Journal of Leukemia
ISSN: 2329-6917

Wang et al., J Leuk 2014, 3:1
DOI: 10.4172/2329-6917.1000161

Research Article Open Access

Myeloid Neoplasms Associated with t(3;12)(q26.2;p13) Are Clinically Aggressive and Frequently Harbor *FLT3* Mutations: A Report of 8 Cases and Review of Literature

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Abstract

The t(3;12)(q26.2;p13) involving *EVI1* and *ETV* 6 is a rare recurrent translocation that has been identified in myeloid neoplasms. The clinicopathologic features of these are not well characterized.

We identified 5 cases of acute myeloid leukemia (AML) and 3 cases of myelodysplastic syndrome (MDS) associated with t(3;12)(q26.2;p13). There were 5 men and 3 women, with a median age of 60 years. The AML cases included 2 *de novo*, 2 arising from prior MDS and 1 relapsed AML. The median bone marrow blast count was 50% (range, 35-91%). Dysplasia was noted in all cases. Of the 3 MDS cases, two were classified as refractory anemia with excess blasts and one therapy related. Two that had follow up data rapidly evolved to AML within 6 months.

Conventional cytogenetic analysis showed t(3;12)(q26.2;p13) in all neoplasms and additional abnormalities in 5 patients, Including chromosome 7 abnormalities in 3 patients. Fluorescence *in situ* hybridization confirmed *ETV6* rearrangement in all 3 cases assessed and *EVI1* rearrangement in both cases assessed. *FLT3-ITD* was identified in 3 of 5 cases assessed. The median overall survival was 12 months (range, 7-58 months).

We conclude that t(3;12) can occur as either a primary or secondary event in myeloid neoplasms. The t(3;12) is associated with multilineage dysplasia, chromosome 7 aberrations and an aggressive clinical course.

Keywords: Myeloid neoplasms; t(3;12)(q26.2;p13); *EVI1; MECOM; ETV6; FLT3;* Chromosome 7

Introduction

Disruption of chromosome locus 3q26 is an uncommon recurrent cytogenetic abnormality that occurs in a small percentage of cases of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). The ecotropic viral integration site 1 (*EVI1)* gene, located on chromosome 3q26.2, also known as *MECOM* gene, has been shown to be activated in at least a subset of these meyleoid neoplasms. *EVI1* is activated in various AML associated cytogenetic abnormalities, such as inv(3)(q21q26.2) or t(3;3)(q21;q26.2)/*EVI1-GATA1.*

The t(3;12)(q26.2;p13) is a rare recurrent event in cases of AML, MDS, and blast phase of CML [1-3]. The *ETV6* gene (ETS variant 6), also called Translocation Ets Leukemia (*TEL*), is located on 12p13 and encodes for a transcription factor that is a target of deletions and translocations in both myeloid and lymphoid malignancies. Various partner genes in reciprocal translocations involving 12p13 have been described. *ETV6* rearrangements are much less frequent in myeloid neoplasms [4].

The clinical and molecular features of myeloid neoplasms associated with t(3;12)(q26.2; p13) are not as well understood as those associated with inv(3)/t(3;3). In this study, we comprehensively described features of 8 patient with myeloid neoplasms associated with t(3;12)(q26.2; p13).

Materials and Methods

We searched the database of the Clinical Cytogenetics Laboratory for cases of myeloid neoplasms associated with t(3;12)(q26.2;p13) detected by conventional cytogenetic analysis. Two cases were also obtained from the Department of Pathology, Vanderbilt University School of Medicine and Cleveland Clinic, respectively. The diagnosis was based on the 2008 WHO criteria. Wright-Giemsa-stained bone marrow (BM) aspirate smears and touch imprints and H&E-stained core biopsy and clot sections were reviewed. This study was conducted according to an institutional review board-approved protocol.

