Lymphocytic Hypophysitis: Occurrence in Two Men

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TWO MEN UNDERGOING transsphenoidal exploration for pituitary adenoma were found to have lymphocytic hypophysitis. Both presented with frontal headaches, lethargy, and diminished libido. Laboratory investigations showed markedly depressed serum testosterone levels, and magnetic resonance imaging demonstrated pituitary enlargement, with optic chiasm involvement. Intraoperatively, the dura was adherent to the pituitary in each case. The excised glands were effaced by a dense lymphoplasmacytic infiltrate and fibrosis, without granulomas. Nonspecific peripheral enhancement on imaging suggested a diagnosis other than adenoma, but more experience with peripheral enhancement in lymphocytic hypophysitis is needed. The diagnosis was histological and required surgical intervention. Long-term pituitary replacement therapy is usually required. (Neurosurgery 34:159–163, 1994)

Key words: Granuloma, Hypophysitis, Lymphocytic, Pituitary

Lymphocytic hypophysitis occurs almost exclusively in women during pregnancy or immediately postpartum, but may occur unrelated to pregnancy, and is now being recognized more frequently as a cause of hypopituitarism (2, 3, 8, 16, 17). The disorder, characterized by lymphocytic infiltration and destruction of the anterior pituitary gland, is histologically typical of many autoimmune diseases; thus, patients with lymphocytic hypophysitis may also have thyroiditis, pernicious anemia, adrenalitis, or parathyroiditis (3). The first report (1962) on lymphocytic hypophysitis emerged from an autopsy conducted on a patient with Hashimoto’s thyroiditis; many subsequent cases were also diagnosed postmortem (3, 6). Other cases, however, have been recognized after anterior hypophysectomy for putative adenoma (2, 3, 6, 8, 17, 20). Depending on the stage of the disease, the pituitary gland may be either enlarged by inflammation or shrunken by atrophy and fibrosis (3).

There appear to be only four cases on record of lymphocytic hypophysitis in male patients (6, 17, 19, 26). Until Guay et al.’s (6) 1987 account, the condition was thought to be an autoimmune disease, exclusively of pregnancy and the puerperium. The two patients that we add to the literature involve men who presented with clinical and radiological features of pituitary adenoma, yet who had pathological findings of lymphocytic hypophysitis.

PATIENTS 1 AND 2

Two men, one white and one black, 47 (Patient 1) and 27 (Patient 2) years old, respectively, presented with frontal headaches, lethargy, and diminished libido of 1 year’s duration. The older man suffered from cold intolerance, failure to ejaculate, and symptoms of inflammatory arthritis. The younger man reported polydipsia and polyuria. Neither had visual changes, seizures, nausea, vomiting, or motor deficits. In both men, axillary and pubic hair distribution was normal, fundi were flat, visual fields full, and their thyroid glands and testes were normal to palpation. There was no recognizable prodromal illness, and the men were not under unusual immunological challenge. They were investigated at different institutions before referral for definitive treatment.

Serum prolactin, cortisol, growth hormone, thyroid function, and serum osmolality were within the normal ranges used by the referring sources. However, severely depressed serum testosterone levels were well below the normal range of 300 to 1000 ng/dl (Table I). Other laboratory findings in Patient 1 included the following: white cell count, 3.4 x 10^3/µL; hematocrit, 42%; moderately elevated erythrocyte sedimentation rate; serum glucose, 170 mg/dl; and liver function indices within normal range. Further laboratory findings in Patient 2 included the following: white cell count, 6.2 x 10^3/µL; hematocrit, 35.6%; serum angiotensin converting enzyme, 9 U/L (normal 8–52 U/L); serum glucose, normal range; cerebrospinal fluid, clear/colorless (40 red cells and 328 white cells/µL); and glucose/protein, 87 and 51 mg/dl, respectively.

