Spontaneously Resolving Lymphocytic Hypophysitis as a Cause of Postpartum Diabetes Insipidus

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A previously healthy 34-year-old woman developed diabetes insipidus 5 months after an uncomplicated pregnancy and delivery. MRI showed marked thickening of the pituitary stalk and prominence of the median eminence of the hypothalamus, with a somewhat small anterior pituitary gland. Further endocrine testing documented mild hyperprolactinemia and evidence of Hashimoto’s disease (elevated TSH and an elevated titer of antimicrosomal antibodies). The radiographic abnormalities resolved spontaneously over the next 3 months, leaving a partially empty sella turcica. The prolactin level also normalized, but diabetes insipidus persisted. Although the diagnosis was not biopsy-proven, this case has a number of features that are typical of lymphocytic hypophysitis (which are discussed); however, unlike the typical presentation of lymphocytic hypophysitis (in which anterior pituitary involvement is prominent, usually as a pituitary mass with anterior pituitary hypofunction), this case is unusual in its presentation with diabetes insipidus and in the localization of radiographic abnormalities to the pituitary stalk and hypothalamus. These features expand and further define the spectrum of the clinical presentation of lymphocytic hypophysitis. This patient’s course confirms the recent observations of others that the natural history of this disorder may be that of a self-limiting disease with spontaneous resolution. As a result, the risks associated with confirmation of the diagnosis by biopsy (or surgical resection of involved tissue) are unnecessary and inappropriate if the clinical presentation is consistent with lymphocytic hypophysitis, and if subsequent follow-up demonstrates the anticipated radiographic normalization (as seen here and in other cases). Empty sella syndrome may represent the end stage of lymphocytic hypophysitis in some patients.

lymphocytic hypophysitis is an uncommon endocrine disorder of presumed autoimmune etiology. It usually affects women of childbearing age, with onset of symptoms in late pregnancy or in the early postpartum period. It usually presents as a pituitary mass, frequently with clinical evidence of anterior pituitary hypofunction. The case presented here is atypical in that diabetes insipidus was the first clinical manifestation of the disorder, and the anatomic involvement appeared to be limited to the pituitary stalk and hypothalamus. The anatomic abnormalities resolved spontaneously (which is a common outcome of this disorder, even though neurosurgical intervention is commonly employed), resulting in a partial empty sella (which may be the end stage of the disease).

Case Report

A 34-year-old white female developed acute and severe symptoms of thirst on the day of her daughter’s high school graduation. Her symptoms persisted without improvement after that, in association with increased urination. She estimated her fluid intake at 5 gallons daily, and she had to get up every hour through the night because of the need to urinate, in association with severe thirst. Attempts to limit her fluid intake did not have any noticeable effect on her urine volume. The
patient's prior medical history was notable for the birth of a healthy child 5 months before the onset of her symptoms; the pregnancy and delivery were unremarkable and uncomplicated, with no problems of hypertension, blood loss, or other difficulty. She breastfed the infant and had no problems with lactation. Her menses had not yet resumed at the time of her presentation. She denied any other problems except for occipital headaches (which had subsequently resolved spontaneously), nausea and occasional vomiting, an episodic sensation of "numbness" around her lips and eyes, and a weight gain of 15 pounds over the previous 6 weeks. Her prior evaluation had included normal serum electrolytes, a serum glucose of 77 mg/dL, normal thyroid function tests (T<sub>4</sub> 7.0 µg/dL [normal 4.5-12.5], T<sub>3</sub>RU, 35% [normal 35-45], free T<sub>4</sub> index, 2.4 [normal 1.6-5.6]), and a normal CT scan of the head.

