Pseudo-progressive bone lesion in a relapsed infant leukemia after chimeric antigen reseptor T-cell therapy

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Title

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Abbreviation

CAR T-cells	chimeric antigen receptor redirected T cells
ALL	acute lymphoblastic leukemia
EL	extramedullary lesion
CR	complete remission
BM	bone marrow
HLA	human leukocyte antigen
cGVHD	chronic graft-versus-host disease
CRS	cytokine release syndrome
HSCT	hematopoietic stem cell transplantation

To the Editor,

Chimeric antigen receptor redirected T cells (CAR-T cells) have enabled us to offer a promising treatment for relapsed or refractory acute lymphoblastic leukemia (ALL).[1] However, there is little information about adverse events associated with the administration of CAR T-cells.[2,3] The changes in extramedullary lesion (EL) of relapsed or refractory ALL after CAR T-cell therapy have been recognized only in a few cases.[4,5] We report herewith pseudo-progression as an augmented immune response to the EL in a boy with relapsed infant ALL after CAR T-cell therapy.

A 10-year-old boy received Tisagenlecleucel because of intractable treatment course of ALL. This patient had received a diagnosis of infant ALL with *MLL-ENL* fusion gene at age 4 months. Complete remission (CR) was obtained after the first induction therapy, but a bone marrow (BM) relapse occurred during the course of the salvage chemotherapy. At 14 months of age, he received umbilical cord blood transplantation from an unrelated human leukocyte antigen (HLA)-one locus mismatched donor that led to the second CR. He then underwent a haploidentical BM transplantation from his mother at age 2 because of the second BM relapse. The third CR was achieved after the last BM transplantation, but BM and testicular relapses of ALL occurred at age 7 years. Repeated infusions of mother's lymphocytes controlled the disease on the developing chronic graft-versus-host disease (cGVHD) until age 9 years, when EL including the left leg bone led to limping. Five courses of blinatumomab failed to control the progressive disease.

Tisagenlecleucel was administered in the non-remitting state following lymphodepleting chemotherapy with fludarabine and cyclophosphamide. Grade 2 cytokine release syndrome (CRS) developed with fever and dyspnea on day 3, and then required tocilizumab for the appreciable control. Prior to CAR-T therapy, his left leg with the bone lesion started to be swollen. The painful leg size increased with heat after CRS occurred. The second dose tocilizumab on day 6 and methylprednisolone on day 7 led to a defervescence and resolution of the affected leg pain. The local inflammation improved by day 14 to the size of contralateral leg (**Supplementary figure**). One month later, he obtained cellular and molecular CR without EL.

Pseudo-progression after immunotherapies have been described in malignant tumors including high-grade glioblastomas, non-small-cell lung carcinoma, and melanoma, but less commonly in hematological malignancies. **Table 1** summarizes all reported cases of leukemia and lymphoma that presented pseudo-progression during CAR-T therapy.[2-5] This patient showed a rapid enlargement of EL with heat and pain after administration of CAR-T cells. Clinical course and serum interleukin-6 dominant cytokine profile (*data not shown*) along with the time course of CRS indicated a pseudo-progression but not true-progression of EL. The present patient received CAR-T cells after hematopoietic stem cell transplantation (HSCT). He had controlable cGVHD without immunosuppressants on mixed donor chimerism (mother 99.3%) after repetitive HSCT at the time of CAR-T cell infusion. This condition might augment the immune response to leukemic cells. According to the CRS magnitude and EL sites, careful management are needed for pseudo-progression after CAR-T cell therapy.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest in association with this report.

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REFERENCES

1. Maude SL, Frey N, Shaw PA, et al. Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia. *N Engl J Med.*2014;371:1507-1517.

2. Wang J, Hu Y, Yang S, et al. Role of Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Predicting the Adverse Effects of Chimeric Antigen Receptor T Cell Therapy in Patients with Non-Hodgkin Lymphoma. *Biol Blood Marrow Transplant.*2019;25:1092-1098.

3. Danylesko I, Shouval R, Shem-Tov N, et al. Immune imitation of tumor progression after anti-CD19 chimeric antigen receptor T cells treatment in aggressive B-cell lymphoma. *Bone Marrow Transplant.* 2020;18- doi:10.1038/s41409-020-01156-y.

4. Denton CC, Gange WS, Abdel-Azim H, et al. Bilateral retinal detachment after chimeric antigen receptor T-cell therapy. *Blood Adv.* 2020;4:2158-2162.

5. Huang J, Rong L, Wang E, Fang Y. Pseudoprogression of extramedullary disease in relapsed acute lymphoblastic leukemia after CAR T-cell therapy. *Immunotherapy* 2021;13:5-10.

Figure legends

Supplementary figure A. Clinical presentation of the patient after the the

administration of CAR T-cells. **B, C.** MRI changes of the leg with pseudo-progression**;**

Before CAR-T treatment and After CAR-T treatment (one month after administration)

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`Tables Letter-pseudoPG CART 20210503 (2).pdf` available at https://authorea.com/users/412139/articles/520907-pseudo-progressive-bone-lesion-in-a-relapsed-infant-leukemia-after-chimeric-antigen-reseptor-t-cell-therapy

Supplementary figure