Journal of Leukemia
ISSN: 2329-6917

Pennisi et al., J Leuk 2015, S1:S1-007
DOI: 10.4172/2329-6917.S1-007

Case Report Open access

Acute Lymphoblastic Leukemia evolving from atypical Chronic Myelogenous Leukemia: Case Report and Review of the Literature

Angela Pennisi, Sarah Jewell, Jonathon Gralewski, Daisy Alapat, Bellamy William, Yogesh Jethava and Pooja Motwani*

Division of Hematology and Oncology, Winthrop P. Rockefeller Cancer Institute, University of Arkansas for Medical Sciences, Little Rock, Arkansas

***Corresponding author**: Pooja Motwani, Division of Hematology and Oncology, Winthrop P. Rockefeller Cancer Institute, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA, Tel: (501) 526-6990; E-mail: PMotwani@uams.edu

Rec date: July 27, 2015; **Acc date:** August 17, 2015; **Pub date:** August 27, 2015

Abstract

Atypical chronic myeloid leukemia (aCML) is a rare chronic myeloproliferative disorder characterized by leukocytosis, absence of Philadelphia chromosome or BCR-ABL rearrangement, and marked myeloid dysplasia. The diagnosis of aCML is difficult and challenging, more so if the initial presentation is with blast crisis. In the absence of characteristic mutational profile, blast crisis of aCML can lead to significant diagnostic dilemma. We describe a case of refractory acute lymphoblastic leukemia (ALL), needing critical evaluation of hemopathological and cytogenetic abnormalities. It was hypothesized that patient had undiagnosed aCML and presented with lymphoid blast crisis. To our knowledge, this is the first described case of aCML presenting with lymphoid blast crisis.

Keywords: Atypical Chronic Myeloid Leukemia (aCML); Acute Lymphoblastic Leukemia (ALL); t(2;13)

Case Summary

A 48 years old female with no significant past medical history, presented in July 2014 at outside hospital with fatigue, low grade fever, and cervical lymphadenopathy. At the time of diagnosis, patient had leukocytosis with total white blood cells count (WBC) of 25 K/ (range , hemoglobin was 8.8 g/dL (range) and platelet count was 302K (range . The flow cytometry of bone marrow aspirate showed an increased blast population (53%) positive for CD34, TdT, CD20, and CD10, consistent with the diagnosis of acute B lymphoblastic leukemia. However flow also demonstrated abnormal myeloid precursors (2%). This finding was not considered significant due to the clonal size. Metaphase cytogenetic analysis revealed t(2;13)(p16;q12) with normal female karyotype of 46,XX. The FISH for BCR-ABL and other ALL related cytogenetic abnormality was negative. Considering the diagnosis of B-ALL, patient was started on induction chemotherapy with Rituximab Hyper-CVAD Part A (Rituximab 375 mg/m^2 IV over 2 to 6 hours once on days 1, Cyclophosphamide 300 mg/m^2 IV over 2 hours Q12H on days 1 to 3, Vincristine 2 mg IV once on days 4 and 11, Doxorubicin 50 mg/m^2 IV over 24 hours on day 4, Dexamethasone 40 mg PO/IV once daily on days 1 to 4, 11 to 14). residual 5% lymphoblasts with persistent leukocytosis (WBC 20.77 K/µL) and worsening anterior cervical lymphadenopathy, hence signifying induction failure. Subsequently the patient received salvage treatment with Larson 8811 regimen. Induction consisted of Cyclophosphamide 1200 mg/m^2 IV once on day 1, Daunorubicin 45 mg/m^2 IV once daily on days 1 to 3, Vincristine 2 mg IV once on days 1, 8, 15, 22, Prednisone 60 mg/m^2 PO once daily on days 1 to 21 and PEG-L-Asparaginase 2500 units/m^2 SC once on days 5 and 19. The patient achieved complete remission (CR) per bone marrow performed in September 2014. However, the abnormal myeloid population persisted. Since patient had achieved CR, she continued on Larson 8811 protocol. Unfortunately the patient relapsed in January 2015. Subsequently she was treated with Blinatumomab, liposomal Vincristine and combination chemotherapy consisting of Cisplatin, Cyclophosphamide and Cytarabine. With each round of chemotherapy, bone marrow aspirate flow cytometry and cytogenetic studies were performed. The consistent feature in each cytogenetic study was presence of t(2;13) and increasing population of myeloblasts (Table 1). Patient was referred to hospice and passed in May 2015.

