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Case Report Section

T-cell acute lymphoblastic leukemia with t(4;11)(q23;p15) and NUP98/RAP1GDS1 gene fusion: Case report and review of literature

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Clinics

Age and sex
15 years old male patient.

Previous history
no preleukemia
no previous malignancy
no inborn condition of note

Organomegaly
No hepatomegaly , no splenomegaly , enlarged lymph nodes (Significant lymphadenopathy involving bilateral cervical, posterior auricular, submandibular, supraclavicular, and inguinal lymph nodes.), no central nervous system involvement

Blood

WBC : 72.8X 10^9/l
HB : 9.4g/dl
Platelets : 72X 10^9/l
Blasts : 94%
Bone marrow : Hypercellular with near-replacement with L2 lymphoblasts.%

Note: Serum chemistries were significant for LDH of 923 U/L and uric acid of 7.8 mg/dL.

Cyto-Pathology Classification

Phenotype

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

Immunophenotype

Flowcytometry of bone marrow aspirate revealed a predominant abnormal CD45 dim lymphoblasts population (97%) expressing CD3, CD5, CD7, CD10, TdT, cytoplasmic CD3, thymic associated marker CD1a, and partial expression of CD8, CD2, and CD30 antigens.

Rearranged Ig Tcr: not performed.

Electron microscopy: not performed.

Diagnosis

T-cell acute lymphoblastic leukemia of thymic origin.

Survival

Date of diagnosis: 05-2015

Treatment

Patient started chemotherapy on May 15th with vincristine, bortezomib, and daunorubicin.

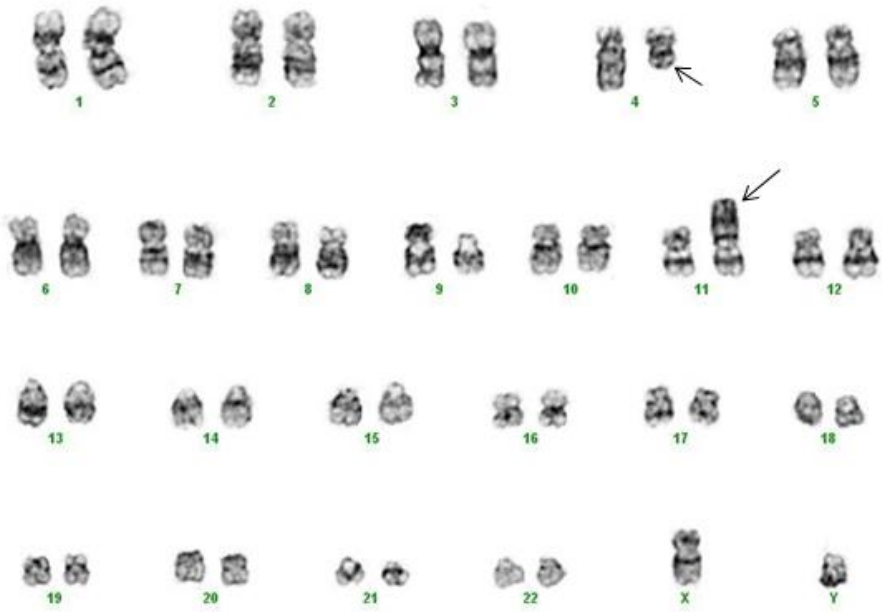

Figure 1: G-banded karyotype showing an apparently balanced t(4;11)(q23;p15) [arrows], and deleted 9p

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Three days later, he received PEG-asparaginase. On Day 29, bone marrow evaluation revealed morphologic and cytogenetic remissions.

The minimal residual disease (MRD) was negative (<0.01%), therefore the leukemia was classified as standard risk.

Complete remission : Complete remission was obtained.

Treatment related death : no

Relapse : no

Status: Alive

Last follow up: 12-2015

Survival: 7 months

Karyotype

Sample

Bone marrow

Culture time

24 and 48h with 10% GCT.

Banding

GTG

Results

46,XY,t(4;11)(q23;p15),del(9)(p13)[20] (Figure 1).

Other molecular cytogenetics results

Fluorescence in situ hybridization (FISH) using the T-cell leukemia DNA probe panel including LSI CDKN2A/CEP-9, LSI BCR/ABL dual fusion translocation probe, MLL and TRA/B breakapart probe(Abbott Molecular, Downers Grove IL, USA) and TCR-B breakapart (Cytocell, Cambridge, UK)] were performed on the harvested bone marrow pallet. The hybridization revealed a monoallelelic deletion of CDKN2A/9p21 gene region in 95% of interphase cells. The remaining probes had a normal hybridization pattern.

