

Case Report

No Adverse Effect of Residual Neoplastic Mast Cells in Systemic Mastocytosis Associated with Acute Myeloid Leukemia with T(8;21) (Q22;Q22); Runx1-Runx1t1 after Bone Marrow Transplantation

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Abstract

Mast cells are often increased in acute myeloid leukemia (AML) with t(8;21), however, concurrent development of systemic mastocytosis (SM) is rare. Here we report the case of a 22-year-old man with concurrent AML and SM. Although he achieved remission with chemotherapy, he relapsed with development of a myeloid sarcoma in the brain. After successful matched sibling hematopoietic stem cell transplant, neoplastic mast cells carrying both the RUNX1-RUNX1T1 translocation and the c-kit point mutation D816 V persisted in the marrow for up to 18 months after transplantation. Despite this, leukemia remains in continuous complete remission for 8.75 years. This observation suggests that neoplastic mast cells in SM-AML with t(8;21) have no adverse effect on hematopoiesis after bone marrow transplantation.

INTRODUCTION

Mastocytosis encompasses a spectrum of disorders in which there is pathological accumulation of mast cells in tissue and bone marrow. The World Health Organization (WHO) classification of mastocytosis includes four categories of systemic mastocytosis (SM): (1). indolent SM, (2). aggressive SM, (3). SM with associated clonal hematologic non-mast cell lineage disease (SM-AHNMD), and (4). mast cell leukemia. Approximately 20-30% of SM patients develop a second hematologic disorder (i.e. SM-AHNMD). In most cases this clonal myeloid disorder is either myelodysplastic syndrome or acute myeloid leukemia [1].

At present the published cases of SM associated with acute myeloid leukemia (SM-AML) cover the spectrum of FAB subtypes, with a majority representing either the M2 or M5 subtype [2].

Based on cytogenetic abnormalities, the t(8;21) (q22;q22) (RUNX1-RUNX1T1) positive AML is the most common subtype of SM-AML. In a recent study of 40 AML patients with the t(8;21), four (10%) were found to have SM, and eight (20%) had benign mast cell hyperplasia [3]. To date only limited information about the relationship between the two coexisting clonal disorders has been published.

Cases of AML in which t(8;21) is the sole cytogenetic abnormality generally have a more favorable outcome. However, SM-AML with t(8;21) carries a poor prognosis [4]. Therefore, the pathological role of the neoplastic mast cells in SM-AML with t(8;21) deserves further evaluation.

In this report, we demonstrate presence of the RUNX1-RUNX1T1 gene rearrangement associated with t (8;21) in mast

cells from a patient who had SM-AML with t(8;21). The findings show that a common cytogenetic abnormality exists in both the myeloid blast and the mast cell compartments. In addition, we demonstrate that even though neoplastic mast cells were detected in bone marrow up to 18 months after successful matched sibling hematopoietic stem cell transplant, the leukemia remained in complete remission for 8.75 years, suggesting that the neoplastic mast cell population has no adverse effect on hematopoiesis under the setting of bone marrow transplantation (BMT).

MATERIALS AND METHODS

Case report

A previously healthy 22-year old-man presented in February 2004 with an elevated total leukocyte count of 18,000/ml, a hematocrit of 30%, and platelet count of 49000/ml with 48% circulating blasts. The bone marrow smear revealed 60% blasts. The complete karyotype was 46 XY, t(8;21) (q22;q22). Therefore he was diagnosed with AML-M2 according to FAB criteria, and AML with t(8;21) according to the WHO classification. Induction chemotherapy (idarubicin and cytarabine, 3+ 7 protocol) was administered, and the patient entered complete remission (CR). He also received 3 cycles of consolidation chemotherapy with high-dose cytarabine, that ended in May 2004. His second cycle of chemotherapy was complicated by unexplained right facial swelling which resolved spontaneously. Bone marrow biopsy specimens obtained in April and May 2004 demonstrated no evidence of residual acute leukemia. The patient remained in CR until December 2004, when he presented with 2 weeks of increasing headaches, word finding difficulty, blurry vision, photophobia and several days of nausea and vomiting. An MRI confirmed the presence of a 5x 4x3 cm left middle cranial fossa mass with 6mm rightward shift, subalpine and left uncial herniation and Dural involvement. He underwent a left temporal craniotomy with excision of this mass and Omay reservoir placement. There was some residual tumor associated with the dura that could not be removed. The surgical specimen demonstrated an extensive blast infiltration, and the diagnosis of a myeloid sarcoma was established. A bone marrow biopsy at this time confirmed marrow relapse with 50% blasts. The patient was reduced with FLAG (fludarabine, cytarabine and G-CSF)-Idarubicin, and his CNS disease was treated with intrathecal cytarabine and radiation.

