Therapy-related Myelodysplastic Syndrome with Trisomy 1q due to der(1;7) and Megakaryoblastic Proliferation Developing during Complete Remission of Therapy-related Acute Myeloid Leukemia with t(8;21)

Chikara Sakai, Keiko Matsubayashi*, Takashi Saotome, Akihiro Ishii and Kyoya Kumagai

Abstract

Therapy-related acute myeloid leukemia (t-AML) with t(8;21) and therapy-related myelodysplastic syndrome (t-MDS) with trisomy 1q due to der(1;7) developed in the same patient with T-cell lymphoma at intervals of six years. After the development of t-MDS with trisomy 1q, during complete remission of t-AML, the number of megakaryoblasts increased to maximally 74% of leukocytes in the blood. This is a very rare case of two separate therapy-related myeloid malignancies (early t-AML and late t-MDS) and is also a notable case of t-MDS with trisomy 1q due to der(1;7) accompanied by megakaryoblastic proliferation.

Key words: T-cell lymphoma, topoisomerase II inhibitors, alkylating agents, CD41

Introduction

Therapy-related acute myeloid leukemias (t-AML) or therapy-related myelodysplastic syndromes (t-MDS) are divided into two subtypes (1). One subtype is caused by alkylating agents such as cyclophosphamide and melphalan, usually presents with preleukemic phase, frequently shows unbalanced chromosomal abnormalities such as –5, 5q–, –7, 7q+, and is refractory to chemotherapies. Another subtype, which is induced by topoisomerase II inhibitors including etoposide or anthracyclines, has no preleukemic phase, often demonstrates balanced translocations such as t(9;11), t(8;21), t(15;17), and, like de novo AML with the same karyotypes, responds well to conventional chemotherapies (2–5).

Recently we experienced t-AML with t(8;21) and t-MDS with trisomy 1q due to der(1;7) in the same patient at intervals of 6 years. Furthermore, after the development of t-MDS with trisomy 1q, megakaryoblastic proliferation ensued.

Case Report

A 41-year-old woman was referred to our hospital in August 1990 because of multiple subcutaneous masses. The patient had no remarkable past history or family history and had been well until one month before hospitalization. Peripheral T-cell lymphoma was disclosed by the biopsy of a subcutaneous tumor and then she was treated with CHOP (adriamycin, cyclophosphamide, vincristine, prednisolone) therapy and MEVP (mitoxantrone, etoposide, vindesine, prednisolone) therapy (6), resulting in partial response. Subsequently, to achieve a complete response, several combination chemotherapies including etoposide, cisplatin, carboplatin, cytarabine, enocitabine (BH-AC), ranimustine (MCNU), procarbazine, and bleomycin were given to her until October 1991, leading to a complete remission. Up to that point, the cumulative doses of adriamycin, cyclophosphamide, etoposide were 400 mg, 5,500 mg, 4,500 mg, respectively. At the end of February 1992, however, severe headache occurred and a mass lesion was discovered in the cerebellum by the computed tomography. Immediately the cerebellar tumor was resected surgically. Pathologically this
tumor was composed of large lymphoid cells with pleomorphic, polylobated nuclei with prominent nucleoli (Fig. 1) and these cells were stained by MT-1 (anti-CD43) and UCHL-1 (anti-CD45RO) but not by L26 (anti-CD20), indicating a T-cell lymphoma. Because there were no lymphomatous lesions below the neck at that time, she was treated with whole brain irradiation (50 Gy) and gained a complete remission again. During whole brain irradiation, anemia and thrombocytopenia developed rapidly and a transfusion of red cells was required. Because the platelet count decreased to 44,000/μl, the bone marrow aspiration with chromosomal analysis was performed. The myelogram showed that 13.5% of marrow cells were myeloblasts with Auer rods accompanied by maturation arrest in immature granulocytes. The cytogenetic study revealed a translocation t(8;21)(q22;q22) (Fig. 2) in 19 out of 20 marrow cells. In July 1992 when myeloblasts increased to 40% in the bone marrow, the induction chemotherapy with daunorubicin, enocitabine, 6-mercaptopurine (6-MP), and prednisolone was started, resulting in a hematological and cytogenetic complete remission of AML (Table 1). Thereafter she received several maintenance chemotherapies comprising daunorobicin, aclorubicin, cytarabine, enocitabine, 6-MP, etoposide, vindesine, vincristine, and ranimustine for three years.

