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Unbalanced translocation der(11)t(11;12)(q23;q13): a new recurrent cytogenetic aberration in myelodysplastic syndrome with a complex karyotype

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Abbreviated title: der(11)t(11;12)(q23;q13) in MDS

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Abstract

Cytogenetic abnormalities are observed in approximately one half of cases of myelodysplastic syndrome (MDS). Partial or complete chromosome losses and chromosome gains are frequently found, but there is a relatively high incidence of unbalanced translocations in MDS. We describe here two cases of MDS with an unbalanced translocation der(11)t(11;12)(q23;q13). Both patients were 69-year-old and diagnosed as refractory anemia with excess of blasts in transformation (RAEB-t) according to the high percentage of blasts in the peripheral blood. Cytoplasmic hypogranulation of neutrophils was evident as a dysplastic change. The blasts were positive for CD4 and CD41a as well as CD13, CD33, CD34 and HLA-DR in both cases. Chromosome analyses showed complex karyotypes including der(11)t(1;11)(q11;p15)t(11;12)(q23;q13) in case 1 and der(11)t(11;12)(q23;q13) in case 2 and several marker chromosomes. Spectral karyotyping confirmed the der(11)t(11;12)(q23;q13) and clarified the origin of marker chromosomes, resulting in del(5q) and del(7q). Fluorescence in situ hybridization (FISH) analyses with a probe for MLL demonstrated that the breakpoints at 11q23 were telomeric to the MLL gene in both cases. FISH also showed that the breakpoint at 11p15 of the case 1 was telomeric to the \textit{NUP98} gene. Considering another reported case, our results indicate that the der(11)t(11;12)(q23;q13) is a recurrent cytogenetic abnormality and may be involved in the pathogenesis of advanced-stage MDS.
1. Introduction

Myelodysplastic syndrome (MDS) is a clonal hematopoietic stem cell disorder characterized by ineffective hematopoiesis that leads to bone marrow failure and/or leukemic transformation. Clonal cytogenetic aberrations are found in 30 to 50% of de novo MDS and 80% of secondary MDS [1, 2]. In contrast to acute myeloblastic leukemia (AML) having preferentially balanced translocations, total or partial chromosome losses and chromosome gains are predominantly observed and balanced translocations are rare in MDS [1-3]. Although several chromosomal changes including 5q-, -7, and +8 are strongly associated with MDS, neither aberration is specific to MDS [2, 4].

Unbalanced translocations, which are created if one of the two derivative chromosomes is lost, are frequently found in MDS [2]. They are usually detected as a part of complex karyotypes, diagnostically nonspecific and related to disease progression [5]. Some recurrent unbalanced translocations, such as der(17)t(5;17)(p11;p11) leading to 17p deletion and der(16)t(1;16)(q11;q11) resulting in 1q trisomy, have been reported and characterized in MDS [2, 3].

On the other hand, chromosomal translocations involving 11q23 have been observed in a variety of hematological malignancies including acute lymphoblastic leukemia (ALL), AML and MDS [6]. The majority of these translocations result in the rearrangement of the MLL gene, although the incidence of MLL rearrangements in MDS has not been defined [3]. In addition, most typical 11q23 translocations, such as t(4;11), t(9;11) and t(11;19), are not found in MDS. Therefore, the pathological roles of 11q23 rearrangements in MDS remain to be completely elucidated.

We describe here two cases of MDS with an unbalanced translocation der(11)t(11;12)(q23;q13) involving 11q23 as a part of complex karyotypes.
The results indicate that the der(11)t(11;12)(q23;q13) is one of the non-random aberrations and may be implicated in the pathogenesis of advanced-stage MDS.
2. Materials and methods

