De Novo Monocytic-M5b AML with t(8;16) (p11.2; p13.3) KAT6A/CREBBP fusion and FLT3-TKD mutation: Analysis of Mitelman Database

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Abstract

t(8;16) in AML is usually associated with cytotoxic therapies and de novo finding is very rare. This subtype is known to have unique characteristics such as hemophagocytosis, DIC, leukemia cutis and varying levels of CD45 expression. Prognosis is poor with overall survival ranging from 4.7 to 18.2 months. The cytogenetic abnormality is **mostly associated with M4 or M5 types of AML** as shown in our descriptive analysis of Mitelman database. Our patient had relapse of AML during consolidation and subsequently developed DIC during an admission from fall.

Background

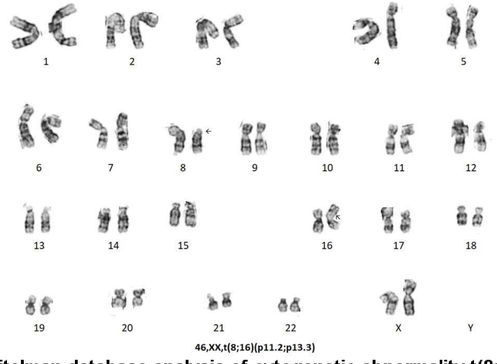
- t(8;16) (p11.2; p13.3)/KAT6A-CREBBP fusion is a rare cytogenetic abnormality usually associated with treatment related AML (t-AML)
- Usually exhibits **unique characteristics such as hemophagocytosis, disseminated intravascular coagulation (DIC), leukemia cutis, monoblastic or myelomonocytic differentiation while accounting for <0.5% cases of AML** and being more common in females [1–3].
- While having t(8;16) as the sole abnormality is rare, having other associated mutations is even rarer [1] as in our patient who had an FLT3-TKD mutation.
- Reported overall survival in such patients is poor and varies from **4.7 to 18.2 months** [1,4].
- Patients with de novo AML with t(8;16) or t-AML with t(8;16) without adverse prognostic factors (e.g., complex karyotype) have a good outcome [1].

Case

- Female in her mid 40s with no past history of MDS or treatment for leukemia/lymphoma or solid organ malignancy was found to have 16% blasts on her CBC during evaluation for chest pain/shortness of breath.
- Flow cytometry and FISH studies on bone marrow biopsy confirmed diagnosis of **monocytic AML with t(8;16) KAT6A/CREBBP fusion** in 87.2% of nuclei in addition to FLT3-TKD mutation.
- Flow cytometry revealed expression of monocytic markers [CD11b (partial), CD14 (partial), HLA-DR, CD36 (partial), CD64], myeloid markers (CD13, CD15, CD33) and aberrant expression with CD45 (dim), cMPO, CD56 (partial), CD71 and CD38.
- **Started 7+3 induction regimen** with cytarabine and daunorubicin; **Midostaurin added for FLT3-TKD mutation**.
- Day 33 bone marrow biopsy with no evidence of leukemic cells so was planned for HiDAC consolidation.

- **Readmitted for relapsed AML** while having received 1 cycle of HiDAC without midostaurin at a different facility. She was started on FLAG-IDA induction regimen (fludrabine+cytarabine+G-CSF and idarubicin).
- Day 17 bone marrow biopsy was performed with no flow cytometry evidence of leukemic cells, with a **CR+MRD negative status** so was discharged with follow up at BMT clinic.
- Readmitted after a fall and developing large intracranial hematoma that was surgically evacuated. Patient developed **DIC** and care was transitioned to comfort measures due to lack of improvement.

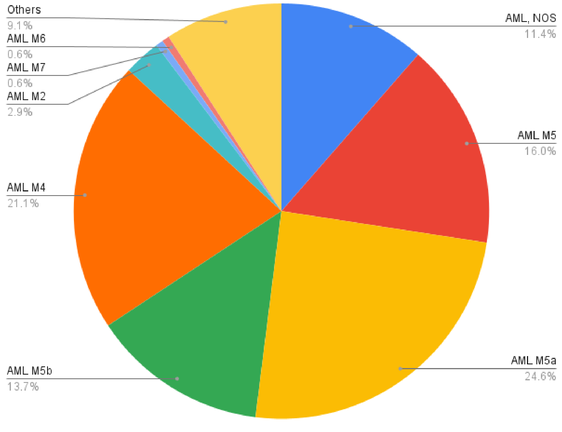
Results



46,XX,t(8;16)(p11.2;p13.3)

Mitelman database analysis of cytogenetic abnormality t(8;16)

n=175 as of 04/18/2022 (database updated quarterly)



Discussion

- t(8;16) usually occurs after treatment for AML and around 50% of patients are deceased in 10 months [3].
- The gene involved in 8p11 is **KAT6A** (previously known as MOZ or MYST3) [5] and **encodes the zinc finger MYST3 protein** with **acetyltransferase activity in the nucleus** [6]. CREBBP (CREB-binding protein) in 16p13 is the most common partner gene for KAT6A.
- **CREBBP protein plays a transcription regulatory role by interacting with DNA-binding protein CREB and thus histone acetylation** [5]. Thus, KAT6A and CREBBP are essential in embryogenesis, cell differentiation, apoptosis and proliferation by means of their histone acetyltransferase activity [7] and the chimeric gene is believed to be leukemogenic through aberrant chromatin remodeling [5,8]. It is unknown if the chimeric gene produces a functional transcript that could contribute to leukemogenesis.
- Her other treatment options included gliterninib. While she was planned to receive an allogeneic SCT, she was transitioned to comfort measures due to complications from her fall and DIC.

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