

Original Article

Trisomy 11 as an isolated abnormality in acute myeloid leukemia is associated with unfavorable prognosis but not with an *NPM1* or *KIT* mutation

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Abstract: Trisomy 11 (+11) as an isolated abnormality is a rare event in patients with acute myeloid leukemia (AML) and is associated with poor prognosis. We describe the clinicopathologic features of 18 AML patients with isolated +11 and their mutation status of *NPM1*, *FLT3*, *NRAS*, *KRAS*, and *KIT*. Fourteen patients had *de novo* AML and 4 patients had a history of myelodysplastic syndrome (MDS). Fifteen patients had a progressive clinical course with refractory or relapsed disease. The median overall survival was 5 months (range, 2 to 48 months). Only 1 patient achieved complete remission after undergoing stem cell transplantation. The bone marrow median blast count was 65% (range, 22 to 86) and 14 patients had blasts >50%. The most common type of AML was AML without maturation (7 patients) classified by the World Health Organization classification system, or M1 (10 patients) by the French-American-British (FAB) system. *FLT3* mutations were detected in 3 of 15 (20%) cases tested. *RAS* mutation was present in 1 of 16 (6%) cases and there was no evidence of *NPM1* or *KIT* mutations (each tested in 12 cases). Our findings confirm previous reports that isolated +11 is associated with a poor prognosis in patients with AML and tends to be associated with FAB-M1 morphologic features. No evidence of *NPM1* or *KIT* mutations were identified.

Keywords: Isolated trisomy 11, acute myeloid leukemia, gene mutations, prognosis

Introduction

Acute myeloid leukemia (AML) is a clinically and genetically heterogeneous neoplasm. In addition to the patient age, cytogenetic findings play a major role in the classification and prognosis of AML allowing for stratification into favorable, intermediate, and poor risk categories [1]. Although highly useful, approximately 40% of AML patients lack cytogenetic abnormalities. Molecular studies in this subgroup of patients have shown various gene mutations, some of which proven to have prognostic importance [1]. Some gene mutations associated with AML have been incorporated into the most recent classification system of the World Health Organization (WHO) [2].

Structural chromosomal abnormalities, such as translocations, generally constitute most of the nonrandom changes in hematopoietic neoplasms. In contrast, chromosomal gains, apart

from chromosome 8, occur less frequently [3]. Unlike structural abnormalities that may lead to specific gene rearrangement, the pathogenetic significance of trisomies is unclear in most AML cases. Autosomal trisomy may occur as a secondary event in association with other cytogenetic abnormalities. However, the presence of a trisomy as part of a complex karyotype usually does not significantly influence prognosis in AML patients. The situation appears to be different for isolated autosomal trisomies as a primary cytogenetic abnormality in AML patients. Others have shown that a number of different isolated trisomies in AML are associated with an adverse outcome [4]. Of these, trisomy 11 (+11) is one of the most rare isolated abnormalities associated with AML. In a study by Heinonen and colleagues, isolated +11 was identified in 13 of 1496 adult AML patients (<1%) [5].

In this study, we focused on patients with AML associated with +11 as an isolated cytogenetic

abnormality. We analyzed the clinicopathologic, immunophenotypic, and cytogenetic data in these patients and we also assessed the mutation status of the *NPM1*, *FLT3*, *RAS*, and *KIT* genes.

Materials and methods

Clinical, morphologic, and Immunophenotypic analysis

We identified AML patients with isolated +11 in the cytogenetic database of the Clinical Cytogenetics Laboratory, in the Department of Hematopathology, The University of Texas MD Anderson Cancer Center. These patients were treated at MD Anderson Cancer Center between 1999 and 2009. This study was approved by the Institutional Review Board.

Clinical, follow-up, and laboratory data were collected at time of diagnosis of AML from the medical records. Laboratory data included a complete blood count in all patients. All patients underwent bone marrow aspiration and biopsy and each case was classified morphologically using the 2008 WHO and the older FAB classifications. Myeloperoxidase was assessed using a standard cytochemical method on bone marrow aspirate smears of all cases.

Flow cytometry Immunophenotypic analysis was performed on peripheral blood and/or bone marrow aspirate material in a subset of patients at M.D. Anderson Cancer Center as previously described [6]. The antibody panels used were highly variable, however, in all cases at least 3-color analysis was performed and myeloblasts were gated for analysis using CD45 and side scatter. CD45 was paired with peridinin chlorophyll alpha protein and either fluorescein isothiocyanate or phycoerythrin conjugated antibodies that included CD13, CD33, CD34, CD117, HLA-DR, and pan-B and pan-T cell antibodies.

