rarely seen with primary pituitary adenomas (3).

The other granulomatous diseases that can involve the hypothalamus or the pituitary gland include tuberculosis, granulomatous hypophysitis, and eosinophilic granuloma. Tuberculosis can produce a picture similar to that of central nervous system sarcoidosis, with a basilar meningitis and findings suggestive of an intrasellar tumor. As many as 4% of cases of late generalized tuberculosis can lead to hypopituitarism from either hematogenous or direct spread through the meninges. Concurrent infection elsewhere is likely to be present. Granulomatous hypophysitis is a rare condition that may present with a sellar-suprasellar mass and hypopituitarism and is most commonly seen in middle-aged and older women. The hypothalamus is not likely to be involved in this disease, and, therefore, diabetes insipidus is less common. On pathological examination, the pituitary gland is infiltrated with inflammatory cells and lymphocytes, granulomas, and multinucleated giant cells. The granulomas are characterized by central necrosis and are not as distinct as those of sarcoidosis or tuberculosis (1–3).

Kalman D. Post
New York, New York


Lymphocytic Hypophysitis: Case Report

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WE REPORT A rare case of lymphocytic hypophysitis in a 52-year-old man who presented with a combination of hypopituitarism and diabetes insipidus. Magnetic resonance imaging with a contrast medium revealed an expanding sellar mass and thickening of the pituitary stalk with homogeneous enhancement. These findings may be useful in differentiating lymphocytic hypophysitis from pituitary adenoma. The unique clinical and radiological features of this case are discussed. (Neurosurgery 36:1016–1019, 1995)

Key words: Diabetes insipidus, Lymphocytic hypophysitis, Magnetic resonance imaging, Pituitary stalk

Lymphocytic hypophysitis is a rare inflammatory disease of the pituitary gland that is being recognized increasingly as a cause of hypopituitarism. Although it is well described in women during the peripartum period, only five cases in men have been reported (3, 8, 15–17). Diabetes insipidus has been described in eight patients with lymphocytic adenohypophysitis (6, 8, 13–15, 18). We report a unique case of lymphocytic hypophysitis in a 52-year-old man who presented with hypopituitarism, diabetes insipidus, and magnetic resonance imaging (MRI) evidence of an expanding sellar mass, with thickening of the pituitary stalk.

CASE REPORT

A 52-year-old man was referred for evaluation of a possible pituitary tumor. His complaints consisted of a 3-month history of general fatigue, impotence, polyuria, and polydipsia. Two months before admission, he had experienced persistent nausea and vomiting, but without an associated headache. His medical history was unremarkable, and there was no family history of endocrine or autoimmune problems.

A physical examination revealed evidence of decreased libido, dry skin, and sparse pubic and axillary hair. His vital signs were stable. During the neurological examination, he was fully oriented. Ocular fundi, visual fields, and visual acuity were normal bilaterally. The remainder of the neurological examination was also within normal limits.

A lumbar puncture revealed an opening pressure of 150 mm H₂O and total protein and glucose concentrations of 36 mg/dL and 64 mg/dL, respectively, in the cerebrospinal fluid. The cerebrospinal fluid contained 30 nucleated cells, 75% of which were lymphocytes and plasma cells.

Routine laboratory examinations were unremarkable. The urinary volume collected during a 24-hour period was 4000 mL, and the specific gravity was 1.003. Endocrinological examinations, involving the simultaneous intravenous administration of growth hormone-releasing hormone (0.1 mg), corticotropin-releasing hormone (0.1 mg), thyrotropin-releasing hormone (0.5 mg), and luteinizing hormone-releasing hormone (0.1 mg), revealed hyposecretion of all pituitary hormones (T3, T4).

