Lymphocytic Hypophysitis.

Report of 3 New Cases and Review of the Literature

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Introduction

Lymphocytic hypophysitis is being recognized with increasing frequency as a cause of hypopituitarism, primarily in women during late pregnancy or during the postpartum period. It is characterized by lymphocytic infiltration and destruction of the anterior pituitary. Depending on the stage of the disease the pituitary may be enlarged secondary to inflammatory infiltration or small and atrophic with destruction of pituitary tissue and replacement with fibrosis. Patients may present with symptoms of an expanding intrasellar mass or with varying degrees of pituitary dysfunction. We report our experience with 3 patients who presented to our institution with symptoms of a pituitary mass lesion and hypopituitarism in the postpartum period, and we review an additional 27 well-documented previously reported cases of this disease.

The first case of lymphocytic adenohypophysitis was described in 1962 by Goudie and Pinkerton (20) in a 22-year-old woman who developed postpartum hypothyroidism and amenorrhea. An appendectomy was performed 14 months after childbirth, and 8 hours after operation she developed shock and died. At autopsy, she had lymphocytic thyroiditis, severely atrophic adrenals, and a small pituitary with extensive lymphocytic infiltration in the atrophic residuum. No giant cells or granulomas were seen and the pathology was distinct enough to differentiate it from healed postpartum pituitary necrosis (the Sheehan syndrome) and granulomatous hypophysitis. The concurrence of lymphocytic thyroiditis and hypophysitis during the postpartum period led the authors to believe that these were linked autoimmune diseases. It became clear that lymphocytic hypophysitis could occur in postmenopausal women, without associated inflammation of thyroid, adrenals or other organs (although these glands were usually small because of the lack of trophic pituitary hormones), and that the pituitary could be of normal size or even enlarged (11, 17, 22, 30).

Quencer (51) reported the first case of lymphocytic hypophysitis in a living patient in 1980. Since this first antemortem diagnosis, there have been an additional 21 cases reported in the English literature (2, 4, 8, 16, 21, 23, 25, 33, 37–39, 47, 49, 54, 64, 69, 70). Case reports have also appeared in the Japanese literature (1, 29, 40, 44). Of the 21, 5 were diagnosed at autopsy and the remaining 16 were diagnosed from tissue samples obtained at surgery. Many of these cases had a wide spectrum of abnormalities, as revealed by computed tomography of the pituitary/sella and endocrinological evaluations. Since a large part of the pituitary was often removed at surgery, the probability of recovering pituitary function without intervention is unknown. In addition, the use of corticosteroids or other immunosuppressive agents has not yet been tested.

We present 3 cases of lymphocytic hypophysitis diagnosed at our institution and review the previous cases to further define the epidemiologic, endocrinologic, radiographic, diagnostic, prognostic, and therapeutic features of this disease.

Case Reports

Case 1

A 29-year-old black woman, 7 weeks postpartum, presented with loss of vision in her left eye.

The patient had no previous medical problems and became pregnant in September 1986, soon after stopping oral contraceptive pills. Her pregnancy was unremarkable until the mid-seventh month, when she developed bifronto-temporal headaches. The headaches worsened over the following month, and the patient noticed loss of peripheral vision in her left eye as well as blurriness while reading.

She had a normal delivery of a healthy baby but after delivery she had no breast engorgement and could not lactate. Headaches and visual loss worsened slightly, and she complained of mild myalgias. Menses did not return. Her 30-lb weight gain persisted.

Neurologic evaluation revealed a left temporal hemianopsia with a right superior quadrantanopsia. Physical examination was
otherwise normal. Both computed tomographic (CT) and magnetic resonance imaging (MRI) scans showed a large intrasellar mass with suprasellar extension and compression of the optic chiasm (Fig. 1). Laboratory evaluation revealed panhypopituitarism: total T4 was 3.3 μg/dL, TRUS 0.8, and TSH 1.0 μIU/mL; basal cortisol was ≤ 0.4 μg/dL with increases to 7.5 at 30 min and 11.0 at 60 min post-cortisone; LH 0.75 mIU/mL, FSH 2.85 mIU/mL, estradiol 30 pg/mL; prolactin 1.0 ng/mL and GH 0.6 ng/mL.

The patient was treated with hydrocortisone and levotyroxine. During transphenoidal surgery, a large, extremely firm pituitary was found and resected, because the frozen section examination was consistent with an adenoma. Final microscopic examination revealed widespread lymphocytic infiltration with acellular fibrosis (Fig. 2). Small nests of mixed pituitary cells were present, mostly acidophils and chromophobes, which stained for ACTH and GH. No adenomatous tissue was found.

The patient had transient diabetes insipidus but otherwise did well postoperatively. Her headaches and visual disturbances resolved. Hormone replacement was continued.

Case 2
A 34-year-old white woman, 6 months postpartum, presented with symptoms consistent with an intrasellar mass and hypopituitarism. Approximately 2 years before admission, she discontinued oral contraceptive pills and had difficulty becoming pregnant. With clomiphene therapy, she was able to conceive. Her pregnancy was uncomplicated until the eighth month when she developed bifrontal headaches and retro-orbital pain as well as blurring of vision. This was not further evaluated, and after the uncomplicated delivery of a healthy child, the symptoms resolved. After delivery, the patient was unable to lactate and was amenorrheic. Subsequently, she developed progressive symptoms of fatigue, facial puffiness, weakness, and orthostatic dizziness. Physical examination was remarkable for mild orthostatic hypotension. Visual fields and acuity were normal. Laboratory evaluation revealed hypopituitarism: total T4 2.3 μg/dL, free T4 0.65 ng/dL, T3RA 92 ng/dL, and basal TSH 3.2 μIU/mL with increase to only 4.7 30 min post/TRH; basal cortisol 0.3 μg/dL; LH 2.65 mIU/mL, FSH 8.9 mIU/mL, estradiol 20 pg/mL; prolactin < 1.0 ng/mL and GH 5.0 ng/mL. A CT scan performed 5 months postpartum showed an intrasellar mass with suprasellar extension to the vicinity of the optic chiasm (Fig. 3).