Cytogenetic analysis and fluorescence in situ hybridization (FISH)

Cytogenetic analysis and FISH analysis were performed on bone marrow aspirate specimens according to standard protocols as previously described [7]. Twenty G-banded metaphases were analyzed whenever possible, and cytogenetic diagnosis was made according to the criteria recommended by the International System

for Human Cytogenetic Nomenclature [8]. Only cases with an isolated +11 as the primary change were included in the study. Fluorescence in situ hybridization using a probe SLI CEP11 for chromosome 11 centromere (Vysis/Abbot Molecular Inc., IL, USA) was performed to confirm the routine cytogenetic results when needed. The cutoff value for the SLI CEP11 was 1.8%.

Molecular studies

Genomic DNA was extracted from fresh bone marrow aspiration specimens for mutational analyses using the Autopure extractor (Qiagen/Gentra, Valencia, CA, USA). *FLT3* (internal tandem duplication [ITD] and codon 835) and *NPM1* (exon 12) mutations were screened using polymerase chain reaction (PCR) followed by capillary electrophoresis on an ABI Prism 3100 Genetic Analyzer (Applied Biosystems, Carlsbad, CA, USA) as previously described [9]. For the *FLT3* codon 835/836 tyrosine kinase domain (TKD) point mutation analysis, PCR products were digested with EcoRV before capillary electrophoresis. Mutations in *NRAS* and *KRAS*, and *KIT* genes were assessed by PCR followed by direct sequencing, Sanger sequencing, or pyrosequencing, according to previously described protocols [9,10].

Results

Clinical, morphologic, and immunophenotypic characteristics

We identified 18 AML patients with isolated +11 from a total of 20,029 AML patients diagnosed at MDACC between 1999 and 2009, showing a frequency of 0.09%. As shown in **Table 1**, there were 11 men and 7 women. The patient ages ranged from 33 to 98 years, with a median of 69 years. Twelve (67%) patients were older than 60 years. All patients presented with anemia, with a median hemoglobin of 88 g/L, range, 69-109 g/L (normal range 140-180 g/L). Sixteen (89%) patients had thrombocytopenia with a median platelet count of 65 x 10⁹/L (normal range, 140-440 x 10⁹/L). Fourteen (78%) patients had leukocytopenia and one patient had marked leukocytosis with a white blood cell count (WBC) of 46 x 10⁹/L (normal range, 4-11 x 10⁹/L). The median WBC was 2.35 x10⁹/L (range, 0.1-46 x10⁹/L).

Morphologically, the median bone marrow blast

Acute myeloid leukemia with isolated trisomy 11

Table 1. Clinicopathologic findings in 18 cases of isolated trisomy 11 AML

Case	Age/Sex	FAB Classification	WHO classification	WBC (x10 ⁹ /L)	Hb (g/dl)	Plt (10 ⁹ /L)	Blasts	OS (Months)
1 ^a	77/F	M1	AML with myelodysplasia-related changes	1.4	7.4	72	68%	6
2	76/F	M0	AML with minimal differentiation	5.4	8.1	95	50%	NA
3	54/F	M1	AML without maturation	3.5	7.1	50	85%	5
4	85/F	M1	AML without maturation	2.8	7.4	34	25%	48
5 ^a	71/M	M1	AML with myelodysplasia-related changes	2.1	10.6	38	57%	3
6	33/M	M2	AML with maturation	3.9	6.9	58	55%	6
7	57/M	M2	AML with maturation	1.4	7.9	68	55%	NA
8	67/M	M1	AML without maturation	2.6	8.1	143	67%	9
9 ^a	68/M	M0	AML with myelodysplasia-related changes	2.4	10.9	94	22%	8
10	48/M	M6	Acute erythroid leukemia	1.5	7.3	117	49% ^b	4
11 ^a	67/M	M1	AML with myelodysplasia-related changes	2.3	9.3	128	69%	2
12	70/M	M2	AML with maturation	5.4	9.6	242	33%	alive
13	98/M	M5a	Acute monoblastic leukemia	10.2	10.3	30	79%	NA
14	74/F	M1	AML without maturation	46	9.6	32	86%	2
15	52/M	M1	AML without maturation	0.1	9.7	11	68%	42
16	59/F	M1	AML without maturation	1.5	9.5	14	53%	4
17	80/F	M2	AML with maturation	0.6	8.3	63	68%	5
18	75/M	M1	AML without maturation	0.9	10.2	65	65%	4

AML, acute myeloid leukemia; FAB, French–American–British; WHO, World Health Organization; WBC, blood cell count; Hb, hemoglobin; Plt, platelet; OS, overall survival; NA, not available.

^a Patient presented with previous myelodysplastic syndrome.

