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Long-term persistence of nonpathogenic clonal chromosome abnormalities in donor hematopoietic cells following allogeneic stem cell transplantation

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Abstract

We describe two unrelated patients who exhibited multiple chromosomal abnormalities in donor cells after allogeneic peripheral blood stem cell transplantation (PBSCT). The patients were diagnosed with chronic myeloid leukemia and chronic lymphocytic leukemia, respectively, and both underwent non-myeloablative conditioning with cyclophosphamide and fludarabine followed by PBSCT from their HLA-matched opposite-sex siblings. Post-transplant bone marrow cytogenetics showed full engraftment, and the early post-transplant studies demonstrated only normal donor metaphases. Subsequent studies of both patients, however, revealed a population of metaphase cells with abnormal, but apparently balanced, karyotypes. Chromosome studies performed on peripheral blood cells collected from both donors after transplantation were normal. Both patients remained in clinical remission during follow-up of up almost 6 years, despite the persistence of the abnormal clones. Chromosomal abnormalities in residual recipient cells after bone marrow or PBSCT are not unusual. In contrast, only rare reports of chromosome abnormalities in donor cells exist, all of which have been associated with post-bone marrow transplant myelodysplastic syndrome or acute leukemias. Ours is the first report of persistent clonal non-pathogenic chromosome aberrations in cells of donor origin.

1. Introduction

Although rare, chromosome abnormalities resulting in hematological neoplasms in donor cells after allogeneic bone marrow or peripheral blood stem cell transplantation (PBSCT) have been reported. Such cases typically involve myelodysplastic syndrome (MDS) or acute leukemias, and have included abnormalities such as 11q23 (*MLL* gene) translocation [1], monosomy 7 [2], t(8;21) [3], and 6q- [4]. Hypotheses offered to explain the development of donor cell leukemia include transfer of oncogenic material from host to donor cells; immunosuppression

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following bone marrow transplant, leading to inadequate immune surveillance; leukemic transformation of engrafted cells; and occult leukemia in the donor [3].

We describe two cases that showed persistent, apparently balanced, clonal chromosome abnormalities in donor cells after PBSCT. In contrast to prior reports, these rearrangements have not resulted in any disease process in the recipients.

2. Case reports

2.1. Case 1

A 66-year-old man was diagnosed with chronic-phase CML in October 1999. His bone marrow showed 100% Philadelphia (Ph) chromosome-positive metaphases without additional karyotypic abnormalities. He received hydroxycarbamide and interferon alpha until December 1999, when a repeat bone marrow biopsy showed progression to lymphoid blast crisis. The patient was then induced into a second chronic phase after three cycles of hyper CVAD (cyclophosphamide, doxorubicin, vincristine, dexamethasone, methotrexate, and cytarabine). He subsequently received non-myeloablative conditioning with cyclophosphamide and fludarabine, followed by a granulocyte colony stimulating factor (G-CSF) mobilized allogeneic PBSCT from his HLA-identical 78 year old sister, and was given cyclosporine A and mycophenolate mofetil for prophylaxis of graft versus host disease (GVHD). Approximately 2 weeks post-PBSCT, a bone marrow aspirate revealed full engraftment with 100% 46,XX donor cells, consistent with remission. For this specimen as well as for all other cytogenetic studies performed on this patient's cells, unstimulated bone marrow or peripheral blood specimens were cultured for 24 or 48 hrs according to standard procedures.

A subsequent bone marrow aspirate obtained 5 months post transplant revealed recurrence of recipient male cells with highly complex karyotypic abnormalities (including double Ph chromosomes) in 18% of the cells (Table 1). Donor cells comprised 82% of the metaphase cells; 11% of these donor cells showed an abnormal karyotype with two apparently balanced reciprocal translocations: 46,X,t(X;20)(q13;q13.3),t(6;12)(p21.1;q24.3) (Fig. 1). Evidence of disease relapse prompted withdrawal of cyclosporine to promote a graft-versus-leukemia effect. One month later, the bone marrow chromosome analysis once again showed a 46,XX karyotype consistent with leukemia remission and full engraftment with female donor cells.

