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First reported case of a spontaneous and healthy pregnancy in a woman with persistent CAR T-cells 5 years after treatment for diffuse large B-cell lymphoma

Ethan Abraham Canty ,[1] Lori Broderick,[2] Daniel Flaherty,[3] Marin Xavier,[4] Sunita D Nasta,[5,6] Lina Dajani,[7] Andrew A White[8]

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For numbered affiliations see end of article.

Correspondence to
Dr Ethan Abraham Canty; ethan.canty7@gmail.com

ABSTRACT

Chimeric antigen receptor T-cell (CAR T-cell) therapy has significantly advanced cancer treatments and remission rates; however, questions exist regarding the impacts on both fertility and immune effects on infants born to mothers who have undergone CAR T-cell therapy. There are no known reported cases of persistence of CAR T-cells after cancer therapy in pregnancy. Here, we present a case of a woman with relapsed refractory diffuse large B-cell lymphoma who undertook an experimental CAR T-cell therapy, had persistence of CAR T-cells 5 years after achieving remission, spontaneously became pregnant and delivered a healthy male infant. Our case provides an example of a healthy pregnancy despite the persistence of CAR T-cells and the resultant healthy newborn without evidence of immunologic or other health effects from the CAR T-cells.

Chimeric antigen receptor T-cell (CAR T-cell) therapy for cancer treatment has provided significant advancements in the treatment and remission of several types of cancer.[1] CAR T-cells typically persist for a few months after undergoing infusion; however, some studies have shown persistence for many years after therapy.[2–4] Given the possibility of extended persistence, some women of childbearing potential may desire pregnancy while active CAR T-cells remain. Limited data exists regarding fertility outcomes and safety.[5] There is no established fertility guidance for patients who have undergone CAR T-cell therapy for cancer treatment and no research on the impact of CAR T-cells on a developing fetus.[5] We discuss a case of a woman in her early 30s with a history of diffuse large B-cell lymphoma treated with an experimental CAR T-cell therapy with persistent CAR T-cells despite treatment 5 years prior, who subsequently became pregnant and gave birth to a healthy boy.

CASE

A healthy woman in her early 30s was diagnosed with diffuse large B-cell lymphoma. She initially underwent six cycles of DA-EPOCH-R, only took leuprorelin for fertility preservation, but failed to achieve metabolic complete response. She was randomized to a clinical trial (ZUMA-7 trial) using axicabtagene ciloleucel CAR T-cell therapy to treat refractory diffuse large B-cell lymphoma and achieved metabolic complete response.[6] She developed persistent CD19+aplasia with symptomatic hypogammaglobulinemia requiring intravenous immunoglobulin (IVIG) replacement. After two separate hospitalizations for aseptic meningitis and debilitating headaches after IVIG, she transitioned to weekly subcutaneous immunoglobulin replacement with significant improvement in IVIG related side-effects. Though her B-cell aplasia and hypogammaglobulinemia were assumed to be secondary to CAR T-cell therapy, a pre-existing subclinical common variable immunodeficiency could not be excluded. No pathogenic variants on a broad genetic immunodeficiency panel of 417 genes were found 5 years after CAR T-cell therapy. Without hormonal therapy or fertility treatment, she presented with a spontaneous pregnancy 5 years after treatment. Follow-up laboratories demonstrated CAR T-cells (CD3+FMC63+) that were 0.1% of lymphocyte gate and 0.0% of total cells with an absolute count of 4 cells/µL of CD19+CAR T-cells and 0 CD19+CD22+ B cells. T-cell clonality screening confirmed the presence of CAR T-cells.

