

Lymphocytic Adenohypophysitis of Pregnancy with Complete Recovery

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A case of lymphocytic adenohypophysitis in a postpartum woman who became symptomatic during her 8th month of pregnancy is presented. The clinical presentation, endocrine findings, pathological findings, and operative management are discussed. Transient hypopituitarism is documented. Unlike most previously published cases, this woman had complete recovery of anterior pituitary function. (*Neurosurgery* 20:791-793, 1987)

Key words: Autoimmune disease, Hypopituitarism, Lymphocytic adenohypophysitis, Pituitary, Pregnancy

INTRODUCTION

Lymphocytic adenohypophysitis is an inflammatory disorder of the pituitary gland characterized by diffuse infiltration of the anterior pituitary with lymphocytes and plasma cells (3). The disease is rare and has been reported only in women, often coincident with pregnancy. The disorder presents with symptoms of hypopituitarism and an expanding sellar mass. It was originally reported only as a postmortem finding, but more recent cases have been diagnosed by surgical biopsy (1, 3, 15, 18-21). Lymphocytic adenohypophysitis should be considered in the differential diagnosis of gestational or postpartum hypopituitarism, especially after a delivery uncomplicated by excessive hemorrhage with hypotension. In the past, women who presented with pituitary dysfunction after delivery were treated with chronic hormone replacement therapy for presumed permanent hypopituitarism.

We report a case of hypophysitis in a 27-year-old woman who became symptomatic during the 8th month of her pregnancy. Clinical evaluation and endocrine testing revealed evidence of pituitary insufficiency. Subsequent testing revealed a spontaneous recovery of anterior pituitary function. The clinical and operative management of lymphocytic adenohypophysitis are discussed in this report.

CASE REPORT

A 27-year-old woman presented to the Neurosurgery Service of the Massachusetts General Hospital for evaluation of a sellar mass 10 days after giving birth to a full-term, normal, male infant.

The patient had a normal menstrual history, and this was her first pregnancy. During the last 2 months of her pregnancy, she had noted over several days the onset of visual impairment described as a haze in front of her eyes. She did not seek medical advice about this symptom, and her pregnancy was otherwise unremarkable. She spontaneously delivered a full-term healthy boy without hypotension or excessive blood loss.

For several days after the delivery, the patient had recurrent episodes of vomiting and severe fatigue and she complained of a severe occipital headache with visual blurring. She was unable to nurse her infant due to postpartum failure of lactation. An intermittent fever to 103°F was noted, with negative blood, urine, and vaginal cultures and a normal plain roentgenogram of the chest. She was treated empirically with

broad spectrum antibiotics for suspected endometritis, and she became afebrile over the next several days. On the 8th postpartum day, the patient was noted to have right ptosis. A computed tomographic (CT) scan demonstrated a sellar mass. She was then transferred to this institution for further evaluation.

Admission examination showed a lethargic woman with a broad nose and prominent jaw. The neurological exam was remarkable only for slight ptosis. Formal visual field testing demonstrated a superior bitemporal quadrantanopsia that was thought to represent chiasmal compression. There was no galactorrhea, and she was clinically euthyroid. A repeat CT scan showed an intrasellar mass with suprasellar extension (Fig. 1). A lumbar puncture demonstrated clear cerebrospinal fluid with a cell count of 0 cells/mm³, a glucose level of 57 mg/dl, a protein content of 34 mg/dl, and an opening pressure of 16 cm H₂O.

The serum glucose and electrolyte levels were normal, and the leukocyte count was 8000. Endocrinological evaluation revealed adrenal insufficiency with an a.m. cortisol level of 5 µg/dl (normal, 8 to 21 µg/dl) and an adrenocorticotrophic hormone (ACTH) level below 10 pg/ml (normal, 20 to 100 pg/ml). There was no response to cosyntropin stimulation (the serum cortisol level was 0.8 µg/dl at 60 minutes). The thyroxine level was 8.8 µg/dl (normal, 4.0 to 12.0 µg/dl), and the T₃ resin uptake was 18% (normal, 25 to 35%). Thyroid-stimulating hormone (TSH) was undetectable at less than 0.5 µU/ml (normal, up to 3.5 mU/ml) and did not respond to exogenous thyrotropin-releasing hormone (TRH) (200 µg i.v.) (TSH was 0.5 µM/ml at 0, 10, 20, 30, and 60 minutes, respectively). The serum prolactin level was 1.4 ng/ml with a markedly blunted response to TRH stimulation (serum prolactin levels at 10, 20, 30, and 60 minutes were 1.7, 2.0, 1.9, and 1.9 ng/ml, respectively). The luteinizing hormone level was 11.3 mIU/ml (normal, 7 to 24 mIU/ml), and the follicle-stimulating hormone (FSH) level was 18.5 mIU/ml (normal, 14 to 35 mIU/ml). The serum growth hormone (GH) level was <1 ng/ml.