Since the patient was not responding to any form of treatment for ALL, the complete histology, cytogenetic abnormalities, and flow results were critically reviewed. Clearly, the patient had different blast populations from the beginning; predominant lymphoid blast population and lesser prominent myeloid blast population upon presentation. However, based on the progressive increase in myeloid blast population and the persistence of t(2;13), described to date in only one case of aCML [1]{Grand, 2007 #13}, it was hypothesized that patient, in fact, had aCML and presented with lymphoid blast crisis.

Discussion

Atypical chronic myeloid leukemia is a rare subtype of myelodysplastic/myeloproliferative neoplasm, largely defined morphologically and initially described as a subtype of myeloid neoplasm resembling chronic myeloid leukemia, but lacking pathognomonic Philadelphia chromosome. In the 2008 World Health Organization (WHO) classification, aCML is defined by "persistent leukocytosis (WBC ≥ 13×109/L) with immature circulating myeloid precursors (≥10% of leucocytes) and marked dysgranulopoiesis, with absent/minimal monocytosis (<1×109/L and <10% of leukocytes) or basophilia (often <2%)". In approximately 15-40 percent of patients, aCML evolves to AML, whereas the remainder die of bone marrow failure [2,3]. The presence of BCR-ABL1 or rearrangements of PDGFRA, PDGFRB or FGFR1 precludes a diagnosis of aCML.

				% Blasts in Bone Marrow	% Blasts in Flow Cytometry		
Date	**Diagnostic Exam***	**BM Cellularity (%)**	**Circulating Blasts**	**B-Lymphoblast**	**B-lymphoblast**	**Myeloblast**	**Immunophenotype**
Day 1	BM, FC	>95	Yes (59%)	90	53	2	B-Lymphoblast: (+): CD45, CD34(heterogenous), CD10 (variable), TdT, CD79a, CD19, CD20 (variable) B-Lymphoblast (-): CD117, CD13, MPO, CD33, cCD3
							Myeloblast (+): CD34, CD117, CD33, CD13 (dim) Myeloblast (-): CD19, CD14, CD3
Day 14 (7/18/14)	BM, FC	5-10	No	<1	0.3	2	B-Lymphoblast (+): CD45, CD19, CD34, CD10 (subset) B-Lymphoblast (-): CD20
							Myeloblast (+): CD34, CD117, CD33, CD13 (dim) Myeloblast (-): CD19, CD14, CD3
Day 28 (8/1/2014)	BM, FC	90	Yes (2-3%)	8	5	2	B-Lymphoblast (+): CD34, CD19, CD10 (variable) B-Lymphoblast (-): CD33, CD20
							Myeloblast (+): CD34, CD117, CD33, CD13 (dim) Myeloblast (-): CD19, CD14, CD3
Day 61 (9/3/2014)	BM, FC	60	No	<1	0.1**	0.3**	No Evidence of Residual Disease, 0.3% of all cells are CD34 positive
Day 184 (1/4/2015)	FC- PB	-	-	-	51***	6	B-Lymphoblast: (+): CD45, CD34(heterogenous), CD10 (variable), TdT, CD79a, CD19, CD20 (variable) B-Lymphoblast (-): CD117, CD13, MPO, CD33, cCD3
							Myeloblast (+): CD34, CD117, CD33, CD13 (dim) Myeloblast (-): CD19, CD14, CD3
Day 194 (1/14/2015)	BM, FC	90	Yes (10-20%)	60	24	6	B-Lymphoblast: (+): CD45, CD34, CD10 (variable), CD19 B-Lymphoblast (-): CD117, CD13, MPO, CD33, cCD3
							Myeloblast (+): CD34, CD117, CD33, CD13 Myeloblast (-): CD19, CD14, CD3
Day 249 (3/10/2015)	BM, FC	50	Yes (rare)	10	5	6	B-lymphoblast (+): CD34, CD19, CD10 (variable) Myeloblast (+) : CD34, CD117, CD33, CD13

