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Case Report

# Potential indication of chemotherapy for hypodipsia and arginine vasopressin deficiency secondary to hypothalamic-pituitary Langerhans cell histiocytosis: a case report and literature review

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## Highlights

- We report the sixth case of impaired OTT and AVD due to HP-LCH.
- This is the first case where hypodipsia resolved during chemotherapy for LCH.
- Hypodipsia and AVD due to solitary HP-LCH may be indications for chemotherapy.

**Abstract.** Hypothalamic-pituitary Langerhans cell histiocytosis (HP-LCH) is often associated with arginine vasopressin deficiency (AVD). Patients with AVD caused by HP-LCH rarely develop an impaired osmotic threshold for thirst (OTT). Improvement in OTT among such patients has not been reported in the literature. To our knowledge, here we report the first case of AVD due to HP-LCH in which hypodipsia resolved during chemotherapy. A nine-year-old Japanese girl presented with polydipsia, polyuria, anorexia, and hypernatremia (149.8 mEq/L) and was diagnosed with AVD secondary to HP-LCH. Visual analog scale examination showed a reduced OTT following the water deprivation test. During chemotherapy for Langerhans cell histiocytosis (LCH), serum sodium concentrations became stable between 138.9 and 142.9 mEq/L under the replacement of desmopressin. Repeated visual analog scale examinations showed that she experienced a sense of thirst at a serum sodium concentration of 142.3–144.6 mEq/L, at which she did not experience any thirst prior to the initiation of chemotherapy. These data suggest that chemotherapy directly improved the OTT in our patient. Improved mechanical compression or infiltration of the hypothalamus related to OTT may lead to the recovery of the sense of thirst. This report highlights the potential role of chemotherapy for solitary HP-LCH in patients with hypodipsia and AVD.

**Key words:** arginine vasopressin deficiency, hypodipsia, hypothalamic-pituitary, Langerhans cell histiocytosis

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## Introduction

Patients with Langerhans cell histiocytosis (LCH) develop single or multiple lesions throughout the body, including the bones, skin, or hypothalamus-pituitary tract. Hypothalamic-pituitary LCH (HP-LCH) is often associated with arginine vasopressin deficiency (AVD). The presence or absence of thirst is of great importance in the management of patients with AVD. Patients with a preserved osmotic threshold for thirst (OTT) spontaneously drink water to avoid hypernatremia, which can result in serious central nervous system complications, including subarachnoid or subdural hemorrhage. To the best of our knowledge, patients with AVD due to HP-LCH rarely develop impaired OTT, and no studies have reported an improvement in impaired OTT in such cases. To date, a robust therapeutic strategy for treating impaired OTT in patients with AVD due to HP-LCH has not been established. Here, we report a case of AVD caused by HP-LCH in which hypodipsia resolved during chemotherapy.

## Case Report

The patient was a healthy Japanese girl with normal intelligence. At 9 yr of age, the patient presented with polydipsia, polyuria, and anorexia. Her fluid intake ranged from 2,000 to 2,500 mL/d, and her 24-h urine volume was approximately 3,000 mL/d. She lost 3 kg in a month prior to the presentation. Her growth chart showed insufficient weight gain but normal growth velocity (**Fig. 1**). During the initial examination, the patient had a serum sodium concentration of 149.8 mEq/L. Water deprivation test showed a urine specific gravity of 1.004, urine osmolality of 117 mOsm/L, and plasma arginine vasopressin (AVP) of 0.5 pg/mL, despite serum sodium concentration of 151 mEq/L and serum osmolality of 305 mOsm/L. The visual analog scale (VAS) indicated a reduced OTT (1, 2) and hypodipsia. She had little thirst but did not want to drink water at a serum sodium concentration of 151–151.5 mEq/L (**Fig. 2A**). Contrast-enhanced magnetic resonance imaging revealed enlargement of the pituitary gland and stalk (**Fig. 3A**). Pathological findings of the biopsy

