AML with t(8;16) shows unique clinical, morphological and cytogenetic features
INTRODUCTION

- t(8;16) (p11.2;p13.3) is a recurrent, myeloid-specific cytogenetic abnormality detectable on routine cytogenetic karyotypic analysis.
- Rare (0.7% of AML) but comprises 6.5% of AML of the M4/M5 FAB subtype.
- Initially described in pediatric leukemias and is the second most common recurrent cytogenetic abnormality in rare cases of congenital leukemia.
- Aggressive and often therapy-related with frequent resistance to standard chemotherapy, similar to AML with MLL rearrangements (though, outcome may even be inferior).
Acute Myeloid Leukaemia and Related Precursor Neoplasms (WHO)

- Acute myeloid leukaemia with recurrent genetic abnormalities
- Acute myeloid leukaemia with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- Acute myeloid leukaemia, not otherwise specified
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm
AML with balanced translocations/inversions (WHO 2008 classification)

- Acute myeloid leukaemia with t(8;21)(q22;q22); RUNX1·RUNX1T1
- Acute myeloid leukaemia with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB·MYH11
- Acute promyelocytic leukemia with t(15;17)(q22;q12); PML-RARA
- Acute myeloid leukaemia with t(9;11)(p22;q23); MLLT3·MLL
- Acute myeloid leukaemia with t(6;9)(p23;q34); DEK-NUP214
- Acute myeloid leukaemia with inv(3)(q21q26.2) or t(3;3)(q2/;q26.2); RPN/·EVI1
- Acute myeloid leukaemia (megakaryoblastic) with t(1;22)(p13;q13); RBMI15-MKL1
Pie chart based on 246 patients analyzed for the presence of mutations in the NPM1 and CEBPA genes, FLT3-ITD, FLT3-TKD and MLL-PTD. Each sector indicates the percentage of patients harboring one or more of the aforementioned mutations. WT indicates patients with only wild-type alleles of the genes testing.

From Mrózek et al* and adapted from Dohne et al**

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**Döhner K et al, Blood. 2005 Dec 1;106(12):3740-6.
AML with t (8;16)

- Initially reported as a malignant histiocytosis (Schouten et al), AML with t(8;16) commonly shows blast hemophagocytosis, DIC, and extramedullary infiltration.
- Often a monocytoïd leukemia but difficult to classify based on unusual cytochemical staining (parallel MPO/NSE positivity in blasts).
- Thought to be an initiating event in leukemogenesis and fuses MYST3 (8p11), which encodes for a histone acetyltransferase, to CREBBP (16p13), which encodes for a transcriptional co-activator and acetyltransferase, generating a novel fusion protein that inhibits RUNX1 regulated transcription, leading to differentiation block.
- Variant translocations related to t(8;16) include t(10;16)(q22;p13), t(8;22)(p11;q13), inv(8)(p11q13), t(8;20)(p11;q13) and show similar features, including blast erythrophagocytosis.
- Although >100 cases of t(8;16) have been reported, infants and children are underrepresented in recent studies.
<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Sex</th>
<th>WBC</th>
<th>Sites</th>
<th>Subtype</th>
<th>Immunophenotype‡</th>
<th>Karyotype</th>
<th>DIC, Hemophagocytosis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5y</td>
<td>F</td>
<td>18,600/ul</td>
<td>Bone marrow, peripheral blood</td>
<td>De novo FAB M5a</td>
<td>CD34-, CD117-, MPO+, NSE+, CD4+, CD56+, TdT-, CD163-</td>
<td>46,XX, der(7)t(6;7)(q15;q31), t(8;16)(p11.2;p13.3)[14]/46,XY[6]</td>
<td>Minimal blast hemophagocytosis</td>
<td>Alive, 19 months s/p transplant</td>
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<tr>
<td>2</td>
<td>8y</td>
<td>F</td>
<td></td>
<td>Bone marrow, peripheral blood</td>
<td>Therapy-related FAB M5b</td>
<td>CD34-, CD117?, MPO-, NSE+, CD2+, CD19+, TdT-</td>
<td>46,XX, t(5;10)(p15.3;q24), del(7)(q31), t(8;16)(p11.2;p13.3), inv(17)(p13q23)[16]/46,XX, t(1;15)(q21;q24), t(5;10)(p15.3;q24), t(6;7)(q27;p15), t(8;16)(p11.2;p13), t(13;17)(q14;p13)[1]/46,XY[3]</td>
<td>None</td>
<td>DOD, &lt;1 year following diagnosis</td>
</tr>
<tr>
<td>3</td>
<td>1m</td>
<td>M</td>
<td>381,000/ul</td>
<td>Peripheral blood, skin, CSF</td>
<td>De novo FAB M4</td>
<td>CD34-, CD117-, MPO+, NSE+, CD56(dim+), TdT(dim+)</td>
<td>46,XY, t(8;16)(p11.2;p13.3) [inc2]/46,XY[2]</td>
<td>DIC</td>
<td>Alive, 19 months s/p reinduction and URD cord blood transplant</td>
</tr>
<tr>
<td>4</td>
<td>14y</td>
<td>F</td>
<td>171,000/ul</td>
<td>Peripheral blood, bone marrow</td>
<td>De novo FAB M4</td>
<td>CD34-, CD56+, CD15+, CD4+</td>
<td>t(8;16)(p11.2;p13.3) nuc ish(5' KAT6A, 3' KAT6A)x2 (5' KAT6A sep 3' KAT6A ax1)[25/100]</td>
<td>DIC hemophagocytosis</td>
<td>DOD, 2 months after bone marrow transplant</td>
</tr>
<tr>
<td>5*</td>
<td>20m</td>
<td>M</td>
<td></td>
<td>Skin</td>
<td>Therapy-related</td>
<td>No flow</td>
<td>t(8;16)(p11.2;p13.3) by FISH</td>
<td>Hemophagocytosis</td>
<td>Alive 1 year after bone marrow transplant</td>
</tr>
</tbody>
</table>

