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Case Report

Steroid-Dependent Graft-Versus-Host Disease Following Second Syngeneic Transplant for Multiple Myeloma

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Abstract

Steroid-dependent graft-versus-host disease requiring photopheresis has not been previously reported. Herein, we present a case of steroid-resistant graft-versus-host disease following second syngeneic transplant for multiple myeloma. The patient experienced an uneventful clinical course following first transplant. Despite receiving her second transplant from the same product following similar conditioning, she developed acute and chronic graft-versus-host disease and was unable to taper her immunosuppression. Patient was initiated on photopheresis and subsequently experienced significant improvement in her symptoms and reduction of her immunosuppression.

Keywords: Syngeneic, Multiple myeloma; Graft-versus-host disease; Photopheresis

Abbreviations

CML: Chronic Myeloid Leukemia; FISH: Florescent In-Situ Hybridization; FLC: Free Light Chain; GSF: Granulocyte Colony-Stimulating Factor; GVHD: Graft-Versus-Host Disease; ISS: International Staging System; MM: Multiple Myeloma; MMF: Mycophenolate Mofetil; SGVHD: Syngeneic Graft-Versus-Host Disease

Introduction

Graft-versus-host disease (GVHD) is an uncommon complication of syngeneic transplant. All but one of the previously reported cases has occurred following initial transplant. Further, the vast majority of cases are low grade and either self-limited or steroid responsive. Herein, we present the clinical and laboratory characteristics of a patient who developed steroid-dependent Grade II acute and moderate chronic graft-versus-host disease following her second syngeneic transplant for multiple myeloma (MM).

Case Presentation

Patient was a 60-year-old G0P0 Caucasian female, who was diagnosed with Stage I (International staging system [ISS]) [1] non-secretory multiple myeloma in 2011 following a compression fracture of her lumbar spine. On presentation, her kappa free light chain (FLC) level was 23.7 mg/dL. Bone marrow biopsy demonstrated >60% CD138+ plasma cells, with RB1 monosomy and translocation t (11;14) on fluorescent in-situ hybridization (FISH). Her hemoglobin was 12.4 g/dL and her creatinine was 0.68 mg/dL. Patient received three cycles of chemotherapy with bortezomib and dexamethasone. In July of 2011, she was conditioned with 200 mg/m^2 melphalan and preceded to syngeneic transplant from her identical twin sister, who was verified by HLA-matching. She did not receive GVHD prophylaxis. Transplant utilized a granulocyte colony-stimulating factor (GSF) mobilized peripheral blood stem cell graft containing 5.50 x 10^6 CD34+ cells/kg, 22.47 x 10^7 CD3+ cells/kg and 6.83 x 10^8 total nucleated cells/kg. Her admission was otherwise uneventful and she recovered her counts on day +10 and was discharged home on day +13. She experienced no rash or liver enzyme abnormalities. She reported some brief episodes of diarrhea and abdominal discomfort, but responded to symptomatic treatment. The patient had resolution of her kappa FLC and her 100 day bone marrow biopsy demonstrated hypocellular marrow with trilineage hematopoiesis and no evidence of disease. The patient had a complete response per International Myeloma Working Group criteria [2]. She was placed on 10 mg/day of lenalidomide as maintenance therapy.

Two and a half years after initial transplant, the patient developed neutropenia. Although her kappa FLC was only minimally elevated (2.85 mg/dl), bone marrow biopsy revealed a hypoplastic bone marrow with 20% plasma cells and patient was diagnosed with disease recurrence. She underwent three cycles of chemotherapy with cyclophosphamide, bortezomib, and dexamethasone. Patient was again conditioned with 200 mg/m^2 of melphalan and received her second syngeneic transplant in January of 2014. The graft for the second transplant was derived from cryopreserved pheresis product unutilized in the patient's prior transplant and contained 5.5 x 10^6 CD34+ cells/kg, 22.47 x 10^7 CD3+ cells/kg and 6.82 x 10^8 total nucleated cells/kg. She recovered her counts on day +11.Hospital course was uneventful and patient was discharged on day +15.

