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Case Report
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CAR T-cell Infusion Following Checkpoint Inhibition Can Induce Remission in Chemorefractory Post-transplant Lymphoproliferative Disorder of the CNS

Wiebke Rösler[1], Andrea Bink[2], Marina Bissig[1], Lukas Imbach[3], Ewerton Marques Maggio[4], Markus G. Manz[1], Thomas Müller[5], Patrick Roth[3], Elisabeth Rushing[6], Corinne Widmer[1], Thorsten Zenz[1], Seraina von Moos[5], Antonia M. S. Müller[1,7]

Correspondence: Wiebke Rösler (Wiebke.roesler@usz.ch); Antonia M. S. Müller (antonia.mueller@meduniwien.ac.at).

We present the successful treatment of a patient with post-transplant lymphoproliferative disorder (PTLD) of the central nervous system (CNS) with checkpoint inhibition, followed by infusion of chimeric antigen receptor T cells (CAR-T). CD19-directed CAR-T cells are an effective treatment option for patients with relapsed/refractory (r/r) aggressive B-cell lymphoma. Although some first experience of the use of CAR-T cells in patients with CNS lymphoma has been published, reports on the treatment of PTLD with CAR-T are scarce. In addition to our case, we provide a review of the available literature on the treatment of CNS lymphoma and PTLD with CAR-T cells.

CAR-T cells targeting CD19 are currently approved for patients with r/r diffuse large B-cell lymphoma (DLBCL), high-grade and primary mediastinal B-cell lymphoma after >2 lines of chemotherapy. In early studies and in phase I/II clinical trials, cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were frequently observed.[1,2] Although patients with active lymphoma of the CNS were excluded from most clinical CAR-T trials, there is now growing evidence for the use of CAR-T in these patients without evidence of increased neurotoxicity.[3–6] CAR-T therapy for treatment of PTLD has not been studied systematically. Data are limited to case reports with heterogeneous outcomes and treatment is typically challenging.[7–12] Here, we present the case of a chemorefractory patient with an EBV-associated DLBCL with secondary CNS involvement undergoing checkpoint inhibition followed by CAR-T-cell therapy. The patient provided her informed consent and procedures were in accordance with the ethical standards of the responsible committee. Moreover, we performed a review of the literature on the treatment of CNS lymphoma and PTLD with CAR-T.

CASE DESCRIPTION

The patient was born with a congenital urogenital-tract (UGT) malformation due to a caudal regression syndrome, which lead to frequent UGT infections and chronic renal failure. At age 18, she required hemodialysis, and soon after underwent cadaveric renal transplantation (RTx; 6/8 HLA-mismatch, no donor-specific antibodies, CMV D–/R–, EBV D+/R-). Pharmacological immunosuppressive therapy (IST) consisted of tacrolimus (TAC), mycophenolate mofetil (MMF), and prednisone (PDN). Four months post RTx, the patient presented with fevers, an UGT infection (ESBL-producing *Escherichia coli*), and a primary EBV infection originating from the transplanted kidney. Following reduction of IST (TAC and MMF)—as was standard management of EBV replication at our institution at the time—the viral load decreased (Figure 1A). Shortly after, the patient was admitted to the hospital with emesis and abdominal pain due to multiple ulcerations in the stomach and the duodenum, which histologically revealed the diagnosis of an monomorphic PTLD in the form of an EBV+ DLBCL, NOS, non-GCB type, with PD-1L expression in 20%–30% of lymphoma cells (Figure 1B, left panel), Ann-Arbor stage IV (stomach, intestines, retroperitoneal lymph nodes; Figure 1C), IPI 3 (aaIPI: 2). The lymphoma had an XX (host-type) karyotype. With diagnosis of the DLBCL, first-line chemotherapy with R-CHOP was initiated. MMF was stopped; TAC and PDN were continued. Treatment was complicated by recurrent massive gastrointestinal bleedings, perforations, and infections. The patient spent 3

