CLINICAL CASE SEMINAR: Lymphocytic Hypophysitis: Clinicopathological Findings*

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ABSTRACT

This report describes the clinicopathological features of 16 patients with lymphocytic hypophysitis and compares the results with the published literature. There were 2 males and 14 females in this series. In 10 of the 14 females (71%), the presentation was associated with pregnancy. Nine patients (56%) presented with symptoms of an expanding pituitary sellar mass, 10 (63%) had anterior pituitary hypofunction, 3 had diabetes insipidus (19%). Progressive undiagnosed hypopituitarism led to the demise of 3 patients (19%). Hypopituitarism was encountered in 6 patients (38%), and elevated growth hormone levels (GH) resulted in IGF-1 excess in one patient. Computed tomography (CT) and magnetic resonance (MRI) imaging revealed features of a pituitary mass mimicking an adenoma in 10 cases (63%). Four patients (25%) had associated autoimmune thyroiditis. Morphologic examination of the pituitary and immunohistochemistry showed a polyclonal lymphoplasmacytic infiltrate as well as occasional neutrophils, eosinophils, and macrophages; the chronic inflammatory process resulted in focal or diffuse adenohypophysial destruction of variable severity with associated fibrosis. The inflammatory infiltrate involved the neurohypophysis in 2 cases and one of the patients had diabetes insipidus; the posterior lobe of two other patients with diabetes insipidus was not examined morphologically.

We conclude that lymphocytic hypophysitis should be considered in the differential diagnosis of females with pituitary enlargement progressing in the peripartum period as well as those patients in whom pituitary hormone deficiency and/or excess is noted in association with an existing autoimmune disorder. This clinical suspicion should probably also be extended to include patients presenting with rapid growth of pituitary masses associated with compressive symptoms with or without pituitary hormone dysfunction. Because of the insistent endocrine and compressive features of this condition in most instances, conservative treatment on the basis of clinical suspicion alone may obviate the need for aggressive pituitary surgery. (J.C. Endocrinol Metab 80: 2302–2311, 1995)

LYMPHOCYTIC hypophysitis is a rare inflammatory lesion of the pituitary gland. Nearly 100 cases have been reported since the first description of the entity in 1962 (1). The disease shows a striking female predilection of approximately 8.5:1 and commonly affects young women during late pregnancy or in the postpartum period. Many reports strongly support the original suggestion of an autoimmune pathogenesis of this lesion and associate it with other autoimmune disorders, primarily thyroiditis and adenitis and less commonly atrophic gastritis and lymphocytic parathyroiditis (1–18).

Clinically, lymphocytic hypophysitis may have an acute onset and occasionally leads to severe complications, even a lethal outcome. In addition, the clinical presentation and radiologic findings may mimic pituitary adenoma. The diagnosis can only be clearly established by histologic examination.

We describe 16 histologically-proven cases of lymphocytic adenohypophysitis; this represents the largest series reported to date. The clinicopathologic findings are analyzed and compared with those published in the literature.

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Patients and Methods

Sixteen cases of lymphocytic hypophysitis were studied; 3 were diagnosed at autopsy, and 13 were from pituitary surgical material. Twelve of these cases represent original descriptions, whereas 5 (Table 1, cases nos 5, 12, 13, and 15) have been previously reported (2, 11, 17, 19).

Morphologic methods

For light microscopy, 4–6 μm thick sections of formalin-fixed paraffin-embedded tissues were stained with hematoxylin-eosin and periodic acid-Schiff (PAS) technique.

For immunocytochemistry, the avidin-biotin-peroxidase complex (ABC) technique was employed. Antibodies were directed against human growth hormone (GH), prolactin (PRL), corticotropin (ACTH), I-131 β-thyroid stimulating hormone (β-TSH), β-follicle stimulating hormone (β-FSH), β-luteinizing hormone (β-LH), α-subunit of pituitary glycoprotein hormones (α-SU), vasopressin, 5-100 protein, glial fibrillary acidic protein. Immunostains for histiocytosis X used the DND-3 antibody and for macrophages the CD68 antibody was applied. In some instances, the surgical material was not sufficient for thorough evaluation; thus limited the number of immunocytochemical stains.

