Early Secondary Graft Failure After Complete Donor Chimerism With Subsequent Autologous Hematopoietic Reconstitution Following Haploidentical Sibling Allogeneic HSCT for Relapsed B-Cell Acute Lymphoblastic Leukemia

Rene A. Amadore Jr. MD[1]; Lynn B. Bonifacio MD[1,2]

[1]Division of Hematology, Department of Medicine, University of the Philippines- Philippine General Hospital
[2]National Kidney and Transplant Institute, East Avenue, Diliman, Quezon City

BACKGROUND

Secondary graft failure (SGF) following initial engraftment complicates 5–10% of allogeneic HSCT, with higher rates in haploidentical settings. SGF with persistent complete donor chimerism—poor graft function (PGF)—is less common. Spontaneous autologous reconstitution after SGF is rare in adults.

CASE

A **47-year-old male** with Philadelphia chromosome–negative B-cell acute lymphoblastic leukemia (**B-ALL**) in second complete remission underwent **haploidentical** peripheral blood **allo-HSCT** (Day 0). Conditioning consisted of **fludarabine/melphalan/ATG** with **intermediate-dose post-transplant cyclophosphamide** (30 mg/kg on Days +3 and +4), plus tacrolimus/mycophenolate mofetil. **CD34$^+$ dose was 6.9 × 10^6/kg**. Neutrophil engraftment occurred by Day +14 with platelet engraftment by Day +18. From Day +22, progressive cytopenias with high-grade fever and rising CMV viremia developed despite **100% donor chimerism** on Day +30. **CMV DNAemia rose from 384 IU/mL** to a peak of 3736 IU/mL. Day +37 bone marrow showed hypocellularity, no measurable residual disease, and X/Y FISH with 100% XY signals despite a female donor, suggesting **early graft loss**. Day +48 septic shock required vasopressors and granulocyte infusions. **Stem cell boost (CD34$^+$ 5.3 × 10^6/kg)** was administered on Day +62. Repeat STR chimerism on Day +95 demonstrated **100% recipient alleles** with persistent hypocellular marrow and **no relapse**, consistent with spontaneous **autologous hematopoietic reconstitution**.

Six convergent mechanisms likely drove graft failure: (1) **Haploidentical donor status**—incidence ~10% versus 3–5% for matched siblings, driven by HLA disparity and bidirectional alloreactivity; (2) **CMV DNAemia at 3736 IU/mL**—independent risk factor for poor graft function (hazard ratio 6–9) via direct progenitor infection and stromal dysfunction; (3) **Reduced-dose post-transplant cyclophosphamide**—standard 50 mg/kg is critical for alloreactive T-cell depletion, whereas 30 mg/kg predisposes to incomplete host-versus-graft abrogation; (4) **Valganciclovir myelosuppression**—necessary for CMV control but inherently marrow-suppressive, compounding pancytopenia; (5) **Paradoxical stem cell boost**—donor lymphocyte infusion in inflamed microenvironment may trigger alloimmune injury to residual donor progenitors, creating competitive advantage for surviving host stem cells; and (6) **Suboptimal stem cell ablation**—fludarabine-melphalan-ATG with three years of prior maintenance chemotherapy may have selected for a resilient host progenitor pool capable of re-expansion.

Follow-up through Day +183 confirmed sustained autologous hematopoiesis

Table 1. Serial Hematologic and Chimerism Parameters During Autologous Recovery

Parameter	Day +95	Day +178	Day +183
Chimerism	100% recipient	100% recipient	100% recipient
Hemoglobin (g/L)	72	73	88
WBC (×10^9/L)	2.6	6.62	3.31
Platelets (×10^9/L)	11	13	23
CMV (IU/mL)	200	Undetectable	Undetectable
G-CSF	Weekly	Reduced	Discontinued

Day +183 bone marrow demonstrated hypocellularity, trilineage hematopoiesis without dysplasia, few megakaryocytes, and flow cytometry compatible with remission. **No graft-versus-host disease, infection, or bleeding.**

CONCLUSION

This case illustrates early SGF transitioning from PGF to autologous reconstitution in a haploidentical setting—a rare trajectory. Six convergent mechanisms, with CMV viremia and haploidentical mismatch as primary drivers, underscore the multifactorial nature of graft failure. Stable autologous recovery without relapse at six months supports conservative management with close monitoring in selected patients, potentially obviating immediate re-transplantation.

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