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Chromosomal Abnormalities at 11q23 after Topoisomerase II Inhibitor Treatment: A Report of Three Cases

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It has become apparent that the *MLL* (myeloid-lymphoid leukemia or mixed-lineage leukemia) gene is frequently rearranged in patients with secondary leukemia or myelodysplasia associated with chemotherapeutic regimens including topoisomerase II inhibitors (topo II inhibitors). Few studies have been reported on hematological or chromosomal abnormalities associated with topo II inhibitor therapy in Korea. We report three cases with topo II inhibitor therapy-related 11q23 abnormalities. First, a 10-year old female with a therapy-related chromosomal abnormality t(11;16)(q23;p13.3) without bone marrow abnormalities; second, a 67-year old male with therapy-related myelodysplastic syndrome (MDS) with add(11)(q23) and advanced to acute myeloid leukemia with t(2;11)(p23;q23) within a year; and third, a 42-year old male with therapy-related acute myeloid leukemia (AML) with 11q23 abnormality demonstrated by fluorescence *in situ* hybridization (FISH) analysis using a *MLL* gene probe and which later proved to be t(9;11)(p22;q23). The chemotherapeutic agents for the primary malignancies (ovarian primitive neuroectodermal tumor, PNET; squamous lung cell carcinoma; and Ewing's sarcoma/PNET, respectively) consisted of topo II inhibitiors as well as alkylating agents. The latent periods from primary therapy to identification of 11q23 abnormalities were relatively short at 9 months, 35 months, and 22 months, respectively. Patients treated with topo II inhibitors are at risk for developing secondary MDS or leukemia that has distinct features from those associated with alkylating agents. The genetic basis and optimal treatment for clonal changes from topo II inhibitor therapy remain to be determined. A close follow-up of cytogenetic and/or FISH study with a *MLL* gene probe for patients with a history of topo II inhibitor treatment would be very useful for diagnosis and prediction of secondary hematologic malignancies. *(Korean J Clin Pathol 2002; 22: 57-62)*

Key words : *Topoisomerase II inhibitors, Secondary hematologic malignancy, MLL gene*

INTRODUCTION

One of the unfortunate consequences of the successful treatment of cancer/leukemia is the subsequent development of a therapy-related myelodysplastic syndrome (t-MDS) or acute leukemia. Two major drugs associated with t-MDS or

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therapy-related acute leukemia have been known to be alkylating agents and DNA topoisomerase II inhibitors (topo II inhibitors). Treatment of patients with alkylating agents has been associated with t-MDS or therapy-related acute myeloid leukemia (t-AML) with loss of chromosomes 5 and/or 7[1]. More recently, several balanced translocations have been identified after the use of drugs targeting topo II (most commonly epipodophyllotoxins). These translocations usually involve the *MLL* (mixed lineage leukemia) gene at chromosome band 11q23[2-4] or less often the *AML1* gene at 21q22 [5]. Variant reciprocal partners of 11q23 include chromosomes 1, 2, 3, 16, 17, and 19[6-9]. Few studies have been reported on hematological or chromosomal abnormalities associated with topo II inhibitor therapy in Korea. Three cases are presented here, in which they had reached successful remission for primary cancers with regimens including topo II inhibitors but subsequently developed chromosomal abnormalities involving 11q23.

CASE REPORTS

Case 1

A 10-year-old female was diagnosed as ovarian primitive neuroectodermal tumor (PNET) with bone marrow metastasis in January 1998. The initial karyotype of bone marrow cells was 46,XX[20]. The oophorectomy with omentectomy followed by five cycles of high dose chemotherapy (doxorubicin, etoposide, cyclophosphamide, cisplatin) between January 1998 and May 1998 was done. In June 1998, autologous peripheral blood stem cell transplantation (auto-PBSCT) was done after mobilization. In December 1998, the gallium scan showed increased uptake in the L2-L4 spine and one cycle of polychemotherapy with ifosfamide and etoposide and another cycle with cyclophosphamide, doxorubicin, vincristine followed by interleukin-2 therapy were started under the impression of relapse. During the first cycle, the patient received radical radiation therapy (total dose 3000 Gy). The total doses of etoposide and doxorubicin were 1,275.8 mg/m^2 and 181.4 mg/m^2, respectively. By routine cytogenetic study with bone marrow specimen in October 1999, an abnormal clone with t(11;16)(q23;p13.3) were identified (Fig. 1), but the bone marrow cells showed no morphological abnormality. No specific therapy has been done and the patient is still alive (Table 1).