Multicolor flow cytometry immunophenotypic analysis was performed on BM aspirate specimens using a FACScan instrument (Becton-Dickinson, San Jose, Calif) as described previously [5]. The blast population was gated using right-angle side scatter and CD45 expression. The panel of monoclonal antibodies included reagents specific for CD3, CD5, CD7, CD13, CD14, CD19, CD33, CD34, CD38, CD64, CD117, HLA-DR, TdT, and myeloperoxidase (Becton-Dickinson).

BM aspirate specimens were analyzed by conventional cytogenetic analysis as described previously [6]. Karyotypes were reported according to the 2013 International System for Human Cytogenetic Nomenclature [7].

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Received July 18, 2014; **Accepted** September 20, 2014; **Published** September 25, 2014

Citation: Wang XI, Lu X, Yin CC, Zhao L, Bueso-Ramos CE, et al. (2014) Myeloid Neoplasms Associated with t(3;12)(q26.2;p13) Are Clinically Aggressive and Frequently Harbor *FLT3* Mutations: A Report of 8 Cases and Review of Literature. J Leuk 3: 161. doi:10.4172/2329-6917.1000161

Fluorescence *in Situ* Hybridization (FISH) was performed using a LSI *ETV6* dual color, breakapart probe (Vysis-Abbott Molecular, Inc), which hybridizes to band 12p13. The *EVI1* dual-color, breakapart DNA probe (Leica/Kreatech Inc.) was used to detect *EVI1* gene rearrangement at 3q26. For each specimen, 200 interphases were analyzed. The FISH images were captured and analyzed by Applied Imaging software- Cyto Vision software (Leica, Inc).

Analyses for *FLT3* Internal Tandem Duplication (*ITD*) and codon 835/836 point mutation were performed by polymerase chain reaction (PCR)-based amplification of genomic DNA and capillary electrophoresis as described previously [8]. Codons 12, 13, and 61 of *KRAS* and *NRAS* were sequenced following PCR amplification using Sanger sequencing or a pyrosequencing-based method as previously described [9]. *NPM1* mutations spanning codons 956 to 971 of exon 12 were detected by PCR followed by capillary electrophoresis as described previously [10]. *KIT D816V* mutation was detected by direct Sanger sequencing on an ABI Prism 3100 Genetic Analyzer [10,11].

The overall survival (OS) was calculated from date of diagnosis of either MDS or AML associated with t(3;12)(q26.2;p13) until death from any cause or date of last follow-up.

Results

Clinical findings

The clinical and morphological features are summarized in Table 1. Of the 8 patients with t(3;12)(q26.2;p13), there were 5 men and 3 women, with a median age of 60 years (range, 33-79 years). Presenting symptoms include fever, chills, general malaise, weakness and night sweats (cases 1, 2), fatigue (cases 3, 5, 6, 8), gum bleeding (case 4) and upper airway infection (case 7). Physical exam found lymphadenopathy (cases 1, 4) and a palpable spleen (case 1). None had myeloid sarcoma involving soft tissue at the diagnosis. Five cases were classified as AML and 3 cases MDS. All patients had anemia with a median hemoglobin level of 8.9 g/dL (range, 6.8 to 12.3 g/dL [68-123 g/L]; reference range, 14-18 g/dL [140-180 g/L] for men and 12-14 g/dL [120-140 g/L] for women) and thrombocytopenia with a median platelet count of 52 × 10^9/L (range, 24-111 × 10^9/L; reference range, 140-440 × 10^9/L). The median white blood cell (WBC) count was 62.6 k/uL (rang, 1.9-129.5 k/uL) for the 5 cases of AML with a median peripheral blood blast count of 31% (range, 21-88%). The patients with MDS had a median WBC of 4.0 k/uL (range, 1.8-7.6 k/uL) with a median peripheral blood blast count of 1% (range, 0% to 3%).

Serum chemistry results were generally unremarkable except the lactate dehydrogenase level was elevated in 2 of 6 patients assessed: 489 IU/L and 4183 IU/L, respectively, (reference range, 313-618 IU/L). The β2-microglobulin level was elevated in 1 patient, 7.3 mg/L (reference range, 0.6-2.0 mg/L).

