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Case Report Section

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A new case of t(4;12)(q12;p13) in a secondary acute myeloid leukemia with review of literature

Sarah M Heaton, Frederick Koppitch, Anwar N Mohamed

Cytogenetics Laboratory, Pathology Department, Wayne State University School of Medicine, Detroit Medical Center, Detroit MI, USA (SMH, FK, ANM)

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Clinics

Age and sex
57 years old male patient.

Previous history
No preleukemia. Previous malignancy Hodgkin's Lymphoma, stage IVA at age 25 year, treated with ABVD for 12 months. Tumor mass in the upper cervical spine diagnosed at age 27 year, treated with laminectomy and five doses of radiation. No inborn condition of note.

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

Blood

WBC : 0.8X 10^9/l
HB : 9.7g/dl
Platelets : 21.0X 10^9/l
Blasts : 18%
Bone marrow : Variably cellular with 20% myeloblasts and dysplastic changes in the erythroid and myeloid cell lines.

Cyto-Pathology Classification

Cytology
His bone marrow showed 60% blasts, and dysplastic changes were noted in the erythroid and myeloid cell lines.

Immunophenotype
Flow cytometry (FCM) revealed that the blasts were of myeloid lineage expressing CD13, CD33, CD34, CD117, HLA-DR, and CD56.

Diagnosis
Acute myeloid leukemia (AML) with dysplastic changes.

Survival

Date of diagnosis: 08-2007

Treatment
He was treated with Idarubicin+Ara-c (3+7) regimen. Because of 15% residual blasts in bone marrow, patient received additional 2+5 therapy, and then he underwent consolidation with Ara-C. Result of karyotype: 46,XY[20]. On April 2008, the patient received a matched unrelated female donor stem cell transplant (SCT). 30 days post transplant; bone marrow revealed no morphological evidence of leukemia and the karyotype was 46,XX[20]. On June 2008; patient developed pancytopenia; WBC: 2.2 x 10^9/l; Hb: 11.6 g/dl; platelets: 18.0 x 10^3/l. His bone marrow showed an increased dysplastic changes and <5% blasts, suggestive of possible early relapse. The karyotype became abnormal (see below). On June 2010; bone marrow was hypocellular with 20% blasts and dysplastic changes in the erythroid and myeloid lineages. FCM revealed myeloblasts expressing CD4, CD7, CD33, CD34, CD56, CD117 and HLA-DR. myeloperoxidase was negative. Non-specific esterase was positive in occasional blasts. Cytology: AML possibly of monocytic origin (AML-M5).
Treatment related death : no

Figure 1. G-banded karyotype showing the balanced t(4;12)(q12;p13) translocation.

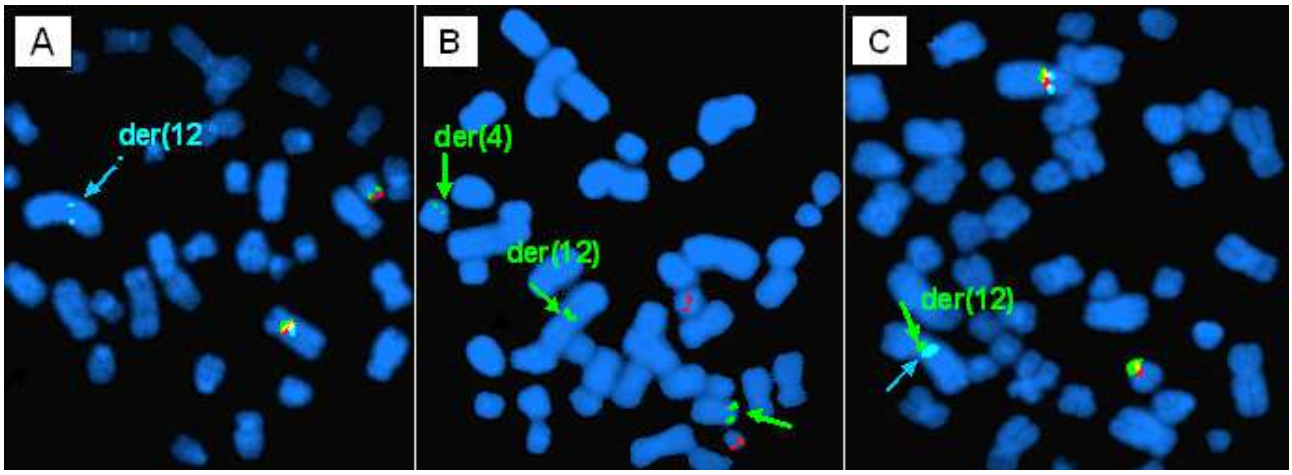

Figure 2. FISH on abnormal metaphases; **(A)** Metaphase hybridized with LSI 4q12 tricolor DNA probe showed a translocation of PDGFRA (SA) to derivative chromosome 12 (arrow), with the dual fusion of spectrunOrange (SO) and spectrunGreen (SG) remained on derivative 4. **(B)** Metaphase hybridized with LSI ETV6/RUNX1 ES dual color probe revealed a split of ETV6 (SG) with the smaller signal being translcated to derivative 4 (arrows). **(C)** Metaphase hybridized with both LSI 4q12 and ETV6/RUNX1 probes showed PDGFRA (SA) translocted to derivative 12 adjacent to ETV6 locus (arrows).