Case 2

A 65-year-old man was diagnosed of a squamous cell carcinoma of lung (TIII/N0/M0) in July 1996. After surgical resection of tumor, he received three cycles of adjuvant chemotherapy with etoposide and cisplatin during the period between July 1996 and October 1996. The total dose of etoposide was 296.5 mg/m^2. During a routine check up in July 1999, bone marrow cells showed dysplastic features and cytogenetic study revealed 46,XY,add(11)(q23)[20] (Fig. 2A). FISH analysis using *MLL* gene probe (Vysis Inc., IL, USA) demonstrated the presence of *MLL* gene rearrangement with splitting of the signal between the two derivative chromosome suggesting a translocation (Fig. 2C). No specific therapy was accompanied. In July 2000, a few blasts (5%) were detected in peripheral blood. The bone marrow study showed an acute myeloid leukemia with multilineage dysplasia. The bone marrow karyotype was 46,XY,t(2;11)(p23;q23)[20] (Fig. 2B). In spite of chemotherapy with idarubicin and ara-C, he could not attain remission and died of septic shock 12 months after the diagnosis of secondary leukemia.

Case 3

A 42-year-old man was diagnosed of Ewing's sarcoma/PNET with no metastasis in February 1998. After wide excision of the mass, he was treated with chemotherapy consisted of vincristine, doxorubicin, cyclophosphamide, etoposide, ifosfamide and radiotherapy between February 1998 and July 1998. The total cumulative doses of doxorubicin, etoposide,

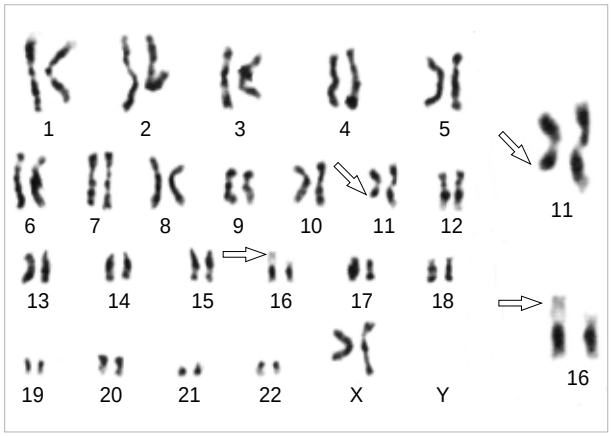

Fig. 1. Karyotype and partial karyotype from case 1 bone marrow cells. The karyotype after topo II inhibitor therapy was 46,XX,t(11;16)(q23;p13.3)[7]. Arrows show the breakpoints of the chromosome rearrangement.

and ifosfamide were 73.5 mg/m^2, 1,450 mg/m^2, and 24,803 mg/m^2, respectively. He had remained well until November 1999, when he presented with fever, chill, and immature cells in peripheral blood. Bone marrow study confirmed the diagnosis of acute monocytic leukemia, M5b. Although the bone marrow had no mitotic cells, FISH study using the *MLL* gene probe showed split signals in 97.5% (195/200) interphase nuclei, indicating an *MLL* gene rearrangement (Fig.

Table 1. Summary of patients with treatment-related chromosomal abnormality involving 11q23

	Case 1	Case 2	Case 3
Age*/Sex	9/F	65/M	42/M
Primary Malignancy	Ovarian primitive neuroectodermal tumor (PNET)	Lung squamous cell carcinoma	Ewing sarcoma/PNET
Initial Karyotype	46,XX[20]	Not done	Not done
Initial bone marrow findings	Marrow involvement of PNET	Not done	No involvement
Topo II Inhibitors	Etoposide (1,275.8 mg/m^2) and Doxorubicin (181.4 mg/m^2) + aa	Etoposide (2,96.5 mg/m^2) +aa	Etoposide (1,450 mg/m^2) Doxorubicin (73.5 mg/m^2) Ifosfamide (24,803 mg/m^2) +aa
Other treatments	Surgery, Auto-PBSCT, Radiation therapy	Surgery	Surgery, Auto-PBSCT
Preceding MDS	No	Yes	No
Latency period (month)	9	MDS: 35 AML: 47	22
CBC (Hb-WBC-Platelet)	9.7 g/dL-3,550/μL-115K/μL	12.3 g/dL-6,100/μL-77 K/μL	8.9 g/dL-84,660/μL-24 K/μL blast(+; 5%), Immature monocyte (+)
Bone marrow findings	No abnormality	AML with multilineage dyspoiesis	AML, M5b
Cytogenetic analysis	46,XX,t(11;16)(q23;p13.3)[7]	MDS: 46,XY,add(11)(q23)[20] AML: 46,XY,t(2;11)(p23;q23)[20]	No mitotic cell 46,XY,t(9;11)(p22;q23)[13]/46,XY[7])†
Fluorescence in situ hybridization (FISH) with MLL gene probe	Not done	MDS: 95% split signal	97.5% (195/200 cells) split signal
Length of Survival/ Present Status	No specific chemotherapy, Alive (23 Months)	MDS: No speific chemotherapy, AML: Chemotherapy Death, 12 months after diagnosis of secondary AML	Chemotherapy and auto-PBSCT Relapse, 11 months later after PBSCT Death, 22 months after diagnosis of secondary AML

