



# Myeloid neoplasms associated with t(3;12)(q26.2;p13) are clinically aggressive, show myelodysplasia, and frequently harbor chromosome 7 abnormalities

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Received: 19 May 2020 / Revised: 12 August 2020 / Accepted: 13 August 2020 / Published online: 27 October 2020  
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## Abstract

Sporadic reports of t(3;12)(q26.2;p13) indicate that this abnormality is associated with myeloid neoplasms, myelodysplasia, and a poor prognosis. To better characterize neoplasms with this abnormality, we assessed 20 patients utilizing clinicopathological data, cytogenetic, and targeted next-generation sequencing analysis. We also performed literature review of 58 prior reported cases. Patients included ten men and ten women with median age 55.8 years (range, 27.8–78.8). Diagnoses included 11 acute myeloid leukemia (AML, 5 de novo and 6 secondary), 5 myelodysplastic syndromes (MDS, 3 de novo excess blasts-2 and 2 therapy-related), 2 chronic myeloid leukemia *BCR-ABL1*-positive blast phase (1 de novo and 1 secondary), 1 primary myelofibrosis (secondary), and 1 mixed-phenotype acute leukemia T/myeloid (MPAL, secondary). Morphologic dysplasia was identified in all AML cases (5/5), MDS cases (4/4), therapy-related cases (3/3), half of myeloproliferative neoplasm cases (1/2), and one MPAL case assessed. The t(3;12) was detected de novo and in subsequent workups in 9 and 11 patients, respectively. Seven patients had t(3;12) only and eight patients had additional chromosome 7 abnormalities. Fluorescence in-situ hybridization detected *MECOM* ( $n = 11$ ) and *ETV6* ( $n = 7$ ) rearrangements in all cases assessed. *FLT3* internal tandem duplication was identified in five (25%) patients. We identified 13 genetic abnormalities in the de novo group ( $n = 9$ ), and 25 in the secondary disease group ( $n = 11$ ). All patients received chemotherapy, with seven allogeneic and two autologous stem cell transplantations. At last follow-up, 14 (70%) patients died with median survival of 6.3 months (range, 0.1–17.3) after detection of t(3;12). In summary, t(3;12)(q26.2;p13) is a rare cytogenetic abnormality in myeloid neoplasms. Myelodysplasia, chromosome 7 abnormalities, and high blast counts are common, and the prognosis is poor. Given the close relationship between the presence of this cytogenetic abnormality and the MDS-related changes, we recommend adding t(3;12)(q26.2;p13) to the list of AML with myelodysplasia-related changes defining abnormalities of the World Health Organization 2017 classification of myeloid neoplasms.

## Introduction

The *MECOM* locus consists of the *MYELODYSPLASTIC SYNDROME 1 (MDS1)* and *ecotropic viral integration site-1 (EVII)* genes located at 3q26.2. *EVII* was first identified as a pro-viral insertion site in murine leukemia [1]. *MECOM/3q26.2* rearrangement has been observed in various myeloid neoplasms, such as acute myeloid leukemia

(AML), myelodysplastic syndromes (MDS), myelodysplastic/myeloproliferative neoplasms, and chronic myeloid leukemias [2–6]. Patients with myeloid neoplasms associated with *MECOM/3q26* abnormalities have a poor response to chemotherapy and a poor outcome.

*MECOM/3q26* abnormalities result in overexpression of *MECOM*. Overexpression can be achieved via two mechanisms. The first mechanism involves juxtaposition of regulatory sequences near *MECOM* as a result of inv(3)(q21q26), t(3;3)(q21;q26), t(3;7)(q26;q21), or t(3;17)(q26;q22) [7–11]. The second mechanism results in fusion of the regulatory sequences near the *MECOM* gene as occurs in t(3;21)(q26;q22) and t(3;12)(q26;p13) where *MECOM* fuses with *RUNX1* or *ETV6* (formerly called *TEL*), respectively [7, 12]. Overexpression of *MECOM* as a result of *MECOM/*

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*ETV6* fusion is driven by the *ETV6* promoter resulting in cell proliferation and malignant transformation [13]. However, the mechanism by which *MECOM* induces leukemogenesis is not well understood.

Although myeloid neoplasms associated with *MECOM* abnormalities have been reported, in most of these studies the t(3;21)(q26;q22) or inv(3)(q21q26) were the focus. Myeloid neoplasms associated with t(3;12)(q26.2;p13) have received very little attention in the literature, mostly as case reports, rare case series, or as a minor mention in larger studies [12–40]. In this study, we characterize the clinicopathological features of 20 patients with myeloid neoplasms associated with t(3;12)(q26.2;p13).

## Materials and methods

### Case collection

We searched the files at our institution from January 1, 2000 through December 31, 2018 for hematologic neoplasms assessed by conventional cytogenetics and shown to carry t(3;12)(q26.2;p13). The following data were collected and analyzed: clinicopathological parameters, treatment regimens, response, and follow-up data. This study was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center.

We reviewed peripheral blood smears, bone marrow (BM) aspirate smears, and touch imprints that were stained with Wright–Giemsa. We also reviewed aspirate clot specimens and decalcified BM core biopsy specimens stained with hematoxylin and eosin.

### Cytogenetic analysis

Conventional cytogenetic analyses were performed on G-banded metaphase cells using standard methods. Twenty metaphases were analyzed and the results were reported according to the current International System for Human Cytogenetic Nomenclature. Fluorescence in-situ hybridization (FISH) analysis was performed on cultured BM cells or air-dried aspirate smears following standard protocols. The presence of t(3;12)(q26.2;p13) was confirmed by FISH analysis to involve either *MECOM* (Leica/Kreatech Inc.), *ETV6* (Abbott), or both using a dual color, break-apart DNA probe. A total of 200 interphase nuclei were analyzed.

### Mutation analysis

Next-generation sequencing analysis using a 28- or 81-gene panel was performed on ten cases following the instructions described previously [41]. Mutation analysis for *PTPN11*, *GATA binding protein 2* (*GATA2*), *KRAS*, *NRAS*, and

*RUNX1* was included in both gene mutation panels. In the remaining ten cases, PCR-based DNA Sanger sequencing and reverse transcriptase PCR were performed to assess the following genes: *C-KIT*, *NRAS*, *KRAS*, *FLT3*, *NPM1*, *CEBPA*, *IDH1*, *IDH2*, *DNMT3A*, and *JAK2*. For all 20 cases, reverse transcriptase PCR was used to assess for *BCR-ABL1*

## Results

### Clinicopathological characteristics

Patients included ten men and ten women with a median age of 55.8 years (range, 27.8–78.8) at time of initial diagnosis (Table 1). The t(3;12)(q26.2;p13) was detected at time of initial diagnosis in 9 patients and was detected over the clinical course in the other 11 patients. At t(3;12) detection, morphologic myelodysplasia was observed in the majority of patients (11 of 12, 92%) assessed (Fig. 1). One patient did not initially show myelodysplasia, but demonstrated myelodysplasia during the disease course (case #1). Of the remaining eight patients that precluded assessment of myelodysplasia at time of t(3;12) detection, six had too few cells in the aspirates and/or touch imprints for assessment but showed myelodysplasia at a later time point. The other two cases were too limited in quality, precluding reliable assessment. All three therapy-related cases showed evidence of dysplasia (one t-AML and two t-MDS).

At the time t(3;12) was detected, 11 patients had AML and 1 patient had mixed-phenotype acute leukemia T/myeloid not otherwise specified (MPAL), per World Health Organization 2017 (WHO 2017) classification of myeloid neoplasms. These patients consisted of AML with myelodysplasia-related changes (AML-MRC,  $n = 8$ ), acute monoblastic leukemia ( $n = 1$ ), not otherwise specified ( $n = 1$ ), therapy related ( $n = 1$ ), and MPAL ( $n = 1$ ). The t-AML patient had plasma cell myeloma (treated with bortezomib plus dexamethasone) and developed lung carcinoma 4 years later (treated with radiation). The myeloma was treated with autologous stem cell transplant (SCT) 6 months after the radiation. Five years after SCT, he developed t-MDS with 7% blasts. Twenty months after the MDS diagnosis, his disease evolved to t-AML with t(3;12) and 40% BM blasts. Of the 11 AML cases, 5 arose de novo and 6 were secondary-not including the secondary MPAL case. The MPAL patient initially had AML and evolved, as defined as progression in disease without prior complete remission, with phenotypic shift to MPAL after 25.4 months. In the AML group, the interval from initial disease to AML ranged from 0 to 10.5 years. For the eight AML patients with available data, the median BM blasts were 48% (range, 17–91%). Complete blood count (CBC) in these patients

