Therapy-related T-cell lymphoblastic lymphoma and inv(11)(q21q23) following acute promyelocytic leukemia chemotherapy

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Abstract Acute promyelocytic leukemia (APL) with the unique t(15;17) translocation has a high complete remission and disease-free survival rates following chemotherapy with all-*trans*-retinoic acid. Chemotherapy complications including secondary malignancies are rare. In this report we present therapy-related T-lymphoblastic lymphoma following APL treatment. The bone marrow analysis showed MLL and MAML2 genes rearrangement that can explain the molecular basis for the lymphoma development.

Keywords T-cell lymphoblastic lymphoma · inv(11)(q21q23) · Acute promyelocytic leukemia

Introduction

Acute promyelocytic leukemia (APL) accounts for 5–10% of acute myelogenous leukemia (AML) [1] and is associ-

ated with a distinct balanced translocation between chromosomes 15q22 and 17q21. The t(15;17)(q22;q21) results in fusion of the promyelocytic leukemia gene (*PML*) and retinoic acid receptor α gene (*RARA*) in the majority of cases [2]. The all-*trans* retinoic acid (ATRA)-based regimen is able to achieve complete remission in 90–95% of such cases [2].

Therapy-related myeloid neoplasm following APL chemotherapy is a rare event, ranging from 0.97% to 6.5% in different studies [3]. Therapy-related T-lymphoblastic lymphoma (T-LBL) following APL treatment is extremely rare, with only one case having been reported in the literature [4]. In this case, the lymphoblastic lymphoma had an abnormal cytogenetic of add(12q) [4]. Therapy-related T-lymphoblastic lymphoma following AML with inv(16) and t(8;21) is also a unique phenomenon [5, 6].

In this report, we describe a patient who developed of T-lymphoblastic lymphoma following APL chemotherapy while she was in complete remission. Cytogenetic study revealed a distinct inv(11)(q21q23) involving mixed lineage leukemia (*MLL*) and mastermind-like 2 (*MAML2*) genes.

Clinical history

This is a 35-year-old Caucasian female who was diagnosed with acute promyelocytic leukemia in April 2007 with t(15;17)(q22;q21), detected by both conventional cytogenetic analysis and fluorescence in situ hybridization (FISH) studies. She was subsequently treated with ATRA, Mitoxantrone, and idarubicin as per AIDA protocol (all-*trans* retinoic acid + idarubicin) [7]. Her bone marrow (BM)

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biopsy post-induction chemotherapy (July 2007) showed no morphologic and cytogenetic evidence of APL. She completed her consolidation chemotherapy in September 2009 and achieved complete remission as was evident in the subsequent BM biopsies. However, the BM biopsies and cytogenetic studies in 2008 revealed mild erythroid dysplasia with *inv(11)(q21q23)* without the presence of the *t(15;17)*. These abnormalities persisted in the follow-up BM biopsies (until 2010), indicating a therapy-related myelodysplastic syndrome.

In September 2010, she was admitted to William Beaumont Hospital with a 3-day history of progressive shortness of breath, diffuse facial swelling, mild left ptosis, flushing, and clavicular nodule. Her LDH was increased to 420 U/L. CT scan showed a large anterior mediastinal mass measuring $10.9 \times 7.5 \times 1.7$ cm between the aortic arch and superior vena cava, leading to complete compression of superior vena cava. This mass extended superiorly to the level of the thoracic inlet and abutting the brachial cephalic artery. There was also an enlarged left supraclavicular lymph node measuring 2.5×3.0 cm. PET scan showed increased uptake in the superior mediastinal mass with a maximum standardized uptake value greater than 8. A supraclavicular lymph node biopsy revealed monomorphic proliferation of small to medium-sized lymphoid cells with fine chromatin and distinct nucleoli. Concurrent flow cytometry demonstrated an aberrant immature T-cell population expressing CD4, CD8, and TdT, phenotypically consistent with

precursor T-cell lymphoblastic lymphoma. Staging BM biopsy was negative for involvement by T-LBL and APL. Conventional cytogenetic analysis on the left supraclavicular lymph node was unsuccessful.

She was treated with hyper CVAD regimen and prophylactic intrathecal chemotherapy per the MD Anderson protocol [8].

She achieved complete remission after six cycles of chemotherapy as was evident clinically, with a negative bone marrow biopsy and PET scan done post-induction.

Material and methods

Cytogenetic analysis

Representative samples of the bone marrow and supraclavicular mass were received for cytogenetic analysis. Standard culture and harvest procedures were performed. Briefly, the tissue was disaggregated mechanically and enzymatically and cultured in RPMI 1640 media supplemented with 20% fetal bovine serum for 24–48 h. Cells were exposed 45 min to Colcemid ($0.02 \mu\text{g/mL}$). Subsequently, the cells were treated with hypotonic solution (0.075 M KCl for 20 min), and fixed with methanol and glacial acetic acid (3:1). Metaphase cells were banded with Leishman stain. The karyotypes were described according to the International System for Human Cytogenetic Nomenclature (ISCN 2009) [9].

