

De Novo Inversion (16) Acute Myeloid Leukemia in Association with Trisomy 22, Deletion 7q And FLT3 (ITD) Associated with Complete Remission

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Clinical practice points

➤ Acute myeloid leukemia (AML) is a heterogeneous neoplastic disorder characterized by the accumulation of immature myeloid blasts in the bone marrow.

➤ More than 90% of the patients with inv (16)/t (16;16) AML harbor secondary chromosome aberrations and mutations affecting N-RAS, K-RAS, KIT, and FLT3.

➤ 7q deletions represent a more frequent genetic alteration occurring in approximately 10% of CBF-AML cases.

➤ Our case presents an elderly patient who has de novo AML with inv (16) in association with trisomy 22, del 7 and FLT3 (ITD) mutation; this is a rare cytogenetic combination.

➤ Several factors that indicate an unfavorable prognosis were present in our case; however, our case achieved complete response, possibly reflecting that trisomy 22 in association with inv (16) is a dominant favorable prognosis regardless of other risk factors.

Keywords: Inversion 16 AML, Trisomy 22 AML, Deletion 7 AML, FLT3 (ITD)

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Introduction

Acute myeloid leukemia (AML) is a heterogeneous neoplastic disorder characterized by the accumulation of immature myeloid blasts in the bone marrow with or without the involvement of peripheral blood [1]. The recent World Health Organization (WHO) classification of neoplasms divides AML into distinct disease entities on the basis of underlying morphology, cytogenetics, immunophenotype and clinical data [2]. One of the most recurrent cytogenetic abnormalities in AML is inv (16) (p13q22), which is usually associated with acute myelomonocytic leukemia with eosinophilia (AML M4-Eo by the French-American-British classification) [3]. On cytogenetic analysis, inv (16) is detected in approximately 8% of adults diagnosed with AML [4]. More than 90% of patients with inv (16)/t(16;16) AML harbor secondary chromosome aberrations (e.g., trisomy 22) and/or mutations affecting N-RAS, K-RAS, KIT, and FLT3 [5]. 7q deletions represent a more frequent genetic alteration occurring in approximately 10% of CBF-AML cases [6]. We present a case of de novo AML that involved inv (16) associated with trisomy 22, 7q deletion and FLT3 (ITD) mutation.

Case Report

A 72-year old white female patient presented to the hospital with fatigue, malaise, rhinorrhea, cough, and dyspnea with exertion. She denied having fever, night sweats, weight loss, decreased appetite, or bleeding. Her physical examination was unremarkable. Her Complete Blood Count (CBC) revealed a total White Blood Cell (WBC) count of $19.4 \times 10^3/\mu\text{L}$ with 10% circulating blasts, 6% neutrophils, 26% lymphocytes, and 56% monocytes. Her hemoglobin was 6.40 g/dL and hematocrit was 18.4%. The platelet count was $10 \times 10^3/\mu\text{L}$, and reticulocytes measured $0.0178 \times 10^6/\mu\text{L}$. Creatinine was 2.7 mg/dL, lactate dehydrogenase (LDH) was 490 U/L, and uric acid was 13.7 mg/dl. The peripheral blood smear showed dysplastic monocytes, immature monocytes, immature granulocytes, and blasts. Bone marrow aspirate and biopsy showed 100% cellularity with approximately 40% blasts and immature mononuclear cells with

features suggestive of monocytoid differentiation and numerous eosinophils. Flow cytometry analysis of the bone marrow aspirate showed approximately 22% blasts expressing CD45, CD13, CD33, CD117, HLA-DR, CD34 and myeloperoxidase. CD4 and CD7 were faintly expressed, and CD10, TdT, CD19, CD20 were negative in blast population. Based on the clinical presentation and pathologic findings, a diagnosis of acute monoblastic leukemia was made.

Cytogenetic Analysis

A 24-h culture with 2-h mitotic arrest on unstimulated bone marrow cells was applied, and the chromosomes were analyzed using Trypsin-Giemsa (GTG) banding of 20 metaphases at a ~450 band resolution. The karyotype was defined according to the International System for Human Cytogenetic Nomenclature 2009 guidelines [7].

Fluorescence *in Situ* Hybridization

Fluorescence *in Situ* Hybridization (FISH) analysis was done using DNA FISH probes (Abbott Molecular, Inc) specific for the pericentromeric region of chromosome 8, putative tumor suppressor gene regions at 5q31, 7q31, 20q12 and RUNX1T1/RUNX1 [t(8;21)], CBFβ (inv 16), KMT2A (11q23) and PML/RARA [t(15;17)] oncogenes. The FISH analysis targeting *MYC* utilized a dual color probe cocktail with specificity for the 3' and 5' ends of the gene.

