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Acute Lymphoblastic Leukemia With Near-haploid Karyotype and Philadelphia Chromosome

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Abstract. *Background/Aim: In precursor B-cell lineage acute lymphoblastic leukemia (BCP-ALL), leukemic cells harbor genetic abnormalities that play an important role in the diagnosis, prognosis, and treatment. A subgroup of BCP-ALL is characterized by the presence of a Philadelphia (Ph) chromosome and a chimeric BCR::ABL1 gene, whereas in another subgroup, leukemic cells exhibit near-haploidy with chromosome number 24-30. This study presents the third documented case of BCP-ALL in which a near haploid clone concurrently displayed a Ph chromosome/BCR::ABL1. Case Report: Bone marrow cells obtained at diagnosis from a 25-year-old man with BCP-ALL were genetically investigated using G-banding, fluorescence in situ hybridization, and array comparative genomic hybridization. Leukemic cells had an abnormal karyotype 28<n>,X,-Y,+6,+10,+18,+21,+ der(22) t(9;22)(q34;q11)[13]/28,idem, del(10)(q24),der(12) t(1;12)(q21;p13)[2]/46,XY[3], retained heterozygosity of the disomic chromosomes 6, 10, 18, and 21, had breakpoints in introns 1 of ABL1 and BCR, and carried a BCR::ABL1 chimera encoding the 190 kDa BCR::ABL1 protein. Conclusion: The coexistence of the BCR::ABL1 chimera and near-haploidy in the same cytogenetic clone suggested a possible synergistic role in leukemogenesis, with the former activating signaling pathways and the latter disrupting gene dosage balance.*

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Precursor B-cell acute lymphoblastic leukemia (BCP-ALL) is a hematological malignancy characterized by uncontrolled proliferation of precursor lymphoid cells committed to the B-cell lineage (1). BCP-ALL affects individuals of any age, but it is more commonly diagnosed in children and adolescents. It is one of the most prevalent types of leukemia in pediatric populations with peak incidence between 2 and 5 years old. However, BCP-ALL can also affect adults, and there is a second peak in incidence among adults over the age of 50 (1). Leukemic cells carry cytogenetic aberrations that play an important role in the diagnosis, prognosis, and treatment of BCP-ALL (2-4). A subgroup of BCP-ALL is characterized by the presence of a Philadelphia chromosome which is the der(22)t(9;22)(q34;q11) of the balanced t(9;22)(q34;q11) chromosomal translocation. The translocation fuses the BCR activator of RhoGEF and GTPase (*BCR*) gene from 22q11 with the ABL proto-oncogene 1, non-receptor tyrosine kinase (*ABL1*) gene from 9q34 generating a chimeric *BCR::ABL1* gene on the der(22)t(9;22)(q34;q11) (5). *BCR::ABL1* encodes a chimeric tyrosine kinase that activates various signaling pathways (6, 7). BCP-ALL with Philadelphia chromosome had a poor prognosis, but the development of increasingly effective tyrosine kinase inhibitors since the early 2000s have dramatically improved their prognosis (5, 8-12).

Hypodiploidy (less than 46 chromosomes) is a rare recurrent chromosomal abnormality, which is found in another subset of BCP-ALL (13-15). Leukemic cells with hypodiploidy may also undergo endoreduplication resulting in an exact or near-exact doubling of chromosome numbers termed as "masked hypodiploidy" (16, 17). Hypodiploidy is divided into three subgroups: near-haploidy with chromosome number 24-30, low hypodiploidy (31-39 chromosomes), and high hypodiploidy (40-45 chromosomes) (13-15, 18-20).

