Acute myeloid leukemia with t(12;13)(p13;q12) and ETV6 involvement; Case report and review of literature

William R. Perry, Deborah Schloff, Anwar N. Mohamed

Cytogenetics Laboratory, Pathology Department, Wayne State University School of Medicine and Detroit Medical Center, Detroit, MI, USA; amohamed@dmc.org

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Abstract

Case report on acute myeloid leukemia with t(12;13)(p13;q12) and ETV6 involvement; Case report and review of literature.

Clinics

Age and sex
61 years old male patient.
Previous history
No preleukemia; no previous malignancy; no inborn condition of note
Organomegaly
No hepatomegaly, no splenomegaly, no enlarged lymph nodes, no central nervous system involvement

Blood
WBC: 5.4X 10^9/l
HB: 6.8g/dl
Platelets: 56X 10^9/l
Blasts: 22% myeloblasts
Bone marrow: 60% cellularity; 30% intermediate-to-large size blasts with open chromatin and no Auer rods; decreased trilineage hematopoiesis; significant dysplasia of erythroid elements.

Cyto-Pathology

Classification

Phenotype
Bone marrow and peripheral blood smear findings were both morphologically consistent with acute myeloid leukemia (AML).

Immunophenotype
Flow cytometry of the bone marrow sample showed a myeloblast population representing 33% of the cells that were positive for CD34, CD33, CD117, CD11b, CD11c, CD13, and cytoplasmic MPO.

Rearranged Ig Tcr
No.

Electron microscopy
not performed

Diagnosis
Acute Myeloid Leukemia, NOS (WHO, 2016).

Survival

Date of diagnosis
12-2017

Treatment
The patient began induction chemotherapy regimen on 1/7/2018 consisting of 7 days of daily cytarabine infusion and 3 days of daily daunorubicin. On 2/15/2018 he was treated for refractory AML with a five-day course of mitoxantrone, etoposide, and cytarabine.

Complete remission: no
Treatment related death: no
Relapse: Remission never achieved.
Status Alive
Acute myeloid leukemia with t(12;13)(p13;q12) and ETV6 involvement; Case report and review of literature. Perry WR et al. Atlas Genet Cytogenet Oncol Haematol. 2019; 23(8)

Last follow up
03-2018
Survival
3 +months

Karyotype
Sample Bone marrow aspirate.
Culture time 24h
Banding GTG band level: 350-400
Results
47,XY,t(12;13)(p13;q12),+21 [20]

Karyotype at Relapse
Karyotype following completion of induction chemotherapy 2/7/2018;
46,XY,t(12;13)(p13;q12)[3]/47,XY,t(12;13)(p13;q12)[3]/47,XY,t(12;13)(p13;q12)[3]/47,XY,t(12;13)(p13;q12)[3]/47,XY,+21[8]/47,XY,+8+t(12;13)(p13;q12)[4]/48,XY,+8, t(12;13)(p13;q12),+21[5] [Figure 1]

Other molecular cytogenetics techniques
Fluorescence in situ hybridization (FISH) using ETV6 LSI break apart probe (Abbott Molecular, Des Plaines, IL USA).

Other molecular cytogenetics results
Fluorescence in situ hybridization (FISH) with ETV6 probe revealed one fusion signal and split signal corresponding to the t(12;13)(p13;q12) however, the partner gene on chromosome 13q12 was not tested [Figures 2].

Results:
A nonsense variant (.c.2693G>A) in the ASXL1 gene was detected using the Illumina TruSight Myeloid Panel: Nonsense variants in ASXL1 gene are associated with poor prognosis (Metzeler et al, 2011).

