Probable Lymphocytic Hypophysitis Diagnosed by Short-term Serial Computed Tomography and Gallium-67 Scintigraphy
—Case Report—

Hideki MURAKAMI, Yuichi HIROSE, Masachika SAGOH, and Takuro HAYASHI

Department of Neurosurgery, Ashikaga Red Cross Hospital, Ashikaga, Tochigi

Abstract
A 61-year-old female presented with headache, malaise, and left oculomotor nerve paralysis. Computed tomography (CT) demonstrated a diffuse pituitary mass and enlarged pituitary stalk with homogeneous contrast enhancement. Her symptoms gradually resolved without treatment. Gallium-67 scintigraphy showed abnormal uptake in the pituitary lesion. Serial CT every 2 weeks after admission showed homogeneous contrast enhancement and shrinking of the pituitary mass to a normal size 12 weeks after the onset. The final diagnosis was lymphocytic adenohypophysitis without biopsy. Recurrence has not been observed for 8 years after discharge. The patient did not need hormone replacement therapy. Histological examination is not always necessary to diagnose probable lymphocytic adenohypophysitis with the characteristic feature of rapid onset, abnormal gallium-67 uptake in the lesion, and resolution of symptoms in the acute stage with shrinking of the lesion on neuroimaging.

Key words: gallium-67 scintigraphy, inflammation, lymphocytic hypophysitis, repeat computed tomography, spontaneous regression

Introduction
Lymphocytic adenohypophysitis is a nonspecific inflammatory disorder of the pituitary gland. The treatment and natural history remain unknown. The symptoms progress more rapidly than those of common pituitary adenoma, and the clinical profile resembles those of pituitary apoplexy and acute swelling of pituitary adenoma during pregnancy. However, lymphocytic adenohypophysitis has features closely resembling those of pituitary adenoma on neuroimaging. Therefore, the preoperative differential diagnosis of lymphocytic adenohypophysitis from pituitary adenoma is difficult. Histological examination is the only means at present for definitive diagnosis and a biopsy is considered essential. However, biopsy or decompressive surgery may cause postoperative hypopituitarism.

We treated a 61-year-old postmenopausal female under a diagnosis of lymphocytic adenohypophysitis within 2 weeks after admission based on serial computed tomography (CT) and gallium-67 scintigraphy.

Case Report
A 61-year-old female complained of headache with fever and double vision on June 18, 1990. She received medication at her local general practitioner's clinic. However, her double vision gradually worsened. She was referred to our hospital on July 13, 1990. Physical and neurological examinations found no abnormalities except for double vision in all directions. Twelve days later, she noticed palpable ptosis on the left side and her headache continued to worsen, accompanied by nausea, vomiting, and general fatigue. CT showed a mass extending superiorly from the sella turcica with homogeneous contrast enhancement. She was admitted on July 25, 1990.

Physical examination was normal, and found no evidence of thyromegaly or lymphadenopathy. There was no history or evidence of skin change or...
alteration in body hair distribution. She had undergone a hysterectomy in 1982 and had entered menopause. Neurological examination identified no meningeal signs. Her pupils were anisocoric (right 2 mm, left 3 mm) and reactive to light. Partial left third cranial nerve paresis had resulted in ptosis and diplopia. Formal visual testing demonstrated no abnormality in either eye. Complete blood cell count, chest radiography, and electrocardiography found no abnormalities. Serum carcinoembryonic antigen level was 3.5 ng/ml (normal <6.0) and alpha-fetoprotein level was 0.1 ng/ml (normal <7.6). Basal levels of pituitary-related hormones showed hyposecretion (Table 1). Antithyroglobulin antibody level was 7.1 µg/ml (normal <1.5) and no antimicrosomal antibody was detected.

