Stereotactic radiotherapy for the treatment of lymphocytic hypophysitis

Report of two cases

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Lymphocytic hypophysitis is a rare inflammatory disorder of the pituitary gland. Standard therapy consists of transsphenoidal resection or oral administration of corticosteroid medications. Two patients with symptomatic lymphocytic hypophysitis, which recurred after standard therapy, were treated with low-dose stereotactic radiotherapy. On imaging studies both lesions demonstrated a response to radiation and each patient experienced relief of symptoms. There has been no adverse sequelae of the radiation treatment.

The authors conclude that stereotactic radiotherapy represents an effective, noninvasive treatment option for patients with lymphocytic hypophysitis, particularly if the disease is recurrent after surgery or resistant to corticosteroid medications.

KEY WORDS • lymphocytic hypophysitis • stereotactic radiotherapy

LYMPHOCYTIC hypophysitis is an unusual inflammatory disorder of the pituitary gland.1-4 There is a distinct female preponderance associated with this disease, and patients typically present during the peripartum period with dysfunction of the adenohypophysis and visual complaints.5-6 Imaging studies demonstrate a homogeneously enhancing intrasellar mass, often with suprasellar extension, which mimics a nonsecretory pituitary adenoma.7-10 The disorder is characterized by diffuse infiltration of the adenohypophysis or infundibulum by a polyclonal population of mature lymphocytes and plasma cells.11,12 The natural history of lymphocytic hypophysitis is uncertain. Although spontaneous regression has been described, if untreated this disorder usually results in relentless destruction of the pituitary gland.13,14

The standard therapy for lymphocytic hypophysitis is resection or administration of high-dose steroid medications.15-23 Although generally effective, these therapies have occasionally been associated with both recurrent disease and morbid states.24,25 There have been no reports on the use of ionizing radiation for the treatment of this rare condition; however, benign lymphoid infiltrates in other locations have proved responsive to moderate-dose radiotherapy.6,10,13 The authors report on the cases of two patients with lymphocytic hypophysitis who were treated with stereotactic radiotherapy. In both cases the disease had recurred following conventional therapy.

Case Reports

Case 1

This 58-year-old man was referred to the Division of Neurological Surgery in May 1996 for evaluation of a possible pituitary adenoma. The patient noted a 2-year history of decreased libido and bitemporal headache.

Examination. The results of the physical examination were unremarkable, except for the presence of an upper outer quadrant anopia in the left eye. An MR image demonstrated an enlarged pituitary gland with a tumor that extended through the diaphragma sellae, filled the suprasellar cistern, and displaced the optic chiasm superiorly. The mass enhanced homogeneously in response to Gd-diethyleneetriamine pentaacetic acid.

In this patient the total testosterone level was 40 ng/dl (normal 250–1000 ng/dl). The morning cortisol concentration was 2 µg/dl (normal 8–25 µg/dl) and the adrenocorticotropic level was 8 pg/ml (normal 9–52 pg/ml). The total thyroxin level was 3 µg/dl (normal 5–11 µg/dl), the total 3, 5, 3'-triiodothyronine level was 89 ng/dl (normal 75–175 ng/dl), and the concentration of thyroid-stimulating hormone was 0.2 µIU/ml (normal 0.3–4.7 µIU/ml). The prolactin level was 55.6 ng/ml (normal 5.4–19.4 ng/ml). Concentra-
tions of follicle-stimulating and luteinizing hormones were each less than 1 mIU/ml (normal 1.6–9 and 2–12 mIU/ml, respectively). The concentration of growth hormone was 1.3 ng/ml (normal 0.7–6 ng/ml) and that of somatomedin C was 338 ng/ml (normal for age 60–220 ng/ml). The urine specific gravity was 1.014 (normal 1.005–1.03) and the serum level of sodium was 148 mmol/L (normal 136–146 mmol/L).

First Operation. The patient was given anterior pituitary hormone replacement therapy and underwent transsphenoidal surgery for tumor removal in June 1996. The floor of the sella turcica was noted by the neurosurgeon to be extremely thin. The intrasellar tumor was firm and fibrous, which was judged to be inconsistent with a typical pituitary adenoma. Examination of a frozen-section specimen revealed a lymphoplasmacytic infiltrate. The intrasellar portion of the tumor was removed and a postoperative MR image revealed a residual, homogeneously enhancing suprasellar tumor.

The specimen obtained at surgery revealed a dense lymphoplasmacytic infiltrate composed of a polyclonal population of mature T and B lymphocytes (Fig. 1). The tumor cells demonstrated focally positive immunohistochemical staining for CD3, CD20, CD43, CD45, and both \( \kappa \) and \( \lambda \) light chains. No definite pituitary parenchyma could be identified within the surgical specimen. The final histopathological diagnosis was lymphocytic hypophysitis.

