

CASE REPORT

Mixed phenotype acute leukemia with t(9;22): success with nonacute myeloid leukemia-type intensive induction therapy and stem cell transplantation

Onyee Chan^{1,2} , Abdur Rehman Jamil^{1,2}, Rebecca Millius^{2,3}, Ramandeep Kaur² & Faiz Anwer^{1,2,4}

¹Department of Medicine, University of Arizona, 1501 N. Campbell Ave., Tucson, Arizona 85724, USA

²Banner University Medical Center – Tucson, University of Arizona, 1501 N. Campbell Ave., Tucson, Arizona 85724, USA

³Department of Pathology, University of Arizona, 1501 N. Campbell Ave., Tucson, Arizona 85724, USA

⁴Department of Hematology, Oncology, Blood & Marrow Transplantation, University of Arizona, 1501 N. Campbell Ave., Tucson, Arizona 85724, USA

Correspondence

Faiz Anwer, Division of Hematology, Oncology, Blood & Marrow Transplantation, Department of Medicine, University of Arizona, Tucson, AZ 86724, USA. Tel: 520-626-0662; Fax: 520-626-8944; E-mail: anwerf@email.arizona.edu

Funding Information

No sources of funding were declared for this study.

Received: 18 July 2016; Revised: 19 October 2016; Accepted: 8 November 2016

Clinical Case Reports 2017; 5(4): 435–439

doi: 10.1002/ccr3.763

Introduction

The Philadelphia chromosome (Ph⁺) is derived from t(9;22)(q34; q11) or variants and carries the chimeric BCR/ABL1 fusion gene which is classically associated with chronic myeloid leukemia (CML) [1]. Chimeric BCR/ABL1 fusion transcript e13a2(b2a2)/e14a2(b3a2) encodes for a 210-kDa protein (P210), e1a2 encodes for a 190-kDa protein (P190), and less commonly e19a2 encodes for a 230-kDa protein (P230) resulting in constitutively active tyrosine kinase that leads to oncogenic transformation of cell to leukemia [2].

Ph⁺ is found in 15–30% of adults and 2–5% of children with acute lymphoblastic leukemia (ALL), and on rare occasions, <3%, in acute myeloid leukemia (AML) [3]. Ph⁺ lymphoma and myeloma have been described in the literature [4, 5].

Among mixed phenotype leukemia with abnormal cytogenetics, up to 20% are reported Ph⁺ [6]. Acute leukemia

Key Clinical Message

Mixed phenotype acute leukemia with t(9;22) is a rare disease with poor prognosis, and information on optimal treatment is limited. We describe a case where our patient experienced positive outcome after nonacute myeloid leukemia-type intensive induction therapy followed by postremission therapy with stem cell transplant.

Keywords

Acute myeloid leukemia, allogeneic stem cell transplantation, de novo acute myeloid leukemia, leukemia in central nervous system, mixed phenotype acute leukemia, Philadelphia chromosome, tyrosine kinase inhibitor.

presenting with Ph⁺ blasts can mean CML in myeloid blast crisis (CML/MBC), Ph⁺ ALL, Ph⁺ AML, or Ph⁺ mixed phenotype acute leukemia. Certain features such as the presence of basophilia, often seen in CML/MBC, or the absence of basophilia commonly seen in Ph⁺ AML can help distinguish one from the other [7]. However, it can be very challenging to delineate these separate entities even in expert hands. Efforts are being made to characterize the genetic differences between the malignancies to better manage treatment as these patients typically have poor prognosis [3].

Mixed phenotype acute leukemia patients with t(9;22) or 11q23 cytogenetic abnormalities have very adverse prognosis [8]. Central nervous system (CNS) involving leukemia add to the disease complexity as extramedullary AML with marrow involvement is considered independent adverse prognostic factor with 5-year survival rate ranging from 20% to 30% [9].

