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Case Report

Epstein Barr Virus-Positive Lymphoproliferative Disorder Following Lymphodepletion for MAGE A4 Adoptive Cellular Therapy in a Patient with Synovial Sarcoma: A Case Report

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Lymphoproliferative · T-cell · Synovial · Sarcoma

Abstract
Lymphoproliferative disorder (LPD) associated with viral reactivation is a known risk of immunocompromised patients. With development of novel cellular therapies utilizing lymphodepletion regimens in advanced cancer, the risk of LPDs should be a consideration. Here, we report a case of a 61-year-old treated male with history of metastatic synovial sarcoma and multiple treatment lines treated with cell therapy (lymphodepleting chemotherapy and afami-cel, formerly ADP-A2M4, T-cell treatment) on clinical study that developed Epstein Barr virus-positive LPD. Patient was treated with rituximab and achieved a complete response. New cellular therapies present promising treatment options for patients and adverse events should be monitored carefully.

Introduction

Chemotherapy toxicity is well described in the literature and associated with significant risks which include development of new malignancies. Repeated chemotherapy exposure can lead to development of abnormal hematological function and leave some patients prone to development of prolonged cytopenia upon subsequent treatment and longer recovery times which may leave them prone to opportunistic infections. In some cases, chemotherapy can be

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associated with serious risks which include the development of new malignancies and aplastic anemia. For patients with metastatic synovial sarcoma, cytotoxic chemotherapy remains the mainstay of treatment with doxorubicin and ifosfamide combinations.

Viral reactivation is a known risk associated with chemotherapy and immunosuppressive therapy [1]. Cytomegalovirus (CMV) and Epstein Barr virus (EBV) are commonly found in the human population and typically suppressed in patients. EBV is the most common human tumor virus, and primary infection frequently occurs in childhood and remains for lifetime of host. To minimize risk to patients during chemotherapy, antiviral supportive measures are often recommended such as acyclovir allied with granulocyte colony-stimulating factors to stimulate bone marrow for immune recovery. Viral reactivation events typically will be re-suppressed by immune system as chemotherapy course is completed, and recovery to a normal immune environment is established. In transplant patients, lymphoproliferative disorders (LPDs) are observed in 2–10% patients [2–5]. For EBV-associated LPD events, rituximab is an effective therapeutic option which targets CD20 EBV+ cells [6].

Novel autologous cellular therapies such as afami-cel aim to enhance the patient's own T-cells to target tumor antigens (Fig. 1) [7]. Adaptimmune Therapeutics' afamitresgene autoleucel (afami-cel) is an investigational autologous engineered TCR. T-cell therapy intended to target MAGE-A4-expressing solid tumors. [8] As previously described [9], afami-cel-specific peptide enhanced affinity receptor (SPEAR) T-cells are genetically engineered with self-inactivating lentiviral vector to target MAGE-A4-expressing tumors, including synovial sarcoma. MAGE-A4 is a cancer/testis antigen expressed in many solid tumors that promotes cell growth by preventing cell cycle arrest and apoptosis [8]. Treatment involves lymphodepleting chemotherapy to aid with engraftment of cells and to reduce any tumor suppressive effects such as T-cell regulatory cells. Cell therapy not only represents a new promising treatment modality for patients but also represents risks of viral reactivation for patients receiving treatment.

Case Report

Our 61-year-old male patient initially presented in 2018 with a mass on the lower right side of his neck. A core needle biopsy revealed monophasic synovial sarcoma, t(X;18)(p11;q11). Staging scans did not show distant metastases. He received 2 cycles of doxorubicin and ifosfamide (AIM) chemotherapy, followed by 60 Gy of radiation therapy to the neck, and 2 additional cycles of AIM. He developed biopsy-proven lung metastasis 6 months after completing chemotherapy. He was treated with pazopanib and pembrolizumab without response. Pazopanib is a potent oral multi-target inhibitor against receptor tyrosine kinases including VEGFR-1, -2, and -3, PDGFR, and c-Kit. Pembrolizumab is a humanized monoclonal antibody directed against the checkpoint protein, programmed cell death-1, which stimulates the immune system's response against tumor cells.