2.1. Case Histories

2.1.1. Case 1

A 69-year-old woman was referred to our hospital for precise examination of anemia in July 2002. Peripheral blood showed hemoglobin 8.6 g/dl, platelets 111 x 10^9/l and white blood cells 4.3 x 10^9/l with 20% blasts, 1% promyelocytes, 3% myelocytes, 2% metamyelocytes, 3% bands, 23% segmented neutrophils, 3% monocytes and 45% lymphocytes. Bone marrow was hypercellular with 6.2% blasts. They were negative for myeloperoxidase staining and looked like magakaryoblasts. Dysplastic changes, such as degranulation of neutrophils and megaloblastic morphology of erythroblasts, were observed in the bone marrow cells. Surface marker analysis by three-color flow cytometry with CD45 gating revealed that the blasts were positive (more than 20%) for CD4 (56.3%), CD13 (90.8%), CD33 (96.2%), CD34 (67.1%), CD41a (84.3%) and HLA-DR (88.3%). She was diagnosed as MDS, refractory anemia with excess of blasts in transformation (RAEB-t) in the French-American-British (FAB) classification, or RAEB-I in the World Health Organization (WHO) classification. After one course of combination chemotherapy with cytarabine, daunorubicin, 6-mercaptopurine and prednisolone, she received non-myeloablative allogeneic stem cell transplantation from HLA 2 loci mismatched sibling donor in October 2002. She achieved a hematological and cytogenetic complete remission.

In May 2003, she was readmitted to the hospital because pancytopenia appeared again. Peripheral blood showed hemoglobin 9.9 g/dl, platelets 28 x 10^9/l and white blood cells 1.2 x 10^9/l with 1% blasts, 1% bands, 17% segmented neutrophils, 2% monocytes and 79% lymphocytes. Bone marrow was normocellular with 12.4% blasts. Dysplastic changes were also
observed in the bone marrow cells. Immunophenotypic analysis revealed that the blasts were positive for CD13 (96.5%), CD33 (96.2%), CD34 (94.8%), CD41a (34.2%) and HLA-DR (86.1%) but negative for CD4 (8.7%). The diagnosis as MDS at the relapse after allogeneic stem cell transplantation was made. She received palliative therapy with transfusion and antibiotics, but died of disease progression in July 2003.

2.1.2. Case 2

A 69-year-old man was admitted to our hospital for the treatment of esophageal carcinoma in July 2003. He had no past history of chemotherapy and radiotherapy. On admission, peripheral blood showed hemoglobin 9.3 g/dl, platelets 62 x 10^9/l and white blood cells 2.9 x 10^9/l with 13% blasts, 1% myelocytes, 1% metamyelocytes, 8% bands, 31% segmented neutrophils, 3% eosinophils, 4% monocytes and 39% lymphocytes. Bone marrow was normocellular with 6% myeloperoxidase-positive blasts. Tri-lineage dysplasia, such as degranulation and pseudo-Pelger anomaly of neutrophils, multi-nuclei of erythroblasts and micromegakaryocytes, was observed in the bone marrow cells. Surface marker analysis revealed that the blasts were positive for CD4 (49.1%), CD13 (95.3%), CD33 (98.9%), CD34 (87.2%), CD41a (32.4%), CD56 (21.6%) and HLA-DR (78.3%). He was diagnosed as RAEB-t in the FAB classification or RAEB-I in the WHO classification. He is now under treatment with transfusion and antibiotics.

2.2. Chromosome analysis and Spectral Karyotyping (SKY)

Chromosome analyses were performed on short-term culture of the cells obtained from bone marrow by the G-banding technique. Karyotypes were described according to the International System for Human Cytogenetic Nomenclature (ISCN 1995) [7]. Spectral karyotyping (SKY) was carried
out with SkyPaint™ kit (Applied Spectral Imaging, Migdal Ha’Emek, Israel) according to the manufacturer’s instructions. A total of 5 metaphase spreads were analyzed for spectral karyotyping.

2.3. Fluorescence in situ hybridization (FISH) analysis

Probes used in FISH analyses were LSI MLL Dual Color, Break Apart Rearrangement Probe, LSI CSF1R/D5S23, D5S721 Dual Color Probe, LSI D7S486, D7S522/CEP 7 Dual Color Probe (Vysis, Downers Grove, IL, USA) and NUP98/D11Z1 Dual Color Probe (SRL Inc., Tokyo, Japan).

