Lymphocytic and Granulomatous Hypophysitis: Experience with Nine Cases

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OBJECTIVE: Lymphocytic hypophysitis and granulomatous hypophysitis are rarely encountered. The aim of this study was to demonstrate their clinical peculiarities among pituitary disorders and to provide an approach for their clinical management.

METHODS: In a retrospective study, we reviewed our surgical experience with nine patients harboring hypophysitis. The series included six cases of lymphocytic hypophysitis, two cases of granulomatous hypophysitis, and one case with evidence of coexisting lymphocytic and granulomatous hypophysitis.

RESULTS: A striking similarity of clinical signs was found for our nine patients. Headache or aseptic meningitis, thickening of the sphenoid sinus mucosa, pituitary stalk enlargement, and tongue-shaped extension of the lesion along the basal hypothalamus were characteristic signs. Lymphocytic hypophysitis was not associated with pregnancy in any of the seven cases. No recurrence has been observed in six cases with total removal of the inflammatory tissue.

CONCLUSION: Lymphocytic hypophysitis and granulomatous hypophysitis represent related inflammatory disorders. Their conspicuous clinical features frequently allow preoperative diagnosis of hypophysitis. In view of their sometimes insidious clinical course, early surgical exploration is justified. (Neurosurgery 40:713–723, 1997)

Key words: Granulomatous hypophysitis, Lymphocytic hypophysitis, Pituitary surgery

Lymphocytic hypophysitis was first described in 1962 (13), but it was not until the 1980s that reports on surgically treated cases appeared in the literature (21). Histologically, lymphocytic hypophysitis is characterized by infiltration of the anterior pituitary gland with lymphocytes and plasma cells and by fibrosis; it finally leads to destruction of the gland (2, 7, 13). Several lines of evidence suggest an autoimmune background (7) with a reaction directed against the anterior pituitary. It is generally considered that lymphocytic hypophysitis is temporally related to pregnancy (2, 18). Approximately 60 cases of lymphocytic hypophysitis have been reported in the literature (30), and only a few of them have involved men (18, 25, 28, 38) or female patients without associated pregnancy (20, 40). However, in our surgical series of 2362 pituitary lesions, we have encountered five female patients harboring lymphocytic hypophysitis, with no case being related to pregnancy, and two additional male patients with lymphocytic hypophysitis.

Granulomatous hypophysitis is another inflammatory disorder of the pituitary gland; it is characterized by granulomas with epithelioid histiocytes and multinucleated giant cells but also shows lymphocyte collections (10, 34, 36). Granulomatous hypophysitis has been long recognized as an isolated disorder of the pituitary gland. It is distinct from systemic giant-cell disorders such as tuberculosis, sarcoidosis, or syphilis (10, 33, 35, 36). Because of their ultrastructural similarities and the evidence of an autoimmune disorder in granulomatous hypophysitis and lymphocytic hypophysitis, it has been suggested that the two entities have the same pathogenetic background or even represent different stages of the same disease (15, 22, 25, 41). A case suggestive of giant-cell hypophysitis in the postpartum period has also been described (8). The first operation for granulomatous hypophysitis in a patient who presented with unilateral ophthalmoplegia was reported in 1980 (39). Since then, only a few surgical cases have been reported (9, 34). With our series of inflammatory...
lesions, we add two additional cases of granulomatous hypophysitis to the literature.

We present the clinical features of our patients with lymphocytic and granulomatous hypophysitis. The striking similarity of their clinical presentation is shown. Awareness of the characteristic clinical features will aid the preoperative recognition of hypophysitis and the choice of correct further management. The role of surgery and the surgical outcomes are presented.

\[
\frac{7}{2362} = 0.3\% 
\]

**RESULTS**

**Patient and Methods**

From December 1982 to December 1995, 2362 operations for lesions in the pituitary region were performed in our department. Pituitary adenomas predominated (2031 operations). Only nine operations (0.38%) were performed for lymphocytic and granulomatous hypophysitis. The mean patient age was 35 years (range, 16–82 yr). There was no evidence of infectious disease in any of the nine cases.

Preoperatively, all patients were evaluated by magnetic resonance imaging (MRI). Contrast medium was used in all but one patient. Plain cranial x-rays were available to evaluate the size and bony changes of the pituitary fossa.

For ophthalmological investigation, visual acuity and visual field examination was performed before surgery and 1 week and 3 months after surgery. Endocrinological assessment in all patients included dynamic testing with adrenocorticotropic hormone, thyrotropin-releasing hormone, and gonadotropin-releasing hormone stimulation before surgery and 1 week and 3 months after surgery. We determined basal and stimulated cortisol, thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, growth hormone, and prolactin levels and measured triiodothyronine, thyroxine, and estradiol or testosterone levels according to the gender. Adrenocorticotropic hormone stimulation provides only indirect information about hypothalamic and pituitary function of the adrenal axis. However, it is a practical test that produces results that are closely correlated with the results of an insulin tolerance test (37). An additional insulin tolerance test was available for six patients preoperatively and three patients postoperatively.

**Clinical presentation**

The major presenting symptom for each patient is listed in Table 1. The duration of the symptoms ranged from 4 to 24 months. Headache was the most frequent complaint (Table 1) and was apparently related to the disease in seven patients. A chiasmal syndrome was found in two patients. Neurologically, a sixth nerve palsy was found in one patient (Patient 7).

