

Long-term Remission of Extramedullary Relapse From Acute Promyelocytic Leukemia After Treatment With Arsenic Trioxide, Intrathecal Chemotherapy, and Brain Irradiation

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Acute promyelocytic leukemia (APL) represents approximately 10–15% of acute myeloid leukemias (AMLs) in adults. It occurs in a younger population compared to other AML subtypes (40 years old vs 70 years old). Unlike with the other AML subtypes, there is no apparent increase of incidence with age.¹ The cure rate with conventional chemotherapy and all-*trans*-retinoic acid (ATRA) therapy is high.² However, marrow and extramedullary relapses do occur and may necessitate unique therapeutic approaches depending on the location, clinical presentation, and timing of relapse.² In this report we describe the clinical details of a patient who presented with relapse in the central nervous system (CNS) and was treated successfully with a combination of systemic therapy with arsenic trioxide (Trisenox, Cephalon) and intrathecal chemotherapy, along with irradiation of the brain.

Case Report

A 35-year-old white man with no significant past medical history presented to the urgent care center with new onset of malaise and low-grade fever. Prior to this presentation, he was feeling well and was physically active. He had played basketball and tennis and exercised on a regular basis until 2–3 weeks earlier, when he noticed significant fatigue. These symptoms grew progressively worse to the point where the patient was no longer able to do his normal physical activities. Upon further questioning, the patient stated that he had a 25-pound weight loss, which he attributed to intentional weight loss. He also admitted to having intermittent gingival bleeding. The patient denied any fevers, chills, night sweats, nausea, or vomiting prior to presentation. The patient also denied any chest pain, shortness of breath, or gastrointestinal/genitourinary problems. Upon presentation, a complete blood count

was done, which showed pancytopenia. A bone marrow aspiration and biopsy showed hypercellular marrow with hypergranular promyelocytes consistent with APL. Cytogenetic studies showed a t(15;17) translocation (Figure 1A), confirming the diagnosis of APL-M3.

Following detailed discussion with the patient and his family regarding various treatment options, he was started on ATRA, along with daunorubicin begun on day 7. The patient tolerated his treatment well and his trilineage cytopenia improved. A repeat bone marrow biopsy 2 months after chemotherapy plus ATRA showed no evidence of abnormal promyelocytic cells. A subsequent bone marrow biopsy 4 months after initiation of treatment showed normal M:E ratio. The myeloid series revealed full maturation to segmented forms. Erythroid maturation was essentially normoblastic. Megakaryocytes were present and appeared normal.

One month later, the patient presented to his primary care physician with right ear discomfort. On examination the patient was found to have a greenish mass within the right external canal, with significantly decreased hearing localized to the same side. The rest of the exam was unremarkable. Computed tomography (CT) of the temporal bone was performed and revealed a 13 × 8 mm lobular soft tissue mass involving the medial aspect of the right external ear canal extending to the level of the tympanic membrane. The middle and inner ear were normal. Biopsy of the mass was consistent with granulocytic sarcoma (chloroma). Cerebrospinal fluid was significant for 13 white blood cells (WBCs) with 87% blasts. Bone marrow analysis was consistent with relapsed APL. The patient was then treated with whole-brain radiation, intrathecal chemotherapy consisting of hydrocortisone/cytarabine and methotrexate, and systemic therapy consisting of arsenic trioxide for reinduction and consolidation. The patient responded well to therapy and regained full hearing capability in the impaired ear. The patient achieved complete remission (CR) and subsequently received three more cycles of consolidation therapy with arsenic trioxide,