The patient was begun on cortisol replacement and, 7 days after admission, was brought to the operating room for transphenoidal biopsy of a presumed nonsecreting pituitary adenoma. The biopsy demonstrated diffuse infiltration of the anterior pituitary by lymphocytes, with no evidence of pituitary tumor (Fig. 2). The tissue contained immunoreactive prolactin cells. Immunocytochemical analysis of immunoglobulin revealed a polyclonal population consistent with

chronic inflammation. Postoperatively, the results of the patient's neurological examination were normal, with resolution of the superior quadrantanopsia. She was discharged on prednisone therapy, 7.5 mg/day.

A TRH test performed 1 month after operation showed some recovery of TSH reserve, with serum TSH levels at 1, 10, 20, and 30 minutes of 2.5, 0.6, 1.9, and 0.9 $\mu\text{U/ml}$, respectively, after TRH stimulation. The results of basal thyroid function tests remained low to normal, with a T_4 of 5.3



FIG. 1. CT scan with intravenous contrast agent demonstrates an enhancing sellar mass. Coronally reconstructed views demonstrated suprasellar extension of this lesion.

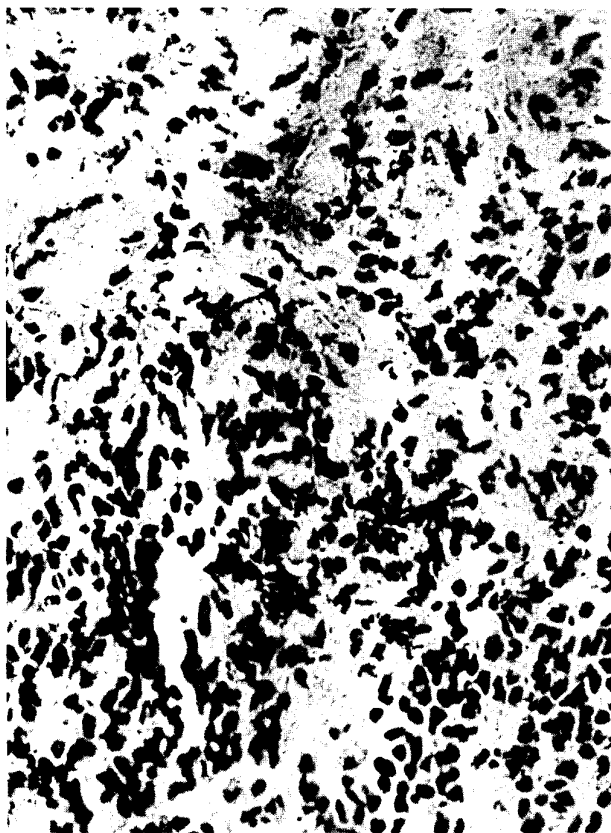


FIG. 2. Anterior pituitary gland demonstrating extensive lymphocytic infiltrate with interstitial fibrosis and some plasma cells. (Hematoxylin and eosin, original magnification $\times 200$.) Immunocytochemical study revealed immunoreactive prolactin cells.

$\mu\text{g}/100\text{ ml}$ and a $T_3\text{R}$ of 20%; the thyroid replacement level was not given. A TRH test repeated 12 months after operation showed recovery of TSH reserve with serum TSH concentrations of 0.9, 3.5, 5.4, and 5.8 $\mu\text{U/ml}$ at 0, 10, 20, and 30 minutes after TRH stimulation. Her prednisone dose was gradually tapered. An insulin tolerance test performed 5 months after operation revealed normal ACTH and GH levels (serum cortisol levels were 14.9, 26.8, and 26.5 $\mu\text{g/dl}$, respectively, at 0, 30, and 60 minutes) and serum GH concentrations of 3 and 26 ng/ml at 0 and 60 minutes, respectively. She has continued to have no neurological deficit for 1 year of postoperative follow-up. She currently requires no hormonal replacement therapy and has a normal menstrual cycle.

DISCUSSION

Lymphocytic adenohypophysitis is a rare disorder of unknown cause. Seven cases of lymphocytic adenohypophysitis have been identified at autopsy (6, 7, 10, 13, 14, 16, 22) and 10 were proven by surgical biopsy (1, 3, 15, 18–21), most reported in the medical or pathological literature. All patients have been women, ranging in age from 22 to 74 years. In 82% of the patients, there was a close temporal association with pregnancy, with symptoms of the disease occurring during gestation or within 14 months after delivery.

