VIA MEDICA

CLINICAL VIGNETTE

Acta Haematologica Polonica 2022
Number 5, Volume 53, pages 357–359
DOI: 10.5603/AHP.a2022.0049
ISSN 0001–5814
e-ISSN 2300–7117

Clinical remission with autologous recovery after allogeneic hematopoietic cell transplantation for juvenile myelomonocytic leukemia

Tomasz Styczyński[1#], Jagoda Sadlok[1#], Monika Richert-Przygońska[2], Robert Dębski[2], Krzysztof Czyżewski[2*]

[1]Student Scientific Society, *Collegium Medicum,* Nicolaus Copernicus University in Toruń, Bydgoszcz, Poland
[2]Department of Pediatric Hematology and Oncology, *Collegium Medicum,* Nicolaus Copernicus University in Toruń, Jurasz University Hospital 1, Bydgoszcz, Poland

Autologous hematological reconstitution after allogeneic hematopoietic cell transplantation (allo-HCT) is a rare phenomenon in which recipient-derived hematopoiesis remains active after an engraftment procedure due to blood cancers. These events develop early (average 1–1.5 months after allo-HCT) and most often give rise to aplasia or leukemic relapse [1–3]. In uncommon scenarios, long disease-free survival is possible in the majority of cases concerning patients with chronic phase of chronic myeloid leukemia (CML) [1–5]. Autologous recovery has also been reported in chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML) [3, 4]. The autologous reconstitution is being diagnosed with an assessment of post-transplant chimerism, which is usually divided as: full donor chimerism (>95%), or mixed donor chimerism (5–95%), or absent donor chimerism (<5%). Generally, a lower percentage of donor chimerism after allo-HCT indicates a higher risk of disease relapse [6].

The objective of this study was to present the case of a 3-year-old boy with juvenile myelomonocytic leukemia (JMML) with long-term hematological and clinical remission after allo-HCT presented with autologous recovery and full autologous chimerism.

A 3-year-old boy with leukocytosis, anemia and hepatosplenomegaly was diagnosed with JMML based on genetic tests which revealed monosomy 7 and *PTPN11* gene mutation. The patient was treated with chemotherapy (thioguanine + cytarabine), which had to be discontinued due to rapidly progressing myelosuppression. Myelogram showed 4.6% of blasts. Three months later, allo-HCT from an unrelated HLA-matched male donor was performed with treosulfan, fludarabine and thymoglobuline conditioning regimen and graft-versus-host disease (GvHD) prophylaxis (cyclosporin A, methotrexate) was initiated immediately. No severe complications were observed in the early post-transplant period. In myelogram on day +29, remission and hematological recovery were confirmed. Chimerism testing revealed a low percentage of donor DNA (12% donor chimerism by day +30 then 1% donor chimerism by day +60) followed by full recipient chimerism in all subsequent tests between day +100 up to 4 years after transplantation, which indicated autologous reconstitution.

Chimerism was assessed by tests of different microsatellite regions, using the variable number of tandem repeats (VNTR) method (Medigen, Warsaw, Poland) (Figure 1). Already on day +100, a graft rejection was diagnosed whereas full clinical and hematological remission was achieved. Genetic tests were repeated multiple times between day +100 up to 4 years after allo-HCT, and all revealed absence of mutation in *PTPN11* gene. It was decided that the patient should stay in an observational group with periodic full blood cell count with manual smear, abdominal ultrasound examination and minimal residual disease assessment in bone marrow (*PTPN11* gene analysis with chromosome 7 monosomy assessment by fluorescence in situ hybridization). To date, the patient remains in a good condition and in hematological and molecular remission.

Our presented case of JMML followed by autologous recovery with full hematological remission is extremely rare [7]. It proves that acquiring a donor chimerism is not

*Address for correspondence: Krzysztof Czyżewski, Department of Pediatric Hematology and Oncology, *Collegium Medicum*, Nicolaus Copernicus University in Toruń, Skłodowskiej-Curie 9, 85-094 Bydgoszcz, Poland, phone +48 52 585 4803, fax +48 52 585 4087, e-mail: k.czyzewski@cm.umk.pl

Received: 25.06.2022 Accepted: 21.08.2022

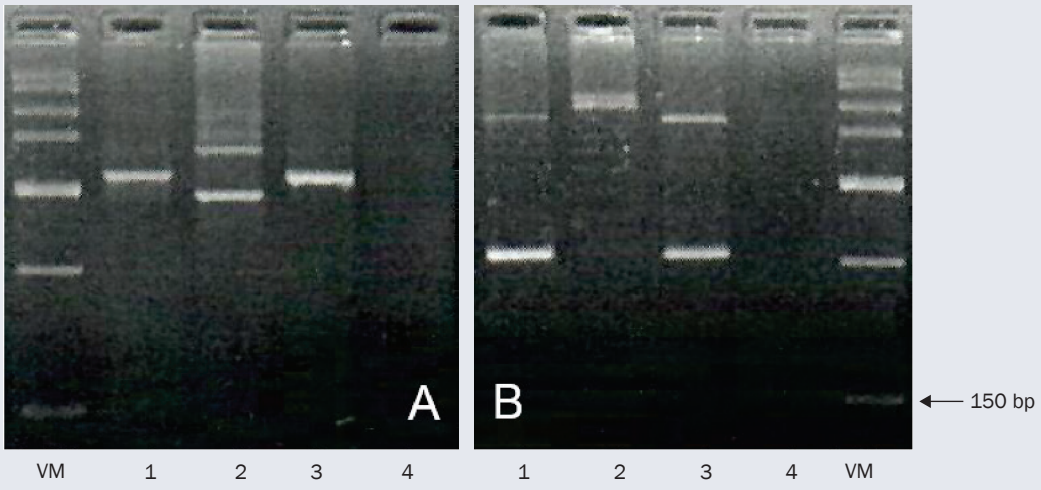

Figure 1. Result of chimerism study with variable number of tandem repeats method at 4 years after allogeneic hematopoietic cell transplantation (allo-HCT): **A**. *Locus* MCT-118; **B**. *Locus* YNZ-22; VM — volume marker; 1 — recipient before HCT; 2 — donor; 3 — recipient after HCT; 4 — negative control

necessary to achieve long-term disease-free survival. Our patient was in good clinical state throughout the course of treatment and did not develop any serious complications. Due to the fact that predicting the course of leukemia among patients with autologous recovery is extremely difficult, frequent analysis of post-transplant chimerism and minimal residual disease can help to distinguish cases with a higher chance of relapse [2, 3].

The mechanisms which lead to autologous recovery with simultaneous maintenance of hematological remission are as yet unknown [1–4]. One possibility is a short immune reaction of engrafted cells soon after allo-HCT which helps with the eradication of leukemic cells [4]. Other authors have hypothesized that residual donor lymphoid activity, which cannot be measured using available methods, enables the maintenance of remission [1–3]. It has also been hypothesized that autologous recovery occurs more frequently in cases with an unrelated donor HCT [1, 2].

Acknowledgements
The authors wish to thank the nurse team chaired by Ewa Dembna for their excellent care of the patients.

Authors' contributions
KC, TS — design of study; RD, MRP, KC — provision of clinical data; all authors — analysis of clinical data; TS, JS — literature search, data analysis and writing manuscript; all authors — critical revision and final approval

Conflict of interest
None.

Financial support
None.

Ethics
The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

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