First Postoperative Course and Treatment. After surgery the patient was given high-dose corticosteroid therapy (40 mg/day prednisone, tapering to 7.5 mg/day over a 6-week period) and 1-desamino-8-d-arginine vasopressin for new-onset diabetes insipidus. The postoperative antinuclear antigen titer was 1:160 (normal < 1:40). Magnetic resonance imaging was performed every 3 months and the man remained stable until June 1997, when enlargement of the residual suprasellar tumor was noted.

Second Operation. The patient underwent a right frontal craniotomy and subtotal tumor resection. The specimen obtained intraoperatively was consistent with lymphocytic hypophysitis and was identical in appearance to the initial surgical specimen.

Second Postoperative Course and Treatment. A postoperative MR image revealed a residual enhancing tumor beneath the third ventricle. The second operation was complicated by a CSF leak, right frontal pneumocele, and osteomyelitis requiring multiple surgical procedures. The patient was again followed up with sequential MR imaging and remained stable until February 2002 when he complained of progressive headaches. An MR image revealed that the residual tumor had increased from 10 to 12 mm in its greatest dimension. The tumor remained homogeneously enhancing and compressed the optic chiasm.

Stereotactic Radiotherapy. In April 2002 the patient began a course of stereotactic radiotherapy in which he received 2400 cGy (12 treatments of 200 cGy) delivered to the 90% isodose line, which encompassed the contrast-en-
Fig. 2. Case 1. Coronal T₁-weighted contrast-enhanced MR image demonstrating the dosimetry for the 18-field treatment plan. The 30, 50, 80, and 90% isodose lines are displayed. The lesion is surrounded by the \textit{thick orange line} and a portion of the optic nerve and chiasm by the \textit{thick magenta line}.

Fig. 3. Case 1. Coronal T₁-weighted contrast-enhanced MR image obtained at the 6-month follow-up examination, demonstrating the response of the lymphocytic hypophysitis to stereotactic radiotherapy.

hancing edge of the tumor plus an additional 3-mm margin of healthy parenchyma (Fig. 2). The tumor measured $12 \times 15 \times 10\ mm$ and had a volume of 0.9 cm³ at the time of treatment planning. The patient was immobilized daily by placement in a custom-fitted thermoplastic face mask. The source of radiation was a dedicated 6-MV linear accelerator equipped with a micromultileaf collimator (Novalis, Heimstetten, Germany). Treatment was delivered using a single isocenter and 18 noncoplanar beams, each of which was individually conformed to the beam's eye view of the target by the collimator. The patient tolerated daily immobilization and radiotherapy without any acute complications. His headaches resolved within 2 weeks after he completed the stereotactic radiotherapy. A follow-up MR image obtained 3 months after completion of the radiotherapy demonstrated no change in the size of the suprasellar tumor. An MR image obtained 6 months later exhibited a reduction in the size of the contrast-enhancing tumor (Fig. 3). The lesion measured $7 \times 8 \times 9\ mm$ on the latest imaging study. There has been no change in the patient's endocrine function.

Case 2

This 75-year-old man was transferred from another hospital to the neurological surgery service in November 2001 with a possible pituitary adenoma. His history included 2 months of headache, polydipsia, and polyuria.

Examination. The results of the physical examination were unremarkable. An MR image with contrast enhancement demonstrated enlargement of the pituitary gland and thickening of the infundibulum, both of which enhanced homogeneously. There was no suprasellar extension or optic chiasm compression.

In this patient the urine specific gravity was 1.004 and the serum level of sodium was 148 mmol/L. The morning concentration of cortisol was 3 μg/dl and the adrenocorticotropic hormone level was 5.5 pg/dl. The total thyroxin level was 0.54 μg/dl and the thyroid-stimulating hormone level was 0.275 μIU/ml. The concentration of growth hormone was 1.6 ng/ml and that of somatomedin C was 118 ng/ml. The total and free testosterone levels were 20 ng/dl and 3 pg/ml respectively. The concentrations of follicle-stimulating hormone and luteinizing hormone were each less than 1 mIU/ml. The prolactin level was 9 ng/ml. (Normal values for these hormones are identical to those given for Case 1.) An analysis of the patient’s CSF obtained by lumbar puncture revealed nine white blood cells (normal 0–5 cells) with 92% lymphocytes. The glucose level was 69 mg/dl (normal 43–75 mg/dl) and the protein level was 43 mg/dl (normal 15–45 mg/dl).

