

NOTE

Spontaneous Regression of Isolated Neurohypophyseal Langerhans Cell Histiocytosis with Diabetes Insipidus

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Abstract. In pediatric and adolescent patients, the most common causes for a thickened pituitary stalk with central diabetes insipidus are germ cell tumors, lymphocytic infundibuloneurohypophysitis (LIN), and Langerhans cell histiocytosis (LCH). We describe here a 13-year-old girl who had an abrupt onset of polyuria and polydipsia. Magnetic resonance imaging of the brain revealed thickening of the pituitary stalk, and loss of the physiological hyperintense signal of the posterior pituitary gland. Based on a histopathology, she was diagnosed as having LCH. Another LCH lesion was not detected. The prognoses for LCH patients with single-system and single-site are generally good so we decided on only simple observation. The lesion spontaneously regressed 3 months later, resembling a typical self-limiting course of LIN. In conclusion, the present case suggests that 1) radiological differential diagnosis between LIN and LCH is so difficult that histological confirmation is crucial for correct diagnosis, 2) some past cases of histologically-unconfirmed LIN can include LCH, 3) solitary neurohypophyseal LCH can shrink spontaneously up to near remission level.

Key words: Germ cell tumor, Lymphocytic infundibuloneurohypophysitis, Langerhans cell histiocytosis, Central diabetes insipidus, Spontaneous regression

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CENTRAL diabetes insipidus (CDI) is a rare disorder that may be caused by a variety of diseases. In pediatric and adolescent patients, up to 50% of cases are idiopathic [1], the most common known causes for the thickened pituitary stalk with CDI are germ cell tumors (GCT) [2, 3], lymphocytic infundibuloneurohypophysitis (LIN) [4], and Langerhans cell histiocytosis (LCH) [3, 5]. The differential diagnosis between these diseases using tumor markers and radiological examinations is difficult, and only histopathological proof leads to a definitive diagnosis. We report a case of spontaneous regression of isolated LCH on the in-

fundibulum with CDI. This case would have been misdiagnosed as LIN if a biopsy had not been performed.

Case report

A 13-year-old Japanese girl suddenly presented with polydipsia and polyuria on February 7, 2006. She was suspected of having diabetes insipidus by a local pediatrician and was referred to us for further examination and treatment. She was a well-developed and well-nourished girl. She had normal puberty development and regular menstruation, and had never experienced visual disturbance. The maximum urine osmolality remained at only 133 mOsm/kg in a 4-hour water deprivation test, and her plasma osmolality and arginine vasopressin were 291 mOsm/kg and 0.80 pg/ml, respectively. After a desmopressin test her urine osmolality had increased to 408 mOsm/kg and urine volume decreased. She was diagnosed as having CDI

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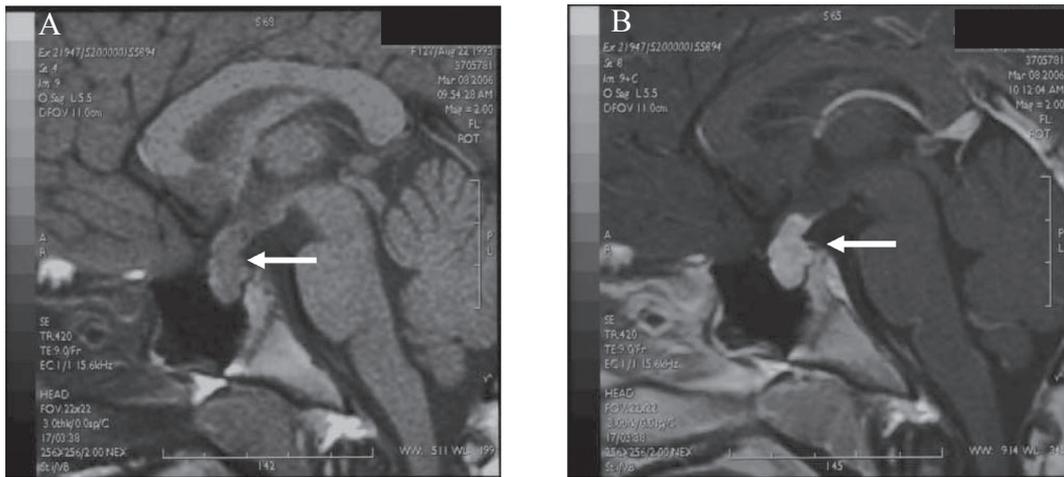


Fig. 1. T1-weighted magnetic resonance (MR) images. A and B: sagittal images before (A) and after gadolinium enhancement (B) show a thickening of the pituitary stalk (13×11×11mm) and the loss of the physiological hyperintense signal of the posterior pituitary gland. The mass was homogeneously contrast-enhanced.

