

Myelodysplasia-related acute myeloid leukemia and acute promyelocytic leukemia: concomitant occurrence of two molecularly distinct diseases

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Abstract

Concurrent presentation of acute promyelocytic leukemia (APL) with other hematologic diseases in the absence of previous chemotherapy or ionizing radiotherapy treatment is very rare. We present a case of simultaneous occurrence of APL with myelodysplastic syndrome (MDS)-related acute myeloid leukemia (AML). A 43-year-old female presented with 3 month of history fatigue, night sweats, chills and pancytopenia. Bone marrow aspirate and biopsy demonstrated 20% myeloid blasts with dysplastic changes admixed with abnormal promyelocytes. Cytogenetic analysis showed tetraploidy and deletion in chromosomes 5q and 7q and polymerase chain reaction showed presence of PML/RARA mRNA transcripts, confirming the presence of concurrent APL and MDS-related AML. Induction chemotherapy with cytarabine and daunorubicin was initiated along with all-trans retinoic acid. This is the first case to be reported in the literature of concurrent occurrence of APL with MDS-related AML. Treatment with 7 + 3 regimen and ATRA was successful in inducing complete remission.

Introduction

Myelodysplastic syndromes (MDS) represent the most common category of acquired bone marrow failure syndrome in adults.¹ They are a diverse group of clonal bone marrow disorders of hematopoietic stem cells characterized by ineffective hematopoiesis, dysplasia in one or more of the major myeloid cell lines, peripheral cytopenias and increased risk of development of acute myeloid leukemia (AML).² Failure of cellular differentiation is associ-

ated with evolution to secondary AML.¹ AML, a very heterogeneous disease clinically, morphologically and genetically, is divided into different subtypes; one such subtype is acute promyelocytic leukemia (APL) that is characterized by the fusion of promyelocytic leukemia (*PML*) gene on chromosome 15 with the retinoic acid receptor alpha (*RARA*) gene on chromosome 17.² As a consequence, the PML-RARA oncoprotein disrupts the interaction of retinoic acid and RARA causing the arrest in maturation of hematopoietic progenitors at the promyelocyte stage.² APL comprises about 10%-15% of all cases of adult AML and represents the most curable type.^{3,4} APL usually manifests *de novo*, but there are few reports of its concomitant occurrence with chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), mainly attributed to previous use of chemotherapy and/or radiotherapy.^{5,6} Concurrent occurrence of APL with other hematologic diseases in the absence of therapy is even rarer; there are few anecdotal reports of plasma cell myeloma and myeloproliferative neoplasms co-existing with APL in the absence of therapy.^{7,8} Herein, we present a case of concomitant occurrence of APL with MDS-related AML.

Case Report

A 43-year-old female of Caucasian ancestry was evaluated in hematology clinic for symptoms of progressive fatigue, generalized bone pains, and night sweats of 3 months duration, and a complete blood count obtained by her primary care physician showing pancytopenia with white blood cell count of $1.5 \times 10^3/\mu\text{L}$, absolute neutrophil count of $0.8 \times 10^3/\mu\text{L}$, hemoglobin of 9.8 g/dL with an MCV 99 fL, and a platelet count of $116 \times 10^3/\mu\text{L}$. Her past medical history was significant for eosinophilic esophagitis and generalized anxiety disorder. She did not have any history of tobacco, alcohol or other substance use, and no history of exposure to chemotherapy or ionizing radiation. There wasn't any family history of primary hematologic disorders. On examination, the patient appeared well, without any signs of mucocutaneous bleeding or splenomegaly.

Peripheral blood film showed anisocytosis and polychromasia in the red cell lineage but without any noticeable morphologic abnormalities in the leukocytes or platelets. Bone marrow biopsy was hypercellular with a cellularity-to-fat ratio of 80:20. The myeloid blasts were increased estimated to be 20% with admixed abnormal promyelo-

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cytes (20%). There was myelofibrosis (grade 2+), dysmyelopoietic changes with pseudo Pelger-Huet cells, decreased erythropoiesis and abnormal megakaryocytes (Figure 1). Cytogenetic analysis by Giemsa banding showed tetraploidy and deletion in chromosomes 5q and 7q [92, XXXX, del (5)(q22q35), del (7)(q22q34)] in 6 of the 20 metaphases.