Replacement therapy with hydrocortisone and levotyroxine was begun, and the patient was referred for surgery. Menses resumed after 1 month of therapy. Transphenoidal sellar exploration showed the pituitary to be extremely firm and tough. A small piece of pituitary tissue was resected. Microscopic examination revealed dense fibrous surrounding a lymphocytic infiltrate and scant pockets of pituitary epithelium (Fig. 4). An MRI scan taken 3 months after the CT scan revealed a small pituitary, approximately one-fifth the size seen on the previous scan (Fig. 5). Hormone therapy continues, but attempts to withdraw treatment will be made.

Case 3
A 38-year-old woman, approximately 6 weeks postpartum, presented with symptoms of a sellar mass and hypopituitarism.

The patient had conceived, carried, and delivered a healthy daughter without complications in January 1986. One month after delivery, she developed severe joint pains. Erythrocyte sedimentation rate and rheumatoid factor were normal and thyroid function tests were low normal. Lactation ceased after 2 months. Menses returned at 5 months postpartum with irregular cycles. The joint pains abated in severity but the patient had generalized, persistent fatigue.

Approximately 6 months after the birth of her first child, she tried to become pregnant again and she finally conceived after an additional 7 months. Throughout the pregnancy she was fatigued, anorexic, and nauseated and she experienced orthostatic dizziness. Left frontal headaches began in the second month of pregnancy. A CT scan in the fifth month of pregnancy showed a parietal arachnoid cyst but was otherwise negative. Cervical spine x-rays showed degenerative arthritic changes. In May 1988, after pitocin-induced labor, she delivered a healthy baby.

Postpartum, she did not lactate. Menses did not return, and the headaches continued. The patient denied having visual disturbances but reported decreased libido over the previous 2 years and decreased axillary and pubic hair. She also complained of slight polydipsia and polyuria of 3 L per day. Physical examination revealed a standing BP of 70/50 and a sallow complexion. Deep tendon reflexes were slightly delayed and scalp hair was coarse. Formal visual field testing was normal.

Endocrinologic evaluation revealed morning plasma cortisol < 1.0 μg/dL, free T4 1.0 ng/dL, TSH 2.5 μIU/mL, estrogen < 25 pg/mL, LH 1.5 mIU/mL, FSH 4.1 mIU/mL, prolactin 2.4 ng/mL, and GH < 0.5 ng/mL. MRI scan (Fig. 6) showed a 1.5 cm mass of the pituitary with suprasellar extension to the optic chiasm as well as a 2 cm left parietal arachnoid cyst. The patient was treated with hydrocortisone and levotyroxine. Dizziness, nausea, and fatigue improved.

Transphenoidal sellar exploration was performed 10 weeks postpartum. Frozen sections of the intraoperative biopsy were consistent with fibrous adenoma. Final pathologic examination, however, showed islands of adenohypophysal cells surrounded by fibrous connective tissue, lymphocytes and lymphoid follicles, diagnostic of lymphocytic hypophysitis (Fig. 7).

Results

Epidemiology

Twenty-nine of the 30 cases of adenohypophysitis so far reported, including the cases presented here, have been females (Table 1). One 52-year-old male patient was reported by Guay in 1987 (Case 24). Aside from his gender, he was a classic case, whose presentation, endocrinologic evaluation, CT scan, gross and microscopic appearance of pituitary at surgery were all typical of lymphocytic hypophysitis.

The age range of affected patients was 18 to 74 years (mean, 32.6). Of the 29 female cases reported, 4 (14%) were post-menopausal. Years from menopause varied from 1 year (Case 26) to 24 years (Case 2).

Twenty-five of 29 female cases (86%) occurred in women of menstrual age. Of these 25 patients, 24 (96%) occurred in women surrounding the puerperium and 1 occurred in a 31-year-old woman with no previous pregnancies (Case 10). Race was reported in 9 patients, of whom 4 were black, 3 were white, 1 was Asian, and 1 was Filipina.
Fig. 1. Case 1. A. T1 sagittal MRI showing sellar mass (diamond) with suprasellar extension in Case 1. Optic chiasm (arrow) is elevated. B. T2 coronal MRI of the same patient demonstrating the sella and suprasellar mass (arrow).
Women affected in the child-bearing period had had between 1 and 5 pregnancies. Of the 21 cases whose parity was known, 8 were primiparous and 13 were multiparous.

**Presentation/symptomatology**

Of the 24 women in whom lymphocytic hypophysitis occurred in the child-bearing period, 13 had their first symptoms during pregnancy (Cases 10–13, 15, 16, 20, 25, 27–30), 10 developed symptoms in the post-partum period (Cases 1, 3, 6–9, 14, 17, 18, 21) and 1 patient (Case 22) became symptomatic during early labor (and died of probable adrenal insufficiency).

The earliest recorded symptoms occurred in 3 patients during the second, fourth, and sixth months of pregnancy (Cases 30, 20, 10). All other patients who had evidence of the disease in the antepartum period developed symptoms in the last trimester. All of these patients had symptoms suggestive of sellar mass: headaches (frontal, temporal, or retro-orbital) and/or visual disturbances including visual field defects, decreased visual acuity, visual blurring, and diplopia.

Only 2 women had symptoms suggestive of pituitary deficiency during pregnancy (Cases 11, 30). They both had nausea and anorexia, with vomiting and weight loss in the former and orthostatic dizziness in the latter, suggestive of hypoadrenalism (and confirmed by laboratory evaluation).

