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Case Report

Central diabetes insipidus developing in a 6-year-old patient 4 years after the remission of unifocal bone Langerhans cell histiocytosis

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Abstract. A six-year-old boy was referred with a one-and-a-half months history of polyuria and polydipsia. At the age of two, he had a single lytic bone lesion in his femoral head, diagnosed as Langerhans cell histiocytosis (LCH) by biopsy at another hospital. As no other affected organs were detected and the affected bone lesion was self-limited, he was not followed up afterward and was doing well. He was diagnosed with diabetes insipidus (DI) by confirming hypernatremia (Na: 148 mEq/l) with hyperosmolar serum (s-Osm 298 mOSM/kg) and inappropriately diluted urine (u-Osm 205 mOSM/kg). His polyuria and polydipsia improved dramatically using the perioral diuretic hormone, and other pituitary functions were not impaired. Magnetic resonance imaging revealed an enlarged pituitary stalk. Sensitive and specific biomarkers of germ cell tumors, including alpha-fetoprotein, placental alkaline phosphatase, and ß-hCG in the cerebrospinal fluid, were not detected, indicating relapse of LCH. Genetic analysis revealed a BRAF V600E mutation in the primary bone lesion. We recommend systematic follow-up of patients with a history of LCH, even non-CNS single-system single-site disease, especially with BRAF V600E mutation.

Key words: diabetes insipidus, Langerhans cell histiocytosis, germinoma

Introduction

Langerhans cell histiocytosis (LCH) is a rare disease with an incidence of less than 10 per million per year (1, 2) and is characterized by the clonal proliferation of pathogenic Langerhans cells. The phenotypes and clinical courses are diverse, ranging from spontaneously remitting single-organ disease to life-threatening multisystem involvement (3). The most frequent central nervous system (CNS)-related complications of LCH are central diabetes insipidus (CDI). CDI may be present at the time of LCH diagnosis but often appears several years after the diagnosis of LCH. Patients with multisystem disease and/or CNS-risk lesions have a significantly increased risk of CDI (4, 5). CNS-risk lesions are craniofacial lesions, particularly in the ear, eye, and oral regions (6). On the other hand, in non-CNS risk single-system single-site affected LCH, the risk of CDI has been reported to be extremely low (7).

We report the case of a 6-yr-old boy who had a history of LCH with non-CNS risk single site bone lesion at 2 yr of age and developed CDI 4 yr after with no sign of disease.

Case Presentation

The patient was a 9-yr-old Japanese boy. At the age of 2 yr, he visited the orthopedic department of the university hospital because of left leg pain. The patient had a definitive diagnosis of LCH by biopsy of a left femur lesion, and the affected single bone lesion was self-limited. Since no symptoms other than leg pain were observed, the presence or absence of other lesions, including the pituitary, was not investigated. Subsequently, the patient was not placed on a regular check-up after 3 mo of follow-up at the orthopedic

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department. The patient had no signs of disease but presented with a half months history of polydipsia and polyuria at the age of 6 yr and 5 mo. His height was 117.5 cm (+ 0.3 SD), and his weight was 21.25 kg (+ 0.1 SD). His height velocity did not decline, but he presented weight loss after the onset of polydipsia and polyuria (**Fig. 1**). Initial investigations revealed hypernatremia (Na: 148 mEq/L), hyperchloremia (Cl: 113 mEq/L), and hyperosmolar serum (s-Osm 298 mOSM/kg) with inappropriately diluted urine (u-Osm 205 mOSM/kg).

Moreover, the 24-h urine volume was 7570 mL/m^2. Blood examination revealed normal complete blood counts and blood chemistry values, as described above. Complete CDI was diagnosed after a water deprivation test followed by pitressin stimulation (**Table 1**) and started treatment with oral l-deamino-8-D-arginine vasopressin (DDAVP), which improved polyuria. Magnetic resonance imaging (MRI) revealed an enlarged pituitary stalk with gadolinium enhancement and an absence of the posterior pituitary bright spot on T1 sequences (**Figs. 2A, B**), which suggested relapse of LCH. Alpha-fetoprotein (AFP), beta subunit human chorionic gonadotropin (ß-HCG), and placental alkaline phosphatase (PLAP) in the cerebrospinal fluid (CSF) were not detected. The anterior pituitary function was not impaired in the stimulating tests (**Table 2**). A skeletal survey suggested no evidence of bone lesions. He received systemic chemotherapy with the Special C regimen (8) to prevent progression to other CNS-related sequelae and is doing well with replacement therapy with oral DDAVP (120 µg/d) more than 3 yr after the onset of CDI. Subsequent genetic analysis using a biopsy specimen of a primary LCH lesion of the femur revealed the BRAF V600E mutation, which is reported to be found in almost half of LCH patients (9).

