Acute graft-versus-host disease after double lung transplant confirmed by short tandem repeat analysis to identify donor chimerism in the skin

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Key words: chimerism; graft-versus-host disease; lung transplantation; organ transplantation; short tandem repeat; solid organ transplantation.

INTRODUCTION

Acute graft-versus-host disease (GVHD) is a severe complication of hematopoietic stem cell transplantation and solid organ transplants (SOTs).[1] Although GVHD is rare in lung transplant patients, mortality exceeds 80%.[2] Currently, the diagnosis of GVHD after SOT is based on clinical manifestations, demonstration of donor chimerism, and histopathologic evidence.[3] We present a case of grade IV acute GVHD after double lung transplant confirmed by the detection of peripheral donor cell chimerism in microdissected lymphocytic inflammatory infiltrates in the skin using short tandem repeat (STR) analysis.

Abbreviations used:

GVHD:	graft-versus-host disease
PTD:	posttransplant day
SOT:	solid organ transplant
STR:	short tandem repeat

CASE REPORT

A 61-year-old man with chronic obstructive pulmonary disease underwent bilateral lung transplant in March 2014. HLA antigen mismatch between the donor and recipient was 9 of 10 antigens, with HLA-A2 being the only shared antigen. Posttransplant medications included prednisone, tacrolimus, azathioprine, and trimethoprim/sulfamethoxazole. On posttransplant day (PTD) 28, the patient developed leukopenia and trimethoprim/sulfamethoxazole was switched to pentamidine and azathioprine was discontinued. On PTD 113, the patient developed fever, worsening oral erosions, and rash. Laboratory tests showcased anemia and leukopenia with normal liver function tests (Table I).

Physical examination revealed erythematous atypical targetoid papules on the bilateral dorsal hands and forearms as well as oral erosions. Punch biopsy demonstrated vacuolar interface dermatitis with basal vacuolar degeneration, dyskeratotic keratinocytes, and a superficial perivascular lymphocytic infiltration involving the dermoepidermal junction. The patient was diagnosed with erythema multiforme and, after clinical improvement, discharged on PTD 117 with prednisone, tacrolimus, and azathioprine.

On PTD 122, he presented with fever, weakness, oral erosions, and rash. Dermatologic examination was significant for generalized morbilliform eruption with rare, atypical targetoid papules. His back was Nikolsky-positive, and mucosal surfaces were spared. Piperacillin-tazobactam and vancomycin were started for possible pneumonia. Laboratory

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Funding sources: None.
IRB approval status: Not applicable.

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JAAD Case Reports 2023;36:24-7.
2352-5126

https://doi.org/10.1016/j.jdcr.2023.03.016

Table I. Laboratory test values after double lung transplantation

Laboratory test parameter	Reference values	PTD 113	PTD 122
Hematocrit	37.0%-50.0%	25.3%	23.7%
White blood cell count	4.0-11.0 × 103/uL	1.6 × 103/uL	3.8 × 103/uL
ALP	40–129 U/L	103 U/L	113 U/L
AST	10–50 U/L	30 U/L	17 U/L
ALT	10–50 U/L	26 U/L	21 U/L
Total bilirubin	0.2–1.3 mg/dL	0.3 mg md/dL	0.5 mg/dL
Mycoplasma IgM	<0.90		1.38
Mycoplasma IgG	<0.90		0.85

ALP, Alkaline phosphatase; *ALT*, alanine transaminase; *AST*, aspartate transaminase; *IgM*, immunoglobulin M; *PTD*, posttransplant day.

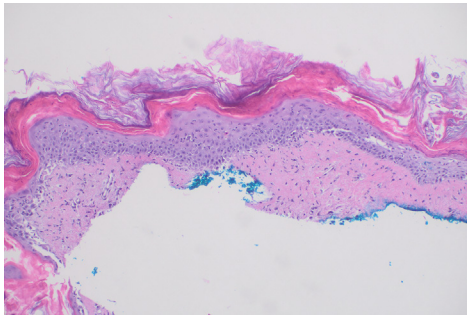

Fig 1. Vacuolar interface dermatitis with dyskeratotic keratinocytes and satellite cell necrosis. (Hematoxylin-eosin stain; original magnification: ×100.)

tests revealed anemia and leukopenia with normal liver function tests (Table I). Skin biopsy demonstrated vacuolar interface dermatitis with dyskeratotic keratinocytes and satellite cell necrosis (Fig 1).

Mycoplasma immunoglobulin M was minimally reactive, whereas mycoplasma IgG was negative (Table I). The patient was transferred to the intensive care unit for fever, tachycardia, worsening desquamation, and new mucous membrane involvement. Intravenous immunoglobulin 1 g/kg daily for 3 days was started for suspected Stevens-Johnson syndrome, possibly from piperacillin-tazobactam.