In the 10 women who developed symptoms in the postpartum period, the time range was between 2 weeks and 14 months after delivery. These patients had symptoms of a sellar mass (as above) and partial or panhypopituitarism. Generally, those who presented at the later end of this range, 14 months after delivery (Case 1), 13 months after delivery (Case 18), and 12 months after delivery (Case 3), had symptoms only of hypopituitarism without suggestion of mass.

One patient (Case 9) was an exception, a 22-year-old woman who developed headache and galactorrhea 14 months postpartum and committed suicide because of fear of recurrent pregnancy. At autopsy, she had a classic pathologic picture of lymphocytic hypophysitis, with prominent inflammation, and the pituitary bulging out of the sella and compressing
the optic chiasm. This was the only case in which pituitary enlargement was found so many months after a pregnancy.

All patients (except for the 1 who died in labor) had uncomplicated normal spontaneous vaginal deliveries without hemorrhagic or septic shock.

Of the 13 patients who initially presented with symptoms of a mass effect, most developed hypopituitarism. In 4 cases (Cases 11, 14, 16, 29) the initial symptoms of headache and visual disturbances resolved postpartum. In other cases in which visual disturbances persisted postpartum, operative intervention was rapid, so that the frequency of spontaneous resolution of the pituitary mass and its associated symptoms is unknown.

Of all 30 reported patients, 27 (90%) had evidence of partial or panhypopituitarism at some time during the course of the disease before surgical intervention. Symptoms and signs of hypoadrenalism were classic. Nine patients died of probable adrenal insufficiency (Cases 1–5, 7, 17, 18, 22). Symptoms and signs of hypothyroidism were also classic. Other symptoms of hypopituitarism included inability to lactate in 8 patients (Cases 11, 17, 18, 20, 25, 28–30); amenorrhea in 11 patients (Cases 1, 6, 9, 11, 12, 16–19, 28, 30); impotence and testicular atrophy in 1 (Case 24). Galactorrhea (without breast feeding and continuing longer than 5 months postpartum) was present in 4 patients (Cases 6, 9, 12, 26). Three patients had no evidence of abnormal pituitary function (Cases 14, 23, 27).

Visual field defects were found in 9 patients (Cases 10, 13–15, 20, 23, 25, 27, 28). Decreased visual acuity was found in 4 (Cases 10, 15, 20, 28). One patient (Case 8) had a unilateral sixth cranial nerve palsy and papilledema (which resolved after hypophysectomy).

None of the patients had clearly documented polyuria or polydipsia consistent with posterior pituitary or hypothalamic dysfunction.

**Laboratory evaluation**

Basic laboratory evaluations (chemistries and blood counts) were normal in most cases. Exceptions included hyponatremia (Cases 2, 5) and hypoglycemia (Cases 3, 5, 7, 17) in association with hypoadrenalism; hypercalcemia in association with transient thyrotoxicosis and adrenal insufficiency (Cases 7, 21); and multifactorial anemias in several patients.
LYMPHOCYTIC HYPOPHYSITIS

Four patients had lumbar punctures with CSF analysis. In 2, CSF was normal (Cases 18, 25). In Case 8, CSF pressure was increased. In 1 patient with presumed viral meningitis, CSF showed a lymphocytic pleocytosis and a slightly elevated protein concentration (Case 26).

Radiographic imaging

Fifteen of the 19 patients who had CT scans (Cases 6, 8, 10–16, 19–21, 23–29) (79%) showed intrasellar masses at initial scanning. Contrast enhancement was seen in all 13 cases in which contrast scanning was reported. Suprasellar extension was seen in 13 cases (72%). In 2 patients (Cases 26, 19) initial CT was normal but repeat scans 4 and 8 months later showed sellar masses. In 1 patient (Case 8), the CT was normal at presentation and remained normal when repeated, although the skull x-ray showed an enlarged sella. In 1 case (Case 20), CT at 4 months into pregnancy showed a mass which decreased in size during the third trimester but enlarged again postpartum.

Four patients had MRI scanning at some point in the course of the disease. In the first (Case 27), a non-contrast CT was normal but the MRI showed an intrasellar mass. In our first patient (Case 28), both CT and MRI showed a large pituitary mass with extension to the optic chiasm. In our second patient (Case 29), MRI showed a normal-sized pituitary with resolution of a large mass present on CT 3 months earlier. Our third patient (Case 30) had a large pituitary mass on MRI.

Four patients had sellar polytomography revealing sellar enlargement (Cases 12, 13, 14, 16) and thinning of the sellar floor (Case 13) or dorsum sellae (Case 14). Ten patients had plain skull radiographs which showed sellar enlargement in 3 (Cases 6, 8, 11); erosion of the dorsum sellae in 4 (Cases 6, 10, 15, 23); and normal findings in 4 (Cases 17, 24, 26, 27).

Angiography was performed in 4 patients (Cases 11, 15, 23, 26). In 3 of these, there was suprasellar displacement of the right internal carotid or elevation of the right anterior cerebral artery. In 1 (Case 26), angiography was normal. In no cases was a tumor blush or any abnormal vascularity seen.

Endocrinologic evaluation

Endocrine function varied from normal to partial or panhypopituitarism. Prolactin levels were variable. Panhypopituitarism here is defined as hypocortisolism (with inappropriately low ACTH), hypothyroidism (with low TSH or insufficient TSH response to TRH), and hypogonadism (amenorrhea with or without low gonadotropins and estrogen).

Panhypopituitarism occurred in 8 of 21 patients (38%) in whom the above axes were objectively assessed (Cases 11, 13, 15, 16, 18, 24, 28, 30).

Hypothyroidism and hypoadrenalism without definitive hypogonadism occurred in 5 more patients (Cases 8, 20, 25, 26, 29). In Cases 8 and 25, patients menstruated normally. In our second patient (Case 29), amenorrhea resolved at 6 months postpartum. Hypoadrenalism and hypogonadism occurred in 2 patients (Cases 17, 21).

