the rash persisted over a three-month period, wherein she was treated with increasing doses of prednisone, 20 to 40 mg orally daily, and vincristine sulfate, 5 to 9 mg intravenously every two weeks for six doses. The submandibular glands diminished significantly from 6x3 cm and 4x3 cm to 2x2 cm and 3x2 cm after six monthly cycles of cyclophosphamide (Cytoxan), 900 mg; vincristine sulfate, 1.0 mg; and prednisone, 100 mg orally for five days. She subsequently returned to Syria and was lost to follow-up.

**Comment**

Since Lichtenstein et al. postulated in 1953 that Hand-Schüller-Christian disease, Letterer-Siwe disease, and eosinophilic granuloma of bone represent different manifestations of a single nosologic entity, which he termed histiocytosis X, it has become apparent that this disease can involve any organ system. Many permutations of bony disease, visceral disease, and soft-tissue involvement have been reported, with single or multiple osseous lesions typifying the adult form. Visceral disease, including liver, spleen, lung, or lymph nodes, implies a worse prognosis in adults. The appearance of typical histiocytes in the pericardial effusion probably represents sloughing from the infiltrated pericardium. Recently, Guardia et al. reported two cases of histiocytosis X with pleural involvement and resulting pleural effusion. These three cases demonstrate that histiocytosis X can present with infiltration of mesothelial structures. Cardiac disease in any form seems rare.

**References**


---

**Lymphoid Hypophysitis**

An Unusual Cause of Hyperprolactinemia and Enlarged Sella Turcica

Carlos J. Portocarrero, MD; Alan G. Robinson, MD; Andrew L. Taylor, MD; Irwin Klein, MD

LYMPHOID hypophysitis is an inflammatory process characterized by the presence of isolated lymphoid follicles and diffuse lymphocytic infiltration of the anterior pituitary. The entity has been reported as an autopsy finding in six cases and as an antemortem diagnosis in one previous patient. The following article describes a woman who underwent transphenoidal pituitary exploration for a suspected prolactin-producing pituitary tumor. Routine histological examination of the surgical specimen, there were the characteristic inflammatory changes of lymphoid hypophysitis without evidence of a tumor. This article documents the occurrence of elevated prolactin and enlargement of the sella turcica owing to lymphocytic infiltration of the adenohypophysis.

**Report of a Case**

A 25-year-old woman was admitted for evaluation of persistent throbbing headaches that had persisted for six months. Five months before, she had a normal vaginal delivery of her fifth child and since that time had persistent galactorrhea and amenorrhea, despite a lack of breast feeding. She had no other symptoms of endocrine dysfunction and was taking no medications. Her height was 163 cm, weight, 84 kg; blood pressure, 110/70 mm Hg; and pulse rate, 80 beats per minute. A white fluid was easily expressed from both nipples. The remainder of the examination findings, including the size and consistency of the thyroid gland, were within normal limits. A complete blood cell count and an ESR were normal, as were the serum electrolyte, calcium, and phosphorus levels. Visual fields by Goldmann perimetry were normal. The sella turcica was symmetrically enlarged on polytomography without erosion of bone, measuring approximately 2,000 cu mm. Coronal and axial computed tomography of the brain showed diffuse enhancement of the pituitary gland without evidence of suprasellar extension.

Because of headaches, abnormal radiological findings, and an elevated serum prolactin level (Table), a presumptive diagnosis of pituitary tumor was made, and, four weeks later, she underwent transphenoidal exploration. Additional preoperative endocrine evaluation included a morning cortisol level of 8 μg/dl, a luteinizing hormone level of 14 mIU/ml, and a follicle-stimulating hormone level of 10.5 mIU/ml. All were within normal limits. No dynamic endocrine testing was performed before surgery. At surgery, no discrete tumor was found, but the gland was abnormally dark. A frozen-section biopsy specimen could not rule out a pituitary adenoma, and approximately 35% of the adenohypophysis was resected. On the permanent sections, there was extensive stromal fibrosis and chronic, inflammatory cell infiltrate with well-differentiated lymphocytes and focal, germinal, center-like lymphoid follicles. Fi-
Lymphoid Hypophysitis—Portocarrero et al

Section of anterior pituitary lobe obtained at surgery showing marked lymphocytic infiltrate forming germinal center-like lymphoid follicle (hematoxylin-eosin, ×120).

brosis and inflammation divided the pituitary into small clusters of eosinophilic and noneosinophilic cells (Figure). A small fragment of neurohypophysis was free of inflammatory changes. The pathological condition was identical to previously reported cases of lymphoid hypophysitis. No edema was seen, and there was no granulomatous inflammation or multinucleated cells. On the 11th postoperative day, the patient had a normal prolactin level (Table).

