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CASE REPORT

Where time is of the essence: A case of acute promyelocytic leukemia and review of the literature

Jinendra Satiya[1], Nadir Bhuiyan[2]. Venkat Kalidindi[3]

[1]*Division of Internal Medicine, University of Miami/JFK Medical Center Palm Beach Regional GME Consortium, Atlantis, Florida, United States*

ABSTRACT

Acute promyelocytic leukemia (APL) represents a medical emergency with a high rate of early mortality. It has a high predilection for disseminated intravascular coagulation and in the absence of treatment, can be rapidly fatal. Without treatment, the median survival is less than 1 month. The coagulopathy in APL is complex and can be attributed to a combination of thrombocytopenia, disseminated intravascular coagulation and hyperfibrinolysis. White blood cell count at presentation is an important predictor of early hemorrhagic death. With the discovery of all-trans retinoic acid and arsenic trioxide, acute promyelocytic leukemia has transformed from a devastating disease into one of the most curable malignancies. Patients should be monitored for the development of differentiation syndrome, seen in 25 % of patients within 2-21 days of initiation of treatment. Early death is still a key issue, particularly in the elderly population, reiterating the importance of rapid diagnosis and treatment. We report the case of a 48 year-old-male diagnosed with the microgranular variant of acute promyelocytic leukemia M3 subtype and treated with all-trans retinoic acid and arsenic trioxide who achieved complete hematological remission.

Key words: acute promyelocytic leukemia, microgranular variant, fluorescence in situ hybridization, all-trans retinoic acid, arsenic trioxide

INTRODUCTION

Acute promyelocytic leukemia (APL) is a rare form of leukemia characterized by the balanced reciprocal translocation between the promyelocytic leukemia gene on chromosome 15 and the retinoic acid receptor α (RARα) gene on chromosome 17. It accounts for 10-15% of newly diagnosed acute myeloid leukemias each year.[1,2] Potentially fatal coagulopathy, and distinct morphologic and cytogenetic abnormalities characterize APL as a unique subtype of AML. Combination treatment with all-trans retinoic acid receptor α (ATRA) and arsenic trioxide (ATO) has remarkably improved the survival rates in these patients. Early death (mortality in the first 30 days after initiation of therapy) continues to be the foremost cause of treatment failure.[3] Our case reiterates the importance of initiating treatment for APL even if the diagnosis is suspected but not yet confirmed. When the typical bilobed cells are seen on a peripheral blood smear, a fluorescence in situ hybridization (FISH) should immediately be ordered to confirm the diagnosis and empiric treatment started in the interim.

Correspondence:
Jinendra Satiya, MD
Division of Internal Medicine,
University of Miami, JFK Medical Center Palm Beach Regional GME Consortium
5301 Congress Avenue, Atlantis, FL 33462
E-mail: jls430@med.miami.edu
Tel: 954-248-8503

CASE REPORT

We present the case of a 48-year-old male with no past medical history who presented with nose bleeds and gingival bleeding for the past two weeks. He was hemodynamically stable at presentation. Physical examination was significant for petechiae on the hands and legs. His white blood cell count was 2300 cells per cubic millimeter, hemoglobin was 7.5gms/dl and platelets were 4000 per microliter. Peripheral smear showed the presence of promyelocytes, blast cells and Auer rods. HIV and hepatitis serologies were negative. On day two of hospitalization, he was started on all-trans retinoic acid (ATRA) based on the presence of typical bilobed cells on the peripheral blood smear at a dose of 45 mg/m2 PO per day in two divided doses. Fluorescence in situ hybridization (FISH) was positive for the PML/RARA (retinoic acid receptor alpha gene) fusion gene. Flow cytometry revealed atypical promyelocytes positive for cluster of differentiation (CD) 13 (38.1%) and CD33 (88.5%) and negative for CD5, CD10, CD14, CD19,

