demonstrating a significant association with aHUS, age-related macular degeneration, or C3 glomerulopathy and others considered as predisposing genetic factors for aHUS or affecting the disease penetrance and severity.

Some genetic variants are presently not considered disease causative by many experts because their functional pathogenic role has not always been demonstrated. Nevertheless, it is remarkable and worth sharing with the scientific community that the described patients exhibit a post-HSCT acquisition (from the donor) of uncommon gene changes involving the complement system. A proof of concept would be the direct detection in blood of mutated proteins, which is currently out of reach for most laboratories. Mechanisms linking mutations to TMA remain poorly understood and likely differ for individual proteins involved; reduced expression of the mutated allele (with low circulating levels of normal protein) and critical changes in affinity for binding substrates of mutated proteins may be at play.

Given the frequencies of the observed variants, the probability that they occur in combination with such a rare disease by chance in 6 of 16 patients is extremely low, making a pathogenic link between mutation and TMA plausible. We expect that extending the screening of both recipients and donors for complement gene mutations in patients with HSCT-TMA may allow the identification of additional cases and may also provide important insights into the pathophysiology of the condition itself.

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Inversion 3 Cytogenetic Abnormality in an Allogeneic Hematopoietic Cell Transplant Recipient Representative of a Donor-Derived Constitutional Abnormality

Ajoy Dias [1], Aref Al-Kali [1], Daniel Van Dyke [2], Dietger Niederwieser [3], Vladan Vucinic [4], Johannes Lemke [5], Christel Muller [4], Sebastian Schwind [4], Anne-Christin Teichmann [4], Ruth Bakken [5], Linda J. Burns [6], Mark Litzow [1,*]

[1] *Division of Hematology, Mayo Clinic, Rochester, Minnesota*
[2] *Cytogenetics Laboratory, Mayo Clinic, Rochester, Minnesota*
[3] *Division of Hematology and Medical Oncology, University of Leipzig, Leipzig, Germany*
[4] *Institute of Human Genetics, University of Leipzig, Leipzig, Germany*
[5] *Medical Services, National Marrow Donor Program/Be The Match, Minneapolis, Minnesota*
[6] *National Marrow Donor Program/Be The Match, Minneapolis, Minnesota*

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* Correspondence and reprint requests: Mark Litzow, MD, Mayo Clinic, 200 First St SW, Rochester, MN 55905.
E-mail address: Litzow.mark@mayo.edu (M. Litzow).
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A B S T R A C T
Allogeneic hematopoietic cell transplantation (HCT) is an important treatment for many severe hematologic disorders; however, HCT can be associated with significant complications, including organ toxicity, graft-versus-host disease, and relapse. Another serious, but rare, complication is the transmission of hematologic and nonhematologic diseases from the donor to the recipient. With older donors, the risk of an abnormality may be increased. Here we describe the transmission of an inversion 3 constitutional cytogenetic abnormality from an unrelated donor to a recipient, and review the clinical implications of the discovery of donor-derived constitutional cytogenetic abnormalities.
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INTRODUCTION

Hematopoietic cell transplantation (HCT) is currently the sole curative option for a variety of hematologic and nonhematologic disorders [1,2]. HCT is now available at more than 1500 centers in more than 75 countries [3]. Complications after HCT are well recognized and include graft rejection; severe, sometimes fatal infections; sinusoidal obstruction syndrome; and acute and chronic graft-versus-host disease, which can potentially lead to significant morbidity and mortality [4]. Rapid advances in HLA typing with resultant high-resolution donor–recipient matching, new immunosuppressive therapy protocols, early detection and pre-emptive treatment of infection, improved supportive care, and use of reduced-intensity conditioning have contributed to the increasing use of HCT and have shifted patients and related donors toward older ages [5-8]. With the increase in allogeneic HCT in older patients who may have older sibling donors, the potential for transmitting diseases with higher prevalence in older patients may increase.