In addition, we investigated RAP1GDS1 and NUP98 as candidate genes for the t(4;11)(q23;p15) breakpoints. FISH using two differentially labeled DNA probes was performed. The BAC RP11-64A22/4q23 covering the centromeric portion of RAP1GDS1 gene locus was labeled green, while the RP11-348A20/11p15.4 covering NUP98 gene locus was labeled orange (BlueGnome, Illumina Cambridge UK). The hybridization revealed a dual fusion signals on the der(4) and der(11) chromosomes (Figure 2). These results indicated that the t(4;11)(q23;p15) fused the NUP98 gene with RAP1GDS1.

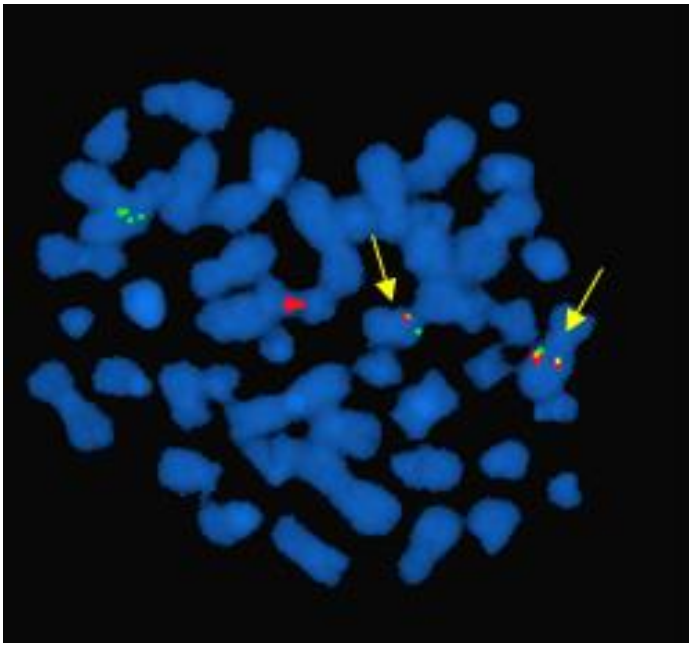

Figure 2: Dual color FISH on a metaphase with t(4;11)(q23;p15) using the DNA probes BAC RP11-348A20/11p15.4 and RP11-64A22/4q23 showing a dual fusion signals hybridized on der(4) and der(11) (arrows) while the green signal and orange signal on normal chromosomes 11 and 4, respectively.

Comments

In this report, a 15 year-old-African American boy presented with progressive neck mass for the last 4 weeks. He was found to have a high WBC and anemia. Following bone marrow evaluation, he was diagnosed with T-cell ALL of thymic origin. Cytogenetic testing at time of presentation exhibited t(4;11)(q23;p15) and deletion of 9p13->pter [Figure 1]. The later resulted in a monoallelic deletion of CDNK2A/9p21 gene locus. Furthermore, FISH characterization of the t(4;11)(q23;p15) breakpoints revealed fusing of NUP98 gene at 11p15 to RAP1GDS1 gene at 4q23. [Figure 2]

NUP98, like KMT2A (MLL) gene, is shown to fuse to a various partner genes and presently at least 28 different partners have been detected in a wide range of hematologic malignancies, including acute myeloid leukemia, chronic myeloid leukemia in blast crisis, myelodysplastic syndrome, and ALL. This suggests that different fusion partner genes may have impact on diversity of leukemia phenotypes. Approximately 10% of patients with NUP98 fusions have T-lineage ALL but so far no B-cell malignancies have been reported to have a NUP98 fusion gene. The NUP98-RAP1GDS1 gene fusion resulted from t(4;11)(q21-23;p15) has been reported in seven leukemia cases including our present case [Table 1]. All cases had additional chromosomal abnormalities. The first report in 1999 by Hussey et al described three patients with T-cell ALL exhibiting t(4;11) in which NUP98-RAP1GDS1 fusion transcripts were detected in their bone marrows. Interestingly, this study and for the first time showed that RAP1GDS1 gene has been implicated in human leukemia. Subsequently, NUP98-RAP1GDS1 gene fusion product was confirmed in two other female patients with t(4;11) T-cell ALL (Mecucci et al). Both reports indicated that the chimeric NUP98-RAP1GDS1 transcripts have the dominant leukemogenic properties. The next patient, a 60 year old female, was reported to have acute myeloid leukemia (AML-M0) with t(4;11)(q13;p15) [Table 1 case 6). FISH on this case showed a break within NUP98 gene, and RT PCR exhibited NUP98-RAPGDS1 fusion transcripts. The RAP1GDS1 fusion point in this case was identical to the one published in T-ALL cases while the breakpoint in NUP98 was different.

