Case Records of the Massachusetts General Hospital

Weekly Clinicopathological Exercises
Founded by Richard C. Cabot

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Case Records of the Massachusetts General Hospital

Case 34-2000

PRESENTATION OF CASE

A 71-year-old woman was admitted to the hospital because of a pituitary mass.

During the five years before admission, the patient had been tired and anorectic, her joints had ached, and her neck and shoulders had become stiff. A diagnosis of polymyalgia rheumatica had been made, and she had refused to take prednisone. She had become depressed after the death of her husband 12 years before admission. Because she frequently traveled within the United States to visit her daughters, her medical care was fragmented and inconsistent. Laboratory tests performed six years before admission showed hyperlipidemia, with normal thyroid function. The results of other laboratory studies are shown in Tables 1 and 2.

Thirty-one months before admission, the patient was referred to this hospital for evaluation because of fatigue. She had smoked two packs of cigarettes daily for many years but had discontinued smoking two years earlier. A test of thyroid function was again performed at the time of this referral (Table 2).

On physical examination, the woman was thin and appeared to be depressed; no other abnormalities were noted. Tests for rheumatoid factor and antinuclear antibodies were negative. The results of other laboratory tests are presented in Tables 1, 2, and 3. Radiologic examination of the chest revealed bilateral reticular and cystic changes in the upper lobes of the lungs, particularly in the apex of the right lung; the mediastinum appeared normal. The results of pulmonary-function studies were normal except for evidence of small-airway disease and increased lung volumes — findings that were suggestive of air trapping. A specimen of arterial blood, drawn while the patient was at rest and breathing ambient air, revealed that the partial pressure of oxygen was 100 mm Hg, the partial pressure of carbon dioxide was 36 mm Hg, and the pH was 7.41.

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**Table 1. Blood Chemical Values.*

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>6 YEARS BEFORE ADMISSION</th>
<th>31 MONTHS BEFORE ADMISSION</th>
<th>21 MONTHS BEFORE ADMISSION</th>
<th>6 MONTHS BEFORE ADMISSION</th>
<th>3 MONTHS BEFORE ADMISSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (mg/dl)</td>
<td>294</td>
<td>249</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>58</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>210</td>
<td>176</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>128</td>
<td>151</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>Normal</td>
<td>72–166†</td>
<td>147</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>Normal</td>
<td>51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(U/liter)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/liter)</td>
<td>129</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Potassium (mmol/liter)</td>
<td>4.2</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Chloride (mmol/liter)</td>
<td>93</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbon dioxide (mmol/liter)</td>
<td>29</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmolality (mOsm/kg of water)</td>
<td>264</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*To convert the values for total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for glucose to millimoles per liter, multiply by 0.05551.

†The range of values is based on three measurements.

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Ten months later (21 months before admission), the patient reported stiffness in her hands and knees, persistent fatigue, and a poor appetite. Her medications were a multivitamin supplement and a calcium supplement. Physical examination revealed no abnormalities. Laboratory tests were performed (Tables 1 and 2). Six months later, the patient reported that she had begun taking prednisone (15 mg daily) three months earlier and was currently taking 7.5 mg daily. She felt well except for anorexia, lack of energy, and pain and tingling in her legs.

Eight months later (six months before admission), the patient entered another hospital because of an unwitnessed collapse and a temperature of 39.4°C with rigors. When she recovered consciousness, she was confused and disoriented. Physical examination, routine laboratory studies, and a computed tomo-

graphic scan of the brain revealed no abnormalities. A magnetic resonance imaging (MRI) study, performed after the administration of gadolinium, disclosed a pituitary mass, 11 mm in vertical dimension, that extended into the suprasellar cistern just inferior to the optic chiasm. Multiple small, discrete areas of increased $T_2$-weighted signal were present in the subcortical periventricular white matter and near the frontoparietal junction, especially on the left side.

Laboratory tests were performed (Tables 1 and 3). The results of lumbar puncture are presented in Table 4. Two blood cultures and a urine culture yielded no organisms. Tests for rheumatoid factor and anti-nuclear antibodies were negative. An electrocardiogram revealed sinus tachycardia at a rate of 118 beats per minute, with a tendency toward low voltage throughout; a mean QRS axis of $-30$ degrees; and nonspecific ST-segment and T-wave abnormalities. Electroencephalographic examination showed focal slowing over the left posterior temporal region and generalized, slight-to-moderate slowing of the background rhythm; no epileptiform activity was detected. An antibiotic was given, and her symptoms resolved.

