

Leukaemia Section

Short Communication

t(5;17)(q35;q21) NPM1/RARA

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Abstract

Acute promyelocytic leukemia (APL) is characterized by distinct clinical and biological features and by the reciprocal translocation t(15;17)(q22;q21) in the majority of patients. The translocation generates the fusion of the promyelocytic leukemia (PML) gene to the gene for retinoic acid receptor alpha (RARA) and these patients are responsive to differentiation treatment with all-trans retinoic acid (ATRA). Rare cases of patients with a morphological diagnosis of APL have variant chromosome translocations, which fuse RARA gene with partner genes other than PML, such as in the variant translocation t(5;17)(q35;q21) that fuses the N-terminus of nucleophosmin (NPM1) gene at 5q35 to the retinoic acid receptor alpha at 17q21.

Keywords

Chromosome 5; chromosome 17; Acute myeloid leukaemia; Acute promyelocytic leukemia; RARA; NPM1

Clinics and pathology

Disease

Acute myeloid leukemia (AML)

Phenotype/cell stem origin

Acute promyelocytic leukemia (AML-M3 according to the FAB classification)

Etiology

Exceptional; only 7 cases with balanced t(5;17)(q35;q12-21) translocation and the underlying NPM1/RARA fusion have been identified (5 males and 2 females, aged 2.5 to 52 years).

There were 2 adult males, aged 29 and 52 years and 4 patients were pediatric cases, among them 2 were 12-year-old males and 2 were 2.5 and 9-year-old females (Table 1).

Clinics

Disseminated intravascular coagulation was present at diagnosis in one case; remission obtained with chemotherapy and/or ATRA; first relapse at 7 and 5 months in 2 cases (Corey et al., 1994 ; Hummel et al., 1999). The 6-month-old boy described by Otsubo et al., presented with cutaneous mastocytosis and aleukemic leukemia cutis that regressed without any therapy within 6 months. Both adult patients also presented with myeloid sarcoma, therefore it is likely that it may occur frequently in NPM1/RARA associated APL (Nicci et., 2005; Kikuma et al.,2015).

Cytology

Hypergranular and hypogranular bilobed promyelocytes; absence of Auer rods; typical microspeckled pattern with anti-RARA antibodies; terminal differentiation of blasts and promyelocytes in vitro with ATRA.

	Sex/Age (years)	Karyotype	Clinics
1.	F/2.5	46,XX,t(5;17)(q32;q12) 48,XX,t(5;17),+2mar	Therapy with ATRA while in partial remission, relapsed within 2 weeks of ATRA cessation.
2.	M/12	47,XY,t(5;17)(q35;q21),der(8)(p23), der(10)(q26),del(12)(q13q22),del(1)(q12q14),-16,-18,+21,+22,+mar	Treated initially with chemotherapy, relapse occurred after 5 months. After therapy with ATRA remission was obtained, followed by bone marrow transplantation, but relapsed and remained refractory to further therapy.
3.	F/9	46,XX,ins(3;5)(q26;q13q13),t(5;17)(q34;q21)	Therapy with ATRA as a part of induction therapy; alive in remission at 29 months.
4.	M/12	46,XY,t(5;17)(q35;q21),del(12)(p13)	Died of cerebral hemorrhage after 5 days of ATRA treatment.
5.	M/29	46,XY,t(5;17)(q35;q21)	Presented with granulocytic sarcoma; therapy with ATRA resulted in complete cytogenetic but not a molecular remission, relapsed at 22 months; treated with one course of arsenic trioxide.
6.	M/4	46,XY,t(5;17)(q35;q12),i(21)(q10)	Presented with cutaneous mastocytosis and leukemia cutis at the age of 6 months with spontaneous regression within 6 month; followed by leukemia development at 4 years; remission to ATRA.
7.	M/52	46,XY,t(5;17)(q35;q12)	Preceded by myeloid sarcoma; induction therapy including ATRA resulted in complete hematological and molecular remission.

Table 1. Reported cases with t(5;17)(q35;q12-21) and confirmed NPM1-RARA fusion. **Abbreviations:** M, male; F, female; ATRA; all-trans-retinoic acid. 1. Corey et al., 1994 and Redner et al., 1996. 2. Hummel et al., 1999; 3. Grimwade et al., 2000; 4. Xu et al., 2001; 5. Nicci et al., 2005; 6. Otsubo et al., 2012; Kikuma et al., 2015.