The pregnancy was complicated by placenta previa and third trimester bleeding, but she ultimately delivered the baby at term. She also had persistent presence of CAR

Table 1 Lymphocyte subset panel and immunoglobulins at birth—mother and infant

	Mother	Infant
Absolute CD3	1860 (570–2400) cells/µL	3627 (1400–6800) cells/µL
Absolute CD4	657 (430–1800) cells/µL	2696 (1000–4800) cells/µL
Absolute CD8	1058 (210–1200) cells/µL	821 (200–2700) cells/µL
CD4:CD8 ratio	0.62 (0.8–3.9)*	3.35 (1.00–2.6)*
Absolute CD19	0 (91–610) cells/µL*	620 (140–2000) cells/µL
Absolute CD45RA	246 (150–870) cells/µL	2464 (900–4500) cells/µL
Absolute CD45RO	354 (190–1050) cells/µL	111 (98–1300) cells/µL
Absolute natural killer cells	149 (78–470) cells/µL	324 (500–3100) cells/µL*
IgG	724 (552–1631) mg/dL	792 (397–1765) mg/dL
IgM	11 (33–293) mg/dL*	6 (6–21) mg/dL
IgA	16 (65–421) mg/dL*	<5 (5–34) mg/dL*

*Abnormal value.

T-cell DNA throughout the pregnancy. Questions arose regarding the potential impact of CAR T-cells on the baby if they crossed the placenta. With this in mind, at delivery, both mother (G5P3) and infant (37.0 weeks gestation) were tested for the presence of CAR T-cells in blood and mother's breast milk, and both mother and infant had their T and B-cell subsets evaluated at delivery. We used the Eurofins/Viracor ExPeCT anti-CD19 (FMC63) CAR T Test to assess the presence of CAR T-cells. The mother had 205.3 copies/µg CAR T-cells in her blood, 30.19 copies/µg in her breast milk, and continued to have undetectable CD19+B cells (table 1). The male infant had 0 copies/µg CAR T-cells in his blood and normal T and B-cell subsets for age suggesting no transplacental migration of maternal CAR T-cells (table 1). Given the presence of CAR T-cells in the breast milk and the unknown risk this could confer to the infant, the mother elected not to breastfeed to reduce the risk of CAR T-cell engraftment into the infant via the gastrointestinal tract. Neither the mother nor the infant experienced peripartum complications.

DISCUSSION

CAR T-cell therapy is an expanding modality for treating oncologic processes and research is currently ongoing for the treatment of rheumatologic conditions,[7 8] but limited data exists on the long-term fertility impact on women who undergo CAR T-cell therapy. We present the first case of a woman successfully treated with CAR T-cell therapy for diffuse large B-cell lymphoma who spontaneously became pregnant and gave birth to a healthy infant, despite persistence of CAR T-cells. Her infant did not have the presence of, nor evidence for immunologic effect of the CAR T-cells at birth.

Recent data indicates that CAR T-cells can be persistent post-treatment, but the length of persistence depends on the product used and the oncologic process being treated. Patients with chronic lymphocytic leukemia have had CAR T-cells persist for 10 years.[2] In contrast, patients with B-cell lymphoma[5] or acute lymphoblastic leukemia[3] have CAR T-cells observed for shorter durations; only 6 months or 2 years, respectively. When comparing the different types of CAR-T cell therapies, one study found that 4-1BB-based CAR T-cell products, such as Kymriah (tisa-cel), may persist for several years when compared with CD28-based CAR-T cells (eg, axi-cel) which show shorter persistence.[9] Overall, recent data suggests that for hematological malignancies, persistence of CAR T-cells may correlate with improved outcomes and survival; however, this has not been fully validated.[10 11] Specifically for B-cell lymphoma, persistence at 6 months post-therapy completion may correlate with improved survival rates.[9] In our case, the CAR T-cell persistence may explain the treatment's long-term success, but further research is necessary.