He subsequently transferred care to our institution in February 2021 and enrolled in the phase 2 clinical trial of afami-cel (SPEARHEAD-1; NCT04044768). HLA×02 and MAGE-A4 positive participants in this trial undergo leukapheresis, and their isolated T-cells are transduced with the MAGE-A4 T-cell receptor and expanded (Fig. 2).

Our patient underwent apheresis in March 2021. Lymphodepletion with fludarabine 20 mg/m^2 (planned reduction from 30 mg/m^2 per protocol due to renal function) and cyclophosphamide 600 mg/m^2 and T-cell infusion with a dose of 4,893.4 × 10^6 transduced cells occurred in May 2021. Acyclovir treatment was initiated at the time of infusion at a dose of 800 mg twice daily.

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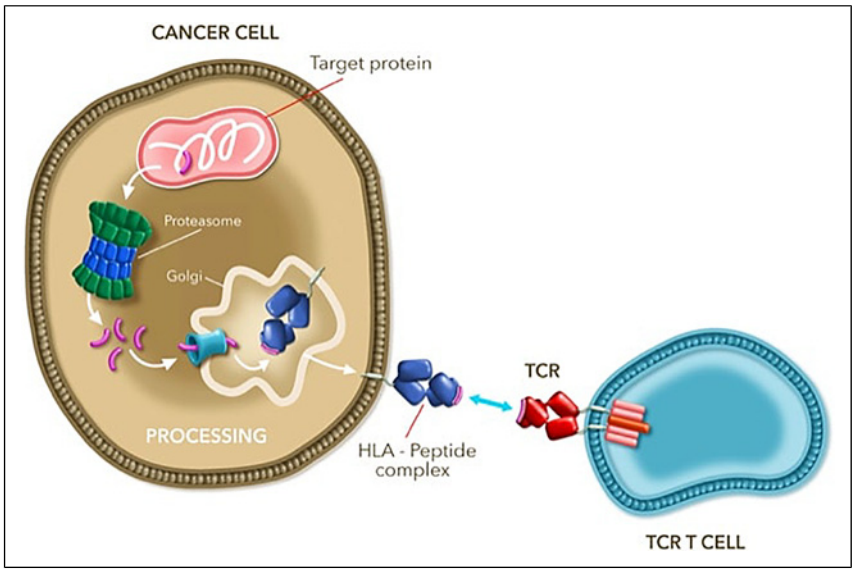

Fig. 1. Schematic of how affinity enhanced TCR s recognize and bind cancer cells. Graphic from Adaptimmune Co. website [7]. TCR, T-cell receptor.

The patient experienced grade 2 cytokine release syndrome (CRS) on day +2 and grade 1 immune effector cell-associated neurotoxicity syndrome and required treatment with tocilizumab and dexamethasone, oxygen for transient hypoxia, and iv saline bolus for hypotension. Tocilizumab is a humanized mouse monoclonal antibody that is designed to bind both mIL-6R (membrane bound receptor for IL-6 and sIL-6R [soluble receptor for IL-6]) and can inhibit both classical and trans-signaling pathway to treat cytokine storm. These adverse events were resolved by day +8.

The patient experienced prolonged cytopenias which manifested initially as grade 3 neutropenia on day +2 with further multiple neutropenia occurrences with final resolution on day +63. The worst grade experienced was grade 4 lasting 4 days, and patient required granulocyte colony-stimulating factor support.

The patient achieved a confirmed partial response per RECIST 1.1. on study with maximum reduction in target lesions of 67.6% at week 24 following infusion. Interestingly, routine surveillance PET/CT in October 2021 showed new intensely hypermetabolic bilateral adrenal masses. Biopsy of right adrenal gland showed a polymorphic LPD, EBV-positive, suspected to be secondary to treatment-related immunodeficiency. Next-generation sequencing by Heme Stanford Actionable Mutation Panel for Hematopoietic and Lymphoid Malignancies (Heme-STAMP) showed a variant of unknown significance (SOCS1 S143_F144insYGSRES), which does not lend support for recurrent genetic alterations found in hematolymphoid neoplasms. Note that there was no reported target or non-target lesion in the adrenal gland at baseline.

