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Case Report

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Progressive Multifocal Leukoencephalopathy After Chimeric Antigen Receptor T-Cell Therapy for Recurrent Non-Hodgkin Lymphoma

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Abstract

Chimeric antigen receptor (CAR) T-cell therapy targeting cluster of differentiation (CD)19 has had a transformative impact on patient outcomes in a subset of patients with relapsed/refractory non-Hodgkin lymphoma. We present a patient with refractory large B-cell lymphoma in complete remission for 2 years following treatment with CD19-targeted CAR T-cell therapy, who presented with 2 weeks of progressive aphasia. Imaging revealed a left occipital brain lesion and biopsy demonstrated features diagnostic of progressive multifocal leukoencephalopathy. Further evaluation revealed severe hypogammaglobulinemia and a low CD4 count. She was treated with pembrolizumab and intravenous immunoglobulin resulting in decreased cerebrospinal fluid viral load without clinical improvement and died 8 weeks after presentation. This case highlights that there is potential for severe opportunistic infections after CAR T-cell therapy, including fatal progressive multifocal leukoencephalopathy. Strategies to enhance post-treatment immune reconstitution are essential to further harness the unique potency of CAR T-cell therapy.

Keywords: Chimeric antigen receptor; CAR T-cell therapy; Progressive multifocal leukoencephalopathy; Opportunistic infection

Introduction

Progressive multifocal leukoencephalopathy (PML) is a devastating opportunistic infection caused by reactivation of John Cunningham virus (JC virus, also known as human polyomavirus 2) within the central nervous system that is characteristically observed in settings of profound immunosuppression [1]. There is increasing evidence that iatrogenic immunosuppression in the setting of immunomodulatory therapies may have an impact on the rising incidence of PML [2]. Specifically, chimeric antigen receptor (CAR) T-cell therapy targeting cluster of differentiation (CD)19 induces durable complete remissions in a subset of patients with relapsed/refractory B-cell lymphomas, dramatically impacting outcomes in this patient population. Unfortunately, the administration of CAR T-cells following lymphodepleting chemotherapy is associated with significant toxicity [3]. The impact of therapy on long-term immune dysregulation has not been well delineated although there is increasing awareness of the incidence of opportunistic infection [4, 5].

We present a patient treated with CAR T-cells for refractory non-Hodgkin lymphoma who was diagnosed with PML 2 years after infusion. This case highlights the potential for severe opportunistic infections in this population, possibly related to persistent lymphopenia, hypogammaglobulinemia, and immune dysregulation after CAR T-cell infusion.

Case Report

Investigations

A 68-year-old woman with history of recurrent/refractory non-Hodgkin lymphoma in complete remission since CAR T-cell therapy 2 years prior presented with 2 weeks of progressive word finding difficulty. Her oncologic history dated back to 2007 (56-years-old at that time) when a mass was discovered in her left breast. Biopsy revealed involvement by a B-cell non-Hodgkin lymphoma with follicular derivation. Her treatment course after diagnosis was notable for multiply recurrent disease following standard induction chemoimmunotherapy, high-dose chemotherapy with autologous stem cell rescue, several subsequent salvage chemotherapies, and targeted therapies (Fig. 1). Despite these efforts, transformation into diffuse large B-cell lymphoma (DLBCL) occurred in August 2016. Her treatment course was also notable for persistent lymphopenia and hypogammaglobulinemia (Fig. 1). In April

