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Case Report

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Successful Treatment of Refractory Post-Transplant Lymphoproliferative Disorder With Chimeric Antigen Receptor T-Cell Therapy in a Heart Transplant Recipient

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Abstract

Post-transplant lymphoproliferative disorders (PTLDs) are opportunistic malignancies that complicate the success of hematopoietic stem cell or solid organ transplantation. These disorders often arise post-transplant due to the immunosuppression required for minimizing the risk of rejection of donor tissue. First-line treatment of these disorders includes limiting immunosuppression when permissible. Subsequent treatment includes the use of monoclonal anti-CD20 antibody (rituximab), and/or combination chemotherapy. Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment paradigm in many lymphoid malignancies. It is not approved for PTLD due to exclusion of PTLD patients from pivotal clinical trials. Also, its utilization post-transplant can be complex and multidisciplinary care is of utmost importance for successful administration of a potentially curative treatment. We present a 68-year-old patient with history of heart transplant for non-ischemic cardiomyopathy, diagnosed with PTLD that was refractory to treatment using current guidelines until successfully receiving CAR T-cell therapy.

Keywords: Post-transplant lymphoproliferative disorder; CAR T-cell therapy; Heart transplant

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Introduction

Post-transplant lymphoproliferative disorder (PTLD) is a heterogeneous group of disorders in patients who undergo either solid organ or hematopoietic stem cell transplant due to immunosuppressive therapy [1]. There is a fine balance post-transplantation between immunosuppression to prevent graft rejection while maintaining sufficient cellular immunity to prevent PTLD [2]. Heart transplant patients have an estimated 0.9% risk of developing PTLD; this risk is about four times that of adult kidney transplant recipients [3]. Malignancy is the leading cause of death at 5 years post heart transplant [4]. One factor that is associated with developing PTLD is when both the donor and recipient are Epstein-Barr virus (EBV) positive. The dominant theory for development of PTLD is that immunosuppressive therapy leads to T-cell depletion allowing EBV-infected B cells to proliferate without regulation.

Chimeric antigen receptor (CAR) T-cell therapy is an emerging modality of treatment for B-cell malignancies including relapsed/refractory diffuse large B-cell lymphoma (DLBCL) and B-cell acute lymphoblastic leukemia (B-ALL). CAR T-cell therapy was approved by the FDA in 2017 [5]. This therapy includes using autologous T cells collected via apheresis from the patient which are modified and expanded *ex vivo*. These cells are manufactured to have a CAR specific to the patient's malignancy. Previous solid organ transplantation is a universal exclusion criterion in CAR T-cell therapy trials. There are a few reports of successful CAR T-cell therapy in refractory PTLD in heart transplants, but mostly in patients under age 25 [2, 6]. In this case report, we present a 68-year-old male patient with refractory PTLD, monomorphic DLBCL subtype, who successfully responded to CAR T-cell therapy.

Case Report

We present the case of a 68-year-old male who underwent orthotopic heart transplant in 2021 for a diagnosis of non-ischemic cardiomyopathy. He was diagnosed with dilated cardiomyopathy secondary to alcohol use 20 years prior.

