

# Severe, Late-onset Graft-Versus-Host Disease in a Liver Transplant Recipient Documented by Chimerism Analysis

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**ABSTRACT:** A 52-year-old liver transplant recipient presented 8 months after transplantation with oral thrush, then 3 days later with oral ulcers and a diffuse rash, and 5 days later with an acutely reduced white blood cell count, rash, fever, and diarrhea. Bone marrow biopsy revealed severe aplasia. Although graft-versus-host disease (GVHD) was considered, the late onset of these symptoms was felt to render this etiology unlikely because GVHD usually occurs 2 to 6 weeks after transplantation. All potentially myelosuppressive medications were discontinued, and the patient was treated with high doses of hematopoietic growth factors. Because his symptoms continued, chimerism analysis was performed, which indicated that 96% of the peripheral blood mononuclear cells were of liver-donor origin. Ultimately, the patient underwent an allogeneic peripheral blood hematopoietic progenitor cell transplant from a human leukocyte antigen-

identical brother, but he died 5 days after transplantation of overwhelming *Candida krusei* infection. To our knowledge, this is the first chimerism-analysis–documented case of severe acute GVHD presenting so late after liver transplantation. It is of note that the patient had no known risks for GVHD in that he was relatively young and shared only one major human leukocyte antigen with his donor. Consideration should be given to GVHD as a cause of bone marrow aplasia at any time after organ transplantation. Storage of cell pellets from all transplant recipients and donors is highly recommended to facilitate the diagnostic evaluation. *Human Immunology* 66, 28–31 (2005). © American Society for Histocompatibility and Immunogenetics, 2005. Published by Elsevier Inc.

**KEYWORDS:** liver transplantation; graft versus host disease; chimerism analysis; HLA

## ABBREVIATIONS

BM bone marrow  
GVHD graft versus host disease  
HLA human leukocyte antigen  
HPC hematopoietic progenitor cells

MC mononuclear cell  
PB peripheral blood  
WBC white blood cells

## INTRODUCTION

Graft-versus-host disease (GVHD) occurs when a transplant donor's T lymphocytes differentiate into effector

cells that mount an immune response against recipient tissues. This is a frequent complication of allogeneic hematopoietic progenitor cell (HPC) transplantation because of the planned infusion of large numbers of immunocompetent cells into an immunocompromised host. In solid organ transplantation, GVHD is an infrequent but serious complication and generally only occurs for transplants involving organs with relatively large numbers of passenger lymphocytes, notably for liver and intestine transplantation. Skin and gut manifestations of GVHD in liver transplant recipients resemble those observed in

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Received June 29, 2004; revised September 24, 2004; accepted September 24, 2004.

HPC transplant recipients, including skin rash and diarrhea. However, liver transplant recipients with GVHD typically lack evidence of liver dysfunction and instead have severe pancytopenia and bone marrow (BM) aplasia not usually seen in HPC transplant recipients. The diagnosis of GVHD in organ transplant recipients is largely a clinical one, but recently, more sophisticated testing that allows the detection of donor organ-derived cells in affected tissue sites can confirm the clinical suspicion and prevent institution of inappropriate therapy. For example, a skin rash with infiltrating donor lymphocytes should probably not be treated as a drug-induced toxicity with concomitant reduction of a particular drug.

The primary risk factor for the development of GVHD in organ transplant recipients is considered to be a relatively low degree of human leukocyte antigen (HLA) mismatching between the donor and recipient, such as in cases of related-donor (usually parent to child) liver transplants or donors homozygous for antigens at most or all HLA loci. A recent meta-analysis [1] of factors increasing the risk for GVHD concluded that in addition to low HLA mismatching, a relatively large age discrepancy (>40 years) between donor (younger) and recipient (older) and recipient age over 65 years were contributing risk factors, presumably as a result of loss of immune responsiveness (against donor lymphocytes) as a function of age. Organ transplant-related GVHD has only been documented to occur for the first time within the first few months after organ transplantation [1], when immunosuppression of the recipient is at its highest level and presumably because donor lymphocytes surviving beyond that time have become tolerant to recipient mismatches. We describe here a liver transplant patient presenting for the first time 8 months after transplantation with clinical and subsequent confirmatory chimerism evidence of GVHD.

## CASE REPORT

This case involves a 52-year-old Hispanic man, blood type O positive, who received an orthotopic liver transplant for end-stage liver disease from alcoholic cirrhosis. The donor was a 53-year-old woman, blood type O positive, who died from a subarachnoid hemorrhage. She had normal liver enzymes. All pretransplant crossmatch tests were negative. The patient underwent an uneventful liver transplantation with typical preparation of the organ, including perfusion with recipient blood, and was discharged 7 days after surgery. According to the routine protocols at our institution, he did not receive any antilymphocyte induction therapy, and his immunosuppression over the next 8 months consisted of low-dose tacrolimus, mycophenolate mofetil (tapered off after 14

weeks), and prednisone (5 mg daily). He had no episodes of rejection and had normal liver enzymes, with gradual resolution of the renal insufficiency that had predated his transplant.

At 8 months after transplant, the patient presented with oral thrush, which was treated with fluconazole. Three days later, he presented with a sore throat, oral ulcers, and a diffuse rash; fluconazole therapy was stopped. His white blood cell (WBC) count, which had been normal, was 2500/ $\mu$ l and then acutely dropped over the next 5 days to 0.1  $\mu$ l/ml, accompanied by severe anemia and thrombocytopenia. The patient was admitted with a 1-day history of temperature to 40°C, diffuse maculopapular rash, diarrhea, and abdominal pain. Blood cultures were negative, as were tests for cytomegalovirus. A BM biopsy on the second hospital day revealed no aspirable elements and an overall cellularity of 10%. Special stains for mycobacteria and fungi were negative. Although GVHD was considered, the majority of the staff believed that the long interval between transplantation and the patient's presentation made GVHD unlikely. Instead, it was believed that the rash and marrow aplasia were a result of drug therapy including valganciclovir and Septra. Both of those drugs were discontinued, and he was treated with broad-spectrum antibiotics and large doses of erythropoietin and Filgrastim. Because he clinically stabilized, he was discharged to home with oral antibiotics and growth factors.

The patient was subsequently readmitted 5 days later with recrudescence of the rash and fever. Meanwhile, a skin biopsy that had been performed during his first admission was read by a hematopathologist as consistent with grade II GVHD. Chimerism analysis of separated peripheral blood (PB) mononuclear cells (MNCs) and granulocytes and total BM nucleated cells (the sample was too acellular to analyze separated BM MCs) was then performed. Stored, pretransplant WBC pellets from both the recipient and donor were available for comparison. DNA from all samples was extracted by means of a standard Qiagen protocol. The chimerism analysis was done with an ABI sequencer with a Promega PowerPlex System in which ten polymorphic, single tandem repeat system alleles and the X versus Y chromosome marker Amelogenin were simultaneously amplified and labeled with different fluorescent dyes. Polymerase chain reaction products with different size (repeat number) polymorphisms were then separated from each other by their rate of migration in a capillary gel. The results indicated that all systems tested were informative in one or both directions (Table 1) and that virtually all (96%) of the PB MCs (largely lymphocytes) were of liver donor origin (Figure 1, third panel). The PB granulocyte fraction was 75% donor, 30% recipient (data not shown). The BM total nucleated cells appeared to be only 30% of donor

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