Discussion

CDI is a heterogeneous disease characterized by polyuria and polydipsia due to antidiuretic hormone or vasopressin deficiency. CDI has underlying causes such as brain tumors (including germinoma,

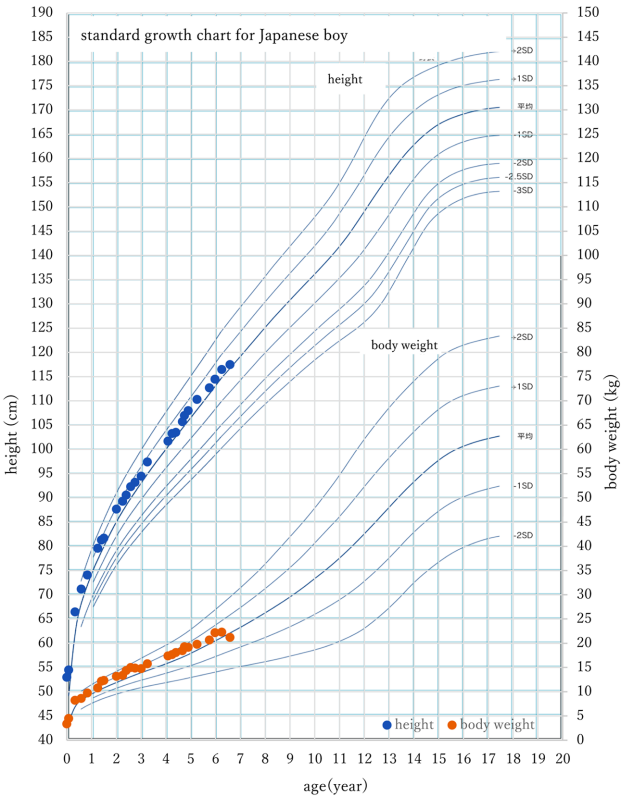

Fig. 1. Growth chart.

Table 1. A water deprivation test followed by pitressin stimulation

Time (h)	0	0.5	1	1.5	2.5	3.5	4.5
Body weight (kg)	21.5	21.4	21.1				
Urine volume (mL)		70	75	50	50	25	75
Urine-Osm (mOSM/kg)	152	159	156	313	539	427	215
Urine-SG	1.005	1.004	1.005	1.008	1.014	1.012	1.006
Serum-Osm (mOSM/kg)	298		300				
Serum-Na (mEq/L)	147		148				
AVP (pmol/L)	0.55		0.92				

Subcutaneous injection of pitressin 5 U/m^2 at 1 h.

Table 2. A stimulating test with L-arginine, CRH, TRH, and LHRH

	0 min	15 min	30 min	60 min	90 min	120 min
GH (ng/mL)	8.18		2.23	2.87	5.36	1.81
ACTH (pg/mlL)	22.4	196	180	82.8	26.6	12.6
Cortisol (µg/dL)	15.3	21.5	21.6	25.5	22.3	19.5
TSH (µIU/mL)	3.24		15.8	11.1	6.97	4.92
PRL (ng/mL)	14.12		49.08	31.18	16.96	13.45
LH (mIU/mL)	< 0.10		1.04	1.21	1.24	1.19
FSH (mIU/mL)	0.52		2.30	3.27	4.00	4.43

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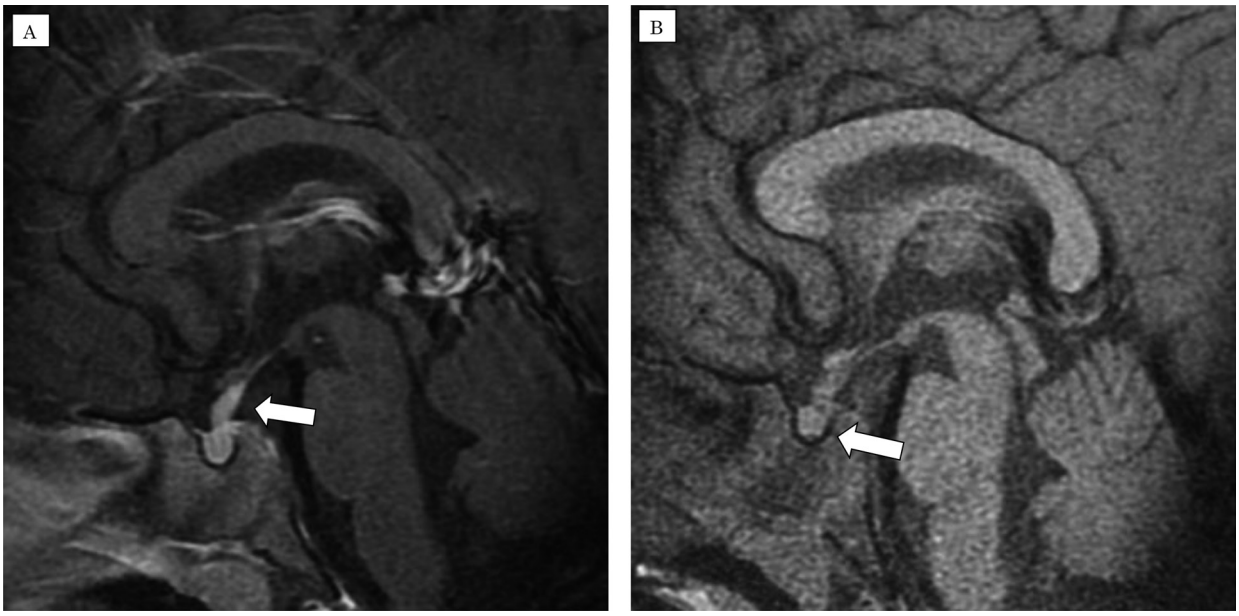

