Two Cases of Lymphocytic Hypophysitis Presenting with Diabetes Insipidus: A Variant of Lymphocytic Infundibulo–Neurohypophysitis

Hiroshi Nishioka, M.D., Hiroshi Ito, M.D., Toshiaki Sano, M.D., Ph.D., and Yoshinori Ito, M.D.

*Department of Neurosurgery, Tokyo Medical College, **Department of Pathology, University of Tokushima School of Medicine, and †Department of Neurosurgery, Kasumigaura Hospital, Tokyo Medical College, Japan


BACKGROUND
It has been thought that neurohypophysial involvement manifesting as central diabetes insipidus in lymphocytic hypophysitis is uncommon. Although cases with such an association have been reported recently with increasing frequency, the relationship with lymphocytic infundibulo-neurohypophysitis remains unclear.

METHODS AND RESULTS
Two postmenopausal women who presented with diabetes insipidus are reported. Adenohypophysial function was normal in both cases, apart from growth hormone secretion. Magnetic resonance imaging revealed a sellar mass lesion mimicking pituitary adenoma, with loss of the hyperintense signal of the neurohypophysis in both cases and thickening of the stalk in one case. The lesion was located behind the residual adenohypophysis during transsphenoidal biopsy; however, histologic examination showed chronic inflammation of the adenohypophysis, findings identical to those of lymphocytic adenohypophysitis. Although the principal site of the inflammation was considered to be the neurohypophysial system, adenohypophysitis was also involved in the lesion. We suggest that these cases represent a variant of lymphocytic infundibulo-neurohypophysitis.

CONCLUSION
To avoid unnecessary surgical intervention, it is important to note that some variants of lymphocytic infundibulo–neurohypophysitis may form a mass lesion not localized in the neurohypophysial system but involving the adenohypophysis, thus resembling adenomas and other tumors.

KEY WORDS
Diabetes insipidus, lymphocytic hypophysitis, lymphocytic infundibulo–neurohypophysitis, pituitary gland, transsphenoidal surgery.

With recent advances in radiologic investigations and technical refinements of transsphenoidal surgery, chronic inflammatory lesions of the pituitary gland are being reported with increasing frequency. The most common among them is lymphocytic adenohypophysitis, which can cause hypopituitarism and visual disorders mimicking non-functioning adenomas. It is reported that the adenohypophysis is the principal site of inflammation, whereas the neurohypophysis is spared in this disease [4]. On the other hand, inflammation of the neurohypophysial system, the lymphocytic infundibulo–neurohypophysitis, is known to be a cause of central diabetes insipidus. The adenohypophysitis of lymphocytic infundibulo–neurohypophysitis is reported to be normal and such cases lack signs of hypopituitarism [9,11]. Consequently, these two lesions present with distinctly different clinicopathologic features.

We report two cases of chronic inflammatory lesions of the pituitary gland that presented with diabetes insipidus and without hypopituitarism. Unlike lymphocytic infundibulo–neurohypophysitis, however, the adenohypophysis was also shown to be involved in the lesion by magnetic resonance imaging.
Results of Triple Stimulation Test in Two Cases

<table>
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<th>Case 1</th>
<th>Case 2</th>
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<td><strong>Basal</strong></td>
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<td>GH (0.66–3.68 ng/mL)</td>
<td>0.57</td>
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<td>Prolactin (1.4–14.6 ng/mL)</td>
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<td>ACTH (9–52 pg/mL)</td>
<td>15</td>
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<td>TSH (0.34–3.5 μ U/mL)</td>
<td>0.57</td>
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<td>LH (5–20 mIU/mL)</td>
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Abbreviations: basal, basal level; peak, peak level of the triple stimulation test; GH, growth hormone; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; ( ), normal range.

(MRI) and histologic studies. The relationship with lymphocytic infundibulo–neurohypophysis and the management of these cases are discussed.

**Case Reports**

**Case 1**

A 53-year-old postmenopausal woman suddenly developed polydipsia and polyuria 1 month prior to admission. She had experienced three normal full-term deliveries more than 20 years previously. She had no previous medical problem.

