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Management of differentiation syndrome in an elderly patient with acute promyelocytic leukemia who developed refractory anemia with ring sideroblasts

Ryan A. Denu^{1,2}, Rodolfo Henrich Lobo³, and Ryan J. Mattison^{2,4}

¹Medical Scientist Training Program, University of Wisconsin-Madison, School of Medicine and Public Health, Madison, WI, USA

²Department of Medicine, Division of Hematology/Oncology, University of Wisconsin, Madison, WI, USA

³Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, WI, USA

⁴University of Wisconsin Carbone Cancer Center, University of Wisconsin, Madison, WI, USA

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Acute promyelocytic leukemia (APL) is a type of acute myeloid leukemia (AML) characterized by the t(15;17) translocation affecting the PML and RAR α genes on chromosomes 15 and 17, respectively [1]. Differentiation syndrome, previously known as retinoic acid syndrome, is a life-threatening cytokine release syndrome that occurs in about 20% of patients (reported literature suggests a range from 2–27%) with acute promyelocytic leukemia (APL) treated with all-trans retinoic acid (ATRA) or arsenic trioxide (ATO) [2–4]. The syndrome typically occurs during induction, but can also occur in relapsed or refractory APL that is treated with these agents. Patients can experience dyspnea, hypotension, fever, weight gain, peripheral edema, acute renal failure, and pleuropericardial effusion due to the release of inflammatory cytokines. An increased incidence of differentiation syndrome has been reported in patients with an elevated white blood cell (WBC) count at diagnosis, a rapidly increasing WBC count, expression of CD13 on APL blasts, higher age, or an elevated body mass index (BMI) [4–7]. Additionally, WBC count over 5000/uL and abnormal serum creatinine have been correlated with severe differentiation syndrome [4]. Severe differentiation syndrome is characterized by the presence of 5 of the 7 signs and symptoms initially presented by Frankel et al., and these patients have worse survival [3,4]. Differentiation syndrome is typically treated with corticosteroids after symptoms appear [3]. Early addition of chemotherapy to ATRA can also reduce differentiation syndrome-related mortality [4,8], albeit not without adverse effects. These two interventions have the potential to reduce mortality from differentiation syndrome to less than 1% [2]. However, patients with differentiation syndrome have an increased risk of relapse that is independent of WBC count [2,4,8].

Treatment-related myeloid neoplasms have been well-reported following chemotherapy for solid tumors and lymphomas,[9] but not as much for acute myeloid leukemia (AML) or APL specifically. Reports suggest that approximately 1–7% of APL patients treated with chemotherapy later developed MDS or AML [10–12]. Here we report an interesting case of an elderly patient with APL who developed differentiation syndrome, tolerated anthracycline treatment, but subsequently developed refractory anemia with ring sideroblasts.

A 79 year old gentleman with past history of hypertension, gastroesophageal reflux disease, and osteoarthritis presented to his primary care physician with petechial rash and increased bruising over arms and legs for the previous two weeks. Complete blood count (CBC) revealed thrombocytopenia, and he was then directly admitted to an outside hospital. He experienced increased exertion-related dyspnea and chest pain. Electrocardiogram demonstrated ST depressions, and he was diagnosed with non-ST elevation myocardial infarction.

He was subsequently transferred to our institution for evaluation of possible hematologic malignancy. CBC revealed a white cell count of 17,800/ μ L, platelet count of 4000/ μ L, and hemoglobin of 8.9 g/dL. Peripheral blood smear showed 21% promyelocytes, reverse transcriptase polymerase chain reaction was positive for the PML-RAR α fusion gene, and bone marrow biopsy demonstrated 95% cellularity with 68% CD45 dim blasts, all contributing to the diagnosis of APL. Given that his WBC count was over 10,000/ μ L, his APL was high risk. Nevertheless, he was started on ATRA and ATO to spare toxicity from anthracycline, as there is a higher incidence of early deaths during or shortly after induction chemotherapy in older APL patients [13]. He was also treated with allopurinol 300mg QD and hydroxyurea 1g TID to prevent tumor lysis syndrome, and he received several transfusions.

The patient's respiratory distress worsened on hospital day 4. Chest X ray demonstrated diffuse, fine, bilateral alveolar opacities, consistent with acute lung injury. The differential diagnosis included differentiation syndrome, diffuse alveolar hemorrhage, transfusion-associated cardiac overload, and transfusion associated lung injury. Given his recent treatment with ATRA, we thought differentiation syndrome was most likely, and therefore treated him with dexamethasone 10mg BID. Originally his significant oxygen requirement was thought to be due to pulmonary edema, and he was cautiously diuresed with IV furosemide. He was then transferred to the ICU and intubated on hospital day 5 due to worsening respiratory failure. He was treated with idarubicin on hospital day 5, given on alternate days for a total of 3 doses (12mg/m² x 2.31 m² per dose), with the goal of reducing his leukocytosis and improving the pulmonary sequelae of differentiation syndrome.

The patient's respiratory distress improved and he was extubated on hospital day 9. ATRA was restarted on day 14. His dexamethasone dose was tapered and finally stopped on day 28. We waited for his blood counts to recover, and he was subsequently discharged on day 41. The patient returned to clinic for follow up 3 weeks later. Bone marrow biopsy performed 63 days after induction demonstrated morphologic remission with no abnormal promyelocytes and no elevation in blasts. We then began consolidation therapy with ATRA and ATO, as per the Italian regimen [14]; that is, 4 weeks on and 4 weeks off ATO, 2 weeks on and 2 off with

concomitant ATRA. The patient underwent a total of seven 4-week long cycles. Following consolidation therapy, the patient showed a complete molecular remission (i.e. no PML-RAR α detected by PCR).

