



## ACUTE MYELOBLASTIC LEUKEMIA AND COMPLEX CYTOGENETIC ABNORMALITIES IN A 16-YEAR OLD ADOLESCENT: A CASE REPORT AND LITERATURE REVIEW

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### ABSTRACT

We present the case of a 16-year-old adolescent with no significant personal or family medical history who developed acute myeloid leukemia (AML) with complex cytogenetic abnormalities. Initially, the patient was treated for prolonged fever and bilateral submandibular lymphadenopathy, with significant pancytopenia and clinical signs suggestive of a hematological disorder. The diagnosis of AML was confirmed by lymph node biopsy, bone marrow examination, and cytogenetic analysis. The patient's evolution required induction chemotherapy, followed by therapeutic intensification and the search for a bone marrow transplant donor. This case highlights the importance of cytogenetic and molecular investigations in the diagnosis and prognosis of pediatric AML.<sup>[1]</sup>

### INTRODUCTION

Acute myeloid leukemia (AML) is a rare hematopoietic malignancy in adolescents. It accounts for 15-20% of acute leukemias in children, with an annual incidence of 7 cases per million children under 15 years, presenting with a complex clinical and biological profile. The average age at diagnosis is 6 years. In 95% of cases, pediatric AML appears de novo. The progression of AML depends heavily on the cytogenetic and molecular abnormalities found in patients, influencing treatment strategies and prognosis. With the development of new diagnostic and therapeutic techniques, the prognosis has significantly improved in recent years, with event-free survival and overall survival rates of 50% and 70%, respectively. Cytogenetic abnormalities are found in 70% of pediatric AML cases, with a complex karyotype present in 10% of de novo pediatric AML cases. Cases with complex cytogenetic abnormalities, such as the one presented here, require tailored management, including intensive chemotherapy and sometimes allogeneic hematopoietic stem cell transplantation.<sup>[2]</sup>

### CASE REPORT

A 16-year-old adolescent, without significant personal or family medical history, presented with prolonged fever and bilateral submandibular lymphadenopathy. The febrile state did not respond to initial antibiotic and

corticosteroid treatment. A complete physical examination revealed no other abnormalities.

The blood count showed severe pancytopenia with anemia of 7.5 g/dL (normochromic normocytic arrythropoietic), leukopenia at 0.320 G/L with neutropenia at 0.110 G/L, and thrombocytopenia at 32 G/L. These results prompted further investigation. A lymph node biopsy showed cellular infiltration with strong expression of CD34, MPO, TDT, and Bcl2 on immunohistochemistry, within the mixed salivary glands, suggesting a myeloid-type blastic tumor proliferation.

The bone marrow examination confirmed the diagnosis of AML, and immunophenotyping of the blasts revealed immature markers (CD34, HLA-DR) as well as monocytic markers (CD33 and MPO). These characteristics confirmed the myeloid nature of the leukemia.

### Results of Complementary Investigations

- **Cytogenetics:** Cytogenetic analysis revealed a complex and hyperdiploid karyotype with clonal chromosomal abnormalities (both numerical and structural), including trisomy of the MLL locus at 11q23. The detailed karyotype was as follows: 56, XY, +6, -7, +8, +8, +10, +11, del(11)(q22)x2, +14, +14, +19, +21, +22, +mar(21)/46, XY (9).

- **FISH (Fluorescence In Situ Hybridization):** The trisomy of the MLL locus was confirmed by FISH, an important prognostic factor in AML.
- **Molecular Profile :** Molecular testing for mutations in the CEBPA, FLT3, and NPM1 genes was negative, excluding mutations commonly associated with AML.

A family history investigation for exposure to ionizing radiation, benzene, or cytotoxic treatments was negative.

### Treatment and Management

The patient received induction chemotherapy according to the ELAM02 protocol, resulting in a partial response after the first treatment phase. After evaluation, therapeutic intensification was implemented, and complete cytological remission was achieved.

