

A Case of Treatment-Related Myelodysplastic syndrome and Acute Myelogenous Leukemia Following High-Dose Chemotherapy with Autologous Stem Cell Transplantation for Non-Hodgkin's Lymphoma

Treatment-related myelodysplastic syndrome (t-MDS) and acute myelogenous leukemia (t-AML) are now well established as complications of cytotoxic chemotherapy. We experienced a 28-yr-old female patient who developed t-MDS/t-AML with characteristic chromosomal abnormalities including 11q23 chromosomal rearrangement following high-dose chemotherapy with autologous stem cell transplantation (ASCT) for non-Hodgkin's lymphoma. The patient was admitted with bulky abdominal masses of B cell lineage non-Hodgkin's lymphoma. After 2 cycles of systemic chemotherapy of the Vanderbilt regimen, the patient underwent ASCT with high dose chemotherapy of the BEAC regimen. She also received radiation of 48 Gy for the residual periportal lymphadenopathy. The initial cytogenetic analysis of the infused mononuclear cells revealed a normal karyotype. Twenty two months after the ASCT, pancytopenia was noted and her bone marrow aspirate showed dysplastic hemopoiesis with myeloblasts up to 12% of non-erythroid nucleated cells. The patient was diagnosed as t-MDS (refractory anemia with an excess of blasts). Cytogenetic analysis showed complex chromosomal abnormalities including 11q23 rearrangement, which is frequently found in topoisomerase II inhibitor-related hematologic malignancies. Four months later, it was noted that the t-MDS had evolved into an overt t-AML. Cytogenetic analysis showed an evolving pattern with more complex abnormalities. The patient was treated with combination chemotherapy, but her leukemic cells were resistant to the therapy.

Key Words : Myelodysplastic Syndromes; Leukemia, Myelocytic, Acute; Transplantation, Autologous; Gene Rearrangement

Geundoo Jang, Sang-We Kim,
Cheolwon Suh, Eun-Kyoung Kim,
Hyeseung Bahng, Young Hoon Jeong,
Il Gwon Park, Woo-Kun Kim,
Sang-Hee Kim, Eul-Ju Suh*,
Chan-Jeoung Park*, Hyun-Sook Ji*,
Jung-Shin Lee

Department of Medicine, Department of Clinical Pathology*, University of Ulsan, College of Medicine, Asan Medical Center, Seoul, Korea

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Address for correspondence

Sang-We Kim, M.D.
Department of Medicine, University of Ulsan,
College of Medicine, Asan Medical Center,
388-1 Poongnap-dong, Songpa-gu, Seoul 138-736,
Korea
Tel : +82.02-3010-3215, Fax : +82.02-3010-6961
E-mail : swkim@amc.seoul.kr

INTRODUCTION

It has been reported that a high dose chemotherapy with autologous stem cell transplantation (ASCT) enhances patient's survival rate and suppresses the recurrence rate in chemo-sensitive primary tumors such as non-Hodgkin's lymphoma (1). However, the treatment also produces delayed toxicities including treatment-related myelodysplastic syndrome (t-MDS) and acute myelogenous leukemia (t-AML). Among the chemotherapeutic agents, etoposide, a topoisomerase II inhibitor is well-known to cause t-AML with a characteristic chromosomal abnormality of 11q23 rearrangement (2). We report here a case of a 28-yr-old Korean woman with t-MDS and t-AML with progressively evolving cytogenetic abnormalities including 11q23 rearrangement after BCNU/etoposide/Ara-C/cytosine arabinoside high-dose chemotherapy and ASCT for non-Hodgkin's lymphoma.

CASE REPORT

A 28-yr-old, four months pregnant woman was admitted with complaints of an icteric skin change and right upper quadrant abdominal mass. Her blood pressure was 120/80 mmHg, pulse rate 100/min, respiration rate 18/min, and body temperature 36.0°C. Her skin and sclera were icteric. Respiratory and heart sounds were normal. A huge non-tender, 10 × 10 cm sized hard mass was palpable on the right upper quadrant of the abdomen.

