Case Report

Acute Myeloid Leukemia with t(11;17)(q23;q21)

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Received: July 14, 2015; Accepted: August 10, 2015; Published: August 12, 2015

Abstract

Acute promyelocytic leukemia (APL) is characterized by the presence of t(15;17), which generates the PML-RARα transcript and by a good response to treatment with retinoids; However, in some variant types as APL with t(11;17) this benefit is not well established. We present the case of a patient who received chemotherapy associated with acid trans-retinoic (ATRA) who achieved complete molecular response and a long term follow-up survival.

Keywords: APL; PLZF-RARα

Introduction

Acute myeloid leukemia with t(11;17)(q23;q21) is a variant of APL, with morphologic characteristics that differentiate from the classic form and in which there is little experience of treatment.

Case Presentation

A woman of 49 years old, diagnosed with rheumatoid arthritis in January 2011 and undergone to treatment with corticosteroids, methotrexate and hydroxychloroquine was controlled since March 2012 by leukopenia.

On May 31st of 2012 she consulted for presenting anemia (Hb: 97 g/L), leukopenia (1.16 x 10^9/L) and neutropenia (0.2 x 10^9/L), attributed to the treatment with methotrexate, which was suspended and instead, a dose of granulocyte colony stimulating factors (G-CSF) was given to the patient; 24 hours later she developed abdominal pain, nausea, vomiets, hematuria and oliguria. Three days later she failed on a relevant renal insufficiency (creatinine: 7.6 mg/dl), deeper anemia and thrombocytopenia. She was treated with hemodialysis, transfusions of red blood cells and platelets and steroids. Nine days later she transferred to our hospital with suspicion Thrombotic Thrombocitopenic Purpura, so that dialysis and plasma transfusions was rebooted.

Physical examination, abdominal ultrasonography and renal Doppler, showed no abnormalities.

Biochemical profile: Urea: 145 mg/dL (10-50), Creatinine: 4.61 mg/dL (0.1-1.1), LDH: 422 u/L (26-245) and rest of parameters were within normal limits.

Blood test revealed: Hb: 82 g/L, MCV: 94.6 fl, WBC: 7.9 x 10^9/L (52% of cells in medium size, round nucleus and pseudo-pelger with wide cytoplasm and fine granulation), Platelets: 92 x 10^9/L (Figure 1). Erythrocyte morphology: 2 schistocytes/1000 erythrocytes (Figures 1, 2).

Coagulation test: Kaolin cephalin clotting time: 32” (24-35), Prothrombin activity: 66% (70-120), Fibrinogen: 236 mg/dL (200-400), D-dimers: 11880 ng/mL (0-500), Fibrin monomers: absent.

Bone marrow aspiration (BMA) showed a hypercellular image, with 71% of cells similar as the peripheral blood; no faggot cells or Auer rods were seen and reaction with peroxidase was strong. (Figure 3-9).

Immunophenotyping: these cells were: CD45 +, MPO +, CD13 +, CD33 +, CD117 +, DR-, CD34 -, CD56 -, CD11c +, CD32 +, CD64 -, CD38 +, CD11b-, CD16-, CD14-, CD4- (Figure 10).
The cytogenetics and molecular studies on BM were:

- **Rearrangement PML-RARα** (q21; q22) t(15;17) (RT-PCR): negative.

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**Figure 3**: Bone marrow aspirate which shows an hypercellular and monomorphic image, constituted by a blast population of medium size, with a round eccentric nucleus and a large cytoplasm with fine granulation, without Auer rods (MGGx200).

**Figure 4**: Bone marrow aspirate: blasts (MGGx1000).

**Figure 5**: Bone marrow aspirate: granular blasts with presence of blebs in their outline (MGGx1000).

**Figure 6**: Bone marrow aspirate: blasts with a mature appearance nucleus and great fragility (MGGx1000).

**Figure 7**: Bone marrow aspirate: blasts and an erythroblast with lackluster chromatin (MGGx1000).

**Figure 8**: Bone marrow aspirate: blast with blebs and probably degranulated cells (MGGx1000).

**Figure 9**: Bone marrow aspirate: strong myeloperoxidase activity (Px1000).

**Figure 10**: Immunophenotype on bone marrow: the blast population was characterized by markers CD45 +, CD13, CD33 +, CD117 + DR - CD56 + CD11c +, CD32 +, CD64 +, CD38 +, MPO +, CD34-, CD11b-, CD16-, CD14-. 
• **FISH:** nucish 15q22 (PMLx2), 17q21 (RARax3) [23/100] (Figure 11).

