

Solid-Organ Graft-Versus-Host Disease After Liver Transplant: A Case Report

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Solid-organ transplant graft-versus-host disease (SOT-GVHD) is a rare complication of organ transplant that is associated with high mortality. The initial signs and symptoms are vague, so this disease is easily confused with other posttransplant complications. A case of SOT-GVHD occurred after orthotopic liver transplant for liver failure due to hepatitis C in a patient in a Veterans Affairs intensive care unit. The patient had dehydration, acute kidney injuries, rashes, diarrhea, and pancytopenia. Results of skin biopsy, bone marrow biopsy, and cytogenetic studies were consistent with SOT-GVHD. Despite supportive care including antibiotics, antiviral and antifungal therapy, high-dose steroids, antithymoglobulin and neupogen, the patient died of overwhelming sepsis. Owing to the rarity of SOT-GVHD, no evidence-based guidelines or recommendations for treatment exist. Treatment includes high-dose corticosteroids and antibiotic, anti-fungal, and antiviral prophylaxis. Treatment of liver transplant-related GVHD with anti-tumor necrosis factor α agents has been successful. (*Critical Care Nurse*. 2016;36[3]:e7-e11)

Solid-organ transplant graft-versus-host disease (SOT-GVHD) occurs in 2 forms. The more common type is antibody mediated.¹ In this form, antibodies from cells from a donor with blood type O attack recipients' red blood cells in recipients with blood type A, B, or AB, leading to mild transient, hemolytic anemias.¹ The second form of SOT-GVHD is a cellular type.¹ Cellular SOT-GVHD is a rare complication following organ transplant.²⁻⁵ In this condition, donor-derived T cells have a reaction to histoincompatible cells in the skin, liver, gastrointestinal tract, and bone marrow, leading to complications in these organs.⁶ This particular form of SOT-GVHD occurs through a multistep process. First, allograft-associated lymphocytes engraft and proliferate in the recipient's bone marrow. Next, donor-origin effector cells produce an immunological attack against immunologically disparate host tissue.² Unfortunately, this diagnosis carries a high mortality, partly because of delays in diagnosis, as it typically has signs and symptoms similar to those of more common diseases such as infection.⁶ GVHD is an important disease about which intensive care nurses must be aware. Treatment must be rapidly instituted. This disease should be considered in patients with transplants in the past and vague signs and symptoms. We present a case of a patient who had SOT-GVHD develop after orthotopic liver transplant.

A 65-year-old man initially underwent orthotopic liver transplant in our facility for end-stage liver failure due to infection with hepatitis C virus with resultant stage T3b Nx hepatocellular carcinoma. He is noted to have type O Rh+ blood. Donor liver was from a female patient of blood group type O Rh+. A total of 4 units of O Rh– packed red blood cells and 8 units of fresh frozen plasma were administered. No blood products were leukoreduced or irradiated.

His initial posttransplant course was notable for cytomegalovirus-positive conversion within the subsequent month. He had several other hospital admissions for dehydration, acute kidney injuries, rashes, and diarrhea. These symptoms are vague and not uncommon in transplant recipients, leading to uncertainty of diagnosis. GVHD, however, must be considered in such patients. At 3 months after transplant, he went to an outside hospital where he was found to have a white blood cell count of $0.1 \times 10^9/L$ with neutrophils of $0.04 \times 10^9/L$, prompting his transfer to our transplant center. He had started treatment with filgrastin with discontinuation of dapsone and valgancyclovir. With his ongoing rash, he had a skin biopsy. His biopsy showed basal vacuolar changes with multiple ectopic keratinocytes, in association with a superficial perivascular and interstitial mixed infiltrate with prominent melanophages. These findings were consistent with graft-versus-host disease grade 2. Bone marrow biopsy showed aplastic anemia with overall pancytopenia. The biopsy was negative for cytomegalovirus, Epstein-Barr virus, and parvovirus. Cytogenetic studies, however, were significant for evidence of chimerization with the finding of a 46,XX karyotype. This female karyotype in a male patient demonstrates complete graft-versus-host disease with infiltration of bone marrow with female cells most likely from the donor liver,

leading to immunological attack of the graft bone marrow on our patient. Further testing was not performed as it would not change the patient's management and it was considered unethical to charge the patient for testing to verify the origin of the graft-versus-host disease (less likely blood products vs more likely liver transplant because of the larger lymphoid tissue).