The initial laboratory findings were as follows: white blood cell count 7,800/ μ L (seg 91%, lymphocyte 6%, and monocyte 3%), hemoglobin 8.3 g/dL, hematocrit 24.5%, and platelet count 296,000/ μ L on complete blood cell count (CBC), blood urea nitrogen 5 mg/dL, creatinine 0.5 mg/dL, protein 6.4 g/dL, albumin 4.0 g/dL, aspartate aminotransferase 38 IU/L, alanine aminotransferase 37 IU/L, total bilirubin 11.1 mg/dL, and direct bilirubin 5.6 mg/dL on blood

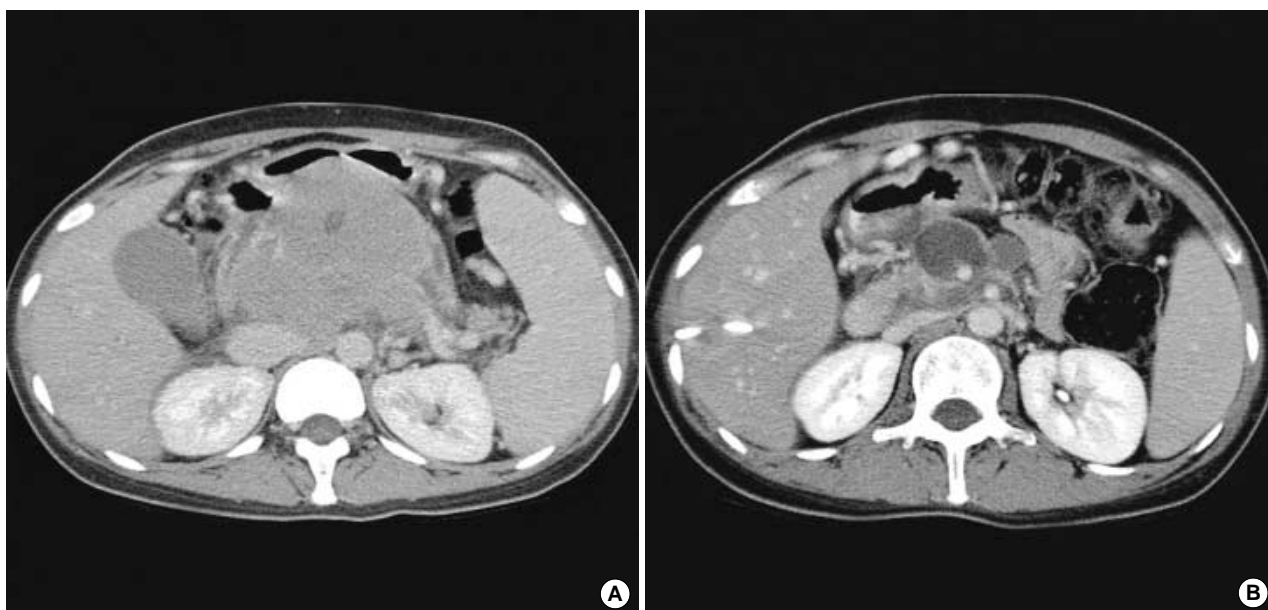


Fig. 1. (A) A bulky mass is noted by abdominopelvic CT scan at the initial diagnosis; (B) The mass size decreases after 2 cycles of chemotherapy of the Vanderbilt regimen.

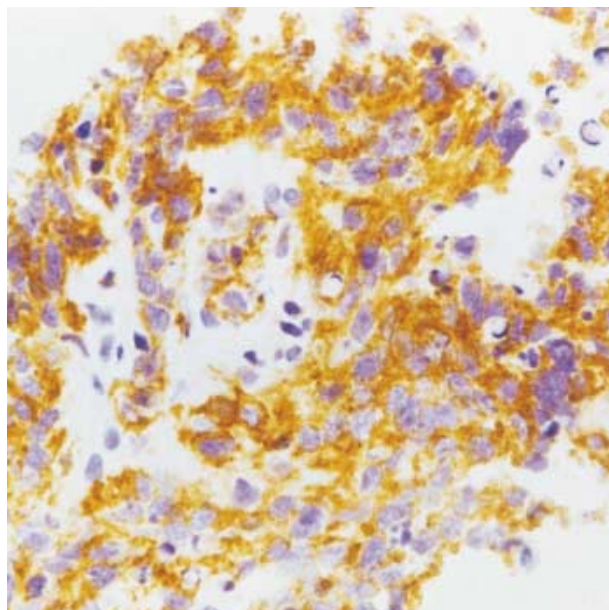


Fig. 2. Light microscopic finding ($\times 200$) of B cell lineage non-Hodgkin's lymphoma showing positive immunohistochemical staining against a pan B antigen (L-26).

chemistry. Bilirubin was +++, urobilinogen +, WBC \pm on routine urinalysis. No abnormality was found on chest radiography and computed axial tomography (CT) scan of the chest. A bulky mass compressing the common bile duct (Fig. 1A) with an involvement of porta caval space and another mass near the left common and internal iliac arteries were detected on CT scan of the abdomen and pelvis. The mass

proved to be a malignant lymphoma of B cell lineage by positive immunohistochemical staining against pan B (L-26) (Fig. 2) with percutaneous needle biopsy. There was no evidence of bone marrow involvement by lymphoma and the result of chromosomal study was normal.