In December 2021, he was treated with 2 cycles of trabectedin for disease progression of sarcoma which were complicated by rhabdomyolysis, CMV reactivation, and non ST-segment elevation myocardial infarction. Trabectedin is an alkylating agent that binds guanine residues in the minor groove of DNA, which interferes with genetic transcription processes and induces lethal single-strand and double-strand DNA breaks. Trabectedin was discontinued in February 2022. Imaging showed favorable response to pulmonary and pleural lesions after treatment with trabectedin.

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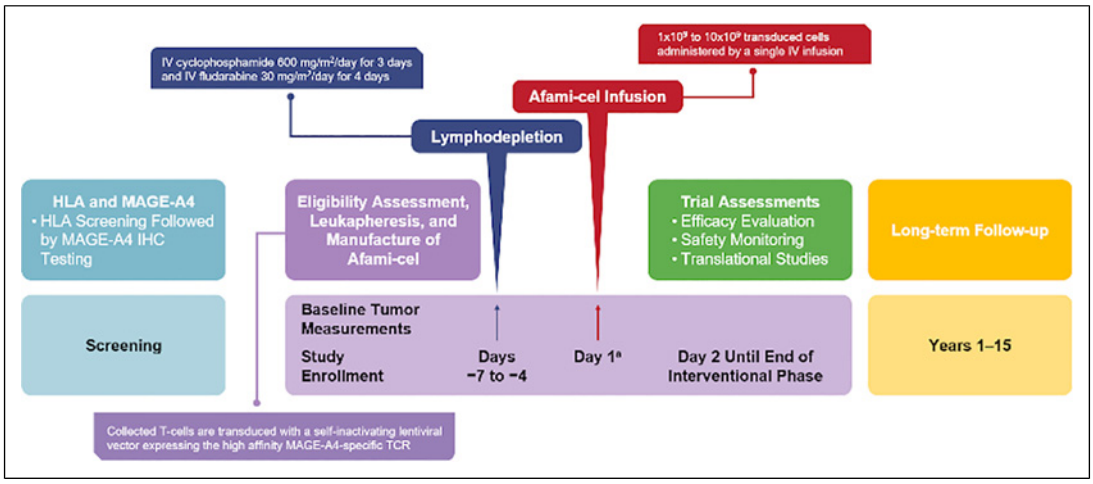

Fig. 2. SPEARHEAD-1 Trial Design (SPEARHEAD-1 study in subjects with advanced synovial Sarcoma or myxoid/round cell liposarcoma, NCT04044768).

