



A novel unbalanced whole-arm translocation der(3;10)(q10;q10) in acute monocytic leukemia

Yamamoto, Katsuya ; Okamura, Atsuo ; Wakahashi, Kanako ; Katayama,
Yoshio ; Shimoyama, Manabu ; Matsui, Toshimitsu

(Citation)

Cancer genetics and cytogenetics, 199(2):134-138

(Issue Date)

2010-06

(Resource Type)

journal article

(Version)

Accepted Manuscript

(URL)

<https://hdl.handle.net/20.500.14094/90001487>



A novel unbalanced whole-arm translocation der(3;10)(q10;q10) in acute monocytic leukemia

Katsuya Yamamoto*, Atsuo Okamura, Kanako Wakahashi, Yoshio Katayama, Manabu Shimoyama, Toshimitsu Matsui

Hematology/Oncology, Department of Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

*Corresponding author: Katsuya Yamamoto

Address: Hematology/Oncology, Department of Medicine, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

TEL: +81-78-382-5885

FAX: +81-78-382-5899

E-mail: kyamamo@med.kobe-u.ac.jp

Abstract

We describe here a novel unbalanced whole-arm translocation der(3;10)(q10;q10) in a 58-year-old man with acute monocytic leukemia. Bone marrow was massively infiltrated with 22.2% monoblasts, 55.4% promonocytes and 5.6% monocytes. These monocytic cells were positive for myeloperoxidase and α -naphthyl butyrate esterase stainings. Surface marker analysis revealed that they were positive for CD4, CD13, CD33, CD56 and HLA-DR but negative for CD14 and CD34. Chromosome analysis of the bone marrow cells showed 46,XY,+3,der(3;10)(q10;q10)[18]/46,XY[2]. Spectral karyotyping confirmed der(3;10)(q10;q10) as a sole structural abnormality. By acquisition of a normal chromosome 3 but not a chromosome 10, the der(3;10)(q10;q10) resulted in trisomy 3q and monosomy 10p. Thus, the +3,der(3;10)(q10;q10) is supposed to play a crucial role in the pathogenesis of acute monocytic leukemia by the gain of 3q or the loss of 10p.

1. Introduction

Acute monoblastic leukemia and acute monocytic leukemia are myeloid leukemias in which 80% or more of the leukemic cells are monocytic lineage including monoblasts, promonocytes and monocytes. In the newly revised World Health Organization (WHO) classification, they are now categorized in “acute myeloid leukemia, not otherwise specified (AML, NOS)” with no recurrent genetic abnormality [1]. Nevertheless, myeloid-associated, non-specific cytogenetic abnormalities are present in the majority of cases.

Unbalanced whole-arm translocations, which involve breakage and reunion of nonhomologous chromosomes at their centromeres, are relatively rare acquired cytogenetic aberrations in hematological malignancies [2]. Some of these translocations, such as der(1;7)(q10;p10), der(7;12)(q10;q10), and der(9;18)(p10;q10), have been reported as a sole and recurrent anomaly, indicating that they could be primary genetic changes [2-5]. Among them, the most frequent der(1;7)(q10;p10) has been clinically and molecularly characterized. It constitutes a distinct entity in myeloid malignancies including AML and myelodysplastic syndrome (MDS) [3]. However, clinical importance of other unbalanced whole-arm translocations remains to be completely clarified. We describe here a novel unbalanced whole-arm translocation der(3;10)(q10;q10) in a patient with acute monocytic leukemia.

2. Materials and methods

2.1. Case History

A 58-year-old man was admitted to our hospital because of anemia and leukocytosis in July 2009. He had no past history of antecedent hematological disorder and chemoradiotherapy. There was no abnormal physical finding caused by extramedullary masses. Peripheral blood showed hemoglobin 72 g/L, platelets 84×10^9 /L and white blood cells (WBC) 25.8×10^9 /L with 3% blasts, 5% myelocytes, 2% metamyelocytes, 8% band forms, 29% segmented neutrophils, 10% promonocytes, 31% monocytes, and 12% lymphocytes. Bone marrow was marked-