Fig. 2. A) An enlarged pituitary stalk with gadolinium enhancement (white arrow). B) Loss of the pituitary bright spot on T1 sequences (white arrow).

craniopharyngioma), Langerhans cell histiocytosis, sarcoidosis, lymphocytic infundibulo hypophysitis, trauma, congenital malformation, and familial/genetic CDI. CDI of unknown etiology is classified as idiopathic. The estimated frequency of idiopathic CDI varies widely, ranging from 3 to 50.6% (10–15). The differences may be due to MRI resolution, region, and follow-up period. Some cases diagnosed as idiopathic on the first MRI were later diagnosed as LCH or germinoma upon subsequent follow-up.

Germinoma presents CDI at a relatively higher frequency in Asians than in other regions. Among the CDI cases, germinoma was reported to account for 32% in Taiwan (12), 22% in China (15), and 8–11% in Europe and America (10, 11, 13, 14). It is known that ß-HCG in CSF is a sensitive and specific biomarker in differentiating germinomas. PLAP is used as a decisive biomarker to differentiate germinomas. The sensitivity and specificity of PLAP in CSF for germinomas were 94 and 97%, respectively, with a cutoff value of 30 pg/mL (16). Since PLAP and ß-HCG in CSF were negative in this case, the possibility of germinoma was considered extremely low. Idiopathic central diabetes insipidus should be differentiated from lymphocytic infundibulo-neurohypophysitis (LIN), in which anterior pituitary function is usually preserved (17). A definitive diagnosis was made by biopsy. Recently, it has been reported that autoantibodies to rabphilin-3A may serve as a biomarker for the diagnosis of lymphocytic infundibulo hypophysitis and be useful for the differential diagnosis of patients with CDI (18). However, it is not yet available for clinical application. As a limitation of this case report, the possibility of CDI due to other causes, including LIN, cannot be ruled out because no pathological diagnosis has been made.

The frequency of LCH in the causes of CDI has been reported to be 3–19%. On the other hand, CDI occurs in 12–19% of LCH patients (6, 19–21). It has been reported that multisystem and single-system diseases involving CNS-risk lesions, such as cranial bones, have a high risk of developing CDI (6). In contrast, LCH with single-system, single-site bone in non-CNS-risk lesions has an extremely low risk of CDI. In a previous study, none of the 99 patients diagnosed with the single-site bone disease with non-CNS risk developed CDI (7). Relapse occurred in 17.6, 18–36.8%, and 46–49% of the patients with the single-system unifocal disease, single-system multifocal disease, and multi-system disease, respectively (19, 22, 23). One study reported that 88% of relapses occurred within the first 2 yr of follow-up (19). Another study reported that relapse occurred during the first 10 yr after diagnosis (20). Although most relapses occur within 2 yr, there is still a risk of relapse afterward (23).

In this case, systemic evaluation for LCH, including pituitary MRI examination, was not performed at the age of two. However, there was no pain in the bone and no significant symptoms, such as fever, polydipsia, and polyuria. In the case of CDI, polydipsia and polyuria progress subacutely, and it is unlikely that CDI developed at the age of two years. Moreover, since there was no retardation in the growth rate, endocrinological abnormalities are unlikely to have occurred for many years.

BRAF encodes one of the kinases involved in the MAPK (RAS-RAF-MEK-ERK) signaling pathway and is considered a potential tumor driver gene. The BRAF V600E mutation is the most common in BRAF and is detected in about half of LCH cases and about 40% of single-system unifocal disease (9). A previous study

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reported that BRAF V600E was more frequently detected in advanced LCH, and CDI occurred at a higher rate in patients with BRAF V600E than in those with wild-type BRAF (24). Another study reported that the BRAF V600E mutation was associated with an increased risk of relapse (25). The recurrence of CDI in this patient might be associated with the BRAF V600E mutation.

Conclusion

Central diabetes insipidus is a serious complication of Langerhans cell histiocytosis. CDI has a severe impact on the quality of life of patients with LCH. Most CDI cases are irreversible and require replacement therapy with DDAVP for a lifetime (4). Long-term follow-up is recommended even in cases with non-CNS risk single-site bone lesions, especially those with the BRAF V600E mutation.

Conflicts of Interests: The authors have no conflicts of interest to declare.

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