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Case Report

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Cryptic NUP214-ABL1 fusion with complex karyotype, episomes and intra-tumor genetic heterogeneity in a T-cell lymphoblastic lymphoma

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Abstract

T-lymphoblastic lymphoma (T-LBL) is a rare and aggressive form of non-Hodgkin's lymphoma and little is known about their molecular background. However, complex karyotypes were already related to this group of malignancy and associated with poor outcome. Here, we describe a 17-year-old female being diagnosed with T-LBL and a normal karyotype after standard G-banding with trypsin-Giemsa (GTG)-banding. However, further analyses including high-resolution molecular approaches, array-comparative genomic hybridization (aCGH), multiplex ligation-dependent probe amplification, fluorescence *in situ* hybridization and multicolor chromosome banding revealed a cryptic complex karyotype, *NUP214-ABL1* gene fusion, episomes and intra-tumor genetic heterogeneity. In addition, homozygous loss of *CDKN2A*, as well as amplification of oncogene *TLX1* (*HOX11*) were detected. Actually, *NUP214-ABL1* fusion gene replicated autonomously in this case as episomes. Overall, highly amplification of *NUP214-ABL1* fusion gene defines possibly a new subgroup of T-LBL patients which accordingly could benefit from treatment with tyrosine kinase inhibitors. As episomes are missed in standard karyotyping aCGH should be performed routinely in T-LBL to possibly detect more of such cases.

Keywords: T-cell lymphoblastic lymphoma, *NUP214-ABL1* fusion, complex karyotype, episomes, intra-tumor genetic heterogeneity, molecular cytogenetics, array comparative genomic hybridization

INTRODUCTION

Lymphoblastic lymphoma (LBL) is a rare and aggressive form of non-Hodgkin's lymphoma (NHL). LBL develops from immature B cells committed to the B- (B-LBL) or T-cell lineage (T-LBL). LBL is morphologically indistinguishable from acute lymphoblastic leukemia (ALL) and 90% of it have a T-cell phenotype. LBL also accounts for approximately 2% of all NHL cases and occur in adult, children and adolescent, with a male predominance (three time more male are affected)[1-2].

Chromosomal abnormalities in T-LBL are not well defined and cytogenetic data in T-LBL is limited. However, a few published cytogenetic studies revealed that typical chromosomal aberrations identified in T-cell ALL (T-ALL) are also present in T-LBL. These include translocations of T-cell receptor (*TCR*) gene to genes encoding transcription factors such as *TAL1*, *TLX1*, *LMO2*, and *LYL1*. In particular, the translocation t(9;17)(q34;q22~23) is typically found in T-LBL[1-4]. However, no single recurrent and typical genetic alteration for T-LBL could be identified. This is in contrast to other malignancies like translocation of *ALK* gene in anaplastic large cell lymphoma, *MYC* gene in Burkitt lymphoma or *BCL2* gene in follicular lymphoma.

Here we present the comprehensive analysis of a T-LBL case with a normal karyotype, according to standard G-banding with trypsin-Giemsa (GTG)-banding, using high resolution molecular methods, identifying also some intra-tumor genetic heterogeneity besides unusual acquired genetic alterations. Also here we report *NUP214-ABL1* gene fusion in this patient, which appears cryptic due to its localization in episomes.

CASE REPORT

A seventeen-year-old female patient, who was initially diagnosed in South Africa with T-ALL, presented in the clinic in Poland with abdominal pain, accompanied by diarrhea and vomiting; she was here initially treated only symptomatically. A few days before, a blood test already revealed hyperleukocytosis (589×10^9/l) with presence of 94% lymphoblasts in blood smear, hemoglobin 8.5 g/dl, and platelet count 53×10^9/l. Bone marrow findings were: hypercellularity with 95% lymphoblasts, lack of megakaryocytes and Periodic-Acid-Schiff (PAS) staining identified in 70% of the blasts thick grains (data not shown). Ultrasound of abdomen showed enlargement of the spleen to 152 mm, and presence of fluid in the lower pelvis. Cervical lymph nodes were bilaterally enlarged with diameters of 3-4 cm, and small submandibular nodes were bilaterally enlarged to 2 cm in diameter.