The Mitelman database of chromosome aberrations and gene fusions in cancer (Database last updated on October 16, 2023) contains 18999 entries of BCP-ALL with aberrant chromosomal aberration. Only 162 of them have a near-

haploid karyotype with chromosome number 24-30 (162/18,999=0.85%) (21). Near-haploid neoplastic B-cells are characterized by commonly loss of chromosomes 3, 7, 9, 15, 16 and 17 and retention of disomies of chromosomes X, Y, 8, 10, 14, 18, and 21 (14, 15, 20). Somatic genetic alterations targeting receptor tyrosine kinase and RAS signaling, deletion of the IKAROS family zinc finger 3 (*IKZF3*) gene, and deletions of a histone cluster at chromosome 6p22 have been reported in 70.6%, 13.2%, and 19.1%, of BCP-ALLs with a near haploid karyotype, respectively (13). Moreover, a recurring acquired genetic alteration involving the phosphoprotein membrane anchor with glycosphingolipid microdomains 1 (*PAG1*) gene, located on chromosome sub-band 8q21.13, was identified in 10.3% of near haploid BCP-ALL cases. The majority of these *PAG1* alterations manifested as homozygous deletions affecting the upstream region and the first exon of the gene, resulting in a complete loss of *PAG1* expression (13).

Near-haploidy in BCP-ALL is generally recognized as a high-risk cytogenetic abnormality (22-24). BCP-ALL patients with near-haploidy often have a less favorable prognosis compared to those with standard-risk cytogenetics (25, 26). High-risk cytogenetics are associated with an increased likelihood of treatment resistance and a higher risk of relapse (25, 26).

We report here an intriguing case of BCP-ALL in which a near haploid clone concurrently displays a Philadelphia chromosome and a chimeric *BCR::ABL1* gene.

Materials and Methods

Ethics statement. The study was approved by the Regional Ethics Committee (Regional komité for medisinsk forskningsetikk Sør-Øst, Norge, http://helseforskning.etikkom.no; 2010/1389/REK sør-øst A). Written informed consent was obtained from the patient. The Ethics Committee's approval included a review of the consent procedure. All patient information has been de-identified.

G-Banding and karyotyping. Bone marrow cells obtained at diagnosis were cytogenetically investigated (27, 28). Chromosomal preparations were G-banded using Leishman's stain (Sigma-Aldrich, St. Louis, MO, USA) and karyotyped according to the 2020 Guidelines of the International System for Human Cytogenomic Nomenclature (29).

Array comparative genomic hybridization (aCGH) analysis. aCGH was performed using CytoSure array products (Oxford Gene Technology, Begbroke, UK) following the company's protocols (30, 31). The reference DNA was Promega's human genomic male DNA (Promega, Madison, WI, USA). The slides (CytoSure Cancer +SNP array, 4x180k) were scanned in an Agilent SureScan Dx microarray scanner using Agilent Feature Extraction Software (version 12.1.1.1) (Santa Clara, CA, USA). Data were analyzed using CytoSure Interpret analysis software (version 4.11.36) (Oxford Gene Technology). Apart from copy number variation (CNV), the software detects allelic imbalance and loss-of-heterozygosity based on the B-allele frequency methodology and single nucleotide polymorphism (SNP) (32). Annotations are based on human genome build 19.

Fluorescence in-situ hybridization (FISH) analysis. FISH was performed on interphase nuclei of bone marrow cells from the patient using CytoCell *BCR/ABL(ABL1)* translocation, dual fusion probe and CytoCell myProbes ABL1 breakapart FISH probe (Oxford Gene Technology).

Case Report and Results

A 23-year-old previously healthy man was admitted to a local hospital due to poor general condition, night sweats, and increasing pancytopenia over a few weeks. A few months before admission, he had a perianal abscess that was successfully drained, and a perianal fistula was diagnosed. Prior to admission, he also had tonsillitis with streptococci and received antibiotic treatment. Blood and bone marrow flow cytometry at the time of admittance showed 46% and 94% blasts, respectively, consistent with B-cell precursor acute lymphoblastic leukemia (BCP-ALL). He was consequently transferred to our university hospital for induction treatment.

Upon clinical examination, he was in relatively good general condition. There were no enlarged lymph nodes in the neck, axillae or groin, and no hepatosplenomegaly or testicular tumors were observed. However, a probable perianal fistula opening was identified. He was afebrile and had stable circulatory and respiratory status.

Blood tests revealed anemia (Hb 8.4 g/dl, normal range 13.4-17.0), a normal leukocyte count (7.3×10^9/l, normal range 3.5-10.0), neutropenia (0.4×10^9/l, normal range 1.5-7.3), and thrombocytopenia (30×10^9/l, normal range 145-390×10^9/l) after platelet transfusion before transfer from the local hospital. There were no signs of disseminated intravascular coagulation (DIC), spontaneous tumor lysis or renal failure, but lactate dehydrogenase (LDH) was elevated to 324 U/l (normal range 105-205 U/l). Blood and bone marrow smears were completely dominated by small to medium-sized blasts with scant cytoplasm. No granules or Auer rods we observed.

