

## Case Report

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# A confirmation of ASXL1 as biological marker of normal cytogenetic acute myeloid leukemia with myelodysplasia-related changes (AML-MRC): A case successfully treated with CPX-351

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### Abstract

We here report the case of a 56 yr old patient affected by acute myeloid leukemia with myelodysplasia related changes (AML-MRC), ASXL1+, successfully transplanted after CPX-351 treatment. Prats-Martin et al. retrospective study identified clinical, cytomorphological, cytogenetic features associated with AML-MRC ASXL1+ such as: higher leukocyte count at diagnosis ( $p=0.005$ ), higher frequency of micro-megakaryocytes ( $p=0.031$ ), with a trend toward a higher presence of megakaryocyte dysplasia ( $\geq 50\%$ ) ( $p=0.071$ ), a lower number of blasts in bone marrow ( $p=0.009$ ) with myelomonocytic/monocytic morphological features ( $p=0.001$ ), absence of cytogenetic abnormalities related to myelodysplasia and TP53 mutations ( $p.035$ ). Up to 56% of patients with AML-MRC, displaying a normal karyotype, were ASXL1+. These morphological and biological patterns are similar to those observed in our patient, suggesting that ASXL1 might be a biological marker of AML-MRC with normal karyotype, when other morphological data are lacking. The prognosis of these patients is very poor in the Prats-Martin cohort, with 3 months median overall survival. In our case CPX-351 allows a successful bridge to transplant, with good tolerance and sufficient control of the disease, 18 months after allogeneic transplant.

**Keywords:** Acute myeloid leukemia; Myelodysplasia related changes; CPX-351; ASXL1; Normal karyotype.

**Abbreviations:** AML-MRC: Acute Myeloid Leukemia with Myelodysplasia Related Changes; CMML: Chronic Myelomonocytic Leukemia; AML-NOS: AML without other Specifications.

### Introduction

AML With Myelodysplasia-Related Changes (AML-MRC) represent 25–34% of all AML cases and are more frequent in elderly patients, with a median age of 73 years [1,2]. AML-MRC have worse prognosis than nonMRC AML with both reduced complete remission rate and overall survival, due to low responsiveness to standard intensive induction chemotherapy regimens,

likely related to both disease biology and patients clinical characteristics [3].

According to the 2016 WHO Classification, the current AML-MRC designation applies to patients with AML who have 20% or more blasts in the blood or bone marrow and who meet any of the following criteria: A history of MDS or MDS/MPN, such as Chronic Myelomonocytic Leukemia (CMML); an MDS-relat-

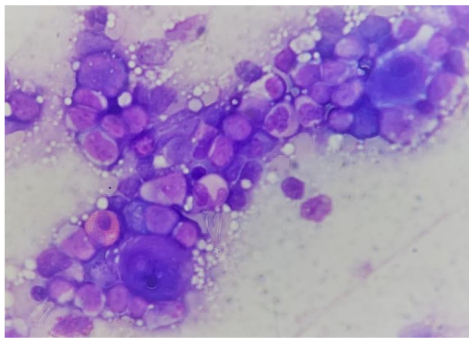
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ed cytogenetic abnormality; or multilineage dysplasia in 50% or more of two or more cell lineages (ie, dysgranulopoiesis, dyserythropoiesis, or dysmegakaryopoiesis; in the absence of NPM1 or biallelic CEBPA mutations (if the diagnosis is based on multilineage dysplasia alone) [4].

In recent years, the use of sequencing gene panels has allowed to evaluate the presence of mutations in myeloid neoplasms and in secondary AML with history of MDS such as ASXL1 (21%-35%), TP53 (22%), RUNX1 (15%-17%), TET2 (15%), IDH1 or IDH2 (25%), DNMT3A (8%-9%), NPM1 (8%), and FLT3 (2%-7%)[5]. In particular ASXL1 loss of function mutations and TP53 mutations showed a poor prognostic significance [6,7].

### Case report

A previously healthy 56-year-old male, with no medical history of interest, was diagnosed with AML after presenting with anaemia (4.4 haemoglobin g/dL), thrombocytopenia (platelets  $11 \times 10^6$  cells/mL), and leucopenia (white blood cells  $2800 \times 10^6$  cells/mL) with peripheral blastosis (14%) and evidence of severe dysgranulopoiesis, anisopoikilocytosis, platelet anisocytosis with giant platelets. Bone marrow cytology showed 50% myelomonocitoid blasts infiltration, with severe dysplasia of all 3 lineages in more than 50% of cells with high number of megakaryocytes (Figure 1); these findings were confirmed by bone marrow histology. Cytogenetic was 46,XY [21], and the patient's mutational analysis was negative for NPM1 and FLT3-ITD and TKD. NGS showed ASXL1 mutation (c.1782C>A) with VAF 45%, associated with NRAS (c. 176>A), GATA2 (c1075T>G) mutations. Extramedullary disease consisted in splenomegaly (20 cm) confirmed at CT scan, neurological symptoms were absent.