Table 1: Bone marrow evaluation- parameters

*Following abbreviations: BM: Bone Marrow; FC: Flow Cytometry; Cyto: Cytogenetics; FISH: Fluorescence in situ hybridization; PB: Peripheral blood

**Clinicopathological remission based on clinical impression, bone marrow examination and immunophenotype (0.1% lymphoblasts and 0.3% myeloblasts)

***Recurrence of acute leukemia based on immunophenotype of peripheral blood (51% lymphoblasts); consistent with phenotype as initial consult

The activating JAK2 V617F mutation has been reported in some cases of aCML [4,5] and approximately 30 percent of cases are associated with acquired mutations of NRAS or KRAS [6]. Karyotypic abnormalities are reported in up to 80 percent of patients with aCML. The most common abnormalities are +8 and del(20q), but abnormalities of chromosome 13,14,17,19 and 12 are commonly reported as well [2,7,8]. Translocation (2;13)(p16;q12) has been described in only one case to date, a 32 year old female patient with aCML [1]. The patient was initially treated with hydroxyurea and subsequently underwent unrelated donor bone marrow transplantation. She relapsed cytogenetically at 4 years, but responded to donor lymphocyte infusion, achieving sustained cytogenetic and molecular (nested reverse transcription polymerase chain reaction) remission. The fusion protein resulting from the t(2;13)(p16;q12) encodes a 66 kDa protein which retains the two coiled –coil domains of SPTBN1 and the tyrosine kinase domain of FLT3. Expression of SPTBN1-FLT3 in cell lines lead to constitutive phosphorylation of the fusion protein and the downstream substrate extracellular signal-regulated kinase 1/2. The translocation results in fusion between exon 3 of SPTBN1 (spectrin, β, nonerythrocytic 1) at chromosome 2p16 and exon 13 of FLT3 (FMS Like Tyrosine Kinase) at chromosome 13q12. SPTBN1 is an actin crosslinking and molecular scaffold protein that links the plasma membrane to the actin cytoskeleton, and function in the determination of cell shape, arrangement of transmembrane proteins, and organization of organelles, while FLT3 is grouped into

the class III receptor tyrosine kinase (RTK) family. It is a transmembrane tyrosine kinase receptor that stimulates cell proliferation upon activation and plays an important role in growth and differentiation of hematopoietic stem cells. Mutations in the FLT3 gene occur in about 30-40 percent of acute myeloid leukemia (AML) with normal cytogenetic. At present, three different activating FLT3 gene mutations are known: the most common are internal tandem duplications (FLT3-ITD) of different length that result in ligand-independent activation of the FLT3 receptor and a proliferative signal, which can be detected in approximately percent, point mutations in the activation loop of the second tyrosine kinase domain (FLT3-TKD), detectable in about 6-8 percent, and point mutations in the juxtamembrane (JM) as well as extracellular domain of the receptor, which are very rare (~2 percent). While FLT3-ITD has been showed to be associated with poor prognosis for AML [9,10] the other two mutations do not appear to be associated with the same poor outcome [11].

There are numerous FLT3 kinase inhibitors under investigation for the treatment of AML, including CEP701 (lestaurtinib), sunitinib malate (SU11248), sorafenib, and PKC412 (midostaurin) have been initiated and evidence of antileukemic activity has been seen in phase 2 studies. Most responses were incomplete and transient.

