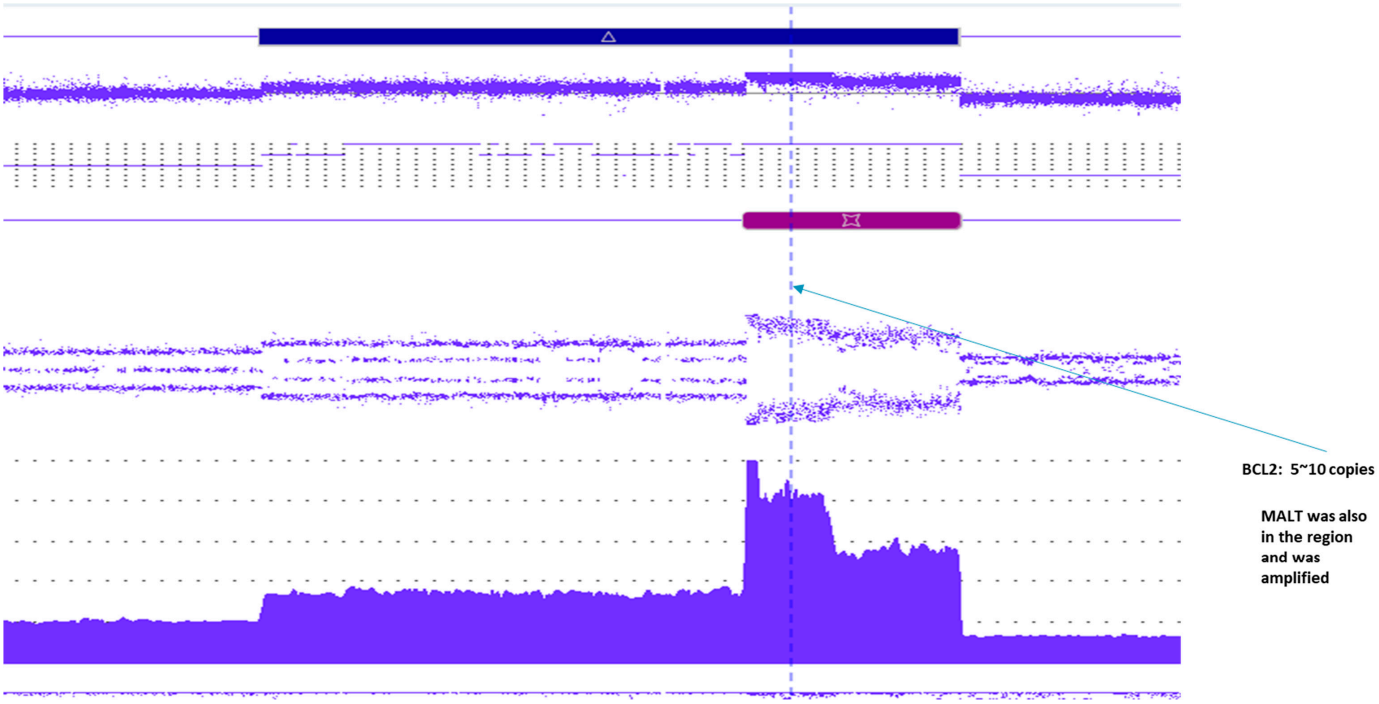

Figure 6. Amplification of *BCL2* at 18q21.

The patient was treated with multiagent systemic and intrathecal chemotherapy for his DLBCL and had refractory disease in the right renal cortex that was unresponsive to additional chemotherapy. He then underwent subsequent CD19 CAR T-cell therapy. CD19-directed chimeric antigen receptor CAR T-cell therapy is a valuable new treatment option for patients with relapsed/refractory B-cell NHL. CD19 is a biomarker for normal and neoplastic B cells, as well as follicular dendritic cells. Post-CD19 CAR T-cell therapy, the patient was found to be in remission from DLBCL. However, with the finding of worsening

thrombocytopenia, subsequent bone marrow evaluation in 2022, including myeloid NGS (Table 1), cytogenetics, and FISH results, showed a diagnosis of myelodysplastic syndrome.

