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Acute myeloid leukemia with variant t(8;10;21)

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ABSTRACT

The t(8;21)(q22;q22) is one of the most common chromosomal abnormalities in acute myeloid leukemia (AML). Approximately 3–4% of AML cases are associated with additional chromosomal abnormalities. Their impact on the prognosis of the disease remains to be established. Here we report a case of t(8;10;21) AML with mutated c-KIT that shared key morphological features with classical t(8;21) leukemias, including the M2 morphology pattern and CD34, HLA-DR phenotype. The 63-year-old female was treated with two inductioncontaining Daunoribicine and Cytarabine and four cycles of intermediate-dose Cytarabine (1.5 g/m^2) and achieved long-lasting remission.

1. Introduction

The translocation t(8;21)(q22;q22) is one of the most common chromosomal abnormalities in acute myeloid leukemia (AML). This subtype is strongly associated with French-American-British (FAB) subtype M2 (WHO). Clinically, the disease is associated with a high remission rate with standard chemotherapy and prolonged survival when high-dose Cytarabine is administered [1–3]. Approximately 3–4% of t(8;21)(q22;q22) AML cases are associated with additional chromosomal abnormalities [4]. Their impact on the characteristics and outcomes of the disease is not completely understood.

2. Case presentation

A 63-year-old female was admitted for fatigue lasting one month and progressive dyspnea. The laboratory work-up revealed 60 × 10^9/L of white blood cells, hemoglobin level of 74 g/L and 15 × 10^9/L of platelets. As the differential white blood cell count contained 51% of myeloblasts with Auer rods, the bone marrow cytology was performed the next day.

The bone marrow aspirate smears were hypercellular, with massive (66%) infiltration by myeloblasts. The myeloblasts varied in diameter between 12–16 μm, and had round nuclei with one to four nucleoli and fine nuclear chromatin. The cytoplasm was scanty, moderately basophilic, often containing azurophilic granules and sporadic Auer rod or pseudo-Chédiak-Higashi inclusion. The proportion of promyelocytes was also elevated (9%), often having atypically shaped nuclei and granulation defects. More mature granulocytes were also often dysplastic – hypogranularity, agranularity, and unusually small myelocytes as well as pelgeroid changes were present. Erythropoiesis and megakaryopoiesis were almost absent (Fig. 1).

The marrow blasts (42% of marrow cells) expressed CD34, CD17, HLA-DR…, CD33, CD56, CD38, MPO and aberrantly CD19. In addition to the blasts, the marrow contained 36% of immature cells of myeloid origin.

Routine cytogenetic analysis revealed complex chromosomal changes involving three chromosomes: 8, 10, and 21. The observation of breakpoints at 8q22 and 21q22 suggested rearrangements of the RUNX1 and RUNX1T1 genes. FISH analysis using a dual-color, dual-fusion RUNX1-RUNX1T1 probe revealed a specific RUNX1-RUNX1T1 fusion signal on the derivative chromosome. M-FISH analysis using a multicolor 24XCyte probe confirmed the results of routine chromosome analysis and revealed that part of the chromosome 8 material was translocated to chromosome 10, part of chromosome 10 moved to chromosome 21, and part of chromosome 21 was attached to chromosome 8 (Fig. 2A and 2B). The results of classical cytogenetic, FISH and