Here, we present a challenging case of Ph⁺ AML with CNS involvement treated with intensive chemotherapy,

tyrosine kinase inhibitor (TKI), CNS directed therapy, and achieved lasting remission after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Patient is in complete remission for over 18 months despite its poor prognosis and remains on maintenance TKI for relapse prevention.

Case Presentation

A previously healthy 61-year-old man presented with easy bruising, slow wound healing sustained during routine household chores, and general malaise for the past 3 months. Physical examination revealed petechiae on lower extremity, mild splenomegaly, and axillary adenopathy. Ultrasound of the abdomen confirmed enlarged spleen measuring 13.3 cm. Initial laboratory workup was concerning for leukemia (Table 1). Complete blood count (CBC) showed significant leukocytosis with white blood count of 150,100/ μ L, normocytic anemia with hemoglobin of 6.7 g/dL, and thrombocytopenia with platelet count of 37,000/ μ L. The differential was notable for 84.6% blasts and absence of basophilia. Lactate dehydrogenase (LDH) was markedly elevated at 785 IU/L.

Bone marrow biopsy (BMB) showed diffuse infiltration by numerous blast cells, which effaced the normal marrow architecture (Fig. 1A). A large number of blast cells were also evident on the aspirate (Fig. 1B). Cytogenetics

and fluorescence in situ hybridization (FISH) analysis revealed the loss of chromosome 7 and the presence of Philadelphia chromosome: 45,XY,-7, t(9;22)(q34;q11.2) [19]/46,XY[1]. Blasts had minimally differentiated phenotype. Morphologically these cells were atypical with immature expression of CD34 and co-expression of CD13 and HLA-DR favoring an early myeloid differentiation rather than lymphoid origin. Flow cytometry on the marrow aspirate showed an abnormal population of cells expressing dim CD45, moderate CD19, dim CD13, bright CD34, HLA-DR, with a subset expressing dim CD117, dim MPO, and dim TdT is identified, comprising 72% of total events. An atypical subset of CD14 + CD64 + monocytes expresses dim CD2. These blasts were negative for surface kappa and surface lambda light chain immunoglobulins, as well as CD10, CD11b, CD14, CD16, CD64, CD56. Molecular studies showed BCR/ABL p190 mRNA PCR of 33.8% on international scale and negative

Table 1. Initial laboratory workup.

Name	Value	Reference	Unit
White cell count	150.1	3.4–10.4	1000/ μ L
Red blood cell count	2.26	4.4–5.6	10e6/ μ L
Hemoglobin	6.7	13.5–17.5	g/dL
Hematocrit	20.6	40.0–48.0	%
MCV	91.2	80–100	fL
MCH	29.6	27.0–34.0	pg
MCHC	32.4	32.0–35.0	%
RBC distribution width	17.1	<14.6	
Mean platelet volume	6.7	5.5–9.0	fL
Platelet count	37	150–425	1000/ μ L
Neutrophils	0.8		%
Lymphocytes	7.7		%
Eosinophils	0		%
Monocytes	5.1		%
Basophils	0		%
Myelocytes	0.9		%
Blasts	84.6		%
Myelocytes (Absolute)	1.35	0	1000/ μ L
Neutrophils (Absolute)	1.20	1.8–7.8	1000/ μ L
Lymphocytes (Absolute)	11.56	1.0–4.8	1000/ μ L
Eosinophils (Absolute)	0.0	0.0–0.3	1000/ μ L
Basophils (Absolute)	0.0	0.0–0.1	1000/ μ L
Blasts	126.98	0	1000/ μ L
LDH	785	125–243	IU/L