14 yo with ho leukemia

- 14 yo with respiratory failure, cytopenia
- History of leukemia with t (8;16), 2 months s/p transplant
- Transfusion reaction (Trali) vs relapsed leukemia
- DIC: fulminant course
20 month old male with 5 week history of growing papules on posterior scalp
- Non-tender, Firm

History of stage 4 neuroblastoma
- Diagnosed at 13 months of age
- Received 8 cycles chemotherapy Cyclophosphamide, Etoposide, Carboplatin, Doxorubicin
Extramedullary AML

- **Myeloid sarcoma**
  - positive for CD68-KP1, CD43, CD33, Lysozyme, Myeloperoxidase (MPO), CD45

- Also known as:
  - Extramedullary acute myeloid leukemia (AML).
  - Chloroma

- A t(8;16) translocation was present in tumor cells analyzed by FISH
  - Fuses MOZ (monocytic leukemia zinc finger) to CREB-binding protein
  - Found in *de novo* and therapy-related AML
Myeloid Sarcoma

- Tumors of myeloid origin occurring at extramedullary locations
- Typically occur in the setting of overt bone marrow involvement
- Treatment is chemotherapy
  - Local recurrence or frank leukemia typically develops within several months without treatment
Discussion

- Neuroblastoma can have cutaneous metastases
- Pathology confirmed isolated cutaneous myeloid sarcoma, occurring on therapy
- Our patient remains in remission ~1y post-HCT
Acute myeloid leukemia with t(8;16)(p11.2;p13.3) is **not yet a distinct entity** in the WHO 2008 Classification.

An **aggressive** course is typical, but evidence for disseminated intravascular coagulation and hemophagocytosis must be sought.

**Pediatric AML with t(8;16) is underrepresented in recent literature** but shows similar features to adult cases.

Diagnostic pearls include:

- Monocytic/monoblastic differentiation with cytoplasmic vacuolization
- MPO/NSE dual positivity – how to classify?
- CD34-/CD117- blasts that often show CD56 and may rarely have dim TdT expression
- The 8p11 fusion gene, MYST3 (MOZ), is involved in both de novo and therapy-related cases and may be crucial in the understanding of leukemogenesis, which could provide therapeutic targets

With further investigation, **AML with t(8;16)(p11.2;p13.3) may meet criteria to stand alone as a distinct diagnostic entity**
Pediatric acute myeloid leukemia with t(8;16)(p11;p13), a distinct clinical and biological entity: a collaborative study by the International-Berlin-Frankfurt-Münster AML-study group

Eva A. Coenen, C. Michel Zwaan, Dirk Reinhardt, Christine J. Harrison, Oskar A. Haas, Valerie de Haas, Vladimir Mihál, Barbara De Moerloose, Marta Jeison, Jeffrey E. Rubnitz, Daisuke Tomizawa, Donna Johnston, Todd A. Alonzo, Henrik Hasle, Anne Auvrignon, Michael Dworzak, Andrea Pession, Vincent H. J. van der Velden, John Swansbury, Kit-fai Wong, Kiminori Terui, Sureyya Savasan, Mark Winstanley, Goda Vaitkeviciene, Martin Zimmermann, Rob Pieters and Marry M. van den Heuvel-Eibrink
Findings

- 62 pediatric patients from 18 countries (median age: 1.2 years), 2 therapy related
- 7 congenital cases showed spontaneous resolution but 4 relapsed eventually
- Extramedullary disease: 66%
- CNS involvement: 15%
- DIC: 39%
Conclusion

- t(8;16)(p11.2;p13.3) or 8p11.2 MYST3 rearrangements are recurrent cytogenetic abnormalities in acute myeloid leukemia and may best be distinct in the WHO classification
- An aggressive clinical course is typical (including DIC)
- Pediatric AML with t(8;16) is underrepresented but may present as a congenital leukemia
- Spontaneous remissions common but clinical follow up very important
References

Acute myeloid leukaemia with 8p11 (MYST3) rearrangement: an integrated cytologic, cytogenetic and molecular study by the groupe francophone de cytogenetique hematologique

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The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes

James W. Vardiman, Jürgen Thiele, Daniel A. Arber, Richard D. Brunning, Michael J. Borowitz, Anna Porwit, Nancy Lee Harris, Michelle M. Le Beau, Eva Hellström-Lindberg, Ayalew Tefferi, and Clara D. Bloomfield

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References