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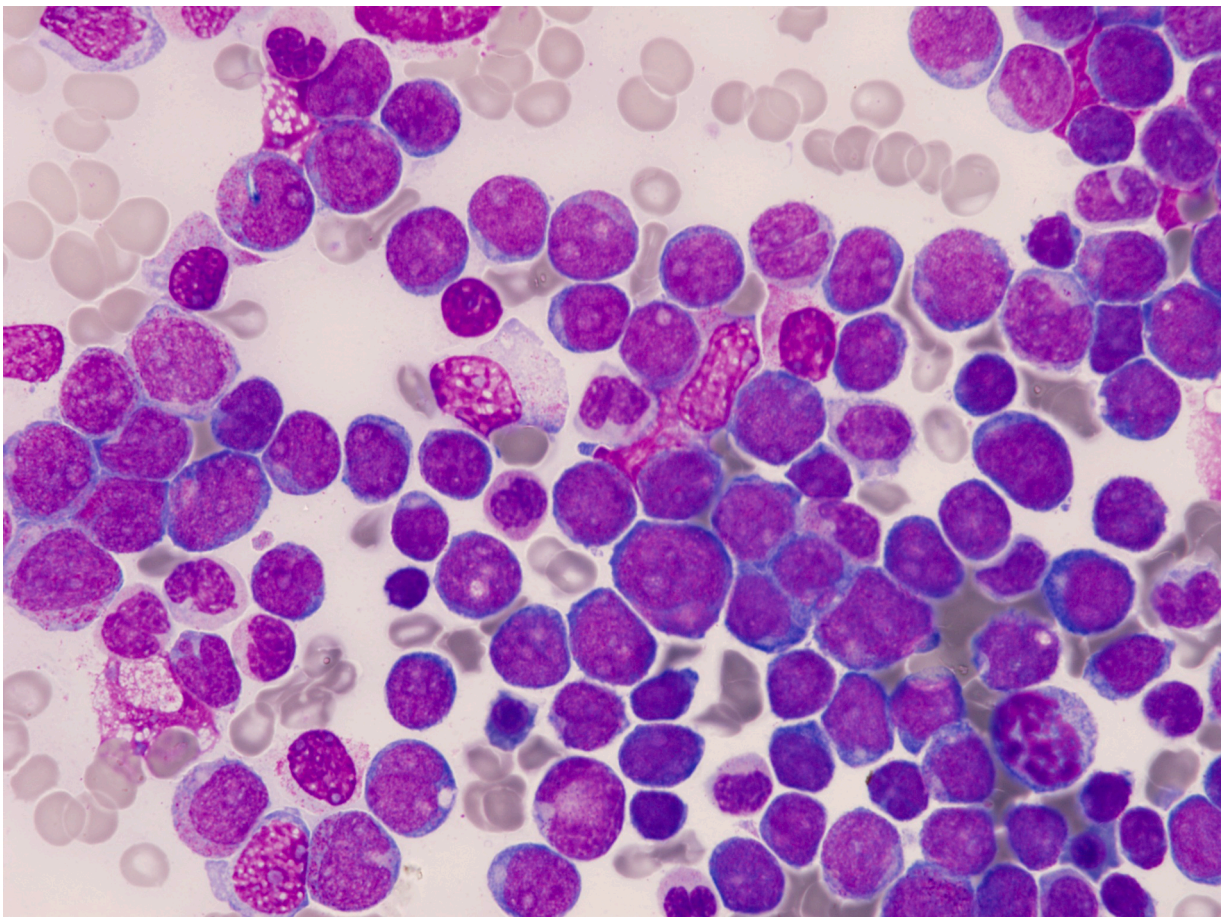

Fig. 1. The bone marrow aspirate. The bone marrow aspirate smears were hypercellular, with massive (66%) infiltration by myeloblasts. The myeloblast varied in diameter between 12–16 μm, and had round nuclei with one to four nucleoli and fine nuclear chromatin. The cytoplasm was scanty, moderately basophilic, often containing azurophilic granules and sporadic Auer rod or pseudo-Chédiak-Higashi inclusion. The proportion of promyelocytes was also elevated (9%), often having atypically shaped nuclei and granulation defects. More mature granulocytes were also often dysplastic – hypogranularity, agranularity, and unusually small myelocytes as well as pelgeroid changes were present. Erythropoiesis and megakaryopoiesis almost were absent.