Five months before admission, the patient returned to this hospital. She was taking 7.5 mg of prednisone daily. Physical examination revealed no abnormalities; she had gained about 4 kg in weight since her visit to this hospital 16 months earlier. Endocrine laboratory tests were performed (Table 2). Levothyroxine (50 mg daily) was administered, and the dose of prednisone was reduced to 5 mg daily. Three months before admission, laboratory tests were again performed (Tables 1 and 2). The patient continued to feel tired and depressed, with muscle aches and anorexia, and had lost 2 kg in weight. She left for

| Table 2. Endocrine Laboratory Values.* |
|-------------------------------|----------------|----------------|----------------|----------------|
| **VARIABLE**                  | 6 YEARS BEFORE ADMISSION | 31 MONTHS BEFORE ADMISSION | 21 MONTHS BEFORE ADMISSION | 5 MONTHS BEFORE ADMISSION | 3 MONTHS BEFORE ADMISSION |
| Thyrotropin (µU/ml)           | Normal           | 0.68            | 0.20            | 0.07            |                   |
| Total thyroxine (µg/dl)      | Normal           | 4.6             | 7.5             |                |                   |
| Cortisol (mg/dl)             | In the fasting state | 8.9             | 1.5             |                |                   |
|                             | 60 min after intravenous injection of cosyntropin | 24.8             | 11.9            |                |                   |
| Total triodothyronine (ng/dl) | Normal           | 78              | 87              |                |                   |
| Thyroid hormone-binding index | Normal           | 0.83            | 0.92            |                |                   |
| Free thyroxine index         | Normal           | 3.8             | 6.9             |                |                   |
| Prolactin (ng/ml)            | Normal           | 3.3             |                 |                |                   |
| Alpha subunit                | <0.2             |                 |                 |                |                   |
| Follicle-stimulating hormone (U/liter) | Normal           | 3.3             |                 |                |                   |

*To convert the values for total thyroxine to nanomoles per liter, multiply by 12.87. To convert the values for total triodothyronine to nanomoles per liter, multiply by 0.01536.

| Table 3. Hematologic Laboratory Values. |
|-------------------------------|----------------|----------------|
| **VARIABLE**                  | 31 MONTHS BEFORE ADMISSION | 6 MONTHS BEFORE ADMISSION | 31 MONTHS BEFORE ADMISSION |
| Hematocrit (%)                | Normal           | 36.6            |                   |
| Mean corpuscular volume (µm$^3$) | Normal           | 92              |                   |
| Erythrocyte sedimentation rate (mm/hr) | 56             | 45–53           |                   |
| White-cell count (per mm$^3$) | Normal           | 10,200          |                   |
| Differential count            | Normal           | Normal          |                   |
| Platelet count (per mm$^3$)   | Normal           | 354,000         |                   |
| Prothrombin time              | Normal           | Normal          |                   |
| Partial-thromboplastin time   | Normal           | Normal          |                   |
Another city a few days after this evaluation. Shortly thereafter, an ophthalmologist found bilateral superior arcuate visual-field defects.

One month later, an MRI study of the brain (Fig. 1), performed before and after the administration of gadolinium, disclosed a mass in the pituitary gland that was 13 mm in vertical dimension, 16 mm in transverse dimension, and 12 mm in anteroposterior dimension. The mass was enhanced with contrast material and was slightly heterogeneous. It displaced the optic chiasm superiorly, extended into the hypophysial stalk, and displaced both carotid arteries laterally.

There was patchy hyperintensity of the T2-weighted signal in the subcortical white matter, probably related to microangiopathic changes. The findings on radiologic examination of the chest were unchanged from those on examination 29 months earlier.

Two months later, the patient was admitted to the hospital for a diagnostic procedure.

**DIFFERENTIAL DIAGNOSIS**

**Dr. Joseph R. Madsen**: The findings in this case that must be explained by my diagnosis include hyperlipidemia, the elevated erythrocyte sedimentation rate, several hormonal abnormalities, hyponatremia on at least one occasion, and the MRI abnormalities. I shall discuss the clinical issues before addressing the radiographic lesion, which is at the center of the case.