**Figure 1:** Megakaryocytic erythroid and myeloid dysplasia in bone marrow aspirate at diagnosis.

Induction with the liposomal daunorubicin and cytarabine formulation, named CPX-351, at the dosage of 44/100 mg/sm was administered with a scheme of three infusions every other day. Table 1 resumes hematological recovery and extrahematological toxicity after CPX-351 and Transplant. A mild hypersensitivity reaction with skin rash was documented after the last administration, resolving spontaneously in few hours. Day +21 bone marrow evaluation showed a CR with Multiparametric Fluorocytometry (MPFC) MRD 2.9% positivity and WT1 overexpression (583.77/10,000ABL copies). Two consolidations, the first on an inpatient and the second on an outpatient basis, were performed at the standard dosage of 29/66 mg/sm at day 1 and 3, with a 10 mg dexamethasone i.v. premedication. We did not

observe any infusional reaction or extrahaematological adverse events. Bone marrow evaluations showed CR with a reduced MPFC MRD positivity after the second consolidation, decreasing from 1.4% to 0.9%, and WT1 normalization (246/10,000 ABL copies). Patient received allogeneic peripheral haematopoietic cells MUD transplant with 11/12 HLA compatibility, and a major ABO incompatibility, after a Busulfan-Fludarabine myeloablative conditioning. The day +30 bone marrow evaluation showed a CR with negative MPFC MRD, a normal peripheral blood WT1 (2.64/10,000 ABL copies), with a mixed chimerism (83.8%) nevertheless a complete lymphoid chimerism (98%) was observed. We therefore decided to rapidly taper cyclosporine and begin pre-emptive treatment with Azacytidine 50 mg/sm/d. s.c. for 5 days from day +45, for 12 courses. At 18 months patient is still in CR, MRD negative without evidence of aGVHD.

### Discussion

Here we illustrated a case of AML-MRC ASXL1 positive (ASXL1+) whose diagnosis was based on assessment of multilineage dysplasia at bone marrow cytology and histology.

It's known that ASXL1 mutations have an higher frequency in AML-MRC than other AML (35% vs 10.8-14.5%) [7-9]. Prats-Martin et al. analysed ASXL1 gene mutations in 61 patients with AML-MRC and 46 controls with AML Without Other Specifications (AML-NOS) confirming the higher frequency of ASXL1 mutations in patients with AML-MRC (31%), compared to control group of patients with AML-NOS (4.3%) [10].

They identified clinical, cytomorphological, cytogenetic features associated with AML-MRC ASXL1+ such as: higher leukocyte count at diagnosis ( $p=0.005$ ), higher frequency of micromegakaryocytes ( $p=0.031$ ) with a trend toward a higher presence of megakaryocyte dysplasia ( $\geq 50\%$ ) ( $p=0.071$ ), a lower number of blasts in bone marrow ( $p=0.009$ ) with myelomonocitic/monocitic morphological features ( $p=0.001$ ), absence of cytogenetic abnormalities related to myelodysplasia and TP53 mutations ( $p.035$ ) [9,6,10]. Up to 56% of patients with AML-MRC, displaying a normal karyotype, were ASXL1+ [10]. This morphological and biological pattern is similar to that observed in our patient, a part from leukocytopenia. Our patient had a normal blood count, at the last evaluation done five years before, and did not report previous symptoms. He had a 50% myelomonocitoid blasts infiltration with trilineage dysplasia, especially megakaryocyte dysplasia, normal karyotype, lack of myelodysplastic related mutations other than ASXL1. This case confirms that ASXL1 mutation might be a biological marker of AML-MRC with normal karyotype, and suggests its possible role in the diagnosis of this entity, when other morphological criteria are lacking.

Similar leukemia is unfortunately characterised by a poor prognosis with a median OS of 1.5 months vs 9 to 12 months in those patients eligible to intensive induction chemotherapy [11-13]. In Prats-Martin retrospective analysis ASXL1+ and ASXL1- AML-MRC showed respectively 100 days vs 362 days median overall survival [10].

In our experience this poor prognosis resulted to be well counteracted by the infusions of CPX-351, which allowed a bridge to allogeneic transplant, with an excellent extrahema-

**Table 1:** Hematological recovery and extrahematological toxicity after CPX-351 and Allogeneic Transplant.

	Induction	1st Consolidation	2nd Consolidation	Allogeneic Transplant**
N >1000 x 10 <sup>6</sup> /ml	+13	+13	+18	+23 (>1500 x10 <sup>6</sup> /ml)
PLT >100.000 x 10 <sup>6</sup> /ml	+31	+20	+21	+28
CPX-351 reaction	Mild rash (30% BSA) after last infusion	None after 10 mg Dexamethasone i.v. premedication	None after 10 mg Dexamethasone i.v. premedication	
Extrahematological toxicity*	Grade III febrile neutropenia (d.+4)			Grade III staphylococcus epidermidis sepsis(d.+10); Grade III oropharyngeal mucositis (only analgesic opioid therapy without total parental nutrition)

\*Extrahematological toxicity graded on the basis of NCI-CTCAE version 5 classification.

\*\*Erytroid transfusional dependence is still ongoing with a median of 6 monthly blood transfusions, probably related to the major ABO incompatibility.

tological tolerance and a satisfactory clearance of the disease. Other standards approaches (3+7) showed a very poor median overall survival of 3 months and CPX-351 have demonstrated an higher transplant rate in all secondary AML patients in phase III studies [14,15]. Further studies are therefore warranted in the extremely unfavorable setting of AML-MRC ASXL1+, aimed both to elucidate the role of ASXL1 in the biological characterization and pathogenesis of this entity and to identify possibly target therapies, able to overcome the detrimental prognosis of this disease.

### Declarations

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**Disclosure of potential conflicts of interest:** Debora Capelli, Diego Menotti, Francesco Saraceni, Alessandro Fiorentini, Attilio Olivieri declare that they have no conflict of interest. Patient gave written informed consent to the treatment of personal data, according to the Declaration of Helsinki and our Institutional Review Board protocol.

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