

Agranulocytosis as a Part of Secondary Graft Failure after Allogeneic Stem Cell Transplantation

Bimalangshu R Dey^{1*} and Sidhertha Podder²

¹Hematology/Oncology unit, Massachusetts General Hospital, Boston MA, USA

²Internal Medicine, Jamaica Hospital Medical center, Jamaica, NY, USA

Abstract

Secondary graft failure after myeloablative allogeneic Stem Cell Transplantation (SCT), although rare, is a serious complication and usually requires a second allogeneic SCT to restore normal donor-derived hematopoiesis. Here, we are presenting a patient with acute myeloid leukemia who developed secondary graft failure following HLA 9/10 Ag-matched unrelated donor SCT. The clinical context and the marrow findings raised the suspicion of an immune-mediated mechanism to be the likely cause of graft failure. He received immunosuppressive therapy (Horse ATG, cyclosporine, corticosteroid) that resulted in restoration of full donor-derived hematopoiesis with essential normal peripheral blood counts, and thus obviating the need for a second allogeneic SCT.

Keywords: Allogeneic stem cell transplantation; Acute myeloid leukemia; Bone marrow transplantation

Introduction

Allogeneic hematopoietic stem cell transplantation (allo SCT) represents a curative therapeutic strategy for various malignant and non-malignant hematological diseases. Graft failure following conventional myeloablative allo-SCT is rare, but can occasionally pose as a significant problem. Graft failure after unrelated donor allo-SCT is slightly higher in incidence than that following related donor transplants. Most graft failures occur within 100 days, those observed after day +100 are infrequent [1].

Primary graft failure is defined as when there are no signs of hematopoietic recovery within 28 days following myeloablative conditioning and stem cell infusion, and patients continue to have significant neutropenia ($<0.5 \times 10^9/L$) and/or thrombocytopenia ($<30 \times 10^9/L$) [2].

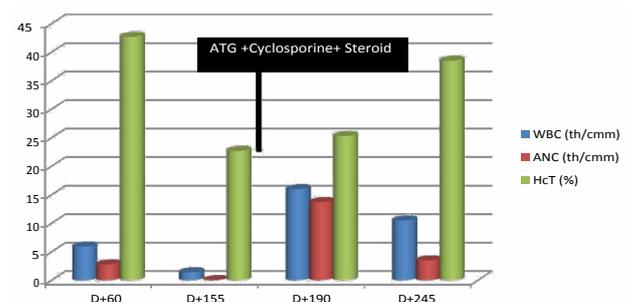
Secondary or late graft failure has been defined as the development of inadequate marrow function after initial engraftment has been achieved.

Case Description

Here, we are describing a 46 years old gentleman with a history of acute myeloid leukemia, subtype M4, who was diagnosed when he presented with cutaneous/ gingival/ CNS involvement and was treated with multiple rounds of systemic and intrathecal chemotherapy with the achievement of a complete remission, both systemic and CNS wise. He then underwent 9/10 matched unrelated donor hematopoietic stem cell transplant following myeloablative conditioning with busulfan/ cyclophosphamide. The donor was male. GVHD prophylaxis consisted of rabbit atthymocyte globulin, tacrolimus and methotrexate. Donor derived hematopoietic engraftment occurred approximately 2 weeks following SCT. Because of mild cutaneous graft-versus-host disease (stage II), he was treated with low dose prednisone with essential resolution of skin rash. Molecular based chimerism analysis performed at 30 and 100 days post-SCT confirmed him to have achieved full donor chimerism. Day +60 he revealed complete recovery of peripheral blood counts. About day +155, when he was essentially asymptomatic, a routine laboratory study revealed hemoglobin of 13.5, hematocrit 38.8, WBC count 1.7 with ANC of 0.00 and absolute lymphocytes 1.63, platelet 96,000 (Graph 1). Findings on physical examination were

unremarkable and his ECOG performance status was 0 (excellent). The etiology was unclear but differential included drug, toxin, and infection or enhanced immune activity while he was on reduced dose of immunosuppression. The modest rise in platelet counts on adjusted (increased) dose of steroid and tacrolimus would support an immune hypothesis. The onset of severe anemia may point to bone marrow failure or secondary engraftment failure. Testing for donor specific antibodies (DSA) to HLA A2 (locus of mismatch) was 0%, DSA was 95% for DR10, DQ6, DR53, DQ5, DQ1, and weak DQ2.

He was maintained on a low dose of prednisone (10 mg daily) and Tacrolimus (0.5 mg daily) for the first several days. Subsequent Bone marrow findings were remarkable for 20% marrow cellularity, preserved erythroid and megakaryocytic compartment, but marked



Graph 1: Indicates WBC, Absolute neutrophil count (ANC) and Hematocrit count (Hct) during the Day +60, Day +155, Day +190 and D+245 days of post transplantation.

***Corresponding author:** Dr. Bimalangshu R Dey, MD, PhD, Hematology/Oncology unit, Massachusetts General Hospital 100 Blossom St, Boston MA 02114, USA, Tel: 617-724-1124; Fax: 617-724-1126, E-mail: bdey@partners.org

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myeloid hypoplasia; there was no evidence of leukemia. The T-cell population had an inverted CD4: CD8 ration (0.13); chimerism analysis revealed >98% bone marrow cellularity deriving from donor origin.

Infectious etiologies for agranulocytosis were ruled out. His immunosuppression with prednisone 10 mg daily and Tacrolimus 0.5 daily was continued until infectious disease work up was completed. He received Neupogen 480 mg subcutaneous daily. There was no improvement in neutrophil counts, and soon he also became severely anemic (HCT 25%). A repeat BM biopsy showed severe myeloid and erythroid hypoplasia. There was quite an impressive presence of large granular lymphocytes with inverted CD4/CD8 ratio. There was no evidence of recurrent acute myeloid leukemia. An immune pathology was entertained and immunosuppressive therapy (IST) with horse antithymocyte globulin (ATG), methylprednisone and cyclosporine (CSA) was given (tacrolimus discontinued). The regimen was horse ATG 3123 mg (40 mg/kg) IV qd days 1-4, Methylprednisone 78.3 mg IV days 1-4 then 78 mg PO qd days 5-15, and cyclosporine 200 mg PO q12 starting day 1. He tolerated the regimen without any significant difficulties. Within a week of the initiation of IST, there noted to be a gradual recovery in neutrophil counts, which was soon, accompanied by an improvement in both RBC and platelet counts. Approximately three months after the IST, on therapeutic dose CSA and low dose prednisone (5 mg daily), and his CBC are within normal limits.

Discussion

The exact cause of acute onset of agranulocytosis was unclear.

Exposure to infection/drug/toxin was felt to a possibility without any documented source of infection. The other possibility was thought to be an enhanced immune reactivity given the patient was off the prednisone at that time and he was receiving the tapering dose of tacrolimus. Second bone marrow biopsy was impressive for presence of large granular lymphocytes with inverted CD4/CD8 ratio. Finally, patient recovered fully with immunosuppressive therapy. The bone marrow findings and the spectacular response to IST raise the possibility of an immune mechanism underlying the onset of agranulocytosis and severe anemia.

While secondary engraftment failure is traditionally rescued by a second allogeneic SCT, our case illustrates that a dysregulated immune system may play a role in the pathogenesis of secondary graft failure, where IST can be a successful strategy in many such patients. The immune mechanism of secondary engraftment failure is a field of research and need to be explored for the better survival following bone marrow transplantation.

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