

Lymphocytic Adenohypophysitis: Clinical, Radiological, and Magnetic Resonance Imaging Characterization

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Lymphocytic adenohypophysitis is a rare nonneoplastic cause of a pituitary mass. We report the case of an 18-year-old woman who presented with complaints of headaches and visual disturbances after an otherwise uncomplicated pregnancy and delivery. She had an elevated serum prolactin level and a pituitary mass visualized by magnetic resonance imaging (MRI). The tissue removed by transsphenoidal resection was an inflammatory mass composed of lymphocytes, plasma cells, and moderate fibrosis surrounding islands of hyperplastic lactotrophs. This is the first case of lymphocytic adenohypophysitis visualized by MRI. As in this case, lymphocytic adenohypophysitis is frequently confused with a prolactin-secreting pituitary tumor before operation and pathological examination of the tissue. The clinical characteristics and radiological features of and an approach to managing patients with lymphocytic adenohypophysitis are reviewed and discussed. (*Neurosurgery* 22:937-941, 1988)

Key words: Autoimmune disease, Lymphocytic adenohypophysitis, Magnetic resonance imaging, Pituitary tumor, Pregnancy, Prolactin, Transsphenoidal microsurgery

INTRODUCTION

Normal pregnancy is associated with alterations in immune function, as well as structural and functional changes in the pituitary gland and other endocrine organs. Prolactin levels rise during pregnancy and the anterior pituitary gland enlarges due to lactotroph hyperplasia caused by high concentrations of estrogen. This effect of estrogen is thought to be responsible for the reported cases of rapid expansion of prolactin-secreting pituitary adenomas during pregnancy (8, 20). We report the case of an 18-year-old woman who developed headaches, visual disturbances, and radiological evidence of a mass arising in the sella turcica toward the end of an otherwise uncomplicated pregnancy. Although the initial clinical diagnosis was prolactinoma, the pathological specimen demonstrated lymphocytic adenohypophysitis, a rare, nonneoplastic cause of an expanding pituitary mass lesion. This pathological entity was first described in 1962 by Goudie and Pinkerton (10) and, since then, 18 additional patients have been reported (1, 2, 4, 5, 9-15, 17-19, 21-23). With 1 exception, all were women, the majority of whom developed symptoms toward the end of a normal pregnancy or during the early postpartum period. Our case is the first in which the radiological abnormalities of lymphocytic adenohypophysitis were visualized with magnetic resonance imaging (MRI).

CASE REPORT

An 18-year-old woman (gravida 3 para 2) was admitted to the hospital with complaints of headaches, blurred vision, and a pituitary mass noted on an MRI scan. Six weeks earlier, she had delivered a full-term male infant by cesarean section. Two weeks before delivery, she had developed severe headaches located in the frontal area with radiation to the occiput. The headaches subsided shortly before delivery, but 1 week postpartum she had experienced the onset of blurred vision involving the left temporal visual field. An ophthalmologist noted blurred disc margins bilaterally and a bitemporal hemianopsia.

The patient had breast fed since delivery and did not note

either deficient or excessive milk production. Her menses had always been regular. She denied nonpuerperal lactation, anorexia, nausea, vomiting, abdominal pain, postural dizziness, cold intolerance, constipation, fatigue, polyuria, or nocturia.

The blood pressure was 120/90, and the pulse was 88 per minute and regular. The pupils were equal, round, and reactive to light and accommodation. There was mild restriction of the temporal visual field on the left, with normal visual fields on the right to confrontation. The superior margins of both optic discs were blurred. The remainder of the physical examination, including a complete neurological evaluation, was normal.