The MLL probe is a mixture of a 350 kb portion centromeric of the MLL gene breakpoint cluster region labeled in SpectrumGreen and a 190 kb telomeric portion labeled in SpectrumOrange. In a normal cell hybridized with the MLL probe, the expected signal pattern is two orange/green (yellow) fusion signals. In a cell with a MLL translocation, one orange, one green and one fusion signals are observed.

The CSF1R/D5S23, D5S721 Dual Color Probe is a mixture of the approximately 160 kb SpectrumOrange labeled CSF1R probe and the approximately 450 kb SpectrumGreen labeled D5S23, D5S721 control probe. The CSF1R probe is located in the 5q33-q34 region. The D5S23, D5S721 probe located at 5p15 serves as an internal control for chromosome 5 to determine deletion of the whole chromosome 5 versus 5q-. In a normal cell, the expected pattern is the two orange and two green signals. In a hybridized abnormal cell containing the 5q33-q34 deletion, one orange and two green signals will be observed.

The D7S486, D7S522/CEP 7 Dual Color Probe is a mixture of the approximately 200 kb SpectrumOrange labeled D7S486 and D7S522 probe located at 7q31 and the centromere of chromosome 7 (D7Z1) probe labeled with SpectrumGreen. In a normal cell, the expected pattern is the two orange and two green signals. In a hybridized abnormal cell containing the
deletion of 7q31, one orange and two green signals will be observed.

The NUP98/D11Z1 probe is a mixture of the NUP98 probe labeled with SpectrumOrange spanning approximately 210kb containing the exon 20 of the NUP98 gene and D11Z1 probe labeled with SpectrumGreen covering a centromere of chromosome 11 [8]. The expected pattern in a normal nucleus is the two orange and two green signals. In a nucleus harboring a NUP98 translocation, three orange signals and two green signals are observed.
3. Results

3.1. Case 1

Chromosome analysis at the initial diagnosis showed the complex karyotypes as follows:
43,XX,-1,add(2)(q35),-3,-5,-7,der(11)t(1;11)(q11;p15)t(11;12)(q23;q13),
-12,-18,add(19)(p13),-22,-22,+mar1,+mar2,+mar3,+mar4,+mar5[2]/44,
 idem,+mar6[3]/45,idem,+8,+19,-add(19),-mar2,+mar6,+mar7[1]/46,XX[5].
After stem cell transplantation, the karyotype was 46,XX in all 20 metaphase spreads. At the relapse, the karyotypes were similar to those at the initial diagnosis as follows (Fig. 1A):
44,XX,-1,add(2)(q35),-3,-5,-7,der(11)t(1;11)(q11;p15)t(11;12)(q23;q13),
-12,-18,-19,-22,-22,+mar1,+mar2,+mar3,+mar4,+mar5,+mar6,+mar7[1]/
43,idem,-15[3]/46,XX[7].
To identify the origin of additional chromosomes and marker chromosomes, we applied SKY analysis on metaphase spreads of the same sample preparation obtained at the relapse. SKY analysis revealed that marker chromosomes were derived from several unbalanced translocations. Therefore, the karyotype at the relapse was revised as follows (Fig. 2A):
42,XX,der(1)del(1)(p?)t(1;3)(q21;?),der(2)t(2;5)(q35;?),-3,del(5)(q?),der(7)
t(5;7)(?;?),der(11)t(1;11)(q11;p15)t(11;12)(q23;q13),-12,-16,der(18)t(18;22)
(q21;q?),der(19)t(7;19)(?;?),-22,der(22)t(7;22)(?;p11).
To confirm some of the SKY findings, we performed FISH analyses with CSF1R (5q33-34) and D7S486, D7S522 (7q31) as a probe on interphase nuclei because chromosome abnormalities of 5q and 7q are important in the pathogenesis of MDS. The regions of 5q33-34 and 7q31 were deleted although the region of 5p15 and the centromere of chromosome 7 were preserved (Fig. 3A, 3B). The results indicated that aberrations of chromosomes 5 and 7 were derived from unbalanced translocations or par-
tial deletions, but not total losses of chromosomes 5 and 7 shown by G-banding.

