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11q23 Aberration Is an Additional Chromosomal Change in De Novo Acute Leukemia After Treatment With Etoposide and Mitoxantrone

Atsushi Ohshima, Ikuo Miura, Akihiko Chubachi, Keiko Hashimoto, Takashi Nimura, Seiko Utsumi, Naoto Takahashi, Yasuhide Hayashi, Masao Seto, Ryuzo Ueda, and Akira B. Miura

Third Department of Internal Medicine, Akita University School of Medicine, Akita (A.O., I.M., A.C., K.H., T.N., S.U., N.T., A.B.M.); Department of Pediatrics, University of Tokyo, Tokyo (Y.H.); and Laboratory of Chemotherapy, Aichi Cancer Center Research Institute, Aichi (M.S., R.U.), Japan

We report on 2 patients with acute leukemia who had an 11q23 chromosomal aberration as an additional change after treatment with etoposide and mitoxantrone, agents that affect topoisomerase II (Topo II). One patient with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (L2) received chemotherapy, including 1,000 mg of etoposide and 75 mg of mitoxantrone. She relapsed 10 months later. Analysis at time of relapse showed a chromosomal aberration of del(11)(q23) as an additional cytogenetic change. The other patient was diagnosed with acute monoblastic leukemia (M5a) and received two autologous peripheral blood stem-cell transplantations. Her cumulative doses of etoposide and mitoxantrone were 6,000 mg and 42 mg, respectively. She also relapsed, and analysis at that time revealed del(11)(q23) as an additional chromosomal aberration. The mixed lineage leukemia/myeloid-lymphoid leukemia (MLL) gene was not rearranged in either case, making these cases distinct from previously described therapy-related leukemias caused by Topo II inhibitors. Based on these two cases, it may be that Topo II inhibitors can cause clonal evolution affecting chromosome band 11q23.

Key words: etoposide, mitoxantrone, 11q23, MLL

INTRODUCTION

Acute leukemia occurring after the treatment of other malignant disorders (therapy-related acute leukemia or t-AL) has become an increasingly significant problem with the broader use of chemotherapy and more intensive regimens [1]. Alkylating agents and radiation therapy are associated with t-AL, often involving chromosomes 5 and 7 [1]. Etoposide has also been reported as a putative cause of t-AL [3–5], in which chromosome band 11q23 is commonly affected [6,7]. Recently, high-dose etoposide has been used in treating acute leukemia, particularly for a conditioning regimen in autologous bone-marrow transplantation or peripheral blood stem-cell transplantation. Here we report on 2 patients diagnosed with acute leukemia who gained a chromosomal aberration of 11q23 after treatment with etoposide and mitoxantrone.

CASE REPORTS

Patient 1

A 24-year-old woman was diagnosed as having Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (L2, FAB classification) in January 1992. She achieved complete remission but relapsed in December 1992, in spite of intensive chemotherapy, including a total dose of 1,000 mg of etoposide and 75 mg of mitoxantrone. Chromosome analysis showed del(11)(q23) as an additional change (Fig. 1a). Using the mixed lineage leukemia/myeloid-lymphoid leukemia (MLL) *Bam*HI 0.9-kb cDNA

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Address reprint requests to Ikuo Miura, M.D., Third Department of Internal Medicine, Akita University School of Medicine, 1-1-1 Hondoo, Akita 010, Japan.