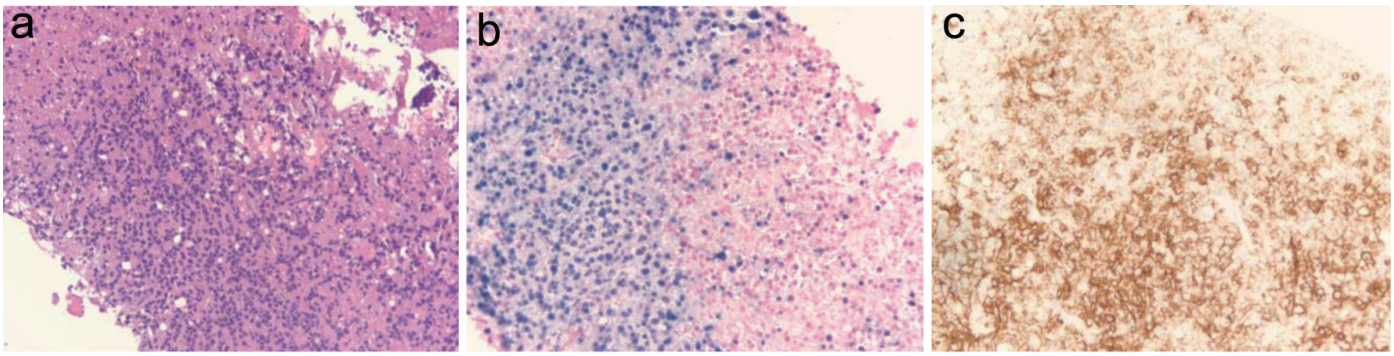

Figure 1. (a) Liver core biopsy showing monomorphic proliferation of neoplastic cells (at × 20 magnification). (b) Ebstein-Barr virus (EBV) stain showing positive nuclear staining of EBV-infected cells (at × 20 magnification). (c) CD20 stain showing positive membranous staining of B cells (at × 20 magnification).

Post-transplant the patient was initially treated with an immunosuppressive regimen of tacrolimus, mycophenolate mofetil, and prednisone.

Five months after transplantation, the patient presented to the hospital with abdominal pain and diarrhea. Infectious workup revealed *Clostridium difficile (C. difficile)* infection and persistent leukopenia from transplant immunosuppression. Due to low risk of rejection and concern for complications from immunosuppression, his mycophenolate was discontinued while tacrolimus and prednisone were continued. Imaging studies included computed tomography of the abdomen/pelvis (CTAP), which revealed new hypodense liver lesions. These findings were followed up with a liver magnetic resonance imaging (MRI) and ultrasound-guided biopsy. Liver biopsy showed EBV+ DLBCL consistent with monomorphic PTLD (Fig. 1a, b). Subsequently, he was started on rituximab 375 mg weekly and received four total infusions over the course of 4 weeks. After four cycles of weekly rituximab, positron emission tomography (PET)/CT was performed and revealed progression of disease with new lung involvement (Fig. 2a). Due to the lack of response demonstrated on imaging, his treatment was then escalated to rituximab, cyclophosphamide, etoposide, vincristine, prednisone (R-CEOP) regimen. Etoposide was used in place of anthracyclines to minimize cardiotoxicities due to post-heart transplant status.

He received two cycles of R-CEOP before presenting to the emergency department (ED) with neutropenic fever and respiratory failure. A bronchoscopy and bronchoalveolar lavage were done to further evaluate the etiology of his respiratory failure. The bronchoscopy revealed a near complete obstruction of the middle lobe bronchus and biopsy confirmed findings consistent with PTLD. Since the patient was now refractory to two lines of PTLD therapy, CAR T-cell therapy was considered. This idea was discussed at a multidisciplinary tumor board which concluded that despite off-label use, CAR T-cell therapy was the next best step to give the patient a chance of curative treatment. Additionally, this plan was brought to and considered by the heart transplant team who recommended a year from transplant pass before CAR T-cell therapy.

In order to allow time for a year to pass and the logistics of preparing therapy, he received two cycles of rituximab plus gemcitabine and oxaliplatin (GemOx) as a bridge to CAR T-cell treatment. The subsequent PET/CT showed further disease progression (Fig. 2b). Tacrolimus was discontinued and prednisone dose was increased 1 week prior to T-cell collection to optimize successful apheresis. Tacrolimus was restarted post apheresis until it was subsequently stopped again during lymphodepletion. Lymphodepletion was initiated with fludarabine and cyclophosphamide (Flu/Cy) prior to infusion of axicabtagene ciloleucel. The total time between apheresis and CAR T-cell infusion was 26 days. On day +3 post CAR T-cell therapy, he developed grade 1 cytokine release syndrome (CRS) with symptoms of fever treated with one dose of tocilizumab. He then developed confusion on day +4 with an immune effector cell-associated neurotoxicity syndrome (ICANS) score of 1, but CT of head, MRI of brain, and electroencephalogram (EEG) had no significant findings. He developed a slight tremor on day +10 and was evaluated by neurology who deemed it to be benign tremor most likely due to hypophosphatemia not CRS or neurotoxicity. He was discharged on day +24 and tacrolimus was restarted on day +30.

