COMMENTARY

blood advances

TO THE EDITOR:

Malignant progression of donor-engrafted clonal hematopoiesis in sibling recipients after stem cell transplantation

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The recent study of Boettcher et al[1] describes 5 cases of donor-engrafted clonal hematopoiesis (CH), one of which progressed into myelodysplastic syndrome (MDS) in both donor and recipient. We share our experience with 4 additional cases of donor-engrafted CH in which all recipients evolved into a donor cell–derived hematologic neoplasm (DCHN). All patients had received an allogeneic stem cell transplant from an HLA-identical sibling resulting in long-term complete remission and full donor chimerism.

Case 1. A 43-year-old female patient with MDS with excess blasts-2 (MDS-EB2) received a peripheral blood stem cell (PBSC) transplant from her 45-year-old sister. A second PBSC transplant from the same donor was performed for a relapse of the original disease 20 months after the first transplant. As reported previously,[2] the discovery of JAK2 p.(V617F) mutations led to the retrospective analysis of both donor and recipient samples, as the donor had a history of a portal venous thrombosis before the first PBSC donation. We identified a JAK2 p.(V617F) mutation in pretransplant donor samples and posttransplant donor and recipient samples. Twenty years posttransplant, the recipient exhibited an exponential increase in JAK2 p.(V617F) mutational burden with clinical progression toward a myeloproliferative neoplasm (MPN)–type polycythemia vera with secondary myelofibrosis. Treatment was needed with phlebotomies, hydroxyurea, and ruxolitinib. In contrast, the donor so far remained untreated as no further myeloproliferative features were observed, despite a gradual increase in JAK2 p.(V617F) mutational burden as high as 100% (Figure 1). Interestingly, we performed shallow whole-genome sequencing analysis and observed an identical del(20)(q11q13) in recent blood samples from both donor and recipient (supplemental Data), suggesting donor-engrafted CH with both a JAK2 p.(V617F) and del(20q) abnormality.

Case 2. A 68-year-old man with MDS with multilineage dysplasia received a PBSC transplant from his 63-year-old-brother. Three and a half years later, the patient developed a donor cell leukemia with 21% myeloblasts in the bone marrow aspirate and full donor chimerism. Next-generation sequencing (NGS) analysis revealed 3 pathogenic variants: SFRS2 p.(P95H), DNMT3A p.(W314*), and RUNX1 p.(R346Afs*248). Sequencing of the healthy donor's peripheral blood showed identical SFRS2 and DNMT3A variants, although at a lower variant allele frequency (VAF) (Figure 2).

Case 3. A 30-year-old man with acute myeloid leukemia with maturation (AML FAB M2, not otherwise specified) received a PBSC transplant from his 35-year-old brother. Seventeen years later, the patient developed acute monoblastic leukemia with full donor chimerism. NGS analysis revealed 5 pathogenic variants: ASXL1 p.(G646Wfs*12), EZH2 p.(E745K), FLT3 p.(I836del), SETBP1 p.(D868N), and TET2 p.(Q219*). Sequencing of the healthy donor's bone marrow at the time of the DCHN showed an identical EZH2 variant (Figure 2). Morphological evaluation of the peripheral blood and bone marrow revealed borderline thrombocytopenia and mild but significant megakaryocytic dysplasia, preferably diagnosed as idiopathic dysplasia of unknown significance (IDUS).[3]

Case 4. A 32-year-old man with Burkitt's lymphoma received a PBSC transplant from his 42-year-old sister. Nineteen years later, the patient exhibited persistent macrocytic anemia. Morphological examination of the bone marrow showed MDS with ring sideroblasts and multilineage dysplasia. NGS

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All data-sharing requests may be submitted to the corresponding author (Dominik Selleslag; e-mail: dominik.selleslag@azsintjan.be).

The full-text version of this article contains a data supplement.

