Myeloid Sarcoma: Extramedullary Relapse After Allogeneic Bone Marrow Transplant for Chronic Myelogenous Leukemia

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INTRODUCTION

Myeloid sarcoma (MS) is an extramedullary tumor of myeloid precursor cells, which can precede or occur concomitantly with acute myeloid leukemia, myelodysplastic syndrome, or myeloproliferative neoplasms. Although MS can involve any organ, it is more common in the central nervous system (CNS) and gonads, sites known as "pharmacologic sanctuaries" where leukemic cells can survive despite systemic chemotherapy. Less often, this tumor can be the manner of relapse after allogeneic bone marrow transplantation.

The diagnosis is based on morphology and immunophenotype by either flow cytometry or immunohistochemistry of paraffin-embedded tissue, and confirmed by FISH or molecular studies. Myeloid sarcomas usually express the leukocyte common antigens CD45, CD13, CD33, CD43 and lack T-cell and B-cell antigens.

Case Study

We report a patient who relapsed with myeloid sarcoma 2 years after allogeneic bone marrow transplantation, with paraparesis due to an epidural tumor and cerebrospinal involvement.

The patient, a 58 year-old woman with a history of chronic myelogenous leukemia diagnosed in 2005, was initially treated with Imatinib, then switched to Dasatinib, to which she became resistant and developed blast crisis in 2009. A CBC in 2009 revealed anemia (Hgb 8.6), thrombocytopenia (plt count 62 $X10^9$/L) and leukocytosis (WBC 33.6 $X10^9$/L) with 62% blasts. Review of peripheral blood morphology was consistent with blast crisis of chronic myelogenous leukemia.

Cytogenetic analysis showed an abnormal female karyotype: 46, XX, t(2;7)(p21;p15),t(9;22)(q34;q11.2) in 15 out of 20 metaphases analyzed. Fluorescent in situ hybridization was positive for the BCR/ABL fusion.

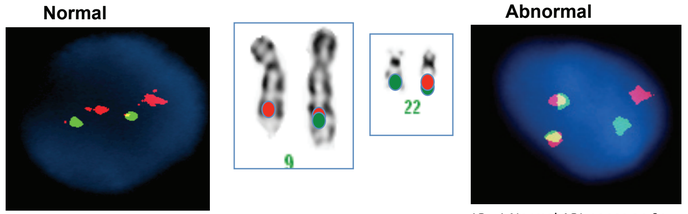

Figure 1: FISH analysis showing presence of Philadelphia chromosome

Qualitative BCR/ABL by RT-PCR detected major breakpoint cluster regions M-BCR b3a2 and M-BCR b2a2 fusion transcripts of BCR/ABL1, encoding the 210 kDa chimeric tyrosine kinase protein . The 210 proteins are characteristic for chronic myelogenous leukemia.

Bone marrow biopsy and aspiration showed a hypercellular marrow with increased blasts and a diffuse increase in reticulin fibers, consistent with blast crisis of chronic myelogenous leukemia.

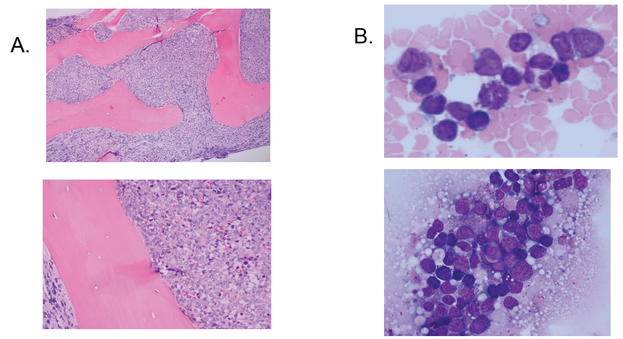

Figure 2: Bone marrow aspirate, regular (A) and magnified view (B), demonstrating hypercellularity and blast crisis respectively.

