

## Case Report

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# Acute Promyelocytic Leukaemia with Differentiation Syndrome Treated Successfully with ATRA-ATO Therapy: A Case Study

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### Abstract

*Acute promyelocytic leukemia (APML) is the first malignant disease highly curable with targeted therapy directed at a unique molecular abnormality. The characteristic bleeding diathesis due to the combined effect of thrombocytopenia and disseminated intravascular coagulation is the most notorious manifestation of the disease, which historically has accepted for high mortality rate during induction. Acute promyelocytic leukemia is one of the few hematologic diseases that can be diagnosed with certainty by morphological examination of blood film and bone marrow aspirate by the practicing hematologist. Such step facilitates early institution of all-trans retinoic acid (ATRA) before molecular confirmation of the diagnosis. Therefore, ATRA therapy as well as aggressive blood product support is critical to reduce early mortality. Early diagnosis and prompt institution of appropriate therapy is essential as APML is a medical emergency and without rapid management patient may succumb due to bleeding diathesis. Also the prognosis of APML is much better than other subtypes of acute myeloid leukemia. ATRA plus anthracycline based chemotherapy for induction and consolidation followed by maintenance ATRA with low dose chemotherapy is currently the standard of care. However the combination of ATRA and arsenic trioxide (ATO), with minimal chemotherapy to control leukocytosis, is very effective therapy for newly diagnosed APML patients. The combination may replace conventional approaches to most, if not all, patients in the very near future. Here we report a case of APML of female who got admitted with fever, cough and pupuric rash throughout the whole body.*

**Key Words:** All-trans retinoic acid (ATRA), Arsenic-trioxide (ATO), Acute promyelocytic leukaemia (APML), Differentiation syndrome (DS), Promyelocytic leukaemia-retinoic acid receptor alpha gene (PML-RARA gene).

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### Introduction

Acute promyelocytic leukaemia (APML) is a subtype of acute myeloid leukaemia (AML) with specific clinical

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and biological features. The genetic hallmark of the disease is the balanced reciprocal translocation of (15:17) (q<sup>22</sup>:q<sup>11</sup>), leading to the fusion of promyelocyte (PML) gene with the retinoic acid receptor alpha (RARA) gene. The resulting PML-RARA hybrid oncoprotein is responsible for the block of differentiation of leukaemic promyelocytes and is able to induce Leukaemia.<sup>1,2</sup>

Interesting, biologic studies that were carried out after the empirical use of all- transretinoic acid (ATRA) and arsenic trioxide (ATO) showed that either RARA and PML moieties of the hybrid contain binding sites for these agents and that both ATRA and ATO were able to induce disease remission through degradation of oncoprotein, thus acting as complementary targeted agents.<sup>3</sup>

APML is a rare disease, accounting for 5%-10% of AML of the adult, with an estimated incidence of 0.1/100000 in western countries.<sup>4</sup> The disease presentation is frequently accompanied by a consumptive coagulopathy that can cause life threatening haemorrhages (most severe one occurring in brain and lungs) and more rarely thrombosis. A rapid diagnosis of APML and the initiation of adequate anti leukaemic and supportive therapy are of paramount importance to prevent early death, which is correctly considered the most important obstacle to the final cure of this disease. With the introduction of differentiation therapy with ATRA combined with conventional chemotherapy and the subsequent advent of ATO, APML has been transformed from the most rapidly fatal to the most frequently curable form of acute leukemia with long time survival rates up to 90%.<sup>5</sup>

### Case Report

A 36 years old lady got admitted in CMH Dhaka with the complaints of fever and cough for 1 month, chest pain for 7 days and weakness in left side of body for 2 day. On examination, she was found anaemic, having purpuric rash in buccal mucosa and petechiae all over the body. Bony tenderness and swelling of left lower limb were also present. There was no lymphadenopathy, hepatosplenomegaly or gum hypertrophy.

