Novel Case of 9;22;15 Translocation in Ph+ Mixed Phenotype Acute Leukemia

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Abstract

Mixed phenotype acute leukemia is a rare hematopoietic malignancy of both myeloid and lymphoid lineages. The Philadelphia chromosome, most well-known for causing CML and common in ALL, is present in 20% of these cases. While Ph+ is a poor indicator of survival among MPAL cases, previous research shows that these patients do have a positive response to tyrosine kinase inhibitors and allogenic hematopoietic stem cell transplantation (allo-HSCT). Here, we present a novel case of a patient with Ph+ MPAL notable for a 9;15;22 translocation that was treated with cycle 2B HyperCVAD + dasatinib, and after four months of treatment, the patient now has minimal residual disease but is unfortunately not in remission.

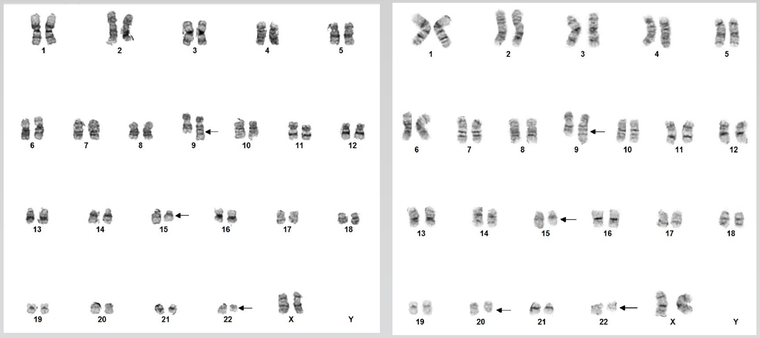

Figure 2. Two abnormal clonal cell populations; left 46,XX,t(9;22;15)(q34;q11.2;q15) and right 46,XX,t(9;22;15)(q34;q11.2;q15),del(20)(q11.2q13.3)

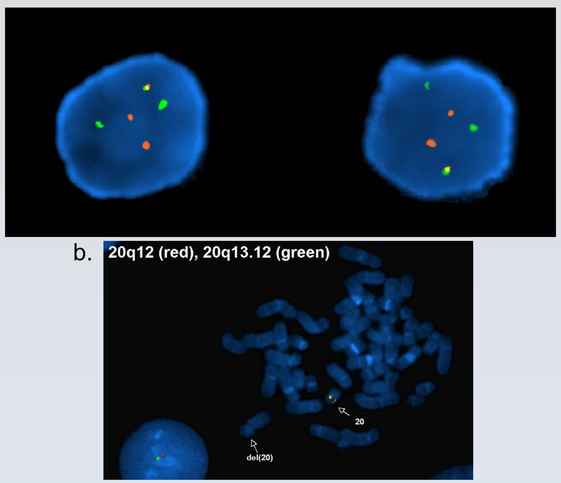

Figure 3. a. Bcr-Abl FISH was positive in 494 of 500 (98.8 %) of nuclei surveyed. b. Deletion of 20q visualized with FISH

Background

The Philadelphia chromosome is one of the most well-characterized chromosomal rearrangements known to oncology. Although most commonly present in chronic myelogenous leukemia, it may also be present in acute leukemias with it being present in 25% of ALL cases (1). In rare cases of mixed phenotype leukemia (MPAL), the Philadelphia chromosome is present in 20% of these cases (1). While Ph+ is a poor indicator of survival among MPAL cases, previous research shows that these patients do have a positive response to tyrosine kinase inhibitors and allogenic hematopoietic stem cell transplantation (allo-HSCT) (2, 3).

Case

A 33-year-old female with unremarkable past medical history presented to the emergency department with fatigue, fever, and flank pain. The initial concern was for a kidney stone. CBC with differential showed a significant leukocytosis of 149.8*10^9/L with both left shift and marked lymphocytosis, along with mild anemia with a hemoglobin of 9.3 mg/dL. Peripheral blood smears showed 50% blasts, while bone marrow biopsy showed 55.6% blasts along with decreased mature lymphoid and erythroid cells (Figure 1).

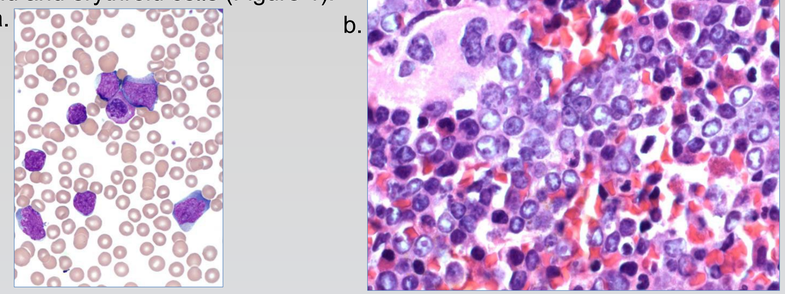

Figure 1. a. Peripheral blood showing blasts and b. bone marrow biopsy showing 100% cellularity and significant blast infiltration

Cytogenetic testing showed two different clones with the most common clone being 46,XX,t(9;22;15)(q34;q11.2;q15) and 46,XX,t(9;22;15)(q34;q11.2;q15),del(20)(q11.2q13.3), 98.8% of which had a positive FISH for Bcr-Abl (Figures 2, 3).