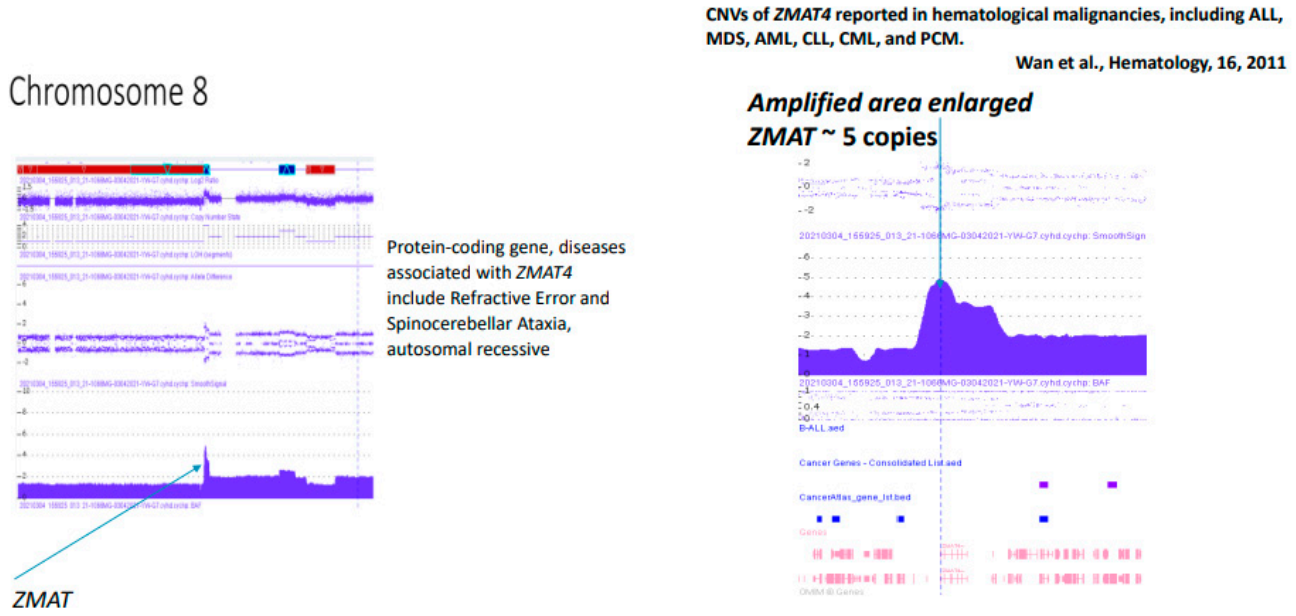

Figure 7. Chromosome 8p11.21—*ZMAT4* (zinc finger, matrin type 4)~5 copies [17].

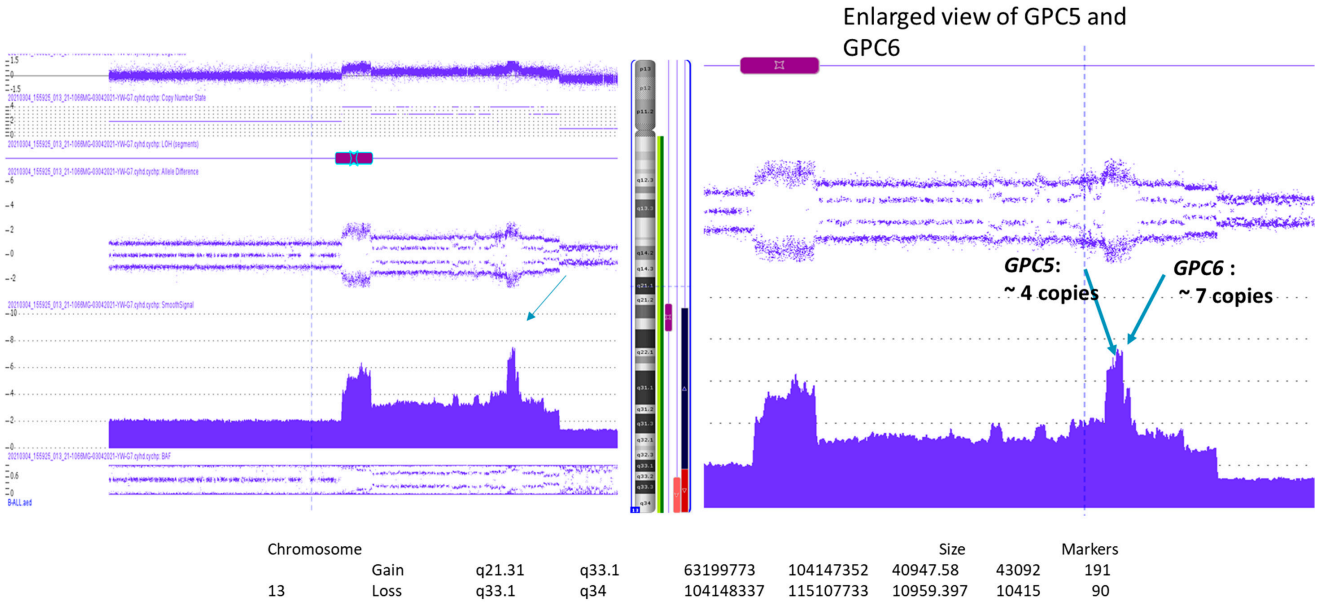

Figure 8. Amplification of 13q31.3q32.1, *GPC5*~4 copies, *GPC6*~7 copies.

Table 1. BM myeloid NGS results.

Gene	Alteration	Allele Frequency	Class	Clinical Significance
TP53	p.Arg175His	68.99	Tier 1	Strong clinical significance
CUX1	p.Leu437 *	11.06	Tier 2	Potential clinical significance
DDX41	p.Pro70Ser	45.39	Tier 3	Uncertain significance

Karyotype: 46,XY,del(5)(q22q35)[7]/44~50,XY,t(1;16)(q21;p13.3),add(3)(q23),add(5)(q35),del(7)(q22),-9,-21,+1~5mar[cp13] − 3/18/22. FISH: loss of 5q31 with EGR1 in 16.5% of cells and loss of D7S486 at 7q31 in 23.5% of cells.

The patient underwent an allogeneic stem cell transplant in 2022, but recurrent MDS was found several months later, for which the patient elected no further therapy and died from disease in late 2022.

4. Discussion

Exploration of the genetic landscape through various techniques for genome-wide screening of genetic alterations for the discovery of oncogenic targets has been reported [18,19].

The case described here highlights DLBCL arising from relapsed Hodgkin lymphoma, including deregulation of various oncogenic targets affecting specific pathways that contribute to the molecular pathogenicity of this disease entity. This could be attributable to chromoanagenesis. This case also illustrates the importance of a comprehensive evaluation of morphology, and molecular and chromosomal karyotype with gains and losses detected by G-banding, FISH, and an SNP array. As in this case, an SNP array can identify distinct CNV patterns in addition to abnormalities detected by other methods. The SNP array technique is unbiased and scans the entire genomic DNA with a comprehensive characterization of CNV, cnLOH, marker chromosomes, and genes implicated in apoptosis [20,21]. Amplifications of *BCL2*, *KMT2A*, and cnLOH of *TP53* have diagnostic and prognostic significance (discussed below), and were clearly identified by the SNP array in this case.

