Case Report

A novel 11;18 translocation in a case of acute myeloid leukemia with maturation

Sandhya Devi G., Faiq Ahmed, Kavita Khadke, Sudha S. Murthy, Senthil J. Rajappa[1]

Departments of Laboratory Medicine, [1]Medical Oncology, Basavatarakam Indo American Cancer Hospital and Research Institute, Hyderabad, India

Acute myeloid leukemia with maturation (AML-M2) is associated with the 8;21 translocation. For the first time in an adult patient with AML-M2, a novel unbalanced translocation involving the short arm of chromosome 11 and long arm of chromosome18 with new breakpoints is presented. CD82 on band 11p11.2 and GATA 6 on 18q11.2 may play a role in the pathogenesis of de novo AML M2. The report with translocation (11;18)(p11.2;q11.2), as the sole cytogenetic abnormality provides more data on the leukemogenesis of de novo AML M2.

Key words: Acute myeloid leukemia with maturation 2, CD82, chromosomal abnormality, GATA6, immunophenotyping, translocation 11;18

Introduction

Acute myeloid leukemia (AML) is a heterogeneous malignancy with varied clinico pathological presentation associated with several molecular genetic aberrations underlying the pathogenesis.[1,2] The 2009 WHO classification of tumors of the hematopoietic and lymphoid neoplasms uses genetic findings in addition to morphologic, immunophenotypic, and clinical features to define distinct subtypes of AML. Cytogenetic analysis is a key component to the evaluation of all patients with newly diagnosed or suspected acute myeloid leukemia.[3] Most AML have specific non-random, clonal chromosomal abnormalities associated with morphologically and clinically distinct subsets of the disease such as the well known 8;21 translocation in AML M2, 15;17 translocation in acute promyelocytic leukemia-M3 etc., with prognostic, and therapeutic importance.[1,4] Here we report a case of AML-M2 having a unique chromosomal abnormality the 11;18 translocation with new breakpoints.

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Case Report

A 42-year-old male was admitted with complaints of shortness of breath, cough and generalized weakness since 15 days. The abdomen, cardiovascular and central nervous system were unremarkable. The patient was a known diabetic and hypertensive on regular treatment. On examination, the patient was pale. There was no lymphadenopathy or petechia. He was tachypnoeic and had features suggestive of pneumonia.

Complete blood picture revealed low hemoglobin of 8.3 gm/dl, total leucocyte count of 37.1 $\times$ $10^3/\mu l$ and platelet count of 22 $\times$ $10^3/\mu l$. Peripheral smear showed anisocytosis, leukocytosis and prominence of blasts (64%). These were 3-4 times the size of mature lymphocytes with moderate amount of cytoplasm. Few of them showed Auer rods. The nuclei showed 2-3 nucleoli. Platelets were moderately reduced. No dysplasia was noted in the background myeloid series [Figure 1].

Bone marrow aspirate was particulate with increased cellularity. Blasts accounted for 84% of the marrow nucleated cells with maturing myeloid precursors.

Address for correspondence: Dr. G. Sandhya Devi, Department of Laboratory Medicine, Basavatarakam Indo American Cancer Hospital and Research Institute, Rd No 14, Banjara Hills, Hyderabad - 500 034, India. E-mail: sandhyag@induscancer.com

Erythroid precursors and megakaryocytes were markedly reduced. Myeloperoxidase (MPO) positivity was seen in 15% blasts [Figure 2]. The cells were negative for PAS and ANAE.

Immunophenotyping was done on peripheral blood using lyse/wash technique and was acquired on dual-laser four-color FACS Calibur (Becton Dickinson, San Jose, CA, USA). The results were analyzed using the Cell Quest software utilizing both forward scatter/side scatter and CD45/side scatter gating strategies. The gated population of cells showed bright positivity for HLA-DR, moderate positivity for CD34, CD33, dim to moderate positivity for CD117, CD13. The neoplastic cells were negative for CD10, CD19, CD7, CD22, CD5, CD7, CD2, CD5, CD14, CD56 [Figure 3].

