case report

Megakaryocytic blast crisis at presentation in a pediatric patient with chronic myeloid leukemia

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Hematol Oncol Stem Cell Ther 2010; 3(1) 42-46

Patients with chronic myeloid leukemia (CML) infrequently present in blast crisis (BC). While most BC are of myeloid origin, megakaryocytic BC is rare, especially at the time of CML diagnosis. We describe the first pediatric patient presenting with megakaryocytic leukemia and having BCR-ABL1 translocation as the single chromosomal abnormality. Clinical features were more suggestive of CML in megakaryocytic blast crisis than Philadelphia chromosome positive de novo AML. The patient was treated with AML-directed chemotherapy and imatinib mesylate followed by umbilical cord blood stem cell transplantation. The patient was in complete molecular response 16 months after stem cell transplantation.

Patients with chronic myeloid leukemia (CML) infrequently present in blast crisis (BC). While most BC are of myeloid origin, megakaryocytic BC is rare, especially at the time of CML diagnosis. We describe the first pediatric patient presenting with megakaryocytic leukemia and having BCR-ABL1 translocation as the single chromosomal abnormality. Clinical features were more suggestive of CML in megakaryocytic blast crisis than Philadelphia chromosome positive de novo AML. The patient was treated with AML-directed chemotherapy and imatinib mesylate followed by umbilical cord blood stem cell transplantation. The patient was in complete molecular response 16 months after stem cell transplantation.

Chronic myeloid leukemia (CML) is a clonal disorder of pleuripotent hematopoietic stem cells characterized by a balanced, reciprocal translocation involving chromosomes 9 and 22. It has a triphasic course: chronic phase (CP), accelerated phase (AP) and blast crisis (BC). At the time of disease progression, approximately 65% of CML patients evolve to myeloid BC, while the remainder has either a lymphoid or mixed-lineage phenotype. Rarely, patients with CML can present directly in a blast crisis. BC with features reminiscent of acute megakaryocytic leukemia (AMKL) is rarely encountered; only five reported cases were found in the literature that describes AMKL as first presentation of CML. (Table 1)[1-5] All of these patients were adult. We believe this is the first reported case of a pediatric patient with CML who presented in megakaryocytic blast transformation.

CASE

A 9-year-old girl presented with progressive abdominal distension of 8 weeks duration without any associated symptoms. Her medical history did not include any preexisting hematological or chronic disease. Physical examination only found splenomegaly reaching the iliac crest. Laboratory tests showed a hemoglobin of 9.4 gm/dL, white blood cell count of 36×10^9/L and platelets of 582×10^9/L. The peripheral smear showed 31% blast cells. Wright-Geimsa stained peripheral blood and bone marrow aspirate smears reviewed by a hematopathologist showed that there were more than 50% medium sized blasts in the bone marrow, with a low nuclear:cytoplasmic ratio and multiple nucleoli. The cytoplasm was granular with some cytoplasmic blebs (Figure 1). There was a reduction in the number of megakaryocytes, but no increase in either basophils or eosinophils. Immunophenotyping of these blasts by FACSCalibur flowcytometer (Becton Dickinson immunocytometry systems, San Jose, CA, USA) showed more than 20% of the gated cells positive for the myeloid markers CD13, CD33 and CD117 and for platelet

Table 1. Clinical characteristics of the patients with megakaryocytic blast crisis of CML at presentation.

