Lymphocytic adenohypophysitis: A pituitary mass lesion occurring in pregnancy

Proposal for medical treatment

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Lymphocytic adenohypophysitis is a nonneoplastic, autoimmune cause of pituitary enlargement and insufficiency. Forty-eight of the 50 reported cases have occurred in women, nearly all in association with pregnancy. Left undiagnosed and untreated, it can progress to pituitary insufficiency and death. Histologic studies show characteristic changes of autoimmune disease with lymphocytic infiltration and destruction of anterior pituitary tissue with fibrotic replacement. Lymphocytic adenohypophysitis is currently diagnosed after other pituitary mass lesions are excluded and has been treated with a combination of neurosurgery and end-organ hormone replacement. However, with improved knowledge of the pathophysiologic characteristics and natural history of the disease and with the ability to make a prospective diagnosis, we believe glucocorticoids may suppress the inflammatory response and protect remaining pituitary tissue. Two previously unreported pregnancy-associated cases are described, including one prospectively diagnosed and treated without neurosurgery during pregnancy. Obstetrician-gynecologists must place lymphocytic adenohypophysitis in the differential diagnosis of pituitary enlargement associated with pregnancy, since treatment is available and the sequelae may be life-threatening. (Am J Obstet Gynecol 1991;164:1549-55.)

Key words: Lymphocytic adenohypophysitis, pituitary, pregnancy complications, neurosurgery, pituitary insufficiency

Lymphocytic adenohypophysitis is a nonneoplastic, autoimmune cause of pituitary enlargement and insufficiency. Of 50 reported cases in the world literature, 48 have occurred in women, and nearly all have occurred during pregnancy, the puerperium, or the first postpartum year. Despite this association with pregnancy, there is rare mention of this disease in the obstetric and gynecologic literature. If left undiagnosed and untreated, it can progress insidiously or quickly to pituitary insufficiency and death. Obstetrician-gynecologists and neurosurgeons must therefore include lymphocytic adenohypophysitis in the differential diagnosis of pregnancy-associated pituitary enlargement. Often mistakenly diagnosed as a prolactin-secreting adenoma, the etiology, pathology, and therapy of the two differ fundamentally. Lymphocytic adenohypophysitis is currently treated with a combination of neurosurgery and end-organ hormone replacement, often resulting in significant chronic morbidity, whereas prolactin-secreting adenomas may be more easily managed medically and usually without long-term sequelae. With improved knowledge of the pathophysiology of lymphocytic adenohypophysitis, the ability to make a prospective diagnosis among symptomatic peripartum women, and recently acquired experience in treatment, we believe that a trial of medical therapy may be warranted before routine neurosurgical exploration is performed. We report here our experience with two previously unreported cases of this unusual cause of pituitary enlargement in young peripartum women including the first case prospectively diagnosed and treated without neurosurgery during pregnancy.