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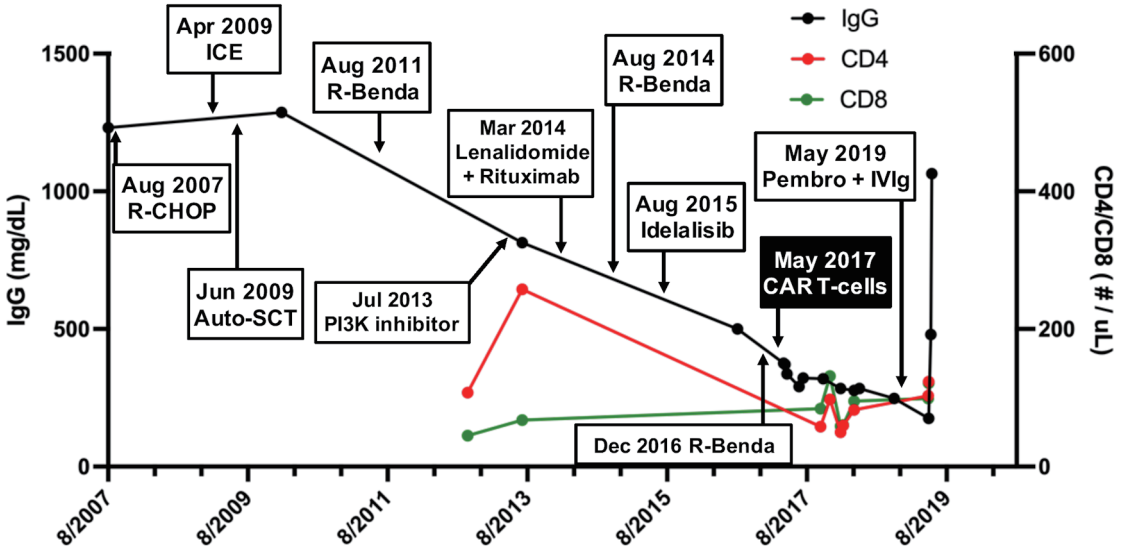

Figure 1. Serum immunoglobulin (IgG) levels and CD4 T-cell counts in response to various lymphoma treatments. A steady decline in serum IgG levels (black) and absolute CD4 counts (red), reaching a nadir after infusion of CD19-targeted CAR T-cells in May 2017. Absolute CD8 counts (green) were relatively preserved. R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; ICE: ifosfamide, carboplatin, etoposide; Auto-SCT: autologous stem cell transplant; R-benda: rituximab, bendamustine; CAR: chimeric antigen receptor; Pembro + IVIG: pembrolizumab, intravenous immunoglobulin; CD: cluster of differentiation.

2017, she underwent lymphodepletion with fludarabine and cyclophosphamide followed by CD19-targeted CAR T-cell therapy (lisocabtagene maraleucel) as part of a clinical trial (see reference [6] for additional details), and was in complete remission since May 2017. Following CAR T-cell infusion, her clinical course was uneventful and only notable for persistent hypogammaglobulinemia. Notably, a bone marrow biopsy done prior to CAR T-cell administration was free of any significant pathology. Similarly, her hemoglobin and platelet levels normalized after CAR T-cell administration, with only residual lymphopenia and continued hypogammaglobulinemia (Fig. 1).

In April 2018, approximately 1 year after CAR T-cell therapy, she noticed symptoms of simple visual hallucinations. Neurological exam revealed right inferior quadrantanopia and brain magnetic resonance imaging (MRI) demonstrated signal abnormality on fluid-attenuated inversion recovery (FLAIR) images in the left occipital pole (Fig. 2b), which was not present at the time of CAR T-cell infusion (Fig. 2a). Follow-up imaging in October 2018 again revealed FLAIR signal abnormality in the left occipital lobe, with extension into adjacent areas compared to prior scans (not shown). This was thought to represent evolving sequelae of infarction.

The patient was enrolled and cared for on a clinical trial approved by the Dana Farber/Harvard Cancer Center (DF/HCC) Institutional Review Board (IRB). As per IRB policies, all study treatments and procedures were performed after informed consent was obtained.

Diagnosis

In April 2019, 2 years after CAR T-cell therapy, she presented with 2 weeks of progressive word finding difficulty. Physical exam revealed alexia without agraphia, non-fluent aphasia, and right homonymous hemianopia. Brain MRI revealed further expansion of FLAIR hyperintense signal in the left occipital lobe and an area of new enhancement (Fig. 2c). Due to worsening symptoms and evolving imaging findings, a malignant process was suspected. Stereotactic brain biopsy was performed to obtain a tissue diagnosis.