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

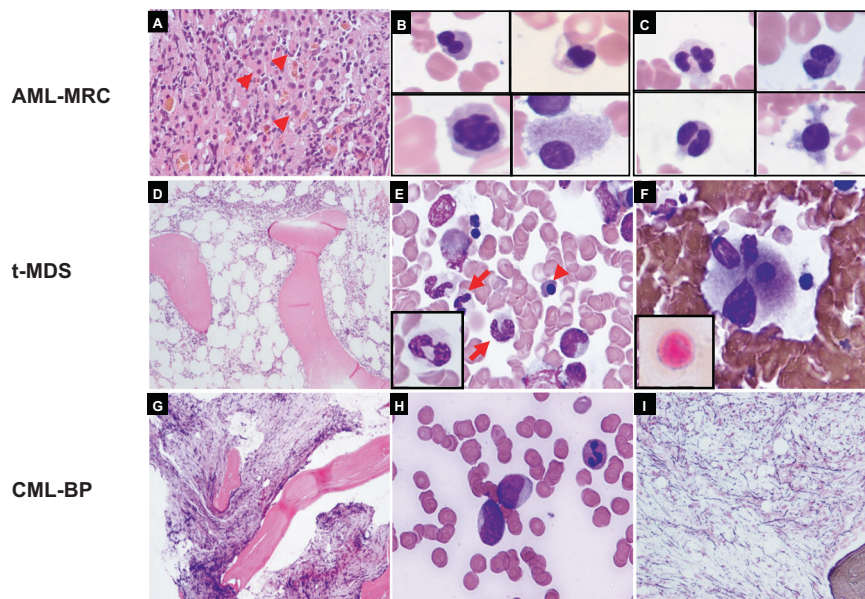
| Case # | Age/Sex | Diagnosis at t(3;12)               | BM Blasts (%) | PB Blasts (%) | WBC (K/ $\mu$ ) | Hgb (g/dL) | Plt (K/ $\mu$ ) | DYSPLASIA             |                       |                      |      |         |
|--------|---------|------------------------------------|---------------|---------------|-----------------|------------|-----------------|-----------------------|-----------------------|----------------------|------|---------|
|        |         |                                    |               |               |                 |            |                 | GRANS                 | RBC                   | MEGS                 | SCT  | OS (mo) |
| 3      | 34.6/M  | AML-MRC                            | 91            | 88            | 129.5           | 6.8        | 68              | ND                    | ND                    | ND                   | Allo | 150.0   |
| 11     | 32.5/F  | AML-MRC                            | 78            | 74            | 25.4            | 8.7        | 186             | Pres <sup>1,2,3</sup> | Pres <sup>1,4,5</sup> | Pres <sup>8,11</sup> | No   | 15.0    |
| 8      | 54.5/M  | Acute Mono Leuk                    | 63            | 21            | 113             | 8.1        | 74              | ND                    | ND                    | ND                   | No   | 17.3    |
| 10     | 45.3/F  | AML-MRC                            | 56            | 53            | 2.5             | 8.3        | 31              | Abs                   | Abs                   | Pres <sup>8</sup>    | Allo | 15.4    |
| 16     | 65.1/F  | t-AML                              | 40            | 19            | 2.7             | 8          | 54              | Pres                  | Pres                  | ND                   | Aut  | 6.8     |
| 18     | 49.5/M  | MPAL                               | 35            | 45            | 14.8            | 9.7        | 17              | Pres <sup>1,2</sup>   | Pres <sup>1,5</sup>   | Pres <sup>8</sup>    | No   | 4.6     |
| 20     | 78.8/M  | AML-MRC                            | 35            | 31            | 62.6            | 8.2        | 33              | Pres <sup>1,2</sup>   | Pres <sup>1,5</sup>   | Pres <sup>8</sup>    | No   | 0.1     |
| 17     | 27.8/M  | AML-MRC                            | 22            | 0             | 0.3             | 9.4        | 25              | ND                    | ND                    | ND                   | Allo | 4.8     |
| 4      | 57.3/M  | AML-MRC                            | 17            | 3             | 1.7             | 10.3       | 110             | Pres <sup>1,2</sup>   | Pres <sup>1,5,4</sup> | Pres <sup>8</sup>    | No   | 5.8     |
| 12     | 59.8/F  | AML (NOS)                          | ND            | ND            | ND              | ND         | ND              | ND                    | ND                    | ND                   | No   | 6.1     |
| 15     | 34.7/F  | AML-MRC                            | ND            | ND            | ND              | ND         | ND              | ND                    | ND                    | ND                   | Allo | 4.0     |
| 19     | 36.7/F  | AML-MRC                            | ND            | ND            | ND              | ND         | ND              | ND                    | ND                    | ND                   | Allo | 6.8     |
| 2      | 32.5/F  | MDS-EB2                            | 18            | 1             | 1.8             | 7.7        | 36              | ND                    | ND                    | ND                   | No   | 0.9     |
| 9      | 45.8/M  | MDS-EB2                            | 18            | 2             | 1.8             | 11.1       | 92              | ND                    | Pres <sup>5</sup>     | Pres <sup>8,9</sup>  | Allo | 82.3    |
| 14     | 73.3/F  | MDS-EB2                            | 10            | 0             | 1.93            | 10.58      | 112             | ND                    | Pres <sup>1,5</sup>   | Pres <sup>8</sup>    | No   | 2.3     |
| 13     | 63.7/F  | t-MDS                              | 3             | 1             | 2.2             | 9          | 112             | Pres <sup>1,3</sup>   | Pres <sup>1,5,6</sup> | Pres <sup>9,10</sup> | Allo | 31.0    |
| 6      | 57.0/M  | t-MDS                              | 1             | 0             | 4               | 9.8        | 24              | Pres <sup>1,3</sup>   | Pres <sup>1,6,7</sup> | ND                   | Aut  | 11.7    |
| 1      | 57.5/M  | CML, <i>BCR-ABL1</i> -positive, BP | 58            | 53            | 75.9            | 10.9       | 221             | Abs                   | Abs                   | Abs                  | No   | 6.5     |
| 7      | 58.3/M  | CML, <i>BCR-ABL1</i> -positive, BP | 27            | 16            | 3.2             | 8.4        | 61              | ND                    | ND                    | ND                   | No   | 12.0    |
| 5      | 61.8/F  | PMF                                | 4             | 0             | 16.2            | 13.1       | 89              | Pres <sup>2,3</sup>   | Abs                   | Pres <sup>8</sup>    | No   | 1.2     |

*M* male, *F* female, *Age* age at initial diagnosis in years, *WBC* white blood cells, *K* 1000,  $\mu$ l microliter, *Hgb* hemoglobin, *g/dl* grams per deciliter, *Plt* platelets, *PB* peripheral blood, *BM* bone marrow, *Abs* dysplasia absent, *Pres* “dysplastic forms” noted but morphology of dysplasia not described in the report, *Pres*<sup>1</sup> dysplasia with irregular nuclear contours, *Pres*<sup>2</sup> dysplasia with cytoplasmic hypogranularity, *Pres*<sup>3</sup> dysplasia with pseudo-Pelger-Huet forms, *Pres*<sup>4</sup> dysplasia with cytoplasmic vacuoles, *Pres*<sup>5</sup> dysplasia with nuclear cytoplasmic asynchrony, *Pres*<sup>6</sup> dysplasia with megaloblastoid changes, *Pres*<sup>7</sup> dysplasia with basophilic stippling, *Pres*<sup>8</sup> small dysplastic megakaryocytes with nuclear hypolobation, *Pres*<sup>9</sup> dysplastic megakaryocytes with separated nuclear lobes, *Pres*<sup>10</sup> dysplastic megakaryocytes with hypogranulated platelets, *Pres*<sup>11</sup> dysplastic micro-megakaryocyte, *SCT* hematopoietic stem cell transplant, *Aut* autologous hematopoietic stem cell transplant, *Allo* allogeneic hematopoietic stem cell transplant, *ND* not determined, *CML* chronic myeloid leukemia, *MDS-EB2* myelodysplastic syndrome with excess blasts 2, *AML* acute myeloid leukemia, *AML-MRC* acute myeloid leukemia with myelodysplasia-related changes, *Acute Mono Leuk* acute monoblastic leukemia, *PMF* primary myelofibrosis, *t-MDS* therapy-related myelodysplastic syndrome, *BP* blast phase, *NOS* not otherwise specified, *t-AML* therapy-related acute myeloid leukemia, *MPAL* mixed-phenotype acute leukemia T/myeloid not otherwise specified.

showed blasts 26% (range, 0–88%), WBC 14.1 K/ $\mu$ l (range, 0.3–129.5), Hgb 8.3 g/dl (range, 6.8–10.3), and platelets 61 K/ $\mu$ l (range, 25–186). At t(3;12) detection, all of the five AML patients assessed (100%) demonstrated dysplasia as did the one MPAL patient. The dysplastic features identified in this group are as follows: granulocytic precursors (irregular nuclear contours including pseudo-Pelger-Huet forms and cytoplasmic hypogranularity), erythroid precursors (irregular nuclear contours including bi-nucleation and nuclear budding, cytoplasmic vacuoles, and nuclear cytoplasmic asynchrony), megakaryocytes (small, nuclear hypolobation, micro-megakaryocytes). At time of t(3;12) detection, three AML and one MPAL patient had myelodysplasia in all three lineages, while one t-AML patient had myelodysplasia in two lineages, and one AML-MRC had

myelodysplasia in one lineage. Six AML cases were not assessed for dysplasia due to too few non-blast cells. The findings are summarized in Table 1.