ly hypercellular with 22.2% monoblasts, 55.4% promonocytes, 5.6% monocytes, 10.0% other myeloid cells, 1.2% erythroblasts, and 3.6% lymphocytes. These large-sized monoblasts and promonocytes had subtly convoluted nuclei with prominent nucleoli and basophilic cytoplasm with vacuoles and fine azurophilic granules (Fig. 1A). They were positive for myeloperoxidase and α -naphthyl butyrate (ANB) esterase but negative for chloroacetate esterase stainings (Fig. 1B, 1C). The ANB positivity was totally inhibited by NaF (Fig. 1D). Trilineage dysplasia was not apparent in the bone marrow cells. Surface marker analysis with CD45 gating by three-color flow cytometry revealed that the monocytic cells (86.5% of all bone marrow cells) were positive (more than 20%) for CD4 (48.2%), CD13 (28.7%), CD33 (100.0%), CD56 (94.8%) and HLA-DR (97.0%) but negative for CD14 (7.0%) and CD34 (3.0%). Therefore, we made the diagnosis as AML M5b in the French-American-British classification or acute monocytic leukemia in the WHO classification [1]. An induction therapy with idarubicin and cytosine arabinoside was started, and the patient achieved a complete remission (CR). He is now under consolidation therapy and remained in hematological and cytogenetic CR for four months.

2.2. Chromosome and fluorescence in situ hybridization (FISH) analyses

Chromosome analyses were performed by the G-banding technique on unstimulated short-term culture of the cells obtained from bone marrow at the initial diagnosis and after CR. Karyotypes were described according to ISCN 2009 [6]. Spectral karyotyping (SKY) was carried out with a SkyPaint kit (Applied Spectral Imaging, Migdal Ha'Emek, Israel) on five metaphase spreads at the initial diagnosis. Chromosomes were counterstained with 4',6-diaminido-2-phenylindole dihydrochloride (DAPI). FISH analyses with LSI MLL Dual Color, Break Apart Rearrangement Probe at 11q23 and LSI CBFB Dual Color, Break Apart Rearrangement Probe at 16q22 (Abbott Molecular, Des Plaines, IL, USA) were performed on 100 interphase nuclei at the initial diagnosis.

3. Results

Chromosome analysis of the bone marrow cells at the initial diagnosis of acute monocytic leukemia showed 46,XY,+3,der(3;10)(q10;q10)[18]/46,XY[2] (Fig. 2A). SKY analysis confirmed der(3;10)(q10;q10) as a sole structural abnormality (Fig. 2B). Unexpectedly, SKY also revealed the existence of an unrelated clone with trisomy 8 as follows:

46,XY,+3,der(3;10)(q10;q10)[2]/47,XY,+8[2]/46,XY[1] (data not shown). The karyotype after hematological CR converted to 46,XY[20].

To exclude the possibility that leukemic cells had cryptic rearrangements, we next performed interphase FISH analyses. We used probes for *MLL* and *CBFB* genes because translocations involving 11q23 and inv(16)(p13q22) in AML occasionally cannot be detected by G-banding or SKY. None of 100 interphase nuclei showed split signals of *MLL* and *CBFB*, indicating the absence of their cryptic rearrangements (data not shown). Accordingly, it was supported that der(3;10) was a sole structural abnormality.

4. Discussion

We have identified a novel unbalanced whole-arm translocation der(3;10)(q10;q10) in acute monocytic leukemia. To the best of our knowledge, the der(3;10)(q10;q10) has never been described in the literature to date [7]. Furthermore, the der(3;10) was accompanied by an extra chromosome 3. Duplication of a normal copy of one of the chromosomes participating in the translocation occurs in more than one half of the cases with unbalanced translocations [8], such as +1,der(1;7)(q10;p10) and der(5;19)(p10;q10),+19 [3, 9]. In the present case, by acquisition of a normal chromosome 3 but not a chromosome 10, the der(3;10) resulted in trisomy 3q and monosomy 10p. The +3,der(3;10) was found as a sole abnormality in all abnormal metaphase spreads by G-banding, indicating that it could play a crucial role in the pathogenesis of acute monocytic leukemia by the gain of 3q or the loss of 10p. Both unbalanced aberrations are not described in cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related

features in the WHO classification [10]. Thus, considering the absence of previous history of MDS and multilineage dysplasia in the bone marrow, we diagnosed the disease as *de novo* acute monocytic leukemia.

