Lymphocytic Hypophysitis in a Patient with Amenorrhea and Hyperprolactinemia
A Case Report

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Lymphocytic hypophysitis is a rare condition reported to occur only in women. A patient with amenorrhea and hyperprolactinemia was thought to have a pituitary microadenoma but was subsequently found to have lymphocytic hypophysitis and pituitary-specific autoantibodies. Photomicrographs taken upon transsphenoidal surgical exploration revealed the lymphohistiocytic infiltrate of the pituitary. The pituitary reserve was tested. Autoimmune hypophysitis should be included in the differential diagnosis of amenorrhea and galactorrhea.

Introduction
Lymphocytic hypophysitis is a rare condition that has been found only in women. Fourteen cases have been described to date. An autoimmune etiology has been suspected because circulating antipituitary antibodies against the lactotroph have been measured in the serum. On histologic evaluation of the pituitary, lymphocytic infiltrate has been seen. Eleven of the previously described 14 cases had been associated with pregnancy or the postpartum state, and 7 were described postmortem. Of the seven, four were associated with autoimmune disease. A case of lymphocytic hypophysitis associated with antiparietal-cell antibodies and vitamin B₁₂ deficiency was described recently.

Case Report
A 31-year-old woman presented in December 1980 complaining of secondary amenorrhea of three years’ duration. Menarche had occurred at age 13, and the menstrual periods were irregular, at intervals of one to six months, and lasted two to three days. The larche and pubarche were normal. At the age of 21 the patient began taking combination sex steroid contraceptives and started menstruating regularly. After discontinuing oral contraceptives at the age of 28, she became amenorrheic and remained so until referred for evaluation three years later. The patient denied having hot flushes, galactorrhea, severe headaches or visual field disturbances. She denied taking any medicines or illicit drugs.

On physical examination the patient’s height was 160 cm and weight was 55.5 kg. Her blood pressure was 110/70 mm Hg. Fundoscopic examination and visual fields were within normal limits. The hair distribution was normal, as were the results of a thyroid examination. Breast examination revealed no palpable masses, and no secretions could be expressed. The pelvic examination was normal. The vaginal epithelium showed flattening and was not well rugated. No cervical mucus was present.

Laboratory Studies

Antibody Determination. Organ-specific autoantibodies were determined by the methods of Bottazzo. Antibodies to the adrenal gland and ovaries were cross-checked (compliments of Dr. George Bright, University of South Carolina). Antibodies against parietal cells were evaluated at the Nichols Institute, Los Angeles. An indirect immunofluorescence technique, using 6μm stomach sections from 6-month-old
male C3H-HE mice as a substrate and polyvalent goat antihuman immunoglobulins coupled to fluorescein isothiocyanate (Atlantic Antibodies, Scarborough, ME) as a conjugate, was employed.

Radioimmunoassay Method. The prolactin assay was a 125I-labeled prolactin double antibody method using the World Health Organization (WHO) first IRS standard. Percent cross-reactivity against thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and human chorionic gonadotropin (HCG) was ≤ 0.5%. Minimum sensitivity of the assay was 2.5 ng/mL. Slope of the curve was −1.13. Range of the assay was 5–200 ng/mL. The coefficient of variation within the assay was 7.4%, with an N value of 13. Inter-assay variation at 9.6 ng/mL was 13.5%. At 66 ng/mL the interassay variation was 10.4%.

LH assay was a 125I LH double antibody technique using the WHO second IRP standard. Percent cross-reactivity with TSH and FSH was < 3.0% and with HCG, ≤ 17%. Minimum sensitivity was 2.21 mIU/mL, and the slope of the dose-response curve was −1.23. The assay range was 3–200 mIU/mL.

The intraassay variation for LH was 4.0%; the interassay variation at 15.9 mIU/mL was 13.6% and at 46.8 mIU/mL, 10.0%. FSH was assayed using a 125I double antibody technique. The standard used was the WHO second IRP. The percent cross-reactivity for TSH, LH and HCG was ≤ 1.5%. The minimum sensitivity was 1.55 mIU/mL. The slope of the curve was −1.19. The range of the assay was 2–100 mIU/mL. The intraassay variation was 1.5%. The interassay variation at 21.2 mIU/mL was 9.0% and at 48.9 mIU/mL, 2.3%. The reagent source for prolactin, FSH and LH assays was Diagnostic Products, Los Angeles.