Flow cytometry found two distinct cell populations of blasts, one myeloid, positive for myeloblast phenotype (CD34+/CD33+/CD13+/CD117+) with aberrant B-cell markers and one lymphoid, positive for B-cell lymphoblast phenotype (CD34+/19+/CD79a(CYTO)+/10+/Tdt+) with aberrant myeloid markers CD13 and CD33 (Figure 4). The patient was diagnosed with Mixed Phenotype Acute Leukemia (MPAL) based on the 2016 WHO classification given lack of of CML and splenomegaly. The patient was subsequently treated with cycle 2B HyperCVAD + dasatinib, and after four months of treatment, the patient has hypocellular bone marrow for age (50% cellularity) with low level residual leukemic blast cohort identified by flow cytometry (1%).

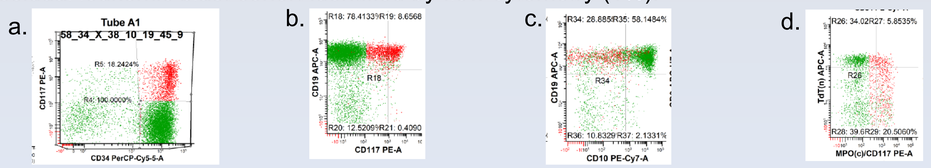

Figure 4. Flow cytometry results showing two distinct myeloid and lymphoid populations. a. CD34, b. CD117, c. CD10, d. MPO

Discussion

Even in the era of dasatinib, other abnormalities in addition to Bcr-Abl continue to have poor prognosis in acute leukemias. Previous studies have shown that remission is possible in Philadelphia chromosome positive mixed phenotype acute leukemias with hyper CVAD and dasatinib, but often require a bone marrow transplant (Table 1). Unfortunately, there is no previous literature showing chromosome 15 translocations in Ph+ MPAL, making it unclear if this abnormality improves or worsens patient prognosis.

Author	Year	Sex	Age	Cytogenetic Abnormality	Treatment	Outcome
Huh et al(6)	2018	F	37	46,XX,t(9;22)(q34;q11)	Induction:HyperCVAD, Imatinib. Consolidation: Dasatinib, Methotrexate, Cytarabine, Allo-HSCT	Remission at 8 months
Lai et al(7)	2018	M	54	46,XY, t(9;22)(q34;q11)	Induction: IA+CVT, Nilotinib, lenalidomide, Consolidation: imatinib (400 mg/d) plus IA+VP, methotrexate+CVAP, VAP, IA +teniposide, VAP+teniposide and CVAP+teniposide	Remission after HSCT
Chan et al(8)	2016	M	61	45,XY,-7, t(9;22)(q34;q11.2)[19]/46,XY[1]	Dasatinib, Hyper-CVAD, AraC, allo-HSCT	Remission at 18 months
Jain et al(9)	2016	M	85	44,-Y,inv(1)(p13p36.1),-6,-7,t(9;22)(q34;q11.2),+mar	Induction: Decitabine, dasatinib, and rituximab-mini-HyperCVAD. Consolidation: Decitabine, dasatinib, and rituximab-mini-HyperCVAD	Remission at 4 weeks
Takata et al(10)	2016	F	69	46,XX, t(9;22)(q34;q11)	dasatinib and prednisolone	Remission 16 months follow-up
Takata et al(10)	2016	F	69	46, XX, t(9;22)(q34;q11.2)[14]/46,idem, -17,+mal[3]/46, XX[3].	dasatinib and prednisolone	No disease progression at 7 months
Kohla et al(1)	2015	M	20s	Clone 1: 46, XY, t(9;22)(q34;q11.2) [22]. Clone 2: 80–88, XXYY, -9[5], t(9;22)(q34;q11.2)[20], -11[6], -13[3], -14[3], -15[2], -18[2], -20[6], -21[3], -22, +der(22) t(9;22)[20][cp20].	HyperCVAD/methotrexate, cytrabin regimen, dasatinib, allo-HSCT	Remission after HSCT
Kawajiri et al(11)	2013	F	71	45,XX, -7, t(9;22)(q34;q11.2)	Induction: Idarubicin, cytarabine, imatinib. Consolidation: high-dose methotrexate, high-dose Ara-C (C1); and single-agent imatinib, After relapse: VP and dasatinib	Remission for 19 months, relapse, then remission for >18 months

Table 1. Literature review of Ph+ Mixed Phenotype Acute Leukemias and their outcomes

Conclusion

Despite advances in targeted therapy for the Bcr-Abl protein in leukemia, the presence the chromosome 15 translocation and mixed phenotype cell lineages makes treatment of this leukemia elusive at this time. Targeting Bcr-Abl alone is not sufficient in Ph+ MPAL cases given their poor prognosis. Bone marrow transplantation has led to remission in some cases of MPAL, but further research on development of individualized targeted therapies is required for better future prognoses for these patients.

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