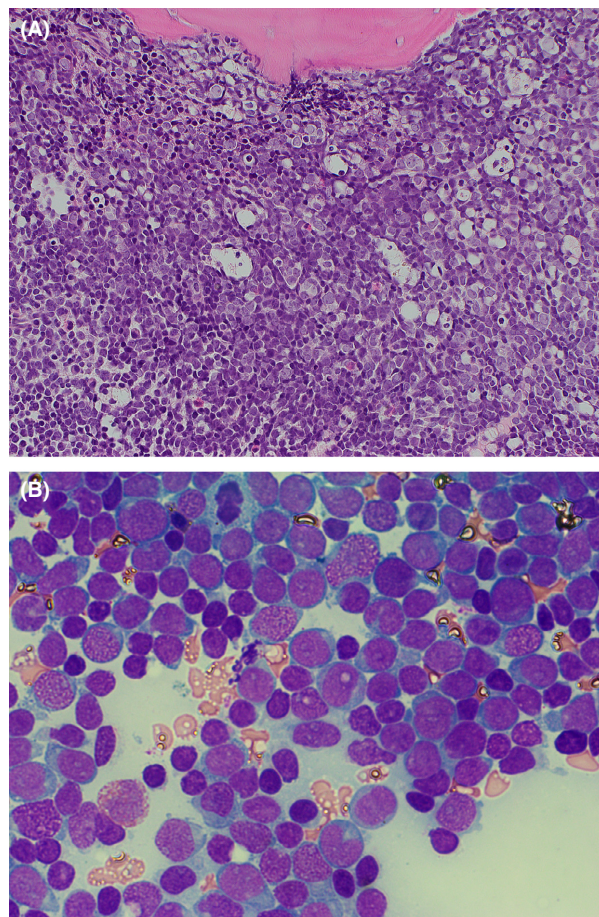


Figure 1. (A) Core biopsy of the marrow showed diffuse infiltration by numerous blast cells, which effaced the normal marrow architecture (H&E, x400). (B) A large number of blast cells are also evident in the marrow aspirate (Wright Giemsa, x1000).

p210. NPM1, FLT3, KIT, and CEPBA mutations were not detected.

On admission, patient was started on hydroxyurea for cyto-reduction along with routine tumor lysis prophylaxis with hydration and allopurinol. Dasatinib was started after 2 days once initial reports became available showing positive Philadelphia chromosome. Patient was then started on hyper-CVAD a few days later after extensive discussions about therapy choice. Five days after admission, patient developed headache, blurry vision, and floaters bilaterally. A computerized tomography (CT) of head was performed, and it did not show any acute intracranial bleed, mass, or midline shift. Blood pressure was normotensive. Ophthalmology was consulted, and they noted the following on fundus examination: Right eye has preretinal hemorrhage near fovea and left eye with intraretinal and preretinal hemorrhage. Their final impression was preretinal hemorrhages on both eyes and intraretinal hemorrhages on left eye secondary to thrombocytopenia. He underwent lumbar puncture (LP), and eight blasts were found in cerebral spinal fluid (CSF) on smear consistent with CNS involvement with leukemia.

Patient was placed on hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) with dasatinib 100 mg daily. Biweekly intrathecal chemotherapy including intrathecal cytarabine (AraC) was initiated with subsequent LP showing clearance of blast cells in CSF. His blurry vision also resolved. Patient completed the 2-course hyper-CVAD regimen with good response. Dasatinib was continued throughout his treatment course, and no significant adverse effect was noted. Kinase domain mutation was not checked. BMB performed 3 months after diagnosis showed mildly hypocellular bone marrow without morphologic or immunophenotypic evidence of AML. Patient achieved complete cytogenetic response (CCyR) and major molecular response (MMR) at this point. Due to the high risk of relapse in Ph+ AML, patient subsequently received allo-HSCT. He had 10/10 HLA-matched haploidentical allo-HSCT from his brother (a total of 4.31×10^6 CD34+ cells were transfused) with conditioning regimen consists of cyclophosphamide 60 mg/kg and total body irradiation (TBI) 1200 centigray (cGy). His course was complicated by chronic graft-versus-host disease (GVHD), but overall patient had been doing well for more than 18 months. Patient continued on dasatinib with plan to stop after 2 years from the date of allo-HSCT. Dose reduction and interruption were performed to improve tolerance due to gastrointestinal-related side effects. His BMB showed 100% donor chimerism and negative cytogenetics. FISH study for t(9;22) was negative, and monthly BCR/ABL p190 mRNA PCR level remained negative. By all tests, patient is in complete remission and minimal residual disease (MRD) negative.