Thyroxin was measured with a commercial radioimmunoassay method, Tetraebad −1.25 (Abbott Laboratories, North Chicago, IL). TSH was measured with a two-sided commercial immunoradiometric assay method, HTSH Riabead (Abbott Laboratories). The T3 uptake assay was measured using a commercial assay kit, Triobead −125 T3 Uptake (Abbott). Cortisol was measured with a commercial radioimmunoassay kit, Rianen (New England Nuclear, Boston). Growth hormone (GH) was measured at Bioscience Laboratories, Van Nuys, CA, using a 125I in-house method. GH standardized against hormone from the National Pituitary Institute was used. Normal ranges for females were less than 15 ng/mL. ACTH was measured at Bioscience

with an in-house radioimmunoassay method. The method was standardized against the 1-24 peptide portion of human ACTH from Organon, Inc, West Orange, NJ. Normal 8–10 AM levels are up to 80 pg/mL.

Endorphins also were evaluated at the Nichols Institute, where samples are extracted routinely with silicic acid. The radioimmunoassay method of Carr et al was used.10

Sections of pituitary tissue 4μm thick were stained for histology with hematoxylin and eosin.

Hypoglycemia was induced with 0.5 U/kg of regular insulin given as an intravenous bolus after a 12-hour fast. The thyrotropin-releasing-hormone (TRH) stimulation test was carried out using 500μg of TRH given as an intravenous bolus.

The dehydration test for measuring the renal concentrating ability was carried out over a 24-hour period by restricting fluids while measuring urine osmolality with conventional methods.

Results of the Laboratory Studies and Treatment

The results of the laboratory studies included a prolactin of 110 ng/mL (Figure 1) (with normal levels < 25 ng/mL), a TSH of 2.0 IU/mL (normal, < 10 IU/mL), T4 of 10.7μg/dL (normal, 5.0–13.7μg/dL), LH of 2 mIU/mL and FSH of 8 mIU/mL. Anteroposterior and lateral coned views of the sella turcica were normal. A TRH stimulation test resulted in an increase in TSH from 2.5 to 13.6 IU/mL and a prolactin response from a baseline to 95 to 131 ng/mL at 20 minutes.

![Figure 1](image-url)

Serum prolactin levels during the patient's clinical course.
were examined, and since the gland was elevated, abnormal tissue could be seen posteriorly on the floor of the sella in the midline. This tissue was fairly discrete and easily separated from the normal-appearing gland. It was removed in several biopsy sections, with several specimens taken from adjacent, normal-appearing pituitary tissue. The gland was split vertically from front to back and then transversely to be sure that no other abnormal tissue lay within it. None was found. The tissue was irregular, yellowish tan and reddish brown, and friable. A review of hematoxylin-and-eosin-stained sections and a reticulin stain showed that portions of the pituitary contained an infiltrate of lymphocytes with an arrangement of cells in a vaguely nodular pattern within a pale, slightly hyalinized stroma. It was not possible to discern any true granulomas or multinucleated histiocytes. No metastases or cellular atypia was noted. Neoplasia was not identified (Figure 2).

A serum prolactin level obtained in the recovery room revealed 160 ng/mL. The patient underwent an uneventful recovery after surgical exploration.

In August 1983 the patient was hospitalized for repeat evaluation and testing of the pituitary reserve. Baseline laboratory studies included a complete blood count, with a white count of 5,900/μL, hemoglobin of 12.1 g/dL, hematocrit of 37.1%, mean corpuscular volume of 90.2 fl oz (normal, 81-99), mean corpuscular hemoglobin of 29.3 pg (normal, 27-31) and mean corpuscular hemoglobin concentration of 32.5 g/dL (normal, 32-36). The differential was 48% segs, 2% bands, 44% lymphocytes, 2% monocytes and 4% eosinophils. The serum sodium, potassium, chloride, carbon dioxide, BUN and glucose were normal. Serum albumin, total protein, calcium, phosphorus, uric acid, creatinine, total bilirubin, creatine phosphokinase, lactate dehydrogenase, alkaline phosphatase, SGOT and cholesterol were all within normal limits. A urinalysis showed a sp gr of 1.005; pH of 6; negative protein, glucose and acetone; 4-6 WBC/high power field (HPF); 2-5 epithelial cells per HPF; and no bacteria. A chest radiograph and ECG were unremarkable. The plasma and urine osmolality were 296 and 123 mosm/L, respectively. The FSH was 15.5 mIU/mL (normal, 5-18), LH was 2.3 mIU/mL (normal, 5-25), baseline TSH was 4.1 IU/mL (normal, 2-10), T₄ was 8.3μg/dL (normal, 5.0-13.7), T₃ uptake was 24.8% (normal, 20.0-30.0) and T₄ free thyroxine index was 8.3 (normal, 4.4-15.7). Prolactin was 90.7 ng/mL (normal, 6-19) (Figure 1). The ANA test, lupus erythematosus preparation and

In April 1981 a computed tomographic (CT) scan of the sella turcica and pituitary gland revealed no abnormality.

