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Trisomy 8 in an allogeneic stem cell transplant recipient representative of a donor derived constitutional abnormality

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Abstract

Trisomy 8 is a common cytogenetic abnormality in myeloid malignancies. It can also be present constitutionally and is associated with a wide range of phenotypes. We report a case of a 20 year old woman with acute myelogenous leukemia (AML) associated with the 11q23/MLL translocation who underwent allogeneic hematopoietic stem cell transplantation (HSCT) from a healthy, unrelated 26 year old female. Cytogenetics on a bone marrow biopsy and aspirate performed 71 days after transplant to evaluate pancytopenia identified trisomy 8 in 6 of 7 cells examined. The bone marrow was hypocellular but normal by morphology and flow cytometry. Fluorescent in situ hybridization (FISH) for the original 11q23/MLL translocation was negative. Chimerism analysis using multiplex polymerase chain reaction (PCR) to amplify an informative short tandem repeat (STR) demonstrated 97% donor cells. These findings were confirmed by repeat bone marrow biopsies at day 110 after transplant and one year after transplant. With resolution of co-morbid illness, the patient's peripheral blood counts recovered and remained normal at one year after HSCT. FISH analysis of a cryopreserved sample of the donor graft showed trisomy 8 in 120 of 200 cells examined. This represents the first reported case of a person with constitutional trisomy 8 mosaicism serving as a stem cell donor. The case illustrates the importance of identifying donor derived constitutional abnormalities to avoid the assumption that these cytogenetic abnormalities after HSCT are representative of malignant disease.

Keywords

Trisomy 8; mosaicism; donor derived leukemia; stem cell transplantation

CASE REPORT

The patient is an African American female who presented at 20 years of age with fatigue and gingival bleeding. She was found to have a white blood cell (WBC) count of 64,900/ul, a hemoglobin of 6.5 gm/dL and a platelet count of 59,000/ul. A bone marrow biopsy and aspirate confirmed the diagnosis of acute monoblastic leukemia without maturation (FAB M5a). Conventional cytogenetics revealed a normal female karyotype. Multiplex fluorescent in situ hybridization (FISH) analysis was positive for an 11q23/MLL translocation and negative for the presence of t(8;21), t(15;17), inv(16) and numeric abnormalities of

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chromosomes 5, 7, and 8. She had no history of any prior chemotherapy or other exposures. She underwent induction chemotherapy with idarubicin and cytarabine and she achieved a complete remission. She subsequently underwent two cycles of consolidation therapy with high dose cytarabine.

A decision was made to proceed with allogeneic transplantation. The best available donor was an unrelated 26 year old female with no reported past medical history who was a single antigen mismatch at HLA-DQ. The donor's peripheral blood counts were normal with a WBC count of 6,800/ul (normal differential) a hemoglobin of 14.7 gm/dL and platelets of 417,000/ul. The patient underwent a repeat bone marrow biopsy and aspirate 3 weeks prior to transplantation which showed a morphologically normal marrow with normal female karyotype and no abnormalities identified on FISH analysis. The transplant conditioning regimen included cyclophosphamide and total body irradiation and graft versus host disease (GVHD) prophylaxis included tacrolimus and methotrexate (1). The patient received a bone marrow graft containing 1.8×10^6 CD34+ cells/kg. Neutrophil engraftment (absolute neutrophil count (ANC)>500/ul) and platelet engraftment (platelet count>50,000/ul) both occurred on day 19 after transplant. Peripheral blood counts were normal day 32 after transplant.

At day 55 after transplant the patient developed gastrointestinal GVHD (stage 3–4) which became steroid refractory but was eventually brought under control at day 85 with combination therapy including prednisone (2mg/kg/day), mycophenolate mofetil and daclizumab. At day 63 her course was further complicated by polymicrobial sepsis and seizures secondary to tacrolimus induced reversible posterior encephalopathy. During these complications the patient was noted to be persistently pancytopenic, requiring intermittent platelet and red blood cell transfusions. A bone marrow biopsy and aspirate were performed on day 71 when the WBC count was 1, 300/ul (ANC 1072/ul), the hemoglobin was 9.7 gm/dL and the platelet count was 53,000/ul (see Table 1). Histological evaluation revealed a 5% cellular marrow and no evidence of leukemia by morphology or flow cytometric analysis. Conventional cytogenetics identified the presence of trisomy 8 in 6 of 7 cells examined (See Figure 1). Chimerism analysis using multiplex polymerase chain reaction (PCR) to amplify an informative short tandem repeat (STR) at the D16S539 locus demonstrated 97% donor cells. Bone marrow biopsy and aspirate were repeated on day 110 after transplant with similar morphologic and engraftment findings. Cytogenetics on this sample identified trisomy 8 in 14 of 20 cells examined. FISH analysis was performed which did not show the 11q23/MLL translocation in 200/200 of cells examined.

