Lymphocytic Hypophysitis: Report of a Case in a Man with Cavernous Sinus Involvement

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Lymphocytic hypophysitis (LH) is a rare inflammatory disease of the pituitary that produces hypopituitarism. It more commonly affects women during pregnancy or shortly after childbirth. Of the 34 reported cases only three have been males. We report the fourth known case of lymphocytic hypophysitis in a male who presented with hypopituitarism, diplopia, and cavernous sinus involvement. To our knowledge this is the second report of involvement of the cavernous sinus by LH. A comparative study of all four male cases is also presented. The findings reveal that the mean age at presentation in the male patients is 52.3, nearly 21 years older than that reported for female cases. Impotence with associated decrease in libido is the most common presenting symptom. Extraocular muscle palsy with associated infiltration of the cavernous sinus is an exclusive finding among male patients with LH. Concerning prognosis, none of the male patients regained pituitary function that had been lost at the time of presentation but required chronic replacement therapy.

KEY WORDS: Lymphocytic hypophysitis; Hypopituitarism; Cavernous sinus

Lymphocytic hypophysitis is a rare inflammatory disease of the adenohypophysis that produces hypopituitarism. It was first described in 1962 by Goudie and Pinkerton [8] in a 22-year-old woman who was 14 months postpartum. She developed shock and died 8 hours following an appendectomy. A postmortem examination revealed a markedly atrophic pituitary with profound lymphocytic infiltration of both the pituitary and thyroid glands. Since then 33 other cases have been reported [1–7,9,11–29]. The vast majority have been women whose condition was diagnosed during pregnancy or within 1 year of childbirth. A strong association with other diseases such as thyroiditis [8,12,26], adrenalitis [14], and pernicious anemia [11,18] have led investigators to suggest an autoimmune etiology.

Pathologically the pituitary progresses through various stages. Initially the gland becomes inflamed and enlarged, producing mass-like symptoms. Further destruction of pituitary cells and replacement with fibrosis leads to symptoms of hypopituitarism. Once the inflammatory process has abated, the pituitary may then become shrunken and atrophic. Partial return of pituitary function may occur but it depends greatly upon the extent of pituitary cell destruction.

The diagnostic process includes differentiation from those disease processes which produce a sellar mass and depressed pituitary function. Pituitary adenoma, Sheehan's syndrome, and granulomatous hypophysitis are all likely possibilities. Biopsy by a transsphenoidal approach can aid in making a definitive diagnosis.

While lymphocytic hypophysitis is well described in women, only three cases have been reported in males. We report one case of lymphocytic hypophysitis in a man who presented with hypopituitarism, right lateral rectus paresis, and evidence of an enlarged pituitary with cavernous sinus involvement on magnetic resonance imaging (MRI). To our knowledge, this is the second report of lymphocytic hypophysitis involving the cavernous sinus.

Case History

A 56-year-old white man presented with a 5-month history of persistent retroorbital headaches and diplopia. He also noted progressive fatigue and weakness, and decreased libido and potency. His appetite was poor, and he had noted an 18-kg weight loss over the previous 6 weeks. He denied any fevers, nausea, or vomiting. His family history included a mother with diabetes mellitus.

Physical examination revealed a thin man who appeared to be older than his stated age. His blood pressure was 124/90 mm Hg supine and 110/90 mm Hg standing; his pulse was 106 and regular. The results of a funduscopic examination were within normal limits. His visual fields were intact to confrontation. However, formal visual field testing revealed slight bitemporal super-
rior quadrant defects. Extraocular muscle examination revealed a right lateral rectus paresis. The remainder of his neurological examination was unremarkable.

Laboratory evaluation revealed a prolactin (PRL) level of 5.2 (8-14.5) ng/mL. A low morning cortisol level of 4.8 (5-29) μg/100 mL was obtained. Thyroid levels were similarly decreased, with a total T4 of 3.7 (4.5-12) μg/100 mL, and a thyroid index of 1.1 (1.35-4.8). Gonadotropic function was also depressed, with a follicle-stimulating hormone (FSH) level of 2.3 (2.4-19.9) mIU/mL, luteinizing hormone (LH) level of 0.1 (0.9-10.6) mIU/mL, and a testosterone level of 1.01 (>280) ng/100 mL.

