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Case Study

Acute Myeloid Leukemia Diagnosed 5 Years after Adult T-Cell Leukemia/Lymphoma

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A case of secondary acute myeloid leukemia (AML) was identified following adult T-cell leukemia/lymphoma (ATL), for which combination chemotherapy had been administered, including epipodophyllotoxin, anthracycline, and alkylating agents. AML with maturation was diagnosed by the cytological findings, cell surface markers, and chromosomal abnormalities. We previously reported two cases of AML accompanied by ATL. In this case of AML after chemotherapy for ATL, we considered that the AML was probably associated with previous chemotherapy for ATL. Although the ATL remained in remission, the therapy-related AML with complex chromosomal abnormalities proved resistant to chemotherapy, and the patient died from complications associated with AML. 〔*J Clin Exp Hematop 55(1) : 29-31, 2015*〕

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INTRODUCTION

Adult T-cell leukemia/lymphoma (ATL) is a unique malignancy derived from T cells infected with human T-cell leukemia virus type-1 (HTLV-1). HTLV-1 infection can also cause several other chronic inflammatory diseases, including HTLV-1-associated myelopathy/tropical spastic paraparesis,[1,2] alveolitis,[3] and uveitis.[4] ATL is a life-threatening disease and its median survival time is short. Many cancers have been reported to be associated with secondary malignancy, including acute leukemia, but few cases of secondary leukemia accompanying ATL have been reported, as secondary leukemia usually needs to occur several years after the primary cancer.[5-7] The main cause of this low frequency of secondary leukemia with ATL is thought to be the short survival time of patients with ATL. We report the case of a patient in whom acute myeloid leukemia (AML) occurred 5 years after the diagnosis of ATL. The course of AML was thought to be associated with the anti-cancer drugs used to treat ATL.

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CASE REPORT

A 50-year-old woman was referred to our hospital with cervical lymphadenopathy in July 2007. The left tonsil was swollen and biopsy identified diffuse, pleomorphic T-cell lymphoma, highly suspected to represent ATL. The specimen showed diffuse infiltrating foci of atypical lymphocytes with hyperlobulated or pleomorphic large nuclei. Immunohistochemically, cells were positive for CD2, CD3, CD4, CD8, and CD30, and most were also positive for Ki-67. However, staining for CD20, CD79a, anaplastic lymphoma kinase, and cytokeratin AE1/AE3 yielded negative results. On the basis of the above findings, the biopsied cells were considered to represent ATL. White blood cell count was 5.11×10^9/L (neutrophils, 54.0%; lymphocytes, 37.2%; monocytes, 4.6%; eosinophils, 1.2%; basophils, 0.06%; large unstained cells, 0.09%). The hemoglobin level was 13.5 g/dL and the platelet count was 237.0×10^9/L. Biochemistry results included: aspartate aminotransferase, 24 IU/L; alanine aminotransferase, 25 IU/L; lactate dehydrogenase, 199 IU/L; alkaline phosphatase, 145 IU/L; anti-HTLV-1 antibody, positive; and soluble interleukin 2 receptor, 1,260 U/mL. Surface lymph nodes were not palpable. On the basis of these data, lymphoma-type ATL was diagnosed. The patient was then treated with combination chemotherapy according to a VCAP-AMP-VECP protocol combining 9 drugs (vincristine, doxorubicin, cyclophosphamide, prednisolone, ranimustine, vindesine, etoposide, and carboplatin) and intrathecal prophylaxis using cytarabine (Ara-C), methotrexate, and prednisolone.[8] The chemotherapy was completed within

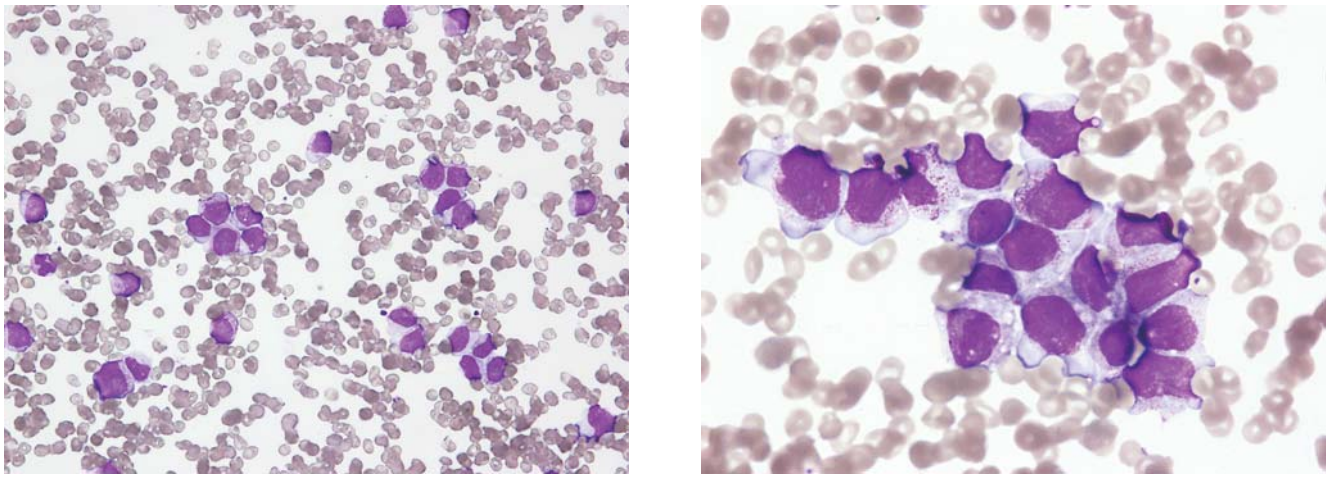

Fig. 1. Cytomorphology of myeloblastic cells. (***1A***) Bone marrow examination reveals numerous myeloblastic cells showing azurophilic granules, but no adult T-cell leukemia/lymphoma cells May-Giemsa stain, ×400. (***1B***) Myeloblastic cells show numerous azure granules indicating acute myeloid leukemia with maturation May-Giemsa stain, ×1,000.

