A Case of Hypopituitarism Due to Granulomatous and Lymphocytic Adenohypophysitis with Minimal Pituitary Enlargement: A Possible Variant of Lymphocytic Adenohypophysitis

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Abstract

A 47-year-old woman complaining of cold intolerance, general weakness and amenorrhea of 10 months duration was diagnosed, by endocrine examinations, as having panhypopituitarism. Skull x-ray films revealed a slightly enlarged sella with double floor sign and MRI showed a low intensity mass in the pituitary. Transsphenoidal exploration disclosed a degenerated pituitary gland, the histology of which showed a granulomatous lesion with moderate lymphocytic infiltration but containing no multinuclear giant cells. No caseous necrosis, causative microorganisms, or BCG antigen were noted. The present case is considered a variant form of lymphocytic adenohypophysitis.

Granulomatous inflammation of the pituitary gland, excluding tuberculosis, syphilis, sarcoidosis and fungal infection, is a rare disorder (Doniach and Wright, 1951; Rickards and Harvey, 1954). Lymphocytic adenohypophysitis is also a rare disorder affecting mainly females and resembling pituitary adenoma because of sellar enlargement. Massive infiltration of lymphocytes is suggestive of its autoimmune nature (Kjaer and Norgaard, 1969).

We report here a patient who had hypopituitarism together with a small intrasellar mass discovered through radiological

imaging, and was diagnosed, by histological examination of the transsphenoidal biopsy specimen, as having granulomatous and lymphocytic adenohypophysitis of unknown etiology.

Case Report

A 47-year-old woman was admitted to our hospital on March 7th, 1986, because of cold intolerance and general weakness. She delivered a child uneventfully at age 26, becoming amenorrheic for 5 years after the delivery, but having normal menstrual periods thereafter. Since May 1985, she had had increasing generalized muscular weakness or pain, cold intolerance and amenorrhea. She visited a hospital, and was given a

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prescription of thyroid hormone, with a diagnosis of hypothyroidism. Her symptoms did not improve, however, and she was referred to our hospital.

Physical examination revealed a pale

woman with a weight of 55 kg and height of 158.5 cm. Blood pressure was 132/100 mmHg and pulse rate was 68 per minute and regular. Axillary temperature was 35.8°C. Her face appeared pale and

Fig. 1. Anterior pituitary function test results.

edematous. The thyroid gland was not enlarged. The breasts were not atrophic and no breast discharge was demonstrated. Neurological examination revealed no abnormalities except for sluggish relaxation of

deep tendon reflexes.

Initial laboratory findings showed mild normocytic anemia and mild liver dysfunction. Urinalysis was negative. Urine volume ranged from 500 to 1200 ml per day;

Fig. 2. Skull X-ray photo. The lateral view of the skull X-ray film shows a slightly enlarged sella and a double floor sign.

the specific gravity of the urine was 1.022. Serum sodium, potassium, calcium, and phosphate were within normal limits. The blood glucose level was 74 mg/100 ml. Serum C3 was 73.3 mg/100 ml, and C4 was 14.6 mg/100 ml. Study of peripheral lymphocytes revealed that OKT-4 was 56.4% and OKT-8 was 13.2%, and that the T4/T8 ratio was high (4.305). Serum angiotensin converting enzyme was 15.7 IU/L and serum TPHA was negative. PPD was positive.

Serum thyroxine (T4) was 0.8 μ g/100 ml; serum triiodothyronine (T3), 52 ng/100 ml;

free T4, 0.25 ng/100 ml; and thyroid stimulating hormone (TSH), 1.7 μ U/ml (measured by a sensitive immunoradiometric assay. The minimal detectable concentration was 0.025 μ U/ml, the normal range was 0.30 to 4.5 μ U/ml) (Mori *et al.*, 1986). The thyroid ⁹⁹mTc-pertechnetate uptake was 0.5% (normal range: 0.4–2.5%). Antithyroid antibodies were negative. The plasma cortisol concentration (3.7 μ g/100 ml) and 24 h-urinary excretion of 17-OHCS (1.0 mg/day) and 17-KS (0.6 mg/day) were low.

Fig. 3. A magnetic resonance image (MRI) of the pituitary region. MRI shows a low density mass of 5 mm in diameter (arrow) in the middle of the anterior pituitary lobe.

Anterior pituitary functions are shown in Fig. 1. Plasma ACTH responses to CRF and insulin-induced hypoglycemia were blunted, although the plasma cortisol response to exogenous ACTH was normal. Plasma GH showed no response to insulin-induced hypoglycemia or GRF. Serum gonadotropin (LH and FSH) responses to LH-RH were blunted. Serum TSH showed a delayed and blunted response to TRH, not associated with any serum T3 increase and measured TSH was considered biologically inactive (Mori *et al.*, 1986). Serum TSH did not respond to sulpiride. Serum prolactin showed almost no response to TRH or sulpiride. The diagnosis of pan-hypopituitarism was established.

Skull X-ray films revealed a slightly enlarged sella with double floor sign (Fig. 2). Magnetic resonance imaging (MRI) showed a low intensity mass (5 mm in diameter) in the middle of the anterior pituitary lobe (Fig. 3).

Pituitary microadenoma was suspected and transsphenoidal exploration of the sella was performed. When the dura was incised and opened, rather hard abnormal dull-white pituitary tissue was observed. In the middle of the anterior lobe a grayish and fragile part was seen. Frozen section of the biopsy specimen revealed chronic inflammation; radical excision was not performed.

