

## Case Report

# Acute Myeloid Leukemia with T(8;16)(P11;P13) and Rapid Clonal Evolution in a Patient with Follicular Lymphoma: A Case Report and Review of Literature

Montoro J<sup>1\*</sup>, Bobillo S<sup>1</sup>, Ortega M<sup>1</sup>, Navarrete M<sup>1</sup>, Gallur L<sup>1</sup>, Palacio C<sup>1</sup>, Blanco A<sup>1</sup> and Vallespi T<sup>1</sup>

<sup>1</sup>Department of Hematology, University hospital Vall d' Hebron, Spain

\*Corresponding author: Montoro J, Department of Hematology, University hospital Vall d' Hebron, 08035, Barcelona, Spain, Tel: 93 2740600; Fax: 93 4894507; Email: mjmontoro@vhebron.net

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## Abstract

We report a case of a 60 year-old woman diagnosed with therapy-related Acute Myeloid Leukemia (AML) t(8;16)(p11;p13) 4 years after receiving chemotherapy for follicular lymphoma. Blasts with monocytic differentiation and erythrophagocytosis were observed, whereas a t(8;16)(p11;p13) was found as the only cytogenetic abnormality. Despite that the patient achieved a complete response after intensive chemotherapy followed by an allogenic stem cell transplantation an early relapse occurred. Interestingly, a clonal evolution was observed at relapse by adding cytogenetic translocation (15;17 (q24;q21) and aberrant chromosome 1. About 150 cases of AML with t(8;16)(p11;p13) and MYST3/CREBBP rearrangement have been reported. This is a rare entity that harbours specific clinical, morphological, molecular, and prognostic features that might make it to be considered a differentiated entity. Finally, to the best of our knowledge, this is the first report on clonal evolution in a case of AML with t(8;16)(p11;p13).

**Keywords:** Acute myeloid leukemia; t(8;16)(p11;p13); MYST3/CREBBP

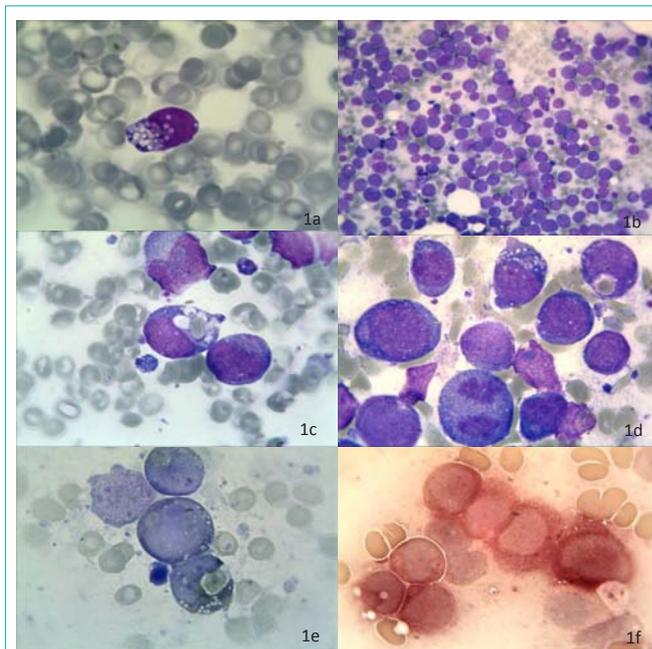
## Introduction

The t(8;16)(p11;p13) is a rare chromosome abnormality found in less than 0.5% of all AML. It has been reported as the *novo* and also associated with previous chemotherapy with a short latency period and poor prognosis. It is characterized by the presence of blasts cells with myelomonocytic and monocytic phenotype and frequent erythrophagocytosis, extramedullary involvement, severe coagulation disorder, and poor response to chemotherapy. Translocation (8;16)(p11;p13) causes fusion of MYST and CREBBP genes, both encoding proteins with histone acetyltransferase activity, that leads to cell differentiation, proliferation and apoptosis. To our knowledge, clonal evolution in AML with t(8;16)(p11;p13) has not been previously described. Herein, we reported a case of therapy-related AML with t(8;16)(p11;p13) that, at relapsed, experienced a clonal evolution. Clinical characteristics and review of the literature are discussed.

