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CLINICAL CASE CHALLENGES

Successful CAR T Cell Therapy in a Heart and Kidney Transplant Recipient With Refractory PTLD

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Post-transplant lymphoproliferative disorder (PTLD) refers to a wide array of immunosuppression-related complications following solid organ transplantation. Improved long-term solid organ transplant graft survival in the last decade has been followed by increased reports of Epstein-Barr virus (EBV)-negative PTLD, which extends well beyond the first 18 months post-transplantation.[1] Recent data from 2018 estimated the incidence of PTLD at 2.24 per 1,000 patient years.[2] Despite substantial advancements in medical therapy, most notably the anti-CD20 monoclonal antibody, rituximab, which alone or in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone has improved survival outcomes for patients with diffuse large B cell lymphoma, outcomes for patients with refractory PTLD remain poor.[3] In the past 5 years, trials have demonstrated the effectiveness of chimeric antigen receptor (CAR) T cell therapy in providing a durable response against refractory diffuse large B cell lymphoma.[4] However, data on the use of CAR T cell therapy in solid organ transplant recipients and heart transplantation specifically are limited. Herein we describe the case of a 23-year-old woman with remote history of heart transplantation with subsequent kidney transplantation who developed refractory PTLD successfully treated with CAR T cell therapy.

CASE PRESENTATION

A 23-year-old woman diagnosed with restrictive cardiomyopathy at birth who underwent heart transplantation at 11 months of age (EBV-/-) and subsequent living-related kidney transplantation (EBV+/-) at 20 years of age for focal and segmental glomerulonephritis was seen in our adult heart transplantation clinic for post-transplantation care. Five years prior, she was noted to have evidence of International Society for Heart and Lung Transplantation cellular rejection of her cardiac allograft (1R/1b), with preserved graft function and without evidence of cardiac allograft vasculopathy or donor-specific antibodies. Her target level of tacrolimus was increased at the time and subsequent annual biopsies had shown no evidence of rejection. At the time of the index clinic, visit she was being managed with triple immunosuppression including tacrolimus with a target goal of 4 to 6 mg/dL, mycophenolic acid 180 mg twice daily, and prednisone 5 mg daily.

At the time of presentation, she described worsening intermittent abdominal pain. Computed tomography of the abdomen and demonstrated thickening of the jejunum. Subsequent esophagogastroduodenoscopy with

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ABBREVIATIONS AND ACRONYMS

CAR = chimeric antigen receptor

CRS = cytokine release syndrome

EBV = Epstein-Barr virus

PTLD = post-transplant lymphoproliferative disorder

small bowel enteroscopy revealed a fungating ulcerated mass in the proximal jejunum. Pathology demonstrated CD20+ monomorphic PTLD with plasmablastic features, EBV-encoded small RNAs, and negative CD30. Positron emission tomography demonstrated a highly heterogeneous soft tissue mass throughout the walls of the midline pelvis with suspected infiltration of the bowel.

Following the diagnosis of PTLD, mycophenolic acid was discontinued, and the patient was initiated on therapy with rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin. She completed 4 cycles; however, repeat positron emission tomography demonstrated focal activity in the small bowel loops with thickened walls in the left lower quadrant and new metabolic activity in the right side of the transverse colon. She underwent repeat endoscopy, which confirmed persistent PTLD.

She was evaluated for autologous stem cell transplantation and CAR T cell therapy. She received 2 cycles of gemcitabine and carboplatin; however, progression of disease was noted. She was subsequently treated with polatuzumab vedotin, an antibody drug conjugate targeting CD79b followed by resection of small bowel residual disease. She underwent collection of peripheral blood mononuclear cells for manufacturing of lisocabtagene maraleucel, a CD19 targeting the CAR T cell product (**Figure 1**). However, the sterility assessment of the cell culture during manufacturing demonstrated an *Escherichia coli* infection. Blood cultures were also positive for *E. coli*. She was admitted and treated with intravenous antibiotics with no evidence of bacteremia. Collection of cells for manufacturing of lisocabtagene maraleucel was repeated without evidence of contamination.