Preoperative laboratory data included normal values for glucose, blood urea nitrogen, creatinine, electrolytes, liver function tests, calcium, and phosphorus. Other data were: hemoglobin, 12.1 g/dl; hematocrit, 36%; white blood cell count, 7700; urinalysis, normal with a specific gravity of 1.025; T₃ resin uptake, 29.8% (normal 35-45%); T₄, 9.3 µg/dl (normal 5.5-11.5 µg/dl); free T₄ index, 2.8 (normal 2.2-4.7); thyroid-stimulating hormone (TSH), 0.7 µU/ml (normal 0-3.5 µU/ml); a.m. cortisol, 24 µg/dl; p.m. cortisol, 9.2 µg/dl; growth hormone, 2.2 ng/ml. The base line serum prolactin value was 129 ng/ml (normal nonpregnant woman, 0-15 ng/ml), a value consistent with either a physiological elevation expected during the postpartum period or a prolactinoma. Antithyroglobulin, antithyroid microsomal, and antiadrenal antibodies were all undetectable.

A chest x-ray film was normal, and skull films were unremarkable, with a normal size sella turcica and no erosions of the sellar floor or posterior clinoid processes. A computed tomographic (CT) scan of the brain and orbits did not demonstrate any abnormalities. Contrast agent was not administered because of a history of an allergic reaction to iodinated contrast material. An MRI scan with sagittal, coronal, and axial images demonstrated a 1- × 1.2-cm mass in the sella turcica. The signal intensity was isointense with the brain parenchyma and appeared homogeneous throughout the mass. The ventricles and sulci were normal, there was no midline shift, and the optic chiasm appeared compressed by the mass. The study was interpreted as demonstrating a

pituitary mass lesion consistent with a pituitary adenoma (Fig. 1).

Because of compression of the optic chiasm with abnormal visual fields, the patient underwent a transseptal transsphenoidal exploration of the sella turcica on the 2nd hospital day. An abnormally firm, tenacious tissue mass was identified. A sample submitted for frozen section was thought to be consistent with a pituitary adenoma, although some lymphocytes were seen, and all visible tumor was surgically resected. The tumor removal was difficult because of the tenacious nature of the mass. Permanent sections of the tissue removed at operation revealed pituitary tissue with hyperplasia of the lactotrophs, as would be expected in a postpartum woman. In addition, there was marked infiltration of the entire tissue by mature and reactive lymphocytes that partially obscured the underlying tissues. There were no lymphoid germinal centers in the tissue submitted, and moderate diffuse fibrosis was evident. No granulomas or multinucleated giant cells were identified. A small amount of neurohypophysis was present and did not have an infiltrate of lymphocytes, such as that which characterized the adenohypophysis. Stains for prolactin using an immunoperoxidase method demonstrated hyperplasia of prolactin-positive cells. Electron microscopy of the specimen showed lymphocytes and plasma cells infiltrating the stroma of the gland (Fig. 2).

Postoperatively, the patient developed diabetes insipidus necessitating treatment with desmopressin. A combined insulin-thyrotropin-releasing hormone (TRH)-gonadotropin-releasing hormone stimulation test confirmed that the patient had developed hypopituitarism with adrenocorticotrophic hormone, TSH, luteinizing hormone, follicle-stimulating hormone, and growth hormone deficiency. After operation, the base line prolactin value was 5.2 ng/ml, and prolactin peaked at 27 ng/ml after the administration of 500 µg of TRH. The patient has done well postoperatively, treated with desmopressin, cortisone acetate, and L-thyroxine.

DISCUSSION

Lymphocytic adenohypophysitis is a rare cause of pituitary enlargement and hypopituitarism (1, 2, 4, 5, 9-15, 17-19,

21-23). This was first recognized as a pathological entity in 1962, but the first case diagnosed antemortem was not reported until 1980. Of the 20 reported patients (including present case), 19 were women. The majority have been diagnosed during the early postpartum period when they presented with evidence of an enlarged pituitary gland or various degrees of hypopituitarism. As in our case, lymphocytic adenohypophysitis is most frequently confused with a pituitary adenoma before operation and pathological examination. Preoperative differentiation of a pituitary adenoma from lymphocytic adenohypophysitis is particularly difficult because of the rapid enlargement of a prolactinoma during pregnancy, though rare, is well recognized (8, 20) and, as in our case, elevated prolactin levels with lymphocytic adenohypophysitis may be increased because of residual nests of lactotroph hyperplasia or compression of the pituitary stalk by the inflammatory mass. Furthermore, in the patient reported, a frozen section obtained intraoperatively was consistent with a pituitary adenoma because of lactotroph hyperplasia that coexisted with the chronic inflammatory infiltrate.