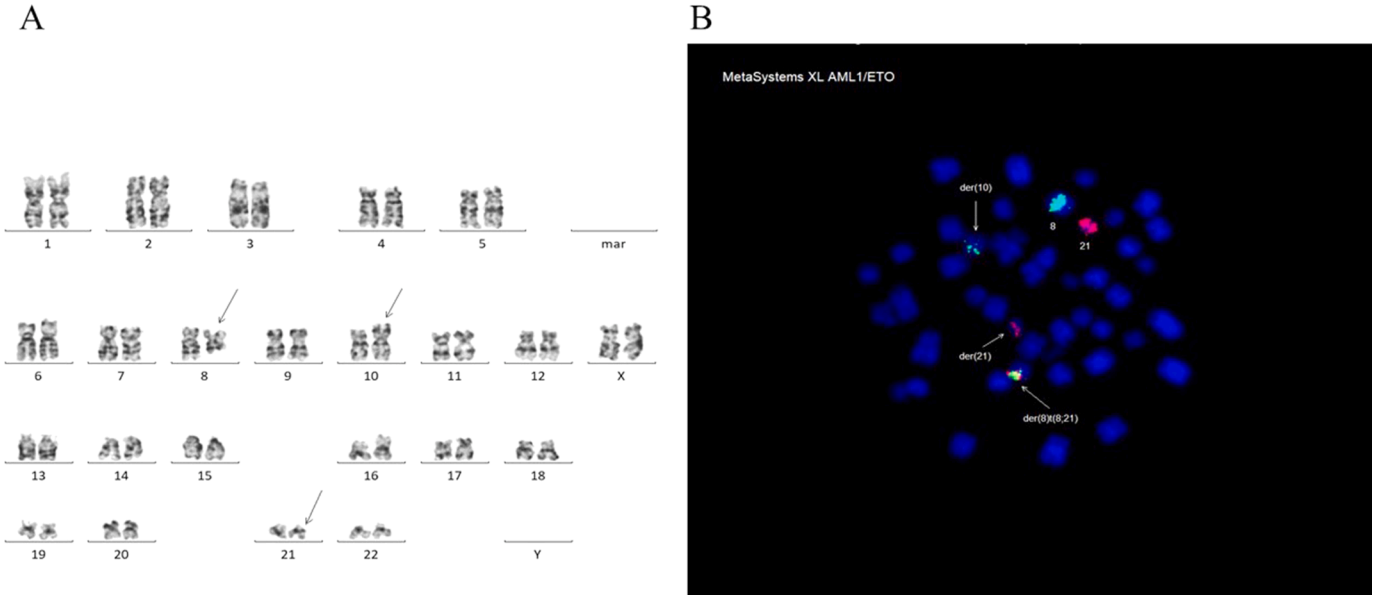

Fig. 2. A. Routine cytogenetic analysis. Routine cytogenetic analysis revealed complex chromosomal changes involving three chromosomes: 8, 10, and 21. B. FISH analysis. Using a dual-color, dual-fusion RUNX1-RUNX1T1 probe revealed a specific RUNX1-RUNX1T1 fusion signal on the derivative chromosome 8.

M-FISH analysis revealed karyotype 46,XX,t(8;10;21)(q22;p14;q22) showing the variant of the t(8;21) translocation involving chromosome 10 as a third chromosome. No other secondary chromosomal changes were found.

The direct PCR sequencing revealed the RUNX1-RUNX1T1 fusion transcript and the direct PCR sequencing of exons 8, 9 and 17 of c-kit gene revealed the mutation NM_001093772.1:c.1250_1256delCTTACGAinsGGGC. Mutations of FLT3-ITD and NPM1 and presence of PML-RARA fusion transcript were ruled out by further examination.

