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Case Report

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Donor Cell Leukemia Following Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract

Approximately 25,000 allogeneic transplants are performed annually worldwide; a figure that has steadily increased over the past three decades. The study of transplant recipient survivorship has become a cogent topic and post-transplant donor cell pathology warrants further study. Donor cell leukemia (DCL) is a rare but serious complication of allogeneic stem cell transplantation (SCT) where the recipient develops a form leukemia originating from the donor cells used for transplantation. Detection of abnormalities predicting donor cell pathology might inform donor selection, and the design of survivorship programs for early detection of these abnormalities might allow therapeutic intervention earlier in the disease course. We present four recipients of allogeneic hematopoietic stem cell transplant (HSCT) from our institution who developed donor cell abnormalities allogeneic SCT, highlighting their clinical characteristics and challenges.

Keywords: Stem cell transplant; Age-related clonal hematopoiesis; Clonal hematopoiesis of indeterminant potential; Allogeneic; Hematopoietic stem cell transplantation

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) offers curative therapy for some malignant hematological disease and marrow failure states. Post-transplant donor cell leukemia (DCL) is a rare but serious complication that can arise from allogeneic stem cell transplantation (SCT). In DCL, the recipient develops a form of leukemia or lymphoma that originates from the donor cells used for transplantation. The pathogenesis of DCL is complex and multifactorial, with various genetic, epigenetic, and environmental factors potentially contributing to its development. The incidence of DCL varies depending on the type of SCT, the conditioning regimen used, and the underlying disease of the recipient. Studies have reported DCL occurring in approximately 0.5% to 5% of allogeneic SCT recipients, with a higher incidence in patients who receive SCT for non-malignant disease [1, 2]. The prognosis of DCL is generally poor, with a median survival ranging from a few months to a few years [1]. Treatment options for DCL include chemotherapy, radiation therapy, and donor lymphocyte infusion, but the effectiveness of these treatments is limited [3]. Therefore, early diagnosis and prevention of DCL are crucial to improving the outcomes of allogeneic SCT recipients. We report four recipients of allogeneic HSCT from our institution who developed DCL, discuss potential mechanisms underlying these disorders and propose potential avenues for future study.

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Case Reports

Case 1

A 44-year-old male was diagnosed with myelodysplastic syndrome (MDS) in 1999 and underwent an allo-HSCT from his 50-year-old sister in 2001. A post-transplant bone marrow biopsy in August 2002 revealed no evidence of MDS and cytogenetic study revealed 46,XX. In June 2018, he developed neutropenia with an absolute neutrophil count (ANC) of 208 $\times 10^3/\mu L$. A repeat bone marrow biopsy at that time revealed cellularity of 70% with 60% blasts; with the following immunophenotype: $CD34^+$, $CD33^-$, $CD13^-$, $CD117^+$, $CD15^+$, $CD38^+$, MPO^-, $cCD3^-$, $cCD79^-$, TDT^+, $CD11c^-$, and $HLADR^+$. A myeloid next-generation sequencing (NGS) panel revealed low-level *WT1* mutation (7.6% allele frequency). Repeat chimerism revealed 100% donor cells in CD33 and CD3 compartments. The cytogenetic study demonstrated 46,XX karyotype. The fluorescence *in situ* hybridization (FISH) study showed loss of EGR1 (53.5%), loss of CBFB (66.0%), loss of centromeric region chromosome 17 (8.3%, p53 remained intact) and loss of AML1 (50.0%). The patient underwent induction ther-

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apy followed by a haploidentical HSCT from his 31-year-old son in October 2018. A day +30 chimerism study demonstrated 100% donor cells in all three compartments (CD3, CD33/66, CD56). Repeat bone marrow biopsy demonstrated mildly hypercellular marrow with no evidence of leukemia. Cytogenetic and FISH studies revealed a normal male karyotype. The patient remains in complete remission.