The most significant consequence of unbalanced whole-arm translocation is the genomic imbalance resulting from the gain and loss of whole chromosome arms. Adeyinka et al. [2] reported that chromosome arms were non-randomly involved in the whole-arm translocations. That is, a loss of 17p was most common, and losses of 7q, 13p, 14p, and 15p, and a gain of 1q were found in more than 10% of cases in 131 hematological malignancies. A gain of 3q and a loss of 10p were observed in three and seven cases, respectively, although the karyotypes of these cases were not fully described. According to the Mitelman database [7], unbalanced whole-arm translocations involving 3q10 or 10q10 were found in 19 cases and 13 cases of hematological malignancies, respectively. Among them, 10 cases of MDS/AML with 3q10 or 10q10 translocations are summarized in Table 1 [2, 11-18]. There was no case having an extra chromosome 3 with 3q10 translocations, whereas acquisition of the partner chromosomes (chromosomes 1 and 12) was observed only in two cases (No. 1 and 5). Thus, trisomy 3q caused by unbalanced whole-arm translocations seems to be a very rare event in MDS/AML. Another two cases with 10q10 translocations (No. 9 and 10) showed monosomy 10p.

Whole or partial trisomy 3 has been reported to be especially associated with lymphoid malignancies. Trisomy 3 represents the most frequent chromosomal abnormality in marginal zone B-cell lymphoma (MZBCL) [19]. Partial trisomy 3q induced by unbalanced translocations involving chromosome 3 is recurrently found in MZBCL as well, and a commonly duplicated region was found to be 3q13.2-3q29 [20]. In addition to MZBCL, gains of chromosome 3/3q occur in other lymphoid B-cell chronic lymphoproliferative disorders including chronic lymphocytic lymphoma, prolymphocytic leukemia and Waldenström's macroglobulinemia [21]. In myeloid malignancies, a few cases of childhood AML showed trisomy 3 and tetrasomy 3q [22]. Gains of partial chromosome 3q by unbalanced translocations were also reported in cases of

juvenile myelomonocytic leukemia [23].

The underlying genetic mechanism by trisomy 3/3q is supposed to be a gene dosage effect rather than a specific gene disruption [20]. Several genes of particular importance in neoplastic transformation are included in the chromosome 3q, such as *PARP9* (*BAL*) at 3q13-21, *RPNI* at 3q21.3, *PBX2P1* at 3q24, *MECOM* (*MDS1-EVII*) at 3q26, *TERC* (*hTR*) at 3q26.2, and *BCL6* at 3q27 [20, 22]. However, it is unknown whether these genes have a gene dosage effect by trisomy 3/3q. On the other hand, monosomy 10p, which could be considered as an alternative mechanism to development of leukemia, has been hardly shown to be correlated with specific subtypes of hematological malignancies. Thus, accumulation of more cases will be necessary to clarify the critical role of der(3;10) in the pathogenesis of acute monocytic leukemia.

References

- [1] Arber DA, Brunning RD, Orazi A, Porwit A, Peterson L, Thiele J, Le Beau MM. Acute myeloid leukaemia, not otherwise specified. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, editors. WHO classification of tumors of haematopoietic and lymphoid tissues, 4th edition. Lyon: International Agency for Research on Cancer, 2008. pp.130-139.
- [2] Adeyinka A, Wei S, Sanchez J. Loss of 17p is a major consequence of whole-arm chromosome translocations in hematologic malignancies. *Cancer Genet Cytogenet* 2007;173:136-143.
- [3] Sanada M, Uike N, Ohyashiki K, Ozawa K, Lili W, Hangaishi A, Kanda Y, Chiba S, Kurokawa M, Omine M, Mitani K, Ogawa S. Unbalanced translocation der(1;7)(q10;p10) defines a unique clinicopathological subgroup of myeloid neoplasms. *Leukemia* 2007;21:992-997.
- [4] Johansson B, Arheden K, Höglund M, Othzén A, Békássy AN, Turesson I, Heim S, Mitelman F. Fluorescence in situ hybridization analysis of whole-arm 7;12 translocations in he-

matologic malignancies. *Genes Chromosomes Cancer* 1995;14:56-62.