Since July 1995, she had been observed without treatment and her condition had been well until June 1998, when thrombocytopenia developed. Examinations of the bone marrow showed hypocellular marrow, 0.5% of myeloblasts, and no apparent cellular atypia. However, the chromosomal analysis revealed a combined trisomy 1q and monosomy 7 due to unbalanced translocation der(1;7) (Fig. 3). A diagnosis of MDS was made. One year later, the same karyotype was seen in 20 of 20 bone marrow cells including 4.5% of blasts. The patient had been asymptomatic initially but, since May 2000, occasionally petechiae and gingival bleeding occurred. In addition, peroxidase-negative blasts (Fig. 4A) and blastoid cells with cytoplasmic blebs (Fig. 4B) together with micromegakaryocytes appeared in the blood. The same karyotype as Fig. 3 was observed also in the peripheral blood cells containing 6% of blasts (or blastoid cells). In March

Figure 1. Histopathology of the brain tumor (HE, ×1,000). Large lymphoid cells with pleomorphic and polylobated nuclei are seen.

Figure 2. The karyotype at the diagnosis of AML [46, XX, t(8;21)(q22;q22)].
2001, when the leukocyte count was 1,800 to 2,300/μl with 17 to 22% of blasts (or blastoid cells), the immunophenotype of the circulating blasts was studied by flow cytometry (FCM) and immunocytochemistry. The data of FCM were as follows: CD13 (+) cells were 9.9%, CD33 (+) 0.7%, HLA-DR (+) 1.9%, CD3 (+) 1.3%, CD5 (+) 1.5%, CD7 (+) 1.2%, CD10 (+) 0.4%, CD34 (+) 28.0%, CD56 (+) 0.2%, and CD41 (platelet glycoprotein IIb/IIIa) (+) 37.4%. Immunocytochemistry demonstrated that both blasts and blastoid cells with cytoplasmic blebs were stained by anti-CD41 antibody (Fig. 4C), indicating megakaryoblasts (7). Since April 2001, because of increase in the circulating megakaryoblasts maximally to 74% of leukocytes and worseness of hemorrhagic tendency, the patient received an intermittent chemother-apy with cytarabine ocfosfate and frequent platelet trans-fusions at an outpatient clinic (8). But ultimately she died of

Table 1. Summary of Cytogenetic Findings

<table>
<thead>
<tr>
<th>Data</th>
<th>Material</th>
<th>Karyotype</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Apr. 1992</td>
<td>BM*</td>
<td>46, XX, t(8;21)(q22;q22)</td>
<td>95% (19/20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46, XX</td>
<td>5% (1/20)</td>
</tr>
<tr>
<td>Aug. 1992</td>
<td>BM</td>
<td>46, XX</td>
<td>100% (20/20)</td>
</tr>
<tr>
<td>Feb. 1994</td>
<td>BM</td>
<td>46, XX</td>
<td>100% (20/20)</td>
</tr>
<tr>
<td>Feb. 1995</td>
<td>BM</td>
<td>46, XX</td>
<td>100% (10/10)</td>
</tr>
<tr>
<td>Mar. 1997</td>
<td>BM</td>
<td>46, XX</td>
<td>100% (13/13)</td>
</tr>
<tr>
<td>Mar. 1998</td>
<td>BM</td>
<td>46, XX</td>
<td>100% (20/20)</td>
</tr>
<tr>
<td>Jun. 1998</td>
<td>BM</td>
<td>46, XX, +1, der(1;7)(q10;p10)</td>
<td>40% (8/20)</td>
</tr>
<tr>
<td>Jun. 1999</td>
<td>BM</td>
<td>46, XX</td>
<td>60% (12/20)</td>
</tr>
<tr>
<td>Aug. 2000</td>
<td>PB**</td>
<td>46, XX, +1, der(1;7)(q10;p10)</td>
<td>100% (20/20)</td>
</tr>
</tbody>
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*bone marrow, **peripheral blood.

