

Treatment of Liver Transplant Graft-Versus-Host Disease With Antibodies Against Tumor Necrosis Factor- α

Gregor Blank,¹ Jun Li,² Thomas Kratt,¹ Rupert Handgretinger,³
Alfred Königsrainer,¹ Silvio Nadalin¹

Abstract

Acute graft-versus-host disease is uncommon after liver transplant. We recently treated a 60-year-old man with liver transplant for hepatocellular carcinoma. After the primary liver transplant graft did not function, revision liver transplant resulted in excellent function. Subsequently, the patient developed watery diarrhea, systemic inflammatory response syndrome, a skin rash on his limbs and trunk, and palmar erythema. Skin biopsy suggested viral exanthems consistent with *cytomegalovirus*. Despite treatment for *cytomegalovirus*, intestinal symptoms worsened. Analysis of peripheral blood with fluorescence-activated cell sorting showed a high proportion of T lymphocytes, with 5% to 10% T cells specific to the second donor, suggestive of graft-versus-host disease. Within 48 hours after beginning therapy with antibodies against tumor necrosis factor- α (infliximab), the skin rash disappeared and endoscopy showed slight improvement of the mucosal regeneration. However, despite antifungal prophylaxis with caspofungin, the patient developed angioinvasive pulmonary aspergillosis and multiple organ failure, and he died. In conclusion, typical clinical symptoms of graft-versus-host disease after liver transplant may include skin rash and gastrointestinal symptoms, and

diagnosis may be confirmed by histologic examination and testing for blood chimerism. A consensus for the treatment of graft-versus-host disease still is lacking, but tumor necrosis factor- α is an encouraging target for therapy to decrease the symptoms of graft-versus-host disease and enable mucosal regeneration.

Key words: Hepatocellular carcinoma, Infliximab, Immunosuppression, Rejection, Therapy

Introduction

Acute graft-versus-host disease (GVHD) is an important complication after hematopoietic stem cell transplant. However, GVHD after liver transplant, first described in 1988,¹ is very rare (incidence, 0.1% to 1%),^{2,3} and usually occurs within the first 6 weeks after transplant.⁴ The most common sites of involvement are the skin and gastrointestinal tract, and GVHD after liver transplant is a progressive and fatal disease with mortality > 85% in adults,⁵ mostly secondary to overwhelming sepsis or gastrointestinal bleeding.^{4,5} The correct diagnosis and proper treatment of GVHD are challenging and no consensus about the best treatment has been established. We recently treated a man who had GVHD after liver transplant, who had a response to antibodies against tumor necrosis factor- α (TNF- α).

Case Report

A 60-year-old man with hepatocellular carcinoma and alcoholic liver cirrhosis, who satisfied the Milan criteria, underwent primary deceased-donor liver transplant in July 2009 (Model for End-Stage Liver Disease score, 25). Because of primary nonfunction of the graft, the patient underwent revision deceased-

From the ¹Department of General, Visceral and Transplant Surgery, University Hospital, Tübingen; the ²Department of Hepatobiliary and Transplant Surgery, University Medical Center Hamburg-Eppendorf, Hamburg; and the ³Department of Pediatric Oncology, University Hospital, Tübingen, Germany

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Corresponding author: Gregor Blank, Department of General Visceral and Transplant Surgery, University of Tübingen, Hoppe-Seyler-Straße 3, D-72076 Tübingen, Germany
Phone: +49 7071 2986600 Fax: +49 7071 294934 E-mail: gregor.blank@med.uni-tuebingen.de

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donor liver transplant on the fourth postoperative day. The second graft had excellent function and no signs of rejection. Immunosuppression consisted of induction with monoclonal antibody to the interleukin-2 receptor (basiliximab) and maintenance with steroids, tacrolimus, and mycophenolate mofetil. Both primary and revision donors and the recipient had positive *cytomegalovirus* (CMV) serology, but no medical CMV prophylaxis was performed. The postoperative course was uneventful, and the patient was discharged from the hospital 5 weeks after revision liver transplant.

The patient developed florid watery diarrhea at 3 months after revision liver transplant and was treated at a local hospital for 4 days with metronidazole because of suspected pseudomembranous colitis. The clinical course deteriorated and the patient developed systemic inflammatory response syndrome. Therefore, he was transferred to the intensive care unit of our tertiary care center. In addition to watery diarrhea, he had a skin rash on his limbs and trunk and palmar erythema, consistent with GVHD. Abdominal computed tomography showed panenteritis, but colonoscopy showed regular mucosa without signs of colitis. Skin biopsy suggested viral exanthems consistent with CMV. The clinical suspicion of GVHD was not confirmed by the colon or skin biopsies.