Morphologic findings

Peripheral blood smears showed circulating blasts in 7/8 cases (range, 1%-88%), anemia with mild to moderate anisopoikilocytosis (5/6 cases), nucleated red blood cells (2/5 cases), absolute monocytosis (3/5 cases).

BM smears showed multilineage dysplasia in all 8 cases. Five of 8 (63%) cases showed megakaryocytic hypoplasia. Small hypolobated

Case number	*1*	2	3	4	5	6	7	*8*
Age/gender	34/M	54/M	58/M	79/M	70/F	61/F	33/F	61/M
Diagnosis	AML, M1	AML, M5a	AML-MRC	AML-MRC	Recurrent AML	RAEB-1	RAEB-2	t- MDS
Peripheral Blood								
WBC (k/uL)	129.5	113	8.9	62.6	1.9	7.6	1.8	4
Hemoglobin (g/dL)	6.8	8.1	8.5	8.2	12.3	9.3	9.3	9.8
Platelet count (k/uL)	68	74	70	33	111	30	36	24
Peripheral blood blast count	88%	21%	32%	31%	10%	3%	1%	0%
Bone Marrow								
Bone marrow cellularity	95%	100%	60%	95%	70%	60%	40%	50%
Bone marrow blasts	91%	63%	45%	35%	50%	8%	18%	1%
Granulocytic series	Decreased, dysplastic	Dysplastic	Dysplastic	Dysplastic	Decreased, dysplastic	Dysplastic	Decreased, dysplastic	Dysplastic
Erythroid series	Decreased, dysplastic	Decreased, dysplastic	Decreased, dysplastic	Decreased, dysplastic	Decreased, dysplastic	Dysplastic	Decreased, dysplastic	Increased, dysplastic
Megakaryocytic series	Decreased, dysplastic	Decreased, dysplastic	Dysplastic	Dysplastic	Decreased, dysplastic	Dysplastic	Decreased, dysplastic	Decreased, dysplastic
Molecular Results								
FLT3 ITD mutation	Positive	Positive	Negative	Positive	NA	NA	Negative	NA
KRAS mutation	Negative	Negative	Negative	Positive (G12D)	NA	NA	NA	Positive (G12A)
NRAS mutation	NA	Negative	Negative	Positive (G13D)	NA	NA	NA	NA
KIT D816V	Negative	NA	Positive	Negative	NA	NA	NA	NA
NPM1 mutation	Negative	NA	NA	NA	NA	NA	NA	NA
Treatment and Survival								
Multiagent chemotherapy	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
BM transplantation	Yes	Yes	No	No	No	No	NA	Yes
Overall (Months)	58	17	7	7	7	11	NA	12
Alive/deceased	Alive	Deceased	Deceased	Deceased	Alive	Deceased	NA	Deceased

NA: not available, MRC: myelodysplasia related changes.

Table 1: Morphology and clinical features of patients at diagnosis.