At the time of her endocrinologic evaluation, physical examination was entirely normal. She complained of thirst, and was found to have a serum osmolality of 294 mOsm/L with simultaneous urine osmolality of 79 mOsm/L. Because of other obligations, she requested that completion of her evaluation be deferred to a later time. Until she could return for completion of testing, she was treated with DDAVP, and she had a dramatic and prompt resolution of her polyuria and polydipsia. She returned to the clinic after discontinuing the DDAVP for a day and limiting her fluid intake prior to her appointment. She was found to have a serum osmolality of 312 mOsm/L with corresponding urine osmolality of 137 mOsm/L. Following subcutaneous administration of DDAVP, urine osmolality increased to 326 mOsm/L at 1 hour and 496 mOsm/L at 2 hours. She restarted DDAVP therapy with excellent results. An MRI scan (Fig. 1) showed a somewhat small pituitary gland, but marked thickening of the infundibulum and a prominent or lobular appearance of the median eminence of the hypothalamus. The high-intensity signal normally seen in the posterior pituitary was absent; absence of this "bright spot" is a consistent MRI finding in central diabetes insipidus [1]. Chest X-ray was normal, with no evidence of granulomatous disease, and ACE level was 15 units/L (normal 10-50).

Because of uncertainty regarding the etiology of the infundibular/hypothalamic abnormalities, an MRI was repeated 3 months following the original study. The follow-up MRI (Fig. 2) showed normalization of the previously thickened infundibulum and interim development of a partial empty sella.

The patient remained amenorrheic 12 months following the birth of her child, and continued to have lactation 6 months after she stopped breastfeeding. Prolactin was elevated at 29 ng/mL (normal less than 15). Thyroid studies revealed T<sub>4</sub> of 6.7 µg/dL (normal 5.5-11.5), T<sub>3</sub>RU of 35.5% (normal 35.9-43.5), and TSH of 13.4 units/mL (normal 0.5-4.5). Antimicrosomal antibodies were positive at 1:6400 (normal less than 1:100). She was treated with L-thyroxine 0.05 mg q.d.

Six months later, she reported increased energy levels with an improved sense of well being, and noted spontaneous menstrual periods for the 2 previous

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Figure 1. A, T1-weighted sagittal MR image shows marked enlargement of the pituitary stalk (arrow). The pituitary gland within the sella is small and lacks a "bright spot." B, T1-weighted coronal MR image shows the enlarged stalk (arrow) again.
months, with continued mild galactorrhea. Prolactin was normal at 11 ng/mL and TSH was 5.2 μunits/mL. The L-thyroxine dosage was increased to 0.1 mg q.d.

One year later, she reported normal menstrual periods with minimal galactorrhea, and was found to have a normal prolactin of 12 ng/mL and TSH of 0.9 μunits/mL. Her diabetes insipidus was well-controlled with the DDAVP, although symptoms would recur if she omitted a dose. A repeat MRI was identical to the second MRI performed 2.5 years earlier (Fig. 2), demonstrating a normal infundibulum and partially empty sella.

Five years following her original presentation, she continued to have symptoms of diabetes insipidus effectively controlled with DDAVP, a TSH of 2.4 μunits/mL on her L-thyroxine therapy, and regular menses with a prolactin of 16 ng/mL.

Discussion

Lymphocytic hypophysitis is a relatively “new” endocrine disease, with the first description of the disorder reported in 1962 [2]. The original descriptions were predominantly from autopsy reports: by 1981, 10 cases had been identified, but the diagnosis was made by biopsy before death in only 3 of these cases [3]. With increasing awareness of the disease, 30 cases were identified in the medical literature by 1989 [4], and a total of 45 cases had been reported by 1992 [5], with the diagnosis made by surgical biopsy in most of the recent cases. The disorder has a striking predilection for females, with 87% of reported cases occurring in women [5]; pregnancy seems to play a particularly important role in the presentation of lymphocytic hypophysitis (for reasons that are obscure), with onset of symptoms closely related to recent pregnancy in 82% of the cases involving women [5]. The presentation of the disease is most commonly that of an expanding pituitary mass in a young woman in late pregnancy or in the early postpartum period, frequently in association with partial or complete hypopituitarism [4]. Microscopic evaluation of involved tissue usually demonstrates diffuse lymphocytic infiltration, with occasional plasma cells and eosinophils also observed [4]. Lymphocytic hypophysitis is generally considered to have an autoimmune etiology, based on its association with other endocrine autoimmune disorders such as thyroiditis or adrenalitis in about 30% of autopsy cases [4], the lymphocytic infiltration that is seen microscopically, and the finding of antipituitary antibodies in at least one case [6].