Given progressive desquamation and other clinical features concerning for GVHD, molecular chimerism studies from peripheral blood and bone marrow were submitted and returned negative for donor DNA. Due to high suspicion of GVHD, STR analysis of paraffin-embedded skin biopsy samples was performed and identified 10% to 20% donor chimerism in microdissected lymphocytes from the upper dermis (Fig 2).

Due to progressive desquamation of approximately 90% of body surface area (Fig 3), the patient was transferred to the burn intensive care unit for grade IV GVHD and treated with methylprednisolone 1 mg/kg. Piperacillin-tazobactam was discontinued.

On PTD 137, owning to melena and respiratory failure requiring intubation, methylprednisolone was increased to 10 mg/kg for 3 days. Esophagogastroduodenoscopy was performed, and biopsies from the gastroesophageal junction and stomach showed rare apoptotic bodies suspicious for gastrointestinal GVHD. On PTD 143, extracorporeal photopheresis was started 3 times weekly for 3 weeks and then decreased to twice a week. Unfortunately, despite complete skin re-epithelialization and resolution of GVHD, the patient died of recurrent pneumonia and bacteremia on PTD 212.

DISCUSSION

Acute GVHD in SOT recipients carries a high risk of mortality in large part due to diagnostic delays related to its low incidence and difficulties in distinguishing GVHD from other posttransplant complications. In contrast to acute GVHD after hematopoietic stem cell transplantation, in which HLA mismatching increases the occurrence of GVHD and posttransplant mortality, a high degree of HLA matching is associated with an increased risk for SOT-associated GVHD. When <2 HLA class 1 alleles are mismatched, the risk of SOT-associated GVHD increases from 1% to 10.3%.[4] Furthermore, when donor-recipient pairs share at least 1 HLA-DR allele, the risk increases to 22.2%.[4] With respect to the association of HLA matching and fatal GVHD, Kamei et al[5] reported that all 8 fatal cases of GVHD after living donor liver transplantation had donor homozygous HLA matching at ≥2 loci (HLA-A, -B and -DR), suggesting that the risk of fatal GVHD after SOT is augmented by the degree of HLA matching. In our case, the donor and recipient were matched at 1 of 10 and mismatched at 9 of 10 antigens, conferring a 1% risk of developing GVHD.[6]

The nonspecific clinical manifestations of GVHD and overlapping histopathologic features with other diagnoses make GVHD primarily a clinical diagnosis.

