Acute Myelogeneous Leukemia (M5a) that Demonstrated Chromosomal Abnormality of Robertsonian 13;21 Translocation at Onset

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Abstract

A 27-year-old woman had congenital lissencephaly syndrome and mental retardation. She had a fever of unknown origin and visited her local physician. Blood test indicated leukocytosis, so she was referred to our hospital for detailed examination. She was diagnosed to have acute myelogeneous leukemia (M5a). The chromosome analysis in blast cells revealed Robertsonian 13;21 translocation. Complete remission was obtained by induction chemotherapy. As normal karyotype (46, XX) was observed in the chromosome analysis of bone marrow cells after remission, it was considered that the patient had acquired Robertsonian 13;21 translocation complicated by acute myelogeneous leukemia. (Internal Medicine 43: 508–511, 2004)

Key words: acute myelogeneous leukemia, acquired Robertsonian translocations, hematologic malignancy, leukemogenesis

Introduction

Centromeric fusion of the long arms of two acrocentric chromosomes is called a Robertsonian translocation (1). This is congenital and is frequently complicated by congenital abnormalities such as Down's syndrome and Turner's syndrome (2). However, very few reports have been discussed a complication of hematologic malignancy. We report a case of acute myelogeneous leukemia (M5a) that demonstrated Robertsonian 13;21 translocation at onset and review the literature on this rare event in hematologic malignancy.

Case Report

The case was a 27-year-old woman with the major complaint of high fever. She was diagnosed with congenital lissencephaly syndrome as a child. As she had mental retardation and epilepsy attacks, she was placed under observation from 1992 by her local physician. A high fever of unknown cause appeared on October 12, 2002. As the result of a blood test indicated leukocytosis, suggesting a blood disease, she was admitted to our hospital for detailed examination. On admission, her body temperature was 38.9°C, anemia was detected in the eyelid conjunctiva and many aphthas were observed in the oral cavity. Chest X-ray did not show any pneumonia. On hematological examination, white blood cell count was markedly increased to $135 \times 10^3/\mu\text{l}$. The red blood cell count was $268 \times 10^6/\mu\text{l}$ and hemoglobin was 9.7 g/dl. The platelet count decreased to $5.2 \times 10^4/\mu\text{l}$. Though the coagulation time result was normal, CRP was increased to 9.1 mg/dl and the LDH level was markedly increased to 1,558 IU/l. The cell count was $488 \times 10^3/\mu\text{l}$ in the bone marrow indicating hyperplasia, and blast cells accounted for 86.4% of them. According to May-Giemsa staining, most of the blasts were immature monocytoid cells (Fig. 1). They were negative to myeloperoxidase staining and positive to non-specific esterase staining. As to surface markers of the blast cell, CD13, CD14, CD33 and HLA-DR were positive. Furthermore, the blood and urinary lysozyme values were high. Accordingly, the patient was diagnosed to have acute myelogeneous leukemia (M5a according to FAB classification). Chromosome analysis of blast cells showed Robertsonian 13;21 translocation (Fig. 2). Induction chemotherapy was immediately started after admission. The blast cells quickly decreased, resulting in complete remission. The chromosome analysis after remission indicated normal karyotype (46,XX). Thereafter consolidation repeated. As the clinical course was favorable, the patient was discharged.

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Figure 1. The bone marrow aspiration showed immature monocytoid cells (May-Giemsa stain, $\times 1,000$).

However, a relapse was observed after two months. Chromosomal abnormality of Robertsonian 13;21 translocation was observed again at relapse as well as first admission in bone marrow. Though reinduction therapy was performed, remission was not gained and the patient died of sepsis ten months after the relapse.

Discussion

We report a case of Robertsonian 13;21 translocation in a patient with acute myelogenous leukemia (M5a). Robertsonian translocations are demonstrated as a mutual translocation between the long arms of D group 13–15 and G group 21–22 in chromosomes (1). Forms of translocation reported in the literature include mutual translocation between D groups, G groups, or between D and G group. The Robertsonian 13;21 translocation in the present case is a D;G trans-

Figure 2. Complete karyotype of the patient showing 45, XX, der (13;21). The acquired Robertsonian translocation is indicated by an arrow. Rearranged chromosome from the same metaphase is shown on the right lower side.