In 3 patients, isolated hypogonadism occurred in

Fig. 4. Case 2. Anterior pituitary biopsy showing marked fibrosis (arrows) separating 2 lymphoid aggregates (L). No residual adenohypophyseoal cells are apparent (hematoxylin-eosin, original magnification × 100).
FIG. 5. Case 2. A. T1 sagittal MRI demonstrating a normal-sized pituitary gland (black arrowhead) and pituitary stalk (white arrow) without suprasellar extension. B. T1 coronal MRI showing the same pituitary gland with a thickened pituitary stalk (arrow).
FIG 6. Case 3. A. T1 sagittal MRI demonstrating sellar mass with suprasellar extension. B. T1 coronal MRI demonstrating sellar mass with suprasellar extension. Optic chiasm is slightly elevated (arrow). C. T2 axial MRI demonstrating the suprasellar component of the mass (arrow).
association with hyperprolactinemia (Cases 6, 12, 19). The first 2 had prolactins of 60 and 61 ng/ml respectively, with galactorrhea. In the latter case, prolactin was 110 ng/ml without galactorrhea.

Isolated but mild hypothyroidism occurred in 1 patient (Case 10); however, a "sick euthyroid" syndrome could not be ruled out in this case.

In 2 patients (Cases 23, 27), pituitary function was completely normal; the latter patient had an elevated prolactin level while nursing in the early postpartum period.

In 9 cases, laboratory data were largely unavailable; 8 of these were diagnosed at autopsy. Endocrinologic abnormalities can be characterized by symptomatic and autopsy information: 1 had panhypopituitarism (Case 1), 3 had combined hypothyroidism and hypoadrenalism (Cases 2-4), and 3 had evidence of isolated adrenal insufficiency (Cases 5, 7, 22). In 1 patient (Case 9), the only clinically significant endocrinologic abnormality was galactorrhea, with the pathologic finding of prolactin cell hyperplasia (14 months postpartum) at autopsy. In the 1 non-autopsy case in which laboratory data were unavailable (Case 14), pituitary function was symptomatically normal.

Adding the objectively proven cases to the clinically-probable cases, there were 9 with panhypopituitarism (30%), 8 with hypothyroidism and hypoadrenalism (27%), 2 with hypoadrenalism and hypogonadism (7%), 3 with hyperprolactinemia/galactorrhea and amenorrhea (10%), 3 with isolated hypoadrenalism (10%), 3 with completely normal pituitary function (10%), 1 with hyperprolactinemia but otherwise normal pituitary function (3%), and 1 with mild isolated hypothyroidism (3%).

Prolactin levels varied from unmeasurable to high. Seven patients had postpartum galactorrhea (Cases 17, 18, 20, 25, 28-30). Three additional patients had low prolactins or prolactin levels that could not be stimulated; lactation ability was unknown in 2 and the third patient was male (Cases 8, 13, 24). Three patients had normal prolactin levels (Cases 14, 15, 23). Eight patients had definitely elevated prolactins (Cases 6, 11, 12, 16, 19, 21, 26, 27).

In summary, 10 patients of 22 known had prolactin levels of <1 ng/ml or inability to lactate (45%), 9 had hyperprolactinemia (41%) and 3 had normoprolactinemia (14%).

Growth hormone was measured in 10 patients before medical or surgical intervention. GH was normal in all. In 5 patients, GH was <1.0 ng/ml, but no dynamic testing was performed to assess responsiveness of this axis (Cases 11, 23, 25, 28, 30). In 5 patients levels were between 1.2 and 5.0 ng/ml (Cases 8, 13, 24, 27, 29). In 1 of these (Case 8), basal GH was 3.0 with insufficient rise to insulin-induced hypoglycemia, suggesting an insufficiency of this axis.

No patients had preoperative diabetes insipidus although 5 patients had transient diabetes insipidus postoperatively (Cases 10, 11, 20, 23, 28) and 3 patients had permanent diabetes insipidus requiring vasopressin therapy (Cases 13, 14, 27).

Treatment/course

Nine patients died from lymphocytic hypophysitis. One additional patient died as a result of suicide when symptoms began. The most likely cause of death in most cases was adrenal insufficiency.

In patients without precipitous decline to death, thyroid and corticosteroid replacement therapy was followed by relief of symptoms. In 1 patient (Case 10), preoperative bromocriptine therapy was accompanied by improvement of visual field defects and visual acuity. In another patient, bromocriptine resolved the galactorrhea but did not change the size of the pituitary mass (Case 26). At least 1 patient had relief of headache when treatment with dex-
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<th>Case No.</th>
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<th>Age</th>
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<td>27</td>
<td>33</td>
<td>18</td>
<td>G,P₁</td>
<td>ap</td>
<td>Headache; pp blurred vision &amp; bilateral visual field defects</td>
<td>CT: N; MRI: M</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>28</td>
<td>Coman</td>
<td>29</td>
<td>G,P₁</td>
<td>ap</td>
<td>Headache &amp; visual loss; pp agalactia, amenorrhea</td>
<td>CT: M, SSE, E; MRI: M</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>29</td>
<td>Coman</td>
<td>34</td>
<td>G,P₁</td>
<td>ap</td>
<td>Headache &amp; visual blurring; pp weakness, agalactia</td>
<td>CT: M, SSE, E</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>30</td>
<td>Coman</td>
<td>38</td>
<td>G,P₁</td>
<td>ap</td>
<td>Headache, fatigue, nausea; pp agalactia</td>
<td>MRI: M, SSE</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: G = pregnancies, P = living offspring, Sx = Stage of pregnancy when symptoms began, ap = antepartum, pm = postmenopausal, pp = postpartum, wt = weight, M = Mass, E = Enhancing, N = Normal, SSE = Supraocular Extension, t = Elevated, ↓ = Insufficient, — = not known.

