Acute graft-versus-host disease after double lung transplantation

Nicole Kim, MD,[a] Nadia Kashetsky, MSc,[b] Yuliya Velykoredko, MD, FRCPC,[c] Michelle Murray, MD, MRCPI, MSc,[d] Lianne Singer, MD, FRCPC,[a,c] Zaid Saeed Kamil, MBChB, FRCPC,[c,e] Danny Ghazarian, MD, ChB, PhD, FRCPC,[c,e] and An-Wen Chan, MD, DPhil, FRCPC[a,c,f]
Toronto and St John's, Canada and Dublin, Ireland

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INTRODUCTION

Graft-versus-host disease (GVHD) is a multisystem disorder occurring when immunologically competent cells are grafted into a recipient whose cells express tissue antigens that are absent in the transplant donor and the recipient is incapable of mounting an effective response against the donor cells.[1]

GVHD is a major complication of allogeneic hematopoietic cell transplant; however, it is uncommonly associated with solid organ transplant and is rarely associated with lung transplantation.[2-8] We report a case of acute GVHD presenting with cutaneous manifestations following double lung transplantation.

Abbreviations used:

GVHD: graft-versus-host disease
POD: postoperative day

CASE REPORT

A 47-year-old Caucasian woman underwent double lung transplantation in March 2018 because of poor pulmonary function in the context of Langerhans cell histiocytosis. Induction immunosuppression, including cladribine, was stopped 1 month prior to the transplant. Postoperatively, cyclosporine (target level, 250-350 ng/mL), mycophenolate mofetil, and prednisone were administered. On postoperative day (POD) 43, there were no signs of acute rejection and no evidence of microorganisms or viral cytopathic effects. On POD 50, the patient developed a painful pruritic eruption on the palms and soles, which became generalized. At that time, the patient was nearing the end of an amoxicillin course for an upper respiratory tract infection. On POD 69, the patient developed watery diarrhea. On POD 71, the patient presented to the Transplant Dermatology clinic with a generalized morbilliform eruption (Figs 1 and 2), vesicles on palms (Fig 3) and soles, and a right buccal mucosa oral ulcer, without fever. Other medications of the patient included trimethoprim/sulfamethoxazole, furosemide, pantoprazole, nystatin, granulocyte colony-stimulating factor, and valganciclovir. Punch biopsies from the back and right thigh showed interface change with apoptotic keratinocytes with adjacent lymphocytes (Fig 4). There were no eosinophils, neutrophils, or viral cytopathic effects. Pathology suggested grade II acute GVHD or erythema multiforme. The differential diagnosis included acute GVHD, drug reaction, and viral exanthem. The diagnosis of acute GVHD was made on the basis of clinical presentation and histopathologic findings.

On POD 73, the patient developed fever, and on POD 74, she was admitted to the hospital and started on intravenous methylprednisolone 90 mg (1 mg/kg) twice daily for 17 days, followed by prednisone. Cyclosporine dose was increased (125 mg twice daily), and other medications, including mycophenolate mofetil, were held. Molecular diagnostics were performed using DNA from peripheral blood

From the Department of Medicine, University of Toronto[a]; Faculty of Medicine, Memorial University of Newfoundland[b]; University Health Network, Toronto[c]; Mater Misericordiae University Hospital, Dublin[d]; Department of Laboratory Medicine and Pathobiology, University of Toronto[e]; and Women's College Research Institute, Toronto.[f]

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Correspondence to: An-Wen Chan, MD, DPhil, FRCPC, Department of Medicine, University of Toronto, 76 Grenville St, Suite 6416, Toronto, ON M5S 1B2, Canada. E-mail: anwen.chan@utoronto.ca.

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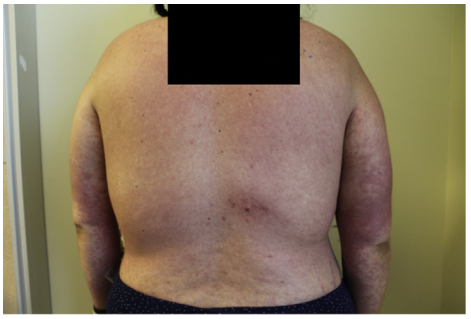

Fig 1. Morbilliform eruption on the trunk and upper extremities due to acute graft-versus-host disease after double lung transplantation.

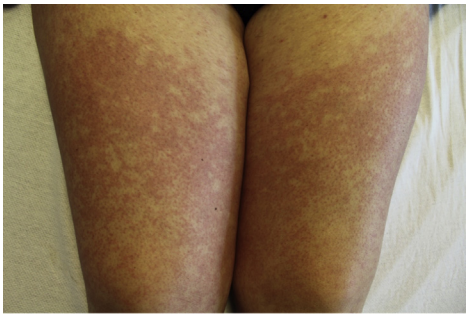

Fig 2. Confluent erythematous papules and plaques on the legs due to acute graft-versus-host disease after double lung transplantation.

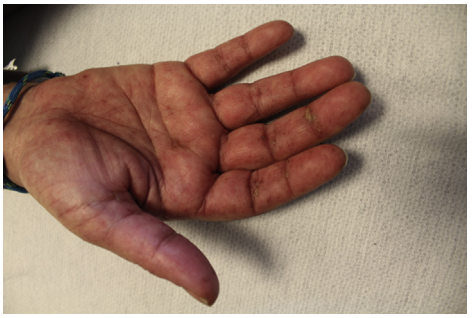

Fig 3. Erythematous papules on the palms due to acute graft-versus-host disease after double lung transplantation.

