Therapy-Related Acute Leukemia Associated With t(11q23) After Primary Acute Myeloid Leukemia With t(8;21): A Report of Two Cases

To the Editor:

Therapy-related acute myeloid leukemias (t-AML) with abnormalities of band 11q23 have been reported with increasing frequency following chemotherapy with topoisomerase II (topo II)-targeting agents such as the epipodophyllotoxins and anthracycline.1 However, reports of t-AML occurring after treatment for an initial de novo AML are rare. We report two patients who were initially diagnosed with AML-M2 associated with t(8;21). Both patients achieved remission with etoposide as part of the treatment regimen, but both subsequently developed t-AML with novel balanced translocations involving 11q23 and with MLL gene rearrangements. Here we consider the possibility that the sequential occurrence of the 11q23 abnormality following the t(8;21) leukemia may be the result of specific, as yet unidentified, biological mechanisms.

Patient 1. A 10½-year-old girl presented at Denver Children's Hospital on 7/1/91 with a 6-week history of headache, abdominal pain, anorexia, fever, and weight loss. The white blood cell (WBC) count was 4.3 x 10^9/L and circulating blasts were identified. A bone marrow (BM) aspirate and biopsy revealed a hypercellular BM with 80% myeloblasts that were myeloperoxidase positive. Some blasts had Auer rods, and the maturing granulocytic elements showed abnormal granulation. The diagnosis of AML-M2 was made and cytogenetic studies on the BM aspirate showed a karyotype of 45,X,-X,t(8;21)(q22;q22) in 19 cells and 46,XX in one cell.

The patient was transferred to Wyler Children's Hospital in Chicago and began therapy with cytosine arabinoside, etoposide (600 mg/m^2 total cumulative dose) and l-asparaginase. During consolidation (2/25/92), a routine BM specimen sent for cytogenetic analysis had a karyotype of 46,XX,t(11;16)(q23;p13) in 18 cells; no cells had Auer rods, and the maturing granulocytic elements showed abnormal granulation. The diagnosis of AML-M2 was made and cytogenetic studies on the BM aspirate showed a karyotype of 45,X,-X,t(8;21)(q22;q22) in 19 cells and 46,XX in one cell. Because of the change in karyotype, chemotherapy was changed to carboplatin; however, the patient subsequently manifested a frank acute leukemia within 4 months. The second leukemia was different from the first in that it had monocytic features, strong NaF-inhibitable nonspecific-esterase activity, and associated trilineage dysplasia; no Auer rods were observed. The second leukemia was felt to be consistent with a t-AML. Additional chemotherapy successfully reduced the number of blasts, but myelodysplasia persisted. A series of subsequent BM specimens showed an increasing population of lymphoid morphology blasts beginning in 10/93 until 12/16/93 when the blasts accounted for 95% of the BM elements. The blasts were TdT positive and had the phenotype of immature T cells, being CD2, CD7, CD5, CD4, CD8, and CD6 positive. Myeloperoxidase and nonspecific-esterase stains were negative. The process was believed to represent a lineage switch from t-AML to a precursor T-cell acute lymphoblastic leukemia (ALL). Cytogenetic analysis of 22 cells from a BM aspirate obtained at the beginning of the lineage switch showed persistence of the t(11;16) clone in six cells, and two additional clones: 48,XX, +X,t(11;16), +12 in 14 cells, and 48,XX, +X,dup(3)(q25q27), +12x(12;15)(p13;q21) in two cells. The t(8;21) was not observed. Pathology slides from this BM aspirate were studied by interphase fluorescence in situ hybridization using probes for the centromeres of the X chromosome and chromosome 12 (Oncor, Inc, Gaithersburg, MD). Three signals were detected for both chromosomes in the granulocytes. Thus, the karyotypic changes detected during the lineage switch were not limited to the malignant clone that evolved into ALL. A reverse-transcriptase polymerase chain reaction (RT-PCR) for the t(8;21) fusion gene was performed using cells from the same aspirate. An amplified band of the expected size was obtained.1 This finding is similar to the results from studies of remission patients, in whom the fusion gene persists despite having had a demonstrated hematologic and cytogenetic remission for several years.2 The patient was treated for ALL, achieved a remission and had a BMT, however, she died on 10/8/94 because of complications from the transplantation procedure.

