

Acute Graft-vs-host Disease Following Liver Transplantation

Carole Bitar, MD; Kathryn Olivier, MD; Caroline Lee, MD; Bethany Vincent, MD; Julie Martin, MD

PRACTICE POINTS

- Acute graft-vs-host disease (GVHD) is a T cell–mediated reaction in which donor T lymphocytes attack host tissue in the setting of immunosuppression.
- Acute GVHD is more common in allogeneic stem cell transplantation but can occur in the setting of solid organ transplantation.
- Symptoms of acute GVHD include rash with or without pruritus, fever, pancytopenia, and diarrhea.
- Early recognition and treatment with systemic steroids can improve mortality.

Acute graft-vs-host disease (GVHD) is a T cell–mediated reaction in which donor T lymphocytes attack host tissue in the setting of immunosuppression. The most common cause of acute GVHD is allogeneic stem cell transplantation, with solid-organ transplantation being a much less common cause. Early diagnosis and treatment are imperative to decrease morbidity and mortality. Dermatologists play a fundamental role in the diagnosis of this condition because skin involvement is among the earliest signs of acute GVHD. We present a case of acute GVHD following liver transplantation, focusing on diagnostic criteria and a comparison to acute GVHD following hematopoietic stem cell transplantation.

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Acute graft-vs-host disease (GVHD) is a T-cell mediated immunogenic response in which T lymphocytes from a donor regard host tissue as foreign

and attack it in the setting of immunosuppression.¹ The most common cause of acute GVHD is allogeneic stem cell transplantation, with solid-organ transplantation being a much less common cause.² The incidence of acute GVHD following orthotopic liver transplantation (OLT) is 0.1%, as reported by the United Network for Organ Sharing, compared to an incidence of 40% to 60% in hematopoietic stem cell transplant recipients.^{3,4}

Early recognition and treatment of acute GVHD following liver transplantation is imperative, as the mortality rate is 85% to 90%.² We present a case of acute GVHD in a liver transplantation patient, with a focus on diagnostic criteria and comparison to acute GVHD following hematopoietic stem cell transplantation.

Case Report

A 68-year-old woman with a history of hepatitis C virus infection, hepatocellular carcinoma, and OLT 1 month prior presented to the hospital with fever and abdominal cellulitis in close proximity to the surgical site of 1 week's duration. The patient was started on vancomycin and cefepime; pan cultures were performed.

At 10 days of hospitalization, the patient developed a pruritic, nontender, erythematous rash on the abdomen, with extension onto the chest and legs. The rash was associated with low-grade fever but not with diarrhea. Physical examination was notable for a few erythematous macules and scattered papules over the neck and chest and a large erythematous plaque with multiple ecchymoses over the lower abdomen (Figure 1A). Erythematous macules and papules coalescing into plaques were present on the lower back (Figure 1B) and proximal thighs. Oral, ocular, and genital lesions were absent.

Dr. Bitar is from the Department of Dermatology, Tulane University, New Orleans, Louisiana. Dr. Olivier and Dr. Lee are from the Department of Dermatology, Louisiana State University, New Orleans. Drs. Vincent and Martin are from the Department of Dermatology, Ochsner Medical Center, Jefferson, Louisiana.

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Correspondence: Julie Martin, MD, Department of Dermatology, Ochsner Medical Center, 1514 Jefferson Hwy, Jefferson, LA 70121 (julie.martin@ochsner.org).