Comments
The t(12;13)(p13;q12) is very rare in hematological malignancies with only 14 cases including the present case have been reported [Table 1]. Six cases were diagnosed with myeloproliferative neoplasms with eosinophilia (MPNeo), five had AML, and the remaining three were pediatric ALL [see TableI for references].
Molecular characterization of the t(12;13) breakpoints revealed the rearrangement of ETV6/12p13 gene in 9/14 cases. On the other hand, FLT3 gene was implicated as the involved partner gene on chromosome 13 in five cases. All five were diagnosed with MPNeo, nevertheless the disease was rapidly fatal in three patients [Table 1]. FLT3 encodes a member of the receptor tyrosine kinase subclass III family of receptors, which is expressed in early hematopoietic progenitor cells (Gilliland & Griffin, 2002; Stirewalt & Radich 2003). Mutations in FLT3 gene are found in approximately 30% of AML cases, yet this gene is rarely involved in translocations. Vu et al reported the first case of t(12;13)(p13;q12) in MPNeo, with the translocation resulting in the creation of an ETV6-FLT3 fusion gene. Reciprocal ETV6/FLT3 and FLT3/ETV6 transcripts were detected by RT-PCR; however, at the protein level, only ETV6/FLT3 was expressed in the patient’s leukemic cells (Vu et al, 2006). The putative oncogenic function gained as a result of the ETV6-FLT3 fusion is the constitutive activation of the tyrosine kinase domains of FLT3. One case of t(12;13)(p13;q12)-related AML involving a ETV6-CDX2 fusion has been described as well (Chase et al, 1999). Although FISH results in the present case revealed the involvement of ETV6 gene in the t(12;13) translocation, it is unknown whether a specific gene may have been affected by the 13q12 locus. Unlike FLT3 gene, ETV6/12p13 translocations is commonly detected in a wide spectrum of hematological malignancies lymphoid and myeloid; with at least 48 chromosomal bands and 30 ETV6 partner genes have been reported. The chimeric oncoprotein resulted from the t(12;13) may have a therapeutic implications. Although the ETV6-FLT3 positive leukemia has shown some sensitivity to FLT3 inhibitors, more cases are needed to appreciate the response.

<table>
<thead>
<tr>
<th>Case #</th>
<th>Age/Sex</th>
<th>Diagnosis</th>
<th>Genes involved</th>
<th>Clinical Status</th>
<th>Survival (months)</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>68Y/F</td>
<td>MPN-eo</td>
<td>ETV6-FLT3</td>
<td>Deceased</td>
<td>21</td>
<td>Vu et al., 2006</td>
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<tr>
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<td>40Y/F</td>
<td>MPN-eo</td>
<td>ETV6-FLT3</td>
<td>Alive - CR</td>
<td>11</td>
<td>Falchi et al., 2014</td>
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<tr>
<td>3</td>
<td>60Y/M</td>
<td>MPN-eo</td>
<td>ETV6-FLT3</td>
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<td>7</td>
<td>Walz et al., 2011</td>
</tr>
<tr>
<td>4</td>
<td>49Y/M</td>
<td>MPN-eo</td>
<td>NR</td>
<td>Deceased</td>
<td>11</td>
<td>Chiyoda et al., 1994</td>
</tr>
<tr>
<td>5</td>
<td>29Y/M</td>
<td>MPN-eo</td>
<td>ETV6-FLT3</td>
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<td>6</td>
<td>33Y/M</td>
<td>T-ALL and MPN-eo</td>
<td>ETV6-FLT3</td>
<td>Alive - CR</td>
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<td>Chonabayashi et al., 2013</td>
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<td>5Y/M</td>
<td>ALL</td>
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<td>9Y</td>
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<td>17Y/F</td>
<td>ALL</td>
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<td>Wlodarska et al., 2011</td>
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<td>10</td>
<td>62Y/F</td>
<td>MDS-RAEB</td>
<td>NR</td>
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<td>Knapp et al., 1985</td>
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<td>51Y/M</td>
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<td>40</td>
<td>Chase, 1999</td>
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<tr>
<td>14</td>
<td>61Y/M</td>
<td>AML</td>
<td>ETV6-?</td>
<td>Alive</td>
<td>3</td>
<td>Present case 2018</td>
</tr>
</tbody>
</table>

Table 1: Clinical data on patients reported with t(12;13)(p13;q12).
ALL: F; female; M; male; acute lymphoblastic leukemia; AML: acute myeloid leukemia; CR: complete remission; MDS-RAEB: myelodysplastic syndrome with refractory anemia and excess blasts; MPN-eo: myeloproliferative neoplasms with eosinophilia; NR: not reported; PTCL: peripheral T-cell lymphoma; Y: years

References


Chiyoda S, Morikawa T, Takahara O. [Atypical chronic myeloproliferative disorder with translocation (12;13)(p13;q12) and tumor formation]. Rinsho Ketsueki. 1994 Dec;35(12):1355-60


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Vu HA, Xinh PT, Masuda M, Motoji T, Toyoda A, Sakaki Y, Tokunaga K, Sato Y.. FLT3 is fused to ETV6 in a myeloproliferative disorder with hypereosinophilia and a t(12;13)(p13;q12) translocation. Leukemia 2006; 20: 1414-1421.
