Lymphocytic Hypophysitis and Pulmonary Sarcoidosis
Report of a Case

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Lymphocytic hypophysitis is one of the causes of hypopituitarism in the postpartum period. Some of these patients have been reported to have other organ-specific autoimmune diseases, and the disease is considered to be autoimmune in nature. The authors describe a unique case of lymphocytic hypophysitis in a young woman. She had hemianopia that developed three days after delivery. Computed tomography scans revealed an intrasellar mass lesion. Secretions of adrenocorticotropic hormone and growth hormone were decreased. Although no organ-specific autoantibodies were detected in her serum, OKT4-positive helper T lymphocytes were increased in peripheral blood. Pituitary biopsy at craniotomy showed typical features of lymphocytic hypophysitis. Pulmonary and eye sarcoidosis developed 11 months after the delivery. This is to the authors' knowledge, the first case of lymphocytic hypophysitis associated with sarcoidosis in other organs. (Key words: Hypophysitis; Sarcoidosis; Hypopituitarism; Hemanopia; Pituitary biopsy) Am J Clin Pathol 1991; 95:506–511

Lymphocytic hypophysitis is a rare disease that is histologically characterized by lymphocytic infiltration in the adenohypophysis. Most cases have been diagnosed as a result of hypopituitarism during pregnancy or in the postpartum period. The radiographic feature of the disease is a space-occupying sellar lesion. This article documents clinicopathologic and immunologic findings of a patient with a unique association of lymphocytic hypophysitis with lung and eye sarcoidosis.

REPORT OF A CASE

A 23-year-old woman was referred to our hospital for evaluation of possible hypopituitarism in August 1986. The patient, who was gravida 1, para 1, had delivered a male baby uneventfully in June 1986. She had complained of left temporal hemianopia, general fatigue, mild fever, and headache that developed three days after the delivery. Physical examination disclosed an apathetic young woman with muscle weakness. Her height was 146.5 cm, weight 40 kg, blood pressure 96–54 mmHg, pulse rate 78 beats per minute, and temperature 36.0 °C. Neurologic examination revealed no abnormalities except hemianopia. Although fever and headache subsided in three days, hemianopia and fatigue persisted. Computed tomographic (CT) scans showed a rounded, contrast-enhancing sellar mass (Fig. 1). She was admitted to our hospital for additional examination.
The serum levels of sodium, potassium, chloride, blood urea nitrogen, creatinine, uric acid, glucose, transaminases, and bilirubin were normal. Endocrineologic studies disclosed secondary adrenal insufficiency. Daily excretion levels of 17-hydroxy cortisol (OHCS) and 17-ketosteroids (KS) were 3.6 μmol and 2.1 μmol, respectively. The level of plasma adrenocorticotropic hormone (ACTH) was less than 2.2 pmol/L. The level of serum T₄ was 6.8 nmol/L (normal, 82-142 nmol/L), T₃, 1.9 nmol/L (normal, 1.6-3.2 nmol/L), and thyroid-stimulating hormone (TSH) 1.7 mU/L (normal, 1.2-3.2 mU/L). Responses of prolactin (PRL), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) to a combined injection of thyrotropin-releasing hormone (TRH) and lutetinizing hormone-releasing hormone (LHRH) were within normal limits (Table 1). IgA, IgM, and IgG levels were 2.06 g/L, 3.71 g/L, and 10.44 g/L, respectively. Surface antigens studies on peripheral lymphocytes showed 84.3% of OKT11, 61.2% of OKT4, 21.3% of OKT8, and 6.8% of CD45RO positive T lymphocytes, especially OKT4-positive helper T lymphocytes, were significantly increased, indicating the activation of immune responses.