The patient was placed on a regimen of pituitary replacement, 1-desamino-8-d-arginine vasopressin, and 60 mg/day prednisone. After 3 weeks, his headache, polyuria, and polydipsia decreased in frequency. An MR image demonstrated reductions in the size of the pituitary mass and the size of the infundibulum. There was no change in the enhancement of the pituitary, but the intensity of infundibular enhancement had decreased. The prednisone dose was decreased to 40 mg/day, but the patient reported a return of headache within 1 week and MR images revealed enlargement of the pituitary–infundibulum mass to its pretreatment dimensions. The dose of steroid medication was escalated to 60 mg/day, with only transient control of the man’s headache and no reduction in the size of the mass on MR images. The prednisone dose was further increased to 80 mg/day and the patient began a course of oxycodone. His headache was controlled, but he began to experience cushingoid habitus, hypertension, and constipation. Attempts to taper the steroid medication resulted in the rapid onset of severe headache. Magnetic resonance images obtained in July 2002 revealed an enlargement of the pituitary stalk, with evidence of optic chiasm compression.

Stereotactic Radiotherapy. In September 2002 the patient began a course of stereotactic radiotherapy and received 2400 cGy (12 treatments of 200 cGy) directed to the 90% isodose line, which encompassed the contrast-enhancing edge of the tumor plus an additional margin of 3 mm of healthy parenchyma. The tumor measured $16 \times 18 \times 23$
has been documented with increasing frequency in men and in menopausal females. The cause of lymphocytic hypophysitis remains obscure, but has been linked to an underlying autoimmune disorder by some investigators. The antinuclear antigen titer was elevated in one of our patients (Case 1), although there was no other evidence of an autoimmune disease in this patient.

Patients with lymphocytic hypophysitis experience symptoms compatible with anterior pituitary gland failure and compression of the optic chiasma. Lymphocytic hypophysitis confined to the infundibulum or neurohypophysis is distinctly uncommon. This disorder can be difficult to differentiate clinically from a pituitary adenoma, and the diagnosis is usually established by histopathological examination of a specimen obtained by transsphenoidal resection. The dense lymphoplasmacytic infiltrate, which was composed of benign, polyclonal mononuclear T and B cells in Case 1, is identical to the microscopic and immunophenotypical description of lymphocytic hypophysitis reported elsewhere.

The patient in Case 2 of this report did not undergo biopsy or resection. The diagnosis in that case was based on the results of imaging, the analysis of the CSF, and the results of laboratory studies. Kristof and colleagues reported the noninvasive diagnosis of lymphocytic hypophysitis based on endocrinological assessment, MR imaging, CSF examination, and the patient’s response to high-dose methylprednisolone. The findings in Case 2, particularly the presence of a lymphocytic pleocytosis in the CSF and the thickening of the infundibulum on MR images, are similar to the criteria proposed by Kristof and colleagues for the presumptive diagnosis of lymphocytic hypophysitis.

The standard therapy for lymphocytic hypophysitis is surgical removal via the transsphenoidal approach. Resection is often incomplete due to suprasellar extension or firm adherence of the sellar tumor to adjacent dura mater. Recurrence following partial removal of lymphocytic hypophysitis has been reported. Moreover, surgical therapy may result in diabetes insipidus or worsening of anterior pituitary function. In Case 1 the disease recurred despite two surgical attempts, one of which resulted in diabetes insipidus. High-dose steroid therapy has been advocated for lymphocytic hypophysitis in an effort to avoid invasive procedures, particularly in patients in whom visual function has not been compromised. The clinical response to corticosteroid medications, however, may be poor or transient, and symptoms frequently return after cessation of therapy. Steroid therapy may be necessary for many months, resulting in serious side effects such as Cushing syndrome, avascular necrosis, and diabetes mellitus. In Case 2 the steroid medication could not be lowered below 80 mg/day without onset of headache, and the patient experienced hypertension and cushingoid symptoms.

There have been no reports of radiotherapy for lymphocytic hypophysitis, although its use has proven to be successful for histopathologically similar conditions elsewhere in the body. Benign lymphoid infiltration of the orbit, also termed "pseudolymphoma," has been treated successfully with radiation. Lanciano and associates treated 26 orbits with 2000 cGy dispensed in 10 fractions. The tumor responded completely in 21 of these cases, and after a median follow-up period of 41 months, 17 cases remained in remission. Soft tissue swelling and proptosis responded com-

**Discussion**

Lymphocytic hypophysitis is an inflammatory process of the pituitary gland first reported in 1962. The condition is rare, accounting for 0.38 to 1.1% of sellar lesions excised during transsphenoidal surgery. Although it typically affects young, pregnant women, lymphocytic hypophysitis

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**Fig. 4. Case 2.** Upper: Magnetic resonance image demonstrating the dosimetry for the treatment plan. The isodose lines and target contour colors are identical to those shown in Fig. 2 (Case 1). Lower: Coronal T1-weighted contrast-enhanced MR image obtained 3 months after stereotactic radiotherapy, demonstrating central tumor hypodensity.
The authors found no correlation of tumor response with the bulk of the lymphocytic infiltrate as measured on computerized tomography scanning. In the study conducted by Keleti et al., 28 orbits were subjected to radiation and the authors reported a 3-year actuarial local control rate of 75% after a median follow-up period of 42 months. There was no significant effect of a dose higher or lower than 3000 cGy on the local control rate. Authors of several small series in which the radiation dose was between 2000 and 2500 cGy have documented 100% control of orbital pseudolymphoma, including patients resistant to corticosteroid therapy. 

