Brief report

Lymphocytic hypophysitis with lachrymal, salivary and thyroid gland involvement

Olivier Lidove\textsuperscript{a}, Jean-Charles Piette\textsuperscript{b}, Frédéric Charlotte\textsuperscript{c}, Nathalie Cassoux\textsuperscript{d}, Jean-Michel Correas\textsuperscript{e}, Thomas Papo\textsuperscript{b,\ast}

\textsuperscript{a}Internal Medicine Unit, Internal Medicine, Bichat Hospital, 46 rue Henri Huchard, 75877 Paris cedex 18, France
\textsuperscript{b}Internal Medicine Department, Pitié-Salpêtrière Hospital, 83 Boulevard de l'hôpital, 75651 Paris cedex 13, France
\textsuperscript{c}Pathology Department, Pitié-Salpêtrière Hospital, 83 Boulevard de l'hôpital, 75651 Paris cedex 13, France
\textsuperscript{d}Ophthalmology Department, Pitié-Salpêtrière Hospital, 83 Boulevard de l'hôpital, 75651 Paris cedex 13, France
\textsuperscript{e}Radiology Department, Necker Hospital 149 rue de Sèvres, 75743 Paris cedex 15, France

Received 14 August 2003; received in revised form 11 November 2003; accepted 25 November 2003

Abstract

We report on hypophysitis associated with a prominent lymphoid infiltration of salivary and lachrymal glands in a 35-year-old woman with a dramatic response to steroids. Four years later, overt Graves' disease developed. To our knowledge, pseudotumoral lymphocytic infiltration of both lachrymal and salivary glands has never been described in association with hypophysitis. Benign lymphocytic hypophysitis may belong to a spectrum that extends from low-grade lymphoid proliferation to autoimmune disease. Such a process may follow a regional tissue distribution including pituitary, thyroid, lachrymal and salivary glands.

© 2004 Elsevier B.V. All rights reserved.

Keywords: Hypophysitis; Graves' disease; Salivary gland; Lachrymal gland

1. Introduction

Lymphocytic hypophysitis is considered an autoimmune reaction in the anterior pituitary and must be included in the differential diagnosis of mass lesions of the sella turcica during pregnancy [1]. Although the literature contains records of more than 100 biopsy-proven cases, the relevant target autoantigens have thus far not been identified. We report on hypophysitis associated with prominent salivary and lachrymal gland lymphocytic infiltration.

2. Case report

A 35-year-old woman was admitted to our hospital in November 1994 because of proptosis related to lachrymal gland enlargement. She was born in Senegal (Africa). Past history was unremarkable. She had three children. Breastfeeding was stopped in June 1994. The patient had no treatment. On admission, she presented with a bilateral proptosis and palpable, symmetrical enlargement of lachrymal and sub-maxillary glands. She did not complain of sicca syndrome or chin hypoesthesia, and she had no hepatomegaly, palpable spleen or peripheral adenopathy. She had regular menses. Bilateral galactorrhea was present. A large blood test panel including blood cell count, electrolytes, creatinine, calcium, C-reactive protein, LDL and transaminases was normal. Tests for autoantibodies including antinuclear factor, anti-Ro/SSA, anti-La/SSB, anti-ENA, anti-dsDNA, rheumatoid factor, antithyeroxperoxidase and antithyroglobulin antibodies were negative. Serum anti-TSH receptor antibody titer was at the upper level of the normal range. Serum angiotensin-converting enzyme was normal. Serum protein electrophoresis was normal. A search for lymphotrophic virus infection including HIV1 and HIV2, HTLV1, CMV and HCV was negative. Anti-EBV antibodies (anti-VCA type) were present at a low titer. Anti-HHV-8 antibodies were repeatedly disclosed by an immunofluorescence assay that was done on PEL (pleural effusion lymphoma) cell line latently infected
with HHV-8 but not with Epstein-Barr virus (BCP-1, provided by P.S. Moore, NYC, USA).

