Lymphocytic Hypophysitis With Subsequent Development of Graves Disease

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Abstract: Lymphocytic hypophysitis (LH), a rare pituitary condition mimicking pituitary macroadenoma, presents most commonly in the peripartum period. This presumably autoimmune disease can occur as an isolated entity or be associated with other autoimmune conditions. The association of LH with Graves disease is extremely rare. We present the clinical course and laboratory evaluation of a woman who developed LH in the third trimester of her fifth pregnancy. The patient then developed overt Graves disease 2 years later. A 21-year-old black woman with an unremarkable medical and obstetric history developed severe headache and partial visual loss during the third trimester of her fifth pregnancy. Evaluation revealed a large partially hemorrhagic pituitary mass with suprasellar extension compressing the optic chiasm. Pathologic evaluation after transsphenoidal surgery confirmed the resected mass to be lymphocytic hypophysitis. Postoperative evaluation documented persistent panhypopituitarism and central diabetes insipidus. She remained clinically stable for 2 years receiving physiological doses of glucocorticoid, levothyroxine, and desmopressin. She then developed symptoms and signs of hyperthyroidism. Levothyroxine was discontinued and additional evaluation was consistent with Graves disease. Patients with severe headache and visual difficulties during pregnancy or the postpartum period should have a detailed neurologic and endocrinologic evaluation. Lymphocytic hypophysitis, a rare pituitary condition, should be considered in the differential diagnosis. It is important to keep close clinical follow up of such patients because they may develop other autoimmune diseases as illustrated by the present case report.

Key Words: lymphocytic hypophysitis, Graves disease

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Learning Objectives

• Recall what is known about the demographic and presenting clinical and radiologic features of lymphocytic hypophysitis (LH) as well as its immunologic aspects.
• Summarize the hormonal abnormalities found in the present patient and previously reported patients with LH, emphasizing those that make it possible to distinguish between LH and pituitary macroadenoma.
• Compare the various treatment options available for patients with LH and the circumstances under which each may be appropriate.

Lymphocytic hypophysitis (LH), an uncommon clinical entity, was first described at an autopsy case in 1962. Since then, more than 125 cases of LH have been reported. The majority of patients (approximately 70%) have been young women presenting during pregnancy or in the postpartum period. Approximately 15% of reported patients were men. Histologically, LH is characterized by diffuse infiltration of the pituitary by lymphocytes and plasma cells and varying degrees of pituicyte destruction. LH may present as an isolated disorder or be associated with other autoimmune diseases. LH is thought to have an autoimmune etiology, and the frequent association of LH with pregnancy may be possibly the result of increased exposure to pituitary antigens or changes in maternal immunologic status. Clinical, LH presents with symptoms of hypopituitarism, secondary adrenal insufficiency, and/or with manifestations of a pituitary mass. Deficiencies of corticotrophin (ACTH), thyrotrpin (TSH), luteinizing hormone, follice-stimulating hormone, and less frequently vasopressin have been found either alone or in combination; serum prolactin levels are elevated in
approximately 50% of patients.\textsuperscript{2–7} The most common manifestations of the pituitary mass are headache and visual field loss, present in 55% to 70% of patients.\textsuperscript{2}

In this report, we describe a patient with a typical presentation of LH during the third trimester of her pregnancy. The patient responded well to initial transsphenoidal surgery and remained clinically stable receiving daily hormone replacement for over 2 years of follow up. Then, on routine screening, the patient was found to have a marked suppression of TSH, elevation of free T4 and free T3, and symptomatology of hyperthyroidism. Additional testing confirmed Graves disease as a cause of hyperthyroidism. Review of the literature showed only 3 previously reported cases of LH and Graves disease.\textsuperscript{8–10}

