**Case Report**

**De Novo Acute Myeloid Leukemia with Combined CBFB-MYH11 and BCR-ABL1 Gene Rearrangements: A Case Report and Review of Literature**

Venkata Rakesh Sethapati, Ra’ed Jabr, Leyla Shune, Wissam El Atrouni, Patrick R. Gonzales, Wei Cui, and Shivani Golem

University of Kansas Medical Center, Kansas City, KS, USA

Correspondence should be addressed to Shivani Golem; sgolem@kumc.edu

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Acute myeloid leukemia (AML) with inv(16)(p13.1q22) resulting in CBFB-MYH11 fusion is associated with a favorable prognosis. The presence of a KIT mutation modifies it to an intermediate prognosis. Additionally, inv(16) can cooperate with other genetic aberrations to further increase cell proliferation. Coexistence of inv(16) and t(9;22) is extremely rare (20 cases). We present a case of a 55-year-old male with elevated white blood cell count. Bone marrow evaluation and flow cytometry analysis were compatible with AML with monocytic features. Cytogenetic studies revealed two-related clones, a minor clone with inv(16) and a major clone with concurrent inv(16) and t(9;22) rearrangements. Fluorescent in situ hybridization studies confirmed these rearrangements. Molecular analysis detected a p190 BCR-ABL1 transcript protein. KIT mutations were negative. The patient was initially treated with standard induction regimen; 7 daily doses of cytarabine from day 1–day 7, 3 daily doses of daunorubicin from day 1–day 3, and 1 dose of Mylotarg (gemtuzumab ozogamicin) on day 1. The detection of t(9;22) led to the addition of daily doses of dasatinib (tyrosine kinase inhibitor) from day 7 onwards. The patient achieved complete remission on day 45. During his treatment course, he acquired disseminated Fusarium infection. Day 180 bone marrow evaluation revealed florid relapse with 64% blasts. Cytogenetic study showed clonal evolution of the inv(16) clone with no evidence of the t(9;22) subclone. Eventually, bone marrow transplantation was contraindicated, and the patient was transferred to palliative care. Literature review revealed that AML with co-occurrence of CBFB-MYH11 and BCR-ABL1 gene rearrangements was involved by only a small number of cases with de novo and therapy-related AML. Most cases were in myeloid blast crisis of chronic myeloid leukemia (CML). Treatment and prognosis among the de novo AML cases varied and majority of them achieved clinical remission. In contrast, these cytogenetic abnormalities in the blast phase of CML had a poor prognosis. As the prognosis and management of AML is dependent upon the underlying genetic characteristics of the neoplasm, it is imperative to include clinical outcome with such rare combinations of genetic alterations.

1. **Introduction**

Acute myeloid leukemia (AML) is one of the most commonly encountered types of leukemias in adults. AML is characterized by clonal expansion of undifferentiated myeloid blasts and consequentially results in impaired hematopoiesis and bone marrow failure. It is a heterogenous disease clinically, morphologically, and genetically. Cytogenetic aberrations and gene mutations play critical roles in the pathogenesis of AML. There are many driver mutations, and the disease can evolve to accumulate more competing clones.

Core binding factor (CBF) leukemias include t(8;21)/RUNX1-RUNX1T1 and inv(16)/t(16;16)/CBFB-MYH11 and are classified as AML with recurrent genetic abnormalities under the World Health Organization (WHO) classification [1, 2]. Inv(16) is found in 5–8% of younger patients with AML and accounts for around 7–10% of all patients with de
A 55-year-old male presented with worsening fatigue. Upon evaluation, he had leukocytosis (white blood cell count—103 × 10^9/L), thrombocytopenia (platelets—25 × 10^9/L), and anemia (hemoglobin—7.6 g/dL). Review of the peripheral blood smear revealed 57% circulating blasts, and flow cytometry was compatible with AML with monocytic features. Myeloblasts comprised 15% of cells and showed expression of CD13, CD33, CD117, CD34, HLA-DR, partial CD123, minimal CD64, CD38, and partial cMPO; the blasts were negative for CD56, CD15, CD11b/C, CD14, TdT, and B and T cell markers. There were around 8% immature monocytic cells present which expressed dim CD45, CD13, CD117, CD33, CD15, partial CD11b, and partial CD64 and were negative for CD34. There were also 14% mature monocytic cells.