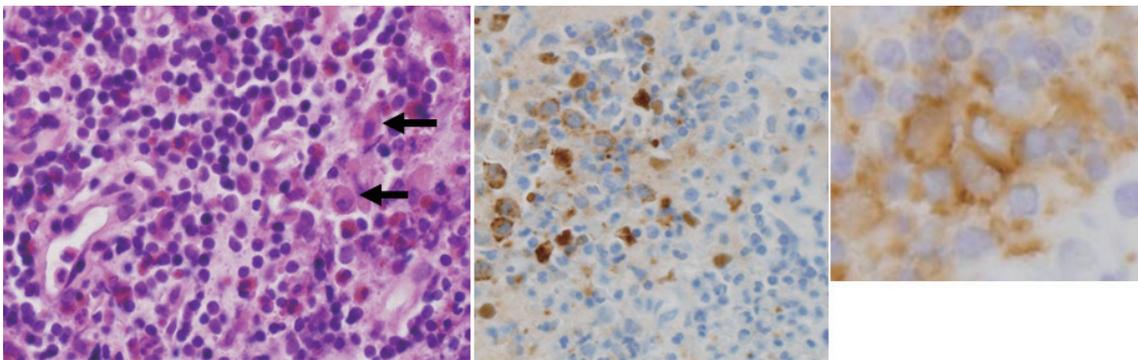


Fig. 2. Photomicrographs of the biopsy specimen. Left: hematoxylin and eosin stain (strong magnification). Note the extensive infiltration of inflammatory cells and the presence of Langerhans cells (black arrow). Middle: immunohistochemical staining for S-100 protein (strong magnification). Right: immunohistochemical staining for CD1a (strong magnification). The extensive positive staining is consistent with histiocytosis. These findings confirmed the diagnosis of Langerhans cell histiocytosis.

based on these results. Anterior pituitary hormones responded normally to a stimulation test with insulin, TRH, and LHRH. Serum tumor markers were not elevated (AFP 1.0 ng/ml, HCG-beta <0.1 ng/ml, CEA 2 ng/ml), but cerebrospinal fluid (CSF) HCG-beta was slightly elevated (0.18 ng/ml, reference value is <0.1 ng/ml). Magnetic resonance imaging (MRI) showed a thickening of the pituitary stalk and loss of the physiological hyperintense signal of the posterior hypophysis, and the mass was homogeneously contrast-enhanced with gadolinium (Fig. 1). The preoperative diagnosis was neurohypophyseal germinoma. The patient underwent endoscopic endonasal transsphenoidal surgery for a biopsy of the lesion. The mass lesion was soft and grayish, and only a few tiny fragments

were biopsied from the lesion. Histopathological examination showed the tumor consisted of granulomatous tissue infiltrated with lymphocytes and occasional eosinophils, as well as areas of large histiocytic cells (Fig. 2). The large cells were positive for S-100 protein and CD1a (Fig. 2), but negative for placental alkaline phosphatase on immunostaining. These findings were compatible with the diagnosis of LCH. A skeletal radiograph survey, bone scintigraphy, a dermatological survey, a chest X-ray and ultrasonography of the abdomen revealed no other LCH lesion. She was diagnosed as having isolated neurohypophyseal LCH. Simple observation, low-dose radiation and chemotherapy were considered in treatment planning. Since LCH patients with single-system and