Whereas established nonmalignant and malignant diseases may be readily discovered, early-stage hematologic diseases and nonmalignant blood disorders might not be detectable by routine donor screening. In many cases, the only way to detect these conditions would be through new and /or expensive diagnostic tests and potentially invasive procedures, which would simultaneously add to the financial and physical burden of donor screening. There are reports of the transmission of constitutional karyotype abnormalities after allogeneic HCT; however, donor evaluation with chromosome analysis remains controversial and is not performed in many institutions.

Here we report the identification of a constitutional inv (3) (p21.3q26.2) balanced chromosome inversion transmitted from donor to recipient in an adult patient with acute myelogenous leukemia (AML) after an HLA-matched unrelated donor HCT, and discuss the clinical implications for the donor and the recipient.

A 54-year-old Caucasian male was diagnosed with *JAK2V617F* mutation–positive polycythemia vera in January 2012. Initial treatment was with aspirin and therapeutic phlebotomy. He exhibited disease progression in February 2014, at which time hydroxyurea was initiated as a cytoreductive therapy. He was then clinically stable until July 2014, when he developed severe thrombocytopenia. A bone marrow biopsy revealed transformation to AML without maturation with 45% blasts. Conventional cytogenetic analysis of the bone marrow aspirate showed a normal diploid male karyotype (46, XY) in all 20 metaphases [Figure 1].

The patient underwent induction chemotherapy with daunorubicin, cytarabine, and nilotinib on a clinical trial with no complications. Bone marrow analysis on day +14 showed residual disease, with approximately 20% $CD34^+$ blasts in a markedly hypocellular marrow. He received reinduction with a second course of daunorubicin, cytarabine, and nilotinib and subsequently entered into a clinical remission. He then received 2 cycles of consolidation with high-dose cytarabine and was in complete remission before undergoing HLA-matched unrelated peripheral blood stem cell transplantation in November 2014 with myeloablative conditioning consisting of busulfan and cyclophosphamide. The National Marrow Donor Program (NMDP)/Be The Match Registry facilitated identification of the 49-year-old male donor.

The recipient's early post-transplantation course was complicated with acute graft-versus-host disease necessitating systemic steroids. Routine bone marrow biopsy at day +100 in February 2015 showed a normocellular marrow with trilineage hematopoiesis with no evidence of AML and 100% donor chimerism. Cytogenetic analysis showed inv (3) (p26q25) in each of the 20 metaphases, suggesting a possible constitutional abnormality present in the donor cells (Figure 1B). The donor center was contacted, and the donor agreed to further testing. Peripheral blood phytohemagglutinin-stimulated karyotyping of donor peripheral blood cells demonstrated a diploid male pattern, with each metaphase having an apparently balanced pericentric inversion of chromosome 3 (46), XY, inv (3), (p26q25) in each of the 20 metaphases tested. He underwent a detailed clinical and hematologic workup, including a bone marrow biopsy, which was morphologically normal but showed the same cytogenetic abnormality. There was no history of miscarriages or infertility in his family frequently associated with inv (3) [9]. The recipient underwent a repeat bone marrow biopsy in November 2015, which showed continued remission with complete donor chimerism but again demonstrated the inv (3) abnormality in all metaphases. He remains in clinical remission.

DONOR-DERIVED CONSTITUTIONAL ABNORMALITIES IN STEM CELL RECIPIENTS AND ITS CLINICAL IMPLICATIONS

Disease transmission is a rare but well-documented complication of HCT with transmissible diseases, including infections, congenital disorders, autoimmune disorders, and hematologic and nonhematologic malignancies [10,11]. Case reports of transmission of donor malignancy in HCT recipients are extremely rare in the literature. Malignancies reported to be transmitted include AML, chronic myelogenous leukemia, lymphoma, and mycosis fungoides [12-16]. Several well-documented cases involving constitutional cytogenetic abnormalities have been reported, with some authors describing cases of relapsed disease showing abnormal post-transplantation karyotypes [17-20]. The nonmalignant aberrations include three main categories of balanced translocation rearrangements, including Robertsonian translocations, reciprocal translocations, and inversions. One in 175 to 250 phenotypically normal subjects carries a balanced rearrangement [9]. The identification of balanced rearrangements is

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