dominance in animals determined that if the number of neoplastic HSCs reaches 0.5% of total HSCs, survival and expansion of the clone are assured. In this particular case, expansion and dominance of a putative V617F mutant cell might have been facilitated by the relatively low total number of HSCs after transplantation, and therefore cannot be considered to reproduce clonal evolution by the relatively low total number of HSCs after transplantation, nance of a putative V617F mutant cell might have been facilitated collected at different times after AML diagnosis.

Clinically relevant events (diagnosis of AML or PV, autologous hematopoietic stem-cell transplantation [HSCT], and onset of pruritus) are marked by arrows on the top of the figure.

To the editor:

Development of original donor cell leukemia after successful engraftment from a second donor

We read with interest the recent review in Blood on donor cell leukemia (DCL) by Flynn and Kaufman.\(^1\) We report a case of DCL occurring in cells from a first allogeneic stem-cell donor after the patient received a successful transplant from a second donor, following loss of the first donor graft.

The patient, a 32-year-old man, presented with severe aplastic anemia in 1995. No precipitating cause of aplasia was identified. Cytogenetic analysis, Ham test, diepoxybutane breakage analysis, telomerase reverse transcriptase, and RNA component of telomerase mutation screening were normal. Treatment with antilympho-

References

DQB1, allelic match. This match was possible because both parents shared A, B, Cw, DRB1, and DQB1 antigens. After a 4-year period of good engraftment with stable, mixed chimerism, donor chimerism fell to 40% in whole blood and cytopenias recurred. A second bone marrow transplantation from donor 1 was performed, using the same conditioning. Engraftment was poor and a third RIC transplantation was performed in November 2005 using the same conditioning regimen and an HLA-matched unrelated male (donor 2). Full donor 2 chimerism of 100% was achieved by day +100 and maintained until day +270. On day +298, neutropenia and thrombocytopenia, but no circulating blasts, were noted. Whole blood donor 2 chimerism was 75% (T-cell chimerism 89%, myeloid cells undetectable). Bone marrow biopsy revealed a diagnosis of refractory cytopenia with multilineage dysplasia. Cytogenetic analysis showed that 40 of 100 cells examined were karyotypically female with monosomy-7. Polymerase chain reaction of minisatellite regions confirmed origin of these cells as donor 1 and subsequently demonstrated mixed chimerism with donor 1 myeloid cells 66%, T cells 1%, and donor 2 myeloid cells 2%, T cells 84%. Bone marrow examination of donor 1 remains normal, with normal cytogenetics. The index patient has since developed acute myeloid leukemia and is undergoing treatment.

To our knowledge, this is the first report of DCL arising in cells from a first donor after successful peripheral blood stem-cell transplantation from a second donor. The causative mechanisms of DCL remain speculative, with bone marrow irradiation implicated as a possible contributory factor in the development of DCL. This patient did not receive radiation therapy. Nevertheless, the appearance of monosomy-7 in the leukemic clone is suggestive of therapy-related myelodysplasia/leukemia. Profound immunosuppression during the course of the treatment, DNA damage, and impairment of DNA repair mechanisms by chemotherapy may have combined to create an aberrant bone marrow microenvironment in which the malignant clone was able to evolve and gain a proliferative advantage over normal cells from donor 2. The failure of donor 2 T cells to maintain a graft versus leukemia effect is probably related to the in vivo T-cell depletion.

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References

To the editor:

Potent graft-versus-leukemia effect in BCR/ABL negative chronic myelogenous leukemia

Five to 10% of patients with chronic myelogenous leukemia (CML) do not have the Philadelphia (Ph) translocation. A smaller number also lack any detectable BCR/ABL rearrangement by interphase fluorescent in situ hybridization (FISH) or real-time polymerase chain reaction (RT-PCR). Although clinically and hematologically similar, BCR/ABL negative (BCR/ABL-) CML has been associated with a worse prognosis. Transplantation remains an option, although successful outcomes have only been reported in a handful of patients.

Ph- CML is uniquely susceptible to graft-versus-leukemia (GVL) effects and molecular studies have shown that BCR/ABL functions as a tumor antigen. In contrast, the efficacy of GVL in BCR/ABL- patients remains poorly defined. For these patients, the prospect of transplantation presents many uncertainties; in the absence of BCR/ABL expression will their disease be as susceptible to GVL?

A 45-year-old woman presented with massive splenomegaly, a white cell count of 8.6 × 10⁹/L, platelet count of 53 × 10⁹/L, and hemoglobin of 110 g/L. The karyotype was 46XX, interphase FISH and RT-PCR for BCR/ABL were negative. BCR/ABL- CML was diagnosed and she was prepared for transplantation from her HLA-identical brother with high-dose busulfan (64 mg/kg) and cyclophosphamide (120 mg/kg). Routine whole blood chimerism testing at day 30 revealed partial donor chimerism of only 56% (Figure 1A) and cyclosporine (CyA) was rapidly tailed to boost donor engraftment. At day 47, upon cessation of immunosuppression, the bone marrow showed marked infiltration with leukemia (Figure 1B) and donor chimerism had further declined to 28% in the peripheral blood and 37% in the bone marrow aspirate.

Fearing the worst, we counseled the patient that she might not survive and offered continuing supportive care. Over the next 30 days, she became increasingly unwell with anorexia, abdominal pain, nausea, jaundice, and hepatosplenomegaly. An ultrasound scan showed diffuse enlargement of the liver and spleen in keeping with progressive CML. She remained profoundly transfusion dependent. Rapidly rising bilirubin and alanine aminotransferase (ALT) levels reached peaks of 733 mM (42.8 mg/dL) and 479 U/L, respectively, at about 90 days. No rash or diarrhea was ever noted.

Unexpectedly, her condition slowly stabilized and she was fit enough for chimerism assessment and bone marrow biopsy at day 125. To our surprise, this revealed 100% donor engraftment in blood and marrow with dramatic and complete clearance of leukemia and some returning erythroid activity (Figure 1B). By 210 days, bone marrow cellularity and reticulin staining were approaching normal (Figure 1B). Liver biopsy confirmed chronic hepatic graft-versus-host disease (GVHD; Figure 1B), and conservative treatment with prednisolone was commenced. An early attempt to withdraw corticosteroids following extracorporeal phototherapy (ECP) was unsuccessful. With stable donor chimerism of 100% at 1 year after transplant, triple immunosuppression was initiated with prednisolone, cyclosporine/tacrolimus, and mycophenolate mofetil.
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