A comprehensive bone marrow evaluation was diagnostic for acute myeloid leukemia involving a hypercellular bone marrow (100% with decreased erythropoiesis, decreased megakaryopoiesis, increased eosinophils, 19% monocytes, and 24% blasts and promonocytes. Morphologically, the blasts appeared large, with irregular and convoluted nuclear contours, dispersed chromatin, and small amounts of basophilic cytoplasm. They were admixed with an increased number of promonocytes that had delicately folded nuclei, dispersed chromatin, inconspicuous nucleoli, and finely granulated cytoplasm. Importantly, there were increased eosinophils that had increased and coarse basophilic granules (Figure 1). Flow cytometry evaluation of the bone marrow biopsy yielded a hemolminated specimen with myeloblasts expressing CD34, CD13, CD33, CD117, and HLA-DR comprising 1.1% of total cells.

Conventional cytogentetics at diagnosis demonstrated two-related clones. Two metaphases had pericentric inversions of chromosome 16 (Figure 2(a)). The second related clone was observed in majority of the metaphases, and each had a Philadelphia chromosome with the classic (9;22) translocation along with an inversion 16 abnormality (Figure 2(b)). Fluorescence in situ hybridization (FISH) assays were positive for CBFB rearrangement and BCR/ABL1 translocation in 94.0–95.0% of the interphase nuclei (Figures 3(a) and 3(b)). A FISH assay for rearrangement of RUNX1T1/RUNXI was normal (Figure 3(c)).

A qualitative reverse transcriptase polymerase chain reaction (RT-PCR) was positive for an e1a2 BCR-ABL1 fusion transcript coding for the 190 kDa BCR-ABL1 fusion protein. A hematologic neoplasm next generation sequencing (NGS) 141 gene panel that was obtained based on the first bone marrow reported only two mutations of unknown significance in TET2 (p.L1322R) and P2RY2 (p.V77A). There were no pathogenic variants detected for FLT3 exon 14 (internal tandem duplication), FLT3 exon 20 (tyrosine kinase domain), NPM1 exon 11, CEBPA, and KIT exon 17 p.D816V at a minimum allelic fraction of 1.0%.

The patient was initially treated with a 7 + 3 cytarabine-based induction regimen: seven daily doses of cytarabine (100 mg/m^2) from day 1 to day 7, three daily doses of daunorubicin (90 mg/m^2) from day 1 to day 3, and a single dose of Mylotarg (gemtuzumab ozogamicin, 4.5 mg/m^2) on day 1. The detection of p190 BCR-ABL1 transcript at day 5 led to the addition of daily doses of 100 mg of dasatinib (tyrosine kinase inhibitor, TKI) from day 7 onwards. Intrathecal cytarabine therapy was omitted due to a low number of platelets. The patient was pancytopenic and needed multiple red blood cells and platelets transfusions. On day 14, peripheral blood showed severe pancytopenia and bone marrow showed a hypocellular (<5%) bone marrow with decreased trilineage hematopoiesis and 1% blasts. Although flow cytometry evaluation revealed a negative immunophenotypic study, FISH studies were positive for t(9;22) and inv(16) in 25.1–27.1% of the interphase cells. Conventional cytogenetics did not yield enough metaphases for a complete study. Dasatinib was stopped on day 21 due to persistent leukopenia. G-colony stimulating factor was given once on day 21 and on day 23. Notably on day 20, the patient’s clinical course was complicated by a skin ulceration in his toes that later resulted in disseminated Fusarium infection (Figure 4). Unable to obtain a bone marrow biopsy to evaluate for hematopoietic recovery, dasatinib was restarted on day 34. On day 45, peripheral blood was significant for absolute lymphopenia and monocytosis. Day 45 bone marrow biopsy showed a hypercellular marrow (80%), increased trilineage hematopoiesis, and less than 1% blasts. Flow cytometry on the same specimen was reported as a negative immunophenotypic study. The conventional cytogenetic study showed normal karyotype.
and RT-PCR analysis for p190 \textit{BCR/ABL1} transcript was undetectable. His clinical status was in complete remission (CR), and the patient was eventually discharged on day 60.