Investigations revealed CBC: Hb:9.6 gm/dl, TLC: 38.49X10<sup>9</sup> /L, N=10%, L=10%, Blasts=80%, Platelet count:21 X10<sup>9</sup>/L, Serum LDH:436 U/L, Plasma fibrinogen : 243mg/dl, Plasma FDP and D-Dimer: Negative. Prothrombin time (PT): 18 sec (control 13 sec), Activated Partial thromboplastin time (APTT): 33sec (control 31 sec), Serum creatinine :1.0 mg/dl, Serum Liver function tests were normal. Bone marrow aspiration was suggestive of Acute myeloblastic leukaemia AML-M3 (>60% Promyelocytes). Bone marrow sample which was sent overseas for quantitative assay of PML RARA and received result was reported as PML/RARA;t(15:17)(q<sup>24</sup>;q<sup>21</sup>):35.4%. So correlating the history, clinical finding and investigation results, the patient was diagnosed as a case of APML (PML-RARA positive).

Treatment was started immediately with conventional ATRA and ATO protocol, blood transfusion support and other supportive management. On 3<sup>rd</sup> day of ATRA and ATO protocol, the patient developed respiratory distress, haemoptysis and passage of black stool and at the same

time swelling of her left lower limb also increased. On examination, there was multiple bruise and echymosis over both forearm and right lower limb. There was dull percussion note, diminished breath sound, reduced vocal resonance in right lower zone of lung with bilateral basal crepitations.

Investigations revealed HB: 10.2gm/dl, TLC: 40.0X10<sup>9</sup>/L, Platelet count: 32.0 X10<sup>9</sup>/L, serum bilirubin : 1.5 gm/dl, plasma fibrinogen :270 mg/dl, D-dimer: Negative, Prothrombin time(PT):18 sec (control 13 sec) and Activated partial thromboplastin time(APTT): 31 sec (control 35 sec). Doppler study of lower limb showed normal limb Vessels. The patient was diagnosed as APML with differentiation syndrome and pleural effusion (right); Inj Dexamethasone along with other supportive measures were started as ATRA syndrome developed and cap ATRA was discontinued. Subsequently the condition of the patient was improved clinically and she received Inj ATO for 45 days. Later on, the patient received inj ATO for 28 day as consolidation protocol.

After consolidation chemotherapy with ATO, her bone marrow sample was examined morphologically and by molecular studies. Bone marrow was in morphological remission (blasts 3%) and hybrid transcript of PML-RARA gene was not detected (Quantitative assay of PML-RARA (t15:17) was 0%).Afterwards, the patient was planned for maintenance chemotherapy with Inj ATO; She completed 6 cycle of Inj ATO as maintenance therapy . Now the patient is stable and asymptomatic and she can perform all routine daily activities. On physical examination, there was no abnormality. All haematological and biochemical parameters were found normal.

### Discussion

APML was first described as an entity in the late 1950s in Norway and France as a hyperacute fatal illness associated with haemorrhagic syndrome.<sup>6</sup> In 1974 Dr Zhen Yi Wang, a chinese haematologist, shared data on the efficacy of ATRA in APML patients. In the early to mid 1990s, ATO was added to the treatment regimen. Over the last 50 years, APML has been transformed from a highly fatal disease to a highly curable one.<sup>7</sup>

APML can be diagnosed in patients of all ages, but median age is typically lower compared with other AML subsets (i.e ~ 40, versus 70 in other AML). A

consumptive coagulopathy is present at diagnosis in 80% of patients and consists of hypofibrinogenemia, thrombocytopenia, prolonged PT, APTT and positive D-dimer.<sup>8</sup> The disseminated intravascular coagulation (DIC) is usually present at diagnosis or is precipitated shortly after chemotherapy is started and is caused by procoagulant activity of the leukaemic promyelocytes, particularly its granular fraction. Because of DIC, thrombocytopenia is disproportionately severe in relation to the degree of bone marrow infiltration. Clinically, APML may manifest in a variety of signs from mild muco-cutaneous haemorrhages (petechiae, echymoses, bruising, gum bleeding, epistaxis etc) to severe internal intracranial or pulmonary bleeding. Less frequently, signs and symptoms related to thrombosis are the initial manifestations of the disease.<sup>9</sup> Due to frequent abrupt onset and the risk of severe haemorrhagic events, immediate institution of ATRA and/or ATO treatment and supportive therapy are critical for the correct management of APML and especially to avoid fatal outcomes.<sup>10</sup> Current recommendations strongly suggest that these measures are started upon clinical suspicion of APL, without the need for waiting for genetic confirmation for correct diagnosis.<sup>11</sup> The suspicion of APL generally arises from morphologic examination of the bone marrow, showing the characteristic infiltrate of abnormal hypergranular promyelocytes.