The hematology/oncology and infectious disease services were consulted and the patient was cared for in the ICU. Throughout his hospital course, he was maintained on neutropenic precautions. He received supportive therapy with irradiated, leukocyte-reduced blood products as needed. Additionally, he was treated with high-dose methylprednisolone (1 mg/kg intravenously daily) as well as cyclosporine (10 mg/kg daily divided into every-12-hour dosing with target levels of 200-400 ng/mL). Filgrastin was discontinued as the patient was not responsive to it. He was treated with a 4-day course of antithymoglobulin. For anti-infectious prophylaxis, he was treated with caspofungin and piperacillin/tazobactam. A potential bone marrow transplant had been discussed but was ultimately decided against, given the high risk of inducing rejection of his orthotopic liver and low certainty of successful treatment.

Unfortunately, his course was complicated by infection with vancomycin-resistant *Enterococcus*, noted on blood cultures, and the patient was treated with daptomycin. He was initially receiving linezolid, but changed to daptomycin to reduce further pancytopenia. The patient continued to have severe protein malnutrition with ongoing diarrhea and gastrointestinal losses. Eventually the patient had septic shock develop, requiring mechanical ventilation for respiratory failure and multiple pressors. At that time, the patient's family elected to change his goals of care to comfort measures only, leading to his death.

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Discussion

SOT-GVHD is a rare and lethal complication of transplant.² Published incidence rates for SOT-GVHD in liver transplant recipients are between 0.1% and 2%.^{2,4} Mortality rates are documented at 75% or greater in liver transplant recipients.^{3,5} There are 2 forms of SOT-GVHD.⁶ In the first and more common form, group O donor antibodies form against cells in patients with disparate blood group types.⁶ The second form is cell mediated.⁶ In this form, donor-derived T cells have a reaction to histoincompatible cells in the skin, liver, gastrointestinal tract, and bone marrow, leading to complications in these organs.⁶ This particular form occurs through a multistep process. First, allograft-associated lymphocytes engraft and proliferate in the recipient's bone marrow. Next, donor-origin effector cells produce an immunological attack against immunologically disparate host tissue.²

SOT-GVHD has an acute phase and a chronic phase. The acute phase is defined as occurring within the first 100 days after transplant.⁷ It typically occurs 1 to 11 weeks after transplant,⁶ with a median onset of 33 days.⁸ Chronic GVHD is defined as occurring more than 100 days after transplant.⁷

SOT-GVHD more commonly occurs after small-bowel and liver transplant, whereas lung and kidney transplants are rarer^{3,5} causes (Table 1). It is hypothesized that the risk factor for SOT-GVHD is related to the amount of lymphoid tissue in the donor organ. Other risk factors include greater HLA match between donor and recipient³ and age greater than 65 years.^{2,4}

SOT-GVHD typically is manifested by fever, diarrhea, rash, and multilineage cytopenia or pancytopenia.² The signs and symptoms are usually quite subtle⁶ and are often confused with early infection in the immunocompromised state. GVHD most likely has many contributing factors. African Americans, for instance, have higher rates than do whites, Hispanics, and persons of Far-Eastern origin.¹⁰ Additionally, cytomegalovirus infection is associated with chronic GVHD development in bone marrow recipients.¹¹ Diagnosis of SOT-GVHD is implied by biopsy-proven histologic features.² Confirmation is made by showing greater than 1%¹² lymphocyte macrochimerism in peripheral blood.² Of note, diagnosis of SOT-GVHD is commonly delayed as the early signs and symptoms mirror those of more common problems such as viral illnesses. Donor chimerism studies should be obtained and GVHD diagnosis should be considered in all solid-organ

Table 1 Prevalence of solid-organ transplant graft-versus-host disease

Organ involved	Prevalence
Small intestine ⁷	5.6%
Liver transplant ⁷	1%-2%
Lung transplant ⁹	Extremely rare, 0.04% reported
Kidney or pancreas ³	Extremely rare, case reports only

transplant recipients with rash, diarrhea, liver dysfunction, and/or pancytopenias. The prognosis for patients with SOT-GVHD is poor. Death is usually due to infections associated with marrow suppression and multiorgan failure. Mortality rates for SOT-GVHD depend on the transplanted organ. Liver transplant patients have a mortality rate of 75%.^{2,4} Lung transplant recipients have a mortality rate of 100%. Other solid-organ transplant patients are reported to have a 30% mortality.²