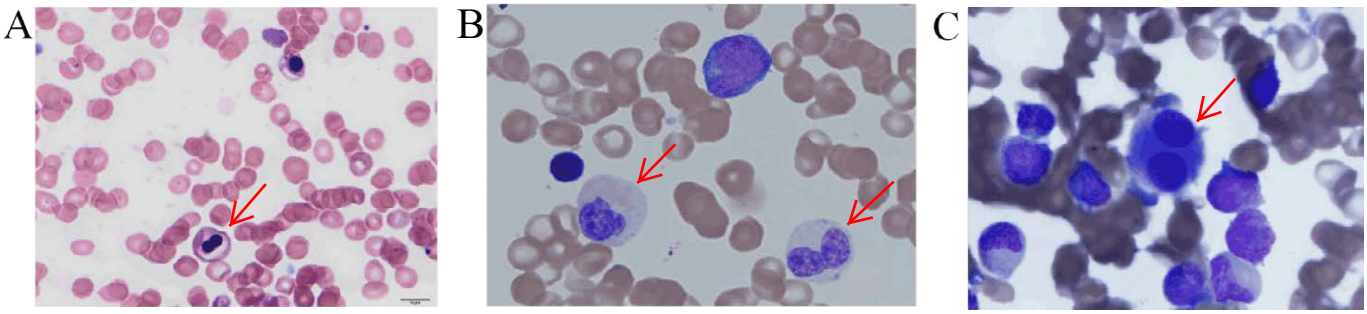

Figure 1: Characteristic cytologic changes of AML or MDS associated with t(3;12)(q26.2;p13) (red arrows)
A: Erythroid dysplasia: a normoblast shows irregular nucleus, case 3
B: Myeloid dysplasia: two myeloid elements show abormal nuclei and cytoplasmic granulation, case 7
C: A dysplastic hypolobated megakaryocyte with two lobes, case 7

case#	diagnosis	Karyotype	*ETV6/EVI1* FISH
1	AML, M1	45,XY,t(3;12)(q26.2;p13),-7[19]	*ETV6*
2	AML, M5a	46,XY,t(3;12)(q26.2;p13), del(11)(q23.1)[20]	*ETV6, EVI1*
3	AML arising from MDS	46,XY,t(3;12)(q26.2;p13),add(7)(q11.2)[18], 46,XY[2]	ND
4	AML arising from MDS	46,XY,t(3;12)(q26.2;p13),del(10)(q22q24)[19], 46,XY[1]	*ETV6*
5	Recurrent AML	46,XX,t(3;12)(q26;p13)[20]	ND
6	RAEB-1	46,XX,t(3;12)(q26.2;p13)[20]	ND
7	RAEB-2	46,XX,t(3;12)(q26;p13) [18] 46,XX[2]	ND
8	t-MDS	46,XY,t(3;12)(q26.2;p13),r(7)[17], 45,XY,t(3;12)(q26.2;p13),-7[3]	*EVI1*

AML: acute myeloid leukemia; M5a: acute monocytic leukemia; MDS: myelodysplastic syndrome; ND: Not Done; t-MDS: therapy related myelodysplastic syndrome; RAEB-2: refractory anemia with excess blasts -2;

Table 2: Cytogenetic Data at Initial Dectection of t(3;12)(q26.2;p13).

megakaryocytes were observed in 7/7 cases (Figure 1). Blasts ranged from 1% to 18% in cases of MDS and 35 % to 91% in case of AML.

The 8 cases were classified as follows. Two *de novo* AML: one was AML without maturation (case 1) and the other acute monoblastic leukemia (case 2). Two were AML that evolved from MDS diagnosed 7 and 11 months earlier and were classified as AML with myelodysplasia-related changes (case 3 and 4). One case of AML was diagnosed at time of relapse (case 5). Two cases of MDS were classified as refractory anemia with excess blasts (RAEB-1 and RAEB-2) (cases 6 and 7) and 1 patient had therapy-related MDS following therapy for 8 months (case 8).

Immunophenotypic findings

Flow cytometric immunophenotypic analysis of BM aspirate specimens from the 5 AML cases showed that the blasts were of myeloid origin. Blasts were positive for CD13, CD33, CD34, CD117, and HLA-DR in all cases. They were also positive for CD5 (partial, 1/3, 33%), CD7 (partial, 2/4, 50%), CD14 (1/2, 50%), CD15 (3/3, 100%), CD38 (2/3, 67%), and CD64 (2/3, 67%).

Cytogenetic findings

All 8 cases carried the t(3;12)(q26.2;p13). Three (37%) cases (cases 5-7) had t(3;12)(q26.2;p13) as the sole abnormality at the time of first detection (Table 2). The other 5 cases (63%) showed additional chromosomal abnormalities, including monosomy 7 (case 1), del(11)(q23.1) (case 2), and add(7)(q11.2) (case 3), del10(q22q24) (case 4), r(7) and monosomy 7 (case 8). In case 5, t(3;12) was not identified in the leukemic blasts at initial diagnosis of AML, but was detected 9 months later at time of relapse. In the whole cohort (n=8), the median number of additional chromosomal abnormalities was 1 (range, 0-2). All 4 patients with available initial karyotypes had other cytogenetic abnormalities prior to detection of t(3;12): add 7 (case 3), monosomy 7 (case 8), t(10;12)(q24;p13) (case 4) and 46,X, t(X;19)(p11.2;p13.1) (case 5) preceded that of t(3;12) by approximately 11, 12, 6 and 10 months, respectively, suggesting that t(3;12) evolved as a secondary event. In cases 1, 2 and 6, the initial karyotype was unknown. There was no cytogenetic follow up for case 7.

