Case Study

A Novel Three Way Translocation in a Child with t(8:21) Acute Myeloid Leukemia (AML-M2) Involving 6q27 with Loss of Y chromosome.

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Abstract:

Background:

The typical t(8;21) (q22;q22) abnormality is associated with acute myeloid leukemia with maturation (AML-M2 based on the French-American-British classification). This protein regulates proliferation, the differentiation, and the viability of leukemic cells. Method: We report a case of 9-year-old boy with a positive RUNX1/CBFA2T1 (AML1/ETO) fusion gene and a karyotype with a 45, X,-Y, t(6;21;8)(q27;q22;q22). Result: This variant translocation involving chromosome region 6q27 with loss of Y chromosome have never been reported before. Child had induction failure after 3+7 chemotherapy and subsequently died due to sepsis. Conclusion: We assume that this translocation may be responsible for the poor prognosis of this case.

Key Words: Variant Translocation, Acute Myeloid Leukemia, Y chromosome

Introduction:

Acute myeloid leukemia (AML) is a heterogeneous bone marrow malignancy, and cytogenetics t(8;21) (q22;q22) abnormality is typically associated with acute myeloid leukemia with maturation (AML-M2 based on the French-American-British classification) (1). This protein is responsible for proliferation, differentiation and the viability of leukemic cells. The translocation fuses the AML1 gene (also called RUNX1) on chromosome 21 with the ETO gene (also referred to as the RUNX1T1 gene that encodes the CBFA2T1 protein) on chromosome 8. This translocation is classified as 'low risk' in patients with AML, and the prognosis after intensive chemotherapy is better for these patients than intermediate or high risk patients (1). The t(8;21) abnormality is found in minority of patients, which is approximately 5%–10% of all AML cases and 10%–20% of AML cases with maturation corresponding to the FAB class AML-M2 [2–5]. Most common abnormality for creating AML1-ETO fusions is simple reciprocal translocation, however, fusion can also occur through variant rearrangements. So, this t(8;21) translocation is often detected together with some additional cytogenetic or molecular genetic abnormalities with variable prognosis (6,7,8). Based on the various published clinical studies, variant rearrangements with t(8;21) includes the del(9q) abnormality in 15%–35% (9), loss of sex chromosomes (4) X (30-40%), Y (50-60%), trisomy 4 and 8 (8%), complex cytogenetics (9-23%) and rarely tetraploid or near tetraploid clones have been reported in literature. (7,10-12). Here we describe a novel three-way translocation in a child with AML that is 45, X,-Y, t(6;21;8)(q27;q22;q22). This variant translocation involving chromosome region 6q27 with loss of Y chromosome has never been described in literature before.

Case:

The patient, 9-year-old boy, was presented to our hospital with complaints of fever off and on since last 3 weeks. Clinical examination showed moderate pallor with just palpable hepatosplenomegaly below costal margin. Complete blood count showed Hemoglobin 7.5 g/dl; leucocyte count 30230/mm3, platelet 15000/mm3 and peripheral blood examination showed 88% blasts. Bone marrow aspiration showed proliferation of peroxidase- positive blasts (97%) with maturation. Flow cytometry was suggestive of AML (T cell markers CD3 (0.1%), CD5 (0.4%), CD7 (1%), CyCD3 (1.2%) were negative, B cell marker CD 19 (21.7%) dim positive, CD10 (0%), CD22 (0.8%) negative, myeloid Marker CD 13 (72.3%), CD33 (88.1%), CD 34 (73%), CD 117 (72.8%), HLA DR (76.1%) moderate positive, CD38 (46.1%), CD45 (99.5%) dim positive, MPO (66.3%) moderate positive. No malignant cells were found in CSF cytospin. A diagnosis of AML (M2) was made. The patient was negative for HIV, hepatitis B and C. He had normal liver and renal function. Fluorescence in situ hybridization (FISH) study for AML1 gene rearrangement using a cosmid probe that covers the breakpoint cluster region of AML1 revealed three signals 2 Orange, 2 Green, 1Yellow, for RUNX1T (ETO)/ RUNX1(AML1) (Fig. 1). A chromosomal analysis (GTG-banding) with 24 hours cultures with appropriate serum and antibiotics revealed a clone of 45, X, -Y, t (6;21;8) (q27;q22;q22) (Fig. 2). One course of induction chemotherapy consisting of cytarabine (200 mg/m2 continuous infusion, days 1–7),