Reference	Age/sex	Clinical presentation	Serum LDH (U/L)	Peripheral blood	Bone marrow (BM)	Cytogenetic/RT-PCR	Treatment	Outcome
Bryant et al[3]	53/F	Paraplegia due to paraspinal mass, splenomegaly	Not provided	WBC: 23.8×10^9/L; platelet: 325×10^9/L; basophils: 11%; blasts: 8%	BM biopsy not performed. Paraspinal mass: myeloid sarcoma showing sheets of megakaryoblasts positive for CD 45, CD43 and CD31	Peripheral blood: 46XX t(9; 22) (q34.1; q11.2). No additional abnormalities	Hydroxyurea and radiation to paraspinal mass	Died of disease 3.5 months after diagnosis
Pelloso et al[2]	25/F	Splenomegaly	1690	WBC: 11.4×10^9/L; platelet: 580×10^9/L; basophils: 8%; blasts: 11%	BM: 23% megakaryoblasts positive for CD33, CD13, CD45, CD41, CD61, CD34	BM: 46XX t(9;22)(q34.1;q11.2) No additional abnormalities. RT-PCR p210 transcript	Daunorubicin and cytarabine followed by imatinib mesylate	Complete morphologic remission in 6 months. No cytogenetic remission
Wu et al[1]	38/M	Fever, night sweats, back pain	7148	WBC: 19.0×10^9/L; platelet: 130×10^9/L; basophils: 2%; blasts: 16%	BM aspirate: dry tap. BM biopsy: hypercellular, majority megakaryoblasts positive for NonSE, CD43, factor VIII, with increased fibrosis	Peripheral blood: t(9;22)(q34;q11), t(13q;14q), t(1p;5q), t(1p;13q)	High-dose cytarabine and etoposide followed by allogeneic SCT from matched sibling donor.	Achieved complete morphological remission 2 months into therapy, however died 35 days after allogeneic BM transplant from complications
Campiott et al[4]	60/F	Syncopal episodes, splenomegaly	1120	WBC: 9.9×10^9/L; platelet: $4{,}100\times10^9$/L; basophils: 7%; blasts: 1%	BM: 56% megakaryoblasts, positive for CD33, CD13, CD45, HLA-DR, CD34, CD41, CD61	BM: 46XX t(9;22)(q34;q11). No additional abnormalities. RT-PCR p210 transcript	Idarubicin and cytarabine followed by imatinib mesylate	Complete hematological remission at 1 month and major cytogenetic response in 4 months
Pullarkat et al[5]	62/M	Fever, back pain, sciatica, paraspinal mass	1661	WBC: 16.2×10^9/L; platelet: 460×10^9/L; basophils: 0%; blasts: 1%	BM aspirate: dry tap. BM biopsy: hypercellular, sheets of megakaryoblasts positive for CD45, CD33, CD41, CD7	BM: 64XY t(9;22)(q34.1;q11.2), +1, +2, +5, +6, +6, +8, +8, +9, +10, +10, +11, +11, +12, +14, +20, +21, +21, +22 Duplicate Ph chromosome in 50% of cells	Imatinib mesylate 600mg daily	No response to Imatinib. Died of sepsis 2 weeks after diagnosis.
Present case	9/F	Splenomegaly	1296	WBC: 36×10^9/L; platlet: 582×10^9/L; basophils 4%; blast 31%	BM: 50% megakaryoblasts positive for CD41, CD42, CD61, CD61	BM: 46XX t(9;22)(q34;q11) No additional abnormalities. FISH 99% positive for BCR/ABL1 RT-PCR p210 transcript	Idarubicin, thioguanine and cytarabine with imatinib mesylate. Umbilical cord blood transplantation.	Complete hematological and cytogenetic response to chemotherapy and IM. On IM major molecular response before UCB-SCT and complete molecular response after SCT 22 months from diagnosis.