Tissue for electron microscopy was obtained in eight cases. Small pieces of tissue were fixed in glutaraldehyde, postfixed in osmium tetroxide, and embedded in an epoxy resin. Ultrathin sections were stained with uranyl acetate and lead citrate and studied with a transmission electron microscope.

Results

Clinical Findings

The cases are summarized in Table 1. Fourteen of 16 patients were female (88%). The women had a mean age of 3
<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex/ Age</th>
<th>Material</th>
<th>Surgical (S)</th>
<th>Autopsy (A)</th>
<th>Clinical presentation</th>
<th>Clinical presentation</th>
<th>Image finding</th>
<th>Other autoimmune associations</th>
<th>Nonsurgical management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/52</td>
<td>S</td>
<td></td>
<td></td>
<td>Hypopituitarism</td>
<td>Headaches</td>
<td>CT: intrasellar lesion</td>
<td>Lymphocytic thyroiditis</td>
<td>Steroid replacement</td>
</tr>
<tr>
<td>2</td>
<td>F/27</td>
<td>S</td>
<td></td>
<td></td>
<td>Hyperprolactinemia</td>
<td>Bitemporal visual loss</td>
<td>CT: normal sella stalk lesion</td>
<td>Thyroiditis</td>
<td>DDAVP</td>
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<td>3</td>
<td>F/?</td>
<td>S</td>
<td></td>
<td></td>
<td>Diabetes insipidus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F/29</td>
<td>S</td>
<td></td>
<td></td>
<td>Hyperthyroidism</td>
<td>Visual defects</td>
<td>CT: sellar mass mild suprasellar extension</td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td>F/28</td>
<td>S</td>
<td></td>
<td></td>
<td>Hyperprolactinemia</td>
<td>Headache</td>
<td>CT: pituitary mass suprasellar and parasellar extension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F/38</td>
<td>A</td>
<td></td>
<td></td>
<td>Diabetes mellitus</td>
<td>Myocarditis</td>
<td>CT: for seizures normal no pituitary views</td>
<td>Nil</td>
<td></td>
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<tr>
<td>7</td>
<td>F/34</td>
<td>A</td>
<td></td>
<td></td>
<td>Post-pregnancy</td>
<td>Septic shock</td>
<td>Nil</td>
<td>Replacement steroids—transient improvement</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M/32</td>
<td>S</td>
<td></td>
<td></td>
<td>Hyperpituitarism</td>
<td>Toxic shock</td>
<td>Nil</td>
<td>Adrenal &amp; thyroid hormone replacement</td>
<td></td>
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<tr>
<td>9</td>
<td>F/31</td>
<td>S</td>
<td></td>
<td></td>
<td>2nd trimester</td>
<td>Visual loss</td>
<td>CT: sellar and suprasellar mass with cavernous sinus extension</td>
<td>Nil</td>
<td></td>
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<tr>
<td>10</td>
<td>F/41</td>
<td>S</td>
<td></td>
<td></td>
<td>Postpartum</td>
<td>Headaches</td>
<td>CT: sellar-suprasellar mass with cystic degeneration</td>
<td>Biopsy; no resection</td>
<td></td>
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<tr>
<td>11</td>
<td>F/24</td>
<td>S</td>
<td></td>
<td></td>
<td>Amenorrhea</td>
<td></td>
<td>MR: large intrasellar mass with suprasellar and cavernous sinus extension</td>
<td>Decadron × 2 months—no response</td>
<td></td>
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<tr>
<td>12</td>
<td>F/32</td>
<td>S</td>
<td></td>
<td></td>
<td>Normal PRL</td>
<td></td>
<td>X-rays: convex diaphragm</td>
<td>No further therapy—progressive improvement</td>
<td></td>
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<tr>
<td>13</td>
<td>F/31</td>
<td>A</td>
<td></td>
<td></td>
<td>Postpartum</td>
<td>Anorexia</td>
<td>Thyroiditis</td>
<td></td>
<td></td>
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<tr>
<td>14</td>
<td>F/29</td>
<td>S</td>
<td></td>
<td></td>
<td>Hyperprolactinemia</td>
<td>Visual defects</td>
<td>Vittigo</td>
<td></td>
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<tr>
<td>15</td>
<td>F/33</td>
<td>S</td>
<td></td>
<td></td>
<td>Hyperprolactinemia</td>
<td>Headaches</td>
<td>Thyroiditis</td>
<td></td>
<td></td>
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<tr>
<td>16</td>
<td>F/29</td>
<td>S</td>
<td></td>
<td></td>
<td>Diabetes insipidus</td>
<td>Visual loss</td>
<td>Parathyroid hyperplasia</td>
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**Notes:**
- CT: computerized tomography
- MRI: magnetic resonance imaging
- BEC: bromocriptine
- PRL: prolactin
- ACTH: adrenocorticotropic hormone
- Ca+: calcium
Lactotroph cell hyperplasia and/or hyperactivity was observed in three patients. Two were female patients who were pregnant or postpartum (12, 14), however lactotroph hyperplasia in one male (case 1) remains unexplained.