In January 2005, the patient was referred to our hospital for a matched sibling allogeneic transplant. A routine bone marrow biopsy prior to his transplant was performed, and revealed no evidence of residual acute leukemia. However, atypical mast cells appeared on the aspirate smears, and the bone marrow biopsy showed multifocal paratrabecular and perivascular aggregates of mast cells. Accordingly, the diagnosis of bone marrow systemic mastocytosis was established. Reviewing the multiple previous bone marrow biopsies and the brain biopsy, the final diagnosis of SM-AHND of the AML subtype was established retrospectively. The patient had no symptoms resulting from mastocytosis at the time of our evaluation.

In February 2005, the patient received an ablative matched sibling allogeneic transplant following conditioning with total body irradiation and high dose cyclophosphamide. His transplant

course was complicated by biopsy proven graft-versus-host disease of his stomach which was treated with high dose glucocorticoids with an excellent response. Evaluation of five post-transplant bone marrow biopsy specimens obtained on day 28, 70, 113, 7 months and 12 months revealed no morphologic, immunophenotypic or cytogenetic evidence of residual leukemic blasts. These samples did however show persistent mastocytosis with multifocal mast cell aggregates. A final bone marrow biopsy was performed (18 months post-transplant) and revealed no evidence of relapse of acute leukemia and in addition showed a significant decrease in the number of neoplastic mast cells and the absence of mast cell aggregates. His leukemia remains in continuous complete remission for 8.75 years.

Histologic and Immunohistochemical Staining

Bone marrow aspirate smears were routinely stained with Wright-Giemsa. The bone marrow trephine biopsy specimens were fixed in 10% neutral buffered formalin, mildly decalcified overnight in edetic acid, and embedded in paraffin. All slides were routinely stained with hematoxylin and eosin. Immunohistochemical stains were performed on routine paraffin sections using the avidin-biotin peroxidase complex technique. Antibodies used included CD117, mast cell tryptase, myeloperoxidase, and CD34. All antibodies were obtained from DAKO, Carpinteria CA.

Flow Cytometric Immunophenotyping

Bone marrow cells were labeled as follows. Briefly, 100 μ l of bone marrow was stained with anti-CD25 (Fluorescein isothiocyanate-conjugated, i.e.; FITC-conjugated) or anti-CD2 (FITC-conjugated), anti-CD117 (Phycoerythrin-conjugated, i.e., PE-conjugated) and anti-CD45 (Peridinin chlorophyll protein conjugated) (all antibodies obtained from Becton Dickinson Immunocytometry System, San Jose, CA) for 20 minutes at room temperature in the dark. Erythrocytes were lysed with buffered NH₄CL at 37° C for 5 minutes then washed in PBS containing 2% FCS. The cells were fixed with 2% paraformaldehyde then analyzed on the FACS Calibur flow cytometry (Becton Dickinson). Data analysis was performed using Winlist software (Verity House, Topsham, ME). The bright CD117 cells with coexpression of CD25 or CD2 were sorted using a FACS Vantage and cytopspin preparation of the purified cells was obtained for FISH analysis.

Cytogenetic studies

Conventional cytogenetic analysis was performed on 24 hour unstimulated bone marrow culture using standard techniques, and analyzed following trypsin Giemsa banding; 20 metaphases were evaluated.

