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All-*trans*-retinoic-acid and arsenic trioxide induced remission in promyelocytic blast crisis

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ABSTRACT

A 78-year-old-male with chronic myeloid leukemia (CML) treated for seven years with dasatinib developed an acute promyelocytic leukemia complicated by disseminated intravascular coagulopathy. A promyelocytic blast crisis was diagnosed by demonstrating co-expression of chimeric *BCL/ABL* and *PML/RARα* translocations by karyotyping, fluorescence in situ hybridization, and quantitative real-time polymerase chain reaction. Promyelocytic blast crisis of CML is a rare event with historically poor outcomes. Treatment of our patient with all-*trans*-retinoic acid (ATRA) and arsenic trioxide (ATO) resulted in complete morphologic remission. We review here the relevant literature of promyelocytic blast crisis and highlight the potential of ATRA/ATO as first line management.

1. Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm originating from a balanced translocation of t(9;22)(q34;q11.2) that results in *BCR-ABL* fusion gene. CML classically evolves through three phases: chronic phase (CP), accelerated phase (AP), and the terminal blast crisis (BC). Since the development of tyrosine kinase inhibitors (TKIs), the progression from CML-CP to AP or BC has been markedly reduced from 20% per year to 1–1.5% per year [1]. CML-BC is characterized by acute leukemic transformation of BCR-ABL mutant cells. The majority of cases (80%) are acute myeloid leukemia (AML) with 20% constituting acute lymphoid leukemia (ALL) [2]. CML-BC management is based on the blast lineage (AML vs ALL) and prior therapy [2]. Generally, a TKI is given in combination with intensive chemotherapy for treatment of AML or ALL CML-BC followed by allogeneic stem-cell transplant if possible in complete remission (CR).

An acute promyelocytic CML-BC is exceedingly rare with no consensus on treatment. Similar to *de novo* acute promyelocytic leukemia (APL), promyelocytic blast crisis is distinguished by a balanced translocation between chromosomes 15 and 17, t(15;17)(q22;q21), resulting in the *PML-RARA* fusion gene. This aberrant retinoid receptor blocks myeloid differentiation and leads to accumulation of immature promyelocytes [3]. Upfront treatment of *de novo* APL with all-trans-retinoic-acid (ATRA) induces differentiation of leukemic promyelocytes into mature granulocytes, and when combined with arsenic trioxide (ATO), results in complete remission rates over 90% [4]. ATRA-ATO has less hematologic toxicities and significantly improved survival and relapse risk when compared to ATRA with chemotherapy in low-intermediate risk patients (defined by WBC less than 10×10^9/L on presentation) [5,6]. The combination of ATRA-ATO acts synergistically with more pronounced reductions of *PML-RARA* transcripts, expedited achievement of CR, and decreased relapse rates compared to ATRA or ATO alone [7]. Here, we describe the treatment of promyelocytic BC with ATRA-ATO in our patient and review the current literature.

2. Case presentation

A 78-year-old Hispanic man with history of Alzheimer's disease, chronic obstructive pulmonary disease, type 2 diabetes mellitus, and hypertension was diagnosed with CML in 2010 with Sokal score of 0.88 (intermediate-risk). He began treatment with imatinib 400 mg daily but approximately six months later it was switched to dasatinib 100 mg daily due to development of dizziness and fatigue. He was intermittently nonadherent with medication and clinic appointments and was lost to follow-up on multiple occasions. In mid-2016, due to development of anemia with hemoglobin (Hb) of 8.9 mg/dL, dasatinib was briefly held and then restarted at a lower dose of 80 mg daily. Six months later, the hemoglobin had improved to 11.9 mg/dL along with

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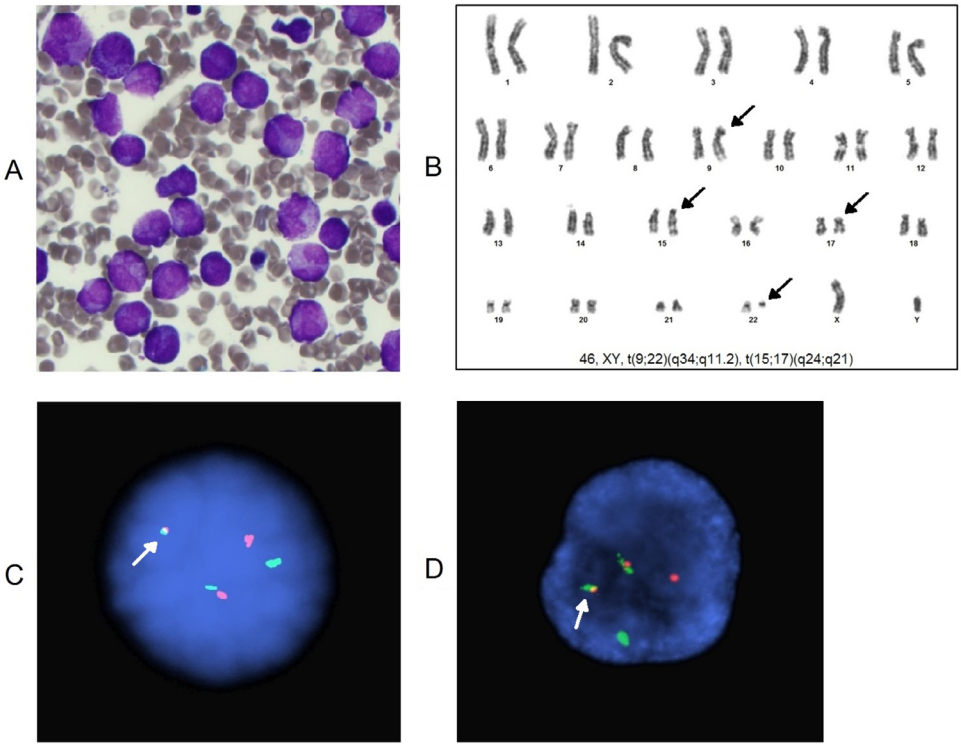

