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Case Report

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Donor cell leukemia after allogeneic hematopoietic stem cell transplantation: a case report

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ABSTRACT

A 48-year-old man was diagnosed Acute myeloid leukemia with FLT3 ITD positive and PML/RARα- negative. Remission was achieved after induction and consolidation chemotherapy. Allogeneic hematopoietic stem cell transplantation was performed from his full matched sibling donor. He relapsed after 5 years and his bone marrow examination revealed PML/RARα-positive Acute promyelocytic leukemia. t(15:17) was positive and FLT-3 ITD was negative. Cytogenetic and molecular analysis confirmed donor cell origin. Donor didn't develop Acute promyelocytic leukemia.

Keywords: Allogeneic hematopoietic stem cell transplantation, donor cell leukemia, leukemogenesis

INTRODUCTION

In recent years, it has become increasingly clear that donor leukemia after allogeneic transplant may be more common than it has been done in the past. Donor-induced leukemias after allo-HSCT can provide important information about the mechanisms of leukemogenesis. The etiology of donor cell leukemia (DCL) is uncertain and the reported literature does not suggest a common mechanism. Mechanisms proposed involve occult leukemia in the donor, transformation of donor cells by antigenic stimulation through host tissue, radiation- or chemotherapy- induced stromal abnormalities, inherent stromal abnormalities, impaired immune surveillance, and fusion of donor cells with residual leukemic cells, resulting in oncogene transfection.

CASE

A 48-year-old man with a 6 months rash on the body was diagnosed with acute myeloid leukemia (AML) on bone marrow including %75 blasts with morphologic features of AML M1. Immunophenotyping revealed expression of CD34, MPO and glycophorin erythroid. Cytogenetic studies demonstrated a normal chromosome, 46, XY. Mutations of t(8:21), inv(16), NPM1 type A, ITD, D835 and t(15:17) genes were examined , but only mutation was found in FLT-3 ITD, and none in other. The patient received two courses of 3+7 chemotherapy including cytarabine 100 mg/m² and daunorubicin 45 mg/m². Follow-up bone marrow aspiration showed 5% myeloid blasts. The patient achieved complete remission with the FLAG (fludarabine 30 mg/m², cytarabine (ARA-C) 2 gr/m²) chemotherapy.

Then he proceeded to allo-HSCT with using busulfan and cyclophosphamide as precondition regimen from a fully HLA-matched sibling donor. No blast was observed in the control bone marrow examination on the 24th day of the transplant. Short tandem repeat (STR) and FISH analysis were consistent with complete donor engraftment. In follow-up the patient presented with skin graft versus host disease (GVHD) which was shown with biopsy. Corticosteroid treatment was started. The patient underwent liver biopsy due to elevated liver enzymes. It was reported as mild activity GVHD, so that mycophenolate mofetil added to treatment. GVHD totally resolved and immunosuppressive medicines were gradually stopped within one year.

The patient was followed up regularly for 5 years in remission. In follow-up neutropenia and thrombocytopenia have developed, bone marrow examination showed morphological features of AML-M3. In cytogenetic study mutation was found in t(15:17). FLT-3 ITD and MLL gene rearrangement were negative. 5th year STR studies indicated full-donor engraftment. The diagnosis of donor-derived AML was made. The patient received induction chemotherapy with ATRA 45 mg/m² and Arsenic trioxide 0.15 mg/kg daily.

DISCUSSION

The cause of DCL is still unclear. It can occur after HSCT for both benign and malignant hematologic diseases.[1,2] It has been shown to develop after chronic myeloid leukemia,[3] acute myeloid leukemia,[4] and acute lymphoblastic leukemia[5] in malignant hematologic disorders and aplastic anemia and thalassemia[6,7] in benign disorders. In the literature, different indications for transplantation and the effectiveness of changes in transplant therapy have been identified. It is likely that the development of leukemia may be greater than pre-and post- HSCT events in the recipient. The health status of the donor and exposure to toxic materials may increase the risk of donor cell acute leukemia in the recipient but these issues are still unclear.

Several mechanisms have been proposed for the development of DCL: a severe proliferative demand for donor cells is often associated with a higher probability of replication error or mutation; an oncogenic process by donor cells triggered by impaired immune surveillance present, especially after transplantation, by the recipient environment in which the original malignancy develops; and due to chronic antigenic stimulation of tumor cells in the recipient, due to small differences in compatibility between the donor and recipient cells if the surveillance of the tumor is adjusted.[2,8-10]

A number of external factors have been assumed to contribute to the rare oncogenic transformation that supports DCL. The most well-known example of post-transplantation malignancy is Epstein-Barr virus-mediated lymphoproliferative disorder (PTLD) that occurs in HCT recipients.[11] Ho et al.[12] reported that the presence of pre-transplantation EBV is a significant risk factor for developing PTLD. EBV is linked to many PTLDs, with a relationship of around 100% in early cases (within one year), EBV negative PTLD accounts for about 20% of all cases and tends to occur late (5 years after transplant), and etiology is unknown.[13]

Another potential contributor to allogeneic cell transformation may be the bone marrow microenvironment. There is growing evidence that suggests cognitive impairment microorganisms can contribute to the pathogenesis of blood malignancies. The marrow microenvironment consists of a complex structure of non-hematopoietic and hematopoietic cells, extracellular matrix as well as soluble and membrane-limiting agents that are used to support normal hematopoiesis. In a similar vein, there is more evidence indicating bone marrow stromal hematopoietic malignancies. Only in the last few years have three mouse models been described showing that major stromal abnormalities can cause malignancy in the hematopoietic compartment. Raaijmakers et al.[14] reported that Dicer1 deletion in mouse osteoprogenitors disorganise hematopoiesis and induces acute myeloblastic leukemia and myelodysplasia. The limitation of our case report is that there is no literature data on the transformation from AML to APL, so we cannot clearly distinguish between DCL and transformation APL.

CONCLUSION

DCL is a rare complication of HSCT and the etiopathology is still unclear. Although recent studies have shown that leukemia is more likely to develop before and after HSCT events in the recipient, new research is still needed, particularly about bone marrow microenvironment, immune surveillance and mutations. As in our case, DCL should be kept in mind in patients with leukemia after HSCT and shown to be donor cell originated by cytogenetic and molecular methods.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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