daunorubicin (60 mg/m2, drip infusion, days 1–3) was given. After first course of chemotherapy child did not go in to remission (bone marrow aspiration showed 10 % blasts with AML minimal residual disease (MRD) of 20%). He was repeated with second course of same chemotherapy. After few days child presented with febrile neutropenia with multidrug resistant Escherichia coli induced septic shock and died.

Discussion

Translocation (8;21) (q22;q22) is a specific abnormality frequently associated cytogenetically in AML-M2. Complex variants of t(8;21)(q22;q22) are occasionally observed with variable prognosis in a small percentage of AML. Mostly three way translocations involved regions of 8q22, 21q22 and a third chromosome. Chromosomes 1, 2, 3, 5, 6, 8, 10, 12, 13, 14, 15, 16, 17, 18, and 20 have been reported as the third chromosome involved in the variant three-way translocation (13). Very rarely, a four-way variant complex translocation is reported (12). In this case, we report an AML-M2 patient involving a new breakpoint 6q27 in a complex three-way t(6;8;21) (q27;q22;q22) with loss of Y chromosome, which has not been reported so far in the literature. FISH analysis with AML1/ETO –specific probes showed co-localization of AML1 and ETO signals on the rearranged chromosome 8 at q22 (figure 1). However, it is unclear that this breakpoint region 6q27 with complex three-way translocation has played any role in leukemogenesis or not. Similar to reported by Udaykumar et al. (13) our patient also had translocation of distal long arm of chromosome 21 at q22 to the long arm of chromosome 8, whereas the end of chromosome 8 was translocated to a third chromosome (6q27) and that remainder of the third chromosome was translocated to chromosome 21, but our third chromosome was 6 involving band q 27 (6q27) instead of theirs 13q14 (figure 2). AML1/ETO protein regulates proliferation, the differentiation, and the viability of leukemic cells. Any event that lead to formation of AML1/ETO fusion from t(8;21) is one of the main cause of leukemogenesis in the variant translocations. (14).

Shinagawa et al. (15) also reported a complex translocation 46,XX,t(6;21;8)(p21;q22;q22) in an adult female that was associated with trisomy 4, not with loss of Y chromosome and involved break point region 6q27 like our case. Assuming in low risk, that patient with t(6;21;8) and trisomy 4 showed good response to chemotherapy and underwent in remission after first course of chemotherapy. A French group (16), 2.5 decades ago reported one out of 148 cases with AML of a three-way translocation of 45,X,- Y, t(6;21;8)(q21;q22;q22) but our case had 45,X, -Y,t(6;21;8)(q27;q22;q22). Holmes et al. (17) described 13 patients with loss of Y chromosome but none had three-way translocation with loss of Y chromosome like ours. Although t(8;21) is associated with a good prognosis, the clinical relevance and implications of this new variant t(6;8;21) (q27;q22;q22) with loss of Y chromosome is yet to be determined. Prognosis of t(8;21) (q22;22) with loss of Y chromosome is reported controversial, including uneasy remission and easy relapse (18) to a weak good prognostic impact (4,7,8). After first course of chemotherapy our patient also did not go in to remission (bone marrow aspiration showed 10 % blasts with AML minimal residual disease (MRD) of

20%) assuming that cytogenetics as bad one. We had planned for hematopoietic stem cell transplant but unfortunately after second course of same chemotherapy that child succumbed to E. coli sepsis.