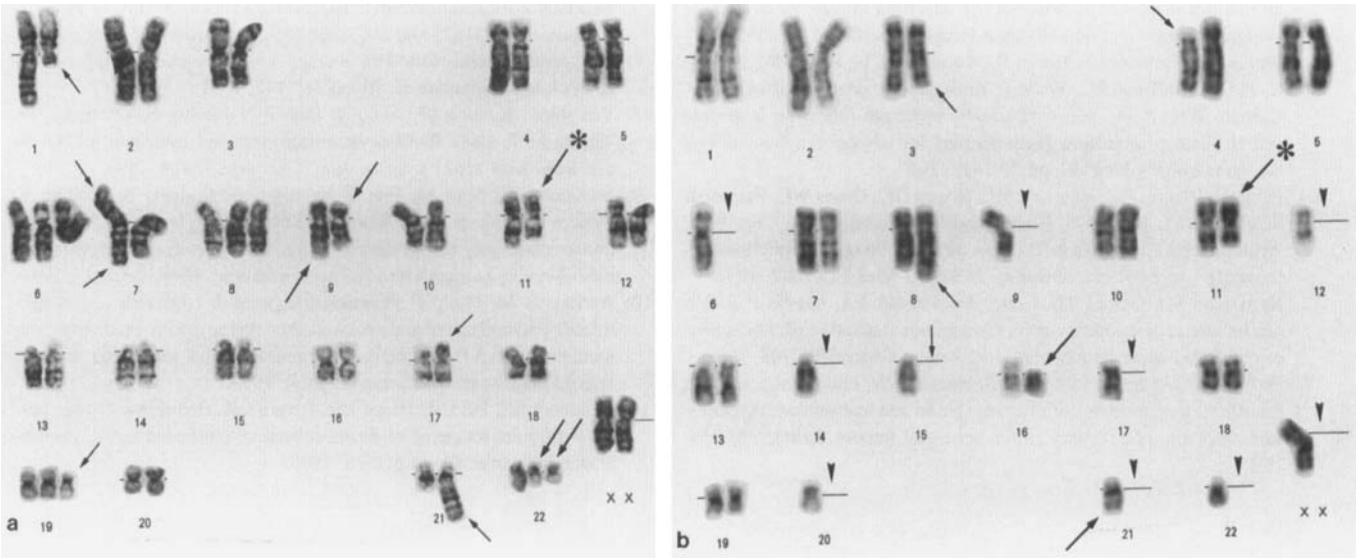

Fig. 1. G-banded karyotypes at relapse show del(11)(q23), denoted by asterisks. Other chromosomal aberrations are indicated by arrows. a: Patient 1. b: Patient 2.

probe (probe x), Southern blot analysis showed that the MLL gene was not involved (data not shown) [8,9]. The patient had resistent leukemia and died of pneumonia after reinduction therapy in February 1993. At necropsy, her bone marrow was found to be replaced by blasts that were positive for α-naphthyl butyrate esterase and inhibited by sodium fluoride.

Patient 2

A 20-year-old woman was diagnosed in April 1992 with acute monoblastic leukemia (M5a, FAB classification) associated with t(16;21)(p11;q13). She attained remission after daunorubicin-based induction therapy. In addition to successive postremission therapy, she underwent two autologous peripheral blood stem-cell transplantations. She relapsed in September 1993. At that time, she had del(11)(q23) as an additional chromosomal change (Fig. 1b) without rearrangement of the MLL gene, which was also determined by Southern blot analysis with probe x [8,9] (data not shown). The patient had cumulative doses of 6,000 mg of etoposide and 42 mg of mitoxantrone. Her relapsed leukemia was refractory to salvage therapy, and she died in February 1994.

DISCUSSION

In addition to alkylating agents and radiation therapy, etoposide, a DNA topoisomerase II (Topo II) inhibitor, has been reported to cause t-AL [2–7]. Another Topo II inhibitor, mitoxantrone, is also reported to be leukemogenic [10]. T-AL associated with Topo II inhibitor treatment is characterized by a monocytic lineage commitment, a lack of myelodysplastic phase, a relatively shorter latency, and an aberration involving chromosome 11q23 and MLL gene rearrangement [1].

We have described 2 patients who each had a 11q23 abnormality in a relapsed clone after treatment with etoposide and mitoxantrone. This change was in addition to the original chromosomal changes of Ph and t(6;21) found at presentation. Previous reports described t-AL cases in which the 11q23 aberration emerged after treatment of nonhematological malignancies or lymphoma [3,6,7]. However, the few t-AL cases with an 11q23 aberration that emerged after treatment for leukemia had no clonal relationship to the original malignancy [4,5,11]. In most of these cases, the MLL gene was rearranged, a situation which is distinct from the cases presented here. To the best of our knowledge, this is the first report of an acute leukemia that acquired an 11q23 aberration as a secondary change after treatment with a Topo II inhibitor.

Exposure to etoposide and mitoxantrone might act on Topo II synergistically and cause t-AL with a smaller amount of etoposide compared to nonhematological malignancies. It follows that these agents could cause not only the secondary leukemia but also clonal evolution, suggesting an even worse prognosis with de novo acute leukemias in relatively short periods. We should keep in mind this additional risk in using large amounts of these agents for initial chemotherapy.

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