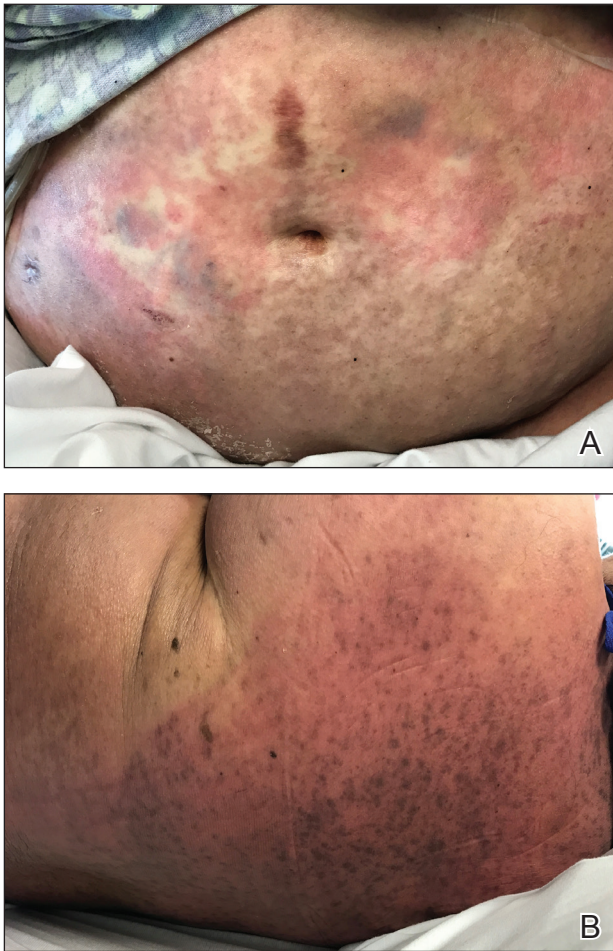


FIGURE 1. Acute graft-vs-host disease following liver transplantation. A, Large erythematous plaque with multiple ecchymoses over the lower abdomen. B, Erythematous macules and papules coalescing into plaques over the lower back.

The differential diagnosis included drug reaction, viral infection, and acute GVHD. A skin biopsy was performed from the left side of the chest. Cefepime and vancomycin were discontinued; triamcinolone ointment 0.1% twice daily and antihistamines as needed for itching were started.

Over a 2-day period, the rash progressed to diffuse erythematous papules over the chest (Figure 2A) and bilateral arms (Figure 2B) including the palms. The patient also developed erythematous papules over the jawline and forehead as well as confluent erythematous plaques over the back with extension of the rash to involve the legs. She also had erythema and swelling bilaterally over the ears. She reported diarrhea. The low-grade fever resolved.

Laboratory review showed new-onset pancytopenia, normal liver function, and an elevated creatinine level of 2.3 mg/dL (reference range, 0.6–1.2 mg/dL), consistent with the patient's baseline of stage 3 chronic kidney disease. Polymerase chain reaction analysis for



FIGURE 2. Acute graft-vs-host disease following liver transplantation. A, Erythematous papules coalescing into plaques over the chest. B, Scattered erythematous papules over the right axilla and right arm.

cytomegalovirus was negative. Histology revealed vacuolar interface dermatitis with apoptotic keratinocytes, consistent with grade I GVHD (Figure 3). Duodenal biopsy revealed rare patchy glands with increased apoptosis, compatible with grade I GVHD.

The patient was started on intravenous methylprednisolone 1 mg/kg for 3 days, then transitioned to an oral steroid taper, with improvement of the rash and other systemic symptoms.

Comment

GVHD Subtypes—The 2 types of GVHD are humoral and cellular.⁵ The humoral type results from ABO blood type incompatibility between donor and recipient and causes mild hemolytic anemia and fever. The cellular type is directed against major histocompatibility complexes and is associated with high morbidity and mortality

Presentation of GVHD—Acute GVHD following OLT usually occurs 3 to 5 weeks after transplantation,⁶ as in our patient. Symptoms include rash, fever, pancytopenia, and diarrhea.² Skin is the most commonly involved organ in acute GVHD; rash is the earliest manifestation.¹ The rash can be asymptomatic or associated with pain and pruritus. Initial cutaneous manifestations include palmar erythema and erythematous to violaceous discoloration of the face and ears. A diffuse maculopapular rash can develop, involving the face, abdomen, and trunk. The rash may progress to formation of bullae or skin sloughing,

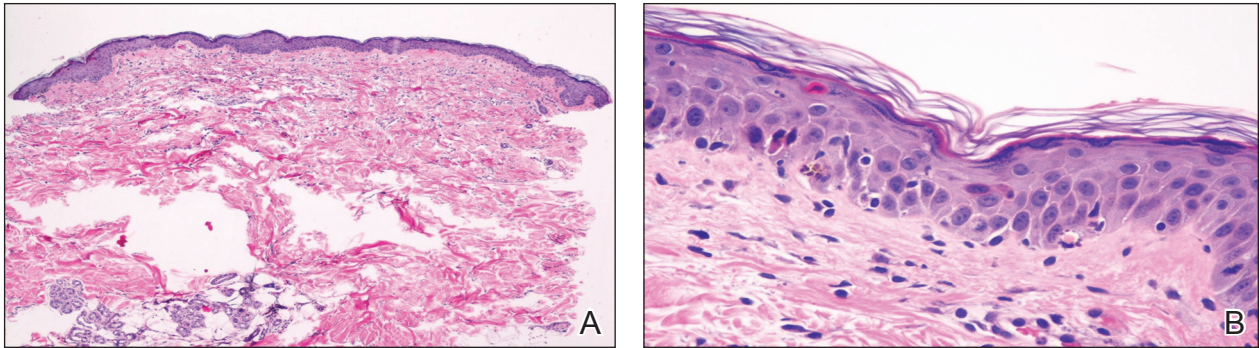


FIGURE 3. Histopathology of punch biopsy specimens from the left side of the chest. A, Vacuolar interface dermatitis with apoptotic keratinocytes, consistent with grade I graft-vs-host disease (H&E, original magnification $\times 20$). B, Close-up of apoptotic keratinocytes (H&E, original magnification $\times 40$).