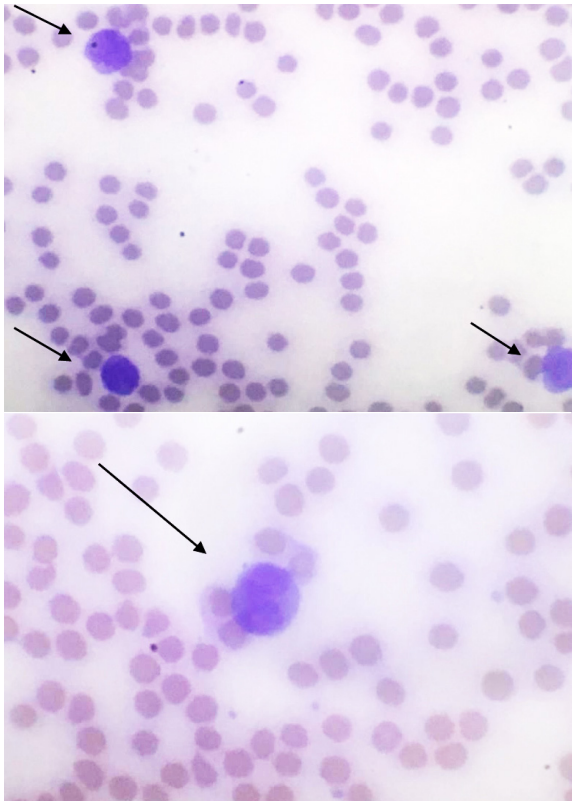

Figure 1, Peripheral blood smear, demonstrating bilobed nucleus with scant neoplasm and no recognizable granules.

CD22, CD34 and human leukocyte antigen (HLA)-DR. D-dimer was high at 650 ng/ml and fibrinogen was low at 90 mg/dl were within normal ranges. Prothrombin time and partial thromboplastin time were within normal ranges. Bone marrow aspiration subsequently performed demonstrated hypocellularity with 30.3% atypical promyelocytes. The patient was diagnosed with the microgranular variant of APL M3. A CT scan of the brain was done prior to starting treatment with ATRA to rule out an intracranial bleed. The patient was transfused with two units of packed red blood cells and six units of platelets through the course of his hospitalization.He was monitored with a complete blood count and dissseminated intravascular coagulation panel daily. His WBC improved to 5200 cells per cubic millimeter, platelets increased to 90,000 per microliter and hemoglobin rose to 11 g/dl. He achieved hematological remission and was subsequently started on arsenic trioxide (ATO) at 0.15 mg/kg/day for 28 days. QT interval was monitored throughout treatment with arsenic trioxide which remained constant at 380 msec. He received consolidation therapy with ATO for two 25-day cycles at 0.15 mg/kg IV per day for five days each week for five weeks each, followed by ATRA (45 mg/m^2 per day orally days 1 through 7. The patient remained stable and was doing well at a six month follow-up with a WBC of 6000 cells per cubic millimeter, platelets of 110,000 per microliter and a hemoglobin of 12 g/dl. He was placed on maintenance therapy with ATRA at 45 mg/m^2 orally for seven days repeated every other week for one year.

DISCUSSION

Acute promyelocytic leukemia represents a medical emergency with a high rate of early mortality, mostly due to hemorrhage. Although not a rapidly-proliferative type of leukemia, by the time patients present with symptoms, the situation is often a life-threatening emergency. It is strongly recommended that treatment is started with a differentiation agent such as ATRA without delay when the diagnosis is suspected. A repeat bone marrow biopsy is performed at 30- 35 days to assess remission. Those that achieve a complete hematological remission can proceed to consolidation therapy with arsenic trioxide (ATO). APL M3 subtype has a high predilection for the development of disseminated intravascular coagulation (DIC). It is recommended that platelets be maintained between 20,000-30,000 per microliter and fibrinogen above 150 mg/dl with transfusion of cryoprecipitate and fresh frozen plasma as required.Patients less than 30 years of age and those who present with a white blood cell count less than 10,000 per microliter have better survival.Risk factors associated with a poor prognosis at diagnosis include a white blood cell count greater than 10,000 per microliter and a platelet count less than 40,000 per microliter. Prognostically our patient was at intermediate risk with a WBC less than 10,000 and a platelet count less than 4000 at presentation.

Survival rates have approached higher than 90% with the discovery of ATRA and ATO-based induction and consolidation regimens.[4] ATRA in combination with arsenic trioxide has proven to be not inferior and may be superior to ATRA plus chemotherapy in the treatment of patients with low-to-intermediate-risk APL. It is also associated with less hematologic toxicity and fewer infections compared to ATRA-chemotherapy which is associated with a higher incidence of cytopenias, mucositis and infections.[5]

The treatment of APL is unique compared to other types of. Treatment phases can be divided into remission induction, consolidation and maintenance. Induction therapy aims to reduce the total body leukemia cell population to below the cytologically detectable level of about 109 cells. ATRA, which promotes the terminal differentiation of malignant promyelocytes to mature neutrophils is key to the induction phase. It must be combined with other agents since remissions induced by ATRA therapy alone are short-lived with a median duration of only about 3.5 months.[6]

ATRA plus ATO is recommended for newly diagnosed APL with low- or intermediate-risk (ie, those with initial WBC count ≤10,000/microL). It is also the preferred therapy for patients, such as older adults, unable to tolerate anthracycline-based therapy. ATO plus ATRA is administered until marrow remission, but should not exceed 60 days. ATRA should be continued until CR is achieved. For chemotherapy-based induction, daily ATRA (45 mg/m^2/day orally divided into two doses), starting on day 0, followed by seven days of cytarabine by continuous infusion (200 mg/

m^2 per day) and four days of daunorubicin (50 mg/m^2 per day), both starting on day 3, can be used.