The patient remained in molecular remission for 32 months until October 2003, when *BCR/ABL1* was detected with a reverse transcription-polymerase chain reaction (RT-PCR) assay. He developed recurrent lymphoid blast crisis in April 2004 and was treated with imatinib (800 mg/day). One month later he received a donor lymphocyte infusion of 2.5×10^7 CD3+ cells/kg, and the imatinib dosage was reduced to 400 mg/day because of neutropenia and thrombocytopenia. Subsequent to this treatment, he became *BCR/ABL1* negative by fluorescence in situ hybridization (FISH), and the bone marrow karyotype again showed 100% 46,XX donor metaphases. Imatinib was discontinued in August 2004. This patient's treatment after PBSCT and relapse have been detailed elsewhere [5].

Shortly after discontinuation of imatinib, a proportion of donor cells once again demonstrated the same abnormal donor female karyotype found previously in the post-PBSCT bone marrow analysis (Table 1). The patient remained in complete molecular remission with engraftment by 100% female donor cells. However, 8% to 35% of the donor cells persistently showed t(X;20) and t(6;12) translocations for more than 6 years following transplantation, until the patient's recent accidental death. The abnormal donor cells detected over the years following this patient were found in both the 24 and 48 hr unstimulated cultures. G-CSF-mobilized PBSCs collected from the patient's donor more than 4 years after transplantation (as a back-up allograft) were

analyzed, and all 50 metaphases from a PHA-stimulated culture showed a normal 46,XX karyotype. As expected, unstimulated cultures did not yield any analyzable metaphases.

2.2. Case 2

A 48-year-old woman was diagnosed with CLL in October 2001, with a CD19+, CD5+, CD23+, kappa+, CD38+ B-cell immunophenotype. The patient showed no response to initial therapy with chlorambucil, and subsequent chemotherapy with fludarabine beginning in February 2002 induced a reduction of lymphocyte count but not of lymphadenopathy. Fludarabine was discontinued in July 2002 because of thrombocytopenia and neutropenia requiring growth factor support. In October 2002, her bone marrow cytogenetic study on cells cultured for revealed a normal 46,XX female karyotype, but FISH demonstrated a *TP53* deletion (17p13.1) in 22% of interphases, without any evidence of trisomy 12, 11q-, or 13q- abnormalities. Since this patient had a mature B-cell lymphoproliferative disorder, her cells were cultured in 2 different ways for all cytogenetic studies: a 48 hr unstimulated culture, as well as a 96 hr culture stimulated with a cocktail of B-cell mitogens [pokeweed mitogen, TPA (4B-phorbol-12-myristate 13), and lipopolysaccharide solution]. Combination chemotherapy with etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) was commenced for cytoreduction as a prelude to non-myeloablative allogeneic PBSCT. In December 2002, she received cyclophosphamide and fludarabine-based conditioning, followed by a G-CSF-mobilized PBSCT from her 6/6 HLA-matched brother. GVHD prophylaxis consisted of cyclosporine A and mycophenolate mofetil.

The patient's post-transplant bone marrow cytogenetic studies showed chimerism (5% to 10% 46,XX recipient cells and 90% to 95% 46,XY donor cells), without any chromosomal aberrations (Table 2). An RT-PCR-based assay chimerism study of polymorphic short tandem repeats (STR) was performed because of persistent lymphadenopathy and a kappa-restricted B-cell population in the peripheral blood. The results revealed that the kappa-restricted B-cells were recipient in origin, confirming persistence of CLL. Cyclosporine A and mycophenolate mofetil were tapered and ultimately discontinued by April 2003 to promote the generation of graft-versus-leukemia effect. Subsequent restaging studies performed 10 months post-transplant revealed complete regression of lymphadenopathy and disappearance of the kappa-restricted monoclonal B-cells. STR-based chimerism studies on B-cells in both the peripheral blood and bone marrow revealed all B-cells had become donor in origin, consistent with remission of CLL. At this time, analysis of a bone marrow aspirate showed a clone with a highly complex, but apparently balanced, karyotype in donor cells which was interpreted as: 46,XY,der(2)inv(2)(p23q23)t(2;11)(q33;q23),der(6)t(2;6)(p23;q15), der(11)t(6;11)(q15;q23) (Fig. 2). This clone was repeatedly detected in 5% to 27% of the donor cells in bone marrow and peripheral blood for 4 years following transplantation, with alternating occasional 100% 46,XY donor karyotype. Over the years, while the abnormal donor cell line was predominantly found in the cultures stimulated with B-cell mitogens, it was also found in the unstimulated culture as well. Despite these karyotypically abnormal cells, the patient's CLL remained in remission during nearly 6 years of follow-up after transplantation. FISH with the *MLL* probe was performed because of the concern that the 11q23 breakpoint might involve the *MLL* locus. Metaphases known to carry the abnormal donor cells with the 11q23 abnormality did not show any evidence of rearrangement of the *MLL* locus.

