t(1;21)(p22;q22) RUNX1/CLCA2

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Clinics and pathology

Disease
Therapy-related acute myeloid leukemia (t-AML)

Epidemiology
Two AML cases positive for the t(1;21)(p22;q22) were reported, a 9 year-old boy (Nadal et al., 2008) and a 64 year-old man (Giguère and Hébert, 2010).

Clinics
The 9 year-old boy presented in September 2004 with an initial diagnosis of acute myeloid leukemia with maturation (AML-M2) with a normal karyotype. In December 2004, he underwent an allogeneic bone marrow transplantation and then relapsed in June 2006. At relapse, the karyotype was 46,XY,t(1;21)(p22;q22)[15]/46,XX[5].


He received a standard induction and consolidation chemotherapy followed by an allogeneic hematopoietic stem cell transplantation. In August 2007, he developed a t(1;21)(p22;q22) positive t-AML.

Complete blood count showed a white blood cell count of 16.4 x 10^9/L, hemoglobin of 86 g/L and platelet count of 34 x10^9/L. The bone marrow aspirate showed 52% of blast cells.

Treatment
The pediatric patient was treated with cytarabine, mitoxantrone and amsacrine. At complete remission, he underwent an allogeneic stem cell transplantation with a conditioning regimen including etoposide and total body irradiation. At relapse, the boy underwent a second bone marrow transplantation.

The adult patient was treated with a standard induction chemotherapy regimen (infusional cytarabine combined with daunorubicine) and two cycles of consolidation therapy with high doses cytarabine, followed by a reduced intensity allogeneic stem cell transplantation. The t(1;21) positive t-AML was not treated with chemotherapy. The patient received palliative care.

Evolution
The boy was alive in April 2012 (Nadal, personal communication). The adult patient died one month and 18 days following t-AML development.

Prognosis
Undetermined.

Genetics

Note
FLT3-ITD (FLT3 internal tandem duplication) mutation was detected in the pediatric patient’s leukemic cells and was absent in the adult patient's cells.
Partial GTG-banded karyotype showing derivative chromosomes 1 and 21 involved in the t(1;21)(p22;q22).

Metaphasic FISH using the LSI RUNX1-RUNX1T1 dual color translocation probe (Abbott Molecular). Three green signals (21q22, RUNX1 gene) are shown (arrows), indicating the presence of a RUNX1 rearrangement. Two normal red signals (8q22, RUNX1T1 gene) were observed.
Cytogenetics

Cytogenetics morphological
Can be easily identified using G-banded chromosomes.

Cytogenetics molecular
FISH using the RUNX1-RUNX1T1 probe showed splitted signals located on derivative chromosomes 1 and 21.
RUNX1 rearrangement was confirmed using the RP11-299D9 BAC probe (BACPAC Resources Center) (Giguère and Hébert, 2010).

 GENES INVOLVED AND PROTEINS

RUNX1
Location
21q22
DNA/RNA
The RUNX1 gene contains 8 coding exons spanning 260 kilobases (kb) of genomic DNA.

CLCA2
Location
1p22.3
DNA/RNA
The CLCA2 gene contains 14 exons which spans 32 kb of genomic DNA. Transcription orientation: telomere to centromere.

Protein
CLCA2 is a member of the calcium-activated chloride channel family.

Additional anomalies
The t(1;21) was the sole anomaly in t-AML cells.

RUNX1 rearrangement was confirmed using the RP11-299D9 BAC probe (BACPAC Resources Center) (Giguère and Hébert, 2010).

Hybrid gene
Description
5’ RUNX1-CLCA2 3’.
Transcript
At least six out-of-frame fusion transcripts were identified (Giguère and Hébert, 2010).
**Fusion protein**

**Note**

In this case, RUNX1-CLCA2 fusion transcripts lead to truncated RUNX1 proteins (Giguère and Hébert, 2010).

**References**

Gruber AD, Pauli BU. Tumorigenicity of human breast cancer is associated with loss of the Ca2+-activated chloride channel CLCA2. Cancer Res. 1999 Nov 1;59(21):5488-91


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