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Co-Expression of RUNX1-RUNX1T1 and CBFB-MYH11 Transcripts in a De Novo Acute Myeloid Leukemia: a First Case Report

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ABSTRACT

Acute Myeloid Leukemia (AML) with recurrent t(8;21)(q22;q22) and inv16(p13q22) genetic abnormalities are termed as Core Binding Factor (CBF)-AML. CBF genetic abnormalities are usually mutually exclusive.

Here, we report a case of an 11-year-old patient diagnosed with a de novo acute myeloid leukemia AML4-eos according to WHO classification. Cytogenetic approaches revealed association of inv(16) and t(8;21)(q22;q22). Molecular testing confirmed the presence of both RUNX1-RUNX1T1 and CBFb-MYH11 fusion genes.

Even though the CBF-AML have usually a good prognosis, it was not the case with our patient. After successful chemotherapeutic treatment the patient experienced a relapse and died one year after initial diagnosis.

To the best of our knowledge, a comparable AML associated with coexistence of RUNX1-RUNX1T1 and CBFB-MYH11 at diagnosis as the primary tumor was not previously reported. Thus, the combination of the here seen fusion genes seems to indicate an adverse prognosis.

Keywords: Acute myeloid leukemia; Core binding factor; RUNX1-RUNX1T1; CBFB-MYH11

INTRODUCTION

Acute Myeloid Leukemia (AML) is characterized by a block in early progenitor differentiation leading to accumulation of immature, highly proliferative leukemic stem cells in bone marrow and blood [1]. The prognostic and therapeutic significance of Karyotype at diagnosis in Patients with AML is now fully established. Two of the most common recurring cytogenetic abnormalities in AML are t(8;21)(q22;q22) and the pericentric inversion of chromosome 16, inv16(p13;q22) or its variant t(16;16)(p13;q22) [2].

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In both subtypes, the cytogenetic rearrangements disrupt genes that encode alpha and beta subunits of core binding factor, a transcription factor that functions as an essential regulator of normal hematopoiesis and myeloid differentiation. t(8;21)(q22;q22) and inv(16)(p13q22) create respectively, the RUNX1-RUNX1T1 and CBFB-MYH11 fusion genes [3]. The RUNX1-RUNX1T1 chimeric protein contributes to leukemogenesis primarily by disrupting normal hematopoiesis via its constitutive transcriptional activity, which increases the capacity of hematopoietic precursors for self-renewal and decelerates their terminal differentiation. CBFB-MYH11 disrupts hematopoiesis because it gathers corepressor complexes, resulting in recruitment of Histone Deacetylase activity and silence of gene function, and sequesters RUNX1 protein in the cytoplasm [3].

CBF genetic abnormalities are usually mutually exclusive. The presence of two chromosome changes in the same leukemic clone of CBF-AML is very rare [4]. Here we report an unusual case with the rare simultaneous presence of inv(16) and t(8;21)(q22;q22) in a morphologically and immunologically typical AML-M4 Eo de novo.

CASE REPORT

An 11-year-old boy without any known adverse medical background was admitted to the hospital in December 2014 with asthenia and a 38.5°C fever. Physical examination showed a tonsillar hypertrophy, splenomegaly 4 cm from the costal margin, normal testicular and neurological examinations. Routine blood examination revealed a severe non-regenerative macrocytic anemia with a Hemoglobin (Hb) level at 3.2 g/dL, White Blood Cell count (WBC) 53 × 109/L with 76% blasts and platelets (PLT) 57 × 109/L.

The bone marrow examination concluded AML FAB type M4 Eo. The karyotype showed t(8 ;21)(q22;q22) and inv(16). Molecular biology confirmed the presence of both RUNX1-RUNX1T1 and CBFb-MYH11 fusion genes.

The patient was given standard treatment for AML including (3+7) induction chemotherapy with meningeal prophylaxis. A complete remission was achieved.

A molecular control of RUNX1-RUNX1T1 and CBFB-MYH11 fusion genes, carried out in July 2015, was negative.

Three months later the patient relapsed, clinical examination revealed peripheral facial paralysis of the left sixth nerve with positive Charles Bell signs and left hypoacusis. The ocular fundus showed stage I papilledema.

The neurological examination was normal and Magnetic Resonance Imaging (MRI) showed a tumor localization of the sphenoid bone extended to the cavum, parapharyngeal space, endocerebral extension, involvement of the 2 petrous bones and bilateral cerebellar epidural involvement, leptomeningeal dissemination at the level of the 2 acoustico-facial bundles localization at the level of the right maxillary sinus.

Routine blood examination showed: WBC 3.5 × 109/L, blasts 27%, Hb 9.6 g/dl and PLT at 6.7 × 109/L.

