Lymphocytic Hypophysitis

Tracy L. Breen, MD,* Kalmon D. Post, MD,† and Sharon L. Wardlaw, MD‡

Abstract: Lymphocytic hypophysitis (LH) is an autoimmune endocrine disorder primarily affecting peripartum young women. Lymphocytic infiltration of the pituitary initially results in pituitary enlargement, which can cause symptoms and radiographic evidence of a mass lesion. Partial or panhypopituitarism may be present. The anterior pituitary is usually affected, although diabetes insipidus can occur. Over time, the pituitary undergoes fibrosis and atrophy; radiography can demonstrate a partial to empty sella. Most patients will have permanent hypopituitarism, but recovery of function has been documented. In the absence of compressive symptoms such as headache or visual impairment, conservative management is recommended because the initial mass lesion seen with LH could spontaneously regress. Hormone replacement therapy should be given as needed. If there are significant neurologic symptoms secondary to a mass effect, a short course of glucocorticoids can be initiated. Further progression of neurologic symptoms warrants neurosurgical intervention. Partial decompression can relieve symptoms while avoiding removal of significant amounts of pituitary tissue. Patients should be monitored for recovery of pituitary function. The incidence of recurrence of LH with future pregnancies is unknown. We report a case of a woman with LH documented by histology who became spontaneously pregnant several years later without recurrence of lymphocytic hypophysitis.

Key Words: hypophysitis, pregnancy, hypopituitarism

(L)ymphocytic hypophysitis is a chronic inflammatory process that is characterized by lymphocytic infiltration and varying degrees of pituitary destruction. It is thought to be an autoimmune endocrine disease, usually affecting peripartum young women, although cases have been reported in both postmenopausal women and a small number of men. Patients present with symptoms of an expanding intrasellar mass and/or with varying degrees of hypopituitarism. Although lymphocytic hypophysitis (LH) is a relatively rare disorder, it is important to include it in the differential diagnosis of an intrasellar mass and hypopituitarism, particularly if the patient is a young woman in the peripartum period. The natural history of the disease is variable. Initially, the pituitary can enlarge and cause compressive symptoms as it undergoes inflammatory infiltration; over time, the gland usually shrinks as a result of fibrosis and atrophy. Most patients will have permanent hypopituitarism, although there have been reported cases of recovery of pituitary function. We review the clinical features of this interesting and possibly underdiagnosed disease. We also report a case of a woman with documented lymphocytic hypophysitis during her first pregnancy who became spontaneously pregnant several years later without recurrence of pituitary disease.

CASE REPORT

The patient is a 28-year-old woman who presented in her 28th week of pregnancy with symptoms of an intrasellar mass lesion. With the exception of slightly irregular menses, she had an unremarkable medical history. At no time was she amenorrheic; she reportedly had a normal prolactin level and easily became pregnant after stopping her oral contraceptive pills. There was no personal or family history of autoimmune endocrine disease. She reported constant bifrontal headache beginning in her 26th week of pregnancy. Two weeks later, she began to note blurring of vision, and evaluation by her ophthalmologist demonstrated bitemporal superior quadrant...
anopsia. Her visual acuity was noted to be 20/50 in the left eye (OS) and 20/30 in the right eye (OD); this deteriorated to 20/70 OS and 20/50 OD over the next 3 days. Her physical examination at that time revealed a blood pressure of 130/72 mm Hg, gravid abdomen, and mild facial plethora. Her laboratory values were significant for mild hypothyroidism: free T4 was 0.6 ng/dL (normal, 0.8–2.7 ng/dL), TSH 1.5 µIU/mL (normal, 0.2–6.0 µIU/mL); basal AM cortisol was 21 µg/dL (normal, 10–25 µg/dL), prolactin 86 ng/mL, and GH 11.5 ng/mL. A brain magnetic resonance image (MRI) revealed a 1.3 × 1.7 × 2 cm intra- and suprasellar mass displacing the optic chiasm upward, consistent with a pituitary adenoma (Fig. 1). In addition to 50 mcg levothyroxine, the patient was started on 4 mg dexamethasone orally every 8 hours. Transsphenoidal surgery was performed 7 days later because her visual defects failed to improve.