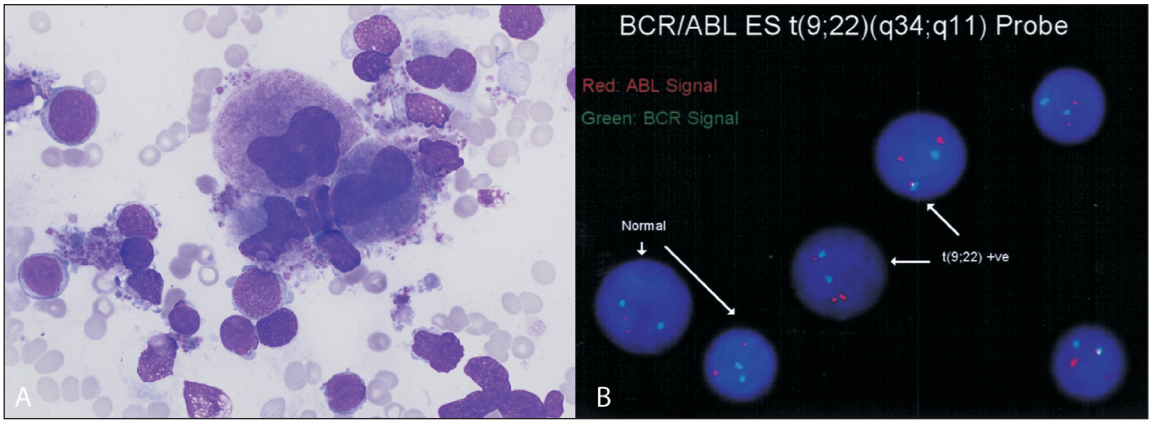

Figure 1 (A) Bone marrow aspirate smear (Wright-Giemsa stain, original magnification ×50) showing leukemic blast cells and megakaryocytes. (B) Metaphase images using the BCR-ABL1 dual color probes demonstrating dual fusion signals (D-FISH) compared to normal.

markers CD41, CD42, CD61 and CD62, with partial positivity for myeloperoxidase. This led to a diagnosis of acute myeloid leukemia (AML) with megakaryocytic differentiation. A cytogenetic study showed karyotype 46XY, t(9; 22)(q34; q11.2). Fluorescent is situ hybridization (FISH) for BCR-ABL translocation showed 99% positive cells. Based on these findings a diagnosis of chronic myeloid leukemia in megakaryocytic blast crisis (CML-BC) was made. Following the initial morphological and flow-cytometric diagnosis of AMKL, the patient was started on induction therapy according to our AML protocol, consisting of idarubicin 12 mg/m^2 IV×3 days, cytarabine 100 mg/m^2/day intravenously continuous infusion×7 days and thioguanine 60 mg/m^2 orally×7 days. Cytogenetic results were received after completion of the first cycle of induction therapy at which time her diagnosis was changed to CML with megakaryocytic BC. Bone marrow evaluation after the first induction cycle revealed a decline in the bone marrow blasts to 7%. There was, however, little if any decline in the size of her spleen. As cytogenetic results were then available, imatinib mesylate at a dose of 340 mg/m^2 was started along with the second induction cycle (idarubicin 12mg/m^2 intravenously×2 days, cytarabine 100 mg/m^2/day intravenously by continuous infusion x 5 days and thioguanine 60 mg/m^2 PO×5 days). Following this she continued on IM alone for a period of ten months. She achieved complete hematological remission (CHR) with regression of the spleen when she was evaluated one month following this induction chemotherapy. FISH for BCR-ABL1 was negative confirming complete cytogenetic response (CCR) as well. Further response evaluation also included quantitative RT-PCR for BCR-ABL1, performed by amplifying the generated cDNA with a BCR exon b2 forward probe and a reverse primer at the ABL exon a4, with a limit of detection at 1/10000; any result <1/10000 underwent nested PCR. By 5 months from diagnosis she had achieved a major molecular response (MMR; >3 log reduction in BCR-ABL1 transcript) with BCR-ABL1 detectable at <1 in 10^4 cells by nested PCR. Stem cell transplant (SCT) work-up was initiated, but unfortunately, as she had no matched-related donor, so a decision was taken to proceed with alternative donor SCT. She was transplanted from a one class II antigen mismatched unrelated umbilical cord blood (UCB) unit, following conditioning with busulfan, cyclophosphamide, antithymocyte globulin, and etoposide. She achieved neutrophil and platelet engraftment by day 20 and 70 post-transplant, respectively. She had no major complication during transplantation, except for transient grade 1 graft-versus-host disease (GVHD) involving the skin. She received imatinib for 4 months post engraftment.

At 6 weeks post SCT she had achieved undetectable BCR-ABL1 transcript by nested PCR. At 26 months from diagnosis and 16 months post-transplantation she remained in complete remission with undetectable BCR-ABL1.