Endocrine test results are shown in Table 1. The only abnormal result was a low TSH, which could not be stimulated by TRH. Magnetic resonance imaging (MRI) confirmed lachrymal gland enlargement and elicited pituitary gland increased volume, with gadolinium enhancement on T1-weighted images (Fig. 1). Of note, orbital fat and muscles were not enlarged. Tm99 thyroid scintigraphy was not performed at this time. Thorax and abdomen CT scans were normal. Lachrymal and salivary gland biopsy specimens were analyzed by optic microscopy, which showed a prominent lymphoid infiltration with a few follicles. Immunohistochemical analysis showed a mixed T(CD3) and B(CD20) cell pattern. Southern blot and PCR study did not detect T or B lymphocyte clonal subsets or EBER (Epstein-Barr encoded RNA). The patient declined a bone marrow biopsy and CSF puncture. Pituitary gland biopsy was postponed because lymphocytic hypophysitis was highly suspected.

High-dose steroid treatment was administered in February 1995 (prednisone 80 mg/day). After 8 days, protoposis had disappeared. At day 30, cranial and orbital MRI was considered normal. The TSH level normalized in April 1995. Steroid dosage was progressively tapered. In April 1996, the patient was asymptomatic and pregnant for the fourth time. Moderate parotid and thyroid gland enlargement was noticed throughout pregnancy. Delivery was normal in November 1996 with a daily dosage of 8 mg prednisone. Blood TSH and FT4 levels remained within the normal range. In June 1997, cranial MRI was performed because of systematic follow-up and showed no recurrence of hypophysitis. In December 1997, prednisone treatment was stopped. By November 1998, the thyroid gland had become significantly enlarged. Levels of FT4 were high with undetectable TSH. Anti-thyroglobulin and antithyroxine antibodies were not detected. Anti-TSH receptor antibodies were positive. Tm99 thyroid scintigraphy showed homogeneous thyroid hypofunction. Graves' disease was considered and carbimazole treatment was started. Pituitary gland MRI was normal. Follow-up with repeated TSH testing and pituitary gland MRI was uneventful.

3. Discussion

The classical presentation of lymphocytic hypophysitis is peripartum hypopituitarism, often with a pituitary mass and visual failure. Secondary adrenal insufficiency, which can be isolated, is a frequent feature which, when undiagnosed, may be fatal. In the early stage, the pituitary gland is enlarged like a pituitary tumor, from which it cannot be distinguished on CT or MRI scanning. In the later stages, the gland may atrophy, leaving an empty sella, as occurs in Sheehan's syndrome. Spontaneous resolution of both the mass and the hypopituitarism has been reported. Neurosurgical intervention has led to irreversible pituitary failure in some cases.

We describe a pituitary gland disease, initially associated with symptomatic salivary and lachrymal gland involvement, which was obviously related to lymphoid infiltration, with a dramatic response to steroids. Because lymphocytic hypophysitis was highly probable, pituitary biopsy was not performed.

To explain such a process, we mainly considered three hypotheses: (1) granulomatosis, (2) lymphoproliferative

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FT4 (10–25 pmol/l)</td>
<td>15</td>
<td>12</td>
<td>16.1</td>
<td>17.5</td>
<td>53</td>
<td>9.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH (0.1–4 mIU/l)</td>
<td>&lt;0.005</td>
<td>&lt;0.005</td>
<td>1.4</td>
<td>0.28</td>
<td>1.1</td>
<td>&lt;0.005</td>
<td>0.6</td>
<td>2.2</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>TRH test TSH T0</td>
<td>&lt;0.005</td>
<td>1.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH T30</td>
<td>&lt;0.009</td>
<td>4.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH T120</td>
<td>&lt;0.005</td>
<td>2.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin (4–14 ng/ml)</td>
<td>16</td>
<td>10</td>
<td>10</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH (10–50 pg/ml)</td>
<td>&lt;10</td>
<td>22.5</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol (µg/l)</td>
<td>105</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oestradiol (30–230 ng/l)</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH (2–12 IU/l)</td>
<td>9</td>
<td>3</td>
<td>2.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LH (1–8 IU/l)</td>
<td>8</td>
<td>6</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVP (1.85–4.8 pmol/l)</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-TPO</td>
<td>32</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibodies</td>
<td>34</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-TG antibodies (N&lt;100 IU/ml)</td>
<td>10.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS antibodies (TRAk) (0–9 U/l)</td>
<td>16.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1) No pituitary reactivity, (2) low response, (3) steroid treatment from February 1995 to October 2000.
The association of sarcoidosis with lymphocytic hypophysitis has been previously described and the question of whether these two entities represent the ends of a continuum has been raised. In our case, a granulomatous process, i.e., sarcoidosis, could have been postulated, but indirect testing (lymphocyte blood count, 24-h urine calcium collection, serum angiotensin converting enzyme, thorax CT scan) was normal. Moreover, multiple histological sampling of salivary and lacrimal glands did not show granuloma. Of interest, in both lymphocytic hypophysitis and granulomatous hypophysitis, ultrastructural studies show activated cytotoxic lymphocytes that interdigitate with pituicytes within periacinar basement membranes [1].