Given that the chimerism data showed 97% donor hematopoiesis there was a high level of suspicion that the trisomy 8 abnormality was of donor cell origin rather than a previously unidentified or newly acquired leukemic clone of recipient cell origin. An aliquot of the donor graft had been cryopreserved before infusion into the recipient. FISH analysis was performed on this specimen which revealed trisomy 8 in 120 of 200 cells examined (See Figure 2). Ultimately, 7 months after HSCT, the patient regained normal hematopoiesis. A repeat bone marrow biopsy performed routinely on the recipient at one year after transplant (corresponding with a WBC count of 6,600/ul, a hemoglobin of 14.0 gm/dL and a platelet count of 195,000/ul) showed a 70% cellular marrow with no evidence of dysplasia. Cytogenetics revealed trisomy 8 in 14 of 25 cells examined. Chimerism analysis showed 100% donor cells. Unfortunately the patient died in remission 18 months after transplant from complications of disseminated varicella-zoster virus infection and hepatic GVHD.

DISCUSSION

Trisomy 8, either alone or in combination with other cytogenetic abnormalities, occurs in 10–20% of patients with AML, myelodysplastic syndrome (MDS) and myeloproliferative disorders (MPD) (2–5). A large study identified trisomy 8 as the sole abnormality in 5.6% of patients with AML; 7.5% of patients with MDS and 7.5% of patients with MPD (6). Occasionally with disease relapse after HSCT, cytogenetic abnormalities not previously identified are discovered.

Trisomy 8 can also be present constitutively. Full constitutional trisomy 8 is almost always associated with early fetal demise. Patients surviving to birth are thus usually trisomy 8 mosaics whose abnormality arose from mitotic non-disjunction during early fetal development. The syndrome is usually diagnosed after presenting with certain morphologic and developmental abnormalities in early childhood. Characteristics include facial dysmorphisms (including prominent forehead, epicanthic folds, prominent lower lip and micrognathia), clinodactyly, camptodactyly, deep palmar creases and scoliosis. The syndrome can also be associated with mild to moderate retardation. Presenting phenotypes can be quite variable and seem to be independent of the degree of mosaicism (7). Interestingly, hematologic abnormalities are not a component of the constitutional syndrome. The use of stem cells from a donor with trisomy 8 mosaicism has never been described.

People with a normal phenotype (or only subtle dysmorphisms apparent only retrospectively) have also been identified fortuitously to be trisomy 8 mosaics during workup for other disorders (7,8). Due to the variable phenotype and need for invasive testing to identify the disorder the precise incidence of constitutional trisomy 8 is unknown. A study in Denmark prospectively performed cytogenetic analysis on the peripheral blood of 34,910 infants and identified only one infant with trisomy 8 (9).

Given the common association of acquired trisomy 8 with hematologic malignancies the question is raised as to whether people who are constitutional trisomy 8 mosaics have an increased risk of developing these disorders (10). Given the rarity of trisomy 8 mosaicism it is difficult to assess whether the presence of this constitutional abnormality is associated with an increased risk of developing hematologic malignancies. There have been several cases reported of both adults and children who are known to be trisomy 8 mosaics who develop hematologic malignancies (11–13). Other cases have been reported as well of patients with hematologic malignancies associated with trisomy 8 who are identified at time of diagnosis of their leukemia to be constitutional trisomy 8 mosaics with normal phenotype (14–16).

