Novel strategy to treat a case of recurrent lymphocytic hypophysitis using rituximab

Case report

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Lymphocytic hypophysitis is an uncommon autoimmune condition that often results in significant morbidity. Although most cases resolve spontaneously or after a short course of steroids, rarely, refractory cases can cause persistent neurological deficits despite aggressive medical and surgical management.

A 41-year-old woman presented with progressive visual loss in the left eye and was found to have a sellar mass. She underwent transsphenoidal surgery because of lesion enlargement. Histopathology was consistent with adenohypophysitis with B-cell predominance. Despite steroid treatment, her neurological condition worsened and she experienced loss of vision in the right eye. Craniotomy with decompression of the right optic nerve was performed. Her condition improved initially, but she continued to have progressive visual compromise over the following months. She was therefore treated with rituximab, a monoclonal antibody against B cells. Her vision improved significantly within a few weeks. There was no clinical or radiographic exacerbation 2 years after starting immunotherapy.

Rituximab, an anti-CD20 antibody that specifically depletes B lymphocytes, can be an effective treatment strategy for patients with steroid-refractory, B cell–predominant lymphocytic hypophysitis.

Key Words • autoimmune adenohypophysitis • immunotherapy • anti-CD20 monoclonal antibody • rituximab • pituitary surgery

Lymphocytic hypophysitis, first described in 1962 by Goudie and Pinkerton,6 is an autoimmune disorder that affects the adenohypophysis and/or neurohypophysis with an incidence of 1 case in 7–9 million persons.2,8 It has a strong female preponderance (8.5:1), with most cases occurring in late pregnancy or the peripartum period. Neurological manifestations of LH include pituitary dysfunction and visual loss related to mass effect.

Primarily, treatment for LH involves hormone replacement therapy and lympholytic agents. Surgery is generally reserved for patients with medically refractory disease. Histologically, LH is characterized by massive infiltration of the pituitary gland by lymphocytes and plasma cells.9 Rituximab (Rituxan, Genentech, Inc.) is a monoclonal antibody against CD20 that selectively induces apoptosis in B lymphocytes. It is approved for various immune-mediated disorders, including B-cell non-Hodgkin lymphoma, CD20-positive chronic lymphocytic leukemia, rheumatoid arthritis, Wegener granulomatosis, and microscopic polyangiitis.21

In this report, we describe the first use of rituximab in the management of LH.

Abbreviation used in this paper: LH = lymphocytic hypophysitis.
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**Second Treatment and Follow-Up.** A transsphenoidal biopsy and/or resection were recommended given the enlargement of the pituitary lesion and the progressive decline in vision. A firm, fibrous gland was encountered at surgery. Intraoperative frozen section was consistent with adenohypophysitis without evidence of tumor. Final histopathology revealed dense, fibrous connective tissue with nests of inflammatory cells, mostly lymphocytes with scattered plasma cells and eosinophils, consistent with a diagnosis of LH (Fig. 3). Immunostaining revealed a significant predominance of B cells.

The patient was discharged home the following day with a course of high-dose steroids; however, she continued to have a steady decline in vision in her left eye. Eighteen months after surgery, she presented with rapid loss of vision in her right eye (20/200 acuity). Magnetic resonance imaging showed that the lesion was now encasing the left carotid artery (Fig. 4). Her serum prolactin level was normal (0.6 ng/ml). She was started on intravenous methylprednisolone, and visual acuity returned to 20/20 in her right eye. However, she only had perception of hand motion in the left eye.

Four months later, she again presented with acute right-sided visual loss. Follow-up MR imaging demonstrated radiographic progression with diffuse enlargement and enhancement of the pituitary gland with extension into both cavernous sinuses and increased compression of the chiasm (Fig. 5). Hyperintense signal of the left optic nerve on T2-weighted MR images was suggestive of edema or optic neuritis. Moreover, there was new dural enhancement along the tuberculum sellae encroaching on the optic nerves bilaterally. Visual acuity in the right eye was 1/200, and the patient was again treated with high-dose methylprednisolone for chronic, recurrent LH. Visual acuity in the right eye returned to 20/20, and she was discharged on an oral prednisone taper.

**Third Treatment and Follow-Up.** Because of the continued relapses and radiographic progression, she underwent a right frontal craniotomy for decompression of the right optic nerve and dural biopsy. Histopathology showed dura mater with mild chronic inflammation and sparse lymphocytes with B-cell predominance—consistent with her first biopsy. Vision in her right eye improved, and she was discharged in stable condition. Despite aggressive medical and surgical management, over the next

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**Fig. 1.** Coronal postcontrast T1-weighted MR image showing an enlarged, heterogeneously enhancing pituitary gland with mild mass effect on the optic chiasm and deviation of the pituitary stalk to the left (arrow).

**Fig. 2.** Magnetic resonance imaging studies obtained 3 months after initial presentation. Coronal (left) and sagittal (right) postcontrast T1-weighted MR images showing extension of the mass (2.1 × 1.2 × 1.3 cm) into the suprasellar cistern and left cavernous sinus. The infundibulum continues to be deviated to the left and is mildly thickened at its attachment to the gland. The optic chiasm is bowed superiorly and is mildly compressed on the left side. The mass appears to be part of the gland itself and is indistinguishable from the normal pituitary gland.