- [5] Bacher U, Haferlach T, Schoch C. Gain of 9p due to an unbalanced rearrangement der(9;18): a recurrent clonal abnormality in chronic myeloproliferative disorders. *Cancer Genet Cytogenet* 2005;160:179-183.
- [6] Schaffer LG, Slovak ML, Campbell LJ, editors. *ISCN 2009: an international system for human cytogenetic nomenclature* (2009). Basel: S. Karger, 2009.
- [7] Mitelman F, Johansson B, Mertens F, editors. *Mitelman database of chromosome aberrations in cancer* (2009). Updated on November 16, 2009, accessed on December 18, 2009. Available at: <http://cgap.nci.nih.gov/Chromosomes/Mitelman>.
- [8] Pedersen B, Nørgaard JM, Pedersen BB, Clausen N, Rasmussen IH, Thorling K. Many unbalanced translocations show duplication of a translocation participant. Clinical and cytogenetic implications in myeloid hematologic malignancies. *Am J Hematol* 2000;64:161-169.
- [9] Yamamoto K, Okamura A, Katayama Y, Shimoyama M, Matsui T. Unbalanced whole-arm translocation der(5;19)(p10;q10) is a novel and recurrent cytogenetic aberration in myelodysplastic syndrome. *Leuk Res* 2009;33:377-383.
- [10] Arber DA, Brunning RD, Orazi A, Bain BJ, Porwit A, Vardiman JW, Le Beau MM, Greenberg PL. Acute myeloid leukaemia with myelodysplasia-related changes. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, editors. *WHO classification of tumors of haematopoietic and lymphoid tissues*, 4th edition. Lyon: International Agency for Research on Cancer, 2008. pp.124-126.
- [11] Davidsson J, Heidenblad M, Bong Å, Johansson B. Array-based comparative genomic hybridization of cytogenetically polyclonal myeloid malignancies. *Cancer Genet Cytogenet* 2006;169:179-180.
- [12] Westbrook CA, Hsu WT, Chyna B, Litvak D, Raza A, Horrigan SK. Cytogenetic and molecular diagnosis of chromosome 5 deletions in myelodysplasia. *Br J Haematol*

2000;110:847-855.

- [13] Side LE, Curtiss NP, Teel K, Kratz C, Wang PW, Larson RA, Le Beau MM, Shannon KM. *RAS*, *FLT3*, and *TP53* mutations in therapy-related myeloid malignancies with abnormalities of chromosomes 5 and 7. *Genes Chromosomes Cancer* 2004;39:217-223.
- [14] Zhao L, Hayes K, Khan Z, Glassman A. Spectral karyotyping study of chromosome abnormalities in human leukemia. *Cancer Genet Cytogenet* 2001;127:143-147.
- [15] Göhring G, Karow A, Steinemann D, Wilkens L, Lichter P, Zeidler C, Niemeyer C, Welte K, Schlegelberger B. Chromosomal aberrations in congenital bone marrow failure disorders—an early indicator for leukemogenesis? *Ann Hematol* 2007;86:733-739.
- [16] Van Limbergen H, Poppe B, Michaux L, Herens C, Brown J, Noens L, Berneman Z, De Bock R, De Paepe A, Speleman F. Identification of cytogenetic subclasses and recurring chromosomal aberrations in AML and MDS with complex karyotypes using M-FISH. *Genes Chromosomes Cancer* 2002;33:60-72.
- [17] Lessard M, Hélias C, Struski S, Perrusson N, Uettwiller F, Mozziconacci MJ, Lafage-Pochitaloff M, Dastugue N, Terré C, Brizard F, Cornillet-Lefebvre P, Mugneret F, Barin C, Herry A, Luquet I, Desangles F, Michaux L, Verellen-Dumoulin C, Perrot C, Van de Akker J, Lespinasse J, Eclache V, Berger R, on behalf of the Groupe Francophone de Cytogénétique Hématologique (GFCH). Fluorescence in situ hybridization analysis of 110 hematopoietic disorders with chromosome 5 abnormalities: do de novo and therapy-related myelodysplastic syndrome-acute myeloid leukemia actually differ? *Cancer Genet Cytogenet* 2007;176:1-21.
- [18] Huret JL, Brizard A, Slater R, Charrin C, Bertheas MF, Guilhot F, Hählen K, Kroes W, van Leeuwen E, Schoot EV, Beishuizen A, Tanzer J, Hagemeijer A. Cytogenetic heterogeneity in t(11;19) acute leukemia: clinical, hematological and cytogenetic analyses of 48 patients—updated published cases and 16 new observations. *Leukemia* 1993;7:152-160.
- [19] Dierlamm J, Michaux L, Wlodarska I, Pittaluga S, Zeller W, Stul M, Criel A, Thomas J,

Boogaerts M, Delaere P, Cassiman JJ, De Wolf-Peeters C, Mecucci C, Van den Berghe H. Trisomy 3 in marginal zone B-cell lymphoma: a study based on cytogenetic analysis and fluorescence *in situ* hybridization. *Br J Haematol* 1996;93:242-249.