Phenotype at relapse: M5-AML

Status: Alive. Last follow up: 06-2010.

Survival: 24 months

Karyotype

Sample: Bone marrow

Culture time: 24 and 48h with 10% conditioned medium

Banding: GTG

Results

46,XY,t(4;12)(q12;p13)[6]/46,XX[14] in June 2008 (post transplant)

Karyotype at Relapse

46,XY,t(4;12)(q12;p13)[12]/ 46,idem,del(7)(q22q36)[4]/ 47,idem,+19[2]/ 46,XX[2], consistent with the recurrence and clonal evolution of the leukemic clone.

Other molecular cytogenetics technics

Fluorescence in situ hybridization (FISH) using LSI 4q12 tricolor and LSI ETV6/RUNX1 ES dual color DNA probes were performed (Abbott Molecular. Downers Grove, IL) on the abnormal metaphase cells.

Other molecular cytogenetics results

Translocation of the PDGFRA gene in Toto, spectrunAqua (SA), to derivative 12 and colocalized with centromeric region of ETV6; Break within ETV6 gene locus, sepctrunGreen (SG) and the telomeric region of ETV6 translocated to derivative 4 (Figure 2 A-C).

Comments

Acute leukemia with t(4;12)(q11-q12;p13) is a rare, nonrandom event with an estimated incidence of 0.6% among adults according to Harada et al. (Harada et al., 1997). This translocation is seen mostly in adult AML but less frequent in pediatric ALL (Hamaguchi et al., 1999). A review of the literature revealed at least twenty-two additional cases with a t(4;12)(q11-q12;p13); eighteen adults and four children. The male to female ratio is 1.5:1 (1.7:1 in adults and 1:1 in children). The majority of patients are adults, aged 18 to 82 with the mean being 58.9 years old (Harada et al., 1995; Harada et al., 1997; Ma et al., 1997; Cools et al., 1999; Hamaguchi et al., 1999; Chaufaille et al., 2003; Manabe et al., 2010). Four children have been reported, aged 3-14 years old, of which three had ALL and the oldest had AML (Harada et al., 1997).

Among the 23 cases including our case with t(4;12) leukemia; 19 had AML; 3 ALL, and one unclassified leukemia. Common features to t(4;12) AML include dysplasia of three hematopoietic lineages (erythroid, myeloid and megakaryocytic), low or absent myeloperoxidase activity, basophilia and a pseudo-lymphoid morphology. The surface markers of the blasts show positivity for CD7, CD13, CD33, CD34 and HLA DR, suggesting that the leukemic cells have an immature myeloid stem cell origin (Harada et al., 1995; Ma et al., 1997; Hamaguchi et al., 1999). Of the reported t(4;12) AML cases; seven were characterized as AML-M0 and four AML-M1. Previous reports suggest that less than 50% of cases achieve remission with intensive induction chemotherapy. Of the patients who do not achieve morphologic remission, none survived beyond six months (Hamaguchi et al., 1999; Chaufaille et al., 2003; Manabe et al., 2010).

The breakpoint at 12p13 in t(4;12) AML is located within or near the ETV6 gene locus. The ETV6 gene has been implicated in both myeloid and lymphoid malignancies (Wlodarska et al., 1998). ETV6 belongs to the ETS family of transcription factors and has two important domains: HLH and an ETS DNA binding domain. Cools et al, found the t(4;12) caused the ETV6 gene recombined to CHIC2 (formerly BLT) (Cools et al., 1999). A number of genes have been mapped to the band 4q12 including mac25, PDGFRA, AFP, and a beta-sarcoglycan gene (Hamaguchi et al., 1999).

The case reported here shared some features to those reported in the literature including positivity for CD7, CD33, CD34, CD117 and HLA-DR, lack of myeloperoxidase activity and dysplastic bone marrow. Unlike other reported cases, bone marrow basophilia and high platelets were not found. Clearly in our case, FISH showed a break within ETV6/12p13 gene, and colocalization of PDGFR1 gene to derivative 12 next to 5' ETV6 region.

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