Prior to CAR T cell therapy, repeat graft assessment showed a left ventricular ejection fraction of 55% to 60% with mild-to-moderate tricuspid regurgitation. A previous coronary angiogram performed 18 months prior had shown no evidence of cardiac allograft vasculopathy, and right heart catheterization showed normal filling pressures with preserved cardiac output. Endomyocardial biopsy showed no evidence of rejection at that time. CAR T cells were infused following a lymphodepleting regimen of fludarabine and cyclophosphamide. She tolerated the treatment well without evidence of cytokine release syndrome (CRS) or neurotoxicity. During CAR T cell treatment, she continued tacrolimus with a goal of 4 to 6 ng/mL and prednisone 5 mg daily. The patient was able to be discharged home 10 days after the infusion.

Three weeks after her CAR T cell infusion, she was found to be COVID-19 (coronavirus disease 2019)-positive by nasopharyngeal polymerase chain reaction following an exposure to an individual with COVID-19. She experienced only mild symptoms and received sotrovimab therapy. Positron emission tomography-computed tomography scans at 1 and 3 months following CAR T cell infusion showed that she was in a complete metabolic response. Echocardiography performed in late April 2022 showed a left ventricular ejection fraction of 60% to 65% and mild tricuspid regurgitation. She is currently doing well over 6 months post-CAR T cell therapy.

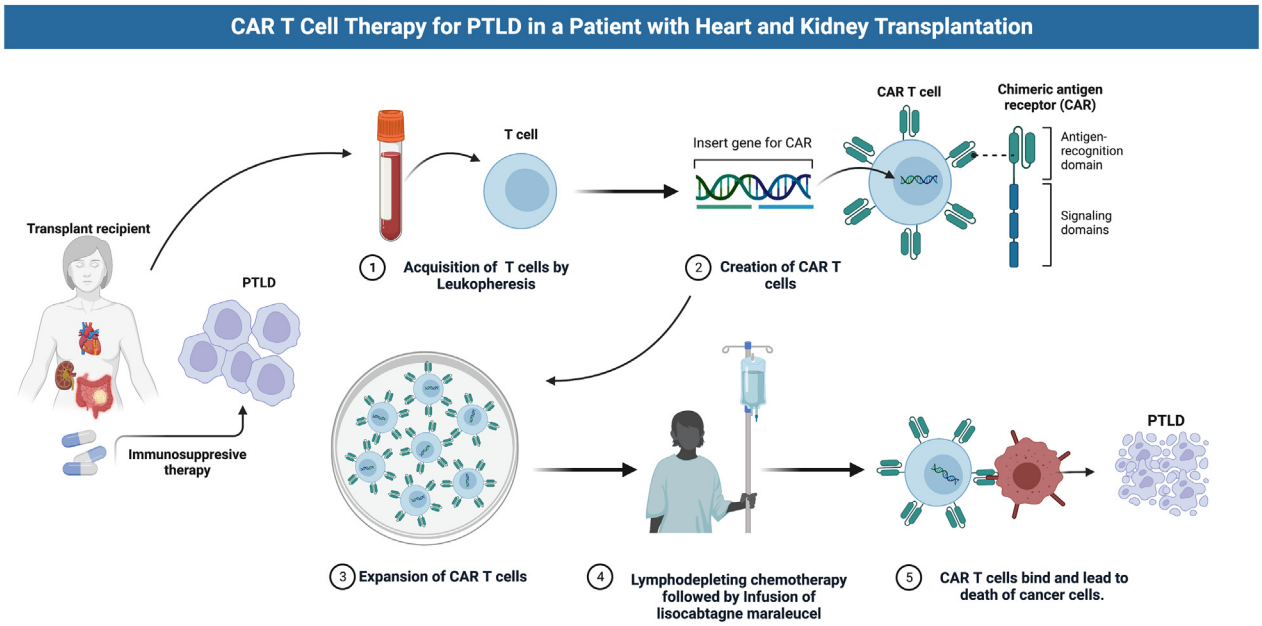
DISCUSSION

We present, to the best of our knowledge, the first case of an adult heart transplant recipient and heart-kidney recipient with PTLD successfully treated with CAR T cell therapy. Use of immunotherapy for cancer treatment in solid organ transplant recipients, specifically heart transplant recipients, presents unique considerations. One must weigh the benefits of cancer therapy against the risks of activation of the immune system leading to allograft rejection, which can have significant hemodynamic consequences, morbidity, and mortality.