Most tumors in the sellar region are pituitary adenomas, but other tumors, such as Rathke’s cyst, craniopharyngioma, germ-cells tumors and metastatic tumors, merit consideration. Hypophyseal non-Hodgkin’s lymphoma is exceedingly rare [2]. A low-grade lymphoproliferative disorder was initially suspected in our patient. Although no adenopathy or hepatosplenomegaly could be elicited, an extranodal lymphoma could have explained lacrimal, salivary and pituitary gland infiltration. B-cell lymphoma arising from mucosally associated lymphoid tissue (MALT lymphoma) is a clonal disorder that can affect lacrimal, salivary and thyroid glands, along with lung and digestive tissues. Moreover, MALT lymphomas have been found in salivary glands and in the thyroid, developing from reactive lymphoid tissue that may accumulate during an autoimmune process. Recently, MALT lymphoma of the pituitary gland has been described in a patient who also had lacrimal involvement [3]. In our patient, the histological hallmark of MALT lymphoma, which typically consists of a lymphoepithelial lesion, was not observed. Moreover, no clonal B cell proliferation could be demonstrated in salivary or lacrimal gland tissues. On the other hand, some atypical lymphoproliferative disorders, such as Castleman’s disease, which is often related to human herpesvirus-8 (HHV-8) infection, may consist of B cell polyclonal proliferation, with rare occurrence of B-cell monoclonal lymphoid contingent [4]. Our patient had serum anti-HHV-8 antibodies. Since HHV-8 seroprevalence may be as high as 50% in Africa, HHV-8 infection may not be significant in this case. Castleman’s disease mostly affects lymph nodes and not salivary, pituitary, or orbital glands. Eventually, pituitary gland lymphoma could be ruled out because of the 5-year follow-up without recurrence.

An autoimmune reaction may be implicated in the genesis of lymphocytic hypophysitis; whether the immune reaction related to this condition is primarily humoral or cell-mediated is not yet clear. Evidence exists for an autoimmune pathogenesis including the association with organ-specific antibodies, i.e., antipituitary antibodies, antimitochondrial, antiparietal and antinuclear antibodies. More recently, serum antipituitary autoantibodies reactive to pituitary cytosolic proteins were found in 70% of biopsy-proven lymphocytic hypophysitis when the incidence of antipituitary autoantibodies in patients with thyroid autoimmune disease was not significantly different from that in controls subjects [5]. In our case, an autoimmune disorder affecting exocrine tissues, especially Sjögren’s disease, was also considered, although no hypophysitis has been described in such a setting. No previous history of systemic disease was noticed. The patient did not suffer from sicca syndrome. Moreover, repeated testing for specific autoantibodies, including antinuclear factors, serum anti-SSA and anti-SSB antibodies was negative. Interestingly, another case of hypophysitis has been described with subsequent dacyroadenitis that could not be attributed to a definite Sjögren’s syndrome. Although transient infraclinal hyperthyroidism was probable at presentation in our patient (Table 1), full-blown Graves’ disease...
The association of sarcoidosis with lymphocytic hypophysitis has been previously described and the question of whether these two entities represent the ends of a continuum has been raised. In our case, a granulomatous process, i.e., sarcoidosis, could have been postulated, but indirect testing (lymphocyte blood count, 24-h urine calcium collection, serum angiotensin-converting enzyme, thorax CT scan) was normal. Moreover, multiple histological sampling of salivary and lacrimal glands did not show granuloma. Of interest, in both lymphocytic hypophysitis and granulomatous hypophysitis, ultrastructural studies show activated cytotoxic lymphocytes that interdigitate with pituicytes within perivascular basement membranes [1].

