t(2;11)(q31;p15) in therapy related myeloid neoplasm: case report and review of literature

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**Clinics**

**Age and sex**
59 years old female patient.

**Previous history**
No preleukemia, no previous malignancy, no inborn condition of note.

**Main items**
Patient diagnosed with breast cancer in 1995, treated with adjuvant chemotherapy consisting of 4 cycles of CAF (cyclophosphamide, doxorubicin and fluorouracil) and CMF (cyclophosphamide, methotrexate and fluorouracil) followed by tamoxifen for 6 years. On 6/2006, she had evidence of recurrence and subsequent liver, ribs, and skull metastases.

She was treated with several other chemotherapies such as taxotere, gemzar, fluvestrant, taxol, bevacizumab and xeloda, and radiation therapy.

On 11/2011, she developed brain metastasis and was successfully treated with gamma knife.

Over her last year, she was on oral cyclophosphamide and doxorubicin.

**Organomegaly**
No hepatomegaly, no splenomegaly, no enlarged lymph nodes, central nervous system involvement (brain metastasis).

**Blood**

**WBC:** 58.7 X 10^9/l
**HB:** 8.7g/dl
**Platelets:** 47 X 10^9/l

**Note:** Peripheral blood showed anemia, thrombocytopenia, neutrophilic leukocytosis with absolute monocytosis.

**Blasts:** 0.9 X 10^9/L, promyelocytes: 0.9 X 10^9/L, myelocytes: 1.5 X 10^9/L, metamyelocytes: 2.3 X 10^9/L, bands: 4.1 X 10^9/L, neutrophils: 29.7 X 10^9/L, monocytes: 17 X 10^9/L; lymphocytes: 2.3 X 10^9/L.

Bone marrow biopsy revealed a hypercellular marrow with 80% cellularity, multilineage dysplasia, 10.2% immature monocytes and 3.2% myeloblasts.

CD34/CD117 showed approximately 10% immature myeloid/monocytic cells. CD64 highlighted the expanded monocytic component. In addition there were scattered metastatic tumor cells positive for AE1/AE3, mammoglobin and BRST1 by immunohistochemistry supporting primary breast origin.

**Cyto-Pathology**

**Classification**

Therapy related myeloid neoplasm best classified as therapy related myelodysplastic /acute myeloid leukemia (t-MDS/AML).

**Immunophenotype**

Flow cytometric of peripheral blood detected 2% myeloblasts expressing CD13, CD33, CD 34, CD117 and HLA-DR, and partially expressing CD14, CD4, CD11d, CD11c and CD64. In addition there were two monocytes gates detected; 18% monocytes were expressing CD13, CD33, and partially expressing CD4, CD11b, CD11c, CD15, CD117, CD64 and CD14.

There was a subpopulation of monocytes representing 6% of gated monocytes were negative CD14, CD19, CD2, CD10, CD7, CD34, CD163 but HLA-DR positive.
Rearranged Ig Tcr
Not performed.

Electron microscopy
Not performed.

Diagnosis
Therapy related MDS/AML

Survival

Date of diagnosis: 01-2013
Treatment: Only supportive therapy
Complete remission: no
Treatment related death: no
Relapse: no
Status: Death
Last follow up: 02-2013
Survival: 0,5 months

Note
Progressed quickly, expired shortly after diagnosis due to lactic acidosis and hypotention.

Karyotype

Sample: Bone marrow aspirate
Culture time: 24h, unstimulated culture and 48 hrs culture with 10% conditioned medium
Banding: GTG

Results

46, XX,t(2;11)(q31;p15)[14]/47,XX,t(2;11)(q31;p15),+8[6] (Figure 1)

Other Molecular Studies

Technics:
Fluorescence in situ hybridization (FISH) using MDS panel DNA probes included EGR1/5q31, D5S23: D5S721/5p15.2, D7S486/7q31, D7Z1/CEP-7, D8Z2/CEP-8, D20S108/20q12, as well as the LSI MLL dual color break apart DNA probe (Abbott Molecular).
FISH results were consistent with trisomy chromosome 8 in 9% of cells and a normal pattern for the remaining loci. In addition, dual color FISH using Signature Genomic DNA probes Rp11-387A1/2q31.1 covering HOXD gene cluster including both HOXD11 and HOXD13 genes was labeled SpectrumOrange, while the RP11-120E20/11p15.4 covering NUP98 gene was labeled SpectrumGreen (PerkinElmer, Spokane, WA).

Figure 1: G-banded karyotype showing t(2;11)(q31;p15) (arrows).

Figure 2: Dual color FISH analysis performed on a metaphase with t(2;11) using BAC probes for NUP98 (RP11-120E20) labeled in green and for HOXD (RP11387A1) labeled in orange, showed the presence of a fusion signal on der(2) (arrow); two orange signals on der(11) and chromosome 2; single green on normal chromosome 11.
The hybridization revealed a fusion signal located on der(2) due to a translocation of NUP98/15p15 (green) to HOXD/2q31(orange) gene region (Figure 2). The remainder of HOXD signal was translocated to 11p15.

**Comments**

The patient presented here was a 59 year old female with a history of breast cancer with several cycles of chemotherapy and radiation therapy due to metastatic recurrences. Seventeen years later, she developed thrombocytopenia along with anemia. Despite the reduction of chemotherapy dosages, her blood cell counts did not recover.