4.1. Genes with Diagnostic and Prognostic Significance

4.1.1. *BCL2*

BCL2 is an apoptotic regulator and promotes cell survival [22]. The *BCL2* proto-oncogene provides B cells with a selective survival advantage and promotes neoplastic expansion [22,23]. It is well known that rearrangement of *BCL2*, an oncogene with the immunoglobulin gene (IG) partner, leads to overexpression of *BCL2*. However, reports on the amplification of *BCL2* are limited. It is unclear if *BCL2* amplification occurs in response to a selection pressure for overexpression [24]. Monni et al. (1999) discuss whether the overexpression of *BCL2* is only due to rearrangement with IG genes and/or also due to amplification of *BCL2* [25]. These authors proposed that these events are probably mutually exclusive, because they have not observed both phenomena in the same case amongst all the lymphomas they have studied [25]. *BCL2* gene overexpression is a negative risk factor and is correlated with severity of malignancy [23].

4.1.2. *KMT2A*

Amplification of the *KMT2A* locus has been described in myeloid neoplasms, particularly acute myeloid leukemia, and myelodysplastic syndrome. It is often associated with a complex abnormal karyotype, and generally portends a poor prognosis [26]. A few cases of *KMT2A* amplification have also been reported in NHL. Starostik et al. (2020) showed amplification of *KMT2A* in five cases of primary gastric DLBCL by array CGH and FISH [27]. Gindin et al. (2014) reported that NHL subtypes associated with *KMT2A* translocations or amplification responded well to standard chemotherapy regimens, with complete remissions from 15 months to 7 years [21].

4.1.3. *TP53*

TP53 is a critical tumor suppressor that governs major defenses against tumor growth by mediating cell-cycle arrest, DNA repair, apoptosis, senescence, and autophagy under cell stress [3]. The negative prognostic impact of *BCL2* mutations in DLBCL has been well described. Molecular mechanisms of *TP53* dysfunction include gene mutations, promoter methylation, allelic imbalance, changes in transcriptional processing and stability of mRNA, malfunction of post-transcriptional modification, or alteration of critical protein/RNA interactions, losses, and cnLOH [3,15]. Disruption of p53-dependent apoptosis is implicated in the development, progression, and invasion of lymphoproliferative diseases [3]. *TP53* mutations occur at a similar frequency in both ABC and GCB subtypes with frequencies of 20–25%, which makes *TP53* one of the most commonly altered genes in DLBCL [3].

Additionally, in patients treated with R-CHOP, *TP53* mutations predict poorer OS and PFS for both GCB and ABC subtypes [3]. Overall, *TP53* mutational status is an independent prognostic indicator of poor survival in patients with DLBCL [3].

4.1.4. *ZMAT4*, *GPC5*, and *GPC6*

Not much information is available in reference to *ZMAT4*, *GPC5*, and *GPC6* amplification at chromosome 8p11.21 and 13q31q32 regions. Copy number variation of *ZMAT4* is reported in hematological malignancies [17]. *GPC5* is overexpressed in lymphoma cell lines with amplification (~4 Mb region in 18% of a total of 45 cases), and its overexpression may contribute to the development and/or progression of lymphomas and other tumors [28]. *GPC5* may function as a tumor suppressor in non-small cell lung cancer [28]. *GPC6* promotes cell proliferation, migration, and invasion in nasopharyngeal carcinoma [29].

5. Conclusions

Evaluation of the genetic landscape in DLBCL cases through various diagnostic methods for genome-wide screening offers a precise framework to explain the genetic heterogeneity, clinical course, and therapeutic considerations of DLBCL [15,18,19]. CNVs, SNVs, and INDELS may influence gene expression through gene dosage imbalances, disruption, fusion, and/or change in cis/trans-regulatory sequences [19]. Additional case studies among a larger cohort of patients may help decipher the molecular mechanisms associated with the complexity and heterogeneity of DLBCL lymphomagenesis and their role in the disease process.

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Conflicts of Interest: The authors declare no conflict of interest.

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