Intraoperatively, there was slightly yellow firm tissue in the sella felt to be consistent with either normal pituitary tissue or lymphocytic hypophysitis. No definite tumor was seen. Frozen sections of the pituitary suggested inflammatory tissue. The sella was explored and partially decompressed. Microscopic examination identified pituitary tissue with focally dense chronic inflammatory infiltrates as well as interstitial widening and fibrosis (Figs. 2 and 3). Prolactin, ACTH, GH, LH, FSH, and TSH were all detected in the gland. The tissue also stained positively for the following lymphoid antigens: leukocyte common antigen (LCA), pan B-cell antigen (L-26), and pan T-cell antigen (UCHL-1). There was no evidence of tumor.

After surgery, the patient noted immediate improvement in her vision. Postoperatively, she developed diabetes insipidus and was treated with DDAVP. Decadron was continued at a dose of 2 mg orally per day; attempts to taper this dose resulted in recurrence of headache and visual complaints. Thyroid hormone was also continued for the remainder of her pregnancy. She delivered a healthy full-term baby but was unable to lactate. Her diabetes insipidus resolved after delivery and corticosteroids were tapered to a maintenance dose. One month after delivery, an MRI was repeated and was without pituitary abnormality (Fig. 4). Her menses returned 1 month postpartum and remained normal. The following year, her levothyroxine and corticosteroid replacement were discontinued. Thyroid function tests, prolactin, and cortisol were all normal. The patient remained euvitally and became spontaneously pregnant 4 years later. Of note,

FIGURE 1. Coronal T1-weighted magnetic resonance image demonstrating a 1.3 × 1.7 × 2-cm intra- and suprasellar mass displacing the optic chiasm upward (arrow).

FIGURE 2. Anterior pituitary with islands of adenohypophyseal cells (large arrow) surrounded by lymphocytes. A lymphoid aggregate (small arrow), interstitial widening, and fibrosis are also seen (hematoxylin–eosin, reticulin stains, magnification × 250).

FIGURE 3. Diffuse lymphocytic infiltration of pituitary is seen with areas of early fibrosis (arrow) (hematoxylin–eosin, magnification × 250).
she had no evidence of pituitary dysfunction or neurologic symptoms during her second pregnancy.

**CLINICAL PRESENTATION**

Lymphocytic adenohypophysitis was first described in 1962. The patient was a 22-year-old woman who was 14 months postpartum when she died of shock after an appendectomy. Her medical history was significant for thyroiditis and amenorrhea that had developed after her pregnancy. Autopsy revealed lymphocytic infiltration of an atrophic pituitary gland, lymphocytic thyroiditis, and atrophic adrenal glands. Several other case reports detailed postmortem examinations showing lymphocytic infiltration of the pituitary without involvement of the other endocrine glands. The first antemortem case of lymphocytic hypophysitis was reported in 1980. Currently, there are approximately 100 reported cases of LH documented by histology in the literature, but the actual incidence of the disease is unknown. Earlier reports in the literature relied on autopsy data because many of these patients died of adrenal insufficiency. More recently, most reported cases have been documented by surgical pathology; however, many suspected cases of lymphocytic hypophysitis are conservatively managed and are never biopsied. It is quite likely that LH is a more common disease than is suggested by the literature.

Patients can present with classic compressive symptoms as a result of an expanding intrasellar mass lesion or with varying degrees of pituitary dysfunction. Such findings can include headaches, visual field defects, decreased visual acuity, diplopia, hypoadrenalism, hypothyroidism, amenorrhea, diabetes insipidus, an inability to lactate postpartum, or galactorrhea not associated with breastfeeding. In a series of 42 patients with LH, 39 were female and 30 presented either during pregnancy or within 14 months postpartum. Of these patients, most had evidence of partial or panhypopituitarism as well as symptoms suggestive of an intrasellar mass.