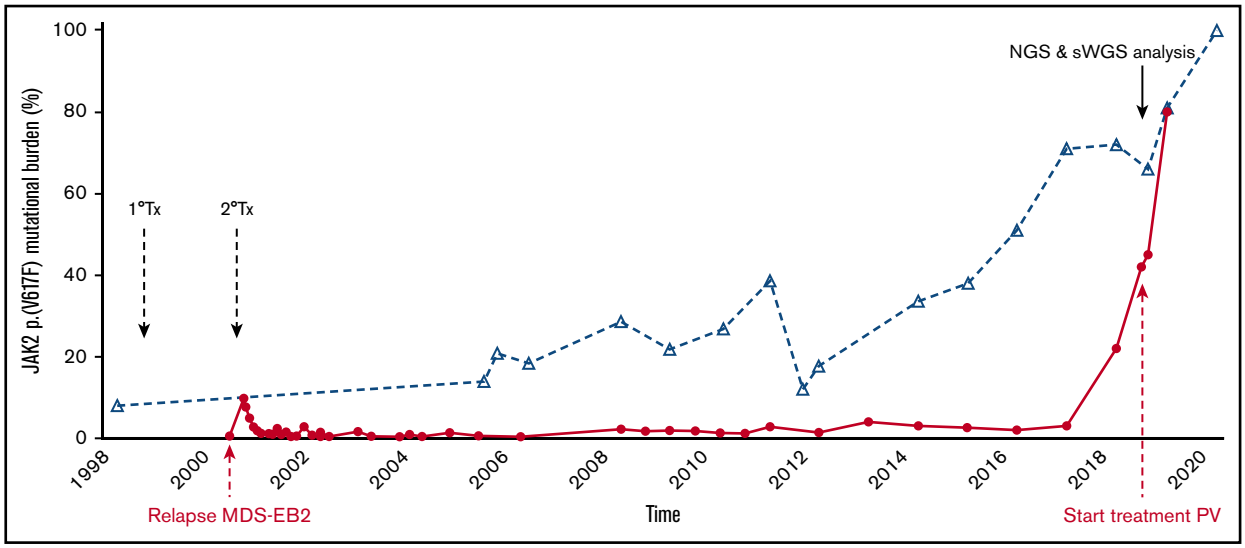

Figure 1. Evolution of JAK2 p.(V617F) mutational burden (%) in peripheral blood from donor and recipient as described in case 1. Donor, blue dashed line (Δ); MDS-EB2, MDS with excess blasts-2; PV, polycythemia vera; recipient, red full line (•); sWGS, shallow whole-genome sequencing; Tx, transplantation.

analysis revealed 1 pathogenic variant: SF3B1 p.(K700E). NGS analysis of the donor's peripheral blood showed the same SF3B1 variant at lower VAF. Further morphological evaluation of the donor's peripheral blood and bone marrow revealed macrocytosis without anemia and significant dysplasia in the erythroid lineage and 13% ring sideroblasts, preferably diagnosed as IDUS (Figure 2).[3]

Approximately 150 cases of DHCN have been published so far, but sequencing data are only reported in about a dozen.[4-6] In our center, we have thus far observed 4 cases of DCHN in 263 HLA identical sibling transplantations and estimated the cumulative incidence at 15 years and 25 years to be 0.5% and 4.7%, respectively; non-DCHN death was considered as a competing risk. The median follow-up time for recipients remaining event free was 8.0 years (supplemental Data).

As shown in the article by Boettcher et al,[1] the 4 cases reported here provide clear evidence of transmission of preexisting CH clones from donor to recipient via peripheral blood stem cells. In addition, they offer some new insights into the behavior of donor-derived CH in the recipient.

A first finding in our cases is the different clinical behavior of donor-derived CH clones in donors and recipients. In all our cases, the donors displayed no clinical signs of a hematological disorder at the time the DCHN developed in the recipient, although the condition of donors in cases 3 and 4 is preferably diagnosed as IDUS. Regular peripheral blood analysis in these 4 donors is performed to monitor progression of CH.

A second key finding is the long interval between acquisition of the CH in the recipient and emergence of DCHN in cases 1, 3, and 4 (20, 17, and 19 years posttransplant, respectively), as was seen in the case of MDS described by Boettcher et al[17] The cumulative incidence at 15 years is comparable to that of other reports,[8] but the estimated cumulative incidence at 25 years is remarkably higher.[5] It should be noted that in contrast to Dietz et al[8] and Engel et al,[5] the cumulative incidence of DHCN in the current study was calculated for a cohort of 263 sibling transplants only. Variations in patient populations and follow-up times may explain the difference in the cumulative incidence of DCHN at 25 years.

A third finding is the consistently higher VAF of the observed pathogenic variants in recipient compared with donor in cases 2, 3, and 4 (Figure 2), a finding also reported by Boettcher et al.[1] NGS analysis of both donor and recipient samples showed that the mutant clones follow distinct trajectories in diverse hematopoietic environments. Cases 2 and 3 suggest that besides the transmission of driver mutations (SFSR2 and DNMT3A in case 2; EZH2 in case 3), additional hits are needed to develop DCHN (RUNX1 in case 2; ASXL1, FLT3, SETBP1, and TET2 in case 3). Additional mechanisms (replicative stress, therapy-induced bone marrow microenvironment injury, impaired immune surveillance, and/or telomere lengthening) may be required for clonal expansion and leukemic development following allogeneic hematopoietic stem cell transplantation.[6,9]

A final finding of interest in our cases is the age of the donors at time of transplantation. With 3 of the 4 donors aged <50 years at time of transplantation, our cases show that younger donors carrying mutations in high-risk genes engrafted in recipients can cause late transformation among long-term survivors of stem cell transplantation. It is notable that the variants detected in our donors at time of DCHN are not exclusively somatic mutations in the most common CH of indeterminate potential genes DNMT3A, TET2, or ASXL1[10] but include variants in other high-risk genes or in multiple genes that are associated rather with pre-AML cases.[11,12] The prevalence and the effect of CHIP in older donors has been studied extensively.[13] In future studies, these phenomena should also be investigated with younger donors.