^b Of non-erythroid cells.

count was 65% (range, 22-86%) (**Table 1**). Four patients had a history of MDS and had morphologic evidence of dysplasia associated with AML. Using the WHO classification these cases were classified as AML without maturation (n=7), AML with myelodysplasia related changes (n=4), AML with maturation (n=4), AML with minimal differentiation (n=1), acute monoblastic leukemia (n=1), and acute erythroid leukemia (n=1). Using the FAB system, 10 cases were M1, 4 M2, 2 M0, 1 M5a, and 1 M6.

Cytochemistry for myeloperoxidase (MPO) was positive in 16 of 18 cases assessed. The two

MPO negative cases were classified using the WHO as AML with minimal differentiation and AML with myelodysplasia-related changes. Using the FAB, both cases were M0. Flow cytometric immunophenotypic data were available for 11 patients. In all cases assessed the blasts were positive for CD13, CD33, CD34, and HLA-DR. CD 117 was expressed in 10 of 11 cases. Myeloperoxidase staining was negative in the 2 patients with the FAB-M0 subtype.

Conventional cytogenetic analysis and FISH

Routine cytogenetic analysis found an isolated

Acute myeloid leukemia with isolated trisomy 11

Table 2. Gene mutations in acute myeloid leukemia with isolated trisomy 11

FLT3 % (# case positive/ # cases tested)	KIT % (# case positive / # case tested)	NPM1 % (# case positive/ # case tested)	RAS % (# case positive/ # case tested)
20% (3/15)	0% (0/12)	0% (0/12)	6% (1/16)

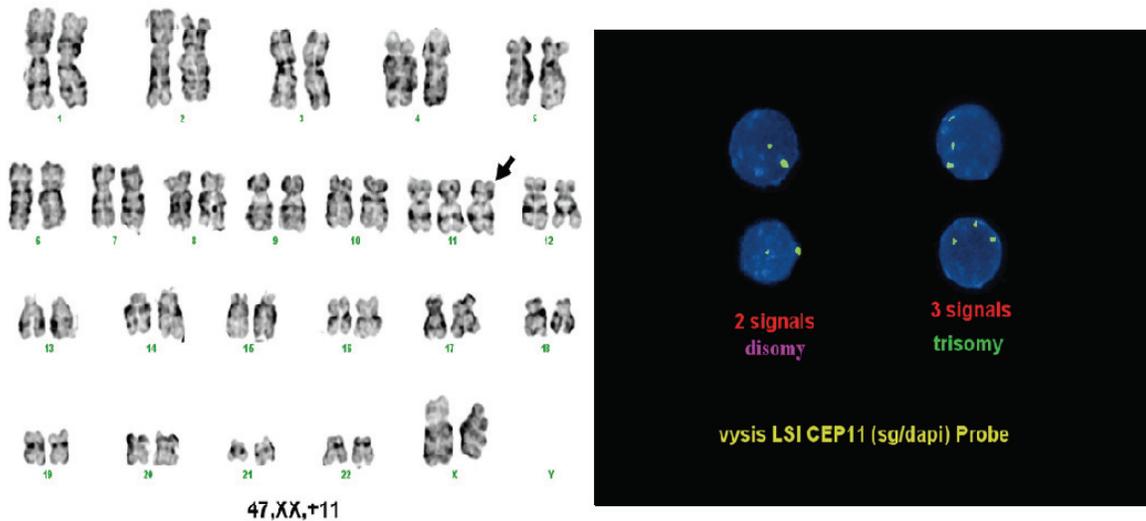


Figure 1. Female karyotype (left) and FISH (right) showing trisomy 11.

+11 as the primary change in all 18 AML patients (**Figure 1**). Trisomy 11 was further confirmed by FISH in 2 cases.

Molecular studies

Molecular testing was performed on all cases with available DNA as is summarized in **Table 2**. *FLT3* mutations were present in 3 of 15 (20%) patient assessed. The three positive cases had an internal tandem duplication of *FLT3* in 2 patients and a point mutation in D835 of the tyrosine kinase domain in 1 patient. One of 16 (6%) cases had an *NRAS* mutation. There was no evidence of *KRAS* mutation in these 16 patients. In 12 patients assessed there was no evidence of *NPM1* or *KIT* mutation.

In a previous study of MDS with +11 by Wang and colleagues [11], control group of AML patients were assessed for partial tandem duplication of the *MLL* gene. In this study, 5 of 11 cases had PTD of the *MLL* gene.

Clinical Follow up

Clinical follow-up data were available for 15 patients, and the median overall survival was 5 months (range, 2 to 48 months) (**Table 1**). Fifteen patients had a progressive clinical course with refractory or relapsed disease. Complete remission was achieved in only 1 patient, who had undergone stem cell transplantation (SCT) (case 12).

