1083-8791/06/1209-0001$32.00/0
doi:10.1016/j.bbmt.2006.04.007

ASBMT American Society for Blood and Marrow Transplantation

Letter to the Editor

Pure White Cell Aplasia (PWCA) Relapsing after Allogeneic BMT and Successfully Treated with Nine DLIs

Pure white cell aplasia (PWCA) is an infrequent, acquired, single-line autoimmune myelopathy [1] characterized by the absence of not only circulating neutrophils but also, more specifically, their precursors in the bone marrow (BM). The defining term was first used in 1983 [2] in analogy to the more frequent and better known pure red cell aplasia, with the understanding that not all "white cells" are affected, but rather only the neutrophil series. PWCA is recognized as an autoimmune myelopathy [1], even if the demonstration of an immune attack by antibodies and/or T lymphocytes may be uncertain. PWCA may present as idiopathic but may also be associated with thymomas. It has been treated more or less satisfactorily with a variety of immunomodulating agents, including corticosteroids, cyclosporin, high-dose immunoglobulins, and thymectomy when associated with thymoma. We report the first case, to our knowledge, of a patient with PWCA who proved refractory to all other treatments but was successfully treated with allogeneic BM transplantation followed by 9 consecutive donor lymphocyte infusions (DLIs).

The patient (UPN 1436) was a North Italian male and 56 years old at the time of this writing (April 2006). No occupational hazards, drug-consuming habits, or thymomas were present. Severe bacterial infections were recurring, including mastoiditis with cranial nerve VII palsy. Severe neutropenia (0.2×10^9/L neutrophils) was detected in 1998. No granulocytic precursors were found in the BM aspirates. He was treated with 3 courses of antilymphocytic globulin (ALG), alternating horse and rabbit products, cyclosporin A (CyA) and granulocyte colony-stimulating factor. Neutrophil reconstitution was obtained for 2 years after horse ALG administration, for 6 months after rabbit ALG administration, and for another 4 months after repeated horse ALG administrations. However, severe neutropenic relapses occurred jointly with severe bacterial infections. In September 2002, he received an allogeneic BM transplant (absolute neutrophil count, 6.9×10^8/kg) from his HLA-identical 53-year-old sister after a reduced intensity conditioning regimen (thiotepa 10 mg/kg, cyclophosphamide [CY] 100 mg/kg). At transplantation, neutrophils amounted to 0.4×10^9/L; the few extant neutrophils were morphologically normal, and large granular lymphocytes were absent on smears. The immunophenotype of peripheral lymphocytes was $CD3^+$ (88%), $CD8^+$ (73.4%), $CD4^+$ (6.7%), $CD19^+$ (3.4%), $CD16^+$ (7%), $CD56^+$ (2.8%), $CD57^-$. The BM aspirate showed normal erythroid and megakaryocytic lineages, lymphoid (20%) and plasmacytic (10%) cells, eosinophils at various stage of maturation, but a total absence of neutrophil precursors. BM biopsy confirmed these findings; total cellularity was estimated at 25%. Cytogenetic examination showed a normal XY karyotype. Seven BM cultures performed during this period showed 24 granulocyte-macrophage colony-forming units (7-59 in our laboratory) and 20 burst-forming units, erythroid (BFU-Es) (7-33). No inhibition of granulocyte-macrophage colony-forming units could be clearly demonstrated in the presence of the patient's serum.

The post-transplantation course was uneventful, with graft-versus-host disease (GVHD) prophylaxis composed of methotrexate-cyclosporin A (MTX-CyA). Time to 500 neutrophils and 50×10^9/L platelets was 20 days. Full donor chimerism was attained on day +20, but from then on a mixed chimerism supervened, with a nadir of donor precursors of 23% on day +42, concomitant with severe neutropenia. A program of escalating DLI was implemented, with a starting dose of 1×10^5/kg and an ending dose of 1×10^7/kg. Nine DLIs were performed in 2 separate blocks (Figure 1) and followed by increasing donor chimerism, as evaluated by cytogenetics and short tandem repeat polymerase chain reaction analysis of T and BM cells. Full donor chimerism was reached on day +740, with complete reconstitution of BM granulocytopoiesis. No GVHD was registered, and infectious complications did not recur.