Donor derived leukemia and MDS are rare complications of HSCT (17–23). These malignant diseases identified in the recipient after transplant may either have existed subclinically in the donor before transplant (with malignant clones infused directly to the recipient) or acquired in donor cells at various times after transplant. Of the former type there have been at least 5 well documented cases in the literature (18–20,22,23). One manuscript reports a case of a 41 year old patient with non-Hodgkin's lymphoma who underwent HSCT from her 50 year old HLA identical sister. The recipient subsequently was identified to have MDS of donor cell origin associated with the del(20q) abnormality. The donor in retrospect had borderline peripheral blood counts, and was a poor mobilizer. The donor underwent a bone marrow biopsy and aspirate which identified MDS also associated with the del(20q) abnormality (23). Other cases have reported inadvertent transmission of AML (20), MDS (22), chronic myelogenous leukemia (CML) (18) and T-cell lymphoma (19) from a donor with subclinical disease to the transplant recipient. In addition to

transmission of malignant disease; donors with constitutional cytogenetic abnormalities have also rarely been reported. Mosaic Turner Syndrome was identified retrospectively in two HSCT donors after this cytogenetic abnormality was identified in the recipient (24).

Trisomy 8 incidentally identified in our asymptomatic donor with normal peripheral blood counts could represent one of two possible clinical scenarios. The first is that the donor is a constitutional carrier of trisomy 8 and the second is that she has an acquired trisomy 8 abnormality representative of a clonal, preclinical pathologic process such as MDS or a myeloproliferative disorder. Given the high percentage (60%) of trisomy 8 cells identified in the donor stem cell graft, the donor's young age, the donor's normal peripheral blood counts, the adequate bone marrow collection, rapid initial engraftment into the recipient and normal bone marrow morphology in the recipient one year after transplant we favor the former possibility. While the recipient was pancytopenic corresponding to hypocellular bone marrows on days 77 and 110 after HSCT, this was in the setting of significant co-morbid illness. Her peripheral blood counts eventually normalized with a 70% cellular morphologically normal marrow at one year after transplant. The donor is being contacted by the donor center for further evaluation and counseling.

If the donor is indeed a constitutional trisomy 8 carrier this finding could have important consequences both for her and for the recipient. While the issue of predisposition to malignancy is uncertain this is a potential concern for both donor and recipient. While our patient's cytopenias early in her course could be explained by her clinical condition it is difficult to rule out the possibility that donor hematopoiesis was particularly susceptible to physiological insult due to the trisomy 8 mosaicism. Indeed due to these uncertainties, if the donor was identified to be a trisomy 8 mosaic prior to HSCT, a different donor may have been selected. Also of note the donor is a young woman of reproductive age and depending on the cell of origin of her trisomy 8, fertility issues may be important.

This case highlights some of the challenges inherent in caring for an unrelated donor. Unrelated donors donate stem cells anonymously to the transplant center and recipient. When a hematologic abnormality is identified in donor cells there is an obligation to inform, evaluate and counsel the donor. This is a particularly challenging predicament when the identified abnormalities are of uncertain clinical significance, as in this case, and may result in subjecting the donor to potentially unnecessary anxiety.

This case report illustrates that the identification of a new trisomy 8 clone in a patient after allogeneic transplant may not represent an evolving or expanding leukemic clone but may in fact be due to donor derived trisomy 8 mosaicism. This entity while rare is extremely important to recognize both for the donor and the recipient.

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Table I

Pertinent recipient peripheral blood and bone marrow assessments after transplant

Variable	Day+32	Day+71	Day+110	D+365
Hemoglobin (g/dL)	13.7	9.7	12.3	14.0
Platelet count (per ul)	179,000	53,000	33,000	195,000
White cell count (per ul)	5,900	1300	2,800	6,600
Absolute neutrophil count	3599	1072	1540	NA
Bone marrow morphology	NA	5% cellular No morphologic evidence of leukemia	3% cellular No morphologic evidence of leukemia	70% cellular No morphologic evidence of leukemia or dysplasia
Cytogenetics (bone marrow)	NA	Trisomy 8 in 6 of 7 cells examine	Trisomy 8 in 14 of 20 cells examined	Trisomy 8 in 14 of 25 cells examined
Chimerism analysis[1] (peripheral blood mononuclear cells)	NA	97% donor origin	98% donor origin	100% donor origin

NA: Not assessed

[1] Chimerism analysis was performed using multiplex PCR to amplify an informative short tandem repeat at the D16S539 locus