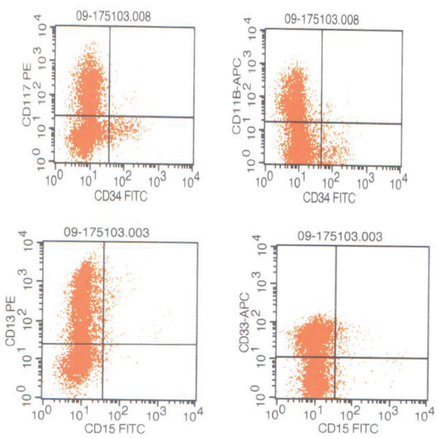

Figure 3: Flow cytometry of the bone marrow showing expression of CD117, CD11B, CD13 and CD33.

She was switched to Nilotinib and received a haplo stem cell transplant from her daughter. Pre-transplant conditioning regimen included 12 Gy total body irradiation (TBI). Her post-transplant course was relatively uncomplicated, however her follow up bone marrow examination did reveal at the molecular level evidence of progressive disease. She was maintained on nilotinib and she went into remission in 2011.

In December 2012, she presented with back pain, nausea, fatigue, and night sweats. MRI of the spine detected a 4.5 cm right paraspinal mass extending to the adjacent neural foramina and soft tissues.

Cerebrospinal fluid contained numerous blasts (30%), left-shifted granulocytes, eosinophilia and basophilia, consistent with leukemic infiltrate.

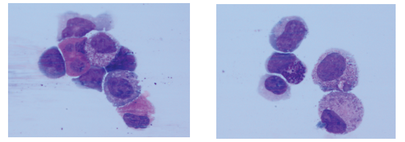

Figure 4: Numerous blasts were detected in the patient's CSF along with other cells consistent with a leukemic infiltrate.

Flow cytometry analysis of the CSF established the blast phenotype as myeloid, with coexpression of CD13, CD33 and CD117. She subsequently received two cycles of intrathecal ARA-C and repeat LP was negative for malignant cells.

Reverse transcription real-time PCR detected the P210 BCR-ABL1 fusion transcript in bone marrow : 0.064%, which gradually increased to 98.947% in March 2013.

Patient's clinical course was complicated with multiple infections (pneumonia, urinary tract infection) septic shock and progressive deterioration despite antibiotics and antifungal medication.

CONCLUSION

Isolated extramedullary relapse is a phenomenon that has been known to occur following allogeneic bone marrow transplantation. A mechanism by which this relapse manifests is thought to be the following: leukemic cells bind with a high affinity to fibroblasts which then localize to non-hematopoietic tissues where myeloid metaplasia occurs leading to the formation of a myeloid sarcoma (1). Typically, the gonads and central nervous system are the most common non-hematopoietic locations for a myeloid sarcoma to form as these organs act as a safe haven by preventing chemotherapeutic treatment from affecting the leukemic cells, thus allowing their continual proliferation (2). In order to achieve continuous complete remission and, consequently prevent an extramedullary relapse, following allogeneic bone marrow transplantation, a combination of high-dose chemotherapy and an allogeneic graft-versus-leukemia effect (where the donor cells attack the leukemic cells) is thought to play a critical role (2). It is interesting to note that the graft-versus-leukemia effect is more typical of allogeneic stem cell recipients who also experienced graft-versus-host disease, where the donor immune reactive cells attack healthy recipient cells, typically in the skin and gastrointestinal tract (3). The patient in this case study did not experience a graft-versus-host/leukemia reaction and thus may have been more susceptible to develop a myeloid sarcoma than one who did demonstrate such an effect. Despite the detrimental consequences of graft-versus-host disease, it is likely that this phenomenon might have a beneficial aspect when it is coupled with the graft-versus-leukemia effect, which can ultimately lead to a decrease in relapse probability.

It has also been noted that the formation of a myeloid sarcoma in a patient in hematologic remission is indicative of a poor overall prognosis (1). Therefore, since this patient was in remission for a number of years before the relapse, it is likely that her outcome will not be favorable and it is probable that she is now expressing end stage disease.

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