Fig. 1 Conventional cytogenetic study revealed an *inv11* (*q21q23*) in the bone marrow (arrow)

46,XX,*inv(11)(q21q23)*

Fig. 2 Rearrangement of *MLL* and *MAML2* genes using break apart probes in the bone marrow (arrows)

Dual-color FISH assay

In an effort to identify the putative genes that are involved in *inv(11)(q21q23)*, the following probes were used: LSI *MLL* break apart probes (Vysis, Abbottpark, Illinois, USA), BAC probes spanning the *MAML2* gene (BlueGnome, Cambridge, United Kingdom), and T-cell receptor beta probes (Dako, Carpinteria, CA, USA).

FISH was performed as previously described [10] on the bone marrow and supraclavicular mass as well as on a metaphase de-stained slide of the bone marrow. Briefly, following pretreatment of the slides, the cells and the probes were co-denatured at 75°C for 5 min and incubated for hybridization overnight at 37°C using the HYBrite instrument (Vysis). Post-hybridization, the slides were washed and counterstained with 4',6-diamidino-2-phenylindole (DAPI II; Vysis). Hybridization signals were analyzed by Olympus BX51 fluorescent microscope in 400 interphase nuclei and ten metaphase cells. Images were acquired by use of the CytoVision Image Analysis System (Applied Imaging, Santa Clara, CA, USA).

Results

Conventional cytogenetic analysis of the bone marrow specimen, 1 year post-induction chemotherapy, identified an *inv(11)(q21q23)* (Fig. 1). This cytogenetic abnormality remained unchanged during the patients' disease course. FISH studies on the interphase and metaphase bone marrow cells using *MLL* and *MAML2* break apart probes revealed rearrangement of both genes (Fig. 2). Conventional cytogenetic analysis on the tissue specimen of the T-LBL was unsuccessful. Paraffin FISH analysis of the involved node demonstrated *MLL* gene rearrangement in the interphase nuclei (Fig. 3), while the FISH study

utilizing *MAML2* probes revealed some non-specific binding which precluded an equivocal interpretation of the status of the gene. An additional FISH study for T-cell receptor beta gene rearrangement was negative (data not shown).

Discussion

APL is a highly curable disease that to achieve durable complete remission, chemotherapy invariably needs to be added to the ATRA regimen. However, complications of chemotherapy including therapy-related neoplasm are at times inevitable.

The *MLL* gene rearrangement with over 80 different partners has been described in acute myelogenous leukemia [11], acute lymphoblastic leukemia [12], and therapy-related myeloid neoplasm [13]. *MLL* has an epigenetic role

Fig. 3 *MLL* gene is rearranged in the supraclavicular lymph node with T-lymphoblastic lymphoma using break apart probes (arrow)

as well as regulatory function in cell cycle, in embryogenesis, and in development [14]. *MLL* also interacts with nuclear receptors and involves in mRNA processing [12]. The *MAML2* gene is widely expressed and binds to the ankyrin repeat domain of NOTCH1 receptor in the nucleus, resulting in activation of NOTCH1 target genes including *HES1* and *HES5* [15]. The t(11;19)(q21;p13) resulting in *CRTC1-MAML2* fusion transcript has been reported in mucoepidermoid carcinoma and Wartin's tumor of the salivary gland [16], and clear cell hidradenoma of skin [17]. This translocation has been shown to activate the *HES1* gene independent of the NOTCH1 signaling [18]. NOTCH1 plays a critical role in T-cell development and *NOTCH1* activation gene mutation is present in >50% of T-ALL/LBL [19].

Metzler et al. reported a case of secondary T-cell acute lymphoblastic leukemia with inv(11)(q21q23) in a mediastinal mass of a young patient who had been treated for AML with inv(16) [5]. Their extensive work-up revealed that the inv(11)(q21q23) had resulted in fusion between *MLL* and *MAML2* genes. Using microarray technique, they showed activation of NOTCH1 downstream signaling pathway genes, including *PTCRA* and *ID1* genes, in the *MLL-MAML2* T-ALL.

Nemoto et al. have also described inv(11)(q21q23) in secondary AML and myelodysplastic syndrome [6]. The patient who developed secondary AML 7 years after being in complete remission from AML with t(8;21), consistently presented an inv(11)(q21q23) during the hematological remission. Interestingly, the patient's disease course was complicated by T-LBL while she was in complete remission. Nemoto et al. demonstrated that the inv(11) in the bone marrow had caused fusion between *MLL* and *MAML2* genes. However, they showed that the *MLL-MAML2* fusion suppresses N1ICD-induced *HES1* promoter activation in a dose-dependent manner, affecting NOTCH1 signaling pathway [6]. These data illustrate different role that *MAML2* gene fusion plays in modification of NOTCH1 signaling.

In the present report, the inv(11)(q21q23) caused rearrangement of *MLL* and *MAML2* genes in the bone marrow. This rearrangement may have stimulated/alterd NOTCH1 signaling pathway in the hematopoietic stem cells that eventually promote development of T-LBL. In our opinion, a better tailored APL chemotherapy regimen or hematopoietic stem cell transplant at the time of therapy-related myeloid neoplasm may avoid such transformation.

Conflict of interest The authors declare that they have no conflict of interest.

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