The PET/CT on day +100 (Fig. 2c) showed resolution of both hepatic and right lower lobe lesions as well as reduction in right parahilar mass. Subsequent PET/CT (Fig. 2d) 5 months post infusion showed further reduction of the parahilar mass and no new lesions.

Discussion

This presentation of a 68-year-old patient status post heart transplant with monomorphic DLBCL subtype PTLD who achieved remission with CAR T-cell therapy is, to the best of our knowledge, one of few examples of this treatment working in an older patient. The details of demographic information, regimen and outcomes of the other reported cases can be found in Table 1 [2, 6-8].

When PTLD develops, the treatment strategy depends on pathological categorization as well as transplant type. PTLD can be classified using the 2017 World Health Organization (WHO) criteria and 2022 International Consensus classification (ICC) into four categories: non-destructive, polymorphic, monomorphic (B-cell, T-cell, natural killer (NK)-cell types), and classic Hodgkin lymphoma [9]. Since PTLD is associated

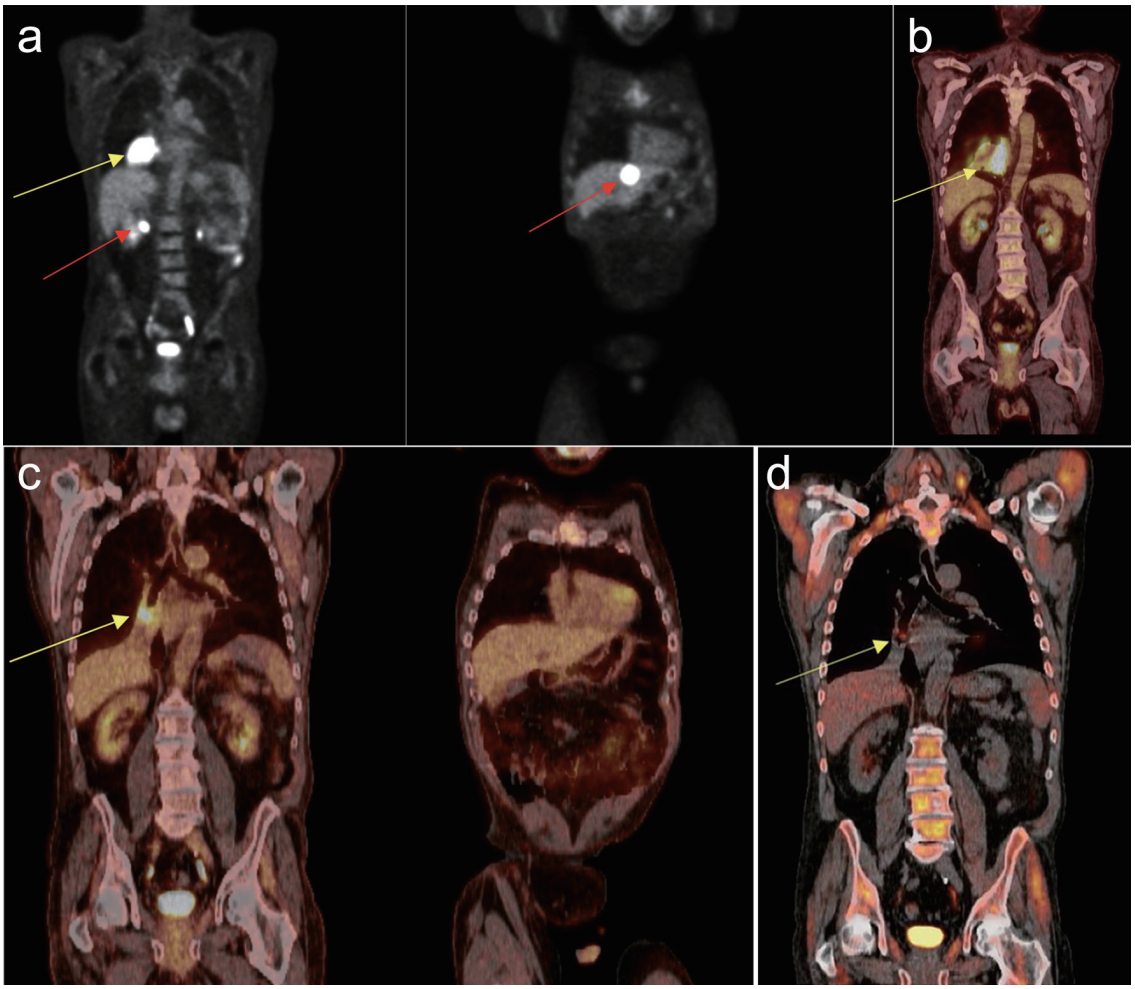

Figure 2. Positron emission tomography/computed tomography (PET/CT) over patient's disease progression and treatment. (a) After rituximab: showing large mass in right lower lobe of the lung (yellow arrow) and lesions in segment 2 and 7 of the liver (red arrows). (b) After rituximab, cyclophosphamide, etoposide, vincristine, prednisone (R-CEOP) showing increase in size of the right lower lobe lesion (yellow arrow) now with central necrosis. Left lobe lesion in the liver resolved, but right lobe lesion remains. (c) After chimeric antigen receptor (CAR)-T cell therapy showing resolution of right lower lobe lesion with reduction in size of parahilar lesion (yellow arrow). Resolution of the liver lesions also noted. (d) Further reduction of the parahilar lesion 5 months post-CAR-T cell therapy (yellow arrow).

with increased immunosuppression, the first-line treatment for most categories includes decreasing immunosuppressive therapy [10]. However, this increases the risk of donor tissue rejections and transplant failure.

Since PTLD often involves B cells, rituximab can be used to target the CD20 antigen when lowering immunosuppression alone is unsuccessful [10]. If decreasing immunosuppression and rituximab alone do not result in remission of PTLD, treatment can be escalated to chemoimmunotherapy. If PTLD is refractory to both single agent rituximab and chemotherapy and the patient is EBV+, EBV-specific cytotoxic T lymphocytes (CTLs) can be considered [11].