*Age at diagnosis of first malignancy. †Karyotype of relapsed AML, M5b cells.
Abbreviation: aa, alkylating agents.

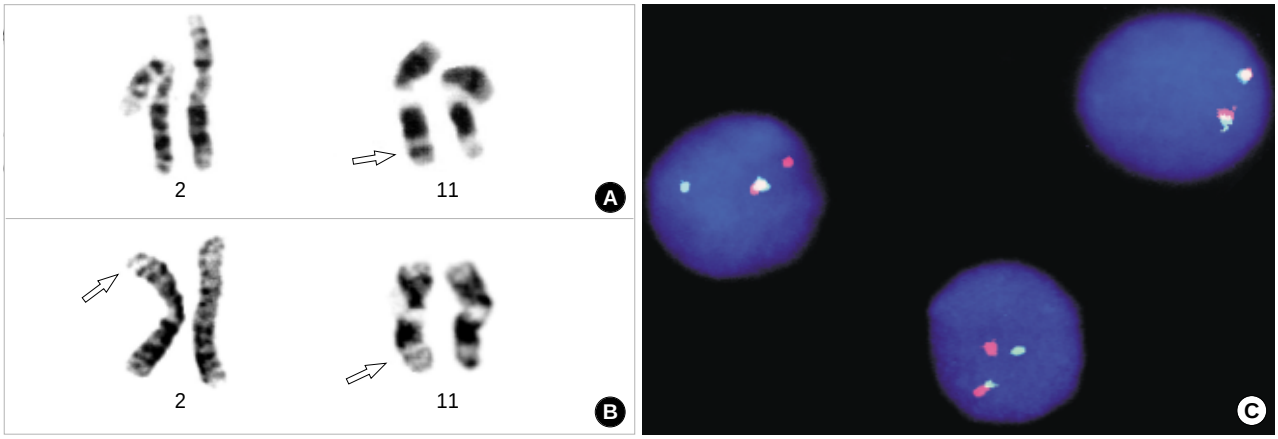

Fig. 2. Cytogenetic studies with case 2 bone marrow cells. (A) Partial karyotypes at diagnosis of t-MDS, add(11)(q23). Arrow indicated unknown material added to 11q23. (B) Partial karyotype at diagnosis of t-AML, der(2)t(2;11)(p23;q23) and der(11)t(2;11)(p23;q23). Arrows indicate the breakpoints of the chromosome rearrangements. (C) FISH analysis using *MLL* gene probe at diagnosis of t-MDS. Splitting of the signal between the two derivative chromosome generated by a translocation was observed.