For two patients, the surgeon was convinced of the existence of an inflammatory lesion. For four patients, an inflammatory disorder was included in the preoperative differential diagnosis. However, for three patients a pituitary adenoma was suspected preoperatively.

**Preoperative neuroradiological findings**

A normal-size pituitary fossa was found in four of the nine cases (Table 2). In another three cases, the pituitary fossa was slightly enlarged. Marked enlargement was encountered in only two cases. A plane sellar floor in the coronal MRI image and in x-rays was found in six cases.

In Figure 1, the appearance of the lesions is shown schematically, by artists drawing according to the preoperative MRI findings. Marked contrast enhancement in MRI was seen in five cases (Table 2); two of these cases had a central hypointense area. Patchy irregular contrast enhancement was demonstrated in another patient. A hyperintense signal without further enhancement after contrast was found for one patient (Patient 2). A tongue-like suprasellar and retrosellar exten-

**TABLE 1. Diagnoses and Clinical Data**

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Diagnosis</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Presenting Symptom</th>
<th>Headache (0/1/2)</th>
<th>Erythrocyte Sedimentation Rate (mm, 1 h/2 h)</th>
<th>White Blood Cell Count (cells/mm³)</th>
<th>Leukocytes in Cerebrospinal Fluid (cells/mm³)</th>
<th>Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lymphocytic hypophysitis</td>
<td>16</td>
<td>F</td>
<td>Meningitis</td>
<td>+</td>
<td>52/71</td>
<td>9,500</td>
<td>3.3 (lymphocytes + polymorphonuclear cells)</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Lymphocytic hypophysitis</td>
<td>35</td>
<td>M</td>
<td>Headache</td>
<td>+</td>
<td>4/12</td>
<td>5,100</td>
<td>5 (lymphocytes)</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Lymphocytic hypophysitis</td>
<td>42</td>
<td>F</td>
<td>Diabetes insipidus</td>
<td>+</td>
<td>10/30</td>
<td>9,200</td>
<td>0 (postoperative)</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Lymphocytic hypophysitis</td>
<td>18</td>
<td>F</td>
<td>Meningitis</td>
<td>++</td>
<td>34/64</td>
<td>1,300</td>
<td>257 (lymphocytes + polymorphonuclear cells)</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Lymphocytic hypophysitis &quot;healed stage&quot;</td>
<td>28</td>
<td>F</td>
<td>Amniorrhoea</td>
<td>0</td>
<td>8/15</td>
<td>7,000</td>
<td>4 (postoperative)</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Lymphocytic hypophysitis</td>
<td>38</td>
<td>F</td>
<td>Headache</td>
<td>++</td>
<td>9/100</td>
<td>7,000</td>
<td>540 (lymphocytes)</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Granulomatous &amp; lymphocytic hypophysitis</td>
<td>40</td>
<td>M</td>
<td>Headache</td>
<td>++</td>
<td>13/30</td>
<td>15,500</td>
<td>1 (postoperative)</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Granulomatous hypophysitis</td>
<td>52</td>
<td>F</td>
<td>Visual deterioration</td>
<td>+</td>
<td>8/14</td>
<td>6,100</td>
<td>10 (lymphocytes + monocytes)</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>Granulomatous hypophysitis</td>
<td>48</td>
<td>F</td>
<td>Headache</td>
<td>++</td>
<td>40/65</td>
<td>7,100</td>
<td>NA* (not available)</td>
<td>No</td>
</tr>
</tbody>
</table>

*NA*, not available.
TABLE 2. Radiological Findings

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>MRIa Signal after Contrast</th>
<th>Extension to Basal Hypothalamus</th>
<th>Pituitary Stalk</th>
<th>Sellar Floor (Coronal View)</th>
<th>Sellar Floor (Thickness)</th>
<th>Pituitary Fossa (Size)</th>
<th>Sphenoid Sinus Mucosa Swelling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hyperintense (hypointense center)</td>
<td>Yes</td>
<td>Thickened</td>
<td>Plane</td>
<td>Thin ventrally</td>
<td>Enlarged</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Hyperintense</td>
<td>No</td>
<td>Thickened</td>
<td>Depressed unilaterally</td>
<td>Normal</td>
<td>Normal</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Hypointense</td>
<td>No</td>
<td>Thickened</td>
<td>Plane</td>
<td>Normal</td>
<td>Normal</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Hyperintense</td>
<td>Yes</td>
<td>Thickened</td>
<td>Plane</td>
<td>Normal</td>
<td>Normal</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Patchy enhancement</td>
<td>No</td>
<td>Normal</td>
<td>Depressed unilaterally</td>
<td>Normal</td>
<td>Normal</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Hyperintense (hypointense center)</td>
<td>Yes</td>
<td>Thickened</td>
<td>Plane</td>
<td>Thin</td>
<td>Slightly enlarged</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Hyperintense (triangular)</td>
<td>No</td>
<td>Thickened</td>
<td>Plane</td>
<td>Normal</td>
<td>Slightly enlarged</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Hyperintense</td>
<td>Yes</td>
<td>Thickened</td>
<td>Plane</td>
<td>Normal</td>
<td>Slightly enlarged</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>NAb</td>
<td>Yes</td>
<td>Thickened</td>
<td>Depressed unilaterally</td>
<td>Thin</td>
<td>Enlarged</td>
<td>Yes</td>
</tr>
</tbody>
</table>

a MRI, magnetic resonance imaging.
b NA, not available.