Cytogenetic and immunophenotypic analyses were done. The latter characterized a T-LBL due to high expression of CD45 (100%), CD2 (96.6%), CD4 (97.3%), CD8 (90%), CD7 (77.1%), CD5 (76.0%), sCD3 (71.2%), CD1a (70.0%) and the lack of TdT, CD19, CD34 and CD38.

Banding cytogenetic analyses were done in unstimulated bone marrow cells according to standard procedures[5] from the material taken at initial diagnoses. A total of 20 metaphases were available and analyzed on a banding resolution of 300 bands per haploid karyotype, revealing a normal female karyotype. Molecular diagnostic polymerase chain reaction (PCR)-based tests for presence of gene fusions *BCR/ABL (*p190 and p210), *TCF3/PBX1*, *MLL/AF4* and SIL/TAL1 were negative (results not shown).

Also genomic DNA isolated from cells fixed in acetic acid-methanol (1:3) was subjected to array-comparative genomic hybridization (aCGH) as well as the multiplex ligation probe amplification (MLPA) studies, as previously reported[6], Finally, fluorescence in situ hybridization (FISH) was done[6-8], revealing a highly complex karyotype [Figure 1 and Table 1] with gene-amplification due to episomes (abbreviated here as epi), which can be reported as:

46,XX,der(2)t(2;7)(q37.3;q25.1),del(4)(p14p16),t(7;10)(q34;q24),del(9)(p21.3p21.3),epi(6;9)(q23.3;q34.12)x20~30[20%]/46,XX,der(2)t(2;7)(q37.3;q25.1),del(4)(p14p16),der(7)(7pter->7q34::10q24.1->10q25.1::2q37.3->2qter),del(9)(p21.3p21.3),der(10)t(10;7)(q23;q34),epi(6;9)(q23.3;q34.12)x20~30[40%]/46,XX[40%].