*Primary thyroiditis
amethasone was begun (4 mg every 6 hours; Case 29).

A total of 20 patients had the diagnosis made at transsphenoidal surgery (17 patients) or bifrontal craniotomy (3 patients). In almost all cases, a mass was present at the time of surgery.

Thirteen patients had partial pituitary resections or biopsies alone and 7 had total hypophysectomies (Cases 11, 13, 15, 24, 27, 28, 30). Total pituitary resections were performed in most of the cases because the frozen section biopsy specimen did not reveal the diagnosis of lymphocytic hypophysitis.

All patients with visual defects and/or headache at the time of surgery had relief of these symptoms postoperatively (Cases 6, 8, 10, 20, 23, 25, 27, 28). The 1 patient who had surgery during her pregnancy (Case 10) subsequently had a normal spontaneous vaginal delivery. In this patient some residual mass was apparent when CT was repeated 2 months postoperatively and the patient had developed panhypopituitarism. In 1 case, long-term follow-up indicated no recurrence of pituitary mass at either 6 months or 2.5 years (Case 26).

Panhypopituitarism continued or developed in those who had total hypophysectomies. Also, in cases where there was significant preoperative pituitary deficiency, most patients did not regain pituitary function. Case 8 did not regain thyroid or adrenal function. Cases 16 and 26 remained panhypopituitarism. Our second patient (Case 29) had a period of amenorrhea postpartum but did regain menses 2 months before surgery. She has, however, remained hypothyroid and hypoadrenal.

Patients who had relatively normal pituitary function or only a preoperative partial deficiency and who had only a partial pituitary resection maintained their presurgical pituitary function. These patients included Case 14, whose pituitary function remained intact; Cases 6 and 12, whose galactorrhea and amenorrhea resolved postoperatively; Case 8, whose gonadal function remained normal; Case 23, whose pituitary function remained clinically intact (a subnormal cortisol response to hypoglycemia was found postoperatively but since this was not performed before surgery, it cannot be considered a decline of function); and Case 19, whose thyroid and adrenal function remained normal after surgery.

Pituitary function became normal in 4 of the 8 patients with hyperprolactinemia. In 2 patients, normalization was immediate after surgery (Cases 6, 27). In 1 case it took 1 year for prolactin levels to return to normal (Case 12). In Case 16, prolactin levels normalized but the patient remained panhypopituitary. In Case 19, mild hyperprolactinemia and amenorrhea persisted for greater than 1.5 years after surgery. In Case 21, the postoperative prolactin level is unknown but the patient subsequently became pregnant. With this second pregnancy she did not develop any further pituitary disease, nor did she have thyroid dysfunction (after her first pregnancy, she had postpartum thyroiditis which evolved from hyperfunction to hypofunction to euthyroidism). In 2 patients (Cases 11, 26), follow-up prolactin levels are unknown.

Three patients regained gonadal function postoperatively, with resolution of hyperprolactinemia (Cases 6, 12, 21). In 1 patient (Case 20), mild hypothyroidism improved after operation and did not require hormone therapy. Corticosteroid replacement was still needed, however. Moreover, in 1 case of well-documented hypothyroidism, hypoadrenalism, hypoprolactinemia with agalactia (Case 25), complete pituitary function returned within 1 year after surgery. Hormone replacement was withdrawn and menses resumed. An insulin tolerance test documented normal adrenal and GH responses to hypoglycemia. TSH responded normally to TRH stimulation.

**Pathology**

Grossly the pituitary can appear small, normal, or large. Frequently it was described as having an unusually firm, tough appearance and feel (Cases 6, 13–15, 18, 20, 24, 27–29). The color varied from dull white (Case 13) or gray (Case 28) to yellow (Cases 14, 15, 20) or purple (Case 6). In 1 case (#10), it was encapsulated by dense pituitary capsule, and in another (Case 8), it was gritty, non-encapsulated and easy to shell out from normal pituitary tissue.

Microscopically, the lesion was characterized by variably dense, diffuse lymphocytic infiltration of a polyclonal nature (Cases 21, 23–25) in the anterior pituitary. Some of the lymphocytes had formed actual follicles with poorly formed or true germinal centers. Plasma cells were also seen, although in smaller numbers than lymphocytes. A few eosinophils were spotted (Cases 8, 13, 20, 21, 24, 28).

A single giant cell was seen in Case 13 and a few foreign body giant cells as well as a tiny area of old hemorrhage were seen in Case 26.

Varying degrees of edema and fibrosis were seen. Amidst the inflammatory infiltrate and fibrosis, small islands of normal pituicytes or isolated pituitary cells were seen. Immunocytochemical stains showed the presence of acidophils, basophils, and chromophobes (Cases 9, 26) although in some cases 1 or more of these cell lines were absent in biopsy specimens: no basophils were seen in Cases 7 or 23, and no corticotrophs were noted in Cases 7 or 8. Lactotroph hyperplasia was seen (as in Cases 7, 9, and 27).

Electron microscopy has shown interdigitation of inflammatory cells with pituicytes (Cases 11, 13, 21,
LYMPHOCYTIC HYPOPHYSEITIS

27).

Multinucleated giant cells, epithelioid histocytes, granulomas, and neoplastic transformation were not seen. In all cases the posterior hypophysis was normal. When cultured, no bacteria, fungi, or acid-fast bacteria were identified (Cases 13, 14, 26).

Immunology

Assays for serum antibodies to pituitary tissue were performed in 5 cases (Cases 8, 13, 19, 21, 23). In Case 8, antibodies to all pituitary cell types were found in the patient’s serum. In Case 19, antipituitary antibody (cell type not specified) was found in addition to antiprolactin antibody at a titer of 1:8. In the 3 other cases, no antipituitary antibodies were found in serum.