On admission, her general physical condition was normal, except for dry skin. Neurologic examination and routine laboratory examinations showed normal results. Her urine volume was 5000–7000 mL/day (specific gravity, 1.002). The plasma antidiuretic hormone level was 0.3 pg/mL (normal, 0.3–3.5). When 5 μg of desmopressin acetate (1-deamino-8-D-arginine–vasopressin acetate trihydrate; DDAVP) was given intranasally twice a day, urine volume decreased to 1500–2500 mL/day (specific gravity, 1.008–1.020). Endocrinologic examinations of the adenohypophyseal hormones and its triple stimulation (thyrotropin-releasing hormone 0.5 mg, luteinizing hormone-releasing hormone 0.1 mg, regular insulin 0.1 IU/kg) test were normal apart from growth hormone (GH), which showed low response (Table 1), despite adequate hypoglycemia (below 40 mg/dL). Examination of cerebrospinal fluid and serologic studies showed normal results, and antinuclear and antipituitary (anticyttoplasm and antecell membrane) antibodies were negative. Skull X ray and computed tomography (CT) were normal. MRI disclosed an intrasellar mass lesion, which was homogeneously enhanced by gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) (Figure 1 A,B). On the T₁-weighted image, loss of the hyperintense signal of the neurohypophysis was observed. However, thickness of the pituitary stalk was normal.

Biopsy of the lesion by a transsphenoidal approach was performed 3 months after the initial onset of her diabetes insipidus. The lesion was an avascular yellow fibrous mass clearly defined from the anteriorly situated residual adenohypophysis, whereas the neurohypophysis could not be identified. Pathologic examination demonstrated diffuse infiltration of lymphocytes and plasma cells associated with fibrosis and edema. Although the biopsy specimen was taken from the center of the fibrous lesion behind the adenohypophysis, a few nests of residual adenohypophysial cells were distributed sparsely in the background (Figure 1 C,D). No adenomas, granulomas, or multinucleated giant cells were present. Some lymphocytes were immunohistochemically stained with UCHL-1 (Dako), whereas L-26 (Dako) was negative.

The patient did well postoperatively, and adenohypophysial functions remained normal. Diabetes insipidus gradually improved and DDAVP became unnecessary 6 months after the surgery.

**Case 2**

A 66-year-old postmenopausal woman gradually developed polydipsia and polyuria 3 years prior to admission. Her polyuria, which had been controlled by DDAVP intranasally, rapidly increased 2 months before admission. She had no previous medical problem.

On admission, her physical condition was unremarkable, and neurologic examination and routine laboratory examinations were normal. Her urine volume was 3000 mL/day (specific gravity, 1.006) with 10 μg of DDAVP nose drops twice per day. The plasma ADH level was 0.2 pg/mL. Peak urinary and plasma osmolality during water deprivation was 196 and 297 mOsm/kg, respectively. Urinary osmolality increased in response to exogenous vasopressin to 419 mOsm/kg. On the other hand, endocrinologic examinations of the adenohypophysial hormones and its triple stimulation (thyrotropin-releasing hormone, luteinizing hormone-releasing hormone, insulin) test were normal apart from GH, which showed low response (Table 1), despite adequate hypoglycemia. Examination of the cerebrospinal fluid and serologic studies showed normal results. Enlargement of the sella turcica was seen on skull X ray. CT and MRI demonstrated a sellar isodense mass lesion with slight suprasellar extension, which was homogeneously enhanced by contrast medium and Gd-DTPA (Figure 2 A,B), respectively. On the T₁-weighted image, loss of the
A (A): Coronal T₁-weighted MRI demonstrates an intrasellar isointensity mass lesion with deviation of the pituitary stalk. (B): The lesion was homogeneously enhanced by Gd-DTPA. (C): Photomicrograph of the surgical specimen demonstrated diffuse infiltration of lymphocytes and plasma cells, fibrosis, edema, with a few nests of residual adenohypophysial cells (Hematoxylin & eosin stain, × 160). (D): Some residual adenohypophysial cells were immunostained with prolactin (Methylgreen counterstain, × 160).

Hyperintense signal of the neurohypophysis and thickening of the stalk were observed.

Biopsy of the lesion was performed by a transsphenoidal approach to establish a histologic diagnosis. An avascular yellow hard elastic mass was found behind the residual adenohypophysis. Pathologic examination demonstrated diffuse lymphocytic infiltration, destruction of the adenohypophysial structures, and replacement by fibrotic tissue (Figure 2 C,D). No adenomas, granulomas, or multinucleated giant cells were present. Most lymphocytes were immunohistochemically stained with UCHL-1, whereas L-26 was negative.

Diabetes insipidus transiently became exacerbated after the surgery, whereas adenohypophysial function remained normal. The patient continues to require DDAVP.