Skull radiography films showed mild demineralization with erosion of the sella turcica. Coronal CT 6 weeks after the onset showed a sellar mass extending into the suprasellar cistern and an enlarged pituitary stalk with homogeneous contrast enhancement (Fig. 1A). Since the progression of the symptoms was more rapid than that of common pituitary adenoma, we suspected pituitary apoplexy, which cannot be detected by CT. However, magnetic resonance (MR) imaging showed no signs of apoplexy. T1-weighted MR imaging showed the same region as an isointense mass intensely enhanced with gadolinium-diethylenetriaminepentaacetic acid, and enlargement of the pituitary stalk and invasion into the cavernous sinus (Fig. 2). CT and MR imaging detected no other masses. Because of the rapid progression of the patient's symptoms, we had to differentiate lymphocytic adenohypophysitis from malignant tumors. Systemic gallium-67 scintigraphy showed abnormal uptake in the pituitary lesion but no other abnormal lesions (Fig. 3).

Surprisingly, the blepharoptosis gradually disappeared from the day of admission without treatment. CT 8 weeks after the onset showed no findings of pituitary apoplexy and a slight shrinking of the pituitary mass (Fig. 1B). The tentative diagnosis was lymphocytic adenohypophysitis. Her double vision also resolved gradually, and serial CT 10 weeks after

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Patient's value</th>
<th>Normal range</th>
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<tr>
<td>T3 (ng/ml)</td>
<td>4.2</td>
<td>5.0-11.5</td>
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<tr>
<td>T4 (ng/ml)</td>
<td>1.3</td>
<td>0.7-1.7</td>
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<tr>
<td>TSH (µU/ml)</td>
<td>0.1-1.5</td>
<td>0.3-0.4</td>
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<td>Cortisol (µg/dl)</td>
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<td>10.5-3.0-15.2</td>
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<tr>
<td>PRL (ng/ml)</td>
<td>8.8</td>
<td>3.1-2.0-30.0</td>
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<tr>
<td>ACTH (pg/ml)</td>
<td>8.1</td>
<td>30.1-6.0-30.0</td>
</tr>
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<td>GH (ng/ml)</td>
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<td>&lt;0.3-&lt;0.5</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
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<td>33.2-12.6-235.7</td>
</tr>
<tr>
<td>ADH (pg/ml)</td>
<td>1.5</td>
<td>0.5-6.3</td>
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onset showed the size of the mass was further reduced (Fig. 1C). Twelve weeks after onset, the pituitary mass had returned to the normal size of the pituitary gland (Fig. 1D). At this time, her symptoms had completely resolved. The final diagnosis was lymphocytic adenohypophysitis based on the clinical course and the disappearance of the mass on follow-up CT.

She was discharged on September 5, 1990. Basal hormonal concentrations returned to normal (Table 1). One year after onset, the pituitary gland became smaller with an empty sella appearance (Fig. 1E). No recurrence has been detected in the 8 years after discharge and she has not needed hormone replacement therapy.

Discussion

Lymphocytic adenohypophysitis is known to resolve spontaneously, and seven previous cases were diagnosed as lymphocytic adenohypophysitis without histological examination. The diagnosis was based on repeat CT 2 to 12 months after the first CT. Since lymphocytic adenohypophysitis is an inflammation, the clinical course is more rapid than that of common pituitary adenoma. Therefore, changes in the size of the mass may be observed by short-term follow-up CT or MR imaging depending on the stage of the inflammation. In our case, a decrease in the size of the mass was observed after only 2 weeks. Therefore, short-term follow-up CT or MR imaging are the best early diagnostic tools to differentiate lymphocytic adenohypophysitis from pituitary adenoma.

Granulomatous hypophysitis is another inflammatory disorder of the pituitary gland with clinical signs closely resembling those of lymphocytic adenohypophysitis. Although no typical CT density pattern can be discerned because of the rarity of this disorder, some cases resembled lymphocytic adenohypophysitis. Langerhans cell histiocytosis is an extremely rare disorder, but one case of Langerhans cell histiocytosis has occurred in the pituitary stalk with clinical signs and MR imaging appearance closely resembling those of lymphocytic adenohypophysitis. However, neither of these disorders has ever resolved spontaneously. Therefore, the diagnosis must be made by histological examination for both disorders.

