Avoiding the Thorns of the Gifted Red Rose: Case Report of Late Diagnosis of Polycythemia Rubra Vera in a Sibling Bone Marrow Transplantation Donor for a Patient with Chronic Myeloid Leukemia

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Dear Editor,

A 25-year-old man presented in 1995 with Philadelphia chromosome-positive chronic myeloid leukemia (CML). He underwent allogeneic hematopoietic stem cell transplantation using his fully-matched 28-year-old brother as a donor, and eventually was cured. He remains with undetectable disease as measured by PCR, sensitive to greater than 5-log.

Twenty-one years later, the donor was diagnosed with JAK2 exon-12-positive polycythemia rubra vera, with normal cytogenetics. Molecular testing was negative for BCR-ABL. A review of his bloodwork and a bone marrow examination done at the time of his stem cell donation showed no morphologic abnormalities. Cytogenetic or molecular testing was not done at that time. His own stem cells, hosted by his sibling, show no sign of a myeloid disorder and do not carry the JAK2 mutation.

Myeloproliferative neoplasms (MPNs) are sporadic in nature, but familial clustering exists. Presumably, a germline predisposition facilitates the gaining of a somatic driver mutation (JAK2, CALR, and MPL) leading to an MPN phenotype [1]. A large population-based study showed that first-degree relatives of MPN patients

have a 5- to 7-fold increased risk of any MPN and a borderline 2-fold increased risk of CML compared with controls [2]. An Italian study reported a prevalence of 7.6% in familial cases within a population of patients with MPN [3]. The coexistence of CML and other MPNs in the same family has been further reported, occurring less commonly than 2 Ph-negative MPNs [1–3]. The coexistence of JAK2, CALR, and MPL somatic mutations in 3 relatives of the same pedigree has also been reported [3].

Significant evidence for a germline predisposition to MPN came from the discovery of a particular JAK2 haplotype in chromosome 9p (the GGCC or 46/1 haplotype), which seems to preferentially acquire the JAK2-V617F mutation. Either this inherited haplotype is genetically unstable and acquires the mutation faster (“hypermutability hypothesis”), or the JAK2-V617F mutation occurs at either 46/1 or the wild haplotype at an equal rate, but there is a selective advantage to the V617F clone on the inherited 46/1 haplotype (“fertile ground hypothesis”) [3, 4].

Another study on a cohort from Iceland identified a germline polymorphism of the

TERT gene [1]. This TERT variant was associated with increased proliferation of myeloid cells and exerted a similar risk of either MPN.

Other genetic factors have been described lately. These include single nucleotide polymorphisms within JAK2 (such as the ones described above) and the erythropoietin receptor [2] and germline variants that may enhance hematopoietic progenitor differentiation and acquisition of driver mutations (ATG2B and GSKIP duplication, RBBP6 mutations, and SH2B3 [LNK] mutations) [1, 3].

Transmission of donor-derived clones through transplantation has been reported [5]. In our case, the overt donor clone developed years after the harvesting and only in the donor's bone marrow.

Screening donors with bone marrow aspirates or extensive genome sequencing as part of the pretransplant evaluation is debatable. Allogeneic hematopoietic stem cell transplantation is often the only treatment option. The identification of latent or constitutional genetic abnormalities subjects healthy donors to potential anxiety and its effect on the clinical outcome is unclear.

Statement of Ethics

No institutional or national ethics committee approval was needed. Every effort was made to preserve the patient's confidentiality.

Disclosure Statement

The authors have no financial conflict of interest to declare.

Author Contributions

Both authors contributed to the writing of this paper.

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