Lymphocytic adenohypophysitis causing pituitary mass

Robert H. Meichner, MD; Silvana Riggio, MD; Herbert J. Manz, MD; and Jerry M. Earll, MD

Lymphocytic adenohypophysitis of the pituitary gland should be included in the differential diagnosis when a pituitary tumor is suspected in association with pregnancy. Seventeen cases of lymphocytic hypophysitis have been described since 1962,1-16 and we now add another case.

Case report. A 24-year-old woman developed headaches, diplopia, and blurred vision in the seventh month of pregnancy. The headaches increased in severity after delivery of a normal child. She was able to nurse for 2 weeks, but discontinued voluntarily. Past history was unremarkable. The only abnormality on physical examination was a right temporal superficial visual field defect. Visual acuity was normal. Normal laboratory data included electrolytes, serum prolactin, and thyroid function studies. Skull films revealed blurred margins of the cortical sphenoid sellae, and contrast CT showed a 2-cm homogeneously enhancing intrasellar mass extending superiorly and to the right. The tumor mass extended to the region of the optic chiasm, and right carotid arteriography revealed that the suprasellar portion of the internal carotid artery was displaced superiorly and anteriorly. There was no evidence of an abnormal vascular blush, abnormal tumor vessels, or early draining veins.

The patient was begun on dexamethasone (4 mg orally every 6 hours), which resulted in marked improvement in her headaches. A subfrontal craniotomy was performed and the vascular structures were found intact, but a bulge of the dorum sellae placed pressure on the right optic nerve. Biopsy demonstrated anterior pituitary tissue with marked focal infiltration by lymphocytes and accompanying fibrosis. Some of the lymphocytes were noted to be in a folliculare-type pattern (figure 1). PAS-orange G and reticulin stains showed many clusters of acidophils and chromophobes, as well as abnormal fibrosis and reticulin. Immunocytochemical studies for ACTH, prolactin, and TSH were negative for the latter two, but showed a positive reaction in small numbers of cells for ACTH (figure 2). Immunoperoxidase studies were performed on paraffin sections. Both kappa and lambda phenotypes were noted, with the majority of plasma cells present expressing kappa chains. IgM, IgG, and IgA heavy chain markers were also noted, with a preponderance of IgG heavy chains consistent with a nonspecific inflammatory reaction. Because of the lack of fresh tissue, T-cell studies were not done.

Postoperatively, the patient developed diabetes insipidus, and therapy with desmopressin acetate (DDAVP) was begun with good results. Repeat visual fields were normal. Angiotensin-converting enzyme was 15 IU/l (normal, 10 to 30 IU/l). VDRL and FTA tests were negative, and qualitative and quantitative immunoglobulins were normal. Hepatitis B sur-
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Figure 1. Only small lobules of adenohypophyseal cells persist in a connective tissue stroma sprinkled with chronic inflammatory cells—the latter are aggregated in larger sheets in the right lower corner (H-E; X100).

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Angiotensin

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Figure 2. Immunocytochemistry depicts occasional adenohypophyseal cells containing fine granules of reaction product for ACTH (arrowheads). Peroxidase-antiperoxidase reaction to ACTH, X250.

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Angiotensin

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face antigen, fluorescent antinuclear antibodies, and extract-

able nuclear antibody were negative. Thyroid

mitochondrial and antiparietal cell antibodies were negative.

Smooth muscle antibodies were positive, and ESR was 9

mm/hr prior to dexamethasone administration. HLA typing

revealed A28, A30, B7, DR2, and DR7. PPD skin test was

negative.

An LH/FSH test produced a normal response over 2 hours.

A thyrotropin-releasing hormone stimulation test was done

measuring TSH, prolactin, and growth hormone. There was

paradoxical response of the growth hormone, which re-

mained less than 1 ng/ml, and the TSH doubled from 5.8 to

12.1 μU/ml in 45 minutes (normal, 15 to 30 μU/ml). The

prolactin response was very brisk, reaching 80 ng/ml in 30

minutes. A 1-hour ACTH test was done with injection of 0.25

mg of cosyntropin IM with baseline and 1-hour cortisol showing

a rise from 2 to 33 μg/dl (normal = 2 X baseline). An

insulin tolerance test that dropped the blood sugar to 10 mg/dl

in 15 minutes revealed a subnormal response of serum cortisol;

growth hormone rose from less than 1 to a peak of 6 ng/ml, and

prolactin remained remarkably constant.

