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(Citation)

Leukemia research, 34(12):e339-e341

(Issue Date)

2010-12

(Resource Type)

journal article

(Version)

Accepted Manuscript

(URL)

<https://hdl.handle.net/20.500.14094/90001485>



Acknowledgements

This work was supported in part by grants-in-aid for scientific research from the Ministry of Health, Welfare and Labor and from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 22591037).

Authors' Contributions

K. Y. provided the concept and design, interpreted the data and drafted the manuscript. M. S., Y. K., and T. M. took care of the patients and collected the data. T. M. revised and gave final approval of the manuscript.

Conflict of interest

All authors declare no conflict of interest.

Unbalanced whole-arm translocation der(18;21)(q10;q10) is a recurrent cytogenetic aberration appearing during progression in myeloid leukemias

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Word count: 1,045

Key words: unbalanced whole-arm translocation; der(18;21)(q10;q10); acute myeloid leukemia

Unbalanced whole-arm translocations are relatively rare acquired cytogenetic aberrations in hematological malignancies [1]. Many of them occur during disease progression as a part of complex karyotypes, although clinical significance of these secondary abnormalities remains to be completely elucidated [2]. We describe here a rare unbalanced whole-arm translocation der(18;21)(q10;q10) which appeared at the relapse of acute myeloid leukemia with myelodysplasia-related changes (AML-MRC). Considering two previously reported cases, the der(18;21)(q10;q10) was shown to be a rare but recurrent cytogenetic aberration appearing during progression in myeloid leukemias.

A 54-year-old man was admitted to our hospital because of anemia and neutropenia lasting for at least six months in April 2008. Peripheral blood showed hemoglobin at 85 g/L, platelet count of 183×10^9 /L and white blood cell count of 3.0×10^9 /L with 1% metamyelocytes, 4% segmented neutrophils, 1% eosinophils, 1% basophils, 19% monocytes, and 74% lymphocytes. Bone marrow was hypercellular with 28.6% myeloblasts, 20.0% myeloid cells, 23.2% erythroblasts, and 17.2% lymphocytes. Myeloblasts were positive for myeloperoxidase but negative for α -naphthyl butyrate esterase and chloroacetate esterase staining. Trilineage dysplasia, including hypogranulation and pseudo-Pelger anomaly of neutrophils, megaloblastic changes of erythroblasts, and binuclear megakaryocytes, was observed in the bone marrow cells. Surface marker analysis with CD45 gating by three-color flow cytometry revealed that myeloblasts were positive (more than 20%) for CD13 (79.6%), CD33 (59.5%), CD34 (62.7%) and HLA-DR (93.4%) but negative for other lymphoid markers. Therefore, considering trilineage dysplasia and a previous history of cytopenia, we made a diagnosis of AML-MRC in the World Health Organization classification [3].

An induction therapy with daunorubicin and cytosine arabinoside was started, and the patient achieved a hematological complete remission (CR). However, the disease relapsed after two months during treatment for complications and preparation for unrelated bone marrow transplantation (BMT) (Table 1). Then, he underwent myeloablative BMT from an HLA matched unrelated male donor after conditioning regimen with total body irradiation

and high-dose cyclophosphamide in August 2008. He obtained complete chimerism and hematological and cytogenetic CR on day 30. Nevertheless, bone marrow examination on day 120 revealed 11.0% blasts, indicating the relapse after BMT. After discontinuation of immunosuppressive agent, best supportive therapies including transfusion and antibiotics were performed. He died of disease progression and pneumonia in February 2009.

The results of cytogenetic analyses during the clinical course were summarized in Table 1. G-banding analysis at the first relapse showed trisomy 21 and der(18;21)(q10;q10) although another unrelated clone was found as a main line (Fig. 1). The clone with trisomy 21 predominated during disease progression. The complex karyotypes at the relapse after BMT also contained der(18;21)(q10;q10),+21 in a stem line. Spectral karyotyping confirmed the structure of der(18;21)(q10;q10) (data not shown).

We have detected an unbalanced whole-arm translocation der(18;21)(q10;q10) in AML-MRC during disease progression. Furthermore, the der(18;21) was constantly accompanied by an extra chromosome 21. 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 [2]. In the present case, by acquisition of a normal chromosome 21 but not a chromosome 18, the der(18;21) resulted in trisomy 21q and monosomy 18p. At the relapse after BMT, the der(18;21),+21 was found as a part of complex karyotypes in all abnormal metaphase spreads. The results indicated that it could play a crucial role in the progression of AML-MRC by the gain of 21q or the loss of 18p, although both are not described in unbalanced abnormalities sufficient to diagnose AML-MRC [3].