Although LH often presents in the peripartum period, it does not necessarily recur with subsequent pregnancies. In addition to the patient that we present here, there have been a few reports of women with LH who have had subsequent pregnancies without recurrence of their pituitary disease. One woman with corticotrophin and prolactin deficiencies as a result of lymphocytic hypophysitis had regression of her pituitary mass and went on to become spontaneously pregnant without recurrence of pituitary enlargement. Another report described a woman with a history of panhypopituitarism secondary to LH who became pregnant by ovulation induction. There was no evidence of LH recurrence during the pregnancy and the patient was able to lactate postpartum. Although most cases of LH have been described in young women, it has also been reported in postmenopausal women and in a small number of men. In 1987, Guay et al. described a 52-year-old man who presented with impotence, decreased facial hair, anorexia, and weight loss. Biochemical testing showed hypogonadism, hypothyroidism, and hypoadrenalism. Computed tomography (CT) revealed an enhancing pituitary lesion with suprasellar extension, whereas histology demonstrated lymphocytic hypophysitis.

Recently, an unusual case was reported of relapsing and remitting lymphocytic hypophysitis not associated with pregnancy. This 48-year-old woman experienced 3 episodes of fever, meningeal symptoms, and pituitary hypertrophy over a period of 9 years. During her second episode of lymphocytic meningitis, laboratory testing showed anterior pituitary insufficiency and autoimmune thyroiditis. She was treated with thyroid and ovarian hormonal replacement therapy as well as replacement hydrocortisone. After 3 months, MRI demonstrated a decrease in her intrasellar mass. Two years later, this patient again presented with lymphocytic meningitis. MRI showed a recurrence of the intrasellar mass; pituitary biopsy confirmed the diagnosis of lymphocytic hypophysitis. The patient was treated with 70 mg prednisone with reported improvement and tapered to a maintenance dose of corticosteroids over the next 6 months. Nine years later, she remained on hormonal replacement therapy; her MRI revealed a partially empty sella.

**RADIOGRAPHIC IMAGING**

Early in the course of the disease, there is often a mass lesion in the sella turcica seen on MRI or CT scan. Such lesions are usually intrasellar and can have suprasellar extension. Differentiating an adenoma from LH may be difficult because both can enhance with intravenous contrast. In pa-
patients with LH and diabetes insipidus, thickening of the pituitary stalk and abnormal signal enhancement have been reported, as well as loss of the hyperintense signal known as the “bright spot” of the normal neurohypophysis.10 Although most cases of biopsy proven LH have been associated with radiographic lesions, this could be misleading because patients presenting without a mass lesion are less likely to be referred to a neurosurgeon. The mass lesion of LH can disappear and result in a partially empty or empty sella. This has been seen in some patients managed conservatively after biopsies documented LH.

**ENDOCRINOLOGIC EVALUATION**

Laboratory evaluation shows pituitary function that ranges from normal to partial or panhypopituitarism. LH usually causes anterior pituitary dysfunction, although diabetes insipidus can also be seen.5,10 Unlike adenomas, in which the order of hormone loss can be associated with anatomic progression of the lesion (first gonadotropins, then TSH and ACTH), LH can result in isolated ACTH and/or TSH deficiencies with normal gonadotropin levels. The prolactin is quite variable, ranging from high, low, or normal. This unusual pattern of hormone deficiencies should alert the clinician to the possibility of LH in the workup of a patient presenting with a pituitary mass and/or hypopituitarism.

**DIFFERENTIAL DIAGNOSIS**

The most common cause of an intrasellar mass is a pituitary adenoma.11 Less common causes include nonpituitary or parasellar tumors and cysts, granulomatous and infectious processes, and vascular lesions such as aneurysms or infarction. In addition to lymphocytic infiltration, primary hypophysitis (defined as not having a definite etiologic agent) can also be characterized by granulomatous or xanthomatous inflammation.12 Secondary hypophysitis can be caused by infections or systemic illnesses such as sarcoid, Wegener’s granulomatosis, and Langerhans cell histiocytosis.

