A 42-year-old female was diagnosed with acute promyelocytic leukemia (APL) with a translocation of chromosomes 15 and 17 involving the *PML* and *RARA* genes. On presentation she met criteria for low-risk disease on the basis of platelet count (50 × 10^9/L) and WBC count (0.8 × 10^9/L). The patient achieved a complete molecular remission after induction chemotherapy with all-trans-retinoic acid (ATRA) and idarubicin (AIDA) and underwent consolidation chemotherapy per the risk-adapted Spanish Cooperative Group for Hematological Malignancies Treatment (PETHEMA) regimen, on completion of which she remained in molecular remission. She subsequently received maintenance therapy with oral ATRA, 6-mercaptopurine, and methotrexate per the Cancer and Leukemia Group B C9710 protocol. Two weeks after completion of maintenance therapy, the patient had a bone marrow examination that demonstrated molecular relapse, on the basis of a positive bone marrow reverse transcriptase polymerase chain reaction (RT-PCR) for PML-RARA that was confirmed on repeat study 4 weeks later. Peripheral blood counts, bone marrow morphology, and cytogenetics were normal. The patient reached molecular remission after two 30-day cycles of arsenic trioxide (ATO) and underwent autologous peripheral blood stem-cell transplantation (SCT) for consolidation, with high-dose busulfan and cyclophosphamide conditioning. Five months after SCT, the patient presented with 1 week of right-sided headache worse with neck flexion, 3 days of intermittent visual loss in her right eye, and paresthesias of the right leg. Magnetic resonance image revealed diffuse leptomeningeal enhancement. Figure 1 shows an axial T1-weighted, gadolinium-enhanced image demonstrating regions of leptomeningeal enhancement (arrows). Cerebrospinal fluid (CSF) analysis revealed blast cells that were CD33 and CD13 positive and HLA-DR negative, and RT-PCR confirmed the presence of PML-RARA transcripts. Figure 2 shows a diffuse infiltrate of myeloblasts and promyelocytes within the CSF (Fig 2A). On high-power view (Fig 2B), several abnormal promyelocytes are noted, with intense azurophilic granules, bilobed nuclei, and dispersed chromatin. Auer rods, single as well as multiple, are present. Bone marrow analysis
revealed the presence of systemic relapse, as evidenced by bone marrow with 28% blasts that were CD33 and CD13 positive and HLA-DR negative, with cytogenetics showing t(15;17). An FLT3 internal tandem duplication (ITD) mutation was also identified in the bone marrow, with 29% variant allele detectable at relapse (11% variant allele was present in the patient’s original diagnostic marrow sample). The patient was treated with twice-weekly intrathecal methotrexate and cytarabine until her CSF cleared. She also completed 12 fractions (total of 24 Gy) whole-brain radiation therapy. Her systemic disease was successfully treated with two 30-day cycles of ATRA plus ATO (ATRA beginning on day 10) that sent her into a third molecular remission.8,9 In view of the patient’s recent autologous SCT, it was felt that a second fully myeloablative transplant would incur an unacceptably high risk of veno-occlusive disease of the liver,10 thus the patient received a matched unrelated-donor nonmyeloablative allogeneic SCT.11 She is currently 6 months post transplantation and has had an uncomplicated course to date, with bone marrow assessment at 6 months demonstrating 99% donor chimera and sustained complete molecular remission.

There are a number of interesting and informative aspects to this case. First, the patient suffered two relapses within 3 years despite presenting initially with low-risk disease as defined by a platelet count more than 40 × 10^9/L and WBC count less than 10 × 10^9/L.1 Patients with low-risk APL treated on the PETHEMA protocol have a cumulative incidence of relapse of just 6.4% within 6 years.2 Notably, this patient had an FLT3-ITD mutation present at diagnosis and at relapse. FLT3 encodes a membrane-bound receptor tyrosine kinase that has a critical role in normal hematopoiesis and is mutated in up to 45% of patients with APL.12 FLT3 mutations are associated with leukocytosis at presentation in APL but have not been independently correlated with response to treatment or with survival.13,14 Second, the patient had striking leukemoid reaction in her second relapse (first morphological relapse). Extramedullary relapse in APL is infrequent, occurring in less than 5% of APL cases and largely predominates in the CNS.15,16 It has been reported to be almost always associated with marrow relapse (as in our patient) and carries a poor prognosis.15 Extramedullary relapse has been shown to occur more frequently in patients with increased WBC count (> 10 × 10^9/L), in younger patients (age < 45 years), and in those with the bcr3 PML-RARA isoform, although only high WBC count remained significant on multivariate analysis.15 The German AML Cooperative Group has shown that high-dose AraC given as part of induction obviates the less favorable clinical predictors at presentation, most notably a low WBC count. The presence of the same FLT3 ITD clone at diagnosis and at relapse suggests that this mutation cooperated with PML-RARA in leukemia initiation and re-emergence. The absence of leukocytosis makes it difficult to attribute the CNS relapse to the FLT3 ITD or to the absence of AraC in her initial therapy, and suggests that there are additional as yet unidentified biologic factors that affect disease course and prognosis in APL. Finally, this report emphasizes the efficacy of ATO in APL therapy.

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**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**  
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