The patient’s free thyroxin concentration was 0.15 ng/mL (normal, 0.85–2.15), and his free triiodothyronine concentration was 1.2 pg/mL (normal, 3.0–5.8). The patient began receiving hydrocortisone (10 mg once a day orally) and thyroid hormone (0.1 mg once a day orally), and his general fatigue lessened. His polyuria and polydipsia were controlled with 1-deamino-8D-arginine-vasopressin (0.025 mL twice daily by nose drops).

His cranial radiographs and sellar polytomography were normal. Computed tomography revealed an isodense sellar mass that was enhanced homogeneously.
TABLE 1. Anterior Hypophysial Function

<table>
<thead>
<tr>
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<th>Preoperative Value</th>
<th>Postoperative Value</th>
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<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Peak</td>
</tr>
<tr>
<td>GH (ng/ml) (&lt;5.0)</td>
<td>&gt;0.05</td>
<td>0.29</td>
</tr>
<tr>
<td>PRL (ng/ml) (1.5–30)</td>
<td>&lt;1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>TSH (µU/ml) (0.3–3.4)</td>
<td>&lt;0.15</td>
<td>0.17</td>
</tr>
<tr>
<td>LH (mIU/ml) (6–34)</td>
<td>&lt;1.0</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>FSH (mIU/ml) (2–22)</td>
<td>1</td>
<td>2.2</td>
</tr>
<tr>
<td>ACTH (pg/ml) (30–60)</td>
<td>&lt;5.0</td>
<td>&lt;5.0</td>
</tr>
<tr>
<td>Cortisone (µg/dL) (2.7–15.5)</td>
<td>2</td>
<td>2.1</td>
</tr>
</tbody>
</table>

* Peak, stimulated peak value; GH, growth hormone; PRL, prolactin; TSH, thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; ACTH, adrenocorticotrophic hormone. TSH and PRL were stimulated by thyrotropin-releasing hormone; GH was stimulated by growth hormone-releasing hormone; ACTH and cortisone were stimulated by corticotropin-releasing hormone; LH and FSH were stimulated by luteinizing hormone-releasing hormone.

neously by the contrast medium. T1-weighted MRI revealed an isointense sellar mass along the pituitary stalk and lacked the hyperintense signal of the posterior pituitary lobe that is seen in most normal subjects (Fig. 1). T2-weighted MRI revealed a low-intensity mass. T1-weighted MRI, after the administration of gadolinium diethylenetriamine-penta-acetic acid, demonstrated a 1.5-cm, well-defined, homogeneous sellar mass with thickening of the pituitary stalk (Fig. 2). Carotid angiography revealed no abnormalities.

OPERATION

A sublabial transsphenoidal exploration was performed. Initially, the floor of the sella and the dura mater were intact. When the dura mater was incised and separated, a firm, dull, yellowish-white mass was evident and it seemed to be somewhat soft compared with a normal pituitary gland. It was removed by curettes and pituitary forcesp and was partially drawn out with a standard suction. The entire portion of visible tumor was surgically resected. Normal pituitary gland could not be identified separately.

The patient's postoperative course was uneventful. Repeated endocrinological examinations revealed a decreased response to hormone stimulation performed according to the preoperative protocol (Table 1). Currently, the patient is doing well, receiving replacement doses of hydrocortisone (20 mg once a day orally), thyroid hormone (0.1 mg once a day orally), and 1-deamino-(8D-arginine)-vasopressin (0.025 mL twice daily by nose drops).

Immunological studies were also performed. Lymphocyte subsets were in the normal range, with a concentration of C3 at 106 mg/dL (normal, 55.0–120), C4 at 40.5 mg/dL (normal, 20.0–50.0), OKT4 at 44% (normal, 35.5–46.9), and OKT8 at 28% (normal, 21.0–32.0). Immunoglobulin fractions also were normal, and tests for antinuclear, antipituitary, antithyroid, and antidiastolic antibodies all were negative.