In the cases in which preoperative endocrine studies have been reported, most patients had variable degrees of hypopituitarism, hyperprolactinemia, or both (1, 2, 11, 13-15, 17, 19, 21-23). Our patient showed normal endocrine function preoperatively with the exception of a prolactin value of 12 ng/ml. Because she breast fed after delivery, the cause of the hyperprolactinemia was difficult to discern and may have been multifactorial.

The cause of lymphocytic adenohypophysitis remains poorly characterized. Histologically, the anterior pituitary gland is infiltrated with small lymphocytes and plasma cells, occasionally arranged in follicles with germinal centers, and there are variable degrees of fibrosis. In a recent study, the lymphocytes were identified as a mixture of both B and T cells with a helper to suppressor ratio of 2:1 (14).

The presence of lymphocytes has led to the speculation that lymphocytic adenohypophysitis is an autoimmune disease, although no specific antigenic stimulus has clearly been identified. Several patients with lymphocytic adenohypophysitis have had associated diseases such as Hashimoto's thyroiditis, silent thyroiditis, idiopathic adrenalitis, and pernicious anemia, diseases considered to have autoimmune causes (10, 12, 14, 18, 23). Our patient lacked clinical evidence of associated

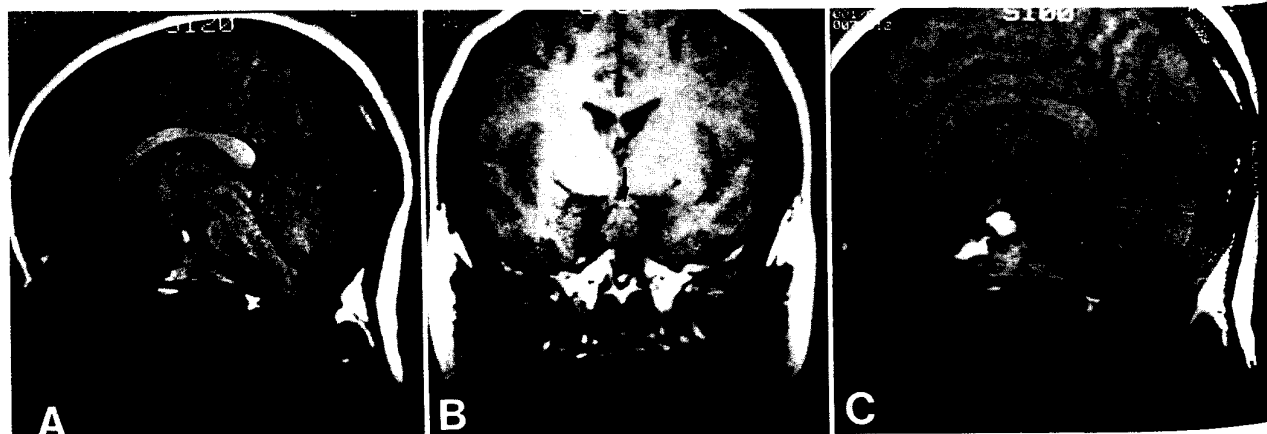


FIG. 1. Sagittal (A) and coronal (B) sections through the sella turcica (T₁-weighted image). A pituitary mass extending superiorly into the suprasellar cistern is demonstrated. The optic chiasm (arrow) is draped over the tumor. C: Postoperative midline sagittal section (T₁-weighted image) shows fat packed into the sella turcica after removal of the tumor. The increased signal intensity of the sellar contents and sphenoid sinus is due to a combination of subacute hemorrhage and fat. Note the lack of compression of the optic chiasm (arrow).