In flow cytometry, 94% of the viable nucleated cells in the bone marrow were B-lymphoblasts with the following phenotype: CD45 bimodal, CD2-, CD3-, CD4 bimodal (72%+, likely artifact), CD5-, CD7-, CD10 bimodal (96%+), CD11b-, CD11c-, CD13-, CD14-, CD16-, CD56-, CD19+, CD20-, CD22+, CD24+, CD33 bimodal (53%+), CD38 weak+, CD64-, CD117-, HLA-DR+, nuTdT+, cyCD3-, cyCD79a+, cyMPO-, cyIgM-, cyCD22 weak+, CD15-, CD49f+, CD58+, CD66b-, CD66c weak+ (24%), CD73- (small subset+, approximately 3-7%), CD81+, CD86-, CD123-, CD133-, CD304 bimodal (57%+), NG2-, TSLPR- compatible with BCP-ALL.

Standard induction therapy was initiated according to the ALLTogether1 protocol, including dexamethasone, vincristine,

daunorubicin, intravenous PEG-asparaginase, and intrathecal methotrexate (33, 34). Later on the same day, molecular pathological examination revealed a *BCR::ABL1* minor fusion transcript corresponding to t(9;22)(q34;q11). Therefore, a tyrosine kinase inhibitor (imatinib) was started as additional treatment. According to Norwegian guidelines, allogeneic bone marrow transplantation (allo-HSCT) was planned upon achieving minimal residual disease (MRD) negativity. He was discharged from the inpatient unit on treatment day 12, and there were no complications, such as tumor lysis, neutropenic fever, or other complications during induction therapy. A significant part of the subsequent treatment was conducted on an outpatient basis.

On treatment day 15, MRD in the bone marrow aspirate was 36% blasts by flow cytometry, with an unchanged flow phenotype. Flow cytometry and molecular pathological examination of the *BCR::ABL1* minor fusion transcript on day 29 indicated a decrease to 2.2% and to 0.8%, respectively. Following induction therapy, the tyrosine kinase inhibitor was switched to dasatinib, and the treatment protocol was changed to the NOPHO ALL 2008 protocol (35) according to the department's procedures, involving 6-mercaptopurine (6MP), vincristine, high-dose methotrexate (5 g/m^2), and intrathecal methotrexate. PEG-asparaginase was omitted to reduce the risk of hepatotoxicity during concurrent treatment with the tyrosine kinase inhibitor.

After a few weeks of respiratory symptoms, a thoracic computed tomography (CT) scan was performed, revealing five nodular consolidations. A CT scan of the sinuses showed pronounced mucosal thickening, and both examinations raised suspicion of invasive mold infection. Bronchial lavage was performed twice without microbiological findings. Empirical antifungal treatment with isavuconazole was initiated for mold infection.

Two and a half months after starting treatment, he achieved minimal residual disease (MRD) of 0.014% based on molecular pathological examination of the *BCR::ABL1* minor fusion transcript in the bone marrow.

The patient underwent allogeneic bone marrow transplantation approximately 4 months after the initiation of treatment. Prior to transplantation, an echocardiogram surprisingly showed a significant decrease in left ventricular function from approximately 60% at the start of treatment to 45%, most likely related to dasatinib treatment, which was subsequently discontinued. MRD was no longer detectable. Originally planned conditioning with ETO/TBI (MAC) was changed to RIC (Reduced Intensity Conditioning) due to heart failure. The modified conditioning regimen involved NCI Cy/Flu/TBI6.

The donor was unrelated, HLA-identical, with blood type AB+, matched to an A+ recipient. Both the donor and recipient were CMV-negative and EBV-positive. Peripheral blood stem cells were used for transplantation. Graft-versus-host disease (GvHD) prophylaxis included anti-thymocyte globulin (ATG) on days -2 to -1 (total 4 mg/kg), cyclosporine from day -1, and methotrexate IV on days +1, +3, and +6. Isavuconazole was administered throughout the transplantation process as mold prophylaxis.