Initial treatment included broad-spectrum antibiotics and antifungal drugs, and the

immunosuppression was reduced to steroids alone. The diagnosis of CMV enteritis was made from histology and polymerase chain reaction studies from colon biopsies and feces. Furthermore, CMV was detected in bronchoalveolar lavage and blood samples. Despite initiating ganciclovir, the patient developed progressive systemic CMV infection and leukopenia. Therefore, 4 weeks after readmission, he was treated with CMV immunoglobulin and foscarnet, and he had subsequent successful control of the systemic CMV infection. However, the intestinal symptoms worsened with progression of the enteritis. Analysis of peripheral blood with fluorescence-activated cell sorting showed a high proportion of T lymphocytes, with 5% to 10% T cells specific to the second donor, suggestive of GVHD. Immunosuppression was intensified, but there was no improvement of the intestinal symptoms (Figure 1) or skin reaction despite a high dosage of steroids (2 mg/kg/d) and sufficient dosage of tacrolimus (trough C0 level, 5 ng/mL).

Using a strategy for therapy-resistant GVHD after hematopoietic stem cell transplant, anti-TNF- α antibody (TNF- α monoclonal antibody [infliximab], 10 mg/kg body weight) was administered in the ninth week after readmission. Within 48 hours after beginning infliximab, the skin rash disappeared and endoscopy showed slight improvement of the mucosal regeneration (Figure 2). However, despite

Figure 1. Follow-Up Colonoscopy 7 Weeks After Readmission, Showing Necrotic Membranes Throughout the Colon

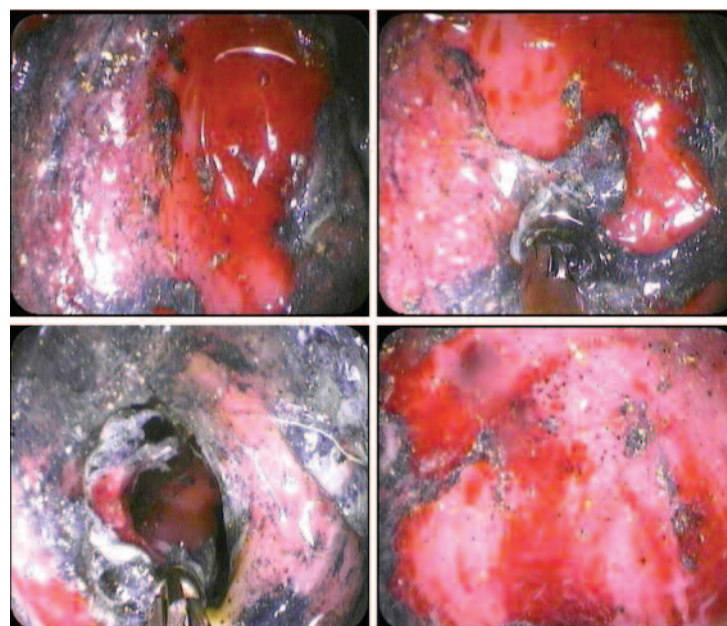
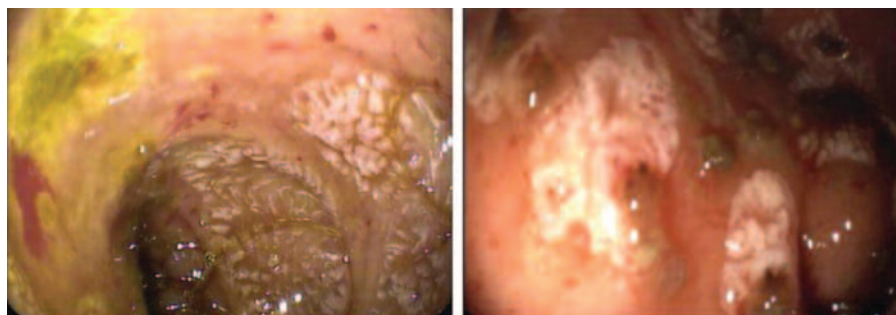


Figure 2. Follow-up Endoscopy Showing Duodenum (Left) and Cecum (Right), With Mucosal Regeneration After Treatment With Antibodies Against Tumor Necrosis Factor- α



antifungal prophylaxis with caspofungin, the patient developed angioinvasive pulmonary aspergillosis and multiple organ failure, and he died 11 weeks after readmission.

Discussion

Although GVHD after liver transplant is rare and usually occurs within 6 weeks after transplant,⁴ cases of late-onset GVHD have been reported up to 8 months after liver transplant.⁶ In the present case, the patient was readmitted 3 months after the liver transplant with florid watery diarrhea, skin rash, and palmar erythema, typical signs of GVHD. The diarrhea may have been caused by impaired intestinal absorption because of lymphocyte infiltration and destruction of the intestinal mucosa.⁷ The diagnosis of GVHD was based on these symptoms and confirmed by biopsy and chimerism studies.