Histological examination of the excised specimen showed degenerated anterior pituitary tissue with moderate lymphocytic infiltration in a fibrous stroma (Fig. 4). No lymphoid follicles or germinal centers were observed. There were granulomatous lesions without infiltration with multinuclear giant cells. No caseous necrosis in the center of the granulomatous lesion or microorganism were detected. An immunohistochemical study using anti-BCG antigen demonstrated no positive findings in the lesion. The residual adenohypophyseal cells showed weak positive immunostaining for ACTH and TSH; GH, LH, FSH, PRL, IgG, IgA and

IgM were negative in immunostaining.

Circulating antibody to pituitary gland, measured by indirect immunocytochemistry against frozen rat pituitary gland, was negative. HLA typing revealed A24(9), A26(10), B39(16), CW1 and DR4.

The postoperative course was uneventful. Anterior pituitary function tests were repeated but remained unchanged compared with the preoperative function tests. Nine months postoperatively, the patient's thyroid and corticosteroid replacement levels were satisfactory.

Discussion

The present case developed hypopituitarism of about 5 years duration and was diagnosed as having idiopathic hypopituitarism. She had a previous history of amenorrhea after delivery of her first child, which was not associated with massive bleeding. Sheehan's syndrome was considered to be unlikely because she could breast-feed the baby and had regular menses afterwards lasting for 17 years. A small mass lesion revealed by MRI led us to explore the pituitary fossa using the transsphenoidal approach. Histological examination of the biopsy specimen revealed the presence of granulomatous and lymphocytic infiltration with considerable destruction of the normal pituitary structure.

Granulomatous hypophysitis has occasionally been reported. Tuberculosis was in the past considered an important factor in the development of granulomatous lesions in the pituitary (Doniach and Wright, 1961; Rickards and Harvey, 1954). However, characteristic giant cells and/or anti-BCG positive staining were not seen in the present case. Most reported cases of tuberculous hypophysitis were associated with impaired posterior lobe function (Doniach and Wright, 1951; Rickards and Harvey, 1954; Kiaer and Norguard, 1969; Taylon and

Fig. 4. Histological findings of the biopsied specimen of the anterior pituitary gland.

Left: Degenerated pituitary gland with moderate lymphocytic infiltrations in the fibrous stroma. No lymphoid follicles or germinal centers are seen.

Right : Granulomatous lesions with no infiltration of multinuclear giant cells or caseous necrosis.

Duff, 1980). However, even after steroid replacement, the patient's ability to concentrate urine was maintained. Syphilis, sarcoidosis and infections resulting from other microorganisms were also considered unlikely. Until now, there have been approximately 20 reported cases of granulomatous hypophysitis of unknown origin (Kiaer and Norguard, 1969; Jose Manuel del Pozo *et al.*, 1980; Taylon and Duff, 1980; Hassoun *et al.*, 1985). The present case should be classified in this category, even though the lack of giant cell formation and posterior lobe dysfunction make the present case somewhat different from the reported cases.

Lymphocytic adenohypophysitis is also quite rare; to our knowledge, 20 cases have been reported (Goudie and Pinkerton, 1962; Hume and Roberts, 1967; Egloff *et al.*, 1969; Lack, 1975; Gleason *et al.*, 1978; Richtsmeier *et al.*, 1980; Mayfield *et al.*, 1980; Asa *et al.*, 1981; Quencer, 1980; Portocarrero *et al.*, 1981; Cebelin *et al.*, 1981; Hungerford *et al.*, 1982; Baskin *et al.*, 1982; Mazzone *et al.*, 1983; Madsen *et al.*, 1985; Sobrinho-Simoes *et al.*, 1985; Jensen *et al.*, 1986; Wild and Kepley, 1986). Nine cases were diagnosed by autopsy, and 11 cases by biopsy. These biopsies were performed due to ballooning of the sella turcica, and signs and symptoms of a pituitary mass lesion. CT and MRI in the present case failed to show apparent enlargement of the sellar content or the existence of a microadenoma-like mass, but X-ray film showed a double floor sign. Interestingly, 14 of the 19 previously reported cases had had their disease onset during pregnancy or the postpartum period. Histopathologically, they showed massive lymphocytic infiltrations with lymphoid follicles and germinal centers, characteristic of autoimmune inflammation. Destructive autoimmune thyroiditis and exacerbations of systemic lupus erythematosus in the postpartum period are commonly associated. Amenorrhea following delivery, together with abnormal radiological

findings, may be indicative of lymphocytic adenohypophysitis in the present case. Of the reported cases which underwent autopsy, most died approximately one year after the onset of the disease. In contrast to them, the present case has several unique features: 1) no lymphoid follicles or germinal centers were present; 2) regular menstrual cycles resumed after a 5 year duration of amenorrhea and continued for 17 years until clinical manifestations of hypopituitarism appeared; 3) even after the onset of clinical manifestations, the disease progressed slowly; 4) remarkable granulomatous changes were coexistent. No antipituitary, antithyroid or other nonorgan specific antibodies were detected, but decreased serum complement concentrations and an elevated ratio of OKT4/OKT8 in peripheral lymphocytes suggest possible autoimmune abnormalities. The present case may have had a mild lymphocytic adenohypophysitis during the postpartum period, but fortunately recovered from it and was able to live a natural life for 17 years. Hume and Reberts (1967) reported a case of lymphocytic adenohypophysitis without germinal centers in a 74-year-old woman. Lymphocytic adenohypophysitis may predominantly affect young women in relation to pregnancy or delivery. Mild cases may be able to survive at this stage. In the present case, gradual progression of granulomatous inflammation may have taken place and finally led to an overt panhypopituitary state. Pituitary hormone deficiencies, especially ACTH deficiency, seem to be critical for prognosis, and in the present case, impaired but considerable secretory reserves of ACTH and TSH were observed through function tests and immunohistochemistry. McKeel (1983) has recently reported that both granulomatous and lymphocytic hypophysitis have common ultrastructural features and possibly represent different stages of a single disease. The present case lends support to his proposal.

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