Figure 3. The karyotype at the diagnosis of MDS [46, XX, +1, der(1;7)(q10;p10)]. Arrow indicates trisomy 1q and arrow head shows monosomy 7.
cerebral hemorrhage in March 2002. Autopsy was not permitted.

Discussion

In the present case, the AML with t(8;21) occurred 18 months after the beginning of chemotherapy for T-cell lymphoma and then the MDS with trisomy 1q due to der(1;7) developed 6 years after complete remission of AML. Up to the occurrence of AML with t(8;21), the cumulative doses of adriamycin, cyclophosphamide, and etoposide were 400 mg, 5,500 mg, and 4,500 mg, respectively. In 137 cases of t-AML or t-MDS reported by Pedersen-Bjergaard et al (1), 47 (73%) of 64 cases previously receiving alkylating agents alone showed unbalanced abnormal karyotypes such as –5, 5q−, –7, 7q+. Conversely, 18 of 20 patients with balanced translocations had received topoisomerase II inhibitors and 4 of 9 patients treated with topoisomerase II inhibitors alone or combined with radiation had a t(8;21)(q22;q22) (1). In another report by the same authors (9), a karyotype t(8;21) was seen in two of 5 cases of t-AML or t-MDS following a combination therapy of etoposide, cisplatin, and bleomycin for germ-cell tumor, and these patients’ cumulative doses of etoposide were 4,250 mg and 5,250 mg. The shortest period between the start of etoposide and the occurrence of t-AML with t(8;21) was only 15 months (9). Therefore, it is most likely that our patient’s AML with t(8;21) was t-AML induced by topoisomerase II inhibitors, etoposide or adriamycin.

The present case’s MDS with combined trisomy 1q and monosomy 7 due to der(1;7) developed about 8 years after the start of chemotherapy for T-cell lymphoma. This karyotype, combined trisomy 1q and monosomy 7 due to der(1;7), had been documented in 1980 for the first time in three patients with myelofibrosis and myeloid metaplasia (10). Since 1985, a der(1;7) had been often reported in MDS (11), and it became evident that a der(1;7) was closely related to t-MDS or t-AML induced by alkylating agents (1, 12–14). Usually a der(1;7) has been associated with poor
prognosis in both de novo and therapy-related MDS (15–17). Hamamoto et al described a unique case (18). Their patient presented as a de novo AML with t(8;21)(q22;q22) and then a MDS with combined trisomy 1q and monosomy 7 due to der(1;7) developed three years after complete remission of AML. Probably also our patient’s MDS with der(1;7) was induced by alkylating agents, especially cyclophosphamide, used about 8 years ago, and developed 6 years after complete remission of the preceding t-AML with t(8;21).

Finally, the present case is very notable one because megakaryoblastic proliferation ensued in the course of t-MDS with der(1;7). Concerning the cytogenetic abnormalities of megakaryoblastic leukemia, a translocation t(1;22)(p13;q13) has been described in infantile acute megakaryoblastic leukemia (AMKL) (19). Dastugue et al (20) showed that a t(1;22)(p13;q13) was the most common abnormality in childhood AMKL but was seldom seen in adult AMKL. In their study, interestingly, a der(1;7)(q10;p10) was observed in two out of 23 cases of adult AMKL, and the authors speculated that, in spite of lack of documented antecedent exposure to chemotherapy or radiotherapy, adult AMKL might be a secondary leukemia (20). Even though a der(1;7) had been described already in AMKL, our case is worthy to be reported in two respects. 1) the megakaryoblastic proliferation (or transition to AMKL) was a late event of t-MDS and its progression to overt AMKL was very gradual, and 2) the trisomy 1q due to der(1;7) was sole chromosomal abnormality observed throughout MDS phase and during transition to overt AMKL.

References


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