CAR T-cell therapy is not FDA approved for PTLD but has been approved for DLBCL [7]. The trials for approval excluded patients on immunosuppressive therapy or prior solid organ transplant, therefore excluding PTLD patients [12]. There is one case of an 18-year-old female receiving CAR T-cell therapy for PTLD after heart transplant and achieving remission [2]. The medical team pursued similar treatment prior to CAR T-cell therapy except that she also received EBV CTLs. CAR T-cell therapy was pursued in our patient due to the biologic similarities of B-cell monomorphic subtype of PTLD to the approved indication of DLBCL. Axicabtagene ciloleucel is one of the CAR T-cell therapies currently approved to target the CD-19 antigen found on B cells, therefore it is plausible that current CAR T-cell therapies will be efficacious in similar B-cell-driven malignancies. Previously, autologous stem cell transplantation was considered a good option for refractory B-cell lymphomas. However, data from the ZUMA-7 trial showed the superiority of CAR T-cell therapy in comparison to standard treatment in terms of overall response rate and complete remission [13]. Additionally, the polatuzumab vedotin, bendamustine and rituximab (Pola-BR), loncastuximab tesirine, and tafasitamab/revlimid regimens were not consid-

Table 1. Key Clinical Factors in Cases Utilizing CAR T-Cell Therapy in PTLD of Heart Transplant Patients

Case	Age at CAR T-cell therapy	Time to PTLD diagnosis	Type of PTLD	Prior therapies	CAR T-cell therapy agent	IS at apheresis	IS at CAR T-cell therapy	Outcomes post-CAR T-cell therapy
Hickmann et al	69	5 months	EBV+ monomorphic	Rituximab, R-CEOP, GemOx	Axi-cel	Stop tacrolimus; increase prednisone	Prednisone	No evidence of PTLD on PET/CT on day +100
Dang et al [2]	18	4 months	EBV+ monomorphic	R-COP, R-COPADM, R-CYVE, EBV CTLs	Axi-cel	Prednisone 5 mg tacrolimus	Unknown	No evidence of PTLD on PET/CT on day +80
Oren et al [6]	23	22 years (3 years s/p kidney transplant)	EBV+ monomorphic	R-CHEOP, gemcitabine/ carboplatin	Liso-cel	Unknown	Tacrolimus, prednisone	No evidence on PET/ CT on +90
Krishnamoorthy et al [8]	54	26 years	EBV- monomorphic	R-CHOP, R-ICE	Axi-cel	-	-	Death on day +44
McKenna et al [7]	76	Unknown	Unknown	R-Benda, radiation	Brexu-cel	-	-	Complete remission