• **Karyotype:** 46, XX, del(5)(q13q31), t(11;17)(q23;q21) [20/30] / 46, XX [10/30] (Figure 12).

• **Rearrangement PLZF-RARα** positive (RT-PCR) (Figure 13).

• **Rearrangement RARα-PLZF** positive (RT-PCR).

Diagnostic: Acute Promyelocytic Leukemia with variant translocation RARα (WHO classification).

Follow up: on 6/28/2013 the patient began induction chemotherapy (Idarubicin, 12 mg/m²/d on days 1, 3 and 5; ARA-C, 500 mg/m² twice daily on days 1, 3, 5 and 7 and Etoposide, 100 mg/m²/d on days 1 through 3) + ATRA, 45 mg/m²/day divided into 2 doses till achieving complete remission.

BMA on day + 37 post-induction showed a 3% blast cells, residual disease (MRD) by flow cytometry of 0.4% and a karyotype: 46, XX, del(5)(q13q31), t(11;17)(q23;q21) [4/50] / 46, XX [46/50]; and PLZF-RARα rearrangement was positive.

After that treatment of consolidation was started (2 cycles of ARA-C, 500 mg/m² / 12 h, on day 1 to 6; Mitoxantrone 12 mg/m²/d on days 4, 5 and 6 and ATRA, 45 mg/m²/d divided into two doses, on day 1 to 15, after which normalized the karyotype, the MRD: 0.072% and the PLZF-RARα and RARα-PLZF rearrangements were negative.

In February 2013 allogeneic hematopoietic stem cell transplantation (HSCT) obtained from peripheral blood of her sister with myeloablative conditioning was done, without significant adverse events.

**Discussion**

APL is included among leukemias with recurrent cytogenetic anomalies and characterized by translocation t(15;17)(q22;q12) PML-RARα. However, in 10% of cases, this alteration is not detected by cytogenetic techniques, either by technical problems, submicroscopic chromosomal insertions or more complex rearrangements. In spite of this, an accurate diagnosis can be done since the PML-RARα transcript would be positive.

In distinction to, approximately 2% of cases of APL carry a fusion gene alternative to the PML (PLZF with t(11;17)(q23q21), NPM1 with t(5;17), NuMA with t(11;17)(q13q21), FIPIL1 with the t(4;17), BCORSTAT5b, the t(X;17), PRKAR1A with rearrangements of 17q).

The most frequent of all of them is the PLZF (promielocytic zinc finger) [1]; this gene also known as Zbtb16 was described at first time in 1993 in a Chinese patient who suffered an atypical APL; It’s located on chromosome 11q23 among a cluster of family zinc finger genes, coding of proteins with high content of cysteine and histidine that require one or more unions of zinc to stabilize its structure [2]; It has a high capacity repressor of transcription and his expression is very high in stem cells and progenitor, but decreases as cells get mature.

The clinical relevance of these variants of APL is without a doubt the different response to treatment with ATRA and Arsenic Trioxide, due to all of them are sensitive with the exception of carriers of the rearrangements with PLZF and STAB5b genes.

In cases of APL with t(11;17)(q23q21) there is evidence of this resistance both in vivo as in vitro, particularly in those patients who have the reverse rearrangement RARα-PLZF, whose product would play an important role in mediating resistance to ATRA [1,3].

Since 1993 there have been reported 16 cases of patients with this variant translocation [4-7], with a very low incidence in women (14 men versus two women) and frequent coagulopathy (11 patients). t(11;17) was detected in all of them by conventional cytogenetics or by FISH, and molecular assays was positive to the PLZF-RARα and
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