Lymphoid Adenohypophysitis Presenting as a Pituitary Tumor

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Lymphoid adenohypophysitis has been reported as a postmortem finding in five patients who died with pituitary insufficiency. We report the first case diagnosed antemortem which presented as an enlarging pituitary mass with hypopituitarism and which was removed by transsphenoidal surgery.

A 23 year old black woman presented with increased intracranial pressure, weight loss and hypoglycemia. Menstrual periods remained regular. Skull roentgenogram revealed an enlarged sella turcica. Plasma cortisol and growth hormone levels did not increase with insulin hypoglycemia. Serum prolactin and thyroid-stimulating hormone (TSH) responses to the administration of thyroid-releasing hormone (TRH) were blunted. Gonadotrophin levels rose normally after the administration of leuteinizing hormone-releasing hormone.

A granular mass was removed by transsphenoidal surgery. Histologically, the anterior pituitary was infiltrated with lymphocytes, lymphoid follicles, plasma cells and eosinophils. Immunocytochemical staining demonstrated thyrotrophs, gonadotrophs and lactotrophs but no recognizable corticotrophic cells within the inflammatory reaction. Circulating antipituitary antibodies were found in the patient's serum. Antibodies to thyroid, adrenal, ovary and pancreas were not detected. Evaluation for possible polyglandular failure demonstrated normal thyroid and adrenal responses to thyroid-stimulating hormone (TSH) and ACTH, respectively.

All six cases of lymphoid adenohypophysitis reported have occurred in women, three within one year postpartum. The inflammatory process has been confined to the anterior pituitary in all cases. Although to date our patient has no other endocrine dysfunction, histologic involvement of other glands including thyroid, parathyroid and gastric mucosa have been described in three other cases. Evidence of an autoimmune etiology exists in some patients with this syndrome. The true incidence is unknown; however, it may become recognized more commonly with the increase in transsphenoidal surgery and should be considered in patients who present with rapidly progressive hypopituitarism and without evidence of a hyperfunctioning pituitary tumor.

Nontumorous lesions causing hypopituitarism with an enlarged sella turcica have been rare and include granulomas [1], aneurysms, familial hypopituitarism [2], basal encephalocoele [3], protrusion of the third ventricle into the sella due to aqueductal stenosis [4] and the empty sella syndrome [5]. In the past, most patients with an enlarged sella turcica and suspected tumor received radiation therapy unless optic...
nerve compression or other neurosurgical complications required surgical intervention. Polytomography of the sella turcica now permits the early detection of small expanding lesions of the pituitary that previously would not have been diagnosed with routine skull roentgenograms. Development of the transsphenoidal approach has resulted in an increase in the surgical treatment of pituitary tumors. Transsphenoidal hypophysectomy and selective adenomectomy also produce excellent tissue specimens for pathologic investigation. These advances may lead to recognition of other pituitary lesions. We report another nontumorous lesion which presents with pituitary insufficiency, increased intracranial pressure and an enlarged sella turcica.

CASE REPORT

A 23 year old black woman, gravida II, para II, was admitted to the Neurology Service in January 1978 because of persistent headache and visual difficulties. She was seven months postpartum following the uncomplicated delivery of her second child. Shortly after starting to take oral contraceptives she noted the onset of headache, which persisted even after she stopped taking the pills three months later. One month prior to her admission a flu-like illness developed followed by fatigue, anorexia, and loss of libido, visual blurriness and diplopia.

Examination revealed a moderately obese woman whose weight was 63.5 kg and height 150 cm. Her blood pressure was 90/60 mmHg. Funduscopic examination revealed bilateral papilledema with hemorrhages and exudates. A right sixth nerve palsy was present. Skull films revealed an enlarged sella, and a computerized tomography (CT) scan of the brain showed no abnormalities. A lumbar puncture revealed an initial pressure of 205 mm water (H₂O).

A diagnosis of pseudotumor cerebri was made. Therapy with prednisone, 60 mg daily, and acetazolamide, 250 mg twice daily, was started. The sixth nerve palsy and headache quickly resolved and the patient felt much improved. The prednisone therapy was tapered and discontinued over the next two months. Therapy with acetazolamide was continued for an additional two months and then stopped because of hypotension. The headaches and visual disturbance recurred.