[1]Department of Medical Oncology and Hematology, University Hospital Zurich, Switzerland
[2]Department of Neuroradiology, University Hospital Zurich, Switzerland
[3]Department of Neurology, University Hospital Zurich, Switzerland
[4]Institute of Pathology and Molecular Pathology, University Hospital Zurich, Switzerland
[5]Department of Nephrology, University Hospital Zurich, Switzerland
[6]Institute of Neuropathology, University Hospital Zurich, Switzerland
[7]Department of Blood Group Serology and Transfusion Medicine, University Hospital Vienna, Austria

HemaSphere (2022) 6:7(e733).
http://dx.doi.org/10.1097/HS9.0000000000000733.
Received: February 8, 2022 / Accepted: April 28, 2022

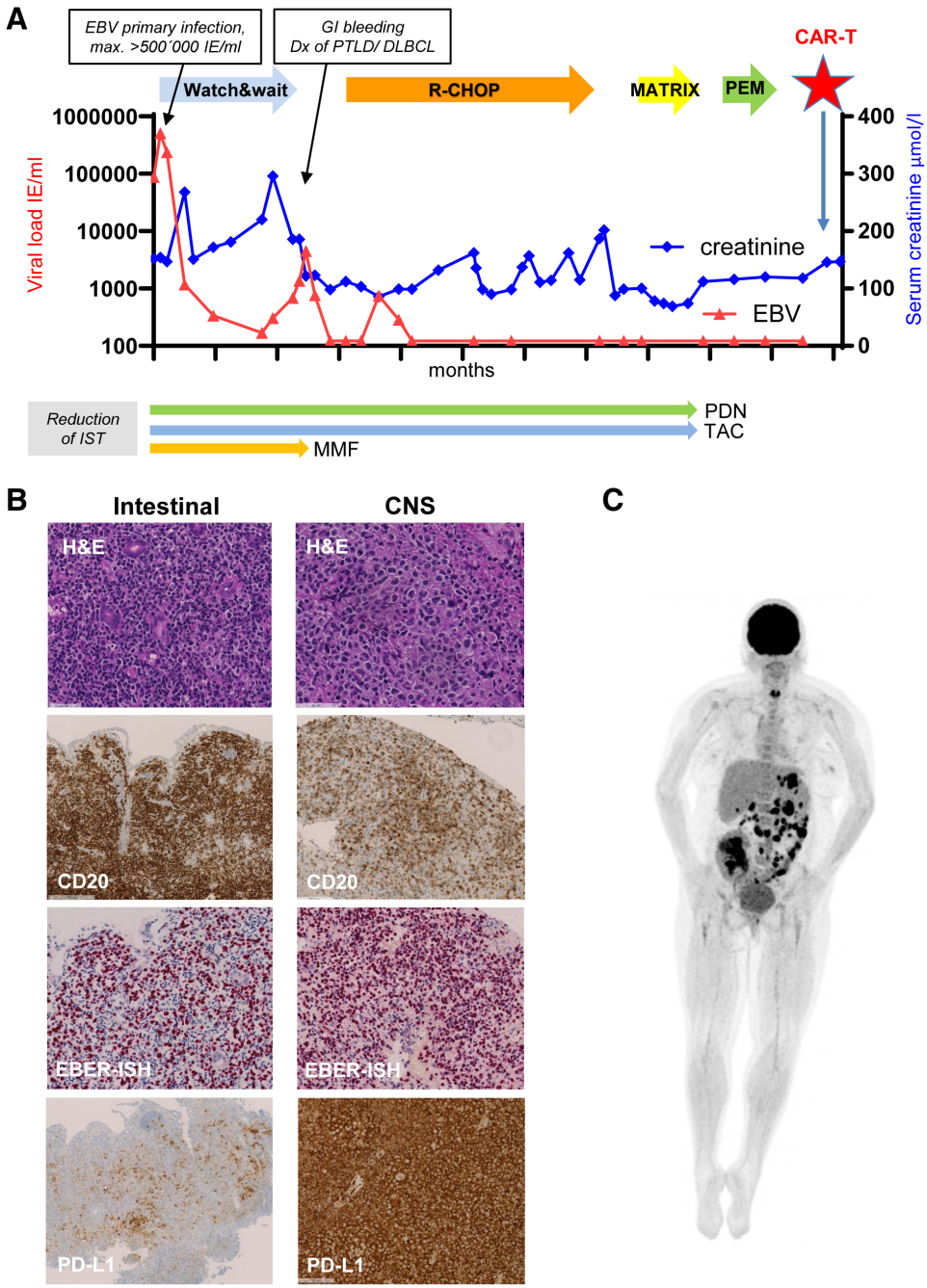

Figure 1. Overview EBV-virusload, pathology and PET-CT scan. (A) Clinical course over 12 mo from the time of EBV reactivation (left y-axis, logarithmic, PCR load in IE/mL) displaying also serum creatinine (in µmol/L) and therapeutic interventions. (B) Histopathology of lymphoma tissue derived from the GI tract (left side) and the CNS (right side), displaying H&E, CD20, EBER-ISH, and PD-L1 stainings. The left panel shows duodenal mucosa diffusely infiltrated by medium to large size lymphoid cells (H&E), with large cells that are strongly and diffusely positive for CD20 and EBER-ISH, providing evidence for EBV infection. In the duodenal mucosa, cells are partially expressing PD-L1 (Klon SP263) in the lymphoma cells. The right panel shows CNS parenchyma diffusely infiltrated by large size polymorphic