Fluorescence in situ hybridization analysis

Fluorescence in situ hybridization (FISH) was performed by the Cytogenetics Laboratory at Seattle Cancer Care Alliance. Dual color FISH with an RUNX1 (AML-1) and RUNX1T1 (ETO) translocation probe (Vysis, LSI AML1/ETO DF cat 32-191006) was performed on cytopspin preparation of the purified cells to evaluate interphase nuclei for the RUNX1-RUNX1T1 gene rearrangement associated with t(8;21). 200 nuclei were evaluated.

C-kit d816v point mutation assay

PCR amplification in combination with sequence specific restriction enzyme digestion and fluorescence-based capillary electrophoresis was used to identify the D816V c-kit point mutation. The assay was developed by Hematologics Inc. PCR was used to amplify a portion of the C-kit region that acquires the D816V mutation. The amplicon products are then digested with the *PleI* restriction enzyme. An intact 138 base pair product will be generated from normal samples. Samples harboring a homozygous D816V mutation have an active *PleI* restriction site and a 68 base pair product will be generated. The different-sized amplicons are identified by fluorescence-based capillary electrophoresis.

RESULTS

Mastocytosis in the pre-transplant marrow

A routine bone marrow biopsy prior to the transplant was performed in our hospital in January 2005, and showed no morphologic, immunophenotypic, or cytogenetic evidence of residual leukemic blasts. However, aspirate smears revealed significantly increased focal aggregates of mast cells with more than 50% displaying atypical morphology with hypogranulated cytoplasm, and some with elongated cytoplasmic extensions (Figure 1A, 1B). The core biopsy showed slight hypocellularity, with multifocal peritrabecular and perivascular aggregates (> 15 cells) consisting primarily of intermediate to large cells with low nuclear to cytoplasm ratio, abundant clear cytoplasm and indented bean shaped nuclei (Figure 1C), occupying approximately 5% of marrow space. Immunohistochemical stains for mast cell tryptase (Figure 1D) and CD117 showed strong staining within the abnormal cells, confirming that these cells were indeed mast cells. In addition, flow cytometry studies identified a population of CD117 (bright) positive mast cells (0.3% of the total non-erythroid cells) with aberrant expression of CD2 and CD25 (Figure 2). Therefore, these findings satisfied one major and two minor criteria for a diagnosis of systemic mastocytosis [1].

Coexistence of acute myeloid leukemia and mastocytosis

After noting these findings, all four previous outside bone marrow biopsies were requested for re-examination of mast cell infiltration. The first biopsy was performed at presentation in February 2004, and aspirate smears revealed 60% myeloid blasts with round to folded nuclei, scant to moderate amounts of blue cytoplasm and occasional

Auer rods (Figure 1A). Ninety percent of the cells were positive for myeloperoxidase. Dysplastic features were seen in maturing granulocytes. In addition, atypical mast cells with decreased granularity were identified. On flow cytometric analysis, these blasts expressed CD34, HLA-DR, dim CD13, dim CD19, dim CD4, partial CD56 and partial CD15. No immunophenotypic study for mast cells was performed at that time. Because there was no core biopsy, we were also unable to verify the presence of large mast cell aggregates in this first biopsy. However, multiple large aggregates of mast cells (>15 cells) with co-expression of CD117 and tryptase were noted in the background of samples