Thus the diagnosis of a meningeal and medullary relapse was made. The patient received a palliative treatment with high-dose corticosteroids, radiotherapy of the brain for 15 sessions between 2 November 2015 and November 20, 2015 at a rate of 2 Gy per session.

The evolution was marked by the aggravation of the cytopenias of the bone and cerebral pains resulting in death after 3 months.

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DISCUSSION

Core-Binding Factor (CBF) acute myeloid leukemia encompasses AML with inv(16) and AML with t(8;21)(q22;q22). CBF AML are categorized as favorable risk AML within the 2017 European Leukemia Net (ELN) genetic risk stratification [5].

Core binding factor is a heterodimeric transcription factor complex that consists of 3 distinct DNA-binding CBFa subunits (RUNX1, RUNX2, and RUNX3), and a common CBFb subunit. RUNX1 was the first CBF gene to be isolated and has been known by a number of names including AML1, PEBPA2B, and CBFA2. The most commonly used name in the literature is AML1. It was renamed as Runt-related transcription factor 1 (RUNX1) by The Human Genome Organization [6].

CBFb and RUNX1 form heterodimers and together bind the consensus TGTGGT DNA sequence and regulate gene expression. RUNX1 protein contains a conserved RUNT Homology Domain (RHD) responsible for binding DNA and CBFb [6]. CBFb does not interact directly with DNA, but allosterically stabilizes the RUNX1-DNA interaction [7] and protects RUNX1 subunit from proteolysis. Both RUNX1 and CBFb are master regulators of definitive hematopoiesis [8].

Two specific cytogenetic types of AML, t(8;21)(q22;q22) and inv(16)(p13q22) or t(16;16)(p13;q22), are called core-binding factor (CBF) AML [9].

The chromosomal aberration t(8;21)(q22;q22) results in the fusion of RUNX1 on 21q22 with RUNX1T1 on 8q22, creating a chimeric fusion gene, RUNX1-RUNX1T1 [10]. The t(8;21)(q22;q22) occurs predominantly in patients under the age of 50. It is seen in about 10% of FAB-M2 AML [11].

The aberrations inv(16) and t(16;16) lead to fusion of CBFb on 16q22 with smooth muscle myosin heavy-chain gene (MYH11) on 16q13, leading to formation of CBFB-MYH11 chimeric gene [12]. The inv(16) is a highly specific marker for FAB-M4Eo. It is seen in about 20% of M4 cases in which there is an increased percentage of abnormal, immature eosinophils in the bone marrow [13].

The t(8;21) and inv(16) subtypes of AML have been usually grouped and reported together in clinical studies because of shown similarities between their molecular and prognostic features [9].

However, more recent studies have demonstrated genetic, clinical, and prognostic differences, supporting the notion that they represent 2 distinct biologic and clinical entities [3].

Here we report a case of an 11-year-old patient diagnosed with a de novo acute myeloid leukemia. At diagnosis, our patient's leukemic clone bore the clinical and morphologic features of AML of the FAB-M4Eo. Cytogenetic analysis showed the presence of both t(8 ;21)(q22;q22) and inv(16). Molecular biology confirmed the presence of both RUNX1-RUNX1T1 and CBFB-MYH11 fusion genes.

To the best of our knowledge, this is the first report in the literature describing the co-expression, at diagnosis, of chromosomal aberrations inv(16) and t(8;21)(q22;q22) in a case of AML-M4.

Battaglia et al. [14] reported a close similar case of a 17-year-old woman with acute myeloid leukemia. Cytogenetic studies of bone marrow metaphases revealed a leukemic clone with the t(8;21)(q22;q22) characteristic of FAB-M2

[14]. The patient was treated and achieved transient remissions. On relapse, her leukemic clone had acquired, in addition to the t(8;21)(q22;q22), the inv(16)(p13q22) characteristic of FAB-M4Eo and a 5q- of the type seen in various acute myeloid leukemias and myelodysplastic syndromes. The patient achieved two further transient remissions, then relapsed and died 21 months after presentation with soft tissue masses, peripheral blast cells, and overwhelming infection [14].

Therefore, Shao et al. [15] reported a case of AML with RUNX1-RUNX1T1 that transitioned to AML with CBFB-MYH11 following autologous peripheral blood stem cell transplantation [15].

The co-expression of translocation t(15;17) and t(8;21) was more common in the literature [16].

While LAM CBF are reputed to have a good prognosis, 25% to 58% of relapse incidences are reported in patients with CBF-AMLs [17].

Moreover, the concomitant occurrence of the 2 anomalies RUNX1-RUNX1T1 and CBFB-MYH11 seems to be associated with a pejorative prognosis as evidenced by our case and that reported by Battaglia et al. [14]. In fact, our patient had a short duration of first remission (three months) and died three months after relapse.

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