Thickening and enhancement of the sphenoid sinus mucosa was observed in four cases. Histological evaluation of the mucosa was performed in three cases. The inflammatory infiltrates of the mucosa resembled the intrasellar pathological findings in two cases, but swelling of the mucosa without histological evidence of inflammation was found in one case.

Endocrinological findings

Mild hyperprolactinemia was observed for five of our patients. Diabetes insipidus was found for five patients (Table 3). Only one patient presented with entirely normal anterior pituitary function preoperatively. Five patients had partial anterior pituitary failure, and three were found to have panhypopituitarism.

Surgical findings

Seven patients were operated on by a transsphenoidal approach. As suspected from MRI findings, thickened mucosa of the sphenoid sinus was found in three cases. The consistency of the thickened mucosa was firm and cartilaginous in one of these cases. In the remaining four cases, the mucosa appeared to be normal. In six cases, the sellar floor was not thinned by the lesion. After the basal dura was opened, the lesions were selectively removed. The consistency and appearance of the lesions are depicted in Table 4. A complete transsphenoidal resection was accomplished in four cases. A partial or subtotal resection was achieved in one case each. Residual normal pituitary tissue was identified in six patients. In one patient (Patient 7), the pituitary gland was enlarged and had a swollen appearance, with no distinct separate lesion. For this reason, only biopsies were taken from the gland.

For two patients, a transcranial approach via a fronto-temporal craniotomy was used because there was an irregular

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*schematic drawings for nine cases of lymphocytic or granulomatous hypophysitis (sagittal sections).*
table 3. ophthalmological and endocrinological findings

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Visual Acuity</th>
<th>Visual Field</th>
<th>Prolactin (mU/L)</th>
<th>Anterior Pituitary Function</th>
<th>Posterior Pituitary Function</th>
<th>Hypothalamic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>Normal</td>
<td>910</td>
<td>N</td>
<td>Down</td>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td>2</td>
<td>Normal</td>
<td>Normal</td>
<td>174</td>
<td>N</td>
<td>N</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>Normal</td>
<td>Normal</td>
<td>250</td>
<td>N</td>
<td>N</td>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td>4</td>
<td>Normal</td>
<td>Normal</td>
<td>953</td>
<td>Down</td>
<td>N</td>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td>5</td>
<td>Normal</td>
<td>Normal</td>
<td>151</td>
<td>Down</td>
<td>Down</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>Normal</td>
<td>Normal</td>
<td>800</td>
<td>Down</td>
<td>Down</td>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td>7</td>
<td>Normal</td>
<td>Normal</td>
<td>1000</td>
<td>Down</td>
<td>NA</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>R, 0.8; L, 0.2</td>
<td>Normal</td>
<td>782</td>
<td>Down</td>
<td>NA</td>
<td>Unchanged</td>
</tr>
<tr>
<td>9</td>
<td>R, 0.2;</td>
<td>Concentric</td>
<td>87</td>
<td>Down</td>
<td>NA</td>
<td>Diabetes insipidus</td>
</tr>
</tbody>
</table>

Note: Normal, less than 500 miliunits/L.

Note: GH, growth hormone; N, normal; ↓, impaired; NA, not available.

Table 4. Surgical Findings and Outcome

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Operative Approach</th>
<th>Consistency/ Appearance</th>
<th>Resection</th>
<th>Complications</th>
<th>Steroid Therapy</th>
<th>Follow-up (months)</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right fronto-temporal</td>
<td>Firm capsule, creamy content</td>
<td>Complete</td>
<td>Wound infection</td>
<td>No</td>
<td>111</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Transsphenoidal</td>
<td>Soft, yellowish</td>
<td>Complete</td>
<td>None</td>
<td>No</td>
<td>43</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Transsphenoidal</td>
<td>Creamy-necrotic (3/5), firm (2/5)</td>
<td>Complete</td>
<td>None</td>
<td>No</td>
<td>104</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Transsphenoidal</td>
<td>Firm, greasy, whitish</td>
<td>Subtotal</td>
<td>None</td>
<td>No</td>
<td>20</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Transsphenoidal</td>
<td>Firm, whitish</td>
<td>Complete</td>
<td>None</td>
<td>No</td>
<td>35</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Transsphenoidal</td>
<td>Creamy, yellowish, fibrotic part</td>
<td>Complete</td>
<td>Yes</td>
<td>No</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Transsphenoidal, 2 times</td>
<td>Firm</td>
<td>Biopsy</td>
<td>Yes</td>
<td>No</td>
<td>29 (12 mo)</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Transsphenoidal</td>
<td>Firm, cartilaginous</td>
<td>Partial</td>
<td>None</td>
<td>Yes</td>
<td>44</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>Right fronto-temporal</td>
<td>Firm</td>
<td>Complete</td>
<td>None</td>
<td>No</td>
<td>12</td>
<td>No</td>
</tr>
</tbody>
</table>

Suprasellar portion. In both cases, total removal of the lesion was accomplished. In one of these cases, the planum sphenoidal and anterior sellar floor were opened to gain access to the intrasellar portion. The pituitary gland was identified in one of the two cases.

Histological findings

In each case, the diagnosis was confirmed histologically (Table 1). Lymphocytic hypophysitis was found for five patients (Table 1). One example of lymphocytic hypophysitis is demonstrated in Figure 2. One lesion suggested the so-called "healed" stage of lymphocytic hypophysitis. For one patient, there were histological features of both granulomatous and lymphocytic hypophysitis. Two lesions were consistent with granulomatous hypophysitis. Whereas numerous giant cells were demonstrated in one lesion (Fig. 3), the other granulomatous lesion was free of giant cells.

