Case Reports

Donor cell–derived myelodysplastic syndrome: From recipient diagnosis to donor trace-back

Joana F. Ribeiro[1][a], Lúcia Vieira[2], Sara Lopes[2], Rute Marcelino[3], Catarina Bolotinha[3], Susana Roncon[2]

[1] Unidade Local de Saúde Gaia e Espinho, Vila Nova de Gaia, Portugal, [2] Instituto Português de Oncologia do Porto Francisco Gentil EPE, Porto, Portugal, [3] Coordenação Nacional da Transplantação, Instituto Português do Sangue e da Transplantação, IP, Portugal; Lisboa, Portugal

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BACKGROUND

Donor cell–derived hematologic neoplasms (DCHN) are rare but severe complications following allogeneic hematopoietic stem cell transplantation (allo-HSCT). Their diagnosis is challenging and requires integration of cytogenetic, molecular and chimerism studies. Beyond recipient management, these cases raise important concerns regarding donor trace-back and biovigilance procedures.

CASE PRESENTATION

We report the case of a male patient with severe acquired aplastic anemia who underwent allo-HSCT from a fully matched unrelated donor. The patient achieved complete donor chimerism and remained clinically stable.

Nearly a decade after transplantation, bone marrow examination showed 5–6% myeloid blasts with dysplasia. Chimerism studies confirmed complete donor origin (>99.8%), supporting the diagnosis of donor cell–derived myelodysplastic syndrome with excess blasts (MDS-EB1).

Following the recipient's diagnosis, the donor was recalled through the national donor registry. Clinical evaluation revealed no evidence of hematologic malignancy and no constitutional symptoms. Laboratory investigation revealed mild transient leukopenia, neutropenia, lymphopenia, macrocytosis, and folate deficiency, with subsequent normalization after folic acid supplementation. Throughout the process, strict donor–recipient anonymity and confidentiality were maintained.

The recipient subsequently underwent a second allo-HSCT and remains in remission.

The case was reported to the Portuguese biovigilance system as a severe adverse reaction (SAR) associated with hematopoietic cell transplantation.

CONCLUSION

This case highlights the diagnostic complexity of DCHN and the importance of integrating chimerism studies and molecular techniques for accurate diagnosis. It also emphasizes the relevance of structured donor trace-back procedures while preserving donor–recipient confidentiality.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an established and potentially curative treatment for a wide range of malignant and non-malignant hematologic disorders. Over recent decades, major advances in knowledge of transplantation biology, refinement of conditioning regimens, and improved prophylaxis and management of graft-versus-host disease (GVHD) and infections have significantly improved patient outcomes and long-term survival rates.

An uncommon but severe complication of allo-HSCT is the development of donor cell-derived hematologic neoplasm (DCHN). DCHN refers to the development of a new

a Corresponding Author. Joana F. Ribeiro, email: joana.ferraz.ribeiro@ulsge.min-saude.pt

hematologic malignancy that results from the donor's engrafted hematopoietic cells after transplantation. This phenomenon, first described in 1971 by Fialkow *et al.*,[1] remains rare, with an estimated incidence of approximately 0.1% according to data from the European Society for Blood and Marrow Transplantation (EBMT).[2] However, the number of reported cases has progressively increased over time, reflecting not only the global growth of allo-HSCT activity but also the availability of increasingly sensitive cytogenetic and molecular diagnostic tools. These have evolved from simple morphological evaluation to karyotype analysis, chimerism testing, short tandem repeat (STR) analysis by polymerase chain reaction (PCR), and more recently, advanced molecular methods such as next-generation sequencing (NGS), which enable accurate determination of donor versus recipient origin of hematopoietic cells after transplantation.[3]

