Case Report

t(1;3)(p36;p21) as the Sole Clonal Abnormality in Refractory Acute Myeloid Leukemia

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Acute myeloid leukemia (AML) is a heterogeneous group of diseases with a multitude of molecular genetic aberrations and variable clinical outcome. Clonal chromosomal abnormalities have been identified in over 50% of AML cases, and have been regarded as one of the most important prognostic markers. We present a case of a 56-year-old Hispanic man with AML with minimal differentiation. Morphologically, the bone marrow was hypercellular with trilineage hypoplasia and 80% blasts. Flow cytometry analysis showed that the blasts were of myeloid immunophenotype. Conventional cytogenetic analysis showed t(1;3)(p36;p21) as the sole cytogenetic abnormality in 5 of 20 metaphases analyzed. The patient received daunorubicin and cytarabine, and achieved first remission. He relapsed 4 months later, and was treated with fludarabine, cytarabine, idarubicin, and G-CSF, and consolidated with high-dose cytarabine. He then received matched related stem cell transplantation. However, the disease relapsed again, and the patient died 11 months after initial diagnosis. To our best knowledge, this is the first report of t(1;3)(p36;p21) as the sole cytogenetic abnormality.

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Key Words: *t(1;3)(p36;p21); acute myeloid leukemia, refractory*

INTRODUCTION

Acute myeloid leukemia (AML) is a clonal hematopoietic stem cell disorder that is characterized by an uncontrolled proliferation of myeloid blasts in the bone marrow and defective production of normal blood cells, which may result in fatal infection, bleeding, and organ failure due to leukemic infiltration.[1] It has been well-recognized that AML is a heterogeneous group of diseases with a multitude of molecular genetic aberrations and variable clinical outcome. Clonal chromosomal abnormalities have been identified in over 50% of AML cases, and have been regarded as one of the most important prognostic markers.[1] Cytogenetic results have been integrated as an important part in the diagnosis, classification, risk stratification, treatment decision, and monitoring responses to therapy in the management of AML patients.

Numerous recurrent cytogenetic abnormalities have been described. Translocation between chromosome 1p36 and chromosome 3p21 is a rare recurrent cytogenetic aberration that has been reported in a variety of hematopoietic neoplasms including non-Hodgkin lymphoma (NHL), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), chronic myelogenous leukemia (CML) and AML. Thirteen cases have been reported to date.[2-9] However, t(1;3)(p36;p21) is part of a complex karyotype in all cases reported. We report the first case of a 56-year-old Hispanic man with AML in which t(1;3)(p36;p21) occurred as the sole cytogenetic abnormality.

CASE REPORT

The patient was a 56-year-old Hispanic man who initially presented with mouth ulcers, eye infection, and fatigue in June 2008. He was found to be cytopenic with a white cell count of 5.9 K/uL, hemoglobin of 8.5 g/dL, and platelet count of 30 K/uL, with 45% circulating blasts. A bone marrow examination performed on June 25, 2008 revealed a hypercellular marrow with trilineage hypoplasia, dysgranulopoiesis, dyserythropoiesis, and 80% blasts. The blasts varied from small to intermediate-sized to large with fine chromatin, prominent nucleolus, and scant to moderate amount of cytoplasm (**Figure 1**). The blasts were negative for myeloperoxidase by cytochemistry. Immunohistochemical studies showed that the blasts were positive for CD34 and CD117, and negative for CD3, CD10, CD20, CD68, myeloperoxidase and terminal deoxynucleotidyl transferase. Flow cytometry immunophenotypic analysis of the bone marrow aspirate material revealed that the blasts were positive for dim CD4, CD11b, CD13, dim CD33, CD34, CD38, CD45, dim CD64, CD117, CD123 and HLA-DR, and were negative for CD2, cytoplasmic CD3, CD5, CD7, CD10, CD14, CD15, CD16, CD19, CD20, CD41, CD56, terminal deoxynucleotidyl transferase and myeloperoxidase. A diagnosis of acute myeloid leukemia with minimal differentiation was made. Cytogenetic study demonstrated a karyotype of 46,XY,t(1;3)(p36;p21) in all the 20 metaphases analyzed (**Figure 2**).