Magnetic resonance (MR) imaging in Patient 1 was obtained on a 1.0 tesla magnet with sagittal T1-weighted images (TR/TE [repetition time/echo time] 600/20, 4.0 mm thick), coronal T1-weighted images (600/20, 3.0 mm thick) and axial T2-weighted images (2500/80, 5.0 mm thick). These demonstrated an asymmetrically enlarged pituitary gland (larger on the right) with right-side depression of the sella floor and suprasellar extension to the optic chiasm, slightly elevated on the right (Fig. 1). There was no cavernous sinus invasion. Signal intensity, homogeneous throughout the pituitary, was isointense to white matter on all imaging sequences. Normal pituitary could not be separated from “tumor.”

In Patient 2, MR was obtained on a 0.5 tesla magnet with unenhanced sagittal
### TABLE 1. Selected Serum Parameters in Two Men with Lymphocytic Hypophysitis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Normal Ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>&lt;4.0 ng/dl</td>
<td>&lt;10.0 ng/dl</td>
<td>300–100 ng/dl</td>
</tr>
<tr>
<td>Prolactin</td>
<td>9.7 ng/dl</td>
<td>11.0 ng/dl</td>
<td>&lt;15 ng/dl</td>
</tr>
<tr>
<td>Cortisol (random)</td>
<td>5.6 μg/dl</td>
<td>5.2 μg/dl</td>
<td>5–18 μg/dl</td>
</tr>
<tr>
<td>Luteinizing hormone</td>
<td>&lt;2.0 IU/L</td>
<td>&lt;2.0 IU/L</td>
<td>2–5 μg/dl</td>
</tr>
<tr>
<td>Growth hormone (random)</td>
<td>1.9 ng/dl</td>
<td>2.2 ng/dl</td>
<td>0.5–2.6 IU/L</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (radioimmunoassay)</td>
<td>2.2 IU/L</td>
<td>Normal</td>
<td>1.5–18.6 IU/L</td>
</tr>
<tr>
<td>Osmolality</td>
<td>27%</td>
<td>Normal</td>
<td>25–35%</td>
</tr>
<tr>
<td>3,5,3'-triiodothyronine uptake</td>
<td>7.4 μg/dl</td>
<td>4.5 μg/dl</td>
<td>0.3–6.0 μIU/ml</td>
</tr>
<tr>
<td>Thyroxine (radioimmunoassay)</td>
<td>1.4 μIU/ml</td>
<td>0.4 μIU/ml</td>
<td>0.3–5.1 μIU/ml</td>
</tr>
</tbody>
</table>

**FIGURE 1.** Patient 1. Coronal magnetic resonance T1-weighted image demonstrates an asymmetrically enlarged pituitary gland with elevation of the optic chiasm on the right (arrow).

T1-weighted images (400/26, 4.0 mm thick), which were repeated together along with coronal T1-weighted images (400/26, 4.0 mm thick) after the intravenous administration of gadopentate dimeglumine (Magnevist, Berlex Imaging, Wayne, NJ). These demonstrated an intrasellar mass inseparable from the normal pituitary gland, showing no cavernous sinus invasion (Fig. 2). The pituitary gland was enlarged, the suprasellar extension elevated the chiasm centrally and probably involved the infundibulum by tracking posteriorly to obliterate the anterior recesses of the third ventricle. There was enhancement of the periphery of the main mass (more prominent on the left) and its suprasellar component. The patients were admitted to The George Washington University Medical Center for elective transsphenoidal resection of a presumed pituitary adenoma.

In Patient 1 (at surgery), the sellar floor was thin, and the pituitary gland was asymmetrically enlarged by a granular, gray, firm, poorly demarcated mass adherent to the dura and covered by a rim of apparently normal pituitary tissue. Intraoperative examination of cytological smears and a frozen section resulted in a diagnosis of granulomatous hypophysitis.