## Case Report

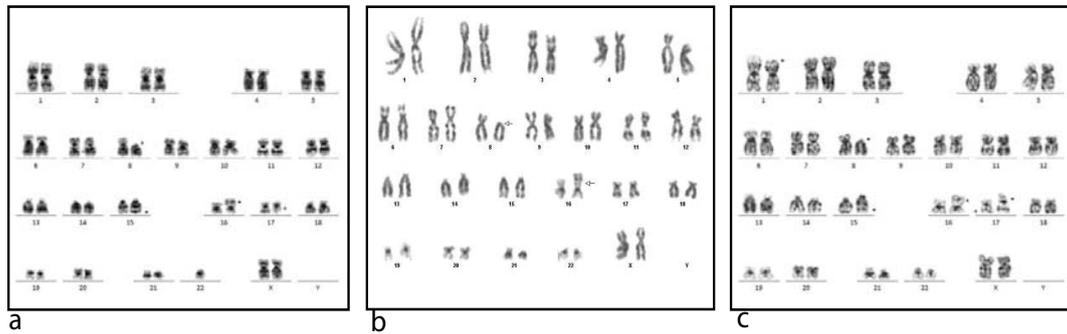
A 60 year-old woman with medical history of follicular lymphoma grade 3b, stage IIIA, FLIPI 3, was admitted in our Department in February 2007. She received chemoimmunotherapy with 6 cycles of standard R-CHOP achieving a complete response. Three years later the lymphoma relapsed with the same histology. She was subsequently treated with 3 cycles of R-ESHAP followed by an autologous peripheral stem cell transplantation conditioned with BEAM (in September 2010, obtaining a very good partial response.

In February 2011 she was admitted due to lower limb pain and fever without evidence of infection or lymphoma relapse. She had large hematomas and nasal spontaneous bleeding. Peripheral blood tests showed hemoglobin 101 g/L, MCV 100 fL, WBC 15.3 x 10<sup>9</sup>/L (neutrophils 46.3 %, lymphocytes 6.7 %, monocytes 10.5%,



**Figure 1:** Morphological features, **Figure 1a:** Peripheral blood blast with cytoplasmic vacuolae, **Figure 1b:** Bone marrow with characteristic blasts infiltration in Giemsa stain, **Figure 1c:** Bone marrow blast with cytoplasmic vacuoles in Giemsa stain, **Figure 1d:** Bone marrow blast with erythrophagocytosis images, **Figure 1e:** Bone marrow blast with myeloperoxidase stain, **Figure 1f:** Bone marrow blast with butyrate esterase reaction.

blast cells 35.2 %), platelet count 18.8 x 10<sup>9</sup>/L, serum LDH 6,009 IU/L, prothrombin time 65%, partial thromboplastin time 42 sec., fibrinogen 0.8 g/L, D-dimer >5000 ng/mL. A bone marrow aspirate



**Figure 2:** Modal karyotype (clonal evolution), **Figure 2a:** Karyotype at diagnosis 46,XX, t(8;16)(p11;p13) [20]. **Figure 2b:** Karyotype at first relapse 46,XX, t(8;16)(p11;p13),t(15;17)(q24;q21) [4]/46,XX[16]. **Figure 2c:** Karyotype after a second cycle of 5-azacitidine 46,XX, t(8;16)(p11;p13) [1]/46,XX, (1;17)(p36;p13),t(8;16)(p11;p13) t(15;17)(q24;q21) [19].

showed infiltration by 86% of monocytic blasts with abundant blue-gray cytoplasm with azurophilic granules and vacuoles, folded nuclei, and prominent nucleoli (Figure 1). Myeloperoxidase stain was positive in 96% of blasts, whereas 86% were dual esterase reaction positive as well. Eritrophagocytosis was present in a large number of blasts. Flow cytometry study showed a CD34 negative blast population with expression of myeloperoxidase and myelomonocytic markers (CD4, CD11b, CD15, CD33 and CD64). Modal karyotype was 46,XX, t(8;16)(p11;p13) as a sole abnormality in all metaphases analyzed (Figure 2). MYST/CREBBP fusion transcript was detected by RT-PCR. Molecular assays for CBFA/MYH11, RUNX1/RUNX1T1, NPM1 mutation, FLT3 mutation, MLLr and CEBPA were negative. She was diagnosed with therapy-related AML according to World Health Organization Classification. She received induction chemotherapy with cytarabine 100 mg/m<sup>2</sup> days 1 to 7, idarubicine 10 mg/m<sup>2</sup> days 1,3 and 5, and etoposide 100 mg/m<sup>2</sup> days 1 to 3, achieving complete remission. As this was considered a high-risk AML, one cycle of 5-Azacitidine (75 mg/m<sup>2</sup>/day for 7 days) was given while waiting for the onset of the allogeneic peripheral blood Stem Cell Transplantation (AlloSCT) procedure. In May 2011 an AlloSCT of unrelated donor with reduced intensity conditioning (fludarabine 30 mg/m<sup>2</sup> days -8 to -3 and busulfan 3.2 mg/m<sup>2</sup> days -2 and -1) was performed. One month later she was admitted to the hospital due to diarrhea and cutaneous rash, being diagnosed with a grade 2 Graft Versus Host Disease (GVHD). At the same time, a bone marrow aspirate was performed showing cytological complete remission but with minimal residual disease by flow cytometry of 1.8%. Interestingly, cytogenetic clonal evolution was observed in the karyotype; 46,XX,t(8;16)(p11;p13), t(15;17)(q24;q21)[4]/46,XX[16] karyotype. The PML-RARa rearrangement was not found. In order to control the progression of the disease, she received a second cycle of 5-azacitidine. In August 2011 she complained again of fever and lower limbs pain. Peripheral blood test showed hemoglobin of 78 g/L, platelet count 7 x 10<sup>9</sup>/L and WBC of 1.9 x 10<sup>9</sup>/L (neutrophils 22%, lymphocytes 46%, eosinophils 2%, monocytes 6%, promonocytes 4%, promyelocytes 4%, blast cells 14%) and LDH of 3,152 IU/L. A bone marrow aspirate disclosed leukemia progression with 96% blasts with the same morphological and immunophenotypic characteristics as the ones at diagnosis. The karyotype showed a new clonal evolution adding a chromosome 1p alteration; 46,XX,t(8;16)(p11;p13)[1]/46,XX,t(1;17)(p36;p13),t(8;16)(p11;p13),t(15;17)(q25;q23) [19]. FISH study for p53 deletion was negative. A body CT scan showed lymph nodes stability. The patient