The patient had an uncomplicated course during the hospital stay, achieving neutrophil engraftment (>0.5) on day +13 and platelet engraftment (>20) on day +15. Trilineage engraftment was confirmed in the bone marrow smear on day +28, and on the same day, donor chimerism was 99% in an unseparated sample.

EBV reactivation occurred with rising EBV DNA levels up to 27,000 IU/ml, but there were no signs of post-transplant lymphoma. This was treated with a dose of rituximab, resulting in a significant decrease in EBV DNA. On day +44, Clostridium difficile toxin was detected in the feces and was treated with vancomycin.

A prophylactic reintroduction of a tyrosine kinase inhibitor (imatinib) will commence once the patient is in a stable condition, with treatment expected to continue for two years.

Diagnostic cytogenetic examination of short-term cultured cells from the patient's bone marrow revealed a near haploid clone described by the karyotype 28<n>,X,-Y,+6,+10, +18,+21,+der(22)t(9;22)(q34;q11)[13]/28,idem,del(10)(q24),der(12)t(1;12)(q21;p13)[2]/46,XY[3] (Figure 1A and B).

Interphase FISH with *ABL1* break-apart probe detected a Red/Green signal, corresponding to the normal *ABL1* locus, together with a green signal, corresponding to terminal (3'-end part of ABL1) in 156 out of 209 nuclei (Figure 2A). FISH with a dual fusion probe for *BCR/ABL1*, detected in 150 out of 201 interphase nuclei, a green, a red signal and a Red/Green signals corresponding to normal *BCR,* normal *ABL1* and *BCR::ABL1* fusion gene (Figure 2B).

aCGH confirmed the results of the main cytogenetic clone seen in G-banding, showing disomy for chromosomes 6, 10, 18, and 21, loss of chromosome Y, loss of most of chromosome 9 from chromosome sub-band p24.3 to sub-band 9q34.11, and loss a region of chromosome 22 from the sub-band q11.23 to q13.33 (Figure 3A-C). Furthermore, aCGH showed that the breakpoint in *ABL1* occurred in intron 1, in a narrow region of 2560 bp in the interval Chr9: 133713031-133715590 (Figure 3B). In the *BCR* gene, the breakpoint was found in intron 1, in a narrow region of 3502 bp between the interval Chr22: 23585229-23588730 (Figure 3C).

BCR::ABL1 chimera with breakpoints in intron 1 of *ABL1* and *BCR* results in the most common *BCR::ABL1* transcript in Ph+ ALL patients, that is the first exon (e1) of *BCR* is spliced to the second exon of (a2) *ABL1* (e1-a2 fusion), coding for a 190 kDa BCR::ABL1 protein (36, 37).

The aberrant chromosomes del(10)(q24) and der(12) t(1;12)(q21;p13) which were present in the small subclone (only 2 metaphases found) were not detected by aCGH. Analysis of allelic imbalance and loss-of-heterozygosity