**Management and Therapy**

Three of the patients were diagnosed at autopsy and no therapy was attempted for the pituitary disorder.

Preoperative therapy with bromocriptine (BEC) was initiated for hyperprolactinemia in two patients. In patient 5, BEC (2.5 mg/day) for 4 days resulted in improvement of her visual acuity and reduction in left temporal hemianopsia; the prolactin level after therapy was 6.7 ng/ml, low for the sixth month of gestation, but a pre-therapy level had not been measured. Despite therapy, the pituitary enlargement remained sufficiently symptomatic to require surgical intervention. Patient 14 received BEC 2.5 mg/day for six months; this suppressed her prolactin levels but did not improve her visual impairment or reduce the size of the pituitary mass on MR imaging.

Patient 16 received therapeutic doses of corticosteroids for one year preoperatively and this did not have any effect on her symptoms. Patient 10 was treated with decadron for 1 month postoperatively with no effect.

Transphenoidal surgery reduced the visual field abnormalities in two patients (cases 5 and 14); in one (case 14) the elevated PRL blood levels normalized following surgery. One patient (case 16) remains blind after a prolonged period of optic nerve compression prior to surgery. One other patient had complete normalization of elevated PRL and GH levels after surgery. Postoperatively, three of our patients (cases 4, 5 and 14) developed diabetes insipidus, which required vasopressin therapy; in two of these patients the episode was transient, but the other patient required ongoing vasopressin replacement.

Seven of the operated patients had preoperative hypopituitarism (cases 1, 4, 5, 8, 11, 12, and 15). In one of these (case 15), pituitary function showed a complete recovery 6 months post-operatively, allowing discontinuation of replacement therapy. Anterior pituitary hormone levels were still normal 11 and 12 months following surgery. In the remainder, surgery did not improve pituitary function, and therapy with thyroid and adrenal hormone replacement continued postoperatively.

One patient (case 10) who required no further postoperative medication has had spontaneous resolution of the pituitary mass documented in serial MR scanning (Fig. 1).

**Discussion**

Lymphocytic hypophysitis has been reported to be predominantly a disease of females, frequently associated with pregnancy or presenting during the postpartum period; in the literature, this association was found in 63% of female patients. In our series, the female to male ratio is 7:1, and 71% of the women the disease was associated with pregnancy. According to the literature, the mean age of presentation in females is 34.5 years (4-7, 13, 14, 16, 20-44) while...
in males it is one decade later (44.7 years) (15, 31, 36, 41, 45-47). We found nearly the same mean ages. Given that autopsies were selected and some surgical specimens represented consultation cases, the current series cannot be used to extrapolate the frank incidence of lymphocytic hypophysitis in the general population.