All patients appeared to have a fairly short survival after diagnosis [Table 1]. Patient no. 1, who showed the longest survival, underwent two matched allogeneic bone marrow transplants but relapsed with an aggressive disease on both occasions. Our patient achieved hematologic and cytogenetic remissions and negative MRD. Currently, the patient is on consolidation chemotherapy and remains in remission. In summary, t(4;11)(q23;p15) is a rare translocation causing NUP98-RAP1GDS1 gene fusion. However it is recurrent and mostly associated with an early T-ALL while one patient had an AML-M0. The risk associated with t(4;11)(q23;p15.4) is not well determined due to low number of cases Although most patients with this translocation had a short survival (Table 1).

Case	Leukemia	Age/Sex	WBC 10^9/L	Karyotype	Fusion Genes	Outcome	References
1	T-ALL L1	21/M	423	46,XY,t(4;11)(q21;p15),+2mar	*NUP98/RAP1GDS1*	Relapsed after 2 matched BMT; died 43 M	Hussey et al., 1999
2	T-ALL L1	25/F	1.8	46,XX,t(4;11)(q21;p14-15), del(12)(p13),+del(13)(q12q14)	*NUP98/RAP1GDS1*	Failure of induction; Died 1M later	Hussey et al., 1999
3	T-ALL L2	49/M	169	46,XY,t(4;11)(q21;p15),del(5)(q13q31)	*NUP98/RAP1GDS1*	BM remission, early relapse, died 14 M	Hussey et al., 1999
4	T-ALL L2	16/F	34	47,XX,t(4;11)(q21;p15),+8	*NUP98/RAP1GDS1*	CR, followed by BMT; 7 m+	Mecucci et al., 2000
5	T-ALL L2	38F	35	47,XX,t(4;11)(q21;p15),+mar	*NUP98/RAP1GDS1*	CR, relapsed in 8 m; died after BMT	Mecucci et al. 2000
6	AML-M0	60/F	3.9	46- t(4;11)(q1?3;p15),?der(8)(p?)	*NUP98/RAP1GDS1*	CR; relapsed and died 8m after diagnosis	van Zutven et al, 2006
7	T-ALL	15/M	72.8	46,XY,t(4;11)(q23;p15),del(9)(p13)	*NUP98/RAP1GDS1*	CR obtained, survival 7M+	Present case, 2015

Table 1: Reported acute leukemia cases with t(4;11)(q21-q23;p15) and *NUP98/RAP1GDS1* gene fusion

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References

Gough SM, Slape CI, Aplan PD. NUP98 gene fusions and hematopoietic malignancies: common themes and new biologic insights. Blood. 2011 Dec 8;118(24):6247-57

Hussey DJ, Nicola M, Moore S, Peters GB, Dobrovic A. The (4;11)(q21;p15) translocation fuses the NUP98 and RAP1GDS1 genes and is recurrent in T-cell acute lymphocytic leukemia. Blood. 1999 Sep 15;94(6):2072-9

Mecucci C, La Starza R, Negrini M, Sabbioni S, Crescenzi B, Leoni P, Di Raimondo F, Krampera M, Cimino G, Tafuri A, Cuneo A, Vitale A, Foà R. t(4;11)(q21;p15) translocation involving NUP98 and RAP1GDS1 genes: characterization of a new subset of T acute lymphoblastic leukaemia. Br J Haematol. 2000 Jun;109(4):788-93

Cimino G, Sprovieri T, Rapanotti MC, Foà R, Mecucci C, Mandelli F. Molecular evaluation of the NUP98/RAP1GDS1 gene frequency in adults with T-acute lymphoblastic leukemia. Haematologica. 2001 Apr;86(4):436-7

van Zutven LJ, Onen E, Velthuizen SC, van Drunen E, von Bergh AR, van den Heuvel-Eibrink MM, Veronese A, Mecucci C, Negrini M, de Greef GE, Beverloo HB. Identification of NUP98 abnormalities in acute leukemia: JARID1A (12p13) as a new partner gene. Genes Chromosomes Cancer. 2006 May;45(5):437-46

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