FIG. 1. Infiltrate of lymphocytes and plasma cells in the adenohypophysis. A: Preoperative T₁-weighted MRI. B: Coronal T₁-weighted MRI. C: Postoperative T₁-weighted MRI. D: Histological section.

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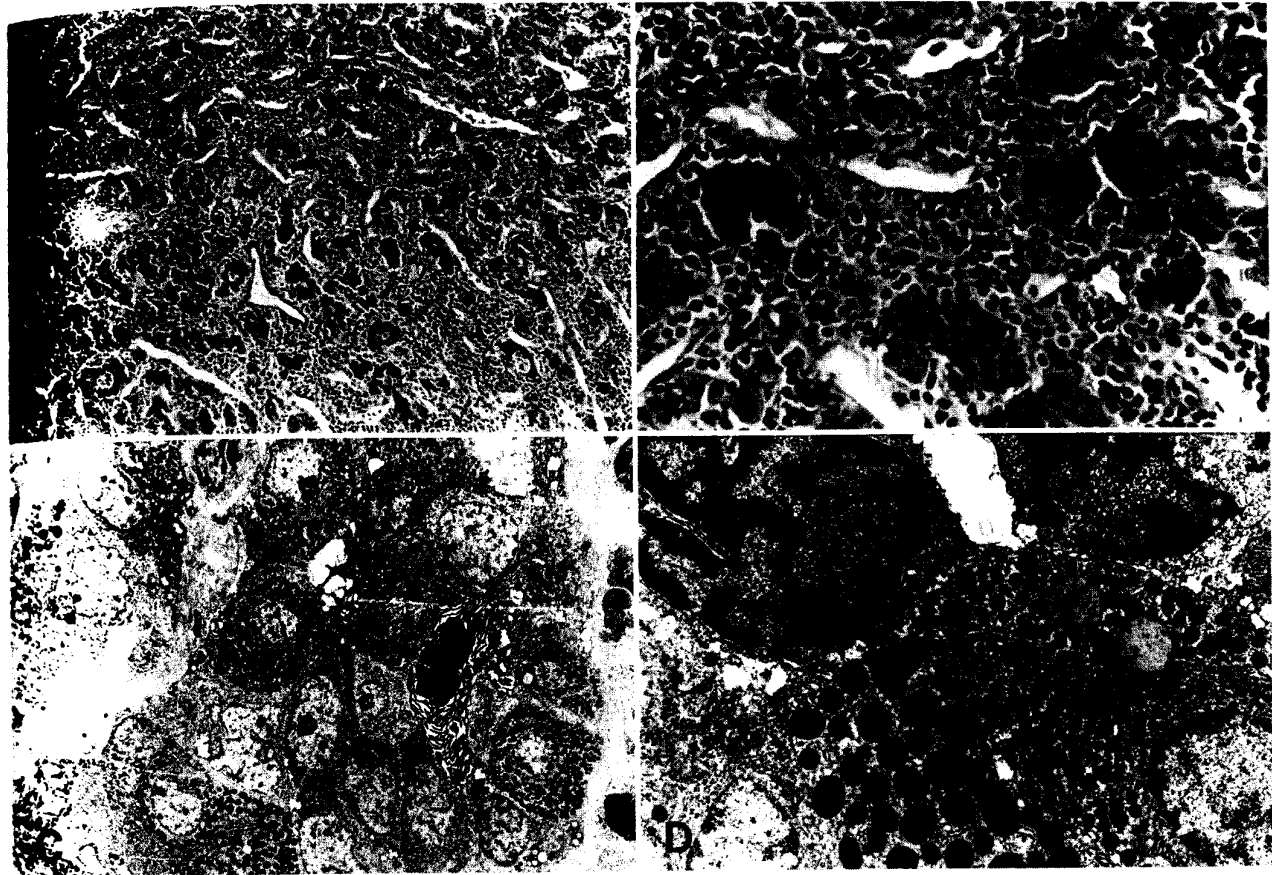