DCHN has been reported in association with several hematologic malignancies, most commonly acute leukemia, and is associated with a poor prognosis, with survival ranging from a few months to a few years.[2] The underlying pathophysiology of DCHN is not fully understood. Proposed mechanisms include the presence of a malignant or pre-malignant clone in the donor, genetic predisposition to develop hematologic malignancies, and the acquisition of somatic mutations in donor cells after transplantation. These events may be facilitated by intense proliferative demands on the transplanted cells, which increases the risk of replication errors, and by post-transplant immunosuppression, which reduces immune surveillance and allows clonal expansion of abnormal cells.[4]

Here, we report a rare case in which donor-derived myelodysplastic syndrome was identified in a transplant recipient nearly a decade after allo-HSCT. This unexpected evolution raised not only significant diagnostic and therapeutic challenges for the patient, but also important implications for the donor. Such cases demand a careful trace-back strategy and long-term donor monitoring, while ensuring strict confidentiality and maintenance of anonymity between donor and recipient. This report illustrates the clinical course, diagnostic pathway, and therapeutic management of the recipient, alongside the rationale for donor trace-back and long-term follow-up in the context of DCHN.

MATERIALS AND METHODS

A retrospective review of a case of DCHN identified at the Portuguese Oncology Institute of Porto (IPO Porto) was performed. Clinical and laboratory data from both the recipient and the donor were retrospectively retrieved from medical records and institutional databases. Recipient-specific diagnostic investigations, including cytogenetic studies, molecular analyses, and chimerism testing, were reviewed. Donor follow-up and biovigilance data were obtained from donor records. A literature review was conducted through PubMed to identify previously published cases of DCHN and relevant studies addressing donor trace-back and post-donation surveillance.

RESULTS - CASE REPORT

In 2015, a six-year-old male patient was diagnosed with severe acquired aplastic anemia, most likely secondary to autoimmune hepatitis. In the absence of an HLA-identical related donor, he underwent an allo-HSCT from a fully HLA-matched (10/10) unrelated donor. The donor was a 44-year-old healthy male who underwent bone marrow harvest from the posterior iliac crests under general anesthesia in the operating theatre. A total nucleated cell dose of 1.63×10^8/kg was infused. The conditioning regimen consisted of fludarabine, cyclophosphamide, and antithymocyte globulin, a reduced-intensity protocol commonly used in severe aplastic anemia. GVHD prophylaxis included tacrolimus and mycophenolate mofetil, and no GVHD occurred. Neutrophil engraftment was achieved on day +24. No post-transplant G-CSF was administered. The post-transplant course was uneventful except for transient febrile neutropenia. The patient achieved complete donor chimerism (>95%) and remained clinically stable for three years.

The donor was followed according to standard post-donation protocols and attended the one-month and one-year evaluations without complications. Both clinical assessment and laboratory investigations, including complete blood counts, were normal. He did not attend the scheduled two-year visit and was subsequently lost to follow-up.

Beginning in 2018, the patient developed progressive cytopenias that were initially managed with intravenous immunoglobulin and corticosteroids, resulting in only partial and transient improvement. Due to persistent and worsening cytopenias, repeated bone marrow evaluations were performed. In 2020, bone marrow analysis revealed myeloid dysplasia with a normal karyotype, while complete donor chimerism was maintained. Despite supportive care, cytopenias persisted and gradually progressed.

In January 2024, bone marrow examination showed 5–6% myeloid blasts with bilineage dysplasia involving the myeloid and megakaryocytic lineages. Cytogenetic analysis demonstrated a normal karyotype (46,XY), and chimerism studies confirmed complete donor origin (>99.8%). NGS identified pathogenic somatic mutations in STAG2, SRSF2, RUNX1, and CEBPA. These findings strongly supported the diagnosis of donor cell–derived myelodysplastic syndrome with excess blasts (MDS-EB1, according to the World Health Organization classification of myeloid neoplasms), occurring nearly a decade after the initial transplantation.