Fourteen authors searched for a wide variety of other serum antibodies, including thyroid microsomal, thyroglobulin, adrenal, ovarian, smooth muscle, mitochondrial, pancreatic islet cell, gastric mucosal, parietal, and nuclear antibodies. Antimitochondrial antibody (ab) was found in 2 patients (Cases 11, 14). Antinuclear ab (titer of 1:80) was found in Case 24, antiparietal ab (titer of 1:40) was found in Case 16, and antismooth muscle ab was found in Case 23.

HLA-typing was performed in 4 patients (Cases 8, 13, 23, 24). The only common antigen expressed was Bw35 (seen in Cases 8 and 13).

Associated endocrine disease

Nine patients (30%) had other endocrine or immune diseases, or chronic lymphocytic infiltration of endocrine organs at autopsy. The abnormalities included postpartum or lymphocytic thyroiditis (Cases 1, 2, 7, 17, 18, 21, 22); pernicious anemia (in Case 2 with atrophic gastritis at autopsy); in Case 16 with low serum B12 and antiparietal antibody; lymphocytic adrenalitis (Cases 4, 17); and focal lymphocytic parathyroiditis (Case 4). One patient had gestational DM (Case 10).

Discussion

Diagnosis/endocrinologic abnormalities

Lymphocytic hypophysitis presents as an intrasellar mass during the last trimester of pregnancy or early postpartum period, or as postpartum hypopituitarism of variable degree. The differential diagnosis may thus include: pituitary adenoma, pituitary necrosis/hemorrhage, aneurysm, granulomatous diseases, and parapariller tumors and cysts. The clinical setting significantly narrows the differential diagnosis. The age distribution and temporal association of lymphocytic hypophysitis with the puerperium leaves lymphocytic hypophysitis, postpartum pituitary necrosis (Sheehan syndrome), and pituitary adenoma as the most probable etiologies in the differential diagnosis. Postpartum pituitary necrosis may have a subtle presentation months or years after delivery, like lymphocytic hypophysitis, but the sine qua non for this diagnosis should be shock or hypotension associated with a complicated hemorrhagic or septic delivery (59). In the later stages, patients with lymphocytic hypophysitis and postpartum pituitary necrosis may have the same appearance on CT: normal, or partially empty or empty sella, the last two reflecting atrophy of the pituitary gland (14).

It may be difficult to distinguish non-secreting pituitary adenomas from lymphocytic hypophysitis. Some authors have commented that the degree of hypopituitarism in lymphocytic hypophysitis is out of proportion to the size of the pituitary mass, particularly with regard to those patients who are truly hypopituitaric, with prolactin deficiency. In patients with lymphocytic hypophysitis, hypopituitarism is present with small masses or even unenlarged pituitaries. In patients with tumors, it would be distinctly unusual to see this degree of hypopituitarism except with a very large mass. The implication is that the hypopituitarism in hypophysitis is more a result of specific pituitary destruction rather than compression and subsequent atrophy of normal pituitary tissue, as is seen with tumors.

Furthermore, tumors are less likely to cause the unusual patterns of endocrinologic abnormalities characteristic of lymphocytic hypophysitis. Tumors often cause a characteristic progressive hormone loss: the levels of GH and FSH/LH are reduced first, followed by levels of TSH and ACTH, and lastly (and rarely) PRL. That is, patients who have tumors large enough to cause TSH and/or ACTH deficiency almost always have loss of GH (detectable by dynamic testing) and gonadal function (52, 63). In contrast, lymphocytic hypophysitis frequently results in isolated ACTH deficiency or combined adrenal/thyroid deficiencies despite normal gonadal function. Moreover, some patients even with agalactia and/or measured prolactin deficiency (Cases 8, 25) still had normal gonadal function. Patients in the postpartum period who do present with these unusual patterns of pituitary hormone levels are more likely to have lymphocytic hypophysitis rather than pituitary adenomas.

Certain pituitary cells appear to be more specifically susceptible to cellular destruction, even though the inflammatory infiltrate is usually diffuse throughout the gland and all pituitocytes are decreased in number. Overall, ACTH cells are the most frequently affected and FSH/LH cells appear to be the most commonly
spared. Prolactin is the most variable hormone in this disease. Deficiency may be caused by specific destruction of the lactotrophic cells. Elevations could be the result of pituitary mass causing stalk compression (31), or residual lactotroph hyperplasia from recent pregnancy (3, 18).

Related cases of postpartum hypopituitarism

Numerous cases of hypopituitarism have been reported in the postpartum period, but because of the lack of mass or headache/visual defects, the patients never underwent surgical exploration of the pituitary (14, 19, 24, 41, 43, 46, 55, 62, 71). These patients were similar to patients with lymphocytic hypophysitis in many respects. Most had minimal or no obstetrical complications. Varying degrees of hypopituitarism were present, including isolated hypocortisolism (55); hypocortisolism and hypogonadism with primary hypothyroidism (19); hypogonadism, hypoadrenalism, hypoprolactinemia (46), panhypopituitarism (43).

In all except 2 of these cases, CT was normal or showed a partially empty or empty sella. Zeller et al (71) reported an 18-year-old woman with secondary adrenal insufficiency, postpartum thyrotoxicosis, and hypogonadism, who was found to have an enhancing pituitary mass with suprasellar extension. Since visual fields were normal, surgery was deferred. She was treated with cortisone acetate and levothyroxine (after hypothyroidism developed). A repeat CT scan done 4 months later showed spontaneous regression of the mass with a pituitary of normal size. A 29-year-old woman reported by Ikeda and Okudaira (24) developed headache and visual field defects associated with a mass during pregnancy. The mass resolved within 4 months postpartum, but she had agalactia and subsequently developed insufficiency of ACTH, GH, and PRL.

