

Novel Application of Extracorporeal Photopheresis as Treatment of Graft-versus-Host Disease Following Liver Transplantation

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ABSTRACT

A 48-year-old man with hepatitis C virus (HCV) cirrhosis complicated by hepatocellular carcinoma underwent liver transplantation. His course was complicated by fever, diarrhea, abdominal pain, and pancytopenia. He developed a diffuse erythematous rash, which progressed to erythroderma. Biopsies of the colon and skin were consistent with acute graft-versus-host disease. Donor-derived lymphocytes were present in the peripheral blood. The patient was treated with corticosteroids and cyclosporine; however, he had minimal response to intensive immunosuppressive therapy. Extracorporeal photopheresis was initiated as a salvage therapy. He had a dramatic response, and his rash, diarrhea, and pancytopenia resolved. He is maintained on minimal immunosuppression 24 months later.

INTRODUCTION

Graft-versus-host disease (GVHD) after liver transplantation (LT) has been well described in the literature.¹ Donor-derived T-lymphocytes attack the recipient's skin, bone marrow, and gut, leading to rash, cytopenia, and diarrhea. The management of GVHD after LT is mostly derived from treatment of GVHD following hematopoietic stem cell transplantation (HSCT).^{2,3} Extracorporeal photopheresis (ECP) is effective in post-HSCT GVHD but has only rarely been used for solid organ transplant-associated GVHD, with only one reported survivor thus far.⁴⁻⁶ It has never been reported with GVHD post-LT.

CASE REPORT

A 48-year-old man with hepatitis C virus (HCV) cirrhosis and hepatocellular carcinoma underwent LT from a 62-year-old woman. The donor human leukocyte antigen (HLA) type was A2,30; B18,44; Bw6,4; C5,-; DR1,17; DR52; DQ2,5. The recipient's HLA type was A26,29; B44,49; Bw4,-; C7,16; DR1,7; DR53; DQ2,5. Induction immunosuppression was basiliximab followed by tacrolimus, mycophenolate mofetil, and prednisone. The early postoperative period was complicated by biopsy-confirmed mild acute cellular rejection, which resolved with steroids. Seventeen days after transplantation, the patient was admitted with fevers, diarrhea, and an erythematous, desquamating rash. He was pancytopenic with a white

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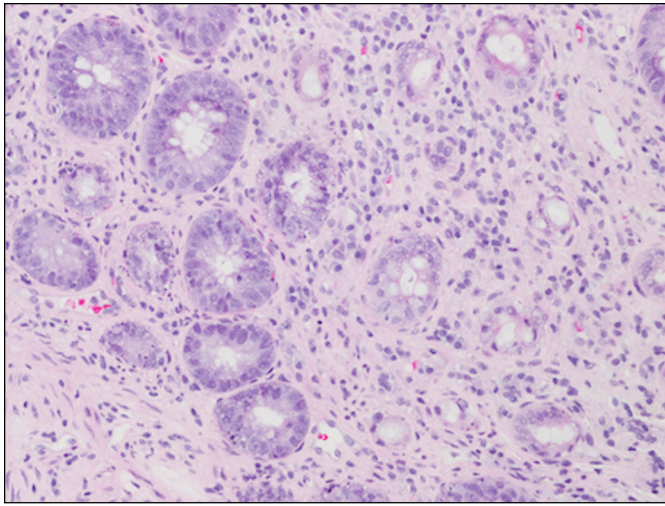


Figure 1. Photomicrograph depicting findings consistent with acute GVHD, including prominent crypt epithelial apoptosis present in the left half of the field and prominent crypt drop-out on the right half of the field (200x magnification).

cell count 400/uL, hemoglobin 8.3 g/dL, and 65,000 platelets/uL. The rash progressed to involve the entire integument and was pronounced in the palms and soles. An infectious workup was negative. Liver function tests were normal, although ferritin was elevated to 27,232 ng/mL (reference range 30–450 ng/mL).

A colon biopsy revealed scattered epithelial apoptosis with crypt destruction (Figure 1). Skin biopsy showed interface dermatitis with dyskeratotic keratinocytes, epidermal necrosis, and superficial perivascular lymphocytic infiltration. The bone-marrow biopsy had decreased cellularity with rare hemophagocytic histiocytes, but normal morphology. Bone-marrow chimerism analysis utilizing short tandem repeats revealed 4% donor DNA, 96% host DNA, and no third-party DNA. Fluorescence in situ hybridization of the marrow showed 1.5% donor-derived cells; 7% of the peripheral blood T-lymphocytes was of female origin.

There was initial concern for secondary hemophagocytic lymphohistiocytosis, and given critical illness, the patient underwent plasma exchange. On the basis of the clinical picture, histology, and bone-marrow findings of donor-derived DNA, it became clear that acute GVHD was the predominant syndrome. The patient was treated with dexamethasone and intravenous immunoglobulins. Tacrolimus was changed to cyclosporine due to thrombocytopenia. He continued to deteriorate over 5 days, and ECP was initiated after obtaining informed consent for off-label use. There was clear improvement of his skin rash, and his fever resolved. Diarrhea, mucositis, and cytopenia resolved, and he underwent 32 sessions of ECP.