Amenorrhea continued until April 1982, when, with a prolactin level of 87 ng/mL (Figure 1), the patient was begun on bromocriptine therapy. The dosage was 2.5 mg twice daily. The prolactin level dropped to 6.3 ng/mL (Figure 1), and normal menses resumed. However, in March 1983 the patient voluntarily discontinued the bromocriptine because of nausea and orthostatic dizziness. Two weeks later a serum prolactin level of 534 ng/mL was measured (Figure 1).

CT scan of the pituitary gland revealed it to be normal in size, shape and texture, but overall it was larger symmetrically than had been noted during the study of April 1981. The patient underwent transsphenoidal exploration of the pituitary gland in June 1983.

At surgery the pituitary appeared relatively normal on first inspection. The margins of the gland
rheumatoid arthritis factor were negative. The auto-
antibody findings are outlined in Table I.

The pituitary reserve was tested. An insulin
tolerance test was performed after an overnight fast,
and the responses of growth hormone, ACTH, cor-
tisol and endorphins to hypoglycemia were measured
(Table II). The fasting blood glucose of 95 mg/dL at
time 0 decreased to 22 mg/dL at 30 minutes. The
growth hormone response of <1 ng/mL at time 0 in-
creased to 6 ng/mL at 60 minutes. ACTH rose from
<10 pg/mL at time 0 to 162 pg/mL at 60 minutes.
The fasting, 8 AM cortisol of 11.5 μg/dL rose to
20.2 μg/dL at 60 minutes, and the endorphin level of
43 pg/mL at time 0 reached a maximum of 698
pg/mL at 60 minutes.

The results of the TRH stimulation test are report-
ed in Table III. Time 0 prolactin and TSH values
were 124.5 ng/dL and 3.9 mIU/mL, respectively.

<table>
<thead>
<tr>
<th>Table II</th>
<th>Pituitary Reserve Testing Two Months After Surgical Exploration of the Pituitary Gland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dL)</td>
<td>95.0</td>
</tr>
<tr>
<td>Growth hormone (ng/mL)</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>ACTH (pg/mL)</td>
<td>&lt;10.0</td>
</tr>
<tr>
<td>Cortisol (μg/dL)</td>
<td>11.5</td>
</tr>
<tr>
<td>Endorphin (pg/mL)</td>
<td>43.0</td>
</tr>
</tbody>
</table>

*Because of severe hypoglycemic symptoms, 50% dextrose was given intra-
venously and followed by a 5% dextrose infusion.

<table>
<thead>
<tr>
<th>Table III</th>
<th>TRH Stimulation Test Two Months After Surgical Exploration of the Pituitary Gland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (minutes)</td>
<td>15</td>
</tr>
<tr>
<td>Prolactin (ng/mL)</td>
<td>123.5</td>
</tr>
<tr>
<td>TSH (mIU/mL)</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Prolactin peaked at 251.6 ng/dL at 60 minutes, and the
TSH reached 12.4 mIU/mL in 30 minutes.

The posterior pituitary reserve in response to
dehydration is presented in Table IV. At time 0 the
urine osmolality was 220 and the serum osmolality,
291. At 24 hours the urine osmolality was 707 and
the serum osmolality, 297.

Postoperatively the patient refused bromocriptine
therapy and opted for serial observation alone. She
has remained amenorrheic. ACTH stimulation stud-
ies performed on August 8, 1984, revealed a change
from 13.8 μg/dL at 8 AM to 27.2 μg/dL at 30 minutes
with 25 IU of ACTH. Fasting prolactin level at 10 AM
18 months postoperatively was 54 ng/mL. The pa-
tient continued to refuse bromocriptine. Dietary
calcium supplementation was prescribed.

Discussion

Goudie and Pinkerton described the first case of lymphocytic hypophysitis in 1962. Sixteen cases, in-
cluding ours, have been described to date. In eight
cases the diagnosis was established from biopsies ob-
tained from surgical exploration of the pituitary gland (Table V). The other seven reported cases
were diagnosed at autopsy from histologic examina-
tion of the gland (Table VI). Eleven of the
previously described cases were associated with preg-
nancy (Tables V and VI). In the three not associated,
the patients' ages were 42, 60 and 74 years. Our case
is unique in that the patient had never been pregnant
and was only 31 years old at the diagnosis.

The histologic findings of lymphocytic hypophysitis
are consistent with an autoimmune etiology. The

<table>
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<tr>
<th>Table IV</th>
<th>Posterior Pituitary Reserve Two Months After Surgical Exploration of the Pituitary Gland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>7 AM</td>
</tr>
<tr>
<td>Urine osmolality (mOsm/L)</td>
<td>220</td>
</tr>
</tbody>
</table>
Table V  Cases Diagnosed at Biopsy, by Author