Patient 2. A 3½-year-old girl was admitted to Ibaraki Children's Hospital (Mito, Japan) on 11/88 with a WBC of 16 x 10^9/L and 15% circulating blasts. A BM study showed 19% myeloblasts (type 11). Most were myeloperoxidase positive and some showed Auer rods. A diagnosis of refractory anemia with excess of blasts (RAEB) was made. Cytogenetic analysis of the initial diagnostic specimen showed a karyotype of 46,XX,t(8;21)(q22;q22) in three cells and 46,XX,t(8;21).del(7)(q32q34) in 16 cells. Although the diagnosis was RAEB, the patient was considered to have an evolving acute myelogenous leukemia and was enrolled on the AML BFM-87 protocol [high dose cytosine arabinoside and etoposide (1,450 mg/m^2 total cumulative dose)]. She achieved a complete remission; maintenance chemotherapy was administered until 10/91 and post-therapy WBC counts ranged from 6 to 10 x 10^9/L with no evidence of residual disease.

On 1/17/92, during routine follow-up, the patient was found to have a WBC count of 133 x 10^9 with 61% blasts. A BM aspirate showed 88% monoblasts, which were 100% positive for NaF-inhibit-
able alpha-naphthyl butyrate esterase. The process was classified as a t(8;21) and was believed to be consistent with an acute monoblastic leukemia. The karyotype was 46,XX,t(11;18)(q23;p11) in 18 cells and 46,XX,t(11;18),i(7)(q10) in two cells. No cells with a t(8;21) were identified. Molecular studies using a 0.84-kb BamHI fragment of MLL cDNA containing exons 5 through 11 as a probe demonstrated an MLL gene rearrangement. RT-PCR for the t(8;21) did not demonstrate the presence of the fusion gene.

After diagnosis of the t-AML, the patient was treated as part of Tokyo Children’s Cancer Study Group ANLL 13 protocol regimen including etoposide and mitoxantrone. She achieved a complete remission but relapsed in 1/93. Despite attempts at reinduction, she died of interstitial pneumonia.

In t-AML, balanced translocations involving 11q23 and MLL rearrangements are strongly associated with epipodophyllotoxin therapy. However, the occurrence of 11q23 abnormalities following the t(8;21) leukemia in these two patients may be more than simply a therapy-related leukemia following a de novo process. Balanced translocations of chromosome band 21q22 and AML1 rearrangements have been associated with topoisomerase-I-targeting chemotherapy, similar to 11q23 translocations and MLL. Here, translocations of both 21q22 and 11q23 have been observed sequentially in the same patients. To assess the likelihood of an association of these two chromosomal abnormalities, we reviewed the literature for reports of the occurrence of both the t(8;21) and rearrangements of 11q23.

Four other cases have been reported with a t(8;21) and an 11q23 translocation in independent clones. Only one case had independent clones at diagnosis. In three cases the t(11q23) was observed after treatment for an initial t(8;21) leukemia. In contrast to the two cases presented here, in two previous cases the t(8;21) reappeared in an independent clone during relapse. No cases of 11q23 translocations preceding the (8;21) were found. An explanation for the occurrence of 11q23 translocations after (8;21) leukemia and lack of the converse may be the fact that patients with AML and a t(8;21) are known to achieve remission more frequently and to have a relatively long disease-free period before relapse, relative to those with 11q23 translocations. To compare the occurrence of 11q23 translocations with a second recurring abnormality, in A. M. we reviewed the literature for cases of t-AML following therapy for an inv(16) leukemia. Patients with the inv(16) at diagnosis are about as common as the t(8;21), and achieve similar remission rates. Only one such case was reported. Therefore, although the numbers are small, there are more reports of 11q23 translocations after therapy for t(8;21) myeloid leukemia (five cases described, including the present cases) than for leukemias with an inv(16).

To explain the rapid onset of t-AML in cases similar to the ones reported here, one of us suggested that a progenitor clone with a mutation conferring susceptibility to etoposide therapy could acquire a t(8;21), and after irradiation of the t(8;21) clone, could give rise to a second clone with an 11q23 translocation. One way that a predisposing clone could occur would be if certain individuals had an inborn susceptibility that makes cells in the hematopoietic lineage prone to illegitimate recombination in MLL following exposure to agents that inhibit topoisomerase II. In such a situation the patient would be predisposed to development of a second leukemia with a topo II-associated chromosome abnormality. Alternatively, the relatively rapid onset and the fact that 21q22 translocations and 11q23 translocations both occur after therapy with topo II-targeting agents, could be due to the type of DNA damage produced. If DNA damage from etoposide has different effects on different parts of the genome, the chromatin structure of the MLL and AML genes may play a critical role in their apparent vulnerability.

These second AML’s are very rare events, but they clearly do occur, possibly more often than is presently recognized because relatively few AML patients are karyotyped both at diagnosis and at “relapse.” Careful study and preservation of material from such patients and their families could provide a valuable resource for critical laboratory studies.

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