Patient was kept on a continued daily dose of 100 mg of dasatinib. However, the patient had gradually increasing Fungitell values and eventually developed fulminant \textit{ Fusarium } infection. He was admitted for bilateral pneumonia on day 120 and was treated with amphotericin (5 mg/kg). He was later enrolled on a clinical trial for an alternative oral-based antifungal medication therapy. His fungal infection was reported to have improved with decreased pulmonary infiltrates and a healed foot wound. The patient returned on day 180 for bone marrow transplant evaluation. His peripheral blood smear was remarkable for pancytopenia and 9% circulating blasts. His bone marrow showed persistent AML with 64% blasts and blast equivalents involving a mildly hypercellular bone marrow (50–60%) with decreased trilineage hematopoiesis. The corresponding flow cytometry on the bone marrow specimen revealed 30% of aberrant myeloid blasts that were positive for CD45 (dim), CD34, CD117, HLA-DR, CD13, CD33, and CD38. Chromosome study showed complete resolution of the t(9;22) subclone (negative by FISH and RT-PCR); however, the inv(16) clone resurfaced with other additional abnormalities significant for clonal evolution (Figure 5). Fungitell values were again high, and CT scan showed findings consistent with pneumonia and pansinusitis. Bronchial lavage cultures and blood cultures were negative for microorganism growth. Bone marrow hematopoietic stem cell transplantation (HSCT) was eventually contraindicated. The patient preferred hospice care and died two months after.

3. Discussion

An inv(16) abnormality is found in 5–8% of younger patients with AML, while the Ph chromosome is a rare event in AML with a reported incidence ranging from 0.5% to 3% [1, 6]. \textit{BCR-ABL1} AML is now included as a new provisional entity in the 2017 revised WHO classification of hematopoietic malignancies [1, 7]. This entity excludes cases with evidence...
of the history of CML. Literature review describes a limited number of cases with AML with BCR-ABL1 translocation that tend to incorporate additional distinct genetic aberrations including inv(16), t(8;21)/RUNX1-RUNX1T1, t(15;17)/PML-RARA, inv(3), 5q deletion, and NPM1 mutation [8, 9].

Our case report similarly illustrates a patient with de novo AML with combined BCR-ABL1 (p190 form) and inv(16) abnormalities.

The Ph chromosome was observed as a subclone in our patient suggestive for “real AML” as Bacher et al. described in his case series [8]. In case #2, their patient had Ph chromosome-positive subclones as a secondary genetic alternation along with inv(16) at initial diagnosis. The patient was treated with hydroxycarbamide and daunorubicin/cytarabine followed by a TKI, imatinib. The patient went into remission but relapsed three months later. At relapse, cytogenetics showed 22 metaphases carrying an inv(16), two of which had an additional t(9;22). The first relapse was treated by intensified chemotherapy using fludarabine, cytarabine, G-CSF, and idarubicin, and again complete

Figure 3: Fluorescence in situ hybridization (FISH) studies on interphase cells showing (a) CBFB and MYH11 rearrangement, dual fusion probe (Cytocell); (b) BCR/ABL1 translocation, dual fusion probe (Cytocell); and (c) normal FISH signal pattern for RUNX1T1/RUNX1 rearrangement, dual fusion probe (Abbott molecular).

Figure 4: Fusarium infection presenting as a skin ulceration in his toes.
remission was achieved. A second relapse occurred ten months from initial diagnosis where 10 of 18 metaphases showed inv(16), while the other eight had evidence of both inv(16) and t(9;22). Their patient’s clinical status after the second relapse is unknown. In contrast, our case at relapse showed complete resolution of the t(9;22) subclone (negative FISH and RT-PCR for BCR-ABL1), but the inv(16) clone resurfaced with other additional abnormalities significant for clonal evolution. This finding substantiates the efficacy of a TKI inhibitor in cases of Ph-positive AML.