PATHOLOGICAL EXAMINATION

The pathological examination revealed edematous adenohypophysis that was diffusely fibrotic and strikingly infiltrated by mature lymphocytes and plasma cells (Fig. 3A). Remnants of the sparse pituitary cells appeared nonreactive after immunoperoxidase staining for anterior hypophyseal hormones. The majority of infiltrating lymphocytes were UCHL-1-positive cells (T cells) (Fig. 3B). There was no evidence of caseous necrosis or epithelioid granulomas, and no neuronal elements were seen. These findings were interpreted as lymphocytic hypophysisis.

DISCUSSION

Lymphocytic hypophysisis presents most often in women during the peripartum period. However, there have been several recent case reports of this disease in men (3, 8, 15–17) and in nonpregnant and/or postmenopausal women (6, 8, 13, 14, 18, 19). The condition usually presents clinically as a pituitary mass lesion with associated hypopituitarism. A few preoperative patients with lymphocytic adenohypophysitis, who also manifested diabetes insipidus, have been reported (6, 8, 13–15, 18). The clinical manifestations among affected men are quite similar. Impotence, with associated decreased libido, is the most common presenting symptom, occurring in all cases. Diabe-

![FIGURE 1. Sagittal T1-weighted MRI demonstrating an isointense sellar mass along the pituitary stalk and the lack of a normal hyperintense signal in the posterior pituitary lobe.](image1)

![FIGURE 2. Coronal (A) and sagittal (B) T1-weighted MRI, after the administration of gadolinium, demonstrating a 1.5-cm sellar mass and thickening of the pituitary stalk (arrow) with homogeneous enhancement.](image2)
tes insipidus has been diagnosed in two men with lymphocytic hypophysitis (8, 15). Lymphocytic hypophysitis may be related to an autoimmune process, as antipituitary antibodies have been found in two previously reported cases (11, 19). However, in this case, the results of immunological studies were unremarkable.

It is difficult to differentiate lymphocytic hypophysitis from a pituitary adenoma with neuroimaging studies. Most of the cases are misdiagnosed preoperatively as pituitary adenomas. Diagnosis is usually made histologically. Levine et al. (9) reported the first case of lymphocytic hypophysitis visualized by MRI. Few authors have reported visualization of the pituitary mass by MRI (2, 4, 6, 8-10, 12, 14, 15, 17). The radiological features are similar to those of a pituitary adenoma. Miura et al. (14) have reported that in formulating a differential diagnosis for lymphocytic hypophysitis preoperatively, it is useful to note swelling of the anterior hypophyseal tissue and the existence of a posterior pituitary lobe on sagittal MRI sections. In our case, T1-weighted, sagittal MRI revealed an isointense sellar mass along the pituitary stalk and lacked the normal hyperintense signal in the posterior pituitary lobe. The sellar mass and neurohypophysis were homogeneously enhanced on MRI with gadolinium diethylenetriamine-penta-acetic acid. Some thickening of the pituitary stalk on computed tomography and/or MRI was found in seven patients with lymphocytic adenohypophysitis who presented with a combination of diabetes insipidus and hypopituitarism (6, 8, 14, 15, 18). We found that sellar pituitary adenomas do not demonstrate thickening of the pituitary stalk on MRI. Therefore, when differentiating lymphocytic hypophysitis from a pituitary adenoma preoperatively, it is important to ascertain whether the MRI shows an expanding sellar mass lesion and thickening of the pituitary stalk with gadolinium diethylenetriamine-penta-acetic acid enhancement. The origin of diabetes insipidus presenting preoperatively is unknown but may result from inflammation extending to the neurohypophysis. To our knowledge, our patient is the third reported case of lymphocytic hypophysitis in a man who presented with hypopituitarism, diabetes insipidus, and evidence of an expanding sellar mass (with thickening of the pituitary stalk) on MRI with a contrast medium.

