

## Lymphocytic Hypophysitis In A Man\*

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**ABSTRACT.** Fewer than 20 patients with lymphocytic adenohypophysitis have been reported, all of them women, and it usually occurs during pregnancy or the postpartum period. We report the recognition of lymphocytic adenohypophysitis in a man. The patient presented with anterior hypopituitarism and an intrasellar mass on computed tomography. Antipituitary antibodies, found in only one of the previous patients, were not

present in this man, although low titer antinuclear antibodies were found. The implications of this latter finding are unclear. The patient's histocompatibility antigen (HLA) types were A2, B8, Bw58, DR1, and DR5. The degree of pituitary failure seemed out of proportion to the size of the mass seen on computed tomographic scan. (*J Clin Endocrinol Metab* 64: 631, 1987)

IN 1962, Goudie and Pinkerton (1) were the first to describe a patient with "anterior hypophysitis." The disease occurred in a woman and was discovered together with Hashimoto's thyroiditis at necropsy. Since then, 15 other patients have been described (2-14). Initially, the disease was usually found during postmortem examination, but more recently it has been detected during pituitary operation. The majority of patients had complete hypopituitarism, but in some, pituitary deficiency was partial (6, 8, 11, 12). Elevated serum PRL levels were found in several instances (7, 9-11). The pathological findings were similar in all patients and resembled those in many autoimmune diseases; there were dense infiltrates of lymphocytes, and plasma cells with interstitial fibrosis and lymphoid follicles with pale germinal centers in the pituitary glands.

All of the patients reported have been women, and in the majority, the diagnosis was made either during pregnancy or within 14 months after childbirth. Associated autoimmune diseases have included thyroiditis (1, 2, 8), pernicious anemia (2), adrenalitis (3), and lymphocytic infiltration of the parathyroid glands (3). Lymphocytic hypophysitis has been postulated to be an autoimmune disease primarily of pregnancy and the puerperium. The present case, to our knowledge, is the first recognition of this disease in a man. The patient presented with hypopituitarism, and at transsphenoidal operation, the patho-

logical findings were diagnostic of lymphocytic hypophysitis.

### Case Report

A 52-yr-old white man sought medical attention after a 1-yr history of impotence and fatigue. He also described decreased beard growth, constipation, intolerance to cold, lack of appetite, arthralgias, and weight loss of 20 kg. He denied nausea, vomiting, diarrhea, abdominal pain, fever, polyuria, headaches, or visual changes. There was no family history of endocrine or autoimmune problems.

Physical examination revealed a well developed man who appeared older than his stated age, with advanced wrinkling of facial skin. Blood pressure was 140/80 mm Hg supine and 120/80 mm Hg standing. Pulse was 72 beats/min and regular. The skin was pale and dry. Axillary hair was normal. Findings on funduscopic examination were normal. The thyroid gland was not enlarged or nodular, and the testes measured 3 × 2 cm and were very soft. Pubic hair was decreased slightly. The relaxation phase of the deep tendon reflexes was markedly delayed. Goldman perimetry revealed normal visual fields.

Laboratory evaluation demonstrated a white blood cell count of 8000/mm<sup>3</sup>, with 42% lymphocytes and 5% eosinophils. Hematocrit was 36%, with normocytic indexes. Serum glucose and electrolyte levels were normal, and no abnormalities indicative of malabsorption were found. The patient regained 10 kg after hormonal replacement.

Hormone levels were measured using standard RIA kits. Serum T<sub>4</sub> was 3.0 μg/dL (normal, 4.5-12.0), T<sub>3</sub> uptake was 17.7% (normal, 22-32%), and TSH was less than 1.0 μU/mL (normal, <1-7). A plasma cortisol level at 1800 h was below 1.0 μg/dL (normal, 2-9). Serum testosterone was less than 10 ng/dl (normal, >280), LH was 2 mIU/mL (normal, 2-20), FSH was 10 mIU/mL (normal, 2-10), GH was 1.2 ng/mL (normal,

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<1-5.0), and somatomedin-C was 93 ng/mL (normal, 92-320). Serum PRL was less than 5 ng/mL (normal, 8-25). Serum osmolality was 290 mosmol/kg (normal, 280-290), with a simultaneous antidiuretic hormone level of 1.3 pg/mL (<0.5 pg/mL for serum osmolality <285 and 2-12 pg/mL for serum osmolality >290).