Similar de novo and therapy-related AML cases with concurrent inv(16) and BCR-ABL1 rearrangements are compared in Table 1 [10–14]. Bustamante and team described a rapid response to single agent treatment with imatinib and demonstrated a negative finding of BCR-ABL1 fusion by FISH or RT-PCR after 3 weeks of therapy. Salem et al. included one patient with de novo AML and one with initial AML with CBFB rearrangement but subsequently acquired a BCR-ABL1 translocation [4]. The former received induction therapy with FLAG-IDA (fludarabine, cytarabine,idarubicin, and G-CSF) regimen and dasatinib with clinical remission in 21 months, and the latter received an induction with 7 + 3 regimen and dasatinib but relapsed after 8 months and died 2 years after initial diagnosis [4]. Miura et al. and Secker-Walker et al. reported stable remissions up to 70 months were achieved after allogenic stem cell transplantation.

We also know that the Ph chromosome can pair up with other abnormalities in AML. Han JY and team presented an AML case with a known prognostically adverse aberration inv(3) and monosomy 7 with Ph chromosome as a secondary abnormality at diagnosis [15]. The patient was treated with induction chemotherapy, but the patient’s course was complicated by neutropenic fever and acute renal failure. Repeated bone marrow examinations showed the presence of persistent leukemia, and the patient subsequently went into hospice care. Mozziconacci et al. described two cases, one in which BCR-ABL1 translocation was in combination with inv(3) where the patient did not respond to initial treatment and died [9]. The other case was a more favorable rearrangement involving acute promyelocytic leukemia where a total of 100 mitoses were analyzed and two metaphases with t(15;17) and t(9;22) were found. The patient was treated with all-trans retinoic acid and chemotherapy and achieved complete remission on day 30. At 3 months, a very low level of MBCR (b2a2) transcript was detected. RT-PCR was still positive at 4 months but negative at 9, 14, 17, and 30 months. 4 years after diagnosis, the patient was still in remission. These findings suggest prognosis of AML with Ph-positive subclones can be associated with the corresponding cytogenetic abnormality.

Interestingly, cases with CML in the blast phase that acquire an inv(16) aberration have a poor prognosis. Salem et al. studied ten patients with combined inv(16) and BCR-ABL1 cytogenetic abnormalities and seven of which were CML cases [4]. In the seven patients, six died with a median overall survival time of 14 months despite intensive chemotherapy and targeted therapy with TKI [4]. Analyzing these cases and cases from Table 1, we can conclude that the p210 form was found in CML cases that transformed into the blast phase, and the p190 form was found in ‘true AML’ with the exception of the case by Ninomiya et al. [16]. The p190 isoform is also more commonly associated with leukemogenesis leading to BCR-ABL1-positive acute lymphoblastic
leukemia than AML [17, 18]. However, the immunophenotypic study from our case is against a lymphoblastic or mixedphenotypic leukemia.

Due to the rarity of this disease, the prognosis is difficult to determine. CBFB rearrangement in AML with no additional mutation is known to have a favorable prognosis. A study with 201 de novo AML patients indicated that the 5-year survival probability was 43% for CBFB-MYH11 rearrangements [19]. Ph-positive AML appears to be an aggressive disease with poor response to traditional AML therapy or TKI alone [1, 4]. Additionally, only limited cases in literature included multigene mutation analysis in these rare co-occurring inv(16) and BCR-ABL1 abnormalities. Our case and the study by Salem et al. did not detect any pathogenic variants. This indicates that these co-occurring abnormalities act independently of other commonly seen mutations in myeloid neoplasms. Our patient had initially shown a favorable response to treatment and achieved CR by day 45 postdiagnosis. He later developed disseminated Fusarium infection, which compromised his leukemic treatment.

Incidence of Fusarium spp. infection in patients with acute leukemia is 0.06% and the survival rate is 4% [20]. Despite enrolling in an investigational antifungal clinical trial, his fungal infection persisted and was not a suitable candidate for HSCT. Overall, we feel that the combination of inv(16) and BCR-ABL1 genetic abnormalities confers an intermediate prognosis.

De novo AML patients with combined inv(16) and t(9; 22) cytogenetic abnormalities seem to benefit from intensive chemotherapy and targeted TKIs. Decisions about HSCT in intermediate-risk AML were less clear-cut in the past, and nowadays, most patients are considered for HSCT in their first CR [21]. Patient fitness, availability of a sibling donor or an alternative donor, a clinical trial option, and the transplant center experience must be considered when making a decision about HSCT. It is important to note that a longer duration of BCR-ABL1 fusion transcript surveillance can be used to establish a standard of care for such Ph-positive AML patients with additional rearrangements [7].