Following the recipient's diagnosis, donor recall was coordinated through the national donor registry according to established donor trace-back procedures and he was re-evaluated, by the collection centre, in April 2024. The donor reported good functional status and absence of constitutional symptoms. Laboratory testing revealed normal hemoglobin levels (14.5 g/dL), mild macrocytosis (mean corpuscular volume, approximately 100 fL), leukopenia (2.34 x 10^9/L) with neutropenia (0.9 x 10^9/L) and lymphopenia (0.9 x 10^9/L), normal platelet count, and no morphological abnormalities on the peripheral blood smear. Biochemical analysis was normal except for folate deficiency. The find-

ings were interpreted as nutritional folate deficiency accounting for the macrocytosis, with transient neutropenia requiring follow-up. Folic acid supplementation (5 mg/day) was initiated, and repeated blood counts were scheduled.

At follow-up in June 2024, complete normalization of blood counts and correction of the folate deficiency were documented. The donor remained asymptomatic. The presence of mutations involving STAG2, SRSF2, RUNX1 and CEBPA raises the possibility of clonal hematopoiesis-related evolution. However, no donor-derived biological samples collected at the time of donation were available for retrospective molecular analysis. Therefore, although no hematologic malignancy was identified in the donor, the possibility of low-level donor clonal hematopoiesis below the detection threshold cannot be completely excluded. Throughout the entire process, strict confidentiality and anonymity between donor and recipient were maintained. The donor was not informed of the recipient's diagnosis; communication focused exclusively on donor safety and medical evaluation.

Following the diagnosis, the patient proceeded directly to a second allo-HSCT, without prior treatment with hypomethylating agents or cytotoxic chemotherapy, from a different fully HLA-matched (10/10) unrelated donor in July 2024, at the age of 15 years. The stem cell source was peripheral blood. Conditioning consisted of a myeloablative busulfan, cyclophosphamide, and antithymocyte globulin–based regimen, and GVHD prophylaxis included tacrolimus and methotrexate. A total $CD34^+$ cell dose of approximately 5 x 10^6/kg and a $CD3^+$ cell dose of 0.99 × 10^8/kg were infused. The post-transplant course was notable for transient febrile episodes during neutropenia, without documented microbiological infection and no major transplant-related complications. Neutrophil and platelet engraftment were achieved by early August 2024 (day +17). Post-transplant chimerism studies demonstrated complete donor chimerism in peripheral blood lineages (>99.7%) and bone marrow (>99.7% donor cells). At the last follow-up in November 2025, the patient remained clinically well, with sustained hematologic recovery and ongoing remission.

This clinical case was reported to the Portuguese biovigilance system as a severe adverse reaction (SAR) in a hematopoietic bone marrow recipient, as it resulted in harm to the patient.

The investigation process was documented within the biovigilance system, and assessments of imputability, recurrence, consequences, and risk impact were undertaken. As the evidence supporting attribution of the SAR to the engrafted hematopoietic cells was conclusive, imputability was classified as certain.

Based on the previously described incidence[2] of 0.1%, and in accordance with the recommendations of the Transplant Procurement Management Guidelines,[5] recurrence of this SAR was considered rare (level 1), whereas the consequences for the recipient were classified as significant (level 3). Following the same guidelines, risk impact was assessed using a matrix combining recurrence and consequence levels. On this basis, the risk impact was classified as level 3, requiring implementation of appropriate therapeutic measures in the recipient and ongoing surveillance of both recipient and donor, coordinated respectively by the transplant center and the donor collection center. Although such measures cannot always be implemented in the context of SAR management, as the underlying causes of certain occurrences may remain unclear and therefore difficult to prevent, in this case therapeutic interventions were introduced to reduce the risk of further harm to the recipient. Moreover, close clinical follow-up of the patient enabled assessment of the effectiveness of the therapeutic measures implemented.

DISCUSSION

Beyond its regulatory implications, this case illustrates the broader clinical value of biovigilance systems in transplantation medicine. Although DCHN remains rare, it may result in substantial clinical consequences including diagnostic delays, need for additional transplantation procedures, and complex donor investigations. Furthermore, the long interval between transplantation and disease development highlights challenges within current biovigilance frameworks, since delayed complications frequently occur beyond routine donor follow-up periods. Although no hematologic malignancy was identified in the donor, the donor age and mutational profile observed in the recipient raise the possibility of an underlying clonal process below the threshold of clinical detection. Increasing use of molecular techniques may further complicate donor evaluation by identifying clonal hematopoiesis of uncertain significance, particularly in older donors. Such findings raise unresolved questions regarding donor screening strategies, long-term surveillance, and ethical considerations surrounding donor recall procedures.