At the time t(3;12) was detected, the five MDS cases included three de novo and two therapy-related disease. In the latter group, one patient was treated for diffuse large B-cell lymphoma, 52 months later a BM biopsy performed due to cytopenia showed MDS with t(3;12), 1% blasts in a 50% cellular aspirate clot with myelodysplasia in the granulocytic and the erythroid precursors; megakaryocytes were markedly decreased in numbers. The other t-MDS patient was treated for breast cancer 12 years prior to development of t-MDS. The five MDS cases showed median BM blasts of 10% (range, 1–18%). The CBC showed blasts 1% (range, 0–2%), WBC 1.9 K/ $\mu$ l



**Fig. 1 Representative myeloid neoplasms with t(3;12)(q26.2;p13).** **a** A representative case of BM core biopsy of AML with t(3;12)(q26.2;p13) (case #11) with a 100% hypercellular marrow with a cluster of dysplastic megakaryocytes, three of which are highlighted by arrowheads. **b** Aspirate shows myelodysplasia in erythroid precursors (top left: irregular nuclear contours; top right: irregular nuclear contours and cytoplasmic vacuolization; bottom left: nuclear cytoplasmic asynchrony) and megakaryocytes (bottom right: hypolobated). **c** Aspirate shows myelodysplasia in granulocytic precursors (top left: irregular nuclear contours and hypogranularity; top right: irregular nuclear contours; bottom left: pseudo-Pelger-Huet form) and megakaryocytes (bottom right: micro-megakaryocyte). **d** A representative case of BM core biopsy of therapy-related MDS with t(3;12)(q26.2;p13) (case #13) with a 30% cellular marrow. **e** Aspirate shows

dysplasia in erythroid precursors with nuclear: cytoplasmic asynchrony and mildly irregular nuclear contours (arrowhead); dysplasia in granulocytic precursors with abnormal nuclear segmentation and abnormally clumped chromatin (arrows) as well as and pseudo-Pelger-Huet form granulocyte (inset). **f** Dysplastic megakaryocytes with separated nuclear lobes as well as the presence of a representative ring sideroblast (inset). **g** A representative BM core biopsy of CML-BP (CML, *BCR-ABL1*-positive, BP) with t(3;12)(q26.2;p13) (case #7) with a hypercellular marrow with extensive myelofibrosis. **h** Aspirate with increased blasts. **i** Reticulin stain demonstrates increased myelofibrosis, trichrome stain showed a few scattered collagen fibers (not shown) giving an overall grade of MF-2 (scale of MF-0–MF-3). Original magnification: **a**  $\times 400$ ; **d**, **g**, **i**  $\times 200$ ; **e**, **f**, **h**  $\times 400$ ; **b**, **c**, inset  $\times 1000$ .

(range, 1.8–4.0), Hgb 9.8 g/dl (range, 7.7–11.1), and platelets 92 K/ $\mu$ l (range, 24–112). At t(3;12) detection, all four MDS patients (100%) assessed for dysplasia demonstrated dysplasia. One MDS-excess blasts-2 (MDS-EB2) patient (#2) was not assessed due to too few non-blast cells. The dysplastic features identified in this group are as follows: granulocytic precursors (irregular nuclear contours including pseudo-Pelger-Huet forms), erythroid precursors (irregular nuclear contours including nuclear budding, nuclear cytoplasmic asynchrony, megaloblastoid changes, and basophilic stippling), megakaryocytes (small, nuclear hypolobation, separated nuclear lobes, and with hypogranulated platelets). At t(3;12) detection, one t-MDS had myelodysplasia in all three lineages, while one t-MDS patient and two MDS-EB2 patients had myelodysplasia in two lineages. The findings are summarized in Table 1.

At the time t(3;12) was detected, three patients were classified as myeloproliferative neoplasms, two had chronic myeloid leukemia, *BCR-ABL1*-positive, blast phase (CML-BP), and one had primary myelofibrosis (PMF). In 1 CML-BP case (#7) and the PMF case, the t(3;12) was detected

later in the disease course. The first patient, after 22 months of CML, *BCR-ABL1*-positive, chronic phase (CML-CP) presented to our institution with 53% myeloid blasts in the blood, 85% hypercellular BM with 58% myeloid blasts in the aspirate and myelofibrosis (MF-2). The second CML-BP patient initially had CML-CP for 1 year and transformed to blast phase with 16% blasts in blood, 30% cellular marrow with 27% blasts in the aspirate and myelofibrosis (MF-2). One patient with PMF presented with 80% hypercellular BM with megakaryocytic hyperplasia with occasional large forms, no increase in blasts, and elevated platelets of 917 K/ $\mu$ l. Of the three MPN patients, two were assessed for dysplasia at t(3;12) detection (case #1 and 5). The PMF patient (#5) demonstrated dysplasia. CML-BP patient (#1) did not demonstrate dysplasia and the CML-BP patient (#7) was not assessed for dysplasia due to too few non-blast cells. The dysplastic features identified in this group are as follows: granulocytic precursors (cytoplasmic hypogranularity and pseudo-Pelger-Huet forms) and megakaryocytes (small with nuclear hypolobation). At t(3;12) detection, one PMF had myelodysplasia in two lineages. The findings are summarized in Table 1. A



predominance of monolobate or bilobate megakaryocytes as seen in myeloid neoplasms with *inv(3)* was not present in this cohort of patients with myeloid neoplasms with *t(3;12)*.

### Cytogenetic and molecular findings

Results of conventional cytogenetic analysis identified the *t(3;12)(q26.2;p13)* in all 20 patients (Table 2 and Fig. 2a). Seven (35%) patients had *t(3;12)(q26.2;p13)* as the sole chromosomal abnormality, and seven (35%) had two cytogenetic abnormalities, and the remaining six (30%) patients had complex karyotype ( $\geq 3$  cytogenetic abnormalities). Apart from *t(3;12)*, chromosome 7 abnormalities were observed in eight patients including monosomy 7 ( $n = 5$ ). One patient (5%) each had *add(7q11.2)*, *del(7q11.2)*, and *del(7q22q36)*. Chromosome 22 abnormalities were observed in five (25%) patients including three with *t(9;22)* as well as monosomy 22 or *idic(22)(p11.2)* observed in one patient (5%) each.

FISH studies were performed to assess *MECOM* in 11 patients and *ETV6* in 7 patients. Rearrangements of *MECOM* and *ETV6* were detected in all tested patients (Fig. 2b, c). Due to an obvious *t(3;12)* abnormality observed in almost all of analyzed metaphases (90–100%) by chromosomal analysis in five cases, no *MECOM* or *ETV6* FISH were performed.

The *de novo* group consisted of the nine patients who had *t(3;12)* at time of initial diagnosis. This included five AML (#3, 8, 10, 11, and 19), three MDS-EB2 (#2, 9, and 14), and one had CML-BP (#1). Eleven patients acquired *t(3;12)* a median of 16.2 months (range, 7.2–60.8) after initial diagnosis (secondary group). This group included six AML (#4, 12, 15–17, and 20), two t-MDS (#6 and 13), one CML-BP (#7), one PMF (#5), and one MPAL (#18).

The *de novo* AML group ( $n = 5$ ) had 11 genetic abnormalities (*BCOR*, *ETNK1*, *FLT3 ITD x2*, *FLT3 exon 15*, *KIT*, *KRAS*, *NRAS x2*, *PTPN11*, and *RUNX1*). The AML group where the *t(3;12)* was detected later in the disease course ( $n = 6$ ) plus the one MPAL patient had 20 genetic abnormalities (*BCR-ABL1*, *BRAF*, *DNMT3A*, *FLT3 ITD x2*, *FLT3 TKD*, *GATA2*, *IKZF1*, *KIT*, *KRAS x2*, *NRAS x2*, *PTPN11 x2*, *RUNX1*, *SF3B1 x2*, *U2AF1*, and *WT1*). The variant allele frequency (VAF) for the former may have a lower trend, median 8.0% (range 7–46%,  $n = 5$ ), compared to the secondary disease group, median 21.0% (range 8–47%,  $n = 9$ ), but was not significantly lower ( $p = 0.21$ ). VAFs reported as “<5%” and mutations without reported VAFs were not included in the calculations. The lack of significance differences in the two groups is likely due to the small sample sizes (Fig. 3).

The *de novo* MDS group ( $n = 3$ ) had one genetic abnormality (*SF3B1*), while the secondary t-MDS group

( $n = 2$ ) where the *t(3;12)* was detected later in the disease course had three genetic abnormalities (*KRAS*, *NRAS*, and *TET2*). The VAF for former group with the *SF3B1* mutation was 10%, while for the secondary t-MDS group is median 11.5% (range 7–16%,  $n = 2$ ). VAFs reported as “<5%” were not included in the calculations.