The patient was diagnosed as malignant B cell lymphoma, and treated with percutaneous transhepatic biliary drainage and artificial termination. Then she was given 2 cycles of chemotherapy of the Vanderbilt regimen (cycle 1; cytoxan 1,500 mg/m² day 1, 2, etoposide 400 mg/m² day 1-3, vincristine 1.4 mg/m² day 8, 22, bleomycin 10 U/m² day 8, 22, methotrexate 200 mg/m² day 15, leucovorin 15 mg/m² q 6 hr for 6 doses 24 hr after methotrexate, prednisolone 60 mg/m² day 1-7, cycle 2; cytoxan 1,500 mg/m² day 29, etoposide 100 mg/m² day 29-31, doxorubicin 45 mg/m² day 1, 2, Bleomycin 10 U/m² day 36, 50, methotrexate 200 mg/m² day 43, leucovorin 15 mg/m² q 6 hr for 6 doses 24 hr after methotrexate, prednisolone 60 mg/m² day 29-35) chemotherapy (3). A partial remission was observed on a follow-up CT scan (Fig. 1B). Cytoxan (4 g/m²) and granulocyte-colony stimulating factor (G-CSF, 10 μ g/kg) were administered for stem cell mobilization, and the BEAC regimen (BCNU 300 mg/m², etoposide 800 mg/m², cytarabine 800 mg/m², and cytoxan 140 mg/kg) was employed for the conditioning of ASCT (4).

On the 27th day after ASCT, her CBC (WBC 3,200/ μ L, Hb 10.9 g/dL, and platelet 119,000/ μ L) suggested a successful engraftment. Follow-up CT scan revealed much more decreased abdominal mass. She received radiotherapy of 48 Gy on periportal area for the residual mass. Afterward, she was followed-up on an outpatient basis in a near complete

remission state.

Twenty two months after the ASCT, her CBC showed a progressive pancytopenia. Her bone marrow examination revealed slightly hypogranular granulocytes with an increase of myeloblasts (12% of nonerythroid nucleated cells, Fig. 3A). She was diagnosed with refractory anemia with an excess of blasts according to the FAB classification. Chromosomal study showed complex abnormalities including trisomy 6 and $t(11;11)(q23;q25)$ (Fig. 4A). Because an HLA-compatible related donor was not available, she had to wait for an HLA-matched unrelated donor from the bone marrow registry receiving a supportive care. The chromosomal study of the patient's frozen mononuclear cells that had been stored

after mobilization did not show any cytogenetic abnormalities.

Four months after the diagnosis of t-MDS, she was readmitted due to cough and purulent sputum. A consolidated lesion was found in the right lower lobe of her lung by chest radiography. Peripheral blood smear revealed blasts up to 27% and bone marrow aspiration and biopsy showed large clusters of myeloblasts (50% of nonerythroid nucleated cells) (Fig. 3B). Chromosomal study showed more complex abnormalities than before (Fig. 4B).

After alleviation of pneumonic consolidation, the patient was treated with cytarabine and idarubicine chemotherapy for t-AML. However her bone marrow on day 14 harbored