All 16 previously reported cases demonstrated clinical evidence of pituitary dysfunction, ranging from amenorrhea and postpartum lactational failure to more nonspecific symptoms, such as fatigue and decreased libido. At least partial laboratory investigation of pituitary function was performed in 13 patients (1, 3, 10, 15, 16, 18–22). Endocrine testing demonstrated varying degrees of hypopituitarism as manifested by depressed serum cortisol levels (1, 3, 15, 18, 19), hypothyroidism (1, 15, 16, 18, 19), and blunted responses of TSH and prolactin to exogenous TRH administration (18). In addition to the clinical and laboratory evidence of depressed pituitary function, 5 patients demonstrated evidence of prolactin hypersecretion manifested clinically by galactorrhea (6, 20, 21) or abnormally high serum prolactin levels (1, 19–21). Ours is the first documented case of recovery from hypopituitarism due to lymphocytic adenohypophysitis.

All 10 patients identified by surgical biopsy (transphenoidal approach in 8 and bifrontal craniotomy in 2) exhibited symptoms consistent with a sellar mass, including headache in 8 and bitemporal field defects in 6. Radiological evaluation of these cases demonstrated a sellar mass lesion in each of the 10 patients. A CT scan in 9 patients showed a contrast-enhancing sellar mass, often with suprasellar extension (1, 3, 15, 19–21). Plain roentgenograms of the skull in 1 patient showed an enlarged sella (18).

The histological features of lymphocytic adenohypophysitis were described in detail by Goudie and Pinkerton (13) and are characterized by extensive infiltration of the anterior pituitary by lymphocytes, as in the present case. The lymphocytes form diffuse sheets surrounding atrophic acini, with the regular reticulin pattern of the anterior pituitary replaced by a patchy network of fine fibers (13). Electron microscopy of the anterior pituitary in this condition reveals interdigitation of pituitary cells with activated lymphocytes (1).

In their original paper on the subject, Goudie and Pinkerton suggested that lymphocytic adenohypophysitis was an autoimmune reaction against the pituitary gland (13). General support for the concept of autoimmune disease of the pituitary comes from the studies of Bottazzo and associates, in which specific autoantibodies to prolactin-secreting as well as human growth hormone-secreting pituitary cells were demonstrated (4, 5).

A specific explanation for the high association of this disorder with pregnancy remains uncertain. General systemic immunological changes with pregnancy include fetal production of "suppressor cells," which theoretically inhibit maternal rejection of the fetal allograft (9). Pathological changes of the pituitary during pregnancy have been well documented, including hypertrophy and hyperplasia of prolactin-secreting cells (2, 11).

Panhypopituitarism after postpartum hemorrhage was described by Sheehan (23, 24). Postmortem examination of the pituitary glands in many of these patients demonstrated infarction of the gland. This was believed to be secondary to arterial spasm in small vessels supplying the hypertrophied pituitary gland of pregnancy, which presumably occurred during a period of hypovolemic shock.

However, cases such as ours, which involve postpartum hypopituitarism after routine deliveries without hemodynamic compromise, may have an alternative explanation. Some of these cases may have an autoimmune cause (12). Engelberth and Jezkova demonstrated antipituitary antibodies in 23 of 128 randomly selected women during the immediate postpartum period (8). In long term follow-up of these patients, 25% of those with antipituitary antibodies later developed clinical signs of hypopituitarism, whereas only 4% of the patients without these antibodies developed similar signs. However, no objective laboratory criteria of pituitary function were obtained in any of these patients. Serum in patients with lymphocytic adenohypophysitis has been assayed for antipituitary antibodies in only 2 cases, with 1 of these patients demonstrating a positive assay for these antibodies (1, 18).

An experimental model of lymphocytic adenohypophysitis has been produced in rats by the injection of pituitary tissue and adjuvant into the hind foot pad (17). Within 13 to 20 days of these injections, lymphocytic infiltration of the anterior pituitary was demonstrated, with histological features broadly similar to those seen in human lymphocytic adenohypophysitis. When the condition was induced in pregnant rats, the pathological changes were found to be most pronounced during the immediate postpartum period (17).

Lymphocytic adenohypophysitis is a distinct clinicopathological entity that should be included in the differential diagnosis of postpartum hypopituitarism, especially after a delivery uncomplicated by hypotension or excessive blood loss. The cause of the disorder remains uncertain, but seems most likely to be autoimmune. Present treatment consists of sellar exploration for both pathological diagnosis and chiasmal decompression and prompt hormone replacement for hypopituitarism. Early diagnosis is important because concomitant pituitary insufficiency is often rapidly progressive.

The clinician must consider the diagnosis of lymphocytic adenohypophysitis in any female patient presenting with a sellar mass lesion during pregnancy or the postpartum period. Because this disorder may be self-limited, resolving spontaneously, it is desirable to avoid major resection for a presumed pituitary tumor, which would cause unnecessary hypopituitarism. In our case, the consistency of the tissue was firmer than that in pituitary adenoma; however, pathological studies are the only way to achieve a certain diagnosis.

The role of high dose steroids to decrease pituitary size is unknown, but a response might be expected given the presumed autoimmune cause of this disorder. Our report also demonstrates the importance of repeat pituitary testing in these patients because hypopituitarism may be transient; these patients may not require long term hormone replacement therapy.

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