### Treatment, response, and prognosis

Nineteen patients had treatment data available. All 19 received chemotherapy, including 14 who received hypomethylating drugs such as decitabine, guadecitabine, or azacitidine; 12 received antimetabolite chemotherapeutic agents such as cytarabine, fludarabine, or clofarabine; 11 (55%) received topoisomerase II inhibitors such as idarubicin, daunorubicin, mitoxantrone, or etoposide; 4 (20%) received immunotherapies such as anti-CD20, anti-CD33, anti-CD45, or anti-CD123; 4 (20%) patients received venetoclax or bortezomib; 3 (15%) received the *FLT3*: inhibitors sorafenib or gilteritinib; 2 (10%) received *BCR-ABL1* tyrosine kinase inhibitors imatinib or dasatinib; and 1 (5%) patient was treated with anagrelide, methotrexate, pembrolizumab, revlimid, or vincristine. Nine (45%) patients underwent SCT: seven allogeneic and two autologous (Table 1). The autologous SCTs were for a patient with DLBCL and one patient with PCM, both of whom later developed therapy-related myeloid neoplasms.

Seven patients relapsed (#1, 3, 10, 15, and 17–19), defined as recurrence of the original disease. Five patients received allogeneic SCT and relapsed after a median duration of 11 months (range 1–28). Two patients (#6 and 16) received autologous SCT for nonmyeloid-related neoplasms before developing t-MDS. Patient (#6) received an autologous SCT for DLBCL, received an allogeneic SCT, and developed MDS then AML 11.1 and 31.2 months after the transplant, respectively. Patient (#15) received two allogeneic SCTs and relapsed 28 and 5 months after the first and second transplants, respectively. Two patients with allogeneic SCT remained in remission after 79.3 and 22 months of follow-up, respectively. Ten patients never achieved complete remission (#2, 4–8, 11, 12, 16 and 20). Four patients were lost to follow-up (two after allogeneic SCT, one after complete response, and one after relapse).

Clinical follow-up was available for all 20 patients. The median follow-up after detection of *t(3;12)* was 6.6 months (range, 0.1–150). During follow-up, ten patients had persistent disease and seven relapsed. Four patients with MDS (#4, 16, 17, and 20) progressed to AML after a median of 9.7 months (range, 6.2–19.5). Of the 14 patients who died by the end of the study, the median survival was 6.3 months (range, 0.1–17.3) after detection of *t(3;12)*.

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

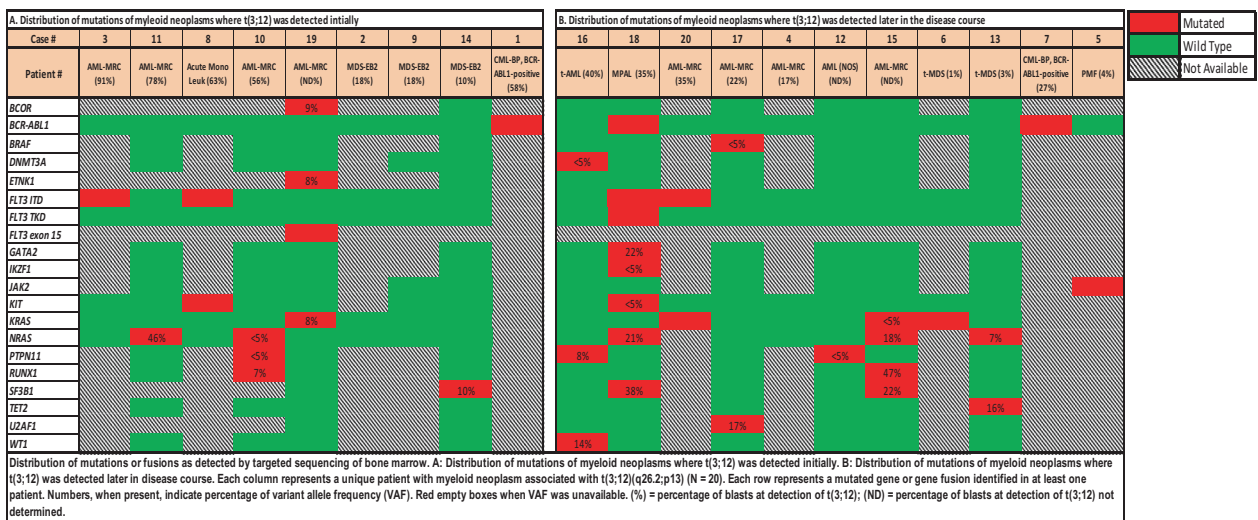
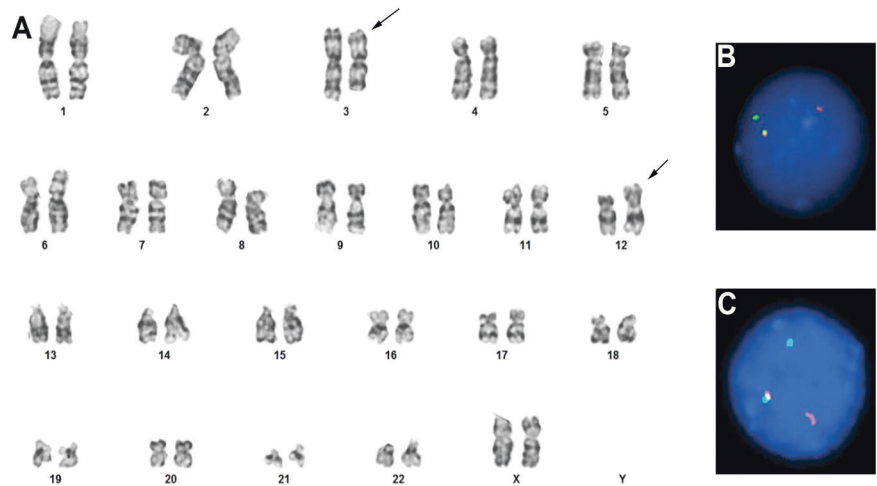
| Case # | Initial Diagnosis | Time to t(3;12) mo | Diagnosis at t(3;12) | Karyotype   | # CG Abn | EVI/ FISH | ETV6 FISH | THERAPY   |  | STATUS |
|--------|-------------------|--------------------|----------------------|---|----------|-----------|-----------|---|--|--------|
|        |                   |                    |                      |   |          |           |           | BEFORE t(3;12)  | AFTER t(3;12)  |        |
| 3      | AML-MRC           | 0.0                | AML-MRC              | 45,XY,t(3;12)(q26.2;p13),-7[19]   | 2        | ND        | Positive  | None  | Ida, Ara-C, Sor, Allo SCT                                | Alive  |
| 11     | AML-MRC           | 0.0                | AML-MRC              | 45,XX,t(3;12)(q26.2;p13),-7[20]   | 2        | Positive  | ND        | None  | Ara-C, Ida, Daun, FLAG, MEC, Dec                         | Dead   |
| 8      | Acute Mono Leuk   | 0.0                | Acute Mono Leuk      | 46,XY,t(3;12)(q26.2;p13)[20]  | 1        | ND        | Positive  | None  | Daun, Ara-C, Ida, Velc, Mit, Etio, Clof, Hyd, 5-aza, Sor | Dead   |
| 10     | Acute Meg Leuk    | 0.0                | AML-MRC              | 46,XX,t(3;12)(q26.2;p13)[19]/46,XX[11]  | 1        | Positive  | ND        | None  | Daun, Dec, CIA, Pred, Allo SCT, 5-aza, CLIA              | Dead   |
| 16     | t-MDS             | 19.0               | t-AML                | 45,XX,t(3;12)(q26.2;p13),-7,idec(22)(p11.2)[16]/46,XX[4]  | > 3      | Positive  | ND        | Velc, Dex, Rads (Lung Adeno), Auto SCT, Lenal, Dec, IMGNG32 (IL-3RA or CD123) | Daun, Ara-c  | Dead   |
| 18     | MPAL              | 25.4               | MPAL                 | 46,XY,t(3;12)(q26.2;p13)[5]/46,idem,t(9;22)(q34q11.2)[4]/47,idem,t(5;15)(q31;q22),+mar[3]/45~48,idem,+1~2mar[cp8] | > 3      | Positive  | ND        | Daun, Ara-c, FLAG, Ara-c, CLAG-M, Anti-CD33, 5-aza                            | FLAG, Hyd, Das   | Dead   |
| 20     | MDS               | 7.2                | AML-MRC              | 46,XY,t(3;12)(q26.2;p13),del(10)(q22q24)[19]  | 2        | ND        | ND        | 5-aza, Jak Inhib  | CLIA, Dec, Ven, Allo SCT, SGI-110                        | Dead   |
| 17     | Hypocellular MDS  | 9.2                | AML-MRC              | 45,XY,t(3;12)(q26.2;p13),del(5)(q31q33),-7[20]  | > 3      | Positive  | ND        | 5-aza, CLIA, Decitabine, Venetoclax   | Allog SCT, DNMT inhib                                    | Dead   |
| 4      | MDS-EB2           | 10.7               | AML-MRC              | 46,XY,t(3;12)(q26.2;p13),add(7)(q11.2)[18]/46,XY[2]   | 2        | ND        | ND        | 5-aza, anti-CD33  | Flud; Ara-c  | Dead   |
| 12     | AML (NOS)         | 11.0               | AML (NOS)            | 46,XX,t(3;12)(q26.2;p13)[3]/41~45,idem,-22[cp6]   | 2        | ND        | Positive  | None  | Ara-C, Ida, Gil, MEC, DNMTi, Dec                         | Dead   |
| 15     | AML-MRC           | 42.5               | AML-MRC              | 46,XX,t(3;12)(q26.2;p13),del(7)(q22q36)[18]/46,idem[cp2]  | 2        | Positive  | ND        | Ara-c, 5-Aza, MEC, Clof, Allo SCT x2, Anti-CD45, aza                          | Flud, Ara-c, Ven, 5-aza                                  | Dead   |
| 19     | AML-MRC           | 0.0                | AML-MRC              | 46,XX,t(3;12)(q26.2;p13),del(6)(q21q25),del(7)(q11.2)[12]   | > 3      | Positive  | ND        | None  | Allo SCT, Mylotarg, Ven                                  | Alive  |
| 2      | MDS-EB2           | 0.0                | MDS-EB2              | 46,XX,t(3;12)(q26.2;p13)[18]/46,XX[2]   | 1        | ND        | ND        | None  | Daun, Ara-c, Allo SCT                                    | Alive  |
| 9      | MDS-EB2           | 0.0                | MDS-EB2              | 46,XY,t(3;12)(q26.2;p13)[10]/46,XY[10]  | 1        | Positive  | Positive  | None  | No F/U   | Alive  |
|        |                   |                    |                      |   |          |           |           |   | CIA, Allo-SCT, Flud ± Clof                               | Alive  |