Discussion

Philadelphia chromosome-positive de novo AML is a rare condition with estimated incidence rate of 0.5–3% [1, 6, 10]. The 2016 revision of the World Health Organization (WHO) classification has recognized mixed phenotype AML with t(9;22) as a separate entity [11]. Distinction between unrecognized CML/MBC and de novo AML is possible on many grounds. Compare to CML/MBC, patients with Ph+ AML lack a history of CML or chronic phase/accelerated phase CML after AML induction chemotherapy. Coexistence of normal metaphases along with Ph+ metaphases, absence of basophilia, and lack of moderate/massive splenomegaly at the time of diagnosis favors Ph+ AML over CML/MBC [3, 12]. Normal karyotype after induction therapy is suggestive of Ph+ acute leukemia, and in CML/MBC, cytogenetic abnormality often persist [13]. In addition to the t(9;22), CML/MBC is associated with trisomy 8, trisomy 19, and isochromosome 17q, whereas monosomy (-7) is associated with Ph+ AML [1, 3, 14]. The p190 BCR-ABL fusion protein is common in Ph+ AML but only rarely present in CML/MBC [1]. On the molecular level, Konoplev *et al.* found 22% of its patients with Ph+ AML had NPM1 mutation and none in patients with CML/MBC [2]. Ph+ AML also has a higher prevalence of FLT3 and KIT genes [2]. While none of the aforementioned features alone is diagnostic of Ph+ AML, the summation provides a good indicator of the correct diagnosis, which is important because of its potential treatment implications.

Outcome of Ph+ AML is generally poor with some studies showed median survival of 9–18 months [1, 14]. The mainstay of treatment includes imatinib and allo-HSCT, but the optimal treatment is not clear because of the limited number of cases and short follow-up reported in literature. With the presence of Ph chromosome, complete response is thought to be unlikely with imatinib alone [1]. Therefore, allo-HSCT is frequently initiated if patient is a transplant candidate. Current recommendation according to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for AML is to treat Ph+ AML as CML/MBC with TKI (alone or with induction chemotherapy) followed by allo-HSCT [15]. A recent study by Chantepie *et al.* showed a promising 68% 2-year overall survival in patients with Ph+ AML after receiving allo-HSCT [10]. There are also reports that showed benefits with using imatinib as interim therapy prior to allo-HSCT and even imatinib or later generations of TKI alone [16–18]. Rebourriere *et al.* reported 21 cases of patients with Ph+ AML in the literature treated with TKI therapy [1]. Eight of the patients received allo-HSCT and three of them continued TKI as maintenance therapy afterward. These

patients did well with at least >18 months survival. It appears TKI after allo-HSCT provides survival benefits, but it is far from conclusive at this point given the limited number of cases reported. More studies will be needed to elucidate the best treatment in this rare subtype of AML.

Any type of AML with CNS involvement is uncommon with incidence rate range from 3.1% to 3.6% [19]. Incidence rate is even lower at 0.37% when CNS involvement is found at diagnosis according to a study conducted by Shihadeh *et al.* [20]. These patients tend to be younger, have a higher white blood cell (WBC) count, lactate dehydrogenase (LDH), and peripheral blood blasts at diagnosis [19, 20]. One study found 80% of patients with CNS involvement had LDH levels >700 IU/L [19]. Other predictive factors include FLT3-ITD, African American ethnicity, and cytogenetic abnormalities of chromosome 11, inv(16), and trisomy(8) [20]. Unlike acute ALL where CNS involvement is more common in which routine intrathecal prophylaxis chemotherapy at the time of diagnosis has shown benefits, such prophylactic measure is not recommended for AML due to the lack of supporting data. Different treatment options include intrathecal chemotherapy, systemic chemotherapy, and brain/craniospinal radiation [20]. It is important to note that AML with CNS involvement confers a worse disease-free and overall survival (OS) compared to those without CNS involvement, so any clinical suspicion should prompt timely diagnostic workup such as lumbar puncture and/or head imaging [19].