Direct and 24 h unstimulated cultures of bone marrow were set up in RPMI 1640 medium containing 15% FBS followed by GTG banding. Chromosomal abnormalities were analyzed in 20 metaphases using Olympus B×41and images captured and karyotyped using Applied Spectral Imaging Ltd Software, Migdal Hatmek, Israel, according to ISCN. Clonal chromosomal abnormality was considered when 2 cells had a gain of a chromosome or a structural abnormality and 3 cells had a loss of chromosome. The karyotype was abnormal with a gain of chromosome 6 and a translocation between the short arm of chromosome 11 and long arm of chromosome 18 between the regions p11.2 and q11.2. The karyotype was 46,XY,+6,t(11;18)(p11.2;q11.2) [Figure 4].

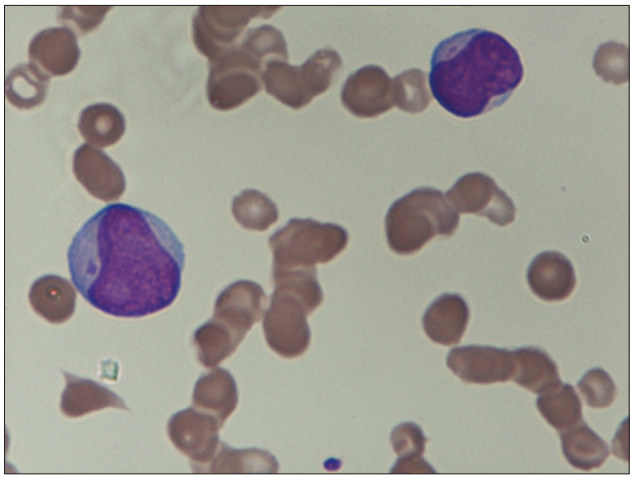

Figure 1: Peripheral smear of an AML-M2 case showing blast with Auer rods

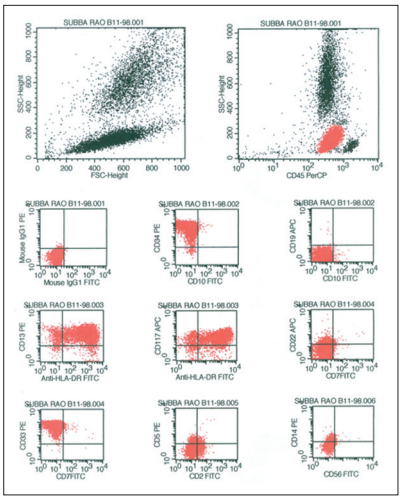

Figure 3: Scatter plots on immunophenotyping - the gated population of neoplastic cells showed bright positivity for HLA-DR, moderate positivity for CD34, CD33, dim to moderate for CD117, CD13 negativity for CD10, CD19, CD7, CD22, CD5, CD2, CD14, CD56