lymphoid cells (H&E), with large atypical cells positive for CD20 and EBER-ISH, providing evidence for EBV infection. In the CNS parenchyma, there is a strong and diffuse PD-L1 (Klon SP263) in the lymphoma cells. (C) PET-CT scan at diagnosis of the DLBCL displaying isolated metabolic activity in mesenteric lymph nodes and the gastrointestinal tract. CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma; Dx = diagnosis; EBV = Ebstein-Barr Virus; GI = gastrointestinal; IST = immunosuppressive therapy; MMF = mycophenolate mofetil; PDN = prednisone; PEM = pembrolizumab; PET-CT = positron emission tomography - computer tomography; PTLD = post-transplant lymphoproliferative disease; TAC = tacrolimus.

months in the hospital and needed multiple interventions (10 endoscopic procedures of the GI, 1 angiography, 2 explorative laparotomies). Five cycles of R-CHOP were administered over 4 months. Positron emission tomography - computer tomography (PET-CT) imaging following cycle 3 revealed a complete remission of the DLBCL. After cycle 5, the patient presented with seizures. Imaging revealed several new CNS lesions (Figure 2A, top panel). Histology confirmed EBV+ DLBCL in the CNS (host type). Immunohistochemistry now demonstrated a higher PD-1L expression of 90% (Figure 1B, right panel) and different fragment lengths of the framework region of the IgH. No other active lymphoma manifestations outside the CNS were present. Systemic salvage chemotherapy (following "MATRix Protocol": rituximab, high-dose methotrexat, cytarabin, thiotepa) was