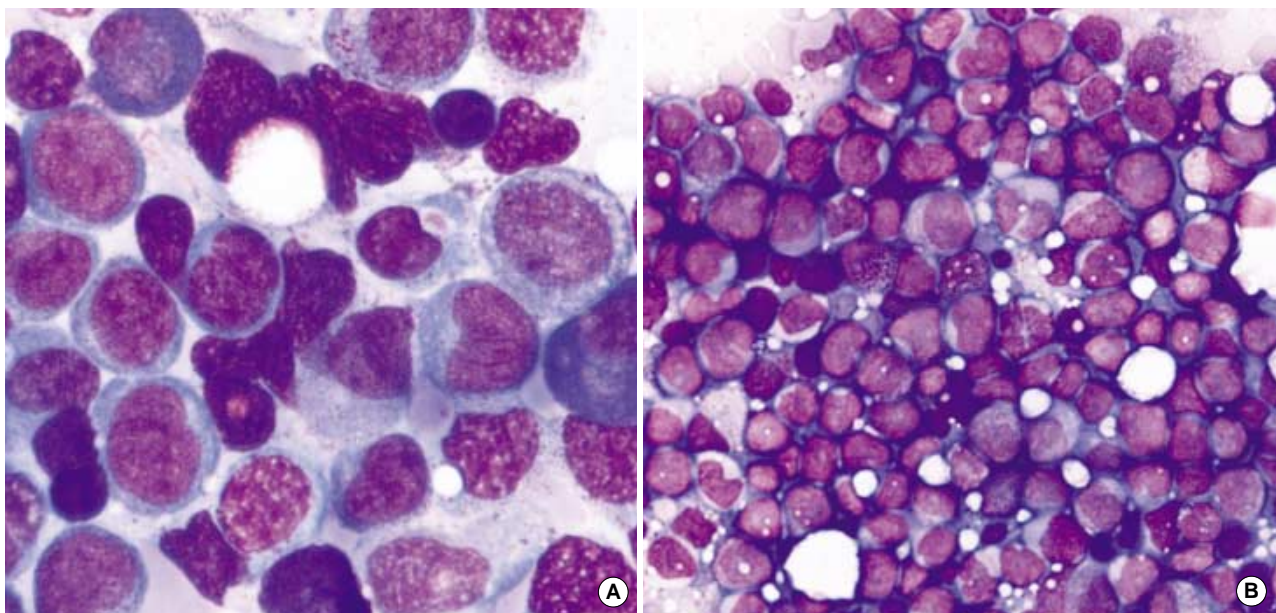


Fig. 3. Light microscopic findings of bone marrow. (A) t-MDS with hypogranular granulocytes and increased myeloblasts (12% of nonerythroid nucleated cells, $\times 1,000$). (B) t-AML with a large cluster of leukemic blasts (50% of nonerythroid nucleated cells, $\times 400$).

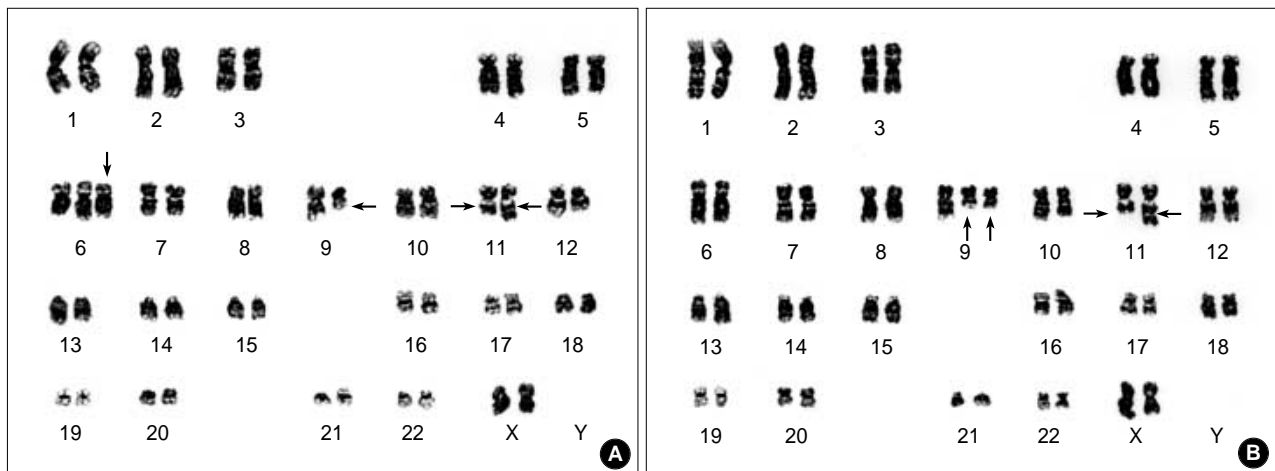


Fig. 4. Cytogenetic analysis of bone marrow. (A) Complex chromosomal abnormalities including $+6$, $del(9)(q12q32)$, and $t(11;11)(q23;q25)$ at the diagnosis of t-MDS. (B) Karyotypic evolution including -6 , $del(X)(q24)$, $+del(9)(q12q32)$ at the diagnosis of t-AML.

persistent leukemic cells. Pneumonic consolidation reappeared along with severe neutropenia. Despite aggressive treatment with broad-spectrum antibiotics, amphotericin B, and G-CSF, the patient eventually succumbed to her disease.

DISCUSSION

The employment of high-dose chemotherapy has improved the survival of patients with malignancies such as non-Hodgkin's lymphoma (1). However its long-term effects are of increasing concern. One of the most serious adverse effects is the development of secondary malignancies including treatment-related leukemia (5).