Although hemianopia spontaneously disappeared in 20 days, the sellar mass did not decrease in size. She underwent a left temporal craniotomy on September 5. An encapsulated and rather hard mass of 1.5 cm in diameter was observed between the optic nerves. Approximately half of the mass was removed; histologic study of the specimen established a diagnosis of lymphocytic hypophysitis during the operation. All of the resected specimen was histologically identified as adenohypophysial tissue (Fig. 2). The infiltrate consisted mainly of lymphocytes, accompanied by plasma cells. Parenchymal cells were scanty, and some necrotic foci were observed. Neither granulomas nor giant cells could be seen in any sections (Figs. 3 and 4).

The patient had an uneventful recovery after the surgical exploration. She required no medication until May 1987, when she noticed weight loss and lassitude. She was hospitalized again for close examination. Her visual fields and ocular movements were normal. Anti-thyroglobulin and antithyroid microsomal antibodies, TSH receptor antibodies, antidiuretic cell antibodies, and antipituitary cell (mouse origin AtT-20 and rat origin growth hormone [GH] cell) antibodies were negative. HLA phenotypes

Fig. 1 (upper, left). Computed tomography (CT) before operation shows a round homogeneously contrast-enhancing intrasellar mass of 17 × 17 mm in size.

Fig. 2 (lower, left). Anterior pituitary biopsy specimen showing massive diffuse mononuclear cell infiltrate and interstitial fibrosis on low-power view. Hematoxylin and eosin (×33).

Fig. 3 (upper, right). Adenohypophysial tissue with interstitial mononuclear cell infiltration. The infiltrate consists mainly of lymphocytes. Hematoxylin and eosin (×165).
TABLE 1. RESPONSES OF TSH, PRL, LH, AND FSH TO A COMBINED INJECTION OF TRH (500 μg) AND LH-RH (100 μg)

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
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<tbody>
<tr>
<td>TSH (mU/L)</td>
<td>1.7</td>
<td>4.6</td>
<td>6.6</td>
<td>7.1</td>
<td>6.5</td>
<td>6.0</td>
</tr>
<tr>
<td>PRL (μg/L)</td>
<td>3.9</td>
<td>28</td>
<td>51</td>
<td>48</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>LH (IU/L)</td>
<td>9.5</td>
<td>14</td>
<td>18</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>13</td>
<td>15</td>
<td>18</td>
<td>21</td>
<td>21</td>
<td>26</td>
</tr>
</tbody>
</table>

TABLE 2. INSULIN TOLERANCE TEST (0.06 U/kg, IV)

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>0</th>
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<th>30</th>
<th>45</th>
<th>60</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.2</td>
<td>2.2</td>
<td>1.9</td>
<td>2.0</td>
<td>2.3</td>
<td>2.2</td>
</tr>
<tr>
<td>ACTH (pmol/L)</td>
<td>&lt;2.2</td>
<td>&lt;2.2</td>
<td>2.3</td>
<td>&lt;2.2</td>
<td>&lt;2.2</td>
<td>&lt;2.2</td>
</tr>
<tr>
<td>Cortisol (nmol/L)</td>
<td>11.0</td>
<td>5.5</td>
<td>13.8</td>
<td>16.6</td>
<td>13.8</td>
<td>13.8</td>
</tr>
<tr>
<td>GH (μg/L)</td>
<td>1.6</td>
<td>1.1</td>
<td>1.7</td>
<td>1.8</td>
<td>1.8</td>
<td>2.2</td>
</tr>
</tbody>
</table>

were A 2, BW 56, CW 1/7, and DR 4. Endocrinologic examinations showed mild hypothyroidism and significant adrenal insufficiency. Serum T4, T3, and TSH levels were 37.3 nmol/L, 0.95 nmol/L, and 5.9 mU/L, respectively. Daily excretion levels of 17-OHCS and 17-KS were 25 μmol and 7.3 μmol, respectively. An insulin tolerance test, in which plasma glucose levels decreased from 4.2 to 1.9 mmol/L, showed impaired responses of ACTH, GH, and cortisol (Table 2). Combined intravenous administration of corticotropin-releasing hormone (CRH) (75 μg) and lysine vasopresin (25 μg) failed to stimulate ACTH secretion; plasma ACTH levels remained less than 2.2 pmol/L throughout the study, however, intramuscular administration of cortrosyn Z for four days increased urine 17-OHCS levels to 53 μmol/day, showing normally responsive adrenal glands. GH responded to 100 μg of growth hormone-releasing hormone (GRH) to the peak level of 11 μg/L, which was slightly low than normal values. Fourteen-hour water deprivation resulted in an elevation of urine osmolality to 801 mmol/kg, indicating normal posterior pituitary function.