Case reports

Case 1. A 26-year-old primiparous woman was seen, 1 month after uncomplicated vaginal delivery, with a 2-month history of daily midline frontal headaches accompanied by diplopia and gradual decrease in visual acuity. During the postpartum period, she had failure of lactation and complained of lethargy and low-grade fever. Her medical history, including gynecologic, was noncontributory. Physical examination revealed bitemporal field defects to confrontation, left greater than right, with acuity of 20/60 on the left and 20/40 on...
the right. A computed tomographic (CT) scan showed a large pituitary mass with suprasellar extension. Laboratory evaluation demonstrated hypopituitarism; insulin-induced hypoglycemia resulted in a basal cortisol level of <1 μg/dl with no increase after stimulation and a growth hormone level of 3.1 mg/ml with no increase. Thyrotropin-releasing hormone challenge (200 μg given as an intravenous bolus) resulted in a prolactin increase from 4 to 8 ng/ml; a gonadotropin-releasing hormone challenge (100 μg) was followed by a luteinizing hormone rise from 4 to 10 mIU/ml, a follicle-stimulating hormone rise from 9 to 20 mIU/ml; and decreased thyroid function (thyroxine index, 0.9; thyroxine, 3.7 μg/dl; triiodothyronine, 17.3 ng/dl). An autoantibody screen was negative, including antinuclear antibodies, latex fixation, antithyroglobulin, and antithyroid micromonos antibodies. The hypopituitarism was attributed to either a pituitary adenoma or adenohypophysitis. With corticosteroid coverage, transphenoidal pituitary exploration was performed. A large, dull, white, tough mass extending almost 2 cm above the sella was subtotally removed. Histologic examination showed infiltration and destruction of anterior hypophyseal acini with lymphocytes and plasma cells (Fig. 1, A) and replacement of normal glandular tissue with lymphoid aggregates and fibrosis (Fig. 1, B). After operation the patient’s visual acuity and fields returned to normal. She was discharged and is being followed up on a regimen of hormone replacement including hydrocortisone, desmopressin acetate, levothyroxine, conjugated estrogens, and medroxyprogesterone acetate.

Case 2. A 30-year-old multiparous woman was admitted to the hospital in her thirty-fifth week of gestation with a complaint of blurred vision. Her antenatal course had been uncomplicated until about 6 weeks before admission, when she noted gradual onset of blurred vision in the left eye that progressively worsened; at admission she was found to have bilateral hemianopsia. Menses had been regular before conception, and there was no history of infertility or galactorrhea. Pregnancy studies, including an ultrasonogram and nonstress tests, were normal. A CT scan showed a large intrasellar mass with suprasellar extension (Fig. 2, A). Laboratory analysis included normal complete blood count and SMA-12 results for pregnancy, and a prolactin level of 185 ng/ml (within normal limits for 35 weeks’ gestation). An overnight adrenocorticotrophic hormone stimulation test was performed. Basal cortisol level was 9 μg/dl with a rise to 13 μg/dl. Dynamic pituitary testing was postponed until after delivery. Tests for rheumatoid factor, antinuclear, anti-double-stranded deoxyribonucleic acid, antimitochondrial, anti-smooth muscle, anti-parietal cell, antimicrobial, and anti-thyroglobulin antibodies were negative. Serologic test for syphilis was negative. The differential diagnosis was lymphocytic adenohypophysitis versus pituitary adenoma. Bromocriptine therapy (2.5 mg twice daily) was started as a diagnostic maneuver and to reduce pressure on the optic chiasma. Amniocentesis was performed; the lecithin/sphingomyelin ratio was 1:8:1 and no phosphatidylglycerol was present. Daily visual field studies were performed and remained unchanged. After 9 days of bromocriptine therapy there was no improvement in symptoms, and a repeat CT scan was obtained that showed no change in the size of the mass. Prednisone therapy (2.5 mg three times a day) was instituted. Nine days later, after completion of 37 weeks’ gestation, the patient was delivered of a 3360 gm infant after an uncomplicated induction of labor. She was maintained on a regimen of prednisone. During the first postpartum week her clinical condition and visual fields remained unchanged, and she lactated normally without breastfeeding. One week after delivery, vision began to improve and subsequently returned to normal. A CT scan performed at that time revealed a decrease in the size of the mass, although significant enlargement persisted. Menses resumed 3 months post partum without breastfeeding. CT scan performed at that time showed a significant decrease in mass size (Fig. 2, B). Dynamic pituitary testing was performed 5 months post partum, after tapering and temporarily stopping steroid therapy for 6 weeks before testing; insulin-induced hypoglycemia showed undetectable growth hormonebefore and after stimulation and a cortisol level of 4 ng/dl with no rise, a thyrotropin-releasing hormone challenge showed a rise in prolactin level from 79 to 337 ng/ml, and a gonadotropin-releasing hormone challenge resulted in a luteinizing hormone rise from 10 to 91 mIU/ml and a follicle-stimulating hormone rise from 7 to 25 mIU/ml. She has been maintained on a regimen of prednisone and is having regular menses. Human leukocyte antigen haplotypes were A28, Aw24(A9), Bw44(B12), B7, Cw7, Dr12, Dr5, MT1, MT2, and MT4.