Repeated peripheral blood chimerism studies 10 days after ECP showed elimination of peripheral female T-lymphocytes. ECP was continued for another 9 months, with a gradual

increase in the interval between treatments with improved clinical status. The patient is currently alive and well on tacrolimus monotherapy with undetectable HCV 24 months after transplant.

DISCUSSION

GVHD in LT is rare, but has a mortality rate of 85%.^{1,7,8} In LT, immunocompetent donor-derived lymphocytes undergo activation following exposure to recipient-derived antigens. Activated donor T-lymphocytes mediate an immune response against recipient tissue.⁷ The target tissues in GVHD following LT are bone marrow, skin, and the gut, with notable sparing of the liver.⁷

The pathogenesis of GVHD in LT occurs in three continuous phases. In the first phase, surgery induces a pro-inflammatory state where host macrophages release tumor necrosis factor α (TNF α) and IL-1, resulting in increased host antigen-presenting cell activity. In the second phase, donor-derived T-lymphocytes residing in the donor liver activate, stimulated by HLA/peptide complex interactions, resulting in IL-2 receptor expression and clonal expansion, ultimately leading to the release of pro-inflammatory cytokines IL-2 and IFN- γ .^{3,7} In the third phase, anti-host T-cells release granzyme and perforin, leading to further inflammation and promotion of GVHD.^{7,9}

In LT, GVHD presents 1–8 weeks after transplant.^{1,7} In 15% of cases, the patient presents with findings only of a rash involving the palms and soles, with eventual bullous transformation and desquamation.^{6,7} GVHD resulting in multi-system organ failure has an 85% mortality rate. The natural history of post-LT GVHD is a relapsing-remitting pattern of diarrhea, rash, fever, and neutropenia, culminating in sepsis and death.⁷

A diagnosis of GVHD after LT is confirmed by biopsy of the affected tissues, which will demonstrate donor-derived lymphocytic infiltration in the appropriate clinicopathological setting.^{7,10} GVHD should be suspected if chimerism is present by polymerase chain reaction or HLA typing of lymphocytes in the peripheral blood with symptoms concerning for GVHD.^{1,6,8,10} Early recognition requires thoughtful synthesis of pathological, laboratory, and clinical data, and prompt treatment is essential.¹⁰

There are no guidelines for treatment of post-LT GVHD. Current therapy is borrowed from GVHD treatment following HSCT and consists of immunosuppression with high doses of corticosteroids or calcineurin inhibitors.^{7,10} However, this is frequently complicated by toxicity and infections.^{6–11}

Salvage therapies in steroid-refractory GVHD after LT are mostly ineffective. Administration of OKT3 or anti-thymocyte globulin (ATG) produces a profound immunosuppression, but is not associated with remission and frequently results in fatal infections.^{7,10} Targeting T-lymphocytes with daclizumab and

basiliximab is associated with remission of skin GVHD, but are usually inadequate in suppressing gut GVHD.^{7,8,10} Anti-TNF α agents are also not effective in treating GVHD and are associated with fungal infections.^{8,10} Decreasing immunosuppression following LT allows host lymphocytes to regain activity against donor lymphocytes with the risk of graft rejection.^{6,8,10} Lastly, T-lymphocyte elimination with ATG or irradiation has not proven to be worthwhile due to the unknown risk of impairing engraftment.^{1,7,12}

ECP has been effective in GVHD following HSCT and is regarded as a second-line treatment, resulting in response rates as high as 80% and up to 50% long-term survival.^{11,13-15} Additionally, ECP has also been somewhat effective in mitigating rejection post-LT.¹⁶ In ECP, patients undergo leukapheresis and incubation with 8-methoxypsoralen, exposure to ultraviolet-A light, and reinfusion.^{9,14,17} Currently, investigations are underway into cryopreservation of apheresed white blood cells for patients unable to tolerate classic ECP; however, this method has not yet been utilized in LT.¹⁸ ECP-treated lymphocytes undergo apoptosis and absorption by dendritic cells and macrophages in the reticuloendothelial system, resulting in the secretion of tissue growth factor- β and IL-10, and promoting immunotolerance.^{9,17,19} Dendritic cells differentiate into type-2 dendritic cells, enhancing the anti-inflammatory response.^{17,20} Additionally, ECP induces a significant increase in circulating CD4⁺ CD25⁺ Treg cells, associated with a tolerogenic phenotype that is present for up to one year following treatment.^{11,16,17,21} Lastly, ECP preserves host responses to foreign antigens, avoiding the increased risk of infection due to immunosuppression.^{4,6,11,15,17,22,23}

We present a case of refractory post-LT GVHD that responded to the novel application of ECP. The patient currently has no evidence of GVHD at 2 years post-transplant. ECP can potentially be used as a salvage therapy in patients with GVHD refractory to treatment following LT, although the optimal use of ECP requires continued study.

DISCLOSURES

Author contributions: All authors wrote and edited the manuscript. STG Hammer provided the pathology images. RH Collins, Jr., is the article guarantor.

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Informed consent was obtained for this case report.

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