This case highlights several important clinical implications. First, DCHN may develop many years after allo-HSCT, emphasizing the need for continued vigilance during long-term follow-up. Second, persistent or progressive cytopenias following allo-HSCT should prompt an extensive investigation, including repeated bone marrow evaluations and, where appropriate, integration of cytogenetic and molecular analyses. Furthermore, chimerism studies alone may be insufficient for establishing the diagnosis of DCHN and should be interpreted alongside morphological, cytogenetic, and molecular findings. Finally, structured donor trace-back procedures and robust biovigilance systems play a critical role in the timely recognition and coordinated management of rare transplantation-related complications while ensuring preservation of donor–recipient confidentiality.

An important limitation of this report is that direct molecular comparison between donor and recipient samples was not performed. Although molecular characterization of the donor by NGS might have provided additional insights into the origin of the DCHN, it was not pursued for ethical reasons, as the results would not have altered the recommended clinical management. Furthermore, identifying such findings in a healthy donor could generate significant

psychological burden and anxiety regarding a potential future malignancy, despite the uncertainty of progression. Therefore, donor origin was inferred based on complete donor chimerism.

CONCLUSION

This case highlights the importance of clinical vigilance in the detection of potential malignant disease transmission and represents an illustrative example of the role of integrated biovigilance systems in the management of rare transplant-related complications. Identification of such events relies on the ability of healthcare professionals to recognize and interpret the recipient's clinical manifestations, establish a possible causal link with the donor and ensure appropriate clinical management. Accurate diagnosis relied on the integration of morphology, cytogenetics, chimerism studies, and NGS, which allowed confirmation of donor origin and exclusion of relapse of the primary disease.

Beyond the clinical implications for the recipient, this case also underlines the importance of structured donor trace-back procedures and post-donation follow-up. The coordinated involvement of transplantation teams, donor registries, and biovigilance systems was essential to ensure timely donor reassessment while maintaining strict confidentiality and anonymity between donor and recipient.

This report illustrates how DCHN represents not only a diagnostic challenge, but also a relevant biovigilance event requiring multidisciplinary management, careful risk assessment, and long-term monitoring strategies. Increased awareness of these rare complications may contribute to earlier recognition and improved reporting practices.

AUTHORS' CONTRIBUTION - CREDIT

Data curation: Joana F. Ribeiro (Equal), Lúcia Vieira (Equal), Sara Lopes (Equal). Investigation: Joana F. Ribeiro (Equal), Lúcia Vieira (Equal), Sara Lopes (Equal). Writing – original draft: Joana F. Ribeiro (Lead). Writing – review & editing: Joana F. Ribeiro (Equal), Lúcia Vieira (Equal), Sara Lopes (Equal), Rute Marcelino (Equal), Catarina Bolotinha (Equal), Susana Roncon (Equal). Conceptualization: Lúcia Vieira (Equal), Sara Lopes (Equal), Susana Roncon (Equal). Formal Analysis: Lúcia Vieira (Equal), Sara Lopes (Equal), Rute Marcelino (Equal), Catarina Bolotinha (Equal), Susana Roncon (Equal). Methodology: Susana Roncon (Lead). Resources: Susana Roncon (Lead). Supervision: Susana Roncon (Lead).

COMPETING INTEREST – COPE

No competing interests were disclosed.

ETHICAL CONDUCT APPROVAL – HELSINKI

This study was conducted in accordance with the principles of the Declaration of Helsinki.

INFORMED CONSENT STATEMENT

All authors and institutions have confirmed this manuscript for publication.

DATA AVAILABILITY STATEMENT

All are available upon reasonable request.

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