Outcome

The mean follow-up period was 45 months (Table 4). Recurrence was observed only in the patient who initially underwent a biopsy for lymphocytic hypophysitis. He under-
went a second operation 1 year later and received several courses of corticosteroids. He still has a fluctuating course, with ongoing disease, more than 2 years after initial presentation. Endocrine functions were unchanged after surgery for six patients (Table 3). In one patient, anterior pituitary function deteriorated. Recovery from diabetes insipidus and improvement of anterior pituitary function, which allowed tapering of the replacement dose, was observed for one patient each.

Illustrative cases

Patient 1

In the summer of 1986, a 16-year-old girl suffered from an episode of headaches, fever, nausea, fatigue, and increased thirst. In September 1986, she was admitted to a medical department with a second episode of similar but more severe symptoms, including vomiting. Her periods were overdue. Severe neck stiffness was noted. Cerebrospinal fluid (CSF) analysis showed 933 white cells/mm³ (lymphocytes and polymorphonuclear cells). No bacteria were found in the CSF. Detailed serological studies of CSF and serum showed no evidence of viral infection. Without specific therapy, the CSF cell count rapidly declined to 63 leukocytes per mm³; the patient was free of fever within a few days. In subsequent weeks, she suffered recurrent episodes of fever, with her body temperature increasing to 39.6°C, and she developed overt diabetes insipidus. Computed tomography and MRI revealed an intrasellar and suprasellar lesion (Fig. 1) with strong peripheral contrast enhancement and a central low-density/intensity portion.

The patient was admitted to our department for surgical therapy. She had lost 17 kg of her body weight within 3 months. Preoperative endocrinological evaluation revealed deficiencies of the adrenal, gonadal, and growth hormone axes. Thyroid function was normal. The prolactin concentration was elevated to 910 milliunits per L. The patient was still feverish, and the CSF cell count obtained immediately before surgery yielded 528 white cells per mm³. Microorganisms were never found in the CSF. Surgery was performed on February 3, 1987. Because the lesion was dumbbell-shaped, an approach via a fronto-temporal craniotomy was used. An extremely firm capsule, which contained creamy fluid, was encountered. The lesion was completely removed. The histological report revealed granulomatous hypophysitis without giant cells.

After surgery, the body temperature of the patient immediately normalized. Three weeks after surgery, the CSF contained 20 leukocytes per mm³; the CSF cell count further declined to 2 leukocytes per mm³ 2 months after surgery. However, the patient gained 40 kg of weight within 3 months. Nine years after surgery, she is doing well and has not suffered a recurrent lesion or additional episodes of meningitis. Her body weight gradually declined, without dieting.

FIGURE 2. Histological appearance of lymphocytic hypophysitis, showing anterior pituitary acini intermingled with lymphocyte infiltrates (Patient 7).

FIGURE 3. Histological appearance of granulomatous hypophysitis, demonstrating multinucleated giant cells, epitheloid cells, and lymphocytes (Patient 9).

Patient 4

From the beginning of May 1994, an 18-year-old female patient complained of severe headaches. By the end of May 1994, she was admitted to a medical department under the diagnosis of meningitis. She had fever, with a body temperature of 39°C, and a stiff neck. A lumbar puncture showed 275 leukocytes per mm³ (lymphocytes and polymorphonuclear cells). Bacteriological examination of her CSF yielded negative results. Serological investigations provided no evidence of viral meningitis, except for increased varicella zoster immunoglobulin G. A therapeutic trial with zovirax was commenced. The body temperature of the patient normalized within a few days. After this episode of meningitis, her fluid intake increased to 16 L per day, and amenorrhea was noticed. A disturbed pattern of sleep and wakefulness since May 1994 and a weight gain of 13 kg since July 1994 suggested hypothalamic dysfunction. Computed tomography and MRI revealed an intrasellar and suprasellar contrast-enhancing mass, with extension into the basal hypothalamus (Fig. 4).

The patient was admitted to our department, in September 1994, for treatment of the intrasellar and suprasellar lesion. A second MRI study demonstrated a slight decrease in size; in particular, the enhancement of the basal hypothalamus had disappeared. An inflammatory origin was apparent. Because the patient appeared to suffer from severe pituitary and hypothalamic dysfunction, surgical resection and confirmation of the diagnosis were attempted. During transsphenoidal surgery, which was performed on September 30, 1994, the thickened basal dura was opened. A whitish, greasy, firm, intrasellar mass was removed. The pituitary gland was encountered in the upper sellar region, toward the sellar entrance. Histologically, lymphoplasm...
mucytic infiltrates of the anterior pituitary gland, with fibrosis, were demonstrated. Three months after surgery, MRI revealed a minor intrasellar contrast-enhancing area. The enhancement of the pituitary stalk had decreased, and the erosion to the hypothalamus had regressed. The CSF cell count had declined to 8 white cells per mm³. The sleep disorder had resolved.