Mutation analysis

Genomic DNA was extracted from patient's peripheral blood. Mutation analysis by a combination of PCR and direct sequencing was performed by Integrated Oncology Group at LabCorp. Somatic mutations were analyzed in AML-associated genes CEBPA, NPM1, c-KIT, and FLT3 (both ITD and TKD).

Results

Cytogenetic analysis of GTG banded metaphases revealed 47 XX chromosomes with deletion of 7q22, inversion of 16 (p13q22) and trisomy 22 (**Figure 1**) in all dividing cells. FISH analysis of the patient's bone marrow revealed 96% CBFβ gene rearrangement in nuclei (**Figure 2A**), and the 7q31 deletion was present in 95% of nuclei analyzed (**Figure 2B**). The results for probes targeting 5q, RUNX1T1/RUNX1, KMT2A and RARA/PML were normal. There were no AML-associated mutations detected in CEBPA, c-KIT, NPM1 and FLT3 TKD genes, however, FLT3 ITD was detected. The patient was considered to have a high risk for development of AML. However, given her advanced age and other comorbidities, she was not considered a candidate for allogeneic stem cell transplant.

A remission induction chemotherapy regimen began with a 7+3 regimen that consisted of cytarabine 100 mg/m² intravenous infusion daily on days 1 to 7 and idarubicin 12 mg/m² intravenous infusion daily on days 1 to 3. The patient tolerated the induction therapy well, but she developed some confusion and seizure-like activity that subsided by the end of the cycle. A post-induction bone marrow biopsy on day 14 showed a hypocellular marrow without any evidence of blasts, and a bone marrow biopsy from

day 28 showed 65% cellularity with trilineage hematopoiesis without detectable blasts by morphology and flow cytometry.

Because of the patient's neurological symptoms during the induction treatment and her advanced age, she received three cycles of consolidation with a 5+2 regimen, consisting of cytarabine 100 mg/m² intravenous infusion daily on days 1 to 5 and idarubicin 12 mg/m² intravenous infusion daily on days 1 and 2. She tolerated the consolidation therapy well with hematological recovery and has remained in remission to date.

Discussion

AML is more commonly found in older patients [8,9]. SEER data indicate a median age at diagnosis of 66 years [8]. The prognosis with AML worsens as the age of the patient increases [10-12]. Based on the current WHO classification system, more than two-thirds [13] of cases of AML can be categorized on the basis of their underlying cytogenetic or molecular genetic abnormalities [14]. In a retrospective study of 35 elderly patients with AML who received intensive chemotherapy, there were 17 cases of remission after induction chemotherapy. Treatment-related mortality occurred at a rate of 22.9%, and the median overall survival (OS) was 7.9 months. Multivariate analysis indicated that significant prognostic factors for OS included performance status, platelet count, blast count, cytogenetic risk category, and intensive chemotherapy. Subgroup analysis showed that intensive chemotherapy was markedly effective in the relatively younger patients (65-70 years) and those with *de novo* AML, better-to-intermediate cytogenetic risk, and normal albumin levels [15]. In a retrospective study, the role of induction and consolidation therapy in patients over the age of 60 showed median OS 11 months with complete remission rate of 58.3%, and treatment-related death was 15.4%. Successful induction was related to good performance. Mortality correlated with failure to achieve Complete Remission (CR). In CR patients, poor karyotype and absence of consolidation correlated with mortality. More than one cycle of consolidation was associated with better OS. Intensive induction in patients with good performance and less than one cycle of consolidation after CR may be the best strategy for improving OS in elderly AML patients [16].

For patients with *de novo* AML, the best clinical approach is the classic cytogenetic analysis including FISH to categorize patients into specific risk groups. Inv (16), detected in approximately 8% of adults diagnosed with AML [4], leads to fusion of the core-binding factor subunit (CBFβ, PEBP2B) gene on chromosomal band 16q22 with the smooth muscle myosin heavy chain (MYH11) gene on 16p13 [17]. Secondary chromosomal aberrations are present in 35% to 40% of inv (16) AML cases, with trisomy 22 representing the most frequent abnormality [18-20]. Trisomy 22 is a favorable prognostic factor for relapse free survival in AML with inv (16) [5]. Trisomy 22 occurs in 18% of patients with inv (16) AML [5]; 7q deletions occur in 10% [6]; and the FLT3 (ITD) mutation occurs in 5% [5]. A study from MD Anderson Cancer Center showed that FLT3-ITD and FLT3-TKD mutations as a group conferred inferior progression-free survival in inv (16) AML [21]. In general AML patients with the FLT3/ITD mutation have shorter remission duration and shorter OS [22]. However the 7q deletion did not