Hematoxylin and eosin (H&E) stained sections from biopsy tissue revealed hypercellular gray matter with bizarre astrocytes (Fig. 2d). Enlarged violaceous nuclei were also observed, suggestive of viral inclusions (Fig. 2d, inset). SV-40 immunostain was strongly positive in large, atypical lesional cells, confirming infection by JC virus (Fig. 2e). Additional immunohistochemical and cytogenetic analyses confirmed the absence of a neoplastic process. Cerebrospinal fluid analysis subsequently tested positive for JC virus DNA by polymerase chain reaction (PCR, > 500,000 viral copies/mL) and serum was positive for anti-JC virus antibodies by enzyme-linked immunosorbent assay (ELISA). Together, these results were diagnostic of PML.

Treatment

During her hospitalization, she was initially treated with dexamethasone, which was discontinued following the diagnosis of PML. Her clinical symptoms gradually worsened with increasing word finding difficulty and worsening mental status. She was subsequently administered three doses of intravenous immunoglobulins (IVIGs), and mirtazapine was administered in an attempt to inhibit viral entry into cells [7, 8]. Pembroli-

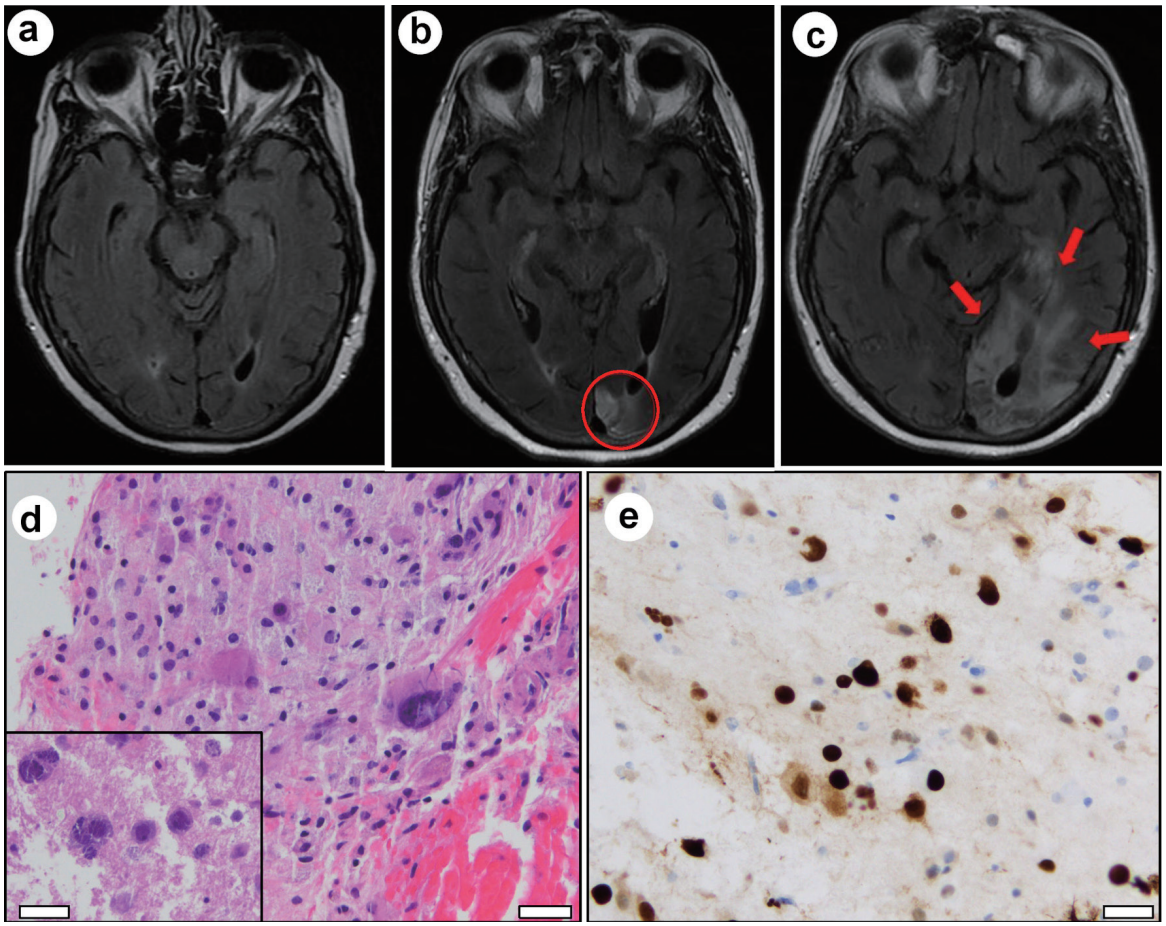

Figure 2. Magnetic resonance imaging evolution and brain biopsy. (a) FLAIR signal abnormality was absent in May 2017 at the time of CAR T-cell infusion and prior to onset of neurological symptoms. (b) FLAIR signal abnormality in the left occipital lobe at the time of initial presentation for visual disturbance in April 2018 (red circle). (c) Expansion of FLAIR signal (red arrows) involving the left occipital lobe and left posterior temporal lobe in April 2019 after presentation with progressive word finding difficulty. Hematoxylin and eosin (H&E) stained sections from left occipital brain biopsy show (d) bizarre-appearing astrocytes and violaceous oligodendroglial nuclear inclusions (inset). Immunohistochemistry demonstrates strong nuclear positivity for SV-40 (e). White scale bars = 100 µm.

zumab was initiated in light of evidence demonstrating efficacy of immune checkpoint inhibitors for PML [9].

Follow-up and outcomes

Despite these efforts, she became increasingly somnolent and passed away after 8 weeks of hospitalization.

Discussion