Comparing Acute GVHD in Hematopoietic Stem Cell Transplantation and in OLT

Attribute	Acute GVHD in Hematopoietic Stem Cell Transplantation	Acute GVHD in OLT
Incidence	40%–60%	0.1%
Onset	During the first 100 days after transplantation	3–5 weeks after transplantation
Skin involvement	Most commonly involved	Most commonly involved
Rash	Similar distribution and clinical presentation	
Fever	+	+
Diarrhea	+	+
Pancytopenia	+	++
Liver involvement	+	–
Mortality	50% ⁸	85%–90%
Treatment	Steroids and steroid-sparing agents	

Abbreviations: GVHD, graft-vs-host disease; OLT, orthotopic liver transplantation; +, present; ++, more common; –, absent.

resembling Stevens-Johnson syndrome or toxic epidermal necrolysis.¹ The skin manifestation of acute GVHD following OLT is similar to hematopoietic stem cell transplantation (Table).^{7,8}

Pancytopenia is a common manifestation of GVHD following liver transplantation and is rarely seen following hematopoietic stem cell transplantation.⁷ Donor lymphocytes engraft and proliferate in the bone marrow, attacking recipient hematopoietic stem cells. It is important to note that more common causes of cytopenia following liver transplantation, including infection and drug-induced bone marrow suppression, should be ruled out before diagnosing acute GVHD.⁶

Acute GVHD can affect the gastrointestinal tract, causing diarrhea; however, other infectious and medication-induced causes of diarrhea also should be considered.⁶ In contrast to hematopoietic stem cell transplantation, in which the liver is usually involved,¹ the liver is spared in acute GVHD following liver transplantation.⁵

Diagnosis of GVHD—The diagnosis of acute GVHD following liver transplantation can be challenging because the clinical manifestations can be caused by a drug reaction or viral infection, such as cytomegalovirus infection.² Patients who are older than 50 years and glucose intolerant are at a higher risk of acute GVHD following OLT. The combination of younger donor age and the presence of an

HLA class I match also increases the risk of acute GVHD.⁶ The diagnosis of acute GVHD is confirmed with biopsy of the skin or gastrointestinal tract.

Morbidity and Mortality of GVHD—Because of the high morbidity and mortality associated with acute GVHD following liver transplantation, early diagnosis and treatment are crucial.⁵ Death in patients with acute GVHD following OLT is mainly attributable to sepsis, multiorgan failure, and gastrointestinal tract bleeding.⁶ It remains unclear whether this high mortality is associated with delayed diagnosis due to nonspecific signs of acute GVHD following OLT or to the lack of appropriate treatment guidelines.⁶

Treatment Options—Because of the low incidence of acute GVHD following OLT, most treatment modalities are extrapolated from the literature on acute GVHD following stem cell transplantation.⁵ The most commonly used therapies include high-dose systemic steroids and anti-thymocyte globulin that attacks activated donor T cells.⁶ Other treatment modalities, including anti-tumor necrosis factor agents and antibodies to CD20, have been reported to be effective in steroid-refractory GVHD.² The major drawback of systemic steroids is an increase in the risk for sepsis and infection; therefore, these patients should be diligently screened for infection and covered with antibiotics and antifungals. Extracorporeal photopheresis is another treatment modality that does not cause generalized immunosuppression but is not well studied in the setting of acute GVHD following OLT.⁶

Prevention—Acute GVHD following OLT can be prevented by eliminating donor T lymphocytes from the liver before transplantation. However, because the incidence

of acute GVHD following OLT is very low, this approach is not routinely taken.²

Conclusion

Acute GVHD following liver transplantation is a rare complication; however, it has high mortality, necessitating further research regarding treatment and prevention. Early recognition and treatment of this condition can improve outcomes. Dermatologists should be familiar with the skin manifestations of acute GVHD following liver transplantation due to the rising number of cases of solid-organ transplantation.

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