Four months after surgery, her amenorrhea and galactorrhea persisted. Her prolactin level was again elevated (Table) and rose to 61 ng/mL after administration of protirelin (thyrotropin-releasing hormone) (TRH). An 8 AM cortisol level was 12.7 µg/dL, and metyrapone test results were normal. A panel of organ-specific antibodies, including thyroglobulin, thyroid microsomal, and adrenal antibodies, was negative. Eight months later, she had had two menstrual periods and her galactorrhea had diminished to a trivial amount. The prolactin level was 22.5 ng/mL and rose to 88 ng/mL with protirelin stimulation.

Comment

In our search of the literature, lymphoid hypophysitis has been reported as an antemortem diagnosis only once before. In that case, and in ours, the patient had clinical, laboratory, and radiological findings of an expanding intraellar mass that prompted pituitary exploration. At transphenoidal surgery, characteristic inflammatory changes of the anterior pituitary were demonstrated. All of the previously reported cases have had evidence of hypofunction of the anterior pituitary with fulminating signs and symptoms of pituitary insufficiency. Six of seven patients had adrenocorticotropic hormone deficiency. In contrast, the present case had hyperfunction with elevated levels of prolactin. It is unlikely that the elevated serum prolactin level was related to her pregnancy five months earlier, since prolactin is in the normal range two to three months postpartum.

Three possible explanations for the hyperprolactinemia are (1) a distortion of the hypothalamic-pituitary venous channels by an enlarged, inflamed gland, resulting in decreased delivery of prolactin inhibitory factor to the adenohypophysis; (2) a direct effect of the inflammatory process on the prolactin-producing cells either to stimulate directly prolactin secretion or to interfere with the normal interaction of prolactin inhibitory factor and its cellular receptor; and (3) the presence of a prolactin-stimulating antibody, arising as a consequence of the inflammatory process. In the postmortem evaluation reported by Richtsmeier et al, hyperplasia of prolactin-secreting cells, perhaps consistent with the patient’s postpartum status, was observed.

Lymphoid hypophysitis is presumably an autoimmune disease. Prior work has demonstrated an association between pituitary inflammatory infiltrates and the presence in serum of antipituitary antibodies. This disease has a predilection for women in the peripartum period, and five of the eight cases reported have occurred within one year after uncomplicated deliveries. Lymphoid hypophysitis may explain some cases of presumed prolactinoma that go into remission without treatment as well as cases of Sheehan’s syndrome that occur in the absence of major obstetric complications.

This study was supported in part by the National Institutes of Health grants No. 5 T32 AM07052 and No. 5 AM00693, and HRSP grant No. W85. Dr Klein is a research associate of the Veterans Administration.

The authors are grateful to Mitchell S. Parker, MD, and Enrique Davila, MD, for help in evaluation of this case.

References


Preoperative and Postoperative Endocrine Evaluation

<table>
<thead>
<tr>
<th>Test (Normal Range)</th>
<th>Preoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11 Days</td>
<td>4 Mo</td>
</tr>
<tr>
<td>Prolactin (5-25 ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>61.0</td>
<td>30.1</td>
</tr>
<tr>
<td>Stimulated with protirelin</td>
<td>61*</td>
<td>88*</td>
</tr>
<tr>
<td>Thyroxine (4.5-11.6 µg/dL)</td>
<td>9.2</td>
<td>7.1</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (0-10 µU/mL)</td>
<td>4.0</td>
<td>4.0</td>
</tr>
</tbody>
</table>

*Maximum prolactin level after administration of 400 µg of protirelin (thyrotropin-releasing hormone).