about 7 months. We evaluated the patient as having reached remission, but the administration of etoposide was initiated at 25 mg on alternate days for about 29 months to prevent ATL relapse. In September 2012, the patient reported feelings of general fatigue, and hematological examination revealed pancytopenia. Bone marrow examination of the patient revealed 93.4% myeloid blasts (Fig. 1) and examination of cell surface markers indicated positive results for CD4, CD13, CD33, and HLA-DR, and negative results for CD3, CD8, CD10, CD19, CD20, CD14, CD34, and CD58, compatible with AML. Chromosomal investigation of bone marrow blasts revealed 46, X, t(X;10)(p11.2;p11.2), t(5;12)(q31;p13), inv(9)(p12q13)[19/20]/46, XX, inv(9)(p12q13)[1/20], and we diagnosed AML with maturation according to the World Health Organization classification. Chemotherapy for AML was started using a combination of Ara-C, aclarubicin, and granulocyte colony-stimulating factor, although severe bacterial infection occurred during chemotherapy. Chest radiography revealed severe pneumonia, for which anti-bacterial drugs were administered. Although chemotherapy was continued with Ara-C and aclarubicin, AML was not controlled and rapidly progressed, and the patient died from the complication of pneumonia in December 2012. No relapse of ATL occurred before the death of the patient.

DISCUSSION

ATL is a disease with poor prognosis, and most ATL patients die within a few years. Median survival is reported to be about 10 months.[9] Rates of secondary leukemia in ATL patients are thus lower than in other malignant diseases, including solid cancer. This has been thought to be due to an insufficient duration for the development of other malignant diseases, including AML. Secondary leukemia is well known to be associated with previous treatment with anti-cancer drugs, particularly alkylating agents and epipodophyllotoxins.[10,11] Cumulative doses of several drugs and the prognosis of the primary malignancy have been reported to contribute to treatment-related cancer.[12] Moreover, the levels of several cytokines are increased and the cytokines produced by ATL cells may be associated with the growth of AML cells.[7] The patient in the present case received several anti-cancer drugs in accordance with the VCAP-AMP-VECP protocol, including alkylating agents and epipodophyllotoxins. In general, secondary or therapy-related AML (TR-AML) accounts for 10-20% of all AML cases.[12] We previously reported data from 90 patients with acute- or lymphoma-type ATL treated in our hospital between October 1999 and July 2006. From those data, the actuarial risk of secondary leukemia among ATL patients in our hospital was 2.1%.[13] The proportion of secondary leukemia among ATL patients in our hospital appears relatively low compared with that in previous reports of other malignancies.[7,12] The main reason for this seems likely to be the short survival of ATL patients, with a median survival time for acute-type ATL of about 10 months.[9] The chemotherapeutic regimens that include epipodophyllotoxins used for ATL are probably involved in the pathogenesis of secondary leukemia, as alkylating agents and topoisomerase II inhibitors are known to induce leukemia more frequently than other chemotherapeutic agents. The administration of etoposide for prolonged periods leads to transforming mutations in normal myeloid cells. Both types of drug act via topoisomerase II and the formation of cleavable complexes can induce a programmed sequence of events eventually leading to cell death.[14] The pathogenesis of TR-AML with t(9;11) may be associated with topoisomerase II-reactive drugs, including anthracyclines.[15] Epipodophyllotoxin-associated secondary AML exhibits a

shorter latency (median, 24-30 months) than alkylating agent-associated secondary AML.[12] In the case of an association with alkylating agents, the peak incidence is 4-6 years following the initiation of cytotoxic chemotherapy for the first malignancy.[12] We previously reported two cases of secondary TR-AML after treatment for ATL; one case involved AML with eosinophilia and a chromosomal change to inv(16)(p13q22), while the second involved AML with maturation and t(8;21)(q22;q22). The latency periods for these cases were 23 months and 21 months, respectively.[13] In the present case, the interval between ATL and AML was 5 years, representing a relatively long period compared with that in other ATL patients, and suggesting that good control by ATL chemotherapy may increase the risk of secondary leukemia. We assume that more time may be needed to accumulate the complex chromosomal abnormalities seen in this case, unlike the two previously reported cases in which the chromosomal changes were relatively simple. The occurrence of TR-AML in this case might have been associated with the combination chemotherapy including etoposide for ATL. Generally, secondary AML is considered to have both poor outcomes and poor response to chemotherapy. As other factors in secondary leukemia, some cytokine levels are increased in patients with ATL and thus may be associated with the pathogenesis of leukemogenesis.[7] The mechanisms of leukemogenesis for secondary leukemia in patients with ATL have not been clarified. In the present case, poor response to chemotherapy may have been associated with the complex chromosomal karyotype, which accumulated during chemotherapy for ATL.

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