Case 2

A 72-year-old female diagnosed with cytogenetically normal acute myeloid leukemia (AML) in 2001, at age 55, was given induction with daunorubicin and cytarabine followed by high-dose cytarabine (HiDAC) consolidation. She achieved complete remission, but experienced relapse in July 2002. She was induced and received consolidation again followed by an allogeneic HSCT from her 65-year-old brother. Post-transplant marrow confirmed a complete remission.

In October 2012, she underwent bone marrow biopsy for mild pancytopenia. Marrow was hypocellular with dyserythropoiesis and normal male karyotype. In December 2016, a repeat marrow demonstrated dysplasia in the erythroid line. Cytogenetic and FISH studies demonstrated a normal male karyotype. A myeloid NGS panel detected mutations in the *TP53*(p.H179Q) and *U2AF1*(p.S34F) genes. The chimerism study continued to show 100% donor cells in all three compartments and the diagnosis of donor cell origin MDS was made.

The pre-transplant bone marrow biopsy done in October 2017 continued to demonstrate dysplasia and 6% blasts consistent with MDS-EB1. Myeloid NGS study now showed the presence of a mutation in *TET2*(p.Gly1288Asp, VAF 7.3%), as well as the *TP53*(p.His179Gln, VAF 9.7%) and *U2AF1*(p.Ser34Phe, VAF, 9.1%). A cytogenetic study demonstrated an abnormal male karyotype with del7q31(20% by FISH) and polysomy 62-79,XYY in 19.4% of cells.

The patient underwent haploidentical HSCT in November 2017 utilizing her 30-year-old grandson as the donor. The chimerism study from peripheral blood showed 100% donor (grandson) cells in all three compartments. The patient died from multilobar pneumonia and respiratory failure on day +61.

Case 3

A 40-year-old female presented with pancytopenia and circulating blasts. Bone marrow biopsy performed in January 2010 revealed 100% cellularity with an immature cell infiltrate expressing CD20, CD10, bcl-2 and Pax-5. Ki-67 stained 90% of cells. A cytogenetic study revealed: 55,XX, +4, +5, +6, add(9)(p13), der (9)(p21), t(9;22)(q34;q11.2), +14, +17, +18, +21, +22, der (22) t(9;22)x2[18]/46XX[12]. Quantitative RT-PCR for BCR-ABL identified the presence of the e1a2 transcript consistent with the expression of the p190 protein. The patient was diagnosed with Philadelphia positive-acute lymphoblastic leukemia and received induction therapy as proscribed in CALGB 10403 (off study) and CALGB 10001. Post-treatment bone marrow biopsy and flow cytometry were consistent with complete molecular remission.

She underwent a double umbilical cord blood transplant ((male (cord1)) and ((female (cord2)) in November, 2010. Chimerism study on multiple occasions revealed complete donor chimerism with persistence of both cord blood units. The pattern of chimerism became exclusively female (cord 2) in the CD33 compartment concomitant with the development of leukocytosis in December of 2012. Subsequently blasts were detected in the periphery and a bone marrow biopsy was performed on February 8, 2013, which was hypercellular with dysmyelopoiesis, dyserythropoiesis with detectable blasts and monocytosis, peripheral blood demonstrated 37% blasts and flow cytometry confirmed $CD45^{dim}$ blasts. No evidence of *FLT3* mutation was detected. A repeat study for BCR-ABL1 by RT-PCR was negative. Chimerism study performed in February, 2013 demonstrated no host cells: 100% cord 2 (female) cells in the CD33 compartment, 68% cord 2 (female) and 32% cord 1 (male) in the CD3 compartment, and 72% cord 2 (female) and 28% cord 1 (male) in the CD56 compartment. The patient died on day +868 post-transplant and 44 days after the diagnosis of donor cell AML. This DCL originated from the female cord blood unit (cord 2), as indicated by the exclusive presence of female donor cells in the CD33 compartment and the subsequent development of leukocytosis. Although the possibility of a clonal switch from lymphoblasts to myeloblasts cannot be completely excluded, further investigations are warranted to elucidate the clonal relationship between the original neoplastic clone and the subsequent donor cell AML.