As in many other cases of PWCA, no serologic inhibition of neutrophilic granulocytopoiesis could

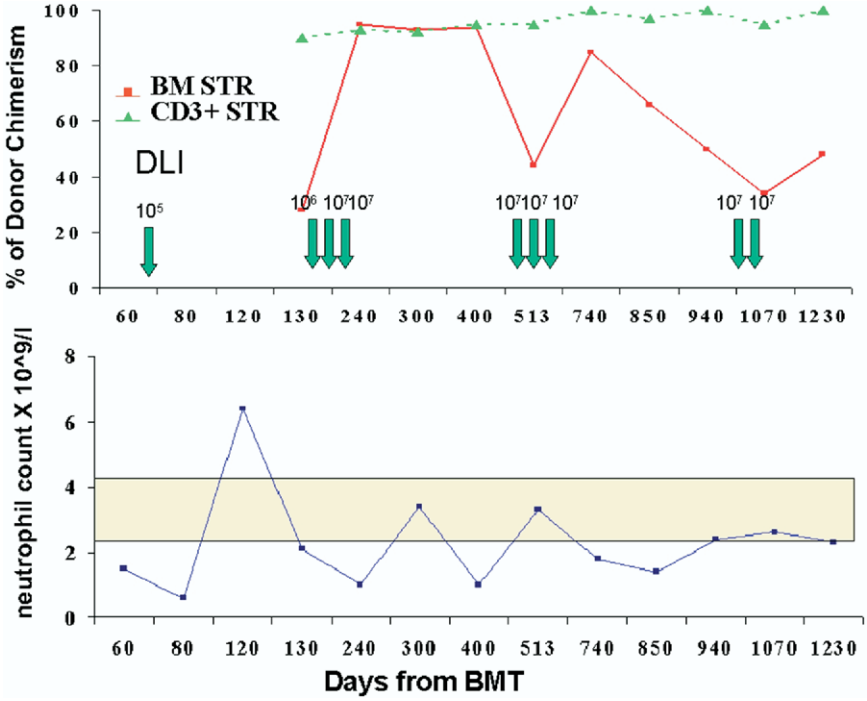

Figure 1. Post-transplantation course of absolute neutrophil count and of blood and marrow chimerism as assessed by short tandem repeat (STR) technology. Shaded area indicates normal absolute neutrophil counts. BMT indicates bone marrow transplantation.

be demonstrated in this patient. However, the presence of eosinophilic precursors in the BM pretransplantation aspirate indicated that the antineutrophil precursor effect started downstream of the division between the eosinophilic and neutrophilic lines. Full donor chimerism in BM and blood could be obtained only after 9 gradually incremental DLIs and coincided with complete remission of granulocytopoiesis in the BM aspirates and of mature neutrophils in the blood. Mixed chimerism after nonmyeloablative allotransplantations has been found to be effective in autoimmune diabetes of nonobese diabetic mice, with reversal of insulitis despite the presence of recipient T cells [4]. A similar experience was reported in some clinical cases of rheumatoid arthritis [5] and psoriatic arthritis [6], but in others full chimerism was necessary [7, 8].

A clinically recognizable graft-versus-autoimmunity effect was found in patients with coincidental diseases after having developed GVHD [9]. In other cases, however, relapses despite full donor chimerism have been reported [10]. A possible interpretation of this last occurrence may be consistent with the concept of long-lived recipient plasmacytes residing in postulated survival niches [11]. However, in this case of persistent, refractory, and relapsing PWCA, attainment of full donor chimerism after 9 consecutive DLIs coincided with complete remission of the disease.

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