**DISCUSSION**

Lymphocytic adenohypophysitis and lymphocytic infundibulo-neurohypophysitis are distinctly different entities, probably caused by different autoimmune processes [4,6,9,14,21]. Lymphocytic adenohypophysitis can cause hypopituitarism and
visual disturbance; however, diabetes insipidus is uncommon. This is because the neurohypophysis has been reported to be histologically normal in most cases [4]. Previous reports have demonstrated a firm fibrous mass encountered immediately beneath the dura of the sella turcica during transsphenoidal surgery. On the other hand, lymphocytic infundibulo–neurohypophysitis is known to be a cause of central diabetes insipidus [9]. It has been reported that the inflammation is localized in the neurohypophyseal system, forming a small mass lesion in the neurohypophysis and/or infundibulum [7], whereas the adenohypophysis has been shown to be spared on MRI [9] and histologic studies [11]. Meanwhile, lymphocytic hypophysitis is a somewhat ambiguous term, used to describe a chronic inflammatory lesion of the pituitary gland involving the adenohypophysis [12].

Clinicopathologic features of the two cases differed from both lymphocytic adenohypophysitis and lymphocytic infundibulo–neurohypophysitis. Unlike the former, they were postmenopausal women presenting with diabetes insipidus. They showed almost normal adenohypophysial function, and residual adenohypophysis was observed during the transsphenoidal surgery. On the other hand, unlike the latter, MRI demonstrated a sellar mass lesion mimicking adenoma, which was not localized in the neurohypophysis. In addition, inflammation of the adenohypophysis was confirmed by histologic study. In our two cases, the lymphocytes were mostly positive for UCHL-1 and negative for L-26, indicating that most of them were T cells. It has been reported that the lymphocytes are mostly T cells, particularly CD4 cells, in most cases with lymphocytic adenohypophysitis [1,5,6,14] and lymphocytic infundibulo–neurohypophysitis [9,11].

Endocrinologic examination demonstrated normal adenohypophysial function apart from GH, which showed low responses to insulin-induced hy-
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poglycemia. Neither patient was obese, and drugs that may influence GH response were not used. The other five adenohypophysial hormones, including responses of ACTH to insulin-induced hypoglycemia, showed normal results. Low responses of GH in elderly cases, however, do not always imply that GH secretion is impaired. Thus, the low responses in our cases may indicate that while adequacy of GH response was not confirmed, neither was there evidence of GH deficiency. Subnormal responses of GH to insulin-induced hypoglycemia has been reported in some cases with lymphoctic infundibulo–neurohypophysitis [9], and in other cases with idiopathic diabetes insipidus [3]. Imura et al [9] suggested that there are derangements in the regulation of GH secretion in some cases with idiopathic diabetes insipidus, in either the hypothalamus or the median eminence.

Although it had been reported that diabetes insipidus is uncommon in lymphocytic adenohypophysitis [4], Thodou et al [21] reported recently that diabetes insipidus is encountered in 14% to 19% of cases of lymphocytic hypophysitis. To our knowledge, diabetes insipidus presenting in histologically diagnosed lymphocytic hypophysitis has been reported in 14 cases [1,8,10,12,13,15–19,22,23]. In these cases, thickening of the stalk, resembling that observed in lymphocytic infundibulo–neurohypophysitis, was frequently noted on MRI [1,10,12,16,18,21]. It is interesting that none of them, apart from one case [17], was in connection with pregnancy. Among them, five cases were quite similar to our two cases; they showed almost normal adenohypophysial function, did not have visual disturbance, and a small sellar lesion was observed on MRI [10,12,13,18]. Furthermore, in three cases in which the surgical findings were described, the residual pituitary tissue was observed anterior to (two cases) or superior to (one case) the fibrous lesion [10,18]. Although inflammation of the neurohypophysitis was not histologically identified in these cases, it is suggested that the principal site of inflammation was the neurohypophysial system, and the adenohypophysitis was secondarily affected by the extent of the inflammatory process. We believe that they represent a variant of lymphocytic infundibulo–neurohypophysitis. In contrast, nine other cases of lymphocytic hypophysitis with diabetes insipidus showed a large sellar mass lesion accompanied by hypopituitarism, and in most cases, visual disturbance [1,8,15–17,19,22,23]. A fibrous lesion was found just beneath the dura during transsphenoidal surgery in these cases. It was suggested that they represent a variant of lymphocytic adenohypophysitis: inflammation of the adenohypophysitis extending to the neurohypophysial system. Consequently, these two types of lymphocytic hypophysitis presenting with diabetes insipidus are quite different and should not be included in the same category. Recently, Ahmed et al [2] reported 2 cases with diabetes insipidus and hypopituitarism, and involvement of the adenohypophysis, neurohypophysis, and hypothalamus, which they termed necrotizing infundibular hypophysitis. It is not certain whether they represent a distinct entity, or whether they represent an extreme form of the latter type of lymphocytic hypophysitis presenting with diabetes insipidus.