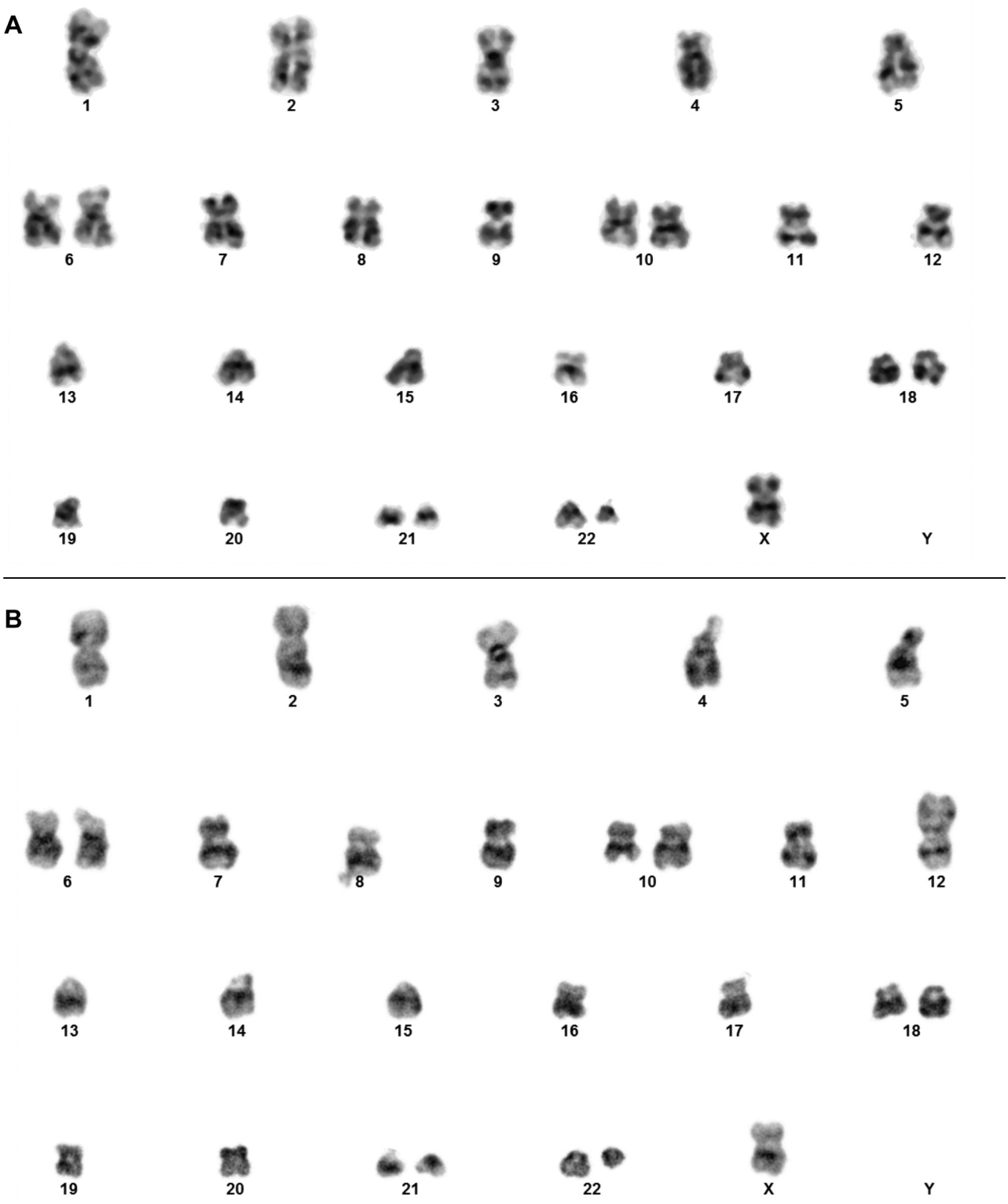

Figure 1. *Cytogenetic analysis of short-term cultured cells from the patient's bone marrow at diagnosis. (A) Karyogram from the main near haploid clone with karyotype 28<n>,X,-Y,+6,+10,+18,+21,+der(22)t(9;22)(q34;q11). (B) Karyogram from the small subclone with the karyotype 28<n>,X,-Y,+6,+del(10)(q24),der(12)t(1;12)(q21;p13),+18, +21,+der(22)t(9;22)(q34;q11).*