This patient’s hyperlipidemia was characterized by an elevation in the serum cholesterol level, especially the low-density lipoprotein fraction. Thyroid function was evaluated because hypothyroidism is a treatable cause of hyperlipidemia. In patients with primary thyroid disease (which, like hyperlipidemia, is prevalent in older people), the level of thyroid-stimulating hormone is the first variable measured during screening, because an elevated value is a sensitive index of hypothyroidism and can predict the value of thyroid hormone replacement as a lipid-lowering strategy.

In the relatively rare cases of secondary hypothyroidism (due to pituitary failure), elevation of thyroid-stimulating hormone obviously does not occur. In the case of this patient, secondary hypothyroidism was eventually recognized, and thyroid hormone was administered. We do not know how the hyperlipidemia responded, but I assume that long-standing, moderate hypopituitarism accounted for it.

Elevation of the erythrocyte sedimentation rate is a nonspecific finding associated with rheumatologic disorders, other inflammatory diseases (including infections), and cancer. Very severe hyperlipidemia by itself can affect the platelets and cause an increase in the erythrocyte sedimentation rate, but the moderate degree of hypercholesterolemia in this patient would not have resulted in such an elevation. The diagnosis of polymyalgia rheumatica that she received was justified by her persistent pain and her age. Criteria for the diagnosis of this disorder are controversial, and there is no pathological gold standard.

When a patient with presumed polymyalgia rheumatica has intracranial or visual symptoms, biopsy of the temporal artery is recommended to rule out temporal (giant-cell) arteritis. Vasculitis and other inflammatory diseases can damage the endocrine organs, including the pituitary gland and hypothalamus. Some definitions of polymyalgia rheumatica require the ex-

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**Table 4. Findings on Lumbar Puncture Six Months Before Admission.**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>FINDING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance of fluid</td>
<td>Clear, colorless</td>
</tr>
<tr>
<td>Cells (per mm$^3$)</td>
<td>3 Lymphocytes</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>59</td>
</tr>
<tr>
<td>Total protein (mg/dl)</td>
<td>50</td>
</tr>
<tr>
<td>Microscopical examination</td>
<td>No microorganisms</td>
</tr>
<tr>
<td>Culture</td>
<td>No microorganisms</td>
</tr>
</tbody>
</table>

*To convert the value for glucose to millimoles per liter, multiply by 0.05551.

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**Figure 1. Sagittal T1-Weighted MRI Scan Obtained after the Administration of Gadolinium, Showing a Mass in the Pituitary Gland.**

The mass extends into the hypophysial stalk, which is prominent.
clusion of other explanations for an elevated erythrocyte sedimentation rate. Accordingly, if we can identify another cause of the elevation in this patient’s erythrocyte sedimentation rate, we can discard the diagnosis of polymyalgia rheumatica.

The first evidence of endocrinopathy in this patient, besides secondary hypothyroidism, was the discovery of hyponatremia and hypo-osmolality 21 months before admission. The result of a cosyntropin stimulation test to evaluate adrenal reserve before the initiation of corticosteroid therapy was normal, however, and after the initiation of corticosteroid therapy her anorexia and lack of energy persisted. The subsequent collapse associated with fever raises the possibility of glucocorticoid insufficiency similar to that in Addison’s disease. A seizure could also have been the cause, but an electroencephalogram showed no evidence of such an event, and an MRI revealed a pituitary mass. Another cosyntropin stimulation test 18 months later suggested a loss of adrenocorticotropic reserve, and the finding of a low level of thyroid-stimulating hormone suggested secondary hypothyroidism, even though the circulating thyroxine and triiodothyronine levels were normal. Thyroxine-replacement therapy was instituted. There was no biochemical evidence of any specific type of secretory adenoma. The level of follicle-stimulating hormone was 3.3 U per liter, a low value in a postmenopausal woman. Thus, every finding pointed to hypopituitarism.

Although the patient did not have diabetes insipidus, her paradoxically low sodium level and low osmolality are compatible with involvement of the posterior as well as the anterior pituitary gland and excess secretion of vasopressin (antidiuretic hormone). Hypersecretion of vasopressin may have been a response to a stimulus such as hypovolemia. For example, neurosurgeons formerly regarded hypopituitarism during subarachnoid hemorrhage as a sign of the syndrome of inappropriate secretion of antidiuretic hormone. Subsequently we learned to evaluate volume status before making this assumption, because restriction of free water may be dangerous if the patient already has hypovolemia. Some destructive or irritative lesions of the neurohypophyseal system can cause excess diuresis rather than diabetes insipidus. For example, vasopressin secretion is often unstable after pituitary surgery or resection of suprasellar masses. Finally, hyponatremia without hypokalemia is typical of adrenocorticotrophic deficiency. I am uncertain whether the hyponatremia with hypo-osmolality was a transient or a persistent feature in this case, but it may reflect abnormal functioning of the posterior pituitary or hypothalamus, even in the absence of overt diabetes insipidus.