Table 1. Acquired Robertsonian Translocations in Hematologic Malignancies; A Summary of the Published Cases

Reference	Sex/age	Diagnosis	Karyotype (acquired Robertsonian translocation)
Levitt et al (5)	F/25	Atypical lymphoid leukemia in ataxia telangiectasia	45, XX, t (13; 15) (q11; p11), t (13; 17) (p11; q11), t (14; 14) (q34; q11), -16, add (18) (q?), +3mar
Mitelman et al (6)	F/60	Acute myelogenous leukemia	47, X, -X, +del (1) (p11), del (5) (q13), t (5; 12) (q21; q24), t (11; 12) (q25; q13), t (13; 14) (q11; p11), +16, +21/46, XX
Morgan et al (7)	M/55	Prolymphocytic leukemia	45, XY, t (9; 10) (p24; q25), t (11; 14; ?) (q13; p12; ?), -13, +t (13; 15) (q11; p12), -15, i (17) (q10), der (20) t (3; 20) (q21; q13)
Fan et al (8)	M/70	Therapy-related myelodysplastic syndrome	45-46, XY, del (5) (q12) [3], +6 [3], +8 [2], -14 [3], -14 [3], +dic (14; 14) (p11; p11) [3], inv (18) (p11 q21) [3], -21 [3] [cp3]/46, XY [40]
Horsman & Kalousek (9)	M/33	Chronic myeloid leukemia in blastic phase	46, XY, t (9; 22) (q34; q11) [1]/49, XY, +8, t (9; 22) (q34; q11), +14, +der (22) t (9; 22) [2]/47, XY, -3, +der (8) t (1; 8) (q?; p?), t (9; 22), add (14) (q?), +t (21; 21) (p11; q11) [2]/46, XY, -3, t (1; 5) (q?; q?), t (9; 22), add (14), +(21; 21) [4]
Horsman & Kalousek (9)	F/66	Myeloproliferative disorder in leukemia transformation	46, XY, +der (1) t (1; 7) (p11; p11), -7 [10]/46, XX, +der (1) t (1; 7), -7, -21, +t (21; 21) (p11; q11) [3]
Horsman & Kalousek (9)	M/44	Acute myelogenous leukemia (M3)	46, XY, -14, +t (14; 21) (p11; q11), t (15; 17) (q22; q12) [20]/46, XY [10]
Ino et al (10)	M/43	Acute myelogenous leukemia (M5b)	45, XY, der (13; 15) (q10; q10) [15]/46, XY [5]
Ma et al (11)	M/68	Acute myelogenous leukemia (M1)	45, XY, der (14; 21) (q10; q10) [5]/46, XY [1]
Chinnappan et al (12)	M/54	Chronic lymphocytic leukemia	38, X, add (Y) (q12), t (1; 9) (q13; q11), -2, 8, der (8) t (8; 14) (q22; q11.2), der (9) (q22), -10, add (10) (q25), der (12) (p11.2 p11.2), der (14; 15) (q10; q10), -16, add (17) (p13), -18, add (18) (q23), add (19) (q13.4), -22
Chinnappan et al (12)	M/76	Acute myelogenous leukemia	44, XY, del (5) (q13 q33), -7add (9) (q34), der (15) t (13; 15) (p11.1; p11.1), der (14; 22) (q10; q10), -18, dic (21; 22) (p11.1; p11.1), +22, r (?14), +r (?14)
Levin et al (13)	-/-	Acute monoblastic leukemia	48, XY, +8, +8, t (13; 15) (p11; q11), -15
Suciu et al (13)	-/-	Acute myelogenous leukemia	47, XX, hsr (1) (q32), t (5; 17) (q11; q11), +8, +11, t (14; 15) (p11; p11), add (19) (p?), +21 "s"
Whang-Peng et al (13)	-/-	Acute erythroleukemia	46, XY, der (5) (q12 q34), -7, +del (12) (p12), +15, -16, add (17) (p?), der (21) t (14; 21) (q12; p11), +r "s"
Olopade et al (13)	-/-	Acute erythroleukemia	47, X, -Y, der (2) t (2; 3) (q31; p23), i (3) (q10), -5, +6, -7, +8, -14, der (14) t (1; 14) (p32; q32), -15, -16, -17, t (17; 21) (q21; q22), der (19) t (14; 19) (q11; q13), +der (21) t (17; 21), +der (?) t (?; 15) (?; q15), +4mar/48, XY, del (5) (q13 q35), +6, -7, +8, +13, der (14; 15) (q10; q10), -17, t (17; 21), add (19) (p13), +der (21), +mar/53, XY, del (5), +6, +8, +13, t (17; 21), der (19), +der (21), +der (?), +2mar
Berger et al (13)	-/-	Acute promyelocytic leukemia	46, XY, add (3) (q29), t (15; 17) (q22; q12), t (21; 21) (p11; q11)/46, XY, der (3), del (11) (p12), t (15; 17), t (21; 21)/46, XY, der (3), t (15; 17), t (21; 21)/45, XY, add (2) (q35), -8, del (11) (p12), -12, t (14; 18) (q32; q21), t (15; 17), +mar
Present case	F/27	Acute myelogenous leukemia (M5a)	45, XX, der (13; 21) (q10; q10) [20]