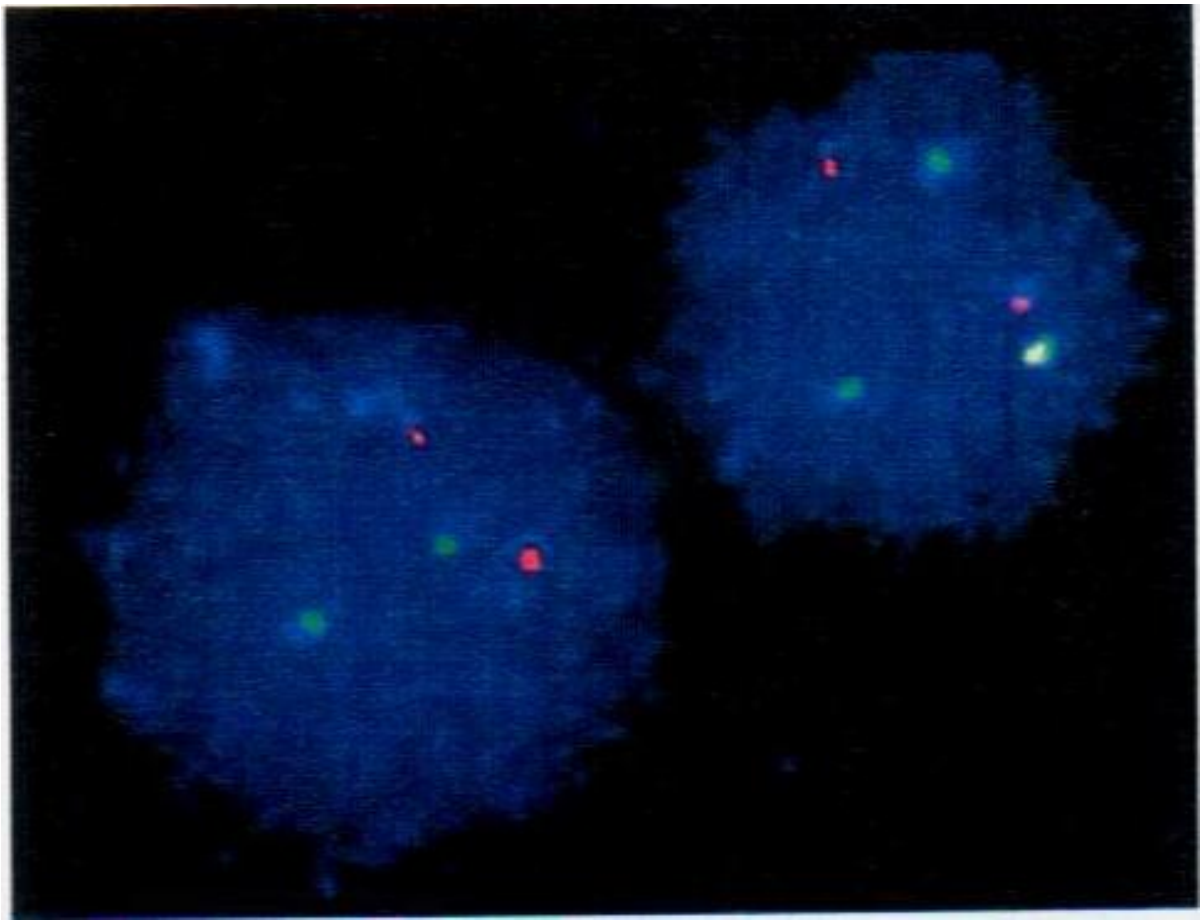

Figure 1: Fluorescence in situ hybridization (FISH) Probe Vysis LS1 Showing RUNX1T1 (ETO)(8q21.3) S. Orange/ LS1 RUNX1(21q22) S. Green