#### Immunological studies

Antipituitary antibodies, tested for by indirect fluorescence on frozen sections of normal human pituitary tissue, were not found. The antiimmunoglobulin (anti-Ig) antiserum used reacted with IgG, IgM, IgA, and  $\kappa$ - and  $\lambda$ -light chains. Antinuclear antibodies were present before operation at a 1:80 titer in a speckled pattern (normal, 1:20) on rat liver, HEP-2 cells, and human pituitary and adrenal tissue but negative on sections of mouse liver. One month after operation the antinuclear antibody titer was 1:40. Three months after operation the antinuclear antibody finding was negative. Antibodies to native DNA, denatured DNA, somatomedin, ribonucleoprotein, SSA (Ro), SSB (La), adrenal cortex, parietal cell, thyroid microsomal, and mitochondrial antigens were negative. The IgG level was 1165 mg/dL (normal, 850-1550), IgA was 198 mg/dL (normal, 80-315), and IgM was 97 mg/dL (normal, 50-200). Histocompatibility antigen (HLA) types were A2, B8, Bw58, DR1, and DR5.

#### Radiological studies

A plain lateral roentgenogram of the sella turcica was normal. A modified coronal computed tomographic (CT) scan revealed an intrasellar mass that measured 1.3 cm and bulged slightly above the anterior clinoid processes (Fig. 1). Its lucent inferior portion was contrasted against a thick dense upper and lateral border. This configuration, although unusual, is consistent with a pituitary adenoma.

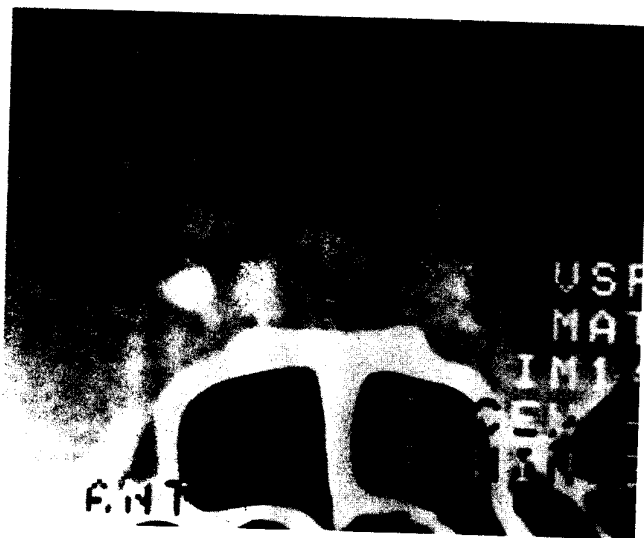


FIG. 1. Coronal CT scan showing an intrasellar mass with slight suprasellar bulging. It measured 1.3 cm in its vertical axis.

#### Operation

The patient received replacement doses of thyroid and adrenal hormones for 1 month before operation. A transnasal transsphenoidal approach to the sphenoid sinus was performed. The pituitary gland appeared abnormal. It was yellow and exceptionally firm. Frozen section indicated the possibility of a pituitary adenoma intermixed with fibrous tissue. No macroscopically normal pituitary tissue could be identified, and a virtually complete hypophysectomy was performed. The patient recovered without incident. Diabetes insipidus did not develop, and he is well taking thyroid, cortisol, and testosterone therapy.