CAR T-cells targeting CD19 have demonstrated striking efficacy in B-cell malignancies including acute lymphocytic leukemia and non-Hodgkin lymphoma [3]. A majority of patients with relapsed/refractory disease achieve complete remission and a subset of patients may achieve durable response. CAR T-cell therapy is associated with significant toxicity in the early post-infusion period including cytopenias, infections resulting from lymphodepleting chemotherapy, and cytokine release syndrome (CRS) [10]. Neurologic toxicities following CAR T-cell infusion may follow CRS and are characterized by symptoms ranging in severity, including aphasia, confusion, altered mental status, and seizure [3].

PML has been described in settings of severe immune compromise resulting in JC viral reactivation and expansion with devastating consequences. It has been previously described in patients with advanced human immunodeficiency virus (HIV) disease with profound CD4 lymphopenia, following allogeneic transplantation in the setting of chronic immune suppression, and in rheumatologic diseases requiring intensive chronic immune suppression [1]. More recently, PML has also been reported in patients with hematologic malignancies on chronic B-cell depleting therapy [2].

Immune dysregulation following CAR T-cell therapy is multifactorial and may result in the emergence of opportunistic pathogens. Patients with lymphoid malignancies undergoing CAR T-cell therapy often have received multiple prior

Table 1. Review of Prior Reports of Progressive Multifocal Leukoencephalopathy (PML) After CAR T-Cell Therapy

Reference	Age/sex	CAR T-cells	Presenting neurologic symptoms (interval[a])	Outcome
Sdrimas et al, 2020 [12]	68/F	Axicabtagene ciloleucel (Axi-cel)	Confusion, aphasia, ataxia, involuntary movements (7 months)	Alive and stable, 12 months after PML diagnosis
Mian et al, 2021 [13]	61/F	Axicabtagene ciloleucel (Axi-cel)	Unsteady gait, dysarthria, loss of taste (14 months)	Deceased, 1 month after PML diagnosis
Current case	68/F	Lisocabtagene maraleucel (Liso-cel)	Visual deficits (11 months); word finding difficulty and worsening visual deficits (23 months)	Deceased, 2 months after PML diagnosis

[a]Interval from CAR T-cell administration to neurologic symptom onset. CAR: chimeric antigen receptor; F: female; PML: progressive multifocal leukoencephalopathy.