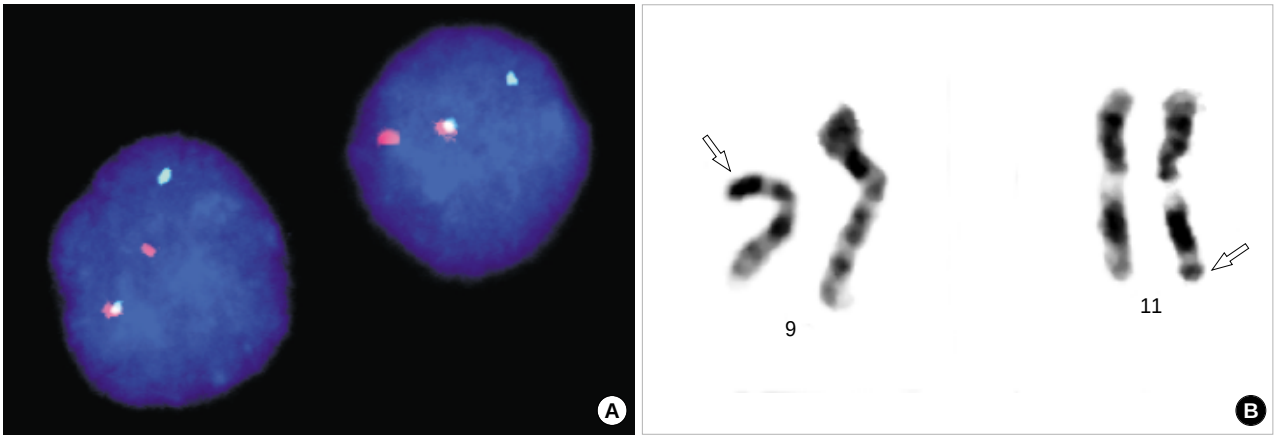

Fig. 3. Cytogenetic studies with case 3 bone marrow cells. (A) FISH analysis using *MLL* gene probe at diagnosis of t-AML, M5b. Splitting of the signal between the two derivative chromosomes generated by a translocation was observed. (B) Partial karyotype at diagnosis of t-AML, M5b in relapse, der(9)t(9;11)(p22;q23) and der(11)t(9;11)(p22;q23). Arrows indicate the breakpoints of the chromosome rearrangement.

3A). After chemotherapy consisted of high-dose ara-C and mitoxantrone followed by auto-PBSCT, relapse occured eleven months later with the bone marrow karyotype of 46,XY,t(9;11)(p22;q23)[13]/46,XY[7] (Fig. 3B). FISH study with *MLL* gene probe showed split signals in 24.0% (120/500) interphase nuclei. Shortly after the polychemotherapy, the patient died of respiratory failure in September 2001, 22 months after the diagnosis of secondary leukemia.

DISCUSSION

Therapy-related hematologic malignancies after high-dose chemotherapy have posed significant consequences of various degree of risk. Prior chemotherapy with large cumulative dose of alkylating agents is the most important risk factor. In addition, topo-II inhibitors therapy, patient age, previous radiotherapy, particularly the use of total body irradiation, and autologous stem cell transplantation have been identified as risk factors[10]. The secondary hematologic disorders associated with topo II inhibitors have following distinct clinical and biologic features compared to those associated with alkylating agents: a shorter latent period; a predominance of monocytic or myelomonocytic features; no preceding MDS; frequent cytogenetic abnormalities involving 11q23[11]. In 1987, Ratain *et al.* reported acute nonlymphocytic leukemia (ANLL) in four of 24 patients with advanced non-small cell lung cancer successfully treated with etoposide and cisplatin with or without vindesine[12]. DeVore *et al.* identified a translocation involving 11q23 in a patient who developed acute monocytic leukemia 33 months after the successful treatment of a germ cell tumor with chemotherapy of etoposide and cisplatin, but not alkylating agents[13]. Additional evidence to support the linkage between epipodophyllotoxins and secondary leukemia was provided by Pui *et al.*, who reported 13 cases of ANLL among 733 consecutive children with acute lymphoblastic leukemia (ALL) in their first remission[14]. These cases were characterized by frequent abnormalities involving 11q23. Twelve of 13 patients in this series who developed ANLL were turned out to have received an epipodophyllotoxin.

Epipodophyllotoxins such as etoposide, teniposide and to a lesser extent anthracyclins such as doxorubicin have been shown to have significant activity against a wide range of solid and hematologic malignancies[15]. It exerts its antineoplastic effects by producing breaks in DNA, which is mediated by their interaction with topoisomerase II, an enzyme that reversibly cleaves DNA[16]. These mechanism provides a logical basis for the induction of secondary leukemia, by causing damage to DNA. The apparent propensity for a locus at 11q23 remains unclear. The most common translocations are t(9;11)(p22;q23) or t(11;19)(q23;p13) in t-AML and t(4;11)(q21;q23) in therapy-related ALL (t-ALL); these are also the most common *MLL* translocations in de novo AML and ALL. The t(11;16)(q23;p13) seen in our case 1 is considered to be the result of the fusion of *MLL* and CBP (CREB binding protein) genes, which were target genes of topo II inhibitors[17-19]. The CBP gene, encoding a transcriptional adapter/coactivator protein, resides on 16p13[20] and was found to be also translocated in AML with t(8;16)(p11;p13)[21]. Borrow *et al.*[21] reported that MOZ and

