

## Case Report Section

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# T-cell acute lymphoblastic leukemia with t(7;14)(p15;q11.2)/HOXA-TCRA/D and biallelic deletion of CDKN2A. Case report and literature review

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### Abstract

Case report and literature review on T-cell acute lymphoblastic leukemia with t(7;14)(p15;q11.2)/HOXA-TCRA/D and biallelic deletion of CDKN2A.

### Clinics

#### Age and sex

9 years old male patient.

#### Previous history

No preleukemia, no previous malignancy, no inborn condition of note, no main items.

#### Organomegaly

No hepatomegaly, splenomegaly, enlarged lymph nodes, no central nervous system involvement.

#### Note

Positive for splenomegaly, bilateral enlarged kidneys, large mediastinal mass, extensive lymphadenopathy of intrathoracic, retroperitoneal, cervical, and axillary regions.  
Cerebral spinal fluid negative for malignant cells.

### Blood

**WBC:** 31.6 X 10<sup>9</sup>/l

**HB:** 8.6g/dl

**Platelets:** 15 X 10<sup>9</sup>/l

**Blasts:** 65%

**Bone marrow:** Dry tap.

**Note:** Peripheral blood showed anemia, thrombocytopenia and leukocytosis.

### Cyto-Pathology Classification

#### Cytology

Peripheral blood smear showed large L2 lymphoblasts with nucleoli, normochromic, normocytic RBCs and markedly decreased platelets.

#### Immunophenotype

Flow cytometric analysis of peripheral blood demonstrated an abnormal CD45dim circulating lymphoblasts (75%) expressing CD2, CD5, CD7, CD8, CD10, cytoplasmic CD3, TdT and partially expressing weak CD30.

Overall, these findings were consistent with T-cell malignancy.

#### Rearranged Ig Tcr

No rearrangements of TCRB and TCRA/D genes by FISH.

#### Electron microscopy

Not performed.

#### Diagnosis

T-cell acute lymphoblastic leukemia (T-ALL).

### Survival

**Date of diagnosis:** 09-2013

**Treatment:** Patient was treated with COG-AALL00434 protocol including vincristine, daunorubicin hydrochloride, prednisone, pegaspargase, and intrathecal cytarabine and methotrexate.

**Complete remission:** yes

**Treatment related death:** no

**Relapse:** no

**Status:** Alive. **Last follow up:** 01-2014

**Survival:** 4 months

**Note:** In remission; on maintenance chemotherapy as of Jan 28, 2014.

## Karyotype

**Sample:** Peripheral blood

**Culture time:** 24 and 48hrs unstimulated cultures

**Banding:** GTG

### Results

46, XY, del(6)(q14q21), t(7;14)(p15;q11.2), del(9)(p13)[12]/92, idemx2, [7]/46, XY[1] (Figure 1)

### Other molecular cytogenetics technics

#### Fluorescence in situ hybridization (FISH)

FISH using Vysis LSI BCR/ABL, CDKN2A/CEP-9 and TCRA/D, as well as Cytocell TCRB DNA probes was performed on peripheral blood harvested pellet.

FISH analysis revealed four copies for TCRB/7q34, TRA/D/14q11.2, BCR/22q11.2, and ABL/9q34 in approximately 50% of cells, representing the pseudotetraploid cell line observed by karyotype. No BCR/ABL gene fusion was detected in any cell line. The hybridization with the CDKN2A/CEP9 probe set produced nullisomy (biallelic loss) of the

CDKN2A in 79% of cells but four copies of the control CEP-9 in 44% of cells and two copies in the remaining 35% while the normal cells had 2 copies of each (Figure 2).

To verify the results of chromosome analysis with respect to t(7;14), confirmatory FISH was performed using Signature Genomic DNA probes BAC probes RP11-1132K14/7p15 (orange) covering the HOXA cluster genes and CTD-2555K7/14q11.2 (green) laying immediately telomeric to the TCRA/D/14q11.2 coding region. The hybridization revealed a fusion pattern; one fusion signal in the pseudodiploid and two fusion signals in the pseudotetraploid cells (Figure 3).