A chest radiograph showed no abnormalities in September 1988. However, bilateral diffuse reticular shadows were demonstrated in May 1989. CT scan revealed fine granular shadows in all pulmonary fields. High uptake of Ga-citrate was shown in both lungs. The serum angiotensin-converting enzyme (ACE) level was 723 nkat/L (normal, 117-417 nkat/L). Serum lysozyme levels were also elevated to 18.0 mg/L (normal, 5.0-10.0 mg/L). Surface markers of peripheral lymphocytes were 69.2% of OKT1, 46.0% of OKT4, 19.6% of OKT8, and 23.2% of slg. OKT4-positive helper T cells were decreased when compared with

![Fig. 4 (left). Small clusters of residual adenohypophyseal cells surrounded by numerous lymphocytes. Hematoxylin and eosin (×660).](image1)

![Fig. 5 (right). Transbronchial lung biopsy specimen showing noncaseating epithelioid granuloma tissue with multinucleated giant cells. Hematoxylin and eosin (×165).](image2)
the data in August 1986. Histologic studies on lung tissue obtained by transbronchial biopsy showed numerous noncaseating epithelioid granulomas with multinucleated giant cells that were consistent with sarcoidosis (Fig. 5). Ocular sarcoid lesions (i.e., nodules on both irides and opacities of both vitreous bodies) were also present.

She had received hydrocortisone at a dose of 10 mg/day from June to compensate for ACTH deficiency. This therapy was continued until July 15, when 15 mg of prednisolone was started for treatment of the sarcoidosis. Serum ACE levels decreased to the normal range in two weeks. Two months after the start of prednisolone therapy, when the lung shadows decreased greatly and sarcoid lesions of both eyes resolved, the dose of prednisolone was reduced to 10 mg/day and maintained thereafter. Pituitary reserve tests performed in October 1987 showed normal secretion of TSH, prolactin, LH, and FSH and low GH response to GRH. Thyroid hormone levels gradually increased to normal ranges during glucocorticoid administration. In January 1988, serum levels of T₄ and T₃ were 95 nmol/L and 1.6 nmol/L, respectively. Her menstrual cycle resumed in March 1988.

**DISCUSSION**

Lymphocytic hypophysitis is a rare disease usually presenting with panhypopituitarism. Since the initial report by Goudie and Pinkerton, 15 15 cases have been reported so far in the literature on the basis of histologic findings (Table 3). All of the patients except one were women,
and in 25 cases the onset of symptoms was related to pregnancy.\textsuperscript{1–12} Either during gestation or up to 16 months after delivery.\textsuperscript{3,13–21} Ten cases were identified at autopsy.\textsuperscript{13–16,20,21,26–29} Symptoms included amenorrhea, nausea, weakness, headache, and visual disturbance.

In some patients with lymphocytic hypophysitis, other endocrine organs were also infiltrated with lymphocytes. Chronic thyroiditis was reported in six patients.\textsuperscript{15,16,20,21,26,28} Five of whom also had adrenal atrophy or adenitis.\textsuperscript{15,16,20,21,28} Pernicious anemia was present in two of the patients\textsuperscript{8,28} and parathyroiditis in one.\textsuperscript{29} Circulating autoantibodies, including antipituitary cell antibodies, were detected in sera from some patients with lymphocytic hypophysitis.\textsuperscript{1,8,11,17,22,25} These findings indicate that lymphocytic hypophysitis is an autoimmune disease. The prevalence of hypophysitis during pregnancy and the puerperal period, when the immune mechanism is disturbed, supports the autoimmune pathogenesis of the disease. The histologic findings of pituitary tissue from this patient agree with those of reported cases with lymphocytic hypophysitis. Diffuse lymphocytic infiltration was observed, whereas giant cells and granulomas were absent. It is clearly different from the lesions of sarcoidosis.