Our patient presented with features that are suggestive of primary Ph⁺ AML including no history of chronic phase, a lack of basophilia, monosomy (-7), and positive p190. His course was complicated by CNS involvement at diagnosis, and he had a number of predictive factors such as high WBC, LDH, blasts, and chromosome 11 abnormalities. Patients with biphenotypic acute leukemia treated with ALL-based induction regimen have reported 87% complete remission (CR) while only 20% of patients treated with an AML-based regimen achieved CR [21]. Based on strongly favorable data of intrathecal component to treat CNS disease, we started our patient on the hyper-CVAD regimen with dasatinib [21]. He was successfully treated and later received allo-HSCT who is now in complete remission for more than 18 months.

Conclusion

Philadelphia chromosome-positive mixed phenotype de novo AML is rare and can be challenging to distinguish from CML/MBC. Features associated with Ph⁺ AML include lack of chronic phase, absence of basophilia or splenomegaly, monosomy (-7), NPM1 mutation, and

presence of p190. CNS involvement in mixed lineage leukemia is an adverse prognostic factor. Any clinical suspicion of neurologic involvement requires timely workup to improve outcome. Non-AML-type intensive induction therapy followed by postremission therapy by allo-HSCT in suitable patients can potentially overcome adverse prognostic factors, achieve complete remission with long-term survival, and be cured.

Acknowledgments

We thank our patient for allowing us to learn from his condition and the staff at the Arizona Cancer Center.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Authorship

OC: reviewed the literature and wrote the article. FA: treated the patient and collected the patient data. FA, AJ, and RK: corrected the manuscript and made helpful suggestions. RM: performed the histological analyses and various stainings. All authors read and approved the final manuscript.

References

1. Reboursiere, E., S. Chantepie, A. C. Gac, and O. Reman. 2015. Rare but authentic Philadelphia-positive acute myeloblastic leukemia: two case reports and a literature review of characteristics, treatment and outcome. *Hematol. Oncol. Stem Cell Ther.* 8:28–33.
2. Konoplev, S., C. C. Yin, S. M. Kornblau, H. M. Kantarjian, M. Konopleva, M. Andreeff, *et al.* 2013. Molecular characterization of de novo Philadelphia chromosome-positive acute myeloid leukemia. *Leuk. Lymphoma* 54:138–144.
3. Soupir, C. P., J. A. Vergilio, P. Dal Cin, A. Muzikansky, H. Kantarjian, D. Jones, *et al.* 2007. Philadelphia chromosome-positive acute myeloid leukemia: a rare aggressive leukemia with clinicopathologic features distinct from chronic myeloid leukemia in myeloid blast crisis. *Am. J. Clin. Pathol.* 127:642–650.
4. Mitani, K., Y. Sato, A. Tojo, F. Ishikawa, Y. Kobayashi, Y. Miura, *et al.* 1990. Philadelphia chromosome positive B-cell type malignant lymphoma expressing an aberrant 190 kDa bcr-abl protein. *Br. J. Haematol.* 76:221–225.
5. Martiat, P., C. Mecucci, Y. Nizet, M. Stul, M. Philippe, J. J. Cassiman, *et al.* 1990. P190 BCR/ABL transcript in a case of Philadelphia-positive multiple myeloma. *Leukemia* 4:751–754.

