Langerhans Cell Histiocytosis Limited to the Pituitary–Hypothalamic Axis

—Two Case Reports—

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Abstract

Langerhans cell histiocytosis rarely presents as a solitary lesion in the pituitary–hypothalamic region, and is indistinguishable from germinoma, which occurs much more frequently, especially in Japanese. A 14-year-old girl and a 9-year-old girl presented with polydipsia and polyuria as the initial symptoms. Magnetic resonance (MR) imaging demonstrated a round mass at the pituitary stalk appearing as isointense on T₁-weighted imaging and hyperintense on T₂-weighted imaging. Endocrinological examination revealed mild hypopituitarism with central diabetes insipidus. Both patients underwent open craniotomy. Histological examination revealed granulomatous tissue with eosinophil infiltration and frequent Langerhans histiocyte clustering, compatible with the diagnosis of Langerhans cell histiocytosis. Low-dose local irradiation of 20 Gy was administered. First patient was followed up for 8 years, and her hypopituitarism gradually improved to a minimal level with only amenorrhea as the residual symptom. Recent MR imaging showed no residual mass at the region. Second patient was followed up for 15 months, and her diabetes insipidus is stable. MR imaging performed 5 months after the treatment showed marked reduction of the mass. These cases reemphasize the importance of histological diagnosis for lesions with similar neuroimaging appearances. Biopsy and low-dose irradiation are an effective treatment for this rare and essentially benign lesion, as opposed to attempting total removal of the mass.

Key words: Langerhans cell histiocytosis, hypothalamus, diabetes insipidus

Introduction

Langerhans cell histiocytosis (LCH), previously known as histiocytosis X, is a systemic disease mainly affecting children and young adults. LCH most frequently involves the skeleton (80%) and skin (50%), but also occurs in the hypothalamic–pituitary axis in the central nervous system (CNS), causing diabetes insipidus (DI) in approximately 25% of patients with systemic disease. However, such CNS involvement is usually part of the systemic disease, and LCH limited to the CNS is rare. We report two cases of LCH limited to the hypothalamic–pituitary axis and discuss the treatment strategy for this rare clinical condition.

Case Reports

Case 1: A 14-year-old girl presented with frequent thirstiness and urination in August 1989. The water deprivation test and pitressin test indicated partial DI. Skull radiography and computed tomography did not detect any abnormal intracranial lesion. Baseline levels of pituitary hormones were within normal limits. She was followed up without treatment for a few months, and she soon became amenorrheic. Magnetic resonance (MR) imaging demonstrated a 5 mm round mass at the pituitary stalk 8 months later. The mass was isointense on the T₁-weighted images and hyperintense on the T₂-weighted images, with homogeneous enhancement by gadolinium (Fig. 1A). She was referred to our...
Fig. 1  A, B: Case 1. Sagittal T₁-weighted magnetic resonance images, at the onset (A) showing a gadolinium-enhanced mass at the pituitary stalk, which had disappeared 8 years after the treatment (B).  C–E: Case 2. Sagittal T₁-weighted magnetic resonance images, at the onset (C) revealing a small enhanced mass at the pituitary stalk (arrow), which was markedly enlarged after 9 months (D). The mass was significantly reduced 5 months after low dose irradiation (E). The apparent reduction in the pineal lesion is due to the difference of the imaging plane.

Fig. 2  A, B: Photomicrographs of the surgical specimens from Case 1 (A) and Case 2 (B) showing granulomatous tissue infiltrated by lymphocytes and occasional eosinophils as well as Langerhans cell histiocytes (arrow). HE stain, original magnification ×100. C: Immunohistochemistry for S-100 protein in Case 2 shows diffuse positivity. Original magnification ×100.
Physical examination detected no abnormal lesion in the skin, and skull radiography found no bone lesions. Serum cholesterol level was within normal limits. The tentative diagnosis was germinoma. She underwent 20 Gy irradiation. However, the size of the mass did not change significantly 2 months following the irradiation, so right frontal craniotomy was performed. The tumor was a grayish-yellow elastic mass arising from the pituitary stalk and hypothalamus. Histological examination showed the tumor consisted of granulomatous tissue infiltrated with lymphocytes and occasional eosinophils, and areas of polymorphous collections of Langerhans cells. Immunostaining was positive for S-100 protein and CD1a, but negative for placental alkaline phosphatase (PLAP). These findings were compatible with the diagnosis of LCH (Fig. 2A).

She had already received low-dose irradiation, so was treated with minimal replacement of cortisol, thyroid hormone, and desmopressin. The replacement was tapered off over 4 years. Eight years after the treatment at the age of 23 years, she had only mild hypopituitarism with amenorrhea. MR imaging showed no detectable mass lesion at the pituitary stalk in July 1998 (Fig. 1B).

**Case 2:** A 9-year-old girl presented with polydipsia and polyuria in March 1997. Physical and neurological examinations found no abnormalities, and laboratory tests were within normal limits. However, the water deprivation test and pitressin test indicated a central DI pattern. MR imaging showed the pituitary stalk as markedly thickened, appearing as isointense on T1-weighted images and hyperintense on T2-weighted images. The lesion was homogeneously enhanced by administration of gadolinium-diethylene triaminopenta-acetic acid. MR imaging also demonstrated a pineal mass with a cyst, with relatively strong enhancement (Fig. 1C).