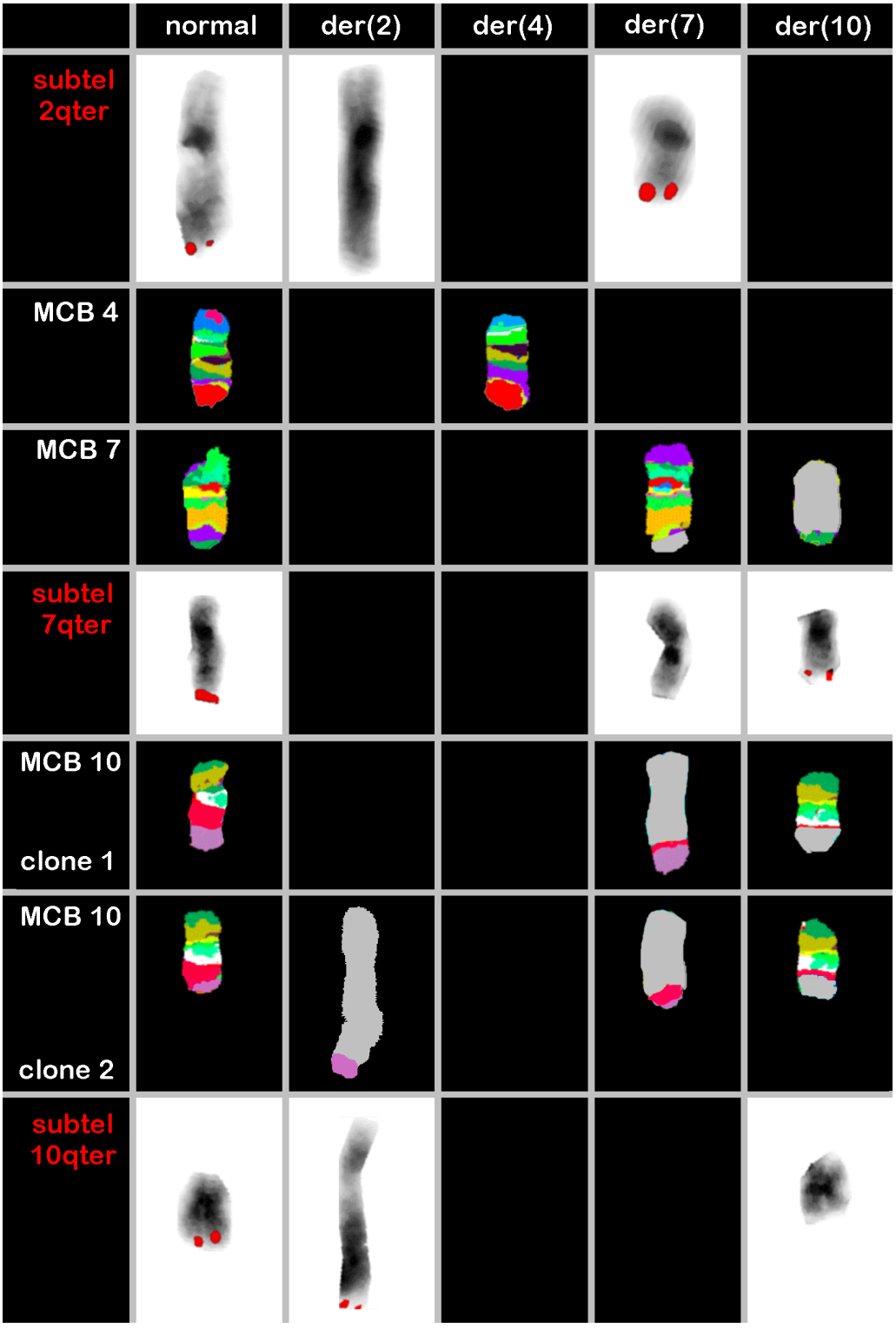

Figure 1. Result of multicolor banding (MCB) probesets for chromosomes 4, 7 and 10 are shown. MCB 10 showed the founder clone and subclone. Locus-specific probes (LSPs) for chromosomes 2, 7 and 10 characterized the breakpoints in 2q37.3, 7p34, 10q24.3 and 10q25.1 [Table 1]. The final karyotype after application of all approaches is summarized in the text. der = derivative chromosome

In the FISH-studies done here, between 15 and 25 metaphases were evaluated per applied probe-set, thus in the final karyotype overall percentages are given for the observed clones.

Table 1. Locus specific probes used for FISH together with their location according to genome browser version NCBI/hg18; this version was used here as some here applied FISH-probes are no longer available in newer genome browser versions. Results obtained are presented using standard (gene) abbreviations and such used according to the international system of cytogenomic nomenclature

Cytoband	Position [NCBI36/hg18]	Genes/locus	Probe	Result (signals on...)
2q37.1	chr2:234,552,641-234,701,765	n.d	RP11-263G22	der(2)
2q37.2	chr2:236,163,266-236,349,539	n.d.	RP11-473L20	der(2)
2q37.3	chr2:238,251,662-238,463,936	n.d.	RP11-497D24	der(7)
2q37.3	chr2:242,433,475-242,633,697	D2S447	2qTEL (Vysis)	der(7)
6q23.3	chr6:135,544,146-135,582,003	*MYB*	SPEC MYB DCBAP (Zytovision)	amp(6)(q23.3q23.3)
7q31.2	chr7:116,099,695-116,225,676	*MET*	SPEC MET/CEN7 (Zytovision)	der(7)
7q33	chr7:133,287,726-133,474,337	n.d.	RP11-639H21	der(7)
7q33	chr7:134,684,542-134,842,811	n.d.	RP11-371N6	der(7)
7q33	chr7:136,263,935-136,416,924	n.d.	RP11-88K4	der(7)
7q33	chr7:137,919,273-138,093,873	n.d.	RP11-269N18	der(7)
7q34	chr7:141,674,679-141,819,906	*TCRB*	n.a.	n.a.
7q34	chr7:142,124,883-142,316,809	n.d.	RP11-39H3	der(10)
7q34-q35	chr7:142,787,852-142,859,896	n.d.	RP11-811J9	der(10)
7q35	chr7:143,536,879-143,690,749	n.d.	RP11-45N9	der(10)
7q35	chr7:145,715,880-145,867,471	n.d.	RP11-97H18	der(10)
7q35	chr7:147,084,270-147,259,380	n.d.	RP11-302C22	der(10)
7q36.3	chr7:158,400,001-158,600,424	VIJyRM2000	7qTEL (Vysis)	der(10)
9p21.3	chr9:21,792,635-21,984,490	*MTAP CDKN2A/B*	SPEC CDKN2A/CEN9 (Zytovision)	del(9)(p21.3p21.3)
9q34.13	chr9:132,579,089-132,752,883	*ABL1*	LSI BCR, ABL (Vysis)	amp(9)(q34.12q34.12)
10q23.31	chr10:89,613,175-89,718,512	*PTEN*	SPEC PTEN/CEN10 (Zytovision)	der(10)
10q24.31	chr10:102,880,252-102,887,526	*TLX1*	n.a.	n.a.
10q24.31-q32	chr10:102,895,115-103,074,760	n.d.	RP11-324L3	der(7)
10q24.32	chr10:104,652,453-104,813,482	n.d.	RP11-724N1	der(7)
10q25.1	chr10:106,748,189-106,912,787	n.d.	RP11-165P9	der(7)
10q25.1	chr10:107,741,530-107,812,754	n.d.	RP11-596L14	der(7)
10q25.2	chr10:112,350,581-112,499,609	n.d.	RP11-364E8	der(2)
10q25.2	chr10:116,774,286-116,971,219	n.d.	RP11-338L11	der(2)
10q26.13	chr10:123,227,834-123,347,962	*FGFR2*	SPEC FGFR2/CEN10 (Zytovision)	der(2)
10q26.3	chr10:134,925,980-135,126,361	D10S2290	10qTEL (Vysis)	der(2)