G-banding and SKY analyses identified t(11;12)(q23;q13) and t(1;11)(q11;p15) translocations, suggesting that the \textit{MLL} gene at 11q23 and the \textit{NUP98} gene at 11p15 may be involved in these translocations. Hence, we performed FISH analyses with MLL and NUP98 probes on metaphase spreads and interphase nuclei at the relapse. However, the MLL signals were located on the der(11) and normal chromosome 11 (Fig.4A). The NUP98 signals were also not split and located on the der(11) and normal chromosome 11 (Fig.5 and data not shown). The results indicated that the breakpoints at 11q23 and 11p15 on the der(11) were telomeric to the \textit{MLL} gene and the \textit{NUP98} gene, respectively.

3.2. Case 2

Cytogenetic analysis showed complex karyotypes as follows (Fig. 1B): 42,XY,add(3)(p25),-5,-7,der(11)t(11;12)(q23;q13),-12,-13,-14,add(16)(q12),-17,-18,-20,+mar1,+mar2,+mar3,+mar4[1]/41,idem,-Y[16]/46,XY[3]. SKY analysis clarified the additional and marker chromosomes as follows (Fig. 2B): 41,X,-Y,der(3)(3qter->3q21::3p25->3qter),der(5)t(5;10)(q11;?),der(7)del(7)(p?)del(7)(q?),der(7)t(7;20)(p13;?)t(7;18)(q11;q11),der(11)t(11;12)(q23;q13),-12,der(13)t(13;17)(q11;q11),-14,der(16)t(14;16)(q13;q12),-17,-18,-20.

FISH analyses with CSF1R and D7S486, D7S522 probes were carried out and showed that the regions of 5q33-34 and 7q31 were deleted although the 5p15 region and centromere of chromosome 7 remained as observed in case 1 (data not shown).

For further characterization of der(11)t(11;12)(q23;q13), we performed FISH analysis with MLL probe. The MLL signals were also remained on
the der(11) and normal chromosome 11 (Fig. 4B), indicating that the breakpoint at 11q23 on the der(11) was telomeric to the *MLL* gene.
4. Discussion

On the basis of G-banding and SKY analyses, we defined an unbalanced translocation der(11)t(11;12)(q23;q13) in two cases of MDS with a complex karyotype. The breakpoints at 11q23 were telomeric to the MLL gene in both cases. Furthermore, in case 1, the NUP98 gene at 11p15 was not rearranged and located on the der(11)t(1;11)(q11;p15)t(1;11)t(11;12).

As shown in Table 1, only three cases of hematological malignancies with t(11;12)(q23;q13) have been described in the literature to date [9-12]. All cases had complex karyotypes. Only the reported CLL case (Table 1) showed a balanced translocation and the t(11;12)(q23;q13) was not found in the stem line, suggesting that this aberration might have different role from others [10]. Common clinical features in these cases could not be found because only limited information was available, but the present two cases had some similar findings. That is, they were older and diagnosed as RAEB-t according to the high percentage of blasts in the peripheral blood. Cytoplasmic hypogranulation of neutrophils was evident as a dysplastic change. Immunophenotypic analyses showed that the blasts were positive for monocytic marker CD4 and megakaryocytic marker CD41a as well as CD13, CD33, CD34 and HLA-DR. There is also another reported case with the der(11)t(11;12)(q23;q13) diagnosed as MDS, RAEB-t [12]. As a result, a total of three cases demonstrated the same phenotype, indicating that der(11)t(11;12)(q23;q13) is a recurrent cytogenetic abnormality in MDS, RAEB-t. Der(11)t(11;12)(q23;q13) may be involved in the pathogenesis of advanced-stage MDS, although it remains to be elucidated whether der(11)t(11;12)(q23;q13) is a primary genetic event or an additional change during disease progression of MDS. Furthermore, there is a possibility that the der(11)t(11;12)(q23;q13) may be a non-random, secondary, disease progression-related anomaly in a broad range of hematological malignan-
cies because the der(11) has been observed in CLL and ALL as well as RAEB-t.