On day +23, patient developed an intensely pruritic rash which covered her entire body. Skin biopsy demonstrated vacuolar alteration of the dermal-epidermal junction with scattered necrotic keratinocytes, mild spongiosis and superficial perivascular inflammatory cell infiltrates, which was consistent with GVHD. Patient had normal LFTs and did not complain of nausea, vomiting or diarrhea. Patient was started on 50 mg of prednisone for suspected stage III GVHD of the skin [3]. Patient's rash was responsive to this treatment. However, it recurred during attempts to taper her steroids and patient was started on tacrolimus on day +37. Her steroids were subsequently tapered and discontinued on day +89.

On day +116, patient developed nausea, vomiting and diarrhea while on 2.5 mg tacrolimus BID. No infectious etiology was identified. Prednisone was restarted at 60 mg/day and mycophenolate

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mofetil (MMF) 1 gram BID was added to her immunosuppressive regimen. On day +187, patient began reporting dry eyes and oral hypersensitivity. She was referred to ophthalmology and started on cyclosporine eye drops. Throughout this time, patient experienced several periods of high volume diarrhea, which were unresponsive to loperamide and required outpatient treatment for dehydration. On multiple occasions, patient's steroid dose was tapered to 10 mg/day and increased to 40 mg/day upon recurrence of her symptoms.

Due to her steroid-dependent moderate chronic GVHD [4], the decision was made to proceed to photopheresis. Port was placed on day 216 and photopheresis was initiated on day +231. Patient received two sessions of photopheresis every other week, which resulted in slow improvement of her gastrointestinal symptoms. Following institution of photopheresis, it has been possible to taper her immunosuppression. After six months, her photopheresis was spaced to two sessions per month. Her photopheresis was discontinued on day +558, with the patient having received a total of 39 pheresis sessions. Patient is currently day +607. At present, our patient remains on 10 mg prednisone ever other day and 0.5 mg/day of tacrolimus, having discontinued MMF.

Discussion

First reported in 1979, GVHD following syngeneic hematopoietic stem cell transplantation (SGVHD) was once considered a rare occurrence [5]. However, recently published data has called this assumption into question. Reported incidence varies by transplant indication, ranging from approximately 10% in the setting of acute leukemia to no reported cases in the setting of aplastic anemia [6-8]. In patients with MM, the two largest series have starkly different rates of SGVHD. Bashey et al reported an incidence of 5% (2/43), while Gharton et al reported an 20% (5/25) [9,10]. Due to a low index of suspicion among providers historically and the small number of syngeneic transplants performed on a yearly basis, it is difficult to ascertain whether the true incidence of SGVHD varies by underlying disease. Our institution has performed 23 syngeneic transplants since 1997, including eight for MM. This is our first case of SGVHD.

An unusual aspect of this patient's presentation is the occurrence of GVHD following the patient's second syngeneic transplant, with no evidence of GVHD during prior transplant. Only one previous case of these phenomena had been reported in a 26-year-old man who developed Grade III acute GVHD involving his liver and skin following a second syngeneic transplant for relapsed Philadelphia chromosome positive chronic myeloid leukemia (CML) [11]. However, unlike our patient, he responded readily to steroids and cyclosporine A and did not develop chronic GHVD.

Another unusual aspect of this case is the relatively recalcitrant nature of the patient's GVHD. SGVHD is generally low grade, characterized by mild symptoms and skin manifestations, and more severe disease is uncommon in the literature. With the exception of two patients, steroid-refractory or -dependent GVHD has not, to our knowledge, been reported [7,8]. Most cases resolve either without treatment or after a short course of steroids; second line treatment is rarely needed. The benefits of extracorporeal photopheresis have been well-documented in other settings, but this is, to our knowledge, the first reported use of photopheresis in a patient with SGVHD [12]. Although the pathophysiology of SGVHD is still not well understood, this case shows that it, like other forms of GVHD, is amenable to treatment with photopheresis.

We believe that this case highlights the need for vigilance regarding the possibility of GVHD occurring with a second syngeneic transplant, even when no GVHD is observed after the first transplant. It also demonstrates the utility of photopheresis for the treatment of steroid-dependent SGVHD.

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