CASE REPORT

In January 2003, a 21-year-old G5, P4 woman was transferred to our hospital from an outside facility for urgent neurosurgic evaluation. The patient gave a history of severe headaches and declining vision dating back to October 2002. At that time, she had a computed tomography scan of the brain reported as normal. The complaints had progressed slowly over the prior 3 months leading to the current episode of a prolonged headache over 24 hours and marked visual loss in the left eye along with moderate visual loss in the right eye. The patient was 35 weeks pregnant at the time. She originally presented to an outlying facility where neurologic evaluation led to a magnetic resonance imaging scan of the brain showing the presence of a large (2.2 \times 2.0 \times 2.2 \text{ cm}) partially hemorrhagic pituitary mass with suprasellar extension compressing the optic chiasm. After neurosurgic evaluation at our institution, she underwent an emergent transsphenoidal surgery for decompression of the mass. The pituitary mass was thought most likely to be a macroadenoma. A successful partial transsphenoidal resection of the pituitary mass was accomplished without any complications and the patient’s vision recovered completely in the right eye and partially in the left eye. During the postoperative period, we evaluated her for panhypopituitarism and central diabetes insipidus. Before surgery, thyroid function tests showed high-normal total T4 and slightly reduced T3 resin uptake. Postoperatively, TSH was 0.52 \text{ uIU/mL} (normal, 0.49–4.67 \text{ uIU/mL}), total T4 was 7.9 \mu g/dL (normal, 4.5–12.0 \mu g/dL), and free T4 was 0.73 \text{ ng/dL} (normal, 0.71–1.85 \text{ ng/dL}). Growth hormone was 0.67 \text{ ng/mL} (normal, <10 \text{ ng/mL}). The patient was discharged a week later with 50 mg levothyroxine daily, 5 mg prednisone in the morning and 2.5 mg in the evening, and desmopressin (DDAVP) nasal spray twice daily. The final pathology report of the resected pituitary mass was consistent with LH. The patient was readmitted to our hospital in the 37th week of pregnancy and delivered a healthy child by cesarean section. She received stress doses of glucocorticoids preoperatively.

The patient has been followed as an outpatient for panhypopituitarism and central diabetes insipidus. She was maintained on DDAVP nasal spray twice to 3 times daily, 5 mg prednisone in the morning and 2.5 mg in the evening, and 75 \mu g levothyroxine daily. At 1, 3, and 15 months after transsphenoidal surgery, pituitary functions were retested after a brief withdrawal of prednisone and DDAVP. She continued to have partial ACTH/cortisol deficiency, growth hormone deficiency, central hypothyroidism, severe gonadotropin/estrogen deficiency, and severe central diabetes insipidus. During routine follow up in April 2005, the patient reported some weight loss and fatigue, which she attributed to a change in diet and taking care of her 5 children. Thyroid function tests performed at that visit revealed a free T4 of 3.4 ng/dL (normal, 0.8–1.8 ng/dL), which was a markedly increase from her previous normal free T4 levels on stable replacement therapy. Levothyroxine therapy was discontinued at that time. She returned 6 weeks later and reported continued weight loss, fatigue, heat intolerance, sweating, and palpitations. The patient had a diffusely enlarged thyroid, tachycardia, and mild hand tremor. TSH was <0.01 mIU/L (normal, 0.40–5.50 mIU/L), free T4 was 5.3 ng/dL (normal, 0.8–1.8 ng/dL), free T3 was 1999 pg/dL (normal, 230–420 pg/dL), and thyroid-stimulating immunoglobulin was 142% (normal, <125%). An I-123 thyroid uptake at 6 hours was 82.6%, confirming the diagnosis of hyperthyroidism. The patient was then treated with metoprolol and 20 mg methimazole daily. She subsequently required 80 mg methimazole daily to achieve adequate control of her hyperthyroidism. She elected subtotal thyroidectomy as definitive treatment of Graves disease.