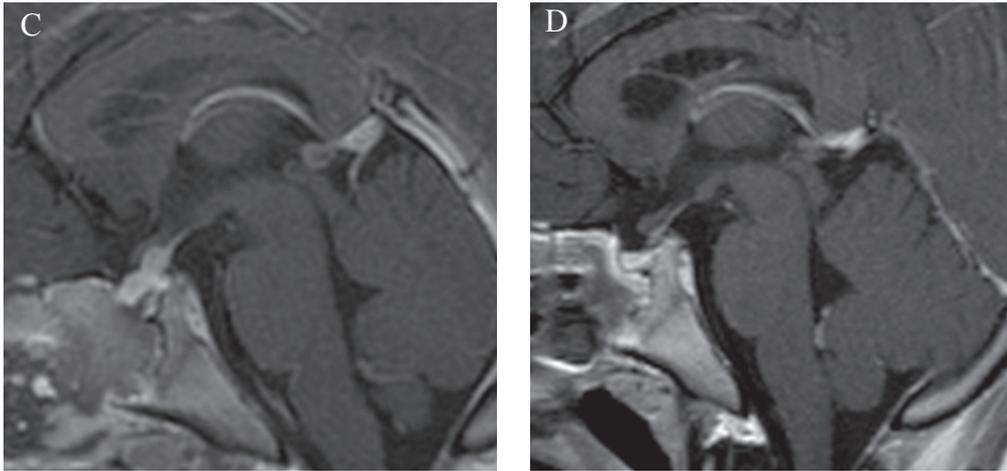


Fig. 3. Postoperative T1-weighted MR images after gadolinium enhancement. C: 14 days after the biopsy; D: 3 months after the biopsy; Sagittal images show that the residual lesion had diminished slightly 14 days after the biopsy, and spontaneously regressed 3 months after the biopsy with no additional therapy.

single-site carry a good prognosis and in some cases spontaneously regress, we decided on only simple observation. Follow-up MRI 14 days later showed that the mass had diminished slightly (Fig. 3C), and three months later showed that the residual lesion had spontaneously regressed (Fig. 3D). Unless the lesion was diagnosed histopathologically the patient would have been misdiagnosed as having LIN. Anterior pituitary hormones maintained normal response to a stimulation test with insulin, TRH, and LHRH 8 months after the biopsy, but her CDI remained unchanged. Normal structures of pituitary stalk and gland were also confirmed on MRI. LCH lesion has not re-grown and no other de novo lesions have been found for more than three years.

Discussion

This report is the first documented case of spontaneous regression of isolated neurohypophyseal LCH. MRI has revealed isolated pituitary stalk thickening in children with CDI, which is associated with GCT [2, 3], LCH [3, 5] and LIN [4]. A definitive diagnosis is needed because these diseases have different prognoses. However, the differential diagnosis between these diseases based on tumor markers and radiological examination is difficult, and only histopathological proof leads to a definitive diagnosis. LIN is an uncommon noninfectious inflammation of the neurohypophyseal system, and the natural course of the disorder is es-

entially self-limited [4]. For definitive diagnosis, a biopsy is necessary to exclude GCT and granulomatous diseases such as LCH; however some cases have been reported without a biopsy [4]. Our case was diagnosed as having LCH by histopathology and the tumor spontaneously regressed 3 months later. The preoperative diagnosis was neurohypophyseal GCT based on a mild elevation of the CSF HCG-beta. However, the biopsy specimen was negated by immunohistology. The diagnostic sensitivity of HCG-beta was insufficient, so the result was probably false-positive. Unless the lesion was diagnosed histopathologically the patient would have been misdiagnosed as LIN. This leads us to conjecture that some past cases of histologically-unconfirmed LIN can possibly include isolated neurohypophyseal LCH.

LCH is an uncommon disorder of unknown etiology, which may occur at all ages and in many systems. Clinical staging of this disease may be either by system (single or multiple organs) or site (single or multiple) in accordance with recent classification methods. Proliferation of LCH in the central nervous system (CNS) most commonly occurs in the hypothalamic-pituitary region. However, lesions arising at the hypothalamic-pituitary axis itself are relatively rare, and even rarer are solitary lesions of the infundibulum (single-system, single-site). Table 1 shows a summary of clinical data in reported cases of isolated neurohypophyseal LCH [5-11]. The table includes many young patients presented with acute-onset DI as well as the patient reported in this paper.

Table 1. Summary of clinical data in reported cases of isolated neurohypophyseal LCH

No. of cases	Author (year)	Age (year) Sex	Chief complaint	Treatment	Course after treatment
1	Tien RD (1990)	57, female	Acute onset polydipsia	Rx20Gy	Not described
2	Scholz M (1995)	46, male	DI, hypothyroidism	Mass lesion resection	*19 months
3	Asano T (1999)	24, female	Polydipsia, fatigue	Rx 20Gy	*7 years
4	Isoo A (2000)	14, female	Polydipsia	Rx 20Gy	*8 years
5	Isoo A (2000)	9, female	Polydipsia	Rx 20Gy	*15 months
6	Takada K (2002)	18, female	Polydipsia	Rx 22.4Gy	Shrinkage after 8 months
7	Inoue T (2005)	33, female	Polydipsia	Mass lesion resection	Not described
8	Horn EM (2006)	18, male	Acute polydipsia, hypogonadism	Rx 21Gy	*2 years
9	Present case	12, female	Acute onset polydipsia	Simple observation	Spontaneous regression