Comment

Management of uncommon diseases that occur during pregnancy has been enhanced by better prospective diagnosis and knowledge of the pathology and natural history of these conditions. Enlargement of the pituitary gland during pregnancy is one such area in which recent anatomic and laboratory studies have contributed to more specific diagnosis and, for some pituitary mass lesions (e.g., prolactin-secreting adenomas), a change from primarily neurosurgical management to medical treatment. In a young pregnant woman with a large expanding pituitary lesion, the most common diagnosis remains a prolactin-secreting adenoma. However, the differential diagnosis must also include lymphocytic adenohypophysitis. The importance of making this diagnosis prospectively is underscored by the natural history of the disease, which has resulted in death in 25% of patients reported with this disease, including the first five in whom it was recognized at autopsy. In a recent review of 30 English language cases, individual patient presentations were summarized.1

Presentation. Lymphocytic adenohypophysitis is a
Lymphocytic adenohypophysitis in pregnancy

Fig. 1. A, Pituitary acinus surrounded by lymphocytes and plasma cells. (Hematoxylin and eosin. Original magnification ×343; bar = 100 μm.) B, Lymphoid aggregates in the anterior pituitary with destruction of normal tissue and replacement by fibrosis. (Hematoxylin and eosin. Original magnification ×205; bar = 100 μm.)

disease predominantly of women (96% of all reported cases). The youngest reported case occurred in a 17-year-old, and the oldest in a 68-year-old; the median reported age at diagnosis was 28 years. Both men were diagnosed in their fifth decade of life. Lymphocytic adenohypophysitis is reported most often in association with pregnancy: 65% of reported cases were multiparous women and 35% had disease associated with a first pregnancy. But it has been reported in women who have never been pregnant (6% of cases). The majority of pregnant patients present with symptoms during the last trimester, although it has been reported in all trimesters. No racial predilection has been detected. The presentation appears to correlate with the apparent stage of the disease process at time of diagnosis. In nearly every case in which diagnosis is made in a living patient, presenting complaints are referable to mass effects of headache and visual changes, symptoms caused by the inflammatory infiltrate, and resulting edema of the pituitary gland. When the condition is not diagnosed antemortem, most patients have had progression to lethargy, anorexia, hypoglycemia,
and frank secondary adrenal insufficiency as a result of acute or chronic hypopituitarism. Most recent reported cases have had presentation symptoms of a space-occupying sellar lesion, i.e., visual disturbances with or without headaches, rather than symptoms associated with adrenal insufficiency. This was the case for the four patients treated at this institution, including two previously reported. In spite of the presenting symptoms referable to cranial compression, 75% of reported peripartal cases of lymphocytic adenohypophysitis had some evidence of partial or panhypopituitarism at some time during pregnancy or the postpartum period, although endocrine evaluation was incomplete in many. Among pregnant patients with sufficient reported information, hypoadrenalism (78%) and thyroid dysfunction (72%) were the most frequent abnormalities found. Primary thyroiditis diagnosed at autopsy or by clinical and laboratory criteria was found in six patients. Some patients may have only isolated defects of a single pituitary factor, e.g., adrenocorticotropic hormone. Measurement of gonadotropins and prolactin is not useful for making the diagnosis of lymphocytic adenohypophysitis during pregnancy but may be helpful in nonlactating (seven cases) and amennorrheic (nine cases) women after an interval following delivery. Only two cases of posterior pituitary dysfunction before neurosurgical intervention have been reported.5,7