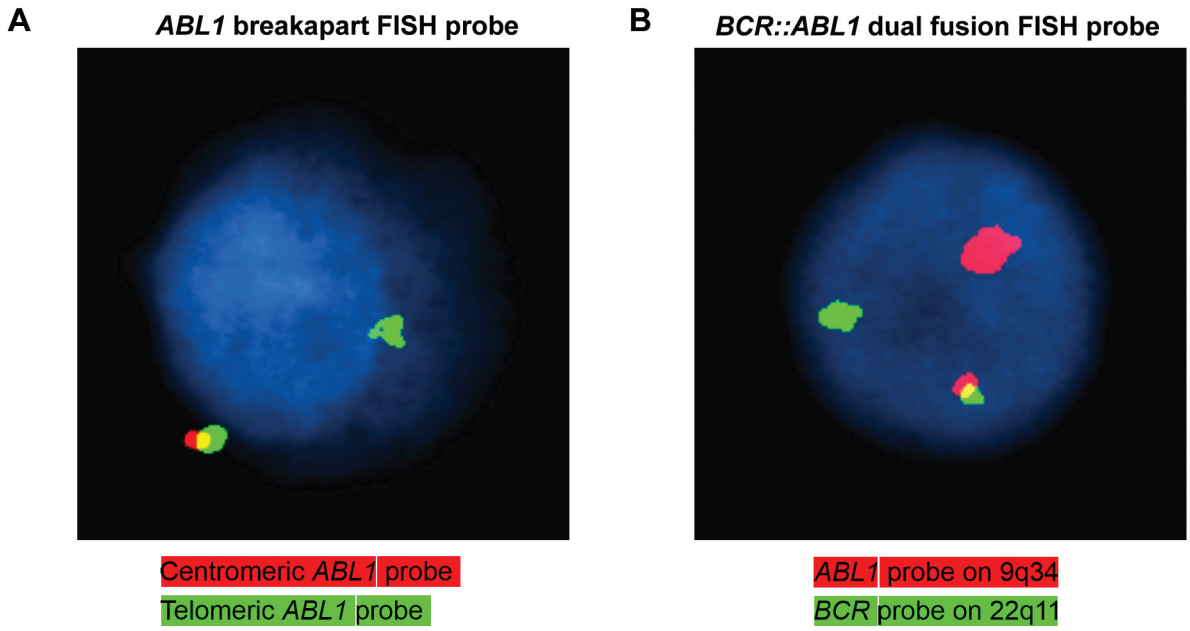

Figure 2. *Fluorescence in-situ hybridization (FISH) of the patient with BCP-ALL. (A) FISH with ABL1 break-apart probe on an interphase nucleus resulted in a red/green signal, corresponding to the normal ABL1 locus, and a green signal, corresponding to terminal (3´-end) part of ABL1. (B) FISH with a dual fusion probe for BCR::ABL1 on an interphase nucleus resulted in green, red and red/green signals corresponding to normal BCR, normal ABL1 and BCR::ABL1 fusion gene.*

showed that the chromosomes 6, 10, 18, and 21 retained heterozygosity (Table I).

Discussion

Near-haploid and Philadelphia chromosome/*BCR::ABL1* chimeric gene are two different recurrent primary genetic aberrations in BCP-ALL (1, 2, 5, 14, 15, 19, 22, 23). The presence of a Philadelphia chromosome/*BCR::ABL1* chimeric gene in a near haploid clone is an extremely rare genetic event. Including the present case there have been only three cases of BCP-ALL with a near-haploid clone harboring a Philadelphia chromosome/*BCR::ABL1* chimeric gene (Table II) (38, 39). The three BCP-ALLs exhibit different chromosome numbers, different retention of disomies, and none of them involved endoreduplication (Table II) (16, 17). In case 1 of Table II, the near-haploid clone had a balanced t(9;22)(q34;q11) together with a normal chromosome 9. Both der(9)t(9;22)(q34;q11) and der(22)t(9;22)(q34;q11) were present within the near haploid clone, indicating that the t(9;22)(q34;q11) translocation occurred after the massive loss of chromosomes and the formation of near haploid clone. In cases 2 and 3 of Table II, the near haploid clone had only the der(22)t(9;22)(q34;q11), which also carried the *BCR::ABL1* chimeric gene, together with a normal chromosome 9. This cytogenetic finding indicated that a balanced t(9;22)(q34;q11) translocation was the first (cyto)genetic event. The subsequent massive loss of chromosomes to generate a near haploid clone also included the loss of the der(9)t(9;22)(q34;q11).

The Mitelman database of chromosome aberrations and gene fusions in cancer (last updated of the database was on January 16, 2024) contains four male BCP-ALL patients with chromosome number 28 and retention of disomies of chromosomes 6, 10, 18, and, 21 (13, 16, 21). Two of those patients also carried a second clone resulting from endoreduplication (13, 16, 21).