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Age</th>
<th>Other autoimmune disease</th>
<th>Headaches</th>
<th>Clinical data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayfield</td>
<td>1980</td>
<td>23</td>
<td>-</td>
<td>+</td>
<td>Puerperal onset. Regular menses. Prolactin, 3.9 ng/mL. Enlarged sella, polytomography. CT scan within normal limits.</td>
</tr>
<tr>
<td>Asa</td>
<td>1981</td>
<td>29</td>
<td>-</td>
<td>+</td>
<td>Nausea, vomiting, 7 months pregnant. Postpartum amenorrhea, no lactation. Hypothyroidism, adrenal insufficiency. Prolactin, 58.7 ng/mL 6 months postpartum. Polytomography, asymmetrical sellar enlargement. CT scan, pituitary fossa mass.</td>
</tr>
<tr>
<td>Mazzone</td>
<td>1983</td>
<td>37</td>
<td>Pernicious anemia</td>
<td>+</td>
<td>Puerperal amenorrhea, hypothyroidism, adrenal insufficiency. Prolactin, 101 ng/mL 9 months postpartum. Polytomography, sellar erosion. CT scan, erosion and ballooning of sellar floor.</td>
</tr>
</tbody>
</table>

gland is homogenously infiltrated with lymphocytes. Giant cells and granulomas are characteristically absent, suggesting a nongranulomatous etiology. Scattered areas of fibrosis representing an end stage destructive process are found sometimes. There is no evidence of tumor.

Adenohypophyisis has been produced experimentally in rats. A single intracutaneous injection of a pituitary extract results in an inflammatory infiltrate of lymphocytes, monocytes and, occasionally, epithelial cells in the anterior lobe of the pituitary gland.

Associated autoimmune disease processes were not uncommon in the previously reported cases. Of seven cases found at autopsy, three had lymphocytic infiltrates involving the thyroid gland, and one had parathyroiditis and adrenalitis. In one patient with thyroiditis, atrophic gastritis was also found at autopsy. Mazzone et al described a case of lymphocytic hypophysitis associated with anti-parietal-cell antibodies and vitamin B	extsubscript{12} deficiency.

All 15 reported cases occurred in women. Furthermore, Bottazzo et al found that of 287 patients with one or more autoimmune endocrine diseases, 19 had sera that reacted with the pituitary glands, obtained at hypophysectomy for breast cancer. Eleven were associated with pregnancy. In four patients the symptoms began in the third trimester, and in the remaining seven the onset of symptoms was postpartum. Symptoms included amenorrhea, galactorrhea, nausea, vomiting, weakness, myalgia, headaches and visual disturbances (Table V). Of the cases found before death, all had been related to pregnancy and the postpartum period. Of the seven patients, only one was reported to have galactorrhea. Prolactin was elevated in three patients.

The mechanism of hyperprolactinemia remains
Table VI  Cases Diagnosed at Autopsy, by Author

<table>
<thead>
<tr>
<th>Year</th>
<th>Age</th>
<th>Other autoimmune disease</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>1962</td>
<td>22</td>
<td>Hashimoto's thyroiditis</td>
<td>Puerperal onset, oligoamenorrhea</td>
</tr>
<tr>
<td>1967</td>
<td>74</td>
<td>Atrophic gastritis, pernicious anemia, lymphocytic hypophysitis</td>
<td>Nulliparous, menopausal onset</td>
</tr>
<tr>
<td>1969</td>
<td>29</td>
<td>—</td>
<td>Puerperal amenorrhea</td>
</tr>
<tr>
<td>1975</td>
<td>42</td>
<td>Parathyroiditis, adrenalitis</td>
<td>Frequent abortions, status post, total abdominal hysterectomy, bilateral salpingo-oophorectomy</td>
</tr>
<tr>
<td>1978</td>
<td>60</td>
<td>Arthralgias</td>
<td>Status post, total abdominal hysterectomy, bilateral salpingo-oophorectomy</td>
</tr>
<tr>
<td>1980</td>
<td>31</td>
<td>Chronic thyroiditis, pancreatitis, adrenalitis</td>
<td>Puerperal death</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>—</td>
<td>Puerperal onset, galactorrhea, suicide, prolactin = 3.9 ng/mL, enlarged sellae on polytomography, CT scan normal</td>
</tr>
</tbody>
</table>

speculative. Antibodies directed against receptor sites on the lactotroph could stimulate the synthesis and/or release of prolactin. Antibodies could likewise interfere with dopamine inhibition at the lactotroph site in the pituitary. Potentially antibodies could interfere with dopamine either in its release into the portal vasculature or in its actual transport in the portal vasculature itself.

Radiographic studies have consisted of tomograms and CT scanning. In all seven cases diagnosed prior to death, tomograms of the sella turcica were abnormal.7-11 CT scans were obtained in all cases, and in only one were the findings described as within normal limits.11

Amenorrhea with hyperprolactinemia requires investigation. Our case, with a prolactin level of 534 ng/mL and a demonstrable change in the radiographic findings, illustrates one rare etiology of nonmalignant hyperprolactinemia.

References