**Anatomy and pathology.** Lymphocytic infiltration of the anterior pituitary occurs rarely. Shanklin8 examined 100 unselected human pituitaries and found a 43% incidence of lymphocytic infiltration, but this was confined entirely to the pars intermedia and pars nervosa with no involvement of the anterior lobe. Simonds and Brandes9 reported the presence of lymphocytes in the anterior pituitary of two of 200 patients with sudden death. These series are in marked contrast to a recent report10 describing mild lymphocytic adenohypophysitis in five of 69 autopsy-obtained pituitaries from women who died during pregnancy, after abortion, or during the postpartum period and emphasizing the association of lymphocytic adenohypophysitis with pregnancy. However, it was not clear how the lymphocytic adenohypophysitis related to each patient’s illness.

Enlargement of the pituitary gland is a normal component of the anatomic and physiologic changes that occur during pregnancy11 and is due principally to hyperplasia of prolactin-secreting cells,12 but such enlargement does not normally induce symptoms of a space-occupying cranial lesion. Our cases were diagnosed with CT technology. In 27 of 30 patients (90%) having CT scans, a sellar lesion was demonstrated at the time of initial scan. Use of polytomography (eight abnormal in eight cases) and plain skull radiography (seven abnormal in 14 cases) has also been reported, and magnetic resonance imaging has been used in the evaluation or follow-up of six patients with lymphocytic adenohypophysitis.13,17 In nearly all abnormal radiologic studies of lymphocytic adenohypophysitis, a suprasellar component was demonstrated, regardless of the imaging technique used. Radiologic features have been reviewed in detail by Levine et al.18 and Miura et al.19

The operative specimens obtained by transsphenoi-
dral resection at our institution were similar to those described in the literature, i.e., firm or tough, dull white-yellow, and adherent to the surrounding structures. Histologic examination showed lymphoid infiltration, diffuse and in aggregates, and fibrosis that nearly completely obliterated normal pituitary architecture. No abnormal cells or oncotic transformation was recognized. Numerous reports have demonstrated the presence of all major T-lymphocyte subpopulations, as well as plasma cells, in these lesions, by means of immunohistochemical staining techniques specific for surface markers and presence of κ-light chains. Review of reported postmortem cases supports the observation that the degree of replacement of normal glandular tissue with lymphocytic infiltrate is correlated with the stage of the disease process at the time of death. Those patients in whom sudden death was preceded by fatigue, anorexia, confusion, weakness, and shock most often had an atrophic gland at autopsy. An enlarged infiltrated pituitary gland also may be found in conjunction with atrophic adrenal glands.

**Association with autoimmunity.** The nature of the histologic findings and the natural history of lymphocytic adenohypophysitis suggest an autoimmune etiology. The histologic characteristics seen in the pituitary are similar to those seen in other autoimmune diseases, i.e., lymphocytic infiltration, obliteration of glandular tissue, and replacement of normal tissue with fibrosis. Many patients also have autoimmune-mediated inflammatory involvement of other organs, including thyroiditis,2,11 pancreatitis, parathyroiditis, pernicious anemia, adrenalitis, and connective tissue inflammation. In one patient15 sarcoidosis of the eye and lung developed 6 months after diagnosis of lymphocytic adenohypophysitis associated with the birth of her second child. Too few human leukocyte antigen haplotypes have been reported to reveal specific genetic associations, although Bw35, found in increased frequency in autoimmune disorders, was reported in two of four cases when tissue typing was performed.

One classification scheme20 defines a process as an autoimmune disease if it fulfills three criteria: (1) detection of circulating autoantibodies to a recognized specific antigen, (2) the production of similar pathologic changes in an experimental animal model produced by injection of antigen, and (3) transfer of the disease by immune serum or cells. In general, patients with lymphocytic adenohypophysitis have had negative general antibody screens, but most have not been screened for antipituitary activity. Antipituitary antibodies have been difficult to demonstrate in patients with lymphocytic adenohypophysitis in whom these studies have been attempted. Difficulties have resulted from the small amount of material obtained from operation, low apparent titer of specific antibodies, and nonspecific binding. Specific antipituitary antibodies have been found in three of six patients tested, but antibodies were not found in patients in other reports. Autoantibodies to the pituitary also have been reported in 23 of 128 unselected postpartum women in one study.2 In that study, in 25% of 16 antibody-positive postpartum women available for follow-up, some symptoms of pituitary insufficiency developed. Experimental animal models of lymphocytic adenohypophysitis have been described. Levine14 produced adenohypophysitis in adult rats with injection of adjuvant and pituitary lymphocytic infiltrate. From preliminary experiments, he suggested that the severity of the process was increased in postpartum animals.