Before developing guidelines to routinely screen all donors for CH by NGS independently of age, more research is required to determine the prevalence of CH, particularly in the population of stem cell donors, and to investigate the relationship of CH and DCHN in a large multicenter cohort. Our findings show that donor

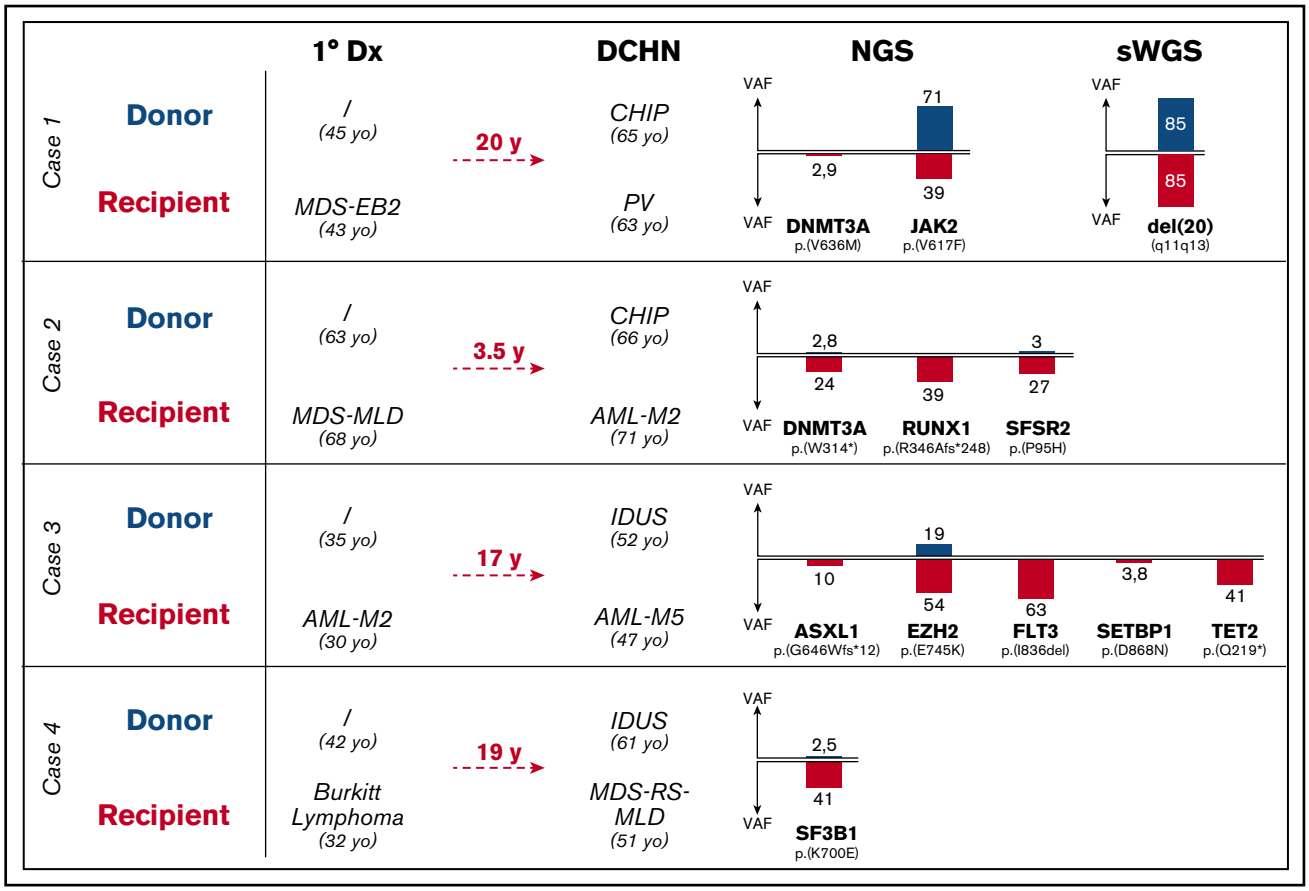

Figure 2. Sequencing data of both donor and recipient after allogeneic hematopoietic stem cell transplantation at time of diagnosis of DCHN. NGS was performed by using a panel of 21 genes relevant to myeloid malignancies. Shallow whole-genome sequencing (sWGS) was performed only of both donor and recipient samples as described in case 1 (details are provided in the supplemental Data). Definitions of hematologic neoplasms are according to the updated (2016) World Health Organization classification and to Valent et al.[3] AML-M2, acute myeloid leukemia with maturation; AML-M5, acute monoblastic leukemia; Dx, diagnosis; CHIP, CH of indeterminate potential; MDS-MLD, MDS with multilineage dysplasia; MDS-RS-MLD, MDS with ring sideroblasts and multilineage dysplasia; yo, years old.

origin of hematologic neoplasms occurring after allogeneic stem cell transplantation should always be excluded.

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