died 2 weeks later due to gastrointestinal bleeding.

## Discussion

The t(8;16)(p11;p13) is a rare chromosome abnormality found in less than 0.5% of adult acute myeloid leukemias. It has been reported as the *novo* and lately it seems that it is heavily associated to previous chemotherapy and/or radiotherapy [1,2]. This abnormality has been described in both sexes and at any age with an increase in childhood [3].

AML with t(8;16)(p11;p13) has several features that allowed it to consider as a single entity in the WHO. Clinically, it presents with frequent extramedullary involvement, specially hepatomegaly, splenomegaly, lymphadenopathies and cutaneous infiltration. In more than 40% of the cases it also presents with coagulation disorders such as disseminated intravascular coagulopathy or primary fibrinolysis, like our patient. Morphologically, prominent erythrophagocytosis and cytoplasmic vacuoles are present almost in the 75% of cases. Furthermore, blasts cells exhibit a myelomonocytic lineage with dual myeloperoxidase and non specific esterase cytochemical staining. It is suspected that this strong positivity to myeloid and monocytic markers is due to a very immature origin of progenitor cell with both potential differentiation, and this could also be related with the resistance to the standard chemotherapy [4]. At the molecular level, the t(8;16)(p11;p13) translocation fuses MOZ (MYST histone acetyltransferase-monocytic leukemia-3) gene, located at 8p11, with CBP (CREB-binding protein), at 16p13, both encoding proteins with histone acetyltransferase activity [5,6]. MYST3 has been shown to modulate gene transcription through activation of the transcription factor complex RUNX1. Moreover, the protein complex MYST3-RUNX1 has been found to increase during normal monocytic differentiation. In its turn, CREBBP protein also regulates transcription by means of histone acetyltransferase activity and by binding to several proteins with key cell cycle functions, such as p53 and nuclear factor nBT. Therefore, an inhibition of RUNX1-mediated transcription by MYST3-CREBBP fusion protein has been hypothesized to be the main mechanism of leukemogenesis in this AML variety [7,8]. However, the precise pathways are mostly unknown. Gene expression profiles of t(8;16) shows high levels of the homeobox genes (HOXA9, and HOXA10), their cofactor MEIS1, and the receptor with tyrosine-kinase activity FLT3, all of the typically up-regulated in MLL-leukemias, another leukemia with very bad

prognosis, leading to the hypothesis of shared pathways in both entities [9].

Prognosis is very poor with a median survival reported less than 6 months. Many patients die in a few days after diagnosis due to coagulopathy or poor condition caused by previous illness that does not avoid intensive chemotherapy treatment [1,4,10]. In those who can receive intention to treat regimens, there is a poor response rate and even in those who respond, an early relapse occurs [11]. Surprisingly, there are described spontaneous remissions [3,12]. In our patient an intensive induction chemotherapy was administered followed by an ASCT as consolidation therapy. Unfortunately, in less than two months progression of the disease arised although she had developed a skin and intestinal acute GVHD. We highlight the rapid clonal evolution of this case at progression with t(15:17) and aberrant chromosome 1 that has not been previously described. At the time of the diagnosis, t(8;16) can appears as a sole abnormality or can be a part of a complex karyotype with no significant differences in survival between these cases and those having t(8;16) with other abnormalities . This clonal progression despite ASCT and GVHD allow us to get a notion about the aggressiveness of this leukemia.

Despite its low incidence, that has not allowed to consider t(8;16)/p11;p13) as an individual entity in 2008 WHO classification, clinical and morphological features make easier to detect cases and afterwards confirming with karyotyping and molecular assays. It is particular very poor prognosis and primary resistant behaviour with standard chemotherapy regimens make these patients essentially candidates for clinical assays with new molecules associated to intensive induction chemotherapy followed by ASCT whenever possible. Due to an expected increase of therapy-related AML we may detect an increase in reported cases in the future and we should be prepared in terms of treatment options.

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