FISH: fluorescence *in situ* hybridization

NUP214-ABL1 fusion could be deduced from aCGH data - the region being amplified ends on one side at *NUP214*- and on other side at *ABL1*-gene - as the amplified region is present as episomes, which are circular, there must be *NUP214-ABL1* fusion.

The patient was treated according to the Polish Adult Leukemia Group (PALG) protocol, with induction therapy consisting of prednisone, daunorubicin, vincristine and PEG-L-asparaginase. No remission was achieved and the patient was re-treated according to fludarabine, cytarabine, and mitoxantrone (FLAM) with consolidation course (metrotrexate, cyclophosphamide and PEG-L-asparaginase) and maintenance treatment. After ten months, the patient relapsed and was now treated according to Hyper-CVAD protocol (cyclophosphamide, vincristine, doxorubicin/Adriamycin and dexamethasone). Still, one month later the patient unfortunately died.

DISCUSSION

Recurrent acquired genetic lesions play a key role in predicting and assessing risks, so are the treatment protocols to be applied. Still, little is known about the copy number alterations (CNAs) accompanying structural abnormalities in T-LBL, such as the *NUP214-ABL1* fusion gene. *ABL1* fusion proteins are sensitive to tyrosine kinase inhibitors, which potentially can be included in future treatment strategy and *NUP214* is a component of the nuclear pore complex, which mediates nucleocytoplasmic transport. *NUP214* is widely