In 2003, soon after the abnormal donor cell line was detected in the patient, a PHA-stimulated peripheral blood karyotype of her donor brother revealed a normal 46,XY karyotype in the 20 metaphase cells examined. He also remained healthy as of his last follow-up in 2008.

3. Discussion

In this report, we document various unusual chromosomal abnormalities in donor hematopoietic cells—detected in two different allogeneic PBSCT recipients—that were not associated with clonal evolution to any malignancy. The first patient, who was diagnosed with CML, received a non-myeloablative PBSCT from his HLA-identical sister. His post transplant bone marrow cytogenetics showed abnormalities involving chromosomes X, 20, 6, and 12 in donor hematopoietic cells. The second patient was diagnosed with CLL and received a similar non-myeloablative PBSCT from her HLA-matched brother. Her post-transplant bone marrow cytogenetics revealed abnormalities in donor hematopoietic cells, involving chromosomes 2, 6, and 11.

Cytogenetic abnormalities have been detected previously in donor cells following bone marrow transplantation (BMT) or PBSCT. To our knowledge, however, all have been related to and resulted in MDS or AML in the recipient after transplantation. Ours is the first report to describe persistent multiple complex chromosomal abnormalities in donor cells post-transplant that were not associated with the development of a malignancy in either the donor or recipient.

The mechanisms underlying the development of chromosomal abnormalities in donor cells are not fully understood. One possible explanation is the effect of chemotherapy and radiotherapy on the engrafted donor cells. Radiotherapy is a well-known mutagenic factor and can cause bizarre cytogenetic abnormalities; however, neither of our patients received radiotherapy. Chemotherapeutic agents are also known to cause genetic instabilities that can lead to malignant transformation [6–8]. Therapy-related MDS/AML (t-MDS/t-AML), which almost always occurs in recipient cells, can be divided into three categories based upon chromosomal findings and latency period after therapy. Unbalanced abnormalities of chromosomes 5 and/or 7 typically occur 5 to 7 years after exposure to alkylating agents. Overt leukemia is often preceded by a preleukemic or dysplastic phase. On the other hand, *MLL* (11q23) and *RUNX1* (21q22) structural rearrangements are associated with topoisomerase II inhibitor therapy, a shorter latency period (generally 1–3 years) before the development of leukemia (often monoblastic), and no preceding dysplastic phase. And, finally, some individuals develop chromosome abnormalities typically associated with primary AML, such as t(15;17), t(8;21), and inv(16); the latency period is generally less than 3 years and, in contrast to the other two categories of therapy-related disease, the prognosis is good [9]. Both of our patients were treated with cyclophosphamide, a nitrogen mustard alkylating agent. Likewise, both received an anti-topoisomerase II drug: doxorubicin in patient 1, and etoposide in patient 2. Furthermore, the donor cells should not have been exposed to chemotherapy in the recipient, since the transplant was given 24 hours after the last dose of chemotherapy, and fludarabine has a very short half-life.

Cytogenetic abnormalities related to MDS/AML have rarely been detected after treatment with interferon-alpha [10], which patient 1 was exposed to, and with fludarabine, which both patients were treated with [11]. Incidence of other karyotypic abnormalities in Philadelphia chromosome-negative cells in patients treated with imatinib varies between 2% and 15% and includes loss of chromosome Y, trisomy 8, chromosome 7 abnormalities, and inv(11) [12–15]. Although cyclosporine A is considered non-mutagenic, sister chromatid exchanges due to cyclosporine use have been reported [16,17].