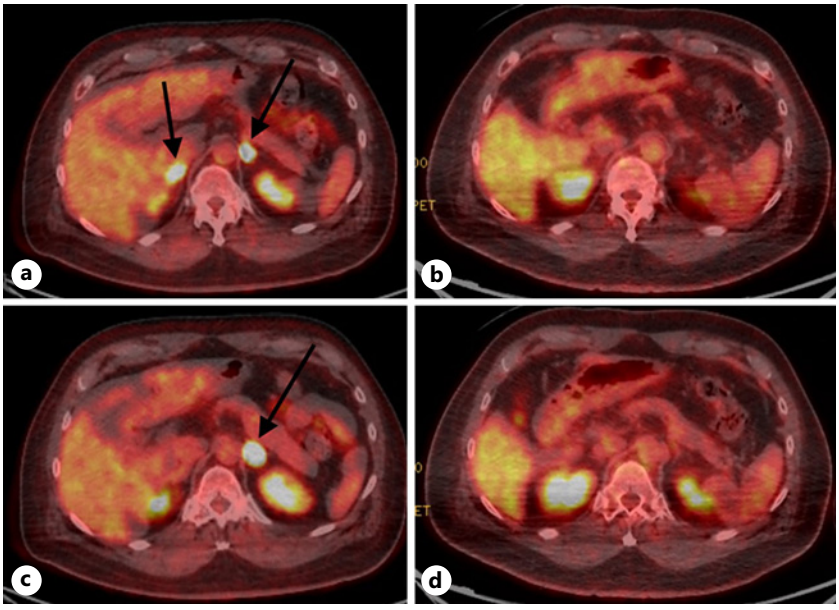

Fig. 3. Adrenal glands before and after completion of rituximab. (Left – March 2022, right – June 2022). Top images highlight the metabolic resolution of right adrenal nodule, and bottom images highlight the decrease of left adrenal nodule. Arrows highlight hypermetabolic adrenal nodules. **a** Right adrenal nodule in March 2022. **b** Right adrenal nodule in June 2022. **c** Left adrenal nodule in March 2022. **d** Left adrenal nodule in June 2022.

For the new diagnosis of secondary EBV LPD, he completed 4 weekly doses of rituximab 375 mg/m^2 in April 2022. PET scan in June showed resolution of lymphoproliferative disease to treatment with metabolic resolution of the right adrenal lesion and decreased size and metabolic uptake of the left adrenal lesion (Fig. 3). Scan also showed interval disease progression off therapy while recovering from trabectedin toxicity with growing pleural and pulmonary nodules, and new hypermetabolic right cervical lymph node.

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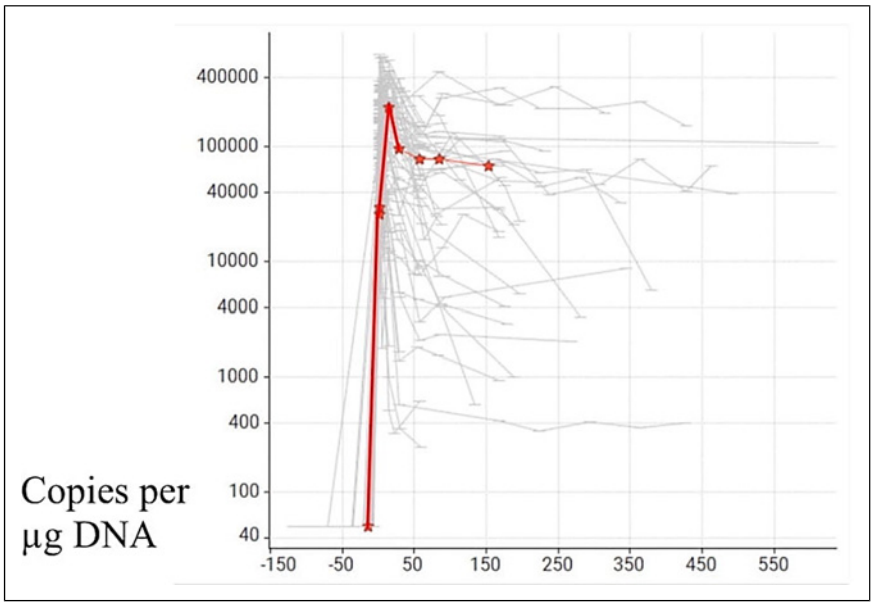

Fig. 4. Persistence profile of subject versus SPEARHEAD-1 cohort 1 patients with patient case highlighted.