The clinical presentation of lymphocytic hypophysitis includes four categories of symptoms. Symptoms derived from mass effects, such as headaches and visual field impairment, were present in 56% of our patients compared with 70% in previously published reports (9, 11-13, 16, 17, 20-24, 26, 27, 29-37, 40, 41, 43-68). Less frequently, diabetes has been reported to cavernous sinus involvement; this has been reported in 6% of patients with lymphocytic hypophysitis (25, 36, 46, 50, 61). Symptoms indicating adenohypophysial dysfunction characterized by partial or total hypothalamic-pituitary function were noted in 63% of patients in this series; this figure is similar to previous reports in which up to 68% of patients were affected (1-3, 5, 7-19, 21, 22, 24, 31, 36-38, 40, 41, 49, 51, 52, 64, 72, 74). Hyperprolactinemia was present in 38% of patients in this series compared with 20% of previously published reports (9, 11, 16, 17, 22, 24, 31, 36-38, 40, 41, 49, 51, 52, 64, 72, 74). Neurohypophyseal involvement manifesting as diabetes insipidus was encountered in 19% of our patients, closely approximating the 14% reported by other investigators (6, 16, 26, 27, 36, 39, 40, 42, 44, 65, 74).

Hyperprolactinemia is a normal finding during pregnancy and the postpartum period, and this explanation has been offered for the hyperprolactinemia that is frequently associated with lymphocytic hypophysitis. Hyperplasia and/or hyperactivity of lactotrophs found by electron microscopy in 2 of our female patients can be attributed to pregnancy. However, of the 18 cases in the literature with reported hyperprolactinemia, 1 was a male (41) and at least 8 were females who were not pregnant or breast feeding (22, 24, 36, 38, 40, 51, 52, 72). In the current series, 2 patients (cases 2 and 16) had no underlying causes of hyperprolactinemia, and features of lactotroph hyperactivity noted in 1 male patient are in discrepancy with his clinical history of hypopituitarism. In many of these patients, therefore, elevated PRL levels may represent an endocrine marker of the disease. Several suggestions have been proposed to explain this increase in serum PRL levels in patients with lymphocytic hypophysitis. Stalk compression resulting in decreased dopamine delivery to the anterior pituitary (stalk section phenomenon) represents a feasible possibility. This theory most likely accounts for hyperprolactinemia associated with suprasellar masses such as in patients 2 and 16 of this series. Alternatively, the inflammatory process may directly alter dopamine receptors and the tonic inhibitory effect of dopamine on PRL release. An autoimmune mechanism involving the production of stimulating antibodies by plasma cells may lead to increased hormone secretion, analogous to the pathophysiologic mechanisms implicated in Graves' disease of the thyroid (24, 51).

Finally, diffuse destruction by the inflammatory process may in some cases result in escape of hormone into the circulation. These latter possibilities may account for PRL hypersecretion in some patients and, possibly, the GH excess documented in our patient 15. One case of combined PRL, GH, and TSH mild hypersecretion in a young nulliparous woman has previously been described in the literature (22).

Selective loss of adenohypophysial cells is likely to be the result of a targeted autoimmune attack (11). The failure to detect corticotroph cells by electron microscopy and/or immunocytochemistry in at least two of our patients (cases 12, and possibly 10 and 13) correlates well with the clinic presentation of cortisole deficiency; this might indicate a true isolated ACTH deficiency. Even though isolated corticotropin deficiency is rare, it represents the most common type of anterior pituitary hormone deficiency encountered in patients with proven or putative lymphocytic hypophysitis (2, 15, 17, 18, 75-77). Isolated TSH deficiency has also been reported (76), and selective absence of gonadotropins has been described (78). The pituitary tissue from one of our patients was found to be nonimmunoreactive for ACTH, TSH, FSH, and LH; clinical correlation was not available in this case (patient 10). This finding may not indicate total absence of these cells, because this result was obtained from a biopsy specimen that may or may not be representative of the entire gland. These results are not totally unexpected in view of the massive parenchymal destruction noted in some cases.

Neurohypophyseal dysfunction manifesting as diabetes insipidus can be attributed either to direct inflammatory invasion, destruction, and/or compression of the posterior lobe or pituitary stalk as shown in two of our cases (patients 2, 16).

Review of previously published reports indicates that nearly 20% of patients present with a history of other autoimmune conditions. Among these, primary hypothyroidism secondary to chronic lymphocytic thyroiditis represents the commonest finding. A similar frequency of 25% was identified in our series. In addition, transient lymphocytic thyroiditis (7, 14) and polyglandular failure have also been reported (78, 79).

