

Reversal of Graft-Versus-Host Disease with Infusion of Stored Autologous Bone Marrow Cells Following Combined Liver-Bone Marrow Allograft Transplantation in Man

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Graft-versus-host reaction was first described following splenocyte transplantation¹ and was correctly attributed to recognition of the host by immunologically competent cells of the graft. Soon, the same phenomenon was recognized in recipients of organs that are rich in lymphoid tissue² and was demonstrated after parent to offspring F₁ hybrid intestinal transplantation in rats.³ An increasing frequency of graft-versus-host-disease (GVHD) has been observed after transplantation of other organs, including the human liver.⁴⁻¹²

In this report, we describe reversal of GVHD in a recipient of a combined liver-bone marrow transplant by infusion of stored autologous bone marrow cells.

Case Report

A 56-year-old man with a gastric leiomyosarcoma with liver metastases underwent upper abdominal exenteration and orthotopic liver allograft transplantation on July 16, 1992. Shortly before operation, the patient was treated with a single dose of 550 rads thoraco-abdominal lymphoid irradiation (TLI). Immediately after operation, 19×10^9 donor bone marrow cells harvested from 10 vertebral bodies were infused IV through a central line. Postoperative immunosuppression was with FK 506 and prednisone.

A skin rash developed within the first postoperative week. The rash, that was initially mild and confined to the areas exposed to the preoperative TLI, progressively worsened and the diagnosis of GVHD was made on a skin biopsy 15 days following surgery. Histologic examination of the skin biopsy revealed a mild, predominantly T lymphocyte infiltrate localized to the upper dermis that was associated with focal exocytosis and spongiosis and with occasional keratinocyte necrosis. The infiltrating cells were recognized as of donor HLA type by immunostaining. A second biopsy on postoperative day 21 revealed more florid changes that included acantholysis and focal cleft formation. A third biopsy one week later showed continued damage to keratinocytes and adnexal cells, with an inflammatory infiltrate of the upper dermis that was signifi-

cantly more conspicuous than in prior biopsies. Immunoperoxidase stains showed the cells to be T lymphocytes of donor origin.

The skin involvement spread to more than 80% of the body surface, including the palms, soles and face. The progression of GVHD was not altered by increases or decreases of FK 506 or prednisone. Throughout this time, 22 to 34% of the circulating lymphocytes were donor phenotype, as determined by flow cytometry using appropriate anti-HLA class I monoclonal antibodies.

On the 42nd and 43rd postoperative days, 2.83×10^8 autologous bone marrow cells/kilograms were infused. The skin rash promptly improved and completely resolved within two weeks after the autologous cell infusion with a reduction of circulating donor lymphocytes which never again exceeded 10% of the total and was in the 3% range on postoperative day 96. The patient who had been gravely ill was restored to a sense of well being and was discharged three weeks following the autologous bone marrow infusion.

Donor-specific alloreactivity was assessed in mixed lymphocyte reaction (MLR) and in cell-mediated lympholysis (CML) pretransplant, during the first month postsurgery and following autologous bone marrow infusion. Pretransplant recipient peripheral blood exhibited proliferative responses to donor or third party irradiated spleen cells. During the first postoperative month, his MLR responses to both donor and third party were significantly suppressed. However, following infusion of the autologous marrow the MLR responses were reestablished, and the patient showed donor-specific CML activity. Restoration of immunocompetence towards the donor coincided with the clinical resolution of the GVHD.

Comment

GVHD in intestinal or hepatic recipients cannot be defined by conventional criteria because the donor origin of the transplanted organs prevents them from becoming a target of GVHD while exposing them to the risk of rejection. Consequently, the most unequivocal finding may be a skin rash such as that observed in approximately 5% of our liver allograft recipients. For years, these dermatologic manifestations were attributed to a drug or to an allergic reaction, until it was realized that systemic chimerism occurs after all successful transplantations, creating the possibility of GVHD in every case.¹²

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Storage of autologous bone marrow could represent a safety net in pilot trials of bone marrow-organ transplantation, until the risk for severe GVHD is better understood or until alternative approaches are developed to prevent GVHD, such as a bone marrow component approach, or by UVB irradiation of the allogeneic bone marrow (Mark Hardy, this issue).

Understanding the difference between the autologous naive cells that had been in storage and the immunocytes in the patient that had become defenseless against attack by cohabitation for six weeks with donor cells would go far in explaining the changes brought about by chimerism. The therapeutic rescue was reminiscent of a tolerance breaking experiment mentioned in the classic article of Billingham, Brent, and Medawar.¹³ However, the incompleteness of the effect in our patient allowed control of the GVHD without rejection of the liver allograft.

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