Approximately 5 months after completion of consolidation therapy, the patient developed transfusion-dependent anemia, and a bone marrow biopsy showed refractory anemia with ring sideroblasts (RARS) present (Figure 2). The bone marrow biopsy revealed about 15% of erythroid cells as ring sideroblasts and 70% cellularity, which is hypercellular for his age. He completed 3 monthly cycles of azacitidine, and has required a total of approximately 20 blood transfusions; therefore, we are monitoring iron labs (ferritin has been elevated) and using deferoxamine to prevent iron overload. After his third cycle of azacitidine, he was hospitalized for shortness of breath and cough. Chest CT demonstrated diffuse bilateral military nodules with diffuse pulmonary fibrosis, but his cultures have been negative. We have continued to treat him with voriconazole and acyclovir. His symptoms are most consistent with eosinophilic pneumonitis, so we have held further treatment with azacitidine at this time. He receives RBC transfusions approximately every 2 weeks for his refractory anemia (transfusion threshold of 8 g/dL hemoglobin) and platelets (transfusion threshold of 10,000/ μ L). A follow-up bone marrow after azacitidine treatment revealed 5% blasts and near red cell aplasia, consistent with refractory anemia with excess blasts-1 (RAEB-1; Figure 1), as well as 1/20 cells positive for t(15;17) by FISH. However, peripheral blood fluorescent in-situ hybridization (FISH) studies did not show a significant burden of APL. He was started on ATRA therapy with prednisone for differentiation syndrome prophylaxis with the goal of improving his blood counts and ameliorating his transfusion burden.

This case brings up an interesting issue about whether his MDS was related to anthracycline treatment versus an underlying predisposition given his APL diagnosis. Anthracycline use is associated with MDS, but studies are typically unable to conclude causality due to the use of concomitant chemotherapeutic drugs as well the presence of confounding factors that can lead to malignancy. It seems rather unlikely that his MDS is due to anthracycline treatment for two reasons: (1) he was only given three doses of idarubicin for a cumulative dose of 36 mg/m², and (2) his MDS developed approximately one year after treatment. In addition, t-MDS related to anthracycline use often shows involvement with the mixed-lineage leukemia (*MLL*) gene located on chromosome 11q23, and our patient's cytogenetic studies were normal. The interval between initial chemotherapy treatment and development of therapy-related MDS is thought to be about 2–3 years for topoisomerase II inhibitors (e.g. anthracyclines) [15], and one study reports a median time from complete remission to MDS in APL patients to be 44 months [12]. In APL, older age, lower relapse risk score, and higher platelet count were associated with greater likelihood of developing therapy-related MDS [12]. An alternative explanation is that our patient's MDS was associated with his APL diagnosis. There is a potentially undiscovered genetic explanation for this association.

Among elderly patients treated for APL, differentiation syndrome and sepsis are the most frequent causes of death [13]. Given the higher likelihood of differentiation syndrome in elderly APL patients, particularly those with high-risk disease, we recommend that all APL patients be treated with corticosteroids during induction. This is consistent with the Italian regimen, which used corticosteroids from day 1 until the end of induction [14]. However,

our patient was treated before this manuscript was published, and their study was done on low and intermediate risk patients under age 71. The use of corticosteroids to treat differentiation syndrome is well accepted, but their prophylactic use has been more controversial. Prophylaxis with prednisone has been shown to reduce the incidence of severe differentiation syndrome but to have no impact on differentiation syndrome-related mortality [4].

In summary, we report the association of a case of APL patient with differentiation syndrome who developed MDS secondary to anthracycline therapy. This case is remarkable in that a 79-year-old with high risk APL tolerated induction with an anthracycline and did not succumb to his differentiation syndrome, which is a common cause of death in elderly APL patients. Early recognition and aggressive treatment is imperative for differentiation syndrome, and corticosteroids should be used as prophylaxis during induction with ATRA in elderly APL patients. Furthermore, patients treated with an anthracycline for induction need to be carefully monitored for MDS. Lastly, this case suggests additional research is needed on the link between differentiation syndrome and development of MDS.

Abbreviations

AML	acute myeloid leukemia
APL	acute promyelocytic leukemia
ATO	arsenic trioxide
ATRA	all trans retinoic acid
BMI	body mass index
FISH	fluorescence in situ hybridization
MDS	myelodysplastic syndrome
RAEB-1	refractory anemia with excess blasts-1
t-MDS	therapy-related myelodysplastic syndrome
WBC	white blood cell

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Figure 1. Diagnosis of RAEB-1 MDS

After presentation with anemia, workup revealed a cellular marrow showing trilineage hematopoiesis with mild dyspoiesis (A), and iron stain showing numerous ring sideroblasts (B). After azacitidine treatment, peripheral blood smear showed many neutrophils with the pseudo Pelger-Huet anomaly present as well as few immature granulocytes (C). The marrow was cellular with marked dysgranulopoiesis and increased blasts. There is a near absence of erythroid precursors (D).