FIG. 2. A: Photomicrograph of the surgical specimen demonstrating a marked inflammatory cell infiltrate of the adenohypophysis. The infiltrate is composed predominantly of lymphocytes and plasma cells, although some neutrophils and eosinophils are noted. Residual nests of adenohypophyseal cells are scattered throughout the tissue (H&E, $\times 100$)

B: Higher power view of the surgical specimen. (H&E, $\times 400$)

C: Electron micrograph of the surgical specimen demonstrating the presence of lymphocytes and plasma cells adjacent to adenohypophyseal cells, which contain typical electron-dense secretory granules. ($\times 1100$)

D: Higher power electron micrograph illustrating lymphocytes adjacent to adenohypophyseal cells. ($\times 7000$)

autoimmune endocrinopathies, and tests for antithyroglobulin antibodies, antithyroid microsomal antibodies, and antiadrenal antibodies were all negative.

Pregnancy is accompanied by alterations in immune tolerance and by exposure of the mother to a variety of "foreign" fetal antigens (6, 7). Patients with autoimmune diseases, such as systemic lupus erythematosus, may experience spontaneous improvement or exacerbation of their disease during pregnancy and frequently have clinical evidence of increased disease activity during the postpartum period. Furthermore, lymphocytic infiltration of the adenohypophysis can be induced in experimental animals after the injection of anterior pituitary tissue, and antipituitary antibodies have been detected in 18% of women shortly after delivery (3, 16). Such circumstantial evidence has led to considerable speculation that lymphocytic adenohypophysitis is an autoimmune phenomenon induced by antipituitary antibodies. Although this remains an attractive hypothesis to explain the pathogenesis of lymphocytic adenohypophysitis, little direct confirmatory evidence has been reported.

The radiological features of this case are noteworthy because our patient is the first reported in the literature in whom the mass was visualized by MRI. An initial CT scan, done

without contrast agent because of an allergy to iodinated dye, failed to demonstrate an abnormality. Previous reports of CT scans in patients with lymphocytic adenohypophysitis have almost uniformly described a contrast-enhancing mass (1, 2, 11, 13, 14, 18, 19, 21, 22). The MRI scan demonstrated a 1- \times 1.2-cm mass in the sella turcica with homogeneous signal intensity throughout the mass. The findings were most consistent with a pituitary adenoma. As on CT scans, the radiological features of lymphocytic adenohypophysitis on MRI scans are quite similar to those of a pituitary adenoma. Table 1 highlights the radiological features of all reported cases.

Lymphocytic adenohypophysitis should be considered in the differential diagnosis of any mass lesion arising in the sella turcica, particularly during pregnancy or the postpartum period. Preoperatively, the differentiation of a pituitary adenoma from lymphocytic adenohypophysitis is extremely difficult, if not impossible. Surgical intervention is necessary to establish a diagnosis and may be necessary to reduce the size of the inflammatory mass, which could be compressing surrounding neural structures, such as the optic nerves (as was the situation in our case). We recommend that intraoperatively a specimen of an unknown tumor mass be submitted for frozen section. If the tissue demonstrates lymphocytic