The fusion protein resulting from the traslocation (2;13)(p16;q12) encodes a 66 kDa protein which retains the two coiled –coil domains of SPTBN1 and the tyrosine kinase domain of FLT3. Expression of SPTBN1-FLT3 transformed Ba/F3 cells (a murine interleukin-3 dependent pro-B cell line) to growth factor independence and was accompanied by constitutive phosphorylation of the fusion protein and the downstream substrate extracellular signal-regulated kinase 1/2 [1]. The growth of transformed cells was inhibited in a dose-dependent fashion by SU11657, PKC412, and TKI258 (CHIR-258), but not by imatinib [1]. Here we present a case of a 48 years old female with refractory B ALL, in which the presence of chromosomal anomaly [t(2;13)(p16;q12)] and coexistence of an increased abnormal myeloblast population could suggest a blastic transformation of the patient's undiagnosed myeloproliferative neoplasm. As t(2;13)(p16;q12) has been described, to date, only in one case of aCML, it was hypothesized that patient had aCML and presented with lymphoid blast crisis, similarly to CML. To our knowledge, this is the first described case of aCML presenting with lymphoid blast crisis. This diagnosis is extremely challenging considering that aCML lacks specific cytogenetic or molecular markers. Further research in aCML and associated cytogenetic abnormalities will help provide a better understanding into the pathogenesis of the disease.

Treatment strategies in our patient would have included induction of a more profound remission using an AML regimen, such as FLAG-IDA, use of one of the investigational FLT3 kinase inhibitor, and consideration for allogenic bone marrow transplant.

References

1. Grand FH, Iqbal S, Zhang L, Russell NH, Chase A, et al. (2007) A constitutively active SPTBN1-FLT3 fusion in atypical chronic myeloid leukemia is sensitive to tyrosine kinase inhibitors and immunotherapy. Exp Hematol 35: 1723-1727.
2. Breccia M, Biondo F, Latagliata R, Carmosino I, Mandelli F, et al. (2006) Identification of risk factors in atypical chronic myeloid leukemia. Haematologica 91: 1566-1568.
3. Kurzrock R, Bueso-Ramos CE, Kantarjian H, Freireich E, Tucker SL, et al. (2001) BCR rearrangement-negative chronic myelogenous leukemia revisited. J Clin Oncol 19: 2915-2926.
4. Jones AV, Kreil S, Zoi K, Waghorn K, Curtis C, et al. (2005) Widespread occurrence of the JAK2 V617F mutation in chronic myeloproliferative disorders. Blood 106: 2162-2168.
5. Levine RL, Loriaux M, Huntly BJ, Loh ML, Beran M, et al. (2005) The JAK2V617F activating mutation occurs in chronic myelomonocytic leukemia and acute myeloid leukemia, but not in acute lymphoblastic leukemia or chronic lymphocytic leukemia. Blood 106: 3377-3379.
6. Vardiman JW (2004) Myelodysplastic/myeloproliferative diseases. Cancer Treat Res 121: 13-43.
7. Hernández JM, del Cañizo MC, Cuneo A, García JL, Gutiérrez NC, et al. (2000) Clinical, hematological and cytogenetic characteristics of atypical chronic myeloid leukemia. Ann Oncol 11: 441-444.
8. Martiat P, Michaux JL, Rodhain J (1991) Philadelphia-negative (Ph-) chronic myeloid leukemia (CML): comparison with Ph+ CML and chronic myelomonocytic leukemia. The Groupe Francais de Cytogenetique Hematologique. Blood 78: 205-211.
9. Marcucci G, Maharry K, Whitman SP, Vukosavljevic T, Paschka P, et al. (2007) High expression levels of the ETS-related gene, ERG, predict adverse outcome and improve molecular risk-based classification of cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B Study. J Clin Oncol 25: 3337-3343.
10. Schlenk RF, Döhner K, Krauter J, Fröhling S, Corbacioglu A, et al. (2008) Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. N Engl J Med 358: 1909-1918.
11. Bacher U, Haferlach C, Kern W, Haferlach T, Schnittger S (2008) Prognostic relevance of FLT3-TKD mutations in AML: the combination matters--an analysis of 3082 patients. Blood 111: 2527-2537.

This article was originally published in a special issue, entitled: **"Leukemia Types"**, Edited by Rohit Mathur