chemotherapy regimens in conjunction with antibody-mediated B-cell depletion, and as a consequence may be immunosuppressed prior to CAR T-cell therapy. Additionally, prolonged B-cell aplasia due to CAR T-cell-mediated depletion of the normal B-cell repertoire with consequent hypogammaglobulinemia is increasingly recognized as a serious complication of CAR T-cell therapy, and may result in an increased risk of opportunistic infection [11]. Hypogammaglobulinemia has been described as soon as 9 weeks and as late as 4 years after infusion [11]. One prospective study reported bacterial, viral, and fungal infections following CD19-targeted CAR T-cell therapy up to 90 days after infusion in 30 of 133 treated patients [4]. Similarly, a retrospective study found that late infections (> 90 days after infusion) were caused by bacteria, respiratory viruses, and (rarely) fungi. Interestingly, 61% of patients in this study had at least one late infection [5].

The impact of CAR T-cell therapy on cell-based immunity may also play a pivotal role for opportunistic infections. For example, lymphodepleting chemotherapy with fludarabine may be associated with prolonged cytopenias via targeting of hematopoietic stem cells as well as functional and quantitative suppression of helper and cytotoxic T-cell populations. In addition, immune dysregulation and cytopenias may be associated with CAR T-cell-induced inflammatory states such as hemophagocytic or macrophage activating syndromes. Finally, hyperstimulation of the CAR T-cell population in the setting of constitutive expression of costimulatory molecules may ultimately result in compensatory activation of tolerance pathways that suppress T-cell immunity.

Our case highlights a devastating late consequence potentially related to prolonged and profound hypogammaglobulinemia, raising an important question on how to optimally monitor patients for long-term effects of CAR T-cell therapy. Similar to other recent reports (Table 1 [12, 13]), CAR T-cells are unlikely the sole contributor to PML development in this patient. Indeed, the patient described here had several other PML risk factors, including history of hematological malignancy, prior rituximab treatment, chronic lymphopenia/hypogammaglobulinemia, and possibly immunosenescence [1] . However, her lymphoma had been in complete remission for 2 years following CAR T-cell infusions. Furthermore, first dose of rituximab was 10 years (and her last dose 2 years) prior to PML diagnosis (Fig. 1). Supporting this notion, one study found that the median time to PML diagnosis following first rituximab dose was 16 months, with almost two-thirds of cases occurring within 2 years of first exposure to rituximab [2]. Thus, it is likely that CAR T-cell therapy significantly contributed to the development of PML in this patient.

Learning points

This case supports the accumulating literature highlighting the importance of vigilance for PML in patients with late neurologic findings, and emphasizes the critical importance of establishing PML as a differential diagnosis by clinicians caring for patients treated with CAR T-cells. Furthermore, there is a critical need for the further interrogation of the late immunologic implications of this highly promising therapy informing surveillance of opportunistic infection and associated complications. Strategies to enhance post-treatment immune reconstitution are essential as we seek to further harness the unique potency of CAR T-cell therapy.

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None to declare.

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There are no financial disclosures or funding sources related to this manuscript.

Conflict of Interest

The authors have no conflict of interest to disclose.

Informed Consent

The patient was enrolled and cared for on a clinical trial approved by the Dana Farber/Harvard Cancer Center Institutional Review Board (IRB). As per IRB policies, all study treatments and procedures were performed after informed consent was obtained.

Author Contributions

JTA, JA, and DA performed the research, analyzed the data, and wrote the manuscript. SS and KS analyzed the data and wrote the manuscript. EJU and HV analyzed the data.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

Auto-SCT: autologous stem cell transplant; CAR: chimeric antigen receptor; CRS: cytokine release syndrome; PML: progressive multifocal leukoencephalopathy; DLBCL: diffuse large B-cell lymphoma; FLAIR: fluid-attenuated recovery inversion; H&E: hematoxylin and eosin; ICE: ifosfamide, carboplatin, etoposide; JC virus: John Cunningham virus; IRB: Institutional Review Board; MRI: magnetic resonance imaging; Pembro + IVIG: pembrolizumab, intravenous immunoglobulin; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-benda: rituximab, bendamustine

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