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2019

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Recommended Citation

Abboud, Ramzi; Han, Se Young; Duncavage, Eric J.; Cashen, Amanda F.; Shirai, Cara Lunn; Welch, John S.; DiPersio, John F.; and Abboud, Camille N., "Serendipity: Decitabine monotherapy induced complete molecular response in a 77-year-old patient with acute promyelocytic leukemia." *Haematologica*, . . (2019).
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Serendipity: decitabine monotherapy induced complete molecular response in a 77-year-old patient with acute promyelocytic leukemia

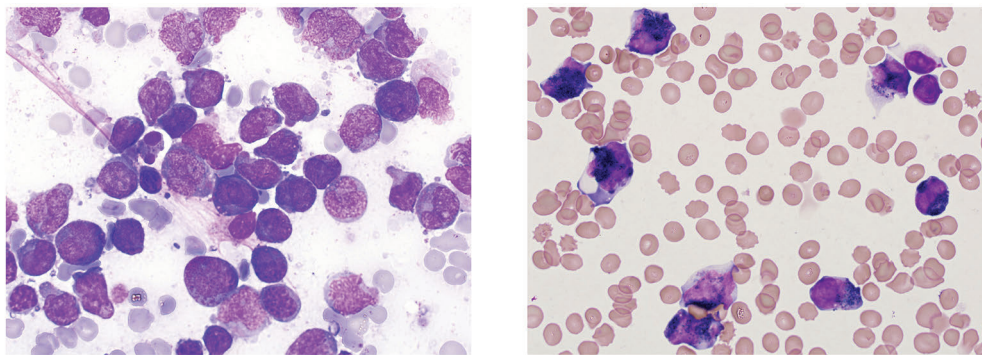
Acute promyelocytic leukemia (APL) is an uncommon but very aggressive subtype of acute myeloid leukemia (AML), accounting for 10-15% of adult AML with 600-800 new cases per year in the United States.^{1,2} Over 95% of cases involve translocation t(15;17)(q22;q21), which results in the promyelocytic leukemia retinoic acid receptor alpha (*PML-RARα*) rearrangement and fusion protein.³ Most of the remaining APL cases harbor a fusion protein involving *RARα* and another partner.⁴ The *PML-RARα* fusion gene initiates APL by blocking differentiation and increasing self-renewal and proliferation of leukemic progenitor cells.

In the 1970s, outcomes in APL were dismal. Anthracycline-based regimens were used, producing long-term survival rates of 15-25%.¹ This changed drastically with the introduction of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) which both target the *PML-RARα* fusion. With modern ATRA and ATO therapy, long-term survival rates approach 95%, in many cases without cytotoxic therapy.⁵

Herein, we present a case of an APL patient with the typical *PML-RARα* fusion, but atypical morphology and immunophenotype, who unexpectedly achieved morphological and molecular remission after treatment with single agent decitabine.

A 77-year-old female with atrial fibrillation and hypertension presented with two months of progressive fatigue and oral ulcers. Family history was significant for a brain tumor (classification unknown) in her mother, and breast cancer in two of her daughters. She consumed