May we review the radiographic findings?

DR. R. GILBERTO GONZALEZ: On the MRI study performed two months before admission, sagittal T1-weighted images obtained before the administration of contrast material reveal a mass enlarging the sella turcica, extending into the suprasellar cistern, and abutting the optic chiasm. The coronal T1-weighted images indicate that the mass probably also extends into the region of the cavernous sinus, where it abuts the internal carotid arteries. After the administration of contrast material (Fig. 1), the mass is intensely enhanced and slightly heterogeneous. It also appears to infiltrate and enlarge the pituitary stalk.

DR. MASDEN: Abnormalities of the pituitary gland and hypothalamus that can cause hypopituitarism include primary and secondary neoplasms, meningitis, sarcoidosis, other inflammatory lesions, subarachnoid hemorrhage, cranial trauma, and trauma from surgery or radiation therapy. The history in this case and the findings in the cerebrospinal fluid rule out all these causes except for neoplasms, inflammatory lesions of the pituitary gland, and sarcoidosis.

Tumors that merit consideration include pituitary adenomas, Rathke’s cyst, craniopharyngioma, germ-cell tumors, lymphoma, and metastatic tumors. The laboratory studies in this case revealed no evidence of an active pituitary adenoma, although growth hormone studies were not performed. Assessment of the level of growth hormone requires dynamic-response tests because of the characteristically pulsatile nature of its secretion. It is unlikely, however, that on physical examination the characteristic facial features of acromegaly would be overlooked; in addition, the sequelae of acromegaly, including diabetes mellitus and hypertension, were not present in this patient.

“Clinically nonfunctioning” adenomas are often immunoreactive for the alpha subunit of the glycoprotein hormones (thyroid-stimulating hormone, follicle-stimulating hormone, and luteinizing hormone) and may be associated with elevated serum levels of the alpha subunit, but in this patient the level was normal. Most important, the appearance of this lesion on MRI is not typical of a pituitary adenoma because of the thickening of the pituitary stalk and the presence of an enhancing mass along the course of the stalk. Also, a pituitary adenoma would not explain the elevated erythrocyte sedimentation rate. A germ-cell tumor would be rare in a patient of this woman’s age, and there are no findings to suggest the presence of a metastatic tumor or lymphoma. Cranioophyngiomas and Rathke’s cysts occur in the area where this mass was found but have different radiologic features.

Inflammatory, tumor-like lesions of the pituitary gland and stalk include abscesses, but the long history of this patient’s illness strongly argues against the diagnosis of an abscess. Two nonsuppurative inflammatory lesions — lymphocytic hypophysitis and granulomatous hypophysitis — deserve serious consideration. These two lesions are not radiographically distinguishable, but they differ in their clinical features.

Lymphocytic hypophysitis is mainly associated with
though they are compatible with it. Ling enough to make the diagnosis of sarcoidosis, although the slight elevation in the aminotransferase level could represent a cardiac manifestation of sarcoidosis, and low voltages on the electrocardiogram could be due to sarcoidosis, and the neurohypophysis is more likely to be involved. The stable lesions on the pulmonary radiographs were negative. The diagnosis was hypophysitis with granulomatous hypophysitis. A distinction between these two lesions cannot always be made, however, first to rule out an infection or neoplasm that might require more specific therapy. In addition, the possibility that the visual-field defects in this patient will rapidly worsen and the potential therapeutic value of transsphenoidal exploration for decompression and biopsy justify transsphenoidal resection of the mass.

DR. CHARLES R. PERAKIS: What erythrocyte sedimentation rates have been reported in other cases of hypophysitis?

DR. MADSSEN: In most cases the rate has been elevated, but in some it has been normal. The elevated levels have been less than 100 mm per hour, and the results of testing did not distinguish lymphocytic from granulomatous hypophysitis.

**CLINICAL DIAGNOSES**

Hypophysitis.

**DR. JOSEPH R. MADSSEN’S DIAGNOSIS**

Hypophysitis, probably granulomatous.