Discussion. All 18 cases of lymphocytic hypophysitis were women, ranging in age from 22 to 74 years (table). Thirty-seven percent had preexisting endocrine disorders, and 22% were associated with autoimmune phe-

nomena. All presented within 1 year postpartum except two, whose ages were 59 and 74, and one who was nulliparous.244 Both menopausal patients were diagnosed at autopsy.2 "Antipituitary" antibodies were reported in one patient.9

Simonds and Brandes17 made serial sections of pituitary glands from autopsies of 200 people with no clinical disorders of the gland: 21 showed areas of lymphocytic infiltration. Gleason et al7 used the term "lymphocytic hypophysitis" if there were epithelioid granulomas and multinucleated giant cells; however, there may be purely lymphocytic infiltration early with a granulomatous component later, in the same disease.6

The first case described antemortem was thought to be pseudotumor cerebri, with a normal CT.9 Abnormal skull radiographs led to biopsy of the pituitary. In another case, electromicroscopy showed activated lymphocytes interdigitating with secretory cells.10 Some pituitary cells exhibited large lysosomal bodies fusing with secretory granules.

An autoimmune disorder was first proposed by Goudie and Pinkerton.1 Levine45 injected pituitary tissue into rats; 13 to 20 days later, there were infiltrates in the anterior pituitary, but not in the adrenals, pan-

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Table. Summary of lymphocytic adenohypophysitis cases

<table>
<thead>
<tr>
<th>Yr</th>
<th>Author</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>1962</td>
<td>Goudie and Pinkerton</td>
<td>22</td>
<td>F</td>
<td>14 mo pp, thyroiditis, nec Dx</td>
</tr>
<tr>
<td>1967</td>
<td>Hume and Roberts</td>
<td>74</td>
<td>F</td>
<td>Gr 0, hypopituitary, pernicious anemia, nec Dx</td>
</tr>
<tr>
<td>1969</td>
<td>Egloff, et al</td>
<td>29</td>
<td>F</td>
<td>1 mo pp, amenorrhea, nec Dx</td>
</tr>
<tr>
<td>1969</td>
<td>Kier and Norgaard</td>
<td>74</td>
<td>F</td>
<td>Gr 1, para 1, nec Dx</td>
</tr>
<tr>
<td>1975</td>
<td>Lack</td>
<td>42</td>
<td>F</td>
<td>Gr 2, para 0, Ab 2, nec Dx</td>
</tr>
<tr>
<td>1978</td>
<td>Gleason, et al</td>
<td>59</td>
<td>F</td>
<td>5 yrs postmenopausal, nec Dx</td>
</tr>
<tr>
<td>1980</td>
<td>Richtsmeier, et al</td>
<td>31</td>
<td>F</td>
<td>Gr 3, para 2, 2 wks pp, thyroiditis</td>
</tr>
<tr>
<td>1980</td>
<td>Quencer</td>
<td>25</td>
<td>F</td>
<td>5 mo pp, amenorrhea, CT +, galactorrhea, Bx</td>
</tr>
<tr>
<td>1980</td>
<td>Mayfield, et al</td>
<td>20</td>
<td>F</td>
<td>Gr 2, para 2, 7 mo pp, CT +, Bx</td>
</tr>
<tr>
<td>1981</td>
<td>Asa, et al</td>
<td>28</td>
<td>F</td>
<td>Gr 3, para 3, 6 mo pp, vision decreased, Bx</td>
</tr>
<tr>
<td>1981</td>
<td>Portocarrero, et al</td>
<td>29</td>
<td>F</td>
<td>6 mo pp, amenorrhea, CT +, Bx</td>
</tr>
<tr>
<td>1981</td>
<td>Cebelin, et al</td>
<td>25</td>
<td>F</td>
<td>5 mo pp, amenorrhea, prolactin up, CT +</td>
</tr>
<tr>
<td>1982</td>
<td>Hungerford, et al</td>
<td>22</td>
<td>F</td>
<td>Gr 3, para 2, 1, 14 mo pp, galactorrhea, nec Dx</td>
</tr>
<tr>
<td>1982</td>
<td>Baskin, et al</td>
<td>27</td>
<td>F</td>
<td>Gr 3, para 2, Ab 1, 8 mo pp, CT +, Bx</td>
</tr>
<tr>
<td>1983</td>
<td>Mazzone, et al</td>
<td>33</td>
<td>F</td>
<td>8 mo pp, vision decreased, CT +, Bx</td>
</tr>
<tr>
<td>1984</td>
<td>Ludmerer and Kissane</td>
<td>37</td>
<td>F</td>
<td>6 mo pp, amenorrhea, CT +, Bx</td>
</tr>
<tr>
<td>1986</td>
<td>Present case</td>
<td>32</td>
<td>F</td>
<td>Gr 1, Ab 1, low thyroid, FSH &amp; LDH, Bx</td>
</tr>
</tbody>
</table>


creas, or thyroid. Conversely, in rats immunized with other tissues, there were no pituitary lesions. Engelberth et al found serum autoantibodies to anterior pituitary tissue in 18% of randomly sampled postpartum women. Failure of lactation, amenorrhea, weight loss, and decreased libido were found in 25% of the women with antibodies and in only 4% of postpartum women with no antibodies. Bottazzo et al found anti-prolactin antibodies in 19 of 287 patients with autoimmune disorders. None had hypopituitary symptoms, and pituitary antibodies have little predictive value for overt pituitary disease.

