Therapy-related Leukemia with Inv(16)(p13.1q22) and Type D CBFB/MYH11 Developing after Exposure to Irinotecan-containing Chemoradiotherapy

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A 40-year-old woman developed therapy-related acute myeloid leukemia (t-AML) with inv(16)(p13.1q22) and a rare type D form of core-binding factor β-subunit gene-myosin heavy chain 11 gene (CBFB-MYH11) fusion transcript approximately 2.5 years after receiving chemoradiotherapy for uterine cervical cancer. t-AML with inv(16)(p13.1q22) and rare non-type A CBFB-MYH11 typically develops after exposure to a topoisomerase II inhibitor, with a short period of latency of one to five years. As the patient had no history of exposure to topoisomerase II inhibitors, among her previously used chemotherapeutics, the topoisomerase I inhibitor, irinotecan, was speculated to be the most plausible cause of t-AML in this case. The present case suggests that irinotecan may cause t-AML resembling that associated with topoisomerase II inhibitors.

Key words: therapy-related acute myeloid leukemia, irinotecan, CBFB-MYH11, inv(16)(p13.1q22)

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Introduction

Approximately 10% of cases of acute myeloid leukemia (AML) develop following exposure to chemotherapy and/or radiation for primary malignancy (1, 2), and the disease is categorized as therapy-related AML (t-AML) according to the WHO classification of tumors of hematopoietic and lymphoid tissues (3). Two subsets of t-AML are generally recognized based on the nature of prior treatments and the characteristics of the disease. The most common type, which usually occurs after the exposure to alkylating agents and/or radiation, with a latency period of 5 to 10 years, is frequently accompanied by the unbalanced loss of genetic material, often involving chromosome 5 and/or 7. This type of t-AML is often preceded by therapy-related myelodysplastic syndrome (t-MDS). The less common type, which occurs after treatment with agents targeting topoisomerase II, has a shorter latency period of one to five years, without the preceding myelodysplastic phase. The majority of these cases are associated with balanced recurrent chromosomal translocations frequently involving MLL at 11q23, RUNX1 at 21q22 or CBFB at 16q22 and morphologically resemble the features of de novo AML associated with these translocations (3-5).

AML associated with the pericentric inversion of chromosome 16, inv(16)(p13.1q22), or the less frequent translocation t(16;16)(p13.1q22) represents 5-8% of all cases of AML. This disorder characteristically exhibits an abnormal eosinophilic component in addition to monocytic and granulocytic differentiation and is thus designated as M4Eo according to the French-American-British classification (3, 6). Molecularly, both inv(16)(p13.1q22) and t(16;16)(p13.1q22) lead to the fusion of the core-binding factor β-subunit gene (CBFB) at 16q22 with the smooth muscle myosin heavy chain 11 gene (MYH11) at 16p13 (7). Although more than 10 types of CBFB-MYH11 transcripts differing in size have been reported to date, more than 85% of fusions are type A, with the less frequent types D and E reported in 5-10% of patients each (7-11). Similar to that observed in de novo
AML, inv(16)(p13.1q22) is one of the most frequently balanced chromosomal translocations in patients with t-AML. Such cases are most frequently associated with exposure to topoisomerase II inhibitors and commonly involve the non-A types of CBFB-MYH11 (1, 10, 12-14).

Irinotecan is an agent that targets DNA topoisomerase I and is currently used to treat lung, ovarian, cervical and colo-rectal cancers worldwide (15). Because only a small number of cases of t-AML developing after irinotecan therapy have been reported (16-18), the risk, as well as clinical and cytogenetic features, of t-AML after exposure to topoisomerase I inhibitors remains unknown. In this report, we describe a case of t-AML with type D CBFB-MYH11 that developed after exposure to irinotecan-containing chemoradiotherapy.