The patient was readmitted in June 1978 because of confusion, nausea, vomiting and weakness. There had been a 20 pound weight loss since her previous admission. She continued to have normal menstrual periods and denied any galactorrhea, polyuria or polydipsia. The blood pressure was 108/60 mmHg. No definite papilledema was present and no vitiligo was noted. The thyroid gland was not palpable and no breast discharge was demonstrated. Deep tendon reflexes were delayed. A random serum glucose level was 45 mg/dl. Lumbar puncture revealed an initial pressure of 270 mmH₂O. Serum thyroxine (T₄) was 2.3 µg/dl (normal 4 to 11 µg/dl), serum triiodothyronine (T₃) was <50 ng/dl (normal 70 to 210 µg/dl), T₃ resin uptake was 31.6 percent (normal 35 to 45 percent) and thyroid-stimulating hormone (TSH) was 4.6 µU/ml (normal 0 to 10 µU/ml). Anterior pituitary function was evaluated (Tables I and II).

Plasma cortisol level was low. Neither plasma cortisol nor growth hormone responded to hypoglycemia. The prolactin and TSH responses to thyrotropin-releasing hormone (TRH) were blunted. However, gonadotrophins responded normally to the administration of LHRH.

Visual fields were normal by Goldmann perimetry. Polytomography of the sella turcica revealed an enlarged rounded sella without focal erosion or soft tissue calcification. A repeat CT scan showed no abnormalities. A pneumoencephalogram did not demonstrate any suprasellar mass or air entering the sella. The patient was thought to have an expanding nonfunctioning pituitary tumor. Transsphenoidal pituitary surgery was performed, and an unusual appearing gritty, nonencapsulated mass was easily shelled out of the pituitary.

Postoperatively the patient made an uneventful recovery. By the seventh day she was receiving only 2.5 mg of prednisone. Anterior pituitary function tests were repeated according to the preoperative protocol and the results were unchanged from the preoperative state.

Ten months postoperatively the patient is well and receiving thyroid and corticosteroid replacement therapy. She continues to have regular menstrual periods and her headaches and visual disturbances have resolved.
MATERIAL AND METHODS

Leutinizing hormone (LH), follicle-stimulating hormone (FSH), growth hormone, prolactin, plasma cortisol, T₄, T₂, T₃ resin uptake and TSH were all measured by conventional radioimmunoassay methods.

Tissue autoantibodies were determined by a standard immunofluorescence method [6]. Control experiments were performed as previously described [7]. Six micron sections for histology were stained with hematoxylin and eosin, methenamine silver, Brown and Brenn, acid-fast, diastase-periodic acid-Schiff, Congo red, Masson trichrome, Movry’s, Herlant’s and Wilder’s stains. Sections were also stained with the immunoperoxidase bridge technique for immunoglobulins G (IgG), A (IgA), M (IgM) kappa, lambda, lysozyme, prolactin and corticotrophin.

RESULTS

Microscopic examination of the tissue revealed acini of anterior pituitary cells separated by large numbers of inflammatory cells (Figure 1). Lymphocytes and plasma cells predominated, but there was also a mild eosinophilic response (Figure 2). Lymphoid follicles were frequently seen. The reticulin framework of the acini was surprisingly intact, with occasional areas of focal disruption or collapse. When the latter occurred, the adenohypophyseal cells were decreased or absent, and there was an admixture of inflammatory cells. The inflammatory reaction stopped rather abruptly at the neurohypophysis. These findings are typical of previously reported cases of lymphoid adenohypophysitis.

Many of the adenohypophyseal cells in the specimen stained positively with orange G; some of these demonstrated positive immunostaining for prolactin. The remaining cells had the staining characteristics of thyrotrophs and gonadotrophs with Mowry’s stain. No corticotrophs could be demonstrated with either the immunostain or histologic stains. Many inflammatory cells demonstrated positive immunostaining for lysozyme, whereas moderate numbers were positive for IgG, kappa and lambda. IgA and IgM positive cells were rarely observed. The adenohypophyseal cells did not
TABLE III  Plasma Cortisol Response to Cortrosyn Infusion

<table>
<thead>
<tr>
<th>Day</th>
<th>Plasma Cortisol (µg/dl)</th>
<th>3 Hours</th>
<th>6 Hours</th>
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<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>9.7</td>
<td>7.6</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>10.3</td>
<td>19.0</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>19.0</td>
<td>22.7</td>
</tr>
<tr>
<td>4</td>
<td>10.3</td>
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NOTE: Cortrosyn (0.25 mg) in saline solution was infused over 8 hours on days 1, 2 and 3. Plasma cortisol was measured before each infusion and at 3 and 6 hours after infusion.