- [20] Gazzo S, Baseggio L, Coignet L, Poncet C, Morel D, Coiffier B, Felman P, Berger F, Salles G, Callet-Bauchu E. Cytogenetic and molecular delineation of a region of chromosome 3q commonly gained in marginal zone B-cell lymphoma. *Haematologica* 2003;88:31-38.
- [21] Wong KF, So CC, Chan JCW, Kho BCS, Chan JKC. Gain of chromosome 3/3q in B-cell chronic lymphoproliferative disorder is associated with plasmacytoid differentiation with or without IgM overproduction. *Cancer Genet Cytogenet* 2002;136:82-85.
- [22] Haltrich I, Kost-Alimova M, Kovács G, Klein G, Fekete G, Imreh S. Multipoint interphase FISH analysis of chromosome 3 abnormalities in 28 childhood AML patients. *Eur J Haematol* 2006;76:124-133.
- [23] Tosi S, Mosna G, Cazzaniga G, Giudici G, Kearney L, Biondi A, Privitera E. Unbalanced t(3;12) in a case of juvenile myelomonocytic leukemia (JMML) results in partial trisomy of 3q as defined by FISH. *Leukemia* 1997;11:1465-1468.

Figure legends

Fig. 1

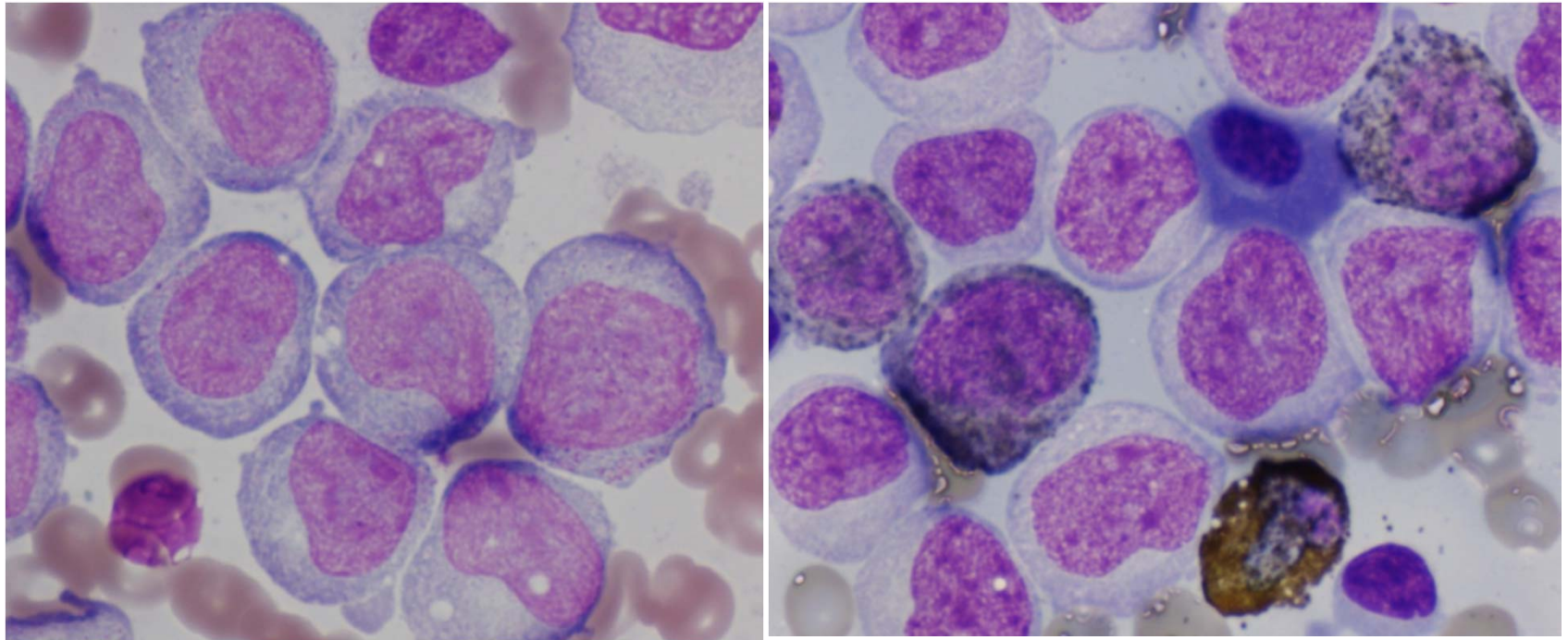
Bone marrow smears at the diagnosis of acute monocytic leukemia (x1000). (A) Large monoblasts and promonocytes are shown (May-Grünwald-Giemsa staining). (B) Monocytic cells show scattered positivity for myeloperoxidase staining. (C) They are positive for α -naphthyl butylate (ANB) esterase but negative for chloroacetate esterase stainings. (D) The ANB positivity is inhibited by NaF.