In Patient 2, the dura was extensively adherent to the capsule of a firm, dense, yellow-white mass. A capsular incision released creamy fluid. The mass was resected, leaving a narrow rim of soft, yellow, apparently normal pituitary tissue along the right sellar wall. Intraoperative cytological smears and frozen sections showed a chronic inflammatory process. Both patients have resumed fully active lives with tailored pituitary replacement therapy.

The lesions from Patients 1 and 2 were histologically similar. Hematoxylin and eosin stained sections showed a diffuse mononuclear infiltrate dominated by mature plasma cells and small lymphocytes, with macrophages and rare eosinophils; a few anterior pituitary cells lay entrapped in a fibrotic stroma impregnated by inflammatory cells (Fig. 3). There were neither diffuse nor compact granulomas (i.e., to suggest sarcoid) or multinucleated giant cells. Marked endothelial cell proliferation was present in Patient 1, with a background of keloidal-like sclerosis in Patient 2. There was no histological evidence of a neoplasm (e.g., adenoma), vasculitis, epidermoid cyst, or craniopharyngioma. Microorganisms or polarizable material were absent.

**DISCUSSION**

The approximately 47 recorded cases of lymphocytic hypophysitis have affected mostly pregnant or immediate postpartum women. Our two patients appear to be the fifth and sixth reported with the condition, all of whom were 27 to 61 years of age at presentation (6, 17–19, 23, 26). Symptoms and signs suggesting anterior hypopituitarism preceded surgical intervention by 1 to 3 years. All six patients had a radiologically demonstrable intrasellar mass, and all underwent transsphenoidal exploration of the pituitary gland for pituitary adenoma. Involvement of the posterior pituitary with concurrent diabetes insipidus was unique to Nussbaum et al.'s patient (17). Inflammation in lymphocytic hypophysitis has been responsible for extraocular muscle palsy, through cavernous sinus infiltration in two men (17, 26). The histopathological findings in the six men have consisted of dense diffuse lymphoplasmacytic infiltrate with fibrosis, residual islands of pituitary, but no granulomas or multinucleated giant cells. Better diagnostic imaging and surgical techniques, such as microsurgical transsphenoidal exploration of the sella, will presumably lead to more frequent recognition of lymphocytic hypophysitis in patients of both sexes.

Cosman et al. (3) and Parent (18) thoroughly summarize what is known about lymphocytic hypophysitis, an uncommon condition affecting mainly postpartum women and characterized by the presence of lymphocytic infiltration of the pituitary gland. The pathological findings are consistent with a chronic inflammatory process, with minimal evidence of neoplasia or granulomatous reaction. The lack of specific localizing signs and symptoms, as well as the variable presentation, make the diagnosis of lymphocytic hypophysitis challenging. The management typically involves surgical intervention to relieve symptoms, but the prognosis is generally good with full recovery.
common disorder characterized by marked lymphoplasmacytic infiltration, fibrosis, and the ultimate destruction of the anterior pituitary gland. The absence of granulomas or giant cells is reported to distinguish lymphocytic hypophysitis from an apparently related disorder, granulomatous hypophysitis (4). However, Asa et al. (1), and others (7, 10, 15), reported ultrastructural similarities between the two conditions, which may represent phases of one process.

The pathogenesis of lymphocytic hypophysitis is thought to be autoimmune, because of its greater incidence in women, particularly in those who are pregnant, and because as many as 30% of affected patients have either thyroiditis, adrenalitis, atrophic gastritis/pernicious anemia, parathyroiditis, or retropertioneal fibrosis (3). Supporting the autoimmune hypothesis are the following conditions: 1) activated lymphocytes interdigitate with pituicytes in different stages of injury (1); 2) lymphocytic and granulomatous hypophysitis show fine structural details identical to those seen in autoimmune thyroiditis (1, 22); and 3) pathological alterations similar to lymphocytic hypophysitis have been induced in rabbits and rats by injection of pituitary tissue mixed with Freund’s adjuvant (9, 11). The latter experiments suggest that the natural history of lymphocytic hypophysitis begins with inflammatory enlargement of the pituitary, progressing to adenohypophysial fibrosis, atrophy, and destruction (3).