Loss-of-heterozygosity based on the B-allele frequency methodology and single nucleotide polymorphism (SNP) (32) showed that the disomic chromosomes 6, 10, 18, and, 21 retained heterozygosity (Table I). This is consistent with previous observations that in neoplasms with near-haploid karyotypes, the disomic chromosomes are both maternal and paternal (19, 40-43). aCGH also revealed that the breakpoints in both the *ABL1* and *BCR* genes occurred in their intron 1. The *BCR::ABL1* chimera, with breakpoints in intron 1 of *ABL1* and *BCR*, results in the most common *BCR::ABL1* transcript in Ph+ ALL patients, where the first exon (e1) of *BCR* is spliced to the second exon of (a2) *ABL1* (e1-a2 fusion), coding for a 190 kDa BCR::ABL1 protein (36, 37). The p190 isoform BCR::ABL1 is insufficient for malignant transformation and additional genetic aberrations

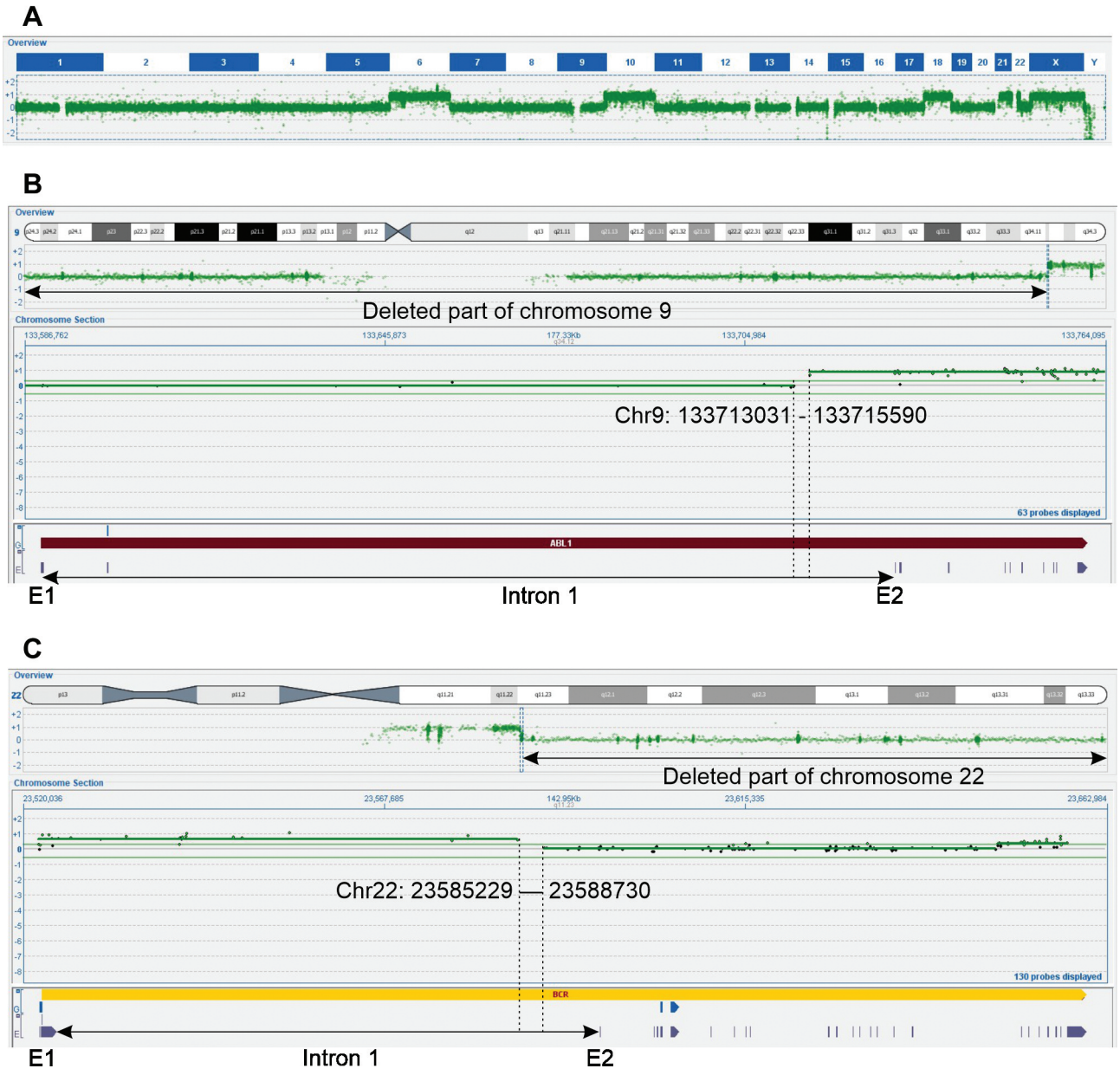

Figure 3. *Array comparative genomic hybridization (aCGH) examination of the bone marrow cells of the BCP-ALL patient. (A) Genetic profile of whole genome showing gains of chromosomes 6, 10, 18, and 21, loss of chromosome Y, loss most of chromosome 9, from chromosome sub-band p24.3 to sub-band 9q34.11, and loss a region of chromosome 22 from the sub-band q11.23 to q13.33 (A, B, and C). (B) aCGH showing that the breakpoint in the ABL1 gene occurred in intron 1, in a narrow region of 2560 bp in the interval Chr9: 133713031-133715590. (C) aCGH showing that the breakpoint in the BCR gene occurred in intron 1, in a narrow region of 3502 bp between the interval Chr22: 23585229-23588730. E: Exon.*

are necessary for the development of Ph+ BCP-ALL (2, 6). Thus, a combination of p190 isoform BCR::ABL1 and near-haploidy may lead to leukemogenesis. The p190 isoform BCR::ABL1 activates signaling pathways (44, 45) whereas near-haploidy may affect thousands of genes disturbing gene dosage balance (42, 46, 47).

Conclusion

We present here the third case of a BCP-ALL in which a near haploid clonal chromosomal aberration harboring a Philadelphia chromosome/*BCR::ABL1* chimeric gene. The coexistence of the *BCR::ABL1* chimera and near-haploidy