A typical finding of GVHD on skin biopsy is epidermal necrolysis,⁸ which also could be consistent with drug rash. More specific findings for GVHD include apoptosis of crypt cells on enteric biopsy.⁹ The evidence of donor lymphocytes in the blood of the recipient is important for the confirmation of GVHD.^{4,5} In the current patient, GVHD initially was not confirmed by the skin biopsies and was masked by CMV disease.

Earlier performance of chimerism studies may have lead to an earlier diagnosis of GVHD. The method may have included short tandem repeats for DNA fingerprinting or the presence of donor-derived T lymphocytes in peripheral blood confirmed by fluorescence in situ hybridization,^{5,10,11} serologic human leukocyte antigen typing of peripheral lymphocytes, polymerase chain reaction followed by sequence-specific oligonucleotide probe hybridization analysis, and sequencing of human leukocyte antigen alleles.^{12,13} There is no accepted

standard for the confirmation of chimerism in GVHD. During liver transplant, 10^7 to 10^{10} donor lymphocytes are transferred to the recipient within the liver graft.⁴ The mean level of donor T cells after liver transplant is approximately 5% on the second postoperative day and decreases subsequently.¹¹ At 8 weeks after liver transplant, recipients still may exhibit 3% donor T lymphocytes in peripheral blood.¹¹ However, patients with GVHD have higher levels of donor T cells.¹¹ In the current case, donor-specific T lymphocytes were 5% to 10% at 5 months after liver transplant.

Although the exact mechanism of GVHD after liver transplant remains unclear, the following risk factors may be important: donor human leukocyte antigen compatibility,³ recipient age > 65 years, age difference > 40 years between donor and recipient,^{2,3} and an immunocompromised state at the time of transplant.¹⁴ Furthermore, CMV infection may induce and influence the severity of GVHD after bone marrow transplant.¹⁵ The prognosis of GVHD after liver transplant is poor, with 85% mortality in adult patients⁵ and 36% mortality in patients < 18 years.⁴

Optimal treatment of GVHD still is undefined. Current available methods include modulation of immunosuppression and blockade of the progression of GVHD. Modulation of immunosuppression includes an increase or decrease of immunosuppression or an increase of recipient T cells. Although high-dose corticosteroids may be the first-line therapy for acute GVHD after stem cell transplant, exclusive corticosteroid therapy or an increase in immunosuppression are ineffective long-term therapies in adults with GVHD after liver transplant.^{2,5,10} Another method includes antilymphocytic agents such as antithymocyte globulin, antilymphocyte globulin, and monoclonal antilymphocyte agents; although this is an improvement over corticosteroids, survival remains poor.^{2,5,6,8} Anti-interleukin-2 receptor antibodies have been used successfully in the

treatment of GVHD after liver transplant.¹³ However, reports of benefits must be tempered by other reports documenting a lack of efficacy.⁵ A completely opposite approach for treating GVHD is a withdrawal of immunosuppression, based on the idea that the host immune system may reject the donor lymphocytes that mediate GVHD.² Both adults¹⁶ and children have been treated successfully by decreasing immunosuppression, despite the risks of worsened symptoms and graft rejection. Infusion of host immune cells to treat GVHD has been successful in 2 cases.^{17,18} Furthermore, extracorporeal photopheresis is used with increasing frequency for treatment of GVHD after bone marrow transplant.¹⁹

Tumor necrosis factor- α is important in the pathogenesis of GVHD,¹⁹ and this could be an encouraging target in therapy. Corroborative results have been published for treating acute GVHD after stem cell transplant. After liver transplant, only 1 previous case of successful treatment of GVHD has been reported with anti-TNF- α antibodies used as third-line therapy.²⁰ In the current case, clinical recovery began 48 hours after the onset of infliximab therapy. However, the patient subsequently developed angioinvasive pulmonary aspergillosis, which led to death. Septic complications are frequent and common causes of death in GVHD, in addition to gastrointestinal bleeding.^{4,5,21} Tumor necrosis factor- α may have a crucial function in the immune response to fungal pathogens,²² and 2 cases of invasive aspergillosis after infliximab therapy have been reported.^{23,24}

In conclusion, typical clinical symptoms of GVHD after liver transplant may include skin rash and gastrointestinal symptoms, and the diagnosis may be confirmed by histologic examination and testing for blood chimerism. A consensus for the treatment of GVHD still is lacking, but TNF- α is an encouraging target for therapy to decrease symptoms of GVHD and enable mucosal regeneration.

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