**Case Report**

A 37-year-old woman was diagnosed with stage IIb uterine cervical cancer and received concurrent chemoradiotherapy consisting of irinotecan, nedaplatin, cisplatin and local radiation (one cycle of irinotecan 160 mg/m² and nedaplatin 80 mg/m², followed by six cycles of cisplatin 70 mg/m²). Fifteen months after starting the therapy, she developed local recurrence. Although she again received irinotecan and nedaplatin (three cycles of irinotecan 160 mg/m² and nedaplatin 80 mg/m²), the cancer progressed, with bladder invasion. Six months after recurrence, the patient was started on a third-line chemotherapy consisting of docetaxel and carboplatin (seven cycles of docetaxel 75 mg/m² and carboplatin with AUC at 5 mg/mL); however, this regimen failed to control the disease and she experienced persistent bladder hemorrhage and abdominal pain. Although she was slightly anemic, most likely due to persistent macrocytic hematuria, the WBC and platelet counts generally remained within the normal range during the third-line therapy. At the time of administration of the sixth cycle, the peripheral blood showed an Hb level of 11.5 g/dL, platelet count of 151x10^9/L and WBC of 4.4x10^9/L. One month later, after the completion of the chemotherapy, the data were as follows: Hb=10.7 g/dL, platelets=106x10^9/L and WBC=3.6x10^9/L. Thereafter, however, both thrombocytopenia and anemia progressed over three months. Consequently, approximately 2.5 years after the start of the initial therapy for cervical cancer, the patient was referred to our department for treatment of the thrombocytopenia. Upon admission, the peripheral blood showed an Hb level of 7.6 g/dL, platelet count of 16x10^9/L and WBC of 3.8x10^9/L with 2% blasts and 52% monocytes. In addition, the bone marrow was hypercellular with 29% blasts, 19.2% monoblasts/promonocytes and 22% eosinophils (Fig. 1A). She was therefore diagnosed with AML, classified morphologically as M4Eo. The leukemic cells were positive for CD13, weakly positive for CD33 and CD34 and negative for CD2. The karyotype was 46,XX.inv(16)(p13.1q22)[12]/46,XX.del(7)(q?),inv(16)(p13.1;q22)[5]/50,XX,+8,+9,inv(16)(p13.1;q22),+21,+22[2] (Fig. 1B), and split signals for CBFB were observed in 96% of the cells according to an interphase FISH analysis. Furthermore, RT-PCR for CBFB-MYH11 revealed a fusion product that was longer than that expected for the type A fusion (Fig. 2A). With approval from the Ethics Committee of Tokyo Medical and Dental University and written informed consent from the patient, we sequenced the CBFB-MYH11 RT-PCR product and found it to be identical to that of GenBank accession number AF249897, corresponding to the type D fusion transcript (Fig. 2B). The patient was thus diagnosed with t-AML with inv(16)(p13.1q22); CBFB-MYH11 and treated with induction therapy comprised of low-dose cytarabine and aclacuribin due to her poor general conditions. She subsequently failed to achieve complete remission after suffering from febrile neutropenia and severe hematuria with renal dysfunction during the induction therapy, which made her general status worse. However, she declined further intensive therapy and was treated supportively.

![Figure 1. Morphological and cytogenetic analyses of bone marrow cells. A: Bone marrow smear obtained at diagnosis (Wright-Giemsa staining, ×1,000). B: A Giemsa-banded karyogram of the bone marrow cells obtained at diagnosis showing 50,XX,+8,+9,inv(16)(p13.1;q22),+21,+22. The arrow indicates inv(16)(p13.1q22).](Image)
In the absence of widespread metastasis of the cervical cancer, the patient displayed a persistent fever with consequent multiple organ failure and died 108 days after starting the induction therapy for t-AML. In this case, the death was most likely due to leukemia or infection.

**Discussion**

We herein reported a case of t-AML with inv(16)(p13.1;q22) that involved the typical features of t-AML caused by topoisomerase II inhibitors. This type of t-AML, in contrast to that induced by alkylating agents or irradiation, usually develops within a relatively short period of time after exposure to chemotherapy or irradiation and is not preceded by MDS (1-3, 5). In the present case, the patient was diagnosed with AML approximately 2.5 years after the start of chemoradiotherapy, not preceded by an apparent MDS phase and not morphologically associated with any significant dysplastic features. The cytogenetic and genetic features of AML in the present case were also typical of the type of t-AML caused by topoisomerase II inhibitors, as this type of t-AML characteristically shows balanced recurrent chromosomal translocations, among which inv(16)(p13.1;q22) with **CBFB-MYH11** is one of the most frequent (1, 12, 14). It is also important to note that the non-A fusion types of **CBFB-MYH11**, such as type D confirmed in the present case, are observed in 40-50% of patients with t-AML, although they are very rare among those with de novo AML with inv(16) (p13.1;q22) (10, 11, 13), thus suggesting that the AML observed in this case was etiologically, but not simply accidentally, related to the prior chemotherapy regimen. It should also be noted that inv(16)(p13.1;q22) is very frequently associated with additional chromosomal translocations, such as trisomies 8, 21 and 22, (10, 11, 19), which were additionally observed in the present patient. Therefore, although complex karyotypic abnormalities are typically observed in cases of t-AML caused by alkylating agents or irradiation, the present case should be considered to be typical of t-AML with inv(16)(p13.1;q22), which usually develops after the administration of therapy with topoisomerase II inhibitors.