Table 2 (continued)

| Case # | Initial Diagnosis          | Time to t(3;12) mo | Diagnosis at t(3;12)       | Karyotype  | # CG Abn | EVI FISH | ETV6 FISH | THERAPY   |                                   | STATUS |
|--------|----------------------------|--------------------|----------------------------|--|----------|----------|-----------|---|-----------------------------------|--------|
|        |                            |                    |                            |  |          |          |           | BEFORE t(3;12)  | AFTER t(3;12)                     |        |
| 14     | MDS-EB2                    | 0.0                | MDS-EB2                    | 46,XX,ins(12;3)(p13;q26.2q21)[11]/46,XX[9]                                   | 1        | Positive | Positive  | None  | 5-aza, Pemb                       | Alive  |
| 13     | t-MDS                      | 0.0                | t-MDS                      | 46,XX,t(3;12)(q26.2;p13)[2]/46,XX[23]  | 1        | Positive | Positive  | TAC, Rad  | DNMTI, Allo SCT                   | Alive  |
| 6      | DLBCL                      | 51.9               | t-MDS                      | 46,XY,t(3;12)(q26.2;p13),r(7)[17]/45,XY,t(3;12)(q26.2;p13),-7[3]             | > 3      | Positive | ND        | RCVAD, Rad, RICE, Auto SCT, MEK 1/2 Inhib, Ara-c, Ida | FLAG                              | Dead   |
| 1      | CML, BCR-ABL/-positive, BP | 0.0                | CML, BCR-ABL/-positive, BP | 46,XY,t(3;12)(q26.2;p13),t(9;22)(q34;q11)[18]                                | 2        | ND       | ND        | None  | Hyd, IFN, IL-2, BCR-ABL1 TKI, DAC | Dead   |
| 7      | CML, BCR-ABL/-positive, BP | 13.5               | CML, BCR-ABL/-positive, BP | 49,XY,t(3;12)(q26.2;p13),+8,+8,-i(8)(q10),i(8)(q10)x2,t(9;22)(q34;q11.2)[19] | > 3      | ND       | Positive  | Ara-c, BCR-ABL1 TKI, Das, Dec                         | Rad to brain                      | Dead   |
| 5      | PMF                        | 60.8               | PMF                        | 46,XX,t(3;12)(q26.2;p13)[20]   | 1        | ND       | ND        | Phlebotomy, Anag, Splen, Hyd                          | No F/U                            | Dead   |

*Acute Meg Leuk* acute megakaryoblastic leukemia; *Acute Mono Leuk* acute monoblastic leukemia; *allo SCT* Allogenic Stem Cell Transplant; *AML* acute myeloid leukemia; *AML-MRC* acute myeloid leukemia with myelodysplasia-related changes; *Anag* Anagrelide; Ara-C Cytarabine; *Auto SCT* Autologous Stem Cell Transplant; *5-aza* Azacytidine; *BP* blast phase; # *CG* Abn number of cytogenetic abnormalities; *CIA* Clofarabine, Idarubicin, and Ara-C; *CLAG-M* Cladribine, Ara-C, Filgrastim(G-CSF), and Mitoxantrone; *CLIA* Cladribine, idarubicin, and Ara-C; *Clof* Clofarabine; *CML chronic myeloid leukemia*; *Das* Dasatinib; *Dam* Daunorubicin; *Dec* Decitabine; *Dex* Dexamethasone; *DAC*: Dexamethasone, High-dose Ara-C, and Carboplatin; *DLBCL* Diffuse Large B-cell Lymphoma; *DNMTI* DNA methyltransferase inhibitors; *Etop* Etoposide; *FLAG Fludarabine, Ara-C, and filgrastim*; *Flud* Fludarabine; *Gil* Gilteritinib; *Hyd* Hydrea; *Ida* Idarubicin; *IFN interferon*; *Lenal* Lenalidomide; *MDS-EB2 myelodysplastic syndrome with excess blasts 2*; *MEC* Mitoxantrone, Etoposide, Ara-C; *Mit* Mitoxantrone; *MPAL* mixed-phenotype acute leukemia T/myeloid, not otherwise specified; *Mylortag* Gemtuzumab Ozogamicin; *ND* not determined; *No F/U* Patient lost to follow up; *Pemb* Pembrolizumab; *PMF* primary myelofibrosis; *Pred* Prednisone; *Rad* Radiation; *RCVAD*: rituximab, cyclophosphamide, vincristine, doxorubicin (Adriamycin), and dexamethasone; *RICE* Rituximab, Ifosfamide, Carboplatin, Etoposide; *SGI-110* 2nd gen hypometh agent; *Sor* Sorafenib; *Splen* Splenectomy; *TAC* Taxol, Adriamycin, Cytosine; *TKI* Tyrosine Kinase inhibitor; *t-MDS* therapy related myelodysplastic syndrome; *NOS* not otherwise specified; *Velc* Velcade, *Ven* Venetoclax.

**Fig. 2 Cytogenetic abnormalities of case #13. a** Conventional study revealed: 46,XX,t(3;12)(q26.2;p13). **b** FISH using *ETV6* dual-color break-apart probe revealed split signals, indicating *ETV6* rearrangement. **c** FISH using *MECOM* dual-color break-apart probe revealed split signals, indicating *MECOM* rearrangement.



**Fig. 3 Distribution of mutations or fusions as detected by targeted sequencing of bone marrow. a** Distribution of mutations of myeloid neoplasms where t(3;12) was detected initially. **b** Distribution of mutations of myeloid neoplasms where t(3;12) was detected later in disease course. Each column represents a unique patient with myeloid neoplasm associated with t(3;12)(q26.2;p13) (n = 20). Each row

represents a mutated gene or gene fusion identified in at least one patient. Numbers, when present, indicate percentage of variant allele frequency (VAF). Red empty boxes when VAF was unavailable. % = percentage of bone marrow blasts at detection of t(3;12); ND = percentage of blasts at detection of t(3;12) not determined.

**Discussion**

The t(3;12) rearrangement is a rare event in hematologic neoplasms. In a study of 9550 cases of hematologic neoplasms with cytogenetic data, only ten (0.1%) had t(3;12) [13, 19]. Here we report 20 patients with hematologic neoplasms associated with t(3;12)(q26.2;p13). Fifteen cases were tested by FISH for *MECOM* (n = 11) and/or *ETV6* (n = 7) rearrangements. All patients in this study group had myeloid neoplasms including AML (n = 11), MDS (n = 5), CML-BP (n = 2), PMF (n = 1), and MPAL (n = 1). In our experience at a large cancer center, we identified no cases of t(3;12) associated with lymphoid neoplasms, which is consistent with the findings in the literature.

A total of 58 reports of t(3;12)(q26.2;p13) have been published in the English literature as case reports, case series, or as karyotypes in larger studies (Tables 3 and 4). There were 34 men and 23 women (gender not reported for one patient) with a median age of 47.5 years (range, 4.8–87). We reviewed these published cases and reclassified the neoplasms, when possible, according to the WHO 2017 [42]. All cases reported in the literature have been myeloid neoplasms. AML was most common with 43 (74%) cases, followed by MDS with 9 (16%) cases, and 6 CML cases (10%, 3 CML-BP, 2 CML-CP, and 1 atypical CML, *BCR-ABL1*-negative).

In our study group, the t(3;12)(q26.2;p13) was present at time of initial diagnosis in 9 (45%) patients and acquired during the course of disease in the other 11 (55%) patients.