location.

Robertsonian translocation is generally considered a harmless chromosomal change. The points of translocations are at or near the centromere, resulting in monocentric or dicentric products in the form of metacentric or submetacentric chromosomes. The long arms of the involved chromosomes are invariably retained or recovered, whereas the reciprocal product, consisting of two short arms, is usually lost. The short-arm chromosomes and possibly satellite stalks are lost by this translocation. However, few numbers of transcribed ribosomal RNA genes are contained in these lost arms, and therefore neither the absence of these small chromosomes nor their presence as extra units seems to affect the phenotype as well as normal karyotype (1).

Although Robertsonian translocations are the most common type of congenital structural changes in newborns with

a frequency of approximately one in 1,117 (3), acquired Robertsonian translocations are rarely encountered in human malignancy (4). The frequency of this acquired translocation is estimated to be one in 10,053 patients with malignancy (5). Acquired Robertsonian translocations are generally found only in malignant cells in patients with malignancy.

Robertsonian translocations may also occur in hematologic malignancy, but only a few studies have been reported. Of reported hematologic malignancy complicated by Robertsonian translocation, the congenital cases account for 97% and the acquired at only 3% (4). To our knowledge, a review of the literature has identified only sixteen previously reported cases of hematologic malignancy with acquired Robertsonian translocations to date (Table 1) (5–13). Karyotype results were presented according to the recommendation by ISCN (1995) (14). The reason for the rarity of acquired

Robertsonian translocations in cancer including hematologic malignancy remains uncertain, but it is suggested that chromosomal recombinations leading to Robertsonian translocations probably occur more frequently in meiosis than mitosis (4).

The present case was complicated with congenital lissencephaly syndrome. Therefore, there may be a possibility that Robertsonian 13;21 translocation is congenital. The formation process of congenital Robertsonian translocation may include the case in which this translocation is already observed in the gamete of parents or when it occurs in the process of cell division to fertilization in spite of the normal gamete of both parents. Moreover, as with the reports of the cases with mosaic type Down syndrome containing 21 trisomy due to Robertsonian translocation, there may be a possibility that Robertsonian translocation occurs in the process of somatic cell division from the zygote with normal karyotype before birth (15, 16). In the present case, unfortunately, it was impossible to obtain tissues other than blood to verify the same Robertsonian translocation seen in blood and chromosome analysis of blood cells in parents because their consent could not be obtained. Therefore, the presence of congenital genetic chimerism could not be completely ruled out. However, considering that the chromosomal abnormality of Robertsonian translocation in the blood cells once disappeared, demonstrating normal karyotype at the time of hematological remission by induction therapy, the present case of Robertsonian translocation is suggested to be of acquired nature as was observed in the cases reported in the literature.

It remains unclear how the acquired Robertsonian translocation contributes to leukemogenesis. However, this phenomenon is postulated to be a mechanism for producing partial trisomy or tetrasomy, contributing to clonal evolution by increasing gene dosage (9). Though fourteen of sixteen cases in the literature revealed numerous additional chromosomal abnormalities other than Robertsonian translocation, no other additional chromosomal abnormalities were observed in the present case at the onset and the same Robertsonian translocation alone in the blood cells was observed at the relapse. This finding suggests that the acquired Robertsonian 13;21 translocation represents the key genetic event in the leukemogenesis. However, as described above, only a few cases of Robertsonian translocation complicated

by a hematologic malignancy have been reported, indicating that the possible association and onset mechanism remain to be elucidated in the future.

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