Discussion

Gains of whole chromosomes are frequently found in hematologic neoplasms, identified as either primary abnormalities or secondary changes in progressive or advanced stages of the disease [3]. Trisomy for chromosomes 8, 13, and 21 comprises approximately 90% of all cases with isolated trisomies, and as an isolated change is often associated with a poor outcome [4]. As an isolated abnormality, trisomy 11 (+11) in AML is a very rare abnormality. The

frequency of isolated +11 at our institution, a major referral center, was 0.09%. In a recent study Wang and colleagues [11] reported a series of cases of MDS with isolated +11. These patients showed a high risk of progression to AML. Heinonen *et al* previously reported a series of 13 AML cases with +11 and suggested that trisomy 11 could be a marker for unfavorable prognosis [5]. Isolated +11 also has been observed uncommonly in other hematologic malignancies, including T-cell acute lymphoblastic leukemia (T-ALL) [12], plasma cell myeloma [13], and chronic lymphocytic leukemia [14]. A current model for AML pathogenesis suggests the importance of two categories of genetic mutation [3]. A class I mutation confers proliferation and cell survival advantages to the clone, whereas a class II mutation impairs cellular differentiation. *FLT3*, *KIT*, and *RAS* mutations are classified as class I mutations, whereas *NPM1* mutation is considered a class II mutation. *FLT3* is a type III receptor tyrosine kinase. Mutations of *FLT3* result in constitutive activation of downstream molecular signaling pathways and aberrant cell growth. *FLT3* mutations are seen in about 30% of AML cases and fall into two main groups: internal tandem duplication and tyrosine kinase point mutation [15]. Both of the mutations render the receptor constitutively activated. *FLT3* mutations occur in approximately 20% of all cases of AML [15]. Rege-Cambrin and colleagues identified *FLT-ITD* mutation in 30% of isolated +11 AML cases, and their study demonstrated an association with a short survival [16]. Our data are in accord with these results. Three of 15 (20%) patients assessed had *FLT3* mutation. These patients had a poor prognosis, but not apparently worse than the group as a whole, suggesting that +11 is the more important prognostic indicator.

The *RAS* (*N-* and *K-*) genes encode a family of membrane-associated proteins that regulate signal transduction on binding to a variety of membrane receptors. They play important roles in the regulatory processes of proliferation, differentiation, and apoptosis. In other studies, presence of a *RAS* mutation did not affect prognosis in AML [17,18]. In this study, an *NRAS* mutation was seen in a single patient (1 of 16 assessed; 6%). There were no *KRAS* mutations. As a group, *RAS* mutations are more common in AML than observed in this series of +11 AML cases [19]. Thus, *RAS* gene mutation does not seem to be important in pathogenesis of +11

AML.

Point mutation at exon 12 of the *NPM1* gene represents one of the most frequent mutations in adult AML, in approximately 30% of unselected AML cases [20]. *NPM1* mutation is usually associated with the FAB M4 or M5 subtypes and is more common in cytogenetically normal AML cases [20,21]. In this study, *NPM1* mutations was not identified in 12 case assessed. This is consistent with previous reports in the literature as our study group all had cytogenetic abnormalities and there was a low frequency of monocytic differentiation. *KIT* gene is infrequently seen in AML with an overall incidence of 3%, and is most frequent in core binding factor AMLs [22]. *KIT* gene was not observed in all 12 patients assessed in this study.

In previous studies of AML associated with +11, mostly appearing in clinical journals, relatively little attention has been paid to the morphologic features of this disease. In addition, most studies have not used the current WHO classification system. In this study, most cases of AML associated with +11 were classified as AML without maturation using the WHO classification or as M1 using the FAB classification. The immunophenotype of the cases assessed in this series showed evidence consistent with a stem cell phenotype with expression of CD34, CD117, and HLA-DR. These results are in accord with an earlier study by Slovak and colleagues [23].

The role of trisomy 11 in the leukemogenesis of AML remains to be defined. It has been speculated that trisomies in general lead to a gene dosage effect that results in increased gene copy number and a survival advantage [3]. Previous studies by others have shown that many +11 AML cases have partial tandem duplication of the *MLL* gene. In one study by Caligiuri and colleagues, up to 90% of cases of AML carrying an isolated +11 had a partial tandem duplication of *MLL* [24]. In this study, 5 of 11 cases assessed had partial tandem duplication of *MLL* [11].

In summary, AML associated with isolated trisomy 11 has a poor prognosis. In this group of 18 cases, the morphologic features most often supported classification as AML without maturation (WHO) or M1 (FAB). The immunophenotype usually has stem cell features. As

shown by others, partial tandem duplication of the *MLL* gene occurs in approximately 50% of cases. *FLT3* gene mutations occur in approximately 20% of cases and there is a very low frequency of mutations of the *NRAS*, *KRAS*, *NPM1*, and *KIT* genes.

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