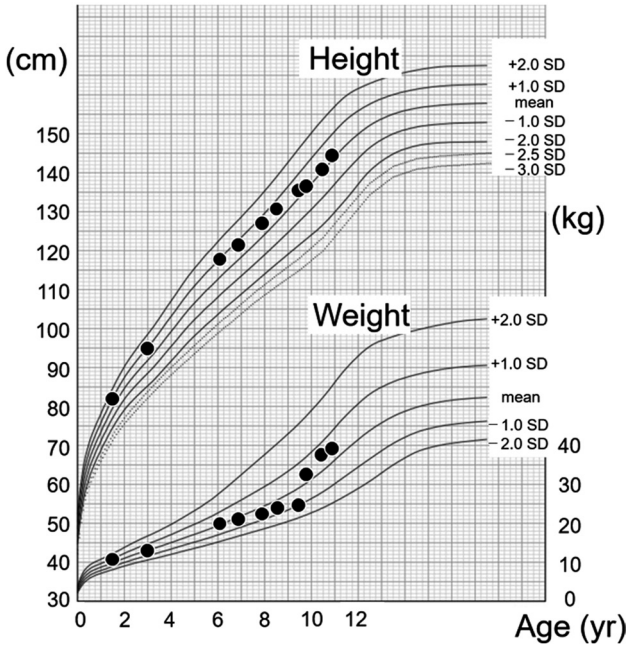


**Fig. 1.** Growth chart. Patient growth was evaluated according to the growth charts of Japanese girls (24).

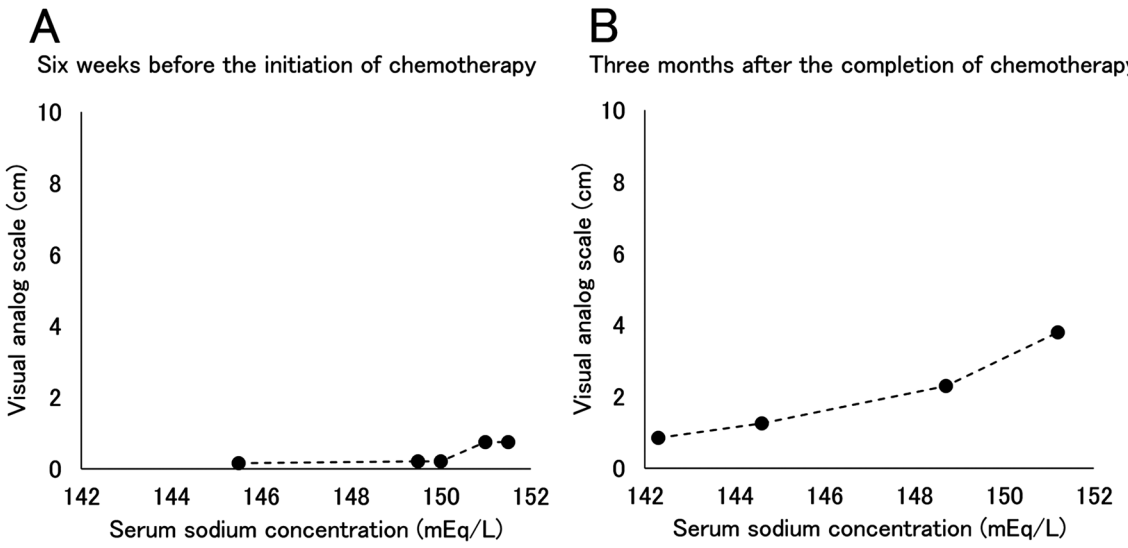


**Fig. 2.** Visual analog scales of thirst assessments before and after chemotherapy. During the water deprivation or hypertonic saline tests, the patient marked her subjective thirst level on a 10-cm scale. A: Six weeks before the initiation of chemotherapy, she had little thirst but did not want to drink water with a serum sodium concentration of 151–151.5 mEq/L. B: Three months after the completion of chemotherapy, she felt thirsty at a serum sodium concentration of 142.3–144.6 mEq/L and wanted to drink water at a serum sodium concentration of 148.7 mEq/L.


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specimens obtained from the pituitary stalk included lymphocyte-like cells with deformed nuclei that were positive for S100 and CD1a and negative for CD3 and CD20, confirming LCH. An endocrinological examination revealed a mild growth hormone deficiency. Positron emission tomography-computed tomography and other imaging studies did not reveal any other lesions. She was diagnosed with AVD and impaired OTT due to HP-LCH and was started on 240 μg of oral desmopressin per day. To avoid severe hyper- or hyponatremia, her body weight was measured twice daily, and water intake was controlled. Chemotherapy was administered according to the JLSG-02 protocol for multisite, single-system, or multisystem disease (3). After induction, a regimen comprising 6 wk of combined treatment with cytosine arabinoside, vincristine, and prednisolone reduced pituitary gland and stalk size (**Fig. 3B**). Subsequently, 24 wk of maintenance regimen A, comprising cytosine arabinoside, vincristine, prednisolone, and methotrexate, was administered. Then, 24 wk of maintenance C regimen comprising vinblastine, prednisolone, methotrexate, and 6-mercaptopurine was administered. The chemotherapy was completed without interruption after 12 mo. Body weight increased rapidly with no apparent increase in growth velocity (**Fig. 1**). During chemotherapy and the follow-up sessions, strict weight control was no longer required. Although she was allowed unrestricted water intake, sodium level was maintained at 138.9–142.9 mEq/L. Oral desmopressin dosage requirements remained unchanged. The enlargement of the pituitary gland and stalk did not recur. The growth rate was maintained at normal levels of insulin-like growth factor 1. Anterior pituitary function, including growth hormone levels, was not impaired. Three months after the completion of chemotherapy, AVP secretory capacity did not improve in the hypertonic saline test. The maximum serum sodium concentration was 151.2 mEq/L, serum osmolality was 308 mOsm/L, and plasma AVP was less than 0.4 pg/mL. Meanwhile, according to VAS evaluation, she felt a sense of thirst at a serum sodium concentration of 142.3–144.6 mEq/L, at which point she did not feel any thirst prior to the initiation of chemotherapy. With a serum sodium concentration of 148.7 mEq/L, the patient wanted to drink water (**Fig. 2B**). This suggests that her sense of thirst had normalized.