#### Pathological studies

Standard histological sections of the anterior pituitary gland showed diffuse infiltration by a polymorphous population of chronic inflammatory cells, most of which were mature lymphocytes (Fig. 2). A lesser number of plasma cells, rare eosinophils, and some focal reactive lymphoid germinal centers were identified. Granulomas or multinucleated giant cells were not seen. There was no evidence of pituitary adenoma or other neoplasm. Malignant lymphoma was excluded by the polymorphous nature of the infiltrate and the presence of germinal centers.

#### Immunohistochemical studies

Deparaffinized tissue sections fixed in Bouin's solution were studied with the avidin-biotin modification of peroxidase-antiperoxidase method reported previously (15) using rabbit anti-



FIG. 2. The anterior pituitary is infiltrated by lymphocytes, and a large germinal center is seen. Normal pituitary cells are seen at the bottom left (hematoxylin and eosin stain; original magnification,  $\times 100$ ).

LH, -FSH, -ACTH, -TSH, -PRL, and -GH antisera. Positive staining was seen with all antisera, indicating the presence of all pituitary cell types. There was no evidence of predominance of any one pituitary hormone.

### Discussion

To our knowledge, this man is the first male patient with lymphocytic hypophysitis to be reported, and therefore, it is evident that the disease affects individuals other than women during pregnancy or the postpartum period. It is likely that the disease is similar to many other autoimmune diseases in that women are affected principally but not exclusively.

Many of the patients reported previously (2-14) had large pituitary mass lesions, and most had various degrees of pituitary insufficiency. Several patients also had elevated serum PRL levels (9-11), probably due to compression of the pituitary stalk. Our patient had signs and symptoms of hypopituitarism, which appeared to be of long duration.

Care must be taken to distinguish lymphocytic hypophysitis from a rare but similar condition, granulomatous hypophysitis, which may present as a pituitary mass with pituitary insufficiency (16). The latter is characterized by epithelioid histiocytes and multinucleated giant cells, but lymphoid follicles are absent. Although this condition may be found in patients with syphilis, tuberculosis, and sarcoidosis, in most the etiology is uncertain. Regardless of the cause, the clinical presentation may be identical.

On CT scan, many patients with lymphocytic hypophysitis have large parasellar masses, whereas others have only intrasellar lesions (17). Our patient had an intrasellar mass with minimal superior bulging. The degree of hypopituitarism seemed out of proportion to the size of the mass. In general, the size of a pituitary mass, at least when it is a tumor, is the major determinant of the degree of hypopituitarism (18), but the extent to which a pituitary mass lesion impinges on or alters hypothalamic-pituitary portal blood flow is another determinant of the degree of pituitary dysfunction that is present. In this regard, this man had a low serum PRL level.

Several findings suggest that autoimmunity is involved in the pathogenesis of lymphocytic hypophysitis. Lymphoid follicles are detected in the lesions, and electron microscopic studies have shown interdigitation of activated lymphocytes with pituitary cells (9). In addition, a number of patients had associated autoimmune endocrinopathies (19). Antipituitary antibodies were positive in one of the three previous patients in whom they were sought (6). Experimentally, autoimmune hypophysitis can be induced by injecting pituitary tissue into mice (20). Similar results (21) have been reported in rabbits, and none of the animals had antipituitary antibodies.

Our study provides some additional support for an autoimmune basis for the disease. As in previous patients, reactive lymphoid germinal centers were present in the lesion. In addition, antinuclear antibodies were detected initially in low titer (1:80); they disappeared after operation. Also, the patient had the HLA-B8 antigen, which has been associated with immunological hyperresponsiveness in normal persons and with a variety of autoimmune diseases (22). Class 2 antigen typing in our patient revealed DR1 and DR5; by contrast, in patients with a number of other autoimmune diseases, striking associations with DR3 (23) have been found.

The absence of antipituitary antibodies in our patient argues somewhat against direct involvement of organ-specific autoantibodies in the disease. However, the direct involvement of such antibodies cannot be excluded, especially early in the pathological process. In this regard, it is well known that not all patients with biopsy-proven chronic thyroiditis have serum antithyroid antibodies (24).

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