CAR: chimeric antigen receptor; CTLs: cytotoxic T lymphocytes; EBV: Ebstein-Barr virus; GemOx: gemcitabine-oxaliplatin; IS: immunosuppression; PET/CT: positron emission tomography/computed tomography; PTLD: post-transplant lymphoproliferative disorder; R-CEOP: rituximab, cyclophosphamide, etoposide, vincristine, prednisone; R-COPADM: rituximab, cyclophosphamide, oncovin (vincristine), prednisone, adriamycin (doxorubicin), methotrexate; R-CYVE: rituximab, cytarabine, etoposide; R-ICE: rituximab, ifosfamide, carboplatin, etoposide.

ered a viable option for this patient due to his preexisting neuropathy [14]. Furthermore, these regimens are not considered curative, and the patient preference was to pursue a curative treatment. At the time of writing, the bispecific T-cell engagers, epcoritamab and glofitamab, have been approved (May 2024) [15]. However, the period of treatment for this patient was before that date.

In the post-transplant setting, one consideration with CAR T-cell therapy is the continuity of the patient's immunosuppression [8]. A balance must be achieved between decreases in immunosuppression increasing risk of rejection and the current level of immunosuppression increasing chance of CAR T-cell failure. This is especially pertinent when the patient is on tacrolimus, a calcineurin inhibitor that blocks production of interleukin-2 (IL-2) and therefore T-cell proliferation. The key moments for changes in immunosuppressive regimens are prior to apheresis to ensure sufficient cells are collected for manufacturing, and during infusion back into the patient to ensure the CAR T-cell function does not get affected by immunosuppressants. To mitigate the risk of CAR T-cell failure in our case, tacrolimus was stopped 1 week before apheresis and then restarted 30 days post-infusion. These considerations were explained to the patient before treatment proceeded, and despite these risks the patient responded well to treatment and achieved remission.

Conclusion

With this example of CAR T-cell therapy being successful in an older patient with PTLD post heart transplant, we hope our case adds to the sparse literature about the use of CAR T-cell therapy post solid organ transplant and highlights the safety and feasibility of this treatment. Multidisciplinary care is of utmost importance to guarantee a successful administration of this potential curative approach. As there are limited guidelines on how to manage immunosuppression changes, this is an area to explore with future research.

Acknowledgments

None to declare.

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Conflict of Interest

All authors have no conflict of interest.

Informed Consent

Informed consent has been obtained for treatment using CAR T-cell therapy, including that this use would be considered off label and did not have specific FDA approval. Patient has the same pathology for which CAR T-cell therapy was approved for.

Author Contributions

Yazan Samhouri MD had full access to all the data and analysis in the study and takes responsibility for the integrity of data and the accuracy of the data analysis. Concept and design: Yazan Samhouri MD. Drafting of the manuscript: all authors. Critical revision of the manuscript: all authors. Administrative and technical support: Yazan Samhouri MD. Supervision: Yazan Samhouri MD.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

PTLD: post-transplant lymphoproliferative disease; EBV: Ebstein-Barr virus; CAR: chimeric antigen receptor; B-ALL: B-cell acute lymphoblastic leukemia; DLBCL: diffuse large B-cell lymphoma; R-CEOP: rituximab, cyclophosphamide, etoposide, vincristine, prednisone; GemOx: gemcitabine-oxaliplatin; EBV CTLs: Epstein-Barr virus cytotoxic T lymphocytes; Axi-cel: axicabtagene ciloleucel; Brexu-cel: brexucabtagene autoleucel; Lis-cel: lisocabtagene maraleucel

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