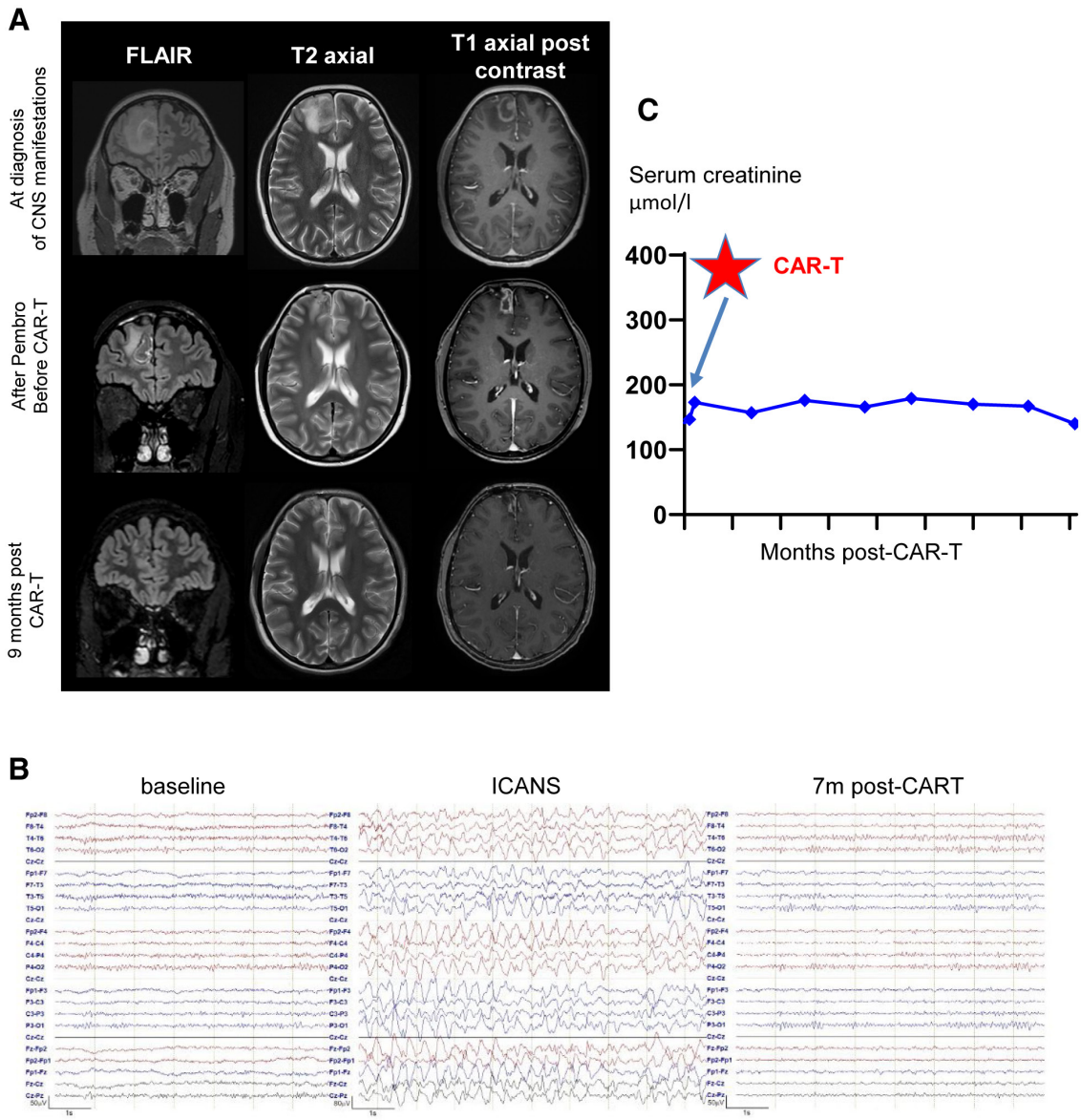

Figure 2. Diagnostics neurology and renal function over time. (A) Serial cMRI images displaying lymphoma lesions in the CNS at diagnosis (upper panel), after Pembro (middle), and 9 mo post CAR-T. Coronal FLAIR, axial T2-weighted and axial T1-weighted post contrast MRI images (from left to right): The right frontal lesion's size and perifocal edema reduce considerably over time. Recent control images (lower panel) show residual signal alterations consistent with gliotic changes. As further lymphoma manifestation a focal contrast enhancement in the left cuneus is shown (upper and middle row) which disappeared completely (lower row). (B) Serial representative EEG epochs are shown at different time points in bi-polar double banana montage. Left: Baseline EEG 3 weeks before CAR-T infusion was unremarkable; middle: EEG on d+6 displays bilateral continuous rhythmic delta activity (at 2–3 Hz) with frontal predominance as an electrophysiological correlate of severe acute encephalopathy. The EEG did not reveal any epileptiform discharges. Right: in the follow-up EEG 6 mo after treatment the encephalopathic EEG pattern was completely resolved. All EEGs were recorded according to international 10/20 montage with addition T1/T2 electrodes. (C) Serum creatinine (in µmol/l) following CAR-T infusion providing no evidence of renal insufficiency of the allograft. CAR-T = chimeric antigen receptor T cells; CNS = central nervous system; EEG = electroencephalogram; FLAIR = fluid attenuated inversion recovery.

given. Only a partial remission (PR) was achieved, but since the patient was in a clinically poor condition (ECOG 2–3) intensive chemotherapy was discontinued. IST with TAC and PDN was stopped and 17 days later, lymphapheresis for production of CAR-T cells was performed. On the day of lymphocyte collection peripheral blood lymphocyte count was 0.232 G/L, comprising mostly T cells (227 $CD3^+$/µL [CD4:CD8 1:1]), and a total of 1.77×10^9 $CD3^+$ T cells were collected for production of tisagenlecleucel (Tisa-Cel). To bridge the time to CAR-T-cell infusion, treatment with the checkpoint-inhibitor pembrolizumab (pembro) was initiated. Pembro was tolerated well. Kidney function remained