The pathogenesis of lymphocytic hypophysitis has been attributed to autoimmunity even from its first description (1). Many indications support this hypothesis. Circulating antipituitary antibodies have been detected in a minority of patients with the disease (4, 7, 50, 72). The association of lymphocytic hypophysitis with pregnancy has been explained by the documentation of antibodies that react with nonhormonal antigens in hyperplastic lactotrophs (80). Antipituitary antibodies have also been detected in patient with the empty sella syndrome (81), idiopathic GH deficiency (82, 83), Cushing's syndrome (84), and different autoimmune isolated and polyendocrinopathies without hypophysitis (80). In an isolated case of ACTH deficiency, the presence of antibodies to corticotroph antigens was detected in secretory granules that contained neither ACTH nor other POMC-derived peptide (75). It has been suggested that the antigen in question could well be a cell-specific factor required for POMC processing. The different methods for detection and quantitation of circulating antipituitary antibodies used in different studies do not allow for reliable conclusions to be made (83, 85, 86). Nevertheless, the exact role of these autoantibodies in the pathogenesis of lymphocytic hypophysitis remains largely unknown.

Specific subtypes of the major histocompatibility complex (MHC) human leukocyte antigens (HLA) can be correlate
with a number of autoimmune endocrine disorders. HLA-DR4, DR5, DRW53/52, DQW3 are commonly detected in patients with Hashimoto’s thyroiditis (87, 88) while HLA-BW35 and A28 are associated with insulin dependent diabetes mellitus (89). HLA-B8 has been associated with immunological hyperresponsiveness in normal persons (90), and DR2 has been present in patients with a variety of autoimmune diseases. All these HLA antigens have also been detected in patients with lymphocytic hypophysitis (5, 11, 25, 31, 35, 45, 46, 50, 61). It is likely that HLA-DR genes are not responsible for the genesis of the autoimmune response per se, but may be closely related, in some subjects, with the genes directly responsible (91).

It has been proposed that the local aberrant expression of HLA-DR antigen by epithelial cells and their subsequent capacity to present surface autoantigens to T-lymphocytes can act as a possible mechanism in the pathogenesis of endocrine autoimmunity. The primary trigger of this abnormal expression might be a viral or other local environmental factor that induces interferon release. Interferon is the best-known inducer of DR expression. The activated T-lymphocytes can then initiate a series of humoral and cytotoxic mechanisms of cell destruction. Consequently the well-known association of endocrine autoimmunity with certain DR subtypes could reflect a genetic predisposition for an abnormal response to viral or other environmental factors (6, 63, 92). HLA positivity has been detected in several organs undergoing autoimmune attack (93–95). Similarly, detection of HLA class II expression on pituitary lymphocytes in lymphocytic hypophysitis may shed light on the probable pathogenetic role of the MHC system in autoimmune pituitary inflammation and destruction. Using immunohistochemistry, McCutcheon and Oldfield (24) could not identify MHC class II positive antigens on pituitary cells from patients with lymphocytic hypophysitis.

Experimentally, subcutaneous injections of human anterior pituitary gland homogenates in Freund’s adjuvant produce a disease histologically characterized by focal lymphoid aggregates and diffuse mononuclear cell infiltration of the pituitary. Interestingly, this adenohypophysitis was found to be more pronounced in pregnant and lactating rats (96, 97). Similar results have been obtained by immunization of rabbits with homologous pituitary tissue in complete Freund’s adjuvant (98).

In patients with lymphocytic hypophysitis, CT or MR imaging has revealed features of an enlarging pituitary mass in up to 95% of patients (83% in the current series) with frequent evidence of suprasellar extension. The radiographic appearance cannot be easily distinguished from a pituitary adenoma. Recent reports, however, point to some possible clues to the correct diagnosis on MR imaging. These include loss of the hyperintense bright spot signal of the normal neurohypophysis, thickening of the pituitary stalk, and enlargement of the neurohypophysis in cases where the latter is also involved (99). These radiographic criteria will need to be prospectively evaluated.

Another interesting observation is that BEC administration may improve visual fields, as it did in one of our patients (case 5) and reduce elevated prolactin levels; however, it does not alter the size of the pituitary mass (cases 9, 14) and (24, 35, 36, 63, 65, 72). Thus an attempt at therapeutic control of a presumed prolactinoma may serve as a diagnostic alternative in patients with hypophysitis.