Fig. 2

(A) G-banded karyotype of the bone marrow cells at the diagnosis of acute monocytic leukemia: 46,XY,+3,der(3;10)(q10;q10). An arrow indicates the rearranged chromosome.

(B) Spectral karyotyping of the metaphase spread after spectrum-based classification (left side, reverse DAPI; right side, SKY). Chromosomes were assigned a pseudocolor according to the measured spectrum. The karyotype is confirmed as follows: 46,XY,+3,der(3;10)(q10;q10). An arrow indicates the rearranged chromosome.

Fig. 1



A	B
C	D

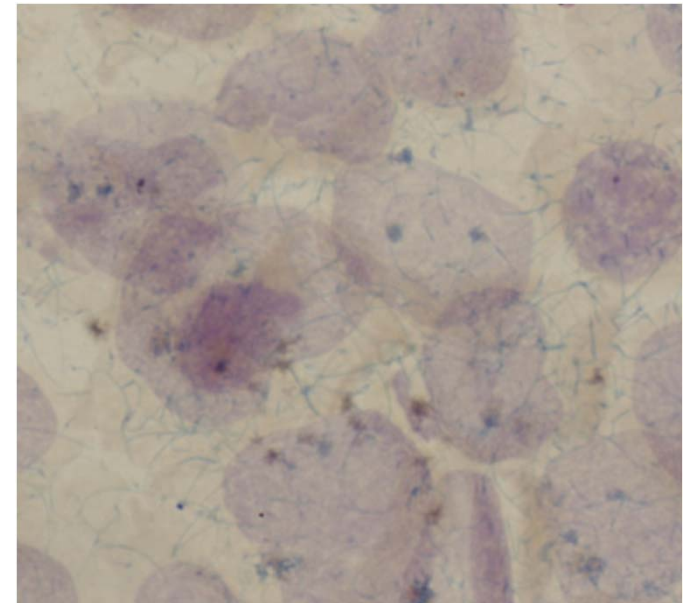
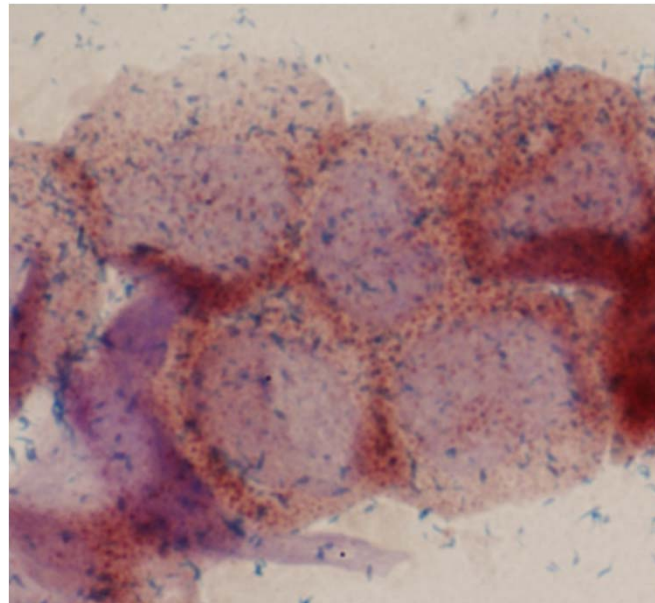
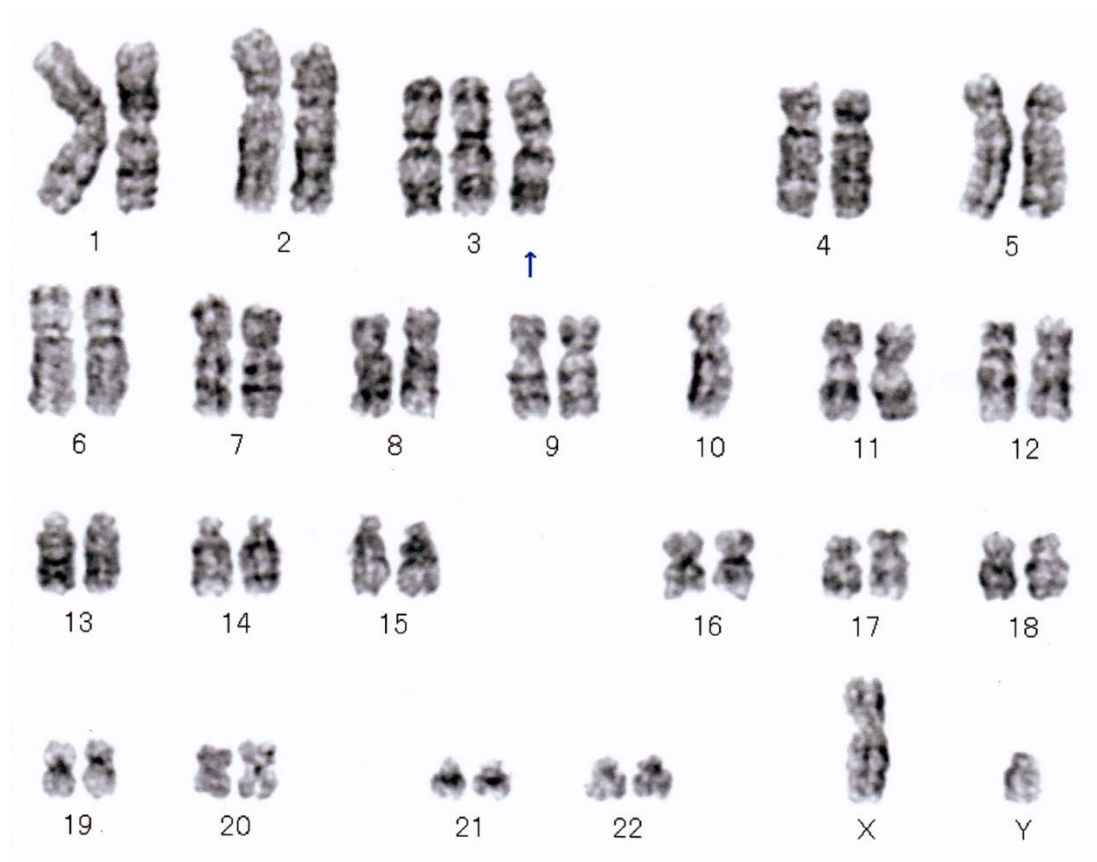