Fluorescence *in situ* hybridization was performed in a subset of cases. *ETV6* rearrangements were seen in all 3 cases assessed and *EVI1* rearrangements were detected in both cases assessed (Figure 2).

Molecular findings

FLT3-ITD was identified in 3 of 5 cases assessed (cases 1, 2 and 4). *KRAS* mutation was detected in 2 of 5 cases (G12D in case 4 and G12A in case 8). *NRAS* mutation (1/3, G13D in case 4) and *KIT D816V* mutation (1/3, in case 3) were also identified.

Clinical Outcome

Clinical follow-up was available for 7 patients. All patients received multi-agent chemotherapy. Three also underwent stem cell transplantation (cases 1, 2 and 8). At last follow-up, 5 patients had died and 2 were alive. For the 3 patients who underwent transplantation, the OS was 12, 17 and 58 months, respectively. The median OS for the 4 patients who did not undergo transplantation was 7 months (range, 7-11 months). There was no significant difference in OS between patients who did or did not undergo transplantation. Of the two cases of MDS that had follow up data (cases 6 and 8), the disease evolved to AML within 2

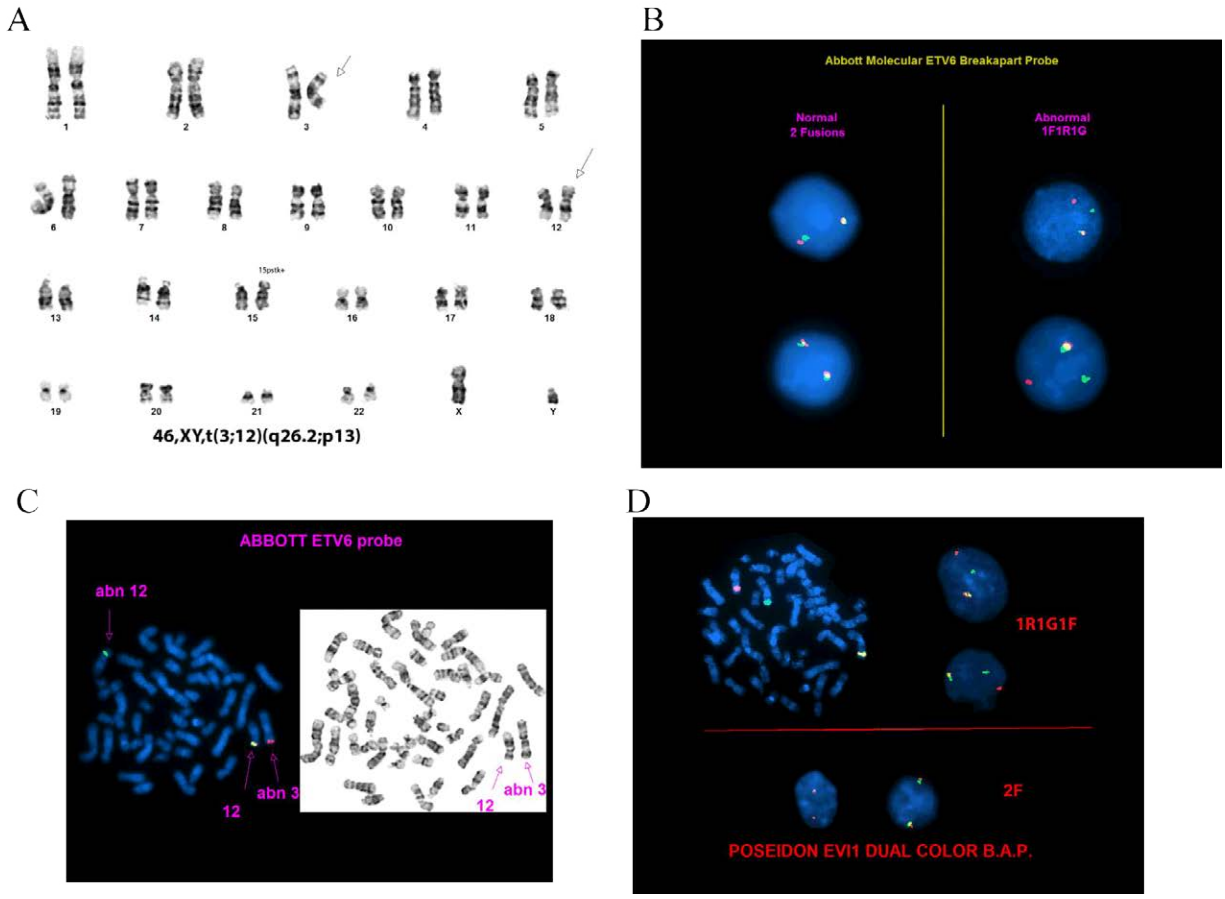

Figure 2: A. Karyotype from a metaphase cell of a patient by G-banding analysis showing the t(3;12)(q26.2;p13). The arrowheads indicate the abnormal chromosomes 3 and 12. There is an increase in length of the stalk on the short arm of chromosome 15 (15pstk+).
B. FISH analysis using LSI *ETV6* break apart probe showing two normal interphase cells (2 fusion signals) on the left and 2 abnormal cells with t(3;12)(q26.2;p13)(3'ETV6+;5'ETV6+) (1F1R1G).
C. The LSI *ETV6* probe on the metaphase shows *ETV6* rearrangement.
D. The Dual-Color *EVI1* break apart probe hybridized to the metaphase showing a rearrangement involving the *EVI1* gene region at 3q26.
The green *EVI1* signal remained on the abnormal chromosome 3 while the *EVI1* red signal was translocated to the abnormal chromosome 12.