Diabetes insipidus is an unusual manifestation of lymphocytic hypophysitis. Histologically, the inflammatory process involves predominantly the anterior pituitary [5], a finding that correlates well with the endocrinological finding of anterior pituitary dysfunction in the majority of cases [5]. In a review of the first 30 reported cases, it was noted that none of the patients had any clinical features to suggest diabetes insipidus [4]. However, one of the cases was reported to develop “mild diabetes insipidus” 4 months after initiation of thyroid hormone and glucocorticoid replacement for anterior pituitary failure in the setting of a pituitary mass with suprasellar extension, later shown by biopsy to represent lymphocytic hypophysitis [7]. Since then, diabetes insipidus has also been described in a 45-year-old woman who had suprasellar extension of an intrasellar mass, which was found to be lymphocytic hypophysitis following surgical resection [8]. Another report included two patients with diabetes insipidus: a 40-year-old man whose CT scan showed a mildly enlarged pituitary gland with some thickening of the pituitary stalk, and a 34-year-old woman whose MRI scan showed diffuse pituitary enlargement with infundibular thickening and extension of the lesion into the suprasellar cistern; both of these patients also had biopsy-proven lymphocytic hypophysitis [9]. The latter case is similar to the case reported here, with infundibular and suprasellar involvement in both patients; both of these women also had hyperprolactinemia at the time of presentation, with normalization of prolactin levels paralleling the spontaneous clearing of MRI abnormalities of the infundibulum, but with failure of the diabetes insipidus to resolve in either case. In a series of 26 patients with central
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diabetes insipidus [1], none of the 23 for whom a specific etiology could be established had lymphocytic hypophysitis, suggesting that lymphocytic hypophysitis is an unusual cause of diabetes insipidus. However, two of the three patients for whom no cause of diabetes insipidus could be defined were young women (25 and 29 years old), and both had uniform thickening of the pituitary stalk as their only MRI abnormality; it is possible that they also had lymphocytic hypophysitis (obstetric history, endocrine test results, and repeat MRI studies were not reported). More recently, a Japanese study [10] of 17 patients with “idiopathic diabetes insipidus” found MRI abnormalities (thickening of the pituitary stalk and/or enlargement of the neurohypophysis) in 9 of the 17, with biopsy confirmation of lymphocytic infiltration in 2 patients.

The natural history of lymphocytic hypophysitis is unknown: the early cases that were identified at autopsy usually died with features suggesting adrenal insufficiency, and the course of subsequently reported cases is difficult to interpret in light of the surgical intervention (pituitary biopsies, partial pituitary resections, and even total hypophysectomies) that have been employed in most cases in order to establish the diagnosis and deal with the presenting pituitary mass [4]. However, in 1986 (only 2 years after the first report of lymphocytic hypophysitis diagnosed in a living patient [11]), a pituitary mass with suprasellar extension was seen to undergo spontaneous regression within 4.5 months of its discovery in a postpartum 18-year-old woman with probable (but not biopsy-proven) lymphocytic hypophysitis [12]. A 37-year-old woman reported in 1986 was found to have a pituitary mass with suprasellar extension during the 7th month of pregnancy, even though she had no surgical intervention and no specific medical therapy (except for hormone replacement for her secondary hypothyroidism and hypoadrenalism), repeat CT 3 months after delivery demonstrated spontaneous disappearance of the mass [13]. More recently, a similar course has been reported in at least three other young women, all of whom presented with a pituitary mass during the late months of pregnancy, and all of whom had spontaneous regression of the radiographic abnormalities in the postpartum period [14–16]. None of these patients had any type of surgical procedure, and their only medical therapy consisted of replacement hormones for anterior pituitary hypofunction. In addition, a biopsy-proven case of lymphocytic hypophysitis has been described in which the sellar mass (which had been discovered in association with postpartum hypopituitarism) underwent spontaneous resolution, leaving a partially empty sella [5], similar to the findings in the case presented here (Fig. 2). The Japanese experience in patients with diabetes insipidus caused by lymphocytic hypophysitis also confirms the self-limited natural course of the disorder [10].