A



B

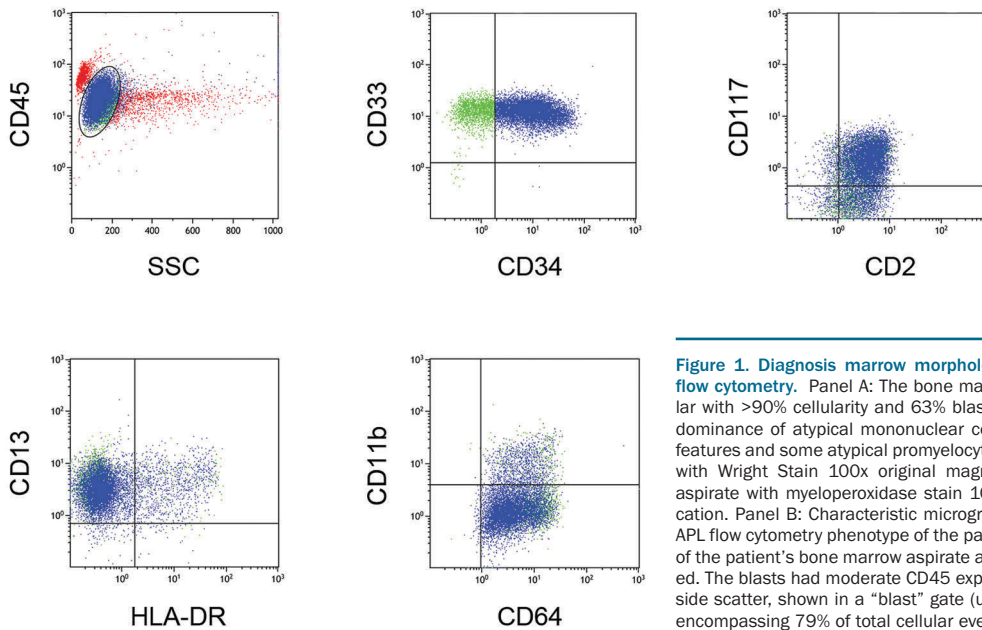


Figure 1. Diagnosis marrow morphologic evaluation and flow cytometry. Panel A: The bone marrow was hypercellular with >90% cellularity and 63% blasts. There was a predominance of atypical mononuclear cells with monocytoid features and some atypical promyelocytes. Top left: aspirate with Wright Stain 100x original magnification. Top right: aspirate with myeloperoxidase stain 100x original magnification. Panel B: Characteristic microgranular/hypogranular APL flow cytometry phenotype of the patient. Flow cytometry of the patient's bone marrow aspirate at diagnosis is depicted. The blasts had moderate CD45 expression and reduced side scatter, shown in a "blast" gate (upper left panel) and encompassing 79% of total cellular events. The blasts were positive for CD33 (bright), CD34 (82%, blue), CD117, CD2 (dim), CD13, and CD64 (dim). The blasts were negative for HLA-DR and CD11b. The blasts were also negative for CD14, CD123, CD19, and CD56 (not shown).

alcohol socially, never smoked, and had no history of illicit drug use. Physical exam including vital signs were normal on presentation, and the patient had no bruises, petechiae, or lymphadenopathy.

Complete blood counts revealed WBC 5600/ μ L, 69% blasts, hemoglobin 9.3 g/dL, and platelets 24000/ μ L. Coagulation panel revealed elevated PT (14.2 seconds) and INR (1.31), and normal PTT (24.6 seconds) and fibrinogen (200 mg/dL). Comprehensive metabolic panel was normal. Serum LDH was 258 units/L and uric acid was 6.3 mg/dL. Peripheral smear morphology revealed a large blast population with no promyelocytes or Auer rods. Bone marrow biopsy revealed AML with maturation (Figure 1A). Flow cytometry identified 79% blasts characterized by co-expression of CD33, CD34, CD117, CD13, CD2 (dim), CD64 (dim) and negative expression of HLA-DR, CD14, CD11b, CD19, CD56, and CD123 (Figure 1B). Cytogenetics revealed a t(15;17) rearrangement which was subsequently confirmed by fluorescence *in situ* hybridization (FISH) as a *PML-RAR α* fusion in 91.5% of cells and 100% of transcripts by quantitative reverse transcriptase polymerase chain reaction (RT-PCR). *FLT3-ITD* testing was positive by standard methods. While the laboratory's protocol is to perform upfront FISH for 7 probes (including *PML-RAR α*) on all suspected cases of AML, only routine cytogenetics was initially requested in this case. As the morphology and flow cytometric findings were not typical for APL, it was originally reported as AML with maturation. Cytogenetic studies

demonstrating a t(15;17) and confirmatory FISH/RT-PCR were reported in the electronic medical record approximately one week after the initial diagnosis of AML with maturation was reported, but did not come to immediate clinical attention.

Given the patient's advanced age and presumed diagnosis of AML, she was treated with a 10-day course of decitabine. Her leukocyte count did not increase during treatment, as might be typical of differentiation syndrome. She developed mild coagulopathy evidenced by elevated INR (peak 1.70), but she had no evidence of bleeding and the fibrinogen and D-Dimer remained normal throughout. Her hospital course was complicated by multifocal embolic infarcts attributed to atrial fibrillation, resulting in expressive aphasia and gait abnormalities. The patient was discharged to inpatient rehabilitation on hospital day 22, and two subsequent cycles of 5-day decitabine consolidation were administered by her local oncologist.

At her first follow-up appointment at our institution, the pre-treatment cytogenetics were reviewed and her diagnosis was amended to APL. A restaging bone marrow biopsy at that time confirmed achievement of complete molecular remission (Figure 2) with cytogenetic remission and negative RT-PCR.