This woman is, to our knowledge, the first patient with lymphocytic hypophysitis associated with sarcoidosis. There are two possible explanations for this combination. First, hypocortisolemia resulting from ACTH deficiency might be associated with the onset of sarcoidosis. The efficacy of glucocorticoid treatment on sarcoidosis suggests the possibility that adrenal insufficiency may play a role in the development of this condition. When patients with sarcoidosis become pregnant, sarcoid lesions may be ameliorated and they may recur in the postpartum period.\textsuperscript{30} This variation is assumed to result from fluctuations in corticosteroid levels. Therefore, postpartum endocrine changes, together with ACTH deficiency, may have been associated with the onset of sarcoidosis in this patient. Second, hypophysitis and sarcoidosis may have common etiologic factors. Although the pathogenesis of sarcoidosis is still a matter of controversy, altered helper T-cell responses appear to lead to sarcoid granuloma formation.\textsuperscript{31,32} Thus, abnormal immune processes may be involved in the development of both disorders. Although no antibodies to thyroid antigens were detected, serum thyroid hormone levels were reduced and TSH levels were slightly elevated. Thyroid function gradually improved during glucocorticoid therapy. The apparent hypothyroidism may have resulted from malnutrition. However, one might also speculate that the prednisolone treatment suppressed autoimmune reactions to thyrocytes.

This unique case shows that lymphocytic hypophysitis cannot be excluded without pituitary biopsy, even in patients with sarcoid lesions in other organs, although sarcoidosis is a more common disease in the sellar area. Radiographic studies, including CT scan, cannot clearly distinguish between pituitary sarcoidosis and lymphocytic hypophysitis. Clinically, normal posterior pituitary function indicates that sarcoidosis is unlikely, and the elevated ratio of T-lymphocytes may be associated with autoimmune mechanisms to adenohypophysyal cells. A definite diagnosis of lymphocytic hypophysitis depends on the histologic features of the pituitary tissue in such cases.

REFERENCES

Intraspinal Neurothekeoma (nerve sheath myxoma)

A Report of Two Cases

WERNER PAULUS, M.D., KURT JELLINGER, M.D., AND GEDEON PERNECZKY, M.D.

Neurothekeomas (nerve sheath myxomas) are rare benign cutaneous tumors. The authors describe two spinal intradural cases that show histologic, immunohistochemical, and electron microscopic features identical to their cutaneous counterparts. The authors' findings suggest histogenesis from Schwann's cells or undifferentiated nerve sheath precursor cells. Neurothekeomas in unusual locations should be differentiated from myxoid neurofibromas, perineuriomas, and soft tissue myxomas. (Key words: Neurothekeoma; Nerve sheath myxoma; Nerve sheath tumors; Electron microscopy; Immunohistochemistry) Am J Clin Pathol 1991;95:511–516

Nerve sheath myxoma was first described by Harkin and Reed as a rare benign cutaneous tumor most often involving the face and arms of young adults. Since then, a large number of cases have been reported under a variety of names, such as neurothekeoma, pacinian neurofibroma, myxomatous perineuroma, bizarre cutaneous neurofibroma, plexiform myxoma, cutaneous lobular neuromyxoma, and perineural myxoma. Nerve sheath myxoma and neurothekeoma are the currently used designations. Rare locations of neurothekeoma include the oral cavity, tongue, and breast. An intraspinal location, described here in two cases, has not been reported previously.