The normal (2 fusion signals) and abnormal signal (1R1G1F) patterns are also shown in two interphases, respectively.

and 6 months, respectively, after detection of t(3;12), with the BM blast count rising from 8% to 71%, and from 2 to 25%, respectively .

Discussion

The t(3;12)(q26.2;p13) was first reported by Secker-Walker et al. in 3 patients as part of a larger series of 66 myeloid neoplasms with chromosomal abnormalities in the 3q26.2 region [12]. To date, 42 patients have been recorded in the Mitelman database, including AML (n=35), CML (n=4), and MDS (n=3) [13]. However, data regarding these cases are limited (Table 3) [1,14]. Our study is the largest series to date and provided both conventional cytogenetic as well as molecular genetic findings that were missing in many of the previous case reports.

In this study, we show that myeloid neoplasms associated with t(3;12) are mostly adults who usually presented with anemia and had poor clinical outcome. Multilineage dysplasia was consistently observed in all patients with frequent small hypolobated megakaryocytes. Karyotypic abnormalities in addition to t(3;12) were common, with monosomy 7 occurring in approximately half of the cases. Furthermore, the t(3;12) was preceded by other karyotypic aberrations in 4 patients whose initial cytogenetic data were available, indicating that the t(3;12) was likely a secondary event or existed as a small subclone initially in these patients. The frequent association with chromosome 7 abnormalities is in accordance with the others reported in Mitelman database (Table 2). The t(3;12)(q26.2;p13) was the sole abnormality in 21 of 38 (55%) cases [12,13]. Nine (24%) cases had additional chromosome 7 abnormalities, with loss of part or all of chromosome 7 (8/9, 89%) being the most common. We also showed *FLT3-ITD* mutations in over half of the cases assessed, a frequency that appears to be higher than the reported overall frequency of 20% to 30% in AML patients [14] and a reported frequency of 18% in balanced t(3q26;v) AML [1].