These published results of treatment for orbital pseudolymphoma imply a role for ionizing radiation in the management of lymphocytic hypophysitis.

Stereotactic radiation treatment is a method used for the accurate, focal therapy of an intracranial target. Treatment delivered in a single large fraction is termed "stereotactic radiosurgery." The dose to the direct brain parenchyma immediately surrounding the target is limited by the steep falloff in dose deposition inherent in the use of multiple collimated beams of radiation. The use of stereotactic radiosurgery for lymphocytic hypophysitis, however, may be limited by the proximity of the tumor to the optic chiasm. The threshold dose for optic neuropathy following stereotactic radiosurgery has been estimated to be 800 cGy. In both patients in this report, the lymphocytic hypophysitis was located within 3 mm of the optic chiasm, an anatomical constraint that would require reduction of the stereotactic radiosurgery dose to the periphery of the tumor to avoid exceeding the tolerance of the optic apparatus.

With stereotactic methods, focal radiation can also be performed by delivering multiple small increments of radiation typical of standard radiotherapy; this is known as "stereotactic radiotherapy." In fact, stereotactic radiotherapy combines the dose-localization advantages of stereotactic radiosurgery with the biological benefits to normal tissue of dose fractionation. Stereotactic radiotherapy has been demonstrated to be accurate, safe, and effective for the treatment of a variety of skull base tumors including acoustic neuroma, craniopharyngioma, and pituitary adenoma. Furthermore, the optic apparatus is known to tolerate a fractionated dose of ionizing radiation of 5000 cGy.

Both patients with lymphocytic hypophysitis in this report demonstrated a rapid clinical response to stereotactic radiotherapy. In the first case, the patient's headaches resolved soon after completion of stereotactic radiotherapy. In the second patient, we were successfully able to discontinue the course of analgesics during treatment and to taper the dose of steroid medication soon after stereotactic radiotherapy without clinical deterioration, which had accompanied prior attempts at dose reduction. The interval from treatment to imaging response varied from 3 to 6 months. The largest tumor dimension decreased from 15 to 9 mm in Case 1. In Case 2 the tumor, which had homogeneously enhanced prior to treatment, demonstrated central hypodensity after stereotactic radiotherapy. Loss of central enhancement has been described after stereotactic radiotherapy for acoustic schwannoma and this has been ascribed to tumor necrosis. The time course of the imaging response of lymphocytic hypophysitis to ionizing radiation delivery is typical of lymphocytic infiltration elsewhere. In the experience Lanciano, et al., had in the treatment of pseudolymphoma, the interval from radiation delivery to complete response of soft tissue swelling and proptosis varied from 2 weeks to 3 months (median 1 month). Fitzpatrick and Mack reported on seven patients with orbital pseudolymphoma who had undergone radiotherapy; in their study all tumors completely responded to treatment within 2 months. A longer follow-up period will be required to establish the duration of the lymphocytic hypophysitis response to stereotactic radiotherapy.

No acute complications were associated with stereotactic radiotherapy in our cases, and the patients tolerated daily immobilization without difficulty. Neither patient experienced exacerbation of headaches during treatment. There has been no decline in visual function in either patient, although the follow-up duration is short. No comment can be made concerning whether any endocrine dysfunction may accompany stereotactic radiotherapy for lymphocytic hypophysitis because the pituitary function in both patients was severely compromised before radiation. In a series of 30 patients who received 4500 cGy during stereotactic radiotherapy for pituitary adenoma, Mitumori and associates reported a 3-year-long freedom from new endocrinopathy of 80%. There has been no recovery of pituitary function following stereotactic radiotherapy in either of our patients. Note also that a recovery of endocrine function is unusual following transsphenoidal surgery.

Conclusions

The results reported here indicate that stereotactic radiotherapy represents a minimally invasive treatment option for patients with lymphocytic hypophysitis, particularly if the disease process is close to the optic chiasm. Patients in whom stereotactic radiotherapy may prove useful for this rare entity include those with disease that is residual or recurrent after attempted surgical removal, those with a presumptive diagnosis of lymphocytic hypophysitis, and those who are resistant to, or intolerant of, high-dose corticosteroid therapy. More experience with stereotactic radiotherapy in patients with lymphocytic hypophysitis is required to establish the long-term benefit of this unique form of radiotherapy.

References


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