**Differential diagnosis.** Lymphocytic adenohypophysitis must be considered in the differential diagnosis of women in the peripartum period with symptoms consistent with a space-occupying cranial lesion. In addition to sella imaging and visual field evaluation, laboratory studies including electrolytes, thyroid function tests, and a basal and adrenocorticotropic hormone-stimulated cortisol should be obtained promptly during pregnancy. A CT scan yields better information for prospective management compared with conventional radiologic studies, although the radiation exposure is somewhat higher. Magnetic resonance imaging poses no known risk to the fetus or mother and, if available, may be expected to yield information helpful in distinguishing lymphocytic adenohypophysitis from other pituitary masses. Bromocriptine (2.5 mg twice daily) should be started immediately. Initial laboratory results, sella imaging, and response to bromocriptine should suggest the direction of further evaluation and the need for prompt initiation of corticosteroid and other hormone replacement.

Postpartum women with failure of lactation and those whose menses fail to resume post partum should be closely questioned and examined for other features referable to pituitary insufficiency. In addition to sella imaging and visual field testing, an insulin-induced hypoglycemia test should be performed and growth hormone, prolactin, and cortisol concentrations assessed. A gonadotropin-releasing hormone and thyrotropin-releasing hormone challenge can be performed the same day. Since thyrotoxicosis is an occasional concomitant finding both during the peripartum period and among patients with lymphocytic adenohypophysitis, thyroid function studies should be performed and blood should be held for antibody studies.

Pituitary insufficiency may be seen in other groups of peripartum patients. Patients with postpartum pituitary necrosis, i.e., Sheehan’s syndrome, can demonstrate a similar pituitary stimulation test profile. However, among lymphocytic adenohypophysitis patients diagnosed in or after labor and delivery, uncom-
plicated vaginal deliveries have been the rule, except for one patient in whom the disease was not suspected and who died in labor of acute adrenal insufficiency.\(^1\) Other cases of pituitary insufficiency in association with pregnancy have been described, usually with imaging consistent with a partially empty or empty sella. Increased secretion of prolactin has been described in patients with lymphocytic adenohypophysitis and an enlarged or normal-sized\(^11\) pituitary. This may lead the unwary to diagnose a prolactin-secreting adenoma and institute bromocriptine therapy without further investigating other pituitary trophic hormone secretion. Glycoprotein-producing pituitary adenomas, also known as (nonsecretory or null-cell adenomas, may present as mass lesions, also unresponsive to bromocriptine. These adenomas may exhibit decreased pituitary trophic hormone secretion, most commonly decreased gonadotropins, and mildly elevated prolactin as a consequence of stalk compression. Increased prolactin secretion may be expected during and some weeks after pregnancy and is insufficient by itself to diagnose a pregnancy-associated pituitary mass. Endocrinologically active pituitary tumors, e.g., growth hormone-producing tumors, usually exhibit some degree of isolated pituitary hyperfunction in association with pituitary enlargement.

**Treatment.** Transsphenoidal chiasmal decompression with initiation of preoperative and postoperative hormone replacement is the traditional diagnostic and therapeutic approach. However, there is reason to believe that, at least for some patients, there may be a less radical initial approach. Most patients reported in the recent literature have undergone only partial surgical resection or pituitary biopsy in the absence of marked chiasmal compression. The main benefit derived from this potentially morbid and expensive procedure may be establishment of the histologic diagnosis. However, consistent clinical features, supportive laboratory findings, and nonresponse to bromocriptine may allow a presumptive, noninvasive diagnosis of lymphocytic adenohypophysitis.