For a female patient presenting with postpartum hypopituitarism, the diagnosis of Sheehan’s syndrome must be considered. Radiographically, Sheehan’s syndrome could initially appear as an enlarged pituitary but then progress to a partially empty sella later in the disease.13,14 It is quite possible that previously reported cases of Sheehan’s syndrome were actually the result of LH because both can present with a partially empty sella and hypopituitarism. Differentiating between these 2 entities necessitates a careful obstetric history detailing acute events at delivery, including hemorrhage and hypotension. The patient with Sheehan’s syndrome typically has evidence of an acute hemodynamic insult, whereas patients with LH could have findings and/or symptoms that predate the delivery. Furthermore, patients with LH often have evidence of other autoimmune diseases.

Because the differential diagnosis of an intrasellar mass and hypopituitarism is fairly broad and the frequency at which LH occurs fairly low, the following features should prompt consideration of LH as opposed to a pituitary adenoma:

1. Any peripartum woman presenting with an intrasellar mass and/or hypopituitarism. Although prolactinomas can increase in size during pregnancy, most women with prolactinomas will describe a history of irregular menses and difficulty with conception.15 In contrast, most patients with LH have a normal menstrual history.

2. An atypical pattern of pituitary hormone deficiencies with the anterior pituitary hormones being most affected. There could be isolated TSH or ACTH deficiencies with intact gonadotropins. Diabetes insipidus can also be present. Such a pattern of biochemical abnormalities would be unusual in an adenoma.

3. Regression of the mass lesion. LH can result in a partially or empty sella, whereas most pituitary adenomas enlarge over time.

4. A personal or family history of other autoimmune diseases.

5. Hypopituitarism out of proportion to the size of the radiographic mass. Panhypopituitarism can be present in LH with only a small radiographic abnormality. This would be less likely to be seen in a micro- or small macroadenoma.

**PATHOLOGY**

Depending on the time course of the disease, the gland could be enlarged or small and atrophied. Grossly, the gland has been described as having a firm consistency. Microscopically, a diffuse lymphocytic infiltrate is seen with destruction of the anterior pituitary. The inflammatory cells can form lymphoid follicles. These cells are a mixed polyclonal population of T and B cells, with plasma cells less frequently seen. There is edema and fibrosis of the anterior pituitary, usually with sparing of the posterior pituitary architecture. Granulomata, giant cells, and histiocytes are not seen in LH.

**PATHOGENESIS**

LH is thought to be one of many organ-specific endocrine autoimmune diseases. Its female and peripartum predominance is consistent with an autoimmune etiology. In one series of patients with LH, 30% of the patients had another autoimmune process with autoimmune thyroid disease occurring most frequently.6 A polyclonal infiltrate is seen histologically, which is similar to other autoimmune diseases. Antipituitary antibodies have been also been reported. In a small number of patients with LH, immunofluorescence has been used to identify antipituitary antibodies directed against adenohypophyseal cells. More recently, an immunoblotting assay was described that detected autoantibodies against a
pituitary cytosolic protein. This protein has been identified as the 49-kDa protein alpha-enolase. Although these antibodies were detected in up to 70% of patients with LH, they were also found in other patients with autoimmune diseases and are not disease-specific. Although antipituitary antibodies could serve as a marker of autoimmunity, we do not currently recommend the routine use of antibody testing to make the diagnosis of LH.

MANAGEMENT

In the past, many patients with LH underwent surgical debulking and resection, which likely contributed to permanent hypopituitarism. There have been many well-described cases of patients whose mass lesions spontaneously resolved without surgical intervention. A small number of patients with LH have been reported to respond to treatment with high doses of glucocorticoids. It remains unclear, however, what role steroids have in the treatment of LH because the natural history is for the mass lesion to regress spontaneously. Unless there are significant compressive symptoms as a result of a mass effect, we do not currently recommend glucocorticoids (other than as replacement) as first-line therapy. A short course of glucocorticoids could be considered in a patient who has compressive symptoms; such a patient should be closely monitored and referred for surgical decompression if there is no response or worsening of symptoms.