According to the Mitelman database, der(18;21)(q10;q10) have been reported in one case of adenocarcinoma and seven cases of hematological malignancies: three cases of AML, one case of atypical chronic myeloid leukemia (aCML), one case of acute lymphoblastic leukemia (ALL), and two cases of multiple myeloma [4]. Among these, one AML case with 48,XY,+8,+21/48,s1,der(18;21)(q10;q10) and the aCML case with 47,XY,der(18;21)(q10;q10),+21,+21/47,XY,der(18;21)(q10;q10)x2,+21 had extra

chromosomes 21 [5, 6], whereas no case had an extra chromosome 18. As a result, a total of three cases exhibited der(18;21),+21, indicating that this is a rare but recurrent cytogenetic aberration in myeloid leukemias. Moreover, the aCML case showed a normal karyotype at presentation. In contrast, der(18;21),+21,+21 or der(18;21)x2,+21, both of which lead to tetrasomy 21q and monosomy 18p, appeared at disease acceleration [6]. The AML case also showed der(18;21),+21 at the diagnosis of AML evolving from MDS [5]. Accordingly, in all three cases, the der(18;21),+21 seems to occur at the transformation or relapse of the disease, supporting that it may be implicated in the disease acceleration rather than the disease onset.

The most functionally important consequence of unbalanced whole-arm translocations is the genomic imbalance resulting from the gain and loss of whole chromosome arms. Adeyinka et al. [1] reported that a gain of 21q and a loss of 18p were observed in one and eight cases of 131 hematological malignancies, respectively. Thus, trisomy 21q by unbalanced whole-arm translocations seems to be a relatively rare event, although trisomy 21 is observed in approximately 5% of AML and 23% of ALL with aberrant karyotypes [7]. Trisomy 21q could result in increased copy number of genes on the entire 21q including *RUNX1*, *TPR22*, and *TFF* at 21q22. It has been shown that intrachromosomal amplification of chromosome 21 (iAMP21) occurs in about 2% of childhood ALL [7]. Among the genes on 21q, iAMP21 always included *RUNX1* [8]. On the other hand, Escher et al. [6] extensively examined all exons of *RUNX1* in the aCML case with der(18;21), but no mutation was detected. The results suggested a possible gene dosage effect for *RUNX1* in myeloid leukemias similar to observations in ALL. However, it has never been elucidated whether *RUNX1* or any other gene is the target of trisomy 21q.

Monosomy 18p has been recurrently observed in chronic myeloproliferative disorders [9, 10]. Namely, monosomy 18p and monosomy 17p were induced by der(17;18)(q10;q10) as a secondary abnormality in the accelerated or blast phase of Philadelphia chromosome-positive CML [9]. Monosomy 18p and trisomy 9p were also brought about by +9,der(9;18)(p10;q10) in polycythemia vera (PV) [10]. Genes that may be lost by this event includes *ERV1*, *YES1*

and *PTPN2* located at 18p11 [9]. Thus, monosomy 18p could be also considered as an alternative mechanism to disease progression. Further investigation for more cases will be necessary to elucidate the critical role of der(18;21) in the pathogenesis of myeloid leukemias.

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Figure Legends

Figure 1

G-banded karyogram of bone marrow cells at the first relapse of AML:

46,XY,der(18;21)(q10;q10),+21. The arrow indicates the rearranged chromosome.