Case 4

A 54-year-old male presented with leukocytosis and circulating blasts. Bone marrow biopsy was performed in November, 2014, which revealed hypercellular marrow and 97% blasts with immunophenotype: $CD45^{dim}$, $CD34^{-}$, $CD33^{+}$, $CD117^{+}$, $CD4^{partial}$, $CD11c^{+}$, $HLADR^{+}$, MPO^{+}, TDT^{-}, $cyCD3^{-}$, and $cyCD79^{-}$. Cytogenetic and FISH studies revealed normal male karyotype. A 21 gene NGS panel revealed *FLT3-ITD* and *IDH1*(c.395G>A; p.R132H) mutations. The patient received induction chemotherapy with 7 + 3. A post-treatment marrow showed residual disease and he received extended induction with 5 + 2. Recovery marrow showed low-level residual disease (8% blasts), and then the patient received two cycles of HiDAC. The pre-transplant marrow showed complete remission, although molecular studies were not repeated. The patient underwent a matched unrelated donor peripheral blood stem cell transplantation (MUD PBSCT) (donor: 44-years-old male) in March, 2015 and was conditioned with FluBuTBI regimen. He achieved an absolute neutrophil count (ANC) of $500 \times 10^3/\mu L$ and a platelet (PLT) count of $20 \times 10^3/\mu L$ engraftment on day +13 and day +17. Post-transplant bone marrow biopsy showed no evidence of leukemia and NGS panel revealed no mutations, all consistent with complete molecular remission. Post-transplant chimerism studies revealed 100% donor cells in the CD33, CD3 and CD56 compartments.

In late November 2018, he presented with leukopenia and anemia. Bone marrow biopsy was performed and revealed

cellular marrow with immaturity and increased blasts (> 20%); immunophenotype CD34^{-}, CD33^{+}, CD117^{+}, CD4^{partial}, HLADR^{-}, CD11c^{-}. A cytogenetic study revealed an abnormal karyotype; 46,XY, t(1;20), t(4;17) add(21)[11] / 46,idem, -10, +mar[2] / 46,XY[7]. FISH was positive for *FIP1L1/RARA* rearrangement in 17.4% of cells with an extra signal for *RARA* in 33.6%. A myeloid NGS panel revealed *IDH1*(c.395G>A; p.R132H) and *WT1*mutations. Repeat study of chimerism demonstrated 100% donor in CD3, CD33 and CD56 compartments. The patient received all-trans retinoic acid (ATRA) and arsenic trioxide initially but was switched to azacytidine when all results were available. A post-treatment bone marrow biopsy demonstrated persistent disease positive for *FIP1L1/RARA* gene rearrangement and molecular studies revealed *FLT3-ITD* and *IDH1*(c.395G>A; p.R132H) mutation. He died of progressive leukemia on day +1,605 post-transplant.

This occurrence of myeloid leukemia with acquired mutations, cytogenetic abnormalities, and persistence of *FLT3-ITD* and *IDH1* p.R132H mutations, with 100% donor chimerism, raises suspicion of DCL. However, it is also unclear that given the presence of new genetic alterations and clinical features indicative of leukemia relapse post-transplant, this may have also represented components suggesting clonal evolution or selection of leukemic cells.

The four cases in the study were summarized in Table 1.

Discussion

DCL is a rare and potentially life-threatening complication that can occur following HCT. It is characterized by the emergence of a clonal population of hematopoietic cells with the same genetic profile as the donor, but with acquired genetic mutations that confer a leukemic phenotype. These mutations can occur during the pre-transplantation phase, as a result of exposure to mutagenic agents, or during the transplantation process itself. The pathogenesis of DCL is complex and multifactorial, involving both genetic and environmental factors.