Fig. 1. Chronic myeloid leukemia – blast crisis characterization (A) Increased promyelocytes seen in bone marrow aspirate using hematoxylin and eosin (H&E) staining; photographed at 1000x magnification (B) Conventional cytogenetics demonstrated an abnormal karyotype - 46, XY, t(9;22)(q34;11.2), t(15;17)(q24;q21). Fluorescent in situ hybridization (FISH) confirmed the presence of (C) t(9;22)(q34;q11.2)/*BCR-ABL*, and (D) t(15;17)(q24;q21)/*PML-RARA* fusions.

an otherwise normal complete blood count (CBC) and differential.

Three months later (seven years after initial diagnosis) he presented to clinic for a routine follow-up. His white blood cell count (WBC) was 1.03 × 10^9/L, Hb 7.8 g/dL, and platelets (Plt) 6 × 10^9/L with 2% blasts and 18% promyelocytes. He was found to have a prothrombin time (PT) of 13.4 s [9.4–12.5 s], activated partial thromboplastin time (aPTT) of 30.5 s [25.1–36.5 s], D-dimer of 10,107 ng/mL [0–232 ng/mL], fibrinogen of 189 mg/dL [200–393 mg/dL], and fibrin monomers and > 80 mg/L fibrin split products were detected. Peripheral blood smear showed abnormal promyelocytes that were strongly positive for myeloperoxidase. Bone marrow biopsy and aspirate revealed 80% cellularity, 88% promyelocytes, 2% blasts, and was notable for replacement of normal marrow elements with sheets of promyelocytes (Fig. 1a). Unstimulated peripheral blood culture revealed a male karyotype with a reciprocal translocation between the long arms of chromosomes 9 and 22–t(9;22)(q34;q11.2) and a reciprocal translocation between the long arms of chromosomes 15 and 17–t(15;17)(q24;q21) in all cells analyzed (Fig. 1b). BCR-ABL1 gene fusions, which detect the t(9;22)(q34;q11.2), were observed in 165 of 200 interphase nuclei using fluorescent in situ hydridization (FISH) analysis. PML-RAR fusions, which detect the t(15;17)(q24;q21.1) were observed in 168 of 200 interphase nuclei scored by FISH analysis (Fig. 1c and d respectively). *BCR-ABL* p210 transcript and the *PML-RARA* long form transcript were elevated to 48.25 and 46.44 international standard-normalized copy number (IS-NCN) respectively. Next-generation sequencing performed by FoundationOne™ Heme panel confirmed *BCR-ABL* and *PML-RARA* fusion transcripts and additionally identified mutation in *ASXL1*.

Flow cytometry was positive for CD45 (dim), CD13, CD2, CD64, CD7 (subset), CD15(subset), CD71, CD123, CD117, and negative for CD34, HLA-DR, CD56, and B-cell markers. These findings were consistent with a promyelocytic blast crisis.

The patient was started on ATRA 45 mg/m^2/daily in two divided doses and ATO 0.15 mg/kg/day. During the first week of treatment, the blasts and promyelocytes gradually decreased and laboratory measures of disseminated intravascular coagulation (DIC) including D-dimer, fibrinogen, fibrin split products, and fibrin monomers trended towards normal (Fig. 2a and b). On day 28 of therapy, his WBC was 1.46 × 10^9/L, Hb 8.1 g/dL, and Plt were 41 × 10^9/L. A restaging bone marrow biopsy and aspirate revealed 5% cellularity with residual and focal marrow fibrosis, trilineage hypoplasia, and less than 1% blasts. Molecular analysis revealed reduced *BCR-ABL* p210 and *PML-RARA* transcript levels to 17.225 IS-NCN and 1.28 IS-NCN respectively (Fig. 2c). FISH analysis from marrow aspirate showed *PML-RARA* and *BCR-ABL* fusion genes in 18/200 and 21/200 cells respectively. Karyotyping showed 1/20 cells with 46,XY,t(9;22)(q34;q11.2). Shortly thereafter, the patient's family decided against pursuing additional treatment due to advanced dementia and all active therapy was withdrawn after 35 days of therapy. The patient was discharged to a long-term care facility and died two months after initiating treatment for BC.

3. Discussion

Promyelocytic BC is a rare entity with only 24 cases reported in the English literature since 1980 (see supplement). Based on our patient's presenting counts (WBC 1.03 × 10^9/L and Plt 6 × 10^9/L), his promyelocytic CML-BC would be categorized as an intermediate-risk APL as per Sanz scoring system [8]. He was therefore treated with ATRA-ATO which constitutes our institute's standard-of-care management for this APL subset. Dasatinib was held secondary to pancytopenia. He tolerated ATRA-ATO therapy well with clearing of peripheral blood blasts and promyelocytes within 20 days (Fig. 2c).

Although there was concern for DIC given the consumptive coagulopathy seen on admission labs, the patient did not experience significant bleeding or signs of organ failure. ATRA-ATO therapy improved the coagulopathy panel within one week (Fig. 2a). A restaging bone marrow biopsy and aspirate on day 28 showed that the patient achieved a morphological CR with incomplete blood count recovery (CRi). The aspirate continued to show *PML-RARA* positivity via FISH and transcript levels, but these were not expected to be negative given the premature timing of biopsy in therapy course. The patient's family decided to withdraw active treatment after consideration of his goals of care, not toxicities.

Considering its rarity, it is not surprising that there is no consensus on the management of promyelocytic BC. Therapies have ranged from