Table I. *Homozygosity observed for each chromosome in the case of BCP-ALL with near haploid clone harboring t(9;22)(q34;q11)/BCR::ABL1. The chromosomes 6, 10, 18, and 21 are in bold.*

Chromosome	SNPs	Homozygous SNPs	Heterozygous SNPs	Unknown Genotype SNPs	% Homozygosity
1	1,180	1,162	18	0	98%
2	1,584	1,578	5	1	100%
3	1,483	1,474	8	1	99%
4	1,101	1,089	12	0	99%
5	1,037	1,030	4	3	100%
6	**1,113**	**679**	**424**	**10**	**62%**
7	1,145	1,133	9	3	99%
8	1,225	1,216	8	1	99%
9	828	807	20	1	98%
10	**946**	**578**	**358**	**10**	**62%**
11	893	888	4	1	100%
12	770	759	9	2	99%
13	758	750	8	0	99%
14	567	560	6	1	99%
15	529	525	2	2	100%
16	530	524	5	1	99%
17	487	483	4	0	99%
18	**571**	**356**	**203**	**12**	**64%**
19	213	210	2	1	99%
20	388	383	5	0	99%
21	**339**	**208**	**129**	**2**	**62%**
22	205	183	21	1	90%
X	878	869	8	1	99%

SNP: Single nucleotide polymorphism.

Table II. *The reported cases of BCP-ALL with near haploid clone harboring a Philadelphia chromosome.*

Case	Sex/Age	Karyotype	Reference
1	F/39	25<n>,X,+9,t(9;22)(q34;q11),+mar[10]/46,XX[8]	Götz, 1992 (38)
2	M/70	27<n>,X,+Y,+14,+21,+22,der(22)t(9;22)(q34;q11.2)[17]/46,XY[3]	Peterson, 2019 (39)
3	M/23	28<n>,X,-Y,+6,+10,+18,+21,+der(22)t(9;22)(q34;q11)[13]/28, idem,del(10)(q24),der(12)t(1;12)(q21;p13)[2]/46,XY[3]	Present case

suggests a potential synergistic role in leukemogenesis, where the former activates signaling pathways and the latter disrupts gene dosage balance.

Conflicts of Interest

The Authors declare that they have no potential conflicts of interest in relation to this study.

Authors' Contributions

IP designed and supervised the research, evaluated aCGH, FISH, and cytogenetic data, and wrote the article. KA performed cytogenetic and FISH experiments. HSW made clinical evaluations and treated the patient. MRT evaluated aCGH, FISH, and cytogenetic data. All Authors read and approved the final article.

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