Patients typically present with symptoms and signs of partial or panhypopituitarism frequently disproportionate to the size of the accompanying intrasellar mass (3, 13, 14, 21, 25). Presently, the diagnosis depends on surgical resection, when an unusually firm pituitary mass, with or without a capsule, and varying from dull white-gray to yellow or even purple, is found (3). Microscopically, the adenohypophysitis is occupied by a dense and diffuse lymphoplasmacytic infiltrate and possibly by germinal centers (3, 17). The infiltrate may have a macrophage and eosinophilic component.

Edema and fibrosis vary with the stage of the disease (3). Typically, islands of pituicytes survive (3). Granulomas and giant cells are not present in lymphocytic hypophysitis and, if observed, suggest the related diagnosis of granulomatous hypophysitis (3). Computed tomography (CT) has been the most commonly used neuroradiological procedure in the reported cases of lymphocytic hypophysitis. In general, CT findings have been limited to an enlarging, enhancing pituitary gland. Enhancement, when remarked on, has been described as diffuse. Scarnarini et al. (24), in reporting giant-cell granulomatous hypophysitis, observed ring-like enhancement in two of five enhancing masses.

Nine cases of lymphocytic hypophysitis (including the two cases reported in this article) have undergone magnetic resonance (MR) imaging (3, 12, 17, 23, 26). All the pituitary glands appeared enlarged, with homogeneous signal intensity isointense to the brain on T1-weighted images. On T2-weighted images, one gland was hyperintense to white matter (Cosman’s Patient 1 [3]), whereas our Patient 2 was isointense. Two MR procedures showed gadolinium enhancement, one homogeneously (26) and another peripherally (our Patient 2). As a rule, macroadenomas enhance diffusely, being indistinguishable from diffusely enhancing lymphocytic hypophysitis.

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The six reported men with lymphocytic hypophysitis form a rare group in whom the findings on imaging tend to mimic macroadenomas. Although non-specific peripheral enhancement is sufficiently unusual to suggest a diagnosis other than adenoma (e.g., giant-cell granulomatous hypophysitis, Scanarini et al. [24]), the value and frequency of peripherical enhancement can only be assessed after more experience has been gained with enhanced MR in the interpretation of this entity. The treatment of lymphocytic hypophysitis is presently limited to surgical resection and hormone replacement, although a limited surgical biopsy in selected cases with medical management and MR follow-up remains an unproven option (3). Corticosteroids, necessary for the treatment of hypopituitarism, are essential in the treatment of lymphocytic hypophysitis, a few patients have experienced a spontaneous and full endocrinological recovery (2, 14). Lymphocytic hypophysitis cannot yet be reliably diagnosed without an operation. Were that possible, careful monitoring and supportive treatment might diminish or even eliminate the need for resection. The overall potential for recovery among patients with lymphocytic hypophysitis remains unknown, but most treated patients require long-term pituitary replacement therapy.

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REFERENCES


COMMENTS

Lymphocytic hypophysitis develops almost exclusively in women, often in association with pregnancy. Although more than 40 cases have been published during the last decade, the causes responsible for this remarkable female predominance and the role of pregnancy in the pathogenesis are still enigmatic. The contribution of Lee et al. is important because their article calls attention to the fact that lymphocytic hypophysitis may occur in men as well. Sex difference is the incidence of certain diseases is well known. Just to mention a few examples, it has been conclusively documented that systemic lupus erythematosus, Graves' disease, and Cushing's disease are more common in women, whereas hemochromatosis and gastric cancer are recognized more often in men.