**Patient 6**

This 38-year-old woman complained of repeated frontal headaches since July 1993. The headaches worsened in September 1994 and were then associated with nausea and vomiting. They were constantly provoked by exercise and followed by physical exhaustion. MRI demonstrated an intrasellar and suprasellar/retrosellar lesion of dumbbell shape, with high peripheral and low central signal intensity in contrast imaging (Fig. 5A). The serum prolactin level was slightly increased to 800 milliunits per L. Insulin-induced hypoglycemia revealed an attenuated growth hormone response. Anterior pituitary function was otherwise normal. A water-deprivation test provided no evidence of diabetes insipidus. The erythrocyte sedimentation rate (ESR) increased to 90 mm during the 1st hour. A lumbar puncture revealed 540 white cells per mm³ (mainly lymphocytes and plasma cells) in the CSF. The angiotensin-converting enzyme concentration was normal (14.8 units/ml). Results of a Tine test were negative. An inflammatory pituitary lesion was suspected, and trial treatment with dexamethasone (3 mg, tds) was commenced in December 1994. Within 2 weeks, the ESR decreased to 5 mm per hour and the CSF cell count declined to 16 per mm³. The prolactin level of the patient normalized. MRI demonstrated marked shrinkage of the suprasellar and hypothalamic portion (Fig. 5B). Consequently, surgery was deferred. The headaches resolved. Dexamethasone was rapidly tapered and eventually discontinued in March 1995, when the patient developed steroid-induced psychosis and suffered from oral mycosis.

In May 1995, the patient became amenorrheal; in June 1995, she noticed fatigue and polyuria, with a fluid intake of 7 L per day. Endocrinological reassessment revealed diabetes insipidus, panhypopituitarism, and hyperprolactinemia (Table 3). MRI showed a re-increase of the lesion, with enhancement of the pituitary stalk and the area below the basal hypothalamus (Fig. 5C).

**Patient 8**

This 52-year-old woman complained of headaches and pain in her right eye for 5 months and noticed fatigue for 3 months. She presented to us with a history of visual deterioration over a 6-week period. Visual acuity was reduced to 0.8 in her right eye and 0.2 in her left eye, and visual fields were concentrically restricted. The white blood cell count and the ESR were within normal limits (Table 1). MRI revealed a dumbbell-shaped, space-occupying lesion with an intrasellar portion and a suprasellar portion that was directed to the retrosellar compartment (Fig. 5A and B). Endocrinological assessment revealed panhypopituitarism, but there was no evidence of posterior pituitary failure. A pituitary adenoma was suspected, and transsphenoidal surgery was performed on September 24, 1992. When the pituitary fossa was opened, a firm cartilaginous mass was encountered. The material within the pituitary fossa was removed. Normal anterior pituitary tissue remained in the posterior part of the fossa. Because of its firm consistency, the suprasellar portion did not enter the pituitary fossa even during jugular vein compression and ventilation with positive end-expiratory pressure. The histological report revealed inflammation of the gland with macrophages, lymphocytes, and plasma cells; scattered giant cells were found. The histological appearance was consistent with the features of both lymphocytic and granulomatous hypophysitis. Further evaluation revealed no evidence of a systemic giant-cell disorder, such as tuberculosis or sarcoidosis, suggesting an isolated lesion in the pituitary region. Findings from the chest x-ray were normal, and the Tine test yielded negative results. Angiotensin-converting enzyme levels were within normal limits. Immunological evaluation failed to show antinuclear, antimitochondrial, or neutrophilic cytoplasmic antibodies, and no immune complexes were detected. As expected, postoperative MRI revealed an unchanged size for the suprasellar portion (Fig. 5C and D). Visual fields and visual acuity were improved, but hypopituitarism persisted. A lumbar puncture revealed 10 cells/mm³, consisting of lymphocytes (30%) and monocytes (70%). Because of the firm consistency, transcranial removal of the residue was rejected. Pathogenetically, an abnormal immune response or an autoimmune disorder was considered. Therefore, we commenced a 6-week trial with the corticosteroid prednisolone, starting with 60 mg daily and...
FIGURE 7. Coronal (A, C, and E) and sagittal (B, D, and F), contrast-enhanced, magnetic resonance images of intrasellar and suprasellar hypophysitis. A and B, before transphenoidal surgery, demonstrating the thickened mucosa of the sphenoid sinus; C and D, after surgery, showing the residual suprasellar portion; E and F, after the second course of prednylidene (Patient 8).

tapering the dose every 5 days (i.e., 48, 36, 24, and 18 mg, ending with a dose of 12 mg). MRI demonstrated shrinkage of the suprasellar residue, from 11 mm to 6 mm in size, under the corticosteroid regimen. After a 2-month interval, a second application of the prednylidene regimen caused further reduction of the suprasellar mass, to 4 mm (Fig. 7, E and F). The CSF cell count was decreased to 8 cells per mm³ after the first trial and to 6 cells per mm³ after the second trial with corticosteroids. Three years after corticosteroid therapy, there is still no evidence of a re-increase of the suprasellar mass.

DISCUSSION

Inflammatory, space-occupying lesions of the pituitary are rare and represent only 0.38% of our surgical series of pituitary lesions. Only 60 cases of lymphocytic hypophysitis have been described in the literature (30). For granulomatous hypophysitis, incidence of 1% among pituitary abnormalities has been described in a surgical series (34). In contrast, minor inflammatory reactions are a frequent finding in normal pituitary glands (30). Isolated granulomas and chronic inflammation may occur throughout the hypophyseal-hypothalamic region. Large granulomas may appear in the hypothalamus and pituitary gland and may cause hypothalamic symptoms as well as anterior or posterior pituitary failure (33, 35). Chronic inflammation of the neurohypophyseal system was demonstrated by Hoshimaru et al. (16), who biopsied two tiny lesions of the pituitary stalk by a transcranial approach and a lesion of the posterior lobe by a transphenoidal approach, in patients with central diabetes insipidus. The pathological examination revealed infiltration with lymphocytes and plasma cells.