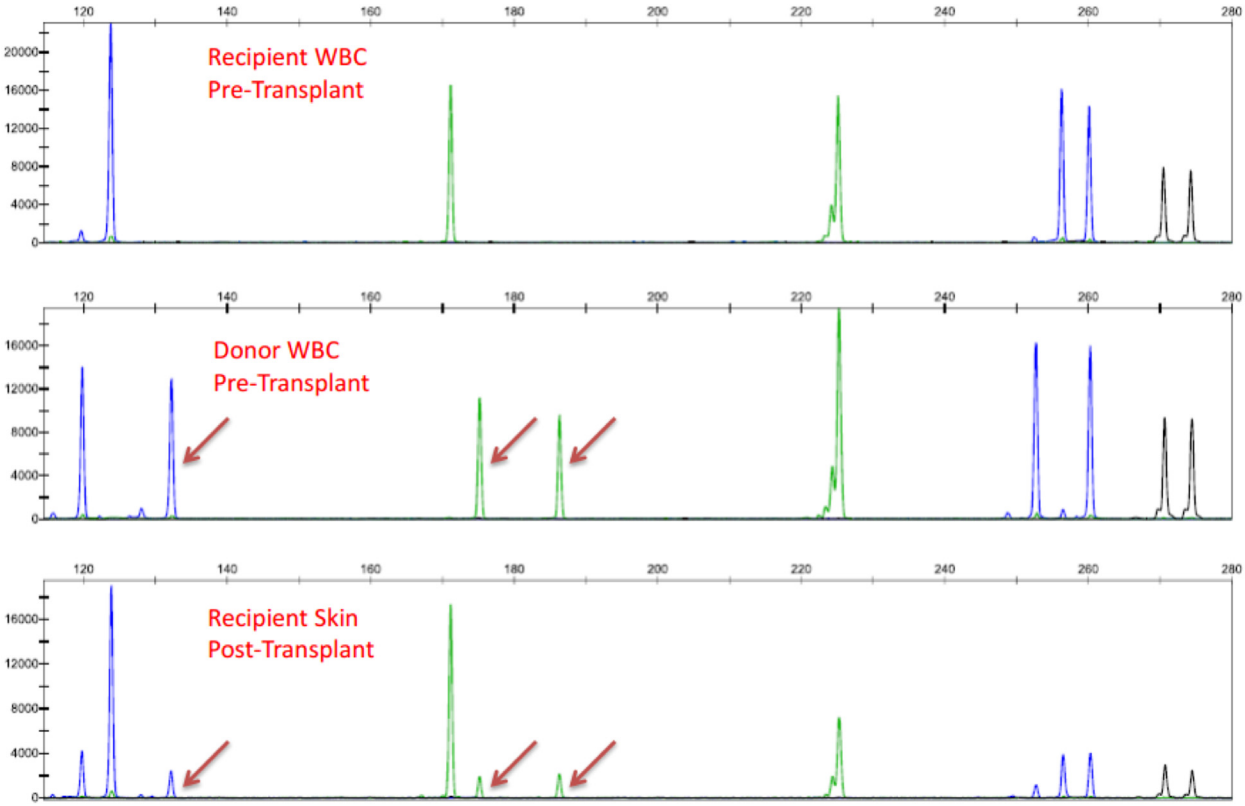

Fig 2. Polymerase chain reaction–amplified short tandem repeats, represented by *colored peaks*, allow molecular differentiation of the donor and recipient. The posttransplant window shows *small blue and green peaks* (*arrows*) in the recipient skin tissue that match donor skin tissue peaks, indicating the presence of donor cells in the recipient tissue. *WBC*, White blood cell.

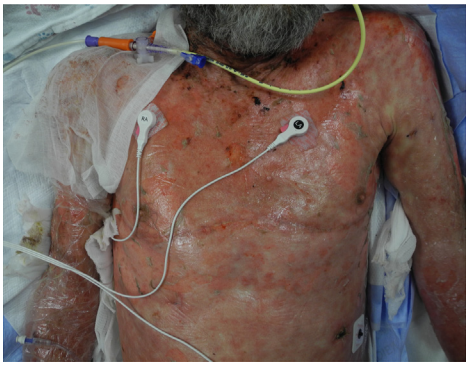

Fig 3. Sheets of desquamation and erosions involving >90% of body surface area due to grade IV GVHD after double lung transplantation.

Although skin biopsy may be useful in evaluating the differential diagnosis of posttransplant skin eruptions, its sensitivity and specificity for diagnosing GVHD have not been definitively established.[7] Stevens-Johnson syndrome and toxic epidermal necrolysis were considered due to the patient's exposure to several high-risk drugs, and the presence of mycoplasma immunoglobulin M raised the possibility of reactive infectious mucocutaneous eruption. The combination of the patient's persistent symptoms, despite discontinuing potential causative drugs, made GVHD the most likely clinical diagnosis.

Currently, the diagnosis of GVHD after SOT requires the demonstration of donor chimerism. Although molecular studies can be used to detect peripheral blood or bone marrow donor chimerism, cases of GVHD after SOT or blood transfusion lacking peripheral blood chimerism but demonstrating chimerism in tissues such as skin have been described.[6,8,9]

In one study, STR analysis of a buccal swab was used to detect donor lymphocytes; however, chimerism was not assessed from the skin biopsy.[6] Unfortunately, the use of peripheral chimerism in diagnosing GVHD is not without its limitations because asymptomatic donor peripheral blood chimerism can be detected 1 to 3 weeks after transplant.[6,10] Consequently, peripheral blood chimerism may neither be specific to nor be an absolute requirement for GVHD after SOT.

Due to the lack of peripheral blood chimerism and a high suspicion of GVHD, we used STR analysis to identify donor chimerism in microdissected lymphocytic inflammatory infiltrates in the upper dermis from a paraffin-embedded skin biopsy. Although the sensitivity and specificity of STR analysis to detect chimerism in the skin and predict GVHD after SOT are not well defined, the presence of donor lymphocytes in the inflammatory infiltrate is likely to be more specific and pathologic given the clinical picture of this patient as opposed to an incidental finding of asymptomatic donor chimerism in peripheral tissue. Unfortunately, widespread use of this test may be limited due to the lack of training and resources needed to perform it as well as prolonged processing times. Nonetheless, STR analysis of the skin provides another method to demonstrate donor chimerism when other techniques fail to show it.

In conclusion, we report a case of GVHD after double lung transplant in which STR analysis was used to identify donor chimerism in the skin. Although detectable chimerism in the skin is suggestive of GVHD, additional studies to evaluate the frequency of asymptomatic donor chimerism in skin biopsy specimens of SOT patients are indicated.

Conflicts of interest

Dr Wysocki received grant funding from Jerry Modell Foundation for the diagnostic and research center. Author Valencia and Drs Kaza, Kim, Oliver, Vandergriff, and Dominguez have no conflicts of interest to declare.

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