

Acute promyelocytic leukemia relapsing into acute myeloid leukemia-M2 with normal cytogenetics

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ABSTRACT

The use of all trans-retinoic acid (ATRA) and combination chemotherapy has made acute promyelocytic leukemia (APL) a potentially curable leukemia. Late sequelae of the treatment of APL have therefore become an important consideration in the overall treatment strategy. We report a patient with APL who achieved complete clinical and molecular remission after treatment with daunorubicin and ATRA. Three years later, she developed acute myeloid leukemia (AML), M2 subtype without any evidence of relapse of the APL clone. Karyotypic analysis showed a normal female karyotype.

Key words: *Acute promyelocytic leukemia, acute myeloid leukemia (AML), secondary AML, therapy related AML*

INTRODUCTION

APL also known as AML, M3 subtype is characterized by the typical morphology and t(15;17) translocation that fuses the PML gene on chromosome 15 to the RARA gene on chromosome 17, which serves as a “clone specific” molecular marker for the diagnosis and monitoring.^[1] Anthracycline and Cytosine arabinoside (Ara-C) based combination chemotherapy introduced in the 1960s, has yielded cure rates of 35-40% in APL, whereas combination of anthracycline-Ara C or anthracycline alone to ATRA, introduced in the early 1990s, has improved this cure rate to 65-70% because of its unique sensitivity to the differentiating action of ATRA.^[2] We report a patient in remission after chemotherapy for APL who developed AML, M2 subtype with no evidence of APL. This clinical syndrome though rare has been increasingly diagnosed and a subject of concern in few patients who are otherwise expected to have a good outcome.

CASE REPORT

A 32-year-old housewife presented with 1 month history of

fever, bleeding per vaginum, and pancytopenia. Peripheral smear and bone marrow were suggestive of infiltration of 90-95% abnormal promyelocytes and blasts, which were strongly myeloperoxidase positive. Coagulation screen was normal. Fluorescence *in situ* hybridization FISH for detection of translocation which fuses the promyelocytic leukemia gene (PML) on chromosome 15q22-q24 to the retinoic acid receptor alpha (RARA) gene on 17q21 PML/RARA translocation carried out by vysis probe/dual color dual fusion method identified PML/RARA translocation. After the first induction course, with ATRA (45 mg/m²/d per oral in 2 divided doses) with daunorubicin (45 mg/m²/d IV over days 1-3) the patient was in morphological complete remission (CR). This was followed by consolidation and maintenance which was completed by April 2009. The patient remained in CR until December 2010, when she presented with fever, weakness, and pancytopenia. Bone marrow examination was compatible with acute myeloid leukemia (AML) French-American-British M2; the karyotype was normal, PML/RARA was negative by both FISH and PCR methods which were repeated twice. The patient attained complete hematological remission after 7 + 3 induction cytarabine (100 mg/m²/d over days 1-7) and idarubicin (12 mg/m²/d over days 1-3) followed by first consolidation with high dose cytarabine. She did not have a full sibling Human leukocyte antigen HLA match. She was taken for autologous hematopoietic stem cell transplant (HSCT) using busulphan and cyclophosphamide conditioning. After a treatment free interval of 9 months, the patient again presented with fever, weakness and pancytopenia

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and diagnosed with second relapse (AML-M2). Patient was explained about the nature of the disease and the available treatment options and their resultant toxicity. She opted for supportive care and finally succumbed to her illness.

DISCUSSION

The patient described in this report was diagnosed with the acute promyelocytic leukemia (APL) according to the typical morphology and PML-RARA rearrangements. Although hematological and molecular remission was achieved, the patient developed AML-M2, 9 months after completion of maintenance therapy. Cytogenetic analysis revealed a normal female karyotype of 46, XX, and there was no morphological or molecular evidence of APL.

Origin of this second AML clone is not clear, three hypotheses are possible: One that this clone co-existed with the original APL clone which arose after effective chemotherapy for APL, or the patient developed it due to therapy (therapy related AML, t-AML) or this can be due to a lineage shift within the myeloid compartment as a virtue of hematopoietic stem cell plasticity.

The incidence of additional cytogenetic abnormalities (ACA) at initial diagnosis (primary) in patients of APL has been found in one-third and it does not influence the outcome of patients of APL and thus are of unknown clinical significance.^[3,4]

In a retrospective analysis over a 12 year study period, secondary clonal cytogenetic aberrations (CCA) following therapy for APL (ATRA with chemotherapy) was seen in 12 out of 123 patients (9.8%), who were in CR. The median time to the emergence of CCA was 27.5 months (range: 2-54 months). Seven patients with secondary CCA are alive without any evidence of leukemia. Four patients were diagnosed with therapy-related myelodysplastic syndrome and acute myeloid leukemia; one patient developed a relapse of APL.^[5]

Advances in the treatment of APL, particularly the incorporation of ATRA in induction and/or maintenance chemotherapy have significantly improved treatment outcome, but has been accompanied by increased reports of t-MDS/AML. The incidence of which as reported by Rome and European groups was 1% and 6.5% respectively.^[6,7] The median latent period from achievement of CR to diagnosis of t-MDS/AML was 34 months (range 25-40 months). All patients presented with the chromosome abnormalities, mostly deletions or loss of the long arm of chromosome 5 and/or 7, or balanced translocations involving the 21q22 band. Prognosis is poor with a median survival of 10

months (range 7-22 months).^[8] Given the poor outcome of chemotherapy for therapy-related disease, allogeneic HSCT is often performed whenever possible.

Relapse of APL after successful therapy with a different subtype of AML has been reported rarely.^[9-11] In some cases, there have been the presence of 2 clones of AML at baseline.^[12,13]

The decade old concept about restriction of leukemic stem cells to a particular phenotype has been refuted recently. Functional characteristics of tumorigenic cells can be reversibly switched on and off due to the cancer stem cell phenotypic plasticity. This facility with which cells from one lineage can transdifferentiate into another depends on how closely related they are to each other and how much their transcription factor machinery overlaps. The best example in this respect is lymphoid blast crisis in chronic myeloid leukemia.

Hematopoietic stem cells and progenitor cells do not grow as self-supporting units; rather they are completely surrounded by the microenvironment of the bone marrow and have a continuing dialog with signals provided by it. While it has long been recognized that intrinsic abnormalities may cause leukemia, it has also become clear that changes in microenvironment composition might lead to disease. How any of these alterations would allow or promote lineage switching in leukemia is currently a topical question.^[14]

We are not sure about the origin of second AML clone in our case. However, this case raises some important questions to be answered in future:

- Is the ACA associated with APL at baseline really benign?
- How to treat a second AML clone when present in addition to APL at baseline?
- Should we monitor patients for CCA after APL therapy when a patient is in CR and if present does it merit treatment?
- Should agents of lower leukemogenic potential be used for APL therapy?

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