Treatment of SOT-GVHD is controversial, with the limited evidence given the rarity and high mortality of cases precluding a strong evidence-based consensus on therapy. Several therapies have been proposed in published case reports and series (Table 2). Treatment is usually initialized with high-dose corticosteroids.² It is likely that a second agent is necessary (second-line therapy) in addition to steroids, owing to the poor response to steroids alone. Additionally, antibiotic, antifungal, and antiviral prophylaxis should be started for potential septic complications in immunosuppressed patients.¹⁴ In patients who do not respond to increasing immunosuppression, reduction of immunosuppressive agents to allow the recipient's immunological recovery and rejection of allograft donor T cells may be tried. Case reports have described successful therapies for GVHD related to liver transplant, including infliximab,¹⁵ etanercept,¹⁶ and alefacept.¹⁷ Ultimately, because of the rarity of the disease, no evidence-based guidelines for therapies exist. However, it is possible that earlier diagnosis of SOT-GVHD may allow improved treatment response. For this reason, lymphocyte macrochimerism should be pursued in solid-organ transplant recipients in whom pancytopenia develops at any time, in particular, within the first 2 months after transplant.

Conclusions

SOT-GVHD is a rare condition with subtle signs and symptoms, which often lead to delays in care and increased

Table 2 Therapies for solid-organ transplant graft-versus-host disease^a

Type	Medication	Dosage	Medication information
First line	Glucocorticoids	Give over weeks, then taper over months if respond	
	Methylprednisolone	2 mg/kg per day in divided doses	
Second line	Mycophenylate	1-3 g daily	Get bone marrow suppression, check complete blood cell count
	Etanercept	0.4 mg/kg subcutaneously twice weekly	Is a recombinant tumor necrosis factor- α receptor fusion protein
	Pentostatin	1.5 mg/m ² intravenously daily for 3 days (cut dose in half for patients with glomerular filtration rate 30-50 mL/min per 1.73 m ²)	Only used for bone marrow transplant patients; is a purine analogue inhibiting T-cell function and proliferation
	Sirolimus	15 mg/m ² loading dose, then 5 mg/m ² for 13 days	Myelosuppression is a common complication
	Antithymocyte globulin (polyclonal antibody)	10-30 mg/kg per day	Can cause serum sickness Can consider if was not already receiving for induction
	Muromonab-CD3 (OKT3; monoclonal antibody to CD3 receptor)	5 mg intravenously daily for 10-14 days	Risk of infections Get cytokine release with initial administration, premedicate with antihistamine and acetaminophen
	Infliximab (anti-tumor necrosis factor monoclonal antibody)	5 mg/kg intravenously at 0, 2, and 6 weeks	Common to have infusion-related reaction, premedicate with antihistamine, acetaminophen, and/or steroids
	Basiliximab (interleukin 2 monoclonal antibody)	20 mg intravenously days 1 and 4, can repeat if needed	Can get anaphylactoid and hypersensitivity reactions
	Daclizumab (interleukin 2 monoclonal antibody)	1 mg/kg intravenously days 1, 8, 15, and 22	Taken off the market, hard to get
	Alemtuzumab (anti-CD52 monoclonal antibody)	10 mg daily intravenously for 5 days, then weekly until symptoms resolve	Can get pancytopenia, check complete blood cell counts
Antibiotics	Broad-spectrum antibiotics and antifungal agents, consider cytomegalovirus prophylaxis		
Granulocyte colony-stimulating factor	For neutropenia as needed		

^a Failure was defined as progression after day 5 or no improvement by day 7.¹³

mortality rate. We describe a case of this particular condition. This diagnosis should be considered in all transplant patients, particularly in patients with pancytopenia or fever and rash within the first 2 months of transplant. Diagnosis is made with biopsy of tissue and lymphocyte macrochimerism. Treatment of this condition is controversial and should include high-dose corticosteroids, broad-spectrum antibiotics, antiviral agents,

and antifungal agents. One should further consider reducing the patient's immunosuppressive agents and use of biological agents such as infliximab. GVHD is an important disease of which intensive care nurses should be aware. Treatment must be instituted rapidly. This disease should be considered as a potential diagnosis in patients who have received transplants in the past and have vague signs and symptoms. **CCN**

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None reported.



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