Further assessment of bone marrow biopsy revealed the diagnosis of t-MDS/AML with absolute monocytosis and monocytic feature. Chromosome analysis identified t(2;11)(q31;p15) translocation in all metaphases and trisomy 8 as a secondary abnormality in a subpopulation of cells.

NUP98 gene rearrangement as a result of t(2;11)(q31;p15) is rare, described in only 8 patients (including the present one). This translocation resulting in NUP98-HOXD13 gene fusion was first described in a 10 year-old patient with therapy-related AML-M6. Subsequently, five other patients have been reported with t(2;11) leukemia; all described to have a de novo AML M4 including three infants. The same translocation was also reported in a 15 year-old patient with chronic myeloid leukemia in blast crisis (CML BC) (Table 1 case #5). In this report, we present the second patient with t(2;11) who was diagnosed with t-MDS/AML after a long history of treated metastatic breast cancer.

The partner gene fused with NUP98 in leukemia harboring t(2;11) was the homeobox genes HOXD13 in all case, and HOXD11 in one patient (Table 1). The NUP98-HOXD13 and NUP98-HOXD11 fusion transcripts were detected in bone marrow of these patients, respectively. In a mouse model, studies have shown that NUP98-HOXD13 transgenic mice developed MDS similar to human, including peripheral blood cytopenia, ineffective hematopoiesis with dysplasia, and increased apoptosis in bone marrow. Within 14 months, all mice died of either leukemic transformation or severe pancytopenia.

In our patient, FISH showed a fusion pattern suggestive NUP98-HOXD13 or HOXD11 gene fusion but not with certainty since the BAC RP11-387A1 probe covers other HOXD genes in the region (Figure 2).

In Summary, t(2;11)(q31;p13) translocation in leukemia is rare but recurrent, and occurs in de novo AML as well as t-MDS/AML, and six out eight of patients were <15 years including three infants (Table 1). Morphologically this translocation appears to be associated with monocytic features, mostly AML M4. The t(2;11) leads to the generation of leukemogenic NUP98 fusion protein.

**References**


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**Table 1: Leukemia cases with t(2;11)(q31;p15) previously reported and the present case.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Leukemia</th>
<th>Age/Sex</th>
<th>WBC</th>
<th>Karyotype</th>
<th>Fusion Genes</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>t-AML</td>
<td>10Y/F</td>
<td>N/A</td>
<td>46.XY,t(2;11)(q31;p15)</td>
<td>NUP98-HOXD13</td>
<td>Complete remission after bone marrow transplant</td>
<td>Raza-Egilmez et al. 1998</td>
</tr>
<tr>
<td>2.</td>
<td>De novo AML M4</td>
<td>62Y/M</td>
<td>100.9</td>
<td>46.XY,t(2;11)(q31;p15)</td>
<td>NUP98-HOXD13</td>
<td>Complete remission following chemotherapy</td>
<td>Arai et al. 2000</td>
</tr>
<tr>
<td>3.</td>
<td>De novo AML M4</td>
<td>10Mon/F</td>
<td>102.9</td>
<td>46.XY,t(2;11)(q31;p15)</td>
<td>NUP98-HOXD13</td>
<td>Complete remission after bone marrow transplant</td>
<td>Shimada et al. 2000</td>
</tr>
<tr>
<td>4.</td>
<td>De novo AML M4</td>
<td>15Y/M</td>
<td>187.9</td>
<td>46.XY,t(2;11)(q31;p15)</td>
<td>NUP98-HOXD13</td>
<td>Progressed quickly poor response to therapy</td>
<td>Taketani et al. 2002</td>
</tr>
<tr>
<td>5.</td>
<td>CML-BC</td>
<td>15Y/F</td>
<td>NA</td>
<td>46.XY,t(2;11)(q31;p15)</td>
<td>NUP98-HOXD13</td>
<td>Complete Remission</td>
<td>Hidaka et al. 2004</td>
</tr>
<tr>
<td>6.</td>
<td>De novo AML M4</td>
<td>11Mon/F</td>
<td>24.4</td>
<td>46.XY,t(2;11)(q31;p15)</td>
<td>NUP98-HOXD13</td>
<td>Progressed quickly, progressed in 2 weeks</td>
<td>Emerenciano et al. 2011</td>
</tr>
<tr>
<td>7.</td>
<td>De novo AML M4</td>
<td>7Mon/M</td>
<td>318.7</td>
<td>46.XY,t(2;11)(q31;p15)</td>
<td>NUP98-HOXD13</td>
<td>Complete Remission</td>
<td>Present case 2013</td>
</tr>
<tr>
<td>8.</td>
<td>t-MDS/AML with monocytosis</td>
<td>59F</td>
<td>59</td>
<td>46.XY,t(2;11)(q31;p15)</td>
<td>NUP98-HOXD13</td>
<td>Progressed quickly</td>
<td>Raza-Egilmez et al. 1998</td>
</tr>
</tbody>
</table>

The patient presented here was a 59 year old female with a history of breast cancer with several cycles of chemotherapy and radiation therapy due to metastatic recurrences. Seventeen years later, she developed thrombocytopenia along with anemia. Despite the reduction of chemotherapy dosages, her blood cell counts did not recover.


This article should be referenced as such: