CASE REPORT

Lymphocytic hypophysitis: Report of an unusual case of a rare disorder

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ABSTRACT. A 36-year-old non-pregnant woman presented with a four-month history of progressive visual deterioration and amenorrhea. The latest gestation was 6 years earlier. Hormonal study revealed central diabetes insipidus, hypopituitarism, and slightly increased prolactin level. Ophthalmologic examination showed bilateral hemianopsia. In the magnetic resonance imaging an intrasellar mass with supra and retrosellar extension was found. The mass showed a polylobular aspect with heterogeneous signal within the tissue. The normal neurohypophysis could not be identified. Pterional craniotomy was performed. The pathological examinations revealed fibrous tissue with heavy inflammatory infiltrate composed of lymphocytes and plasma cells, islands of eosinophilic epithelial cells stained positively for chromogranin, GH, ACTH, and PRL and negatively for antibodies directed against HLA-II antigens. This case of lymphocytic hypophysitis was not related to pregnancy and involved the neurohypophysis. We discuss the features that can help to make a preoperative differential diagnosis.

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INTRODUCTION

Lymphocytic hypophysitis (Lh) is a rare inflammatory lesion of the pituitary gland. Since its first description in 1962 (1) at autopsy of a 22-year-old woman, about 100 cases have been reported, most of them in women and with a close temporal relationship to pregnancy. Only a few of them have involved men or female patients out of the pregnancy or in the postpartum period (2, 3). Clinically, Lh is characterized by symptoms of compressive sellar mass, with varying degrees of hypopituitarism. It has been stated that the loss of pituitary function is out of proportion to the degree of pituitary enlargement, because hypopituitarism results from specific pituitary gland destruction rather than compression and atrophy of normal pituitary tissue (4); the posterior pituitary gland and pituitary stalk are typically spared, so that diabetes insipidus (DI) is not part of the characteristic picture (5). Many reports strongly support the original suggestion of an autoimmune pathogenesis of this lesion (2, 6, 7). The diagnosis can only be firmly established by histologic examination that shows involvement of the anterior pituitary by a dense plasmacytic and lymphocytic infiltrate accompanied by oedema and fibrosis. We report a further case of Lh in a 36-year-old non-pregnant woman, clinically characterized by visual loss, partial hypopituitarism, and DI.

CASE REPORT

A 36-year-old woman with a tumor of the hypothalamic-hypophysal area was referred for endocrinological evaluation. For the previous 4 months she had suffered from progressive visual deterioration of her left eye, and was amenorrheic from that time. During the last two months, she had noticed decreased libido, constipation, and increasing polyuria and polydipsia, without headache or galactorrhea. Her obstetric history consisted of two gestations with spontaneous deliveries at term of healthy infants, the most recent of which had occurred six years earlier. Six months after that delivery she had suffered a not well-documented episode of thyroid dysfunction. She remembered she had been treated with an antithyroid drug. Several weeks later she began to feel tired and withdrew herself from the treatment. The thyroid
function recovered spontaneously. She did not have any family history of autoimmune diseases or DI. The ophthalmologic examination showed bilateral temporal hemianopsia and a central scotoma. Physical examination was otherwise unremarkable. In the pre-operative magnetic resonance imaging (MRI) of the cranium, performed before and after the administration of gadolinium, an intrasellar mass was found. It was isointense with heterogeneity on T1-weighted images. On sagittal planes it featured a tongue-like supraventricular extension. The basal hypothalamus was infiltrated, with partial involvement of the third ventricle. On coronal planes the optic chiasm was displaced upward. The mass showed a polylobular aspect, with nodular areas that were hyperintense on T1 and hypointense on T2, interpreted as calcifications. Contrast-enhanced T1-weighted images revealed heterogeneous pituitary enhancement. There was a ring-like contrast enhancement with central hypointense area. The pituitary stalk was obscured by the mass and could not be differentiated from the lesion. The T1-weighted images lacked the hyperintense signal of the neurohypophysis, and could not be identified. The carotid arteries, sinus cavernous, and sphenoid sinus appeared normal (Fig. 1). The suspected radiological diagnosis was craniopharyngioma. The initial serum biochemistry was normal with Na+: 145 mEq/l, Osm.: 293 mosm/kg. The water deprivation test provided a mild DI; the peak urinary and plasma osmolality were 231 and 294 mosm/kg, respectively. Urinary osmolality increased in response to exogenous subcutaneous desmopressin to 372 mosm/kg (increment 61%). Endocrinological evaluation after triple stimulation revealed: adrenal insufficiency, hypogonadism and decreased growth hormone (GH) secretion, with a slightly increased prolactin (PRL) level (Table 1). Radioimmunoassay was negative for thyroid peroxidase and thyroglobulin antibodies. Her HLA typing was A11/13B51/53Bw4DR52, which is not associated to any autoimmune endocrine disorder. After proper replacement therapy, surgery was performed. Because the lesion was dumbbell-shaped, an approach via a pterional craniotomy was used. A grey, creamy encapsulated mass with some areas of firm tissue was found. Several fragments of rubbery greyish tissue with a total volume of 1 cm3 were submitted for pathologic evaluation. Microscopically, the bulk of the lesion consisted of fibrous tissue with a heavy inflammatory infiltrate composed of lymphocytes and plasma cells. No granulomas or giant cells were identified (Fig. 2). Roughtly the same amount of lymphoid cells was immunohistochomically reactive for T-cell (CD3, Atom) and B-cell (L-26, DAKO) markers as determined on paraffin sections. The plasma cells represented a third of the inflammatory infiltrate and were polyclonal in nature. Several distorted islands of eosinophilic epithelial cells were focally present; these stained positively for chromogranin (DARK-A3, DAKO), GH, ACTH and PRL and negatively for antibodies directed against HLA-I and HLA-II (both from DAKO). Following surgery the visual defect improved, but endocrinological assessment revealed panhypopituitarism (Table 1), with more pronounced hyperpro-

<table>
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<th>Glucose (3.9-6.1) mmol/l</th>
<th>Cortisol (6-26) µg/dl</th>
<th>ACTH (4.7-41) pg/ml</th>
<th>T4 (0.8-2) ng/dl</th>
<th>TSH (0.3-5) µU/ml</th>
<th>PRL (3.6-19) ng/ml</th>
<th>LH mU/ml</th>
<th>FSH mU/ml</th>
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<tbody>
<tr>
<td>Preoperative B/P</td>
<td>4.1/2</td>
<td>2/7.9</td>
<td>10/11</td>
<td>1.1</td>
<td>0.8/5.7</td>
<td>40</td>
<td>2.4/2</td>
<td>1.9/5.7</td>
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<tr>
<td>Postoperative B/P</td>
<td>3.9/1.8</td>
<td>0.28</td>
<td>5.3/6</td>
<td>0.1/0.1</td>
<td>96/114</td>
<td>0.1/0.1</td>
<td>0.1/0.5</td>
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B: basal, P: peak.

Lymphocytic hypophysitis
lactinemia, and DI. The MRI was repeated 2 and 6 months post-operatively and showed a residual 5 mm sellar.

DISCUSSION

Classically Lh has been reported in females during pregnancy or in the post-partum period. More recently it has been suggested that the disease should be considered in the differential diagnosis of any pituitary mass (8).

We present an unusual case of Lh in a woman of child-bearing age without association either with pregnancy or with the post-partum period and with involvement of the neurohypophysis. It has been estimated that in 25% of the cases involving women the disease is not associated with pregnancy, and DI has only been encountered in 14–19% of the patients (2). Including our case, eleven cases of Lh not related to pregnancy and featuring DI have been reported (9). The patient also presented with visual field impairment due to compression by the mass, and partial adenohypophyseal hypofunction, with slight hyperprolactinemia. Elevated serum PRL level suggests that the infiltration of the hypophysial stalk, and not only the destruction of the hypophysial parenchyma by inflammatory infiltration, may play a role in hypopituitarism. It could explain transient endocrine and compressive features of this condition in many instances. The pituitary tissue was found immunoreactive for GH, PRL and ACTH. The latter finding is a rare occurrence, since ACTH cells are the most frequently affected (2, 4). Nearly 20% of patients present with a history of other autoimmune conditions, in this patient the transient thyroid dysfunction was probably a post-partum thyroiditis. At the time of presentation, the thyroid function was normal, and antithyroid antibodies (thyroid peroxidase and thyroglobulin antibodies) were negative. A test for antipituitary antibodies was not performed because the lack of any standard method for detection, which does not allow for reliable conclusions about the usefulness of such a serologic presurgical marker (2). The MRI images are not typical of pituitary adenoma. The latter, if it is not substantially enlarged, generally presents like a homogeneous mass, and contrast enhanced T1-weighted images show a homogeneous tissue. The patient under discussion has a markedly enlarged asymmetric, polylobular sellar mass, with nodular areas, and heterogeneous signal within this tissue. On images obtained after the administration of gadolinium there was a heterogeneous pituitary enhancement of the mass. These images can be seen when pituitary adenomas reach a considerable size and suffer degeneration or haemorrhage. Craniohypophyseal hypofunction was the most common neoplasm in the hypothalamic-pituitary region in children, although it can develop at any age. The polylobular aspect of the lesion resembling cysts and the nodular hyperintense on T1 and hypointense on T2-weighted areas interpreted as calcifications suggested initially the diagnosis of craniopharyngioma. Probably advances in MRI imaging techniques like dynamic MRI studies provide new insights into the diagnosis and pathogenesis of lymphocytic hypophysitis. Recently Sato et al. (10) have reported progressively decreasing pituitary vasculature in patients with lymphocytic hypophysitis or infundibuloneurohypophysitis. Unfortunately we could not perform a dynamic MRI study. The post-operative MRI (performed at 6 months) showed post-surgical changes, thickening of the optic chiasm and an irregular stalk (Fig. 3). Even from the original description of this entity by Goudie et al. (1) an autoimmune pathogenesis has been generally proposed. In one previous report the immunohistochemical study included class I and II MHC antigens (11). As in our case, the cells of the adenohypophysis were negative for class II MHC [a positive finding would have lent further support to the autoimmune hypothesis, since inappropriate expression of class II MHC appears to underlay most examples of endocrine autoimmunity (12)]. As stressed by McCutcheon et al. (11), this observation needs to be confirmed in other cases before any conclusions can be drawn. Making a correct pre-operative diagnosis is of paramount importance if we take into account that there are some cases with spontaneous partial or to
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