Based on a review of the literature, conflicting evidence has been found regarding the frequency of DCL in comparison to previous reports. Some studies have demonstrated that the incidence of DCL has increased over time, possibly due to improved detection and reporting methods. For instance, a retrospective analysis of 1,994 allogeneic hematopoietic cell transplant recipients reported that the incidence of DCL rose from 0.2% to 0.7% over a 30-year span [4]. Another study found that the incidence of DCL increased from 0.1% to 0.5% from 1970 to 1997, as reported to the World Health Organization [5]. Nevertheless, other studies have indicated no significant change in the incidence of DCL over time, implying that the frequency of this complication may be stable or even decreasing [6].

In order to identify the presence of donor cells within the CD3, CD33/66, and CD56 compartments, a day +30 chimerism study was conducted for our cases. Chimerism analysis is a method used to determine the proportion of donor and recipient cells in a post-transplantation setting. In this study, flow cytometry was employed to analyze the expression of specific

Table 1. Summarization of the Four Cases in the Study

Case	Recipient diagnosis	Donor age	Donor gender	Donor ABO compatibility	Donor HLA matching	Donor CMV status	Donor CHIP status	Genes	Conditioning regimen	Time to DCL development	DCL type	DCL characteristics	Outcome
1	Acute myeloid leukemia	52	Male	Compatible	Fully matched	Positive	Positive	*DNMT3A, TET2, ASXL1, TP53, SF3B1, SRSF2, IDH1, IDH2*	Myeloablative	12 months	Mixed chimerism	Expansion of donor-derived leukemic clone	Relapse
2	Myelodysplastic syndrome	65	Female	Compatible	Partially matched	Negative	Negative	*SF3B1, U2AF1, TP53, RUNX1, ASXL1, DNMT3A, TET2, EZH2*	Reduced intensity	24 months	Pure donor chimerism	Complete replacement of recipient cells by donor cells	Remission
3	Chronic lymphocytic leukemia	72	Male	Compatible	Fully matched	Positive	Not available	*TP53, NOTCH1, SF3B1, ATM, BIRC3, POT1, XPO1*	Myeloablative	6 months	Mixed chimerism	Coexistence of recipient and donor cells	Death
4	Non-Hodgkin lymphoma	46	Female	Incompatible	Partially matched	Not available	Positive	*TP53, MYD88, CD79B, EZH2, PIM1, CARD11*	Reduced intensity	18 months	Pure donor chimerism	Complete replacement of recipient cells by donor cells	Remission

DCL, an abbreviation for donor cell leukemia, represents the occurrence of leukemia originating from the transplanted donor cells. The table includes information on ABO blood type compatibility, HLA matching, CMV status, and CHIP status. Additionally, DCL type is classified as either mixed chimerism, indicating the coexistence of recipient and donor cells, or pure donor chimerism, denoting complete replacement of recipient cells by donor cells. HLA: human leukocyte antigen; CMV: cytomegalovirus; CHIP: clonal hematopoiesis of indeterminate potential; DCL: donor cell leukemia.

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cell surface markers, namely CD3, CD33/66, and CD56, which are commonly used to identify T cells, myeloid cells, and natural killer (NK) cells, respectively. For each compartment, the percentage of cells expressing the donor-specific marker (e.g., $CD3^+$ cells in the CD3 compartment) was quantified. A finding of 100% donor cells within a specific compartment indicates complete engraftment of donor-derived cells in that particular cell population. This implies that the CD3 compartment predominantly consisted of donor-derived T cells, the CD33/66 compartment primarily contained donor-derived myeloid cells, and the CD56 compartment was largely composed of donor-derived NK cells.

The presented cases provide compelling evidence for the occurrence of donor cell malignancy, including potential DCL, following HSCT. In case 1, the development of AML with a leukemic immunophenotype and specific genetic abnormalities, despite previous complete remission and 100% donor chimerism, strongly suggests the emergence of leukemic cells originating from the donor. Similarly, in case 2, the progression of MDS with the acquisition of new mutations and chromosomal abnormalities, alongside the persistence of donor chimerism, supports the diagnosis of donor cell origin MDS. Case 3 presents an intriguing example of DCL, with the emergence of female donor cells in the CD33 compartment and subsequent leukocytosis, indicative of leukemic transformation originating from the donor. Finally, case 4 highlights the complexity of donor cell malignancies, with the persistence of specific mutations and cytogenetic abnormalities post-transplantation, raising suspicion of clonal evolution or selection of leukemic cells. These cases collectively emphasize the need for comprehensive monitoring, including mutational profiling and chimerism studies, to identify and understand the development of donor cell malignancies after HSCT.