Recently, it has been reported that diabetes insipidus can be caused by lymphocytic infundibuloneurohypophysitis, which is not a variety of lymphocytic adenohypophysitis (5, 7). MRI has revealed that the anterior pituitary gland and hypothalamus are normal in such cases, but that the hyperintense signal of the normal neurohypophysis observed on T1-weighted MRI is absent. In addition, MRI has demonstrated thickening of the pituitary stalk, enlargement of the neurohypophysis, or both. Ahmed et al. (1) reported two men with necrotizing infundibulohypophysitis who presented with a combination of diabetes insipidus and hypopituitarism. Each was found to have a sellar mass lesion with an abnormally thick and enlarged pituitary stalk that demonstrated intense enhancement with a contrast medium on MRI. Tissue obtained at transsphenoidal surgery performed in these patients revealed necrosis, fibrosis, and chronic inflammation, features inconsistent with lymphocytic hypophysitis. Thus, these findings in patients with lymphocytic infundibuloneurohypophysitis or necrotizing infundibulohypophysitis are distinct from those in our patient.

Received, October 11, 1994.
Accepted, November 23, 1994.
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REFERENCES

Lymphocytic hypophysitis may have a rapid onset and may lead to severe complications, even to death. In some patients, spontaneous regression of the sellar mass and partial or total recovery of pituitary function may occur. Mass effects such as headaches and visual field impairment and/or adenohypophysial hypofunction, characterized by partial or total hypopituitarism, are present in approximately 50% of the patients. Interestingly, prolactin excess may be evident in several cases. Hyperprolactinemia may be caused by stalk compression, release of prolactin from damaged lactotrophs, decreased production of hypothalamic dopamine, loss of dopaminergic receptors, or production of lactotroph-stimulating antibodies. Diabetes insipidus, as noted in the case of Abe et al., is encountered in approximately 20% of patients and may be caused by compression and impairment of the stalk and/or the posterior lobe.

In the majority of patients with lymphocytic hypophysitis, computed tomography or magnetic resonance imaging reveals features of a pituitary mass, often with suprasellar extension. Based on the imaging findings, the lesion is often diagnosed as a pituitary adenoma. In the case of Abe et al., magnetic resonance imaging disclosed a loss of the hyperintense "bright spot" signal of the normal neurohypophysis, a thickening of the pituitary stalk, and an enlargement of the neurohypophysis. This is of particular interest because magnetic resonance imaging changes may be helpful in making the correct diagnosis.

The pathogenesis of lymphocytic hypophysitis has been attributed to an autoimmune process. Circulating antipituitary antibodies, as demonstrated in the case of Abe et al., can be detected only in a few patients.

Lymphocytic hypophysitis is regarded as a medical disease and should be treated primarily with corticoste-roids. If the correct diagnosis is made, surgery can be avoided. Surgery is, however, necessary if conservative treatment is ineffective. Operative intervention is also needed when the diagnosis is uncertain. The correct diagnosis can conclusively be made by histological examination.

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The authors provide a detailed documentation of an unusual case involving a man with lymphocytic hypophysitis presenting with diabetes insipidus. The unusual features of this case are as follows: 1) the patient was a man; 2) he presented with diabetes insipidus; and 3) the imaging studies appeared to show involvement not only of the adenohypophysis but also the neurohypophysis as well as the stalk itself. Although magnetic resonance imaging is certainly not unique for this entity, it does have features that might suggest a diagnosis other than pituitary adenoma. Most adenomas do not enhance so uniformly and strongly and most do not involve the stalk itself. I would agree with the authors that if this specific magnetic resonance image were to be seen again, one should think of a diffuse infiltrating process, such as lymphocytic hypophysitis.

My only disagreement with the workup of this patient is that the authors performed carotid angiography. With modern magnetic resonance imaging, it is rarely necessary to expose patients to the risk of angiography. It is not clear to me why the authors performed a lumbar puncture, but it did provide somewhat interesting findings in that there was a slight increase in cellularity, with 75% of those cells being lymphocytes or plasma cells.

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Neurosurgery, Vol. 36, No. 5, May 1995