Transfer of oncogenic material from host to donor cells is another possible mechanism. Viral or non-viral oncogenic agents released from patient's original leukemic cells might transfect the donor cells, causing a recurrent leukemia of the same type [18–20]. Relapse in donor cells with the leukemia identical to the original leukemia supports this theory [19,20]. In opposition to this theory is the observance that donor-cell leukemias have occurred following PBSCT in

patients with nonmalignant disorders such as aplastic anemia or thalassemias [2,21–23]. Also, most leukemias that develop in donor cells differ in type from the patient's original pre-transplant leukemia [1].

Another possibility is that the chromosomal aberrations were derived from abnormal donor cells infused during transplantation. In such cases, these abnormalities should have been detectable in the donor's hematopoietic cells. Indeed, a case of acute leukemia inadvertently transmitted by bone marrow transplantation has been described [24]. Donors in both of our cases were healthy, had never received chemotherapy, and showed normal peripheral blood karyotypes. However, latent chromosomal abnormalities at very low numbers of cells can be detected in normal healthy individuals; therefore, the finding of a low level, stable, cytogenetically abnormal clone is not conclusive evidence of a neoplastic process [25,26]. However, when transplanted into a suitable environment, even at very low levels, abnormal cells might be stimulated to show clonal growth and even progress to leukemia. Unlike in our patients, such abnormalities are usually only transiently detected and do not persist for years.

Most of the chromosomal abnormalities seen in our cases are not recurrent in hematological malignancies and are not associated with a particular chemotherapeutic agent. The 11q23 breakpoint found in the donor cells in patient 2 does not involve the *MLL* locus, as determined by FISH. The t(X;20)(q13;q13.3) has been reported as a rare recurrent abnormality in patients with MDS [27], but no commercial FISH probes are available to determine if the breakpoints present in our patient are actually the same as in previous reports. The appearance and disappearance of the clonal chromosomal abnormalities in a minor proportion of the donor cells, as well as the lack of any signs of therapy-related disease in the recipients described in our report, suggests that the abnormal cells did not acquire any growth advantages during the post-transplant period.

Although persistence of nonpathogenic clones of donor origin has not been reported, Masuko et al described a case in which clonal abnormalities in recipient cells persisted after a failed allogeneic PBSCT for acute lymphoblastic leukemia. Despite the unsuccessful transplant, the patient remained in remission during 8 years of follow up, although one of the persistent clonal abnormalities in recipient cells was a deletion of 20q—a recurrent aberration associated with myelodysplastic syndrome and AML. The authors concluded that the persistence of clonal abnormalities in host cells without development of MDS or leukemia suggests that another genetic abnormality is needed for the development of malignancy. This may be the case in our patient with the t(X;20). It should be noted that, in particular for deletion 20q, there is evidence that, in the absence of morphological evidence, this chromosome abnormality is not considered definitive evidence of MDS or leukemia [28].

In conclusion, this is the first report of apparently nonpathogenic, complex clonal cytogenetic abnormalities detected over a prolonged interval in donor hematopoietic cells after PBSCT. The maintenance of complete remission in our patients, and the absence of disease in both PBSCT donors, suggests that these abnormalities do not play a role in malignant transformation. These observations suggest that cytogenetic abnormalities in donor cells are not always of clinical significance, which may provide reassurance to patients. Moreover, our findings suggest that clinicians should consider observing similar cases rather than resorting to immediate treatment (e.g., a second transplant). Further studies are needed to characterize the mechanisms leading to the development and maintenance of these cytogenetic changes in the donor cells.

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Figure 1.
Post-transplant bone marrow G-banded karyotype for Case 1 demonstrating a donor female karyotype with two apparently reciprocal translocations: 46,X,t(X;20)(q13;q13.3),t(6;12)(p21.1;q24.3).

Figure 2.

Post-transplant bone marrow G-banded karyotype for Case 2 demonstrating a donor male karyotype with an apparently complex rearrangement involving chromosomes 2, 6, and 11: 46,XY,der(2)inv(2)(p23q33)t(2;11)(q33;q23), der(6)t(2;6)(p23;q15),der(11)t(6;11)(q15;q23).