DISCUSSION

The true incidence of lymphocytic hypophysitis is unknown. It is probably more common than suggested by histologically confirmed cases. The condition is most prevalent in women, occurring during pregnancy or the peripartum period, isolated or in association with other autoimmune diseases. Presenting symptoms and neuroimaging features resemble those of a nonfunctioning pituitary macroadenoma often manifested by visual disturbances, headache, hypopituitarism, hyperprolactinemia, and variable pituitary enlargement.\textsuperscript{4,5} Several conditions should be considered in the differential diagnosis: pituitary adenoma, pituitary necrosis/hemorrhage, parasellar tumors and cysts, aneurysm, granulomatous disease, and LH. In view of the patient’s age and frequent temporal association of LH with pregnancy and puerperium, the differential diagnosis narrows to LH, postpartum pituitary necrosis (Sheehan syndrome), and pituitary adenoma. Distinction between nonsecreting pituitary macroadenomas and LH can be difficult clinically. No specific radiologic features distinguish LH from pituitary tumors.\textsuperscript{2,5} The degree of hypopituitarism in LH is commonly out of proportion to the size of the pituitary mass, especially in those patients who are truly panhypopituitary. In patients with LH, panhypopituitarism may be present with even small pituitary masses or even in patients with unenlarged pituitary glands. In contrast, it would be distinctly uncommon to see this degree of panhypopituitarism with pituitary macroadenomas except with very large tumors. This suggests that the hypopituitarism associated with LH is more the result of specific pituiocyte destruction rather than compression and subsequent atrophy of normal pituitary tissue, as is seen with pituitary tumors.\textsuperscript{4}
In addition, there is a characteristic temporal loss of pituitary hormones associated with macroadenomas that helps distinguish them from LH. Macroadenomas often cause an initial loss of growth hormone, follicle-stimulating hormone, and luteinizing hormone, followed by reduction of TSH and ACTH, and lastly, if at all, prolactin.\textsuperscript{11–14} In contrast, LH frequently results in isolated ACTH deficiency or combined adrenal/thyroid deficiencies despite normal gonadal function.\textsuperscript{15,16} Specific pituicytes appear to be more susceptible to cellular destruction with ACTH-producing cells most frequently affected and gonadotrophs most commonly spared. Prolactin is the most variable affected hormone in this disease. Consequently, patients in the postpartum period who do present with these unusual patterns of pituitary hormone deficiency are more likely to have LH than pituitary adenomas.\textsuperscript{5}

The original case description of LH by Goudie and Pinkerton in 1962 was in a 22-year-old woman who developed postpartum hypothyroidism and amenorrhea.\textsuperscript{1} She died of shock 8 hours after an appendectomy, which was performed 14 months after childbirth. The autopsy revealed lymphocytic thyroiditis, severely atrophic adrenals, and a small pituitary with extensive lymphocytic infiltration in the atrophic residuum. The pathology was distinct enough to differentiate the mass from healed postpartum pituitary necrosis (Sheehan syndrome) and granulomatous hypophysitis. The authors felt that these changes represented linked autoimmune diseases. Since 1980, many case reports were published with an antemortem diagnosis of LH.\textsuperscript{17–19} Currently, approximately 100 cases of LH have been documented histologically.\textsuperscript{5}

LH is commonly associated with other autoimmune diseases, most often with lymphocytic thyroiditis.\textsuperscript{4} In contrast, review of the literature uncovered only 3 cases of LH associated with Graves disease.\textsuperscript{8–10} Our patient had a classic presentation of LH although pituitary adenoma was the primary consideration at the time of presentation. The unusual and rather unique aspect of this case is the subsequent development of overt hyperthyroidism resulting from Graves disease 2 years after the initial presentation. Review of the literature revealed only one other case with a similar timeline of disease progression (LH followed by Graves disease).\textsuperscript{10}