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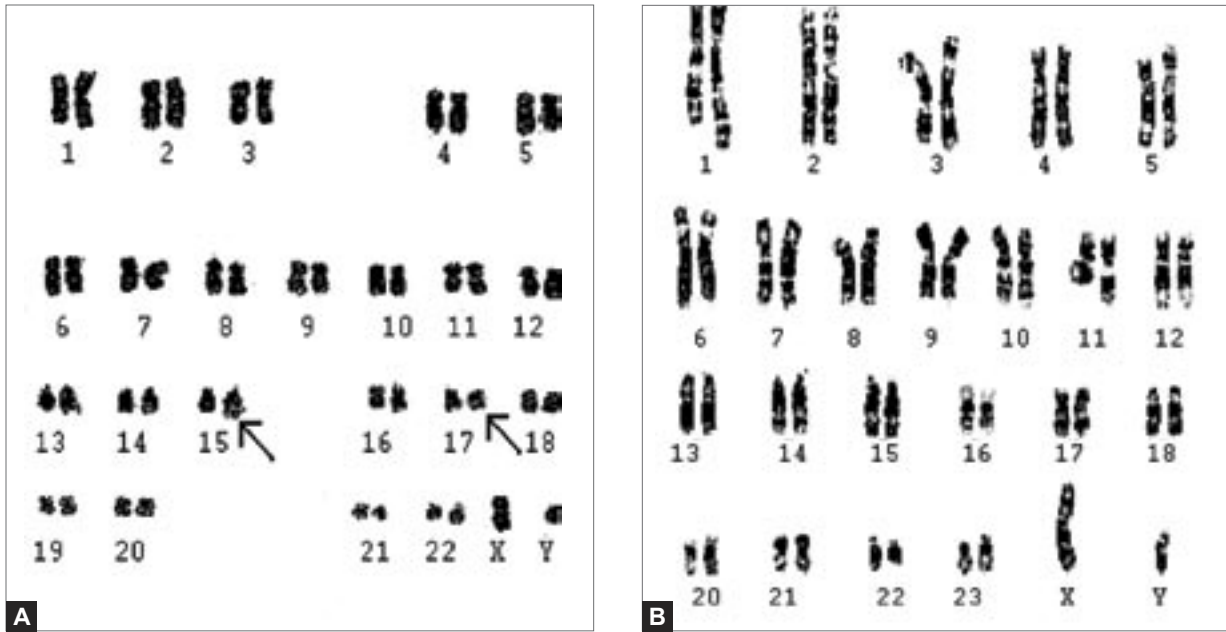


Figure 1. A) Karyotype analysis: 46 XY, t(15;17)(q22;q21) Patient's initial presentation; B) 46 XY After treatment with arsenic trioxide and intrathecal chemotherapy.

followed by maintenance therapy using ATRA, methotrexate, and 6-mercaptopurine.

The patient's last bone marrow biopsy was done in June 2004 after completing maintenance therapy and showed a normocellular marrow with adequate megakaryocytes and erythrocytes and normal-looking promyelocytes consistent with remission. Fluorescence in situ hybridization studies were performed, which showed no promyelocytic-retinoic acid receptor (*PML-RAR α*) fusion complex in 98.4% of the 492 interphase nuclei that were analyzed. Karyotype analysis (Figure 1B) was negative for any abnormalities. The patient is currently doing well.

Discussion

Molecular genetics and pathogenesis

Virtually every APL patient has a balanced reciprocal translocation, t(15;17). This translocation leads to the fusion of the *PML* gene on chromosome 15 and the *RAR α* gene on chromosome 17. The presence of the *PML-RAR α* fusion causes arrest in myeloid differentiation and propagates the clonal proliferation of immature myeloid precursor. In rare cases of APL, variant translocations have been described. Although it is difficult to distinguish them morphologically, they represent alternative fusion partners with *RAR α* , which include promyelocytic leukemia zinc finger gene (*PLZF*), nuclear mitotic apparatus (*NUMA*), nucleophosmin (*NPM*) and *STAT5b*.

Recent studies have improved our understanding of the underlying pathophysiology of APL. As a result of the

PML-RAR α fusion, an increased affinity for the nuclear repressor protein complex was observed. The formation of such a protein complex attracts histone deacetylase, which causes an alteration in the chromatin conformation and thus inhibits transcription.³ Retinoic acid functions in part by stimulating the release of the histone deacetylase from the nuclear corepressor complex. By doing so, it would lead to normal chromatin conformation, normal transcription, and thus differentiation of the cell line.

ATRA was first used in China in 1986 for the treatment of APL and it proved to be a highly effective remission induction agent. ATRA quickly gained worldwide acceptance and has become first-line treatment for APL patients. Combination treatment with ATRA and chemotherapy has dramatically improved outcome and survival in patients with APL. But despite such improvement, relapse occurs within 4–5 years in about 30% of patients on such therapy.³ Several treatment regimens have been used in the treatment of refractory or relapsed APL, consisting of cytarabine, anthracyclines, and autologous and allogeneic stem cell transplantation. Arsenic trioxide, however, has recently become the drug of choice in the treatment of relapsed or refractory APL patients.