An autoimmune pathogenesis is well established for lymphocytic hypophysitis. The existence of pituitary autoimmunity has been demonstrated (6). A 30% incidence of coexistence of lymphocytic hypophysitis with other autoimmune disorders is found in the literature (7, 13, 18). An autoimmune pathogenesis is also suggested by immunohistochemical characterization and ultrastructural evidence showing that cytotoxic lymphocytes intimately contact anterior pituitary cells in lymphocytic hypophysitis (2, 3, 27, 28). The autoimmune hypothesis is further supported by the finding that lymphocytic hypophysitis can be experimentally induced in rats by injection of isologous and homologous pituitary tissue (19). It has been suggested that lymphocytic hypophysitis mainly affects female patients during pregnancy and after delivery (2, 3, 11, 18). Only individual cases have been reported to be independent of pregnancy, and only a few cases have been described in men. It is therefore surprising that all of our cases of lymphocytic hypophysitis were unrelated to pregnancy. Apparently, the occurrence of lymphocytic hypophysitis without associated pregnancy is more frequent that previously considered.

For one of our patients (Patient 5), the healed stage of an inflammation was the likely diagnosis. There was no preceeding pregnancy to suggest postpartum necrosis, and there was no evidence of pituitary atrophy, which would be expected in the case of an infarction. The sellar content was enlarged. The lesion consisted of bundles of fibrotic tissue intermingled with anterior pituitary tissue. After removal, the cavity was surrounded by normal pituitary tissue, as confirmed by a biopsy. We included the case of healed-stage lymphocytic hypophysitis in this series because it supplements the variety of lesions of presumed inflammatory origin that neurosurgeons may face.

Giant-cell-containing granulomatous hypophysitis of the pituitary gland (granulomatous hypophysitis) was first described in 1917 (36) and is considered a clinico-pathological entity with isolated involvement of the pituitary gland (10, 33, 35, 36). Clinical evaluation must exclude specific granulomas (i.e., sarcoidosis or tuberculosis). Association of giant-cell granulomas of the pituitary and systemic giant-cell-containing disorders has become extremely rare, and most publications are historical (5). We have not encountered a single case of pituitary sarcoidosis or tuberculosis. Granulomatous hypophysitis mainly affects the anterior pituitary lobe. However, it may show an extension to the posterior lobe, to the pituitary stalk, or even to the hypothalamus (33). Clinically, hypopituitarism prevails, and middle-aged or elderly women are predominantly affected (33).

Granulomatous hypophysitis and lymphocytic hypophysitis represent disorders with similar pathogenetic backgrounds (8, 15, 22, 25, 41). Cases with evidence of coexistent lymphocytic hypophysitis and granulomatous hypophysitis have been described (23); such a mixed type of hypophysitis was also found in one of our cases (Patient 8). Furthermore, the similarity of clinical signs for lymphocytic and granulomatous

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hypophysitis is conspicuous. The most striking feature of lymphocytic and granulomatous hypophysitis is the increased CSF cell count and related meningocele (Table 1). Two of our patients presented with clinical signs of meningitis, i.e., one patient each with lymphocytic hypophysitis and granulomatous hypophysitis. The CSF was found to be sterile in all cases. A CSF examination was performed for only a few cases in the literature. Increased white cell counts without meningitis have been documented in some cases of lymphocytic hypophysitis (18, 25, 40).

One publication reported on idiopathic meningitis preceding lymphocytic hypophysitis (40). A spontaneously resolving suprasellar mass in conjunction with sterile meningocerebralitis is also suggestive of granulomatous hypophysitis or lymphocytic hypophysitis (17). In 1992, the only report of granulomatous hypophysitis and aseptic meningitis appeared (41). The authors cautiously reported that a relationship between hypophysitis and meningitis was not ascertained. This attitude might have been based on the lack of support from the preceding literature.

We have no doubt that meningitis or CSF leukocytosis is secondary to the pituitary lesion in hypophysitis. For Patient 1 with granulomatous hypophysitis, it was clearly demonstrated that the fever and episodes of meningitis ceased once the inflammatory lesion had been removed. It must be discussed whether the CSF reaction represents an autoimmune reaction extended to the CSF space (41) or simply a dissemination of inflammatory cells. An increased ESR is an additional clinical sign that supports the suspicion of hypophysitis (Table 1).

Headache is a characteristic symptom in inflammatory lesions (Table 1) and is frequently observed in lymphocytic hypophysitis (7, 20, 25) and granulomatous hypophysitis (9, 34). In contrast to headache in pituitary adenomas, headache is frequently associated with nausea and vomiting (9, 24, 25). It is tempting to assume a connection between headache and CSF lymphocytosis (40). However, a clear correlation between the degree of headache and the CSF white cell count cannot be deduced from our series (Table 1).