An MRI of the pituitary gland in coronal section revealed a 1.5-cm intrasellar mass with suprasellar extension abutting the optic chiasm (Figure 1). The mass homogeneously enhanced with injection of Magnevist. Abnormal enhancement of the right cavernous sinus with occlusion of the right internal carotid artery was also noted.

The patient received cortisol and thyroid replacement therapy 1 month prior to surgery. A transsphenoidal approach to the sella was then performed. A very enlarged fibrous gland was encountered, and no obvious tumor was seen. Frozen section evaluation revealed chronic inflammation on a background of dense connective tissue. No further exploration was performed, and the procedure was terminated.

Pathological examination revealed much of the pituitary to be replaced by fibrosis (Figure 2). The remaining gland was diffusely infiltrated with lymphocytes. Reactions to stains for bacteria, acid-fast organisms, and fungi were negative, and no sarcoid granulomas were noted.

Further immunological studies were performed. Antinuclear, antipituitary, antithyroid microsomal, and antiparietal cell antibodies were all negative. HLA typing revealed A1/24, B35, Bw3/4, Cw3/4, DRw11/52, and DQw7.

The postoperative course was complicated by diabetes insipidus, which resolved completely. The patient was discharged on a regimen of cortisol, thyroid, and testosterone replacement therapy. An MRI scan 6 months after surgery revealed no change in the size of the pituitary or the right cavernous sinus involvement. However, the patient’s adrenal and thyroid function had improved with the replacement therapy. His potency had also returned in response to testosterone injections. His diplopia had resolved, and no lateral rectus palsy was noted on examination.

Discussion

Lymphocytic hypophysitis has been described in only three male patients previously. To our knowledge this
patient would be the fourth. As the number of male patients increases, certain similarities can be drawn when the epidemiologic, clinical, endocrinologic, and radiographic features are reviewed. These parameters are presented in Table 1. Presentation occurs in the fifth and sixth decade of life with a range of 40–61 (mean 52.3) years. Interestingly, this age distribution is much higher than that reported for female patients, whose ages range from 18 to 54 (mean 31) years. This older age distribution among men may lend some support to the possibility of lymphocytic hypophysitis being an autoimmune disease. While autoimmune diseases are more prevalent in females, they do occur in men most commonly in the fifth and sixth decades of life.

The clinical manifestations among the male patients are quite similar. Impotence with associated decreased libido is the most common presenting symptom, occurring in all cases. Fatigue is also quite prevalent, affecting three patients. Extraocular muscle palsy secondary to infiltration of the cavernous sinus, noted in two patients, is an exclusive finding among males.
affected with lymphocytic hypophysitis. It was first described by Nussbaum et al. [21] in a patient with bilateral sixth nerve palsies. MRI of the pituitary suggested bilateral cavernous sinus involvement. Our patient had an isolated sixth nerve palsy with unilateral cavernous sinus infiltration. Diplopia alone is a fairly common visual symptom among affected women [4]. However, diplopia with demonstrable extracocular muscle palsy is quite rare. One case of a sixth nerve palsy was reported in a 22-year-old female whose symptoms resolved completely following hypophysectomy [17]. Pseudotumor cerebri was felt to be the likely etiology. Both male patients with diplopia had sixth nerve palsies without associated papilledema.

Laboratory evaluation revealed generalized decreases in adrenal, thyroid, and gonadotropic hormone levels in three patients. Cosman et al. [4] reported that hormone levels decreased in an unusual pattern in lymphocytic hypophysitis. Initially adrenal and thyroid levels become deficient, while gonadal function is spared, suggesting that certain cells of the pituitary may be more susceptible to destruction. Eventually FSH/LH and, lastly, prolactin cells are lost [4]. The panhypopituitarism, with adrenal, thyroid, and gonadotropic hormones affected equally, initially suggests that lymphocytic hypophysitis is less specific and possibly more aggressive in males. One male patient, however, had isolated gonadotropic dysfunction without adrenal or thyroid involvement [21], supporting the likelihood that a spectrum of disease can exist in males.