However, due to the lack of a compatible geno-identical donor for a bone marrow transplant, the patient was transferred abroad in search of a pheno-identical donor.

### DISCUSSION

AML represents a group of malignant tumor diseases related to abnormal clonal proliferation in the bone marrow, blood, and potentially other organs, of myeloid hematopoietic precursors that are arrested at an early stage of differentiation.<sup>[3]</sup> In children, AML is less frequent than acute lymphoblastic leukemia (ALL) and has a poorer prognosis.<sup>[4]</sup> With the development of intensive chemotherapy protocols and progress in hematopoietic stem cell transplantation, prognosis has improved. Diagnosis, prognosis, choice of treatment protocol, and follow-up depend on morphological, cytochemical, immunophenotypic, cytogenetic, and molecular data. Cytogenetic findings allow stratification of children into a favorable prognosis group, who benefit from conventional chemotherapy, and an intermediate or unfavorable prognosis group, who require additional treatment with geno-identical or pheno-identical allogeneic bone marrow transplantation.<sup>[5]</sup> AML in children tends to respond better to treatment due to the higher frequency of cytogenetic abnormalities associated with a favorable prognosis and better treatment tolerance.<sup>[6]</sup> Although the unfavorable prognosis subgroups are less frequent in children, karyotyping remains an essential examination in the evaluation of AML at diagnosis, as cytogenetic abnormalities are one of the most powerful independent prognostic factors of this disease.<sup>[7]</sup>

This case presents several features worth highlighting. First, the initial diagnosis of AML was delayed due to atypical symptoms (prolonged fever and lymphadenopathy), which led to initial management with antibiotics and corticosteroids. The pancytopenia associated with nonspecific clinical signs was a

determining factor in directing the diagnosis toward a hematological disorder.

The complex cytogenetic abnormalities found in this case, particularly the trisomy of the MLL locus (11q23), are associated with a poor prognosis. These abnormalities may complicate the response to treatment and increase the risk of relapse, making patient management particularly challenging. The ELAM02 protocol, combined with chemotherapy intensification, achieved complete cytological remission, but the long-term prognosis remains uncertain, particularly in the absence of a geno-identical bone marrow transplant donor.

The negative results for CEBPA, FLT3, and NPM1 mutations exclude the mutations typically associated with better treatment response or favorable prognosis, reinforcing the importance of monitoring the patient's evolution.<sup>[8]</sup>