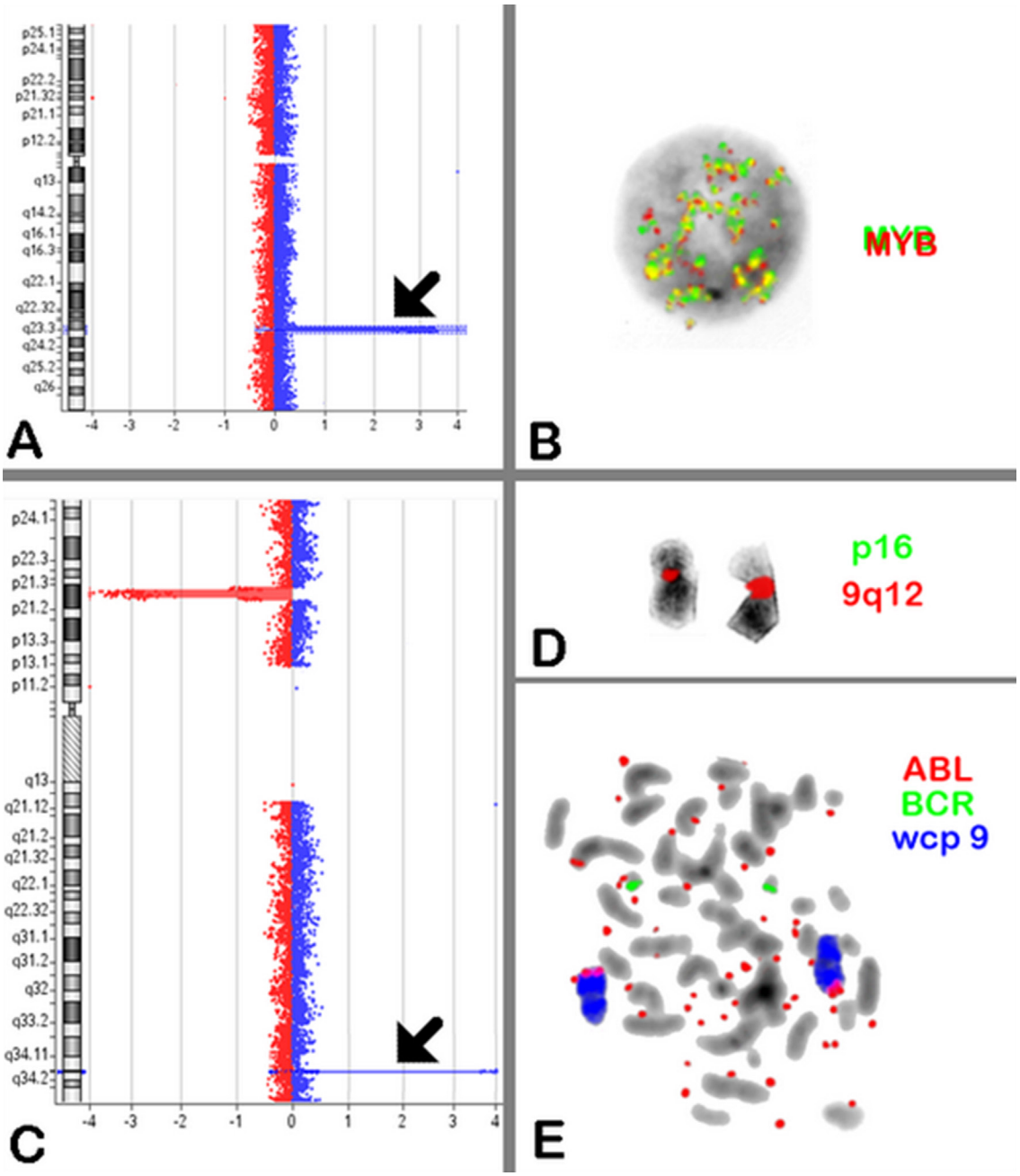

Figure 2. A: Array comparative genomic hybridization (aCGH) analysis of chromosome 6 revealed high level of 6q23.3 amplification containing *MYB* gene (arrow); B: MYB Dual Color Break Apart Probe was applied and showed high level of amplification more than 20 copies/per cell; C: aCGH analysis of chromosome 9 revealed biallelic deletion of *CDKN2A* at 9p21.3 and high level of 9q34 amplification contains *ABL1* and *NUP214* (arrow); D: FISH confirmed the homozygous deletion of *CDKN2A* in metaphase; E: BCR, ABL Dual Color Probe was applied and showed variable number of episomes (20-30) in spread metaphases. aCGH: array-comparative genomic hybridization; FISH: fluorescence in situ hybridization; wcp: whole chromosome paint

expressed and is involved in the pathogenesis of acute myeloid leukaemia associated with the translocation t(6;9)(p23;q34) as *DEK-NUP214* fusion[9-11].

To the best of our knowledge, a cryptic *NUP214-ABL1* fusion yet has only been identified in 6% of individuals with T-ALL and is the second most prevalent fusion gene involving *ABL1*[12-15]. Here we report this for the first time in a T-LBL case, and even detected it as a high level amplification; most probably after inversion, duplication or translocation, gene fusion, circularization and amplification happened. As *ABL1* is one of the best targetable tyrosine kinases, identification of *ABL1* gene fusion is clinically important, as patients may

Table 2. Summary of CNAs detected by aCGH. Recurrent (R) and unique (U) acquired CNAs are correspondingly highlighted in first column. Results obtained are presented using standard (gene) abbreviations and such used according to the international system of cytogenomic nomenclature