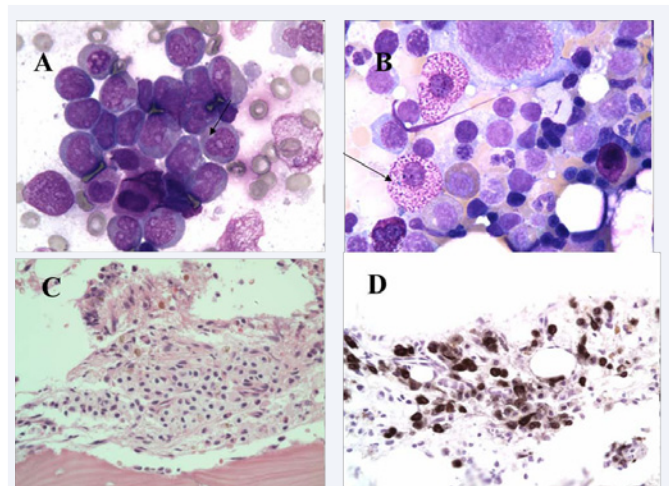


Figure 1 Coexistence of AML and mastocytosis. (A): Myeloblasts with occasional Auer rods (arrow) in the aspirate at initial diagnostic marrow (Wright-Giemsa, X1000); (B): Atypical mast cells (arrow) with hypogranulated cytoplasm in the aspirate at the pre-transplant marrow (Wright-Giemsa, X1000); (C): Mast cell aggregates in the biopsy (H&E, X400); (D): Atypical mast cells with expression of tryptase as demonstrated by immunohistochemistry (X400).

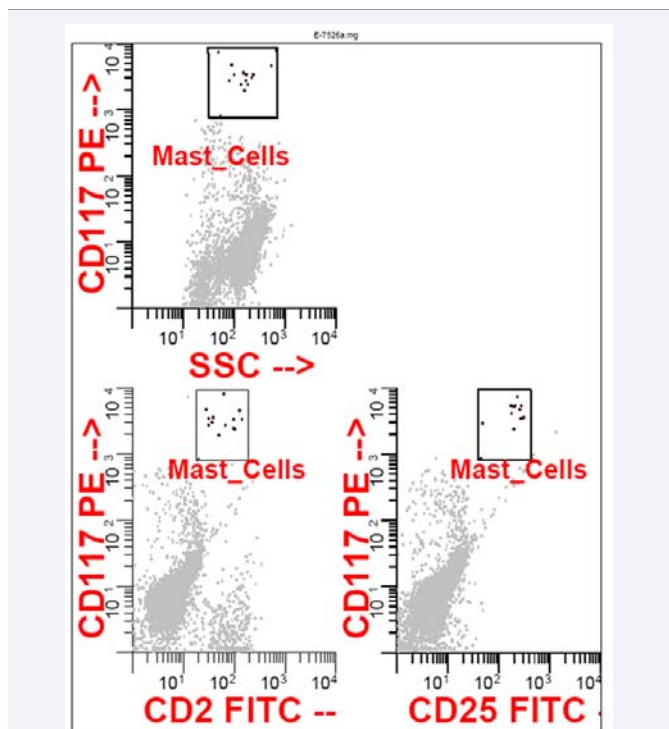


Figure 2 Immunophenotyp of mast cells by flow cytometry. Atypical mast cells express bright CD117 with aberrant expression of CD2 and CD25.

containing diffuse blast cell infiltration on the biopsy performed in December 2004, the time of the original diagnosis of recurrent acute myeloid leukemia. These findings demonstrated the coexistence of AML and mastocytosis in this patient at the time of original diagnosis.

In addition, two bone marrow biopsies obtained during

clinical remission in April and May 2004 (after chemotherapy) also revealed these atypical mast cells on the aspirates with variably size of mast cell aggregates in the core biopsies. These combined findings indicate a persistent mastocytosis existing at presentation with AML and throughout the treatment course independent of the presence or absence of neoplastic blasts.

Coexistence of myeloid sarcoma and mastocytosis

In December 2004, the patient had early relapse of disease with the development of a left middle cranial fossa mass. Hematoxylin and eosin stained histologic sections of brain biopsies demonstrated a highly cellular lesion composed predominately of a monomorphic population of large polygonal cells with large nuclei, irregular chromatin, and variable prominent nucleoli (Figure 3 A). Immunohistochemical staining for myeloperoxidase showed strong positivity in most cells (Figure 3B). Flow cytometry confirmed these cells to be myeloid blasts with co-expression of CD45, HLA-DR, CD13, and CD56. A diagnosis of myeloid sarcoma was established. When this biopsy was re-evaluated by us, the additional immunohistochemical stains for mast cells were performed. Interestingly, we found that there were also loosely scattered mast cells with multiple perivascular dense aggregates in the lesion. These mast cells were positive for tryptase (Figure 3C) and CD117, and negative for CD34 and myeloperoxidase. Therefore, the coexistence of myeloid sarcoma and mastocytosis was established.