Hypoglycemia developed in three patients [10,12] and four patients were hypothyroid [8,9,11]. Two of the previous cases occurred in premenopausal women within one year of an uncomplicated pregnancy [8,10]. Amenorrhea persisted postpartum in both cases in contrast to our patient who continued to have normal menstrual periods. Perhaps suppression of the gonadotrophs by oral contraceptive therapy protected these cells against destruction by the inflammatory process.

Our patient presented with pseudotumor cerebri, a condition not reported in any of the previous cases. Pseudotumor has been reported in association with adrenal insufficiency and withdrawal of corticosteroid therapy [13]. Papilledema and the sixth nerve palsy resolved rapidly with steroid therapy.

Pathologically, lymphocytic infiltration confined to the anterior pituitary occurred in all cases, resulting in atrophy of the pituitary in two cases [8,9], destruction of the anterior pituitary without change in its size in one case [11], and gross enlargement in three cases [10,12]. These differences may reflect the stage or duration of the inflammatory process. In one autopsy study lymphocytic infiltrates have been found in 43 percent of apparently normal pituitaries from people who died of unrelated causes [14]. These infiltrates were most frequently found in the pars intermedia, occasionally in the posterior pituitary, but not in the anterior pituitary. In contrast, lymphoid adenohypophysitis appears to involve only the anterior pituitary. The different embryologic origin and vascular supplies of the anterior and posterior pituitary may allow for selective involvement by a variety of pathophysiologic mechanisms.

Other infiltrative diseases of the anterior pituitary, such as syphilis, granulomatous hypophysitis [15] and sarcoidosis [16], were excluded by the absence of granulomas. Lymphoma was excluded by the presence of lymphoid follicles with germinal centers.

Lymphocytic infiltration of other organs has been described in three cases [8,9,11]. Hashimoto's thyroiditis was present in two patients, one of whom also had pernicious anemia [8,9]. A single parathyroid gland was involved in another patient [11]. A few cases of atrophy of the pituitary gland have been reported with a lymphocytic infiltrate of the pituitary [17]. Although provocative tests were not carried out, clinical pituitary dysfunction was not present in these cases. Our patient demonstrated no evidence of other endocrine gland involvement as determined by circulating antibodies or functional response to trophic hormones. The brief follow-up thus far, however, does not exclude a polyglandular failure syndrome since sequential involvement of glands may be separated by years.

The etiology of lymphoid adenohypophysitis is unknown. There is some evidence for an autoimmune cause. Levine [18] has induced an experimental adenohypophysitis in rats by injecting autologous pituitary tissue with an immunological adjuvant. The severity of
the inflammation was greater in postpartum rats. In human studies pituitary autoantibodies have been demonstrated in 18 percent of women at the fifth to seventh postpartum day [19]. Of those women in whom antibodies were maintained for six to twelve months after delivery, signs of anterior pituitary deficiency developed in 25 percent compared to only 4 percent of those without antibodies. Our patient had circulating autoantibodies to normal pituitary tissue although immunoglobulin was not found on the pituitary cells by immunoperoxidase staining. The pathologic significance of these antibodies is unknown; whether they serve only as markers of disease and are not themselves causative is uncertain. Volpé [20] has suggested that autoimmune endocrine disorders represent an abnormal immune system reacting with normal glandular tissue rather than altered tissue antigens.

Certain HLA types have been associated with autoimmune endocrine disorders. Our patient possessed a BW35 antigen which has been detected in an increased frequency in Grave’s disease among Japanese patients [21]. The other HLA antigens found in our patient have not, to our knowledge, previously been associated with any endocrine syndromes.

Three of six patients presented with evidence of hypopituitarism within one year of childbirth. The onset of the inflammatory process may well have begun much earlier, suggesting that pregnancy may be a factor in the initiation of hypophysitis. Whether pregnancy is associated because of an alteration in immunologic status or an increase in pituitary size and vascularity allowing the release of pituitary antigens into the circulation is speculative.

Many questions about this disease remain unanswered. Although we would not have made the diagnosis without surgery, it is uncertain that the patient needed surgery. The inflammatory process may have resolved with hormonal replacement alone. The relatively rapid development of hypopituitarism in our patient and in the previous cases is not typical of the chronic dwindling course of most patients with pituitary tumors. This rapid course may be a diagnostic clue to distinguishing hypophysitis from other causes of pituitary failure with an enlarged sella. It seems likely that the popularity of transsphenoidal pituitary surgery may result in more recognized cases of this entity, so that the true incidence of this disease becomes established. Lymphoid adenohypophysitis should be considered in patients who present with pituitary insufficiency without evidence of a hyperfunctioning pituitary tumor.

REFERENCES