DI: diabetes insipidus, Rx: radiation therapy, *: No recurrence over period

Treatment of isolated neurohypophyseal LCH is controversial and highly individualized. Simple observation, low-dose radiation and chemotherapy are considered in treatment planning. Low dose radiation therapy has been the treatment in most cases [5, 7-9, 11]. The pathogenesis of LCH has yet to be well elucidated, and it is generally assumed to be a disorder of immune regulation, as evidenced by the presence of other immunologically active cells within the lesions in addition to increased cytokines [12]. The natural history of LCH is poorly understood. In fact, spontaneous regression has been well reported in many body systems including skin, bone, pulmonary and CNS [13]. Yamaguchi *et al.* reported a case of spontaneous

and continuous regression of multifocal LCH in the CNS and speculated on the possibility of spontaneous regression of LCH in CNS lesion [13]. Our case also spontaneously regressed, so simple observation is a reasonable treatment option in some patients with isolated neurohypophyseal LCH. Further clinical study is required to establish a treatment strategy.

In conclusion, the present case suggests that 1) radiological differential diagnosis between LIN and LCH is so difficult that histological confirmation is crucial for correct diagnosis, 2) some past cases of histologically-unconfirmed LIN might have included LCH, 3) isolated neurohypophyseal LCH can shrink spontaneously up to near remission level.

References

1. Maghnie M, Cosi G, Genovese E, Manca-Bitti ML, Cohen A, Zecca S, Tinelli C, Gallucci M, Bernasconi S, Boscherini B, Severi F, Arico M. (2000) Central diabetes insipidus in children and young adults. *N Engl J Med* 343: 998-1007.
2. Mootha SL, Barkovich AJ, Grumbach MM, Edwards MS, Gitelman SE, Kaplan SL, Conte FA. (1997) Idiopathic hypothalamic diabetes insipidus, pituitary stalk thickening, and the occult intracranial germinoma in children and adolescents. *J Clin Endocrinol Metab* 82: 1362-1367.
3. Leger J, Velasquez A, Garel C, Hassan M, Czernichow P. (1999) Thickened pituitary stalk on magnetic resonance imaging in children with central diabetes insipidus. *J Clin Endocrinol Metab* 84: 1954-1960.
4. Imura H, Nakao K, Shimatsu A, Ogawa Y, Sando T, Fujisawa I, Yamabe H (1993) Lymphocytic infundibuloneurohypophysitis as a cause of central diabetes insipidus. *N Engl J Med* 329: 683-689.
5. Tien RD, Newton TH, McDermott MW, Dillon WP, Kucharczyk J. (1990) Thickened pituitary stalk on MR images in patients with diabetes insipidus and Langerhans cell histiocytosis. *Am J Neuroradiol* 11: 703-708.
6. Scholz M, Firsching R, Feiden W, Breining H, Brechtelsbauer D, Harders A. (1995) Gagel's granuloma (localized Langerhans cell histiocytosis) in the pituitary stalk. *Clin Neurol Neurosurg* 97:164-166.
7. Asano T, Goto Y, Kida S, Ohno K, Hirakawa K. (1999) Isolated histiocytosis X of the pituitary stalk. *J Neuroradiol* 26:277-280.
8. Isoo A, Ueki K, Ishida T, Yoshikawa T, Fujimaki T, Suzuki I, Sasaki T, Kirino T (2000) Langerhans cell histiocytosis limited to the pituitary-hypothalamic axis - two case reports. *Neurol Med Chir (Tokyo)* 40:532-535.

9. Takada K, Yamada S, Usui M, Seki K, Matsushita H, Nishihara T. (2002) A case of infundibulo Langerhans cell histiocytosis with the use of a ventriculofiberscope. *Folia Endocrinologica Japonica*. 78 Suppl.: 43-44. (in Japanese)
10. Inoue T, Kawamata K, Aihara Y, Tanaka M, Kubota Y, Kubo O, Hori T. (2005) A case of hypothalamic tumor after radiotherapy for neurohypophyseal germ cell tumor. *Folia Endocrinologica Japonica* 81 Suppl.: 82-84. (in Japanese)
11. Horn EM, Coons SW, Spetzler RF, Rektek HL. (2006) Isolated Langerhans cell histiocytosis of the infundibulum presenting with fulminant diabetes insipidus. *Childs Nerv Syst* 22:542-544.
12. Egeler RM, Annels NE, Hogendoorn PC. (2004) Langerhans cell histiocytosis: a pathologic combination of oncogenesis and immune dysregulation. *Pediatr Blood Cancer*. 42:401-403.
13. Yamaguchi S, Oki S, Kurisu K. (2004) Spontaneous regression of Langerhans cell histiocytosis: a case report. *Surg Neurol*. 62:136-140.