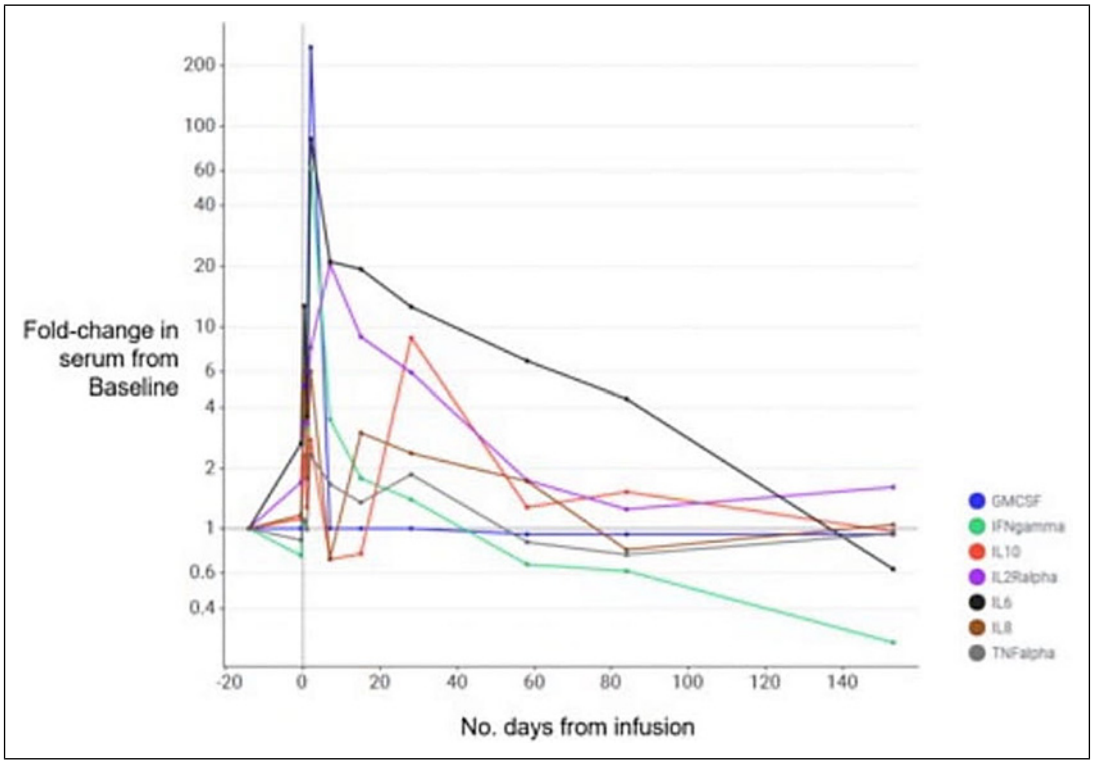

Fig. 5. Serum cytokine levels pre- and post-afami-cel treatment.

On study entry, the patient was CMV IgG and EBV IgG positive (IgM negative). Peak CMV was 2002 IU/ML in January 2022 and peak EBV 3450 in March 2022. In April, following initiation of rituxan CMV and EBV were undetectable and in June 2022 there was undetectable CMV and low positivity EBV, and the LPD event was considered resolved.

Conclusion

Analysis of adrenal biopsy was negative for MAGE-A4 expression. Bone marrow biopsy was negative for involvement by EBV+ LPD. Analysis of the subject's PBMC-derived samples for lentiviral vector showed persistence profile similar to that for other study patients on study. Peak of ~221,000 copies per mg DNA at 2 weeks post-infusion had transiently reduced to ~68,000 copies by ~22 weeks post-infusion (Fig. 4).

Measurements of cytokine levels in subject-derived serum samples taken pre- and post-afami-cel infusion showed transient post-infusion changes in several markers. Greatest magnitude of increase relative to baseline was noted for IFNγ, GM-CSF, and IL-6 (Fig. 5). Peak levels typically occurred within the first week post-infusion and returned toward baseline. Temporal profile for this subject was consistent with other study patients.

The event of LPD was considered related to cyclophosphamide, fludarabine, and afami-cel. This event was likely driven by immunosuppression from chemotherapy agents and could likely have occurred after lymphodepletion for any other therapy, but causality to T-cell therapy cannot be excluded. For patients who have immunosuppression driven by chemo-therapy, viral replication driven events are a potential risk with this therapy. New cellular therapies present promising treatment options for patients, and adverse events should be monitored carefully. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533129).

Statement of Ethics

This study protocol was reviewed and approved by Stanford Institutional Review Board, approval ID #34465. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.Z. and K.G. contributed to conception of the work, data interpretation, and drafting of the manuscript. G.J. participated in data acquisition and data analysis. All authors were involved in revision of the manuscript, approved the final version of the manuscript to be published, and agreed to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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