

# Graft-Versus-Host Disease After Pancreatic Transplantation

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## ABSTRACT

Graft-versus-host disease (GVHD) is a common complication of hematopoietic stem cell transplantation but can rarely occur after solid organ transplants. Small bowel and liver transplants are typically implicated, but solid organ transplant-associated GVHD has also been associated with other organs. We present a 40-year-old diabetic woman who underwent renal followed by pancreatic transplantation over a span of 21 months and ultimately developed acute classic GVHD. The diagnosis proved to be challenging in the context of confounding infections and inconclusive bone marrow and skin biopsy findings. She had multiorgan failure at the time of endoscopic confirmation and died after having minimal response to aggressive immunosuppression.

## INTRODUCTION

Graft-versus-host disease (GVHD) is usually a complication of allogeneic hematopoietic stem cell transplantation that occurs when nonidentical grafted lymphocytes elicit an immune response that leads to organ dysfunction. The acute classic subtype occurs within the first 100 days of transplantation, typically with dermatologic, hepatic, and gastrointestinal (GI) manifestations.<sup>1</sup> Although rarely encountered, GVHD can also occur in other clinical settings, including after blood transfusions in susceptible hosts or after solid organ transplants (SOTs) involving lymphocyte-rich organs.<sup>2,3</sup> Most cases of SOT-associated GVHD involve small bowel or liver transplants with incidence rates of greater than 5% in the former and 1% in the latter.<sup>4,5</sup> There are 15 case reports of GVHD related to pancreas transplants, 7 of which represent simultaneous pancreas-kidney transplants and 2 of which represent sequential pancreas-kidney transplants.<sup>3,6-16</sup> Diagnosis is typically confirmed by performing routine histopathology or polymerase chain reaction (PCR) assays aimed at detecting donor-derived short-tandem repeats (STRs) in involved tissue or peripheral blood to demonstrate the presence of donor T-cell chimerism. Endoscopy is often a critical step in the diagnostic workup because the GI tract is typically affected. Treatment approaches vary significantly: some groups favor aggressive immunosuppression, whereas others opt to decrease the degree of immunosuppression to elicit a host-versus-graft response. Regardless, the prognosis is generally poor. In reported cases of pancreatic transplant-associated GVHD, 9 of 15 patients died, most commonly because of complications related to sepsis.<sup>6</sup>

## CASE REPORT

A 40-year-old woman with a history of diabetes mellitus type 1 complicated by end-stage renal disease and refractory gastroparesis received a living-donor kidney transplant followed by a pancreas transplant 21 months later. Pretransplant induction included antithymocyte globulin with a maintenance regimen that consisted of tacrolimus, azathioprine (initially mycophenolate), and prednisone. Approximately 4 weeks after her pancreas transplant, her course became complicated by progressive abdominal pain, watery diarrhea, multifocal rashes, and pancytopenia. Serial stool PCR assays identified a chronic norovirus infection. Two skin biopsies were performed, primarily because of suspicion for GVHD, and revealed atypical lymphocytic infiltrates and clonal rearrangement

of the T-cell receptor gene, potentially suggestive of a post-transplant lymphoproliferative disorder or lymphoma. She had no history of blood product transfusions at our institution before the onset of her symptoms.

Two months later, she was readmitted to the hospital with abdominal pain, nonbloody diarrhea, and nonbloody emesis. Physical examination at the time of admission was notable for a maculopapular rash along her legs, abdomen, and back. Basic laboratory workup was significant for a hematocrit of 21.5%, white blood cell count of 800 cells/ $\mu$ L, and a platelet count of 109,000 cells/ $\mu$ L. Stool PCR assays were negative for common bacterial pathogens but remained positive for norovirus. Serum PCR assays for cytomegalovirus, BK virus, and Epstein-Barr virus were negative. Human herpes virus 6 serum PCR was detectable at 3.20 log-count copies. STR analysis of the blood was performed and matched the patient's pretransplant genotype. A bone marrow biopsy revealed markedly hypocellular marrow with normal cytogenetic studies and normal flow cytometry analysis, and a repeat skin biopsy featured non-specific findings, including focal acantholysis and superficial epidermal necrosis. In the absence of a clear unifying diagnosis, she was managed supportively. Azathioprine was held in the context of bone marrow suppression.

Two weeks into her hospitalization, she developed persistent febrile neutropenia and profuse hematochezia in the setting of *Enterococcus* enterocolitis and bacteremia. In the context of severe neutropenia, ongoing bowel inflammation, thrombocytopenia, and coagulopathy, her bacteremia persisted and she developed recurrent episodes of hypotension. Her course was also complicated by cholestatic hepatic dysfunction of unclear etiology, hypoxemia secondary to pulmonary edema, and encephalopathy. Endoscopy was requested on several occasions but initially deferred in the setting of pancytopenia.

