Lymphoid Hypophysitis With Selective Adrenocorticotrophic Hormone Deficiency

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- This report describes a 31-year-old woman with evidences of selective adrenocorticotrophic hormone deficiency associated with a remarkable pituitary lesion, lymphoid hyperplasia, clinical manifestations of secondary hypocortisolism, which first appeared during the immediate postpartum period following normal pregnancy, included progressive weakness and mental aberrations, fasting hypoglycemia, transient hypercalcemia, and striking ECG changes. Sudden death resulted from cardiorespiratory collapse. Microscopic examination of the anterior pituitary disclosed focal fibrosis and extensive lymphocytic infiltrations with a marked reduction of basophils; immunostaining techniques demonstrated a selective loss of corticotropin-secreting cells. The histopathology of the pituitary and its association in this case with lymphoid thyroiditis suggest that selective damage to corticotrophs was due to an autoimmune process.

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Selective adrenocorticotrophic hormone (ACTH) deficiency is an uncommon occurrence. Most reported cases could not be related to pituitary neoplasms, and a specific cause has not always been apparent. The following report describes a woman who had manifestations of hypocortisolism during the postpartum period following normal delivery and whose death occurred on an episode of cardiac arrest. Postmortem examination disclosed an unusual pituitary abnormality identical to previously reported descriptions of lymphoid hypophysitis, as well as evidence of chronic lymphocytic thyroiditis. The morphologic appearance of the pituitary and its association with lymphocytic thyroiditis are consistent with the proposition that ACTH deficiency in this case was due to selective damage of corticotropin-secreting cells of the adenohypophysis by an autoimmune process.

REPORT OF A CASE

A 31-year-old, para 3, gravida 3, was hospitalized with a three-month history of generalized muscular weakness that began two weeks after the birth of her third child. The antecedent pregnancy and delivery were uneventful. She nursed the newborn infant until the time of hospitalization. During the month prior to admission, she experienced increasing anorexia and abdominal pain resulting in a 4.5-kg weight loss, as well as myalgias and progressive weakness.

Physical examination disclosed an apathetic young woman with obvious muscle weakness. Blood pressure was 100/65 mm Hg; pulse rate, 75 beats per minute; respirations, 15/min; temperature, 35.9 °C. Breasts were unremarkable except for lactation. The thyroid gland was not enlarged. Neurologic examination showed no specific abnormalities aside from weakness of proximal muscles.

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Initial laboratory evaluation demonstrated mild normocytic anemia; the WBC count was 3,300/cu mm; eosinophils, 8%. Urinalysis findings were normal. Serum calcium level was 12.2 mg/dL; phosphate level, 5.4 mg/dL; glucose concentration, 93 mg/dL; BUN level, 14 mg/dL; creatine phosphokinase level, 32 mU/mL. Serum electrolyte values were normal. Thyroid function studies gave the following values: triiodothyronine uptake, 96% (normal, 40% to 60%); serum thyroxine, 12.0 ng/dL (normal, 4 to 11 ng/dL); free thyroxine index (T), 7.1 (normal, 5 to 6.5); 24-hour iodine 131 uptake, 2% (normal, 15% to 30%). Electromyogram and findings from nerve conduction studies were abnormal, but not diagnostic of a primary muscle disorder or neuropathy. Lethargy and weakness progressed, and the patient became obtunded on the fourth day of hospitalization, when the serum calcium concentration was 16.3 mg/dL. Treatment with intravenously given furosemide and saline resulted in prompt reversal of hypercalcemia. Subsequently, sensorium improved and serum calcium concentrations remained normal despite discontinuation of treatment. During the last four days of life, serum calcium values ranged from 8.9 to 9.7 mg/dL.

Three days prior to death, while fasting in preparation for an upper gastrointestinal tract roentgenographic examination, she again became obtunded following a prodromal period of tremulousness and tachycardia. Intravenous injection of glucose resulted in prompt recovery; plasma glucose level, measured just prior to glucose administration, was 40 mg/dL.

Electrocardiograms showed nonspecific ST-segment and T-wave changes until two days prior to death, when QT intervals became markedly prolonged to 0.60 s and striking T-wave inversions were noted. Serum calcium level at this time was 9.6 mg/dL. On the 16th day of hospitalization, she suddenly became extremely apprehensive; cyanosis developed, followed by respiratory arrest, and she died within two hours.

AUTOPSY FINDINGS

The subject was a well-developed, well-nourished young woman. Lactation was noted. The brain, heart, lungs, liver, kidneys, gastrointestinal tract, peripheral muscles, and bone marrow showed no striking abnormalities.