The *EVI1* proto-oncogene is located on human chromosome 3q26. Its transcriptional activation is relatively common in myeloid malignancies and has been reported in up to 10% of AML, blast phase of CML and MDS. [15] The EVI1 protein is a transcriptional regulator with DNA-binding zinc finger domains. Overexpression of EVI1 is an indicator of poor prognosis in myeloid malignancies. The major cellular effects are promoting proliferation, interfering with myeloid differentiation and preventing cellular apoptosis. In retrovirally-transduced marrow cell recipient mice, coexpression of EVI1 and Trib1 accelerates leukemogenesis [16]. EVI1 binds CCAAT/enhancer binding

Age /Sex	Cytogenetics	Diagnosis	Survival
NA	46,X?,t(3;12)(q26;p13)	AML, NOS (RAEB-T)	NA
29 y/m	46,XY,t(3;12)(q26;p13)	AML, NOS	NA
43 y/m	46,XY,t(3;12)(q26;p13)/46,idem,i(14)(q10)	MDS	NA
61 y/M	46,XY,t(3;12)(q26.2;p13)[20]	AML (FAB-M2)	NA
37 y/M	46,XY,t(3;12)(q26.2;p13)[19]/46,idem,der(9)t(1;9)(q10;p10)[2]	AML (FAB-M0)	NA
53 y/F	46,XX,t(3;12)(q26.2;p13)[20]	AML, NOS	NA
74 y/m	46,XY,t(3;12)(q26;p13)	AML, NOS (de novo)	NA
27 y/m	46,XY,t(3;12)(q26;p13)	AML, NOS (de novo)	NA
61y/f	46,XX,t(3;12)(q26;p13),del(5)(q14q34)	s-AML	NA
77y/f	46,XX,t(3;12)(q26;p13),del(5)(q14q34)	s-AML	NA
67y/f	46,XX,t(3;12)(q26;p13)	s-AML	NA
50y/m	45,XY,t(3;12)(q26;p13),-7	AML, NOS (de novo)	NA
48y/m	45,XY,t(3;12)(q26;p13),-7	t-AML	NA
57y/m	46,XY,t(3;12)(q26;p13)	MDS	NA
64y/m	46,XY,t(3;12)(q26;p13),del(7)(q12)	MDS	NA
13y/F	45,XX,t(3;12)(q26;p13),-7	AML (FAB-M2) (de novo)	10 mon
46y/m	46,XY,t(3;12)(q26;p13)	AML (FAB-M4)	6 mon
NA	46,XY,t(3;12)(q26;p13)	AML, NOS	NA
NA	46,XX,t(3;12)(q26;p13)	AML, NOS	NA
NA	46,XX,t(3;12)(q26;p13)	AML, NOS	NA
NA	46,XY,t(3;12)(q27;p13),add(9)(p24)	AML, NOS	NA
NA	46,XY,t(3;12)(q26;p13)	AML, NOS	NA
NA	46,XY,t(3;12)(q26;p13)/47,idem,+18	AML, NOS	NA
NA	46,XX,t(3;12)(q26;p12)	AML, NOS	NA
NA	46,XX,t(3;12)(q26;p13)	AML, NOS	NA
NA	46,XX,t(3;12)(q26;p13)	AML, NOS	NA
6mon/m	45,XY,-7,del(12)(p11p12)/45,XY,t(3;12)(q26;p12),-7	s-AML	9 mon
79y/f	46,XX,t(3;12)(q26;p13),add(7)(q11)	AML (FAB-M0)	270 mon
52y/m	46,XY,t(3;12)(q26;p13),-7,+r	s-AML (FAB type M2)	NA
60y/m	46,XY,t(3;12)(q26;p13),del(7)(q21q35)	s-AML (FAB type M2)	7 mon
87y/m	46,XY,t(3;12)(q26;p13),del(7)(q21q34)	s-AML (FAB type M2)	10 mon
57y/?	46,XY,t(3;12)(q26;p13)	AML (FAB-M0) (de novo)	15 mon
21y/f	46,XX,t(3;12)(q26;p13)	AML (FAB type M2)	39 mon
24y/m	46,XY,del(1)(p3?2p3?4),t(3;12)(q26;p13)	AML, NOS	NA
59y/f	46,XX,t(3;12)(q26;p13)	s-AML (FAB type M4)	5 mon
70y/m	46,XY,t(3;12)(q26;p13)	s-AML	18 mon
36y/f	46,XX,t(3;12)(q26;p13)	s-AML (RAEB-T)	44 mon
45y/m	46,XY,t(3;12)(q26;p13),t(7;12)(p15;p13)/46,idem,t(2;10)(p23;q22)	AML-MRC (de novo)	9 mon