Chromosome (alteration U or R)	Cytobands	GRCH37/hg19	Size of imbalance [Mb]	Genes
1 (U)	del(1)(p36.31p36.23)	chr1:5,958,728-7,238,618	1.27	*NPHP4, KCNAB2, CHD5, RPL22, RNF207, ICMT, HES3, GPR153, ACOT7, HES2, ESPN, MIR4252, TNFRSF25, PLEKHG5, NOL9, TAS1R1, ZBTB48, KLHL21, PHF13, THAP3, DNAJC11, CAMTA1*
	del(1)(q22.2q22.2)	chr1:91,620,826-91,739,326	0.2	*HFM1*
4 (U)	del(4)(p16.3p14)	chr4:3,072,509-38,882,925	35.8	*HTT, C4orf44, RGS12, HGFAC, DOK7, LRPAP1, LOC100133461, ADRA2C, LOC348926, OTOP1, TMEM128, LYAR, ZBTB49, D4S234E, STX18, LOC100507266, MSX1, CYTL1, STK32B, C4orf6, EVC2, EVC, CRMP1, JAKMIP1, LOC285484, WFS1, PPP2R2C, MAN2B2, MRFAP1, LOC93622, S100P, MRFAP1L1, CNO, KIAA0232, TBC1D14, LOC100129931, CCDC96, TADA2B, GRPEL1, FLJ36777, SORCS2, PSAPL1, MIR4274, AFAP1 AS1, AFAP1, ABLIM2, SH3TC1, HTRA3, ACOX3, METTL19, GPR78, CPZ, HMX1, LOC650293, USP17, USP17L6P, DEFB131, MIR548I2, DRD5, SLC2A9, WDR1, MIR3138, ZNF518B, CLNK, MIR572, HS3ST1, HSP90AB2P, RAB28, LOC285547, NKX3-2, LOC285548, BOD1L, LOC152742, CPEB2, C1QTNF7, CC2D2A, FBXL5, FAM200B, BST1, CD38, FGFBP1, FGFBP2, PROM1, TAPT1, FLJ39653, LDB2, QDPR, CLRN2, LAP3, MED28, FAM184B, DCAF16, NCAPG, LCORL, SLIT2, LOC100505893, MIR218-1, PACRGL, KCNIP4, NCRNA00099, LOC100505912, GPR125,GBA3, PPARGC1A, MIR573, DHX15, SOD3, CCDC149, LGI2, SEPSECS, LOC285540, PI4K2B, ZCCHC4, ANAPC4, SLC34A2, SEL1L3, C4orf52, RBPJ, CCKAR, TBC1D19, STIM2, MIR4275, PCDH7, ARAP2, DTHD1, KIAA1239, C4orf19,RELL1, PGM2,TBC1D1, PTTG2,FLJ13197, KLF3,TLR10, TLR1,TLR6, FAM114A1,MIR574*
6 (R)	amp(6)(q23.3q23.3)	chr6:134,245,761-136,118,354	1.87	*TBPL1, SLC2A12, HMGA1P7, SGK1, ALDH8A1, HBS1L, MIR3662, MYB, AHI1, NCRNA00271*
9 (R)	del(9)(p21.3p21.3)	chr9:20,605,923-21,218,606	0.61	*MLLT3, KIAA1797, MIR491, PTPLAD2, IFNB1, IFNW1, IFNA21,IFNA4, IFNA7, IFNA10, IFNA16*
	del(9)(p21.3p21.3)	chr9:21,252,517-23,002,377	1.75	*IFNA22P, IFNA5, KLHL9, IFNA6, IFNA13, IFNA2, IFNA8, IFNA1, LOC554202, IFNE, MIR31, MTAP, C9orf53, CDKN2A, CDKN2B-AS1, CDKN2B, DMRTA1*
	amp(9)(q34.1q34.1)	chr9:133,658,293-134,092,544	0.43	*ABL1, QRFP, FIBCD1, LAMC3, AIF1L, NUP214*
10 (U)	del(10)(q25.1q25.2)	chr10:111,634,169-112,348,580	0.71	*XPNPEP1, ADD3, MXI1, SMNDC1, DUSP5, SMC3*
15 (U)	amp(15)(q13.3q13.3)	chr15:32,098,670-32,539,666	0.44	*CHRNA7*

CNAs: copy number alterations; aCGH: array-comparative genomic hybridization

potentially benefit from tyrosine kinase inhibitors[16-17].