Given all the similarities between these cases of idiopathic postpartum hypopituitarism (with or without masses) and pathologically proven lymphocytic hypophysitis, it is reasonable to speculate that many of these cases were actually lymphocytic hypophysitis. Other cases labeled as Sheehan syndrome but lacking the characteristic history of shock or hemorrhage may also be lymphocytic hypophysitis. The actual incidence of this entity, therefore, may be much greater than currently recognized. Some cases of idiopathic hypopituitarism in men and in postmenopausal women may likewise be due to lymphocytic inflammation. Moreover, the spectrum of lymphocytic hypophysitis may include cases of idiopathic isolated ACTH and TSH deficiencies (6, 65).

Pathology

The only way to definitely diagnose lymphocytic hypophysitis is through biopsy or at autopsy. The pathologic picture is definitive: lymphocytic infiltration with plasma cells, few eosinophils, edema, and fibrosis. Multinucleated giant cells are characteristically absent. Epithelioid histiocytes and true granulomas, when seen, reflect a distinct disease process, granulomatous hypophysitis, which is not to be confused with lymphocytic hypophysitis. Cases which show this pathology with or without lymphocytic infiltration (9, 27, 34, 56, 66), have been included by some authors in other series, and are specifically excluded here. The overall age predilection is different for granulomatous hypophysitis, which usually occurs in older patients although subsets of this disease may occur in a younger population. The frequent association of lymphocytic hypophysitis with pregnancy is missing for granulomatous hypophysitis. An association with systemic granulomatous disease exists in a subset of patients with granulomatous hypophysitis, and since the pathologic picture is different, the etiologic process may also be different (10, 45, 60). An analogy with thyroid disease can be made: postpartum thyroiditis, which is characterized by lymphocytic infiltration, is probably of autoimmune etiology. In contrast, in subacute thyroiditis, granulomatous infiltrates predominate and the inciting agent may be viral.

Additionally, lymphocytic hypophysitis can be differentiated pathologically from healed postpartum pituitary necrosis (Sheehan syndrome), in that the latter shows mostly acellular fibrosis rather than a lymphocytic infiltrate with fibrosis; furthermore, Sheehan syndrome is usually focal in the areas most vulnerable to ischemic injury rather than diffuse throughout the gland. Finally, the gland is almost always small and atrophic at this stage, never enlarged (58, 60).

Some controversy has arisen regarding the normal appearance of the pituitary at autopsy. Simonds and Brandes (61) studied 200 patients who had died suddenly and found that 10% had some lymphocytic infiltration. In 19 of 21 cases, the lymphocytes occurred in the pars intermedia, pars nervosa, or surrounding blood vessels. In only 2 of 21 cases were any lymphocytes seen in the anterior lobe. Their meaning is unclear without any clinical correlation. Shanklin (67) studied 100 pituitary glands at autopsy and found evidence of lymphocytic inflammation in 43%. Shanklin found, however, not a single area of lymphocytic infiltration in the anterior hypophysis. Clearly, therefore, although the presence of lymphoid tissue in or near the pars intermedia may be a nor-
Lymphocytic hypophysitis is a pathological finding, inflammatory infiltrates in the anterior hypophysis are distinctly unusual and certainly pathological.

Pathogenesis/immunology

The etiology of lymphocytic hypophysitis is unknown but there is some support for the idea that the disease has an autoimmune basis. First, the greater incidence of the disease in females is consistent with autoimmunogenesis. More specifically, the epidemiologic association of the disease with pregnancy and the puerperium is consistent with the multiple complicated immunologic changes that occur at this time (13, 15, 48, 67, 68). Also supporting an autoimmune pathogenesis is the presence of thyroiditis, adrenitis, atrophic gastritis and pernicious anemia, parathyroiditis or retroperitoneal fibrosis in more than 30% of patients with lymphocytic hypophysitis. These coexisting disorders are probably autoimmune in etiology, and are pathologically similar to lymphocytic hypophysitis. Moreover, in some autoimmune endocrinopathies such as the Schmidt syndrome, lymphocytic infiltration of the pituitary has been found in a few cases at autopsy. This finding is a further possible link to the pathogeneses of these disorders (7).

Ultrastructural evidence showing interdigitiation of activated lymphocytes with pituitary cells in varying stages of cell injury and death is support for a destructive process induced by immune cells. Such ultrastructural changes are identical to those seen in autoimmune thyroiditis (53).

Furthermore, experimental animal models of adrenohypophysitis have been produced. In the first model, pituitary tissue and adjuvant were injected subcutaneously into footpads of rats (32). The resultant microscopic appearance of the pituitary is nearly identical to that seen in patients with lymphocytic hypophysitis. No lesions were detected in the pituitaries of rats immunized with adrenal, pancreas, or spinal cord tissue (and adjuvant). In preliminary experiments by the same author, the severity of adrenohypophysitis might have been increased in postpartum animals.

A second animal model for autoimmune pituitary disease has been produced in rabbits (26). Homologous pituitary tissue and adjuvant were injected into the backs of experimental animals. Blood was obtained before and after immunization to look for antipituitary antibodies and lymphocyte stimulation. Five of 7 experimental animals had evidence of pituitary inflammation in the anterior lobe. Although no significant titer of antipituitary antibody was found, evidence of lymphocyte activation was obtained through measurement of H-thymidine uptake in animals before and after immunization. Four of the 5 animals with pituitary inflammation had lymphocytes that were activated against pituitary extract. It is possible, therefore, that cellular mediated immunity is involved in the production of lymphocytic hypophysitis.

If the pathogenesis involves humoral immunity as well, then an autoantibody marker for this disease may be found. So far, it has been found in only 2 of 5 cases in which an assay for antipituitary antibody was performed. The timing of the assay was variable, however, and only 1 static measurement was reported in each case. The situation could be analogous to postpartum thyroiditis, in which antibody titers can increase or decrease intermittently, even disappearing at different times in the course of the disease (42). Antibody was found in 1 of the 2 cases of idiopathic postpartum hypopituitarism in which no biopsy was performed (19, 46).