Extramedullary Relapsed APL

Extramedullary infiltration of promyelocytic cells was rarely seen in the APL population in the pre-ATRA era.⁴ Studies by Evans and colleagues¹⁴ concluded that the mechanism by which ATRA induces differentiation of leukemic clone involves upregulation of cellular adhesion

molecules. It was further hypothesized that such upregulation of the adhesion molecules in the promyelocytes may increase cytokine release, thus increasing the expression of ligands in ICAM1 and VCAM1. (ICAM1 and VCAM1 have been demonstrated to be present on astrocytes in the blood-brain barrier.) Through this mechanism, ATRA was thought to facilitate the entry of malignant promyelocytes into the cerebrospinal fluid. A study by Wiernik and coauthors, after reviewing 23 cases of extramedullary presentation of relapsed APL, suggested that such presentations may occur more frequently with initial treatment with ATRA than other chemotherapeutic agents.⁵ Among the patients in that study, none presented with a manifestation in the auditory canal. Such cases are extremely rare (one in the English literature and several in the Japanese literature⁶). It was proposed that because arsenic deposited well in epidermal tissues,⁵ a therapeutic response of the chloroma at the site of the disease in the external auditory canal was expected in our patient.

Clinical Trials With Arsenic Trioxide in APL

Several studies were undertaken to evaluate the efficacy of arsenic trioxide treatment in relapsed patients. One such study was published in *Blood* in 2001 by Soignet and coworkers, in which 21 patients experiencing their first relapse and 19 patients who were experiencing their second relapse were treated with arsenic trioxide as induction therapy.⁷ Those who achieved CR were offered one consolidation course of arsenic trioxide after induction treatment. Further cycles of arsenic trioxide were given as maintenance therapy for those patients who continued to be in CR. Out of the 40 patients treated with arsenic trioxide, 34 patients (85%) achieved CR. Thirty-one patients (91%) with CR had posttreatment cytogenetic tests negative for t(15;17). Thirty-two patients in CR received consolidation therapy, and 18 of them received additional arsenic trioxide as maintenance. The remainder of the patients received allogeneic (n=8) and autologous (n=3) stem cell transplantation after arsenic trioxide consolidation treatment. The 18-month Kaplan-Meier estimates of overall and relapse-free survival were 66% and 56%, respectively.

A study was conducted evaluating the effectiveness of arsenic trioxide and stem cell transplantation in patients with APL who relapsed after or were refractory to ATRA-based therapy. Arsenic trioxide was proven to be an effective induction therapy in these patients, with a significant CR rate. The role of arsenic trioxide as consolidation and maintenance therapy was also evaluated and showed a relapse-free survival of 56% at 18 months, which is impressive considering the limited number of treatment options available for relapsed patients.

Combination Therapy With Systemic Arsenic Trioxide and Intrathecal Chemotherapy

With the recent studies emphasizing the effectiveness of arsenic trioxide as a salvage treatment for APL patients who relapse after or are refractory to ATRA, it was considered acceptable to choose arsenic trioxide as the treatment regimen in our patient. Extensive research of the literature revealed the rarity of the use of the combination of systemic arsenic trioxide and intrathecal chemotherapy. We found one report¹⁵ of treatment with such a combination. There is still much to be discovered regarding the possible side effects and toxicity of such combination therapy. Further investigation needs to be conducted to document the safety of arsenic trioxide in combination therapy in patients with CNS involvement of APL. A recent study⁴ looked at the incidence, presenting features, and risk factors of extramedullary relapse in APL patients. They concluded that extramedullary relapse occurred more frequently in patients with elevated WBC counts (>10,000 cells/mL). In light of this new information, would such patients benefit from CNS prophylaxis? Because CNS relapse continues to be a rare complication, it will prove to be a challenge to conduct such necessary studies.

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Review

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The majority of newly diagnosed patients with APL are now cured of their disease with ATRA and anthracycline-based chemotherapy. Between 70% and 90% of patients with low- or intermediate-risk disease can be expected to be cured.¹⁻³ Therefore, major attention has been focused on the treatment of patients with high-risk APL, who have a relapse risk of approximately 20%, and on potential long-term complications associated with current treatment.⁴ The latter include cardiac dysfunction associated with increased doses of anthracyclines,⁵ secondary myelodysplastic syndrome,^{6,7} and the development of extramedullary disease after ATRA exposure.⁸⁻¹⁷ Historically, extramedullary disease was a very uncommon occurrence in the pre-ATRA era. Though some reports suggest that prior exposure to ATRA predisposes patients to the development of extramedullary disease¹⁰ others do not confirm this finding.^{11,12}

In this report, Drs. Farhat and Venugopal present the interesting case¹⁸ of a young man with newly diagnosed APL treated with ATRA and daunorubicin who achieved a morphologic CR, but who developed an extramedullary relapse in the external auditory canal 5 months after initiation of treatment. Simultaneously, both the cerebrospinal fluid and the bone marrow demonstrated recurrent disease. The patient responded well to intrathecal chemotherapy, whole-brain radiation, and systemic arsenic trioxide. This case report provides the foundation for addressing several questions. First, why did the patient develop extramedullary disease at all? Second, what is the best treatment for a patient with a relapse in an extramedullary site. Finally, are there ways to prevent recurrent disease, particularly in extramedullary sites?