Following three days of cytoreduction with 3 g hydroxyurea per day, the induction consisting of 7 days of Cytarabine 100 mg/m^{2}and 3 days of Daunorubicin 90 mg/m^2 was started. The bone marrow cytology performed on day 14 of the induction revealed the persistence of leukemic cells (10% of myeloblasts by cytology and 12% by flow cytometry) in hypocellular bone marrow aspirate. According to institutional guidelines, a second induction consisting of 7 days of Cytarabine 100 mg/m^{2}and 3 days of Daunorubicin 45 mg/m^2 was started on day 21 of the first induction. The treatment was well tolerated. The bone marrow cytology performed on day 25 of the second induction revealed aplastic bone marrow aspirate without trilinear haematopoiesis. Consistent with these findings, the peripheral blood smear contained 0.1 $\times$ 10^9/L of white blood cells, a hemoglobin level of 90 g/L, and 10 $\times$ 10^9/L of platelets. With G-CSF (Granulocyte Colony Stimulating Factor) support, the neutrophile recovery was achieved on day 39 of the second induction. The bone marrow cytology performed on day 45 of the second induction revealed incipient remission. The hypocellular bone marrow aspirate with normocellular fragments contained 1.8% of myeloblasts and trilinear hematopoiesis. The amount of RUNX1-RUNX1T1 transcripts decreased by 2 logs after the second induction. The treatment then consisted of 4 cycles of intermediate-dose Cytarabine 1.5 g/m^2 twice daily on days 1, 3, and 5. Regular examinations of the bone marrow confirmed lasting cytological remission; the RUNX1-RUNX1T1 transcript decreased slowly but regularly and dropped to zero upon completion of the fourth consolidation. Further examinations of the bone marrow also confirmed the remission and the patient is disease-free more than 7 years after the diagnosis.

The recent case shared key morphological features with classical t(8;21) AML including the M2 morphology pattern and CD34, HLA-DR… phenotype. As in one of the previously described cases, the recent case contained an elevated proportion of promyelocytes in the bone marrow. Lee and colleagues described a case of t(8;10;21) leukemia in an 11-year-old female that morphologically mimicked chronic myeloid leukemia [5].

In addition to cytogenetic changes, the recent case harboured c-KIT mutation. This is not surprising, as c-KIT mutations commonly occur in core binding factor AMLs. As much as 25% of t(8;21) and 30% of inv(16) harbor the c-KIT mutation [6]. Currently, the prognostic significance of c-KIT mutation is not completely understood. In some, but not all studies the presence of c-KIT mutation was shown to be associated with higher incidence of relapse. [7] However, the prognostic significance of the mutation itself is overcome by the powerful prognostic significance of the minimal residual disease monitoring. [8] Ultimately, the negative MRD status after the 3rd consolidation and the wish of the patient guided our decision not to proceed to the allogenic hematopoietic stem cell transplantation.

However, the treatment options would actually be much more varied. Fludarabine, cytarabine and idarubicine can be effective regimen as well. [9] Specifically, one should mention Gemtuzumab ozogamicin (GO) that was approved by FDA in 2017 for the treatment of newly diagnosed CD33-positive AML. Gemtuzumab ozogamicin improves the outcome in patients with AML, the benefit being particularly clear in patients with favourable cytogenetics. The meta-analysis of five randomized trials showed that the addition of GO to induction therapy provides absolute survival benefit of 20,7% in core-binding factor (CBF) AML. [10]

Additional treatment option is represented by tyrosine kinase inhibitors like avapritinib or dasatinib. The addition of dasatinib into frontline therapy and its further administration as a maintenance therapy reduced the relapse rate in KIT-mutated CBF AML to levels comparable to KIT-wt CBF AML. [11,12]

3. Conclusion

t(8;21) is associated with a high remission rate with standard chemotherapy and prolonged survival when high-dose Cytarabine is administered [3]. The prognostic impact of additional molecular and cytogenetic changes is still a matter of debate. This uncertainty is linked mainly to the rarity of the variants. Whereas t(8;21) accounts for approximately 5–10% of AML [1,2], the additional cytogenetic changes are present in 3–4% [4]. As it is unrealistic to conduct a prospective study, the only way to evaluate their impact on the prognosis is to publish case reports or small patient series.

Authors' contributions

Study conception and design: J.N. Acquisition, analysis and interpretation of data: B.B., J.N., J.S., P.K., V.R., I.K/Z. Drafting of manuscript: J.N. All authors read and approved the final manuscript.

Declaration of Competing Interest

The research has been performed in accordance with the Declaration of Helsinki. All data generated or analysed during this study are included in this published article.

The authors declare that they have no competing interests.

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