Prognosis

The 2.5 years-old child (Corey et al., 1994; Redner et al., 1996) was treated with ATRA while in partial remission and relapsed shortly after ATRA cessation. One of the 12-years old males (Hummel et al., 1999) received chemotherapy in induction and consolidation and relapsed after 5 months; remission was obtained with Ara-C and ATRA therapy followed by allogenic BM transplantation, but relapsed with therapy refractoriness. The second 12-years old male who presented with severe DIC died of cerebral hemorrhage after 5 days of ATRA treatment (Xu et al., 2001). The 9-year-old female was treated with ATRA as a part of induction therapy and was alive in first CR at 29 months (Grimwade et al 2000). The last pediatric patient presented with aleukemic leukemia cutis and t(5;17)(q35;q12) NPM1/RARA fusion at the age of 6-month-old (Kanegane et al., 2009; Otsubo et al., 2012). He showed no sign of leukemia without any therapy after 12 months, except for the presence of NPM1-RARA transcript in the bone marrow, but developed APL at the age of 4 years with complete remission to ATRA. Both adult patients received ATRA as part of induction therapy, resulting in cytogenetic but not a molecular remission in 1 patient who relapsed at 22 months after diagnosis (Nicci et al., 2005), and in complete hematological and molecular remission in the other case (Kikuma et al., 2015).

From these data, the response to ATRA is difficult to assess since it was not part of induction treatment in some cases and due to the limited number of patients. However, patients with NPM1/RARA fusion appear to be sensitive to ATRA (Hummel et al., 1999; Grimwade et al., 2000; Kikuma et al., 2015) and cells bearing the t(5;17) terminally differentiate in its response (Redner et al., 1996), indicating that ATRA can be used to treat NPM1/RARA-positive APL patients. It is also possible that the presence of the additional/complex karyotypic abnormalities may be related to the prognosis in this group of patients.

Cytogenetics

Additional anomalies

Sole anomaly in both adult patients (Nicci et al., 2005; Kikuma et al., 2015) and associated with additional anomalies in pediatric patients: del(12p) in 1 (Xu et al., 2001), i(21)(q10) in 1 (Otsubo et al., 2012) and complex anomalies in 2 cases (Hummel et al., 1999; Grimwade et al., 2000).

Variants

Variant chromosome translocations, which fuse RARA with 1 of the partner genes: PML (promyelocytic leukemia protein) in t(15;17)(q22;q21) that is found in the majority of APL patients; ZBTB16 (zinc finger and BTB domain containing 16, previously known as PLZF)

in t(11;17)(q23;q21) (De Braekeleer et al., 2014); NUMA1 (nuclear matrix-mitotic apparatus protein 1 gene) in t(11;17)(q13;q21) (Wells et al., 1997); STAT5B (signal transducer and activator of transcription 5 beta) in dup(17)(q21.3q23) (Chen et al., 2012); PRKAR1A (protein kinase, cAMP-dependent, regulatory, type I, alpha) in t(17;17)(q21;q24)/del(17)(q21q24) (Catalano et al., 2007); FIP1L1 (factor interacting with PAP 1-like 1) in t(4;17)(q12;q21) (Buijs et al., 2007); NABP1 (OBFC2A: oligonucleotide/oligosaccharide-binding fold containing 2A) in der(2)t(2;17)(q32;q21) (Won et al., 2013); TBL1XR1 (TBLR1, GenBank KF589333) in a complex t(3;17)(q26;q21), t(7;17)(q11.2;q21) (Chen et al., 2014); BCOR (BCL6 corepressor gene) in t(X;17)(p11.4;q21) (Ichikawa et al., 2015) and the recently described new RARA partner IRF2BP2 (interferon regulatory factor 2 binding protein 2) in t(1;17)(q42.3; q21) (Yin et al., 2015).

Genes involved and proteins

NPM1 (nucleophosmin)

Location

5q35.1

Protein

Gene for the nucleolar phosphoprotein nucleophosmin; would participate in ribosome assembly.

RARA (Retinoic acid receptor, alpha)

Location

17q21.2

Protein

Gene for the retinoic acid receptor alpha. Ligand-dependent transcription factor specifically involved in hematopoietic cells differentiation and maturation. Receptor for all-trans retinoic acid (ATRA) and 9-cis RA. After linking with ATRA, RARA binds with RXR (retinoid X receptor protein) to the RARE domain (retinoic acid response elements), a DNA sequence common to a number of genes. The breakpoint lies within the second intron of the gene, as in t(15;17) and t(11;17) translocations.

Result of the chromosomal anomaly

Hybrid gene

Description

Two reciprocal fusion genes are generated: 5'-NPM1 + 3'-RARA on der(5) and 5'-RARA + 3'-NPM on der(17); both fusion genes are transcribed,

the crucial one is NPM1/RARA; two NPM1/RARA chimeric cDNAs are generated, one short and one long differing from 129 bp, with corresponding transcripts of 2.3 and 2.4 kb (alternatively spliced transcripts); in one case, only the short NPM1/RARA isoform could be detected; the 5' end of NPM1/RARA cDNAs contains the first 442 bp of the NPM1 cDNA; the 3' end contains RARA sequences of exon 3 through the 3' end of RARA; a reciprocal RARA/NPM1 transcript is detected: RARA exons 1 and 2 are fused to 3' NPM1 downstream bp 443.

Detection

Nested RT-PCR.

Fusion protein

Description

Two NPM1/RARA proteins, of 563 and 520 amino acids, are encoded (MW 62 and 57 kDa); NPM1/RARA fusion protein acts as a retinoic acid-responsive transcriptional activator: increase of activity in a concentration dependant manner.

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