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Although there are reports of isolated extramedullary relapse in patients with APL, most often in the CNS,^{10,11,13} this patient also had a systemic relapse. Based on the presenting WBC and platelet count, newly diagnosed patients are now classified as low-risk (WBC $\leq 10,000$ cells/mL and platelet count $>40,000$ cells/mL), intermediate-risk (WBC $\leq 10,000$ cells/mL and platelet count $\leq 40,000$ cells/mL), and high-risk (WBC $>10,000$ cells/mL). The relapse rate among patients presenting with low- or intermediate-risk disease appears to be quite low, approximately 3–5%, whereas the relapse rate for patients with high-risk disease is approximately 20%.⁴ The patient presented with pancytopenia, but the specific peripheral blood counts are not reported. It is presumed the patient had intermediate-risk disease and could have been among the few patients who relapse based on the intermediate-risk classification. Relapse in the CNS has been associated with a high WBC count in APL in some^{13,19} but not all reports.¹¹ It is also possible that lack of exposure to cytarabine accounted for the systemic and extramedullary relapse. The patient received ATRA and daunorubicin, but not cytarabine, for induction. The administered consolidation chemotherapy program was not reported. Though there are data to suggest that cytarabine is not required in the treatment of APL if sufficient doses of anthracyclines are given, particularly idarubicin, a trial conducted by the European APL Group randomizing patients to either ATRA and daunorubicin or ATRA with daunorubicin and cytarabine closed early because of an increased relapse rate among patients randomized to the arm without cytarabine.²⁰ Finally, there may be biologic characteristics of the disease that contribute to the risk of relapse. For example, Farhat and Venugopal report that the patient had hypergranular morphology. In the pre-ATRA era the outcome among patients with the microgranular variant was inferior to that of patients with classical hypergranular disease.²¹ However, with exposure to ATRA with contemporary therapy, the outcome appears to be the same.²² Some,²³ but not all,²⁴ reports suggest that expression of CD56, which identifies the neural crest adhesion molecule (NCAM), may predispose a patient to extramedullary disease. Internal tandem duplications of the *FLT3* gene are common in APL and have been associated with the presence of a high WBC count at presentation and a less favorable outcome.²⁶ However, not all studies have reported the same findings.²⁶⁻²⁸ The details of the cytogenetics other than the presence of a typical $t(15;17)$ translocation are not known. However, even if additional cytogenetic abnormalities were present, the outcome does not appear to be different and there are no data to suggest therapy should be any different than that for patients with only the typical $t(15;17)$ translocation. Interestingly, although relapse of APL in the CNS is a common location, isolated relapse in the external audi-

tory canal has been previously reported.^{11,14-17,19} ATRA is well-known to modulate adhesion molecules, such as B1 and B2 integrins, which are important for the adhesion of myeloid cells to stromal cells and fibronectin and to the blood vessel wall during migration, respectively.²⁹ This may provide an explanation for the development of both extramedullary disease and the retinoic acid syndrome in some patients with APL and the association with high WBC counts in some reports. Finally, it is possible that as patients survive longer with effective therapy, extramedullary disease has emerged.

In the case reported here, treatment with both aggressive intrathecal chemotherapy and radiation as well as systemic therapy with arsenic trioxide was indicated. Although few data are available, arsenic trioxide appears to penetrate the cerebrospinal fluid such that levels of only approximately 50% of the systemic levels are attained in the setting of meningeal relapse.³⁰ For systemic relapse, arsenic trioxide is now the treatment of choice.³¹ Approximately 85% of patients will achieve a molecular CR with two cycles of arsenic trioxide. The prevailing view is that patients with an apparently isolated extramedullary relapse should be treated with systemic therapy in addition to therapy directed at the site of extramedullary disease. Following a second remission induced with arsenic trioxide, autologous hematopoietic stem cell transplantation (HSCT) is considered.^{32,33} Allogeneic HSCT is generally reserved for those patients in first hematologic CR who remain persistently molecularly positive following initial appropriate induction, consolidation, and maintenance therapy or those patients who are molecularly positive in second hematologic CR after arsenic trioxide. Gemtuzumab ozogamicin (Mylotarg, Wyeth) is another active agent in these settings.

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