### Array Comparative Genomic Hybridization (aCGH)

Genomic DNA was isolated from peripheral blood using a Puregene kit (Gentra Systems, Minneapolis, MN). The aCGH was performed using a genome wide oligonucleotide + single nucleotide polymorphism based microarray containing 180K-features (SurePrint G3 GGXChip + SNP v1.0 4x180k Agilent Technologies, St Clara, CA). The microarray slide was scanned by Agilent G2565 CA microarray scanner system with data imported to aCGH Analytics Software (Genoglyphix™; Signature Genomic Laboratories). The array design and genomic coordinates are based on NCBI build 37 (hg19).

The aCGH revealed a 33.3Mb terminal monoallelic deletion of chromosome 9p13.3->pter, with 1.39 Mb biallelic deletions in the 9p21.3 region which spans the CDKN2A gene locus (Figure 4). It also detected a large 20.7 Mb interstitial deletion at del(6)(q14.1q16.2) and 1.34 Mb duplication within the 4q32.1 region.

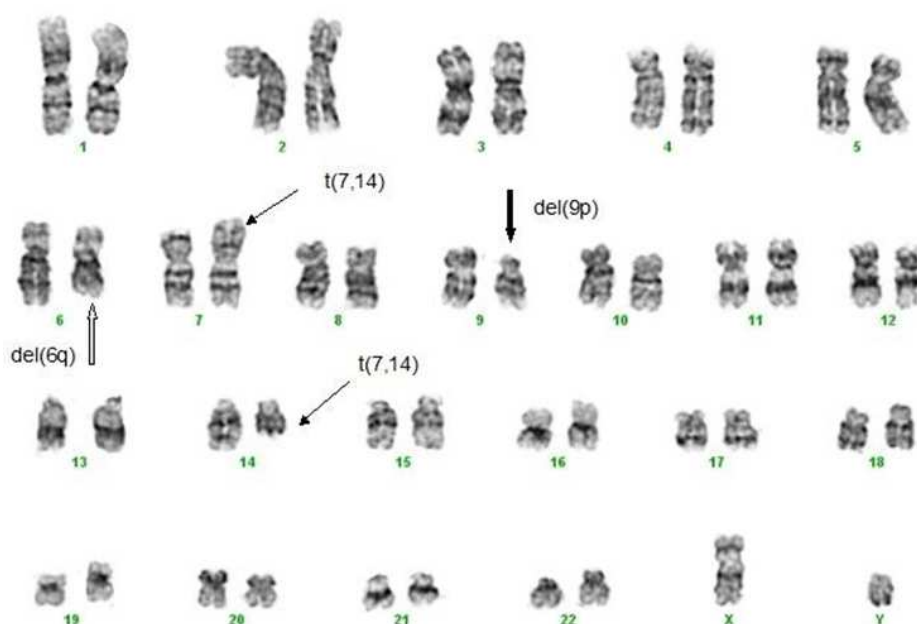


Figure 1: G-banded karyotype of the pseudodiploid cell line demonstrating del(6q) (hollow arrow), t(7;14)(p15;q11.2) (thin arrows), and del(9p) (solid arrow).