For many patients with suspected LH, conservative management is warranted. The clinician should closely monitor visual fields and acuity, neurologic examination, and radiographic imaging. Progressive deterioration in vision or neurologic function should prompt neurosurgical intervention. It is important to discuss with the neurosurgeon the suspicion of LH, because simple decompression as opposed to more extensive resection could be sufficient. Intraoperative frozen sections could assist in the diagnosis. Hormone replacement should be given as needed. Although most patients with LH will remain hypopituitary, it is important to routinely monitor pituitary function. There are several well-documented cases, in addition to our patient, in which pituitary function has been shown to recover. As conservative treatment becomes more common, we anticipate that recovery of pituitary function will be more frequently observed. Because many previously reported patients had significant amounts of pituitary tissue removed at surgery, it is difficult to determine what number of patients will recover function without intervention.

SUMMARY

Lymphocytic hypophysitis is an autoimmune endocrine disorder classically affecting young women in late pregnancy or the postpartum period. It can be manifested by an atypical history is for the mass lesion to regress spontaneously. Unless there are significant compressive symptoms as a result of a mass effect, we do not currently recommend glucocorticoids (other than as replacement) as first-line therapy. A short course of glucocorticoids could be considered in a patient who has compressive symptoms; such a patient should be closely monitored and referred for surgical decompression if there is no response or worsening of symptoms.

For many patients with suspected LH, conservative management is warranted. The clinician should closely monitor visual fields and acuity, neurologic examination, and radiographic imaging. Progressive deterioration in vision or neurologic function should prompt neurosurgical intervention. It is important to discuss with the neurosurgeon the suspicion of LH, because simple decompression as opposed to more extensive resection could be sufficient. Intraoperative frozen sections could assist in the diagnosis. Hormone replacement should be given as needed. Although most patients with LH will remain hypopituitary, it is important to routinely monitor pituitary function. There are several well-documented cases, in addition to our patient, in which pituitary function has been shown to recover. As conservative treatment becomes more common, we anticipate that recovery of pituitary function will be more frequently observed. Because many previously reported patients had significant amounts of pituitary tissue removed at surgery, it is difficult to determine what number of patients will recover function without intervention.

SUMMARY

Lymphocytic hypophysitis is an autoimmune endocrine disorder classically affecting young women in late pregnancy or the postpartum period. It can be manifested by an atypical pattern of hormone deficiencies such as intact gonadotropins with ACTH or TSH deficiencies. The presence of diabetes insipidus should increase the suspicion of LH. Compressive symptoms resulting from an enlarging sellar mass can be present. Alternatively, patients can present with radiographic evidence of a partially empty or empty sella. Full endocrine evaluation and MRI imaging of the pituitary should be performed, in addition to close monitoring of the patient’s visual and neurologic examination. If suspicion for LH is high, and the patient has stable vision and neurologic examinations, one may follow conservatively. A short course of glucocorticoids may be warranted to treat compressive symptoms. If surgical intervention is indicated, an intraoperative frozen section could assist in the diagnosis, thus allowing for simple decompression of the gland. Early in the disease, the pituitary gland enlarges but over time could atrophy as a result of destruction of the gland and accompanying fibrotic changes. Most patients with pituitary dysfunction will remain hypopituitary but should be routinely evaluated for recovery. Women with a history of LH should be closely monitored during future pregnancies because the incidence of recurrence is unknown. However, there have been several reports of subsequent pregnancies without evidence of pituitary hyper trophy. Our patient not only had remission of her mass lesion, but became eutopituitary and went on to have a spontaneous pregnancy 4 years later without recurrence of LH.

REFERENCES