**Fig. 3.** Photomicrographs showing results of histopathological analysis. A: Nests of normal acinar cells surrounded by a dense infiltrate of inflammatory cells are seen on H & E stain. B: Immunostaining with CD3 reveals a minority of T cells. C: Immunostaining with CD20 confirms that the majority of the inflammatory infiltrate is composed of B lymphocytes. Original magnification × 40.
few months, she had several relapses with progressively worsening vision. Follow-up MR imaging demonstrated further enlargement of the mass and involvement of the right cavernous sinus (Fig. 6).

Fourth Treatment and Follow-Up. Because of the predominance of B cells on histological analysis, she was treated with rituximab: 2 1000-mg infusions 15 days apart, repeated every 6 months. Her condition has remained stable since she began this immunotherapy regimen. Vision in her right eye returned to baseline (20/25) at the most recent follow-up 2 years after starting the rituximab treatment. Magnetic resonance imaging demonstrated a smaller heterogeneously enhancing sellar mass with diminished dural enhancement (Fig. 7).

Discussion

Lymphocytic hypophysitis can affect the anterior pituitary (adenohypophysitis), posterior pituitary and stalk (infundibuloneurohypophysitis), or the entire gland (panhypophysitis). Patients usually present with a sellar mass and a host of neurological signs and symptoms, including headache (compression of the dura and diaphragma sellae), visual loss (compression of the optic nerve/chaism), ophthalmoplegia (cranial neuropathy from invasion into the cavernous sinus), hypopituitarism (autoimmune response against acinar cells), diabetes insipidus (compression of the infundibulum or autoimmune destruction of the neurohypophysis), and hyperprolactinemia (compression of the infundibulum). Definitive diagnosis requires histopathological evaluation. Microscopically, a diffuse infiltrate of inflammatory cells, mostly T and B lymphocytes, is seen with nests of normal acinar cells surrounded by necrosis and extensive fibrosis.

Little is known about the actual mechanisms of autoimmune invasion in LH, and the disorder is often managed conservatively. Remission can occur spontaneously in some patients. Most with symptomatic LH require high-dose glucocorticoids, that is, pulse doses of methylprednisolone or prednisone followed by a slow taper over

![Fig. 4](image-url)

**Fig. 4.** Follow-up coronal postcontrast T1-weighted MR image obtained 18 months after the transsphenoidal biopsy, showing persistent enlargement of the pituitary gland, thickened infundibulum, and encasement of the left cavernous carotid artery (arrows).

![Fig. 5](image-url)

**Fig. 5.** A: Coronal postcontrast T1-weighted MR image obtained 22 months after surgery, showing a mass extending into both cavernous sinuses (arrowheads) with compression of the optic chiasm (arrows). B: Axial T2-weighted MR image showing hyperintense signal in the left optic nerve (arrowheads). C: Axial T1-weighted MR image showing diffuse dural enhancement along the tuberculum sellae (arrows) encroaching on the optic nerves bilaterally at the level of the optic canal (arrowheads).

![Fig. 6](image-url)

**Fig. 6.** Follow-up coronal MR image obtained 3 months after craniotomy, showing a larger mass with extension into the cavernous sinus bilaterally and superior displacement of the infundibulum and chiasm.
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Fig. 7. Coronal MR image obtained 2 years after starting rituximab therapy, showing decreased size and enhancement of the sellar mass. The dural enhancement previously seen along the planum sphenoidale and optic nerve/chiasm is also decreased in intensity. There is no suprasellar extension of the gland.

a period of weeks to months. In addition, patients with panhypopituitarism, diabetes insipidus, and hyperprolactinemia benefit from hormone replacement, desmopressin acetate, and Bromocriptine, respectively. Despite good response to these first-line therapies in the majority of patients, relapses are common. Transnasal transsphenoidal resection of the sellar mass is indicated for individuals who are unresponsive to medical therapy, for those whose symptoms recur with the cessation of medical therapy, or as a primary treatment in those who present with significant visual symptoms. Surgical decompression results in favorable outcomes in most patients with visual loss (Table 1). If diagnosis of LH is uncertain, intraoperative frozen section should be obtained to rule out other entities to avoid unnecessary resection of potentially viable glandular tissue. A few cases have been treated with stereotactic radiosurgery. Favorable outcomes have also been reported in patients with visual loss following salvage treatment with lympholytic agents (Table 2).

The choice of lympholytic agent depends on the dominant cell type seen on histology. Unlike other lympholytic drugs, which target T cells, rituximab is a monoclonal antibody directed against the CD20 antigen on the surface of B lymphocytes. The exact mechanism of B-cell lysis remains unknown, but it is believed to be either complement-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity.