Fig. 2

A



B

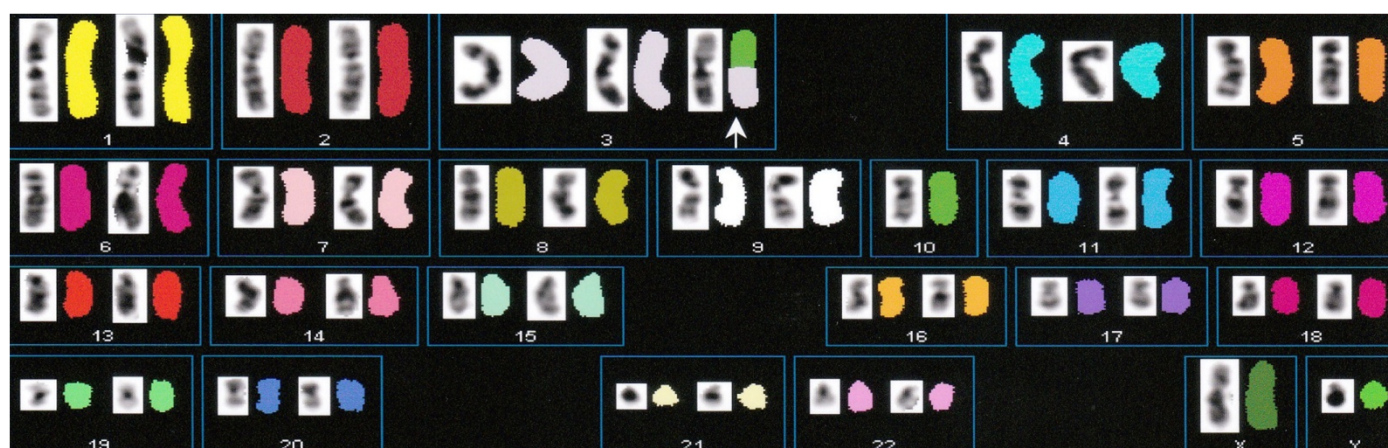


Table 1. Reported cases of acute myeloid leukemia and myelodysplastic syndrome with unbalanced whole-arm translocations involving 3q10 or 10q10

<i>Case No.</i>	<i>Age/ Sex</i>	<i>Diagnosis</i>	<i>Karyotypes</i>	<i>References</i>
1	66/M	AML	47,X,der(Y)t(Y;3)(q12;q21),+8[7]/46,XY,+1, der(1;3)(q10;q10) [3]/46,XY[15]	Davidsson <i>et al.</i> , 2006 [11]
2	NA/M	MDS	49~50,XY, der(3;5)(q10;q10) ,-5,add(7)(?q10),+8,+22,+1~3mar[cp20]	Westbrook <i>et al.</i> , 2000 [12]
3	45/M	t-AML	44,XY, der(3;6)(q10;p10) ,del(5)(q11.2q34),-7,del(12)(p11.2p13)[4]/45,idem,+r[17]/46,idem,+r,+mar[2]	Side <i>et al.</i> , 2004 [13]
4	NA/F	AML	43~47,X,der(X)t(X;17)(p22;q21), der(3;8)(q10;q10) inv(3)(q21q25),del(5)(q31),i(8)(q10),del(9)(q11),+der(9)del(9)(p21)del(9)(q11)x2,der(10)t(3;10)(p22;p13),der(10)t(10;21)(p15;q21),der(12)t(10;12)(q22;q12),del(13)(q21),der(16)t(12;16)(p13;q22),-17,-21[cp5]	Zhao <i>et al.</i> , 2001 [14]
5	6/F	AML	46,XX,i(7)(q10)[2]/45~47,XX,+der(2)t(2;17)(p14;q11), der(3;12)(q10;q10) ,-5,+12,-13,-17,del(20)(q11)[cp10]/46,XX[6]	Göhring <i>et al.</i> , 2007 [15]

6	77/F	AML	44,X,dic(X;14)(q13;p11.2), der(3;17)(q10;q10) ,del(5)(q11.2q31),add(7)(q32),-12,-15,add(16)(p13.1),+1~2mar[cp15]/46,XX[1]	Adeyinka <i>et al.</i> , 2007 [2]
7	78/F	AML-M0	44,XX, der(3;17)(q10;q10) ,der(4)t(4;16)(q34;p13),del(5)(q12q34),-7,del(12)(p13)	Van Limbergen <i>et al.</i> , 2002 [16]
8	53/F	RAEB-2	44,X, der(X;3)(q10;q10) ,der(1)t(X;1)(?;q43),der(4)t(4;11)(q11;?q24),del(5)(q22q35),der(5)ins(5;20)(q15;q?),del(6)(p22),-7,der(22)t(4;22)(q11;p12),+dmin(X)/44,XX,t(1;6)(q12;q26),-3,del(5)(q22q35),der(5)ins(5;20)(q15;q?),der(6)t(6;17)(p22;?),-7	Lessard <i>et al.</i> , 2007 [17]
9	56/M	AML-M5a	45,XY, der(7;10)(q10;q10) ,t(11;19)(q23;p12-13)	Huret <i>et al.</i> , 1993 [18]
10	78/F	MDS	44~48,XX, der(10;17)(q10;q10) , -12,add(16)(p13.3),+1~3mar[cp12]/46,XX[9]	Adeyinka <i>et al.</i> , 2007 [2]
11	58/M	AML-M5b	46,XY,+3, der(3;10)(q10;q10) [18]/46,XY[2]	present case

Abbreviations: NA, not available; F, female; M, male; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; t-AML, therapy-related AML; RAEB, refractory anemia with excess of blasts. Unbalanced translocations involving 3q or 10q are described in bold letters.