**Table 3** Characteristics of 58 Myeloid Cases Associated With t(3;12) Reported In The Literature.

| Case # | Reference | Age/ Sex | Diagnosis      | Karyotype  | # CG Abn | BM Blasts (%) | PB Blasts (%) | WBC (10 <sup>9</sup> /L) | Hgb (g/dL) | Plt (10 <sup>9</sup> /L) | SCT FISH | EVJ FISH | ETV6 FISH | OS (mo) |
|--------|-----------|----------|----------------|--|----------|---------------|---------------|--------------------------|------------|--------------------------|----------|----------|-----------|---------|
| 1      | ACHkar    | 63/F     | AMML           | 47,XX,+8,(3;12)(q26;p13)[18]/47,XX,+8[2]   | 2        | ND            | ND            | 5.4                      | 9.61       | 132                      | ND       | Positive | Positive  | 2       |
| 4      | Beyer     | 29/M     | AML (NOS)      | 46,XY,t(3;12)(q26;p13)[12]   | 1        | ND            | ND            | ND                       | ND         | ND                       | ND       | ND       | ND        | ND      |
| 7      | Bobadilla | 61/M     | AML w/ mat     | 46,XY,t(3;12)(q26;p13)[20]   | 1        | ND            | ND            | ND                       | ND         | ND                       | ND       | Positive | ND        | ND      |
| 8      | Bobadilla | 37/M     | AML w/o mat    | 46,XY,t(3;12)(q26;p13)[19]/46,iderm,der(9)t(1;9)(q10;p10)[2]   | > 3      | ND            | ND            | ND                       | ND         | ND                       | ND       | Positive | ND        | ND      |
| 9      | Bobadilla | 53/F     | AML (NOS)      | 46,XX,t(3;12)(q26;p13)[20]   | 1        | ND            | ND            | ND                       | ND         | ND                       | ND       | Positive | ND        | ND      |
| 10     | Dastugu   | 67/F     | Acute Meg Leuk | 46,XX,t(3;12)(q26;p13)[20]   | 1        | ND            | ND            | ND                       | ND         | ND                       | ND       | Positive | ND        | ND      |
| 11     | Haferiach | 74/M     | AML (NOS)      | 46,XY,t(3;12)(q26;p13)[20]   | 1        | ND            | ND            | ND                       | ND         | ND                       | ND       | Positive | Positive  | ND      |
| 12     | Haferiach | 27/M     | AML (NOS)      | 46,XY,t(3;12)(q26;p13)[4]/46,XY[2]   | 1        | ND            | ND            | ND                       | ND         | ND                       | ND       | Positive | Positive  | ND      |
| 13     | Haferiach | 61/F     | AML-MIRC       | 46,XX,t(3;12)(q26;p13),del(5)(q14q34)[20]  | 2        | ND            | ND            | ND                       | ND         | ND                       | ND       | Positive | Positive  | ND      |
| 14     | Haferiach | 77/F     | AML-MIRC       | 46,XX,t(3;12)(q26;p13),del(5)(q14q34)[3]/46,XX[4]  | 2        | ND            | ND            | ND                       | ND         | ND                       | ND       | Positive | Positive  | ND      |
| 15     | Haferiach | 67/F     | AML (NOS)      | 46,XX,t(3;12)(q26;p13)[10]/46,XX[11]   | 1        | ND            | ND            | ND                       | ND         | ND                       | ND       | Positive | Positive  | ND      |
| 16     | Haferiach | 48/M     | t-AML          | 45,XY,t(3;12)(q26;p13),-7[9]/46,XY[12]   | 2        | ND            | ND            | ND                       | ND         | ND                       | ND       | Positive | Positive  | ND      |
| 17     | Haferiach | 50/M     | AML-MIRC       | 45,XY,t(3;12)(q26;p13),-7[5]/46,XY[15]   | 2        | ND            | ND            | ND                       | ND         | ND                       | ND       | Positive | Positive  | ND      |
| 20     | Haferiach | 48/F     | AML-MIRC       | 46,XX,der(5)t(5;6)(q14;p22),der(6)t(6;7)(p22;q2),der(7)t(5;7)(q?;q1),der(12)t(3;12)(q26;p13)[3]/47,XX,der(5)t(5;6)(q14;p22),der(6)t(6;7)(p22;q?),der(7)t(5;7)(q?;q1),der(12)t(3;12)(q26;p13),+2[19]    | > 3      | ND            | ND            | ND                       | ND         | ND                       | ND       | Positive | Positive  | ND      |
| 21     | Hazard    | 13/F     | AML w/ mat     | 45,XX,t(3;12)(q26;p13),-7  | 2        | 37            | 10            | 6.5                      | 8.2        | 79                       | Yes      | ND       | ND        | 10      |
| 22     | Iwase     | 46/M     | AMML           | 46,XY,t(3;12)(q26;p13)   | 1        | 54            | 53            | 53.8                     | 6.9        | 765                      | ND       | ND       | ND        | 6       |
| 23     | Kim       | 60/M     | t-AML          | 45,XY,t(3;12)(q26;p13),-7[16]  | 2        | 26            | 16            | 4.45                     | 6          | 68                       | ND       | Positive | Positive  | ND      |
| 24     | Langabeer | ?/M      | AML (NOS)      | 46,XY,t(3;12)(q26;p13) [20]  | 1        | ND            | ND            | ND                       | ND         | ND                       | ND       | ND       | ND        | ND      |
| 25     | Lavallee  | 41/F     | AML-MIRC       | 46,XX,t(3;12)(q26;p13)[2]/ 45,iderm, -7[20]  | 2        | ND            | ND            | ND                       | ND         | ND                       | ND       | ND       | ND        | ND      |
| 26     | Lughart   | ?/F      | AML (NOS)      | 46,XX,t(3;12)(q26;p13)[20]   | 1        | ND            | ND            | ND                       | ND         | ND                       | ND       | ND       | ND        | ND      |
| 27     | Lughart   | ?/F      | AML (NOS)      | 46,XX,t(3;12)(q26;p13)[18]   | 1        | ND            | ND            | ND                       | ND         | ND                       | ND       | ND       | ND        | ND      |
| 28     | Lughart   | ?/M      | AML (NOS)      | 46,XY,t(3;12)(q26;p13)[55]   | 1        | ND            | ND            | ND                       | ND         | ND                       | ND       | ND       | ND        | ND      |
| 29     | Lughart   | ?/M      | AML (NOS)      | 46,XY,t(3;12)(q26;p13)[20]   | 1        | ND            | ND            | ND                       | ND         | ND                       | ND       | ND       | ND        | ND      |
| 30     | Lughart   | ?/M      | AML (NOS)      | 46,XY,t(3;12)(q26;p13)[7]/47,iderm,+18[4]/46,XY[8]   | 2        | ND            | ND            | ND                       | ND         | ND                       | ND       | ND       | ND        | ND      |
| 31     | Lughart   | ?/F      | AML (NOS)      | 46,XX,t(3;12)(q26;p13)[13]/46,XX[7]  | 1        | ND            | ND            | ND                       | ND         | ND                       | ND       | ND       | ND        | ND      |
| 32     | Lughart   | ?/F      | AML (NOS)      | 46,XX,t(3;12)(q26;p13)[12]   | 1        | ND            | ND            | ND                       | ND         | ND                       | ND       | ND       | ND        | ND      |
| 33     | Lughart   | ?/F      | AML (NOS)      | 46,XX,t(3;12)(q26;p13)[20]   | 1        | ND            | ND            | ND                       | ND         | ND                       | ND       | ND       | ND        | ND      |
| 34     | Lughart   | ?/F      | AML (NOS)      | 46,XX,t(3;12)(q26;p13)   | 1        | ND            | ND            | ND                       | ND         | ND                       | ND       | ND       | ND        | ND      |
| 35     | Lughart   | ?/M      | AML (NOS)      | 46,XX,t(3;12)(q26;p13)   | 1        | ND            | ND            | ND                       | ND         | ND                       | ND       | ND       | ND        | ND      |
| 56     | Yamamoto  | 45/M     | AML-MIRC       | 46,XX,t(3;12)(q26;p13)   | 1        | 39            | 35            | 9.1                      | 9.6        | 26                       | Yes      | ND       | Positive  | 18      |
| 37     | Nishimura | 49/F     | AML w/o mat    | 46,XY,t(3;12)(q26;p13),add(7)(p13),add(12)(p11.2)[18]/46,XY,t(3;12;5)(q26;p13;q31),add(7)(p13),add(12)(p11.2)[2] Later: 46,XY,t(3;12)(q26;p13),t(7;12)(p15;p13)[5]/46,s,t(2;10)(p23;q22)[3]            | > 3      | 65.4          | 65            | 6.3                      | 6.5        | 46                       | ND       | ND       | ND        | 19      |
| 41     | Peeters   | 33/F     | AML-MIRC       | 46,XX,t(3;12)(q26;p13),del(7)(q22)   | 2        | 16.2          | 8             | 21.8                     | 11.1       | 311                      | ND       | Positive | Positive  | 6       |
| 42     | Poppe     | 41/M     | AML-MIRC       | 45,XY,t(3;12)(q26;p13),-7  | 2        | ND            | ND            | ND                       | ND         | ND                       | ND       | ND       | ND        | ND      |
| 43     | Poppe     | 52/M     | AML-MIRC       | 46,XY,t(3;12)(q26;p13),-7,-t   | > 3      | ND            | ND            | ND                       | ND         | ND                       | ND       | Positive | Positive  | ND      |
| 44     | Raynaud   | 60/M     | AML-MIRC       | 46,XY,t(3;12)(q26;p13),del(17)(q21q35)[20]   | 2        | 44            | 4             | 2.2                      | 9.6        | 174                      | ND       | Positive | Positive  | 7       |
| 45     | Raynaud   | 87/M     | AML-MIRC       | 46,XY,t(3;12)(q26;p13),del(7)(q21;q34)[19]/46,XY,t(3;12)(q26;p13)[1]   | 2        | 61            | 35            | 3.3                      | 8.8        | 113                      | ND       | Positive | Positive  | 10      |
| 46     | Raynaud   | 28/F     | AML-MIRC       | 46,XX,t(3;12)(q26;p13)[30]; 3 years later: 46,XX,t(1;7)(p13;p15),t(3;12)(q26;p13),-6,del(11)(q21q23),der(11)t(11;?)p(11;?),add(17)(p11),del(17)(p12),der(19)t(12;19)(q13;q13),+der(2)t(2;4)(?;q11)[11] | 1        | 46            | 30            | 37                       | 11.1       | 34                       | Yes      | Positive | Positive  | 12      |
| 47     | Raynaud   | 26/M     | Acute Meg Leuk | 46,XY,?mt del(1)(p32;p34),t(3;12)(q26;p13)[15]/46,iderm,del(5)(p1?;4)[115]   | > 3      | 66            | 25            | 8.6                      | 9.7        | 192                      | ND       | Positive | Positive  | 7       |