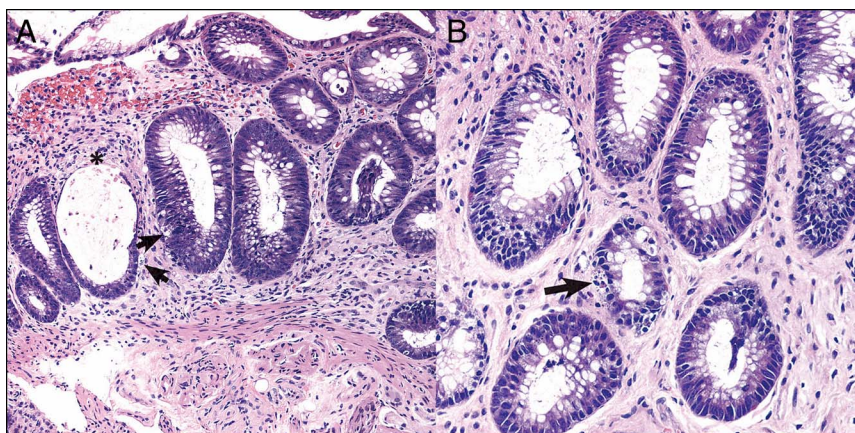
In light of the patient's rapidly deteriorating condition and growing concern for GVHD, flexible sigmoidoscopy with

colonic biopsies was emergently performed, ultimately confirming the diagnosis of GVHD (Figure 1). Tissue from the patient's initial skin biopsy pre-dating her admission subsequently identified donor chimerism with 33% of cells derived from the donor. Pulse-dosed steroids, ruxolitinib, and vedolizumab were initiated with a limited clinical response. There was a progression of sepsis complicated by multiorgan dysfunction and she died. Autopsy revealed jejunal necrosis secondary to *Aspergillus* enteritis in the setting of SOT-associated GVHD.

## DISCUSSION

GVHD is a rare but serious complication of SOTs. It usually presents acutely after liver or small bowel transplants although there have been 15 reported cases of GVHD after pancreas transplants alone or in combination with renal transplants.<sup>3,6-16</sup> The diagnosis of SOT-associated GVHD is challenging, and the management remains controversial.

This case featured many of the typical characteristics identified in previous cases of SOT-associated GVHD. The patient was induced with potent T-cell depleting therapy, including antithymocyte globulin, before her pancreas transplant and developed nonspecific skin rashes, colitis, and hepatic dysfunction. Although GVHD was strongly considered early in her presentation, her diagnosis was delayed in the context of several factors, including confounding infections (norovirus and *Enterococcus*), inconclusive skin and bone marrow biopsy findings, negative STR analysis of the blood, and reluctance to perform endoscopy in a patient with pancytopenia. A treatment strategy focused on aggressive immunosuppression was chosen, but she developed overwhelming sepsis in the context of bacterial and fungal infections and died in the setting of multiorgan failure after limited response to therapy. The overwhelming question among providers centered around the timeliness of the diagnosis: could it have been established earlier, and if so, how?



**Figure 1.** The colonic mucosa at medium magnification revealing (A) markedly reactive crypt epithelium with focal attenuation and loss of epithelium (asterisk), but no lamina propria inflammation. Numerous apoptotic epithelial cells are present (arrows). The colonic mucosa at high magnification showing (B) multiple apoptotic bodies noted in a single crypt (arrow).

In one recent study, investigators tried to identify transplant recipients at risk for SOT-associated GVHD by screening for chimerism in adults with sex-mismatched simultaneous pancreas-kidney transplants using standard XY fluorescence in situ hybridization (FISH) in blood samples collected at approximately 5- and 28-days post-transplant. None of the 7 patients included in the study demonstrated chimerism at either time points, and none ultimately developed GVHD.<sup>6</sup> Although XY FISH and STR PCR-based assays using peripheral blood have been successfully used to diagnose SOT-associated GVHD and are now being used more routinely, the sensitivity and specificity of these modalities to detect chimerism and predict GVHD after SOTs are not well-defined. Consistent with the observations we reported, there have been several other reported instances in which blood-based testing was later inconsistent with tissue-based PCR, FISH, or histopathology.<sup>17-19</sup> Moreover, the availability of STR analysis is limited, even among tertiary care centers, and processing times are sometimes a significant barrier.

Our case highlights that a timely and accurate diagnosis of SOT-associated GVHD can be challenging. However, the GI tract is often one of the earliest and most common organ manifestations, and gut, liver, and pancreatic transplants are commonly implicated in SOT-associated GVHD and associated with high mortality rates. Consequently, gastroenterologists have a critical role in the identification and early diagnosis of this rare but lethal entity. Therefore, until non-invasive testing becomes more reliable, endoscopy remains fundamental and should be performed without significant delay, especially if biopsies from more accessible organs such as the skin or bone marrow are inconclusive.