Assays for serum antibodies were performed in three cases in order to assess for concomitant autoimmune disease. Guay et al. [9] reported in their case an ANA titer of 1:80. Pestell et al. [23] noted an antiparietal cell antibody titer of 1:40 in their patient. Autoantibodies were not present in our case. Their absence, however, does not preclude the presence of an autoimmune process. It has been shown, for example, that not all patients with biopsy-proven lymphocytic thyroiditis have serum antithyroid antibodies [10].

HLA typing may also point to an autoimmune process. Hashimoto’s thyroiditis has been associated with HLA class II alleles DR4 and DRw52/53 [23]. Immune hyperresponsiveness and other autoimmune diseases have been associated with HLA B8 and DR5 [9]. One male patient was noted to have both HLA B8 and DR w52 [23].

Presently all four patients require chronic replacement therapy for hormonal deficiencies that were present at the time of diagnosis. The partial return of function that has been noted in some female patients has not been shown to occur in males. Obviously more extensive follow-up with a greater number of male patients is necessary to assess the true natural history of this disease. While four patients is not an extensive series, review of these cases will, hopefully, aid in a better understanding of lymphocytic hypophysitis in men. For neurosurgeons lymphocytic hypophysitis should now be considered in differential diagnosis for men with hypopituitarism and enlarged pituitary glands.

### Table 1. Summary of All Male Patients Reported with Lymphocytic Hypophysitis

<table>
<thead>
<tr>
<th>Reference/presentation</th>
<th>Endocrine function(^*)</th>
<th>CT/MR scan</th>
<th>Pathology</th>
<th>Associated autoimmunity(^*)</th>
<th>HLA typing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guay et al [9]: 52-year-old male with impotence and fatigue</td>
<td>↓ T↓, ↓ TSH</td>
<td>Intraseellar mass</td>
<td>Lymphocytic infiltration with fibrosis</td>
<td>ANA 1:80</td>
<td>A2 B8</td>
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<tr>
<td></td>
<td>↓ LH ↓ T ↓ PRL</td>
<td></td>
<td></td>
<td></td>
<td>Bw 58 DR1</td>
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<td></td>
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<td>DR5</td>
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<tr>
<td>Pestell et al [23]: 61-year-old male with impotence and fatigue</td>
<td>↓ T↓, ↓ TSH</td>
<td>Diffuse enlargement of the pituitary</td>
<td>Lymphocytic infiltration of the pituitary</td>
<td>Antiparietal cell antibody 1:40</td>
<td>A2/28 B60</td>
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<td></td>
<td>↓ T ↓ PRL</td>
<td></td>
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<td>Bw 62/6</td>
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<tr>
<td></td>
<td>↓ FSH ↓ LH</td>
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<td></td>
<td>DR 4/13</td>
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<td>DRw 52/53</td>
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<td>DQw 1/3</td>
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<tr>
<td>Nussbaum et al [21]: 40-year-old male with impotence, diploria, polyuria, polydipsia</td>
<td>↓ T</td>
<td>Suprasellar mass with bilateral cavernous sinus involvement</td>
<td>Lymphocytic infiltration with fibrosis</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Supler and Mickle (present study): 56-year-old male with impotence, fatigue, diploria</td>
<td>↓ T↓, ↓ T</td>
<td>Suprasellar mass with right cavernous sinus involvement</td>
<td>Lymphocytic infiltration with fibrosis</td>
<td>Autoantibodies negative</td>
<td>A1/24 B35</td>
</tr>
<tr>
<td></td>
<td>↓ PRL ↓ FSH</td>
<td></td>
<td></td>
<td></td>
<td>Bw 3/4</td>
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<tr>
<td></td>
<td>↓ LH</td>
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<td>Cw 3/4</td>
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<td>DRw 11/32</td>
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<td>DQw 7</td>
</tr>
</tbody>
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\(^*\) TSH, thyroid-stimulating hormone; LH, luteinizing hormone; PRL, prolactin.
\(^*\) ANA, antinuclear antibody; N/A = not available.
References