There is considerable evidence to suggest that organ-specific autoimmune endocrinopathies represent primary dysfunctions in immune surveillance. It had been proposed that the fetus may modulate maternal antifetal suppressor cells in order to escape immunologic rejection by the mother. Oeding and Oldstone showed that cord blood lymphocytes inhibited proliferation of maternal lymphocytes, and further marker studies showed these to be suppressor T cells. Froelich et al showed that fetal suppressor cells inhibit both T- and B-cell function of adult lymphocytes.

The lack of specific immunoglobulins in this patient's pituitary is compatible with lymphocytic hypophysitis being governed by a type II (cytotoxic)- or type IV (delayed hypersensitivity)-mediated cell response. It is possible that, once the fetus-induced immune suppression in the mother is removed, the intrinsic disease process, which is perhaps induced by the allografted fetus, proceeds to flare. The predictive value of HLA status in lymphocytic hypophysitis is uncertain, though two of three patients typed in the literature were positive for HLA-B35, and our patient had a DR2 component seen with cytotoxic diseases such as Goodpasture's syndrome and optic neuritis. Until further characteristics or markers are defined, pituitary biopsy is currently necessary, and surgical decompression can be performed at the same time. Early treatment with immune suppressants aimed at T-cell function to prevent eventual endocrine failure may prove useful, once the diagnosis is made, although there is not yet sufficient experience with this regimen.

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References

Alzheimer’s disease: Low cerebral somatostatin levels correlate with impaired cognitive function and cortical metabolism

The most consistent biochemical abnormality found in Alzheimer’s disease involves the acetylcholine and somatostatin-containing neuronal systems. Much is now known about the loss of cholinergic projections from nucleus basalis to cerebral cortex, associated with widespread reduction in cortical choline acetyltransferase (CAT) activity and acetylcholine synthesis. The decrease in CAT activity may correlate with histologic abnormality, cognitive impairment. However, cholinomimetic therapies have had disappointing results, suggesting the cholinergic deficit alone may not be the critical determinant of Alzheimer dementia.

The other biochemical abnormality found consistently in Alzheimer’s disease is low cortical somatostatin content. Little is known about the relationship of this change to either the histologic features or the symptoms of the dementia. Therefore, in Alzheimer patients, we compared somatostatin levels in CSF, intellectual performance, and cerebral metabolism as studied by positron emission tomography (PET) following 5-fluoro-2-deoxyglucose (FDG).

Moreover, in postmortem Alzheimer brain, we compared somatostatin levels and CAT activity in different cortical areas.

Methods. Twenty-four Alzheimer patients (12 men, 12 women; mean ± SEM, age 60 ± 1.5 years) and matched normal control subjects (15 men, 9 women; 59 ± 2.5 years) participated in the CSF study. Alzheimer’s disease was diagnosed by a history of gradually progressive intellectual deterioration without focal motor or sensory signs or other causes of dementia. EEG recordings were generally free of localized abnormality, and CT revealed generalized cerebral atrophy. Dementia symptoms had been present for 1 to 5 years and ranged from mild to moderately severe (Wechsler Adult Intelligence Scale [WAIS] Full Scale IQ from 123 to 64; Wechsler Memory Scale [WMS] from 106 to 58). No subjects received any centrally active drugs for the month preceding the study. CSF was sampled by lumbar puncture at 9 AM from the L3-4 interspace; individuals were fasting and had bed rest overnight. Thirteen successive 1-ml samples were collected, put on ice, then pooled, mixed, realiquoted into 1-ml samples, and frozen at –70 °C for subsequent analysis. Somatostatin values in the Alzheimer and control groups were compared by the Student’s t statistic.

Seventeen Alzheimer patients and 6 of the normal controls had neuropsychological testing and PET scans. The psychometric battery included the Mattis Dementia Scale, WAIS, WMS, Boston Diagnostic Aphasia Examination, and the Rey-Osterreith Complex Figure Test. Test results were compared with