Donor cell derived deletion 7q occurring after allogeneic stem cell transplantation: a case report

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INTRODUCTION

Deletion 7q (del(7q)) is a non-reciprocal chromosomal abnormality which appears to play a **significant role in the development and progression of myeloid malignancies** (myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) and juvenile myelomonocytic leukemia). It is frequently seen in patients **with therapy related myeloid neoplasms** and is associated with poor prognosis (1,3). The resulting compound haploinsufficiency of multiple tumor suppressor genes and dysregulation of gene expression is thought to play a key role in disease development and progression (1,2). Deletion 7q has been found to be a **recurrent genetic abnormality in donor cell leukemia (DCL) and –MDS** with an incidence of up to 36.4% (4).

CASE PRESENTATION

CLINICAL HISTORY & DIAGNOSIS

Our patient initially presented with a diagnosis of **poor risk AML (FLT3+/NMP1-)** at the age of 56. Cytogenetic analysis at diagnosis showed a 3p deletion and translocation t(5;11).

Four years earlier, the patient had been treated for a **follicular lymphoma**.

AML TREATMENT

Standard induction chemotherapy was initiated (Cytarabine and Idarubicine), followed by consolidation with Mitoxantrone and Etoposide. After consolidation he was referred for **alloHSCT, with his HLA-identical sister acting as donor**. Pre-transplant bone marrow aspirate showed a complete morphological and molecular remission without any cytogenetic abnormalities. On pre-donation screening, peripheral blood counts of the donor showed no abnormalities. The conditioning regimen consisted of Fludarabine, oral Busulfan and antithymocyte-globulin (ATG). Graft-versus-host-disease (GVHD) prophylaxis consisted of tacrolimus and mycophenolate mofetil, in addition to the ATG as part of the conditioning. A total of 2,15x10E6 CD34+ peripheral blood stem cells/kg was administered.

POST-TRANSPLANT COURSE

- Transient clonal expansion of **T-cell large granular lymphocytes** (T-LGL) at 2 years post-transplant, present in bone-marrow aspirate and peripheral blood. A spontaneous resolution was seen after 2 years.
- Routine bone marrow analysis 4 years post-transplant identified a **del(7q) in 10 out of 20 cells**, all of them with female karyotype (46,XX,del(7)(q21)[10]), alongside **normal morphology and full donor chimerism**. Retrospective analysis of a previous bone marrow sample showed a del(7q) in 1 out of 20 cells, indicating **progression of the clone**. The donor was contacted and bone marrow analysis showed no morphological or cytogenetic abnormalities.

- **The routine use of cytogenetic analysis in patients post alloHSCT could lead to the early detection of *de novo* clonal abnormalities with an impact on survival.**
- **Detection of donor cell derived clonal abnormalities post alloHSCT should warrant a thorough evaluation of the donor if possible as well as a strict follow-up of the patient for clonal evolution to DCL or donor cell MDS.**
- **Donor cell leukemia is a rare finding but must be considered in all post alloHSCT leukemia or MDS cases.**

KARYOTYPE

DONOR CELL LEUKEMIA

DCL occurs when *de novo* acute myeloid leukemia occurs in engrafted cells of donor origin, which can be found in up to 5% of all relapses post alloHSCT. The pathogenesis is however poorly understood. Possible mechanisms include (5):

1. **Abnormal hematopoietic micro-environment**, pre-existing or induced by delayed effects of cytotoxic treatment.
2. **Defective immune surveillance**, either as a predisposing condition or induced post-transplant by impaired immune reconstitution or immunosuppressive treatment.
3. Prior **genetic susceptibility** to disease existing within donor cells.
4. **Telomere shortening** due to proliferative demand after HSCT.
5. **Fusion of leukemogenic DNA** released from leukemia cells by conditioning with donor cell DNA or **fusion of residual leukemia cells** with donor stem cells.

DISCUSSION

The mechanism of development of del(7q) in our patient is unclear. However, when reviewing our case it seems most likely that a **pre-existing host factor** such as an **impaired bone marrow microenvironment** or **defective immune surveillance** played a significant role in its development in our patient. The past history of a low grade lymphoproliferative disorder, the occurrence of a T-LGL post-transplant and the long latency between transplant and development of the abnormality all support this theory.

There is a high risk of further clonal evolution either to donor cell derived MDS or DCL underlining the need for strict further follow-up.

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