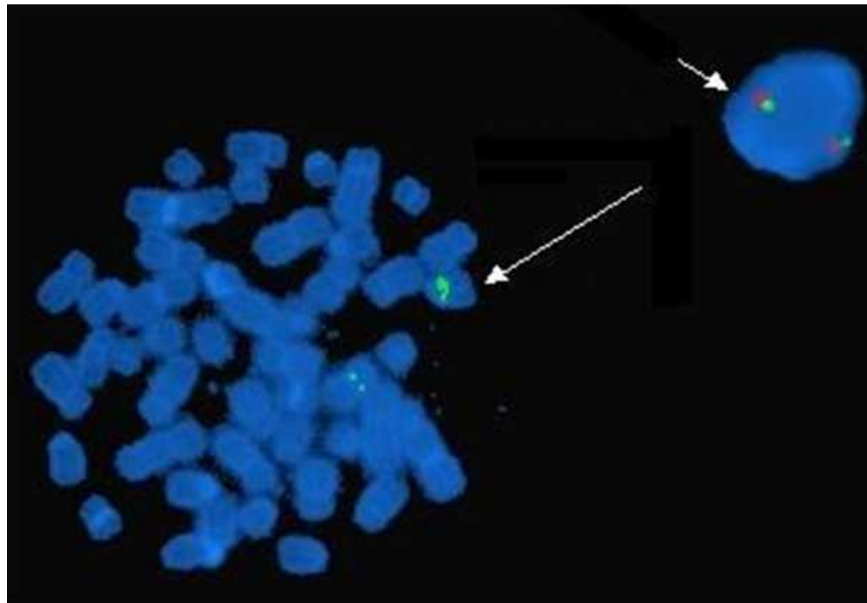


Figure 2: FISH was performed using CDKN2A (orange) and the control CEP 9 (green) DNA probe set. The hybridization revealed biallelic loss of CDKN2A in an abnormal metaphase (long arrow) while the normal diploid interphase cell had two copies of each (short arrow).

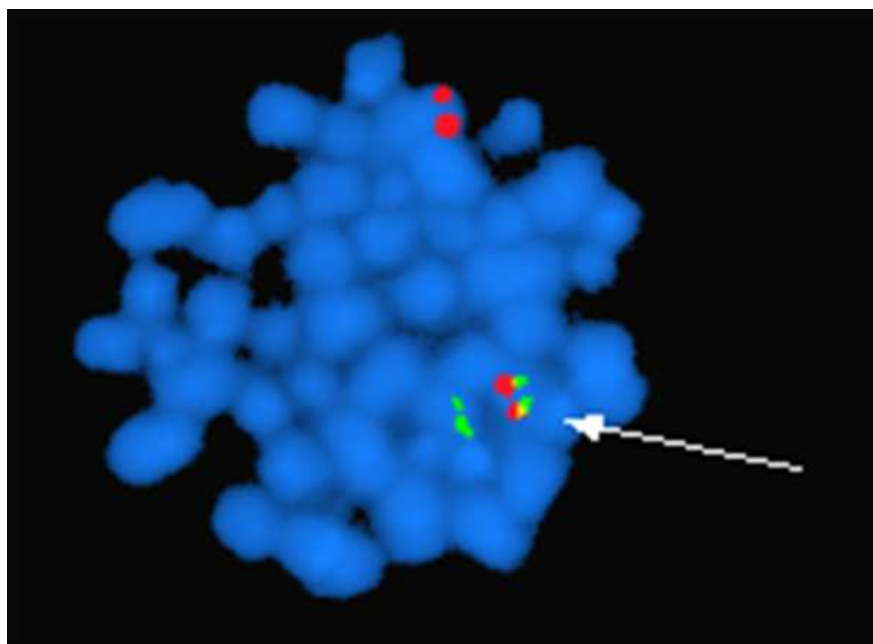


Figure 3: FISH of a t(7;14) carrying metaphase cell demonstrating fusion of HOXA-TCRA/D gene regions (thin arrow).