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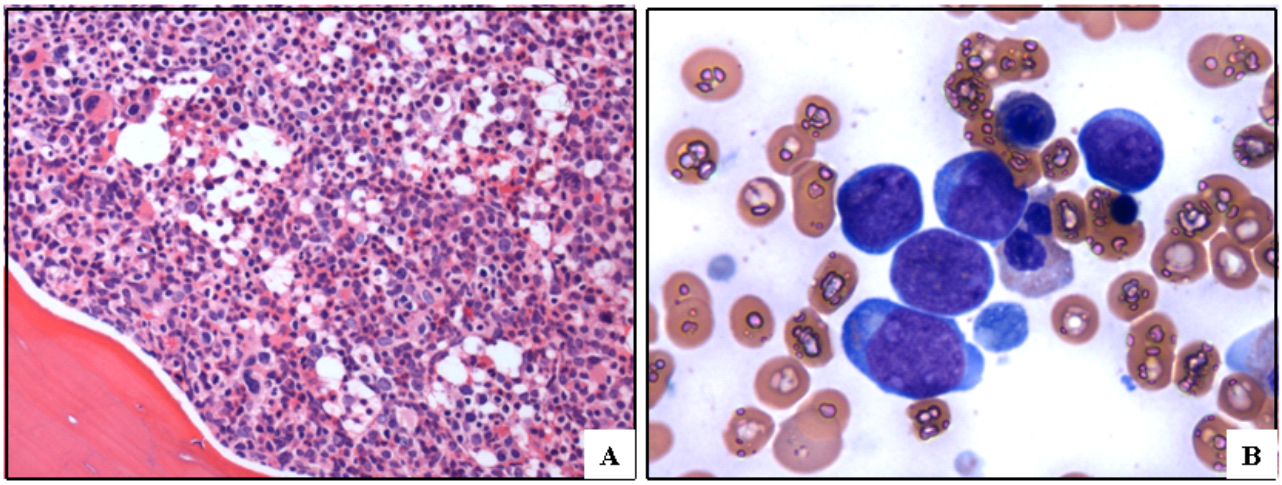

Figure 1. **A.** Bone marrow core biopsy demonstrates a hypercellular marrow with trilineage hypoplasia and markedly increased immature cells (H&E, x200). **B.** Bone marrow aspirate smear shows a cluster of blasts and a dysplastic granulocyte (Wright-Gimesa, x1000).

The patient was admitted to a local hospital, and was treated with induction regimen of daunorubicin and cytarabine (7+3). A repeat bone marrow performed on July 30, 2008 showed no evidence of leukemia. The patient declined further chemotherapy. He remained well until November 2008 when a bone marrow examination revealed relapsed disease. He was treated with a salvage regimen with fludarabine, cytarabine, idarubicin, and G-CSF (FLAG), and came to our institution for further treatment options.

Upon presentation at our institution, his white cell count was 6.9 K/uL, hemoglobin 12.8 g/dL, and platelet count 355 K/uL, with a normal differential count. His serum lactate dehydrogenase level was 581 IU/L, and his serum β2-microglobulin level was 1.8 mg/L. There was no palpable hematosplenomegaly or lymphadenopathy. Bone marrow biopsy showed no morphologic or immunophenotypic evidence of AML. He received consolidation therapy with high-dose cytarabine in December 2008. He then received matched related stem cell transplantation in February 2009. However, the disease relapsed again in April 2009. The t(1;3)(p36;p21) was detected at the time of relapse. The patient decided not to receive any further treatment for AML, and he died 11 months after initial diagnosis.

DISCUSSION

Cytogenetic abnormalities have been regarded as one of the most important prognostic factor in AML. Clonal chromosomal aberrations have been detected in over 50% of AML, with +8, -7/del(7q), +21, -5/del(5q) being the most common.[10] Hematopoietic neoplasms associated with t(1;3)(p36;p21) is a rare entity and has only been described in 2 cases of AML, both were classified as acute promyelocytic leukemia (APL). In both cases, t(1;3) presented as part of complex cytogenetic abnormalities.[3,4] We report a case of AML with t(1;3)(p36;p21) as the sole cytogenetic abnormality.

t(1;3)(p36;p21) has been reported in only 13 cases to date, and has been associated with a variety of hematopoietic neoplasms, including NHL (2 cases of follicular lymphoma, 1 case of diffuse large B-cell lymphoma), ALL (n=3), MDS (n=3), CML (n=2), and AML (n=2).[2-9] There were 7 men and 6 women. Most patients were in the fifties (age range, 7-87 years). Partial clinical information was available on 8 patients,[3] 5 had received chemotherapy for prior malignancies including alkylating agents in 3 cases. Five patients had t(1;3) detected at initial presentation. Two had t(1;3) detected upon relapse, and 1 had t(1;3) at CML progression to accelerated phase. Treatment information was not available for most of the patients. The survival was reported to be very variable, ranging from 25 days to 16 years.[2] The t(1;3)(p36;p21) was a part of complex karyotypes in all 13 cases; accompanying t(9;22)(q34;q11) in CML, t(15;17)(q22;q21) in APL, -7 in MDS, t(14;18)(q32;q21) in follicular lymphoma, and del(6q) in 3 other cases.[3-9] This suggests that the t(1;3)(p36;p21) in those reported cases was a secondary change.