FAB type M0: Acute myeloblastic leukemia with minimal differentiation FAB type M2: Acute myeloblastic leukemia with maturation FAB type M4: Acute myelomonocytic leukemia; AML, NOS: Acute myeoid leukemia not otherwise specified
MDS: Myelodysplastic syndrome; MRC: Myelodysplasia-related changes; RAEB-T: Refractory anemia with excess blasts in transformation
s: secondary; t: therapy related; NA: not available

Table 3: Characteristics of 38 AML and MDS Cases Associated With t(3;12) From the Mitelman Database.

protein-ε (C/EBP-ε) and deregulates terminal differentiation of granulocytes [17]. Kurokawa et al. demonstrated that EVI1 inhibits c-Jun N-terminal kinase (JNK) to suppress stress induced apoptosis [18].

A number of inversions and translocations have been described in human AML and MDS marrow cells involving chromosome 3q26, where the human gene is located. The most common *EVI1* chromosomal rearrangements include inv(3), t(3;3), t(3;12) and t(3;21). The t(3;12)(q26;p13) results in a fusion protein involving *ETV6* (also termed *TEL*), an ETS family transcription factor required for normal hematopoiesis. The prototype of AML/MDS with *EVI1* disruption is inv(3)/t(3;3)/*EVI1-GATA1*, which is recognized as a distinct entity in the current World Health Organization (WHO) classification. These patients often present de novo or arise from prior MDS, with frequent concurrent chromosomal 7 aberrations and have a short overall survival [1,19]. BM typically shows increased small hypolobated megakaryocytes and multilineage dysplasia. It is unclear if cases in which 3q26.2/*EVI1* partners with genes other than *GATA1* behave similarly to those with inv(3)/t(3;3) in clinical presentation and outcome. The t(3;12) is thought to juxtapose *ETV6* upstream of *EVI1* gene resulting in *EVI1* overexpression. We have demonstrated here that these cases are similar to those of AML/MDS

with inv(3)/t(3;3) in many of the features described above and justify their classification in the same subgroup as AML with inv(3)/t(3;3). As inv(3)/t(3;3) is identified following -7 in some cases, we also observed that t(3;12) may emerge several months after other cytogenetic aberrations or during relapsed AML. Interestingly, the emergence of t(3;12) was accompanied by rapid evolution to AML, within 6 months, in the MDS cases. These observations suggest that the t(3;12) may signify a general genetic instability and is a secondary event in many cases that contributes to disease progression. Based on rapid progression to AML, we also believed that the cases with a blast count in the range of MDS be still considered as AML in a similar approach as that of AML with t(8;21) or inv(16).

In summary, we have described 8 cases of AML or MDS with t(3;12)(q26.2;p13). Similar to cases with inv(3)q21q26.2) or t(3;3)(q21;q26.2), they usually show dysplasia, associated with abnormalities of chromosome 7 and a short survival despite multi-agent chemotherapy and bone marrow transplantation. However, unlike cases with inv(3)(q21q26.2) or t(3;3)(q21;q26.2), these cases are frequently associated with thrombocytopenia, megakaryocytic hypoplasia and *FLT3-ITD* mutation. The t(3;12) also occurred following other cytogenetic aberrations, suggesting it existed as a small subclone initially or emerged a secondary event in some cases. Overall, the findings suggest that this group of patients should be classified in the same subgroup as AML with inv3/t(3;3).

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