The pituitary gland was small, approximately 60% to 70% of normal size. Routine hematoxylin-eosin sections showed that the anterior pituitary was made up almost entirely of acrophilic and chromophobic cells (Fig 1). A careful search for basophils with routine stains, Rhodocyan stain, and Glenner-Lilie stain was negative. The acidophils were mainly central in location (Fig 1, top left). The cells beneath the moderately thickened capsule were almost exclusively chromophobes arranged in cords widely separated by loose, edematous connective tissue (Fig 1, top right). Numerous clusters of lymphocytes intermixed with a few plasma cells were distributed throughout the anterior lobe; smaller aggregates of mononuclear cells were scattered between individual secretory cells (Fig 1). Overall, approximately 5% to 10% of the anterior pituitary was infiltrated by inflammatory cells.

There was pronounced prolactin cell hyperplasia. Growth hormone-, thyroid-stimulating hormone-, follicle-stimulating hormone-, and luteinizing hormone-secreting cells were easily recognized by the immunoperoxidase technique. However, the same technique demonstrated no apparent immunoreactive ACTH with either of two antibodies, 1-24 anti-ACTH or 1-39 anti-ACTH.

The combined weight of both adrenal glands was approximately 3.8 g. Sections showed marked atrophy of the inner cortex; the entire zona fasciculata and zona reticularis was only 6 to 10 cells in width (Fig 2). There were numerous foci of lymphocytes and occasional plasma cells scattered among the cells of the inner cortex. The zona glomerulosa was normal.

The thyroid gland, which weighed 20 g, was extensively infiltrated by mononuclear cells, mostly lymphocytes with...
Fig 1.—Anterior pituitary gland shows atrophy, fibrosis, lymphocytic infiltration, and reduction in basophils (hematoxylin-eosin, original magnification ×110). Top left, Subcapsular region with thickened capsule and heavy lymphocytic infiltrate between widely separated cell cords composed largely of eosinophils. Top right, Posterior medial region of anterior lobe with small area of normal posterior lobe. Cells of anterior lobe are largely chromophobes. Lymphocytic infiltrates are present. Bottom left, Area of lateral portion of anterior lobe composed of mixture of chromophobes and acidophils. Bottom right, Area of anterior lobe near posterior lobe shows extensive fibrosis and few residual basophils.

Fig 2.—Atrophic adrenal gland. Micrograph shows entire thickness of cortex (no medulla is present at this level). Double layer of inner cortex (between arrows), including all that is left of the zona fasciculata and zona reticularis, is smaller than the zona glomerulosa (hematoxylin-eosin, original magnification ×70).

Fig 3.—Thyroid shows marked atrophy and degeneration of follicles. There is extensive lymphocytic infiltration and fibrosis of interstitium (hematoxylin-eosin, original magnification ×200). some plasma cells (Fig 3). The mononuclear infiltrate account for more than 15% of the thyroid mass. The parathyroid glands were normal size; two showed normal morphology, and the other two consisted of almost solid sheets of chief cells, suggesting hyperplasia. The ovaries were unremarkable, showing normal postpartum changes.

COMMENT

In this case, the autopsy provided morphologic evidences of adrenal atrophy associated with selective loss of pituitary corticotrophs. Retrospectively, it may be assumed that the progressive weakness, myalgias, gastrointestinal tract distress, emotional disturbances, hypotension, fasting hypoglycemia, and hypercalcemia that occurred during the course of her illness all were manifestations of hypocortisolism. The striking ECG changes probably were also a reflection of adrenal insufficiency. Cortisol deficiency can cause flattening or inversion of T waves and lowered QRS voltage, as well as prolongation of the QT interval, and serum calcium levels were normal when these ECGs were obtained.

Pituitary functions were not specifically evaluated because hypopituitarism was not suspected during life. However, the clinical and autopsy findings strongly support the proposition that pituitary functions other than ACTH secretion were preserved. The presence of normal puerperal lactation attests to the functional competence of the abundant prolactin cells that were observed in the pituitary sections. Although clinical assessment of gonadal function during the immediate postpartum period generally is problematic, microscopic examination of the ovaries in this case did not show follicular atrophy but demonstrated changes compatible with the normal puerperium. Thyroid function tests showed an elevation of the serum free thyroxine index associated with low thyroidal iodine 131 uptake. These seemingly paradoxical findings are now known to be characteristic of the initial thyrotoxic phase of so-called painless or silent thyroiditis. The cause of this recently described entity has not been clearly defined, but thyroid biopsy specimens from affected patients have demonstrated chronic lymphocytic thyroiditis, suggesting that it is an autoimmune disorder, perhaps a variant of Hashimoto's thyroiditis. Thus, the morphologic appearance of the thyroid in this case supports the assumption that the elevated serum thyroxine level was due to silent
thyroiditis. Since this disease seems to have a predilection for the puerperium, it is possible that the onset of hyperthyroidism may have been a precipitating factor in the development of manifestations of hypocoercism during the postpartum period in this patient.4