A significant portion of patients undergoing evaluation for GVHD will have profound cytopenias, often requiring ongoing transfusions, which is a common deterrent to upper and lower endoscopy. In fact, trainees are sometimes taught that neutropenia is a contraindication to rectal examination and endoscopy and that thrombocytopenia precludes endoscopic biopsy although there is limited evidence suggesting an increased risk of infection or bleeding in these settings. Studies have demonstrated that endoscopy and biopsy with appropriate transfusion therapy is safe in neutropenic and thrombocytopenic patients and should be performed in a timely manner.<sup>20</sup> Maintaining a high index of suspicion and promptly obtaining tissue samples from affected organs, including the GI tract, remain the cornerstones for the diagnosis of GVHD.

## DISCLOSURES

Author contributions: S. Saffo wrote the manuscript. C. Peng, N. Kibbi, E. Adekolu, WS Asch, and M. Sanchez edited the article. N. Patel and ME Robert provided the images. M. Sanchez is the article guarantor.

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## REFERENCES

1. Nassereddine S, Rafei H, Elbaresh E, et al. Acute graft versus host disease: A comprehensive review. *Anticancer Res.* 2017;37(4):1547-55.
2. Zhang Y, Ruiz P. Solid organ transplant-associated acute graft-versus-host disease. *Arch Pathol Lab Med.* 2010;134(8):1220-4.
3. Rossi AP, Bone BA, Edwards AR, et al. Graft-versus-host disease after simultaneous pancreas-kidney transplantation: A case report and review of the literature. *Am J Transpl.* 2014;14(11):2651-6.
4. Mazariegos GV, Abu-Elmagd K, Jaffe R, et al. Graft versus host disease in intestinal transplantation. *Am J Transpl.* 2004;4(9):1459-65.
5. Smith DM, Agura E, Netto G, et al. Liver transplant-associated graft-versus-host disease. *Transplantation.* 2003;75(1):118-26.
6. Rashidi A, Brennan DC, Amarillo IE, et al. Mixed donor chimerism following simultaneous pancreas-kidney transplant. *Exp Clin Transplant.* 2018;16(3): 307-13.
7. Asari S, Matsumoto I, Toyama H, et al. Acute graft-versus-host disease following simultaneous pancreas-kidney transplantation: Report of a case. *Surg Today.* 2015;45(12):1567-71.
8. Chang J, Sageshima J, Ciancio G, et al. Successful treatment for graft-versus-host disease after pancreas transplantation. *Clin Transplant.* 2014;28(2):217-22.
9. Gulbahce HE, Brown CA, Wick M, et al. Graft-vs-host disease after solid organ transplant. *Am J Clin Pathol.* 2003;119(4):568-73.
10. Guy S, Potluri A, Xiao G, et al. Successful treatment of acute severe graft-versus-host-disease in a pancreas-after-kidney transplant recipient: Case report. *Transplant Proc.* 2014;46(7):2446-9.
11. Kimball P, Ham J, Eisenberg M, et al. Lethal graft-versus-host disease after simultaneous kidney-pancreas transplantation. *Transplantation.* 1997; 63(11):1685-8.
12. Osband AJ, Laskow DA, Berkowicz T, Mann RA. Quiz page July 2009. Fever and neutropenia following simultaneous pancreas-kidney transplantation: Graft-versus-host disease. *Am J Kidney Dis.* 2009;54(1):A35-7.
13. Rashidi A, Fisher SI. Unwelcome passengers. *Blood.* 2015;125(9):1507.
14. Sharma A, Armstrong AE, Posner MP, et al. Graft-versus-host disease after solid organ transplantation: A single center experience and review of literature. *Ann Transplant.* 2012;17(4):133-9.
15. Weinstein A, Dexter D, KuKuruga DL, et al. Acute graft-versus-host disease in pancreas transplantation: A comparison of two case presentations and a review of the literature. *Transplantation.* 2006;82(1):127-31.
16. Weng FL, Pancoska C, Patel AM. Fatal graft-versus-host disease presenting as fever of unknown origin in a pancreas-after-kidney transplant recipient. *Am J Transplant.* 2008;8(4):881-3.
17. Leventhal J, Abecassis M, Miller J, et al. Chimerism and tolerance without GVHD or engraftment syndrome in HLA-mismatched combined kidney and hematopoietic stem cell transplantation. *Sci Transl Med.* 2012;4(124):124ra28.
18. Kim GY, Schmelkin LA, Davis MDP, et al. Dermatologic manifestations of solid organ transplantation-associated graft-versus-host disease: A systematic review. *J Am Acad Dermatol.* 2018;78(6):1097-101.
19. Meves A, el-Azhary RA, Talwalkar JA, et al. Acute graft-versus-host disease after liver transplantation diagnosed by fluorescence in situ hybridization testing of skin biopsy specimens. *J Am Acad Dermatol.* 2006;55(4):642-6.
20. Tong MC, Tadros M, Vaziri H. Endoscopy in neutropenic and/or thrombocytopenic patients. *World J Gastroenterol.* 2015;21(46):13166-76.

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