Importantly, however, our patient had not previously received topoisomerase II inhibitors prior to developing AML. With the exception of irradiation and platinum-based agents (nedaplatin, cisplatin and carboplatin), which act basically as bifunctional alkylating agents to cause t-AML (1, 20), the patient was treated with only irinotecan (total dose, 640 mg/m²) and docetaxel (total dose, 525 mg/m²). Irinotecan is a semisynthetic derivative of camptothecin categorized as a topoisomerase I inhibitor (15). Topoisomerase inhibitors bind to the enzyme/DNA complex at the strand cleavage stage of the topoisomerase reaction, thereby interacting with topoisomerase I or II. Topoisomerase II inhibitors consist of intercalating agents, such as anthracyclines, and non-intercalating epipodophyllotoxins, such as etoposide. The topoisomerase I inhibitor irinotecan is classified as a non-intercalating drug (15, 21). Because the mutagenic properties of irinotecan in vitro are similar to those of topoisomerase II inhibitors, these drugs are expected to induce a similar type of t-AML (21). However, as shown in Table, only three cases of t-AML developing after irinotecan exposure have been previously reported (Cases #2-4), with the topoisomerase II inhibitor etoposide additionally used in one case (Case #3) (16-18). All three patients developed t-AML within three years after irinotecan exposure, without any documented signs of the t-MDS phase, thus resembling the clinical course of t-AML caused by topoisomerase II inhibitors, although complex karyotypic abnormalities were ob-

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**Figure 2.** Molecular genetic analyses of **CBFB-MYH11**. A: RT-PCR analysis of the **CBFB/MYH11** (A) and β-actin (B) transcripts of the bone marrow mononuclear cells derived from a normal control (1) and the patient (2). The position and length of the **CBFB/MYH11** and β-actin transcripts are indicated in red and black, respectively. M: molecular mass size markers. B: Sequence analysis of **CBFB/MYH11**. The nucleotide sequences around the junction in addition to the deduced amino acid sequences are shown. The number of nucleotides of **CBFB** and **MYH11** at the fusion junction is also indicated.
served in Case #2. Hence, the present case represents the first case of t-AML with inv(16)(p13.1;q22) occurring after irinotecan exposure with the typical features of the type of t-AML caused by topoisomerase II inhibitors. On the other hand, the administration of the antimicrotubule agent docetaxel, which was also used in the present case, has been reported in association with the onset of t-AML in two cases (Cases #5, 6) (22, 23). However, the patient in Case #5 was also treated with the alkylating agent carboplatin in addition to irradiation and presented with features resembling those of t-AML caused by alkylating agents, including an antecedent t-MDS phase and complex karyotypic abnormalities (22). Although Case #6 involved inv(16)(p13.1;q22), the patient was treated with etoposide 18 months before developing t-AML (23). Intriguingly, four cases of t-AML with inv(16)(p13.1;q22) have been reported in association with the other taxane, paclitaxel (13, 24). However, except in one case, the patients were also exposed to etoposide. Therefore, the possible leukemogenic role of paclitaxel in the development of t-AML with inv(16)(p13.1;q22) remains elusive, and based on the mechanism of action and details of previous case reports, we consider irinotecan to be the most plausible causative agent for the onset of t-AML in the present case.

Although inv(16)(p13.1;q22) is associated with a favorable prognosis (3), the prognosis of t-AML with inv(16)(p13.1;q22) is significantly worse than that of its de novo AML counterpart (4, 10). Furthermore, the current patient was unable to receive the standard AML induction therapy due to her poor condition derived from the remaining cervical cancer, and she died approximately four months after receiving chemotherapy for t-AML (Cases #5, 6), although inv(16)(p13.1;q22) was observed in Case #6 (22, 23).

It is notable that only a few cases of t-AML following irinotecan exposure have been reported considering the wide range of clinical use and similar mechanism of action of this drug to topoisomerase II inhibitors (15, 21). This finding may be explained at least partly by the observation that patients treated with irinotecan generally exhibit a shorter overall survival than those treated with etoposide or anthracyclines, which are widely used to treat hematological malignancies. For instance, the overall survival of first-line FOLFIRI therapy, one of the most wildly used combined chemotherapy regimens containing irinotecan for colorectal cancer, is only approximately 20 months (25). However, the overall survival of patients treated with irinotecan is expected to become longer, as various novel molecular targeting agents are now being combined with these regimens (26). Therefore, the number of patients with t-AML following exposure to irinotecan is expected to increase in the near future. Such cases should be analyzed carefully in order to determine the risk, as well as clinical and molecular features, of this condition.

The authors state that they have no Conflict of Interest (COI).

References