In the two cases of APL, the first patient was a 55-year-old woman with a 3-way translocation involving 1p36 and 3p21 showing cytogenetic results of 46,XX,t(1;2;3)(p36;q21;p21),t(15;17)(q22;q11.2)[20]/46,XX [10]. No other clinical information was provided. The patient only survived 64 days.[3] The second patient was a 44-year-old Japanese man who was initially diagnosed as APL with t(15;17) as the sole abnormality. The patient was treated with two courses of induction chemotherapy and achieved complete remission. t(1;3)(p36;p21) occurred at the third relapse (56 months after initial diagnosis). The patient died of sepsis 15 months after the detection of t(1;3)(p36;p21). This indicates that the t(1;3)(p36;p21), as well as its variant

t(1;2;3)(p36;q21;p21) in the other case, was an acquired change that may be related to the patient's chemotherapy as the authors suggested.[4] However, in our case, t(1;3) was the sole cytogenetic abnormality at patient's initial presentation of AML. It was not associated with any prior chemotherapy or radiation therapy, nor was it shown as an evidence of clonal evolution.

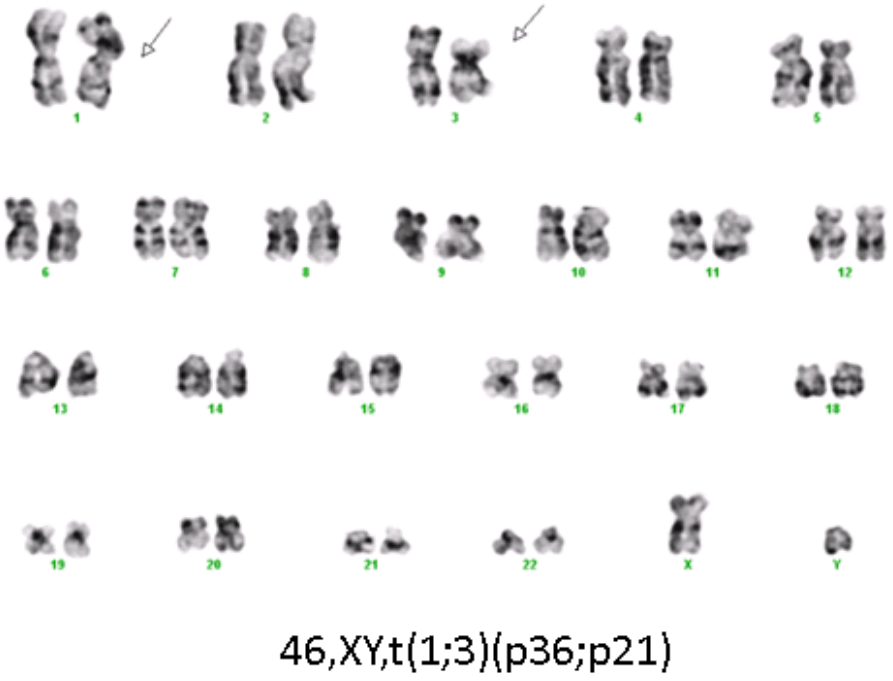

Figure 2. A representative karyotype shows 46,XY,t(1;3)(p36;p21). The arrows indicate translocations between chromosomes 1p36 and 3p21.

A number of genes located at chromosome 1p36 have been reported to be associated with the development of cancers. Among these genes, several have been implicated in the pathogenesis and/or progression of myeloid disorders, including *MDS2* (myelodysplastic syndrome 2 translocation associated) that has been involved in myeloid neoplasms with t(1;12)(p36;p13); *PIK3CD* (phosphoinositide-3-kinase, catalytic, delta polypeptide) that encodes p110delta, an upstream regulator of AKT, and has been involved in AML and other hematopoietic malignancies; *PRDM16* (PR domain containing 16, previously know as *MEL1*) that was initially identified in t(1;3)(p36;q21) myeloid leukemias and has subsequently been described in AML, MDS, and therapy-related myeloid neoplasms; *PRDM2* (PR domain containing 2, with ZNF domain) that has been implicated in leukemogenesis; and *RAP1GAP* (RAP1 GTPase activating protein), the expression level of which is increased in MDS patients.[2] Genes at 3p21 that have been implicated in leukemogenesis include *CCR1* (chemokine (C-C motif) receptor 1) and *CCR9* (chemokine (C-C motif) receptor 9), both have been reported to be expressed in a variety of hematopoietic neoplasms including AML; and *NCKIPSD* (NCK interacting protein with SH3 domain) that was identified as a partner gene with *MLL* in t(3;11)(p21;q23) therapy-related AML.[2] With FISH using BAC/PAC probes, Tri et al. determined the 1p36 breakpoint at 1p36.2 and the 3p21 breakpoint at 3p21.3.[4]

Based on the variable presentations of t(1;3)-associated neoplasms, it is likely that it is heterogeneous at the molecular level. It is also possible that other cytogenetic abnormalities in addition to t(1;3) in the reported cases might play roles in the heterogeneity of these diseases.

In summary, we report the first case of an AML with t(1;3)(p36;p21) as the sole cytogenetic abnormality in a 56-yea-old Hispanic man with immature phenotype, high blast count, resistance to multiple chemotherapy, and a poor clinical outcome. The t(1;3) was detected at initial presentation and was not associated with prior exposure to chemotherapy or radiation therapy.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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