Bayram et al reported a patient with Graves disease who then developed LH 2 years later.\textsuperscript{8} Yamamoto et al described a patient with concurrent Graves disease and LH at the time of initial presentation.\textsuperscript{9} The only case report that showed a timeline of disease progression similar to our patient also exhibited other unusual features.\textsuperscript{10} This patient initially presented with marked lachrymal and salivary gland enlargement, which on biopsy demonstrated prominent lymphoid infiltration. The patient also had an enlarged pituitary gland by magnetic resonance imaging and LH was suspected. However, no pituitary biopsy was done to confirm this suspicion. She was treated with high doses of glucocorticoids that were tapered over the course of 1 year. Approximately 4 years after her initial presentation, she developed Graves disease. At that time, there were no clinical findings consistent with LH and the patient had otherwise normal pituitary function.\textsuperscript{10} Graves disease, thyroiditis, and hypothyroidism represent a spectrum of diseases with a similar pathogenetic mechanism.\textsuperscript{20} Although the pathogenesis of LH has not been defined, the association with other presumed autoimmune disorders (adrenalitis, atrophic gastritis, pernicious anemia, lymphocytic parathyroiditis, systemic lupus erythematosus, Sjögren syndrome, and isolated ACTH deficiency) suggests a similar pathogenic basis.\textsuperscript{7,4,19,21}

There are a number of experimental animal models of LH. In one model, pituitary tissue and adjuvant were injected subcutaneously into the footpads of rats. The microscopic changes noted in the pituitary glands of animals injected with pituitary tissue were nearly identical to those seen in LH. No such lesions were detected in the rats immunized with adrenal, pancreas, or spinal cord tissue (and adjuvant).\textsuperscript{22} Another animal model of autoimmune pituitary disease is described in rabbits. Homologous pituitary tissue and adjuvant were injected subcutaneously into the backs of these animals. Blood samples obtained before and after immunization were tested for antipituitary antibodies and lymphocytic stimulation. Five of 7 experimental animals had evidence of inflammation in the anterior lobe of the pituitary glands, whereas no significant antipituitary antibodies were detected serologically. Four of the 5 animals with pituitary inflammation had lymphocytes that were activated against pituitary extract. These findings support the possibility of cellular-mediated immunity involved in the production of LH.\textsuperscript{23} Antipituitary antibodies reactive to a 49-kDa pituitary cytosolic protein were detected in 70% of patients with biopsy-proven LH and in 55% of patients with clinically suspected hypophysitis. These autoantibodies were also detected in 42% of patients with Addison disease, 20% of patients with pituitary tumors, 15% of patients with thyroid autoimmunity, 13% of patients with rheumatoid arthritis, and 10% of apparently normal subjects. Serologic reactivity to another pituitary cytosolic protein (40-kDa) was present in 50% of patients with biopsy-proven LH.\textsuperscript{24} Because these autoantibodies do not appear to be disease-specific, they are no longer recommended in making this diagnosis of LH.\textsuperscript{5}

Several other forms of hypophysitis distinct from LH are described: granulomatous, xanthomatous, and necrotizing infundibulo-hypophysitis.\textsuperscript{25–28} These forms of hypophysitis have no gender predilection. Their clinical presentation is similar to LH. Coexisting LH and granulomatous hypophysitis is extremely rare.\textsuperscript{27,29}

If clinical features and pituitary tests support LH but compressive visual field disturbances are absent, surgical therapy should be withheld. In such cases, pituitary hormone deficits should be replaced and monitoring done for possible spontaneous resolution of the inflammatory mass. A treatment course with glucocorticoids should be considered as a means to resolve the sellar mass and improve endocrine function, especially if adrenal reserve is compromised. Transsphenoidal surgery may be required to confirm a tissue diagnosis and relieve compression symptoms. The extent of the procedure should be limited so as to conserve viable pituitary tissue, particularly in view of possible spontaneous resolution.\textsuperscript{2}


CONCLUSIONS

Lymphocytic hypophysitis is a rare disorder that predominantly affects women during or after pregnancy. Patients tend to have a good outcome with early diagnosis and appropriate therapy. Although a full understanding of the actual pathogenesis of LH is still being sought, current evidence suggests that LH may be the result of an autoimmune process. Association of LH with other autoimmune disorders occurring before, after, or concurrently with LH emphasizes the importance of continued close follow up of such patients with anticipation of possible development of other autoimmune-mediated conditions.

REFERENCES