Long-term effects of CAR T-cell therapy on the immune system are still being studied, but recent data indicates patients may experience various immunological and hematologic complications after CAR T-cell therapy. Cytopenias have been found to range anywhere from 1% to 66.7% after day 90 of CAR T-cell infusion, and this may be driven by both CAR T-cell effects and prior lymphodepleting chemotherapy.[12 13] At 1-year post-infusion, 60% of patients exhibited persistent CD4+T-lymphocyte depletion (<200 cells per µL).[14] Conversely, CD8+T-lymphocytes exhibited swifter recovery, resulting in a skewed CD4/CD8 ratio (<1.0) observed in 66.7% of patients by 18 months. Notably, the duration of CD4+T-lymphocyte depletion significantly correlated with advanced age, but not with prior treatment lines. Furthermore, a low CD4+count did not demonstrate a negative association with clinical response to CAR-T therapy.[14] Our patient had normal CD4 and CD8 cells post CAR T-cell therapy and has remained with normal numbers and function, based on normal responses to tetanus and mitogen stimulation.

CAR T-cell therapy has shown significant B-cell aplasia. Mechanistically, CAR T-cells can be engineered to target the CD19+antigen expressed on both malignant and healthy B cells. This inherent targeting leads to an anticipated 'on-target, off-tumor' effect—prolonged B-cell aplasia. Up to 98% of patients experience B-cell aplasia within 2 weeks to 1 month after CAR T-cell infusion, potentially persisting for months or even years.[12] The peripheral blood CD19+CAR T-cell DNA copy number negatively correlated with CD19+cell counts, suggesting a link between B-cell aplasia and CAR T-cell persistence.[15] One study found that B-cell aplasia served as a superior indicator of CAR T-cell persistence compared with flow cytometry in a cohort of 30 B-cell acute lymphoblastic leukemia (B-ALL) patients at the 1 year mark.[15]

Interestingly, all patients achieving response exhibited B-cell aplasia, with a 73% probability of relapse-free B-cell aplasia at 6 months.[15] Conversely, loss of B-cell aplasia preceded or coincided with clinical/radiographic relapse in 61.9% of patients, independent of CD19 expression on the relapse biopsy.[16]

B-cell recovery post-CAR T-cell therapy may not equate to complete functional restoration. One study reported B-cell dysfunction in some patients, evidenced by low IgM and/or IgA serum levels and a defective response to *Salmonella typhi* vaccination.[17] Recovered B cells were predominantly naïve.[17] This suggests that functional B-cell reconstitution might take longer than flow cytometry might suggest.[17]

Agammaglobulinemia is very common after CD19 antigen targeting CAR T-cell therapy. At baseline, 27.6% of patients exhibited IgG levels below 400 mg/dL in one study. Following CAR T-cell infusion, IgG levels reached their nadir at 6 months,[16] with another study showing reduced serum IgG levels through the first 9 months after axicabtagene ciloleucel infusion.[14] Of those patients, 44.4% failed to recover serum IgG levels within 18 months.[14] Among patients with normal baseline IgG levels, a significant proportion (29.4%) developed new-onset hypogammaglobulinemia (low IgG) with a median time of 2 months post-infusion.[14]

Fertility data post-chemotherapy depends on several factors, including type of chemotherapy, ovarian suppression, cryopreservation, and assisted reproductive technology.[18 19] Spontaneous pregnancies or those resulting from assisted reproductive technologies range from 20% to 55%.[20 21] Some efficacy in fertility preservation has been shown with ovarian suppression with gonadotropin-releasing hormone antagonists during chemotherapy; however, its impact on long-term fertility is still being reviewed.[18]

Long-term fertility data of patients treated with immunotherapy and CAR T-cell therapy for oncologic diseases is very limited, and there are no established guidelines for fertility preservation.[22 23] Spontaneous pregnancies after CAR T-cell therapy have rarely been reported in the literature. One survey of 66 centers using CAR T-cell therapy found that seven patients became pregnant with a total of five live births.[5] Only two of these live births came from the patient's own eggs.[5] Thus, future research is warranted on long-term fertility data for both men and women who receive CAR T-cell therapy. Our case provides a compelling example of the potential for spontaneous pregnancies in women with diffuse large B-cell lymphoma treated with chemotherapy but cured with CAR T-cell therapy. Furthermore, new guidelines recommend CAR T-cell therapy as second-line treatment without prior high-dose chemotherapy with stem cell salvaging, increasing the number of patients encountered with similar presentations as ours.