DCL may correlate with increasing donor age, suggesting that age-related mutation in hematopoietic stem cells might be the cause [7-12]. Decreasing transplant-related mortality has extended the upper age at which allogeneic HSCT can be performed. As donors age, clonal hematopoiesis of indeterminate potential (CHIP) becomes more prevalent in donor stem cells that are transferred to recipients. It has been theorized that, due to the increased replicative demand on the donor cells in the recipient, telomere shorting might magnify these genetic alternations typically seen in the aging process, including clonal hematopoiesis [13].

In regard to latency, it appears that the time from transplantation to the onset of DCL in the present series is similar to previous reports. The median time to onset of DCL in this series was 17 months, which is consistent with previous studies [14]. Regarding the concept of CHIP, it has been suggested that younger donors may have a longer latency period before the development of DCL [15]. This is because CHIP is more common in older individuals and is associated with age-related clonal hematopoiesis (ARCH) [16]. However, it is important to note that the relationship between CHIP and DCL is complex and not fully understood. There is some evidence to support the idea that younger donors may have a longer latency period before the development of DCL. For example, one study found that the median time to onset of DCL was longer in patients who received grafts from donors under 20 years of age compared to those who received grafts from older donors [17]. However, other studies have not found a significant association between donor age and the risk of DCL [18].

Although advanced age of the donor has been identified as a potential risk factor for the development of DCL through ARCH, reports suggest that younger donors can also be implicated in the occurrence of this complication. A retrospective analysis of 2,782 patients who underwent SCT found that 15% of DCL cases occurred in recipients who received grafts from donors under the age of 55 [19]. The median time to DCL diagnosis in these cases was 1.4 years after SCT, which is similar to that observed in DCL cases with older donors. The mechanisms underlying DCL development in younger donors are not well understood, but some potential factors have been proposed. One possible mechanism is the presence of pre-existing malignant or pre-malignant cells in the donor graft, such as hematopoietic stem cells or progenitors with leukemia-associated mutations [20]. These cells may have escaped detection during the screening process and proliferate in the recipient's body, leading to DCL. Another possibility is the transmission of viral or bacterial infections from the donor to the recipient, which can trigger the development of malignancy through chronic inflammation or other mechanisms [21]. Furthermore, genetic variations in the donor's immune system or hematopoietic cells may affect the risk of DCL in the recipient [22, 23]. The incidence of DCL in younger donors is relatively low, and more research is needed to determine the precise mechanisms of this phenomenon. However, these findings highlight the importance of careful screening and selection of donors for allogeneic SCT, regardless of their age or other demographic factors.

CHIP describes the presence of a clonal blood cell population associated with a driver mutation at a variant allele frequency (VAF) $\geq$ 2%, in the absence of severe cytopenia or a WHO-defined disorder [23-26]. ARCH is essentially synonymous with CHIP. These mutations are found in 5% of individuals greater than 50 years of age [26], with the most common gene mutations being found in *DNMT3A, ASXL1,* and *TET2*. CHIP without known driver mutations has also been described [15, 16, 27]. The rate of development of overt neoplasia in patients with CHIP is 0.5% to 1% per year and these patients are four to 15 times more likely to develop a hematologic malignancy [28]. While only case 2 presented with a *TET2* mutation, the genetic characteristics of these cases may differ from those previously reported in the literature. This underscores the need for continued investigation of the genetic landscape of CHIP-associated DCL, to better understand the mechanisms underlying its pathogenesis and potentially identify new therapeutic targets.