Figure 1

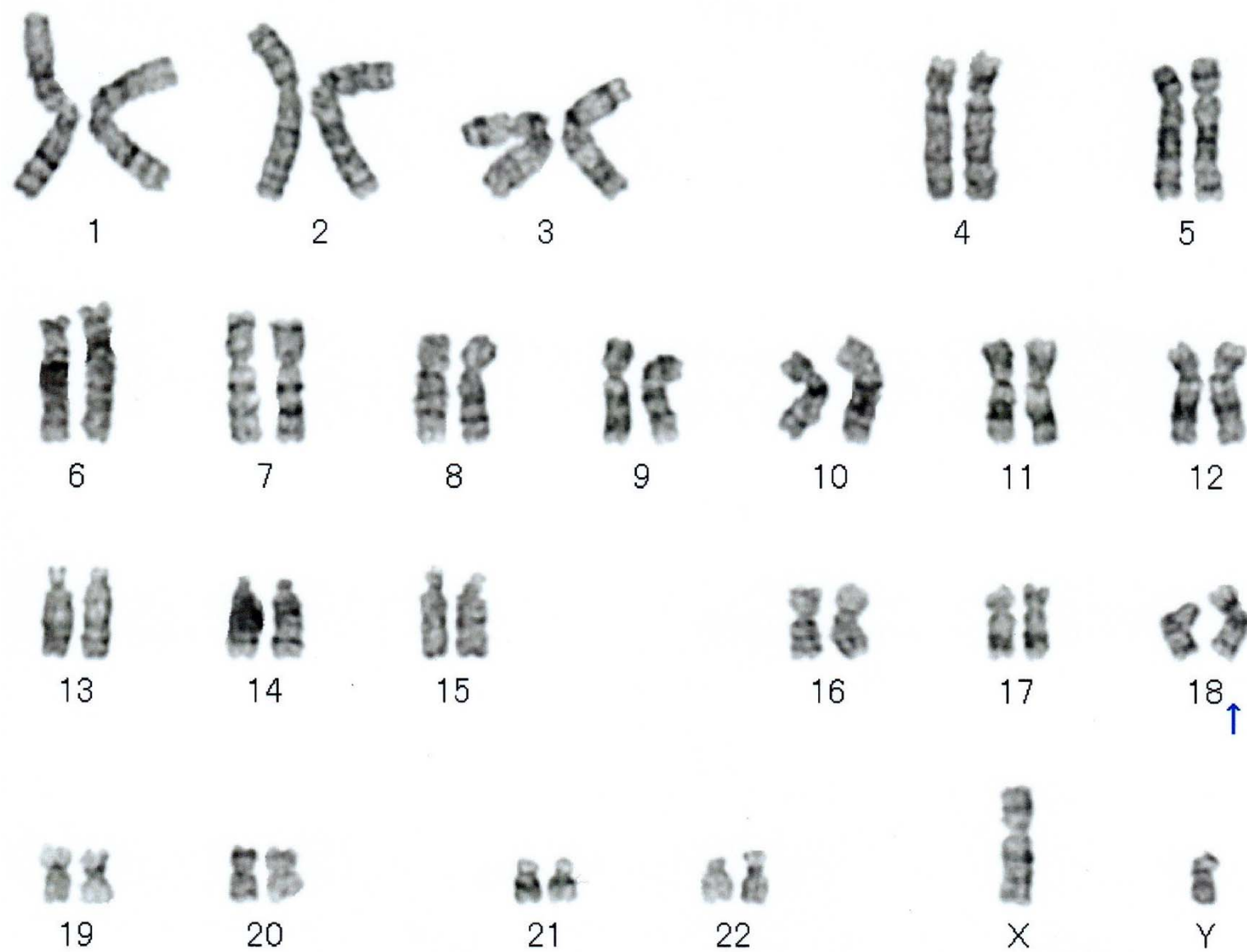


Table Legends

Table 1

Summary of cytogenetic analyses

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; BMT, bone marrow transplantation. The **der(18;21)(q10;q10)** and **+21** are described in bold letters.

Table 1. Summary of cytogenetic analyses

<i>Date</i>	<i>Disease status</i>	<i>Blasts (%) in BM</i>	<i>Karyotypes</i>
April 2008	AML, diagnosis	28.6	47,XY,+4[1]/46,XY[29]
May 2008	CR, after induction therapy	2.2	46,XY[20]
July 2008	AML, first relapse	8.8	46,XY,+8,-16,-17,+mar1[4]/47,XY,+21[2]/46,XY, der(18;21)(q10;q10) ,+21[2]/46,XY[12]
August 2008	AML, first relapse	9.6	47,XY,+21[4]/46,sl, der(18;21)(q10;q10) [1]/46,XY[15]
September 2008	CR, after BMT	0.2	46,XY[20]
October 2008	CR, after BMT	1.2	46,XY[20]
December 2008	AML, second relapse, after BMT	11.0	46,XY,del(6)(q?), der(18;21)(q10;q10) ,+21[2]/46,sl,-2,add(11)(q13),add(12)(q24.1),+mar1[2]/ 46,sl,add(1)(p11),add(5)(q31),add(7)(p11.2),add(8)(q13),add(14)(q24),add(15)(q15)[1]/46,XY[10]