CBP, located on 8p11 and 16p13, respectively, formed a fusion gene in AML cells with t(8;16). Because MOZ and *MLL* have C4HC3 zinc fingers in common, which are thought to promote protein-protein interactions among the chromatin components, it is reasonable to predict that *MLL* may have fused to CBP. The t(11;16) has thus far been reported in patients with t-MDS and therapy-related acute leukemia. Satake *et al.*[17] reported a 7-year-old boy diagnosed as therapy-related chronic myelomonocytic leukemia (CMMoL) with a karyotype of 46,XY,t(11;16)(q23;p13) after chemotherapy including topo II inhibitor, pirarubicin (Hoechst Marion Roussel Inc., Kansas, USA), for ALL. Rowley *et al.*[18] reviewed eleven t(11;16) patients, all of whom had prior therapy with drugs targeting topo II. Three of them presented with a MDS most similar to CMMoL and one had dyserythropoiesis. Six patients presented with AML (4 M4s, 1 M2, 1 M5a) and one with B-ALL. All of the patients achieved a complete remission as a result of their initial therapy but developed a secondary hematologic disorder within 6 to 60 months. Every patient's treatment included a drug that targeted DNA topo II, usually etoposide or teniposide, but also doxorubicin; the doses ranged from 2,200 mg/m^2 to 8,100 mg/m^2. Of them, seven patients received treatment for their secondary diseases, including bone marrow transplantation and four patients are under treatment or are in remission but three are dead. Usually, most patients with secondary hematologic disease and *MLL* translocations are diagnosed as t-AML or less commonly t-ALL with no preceding MDS. But the t(11;16) is unique for its frequent association with t-MDS. In our first case with t(11;16), no apparent dysplastic feature except peripheral pancytopenia was observed and no specific treatment was done for chromosomal abnormality.

In a second case, add(11)(q23), which had been observed at initial diagnosis of t-MDS, was proved to be a translocational rearrangement by FISH analysis and was demonstrated afterwards to be t(2;11)(p23;q23). The t(2;11)(p23;q23) was reported as a novel rearrangements of t-MDS after chemotherapy including topoisomerase II inhibitor[22]. Although small number of cases of de novo MDS and secondary AML and MDS which involve mainly a t(2;11) have been described, the majority had breakpoints at 2p21, not 2p23[23, 24].

The survival of patients with t-MDS and t-AML after chemotherapy was in general poor with six months of median survival[25, 26]. Because of the generally poor response to conventional, intensive antileukemic chemotherapy of patients with t-AML, allogeneic bone marrow transplantation has been attempted.

A critical practical concern is whether patients develop therapy-related leukemia because of chance or because of unusual sensitivity to the topo II inhibitors. One way to approach this issue can be to save material of all such patients. Although the genetic basis and optimal treatment for clonal changes from the topo II inhibitor therapy remain to be determined, close follow-up of cytogenetic study for patients with history of topo II inhibitor treatment would be very helpful for diagnosis and prediction of secondary hematologic malignancy. Especially, FISH using the *MLL* gene probe was very useful in the evaluation of the cytogenetic abnormality at 11q23 in situations where abnormal cells are not dividing in culture or in the cases of translocations too subtle to be detected on conventional cytogenetic analysis.

국문요약

Topoisomerase II (topo II) 억제제 치료 후의 *MLL* 유전자 재배열과 연관된 이차성 혈액질환의 발생보고의 빈도가 전세계적으로 점차 증가되고 있다. 그러나 국내에서는 topo II 억제제 치료와 연관된 혈액학적 혹은 염색체 이상에 대한 보고가 전무한 상태이다. 저자들은 topo II 억제제 치료 후에 골수 이상 없이 t(11;16)(q23;p13.3)의 염색체 이상만을 보인 10세 여아와 add(11)(q23)의 염색체 이상을 보이는 동시에 골수이형성증후군의 골수 양상을 보였다가 1년 후에 t(2;11)(p23;q23)을 보이는 급성백혈병으로 진행된 67세 남자 환자, 11q23 이상을 동반한 급성백혈병을 보이는 42세 남자 환자의 세 증례를 경험하였기에 보고하는 바이다. 세 증례 모두에서 일차 진단된 질환(각각 난소 원시신경외배엽종양, 폐편평상피세포암, Ewing 종양/원시신경외배엽종양)에 대한 치료제로서 알킬화약물(alkylating agent)과 함께 topo II 억제제가 사용되었다. 일차 종양의 진단 시기로부터 염색체 이상을 보이기까지의 시간은 각각 9개월, 35개월, 22개월이었다. Topo II 억제제 치료를 받은 환자들은 이차성 혈액질환이 발생할 수 있는 위험군에 해당하며, 나타나는 양상은 알킬화약물에 의한 이차성 혈액질환의 양상과는 다르다. Topo II 억제제와 연관되어 나타나는 염색체 이상에 대한 유전적 배경이나 이에 대한 적절한 치료법은 아직까지 밝혀지지 않았지만, topo II 억제제로 치료하는 환자들의 경우 이차성 혈액질환의 진단과 발생의 예측을 위해 *MLL* probe를 이용한 FISH법을 포함해서 염색체 이상 유무에 대한 주기적인 추적검사의 시행이 매우 유용할 것으로 생각된다.

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