Table 3 (continued)

| Case # | Reference         | Age/ Sex | Diagnosis                   | Karyotype  | # CG Abn | BM Blasts (%) | PB Blasts (%) | WBC (10 <sup>9</sup> /L) | Hgb (g/dL) | Plt (10 <sup>9</sup> /L) | SCT (10 <sup>9</sup> /L) | EVII FISH | ETV6 FISH | OS (mo) |
|--------|-------------------|----------|-----------------------------|--|----------|---------------|---------------|--------------------------|------------|--------------------------|--------------------------|-----------|-----------|---------|
| 49     | Roumier           | 57/M     | AML w/o mat                 | 46,XY,t(3;12)(q26;p13),ish der(3)(ETV6+)(15)/46,XY[7]  | > 3      | ND            | ND            | ND                       | ND         | ND                       | ND                       | ND        | ND        | 15      |
| 50     | Secker-Walker     | 27/F     | AML-MRC                     | 46,XX,t(3;12)(q26;p13)   | 1        | ND            | ND            | ND                       | ND         | 110                      | Yes                      | ND        | ND        | 39      |
| 51     | Secker-Walker     | 24/M     | AML-MRC                     | 46,XY,del(1)(p32p34),t(3;12)(q26;p13)  | 2        | ND            | ND            | ND                       | ND         | 192                      | ND                       | ND        | ND        | ND      |
| 52     | Shali             | 59/F     | AMML                        | 46,XX,t(3;12)(q26;p13)[8]/46,XX[t4]  | 1        | ND            | ND            | ND                       | ND         | ND                       | ND                       | Positive  | Positive  | 15      |
| 53     | Shiba             | 4.8/M    | Acute Mono Leuk             | 45,X,-7[1]/45,sl,t(3;12)(q26;p13)[18]/46,XY[11]  | 1        | ND            | ND            | 33.9                     | ND         | ND                       | Yes                      | ND        | ND        | ND      |
| 57     | Van de Loosdrecht | 70/M     | t-MDS-EB                    | 46,XX,t(3;12)(q26;p13)[19]/46,XX[3]  | 1        | 8             | ND            | 24.3                     | 7.4        | 212                      | ND                       | Positive  | Positive  | 42      |
| 3      | Doorn-Khosrovani  | NA       | t-MDS-EB                    | 46,X?,(3;12)(q26;p13)  | 1        | ND            | ND            | ND                       | ND         | ND                       | ND                       | ND        | ND        | ND      |
| 18     | Haferlach         | 57/M     | MDS                         | 46,XX,t(3;12)(q26;p13)[19]/46,XY[11]   | 1        | ND            | ND            | ND                       | ND         | ND                       | ND                       | Positive  | Positive  | ND      |
| 19     | Haferlach         | 64/M     | MDS                         | 46,XX,t(3;12)(q26;p13),del(7)(q12)[17]/46,XX[3]  | 2        | ND            | ND            | ND                       | ND         | ND                       | ND                       | Positive  | Positive  | ND      |
| 5      | Beyer             | 43/M     | MDS                         | 46,XX,t(3;12)(q26;p13)[2]/46, idem, t(14)(q10)[31]/46,XY[3]  | 2        | ND            | ND            | ND                       | ND         | ND                       | ND                       | ND        | ND        | ND      |
| 38     | Orciuolo          | 35/M     | MDS                         | t(3;12)(q26;p13)   | 1        | ND            | ND            | ND                       | ND         | 103                      | ND                       | ND        | ND        | 24      |
| 58     | Yamamoto          | 21/M     | MDS                         | 46,XX,t(3;12)(q26;p13)[11]/46,XY[9]; 5 years later: 6,XX,t(3;12)(q26;p13)[7]/46,sl,del(5)(q7)[13] after BMT: 46,XX,t(3;12)(q26;p13),del(7)(q7)[18]/46,sl,-Y,add(2)(q31), del(6)(q7),add(10)(q22)x2,add(21)(q22),pmar[12] | 1        | 2.4           | 0             | 4.1                      | 13.9       | 86                       | Yes                      | Positive  | Positive  | 66.1    |
| 55     | Voutsadakis       | 36/F     | MDS                         | t(3;12)(q26;p13); 3.17 years later: t(3;12)(q26;p13),+22   | 1        | ND            | ND            | 6.5                      | 6          | 91                       | ND                       | Positive  | Positive  | 9       |
| 54     | Taylor            | 47/F     | MDS/MPN-RS-T                | 49,XX,t(3;12)(q26;p13),+8,(9;22)(q34.1;q11.2),+der(12)(3;12),+der(22)(9;22)(q34.1;q11.2)[21]   | 1        | ND            | ND            | ND                       | ND         | ND                       | ND                       | ND        | ND        | ND      |
| 6      | Bobadilla         | 49/M     | CML, BCR-ABL1-positive, AP  | 49,XX,t(3;12)(q26;p13),+8,(9;22)(q34.1;q11.2),+der(12)(3;12),+der(22)(9;22)(q34.1;q11.2)[21]   | > 3      | ND            | ND            | ND                       | ND         | ND                       | ND                       | Positive  | Positive  | ND      |
| 36     | Nakamura          | 26/M     | CML, BCR-ABL1-positive, AP  | 46,XX,t(3;12)(q26;p13),t(9;22)(q34;q11)  | 2        | 1.8           | 1.2           | 600                      | 12.4       | 453                      | Yes                      | ND        | ND        | ND      |
| 2      | Bacher            | 38/F     | CML, BCR-ABL1-positive, BP  | 46,XX,t(3;12)(q26;p13),t(9;22)(q34;q11)  | 2        | 73            | ND            | ND                       | ND         | ND                       | ND                       | ND        | ND        | ND      |
| 39     | Paquette          | 55/M     | CML, BCR-ABL1-positive, BP  | 47,XX,t(3;12)(q26;p13),t(9;22)(p15;q34;q11.2),+21[8]/46,XX[12] > 3   | > 3      | ND            | ND            | ND                       | ND         | ND                       | ND                       | Positive  | Positive  | 55      |
| 48     | Raynaud           | 20/M     | CML, BCR-ABL1-positive, BP  | 46,XX,t(9;22)(q34;q11)[3]/46, idem,t(3;12)(q26;p13)[20]  | 2        | 30            | 23            | 16.5                     | 5          | 92                       | ND                       | Positive  | Positive  | 12      |
| 40     | Peeters           | 26/M     | aCML, BCR-ABL1-negative, BP | 46,XX,t(3;12)(q26;p13),t(9;15)(p21;q15;p13)  | 2        | 25            | ND            | 64                       | 8.7        | 37                       | Yes                      | Positive  | Positive  | ND      |

M male, F female, Age age at initial diagnosis in years, # CG Abn number of cytogenetic abnormalities, WBC white blood cells, K 1000, µl microliter, Hgb hemoglobin, g/dl grams per deciliter, Plt platelets, PB peripheral blood, BM bone marrow, OS overall survival in months, SCT hematopoietic stem cell transplant, ND not determined, AML acute myeloid leukemia, AML w/o mat acute myeloid leukemia without maturation, AML w/mat acute myeloid leukemia with maturation, AMML acute myelomonocytic leukemia, AML-MRC acute myeloid leukemia with myelodysplasia-related changes, Acute Mono Leuk acute monoblastic leukemia, Acute Meg Leuk acute megakaryoblastic leukemia, t-AML therapy-related acute myeloid leukemia, MDS-EB2 myelodysplastic syndrome with excess blasts 2, t-MDS-EB2 therapy-related myelodysplastic syndrome with excess blasts 2, MDS myelodysplastic syndrome, t-MDS therapy-related myelodysplastic syndrome, MDS/MPN-RS-T myelodysplastic syndrome/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis, PMF primary myelofibrosis, CML chronic myeloid leukemia, BCR-ABL1-positive, aCML atypical chronic myeloid leukemia, BP blast phase, CP chronic phase, NOS not otherwise specified, MPAL mixed-phenotype acute leukemia T/myeloid not otherwise specified, OS overall survival.