In conclusion, a case of probable lymphocytic hypophysitis with several notable features is presented here. The diagnosis was not proven by biopsy, but the presentation in the peripartum period with pituitary dysfunction, in association with spontaneously clearing radiographic abnormalities, is very typical for this disorder. Even though the presence of other autoimmune endocrine diseases is far from a uniform feature of lymphocytic hypophysitis [5], the finding of features of Hashimoto’s disease in this case provides further support for the diagnosis: autoimmune thyroid disease seems to be the most common endocrine disease associated with lymphocytic hypophysitis [4, 5]. Lymphocytic thyroiditis has been demonstrated at autopsy in a number of patients with lymphocytic hypophysitis, including the original description of the disease [2], and one of the previously mentioned patients with spontaneously resolving postpartum lymphocytic hypophysitis had clinical features of postpartum lymphocytic (“silent”) thyroiditis with thyrotoxicosis [12].

The case reported here is noteworthy for several reasons:

(1) Although lymphocytic hypophysitis is usually considered a disorder of the anterior pituitary (sometimes with infundibular or hypothalamic involvement), the present case demonstrates that radiographic evidence of disease involvement can be predominantly restricted to the pituitary stalk and hypothalamus, with little evidence of anterior pituitary involvement. Thus, lymphocytic hypophysitis may be included in the differential diagnosis of infundibular/hypothalamic infiltrative processes along with such disorders as sarcoidosis, eosinophilic granuloma, hamartoma, and glioma. (As an aside, it should be noted that the finding of radiographic changes largely restricted to the pituitary stalk does not totally exclude the possibility of anterior pituitary involvement. The pars tuberalis of the adenohypophysis actually covers the pituitary stalk anteriorly and laterally [a feature which is clinically important at times, because the pars tuberalis may occasionally give rise to suprasellar adenomas, and may also function as a reservoir of pituitary tissue that may continue to function even after “total" hypophysectomy].) Thus, it is theoretically possible that the stalk swelling in this case represented adenohypophysitis that was isolated to the pars tuberalis, in which case swelling and inflammation

of the stalk may represent a compensatory mechanism to compensate for anterior pituitary dysfunction.

(2) This case also highlights the fact that lymphocytic hypophysitis may result in acute anterior pituitary failure and severe end-organ dysfunction that may persist for months or even years after diagnosis and treatment. The evaluation of such patients is sometimes difficult, and it is important to keep in mind that even in the absence of regression of suprasellar mass, the patients may be in a state of compensated anterior hypopituitarism for months or even years post diagnosis.

In summary, this case report demonstrates that lymphocytic hypophysitis is an unusual cause of diabetes insipidus, and that it may present with acute anterior pituitary failure and severe end-organ dysfunction that may persist for months or years after diagnosis and treatment.
of the stalk could inhibit axonal transport of vasopressin and thereby cause diabetes insipidus.)

(2) Although lymphocytic hypophysitis typically results in anterior pituitary hypofunction, this patient’s presentation with diabetes insipidus (as well as the later documentation of hyperprolactinemia) is the functional correlate of the pituitary stalk and hypothalamic involvement that was demonstrated anatomically. This supports previous descriptions of lymphocytic hypophysitis as a cause of diabetes insipidus [7–10].

(3) The spontaneous resolution of the radiographic abnormalities supports the observations of others that lymphocytic hypophysitis is a self-resolving disorder in many cases, and that neurosurgical intervention for an apparent pituitary or suprasellar mass in a pregnant or recently postpartum woman may not be essential or even appropriate. Instead, periodic radiographic monitoring (to assure resolution of the lesion) along with evaluation for endocrine deficiency states (which may persist even after anatomic normalization) may be the most appropriate management for this disorder [4, 5, 12–16].

(4) The development of a partial empty sella in this case, as well as in a previously reported patient [5], suggests that lymphocytic hypophysitis may be a cause of some cases of the empty sella syndrome. The observation that antipituitary antibodies are measurable in the serum of 75% of women with the empty sella syndrome [17], combined with the presumed autoimmune nature of lymphocytic hypophysitis, lends support to the previous suggestion that the empty sella syndrome may at times represent the end stage of lymphocytic hypophysitis [4].

References