## Ethics statement

This study complied with all relevant national regulations and institutional policies as well as the

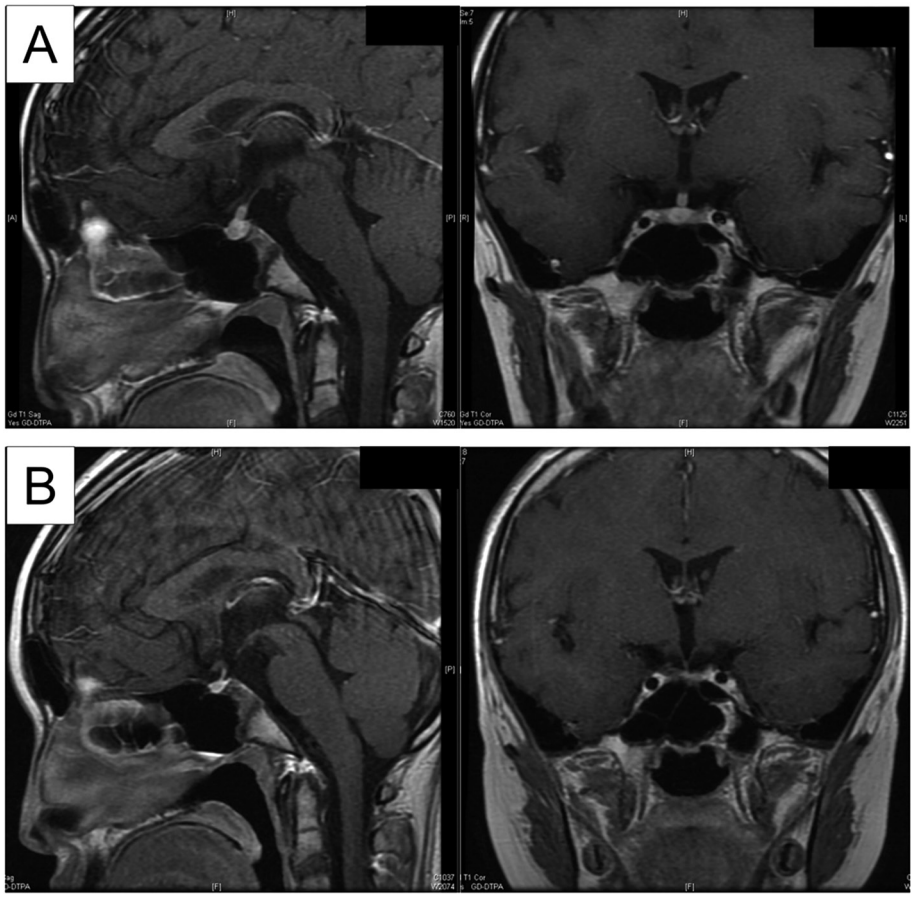


**Fig. 3.** Contrast-enhanced T1-weighted magnetic resonance imaging. A: Before chemotherapy initiation, the pituitary gland and stalk were enlarged. No lesions were observed in the hypothalamus. B: During chemotherapy, the pituitary gland and stalk reduced in size. No newly developed lesions were observed in the hypothalamus.


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tenets of the Helsinki Declaration. We received approval from the ethics committee of Keio University School of Medicine (20150104) and provided opt-out statements.

## Literature Review

A literature search of PubMed and Google Scholar was conducted in October 2023. The following search terms were used: "adipsia," "adipsic," "hypodipsia, " "hypodipsic," "diabetes insipidus, " "arginine vasopressin deficiency," and "Langerhans cell histiocytosis." We found five patients with AVD due to HP-LCH reported as adipsic (4–8), and no patients were hypodipsic. The clinical manifestations of patients were reviewed (**Table 1**).