Our patient's clinical course stands in contrast to reports of earlier experiences of immune checkpoint inhibitor use in patients with heart transplantation. In one analysis of 4 heart transplant recipients, 3 patients developed acute graft rejection and graft failure within 3 months, and mortality was 75% at <36 months.[5] Notably, this was a small group of patients with advanced malignancies. CAR T cell therapy, with a more targeted approach to tumor-specific antigen-mediated immune activation, may represent a more promising option in this population. The lymphodepleting regimen used to condition patients prior to CAR T cell infusion may contribute to protection against rejection by limiting bystander T cell activation. However, the first reports of CAR T cell therapy in solid organ transplant patients have also shown poor outcomes. Krishnamoorthy et al[6] reported 3 solid organ transplant patients with refractory PTLD (2 kidney transplants and 1 heart transplant) who were treated with CAR T cell therapy. Unfortunately, all 3 patients did not respond to CAR T cell therapy and died during the index hospitalization. At the time of death, all 3 patients had unresolved neurotoxicity and/or CRS.

A key aspect regarding management of solid organ transplant patients undergoing CAR T cell therapy is modification of immunosuppression regimen during CAR T cell therapy. Low-dose steroids are not thought

FIGURE 1 **CAR T Cell Therapy for PTLD**



Flow chart depicting the development of post-transplant lymphoproliferative disorder (PTLD) following immunosuppressive therapy, percurrent of T cells followed by generation of chimeric antigen receptor (CAR) T cells, clone expansion, and infusion with subsequent binding of CAR T cells to cancer cells. Illustration generated using BioRender.

to have a significant impact on CAR T cell treatment. High-dose steroids are frequently used in patients who develop severe toxicity, and clinical trial evidence suggests that even at high doses, steroids do not impair efficacy.[7] In this case, the cell cycle inhibitor was stopped prior to therapy and the patient was maintained on low-dose calcineurin inhibitor and prednisone. Adjustment of immunosuppression during CAR T cell therapy is dependent on weighing the risks of graft rejection vs progression of PTLD. In this case in which heart transplantation was performed over 20 years ago with a remote history of cellular rejection over 5 years prior, and without evidence of donor-specific antibodies, it was decided to discontinue mycophenolate mofetil and continue to monitor graft function by echocardiography. Additional strategies that could be considered in these circumstances are the use of assays to detect changes in markers of immune function and donor-derived cell-free DNA for detection of rejection. Considering the poor prognosis and increased risk of mortality in patients with a heart transplant and PTLD, the benefit of CAR T cell therapy was considered to outweigh the risks of potential graft rejection. The consequences of maintenance immunosuppression on CAR T cell efficacy is not fully understood at this time.

Commonly reported and well-studied toxicities associated with the use of CAR T cell therapy including CRS are well documented.[4,8-10] Recent data from a postmarketing pharmacovigilance study using the Food and Drug Administration adverse event reporting system examining data on 2,657 patients receiving CAR T cell therapy found an association with tachyarrhythmias, cardiomyopathies, and pericardial disorders.[9] Other reported cardiotoxicities include hypotension, troponin elevation, reduction in left ventricular ejection fraction, pulmonary edema, and cardiogenic shock. When present, these usually occur in the setting of CRS and generally respond to tocilizumab with or without steroid therapy.[11] Differentiation of cardiac and noncardiac pulmonary edema in patients with preexisting heart failure may be challenging in the setting of CRS.

Previous consensus statements regarding pre-CAR T cell cardiac evaluation include baseline history and physical and targeted cardiac testing like echocardiography and ischemic work-up in selected patients with known disease or symptoms.[4] In this patient with excellent performance status, we proceeded with

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echocardiography, which revealed normal graft function. The patient had a screening coronary angiogram 18 months earlier with no evidence of cardiac allograft vasculopathy.

Our case demonstrates that CAR T cell therapy can be safely used in select heart transplant recipients with refractory PTLD. Additional studies are needed in this patient population to help guide patient selection and management and evaluate long-term outcomes.

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