AML fluorescence in situ hybridization (FISH) showed that 12% of nuclei were tetraploid, however there was no fusion of the *PML* and *RARA* gene regions or the *MYH11* and *CBFB* gene regions. Quantitative real-time polymerase chain reaction (qRT-PCR) detected PML/RARA mRNA transcripts, estimated to be 31.3% (normalized value of PML-RARA to GUSB control gene transcripts), indicating the presence of acute promyelocytic leukemia (APL) clone. OncoHeme next-generation sequencing (<https://www.mayomedicallaboratories.com/test-catalog/Overview/63367>) did not show any pathogenic mutations. The diagnosis was consistent with co-occurrence of APL and MDS-related AML. The patient was admitted for induction chemotherapy with 7 + 3 regimen (cytarabine 125 mg/m²/day for 7 days and daunorubicin 90 mg/m²/day for 3 days) and all-trans retinoic acid (ATRA) 45 mg/m²/day. Post-induction bone marrow biopsy obtained in day 14 presented with residual leukemic blasts but without any mRNA PML/RARA transcripts. She hence underwent second induction with 5 + 2 reg-

imen (cytarabine 100 mg/m²/day for 5 days and daunorubicin 50 mg/m²/day for 2 days). A repeat bone marrow biopsy obtained once peripheral blood cell counts normalized showed both a morphologic and molecular remission. She subsequently received consolidation chemotherapy with 2 cycles of high dose cytarabine (HiDAC, 3 g/m² q. 12 hours on days 1, 3 and 5). Search for a suitable donor for allogeneic hematopoietic stem cell transplant is underway.

Discussion

We present the first case report of a patient with concomitant occurrence of APL and MDS-related AML, and its management. Although reports of concurrent APL and other hematological disease do exist, they are very rare and are usually therapy-related. Lim *et al.* in 2014 described a 60 year old male with APL concomitant with plasma cell myeloma without previous exposure to chemotherapy and radiotherapy.⁷ They proposed that the concurrent presentation of these two entities was a result of abnormal multipotent stem cells, environmental exposure that gave rise to the leukemic clone.⁷ The patient was treated with ATRA; idarubicin was not administered due to sepsis.⁷ Su *et al.* in 2017 reported a case of a 52 year old male with chronic

lymphocytic leukemia (CLL) and APL treated with ATRA and hydroxyurea.⁹ The patient developed acute hypoxic respiratory failure and did not respond to treatment. He developed disseminated intravascular coagulation and eventually died. Mamorska-Dyga *et al.* in 2016 described a young patient with co-existing APL with *JAK2 V617F* positive myeloproliferative neoplasm (MPN).⁸ The patient was induced with ATRA and arsenic trioxide (ATO) and developed thrombocytosis with a bone marrow biopsy that showed reticulin fibrosis, left shift of myeloid lineage and dysplastic changes.⁸ The patient was refractory to ATRA and ATO treatment and was treated with cytarabine and idarubicin, and eventually with hydroxyurea and low dose aspirin.⁸ They hypothesize that the *JAK2 V617F* positive MPN clone was present first and that additional mutations on *FLT3* and *PML/RARA* led to the development of APL.⁸ Akin to many cases, the etiology for MDS-related AML in our patient is not clear. The chromosomal abnormalities found in our patient (tetraploidy, del 5q and del 7q) can occur *de novo* but are more commonly present in therapy-related AML/MDS (tAML/tMDS).^{2,10}[11] The occurrence of therapy related AML as a complication of cytotoxic therapy is well documented and has a poor prognosis.² A study by Duffield *et al.* demonstrated that

about 9% of APL cases in their cohort presented after treatment with cytotoxic chemotherapy or radiation therapy.¹¹ Our patient did not have any past medical history of any other malignant diseases, or prior use of chemotherapy or ionizing radiation. The most common genetic abnormality in APL is the translocation between chromosome 15 and 17 [t(15;17)(q22;q12)] but different translocation partners of *RARA* gene have been described with clinical and pathological findings similar to APL. These include t(11;17)(q23;q21) *ZBTB16/RARA*, t(11;17)(q13;q21) *NUMA/RARA*, t(5;17)(q35;q21) *NPM/RARA*, der(17) *STAT5B/RARA*, der(17) *PRKAR1a/RARA*, t(X;17)(p11;q12) *BCOR/RARA*, and t(4;17)(q12;q21) *FIP1L1/RARA*.¹² These findings are indicative of the key role of *RARA* in the pathogenesis of the disease.² We suspect that the *PML/RARA* translocation is an independent event, causing the distinct APL clone.