Given her complete remission, the patient was treated with four cycles of ATRA and ATO consolidation per LoCocco protocol.⁵ She has experienced significant neurological recovery with mild right facial weakness,

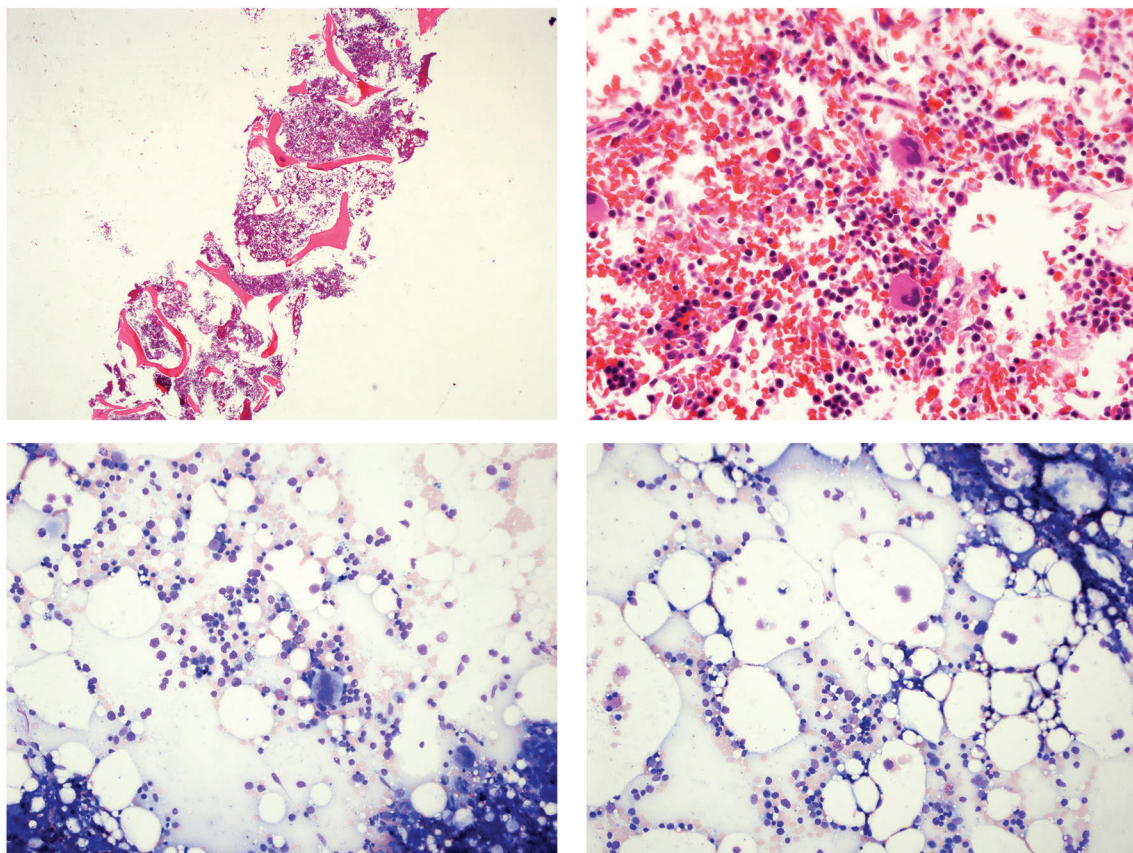


Figure 2. Day 30 marrow morphologic evaluation. D30 Marrow morphologic evaluation. The bone marrow was normocellular for age and showed trilineage hematopoiesis with an erythroid predominance and no increased blasts. Top left: core 2x original magnification. Top right: core 10x original magnification, Bottom row: bone marrow aspirate 40x original magnification.

expressive aphasia, and wide-based gait. She remains independent for ADLs and IADLs. She is now 1,035 days from diagnosis in both morphologic and molecular complete remission with undetectable *PML-RAR α* and *FLT3-ITD*.

Bone marrow morphology was consistent with microgranular variant of APL which lacks the Auer rods and the CD34/HLA-DR negative phenotype typically seen in APL (Figure 1A). Microgranular APL frequently has *FLT3-ITDs*, however it does not itself predict for a worse prognosis compared with classic APL.⁶

Flow cytometry was consistent with microgranular/hypogranular variant of APL.² The APL blasts identified (79% total cells) were characterized by co-expression of CD33, CD34, CD117, CD13, CD2 (dim), CD64 (dim), and were negative for expression of HLA-DR, CD14, CD11b, CD19, CD56, and CD123 (Figure 1B).

