Acute Lymphoblastic Leukemia of the Central Nervous System Presenting with Rapid Weight Gain

Connor P. Hall[1] and Alan Friedman[1]

[1]Johns Hopkins University School of Medicine

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Connor P. Hall[1] and Alan D. Friedman[1]

[1]Division of Pediatric Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Correspondence: Alan D. Friedman, MD

Johns Hopkins University

CRB I, Rm. 253 1650 Orleans St. Baltimore, Maryland 21231 Phone: 410-955-2095; Fax: 410-955-8897 Email: afriedm2@jhmi.edu

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Abbreviations:

ALL	Acute Lymphoblastic Leukemia
CNS	Central Nervous System
BFM	Berlin-Frankfurt-Munster
COG	Children's Oncology Group
MUD	Matched Unrelated Donor
BMT	Bone Marrow Transplant
CAR	Chimeric Antigen Receptor
CBC	Complete Blood Count
WBC	White Blood Cell
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
TSH	Thyroid stimulating hormone
CRH	Corticotropin-releasing hormone
ACTH	Adrenocorticotropic Hormone
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
CSF	Cerebrospinal Fluid

To the editor,

Acute Lymphoblastic leukemia (ALL) of the central nervous system (CNS) often presents asymptomatically; however, CNS disease has also been noted to present with focal neurological defects or seizures.[1] Here, we present an unusual case of overt CNS ALL presenting with rapid weight gain which was completely reversed by administration of CNS-directed leukemia therapy.

A seven-year-old female with history of multiply relapsed pre-B acute lymphoblastic leukemia (ALL) and autism spectrum disorder was admitted with increased fatigue, weight gain, increased appetite, and shortness of breath. Her ALL history started when she was two years old in her native country and was initially treated per BFM ALL-IC 2009. She emigrated to the United States during maintenance therapy and finished per COG protocol AALL0932, Average Risk arm. Since that time, she has relapsed three times. The first occurred six months following her initial therapy, consisted of bone marrow and CNS relapse, and was treated with reinduction therapy followed by myeloablative matched unrelated donor (MUD) bone marrow transplant (BMT). The second relapse occurred in eleven months later, consisted of isolated bone marrow disease, and treated with anti-CD19 CAR-T cell therapy (brexucabtagene autoleucel) followed by a reduced intensity MUD BMT. Ten months after her second relapse, she had her third relapse, again consisted of isolated bone marrow disease, and was treated with blinatumomab and inotuzumab over a seven-month period.

One year later and one month prior to presentation, the patient was noted to be having increasing weight and fatigue. This progressed to the point where she was also noted to have dyspnea. She was also noted to have hyperphagia during this time. On the day of presentation, she developed acute abdominal pain prompting evaluation in the emergency department. She had vital sign irregularities, both tachycardia and tachypnea, although no visible distress. She also had a Cushingoid appearance. CBC was unremarkable, with WBC 8.9K/μL (5.5K-15.5K/μL), absolute neutrophil count (ANC) of 5450/μL (1500-8000/μL), and platelet count 378K (150K-350K/μL). She was mildly anemic, with hemoglobin 11.5 g/dL (11.7-13.8 g/dL), although at her baseline. She had mild elevation in her liver function tests, with AST and ALT 92 U/L (0-31 U/L) and 155 U/L (0-31 U/L), respectively. TSH was mildly elevated at 6.91 IU/mL (0.5-4.5 IU/mL), but Free T4 was normal at 0.8 ng/dL 0.8-1.8 ng/dL). Her chest radiograph was unremarkable. During her admission, she had additional labs to assess her CRH-ACTH-cortisol axis. Her morning cortisol was 26.2 μg/dL with adequate suppression to 1.2 μg/dL with dexamethasone. Her ACTH level was also normal at 34 pg/mL (9-57 pg/mL). She had a CT angiogram to assess for pulmonary embolus which was unremarkable. Lastly, to rule out leukemic involvement of her hypothalamic-pituitary axis or a secondary neoplasm given previous radiation treatment during BMT, a brain MRI was obtained which was unremarkable.

She was discharged after normalization of her vital signs, resolution of abdominal pain, and otherwise unremarkable evaluation. Ultimately, it was decided to send flow cytometry from her peripheral blood and bone marrow aspirate as well as the CSF. Peripheral blood flow cytometry and bone marrow aspirate flow cytometry showed 0.2% and 9.1% abnormal phenotypic cells consistent with a fourth relapse of precursor B-cell ALL. Cerebrospinal fluid analysis also demonstrated 3,114 WBCs/μL with flow cytometry, designating 99% as lymphoblasts. She was started on therapy as detailed in Figure 1A. Upon initiation of intrathecal therapy, she experienced a rapid reduction in CNS leukemia burden and weight (Figure 1A, 1B). She also received intermittent systemic chemotherapy (IV vincristine, oral dexamethasone, oral 6-mercaptopurine), but this was limited given toxicity (sluggishness) and need to preserve peripheral lymphocytes to allow T cell collection. She ultimately proceeded to anti-CD19 CAR-T cell therapy (tisagenleleucel) and achieved remission. She continues to demonstrate no evidence of disease two years later, with continued B-cell aplasia suggesting persistence of CAR T cells, and appropriate weight gain.

We surmise that this patient's rapid weight gain was caused by CNS leukemia, which corrected after administration of CNS-directed leukemia therapy. There have been other rare cases of leukemia presenting with weight gain reported in the literature, each associated with CNS disease.[2-5] We presume that this patient was experiencing hypothalamic obesity because of ALL in the CNS. It is well known that disruptions of the hypothalamus, including oncologic causes, can cause obesity associated with hyperphagia, also known as

hypothalamic obesity. Damage to the hypothalamus by tumors infiltrating the hypothalamus (craniopharyngioma, glioma, etc.), surgery, or radiation are more familiar to oncologists as the cause of this syndrome.[6] Although we did not see a mass on brain MRI or any other imaging signs suggestive of CNS leukemia, it is possible that there was leukemia infiltrate in that region causing a hypothalamic disruption. With the large number of leukemic blasts in the CNS, it is likely that she had diffuse brain parenchymal involvement leading to the clinical manifestations seen here, including rapid weight gain with associated hyperphagia (hypothalamic obesity) and some degree of autonomic dysfunction (tachycardia and tachypnea).

This case highlights the causative association between rapid weight gain and increased appetite with CNS ALL. While most children will remain asymptomatic with CNS involvement, the diagnosis of ALL should be considered with these unique presentations to expedite timely diagnosis and treatment.

Conflicts of Interest: The authors declare no conflict of interest.

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FIGURE LEGEND

FIGURE 1 (A) Drop in CNS leukemic blast count and patient weight after initiation of therapy (top); diagram of therapy provided (bottom). ITT, intra-thecal triple therapy; Cyt, intrathecal cytarabine; Cyt/HC, intrathecal cytarabine and hydrocortisone; DEX, dexamethasone; 6-MP, 6-mercaptopurine; VCR, vincristine. **(B)** Growth curve for the patient showing rapid weight gain over a six-month period, with resolution once CNS-directed therapy was initiated.