The mainstay of treatment for MDS-related AML is induction chemotherapy with anthracycline and cytarabine, and the best chance at cure is consolidation with allogeneic hematopoietic stem cell transplant if the patient is deemed appropriate candidate and if there is availability of a suitable donor.¹³⁻¹⁵ Long term survival rates in patients with first complete remission are often higher than 50%.¹⁵ Since our patient was relatively young and did not have any major comorbidities, induction chemotherapy with 7 + 3 regimen was deemed the most appropriate treatment. On the other hand, the standard treatment for *de novo* APL is anthracyclines and ATRA, which induces terminal differentiation followed by natural apoptosis of malignant cells.¹⁶ The combination of anthracyclines and ATRA induces a complete response in over 90% of patients, and the risk of relapse is 16.5% at 10 years.¹⁷ The main side effects associated with ATRA include the differentiation syndrome which manifests with fever, respiratory distress, weight gain, pleural or pericardial effusions and sometimes renal failure.¹⁶ Other side effects from prolonged use of ATRA include Sweet syndrome which is an acute febrile neutrophilic dermatosis with fever, leukocytosis, raised plaques on the skin and histologically dense, dermal infiltration of the skin with mature neutrophils.¹⁸

In our patient, the combination treatment was successful in inducing remission of both MDS-related AML and APL. She began consolidation therapy with HiDAC.

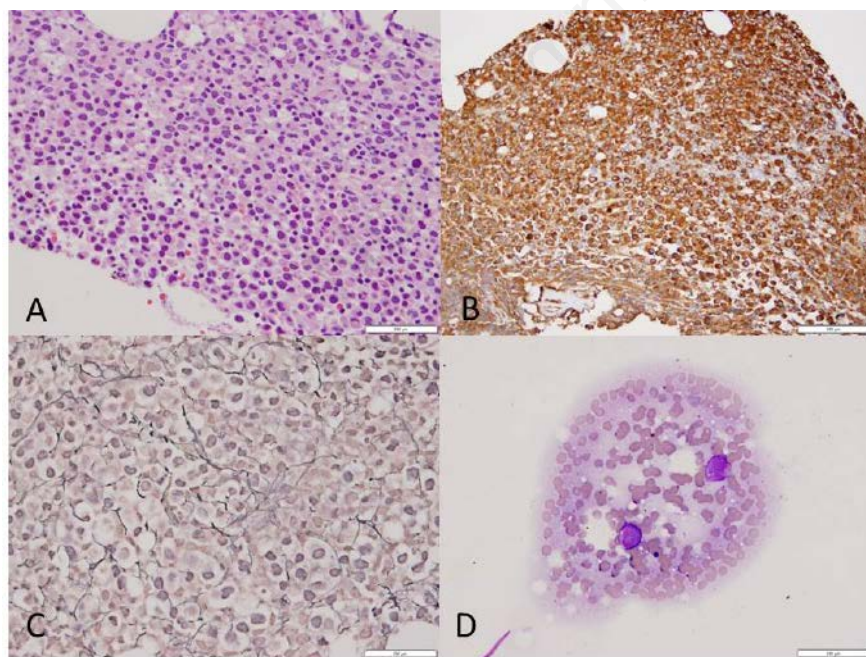


Figure 1. Bone marrow biopsy pathology slides with different stains. A) Bone marrow biopsy 100X hematoxylin and eosin stain showing a hypercellular marrow with increased promyelocytes; B) Bone marrow biopsy 200X MPO stain showing diffuse MPO staining; C) Bone Marrow Biopsy 400X reticulin stain showing grade 1 fibrosis; D) Roll preparation 400X Wright stain showing promyelocyte blasts.

Conclusions

This is the first case report of concurrent occurrence of APL and MDS-related AML, and the description of its management. Treatment with combination of 7 + 3 regimen and ATRA was successful in inducing a complete remission from both APL and MDS-related AML. The optimal consolidation therapy in such cases where there are 2 clones of AML, remains unknown. Our patient received consolidation chemotherapy with 2 cycles of HiDAC, and search for a suitable donor for allogeneic hematopoietic stem cell transplant is underway.

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