Cytogenetic Subgroups	Fusion Gene or Genes Involved	Frequency in Childhood AML	Median Age (Y) (Range)	Special Features (Age, FAB, Phenotype, Treatment)	Secondary CA	Secondary Molecular Abnormalities	Risk Category	References
<b>BALANCED CA</b>								
<b>APL</b>								
t(15;17)(q24;q21)	PML-RARA	6-10%	12 (1-18)	M3 and M3v, Emergency (DIVC), Specific APL treatment (ATRA, ATO)	tri 8, del(9q), ider(17)(q10)	FLT3-ITD	Favorable	[20,39]
<b>CBF leukemias</b>		20-25%						
t(8;21)(q22;q22)	RUNX1-RUNX1T1	12-15%	8	M2, blasts with single and thin Auer rods, dysgranulopoiesis, CD19+, CD66+	loss of X or Y, del(9q), tri 8, del(7q), tri 4	KIT, RAS, FLT3-TKD, FLT3-TKD, ASXL1/2, RAD21	Favorable	[1,40-43]
inv(16)(p13q22)/t(16;16)(p13;q22)	CBFB-MYH11	5-9%	9	M4eo	tri 22, del(7q), tri 8	KIT, RAS, FLT3-TKD, FLT3-ITD	Favorable	[1,40-43]
11q23/KMT2Ar	KMT2A with multiple partners	16-21%	2.2 (0-18)	M4 and M5, infants	tri 8	High EVI1 expression, few mutations	Adverse or Intermediate	[44-46]
t(9;11)(p22;q23)	KMT2A-AF9(MLL1T3)	6-9%	2.6				Intermediate	[44-46]
t(11;19)(q23;p13.1)	KMT2A-ELL	1-2%	4.6				Intermediate	[44-46]
t(11;19)(q23;p13.3)	KMT2A-ENL(MLL1T1)	1%	7.1				Intermediate	[44-46]
t(10;11)(p12;q23)/ins(10;11)(p12;q23q13)*	KMT2A-AF10(MLL1T1)*	2-3%	1.3				Adverse	[44-46]
t(6;11)(q27;q23)	KMT2A-AF6(MLL1T4)	1-2%	12.4				Adverse	[44-46]
11p15/NUP98r	NUP98 with multiple partners	3-5%	11 (1.3-18)				Adverse	[36,47,48]
t(5;11)(q35;p15)**	NUP98-NSD1	3-4%	10.4 (1.2-19.4)	M4/M5 71-77% of NUP98r 10-16% of NK	tri 8, del(5q), CK	FLT3-ITD, WT1 mut	Adverse	[36,46,47,49-51]
t(11;12)(p15;p13)**	NUP98-KMD5A	1-2%	3.2 (0.01-18.5)	10-30% of NUP98r 34% M7, 10% of M7	CK (numerous numerical and structural CA)	Low frequency of mutations	Adverse	[47,48,52]
12p13 abnormalities	NUP98-KMD5A del(12p) ETV6 (12p13.1)	4%					Adverse	[22,28]
t(7;12)(q36;p13)**	ETV6; MNX1	1%	0.5 y (0.2-2.3)	Only infants (4% of infants)	tri 19	unknown	Adverse	[53]
<b>Rare other balanced CA</b>								

Cytogenetic Subgroups	Fusion Gene or Genes Involved	Frequency in Childhood AML	Median Age (Y) (Range)	Special Features (Age, FAB, Phenotype, Treatment)	Secondary CA	Secondary Molecular Abnormalities	Risk Category	References
t(10;11)(p12;q14)	PICCALM-MLL1T10	<1%	older children	Extramedullary disease, granulocytic sarcoma, CD7+	tri 4, tri 19		Intermediate	[46,50,54]
inv(3)(q21q26.2)/t(3;3)(q21;q26.2)	GATA2; EVI1(MECOM)	2%	3 (2-18)	Dysmyelopoiesis and platelet abnormalities	mon 7		Adverse	[1,22,24]
t(3;5)(q25;q35)	NPM1-MLF1	<0.5%	3.5 (2-13)	M2, M4, M6, dysplasia	rare	unknown	Intermediate	[46,50,55]
t(6;9)(p22;q34)	DEK-NUP214	1-2%	12 (2.6-20.4)	M2/M4, dysplasia, basophilic. No infant cases	loss of Y, tri 8, tri 13	FLT3-ITD	Adverse	[56,57]
t(8;16)(p11;p13)	KAT6A-CREBBP	<1%	1.2 (0-16)	Peak in infants, spontaneous remission in a subset of neonates, DIVC, M4-M5, erythrophagocytosis	tri 1q, del(5q), del(7q), del(9q)	High HOXA9/HOXA10 expression	Intermediate	[50,58]
t(16;21)(p11;q22)	FUS-ERG	0.4%	8.5 (2.0-17.5)	no	tri 8, tri 10		Adverse	[50,59]
t(16;21)(q24;q22)	RUNX1-CBFA2T3	0.2%	6.8 (1.0-17)	M1/M2, t-AML	tri 8, loss of Y	Gene expression profile close to RUNX1/RUNX1T1	Favorable?	[50,59]
t(1;22)(p13;q13)	RBM15-MKL1	0.3%	0.7 (0.1-2.7)	Only M7 (5-10% of M7) Hepatosplenomegaly, fibrosis	Mainly no ACA, HD karyotypes		Intermediate	[48,60-64]
inv(16)(p13q24)**	CBFA2T3-GLIS2	2-3%	1.5 (0.3-17.2)	Infants, 20% of non-DS-AMKL, extramedullary disease, CD66++	Low HD karyotypes, tri 3, tri 21	Few mutations	Adverse	[46,48,50,64-67]
t(9;22)(q34;q11)	BCR-ABL1	0.6%		Exclude CML-BP or MPAL mBCR Sensitivity to TKI	Association with inv(16)/CBFB-MYH11		Adverse	[1,14,22]
<b>UNBALANCED CA</b>								
Monosomy 5, del(5q)	/	1.2%	12.5 (0.3-20.7)	M0	del(17p), CK		Adverse	[7,22,28,68]
Monosomy 7 ***	/	3%	7.2 (0-18)	Exclude a primary CA and a predisposition syndrome (GATA2)	/		Adverse	[22,28,69]