TABLE I
Radiological Features of Lymphocytic Adenohypophysitis

Author (Ref.)	Skull Films	Sella Tomograms	CT Scan	Additional Radiological Studies
Goudie (10)	— ^a	—	—	
Hume (12)	—	—	—	
Egloff (5)	—	—	—	
Lack (15)	—	—	—	
Gleason (9)	—	—	—	
Quencer (22)	enlarged sella, erosion of dorsum	enlarged sella, erosion of dorsum	enhancing intrasellar mass without suprasellar extension	
Mayfield (17)	enlarged sella	enlarged, rounded sella without erosions	normal ^b	
Richtsmeier (23)	—	—	—	
Asa (1)	normal size sella, thinning of dorsum	—	lobulated, enhancing mass with suprasellar and lateral extension	
	slight enlargement of sella	slight enlargement of sella	pituitary fossa mass	arteriogram—minimal suprasellar extension with elevation of A ₁ segment of anterior cerebral artery
Portocarrero (21) ^s	—	symmetrically enlarged sella without erosions	diffuse enhancement of pituitary without suprasellar extension	
Cebelin (4)	—	—	—	
Hungerford (13)	enlarged sella with erosion of dorsum	—	uniform enhancement of a pituitary mass with suprasellar extension	arteriogram—elevation of right anterior cerebral artery, no abnormal blush
Baskin (2)	—	—	contrast-enhancing mass with suprasellar extension	arteriogram—normal
	expanded sella, thin floor and dorsum	—	contrast-enhancing mass with suprasellar extension	
Mazzone (18)	—	inferior bulging of sellar floor	elevation of diaphragm sella, ballooning of sellar floor with area of contrast enhancement	
Jensen (14)	—	—	contrast-enhancing mass within the sella	
Guay (11)	normal	—	1.3-cm intrasellar mass with slight bulging above the anterior clinoid processes	
McGrail (19)	—	—	contrast-enhancing intrasellar mass with suprasellar extension	
Levine	normal	—	normal—no contrast given due to history of allergy to iodinated contrast material	MRI—1.0 × 1.2-cm homogeneous mass within the sella

^a — denotes test result not reported by the authors.
^b Early model CT scanner; no thin sections or coronal cuts were possible.

infiltration, an aggressive effort to excise the mass completely should not be attempted. As in this and many previously reported cases, complete resection of the mass often results in hypopituitarism. The inflammatory tissue remaining after a subtotal resection could theoretically be treated with glucocorticoids, although no previous cases have been treated in

this manner; therefore, a response to glucocorticoids must remain speculative. This approach might allow preservation of pituitary function. The tenacious nature of the inflammatory mass almost assuredly contributes to the postoperative pituitary insufficiency in those patients in whom a total resection has been attempted. Even when a frozen section

obtained during operation, definitive diagnosis may need to await examination of permanent sections. In our case, interpretation of the frozen section was extremely difficult because the biopsy contained residual islands of lactotroph hyperplasia that mimicked a pituitary adenoma. A conclusive diagnosis was impossible until the permanent sections were reviewed; however, the presence of lymphocytes in the adenohypophysis or a pituitary mass recognized during the peripartum period should increase one's index of suspicion that the patient might have lymphocytic adenohypophysitis. In this situation, radical attempts at removal of the tissue should be avoided.

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COMMENTS

This is a clearly written report about a condition thought to be rare but perhaps occurring more frequently in pregnant women than previously suspected. Recognition of this condition at the time of operation should be the goal so that the whole anterior lobe is not removed, as was done in this case. Patients with this problem may recover pituitary function if only partial resection is done, and panhypopituitarism may thereby be averted. An MRI appearance of diffuse enlargement of the gland, moderate prolactin elevation, and pathological findings at operation of lymphocytic infiltration should suggest partial resection only as the surgical treatment.

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The authors have presented a well-documented case of lymphocytic hypophysitis. With more than 20 cases already cited in the medical literature, pituitary surgeons may now strongly consider such a diagnosis in a patient with a sellar mass during the gestational or postpartum period.

Biopsy of the mass is necessary to confirm the diagnosis and limit the resection of the viable pituitary tissue. Treatment by low dose glucocorticoids seems to be successful and compatible with normal pituitary function.

If the serum prolactin level is >250 ng/ml, bromocriptine therapy might be initially considered without biopsy, especially in the pregnant patient.

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