**Table 4** Summary of Clinicopathologic Characteristics of Patients With t(3;12).

|   | Current Study         | Previous Studies [11 - 39] | Overall            |
|---|-----------------------|----------------------------|--------------------|
| Case number (N)   | 20                    | 58                         | 78                 |
| Age: median; range (yrs)  | 55.8<br>(27.8 – 78.8) | 47.5 (4.8 - 87)            | 48.5<br>(4.8 – 87) |
| <b>Myeloid Neoplasms with t(3;12): N (%)</b>                            |                       |                            |                    |
| Acute Leukemia  |                       |                            |                    |
| AML   | 11 (55%)              | 42 (72%)                   | 53 (68%)           |
| MPAL  | 1 (5%)                | 0                          | 1 (1%)             |
| MDS   | 2 (10%)               | 6 (10%)                    | 8 (10%)            |
| MDS-EB  | 3 (15%)               | 2 (3%)                     | 5 (6%)             |
| MDS/MPN   |                       |                            |                    |
| MDS/MPN-RS-T  | 0                     | 1 (2%)                     | 1 (1%)             |
| <i>CML, BCR-ABL1</i> -positive  | 2 (10%)               | 6 (10%)                    | 8 (10%)            |
| <i>aCML, BCR-ABL1</i> -negative   | 0                     | 1 (2%)                     | 1 (1%)             |
| PMF   | 1 (5%)                | 0                          | 1 (1%)             |
| <b>Myeloid Neoplasms with t(3;12) as the only CG abnormality: N (%)</b> | 7                     | 29                         | 36                 |
| AML   | 2 (29%)               | 22 (76%)                   | 24 (67%)           |
| MDS   | 1 (14%)               | 4 (14%)                    | 5 (14%)            |
| MDS-EB  | 3 (43%)               | 2 (7%)                     | 5 (14%)            |
| MDS/MPN   |                       |                            |                    |
| MDS/MPN-RS-T  | 0                     | 1 (3%)                     | 1 (3%)             |
| MPN   |                       |                            |                    |
| PMF   | 1 (14%)               | 0                          | 1 (3%)             |

(N) number, Age age at initial diagnosis, yrs years, *t(3;12)* the initial diagnosis of *t(3;12)(q26.2;p13)*, AML acute myeloid leukemia, MDS-EB myelodysplastic syndrome with excess blasts, MDS myelodysplastic syndrome, MDS/MPN-RS-T myelodysplastic syndrome/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis, CML chronic myeloid leukemia, *aCML* atypical chronic myeloid leukemia, PMF primary myelofibrosis, MPAL mixed-phenotype acute leukemia T/myeloid not otherwise specified.

This observation suggests that *t(3;12)* is a driver that can be an initiating event or occurs as a secondary event in disease progression. Seven (35%) patients had *t(3;12)(q26.2;p13)* as the sole chromosomal abnormality, while 13 (65%) patients had either 2 or  $\geq 3$  chromosomal abnormalities. Similar to our experience, cases with *t(3;12)(q26.2;p13)* reported in the literature also frequently had this translocation as a sole chromosomal abnormality ( $n = 29$ , 50%), while 21 (36%) had 2 chromosomal abnormalities, and 8 (14%) had  $\geq 3$  chromosomal abnormalities. However, the over representation of the proportion of our patients (30%) with  $\geq 3$  chromosomal abnormalities as compared to the literature (14%) may reflect a greater percentage of patients

presenting to our institution who had already received multiple prior therapies.

The 29 cases in the literature with *t(3;12)* as the sole cytogenetic abnormality at initial diagnosis included 21 AML and 6 MDS (2 are MDS-EB) and 1 MDS/MPN-RS-T. In addition to *t(3;12)*, monosomy 7 was the most common chromosomal abnormality reported both in literature ( $n = 8$ , 14%) and found in our study ( $n = 5$ , 25%) [19]. Cytogenetic abnormalities in addition to *t(3;12)* such as abnormalities of 7q and chromosome 22 did not significantly differ from the literature. It is important to note that the underrepresentation of other cytogenetic abnormalities reported in the literature may be due to the limited number of cases in this study.

*t(3;12)(q26.2;p13)* is also associated with a resistance to conventional chemotherapy and it confers a poorer prognosis. Of the 20 patients with follow-up information available, 10 patients had persistent disease, while other 7 patients relapsed. Of the 14 (70%) patients that died, the median survival was 6.3 months (range, 0.1–17.3 months) after detection of *t(3;12)(q26.2;p13)*.

The literature reports *MECOM* abnormalities to be a poor prognostic indicator for AML patients [15]. Inappropriate overexpression of *MECOM* can occur via the *t(3;12)(q26.2;p13)* resulting in poorer prognosis [13]. Similar to our results, Kim et al. reported that the *t(3;12)(q26.2;p13)* in myeloid neoplasms results in leukemogenesis by promoting proliferative capacity and suggests a dismal prognosis, measured in a few months [13, 22, 40]. Lugthart et al. reported that patients with *t(3;12)(q26.2;p13)* showed 5-year survival rates of 25–51%. There are reports of patients with *t(3;12)(q26.2;p13)* that did not achieve complete remission with therapy and died of refractory disease [27, 33, 38]. Reports suggest that this translocation is associated with CML-BP, transformation of MDS or chronic myelomonocytic leukemia to AML, and a poor prognosis [12, 32]. One study of four patients had a median survival of 9.5 months (range, 2–12) [30]. Treatment failure in patients with AML associated with *t(3;12)(q26.2;p13)* may also be due to the fact that AML is secondary to MDS with the presence of additional chromosome 7 abnormalities [33]. Similar to the cases we report, the literature reports failure of therapy including patients who have undergone allogeneic SCT transplantation [30, 43].

Morphologic dysplasia was found in 11 of 12 (90%) cases assessed. Furthermore, either MDS defining cytogenetic abnormalities or dysplasia was found in 18 of 20 (90%) cases in our cohort as case #2, 8, and 12 demonstrated dysplasia after the detection of *t(3;12)*. When comparing the subgroups of myeloid neoplasms, morphologic dysplasia was found in all the AML cases (5/5), MDS cases (4/4), half the myeloproliferative neoplasms cases (1/2), and one MPAL case assessed. All of the therapy-related cases (3/3) showed dysplasia.

Of the 58 cases described in the literature to date, 15 (26%) had MDS defining cytogenetic abnormalities. Of the 14 cases in the literature assessed for morphologic dysplasia, 14 cases (100%) demonstrated dysplasia. This is similar to the dysplasia found in the 90% of cases (11 of 12 cases assessed) in our study. Six (10.3%) of the 58 cases had both MDS defining cytogenetic abnormalities and dysplasia.

The role of t(3;12) in leukemogenesis is believed to result from the active promoter *ETV6* inducing overexpression of *EVII* [12, 44]. Ottema et al. demonstrated that cases of inv(3) and t(3;3) exhibited *EVII* overexpression but low or no *MDS1-EVII* transcription (atypical 3q26-rearranged AML) due to translocation of the *GATA2* enhancer to the *MECOM* locus. Given the clinical and biological similarities, the authors conclude that (1) atypical 3q26-rearranged AMLs and AMLs with inv(3)/t(3;3) are one entity and (2) routine analysis determining *MECOM* rearrangements require *MECOM* FISH to assess for *MECOM* rearrangement together with quantitative assessment of the *EVII* and *MDS1-EVII* mRNA expression levels [11]. In the future, it would be interesting to assess the *EVII* expression levels to see if t(3;12) has a similar mechanism of leukemogenesis as 3q26-rearranged AMLs. *MECOM* acts as a transcription factor that targets genes directly through its proximal zinc finger domain [45]. *MECOM* regulates the expression of *GATA2*, *Pbx homeobox 1 (Pbx1)*, *PROMYELOCYTE LEUKEMIA (PML)* gene transcription, and inhibits the transforming growth factor beta (TGF- $\beta$ ) signaling by repressing mothers against decapentaplegic homolog 3 function by interacting with and recruiting corepressor C-terminal-binding protein [46–50]. Experimental evidence suggests that the leukemogenic effects also include promoting cell cycle proliferation by upregulating activator protein 1, blocking the growth inhibitory effects of TGF- $\beta$ , cooperating with RAS/receptor tyrosine kinase pathway activating mutations, and suppressing apoptosis/differentiation [44, 51–53].

In summary, the presence of t(3;12)(q26.2;p13) is a rare abnormality associated exclusively with myeloid neoplasms. Morphologic myelodysplasia was found in all the AML cases (5/5), MDS cases (4/4), therapy-related cases (3/3), half the myeloproliferative neoplasms cases (1/2), and one MPAL case assessed. This translocation is associated with resistance to treatment, rapid disease progression, and a poorer prognosis. Novel therapeutic strategies are needed for this subset of patients with myeloid neoplasms. Given the close relationship between the presence of this cytogenetic abnormality and MDS-related changes, we recommend adding t(3;12)(q26.2;p13) to the list of AML-MRC-defining abnormalities of WHO 2017 classification of myeloid neoplasms.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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