Flow cytometry shows a distinctive pattern of antigen expression including strong positivity for CD33, expression of CD13 and CD 117, infrequent expression of HLADR and CD 34, lack of CD 11a, CD11b and CD14. Although not conclusive for APML diagnosis, the antigenic profile may help in generating alert on a possible diagnosis of APML.<sup>12</sup> The sole morphologic suspicion of APL should always be followed by immediate institution of ATRA and/or ATO therapy and lead to aggressive replacement of platelets, fresh frozen plasma and cryoprecipitate to counteract the ongoing coagulopathy without waiting for genetic confirmation.

A pilot study with combined ATRA and ATO was conducted by Estey et al<sup>13</sup> at the MD Anderson Cancer Centre (MDACC). ATO and ATRA therapy was given concomitantly during induction therapy, followed by four consolidation cycles with intermittent ATO and ATRA, then 6 maintenance cycles with ATO. Overall

complete remission (CR) was 89% (96% in low risk and 79% in high risk patients). With the median follow up of 34 months for eligible patients, this combination therapy was superior in term of EFS or OS to the standard AIDA chemotherapy (2 year EFS :97% versus 86% , p=0.02; 2 year OS :99% versus 91%, p=0.02) and was associated with significantly less myelosuppression and infections.

Another two prospective non-randomized trials using a chemotherapy- free approach were conducted in India and Iran after ATO was administered as a single agent for both induction and consolidation therapy.<sup>14,15</sup> The Indian study reported, at a median follow up of 25 months, 3 year EFS, DFS and OS of 74.8%, 87.2% and 86% respectively.<sup>14</sup> Similar results were reported by investigators from Iran with 2 year DFS and 3 year OS of 63.7% and 87.6% respectively.<sup>15</sup> Both studies showed significantly better outcome for patients with low risk disease. In summary, the results of the two non-randomized studies strongly support ATRA-ATO as the new standard of care at least in low-risk patients with APL. Mathews et al reported that patients who presented with a WBC count less than 5,000/ $\mu$ l and platelet count greater than 20,000/ $\mu$ l, treated with single agent ATO had a survival at 5 years of 100% without a single patients relapsing.<sup>16</sup>

In the study by Rannani et al, the differentiation syndrome developed in 2 of 17 (12%) patients treated with concurrent ATRA and/or ATO.<sup>17</sup> Differentiation syndrome (DS) is a relatively common and potentially life-threatening complication that can occur during the first few days or weeks after the start of ATRA and/or ATO. The complex of clinical signs and symptoms of this complication includes dyspnoea, interstitial pulmonary infiltrate, unexplained fever, weight gain >5 kg, pleuro-pericardial effusion, hypotension, acute renal failure and peripheral oedema.<sup>18</sup> For the treatment of overt or suspected DS, expert panels recommend the prompt use of intravenous dexamethasone 10 mg BD until resolution of signs and symptoms.<sup>19</sup> ATRA and/or ATO treatment should be discontinued only in case of severe DS.

## Conclusion

Early death before treatment or during the initial days of therapy remains the main obstacle to the final cure of APML. The combination of ATRA and ATO with

minimal chemotherapy to control leucocytosis ; is very effective therapy for newly diagnosed APML patients. This combination may replace conventional approaches for most, if not all, patients in the very near future.

**Conflict of interest:** Nothing to declare.

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