No data is available on the impacts of persistent CAR T-cells on a developing fetus and newborn. At delivery, the infant's blood tested negative for CAR T-cell DNA, suggesting that minimal to no CAR T-cells had crossed the placenta to affect the infant, to the best of our knowledge. Assessment of lymphocyte subsets at birth demonstrated normal cell numbers for age, including normal CD19+B cells, which, if the CAR T-cells had been present, would have theoretically depleted these cells. However, more data is required to assess the potential impact of CAR T-cells on a developing fetus and long-term outcomes.

Evidence of CAR T-cells was present in the breast milk in our patient, which prompted discussion on the safety of breastfeeding the infant. Data suggests that the acidic environment of the stomach creates a toxic environment for T cells.[24] Yet, cytotoxic T lymphocytes (CTLs) found in maternal breast milk have demonstrated gut-homing behavior towards Peyer's patches with significant capacity to produce inflammatory and cytolytic markers compared with the CTLs generated by the infant.[25] One study demonstrated that labeled T lymphocytes did not cross the gut wall of infant mice and suggested maternal T lymphocytes do not affect the infant via gut-border crossing.[26] In contrast, another study showed that T lymphocytes could survive the stomach acidity, and had a propensity to migrate to the spleen and thymus.[27] With shared decision-making with the mother, the decision was made in our case to not breastfeed due to the presence of CAR T-cells in the breast milk and the theoretical risk of these CAR T-cells affecting the baby via the gut. However, further research is warranted on whether CAR T-cells can cross the intestinal barrier of infants who are breastfed.

This case is the first known case in the literature of a woman treated with CAR T-cell therapy for diffuse large B-cell lymphoma with resultant remission, persistent B-cell aplasia and hypogammaglobulinemia, who had a spontaneous pregnancy with resultant healthy infant. This case demonstrates the potential for patients with a history of cancer treated with CAR T-cells to undergo a safe pregnancy, including those with prolonged persistence of CAR T-cells after treatment. Furthermore, we highlight a healthy infant who, despite the mother having persistent CAR T-cells in her serum as well as breast milk, did not show evidence of CAR T-cells nor immunologic effects, such as B-cell aplasia. Further follow-up is planned. This case highlights the ongoing need for investigations into CAR T-cell persistence, tissue distributions and guidelines for post-oncologic therapy management of patients of childbearing age.

Author affiliations
[1]Allergy, Asthma and Immunology, Scripps Green Hospital, La Jolla, California, USA
[2]Allergy and Immunology, Rady Children's Hospital, San Diego, California, USA
[3]Internal Medicine, Scripps Mercy Hospital, San Diego, California, USA
[4]Hematology/Oncology, Scripps Clinic, San Diego, California, USA
[5]Lymphoma Program, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA
[6]Hematology/Oncology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA
[7]Internal Medicine, Scripps Clinic, San Diego, California, USA
[8]Allergy, Asthma and Immunology, Scripps Clinic, San Diego, California, USA

Contributors EAC assisted in patient care, designing of the article, and was the main writer of the article. LB provided guidance in patient care as an outside consultant, designing of the article, and editing and writing of the article. DF helped with writing and editing the article. MX provided direct patient care, assisted in designing of the article, and editing the article. SDN provided guidance in patient care as an outside consultant, designing of the article, and editing of the article. LD provided guidance on patient care and editing of the article. AAW provided direct patient care, guidance on designing of the article, and editing of the article. EAC (guarantor, ethan.canty7@gmail.com) takes full responsibility for the integrity of the data and the accuracy of the analyses presented in this manuscript.

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ORCID iD

Ethan Abraham Canty http://orcid.org/0000-0003-2711-7527

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