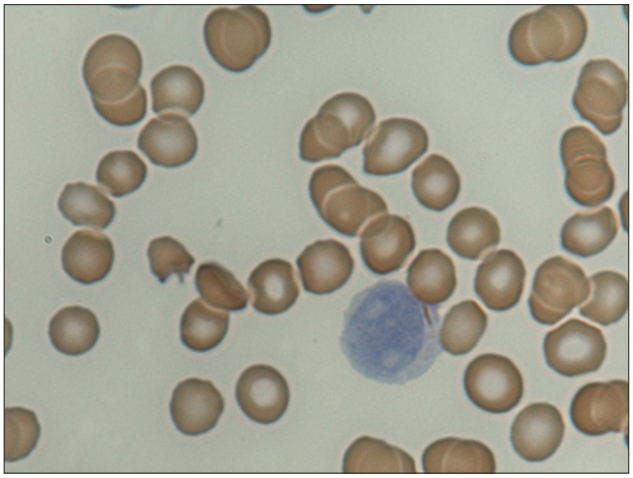

Figure 2: Myeloperoxidase highlighting Auer rods within the blast

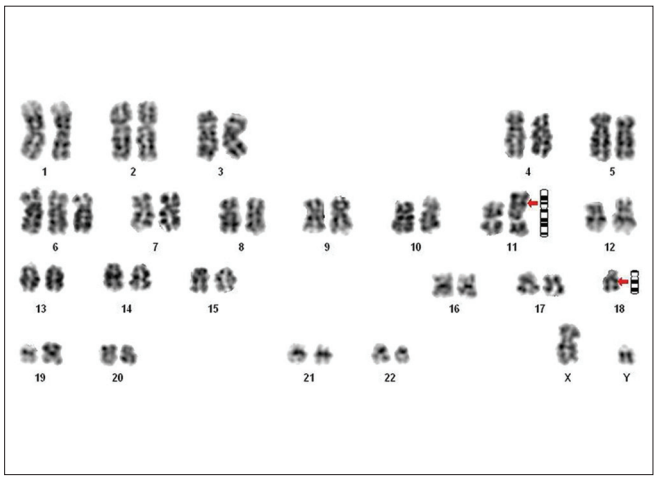

Figure 4: Karyotype of AML M2 case showing 46,XY,+6,t(11;18)(p11.2;q11.2)

The morphology and immunophenotypic features were consistent with the final diagnosis of acute myeloid leukemia with maturation (AML-M2), however with a new translocation having the karyotype 46,XY,+6,t(11;18)(p11.2;q11.2).

Discussion

Age, WBC counts, morphology and pretreatment cytogenetic abnormalities, are predictive of induction success, cumulative incidence of relapse and overall survival in adult patients with de novo adult leukemia. Favorable prognosis is associated with the presence of Auer rods in M1-M4 and M2-M4Eo and adults with translocation 8;21.[1,2,4]

Abnormal karyotypes have been described in 50 % of adult AML and include loss or deletion of chromosme 5/7, gain of chromosome 8, t(9;22)(q34;q11.2),11q23,11p15 or p15.5 translocations, inversion 11[1] partial tandem duplication of the MLL gene in 6-11%, normal cytogenetics, with either FLT3, NPM1, CEBPA, N Ras, K Ras, HRas mutations.[1,3,4] 8;21 translocation with breakpoint at q22;q22 has been reported in 18% of all cases of AML with cytogenetic abnormalities,[4] approximately in 6% adults with AML with maturation.[1,5] The translocation results in fusion of AML1–ETO gene that alters transcriptional regulation and reduces apoptosis.[6] Leukemic blasts show prominent Auer rods, strong myeloperoxidase positivity, homogenous salmon colored granules, cytoplasmic vacuolization, and prominent bone marrow eosinophilia.[4] Flow cytometric analysis shows the expression of myeloid associated markers CD13, CD33, CD117, CD34, HLA-DR and cytoplasmic MPO.[1,4] Other abnormalities described in AML M2 include translocations t(6;9)(p23;q34), t(2;9)(q14;p12), t(5;11)(q35;q13), t(10;11)(p13;q14), t(8;9)(p22;q13), t(8;16)(p11;q13), del12,(p11→p13) and various complex translocations.[1,4]

11;18 translocation has been described in marginal zone B-cell lymphoma-extranodal mucosa-associated type. The juxtaposition of genes BIRC3(AP12) at 11q21and MALT1(18q21) on translocation results in increased activation of NF-kappa B leading to the genesis of lymphoma.[7]

Evidences indicate the occurrence of breakpoints on chromosome 11 at 11q23 and 11p15 or 11p15.5.[1] Review of morphology and immunophenotype of the present case was consistent with the diagnosis of AML-M2, however with a novel 11;18 translocation with new breakpoints at 11p11.2 and 18q11.2 described for the first time. These break points are different from the breakpoints described in 11;18 translocation at 11q21 and 18q21 in marginal zone lymphoma.[7] This report may provide insight on a new abnormality in leukemogenesis of AML-M2.

Continuous characterization of new numerical and structural chromosomal abnormalities, identification of the breakpoints and genes involved has contributed to the understanding of the molecular pathogenesis of leukemogenesis. The rearranged genes are known to encode tyrosine kinases or transcription factors or other proteins that impair the regulation of cell cycle and apoptosis and there by the hematopoietic system.[2] With reference to the present case CD82 gene located on 11p11.2[8] and GATA binding protein 6 (GATA 6) gene mapped to chromosome 18q11.2[9] may be involved in the causation of AML-M2. Both CD82 and GATA6 have been implicated in the causation of many solid tumors.[8,9] Reduced gene expression, gene deletions, mutations, mislocalization of the transcriptional factor (GATA6) and other epigenetic mechanisms contribute to tumorigenecity.[9] However, the underlying mechanism in the causation of hematopoietic neoplasm visa acute myeloid leukemia by these genes is not known.

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