We examined MLL involvement at the 11q23 in the der(11)t(11;12)(q23;q13) and no rearrangement was found in the two cases; it is unknown whether MLL was rearranged in other 3 reported cases. The majority of balanced 11q23 translocations result in the rearrangement of the MLL gene, but it has been shown that there is heterogeneity in the breakpoint in some of 11q23 rearrangements [13]. Namely, a number of 11q23 rearrangements clearly involved regions other than the MLL gene. For instance, breakpoints at 11q23 were telomeric to the MLL gene in ALL with t(11;14)(q23;q11) and malignant lymphoma with t(11;14)(q23;q32) [6, 13]. Recently, Archimbaud et al. reported that AML patients with unbalanced 11q23 abnormalities lacked MLL rearrangement and showed different clinical features such as older, less frequently of M4/M5 subtype, more frequent expression of CD34 antigen, additional chromosomal abnormalities and poor prognosis [14]. These findings indicate that unbalanced 11q23 abnormalities constitute MLL-unrelated different pathologic entity from cases with balanced 11q23 translocations and MLL rearrangement. Lack of MLL rearrangement in the present cases with unbalanced der(11)t(11;12)(q23;q13) is compatible with these observation. Unknown gene(s) located telomeric to the MLL gene may be involved in the der(11)t(11;12)(q23;q13) and associated with the development of MDS.

Chromosome rearrangements at 12q13 are frequently observed in a variety of solid tumors such as myxoid liposarcoma [15, 16]. Furthermore, Seyger et al. reported that 12q13 may be a new recurrent breakpoint in acute non-lymphocytic leukemia (ANLL) and clinically important in ANLL because of an immature phenotype and poor prognosis [17]. As observed in the present cases, the 12q13 translocation is often associated with concomitant dysmyelopoietic changes and occurs as a complex karyotype with
other aberrations accompanying the translocation [17-19]. Chromosome region 12q13 is also known to contain several genes involved in tumorigenesis such as *CHOP*, *CDK4*, *MDM2* and *GLI* [20, 21]. Recently, the *HOXC13* gene was identified at 12q13 in AML with t(11;12)(p15;q13) that results in the formation of a novel *NUP98/HOXC13* fusion [22]. It is possible that these genes at 12q13 might be involved in the der(11)t(11;12)(q23;q13).

It has been reported that many unbalanced translocations show duplication of a translocation participant. That is, a morphologically normal copy of one of the two chromosomes is acquired and this acquisition may compensate for one of the translocated segments [5]. However, the der(11)t(11;12)(q23;q13) is not followed by the gain of a normal chromosome 12 and consequently results in 12p monosomy. Deletions of 12p, such as del(12)(p11) and del(12)(p11p13), are recurrent cytogenetic abnormalities often observed in MDS or AML [23]. Loss of 12p in the der(11)t(11;12)(q23;q13) also may play a possible pathogenetic role by inducing functional loss of tumor suppressor genes [1-3].

In the case 1, the der(11)t(11;12)(q23;q13) was accompanied by an additional translocation t(1;11)(q11;p15) and led to the formation of the der(11)t(11;11)(q11;p15)t(11;12)(q23;q13). The der(11)t(1;11)(q11;p15) has been reported as an additional cytogenetic abnormality in Philadelphia chromosome-positive ALL [24]. In addition, +der(11)t(1;11)(q11;p15) was described in multiple myeloma with a complex karyotype [25]. The *NUP98* gene maps to 11p15 and was initially shown to be involved in t(7;11)(p15;p15) in AML [14]. The *NUP98* gene is now known to be fused to more than 10 partner genes in various hematological malignancies [26]. Hence, we examined the correlation with *NUP98*, but *NUP98* was not involved in the der(11)t(1;11)(q11;p15) and the breakpoint at 11p15 was telomeric to the *NUP98* gene.
The other common aberrations found in the 2 cases were deletions of 5q and 7q. G-banding analysis showed -5, -7, and several marker chromosomes as a part of complex karyotypes, and SKY clarified the origin of the marker chromosomes. Consequently, aberrations of chromosomes 5 and 7 were shown to be the results of unbalanced translocations or partial deletions, but not total losses of chromosomes 5 and 7 in both cases. The results of FISH with CSF1R and 7q31 probes were compatible with these findings. Our results confirmed that the use of SKY combined with conventional G-banding analysis has assisted in the identification of important chromosomal rearrangements [27]. Kakazu et al. also showed by SKY analysis that some chromosome losses identified by G-banding were not complete, but chromosome fragments had been translocated to a variety of partner chromosomes [28]. Deletions of 5q and 7q are most frequent cytogenetic abnormalities and play an important role in the development of MDS [1-3].