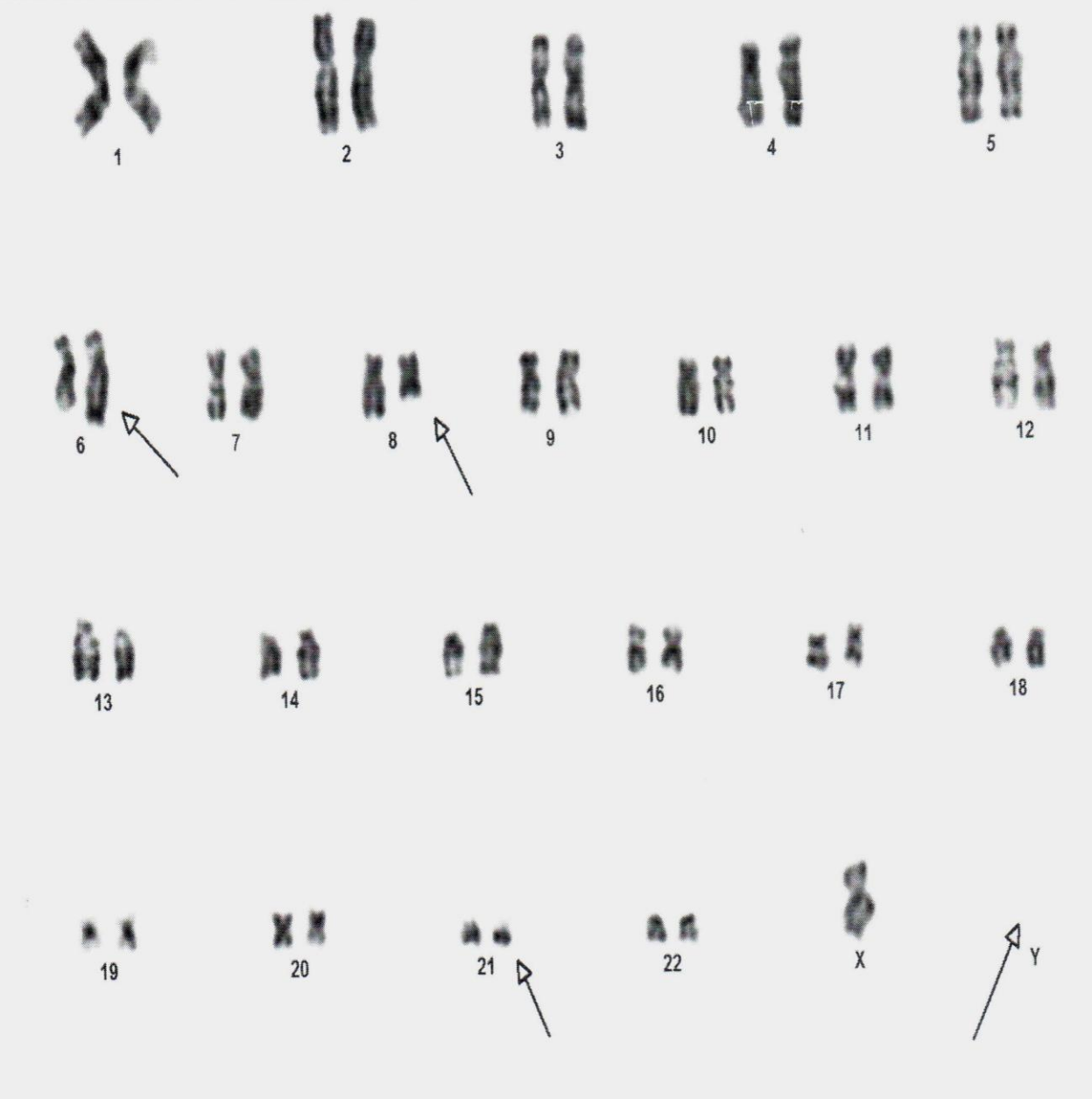

Figure 2: Chromosomal analysis with GTG Banding showing clone of 45, X, -Y, t (6;21;8) (q27; q22; q22)

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