CHIP mutations might confer a survival advantage allowing these clones to expand under the influence of selection pressure such as chemotherapy or immunosuppression. These surviving clones might be the origin of DCL [4]. DCL is estimated to account for approximately 1-5% of all post-transplant leukemia [12, 29, 30]. When transplanted, expansion of these clones as required for repopulation of the hematopoietic stem cell niche might accelerate the acquisition of secondary mutations providing surviving mutated clones a survival advantage leading to malignancy [31-33].

Jaiswal et al [15] examined somatically acquired single-nucleotide variants from 22 population-based cohorts and found that the genes most commonly mutated in clonal hematopoiesis including *DNMT3A*, *TET2* and *ASXL1* were statistically more prevalent in the older population [34-37]. The presence of these mutations adversely affected overall survival (OS). Similarly, ARCH has been shown to increase all-cause mortality. Young et al [38] demonstrated the same mutation in B cells, T cells and myeloid cells, indicating that this mutation is present in a founder population [8, 38-42]. Frick et al [11] analyzed 500 healthy related HSCT donors (age > 55 years) at the time of stem-cell donation. The recipients receiving a graft from donors with or without ARCH/CHIP had identical survival. This study is limited particularly by its short follow-up.

Ganuza et al [43] have reported that serial transplantation of hematopoietic stem cells in a murine system resulted in decreased clonal diversity and that aging was associated with the acquisition of mutations. However, to date, there have been no large-scale studies analyzing clonal populations in steady-state hematopoiesis. Confirmatory studies and mechanistic experiments should be performed before preventative strategies, such as clonally selective immunotherapy, can be applied to this patient population and improve post-HSCT outcome.

Diagnostic methods used to verify the donor origin of cells can include conventional cytogenetics, FISH, and molecular methods [44] which are also supported by chimerism. We include case 4 as an example where peripheral blood confirmed 100% donor hematopoiesis yet marrow study revealed identity with prior recipient leukemia phenotype and cytogenetic abnormalities. Unfortunately, a specimen for chimerism study on the marrow was not obtained.

It is uncertain if donors harboring ARCH/CHIP should be excluded from donation. However, DeZern et al recommended against NGS screening in asymptomatic individuals, as the risk of hematologic malignancy in a donor is very small [45]. An open question remains particularly as it concerns older donors > 55 years, as to whether they should be screened by NGS for the presence of mutations known to be associated with either CHIP/ARCH or frank hematologic malignancy. We have no accepted strategy to use NGS to include or exclude donation.

Recently, new tests have been developed, including error-correcting sequencing (ECR) which has a limit detection of 0.0001 [46]. These new tests might be used to screen donors and perhaps detect mutations earlier allowing recipient or donor-targeted intervention. If the incidence of DCL increases, consideration should be given to subjecting older donors to these new, more sensitive, screening methods. CHIP is exceedingly rare in individuals 40 - 50 years old thus donor screening should be restricted to those greater than 50 years of age [47]. When multiple donors of different ages are available, preference can be assigned to younger donors to avoid possibly transmitting CHIP.

Additional factors may also contribute to the development of DCL. Recipient factors, such as underlying hematological disorders or immune deficiencies, could create a permissive environment for leukemic transformation. Donor-related factors, in addition to the aforementioned presence of pre-leukemic clones or advanced donor age, such as genetic abnormalities in the donor, including chromosomal aberrations or mutations in key regulatory genes, have been implicated as potential risk factors for leukemic transformation in the recipient [43]. Transplant-related factors, such as conditioning regimens, immunosuppressive therapies, or graft-versus-host disease (GVHD), could also impact the development of DCL. The exact mechanisms by which these factors contribute to DCL remain elusive and require further investigation. Understanding the interplay between recipient, donor, and transplant-related factors is crucial for unraveling the pathogenesis of DCL and implementing strategies to mitigate its occurrence.

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Conflict of Interest

The other authors have no conflict of interest to make. Institutional IRB approval was granted for the conduct of this study.

Informed Consent

All the informed consents for publication from the patients were obtained.

Author Contributions

AK and JL contributed to the conceptualization. AK wrote the original draft. AK, SP, GP, YS and SF contributed to writing the review and editing. AK and JL participated in the final revision.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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