Mastocytosis in the post-transplant marrow

Five bone marrow biopsies were performed on day 28, 70, 113, and 7, 12 months after transplant. All biopsies showed no morphologic or immunophenotypic evidence of residual leukemia with a normal karyotype as demonstrated by a conventional cytogenetic analysis. However, atypical mast cells with hypogranulated cytoplasm persisted on the aspirate smears. Flow cytometry showed that these mast cells aberrantly expressed CD2 and CD25 at 0.1%, 0.2%, 0.3%, 0.2% and 0.1% of total non-erythroid cells on day 28, 70, 113, and 7 months, 12 months marrow, respectively. The core biopsies showed variably sized mast cell aggregates (occupying 2 to 5% of the marrow space) as confirmed by immunohistochemical staining for tryptase in these marrows. When serum total tryptase was examined on day 113 post-transplant, it was significantly increased (29 ng/ml, >20ng/ml). These combined results indicate that there was a persistent mastocytosis in post-transplant marrow for at least one year. A final bone marrow biopsy was performed at 18 months after transplant, and revealed scattered individual mast cells without mast cell aggregates.

Detection of the RUNX1-RUNX1T1 gene rearrangement in the neoplastic mast cells

As mentioned above, flow cytometric studies showed aberrant mast cells in post-transplant marrow aspirates. Therefore, using a FACS Vantage cell sorter by gating the population with high side scatter and co-expression of CD117 and CD2 or CD25, we purified these cells. This sorted population was subjected to dual color FISH with a RUNX1-RUNX1T1 translocation probe. This was first performed on day 28 post-transplant sorted bone marrow fractions. Only twenty-eight nuclei were available for analysis from the CD25+/CD117+ fraction. Twenty-five nuclei of

28 analyzed (89.5%) from this fraction showed the typical fusion signal pattern associated with RUNX1-RUNX1T1 rearrangement (Figure 4 A). By contrast, no nuclei of 200 analyzed (0%) from the CD25-/CD117- fraction showed the fusion signal (Figure 4 B). These studies were repeated on day 70 post-transplant sorted bone marrow fractions, and similar results were obtained. On that sample, 187 nuclei of 200 analyzed (93.5%) from the CD2+/CD117+ fraction showed the typical fusion signal as compared to no nuclei from the CD2-/CD117- fraction having this fusion signal. These results convincingly demonstrate that there was a RUNX1-RUNX1T1 gene rearrangement associated with t(8;21) cytogenetic abnormality in these aberrant mast cells.

Detection of the c-Kit D816V point mutation in the neoplastic mast cells:

The sorted mast cells from day 113 post-transplant marrow aspirate were evaluated for the D816V c-Kit mutation. To identify this mutation, PCR amplification in combination with sequence

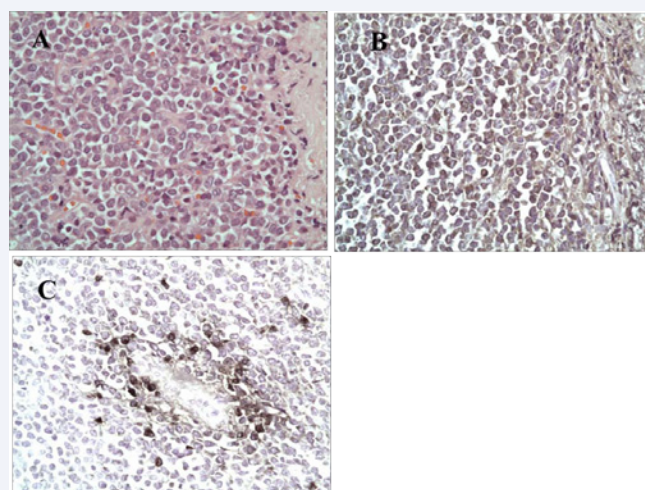


Figure 3 Coexistence of myeloid sarcoma and mastocytosis. Brain biopsy demonstrated a highly cellular lesion composed predominately of blast-like cells (A, H&E, X400) with strong positivity for myeloperoxidase (B), and scattered mast cells with perivascular dense aggregates, which were positive for tryptase as demonstrated by immunohistochemistry (C).