The goal of remission induction treatment is morphological complete remission (CR) with recovery of normal hematopoiesis. Patients who achieve hematologic CR with induction therapy proceed directly to consolidation therapy. Patients who achieve a partial response after the initial course may achieve a CR after additional therapy. Approximately 90 percent of patients will achieve hematological CR with induction therapy. However, without additional therapy, most of these patients will relapse.

For patients with APL who achieve a CR with ATO plus ATRA, consolidation therapy should include ATO. Maintenance therapy: Single agent ATRA – ATRA 45 mg/m2 orally for seven days repeated every other week for one year. Combination maintenance therapy – ATRA 45 mg/m^2 orally daily on an intermittent schedule (eg, 15 days every three months or seven days every two weeks) plus 6-mercaptopurine (MP) 60 mg/m^2 orally every evening plus methotrexate 20 mg/m^2 orally per week as tolerated.

Pregnant patients who suffer from APL in the first trimester are required to decide whether they would like to electively terminate the pregnancy as this will allow the use of standard ATRA-chemotherapy or ATRA-ATO-based therapy which would otherwise be contraindicated. Should the patient elect to continue the pregnancy, then ATRA is excluded in the first trimester because of the risk of fetal malformations. ATO cannot be used in pregnant patients due to its embryotoxicity. Daunorubicin which has a lower chance of crossing the placenta, can be employed.

Patients should be monitored for the development of differentiation syndrome, seen in 25 % of APL patients within 2- 21 days of initiation of treatment. It is characterised by fever, peripheral edema, pulmonary infiltrates, hypotension, renal and hepatic dysfunction and treated with intravenous dexamethasone. Monitoring for QT prolongation and liver enzymes is essential with arsenic trioxide use. Electrolytes should be repleted to maintain potassium >2 mEq/l and magnesium >1.8 mg/dl.

Patients with APL M3 often tend to do better when monitored in the intensive care unit.[7] Without treatment, the median survival is less than 1 month. Current obstacles in APL managementinclude prompt identification and treatment of newly diagnosed cases to reduce the early mortality and to optimize treatment strategies in high-risk patients such as those with a white blood cell count greater than 10,000 per microliter.

CONCLUSION

Acute promyelocytic leukemia (APL), must be quickly recognized and promptly treated. APL represents a medical emergency and it is imperative that treatment be initiated as soon as the diagnosis is suspected, even before genetic confirmation of the diagnosis has been made. Disseminated intravascular coagulation is the defining clinical clue to this subtype of AML characterized by t(15;17). All-trans retinoic acid (ATRA) is the backbone of specific therapy. ATRA and ATO-based induction and consolidation regimens provide patients with a chemotherapy-free regimen with superior efficacy and fewer side-effects.

CONFLICT OF INTEREST

None.

REFERENCES

1. Tallman MS, Altman JK How I treat acute promyelocytic leukemia Blood. 2009 Dec 10; 114(25):5126-35.

2. Chen C, Huang X, Wang K, Chen K, Gao D, Qian S. Early mortality in acute promyelocytic leukemia: Potential predictors. Oncology Letters. 2018;15(4):4061-4069.

3. Tallman MS, Andersen JW, Schiffer CA, et al. All-trans retinoic acid in acute promyelocytic leukemia: Long-term outcome and prognostic factor analysis from the North American Intergroup protocol. Blood. 2002;100:4298–4302.

4. Watts JM, Tallman MS Acute promyelocytic leukemia: what is the new standard of care?Blood Rev. 2014 Sep;28(5):205- 12

5. Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med. 2013 Jul 11;369(2):111-21.

6. Wang ZY, Chen Z. Differentiation and apoptosis induction therapy in acute promyelocytic leukaemia. Lancet Oncol 2000; 1:101.

7. Etienne Lengliné, Emmanuel Raffoux, Virginie Lemiale, et al. Intensive care unit management of patients with newly diagnosed acute myeloid leukemia with no organ failure Leukemia & Lymphoma Vol. 53 ,Iss. 7,2012;13529.