### Table 1: AML cases with concurrent inv(16) and BCR-ABL genetic abnormalities in this study and selected cases from literature review.

| Sex/age | AML subtype | FAB classification | Karyotype | Other mutation assay(s) | Clinical course | PMID |
|---------|-------------|-------------------|-----------|-------------------------|----------------|------|
| M/40    | De novo     | M4eo              | 46,XY,inv(16)(p13q22)[17]/46,XY,idem,t(9; 22)[q34;q11][3] | Not performed | Chemotherapy and HSCT; stable remission | 8250017 |
| F/9     | De novo     | M4eo              | 46,XX,inv(16)(p13q22)[21]/46,XX,t(9;22)(q34;q11),inv(16)(p13q22)[8]/46,XX[10] | Not performed | Chemotherapy and HSCT; died soon after HSCT | 1728947 |
| M/13    | De novo     | M4                | 46,idem,del(7)(q22q32)[16]/46,idem,t(9;22)[19]/q34,q11.2p13.1)[2] | Not performed | Cytarabine, daunomycin, etoposide + gemtuzumab | 20513535 |
| F/40    | De novo     | M1                | 46,XX,inv(16)(p13q22)[4]/46,XX,t(9;22)(q34;q11),inv(16)(p13q22)[18] | Not performed | One cycle of conventional induction therapy Hydroxy carbamamide, daunorubicin / cytarabine and imatinib with relapse in 3 months. Fludarabine, cytarabine, G-CSF and Idarubicine with complete remission but relapsed 10 months later | 11368385 |
| M/63    | De novo     | M4eo              | At diagnosis: 46,XY,inv(16)(p13q22)[20]/46,XY,t(9;22)(q34q11),inv(16)(p13q22)[2] At last relapse: 46,XY,inv(16)(p13q22)[10]/46,XY,+8,t(9;22)(q34q11),inv(16)(p13q22)[8] | Not performed | Imatinib; remission in 3 weeks | 21275954 |
| F/49    | Therapy-related | M4eo           | 46,XX,inv(16)(p13lq22)[5]/46,XX,t(9;22)(q34;q11)[2][7]/46,XX[8] | Not performed | Fludarabine, cytarabine, G-CSF and Idarubicine + dasatinib, stable remission | 22370710 |
| M      | De novo     | M4eo              | 46,XY,inv(16)(p13lq22)[3]/46,idem,t(9;22)(q34;q11.2)[17] | None (NGS, multiple genes) | Gemtuzumab ozogamicin induction + Dasatinib; a first relapse diagnosed 6 months from initial diagnosis. Hospice. | 28253536 |
| M/55    | De novo     | M4eo              | At Diagnosis: 46,XY,inv(16)(p13lq22)[2]/46,sl,t(9;22)(q34q11.2)[20]/46,XX[1],nuc ish(MYH11,CBF)x3(MYH11 con CBF)x2/[190/200]/(ABL1,BCRX3/BLX1 con BCRX2) [188/200] 13-day follow-up: 46,XY[2],nuc ish(ABL1,BCR)x3(ABL1 con BCR)x2/[88/350]/(MYH11,CBF)x3(MYH11 con CBF)x2/[95/350] 45-day follow-up: 46,XY[20] 188-day follow-up: 51,XY,+8,+9,+13,inv(16)(p13lq22),+18,+22[19]/46,XY[1],nuc ish(MYH11,CBF)x3(MYH11 con CBF)x2/[155/200]/(ABL1x2+3,BCRX2+3)[372/500] | None (NGS, multiple genes) | Current case | Current case |
4. Conclusion

Molecularly defined genetic abnormalities in AML have a significant impact on a patient’s management and prognosis. AML presenting with both inv(16) and t(9;22) abnormalities confers an intermediate prognosis. The pathogenic effect of the occurrence of these abnormalities acts independent of other common molecular mutations seen in myeloid neoplasms. These cases are rare and need to be documented and studied further to formulate better management strategies. Such cases may benefit from intensive chemotherapy and TKIs as a bridge to stem cell transplantation. Comorbidities and infectious diseases arising from an immunocompromised state must be taken into consideration when planning treatment regimens to prevent doing more harm than benefit to the patient.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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