Complex cytogenetic abnormalities predominate in advanced-stage MDS and are associated with poor prognoses. In the present cases, complex karyotypes were observed at the initial diagnoses and the pathway of clonal evolution could not be clarified. Hence, at present, it is difficult to evaluate accurately the clinical significance of der(11)t(11;12)(q23;q13). Further cytogenetic and molecular analyses for more cases are needed to elucidate the pathogenesis of der(11)t(11;12)(q23;q13) in MDS.
References


Figure legends

Fig.1. G-banded karyotypes of the bone marrow cells. Arrows indicate rearranged chromosomes.

(A) case 1;
43,XX,-1,add(2)(q35),-3,-5,-7,der(11)t(1;11)(q11;p15)t(11;12)(q23;q13),-12,-15,-18,-19,-22,-22,+7mar.

(B) case 2;
42,XY,add(3)(p25),-5,-7,der(11)t(11;12)(q23;q13),-12,-13,-14,add(16)(q12),-17,-18,-20,+4mar.

Fig.2. Spectral karyotypes of the metaphase spread after spectra based classification (left side, reverse DAPI; right side, SKY). Chromosomes were assigned a pseudocolor according to the measured spectrum. Arrows indicate rearranged chromosomes.

(A) case 1;
42,XX,der(1)del(1)(p?)t(1;3)(q21;?),der(2)t(2;5)(q35;?),-3,del(5)(q?),der(7)t(5;7)(?;?),der(11)t(1;11)(q11;p15)t(11;12)(q23;q13),-12,-16,der(18)t(18;22)(q21;q?),der(19)t(7;19)(?;?),-22,der(22)t(7;22)(?;p11).

(B) case 2;
41,X,-Y,der(3)(3qter->3q21::3p25->3qter),der(5)t(5;10)(q11;?),der(7)del(7)(p?)del(7)(q?),der(7)t(7;20)(p13;?)t(7;18)(q11;q11),der(11)t(11;12)(q23;q13),-12,der(13)t(13;17)(q11;q11),-14,der(16)t(14;16)(q13;q12),-17,-18,-20.

Fig.3. Dual-color FISH analyses with the (A) CSF1R/D5S23, D5S721 and (B) D7S486, D7S522/CEP 7 probes on interphase nuclei of the case 1. (A) Two D5S23, D5S721 signals (green) and one CSF1R signal (orange) are observed. (B) Two D7Z1 signals (green) and one D7S486, D7S522 signal
(orange) are observed.

Fig.4. Dual-color FISH analyses with the MLL probe on metaphase spreads of the case 1 (A) and case 2 (B). Dual-color MLL signals (green and orange) are located on normal chromosome 11 and der(11) and they are not split. Arrows indicate MLL signals.

Fig.5. Dual-color FISH analysis with NUP98/D11Z1 probes on interphase nuclei of the case 1. Two NUP98 signals (orange) are not split. Two D11Z1 signals (green) are also observed.
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<td>69/M</td>
<td>RAEB-t</td>
<td>41,X,Y,der(3)(3qter-&gt;3q21::3p25-&gt;3qter),der(5)t(5;10)(q11?),der(7)del(7)(p?)del(7)(q?),der(7)t(7;20)(p13?)t(7;18)(q11;q11),der(11)t(11;12)(q23;q13),-12,der(13)t(13;17)(q11;q11),-14, der(16)t(14;16)(q13;q12),-17,-18,-20.</td>
<td>Case 2</td>
</tr>
</tbody>
</table>

Abbreviations: M, male; F, female; NA, not available; CLL, chronic lymphoid leukemia; ALL, acute lymphoblastic leukemia; RAEB-t, refractory anemia with excess of blasts in transformation.