stable. After the second cycle of pembro CNS lesions shrunk with decreasing contrast enhancement (Figure 2A, middle panel), and the general condition of the patient improved (ECOG 1). Four weeks after the second dose of pembro, the patient received lymphodepletion (fludarabine 25 mg/m^2 d-4 to d-2, cyclophosphamide 250 mg/m^2 d-4 to d-2) and was infused with 0.9×10^8 CAR^+ viable T cells (1.58×10^6/kg). Following CAR-T cell infusion, she repeatedly developed fevers (>38.5°C), corresponding to CRS°1, and between d+5 to d+8, she showed multimodal cognitive dysfunction including focus (count backwards), aphasia (name objects), and impaired writing, corresponding to ICANS grade 1. Electroencephalogram on d+6 revealed correlates of severe acute encephalopathy but no epileptiform discharges (Figure 2B). CRS and ICANS both resolved without specific interventions and treatments by d+9

post CAR-T infusion. Neither steroids nor tocilizumab were given and on d+15, she was discharged home. Prolonged pancytopenia was observed, particularly of the red lineage. CAR-T cells remained detectable in the blood beyond 7 months post CAR-T infusion; moderate B-cell lymphopenia persists and the patient requires regular intravenous immunoglobulin substitutions. cMR and PET-CT imaging demonstrate an ongoing remission. Without any IST for the past 26 months renal function remains stable (Figure 2C), without histological signs of allograft dysfunction of the transplanted kidney.

PTLD comprises a wide spectrum of lymphoid neoplasms seen after solid organ and allogeneic hematopoietic cell transplantations (allo-HCT) that are associated with immunosuppression or EBV infection.[13] Treatment of PTLD is mostly based on phase II trials, single institution retrospective studies, and expert opinions. Although some early-type and polymorphic PTLD may respond to reduction of IST and rituximab monotherapy, monomorphic PTLD typically requires additional chemotherapy. PTLD involving the CNS is rare (7% of all PTLD), typically has a monomorphic histology and a poor prognosis with a reported 1-year survival of 40%.[14] Adoptive EBV-directed T-cell therapies demonstrate promising effects but are not widely available in clinical routine.[15]