**PATHOLOGICAL DISCUSSION**

DR. DIANE KARLUK: Microscopical examination of the biopsy specimens of the anterior pituitary showed effacement of its normal glandular architecture by a dense inflammatory infiltrate that varied in composition; it was predominantly lymphocytic (Fig. 2) with focal follicle formation but also contained a mixture of lymphocytes, plasma cells, histiocytes, polymorphonuclear leukocytes, and eosinophils. Ill-defined epithelioid granulomas containing multinucleated giant cells (Fig. 3) were present focally; small calcific deposits and larger confluent foci of calcification were seen in some of the giant cells (Fig. 2). Many pituicytes were vacuolated (Fig. 4). Immunophenotyping confirmed the presence of both B and T lymphocytes, and stains for tubercle bacilli and fungi were negative. The diagnosis was hypophysitis with both granulomatous and lymphocytic inflammation.

The differential diagnosis included both a primary inflammatory process of the pituitary gland and a systemic inflammatory process, such as sarcoidosis. Features of this case that argue against the latter diagnosis are the absence of clinical evidence of systemic disease and the wide variety of types of inflammatory cells in the infiltrate. Moreover, pituitary involvement is rarely an initial finding in patients with sarcoidosis, and the neurohypophysis is more likely to be involved than the adenohypophysis.

As Dr. Madsen stated, many cases of hypophysitis fall clinically and histologically into the category of either lymphocytic hypophysitis or granulomatous hypophysitis. A distinction between these two lesions cannot always be made, however, because of their overlapping clinical and histopathological features.

In 1917, Simmonds described elderly women with pituitary inflammatory lesions characterized by lymphocytic hypophysitis.
phocytic inflammation and granulomas with multinucleated giant cells — histologic features similar to those in this case.

In both lymphocytic hypophysitis and granulomatous hypophysitis, ultrastructural studies show activated cytotoxic lymphocytes that interdigitate with pituicytes within periacinar basement membranes.24,25 McKeel25 noted the overlap between these two categories of hypophysitis and suggested an alternative diagnosis of either granulomatous hypophysitis with extensive lymphocytic infiltration or granulomatous lymphocytic adenohypophysitis. He hypothesized that hypophysitis is characterized by a spectrum of histologic features, with a purely lymphocytic adenohypophysitis constituting the predominant early lesion and a granulomatous component occurring during a later phase of the disease. The mixed composition of the inflammatory infiltrates within the same area of tissue also raises the question of sampling bias.

It has been suggested that both lymphocytic hypophysitis and granulomatous hypophysitis have an autoimmune basis. With respect to lymphocytic hypophysitis, the evidence of an autoimmune pathogenesis includes the presence of circulating antipituitary antibodies in patients with biopsy-proved disease. In a study of serum from 115 patients with endocrine disease and 52 controls, Crock26 found that antibodies to a 49-kd cytosolic protein were present in 70 percent of the patients with biopsy-proved lymphocytic hypophysitis, in 55 percent of those with clinically suspected hypophysitis, in 42 percent of patients with Addison's disease, and in 9.8 percent of the controls. This cytosolic autoantigen is not restricted to pituitary tissue but is also present in the adrenal and thyroid glands, brain, liver, and spleen. Antipituitary antibodies have also been detected in patients with the empty-sella syndrome,27 Cushing's disease,28 Grave's disease,29 and polyendocrinopathic disorders without hypophysitis.30 Autoimmune conditions associated with lymphocytic or granulomatous hypophysitis include thyroiditis, adrenalitis, atrophic gastritis,31 Sjögren's syndrome,32 systemic lupus erythematosus,33 Cogan's syndrome,34 and Takayasu's disease.35 The proposal that hypophysitis has an autoimmune pathogenesis rests on the finding that injection...
of pituitary homogenates induces the disorder in mice and rabbits.

In summary, this was a case of hypophysitis with both granulomatous and lymphocytic inflammation in an elderly woman without evidence of infection, neoplasm, or systemic disease.

DR. E. TESSA HEDLEY-WHITE: There is little doubt that a smaller biopsy specimen could have contained only the lymphocytic infiltrate or only the granulomatous infiltration.

DR. MADSEN: After the biopsy, was there further investigation of the possibility of sarcoidosis?

DR. ENRICO CAGLIERO: Further investigation has been delayed for some time because of the patient’s travel schedule. The angiotensin-converting–enzyme investigation of the possibility of sarcoidosis?

ANATOMICAL DIAGNOSIS
Granulomatous and lymphocytic hypophysitis.


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