## Discussion

Herein, we report the first case of impaired OTT that resolved during chemotherapy for LCH. Although we cannot exclude the possibility of spontaneous resolution of the hypothalamic-pituitary lesion, as shown in a single cutaneous or bone lesion of LCH (9), chemotherapy for LCH likely improved the OTT in our patient. We assume that chemotherapy improved the mechanical compression or infiltration of the hypothalamus related to OTT, leading to the recovery of the sense of thirst. Previous studies have shown that i) adipsia in a patient with neurosarcoidosis resolved following anti-tumor necrosis factor-α therapy (10) and ii) postoperative impairment of OTT resolved over time in 10 patients with craniopharyngioma or anterior communicating artery aneurysm (11–15). The resolution of impaired OTT in these cases suggests the plasticity of the OTT, thereby supporting our speculation.

It is possible that the mild hypernatremia observed in this patient was associated with the reversibility of the impaired OTT. On initial examination, the patient with polydipsia and polyuria had a serum sodium concentration of 149.8 mEq/L. Based on the VAS score before chemotherapy, she felt a little thirst, and her serum sodium concentration was 151–151.5 mEq/L. We speculated that when the serum sodium concentration is higher than 151–151.5 mEq/L, she could feel thirsty and drink as much water as needed. Notably, her sodium concentration before replacement or chemotherapy was lower than three 'adipsic' patients with AVD due to LCH (156–181 mEq/L) (**Table 1**). These findings imply that the impaired OTT in our patient was milder than that in previously reported adipic patients. Therefore, we assumed that mildly impaired OTT can be resolved by chemotherapy.

This report highlights the potential usefulness of chemotherapy for the treatment of HP-LCH. The general outline of the therapeutic management of LCH is as follows: Chemotherapy is recommended for patients with multi-site, single-system, or multi-system lesions. Chemotherapy is particularly beneficial for patients with hypothalamic-pituitary lesions, which can help prevent additional hypothalamus-pituitary dysfunction, although it does not ameliorate the current dysfunction (16, 17). For patients with only a solitary bone lesion, such as one in the hands or feet, spontaneous resolution may occur and no treatment is acceptable. Meanwhile, the indications for chemotherapy for solitary hypothalamic-pituitary or cranial bone lesions remain controversial,

**Table 1.** Clinical information of previously studied patients with arginine vasopressin deficiency due to hypothalamic-pituitary LCH reported as "adipsic," and the current patient

| Reference | Sex | Age (yr) | Serum sodium concentration (mEq/L) | Serum osmolality (mOsm/L) | Urine osmolality (mOsm/L) | Arginine vasopressin deficiency | Treatment for LCH | A sense of thirst | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Before treatment | During or after treatment |
| 4 | Male | 22 | NA | NA | NA | + | NA | Adipsic | NA |
| 5 | Female | 36 | 156 | 322 | 100 | + | Chemotherapy (cytarabine), radiotherapy | Adipsic | NA |
| 6 | Male | 46 | NA | NA | NA | + | Chemotherapy (etoposide), radiotherapy | Adipsic | NA |
| 7 | Male | 41 | 181 | 360 | NA | + | Chemotherapy (vinblastine, prednisolone) | Adipsic | NA |
| 8 | Female | 12 | 165 | 316–326 | 143–191 | + | Chemotherapy (prednisolone) | Adipsic | Adipsic |
| Our case | Female | 9 | 149.8 | 298 | 70 | + | Chemotherapy (cytosine arabinoside, vincristine, prednisolone, methotrexate, vinblastine, 6-mercaptopurine) | Hypodipsic | Normodipsic |

LCH, Langerhans cell histiocytosis; NA, not available.


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and active surveillance is an alternative strategy (18, 19). There are only a few series with small numbers of patients or case reports regarding the treatment of LCH with central nervous system lesions (19). In our case of solitary HP-LCH, the mildly impaired OTT was reversed during chemotherapy, implying that chemotherapy could be an alternative strategy for patients with solitary HP-LCH and mildly impaired OTT. Further studies are necessary to determine whether the mildly impaired OTT in patients with solitary HP-LCH is indicated for chemotherapy.

We objectively assessed the patients' OTT using the VAS. Several reports have used the VAS to evaluate the degree of thirst in pediatric patients. However, the appropriate VAS method for pediatric patients aged ≤ 10 yr has not been fully established (20–23). Based on our experience with the present case, we identified two important factors when using the VAS to evaluate OTT in pediatric patients. First, we must confirm that pediatric patients have sufficient comprehension ability prior to the VAS evaluation. The degree of thirst in the patients should be documented using a scale. Second, we must consider the methodological limitations of VAS evaluation that might lead to inconsistencies between different examinations on different days because the same degree of thirst may not be marked at the same position on the scale. This limitation must be recognized when assessing the effects of treatments for hypodipsia or adipsia. Despite these limitations, we believe that the VAS is a valuable tool for objectively evaluating OTT in pediatric patients.

In conclusion, we reported the first case of impaired OTT resolution during chemotherapy for LCH. Patients with hypodipsic AVD secondary to HP-LCH are potential candidates for chemotherapy.

**Conflict of interests:** All authors declare no relevant financial relationships.

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