AVAILABLE REPORTS FROM THE LITERATURE

The use of CAR-T cells for treatment of PTLD has not been studied systematically (Suppl. Table S1). Three successful treatments were reported by Luttwak et al[9] following renal and liver transplantations, with responses in all 3 patients and little toxicity. In contrast, outcomes were unfavorable in 3 patients following kidney and heart transplants reported by Krishnamoorthy et al,[8] who developed CAR-T associated toxicity and early death in all 3 patients. Two promising pediatric cases reported a disease free survival beyond 6 and 16 months, respectively.[7,12] Recently, 3 additional RT recipients with PTLD who were treated with CAR-T cells were reported to have tolerated treatment well, but only 1 of the 3 patients obtained a CR beyond 6 months. No CNS involvement was reported in this cohort of patients.[10]

Patients with CNS lymphoma were initially excluded from the pivotal CAR-T cell trials,[1,2] due to concerns of an increased neurotoxicity. Growing experience, also within clinical trials (TRANSCEND NHL001-Trial, using Liso-cel also in a cohort of CNS lymphoma patients), does not support the fear of intolerable neurotoxicity, but numbers of patients with CNS involvement were low (7/294 infused patients).[4] Feasibility without excess toxicity has also been demonstrated in case reports and small case series (Suppl. Table S2).[3,5,6,11,16,17]

Similarly, little is known on the use of checkpoint inhibition in CNS-PTLD, which has only been described in 1 pediatric allo-HCT recipient so far.[18] Twelve months after start of treatment the patient was in a CR without signs of graft-vs-host disease or graft failure, whereas maintenance therapy with Nivolumab was ongoing. In general, treating solid organ transplant recipients with checkpoint-inhibitors puts the allograft at risk of rejection, but exact numbers of graft loss for different transplanted organs are not available as of yet.

Our PTLD patient presented with a clinically highly aggressive DLBCL after RT. Lacking the response to conventional chemotherapy and considering the poor clinical condition, the decision was made to switch treatment to a short course of immunotherapy—despite of the risk of harnessing renal function of the allograft—until CAR-T cells were manufactured. Twenty months after CAR-T cell infusion, the patient remains in an ongoing CR. Whether the 2 doses of pembro, tisa-cel, or the combination of the 2 immunotherapies eradicated the lymphoma remains unanswered. Given the risk of organ rejection the use of checkpoint inhibition needs to be thoroughly evaluated and discussed with the patient. As planning of lymphocyte collection and production of CAR-T cells requires weeks of time, a bridging strategy is often needed. Our patient was in a clinically poor condition and did not tolerate more chemotherapy. In the light of the high PD-1L expression and the potential synergy between both treatments, we decided to attempt this sequential combination strategy of pembro and CAR-T cells. This case illustrates that checkpoint inhibition followed by CAR-T cell therapy can be safe and efficient in selected patients with PTLD, even when involving the CNS. Treatment was tolerated well. Whether CAR-T cells directed against B cells contributed to suppression of humoral immunity against the allograft and lower the risk of loss of function of the transplanted organ remains to be clarified. Until larger data sets from registries are available experiences, as ours may help to guide treatment decisions in patients with refractory PTLD.

ACKNOWLEDGMENTS

We are grateful to the young patient and her parents to allow us to report on this extraordinary clinical case.

AUTHORSHIP CONTRIBUTIONS

WR and AM treated the patient and wrote the article. SvM and TM guided nephrologic treatment and immunosuppressive therapy. LLI performed EEG analysis and provided those exams plus interpretation. AB analyzed cMRI images and provided results plus interpretation. EM performed additional stains of lymphoma tissues and provided their analysis. ER provided analysis of the CNS biopsy. PR, MB, TZ, and MGM were all critical in the treatment of the patient. All of the above either wrote parts of the article or critically discussed and edited the article.

DISCLOSURE

AM received honoraria from Novartis, KITE/Gilead, and Janssen, Celegene/BMS. Wiebke Rösler has received honoraria as member of the supervisory board of MagForce AG and travel support from Janssen.

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