Episomes are submicroscopic, circular and large acentric DNA fragments that can replicate autonomously. One of the common formation-mechanisms for extrachromosomal elements in cancer cells is episome-replication and unequal segregation during cell division, resulting finally in an increase of copy numbers. Still they that are invisible in banding cytogenetics; this is because episomes are composed of only several hundred kilobases of amplified oncogenes and/or drug-resistance genes, and thus are too small to be visualized by light-microscopy[18-20]. Of interest, we detected a variable number of episomes (20-30) in different cells. However, we suggest that c-*MYB* is also present on the same episomes [Figure 2]; due to lack of material we could not confirm this by FISH.

Additionally, recurrent acquired CNAs in different chromosomal regions were also identified besides unique ones for this case [Table 2]. Taken together, the genomic abnormalities in T-ALL and T-LBL are so similar

that they could be considered as identical diseases in the future[1,4,12,14,15,21-24].

As shown in our case, *NUP214-ABL1* is accompanied with loss of cyclin-dependent kinase inhibitor 2A (*CDKN2A)*, which encodes the tumorsuppressors p16INK4A and p14ARF, and affects cell cycle progression. *CDKN2A* gene deletion can be detected at initial diagnosis or acquired at relapse, suggesting that *CDKN2A* gene deletion is a secondary genetic event and associated with chromosomal rearrangements. This may as a result lead to the aberrant expression of a diverse group of T-cell-specific transcription factors, which again can function as oncogenes, such as *TLX1* and *TLX3*[2,21,25]. The translocation t(7;10)(q34;q24), resulting from the *TRB/TLX1* fusion gene, has been reported in several studies, and is present in 5% of pediatric and 30% of adult with T-cell ALL[25-28].

Overall, in the present T-LBL case we identified substantial intra-tumor genetic heterogeneity and complexity. The founder clone has *TRB*/*TLX1* fusion gene and the subclone has *TRB*/*TLX1* fusion gene plus complex karyotype involving three-way translocation t(2;7;10)(2q37.3;7q34;10q25.1), further developing into a more complex subclone. Interestingly, the breakpoints at 2q37.3, 7q34, 10q24.3 and 10q25.1 were not previously reported in T-LBL[29]. Thus, this data provides genetic support for a multi-step pathogenesis: deletion of a tumor-suppressor gene (*CDKN2A*), deregulated expression of a transcription factor *TLX1* and most likely overexpression of a constitutively activated tyrosine kinase (*NUP214-ABL1*) and oncogene *c-MYB* due to episome amplification and the unique phenotypes of the T-LBL case mentioned above.

To conclude, this study demonstrates the power of high resolution molecular approaches. It may be considered that the use of such approaches is the most efficient and future standard method for screening *ABL1* alteration. Particularly in T-LBL patients this may be advantageous, as *ABL1* modulates T-cell development and plays a role in cytoskeletal remodeling processes in T-cells. Besides, the intra-tumor genetic heterogeneity in cancer has important implications for reservoirs of cells involved in progression of disease and drug resistance therapy. As *NUP214-ABL1* fusion is sensitive to the tyrosine kinase inhibitor, this suggests that new therapeutic approaches in T-LBL may improve outcome and/or decrease treatment-related morbidity.

DECLARATIONS

Authors' contributions

Did the FISH-studies and drafted the paper: Othman MAK
Performed array comparative genomic hybridization (aCGH) analyses and interpretation: Melo JB, Carreira IM, Othman MAK
Provided T-LBL-case including clinical and banding cytogenetic data: Grygalewicz B, Kołkowska-Leśniak A
Planned and organized the study and did final drafting of the paper: Liehr T
All authors read and approved the paper.

Availability of data and materials

All data is provided in this article. Also the patient was mentioned previously in[30] as P61.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The present study was approved by the Ethical Board at the Friedrich Schiller University (Jena, Germany; approval No., 1105-04/03). Consent to participate of the parent of the patient studied here is available on request from the authors of this paper.

Consent for publication

Not applicable.

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