Nor is the finding of antipituitary antibody always abnormal. Engelberth and Jezkova (12) found that 18% of normal women had antipituitary antibodies (abs) in the postpartum period (5th to 7th day postpartum), whereas all were negative for abs during pregnancy and at delivery. Symptoms and signs of pituitary deficiency 6 to 12 months after delivery appeared to be more common in women who had measurable abs (25% vs. 4% in patients with no abs) but there were no objective data to corroborate this. A high titer of abs was also found in a single patient with the Sheehan syndrome. These findings indicate that normal puerperium may result in hypophysial antibodies and/or that antibodies may appear as a result of pituitary necrosis in the Sheehan syndrome. Additionally, Fouplard et al (50) have found that human pituitary ACTH secreting cells normally have an affinity for human antibody through the Fc portion of immunoglobulin.

Further interesting information regarding pituitary autoimmunity includes studies by Bottazzo (5) in which sera from 6.8% of patients with various endocrine autoimmune syndromes contained antibodies to prolactin secreting cells. No clinical evidence of pituitary disease was correlated with the presence of antibodies in 19 patients (although TRH testing yielded a flat prolactin response in 2 patients). The highest incidence of antibody was found in patients with polyendocrinopathies (10 of 92 were positive) and in hyperparathyroidism (2 of 8 were positive). None of the 13 panhypopituitary patients tested positive for antibody.

It has recently been reported (28) that antipituitary antibodies have been measured in the serum of 75% of women with the empty sella syndrome. It is conceivable that in some cases the empty sella syndrome may represent the end stage of lymphocytic
hypophysitis.

Thus, the evidence for autoimmunity in the pathogenesis of adenohypophysitis is intriguing but inconclusive. Further investigation of normal postpartum pituitary immunity, elucidation of pituitary antigens and autoantibodies in lymphocytic hypophysitis is needed.

Lymphocytic hypophysitis may result from an autoimmune reaction to other inciting antigens/factors besides those associated with pregnancy. The 1 postmenopausal female who was diagnosed antemortem had an antecedent viral meningitis syndrome and subsequently developed hypopituitarism. Viral antigen may have stimulated an immune response that crossreacted with pituitary cells in addition to viral particles. In the postmenopausal women diagnosed at autopsy, there were no clear inciting factors, although 2 of these patients had other presumably autoimmune endocrinopathies (thyroiditis and gastritis in 1 and parathyroiditis and adrenalitis in the other). The 1 male with lymphocytic hypophysitis had no previous history of endocrine or autoimmune disease or meningitis. He did have the HLA-B8 antigen, however, which has been associated with some autoimmune diseases. The 1 menstrual-age woman with no previous pregnancies did not have other endocrinologic, immunologic, or viral illnesses preceding the onset of lymphocytic hypophysitis.

Natural history of lymphocytic hypophysitis

Information obtained by combining clinical data as well as radiographic and pathologic data reveals that lymphocytic hypophysitis probably progresses through various stages. Early on, the pituitary becomes edematous, inflamed, and enlarged and may produce mass-like symptoms. Subsequently, pituitary tissue is destroyed and replaced with fibrosis; the sellar mass spontaneously regresses and symptoms of hypopituitarism develop. At this time, the pituitary is usually shrunken and atrophic. The early stage may be subclinical, with no symptoms of pituitary mass but with the ultimate development of postpartum hypopituitarism. The fact that pituitary function may be recovered implies that hypopituitarism may be secondary to compression of tissue by inflammatory mass rather than cellular destruction, or that pituicytes may regenerate with time in certain cases.

Management

Given our current understanding of this disease, a management paradigm can be formulated. In the proper clinical setting, during the puerperium, if a patient develops a pituitary mass causing mild headaches or visual symptoms, the patient should be observed closely without surgical intervention. Visual field examinations and CT scans should be followed carefully. If symptoms resolve and the mass shrinks, surgery may be avoided. Hormone replacement should be provided as needed but attempts to withdraw therapy, with appropriate endocrinologic testing, should be made 6 to 12 months after presentation to see if endogenous pituitary function has recovered. Full endocrinologic recovery was well documented in 1 patient (Case 25).

If a patient with a pituitary mass during the puerperium has severe headaches or marked visual abnormalities, transsphenoidal surgery with biopsy should be performed. If the pituitary has a firm, tough appearance, uncharacteristic for an adenoma, and if the biopsy specimen shows dense lymphocytes with or without fibrosis, then simple decompression should be performed without removal of the gland. A trial of corticosteroid therapy has been suggested in this setting but there are no data to support the efficacy of such treatment.

Further research on adenohypophysitis should include: 1) characterization of normal and pathologic postpartum antipituitary antibodies in order to identify a serologic marker for this disease, 2) determination of factors that render certain pituicytes more susceptible than others, 3) determination of HLA associations, 4) assessment of the effects of immunosuppressive agents, 5) determination of the probability of spontaneous recovery of pituitary function, and 6) determination of the probability of recurrence if a future pregnancy occurs.

Summary

Lymphocytic hypophysitis is an uncommon but increasingly recognized disorder characterized by chronic inflammation and destruction of the anterior pituitary. Three new cases are presented here with a review of the 27 previously reported cases. The disease affects primarily young women in late pregnancy or in the postpartum period but also has been described in postmenopausal women and in one man. It presents as an expanding intrasellar mass or as partial or panhypopituitarism. The etiology may be autoimmune. The natural history of this entity begins with enlargement of the pituitary secondary to inflammatory infiltration and progresses to atrophy of the gland with destruction of pituitary tissue and replacement with fibrosis. At least 1 patient had documented recovery of pituitary function, and the overall potential incidence of recoverable function is unknown. Our improved understanding of this disease has led us to conclude that surgical intervention is not always necessary.