MDS and acute leukemia are clonal neoplastic hematologic disorders from various causes such as familial factor, ionizing radiation, benzene, and chemotherapeutic agents. It is well known that chemotherapy or radiotherapy of primary cancer can induce t-MDS and t-AML especially in patients with Hodgkin's and non-Hodgkin's lymphomas who received high-dose chemotherapy with or without total body irradiation for ASCT (24). These patients represent the highest risk group to develop t-MDS and/or t-AML between 2-8 yr following therapy, and most have chromosomal abnormalities that were not present at the time of diagnosis of the primary cancer (6).

Recently, it has become evident that there are at least two different forms of chemotherapy-related leukemia: alkylating agent-related and topoisomerase II inhibitor-related leukemias. Alkylating agents such as cyclophosphamide, melphalan, busulfan, semustine, and carmustine have been implicated in t-MDS and t-AML. These agents form covalent bonds between the carbon of an alkyl moiety and nucleophilic DNA bases. These induce both intra- and interstrand DNA cross-linkings and breaks and the DNA cross-linking causes a DNA misleading. Although the leukemogenicity of the alkylating agents is not fully known, they may induce leukemia through such mechanisms as point mutations, deletions, and inappropriate recombinations, because of the enhanced and aberrant DNA repair (7, 8). There are evidences that the leukemogenic risk is dose dependent (9, 10) and most t-AML present initially as myelodysplasia and develop within 1 yr from the diagnosis of MDS (11). Cytogenetic studies have shown unbalanced chromosomal aberrations, most commonly the loss of whole chromosomes 5 or 7, or various parts of the long arms of these chromosomes (11, 12). Morphologically, the French-American-British (FAB) subtypes M1, M2, M6, M7 and even undetermined phenotypes have been reported (13).

It is thought that topoisomerase II inhibitors such as etoposide (VP-16) and teniposide induce secondary leukemias by inhibition of the topoisomerase II, which regulates the superhelical rearrangement of the DNA. The enzyme cleaves a

single strand of the DNA duplexes at a specific sites by a covalent binding between its tyrosine residue and 5'-phosphate residue of the DNA, and produces a transient double strand break, which enables the knotted or interlinked DNA to pass (14-16). Thus topoisomerase II inhibitor produces secondary DNA damages such as a complex conversion. In the process of repair, an illegitimate and non-homologous recombination can occur and this may be responsible for leukemogenic potential. Topoisomerase II inhibitor-related leukemia has a relatively short incubation period, median 2 to 3 yr following treatment without a prodromal myelodysplastic phase compared to alkylating agent-related leukemia (13). The chromosomal study may show the characteristic balanced translocations involving chromosome band 11q23 or less often, 21q22 (17-20). Common partner chromosomes for the 11q23 translocations are the chromosomes 1, 2, 4, 6, 9, 10, 16, 17, 19, 22, and X (13). These chromosomal aberrations are more frequently associated with the development of AML M4 or M5 according to the FAB classification (16, 19). The *mixed lineage leukemia (MLL)* gene is located at chromosomal band 11q23 and is frequently involved in t-AML following topoisomerase II inhibitor treatment (21). Recently, Krishnan *et al.* reported 22 patients with morphologic evidence of t-MDS and t-AML among 612 patients who had been treated with high-dose chemotherapy with ASCT for Hodgkin's disease and non-Hodgkin's lymphoma (22). A multivariate analysis of the entire cohort revealed that the stem cell priming with etoposide (relative risk 7.7, *p* value=0.002) was independently associated with an increased risk of developing a secondary leukemia with the 11q23/21q22 abnormalities.

A cumulative dose of etoposide higher than 2-3 g/m² is known to be associated with the development of t-AML, although this association has not been found in all studies (23). In this case, a total of 2.3 g/m² cumulative dose of etoposide was given as well as alkylating agents and irradiation. The patient was diagnosed with t-MDS 22 months after ASCT, which progressed to t-AML after 4 months. The cytogenetic studies revealed a normal karyotype before ASCT, the 11q23 rearrangement within chromosome 11 at the diagnosis of t-MDS, and more complex chromosomal abnormalities at t-AML.

In conclusion, our patient suffered from t-MDS/t-AML following an aggressive treatment for non-Hodgkin's lymphoma. Her characteristic 11q23 rearrangement might be attributed to the use of a high cumulative dose of topoisomerase II inhibitor, etoposide.

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