Based on the available evidence, lymphocytic hypophysitis is regarded as an autoimmune disease. It is not clear, however, why it is more frequent in women than in men. Are female sex hormones involved in the pathogenesis? Does the enlargement of the pituitary gland during pregnancy play a role? Does testosterone have a protective effect? Is the female pituitary more susceptible to immune destruction? The finding that the disease may be found in men indicates that factors other than female sex hormones, pregnancy, and hypersensitivity of the female pituitary may trigger the development of tissue damage.

Although the two well-documented cases of Lee et al. do not pinpoint the underlying mechanism, their article will stimulate further work. One can agree with Lee et al. that, at present, no definitive criteria exist as to how to recognize the disease conclusively without histological confirmation. The two cases described in detail by the authors prove...
Intracranial Suprasellar Angiolipoma: Ultrastructural and Immunohistochemical Features

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THE AUTHORS PRESENT ultrastructural and immunohistochemical characteristics of an intracranial suprasellar tumor displaying features of cavernous angioma with islets of adipose tissue. Electron microscopy revealed thinned-walled vessels separated by a loose collagenous stroma containing nests of mature adipocytes as well as fibroblasts, myofibroblasts, mast cells, and a few macrophages. Intracytoplasmic lipid droplets were also identified in scattered pericytes and smooth muscle cells of vascular walls and in the transitional cells resembling smooth muscle cells and adipocytes. Many adipose tissue cells were positive for S-100 protein with polyclonal antibodies. Other lipidized tumor cells were immunoreactive for some or all of the following: smooth muscle-specific actin, factor XIIIa, vimentin, and, occasionally, for desmin. Ultrastructure and immunohistochemistry indicate that in addition to typical adipocytes, lipidized cells of another nature contribute to the characteristic appearance of the adipose tissue component of angiolipoma. (Neurosurgery 34:163-167, 1994)

Key words: Angiolipoma, Electron microscopy, Immunohistochemistry, Intrasellar tumors

Angiolipomas are benign mesenchymal neoplasms composed of an intimate mixture of blood vessels and mature adipose tissue (2, 9, 13, 17, 20, 23, 26-28). These tumors are most often benign and usually occur in the subcutaneous tissue of the upper extremities and trunk of young adults (2, 9, 13). Within the craniospinal axis, angiolipomas are extremely rare, and almost all have been found in the spinal extradural space (17, 20, 23, 27). Only two patients with intracranial angiolipomas have been reported; on both occasions, the tumors were in close association with the middle cranial fossa and sphenoid sinus (26, 28). Here we describe the immunohistochemical and electron microscopic features of a suprasellar angiolipoma extending to the sphenoid sinus and the perisellar areas of the middle cranial fossa.

CLINICAL HISTORY

The patient, a 65-year-old, right-handed woman who was a native of the Bahamas, was referred to an endocrinologist for evaluation of insidiously progressive easy fatigability and heaviness of the left eyelid of 2 months' duration that was followed within 1 month by frank ptosis, and later by diplopia. There was no other complaint.

At the time of the hospital admission, her mental status and higher cognitive functions were normal. She had normal visual acuity while wearing corrective lenses, and her visual fields were normal to confrontation. There was an incomplete left third nerve palsy with partial involvement of the left pupil. The remaining cranial nerves were intact. The findings of the neurological and general examinations were otherwise unremarkable. Laboratory evaluations of endocrine function revealed normal pituitary function with maintenance of adequate target gland hormone levels.

Computed tomographic and magnetic resonance imaging of the brain with high-resolution and direct coronal views of the sellar region revealed a sellar and left parasellar tumor measuring approximately 5 × 3 × 3 cm (Fig. 1). There was expansion of the sella turcica without significant bone erosion. Cerebral angiography demonstrated an avascular mass extending to the left cavernous sinus. On the basis of both the clinical and radiographic findings, a nonfunctioning pituitary adenoma was suspected.

The patient underwent a left frontotemporal craniotomy. At surgery, a well-circumscribed, seemingly encapsulated, red-purple sellar and left parasellar lesion was found. The tumor appeared to be composed of a meshwork of large,