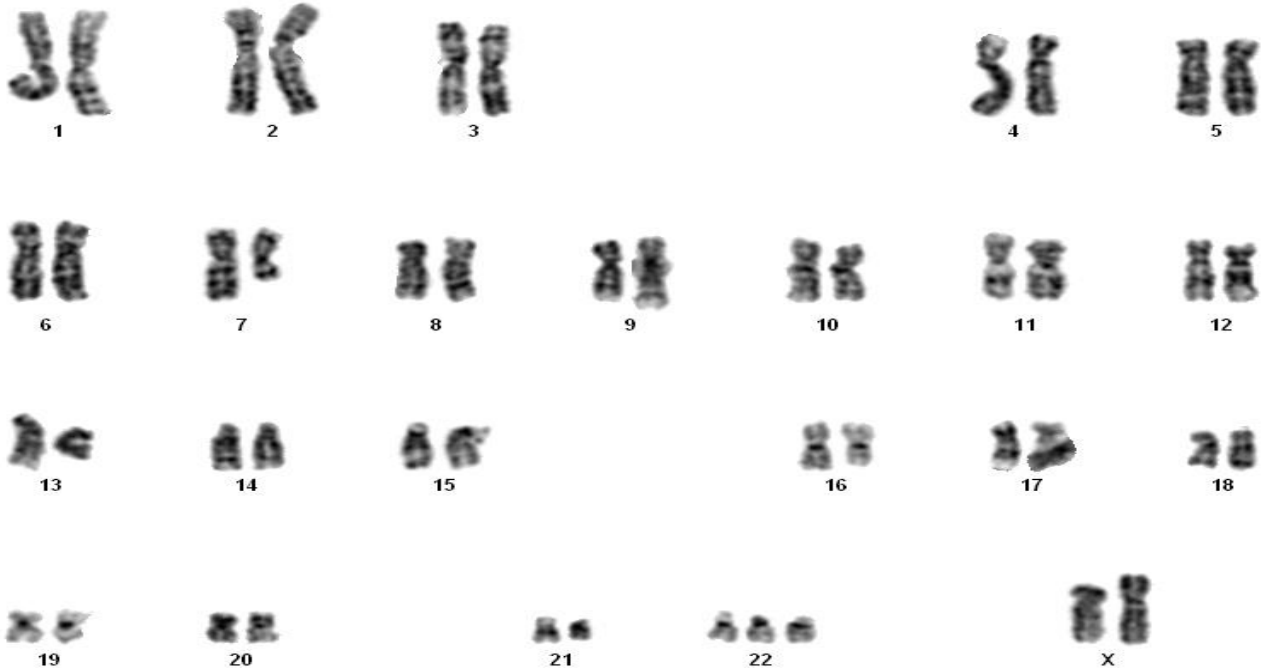


Figure 1 Cytogenetic analysis revealed 47, XX with deletion of 7q22, inversion of 16 (p13q22) and trisomy 22.

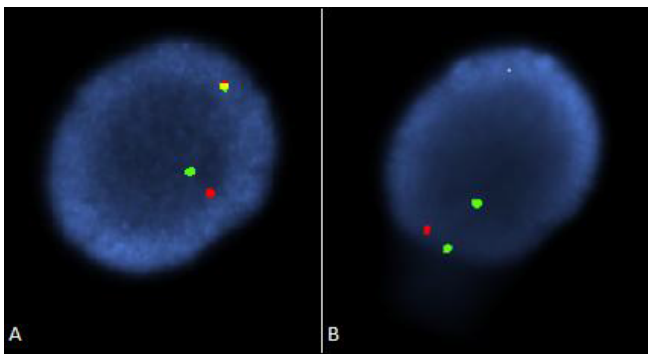


Figure 2 (2A) A metaphase FISH image where there is inversion chromosome 16. (2B) A metaphase FISH image, where it demonstrates 7q31 deletion.

show any effect on the relapse free survival, complete remission or OS [5]. Identification of secondary chromosomal aberrations and gene mutations in inv (16) AML are important to determine favorable and unfavorable prognosis [5].

Our case presents an elderly patient with *de novo* AML who had inv (16) in association with trisomy 22, del 7q and FLT3 (ITD) mutation. Following intensive chemotherapy the patient achieved complete remission. It is difficult to predict the effect of this complex cytogenetic abnormalities on clinical outcomes.

Conclusion

We present the case of an elderly patient with inv (16) AML in association with trisomy 22, del 7q, and FLT3 (ITD) mutation, which is rare a presentation. Although there were several factors that showed unfavorable prognosis in this case presentation, achieving complete response might reflect that trisomy 22 in association with inv (16) confers a dominant favorable prognosis regardless of other risk factors. Although our patient responded well to therapy and remained in remission at 16 months of follow-up, long-term follow-up is needed to accurately assess the prognostic significance of trisomy 22 in inv (16) AML.

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