6. Keung, Y. K., M. Beaty, B. L. Powell, I. Molnar, D. Buss, and M. Pettenati. 2004. Philadelphia chromosome positive myelodysplastic syndrome and acute myeloid leukemia-retrospective study and review of literature. *Leuk. Res.* 28:579–586.
7. Nacheva, E. P., C. D. Grace, D. Brazma, K. Gancheva, J. Howard-Reeves, L. Rai, et al. 2013. Does BCR/ABL1 positive acute myeloid leukaemia exist? *Br. J. Haematol.* 161:541–550.
8. Matutes, E., W. F. Pickl, M. Van't Veer, R. Morilla, J. Swansbury, H. Strobl, et al. 2011. Mixed-phenotype acute leukemia: clinical and laboratory features and outcome in 100 patients defined according to the WHO 2008 classification. *Blood* 117:3163–3171.
9. Solh, M., S. Solomon, L. Morris, K. Holland, and A. Bashey. 2016. Extramedullary acute myelogenous leukemia. *Blood Rev.* 30:333–339.
10. Chantepie, S. P., M. Michallet, D. Blaise, S. Maury, E. Deconinck, R. Tabrizi, et al. 2015. Allogeneic stem cell transplantation (allo-SCT) for de novo Ph+ AML: a study from the French Society of Bone Marrow Transplantation and Cell Therapy. *Bone Marrow Transplant.* 50:1586–1588.
11. Arber, D. A., A. Orazi, R. Hasserjian, J. Thiele, M. J. Borowitz, M. M. Le Beau, et al. 2016. The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. *Blood* 127: 2391–2405.
12. Cuneo, A., A. Ferrant, J. L. Michaux, H. Demuyneck, M. Boogaerts, A. Louwagie, et al. 1996. Philadelphia chromosome-positive acute myeloid leukemia: cytoimmunologic and cytogenetic features. *Haematologica* 81:423–427.
13. Berger, R. 1993. Differences between blastic chronic myeloid leukemia and Ph-positive acute leukemia. *Leuk. Lymphoma* 11(Suppl. 1):235–237.
14. Bhatt, V. R., M. Akhtari, R. G. Bociek, J. N. Sanmann, J. Yuan, B. J. Dave, et al. 2014. Allogeneic stem cell transplantation for Philadelphia chromosome-positive acute myeloid leukemia. *J. Natl. Compr. Canc. Netw.* 12:963–968.
15. O'Donnell, M. R., M. S. Tallman, C. N. Abboud, J. K. Altman, F. R. Appelbaum, D. A. Arber, et al. 2014. NCCN clinical practice guidelines in oncology: acute myeloid leukemia. *NCCN Clinical Practice Guidelines in Oncology, NCCN.org*; 2.2014.
16. Cho, B. S., H. J. Kim, S. Lee, K. S. Eom, W. S. Min, J. W. Lee, et al. 2007. Successful interim therapy with imatinib prior to allogeneic stem cell transplantation in Philadelphia chromosome-positive acute myeloid leukemia. *Eur. J. Haematol.* 79:170–173.
17. Pompetti, F., A. Spadano, A. Sau, A. Mennucci, R. Russo, V. Catinella, et al. 2007. Long-term remission in BCR/ABL-positive AML-M6 patient treated with Imatinib Mesylate. *Leuk. Res.* 31:563–567.
18. Jentsch-Ullrich, K., A. F. Pelz, H. Braun, M. Koenigsmann, M. Mohren, P. Wieacker, et al. 2004. Complete molecular remission in a patient with Philadelphia-chromosome positive acute myeloid leukemia after conventional therapy and imatinib. *Haematologica* 89:ECR15.
19. Rozovski, U., M. Ohanian, F. Ravandi, G. Garcia-Manero, S. Faderl, S. Pierce, et al. 2015. Incidence of and risk factors for involvement of the central nervous system in acute myeloid leukemia. *Leuk. Lymphoma* 56:1392–1397.
20. Shihadeh, F., V. Reed, S. Faderl, L. J. Medeiros, A. Mazloom, M. Hadziahmetovic, et al. 2012. Cytogenetic profile of patients with acute myeloid leukemia and central nervous system disease. *Cancer* 118:112–117.
21. Xu, X. Q., J. M. Wang, S. Q. Lu, L. Chen, J. M. Yang, W. P. Zhang, et al. 2009. Clinical and biological characteristics of adult biphenotypic acute leukemia in comparison with that of acute myeloid leukemia and acute lymphoblastic leukemia: a case series of a Chinese population. *Haematologica* 94:919–927.