Although the management of lymphocytic adenohypophysitis is still controversial, conservative care with steroids has been recommended when gross visual disturbance is absent [4,5,16,20]. In contrast to lymphocytic adenohypophysitis, which tends to be large and can cause visual disturbance, lymphocytic infundibulo–neurohypophysitis is usually a small mass lesion that does not cause visual disturbance [7,9]. In addition, presurgical diagnosis of typical cases can be made by MRI [9], and improvement of the diabetes insipidus cannot be expected to be obtained by transsphenoidal surgery. Therefore, surgical intervention should be avoided in typical cases of lymphocytic infundibulo–neurohypophysitis.

Apart from the mass lesion involving the adenohypophysis, the MRI findings of our two cases—loss of the hyperintense signal of the neurohypophysis in both cases and thickening of the stalk in one case, as well as normal adenohypophysial function except for GH secretion—were identical to those reported in typical cases of lymphocytic infundibulo–neurohypophysitis [9]; however, we failed to obtain a correct presurgical diagnosis. It is important to notice that some variants of lymphocytic infundibulo–neurohypophysitis may form a mass lesion involving the adenohypophysis, thus mimicking adenomas and other tumors.

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COMMENTARY

Nishio et al present two cases of lymphocytic hypophysitis with some special characteristics that are rarely found among the increasing numbers of publications concerning this rare pituitary disease. Interestingly, no impairment of anterior pituitary function either preoperatively or postoperatively was found in either case, except for growth hormone oversecretion. Both patients presented with diabetes insipidus, which resolved after removal of a fibrous mass within the intermediate zone in one. Therefore, in this case with a transient diabetes insipidus, the classification as infundibular hypophysitis must be considered ambiguous. A sagittal MRI with clearly visible involvement of the stalk would have been helpful for comparison in the second case. As should be expected, in the second case the diabetes insipidus persisted after a similar transphenoidal removal of tissue, as in the first case. The statement that this is a presentation of a new entity of infundibular neurohypophysitis cannot be fully supported by the findings of the authors.

We can speculate that both cases had a circumscribed hypophysitis adjacent to cystic or amorphic material within the intermediate zone. This may be similar to a recently described form of a localized reactive or "continue hypophysitis" [1–3]. Most interesting for the neurosurgeon is the presentation of two cases with hypophysitis with minor anterior lobe deficits. Thus, in similar cases, hypophysitis must be taken into consideration in the differential diagnosis of diabetes insipidus.

Dieter K. Lüdecke, M.D.
Takumi Abe, M.D.
Hamburg, Germany

REFERENCES


The authors have presented two cases that are unusual and well studied. They represent an entity that differs from the more typical lymphocytic hypophysitis, as pointed out by the authors. Is this a new entity, or is this perhaps responsible for some of the previously described “idiopathic diabetes insipidus”?

One must keep in mind that adenohypophyseal rests can occur along the infundibulum and basophil invasion may be seen in neurohypophysis. Therefore, it is possible that scant numbers of adenohypophyseal cells may be present in these locations, and the process depicted may represent true infundibulo-neurohypophyseitis.

This pathology affects a different age group and a different portion of the pituitary gland. Whether both represent an autoimmune phenomenon is yet to be determined. Both, however, can be treated medically with steroids and observation, unless there is acute neurologic dysfunction, such as visual loss requiring surgical decompression. If surgery is done, the authors point out that the anterior portion of the gland need not be excised and may recover some function. This is sound advice.

Kalmon D. Post, M.D.
New York, New York

**The trouble with Eichmann was precisely that so many were like him, and that the many were neither perverted nor sadistic, that they were, and still are, terribly and terrifyingly normal. From the viewpoint of our legal institutions and of our moral standards of judgment, this normality was much more terrifying than all the atrocities put together.**

Hannah Arendt (1906–75)
“Eichmann in Jerusalem,” Epilogue