Cytogenetics revealed a t(15;17) rearrangement which was subsequently confirmed by FISH as a *PML-RAR α* fusion in 91.5% of cells and 100% of transcripts by quantitative RT-PCR. A Next generation hematologic malignancy panel was negative for mutations in *ABL1*, *ASXL1*, *ATM*, *BCOR*, *BIRC3*, *BRAF*, *CALR*, *CBL*, *CEBPA*, *CREBBP*, *CSF1R*, *CSF3R*, *DNMT3A*, *EP300*, *ETV6*, *EZH2*, *FBXW7*, *FGFR4*, *FLT3*, *GATA1*, *GATA2*, *GATA3*, *IDH1*, *IDH2*, *IL7R*, *JAK2*, *JAK3*, *KDM6A*, *KIT*, *KMT2A*, *KRAS*, *MPL*, *NF1*, *NOTCH1*, *NOTCH2*, *NPM1*, *NRAS*, *NSD1*, *PAX5*, *PDGFRA*, *PDGFRB*, *PTPN11*, *RUNX1*, *SETBP1*, *SF3B1*, *SRSF2*, *STAG2*, *TERT*, *TET1*, *TET2*, *TP53*, *TSLP*, *U2AF1* and *ZRSR2*.⁴

Our patient is a unique example of APL who fortuitously achieved complete molecular remission with decitabine monotherapy. She was misdiagnosed with non-APL AML due, in part, to the lack of up-front FISH testing for *PML-RAR α* , nonstandard APL morphology, and communication issues in reporting the positive cytogenetic findings. Cases of microgranular variant, while rare, have been described and highlight the importance of cytogenetic analysis.^{6,7} As a result of this case, we now have an institutional policy that all *PML-RAR α* results must be communicated by voice to the treating attending physician.

Several groups have sought the role of DNA methylation in APL. DNA methyltransferase (*DNMT*) is the key enzyme in DNA methylation, a process that plays a major role in leukemogenesis.⁸ Di Croce *et al.*, have suggested that the *PML-RAR α* fusion protein interacts with *DNMT1* and *DNMT3A*, leading to hyper-methylation and subsequent silencing of downstream pathways involved in hematopoietic cell differentiation - such as *RAR α* .⁸ Furthermore, overexpression of *DNMT3A*, in collaboration with *PML-RAR α* , promotes APL leukemogenesis *in vivo*. While ATRA can make changes in posttranslational modification such as histone acetylation, it does not affect DNA methylation in APL cells.⁹ Therefore, there may be a role for hypomethylating agents in combination with ATRA and ATO to improve therapeutic outcomes of APL through activity in an additional pathway.

Decitabine is a well-tolerated hypomethylating agent that alters gene expression resulting in several antileukemic effects. Forkhead box (*FOX*) genes are important in hematopoietic cell differentiation. *FOXC1* transcription levels are low in APL, in contrast to AML.¹⁰ Interestingly, in APL cell lines, decitabine upregulates *FOXC1* transcription to normal levels through hypomethylation of the promoter,^{10,11} which may promote differentiation. Furthermore, decitabine can acti-

vate the TRAIL pathway in APL cells, thus inducing leukemic cell apoptosis.¹² Finally, decitabine has been shown to induce apoptosis in the ATRA resistant APL cell line NB4-R2¹³ as well as HL-60 acute myeloid leukemia cells.¹⁴

Further support of the role of hypomethylating agents is provided by a case of refractory APL with variant translocation *STAT5B/RARA* where decitabine was used in combination with alternating cycles of idarubicin/cytarabine and aclacinomycin/cytarabine inducing a complete and durable response.¹⁵

Although this patient presented with a low WBC CT and low-risk APL clinical features, she harbored the *FLT3-ITD* mutation which some view as an added risk factor in acute myeloid leukemia. Her robust molecular response after decitabine single agent therapy is remarkable. She continues in complete remission 24 months after standard consolidation with ATRA and ATO. This case has prompted us to consider the addition of decitabine to ATRA and ATO induction as an attractive alternative to anthracyclines in high-risk APL.

Our elderly patient with low-risk APL achieved complete morphologic and molecular remission after single agent treatment with decitabine.

In cases of high-risk APL, where many centers use cytotoxic chemotherapy, decitabine may be an efficacious and more tolerable alternative to anthracycline therapy.

Our case is the first to demonstrate the potential efficacy of front-line single-agent decitabine in a patient with *de novo* APL, with the potential caveat that the APL did not have a classic morphology and expressed CD34.

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Funding: RA was supported by the National Cancer Institute of the National Institutes of Health under Award Number R25CA190190.

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doi:10.3324/haematol.2018.209478

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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