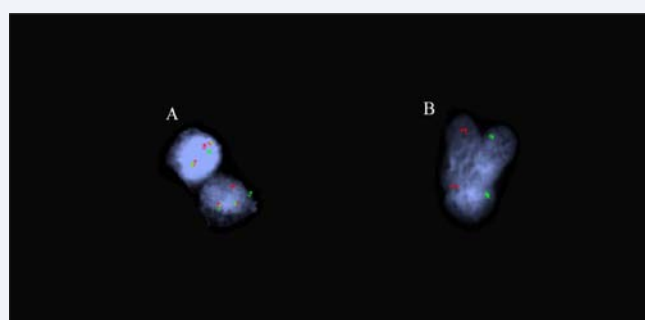


Figure 4 Detection of the RUNX1-RUNX1T1 gene rearrangement in neoplastic mast cells by target FISH analysis. (A) Positive pattern for t(8;21) in the mast cells; RUNX1 is labeled with green and RUNX1T1 is labeled with red; a positive pattern is indicated by two fusions with yellow. (B) Negative pattern for t(8;21) in the control cells.

specific restriction enzyme digestion and fluorescence-based capillary electrophoresis was used. We found that a D816V point mutation was detected in the CD25+/CD117+ sorted mast cell population but not in the sorted CD33+ control cell fraction (Figure 5).

DISCUSSION

Mastocytosis represents a heterogeneous spectrum of diseases in which the pathological hallmark is accumulation of abnormal mast cells in the tissues. Mast cells are thought to be derived from the pluripotent myeloid stem cell and require stem cell factor (SCF) for maturation and development. They play a key role in allergic reactions through release of granules which contain numerous inflammatory mediators. Gain of function mutations in C-kit, the tyrosine kinase receptor for SCF, are often found in patients with systemic mastocytosis, most commonly D816V [5,6]. Tyrosine kinase inhibitors such as imatinib, while able to exhibit preferential cytotoxicity on mast cells with wild-type c-Kit, do not effect mast cells expressing the mutated C-kit with D816V [5,6]. Therefore, it is important to detect such a mutation in this disease due to clinical implication.

Symptoms due to mastocytosis are related to mast cell degranulation or infiltration of various organs. The disease can be classified into distinct clinical categories depending on symptoms and the extent of tissue infiltration [5]. In up to 20% of cases, systemic mastocytosis can be associated with a variety of myeloid stem cell disorders such as myelodysplastic syndromes, myeloproliferative neoplasms or leukemia [1]. These patients must meet criteria for diagnosis of a clonal hematopoietic non-mast cell lineage disease (AHNMD) as well as the WHO criteria for diagnosis of systemic mastocytosis [1]. In such patients, it is important to make both diagnoses since these findings affect prognosis [4,6].

The diagnosis of acute myeloid leukemia (AML) and systemic mastocytosis (SM) can be made concurrently. However, in the majority of these cases, a definitive diagnosis of SM was made after treatment with chemotherapy, when the mast cells infiltrates were more prominent [4]. In our case, SM was not made at the original diagnosis but was originally made at the time of pre-transplant work up. We were able to retrospectively identify persistent mastocytosis coexisting at presentation with AML and remaining through pre- and post-chemotherapy periods regardless of the presence or absence of leukemic blasts. The concurrent diagnosis of SM with AML requires a high index

suspicion based on morphological and immunohistochemical evaluation for a neoplastic mast cell population.