Gallium-67 scintigraphy shows low uptake in normal brain tissues and high uptake in glioblastomas, metastatic brain tumors, malignant lymphomas, sarcoidosis, and brain abscesses, and in regions of inflammation. Gallium-67 uptake in lymphocytic adenohypophysitis or granulomatous hypophysitis is unclear. High uptake of gallium-67 can be expected in lymphocytic adenohypophysitis and granulomatous hypophysitis due to the inflammatory nature of these disorders, and in our case, high uptake of gallium-67 was observed in the pituitary.
lesion. High uptake of gallium-67 was reported in a case of neurohypophyseal germinoma but no abnormal uptake in 15 cases of pituitary macroadenoma. Further studies of gallium-67 scintigraphy in inflammatory disorders of the pituitary gland are required, but this technique is likely to be useful for the differentiation of inflammatory disorders from pituitary adenoma.

We propose the following management paradigm for probable lymphocytic adenohypophysitis. If the disease has a relatively rapid onset with neuroimaging evidence of pituitary mass, gallium-67 scintigraphy shows normal uptake only in the pituitary lesion, and mitigation of symptoms or shrinking of the mass is observed during the course, the disease is highly likely to be lymphocytic adenohypophysitis and requires no biopsy or steroid therapy. If no changes in the size of the mass are observed, the response to steroid therapy should be examined. If symptomatic exacerbation and enlargement of the mass are noted, the lesion is likely to be due to inflammatory disease such as lymphocytic adenohypophysitis or a malignant tumor. However, if the disease progresses, biopsy for differential diagnosis or decompensate surgery is necessary.

Steroid therapy is effective for the treatment of lymphocytic adenohypophysitis. However, it is not clear whether the steroids act as non-specific anti-inflammatory agents or as hormonal replacement. Steroids may suppress the inflammation, but the dose and requirement for steroid therapy vary with the stage of the disease. A case of massive fibrous lymphocytic adenohypophysitis was unresponsive to administration of prednisolone for 2 weeks. On the other hand, as hormonal replacement, the necessity for steroid therapy depends on the deficient hormones. A case of spontaneously resolving lymphocytic adenohypophysitis was treated by desmopressin acetate and L-thyroxine without steroids. In our case, the patient’s symptoms were gradually alleviated without treatment. Administration of steroids was not selected in our case because of the risk of masked diabetes insipidus.

Biopsy is required to establish the histological diagnosis of lymphocytic adenohypophysitis but decompressive surgery is sometimes performed due to narrowing of the visual field. However, non-specific inflammatory changes may occur around and within pituitary lesions such as pituitary adenoma, craniopharyngioma, and Rathke’s cleft cyst secondary to necrosis, infarction, or hemorrhage associated with the lesions. Such findings are named secondary hypophysitis. In such cases, only biopsy alone is not sufficient for the strict diagnosis of lymphocytic adenohypophysitis. Biopsy specimens of lymphocytic adenohypophysitis have showed infiltration of numerous lymphocytes between the normal anterior pituitary cells. Moreover, at the end stage of lymphocytic adenohypophysitis, the pituitary gland is decreased in size with an empty sella appearance. In our case, the pituitary gland was reduced in size with an empty sella appearance and the hypopituitarism resolved completely. Therefore, biopsy or decompressive surgery might have exacerbated the residual pituitary function in this case.

The results of long-term follow-up of lymphocytic adenohypophysitis have only been reported in four cases. All cases were diagnosed by histological examination and required hormone replacement therapy. One case recurred 2 years after the biopsy. The other three cases did not recur for 2.5–3.5 years. Our patient has remained free of recurrence for more than 8 years and hormone replacement therapy was not needed.

In the present case, the diagnosis of lymphocytic adenohypophysitis could be made without biopsy as the mass disappeared without treatment and the course of disappearance could be followed up by serial CT, and recurrence has not been observed for 8 years. These findings will help to clarify the natural history of lymphocytic adenohypophysitis. More details of the natural history of the disease may help us determine the appropriate therapeutic approach for this disorder.

References


Address reprint requests to: H. Murakami, M.D., Department of Neurosurgery, Ashikaga Red Cross Hospital, 3-2100 Honjo, Ashikaga, Tochigi 326-0808, Japan.