DISCUSSION

Progression to BC is part of the natural history for CML. Prior to the imatinib era, patients with CP-CML would develop blast crises at a median of 3 to 4 years.[6] However, this changed somewhat following the introduction of interferon alfa and more so with imatinib. Although over two-thirds of BC in CML patients is of myeloid origin, megakaryocytic blast crises are fairly

rare. Our patient presented with what was initially diagnosed as de novo AMKL and was classified as CML in megakaryocytic BC after cytogenetic studies were reported. Differentiation between de novo AMKL and megakaryoblastic BC of CML is difficult. In pediatric patients de novo AMKL generally occurs in younger children at a median of 22 months.[7] Both de novo AMKL and CML-BC share the same clinical features and bone marrow morphology. However, the presence of high platelet count, splenomegaly, and basophilia may support the diagnosis of CML-BC.[8] Our patient had all of these clinical features: thrombocytosis (platelet count 582×10^9/L), massive splenomegaly and peripheral blood basophilia (4%; absolute basophilic count 1.46×10^9/L). Classically seen in CML, the Philadelphia chromosome (Ph) has rarely been described in de novo AML, including AMKL. These Ph+ de novo AML did not have the additional cytogenetic abnormalities that are seen in about 80% of CML-BC cases. Incidentally, as in our patient, about 20% of CML patients do not develop additional detectable cytogenetic lesions at the time of progression.[9] Three of the five previously reported patients who presented with megakaryocytic BC did not have additional karyotypic changes. Progression of CML signals the development of more aggressive disease with a significantly poorer prognosis when compared to CP patients, even when treated with imatinib. Although hematological responses are seen in up to 50% of patients, the 12-month survival was less than 30%.[10] While use of conventional AML-directed chemotherapy has resulted in very poor outcomes (median survival of 3.5-15 months in responders and 2-6 months in non-responders),[11] the combination of conventional chemotherapy and imatinib has proven to be more effective. Using mitoxantrone and etoposide, Fruehauf et al reported HR in 67% and 100% patients who received IM following and concomitantly with chemotherapy, respectively.[12] Six of the 16 patients on this study underwent allogeneic SCT and achieved a significantly better survival (median 15.7 months; range 4-31) as compared to 4.7 months (range 0-49) for chemotherapy alone. Although there was significant cytoreduction, chemotherapy alone did not achieve CHR for our patient, and only the addition of imatinib to the second induction cycle resulted in CHR and CCR. Subsequent therapy with imatinib alone resulted in further reduction of the BCR-ABL1+ clone achieving a MMR prior to SCT. Three of the five patients previously reported were also treated with imatinib, two in conjunction with AML-directed chemotherapy and one alone. Positive responses were seen only in the two patients who received imatinib with chemotherapy. It is likely that the clonal transformation and acquisition of new chromosomal abnormality favored the use of additional chemotherapy. Following the advent of tyrosine kinase inhibitors the indication or requirement for SCT has been questioned. Certainly in adult patients in CP1, SCT now holds a significantly lower position in treatment options for CML.[13] The situation is more complicated for children where the long-term effects of imatinib are as yet unknown. For patients in advanced-phase CML, allogeneic SCT still provides significant benefit over imatinib alone and, particularly in children, is considered the therapeutic option of choice.[14] When sibling donors are unavailable, alternative donor transplants have also been found to be of benefit. Recent reports have indicated the potential use of UCB as a stem cell source for both adult and pediatric CML patients.[15-17] In one large series of both adult and pediatric patients, children younger than 15 years of age achieved a 74% 2-year EFS, which was marginally better than that for adolescents/young adults and older adults (33% and 15%, respectively; P=.049).[15] This same study and others have reported a worse outcome for patients transplanted in advanced phase (AP/BC) CML. As in our patient, initial use of imatinib to achieve at least a reversion to CP, may result in an improved outcome post SCT.

In summary, we have described the first pediatric patient with CML who presented in megakaryocytic BC. Differentiation from the rarely encountered Ph+ de novo AMKL may be difficult, but these patients do benefit from AML-directed chemotherapy treatment with imatinib used concomitantly. Allogeneic SCT using any donor stem cell source may result in cure for a subset of these patients.

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