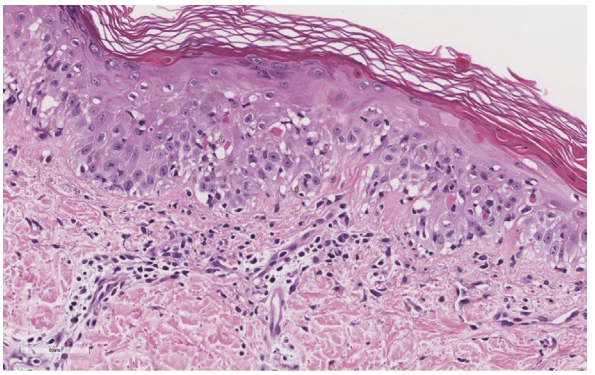

Fig 4. Apoptotic keratinocytes and interface lymphocytes due to acute graft-versus-host disease after double lung transplantation.

and polymerase chain reaction amplification using primers specific for 15 short tandem repeats loci. Mixed profiles of host and donor cell chimerism, where immune cells from the donor and the patient coexist with immune tolerance, were identified. Laboratory tests revealed anemia (hemoglobin, 8.9 g/dL; normal range, 12-16 g/dL), leukopenia (leukocyte count, 0.3 $\times$ 10^9/L; normal range, 4.5-11 $\times$ 10^9/L), lymphocytopenia (lymphocyte count, 0.1 $\times$ 10^9/L; normal range, 0.77-4.5 $\times$ 10^9/L), and neutropenia (neutrophil count, 0.1 $\times$ 10^9/L; normal range, 2.0-7.5 $\times$ 10^9/L). On POD 89, increased levels of aspartate transferase (90 U/L; normal range, 0-35 U/L), alanine transferase (165 U/L; normal range, 0-35 U/L), and bilirubin (1.58 mg/dL; normal range, 0.2-1.2 mg/dL) were noted. On POD 82, colon and rectum biopsies showed reactive or regenerative changes in the large bowel mucosa but no evidence of active GVHD.

There were no viral cytopathic effects suggestive of cytomegalovirus. Infectious workup was negative for herpes simplex, varicella-zoster virus, parvovirus B19, Epstein-Barr virus, and *Clostridium difficile*. Cytomegalovirus was detected at <202 IU/mL on POD 76 and at 1640 IU/mL on POD 94. On POD 94, the patient was started on intravenous ganciclovir at 450 mg twice daily. Since POD 71, skin disease persisted despite treatment. On POD 95, the patient developed severe pancytopenia and was administered granulocyte colony-stimulating factor. On POD 99, confusion developed. Magnetic resonance imaging of the brain confirmed posterior reversible encephalopathy syndrome. Other neurologic deficits were absent, and confusion resolved over 2 days. Adamant about discharge, the patient left the hospital against medical advice on POD 102. The team was informed that the patient passed away on POD 118. The specific cause of death was not provided.

DISCUSSION

Acute GVHD following lung transplantation is a rare entity.[2-7] Cases have been described as a morbilliform rash beginning on the palmoplantar surfaces or the extremities commonly with pruritus,[3,5] resembling rashes seen in acute GVHD following transplantation of other solid organs.[9] In a review of 70 cases of GVHD after solid organ transplant, morbilliform rash was the most common presentation, seen in 87% of patients, which spread over the entire body.[9]

Since the initial presentation of acute GVHD may resemble a drug reaction or viral exanthem, diagnosis is challenging. As lung transplant recipients often receive antimicrobial prophylaxis, which can cause cutaneous drug reactions, tissue biopsy is necessary to help diagnose the etiology of any morbilliform rash. Although no single histologic feature is diagnostic, the presence of keratinocyte necrosis with mild lymphocytic infiltrate is highly suggestive of GVHD.[6] Molecular studies can help diagnose GVHD by evaluating the presence of donor lymphocyte chimerism.[1,7] Chimerism can occur following solid organ transplant in the absence of GVHD. However, this should resolve within a few weeks. Its persistence supports GVHD diagnosis.[5]

GVHD risk factors include the degree of human leukocyte antigen mismatch, older recipient age, higher levels of immunosuppression, myeloablative conditioning regimens, and cytomegalovirus status.[3] In our case, cladribine, prior to the transplant, may have been a predisposing factor to the onset of GVHD, as cladribine may further decrease lymphocytes, offering a favorable condition for GVHD.[2] This is supported by a case where cladribine worsened lymphopenia, also offering a favorable condition for GVHD in a patient who received lung transplant because of Langerhans cell histiocytosis.[2]

No evidence-based treatment guidelines for acute GVHD after solid organ transplantation exist. However, first-line therapy usually consists of increasing immunosuppression with methylprednisolone.[5,8] Other treatments include antiproliferative agents, anti-interleukin 2 receptor antibodies, tumor necrosis factor inhibitors, other monoclonal antibodies, and extracorporeal photochemotherapy.[5,7,8] Treatment is also directed at supporting hematopoiesis with granulocyte colony-stimulating factor and by discontinuing antibiotics and other myelosuppressive medications.[10] Treatments may prolong short-term survival; however, mortality due to acute GVHD after solid organ transplantation is high (77.8%).[4] Almost all cases of GVHD after lung transplant have been fatal, with death occurring between PODs 64 and 163 due to multiorgan failure and septic shock.[5,7,8]

In conclusion, we report a case of acute GVHD after double lung transplantation. Cutaneous manifestations of GVHD were nonspecific and resembled other dermatologic entities. Although GVHD after solid organ transplantation is rare, clinicians must have a low index of suspicion for this entity to facilitate early diagnosis and treatment for this life-threatening condition.

Conflicts of interest

None disclosed.

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