The advent of MRI has greatly contributed to a more precise description of pituitary tumors and their morphological features. The most characteristic finding of lymphocytic and granulomatous hypophysitis is the tongue-like extension along the basal hypothalamus, as demonstrated in five of our cases. Ahmed et al. (1) claimed that stalk enlargement is not a finding in lymphocytic hypophysitis. However, a careful review of the literature supports our findings and demonstrates that stalk enlargement is typical in lymphocytic hypophysitis (18, 25, 40) and granulomatous hypophysitis (15, 41). In some instances, it is not clear whether stalk enlargement is a nonspecific reaction or an extension of the lesion along the stalk.

Marked contrast enhancement in MRI and computed tomography is typical of inflammatory lesions of the pituitary (38). Ring-like enhancement is consistent with central necrosis. Triangular enhancement of the lesion and erosion of the diaphragm sellae are pathognomonic findings of lymphocytic hypophysitis but are found only in some cases (4, 38) (Table 2).

A normal-size or slightly enlarged fossa is another finding indicative of lymphocytic hypophysitis (Table 2) (14, 15, 40). A plane sellar floor was frequently observed in our series and can be explained by the diffuse character of inflammation. In contrast, a unilateral depression is generally found in pituitary adenomas, even if they are small.

Another conspicuous finding in our study was an inflammatory reaction of the sphenoid sinus mucosa, although we cannot eliminate the possibility that mucosal changes were an independent and coincidental finding. Thickened mucosa of the sphenoid sinus was previously described by Ahmed et al. (1) in a case of hypophysitis. Scanarini et al. (34) reported on one case of granulomatous hypophysitis with extension into the sphenoid sinus. In another case, a mucocele was found during transsphenoidal surgery for granulomatous hypophysitis, but the mucocele was not histologically examined for inflammatory changes. Spread of the inflammation from the pituitary fossa into the sphenoid sinus is easily understood, because the lesions may also extend to the hypothalamus and encroach upon the cavernous sinus.

Anterior pituitary failure and hyperprolactinemia are frequent findings in lymphocytic hypophysitis (7, 18, 20, 25, 40) and granulomatous hypophysitis (9, 34). Pituitary failure disproportionate to the relatively small size of the lesion is a suspicious feature (7). Diabetes insipidus may occur in both disorders (15, 25) (Table 3). Although it is considered rare in lymphocytic hypophysitis, we found diabetes insipidus in three patients.

Recovery of pituitary deficiency after surgery for hypophysitis is unlikely (26, 34, 38) (Table 3), although rare cases with complete recovery have been reported (21). Deficiency persisting even after surgical decompression underlines the destructive nature of inflammatory lesions. In contrast to the situation with pituitary adenomas, compression and displacement of the pituitary gland as causes of hypopituitarism apparently play lesser roles. Only hyperprolactinemia, which is generally caused by stalk distortion in nonsecreting lesions, is likely to resolve after surgery (20), as demonstrated for four of five cases in our series (Table 3).

Except for lymphocytic hypophysitis in pregnant or nursing women, inflammatory lesions are often not recognized preoperatively. In most cases reported in the literature, pituitary tumors were suspected preoperatively (1, 9, 34), and it has been claimed that no preoperative finding reliably predicts a granuloma of the pituitary (26). Two of our patients were referred to us under the diagnosis of meningitis and additional pituitary tumor, but the connection between meningitis and the pituitary lesion was not recognized. The reason is the rarity of these inflammatory lesions. With increasing awareness of the disease, the diagnosis can frequently be made preoperatively.

In general, the outcome of surgery for lymphocytic hypophysitis and granulomatous hypophysitis is favorable even if the lesion is only partially removed or biopsied (15, 20, 21, 34, 38). Therefore, the recommendations have been to avoid major resection because of the self-limited course (21) or to defer surgery if vision is not compromised (29). However, the course of the disease can be insidious, and recurrence can.
precipitate severe pituitary and hypothalamic damage. Fluctuating courses and recurrent symptoms have been described by several authors (1, 24, 25, 40), and a late recurrence of symptoms 8 years after pregnancy-related lymphocytic hypophysitis has been described (24). Beneficial effects of corticosteroids have been described (4, 12). However, for most patients who underwent corticosteroid therapy, symptoms recurred during therapy or after tapering and withdrawal of corticosteroids (1, 4, 25, 28); a case unresponsive to corticosteroids has been reported (32). For one of our patients (Patient 6), surgery was initially rejected and corticosteroid therapy was commenced. After withdrawal of corticosteroids, the disease recurred and severe pituitary deficiency developed. Another patient (Patient 7) also showed recurrence after withdrawal of corticosteroids. It remains unresolved whether corticosteroids actually influence the natural course of the disease or merely cause transient quiescence of the disease.

Based on this experience, we advocate early surgical intervention. It excludes the possibility of an infectious disorder and confirms the precise diagnosis. Usually, a transsphenoidal approach is appropriate. Abnormal tissue is removed, but normal-appearing tissue is preserved to prevent pituitary dysfunction. If only an enlarged gland is encountered, one must be content with a biopsy to confirm the diagnosis. For two of our patients, the tumor configuration allowed only transcranial surgery. The morbidity rate is low, and additional postoperative pituitary failure is rarely encountered (Tables 3 and 4). If the suprasellar portion does not enter the pituitary fossa, manipulations above the sellar entrance should be avoided, because they carry the risk of damage to the suprasellar structures. In our series, none of the six patients with complete removal has suffered a recurrence. Enlargement of the stalk might be a secondary reaction in some cases and disappears after removal of the intrasellar (subdiaphragmatic) inflammatory mass. Incompletely removed lesions must be observed under a very close follow-up regimen.