A correct preoperative diagnosis of lymphocytic hypophysitis was suspected in only two of our patients (cases 1 and 44). Our review of the literature also shows that in only few instances was the diagnosis considered preoperatively (7, 24, 33, 44). These findings underscore the lack of any specific and reliable diagnostic clinical, biochemical, or radiographic criteria that would facilitate the correct preoperative diagnosis of this condition.

Histologic examination represents the basis for confirmatory diagnosis of lymphocytic hypophysitis. Evaluation of the affected pituitaries examined in this series revealed a dense polyclonal inflammatory infiltrate with a mixed T and B cell population. Other investigators have reported similar findings (24, 33). The differential diagnosis should include other inflammatory processes such as tuberculosis, sarcoidosis, syphilis, and giant cell granuloma. The presence of multinucleated giant cells generally distinguishes these conditions from lymphocytic hypophysitis. Sheehan’s syndrome (postpartum pituitary necrosis), which may be associated with a similar clinical presentation of gradually progressive hypopituitarism, should also be considered in the differential diagnosis. This disorder can easily be excluded when there is no history of a complicated delivery (100); however, it may be that some patients with presumed Sheehan’s syndrome but no clear history of postpartum hemorrhage or sepsis have lymphocytic hypophysitis (85, 101).

The natural history of lymphocytic hypophysitis is not well established. Progressive severe and permanent hypopituitarism can be effective of the degree of destruction of hypophysial tissue and has resulted in severe fatality complications in 19% of our cases. However, spontaneous partial or total pituitary function recovery and/or mass resolution has been described in some patients with morphologically documented or clinically suspected lymphocytic hypophysitis (7, 13, 14, 16, 21, 43). In these cases, the hypopituitarism may have been caused by compression of hypophysial cells either by the inflammatory infiltrate or edema, rather than by irreversible cell destruction. The majority of patients, however, require active management. BEC administration can improve visual fields and reduce hyperprolactinemia, as described above; however, it does not affect sellar enlargement. Corticosteroids that have been advocated to reduce inflammation and have been effective in some patients (34, 36, 37, 50), but its efficacy in this disorder remains uncertain. In our patients 10 and 42, and in other instances reported, no benefit was achieved (44). One patient received both BEC and prednisolone therapy with transient improvement of the visual field deficit and experienced subsequent deterioration (31). Surgery should be performed in cases associated with progressive conservative features or those in which radiographic or neuroendocrine deterioration is observed during conservative management with corticosteroids and hormone replacement (28, 31). Transsphenoidal surgery is both diagnostic and therapeutic. It has resulted in amelioration of symptoms of a sellar fullness in some patients (26, 28, 29, 33–35, 44, 50, 53, 54, 62, 66). Hyperprolactinemia (9, 36, 38, 49, 51, 64) and pituitary
tion (26, 34, 62) have also been reported to resolve following pituitary surgery in some cases. In two of our cases, progressive and total recovery of pituitary function was observed following transphenoidal biopsy. However, surgical intervention has been associated with further deterioration of visual field defects in one patient (31) and may result in diabetes insipidus, as it did in one of our patients (case 4). Hypopituitarism developed or was worsened following extensive surgery in several reports (22, 29, 31, 37, 64, 65), highlighting the importance of proper diagnosis and conservative management of patients with this lesion. We propose that in cases of suspected hypophysitis, a frozen section should be performed to confirm the diagnosis and to avoid aggressive resection of potentially viable pituitary tissue.

In conclusion, lymphocytic hypophysitis should be considered in the differential diagnosis of pituitary masses in females during pregnancy or in the postpartum period as well as those patients in whom pituitary hormone deficiency is noted in association with a coexisting autoimmune disorder. This clinical suspicion should be extended to include patients presenting with rapidly growing pituitary masses associated with compressive effects with or without hypophysial dysfunction and to those patients with hyperprolactinemia that responds to BEC therapy without an associated reduction in pituitary mass size or compressive symptomatology. The diagnosis can only be clearly established with histologic confirmation. Nevertheless, because of the transient endocrine and compressive features of this condition in many instances, conservative treatment on the basis of clinical suspicion alone may obviate the need for aggressive pituitary surgery.

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