Cytogenetic Subgroups	Fusion Gene or Genes Involved	Frequency in Childhood AML	Median Age (Y) (Range)	Special Features (Age, FAB, Phenotype, Treatment)	Secondary CA	Secondary Molecular Abnormalities	Risk Category	References
del(7q) ***	/	3%	7.6 (0-18)	Exclude a primary abnormality and a pre-disposition syndrome	/		intermediate	[22,28,69]
Trisomy 8 ***	/	10-14%	10.1 (0-18)	Mainly a secondary abnormality Search for a primary CA	/	FLT3-ITD	Discussed	[70]
Hyperdiploidy (48-65 chr.)	tri 8, tri 21, tri 19, tri 6, ....	11%	2 (0-17)	AMKL, infants, Search for a primary CA	/	/	No significance	[56,71]
Complex karyotype <i>f</i>	/	8-17%	3 (0-18)	Exclude a primary CA	/	/	Discussed	[5,6,22,28]
Monosomal karyotype <i>ff</i>	/	3-5%	3.6 (0-17)	Exclude a CBF leukemia	/	/	Discussed/ Adverse even after exclusion of mon 7	[5,6]
Normal Karyotype								
Normal karyotype	/	20-26%	8.8 (0-18)	Search for a cryptic CA		Search for prognostic mutations: FLT3-ITD, CEBPA <sub>del</sub> , NPM1	According to cryptic CA or to mutations	[7,22,28,36,46]

NOTE 1. Risk categories were defined according to Harrison [22] and Von Neuhoff 2010 [28]. Favorable, Intermediate and Adverse correspond to 5-year survival >70%, 50-70% and <50%, respectively. NOTE 2. Infants: children under 2 years. Abbreviations: APL: acute promyelocytic leukemia; CA: cytogenetic abnormality; CK: complex karyotype (at least 3 CAs); CML-BP: chronic myeloid leukemia blast phase; DVC: disseminated intravascular coagulation; HD: hyperdiploid karyotype; mBCR: minor BCR; MPAL: mixed phenotype acute leukemia, mon. monosomy; r: rearrangement; TKI: tyrosine kinase inhibitors; tri: trisomy. \* A complex rearrangement or a cryptic insertion is necessary to create a KMT2A-MLL1T10 fusion gene (see text); thus, FISH with a KMT2A probe is mandatory. \*\* Cryptic abnormality requiring molecular methods for detection: FISH and/or PCR-based method. \*\*\* As a primary abnormality. *f* At least 3 independent CAs in the absence of a WHO-designated recurring translocation or inversion. Some authors include in the definition "with at least one structural abnormality" [5,28]. *ff* Loss of at least two autosomes or loss of one autosome and the presence of a structural abnormality (excluding mar or ring), excluding CBF AML.

## CONCLUSION

This case report highlights the diagnostic and therapeutic complexity of acute myeloid leukemia in adolescents. Early diagnosis, thorough cytogenetic analysis, and a personalized therapeutic approach are essential for optimizing remission and survival chances. Treatment of AML with complex cytogenetic abnormalities remains a challenge, and finding compatible donors for bone marrow transplantation is a key step in patient management.

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