She had no skin lesion or bone pain in any part of the body. She received desmopressin to control the DI and was followed up. Nine months later, her growth curve started to show flattening, and the serum level of somatomedin-C was low at 47 ng/ml. Serum cholesterol level was within normal limits. MR imaging showed the pituitary stalk lesion had enlarged markedly to form a mass of 10 mm in diameter with extension to the hypothalamus in March 1998 (Fig. 1D). She was referred to our hospital for further treatment.

She underwent right frontal craniotomy for open biopsy of the lesion. The tumor was approached between the right internal carotid artery and the right optic nerve. The mass was grayish-brown and consisted of hypovascular elastic tissue. The margin with the normal pituitary stalk was unclear. Several small pieces of tumor were obtained. Histological examination found granulomatous tissue with clustering of Langerhans cells and frequent eosinophilic infiltration (Fig. 2B). Immunostaining was positive for S-100 protein (Fig. 2C) and CD1a, but negative for PLAP. Occasional glial fibrillary acidic protein-positive cells were also observed, which probably represented gliosis induced by tumor cell infiltration. These findings were compatible with LCH. Following the hematologist's recommendation, bone scintigraphy and bone marrow aspiration were performed, but neither found evidence of systemic involvement of the disease. She received 20 Gy irradiation to the lesion, and was discharged with desmopressin replacement therapy.

MR imaging obtained 3 months after the treatment showed marked reduction of the mass (Fig. 1E). The pineal lesion, which was not included in the irradiated volume, showed no change in size and was considered to be a pineal cyst. Surgical resection of this lesion was not planned. At 15 months after the treatment, her DI was stable with the minimum dose of desmopressin.

**Discussion**

Involvement of the hypothalamic-pituitary axis is a well-recognized cause of DI in children or young adults with LCH. MR imaging is the key to the diagnosis, typically showing a mass at the pituitary stalk as hypointense or isointense on the T1-weighted images and isointense or hyperintense on the T2-weighted images, with homogeneous enhancement with gadolinium. The hyperintense appearance of the normal posterior pituitary lobe on T1-weighted image is generally absent, reflecting the regional depletion of pitressin. LCH of the CNS usually occurs as a part of the systemic disease, and such MR imaging findings in patients with known systemic LCH is considered definitive for the diagnosis. The standard treatment is low-dose irradiation with or without mild chemotherapy. However, LCH limited to the pituitary-hypothalamic axis is practically indistinguishable from suprasellar germinoma on neuroimaging. Germinoma is a more common lesion causing DI in children and requires much more aggressive radiochemotherapy. Accurate diagnosis is critical because of the significant difference in the management of these diseases. Histological examination of the tissue including immunohistochemistry for PLAP, a marker for germinoma, is essential. Neither of our cases expressed PLAP, which supported the diagnosis of LCH combined with the positive S-100 protein staining and
Table 1  Treatment of Langerhans cell histiocytosis limited to the pituitary-hypothalamic axis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of cases</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTX</td>
<td></td>
<td>Controlled Recurred Unknown</td>
</tr>
<tr>
<td>total dose &gt; 22 Gy</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>total dose ≤ 22 Gy</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>total dose not described</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>RTX and chemotherapy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Surgery only</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>No treatment</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

RTX: radiation therapy.

The prognosis of LCH varies significantly depending on the extent of the disease. Systemic LCH is generally fatal, whereas localized LCH usually follows a benign course. Therefore, treatment for localized LCH can be directed to prevention of systemic progression. Bone and skin lesions are usually excised and treated with 5 to 6 Gy local irradiation, which leads to complete remission in most patients. However, the optimal treatment of LCH limited to the pituitary-hypothalamic axis is still controversial, largely owing to the extremely low incidence. Only 18 cases of isolated pituitary-hypothalamic LCH have been reported. Eight cases were treated with irradiation, one with irradiation and chemotherapy, two with surgery only, and seven were detected at autopsy without treatment (Table 1). There was no recurrence in the patients treated with irradiation except one case receiving an unknown dose. LCH was controlled in all three cases with low-dose irradiation (≤ 22 Gy), indicating that a low dose is sufficient for most cases of isolated hypothalamic LCH. Therefore, high-dose irradiation should be avoided considering the high risk of inducing panhypopituitarism. Complete microsurgical excision has been recommended without further treatment. Although complete resection may be ideal if performed safely, LCH generally involves tight adhesion to the hypothalamus and a considerable risk of injuring the pituitary stalk. Whether such a rather aggressive approach offers a better prognosis in the long-term period remains unclear. The longest follow-up period reported for surgically resected cases is only 18 months. In contrast, our Case 1 with an 8-year follow-up is a valuable example that shows biopsy and low-dose irradiation without intensive chemotherapy is an obviously safer and effective option for the management of pituitary-hypothalamic LCH.

References


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