Partial losses of pituitary function have been reported in occasional cases of Sheehan's syndrome, but the histopathology of the anterior pituitary in this patient was typical of a chronic inflammatory process rather than avascular necrosis. Indeed, the microscopic picture in this instance was identical to that described in reported cases of lymphoid hypophysitis.6-9 Although selective impairment of ACTH secretion has not been reported in previous reports, the postmortem diagnosis of lymphoid hypophysitis has been associated with varying degrees of hypopituitarism during life. The assumption that lymphoid hypophysitis is an autoimmune disorder is supported by experiments in which similar pituitary lesions were induced in rats by single injections of pituitary tissue preparations plus adjuvants, and also by the clinical association of this pituitary abnormality with other autoimmune endocrine disorders.3-4,9-10

Aside from the possible contributory role of thyrotoxicosis, it is likely that the occurrence of this patient's illness shortly after delivery reflected the onset of hypopituitarism due to the postpartum development or progression of lymphoid hypophysitis. In addition, hypopituitarism also began during the puerperium in two of five previously reported cases.9 Furthermore, a high titer of pituitary antibodies has been noted to appear in a substantial number of women during the first week after uncomplicated deliveries, suggesting that the pituitary may be subject to autoimmune damage more frequently during the postpartum period than might be suspected from the small number of reported cases of lymphoid hypophysitis.11 In the absence of autopsy evidence, it would be extremely difficult to distinguish between autoimmune mechanisms and ischemic injury as a cause of postpartum hypopituitarism. This case draws attention to the diagnostic difficulties presented by lymphoid hypophysitis when it results in partial or selective loss of pituitary function. Awareness of the suspected frequency of lymphoid hypophysitis and its possible predilection for immediate postpartum period may result in earlier recognition and successful treatment of what otherwise could be a potentially fatal condition.

Kalman Kovacs, MD, PhD, FRCPC, performed the prostate cell staining and immunoperoxidase staining studies.

References

T-Storm in Pernicious Anemia

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- A 32-year-old woman first had thyrotoxicosis and severe pernicious anemia (PA) in 1975. The initial serum thyroxine (T4) level, 14.5 μg/dL, rose to 29.2 μg/dL, with no other therapy except cyanocobalamin injection and blood transfusions. She again had thyroid storm and PA in 1978. The serum T4 level was only slightly elevated, but the triiodothyronine (T3) level was normal. She received therapy for both diseases and recovered. Four months later, with a normal hematocrit reading, thyrotoxicosis recurred, with noticeable elevation of T4 and T3. These data suggest that first, thyroid storm can occur with excess T4, only, and its occurrence does not depend on the degree of thyroid hormone elevation; and second, thyroid hormone level can be depressed in severe PA, and a normal T4 level should not rule out thyrotoxicosis in this condition.

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In the majority of patients with thyrotoxicosis there is elevation of both serum thyroxine (T4) and serum triiodothyronine (T3) levels. Thyrotoxicosis occurring only with elevation of T4 (T4-toxicosis) is well known. Recent reports also have documented patients in whom hyperthyroidism developed with excess serum T4, and a normal T3 level (T4-toxicosis).12-13 We describe a patient with severe pernicious anemia (PA) in whom spontaneous thyroid storm developed with only excess serum T4 (T4-thyroid storm).

REPORT OF A CASE

A 32-year-old woman was hospitalized in August 1978, because of thyroid crisis. She had complained of progressive weight loss, heat intolerance, excessive sweating, hyperdefecation, severe weakness, and amenorrhea of two years' duration. Thyrotoxicosis was first diagnosed in 1969, but the patient took antithyroid medications irregularly and was lost to outpatient follow-up. She was seen again in 1975 with pancytopenia and thyrotoxicosis. Pernicious anemia was documented by a low serum vitamin B12 level, a megablastic bone marrow, histamine-fast achlorhydria, and an abnormal Schilling's test. A thyroid scan that was done at the time showed a diffusely enlarged thyroid gland with a uniform "uptake of 76% in 24 hours. She received antithyroid drugs, and she later refused thyroidectomy or therapy. She was again lost to follow-up, and received no antithyroid therapy for many months prior to the present hospitalization.

On examination, the patient appeared very ill, extremely restless, occasionally incoherent in speaking, and obtunded. Her temperature was 41 °C, pulse rate was 180 beats per minute, and blood pressure was 110/80 mm Hg. Thyromegaly and noticeable exophthalmos were present. The heart was not enlarged, but a pulmonic ejection murmur and summation gallop were detected. Rales were heard at both lung bases. There was resting tremor of the hands, and the skin was warm and moist. Severe bilateral proximal

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