It is not clear whether SM-AHNMD represents a single disorder or two clonal entities. Some studies have addressed the question as to whether the Asp816Val c-kit mutation is present in both SM and the associated non-mast cell lineage disorder. Fritsche-Polanz et al examined 101 cases of AML. Seven cases were positive for the D816V mutation in KIT, all of which demonstrated concurrent systemic mastocytosis. The D816V mutation was present in microdissected mast cells in all 4 cases examined; in addition, the mutation was present in microdissected CD34 positive blasts in 2 of the 4 cases tested [7]. In our study, to determine the relationship between mast cells and leukemic clone, bone marrow mast cells were sorted by gating on the population with high side scatter and co-expression of CD117 and CD2 or CD25, and then examined for the presence of the RUNX1-RUNX1T1 gene rearrangement associated with t(8;21). By fluorescence-in-situ-hybridization (FISH) analysis, we demonstrated that the majority of the mast cells had the RUNX1-RUNX1T1 gene rearrangement. These results show a common cytogenetic abnormality existing in both the myeloid blast and neoplastic mast cell compartment, and support the hypothesis that there is a clonal evolution of systemic mastocytosis and AML from a common hematopoietic progenitor. A similar study had been performed earlier by Pullarkat et al in a case of SM-AML with t(8;21) [8] and several t(8;21) AML cases with increased mast cells [9].

Several groups have reported that AML with t(8;21) is the most common subtype of SM-AML [10,11]. Although cases of AML with t(8;21) as the sole cytogenetic abnormality in general has a better prognosis with therapy using high-dose cytarabine, patients with SM and AML with t(8;21) tend to do worse [4,6]. This is consistent with our patient's clinical course as well. Interestingly, he also had relapse of disease in the CNS with the development of a myeloid sarcoma. The development of CNS myeloid sarcomas is seen in patients with the t(8;21) AML, but is extremely rare in SM-AML with t(8;21) [4]. In our case, we were also able to detect neoplastic mast cells in the myeloid sarcoma as well.

In a recent report of ten patients with SM-AML and t(8;21), four patients failed to achieve remission after standard chemotherapy and seven patients have died of relapsed AML [4]. The two survivors (AML in remission 4 years or 1 year after transplant) had both undergone allogeneic marrow transplantation after ablative radiation-based conditioning. In these two patients, host-derived bone marrow mast cells were detected up to a year after transplant [8,12]. In our patient, neoplastic mast cells can be detected in bone marrow up to 18 months after transplant but start to decline at 12 months after transplant. During this time, the patient experienced clinical graft-versus-host disease. Therefore, a "graft-versus-mast cell" effect may have contributed to the decline of mast cells [13]. In all three cases (two previously published cases), neoplastic mast cells persist in the marrow after transplant, but do not cause any symptoms or adverse consequence. In fact, in the case reported here, AML has been in continuous remission for 8.75 years, and he is the longest known survivor. These data suggest that the neoplastic mast cells seem

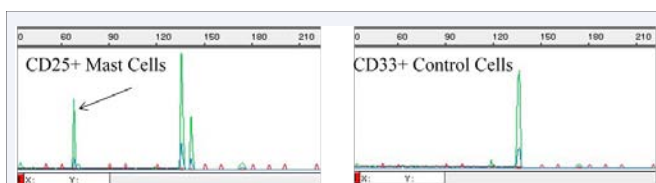


Figure 5 Detection of the c-Kit D816V point mutation in the neoplastic mast cells. A 68 bp digestion product (arrow, indicative for the D816V c-kit point mutation) was detected in the CD25+ sorted mast cell population but not in the CD33+ control cell population. A 138 bp amplicon was present in both the CD25+ mast cell and in the CD33+ control cell specimen.

to be resistant to chemotherapy, and BMT plays an important role in bringing in long term remission through possible graft-versus-mast cell effect. It is therefore possible that it is only under the setting of BMT that the pathological role of residual neoplastic mast cells becomes insignificant. Without BMT, whether or not these neoplastic mast cells contribute to the recurrent disease remains to be determined.

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