Since lymphocytic adenohypophysitis appears to share pathophysiologic features common to many autoimmune disorders, we believe that aggressive initiation of corticosteroid therapy may induce remission, as well as protect remaining pituitary tissue during periods of acute insufficiency. Some experience with corticosteroid therapy has been obtained. One 18-year-old woman, 10 weeks postpartum, was found to have secondary adrenal insufficiency, postpartum thyrotoxicosis, hypogonadism, and a pituitary mass with suprasellar extension.\(^18\) Surgery was deferred due to thyrotoxicosis and because there were no symptoms referable to chiasmal compression. She was treated with cortisone acetate and propranolol hydrochloride and experienced nearly complete resolution of the mass. She continued to have chronic partial pituitary insufficiency of ACTH, growth hormone, thyroid-stimulating hormone, and prolactin production and remains on hormone replacement. At least five patients have been treated with corticosteroids in anticipation of surgical resection with improvement in signs or symptoms.\(^1\) One patient\(^2\) was followed after being placed on steroids when she presented in the thirty-ninth week of gestation with visual field defects. Similar to our case 2, she experienced resolution of her mass but had residual pituitary insufficiency. Another patient,\(^2\) not operated upon, had gradual recovery of thyroid function, but not of ACTH, prolactin, or growth hormone after being placed on corticosteroids post partum.

Specific management should be determined by response to bromocriptine and steroids, as assessed by changes in visual fields, changes in mass size on imaging studies, and recovery or progression of endocrine deficits. Whether patients will be followed prospectively or undergo resection, with evidence of pituitary insufficiency of ACTH, one should not delay in instituting corticosteroids while exploring other etiologies or organ involvement. One of the two men reported with lymphocytic adenohypophysitis developed a typical adrenal crisis resulting in death while undergoing diagnostic workup for panhypopituitarism, despite being placed on corticosteroids early in the crisis.\(^3\) Two patients gradually regained normal pituitary function after transsphenoidal decompression;\(^1\) one patient regained normal thyroid function only;\(^2\) and in one postpartum patient pituitary insufficiency gradually developed where none had existed before operation.\(^2\)

One suspected antepartum case of lymphocytic adenohypophysitis with selective deficiency of prolactin and growth hormone\(^11\) continued to be deficient post partum although a pituitary mass regressed. Another patient in whom the disease was suspected, with symptoms of a pituitary mass but no hormone deficits during pregnancy, did not undergo operation. Post partum she experienced regression of the mass but later pituitary insufficiency of adrenocorticotropic hormone, growth hormone, and prolactin developed.\(^2\) These cases underscore the rationale for continued observation and retesting of these patients. Two patients with lymphocytic adenohypophysitis have achieved a subsequent pregnancy, as would be expected with appropriate hormone replacement.

With time, acute pregnancy-associated maternal immune system alterations resolve after delivery and may enable withdrawal of steroid therapy with careful assessment of residual function. Such patients should be monitored closely for evidence of chronic or acute pituitary insufficiency and for occurrence of features as-
associated with other autoimmune disorders. Corticosteroid therapy may not obviate the need for neurosurgical intervention in some cases of pregnancy-associated lymphocytic adenohypophysitis, but it is hoped that surgery may be reserved for patients with acute chiasmal compressive lesions that are nonresponsive to either bromocriptine or corticosteroids.

In summary, lymphocytic adenohypophysitis must be included in the differential diagnosis of pregnancy-associated pituitary enlargement. If it is diagnosed, a trial of medical therapy with corticosteroids may allow conservation of remaining pituitary tissue and decrease morbidity and costs associated with caring for patients with this unusual pituitary mass lesion.

REFERENCES