Observation alone should be recommended only in the absence of pituitary, hypothalamic, and visual dysfunction. If an inflammatory lesion of the pituitary gland is suspected, the follow-up intervals must be shorter than for asymptomatic pituitary adenomas.

If a residual lesion remains after surgery and symptoms worsen, steroid therapy can still be considered. In view of the results reported in the literature, corticosteroid therapy should be maintained over a longer period of time. One of our patients with histological evidence of lymphocytic hypophysitis and granulomatous hypophysitis was successfully treated with corticosteroids for a residual portion threatening the optic pathways.

Inflammatory lesions of the pituitary gland have been increasingly recognized in the past decade. It remains unresolved whether their incidence is actually increasing. Our presentation should contribute to a better understanding of their clinical peculiarities. Despite recent experience with corticosteroid therapy, surgery remains the mainstay of therapy.

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REFERENCES


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COMMENTS

The authors report a surprisingly high incidence of lymphocytic hypophysitis and/or granulomatous hypophysitis in a very large surgical series of more than 2300 pituitary lesions. Moreover, unlike most cases reported, which are related to pregnancy, these cases were seen in women without relation to pregnancy and in men.

It is interesting that five of the nine cases had a characteristic sagittal magnetic resonance image showing a tongue-like suprasellar and retrosellar extension that reached the hypothalamus. All but one case had widening of the pituitary stalk. Although four of the cases demonstrated thickening of the sphenoid sinus mucosa, I doubt that this common finding is directly related to the process of inflammation within the pituitary. It remains impossible to diagnosis hypophysitis before pituitary biopsy, and the authors think that aggressive surgical resection of abnormal-appearing tissue provides the best chance for long-term remission.

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In large series of sellar lesions, approximately 9% (1) are entities other than pituitary adenomas. Inflammatory lesions make up a small percentage but must be recognized, because the treatment may differ. Lymphocytic hypophysitis has been frequently discussed in the literature in recent years, but it is usually reported among women who are in the late stages of pregnancy or who have recently given birth. This article describes patients, both men and women, with lymphocytic hypophysitis who are not in those situations. Granulomatous hypophysitis, not in relationship to sarcoidosis or tuberculosis, is also occasionally seen.

These entities must be considered in the differential diagnosis. Several hints that differ from those for adenomas are often present. Diabetes insipidus was seen in seven of these patients. This is extremely rare as a presenting sign for non-treated pituitary adenomas. The stalk is often thickened. This may be less helpful, because the stalk may appear thickened when pituitary adenomas compress it from below. Magnetic resonance imaging characteristically shows these lesions extending along the basilar hypophysitis. This is unusual with adenomas. Additionally, with relatively small inflammatory lesions there may be dramatic hypopituitarism, which is not often seen with small adenomas.

Surgery does not always need to be considered. For women with lymphocytic hypophysitis associated with pregnancy, conservative treatment with corticosteroids may suffice, as discussed by the authors. Often however, a conservative operation with decompression of the sella and biopsy of the lesion may be adequate.

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Lymphocytic and Granulomatous Hypophysitis


Anyone who has performed a considerable amount of pituitary surgery has had the problem of obtaining, during the procedure, the pathological report on inflammation. The issues become how much surgery to do, whether to use antibiotics, and what to tell the patient about the remaining pituitary function. Honegger et al. describe these inflammatory lesions well, hypothesizing that the lesions may represent a continuum of problems and describing the results of their management. The rarity of these lesions is impressive, but pituitary surgeons must be ready to deal with them. This will remain an important contribution for some time.

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ANNOUNCEMENT

Foundation for International Education in Neurosurgery Update and Request for Volunteers

The Foundation for International Education in Neurosurgery (FIENS) continues to develop activities that are primarily designed to foster education in developing areas of the world. These initiatives are coordinated with the activities of the World Federation of Neurosurgical Societies, which, through its Education Committee, has sponsored a number of regional educational programs for neurosurgeons in developing areas. The Foundation assists in providing faculty for these larger educational efforts. The major current activities of FIENS consist of programs in Africa. The Foundation has worked with neurosurgeons in Ghana in an attempt to help develop an indigenous neurological training program there. This has involved sending senior level residents and faculty for varying periods of time, usually 3 to 6 months for residents and 2 to 4 weeks for faculty support. FIENS has supported a program in Zimbabwe to provide neurological assistance to the program already in place in that country, and it has supported an African trainee, who currently is a resident at Yale, in the initial steps to develop a neuroscience initiative for Southern Africa. She has been a liaison with the Pan-African Neurosurgical Association, which strongly supports this concept, and we anticipate rapid development. Another new project involves a Senior Neurosurgical Interchange with Peru under the guidance of Dr. Anselmo Pineda and the Peruvian-American Neurosurgical Society. Opportunities exist for volunteer neurosurgeons to go to Peru and visit and work in a number of different medical centers around the country. FIENS maintains a roster of neurosurgeons interested in serving as volunteers. For volunteer experiences of at least 4 to 6 weeks, the Foundation will support the volunteer’s air travel expenses. The host country is ordinarily able to underwrite most of the volunteer’s expenses incurred at work. Further information and volunteer request forms can be obtained from the Office of the Secretary of the Foundation, Dr. David Fairholm: Division of Neurosurgery, Department of Surgery, Room 3100, 910 W. 10th Avenue, Vancouver, BC, Canada V5Z 4E3.

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