In our patient, a B cell–predominant infiltrate was demonstrated on immunohistochemistry. Hence, we believed that rituximab was a rational alternative to other immunosuppressive therapies. Since B lymphocytes play

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**TABLE 1: Literature review of surgical intervention for visual deficits in LH**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients w/ Visual Symptoms (study total)</th>
<th>Symptom</th>
<th>Approach</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosman et al., 1989</td>
<td>9 (30)</td>
<td>decreased acuity, blurring, bitemporal hemianopia, visual loss</td>
<td>transsphenoidal in 6; bifrontal craniotomy in 3</td>
<td>symptom relief in all patients</td>
</tr>
<tr>
<td>Pestell et al., 1990</td>
<td>1 (2)</td>
<td>rt-sided deficits, bitemporal hemianopia</td>
<td>frontal craniotomy</td>
<td>worsened postop vision</td>
</tr>
<tr>
<td>Bitton et al., 1991</td>
<td>1</td>
<td>decreased central &amp; peripheral vision, bitemporal hemianopia</td>
<td>transsphenoidal</td>
<td>normal vision returned</td>
</tr>
<tr>
<td>Supler &amp; Mickle, 1992</td>
<td>1</td>
<td>diplopia, abducent nerve palsy, bitemporal superior quadrantanopia</td>
<td>transsphenoidal</td>
<td>resolution of diplopia &amp; palsy</td>
</tr>
<tr>
<td>Nishioka et al., 1994</td>
<td>1</td>
<td>bitemporal hemianopia, blurred lt vision</td>
<td>transsphenoidal</td>
<td>visual fields &amp; acuity normalized</td>
</tr>
<tr>
<td>Ng et al., 2003</td>
<td>1 (3)</td>
<td>bitemporal hemianopia, bilat decreased visual acuity</td>
<td>transsphenoidal</td>
<td>improved visual acuity bilaterally</td>
</tr>
<tr>
<td>Leung et al., 2004</td>
<td>5 (16)</td>
<td>diplopia in 2 patients, bitemporal hemianopia in 3 patients</td>
<td>transsphenoidal</td>
<td>normal visual fields restored in 3 w/ hemianopia; 1 of 2 patients w/ diplopia improved</td>
</tr>
<tr>
<td>Gutenberg et al., 2006</td>
<td>9 (21)</td>
<td>mono- &amp; bitemporal hemianopia</td>
<td>transsphenoidal</td>
<td>improvement in visual deficits in all patients</td>
</tr>
<tr>
<td>Sinha et al., 2006</td>
<td>1</td>
<td>bilat homonymous hemianopia</td>
<td>transsphenoidal</td>
<td>steady visual improvement, recurrence at 2nd pregnancy, treated conservatively</td>
</tr>
<tr>
<td>Menon et al., 2009</td>
<td>1 (15)</td>
<td>monocular blindness</td>
<td>transsphenoidal</td>
<td>no improvement in vision</td>
</tr>
<tr>
<td>Ray et al., 2010</td>
<td>1</td>
<td>diplopia, rt abducent nerve palsy</td>
<td>transsphenoidal</td>
<td>improved for 2 wks, recurrence treated w/ stereotactic radiation</td>
</tr>
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a central role in the humoral immune response, they may be responsible for autoantibodies directed against the pituitary gland, further supporting the use of an anti-CD20 drug in LH.

Conclusions

We describe the first reported use of rituximab, a monoclonal antibody against B cells, to treat a patient with chronic, recurrent LH. Established medical therapies are not always effective, perhaps because of the variable involvement of T and B cells and other inflammatory cells. Tissue diagnosis may be more important than previously thought and may help to direct the most appropriate treatment. Anti-CD20 therapy using rituximab is a well-tolerated and effective alternative in cases of steroid-refractory LH.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following: Conception and design: Jagannathan, Gauthikonda. Acquisition of data: Schreckinger, Francis. Drafting the article: Schreckinger, Francis, Rajah. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Mittal.

Acknowledgment

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References


TABLE 2: Lympholytic therapy for visual deficits in LH

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients w/ Visual Symptoms</th>
<th>Symptom</th>
<th>Lympholytic Therapy at Relapse</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ward et al., 1999</td>
<td>1</td>
<td>AIRE mutation (polyendocrinopathy w/ LH), keratoconjunctivitis</td>
<td>cyclosporin A, 5 mg/kg/day</td>
<td>visual symptoms resolved at 8 mos</td>
</tr>
<tr>
<td>Tubridy et al., 2001</td>
<td>1</td>
<td>diplopia</td>
<td>methotrexate, 7.5 mg weekly</td>
<td>resolution of symptoms &amp; normal eye movements at 9 mos</td>
</tr>
<tr>
<td>Lecube et al., 2003</td>
<td>1</td>
<td>diplopia</td>
<td>azathioprine, 150 mg/day × 4 wks</td>
<td>symptom free w/o clinical or radiographic evidence of disease at 18 mos</td>
</tr>
<tr>
<td>Papanastasiou et al., 2011</td>
<td>1 (2 total)</td>
<td>diplopia, bilateral abducens nerve palsy, deterioration of visual fields &amp; acuity</td>
<td>azathioprine, 150 mg/day × 10 days, then 100 mg/day × 6 mos, then 50 mg/day × 6 mos</td>
<td>improvement in clinical signs at 4 wks, clinically &amp; radiographically disease free at 2 yrs</td>
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