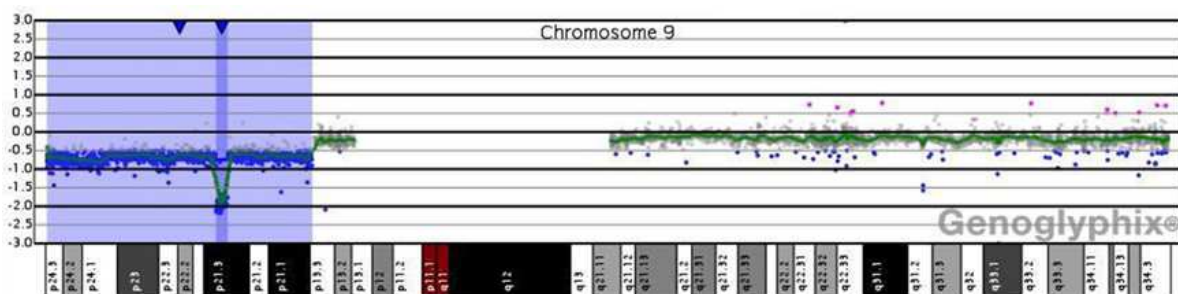


Figure 4: aCGH plot for chromosome 9 showing compound deletions. The light blue region indicates a terminal monoallelic deletion of 33.3 Mb of 9p while dark blue region points to biallelic deletion within the 9p21.3.

## Comments

The patient here presented with progressive cough and neck mass. He was found to have an elevated WBC count with concomitant anemia and thrombocytopenia. Assessment of peripheral blood revealed the diagnosis of T-cell acute lymphoblastic leukemia (T-ALL). Chromosome analysis showed two clones, pseudodiploid and pseudotetraploid, both exhibiting t(7;14)(p15;q11.2), del(6)(q14q21), and del(9)(p13) (Figure 1). However, the pseudotetraploid clone had two copies of these abnormalities indicating it was derived from duplication of the pseudodiploid clone. FISH confirmed juxtaposing of HOXA/7p15 and TCRD/14q11.2 genes in the t(7;14) carrying leukemic cells (Figure 3).

Homeobox (HOX) genes encode transcription factors which act as key regulators in embryonic development and normal hematopoiesis. Recently, the HOXA gene cluster at chromosome 7p15 has been described as a new recurrent breakpoint that occurs in up to 3% of T-ALL. The inv(7)(p15q34) and t(7;7)(p15;q34) place HOXA under the control of T-cell specific enhancer of TCRB, leading to upregulation of HOXA genes particularly HOXA10 and HOXA11. Another rare translocation is t(7;14)(p15;q11.2), previously described in a 29-year-old patient with T-ALL. The translocation resulted in colocalization of HOXA-TCRD genes, and generalized overexpression of the HOXA genes. However the leukemic clone of this case had also t(10;11)(p14;q21), and expressed CALM-AF10 fusion transcript. Therefore, it was concluded that the existence of both HOXA-TCRD and CALM-AF10 in the same leukemic cells may contribute to the global expression of HOXA genes. The t(7;14) in a 31-year old female with T-ALL was also cited but not well documented in a technical report by Garipidou et al 1991.

The present case is believed to be the only other well described case with t(7;14)(p15;q11.2)/HOXA-TCRD translocation. However, our case was lacking t(10;11) which may make the two cases different in clinical presentation and response to therapy. Biallelic deletion of CDKN2A/9p21 as documented by aCGH and FISH was also found in our case (Figures 2, 4). Deletion of CDKN2A, tumor suppressor gene, is the most frequent genomic aberration occurs in over 70% of T-ALL which emphasizes the importance of CDKN2A inactivation in the development of this leukemia. A study pooling 907 individual cases of ALL has demonstrated that CDKN2A deletion, mono- or biallelic, is an independent risk factor for the development of ALL irrespective of cell lineage (B or T-cell). However, the prognostic significance of CDKN2A deletion in cases of pediatric T-cell ALL is currently unknown due to its frequent

association with other recurrent cytogenetic abnormalities. The deletion CDKN2A/9p21 has been previously shown to accompany the common yet nonspecific finding of del(6q), which was also present in this case.

In summary, the t(7;14)(p15;q11.2) translocation is extremely rare resulting in an aberrant juxtaposing of HOXA-TCRD genes. Therefore, TCRD/14q11.2 may consider as a new variant partner for activation of HOXA/7p15 in T-ALL. Although the expression of HOXA genes was not tested in the present case, we assume it was upregulated as documented previously in HOXA-TCRD case and HOXA-TCRB cases.

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