Cytogenetic analyses of Case 1

Table 1

Time from PBSTCT	Karyotype (BM)
– 9 months	46,XY,t(9;22)(q34;q11.2)[20]
– 5 months	46,XY,t(9;22)(q34;q11.2)[18]/46,XY[3]
– 3 months	46,XY,t(9;22)(q34;q11.2)[20]
– 2 months	46,XY,t(9;22)(q34;q11.2)[18]/46,XY[2]
PBSTCT	
+ 1 month	46,XX[30]
+ 5 months	46,XY,t(2;17)(p13;q22), t(9;22)(q34;q11.2),der(9)t(1;9)(q21;q34), der(19)t(19;20)(p13.3;p11.2), –20,der(22)t(9;22)[4]/46,X,t(X;20)(q22;q13.3),t(6;12)(p21.1;q24.3)[2]/46,XX[16]
+ 6 months – +23 months (BM)	46,XX[20]
+ 21 months (PB)	46,XX[8]
+ 24 months	46,X,t(X;20)(q13;q13.3),t(6;12)(p21.1;q24.3)[2]/46,XX[22]
+ 30 months	46,X,t(X;20)(q13;q13.3),t(6;12)(p21.1;q24.3)[7]/46,XX[13]
+ 40 months	46,X,t(X;20)(q13;q13.3),t(6;12)(p21.1;q24.3)[3]/46,XX[17]
+ 42 months	46,XY,t(9;22)(q34;q11.2),add(19)(q13.4)[cp3]/46,X,t(X;20)(q13;q13.3), t(6;12)(p21.1;q24.3)[2]/46,XX[18]
+ 55 months	46,X,t(X;20)(q13;q13.3),t(6;12)(p21.1;q24.3)[1]/46,XX[9]
+ 56 months	46,XX[20]
+ 57 months	46,X,t(X;20)(q13;q13.3),t(6;12)(p21.1;q24.3)[2]/46,XX[18]

BM, bone marrow; PB, peripheral blood; PBSTCT, peripheral blood stem cell transplant.

Table 2

Cytogenetic analyses of case 2

Time from PBSCT	Karyotype
– 2 months	46,XX[20]
PBSCT	
+ 1 month (BM)	46,XX[2]/46,XY[19]
+ 2 months – + 3 months (BM)	46,XX[1]/46,XY[19]
+ 5 months (BM)	46,XY[20]
+ 10 months (BM)	46,XY,der(2)inv(2)(p23q23)t(2;11)(q33;q23),der(6)t(2;6)(p23;q15),der(11)t(6;11)(q15;q23)[5]/46,XY[15]
+ 16 months (PB)	46,XY,der(2)inv(2)(p23q33)t(2;11)(q33;q23),der(6)t(2;6)(p23;q15),der(11)t(6;11)(q15;q23)[6]/46,XY[16]
+ 19 months (BM)	46,XY[20]
(PB)	46,XY[20]
+ 24 months (BM)	46,XY,der(2)inv(2)(p23q33)t(2;11)(q33;q23),der(6)t(2;6)(p23;q15),der(11)t(6;11)(q15;q23)[1]/46,XY[19]
+ 28 months (PB)	46,XY
+ 31 months (BM)	46,XY,der(2)inv(2)(p23q33)t(2;11)(q33;q23),der(6)t(2;6)(p23;q15),der(11)t(6;11)(q15;q23)[2]/46,XY[18]
+ 36 months (BM)	46,XY[20]
+ 44 months (PB)	46,XY,der(2)inv(2)(p23q33)t(2;11)(q33;q23),der(6)t(2;6)(p23;q15),der(11)t(6;11)(q15;q23)[2]/46,XY[18]
+ 48 months (BM)	46,XY,der(2)inv(2)(p23q33)t(2;11)(q33;q23),der(6)t(2;6)(p23;q15),der(11)t(6;11)(q15;q23)[1]/46,XY[19]
+ 61 months (BM)	46,XY[20]

BM, bone marrow; PB, peripheral blood, PBSCT, peripheral blood stem cell transplant