Most tumors in the sellar region are pituitary adenomas, but other tumors, such as Rathke’s cyst, craniopharyngioma, germ-cell tumors and metastatic tumors, merit consideration. Hypophysial non-Hodgkin’s lymphoma is exceedingly rare [2]. A low-grade lymphoproliferative disorder was initially suspected in our patient. Although no adenopathy or hepatosplenomegaly could be elicited, an extranodal lymphoma could have explained lacrimal, salivary and pituitary gland infiltration. B-cell lymphoma arising from mucosally associated lymphoid tissue (MALT lymphoma) is a clonal disorder that can affect lacrimal, salivary and thyroid glands, along with lung and digestive tissues. Moreover, MALT lymphomas have been found in salivary glands and in the thyroid, developing from reactive lymphoid tissue that may accumulate during an autoimmune process. Recently, MALT lymphoma of the pituitary gland has been described in a patient who also had lacrimal involvement [3]. In our patient, the histological hallmark of MALT lymphoma, which typically consists of a lymphoepithelial lesion, was not observed. Moreover, no clonal B cell proliferation could be demonstrated in salivary or lacrimal gland tissues. On the other hand, some atypical lymphoproliferative disorders, such as Castleman’s disease, which is often related to human herpesvirus-8 (HHV-8) infection, may consist of B cell polyclonal proliferation, with rare occurrence of B-cell monoclonal lymphoid contingent [4]. Our patient had serum anti-HIV-8 antibodies. Since HHV-8 seroprevalence may be as high as 50% in Africa, HHV-8 infection may not be significant in this case. Castleman’s disease mostly affects lymph nodes and not salivary, pituitary, or orbital glands. Eventually, pituitary gland lymphoma could be ruled out because of the 5-year follow-up without recurrence.

An autoimmune reaction may be implicated in the genesis of lymphocytic hypophysitis; whether the immune reaction related to this condition is primarily humoral or cell-mediated is not yet clear. Evidence exists for an autoimmune pathogenesis including the association with organ-specific antibodies, i.e., antipituitary antibodies, antimitochondrial, antiparietal and antinuclear antibodies. More recently, serum antipituitary autoantibodies reactive to pituitary cytosolic proteins were found in 70% of biopsy-proven lymphocytic hypophysitis when the incidence of antipituitary autoantibodies in patients with thyroid autoimmune disease was not significantly different from that in controls subjects [5]. In our case, an autoimmune disorder affecting exocrine tissues, especially Sjögren’s disease, was also considered, although no hypophysitis has been described in such a setting. No previous history of systemic disease was noticed. The patient did not suffer from sicca syndrome. Moreover, repeated testing for specific autoantibodies, including antinuclear factors, serum anti-SSA and anti-SSB antibodies was negative. Interestingly, another case of hypophysitis has been described with subsequent dacryoadenitis that could not be attributed to a definite Sjögren’s syndrome. Although transient infrachondral hyperthyroidism was probable at presentation in our patient (Table 1), full-blown Graves’ disease...
occurred 4 years after hypophysitis was initially documented. Pemphigus anemia, autoimmune thyroiditis, Graves' disease, systemic lupus erythematosus and Sjogren's syndrome have all been reported in association with hypophysitis [6,7]. Since hyperthyroidism itself triggers involution of pituitary thyrotropic cells, it is not the hormonal status but rather the autoimmune component of Graves' disease that is thought to relate to hypophysitis. Interestingly, in our case, thyroid hormone levels normalized under steroid treatment and clear-cut Graves' disease developed after prednisone treatment was stopped.

In such a pituitary gland disease, histological sampling by means of surgery should be discussed in order to exclude a tumoral process. In our patient, lymphocytic hypophysitis was highly suspected because of the following factors: female sex, young age, post-partum occurrence and polyclonal lymphocyte infiltration, which was thought to also occur in the pituitary gland since it was already demonstrated in the salivary and lachrymal glands. In such a case, steroid therapy, with close MRI pituitary gland monitoring, may be considered before diagnostic surgery is performed [8]. Indeed, medical treatment could be life-saving, as emphasized by the large proportion of autopsy reports. Moreover, delay in treatment institution may result in steroid inefficacy.

In conclusion, from our observation, we could speculate that benign lymphocytic hypophysitis belongs to a spectrum that extends from low-grade lymphoid proliferation to autoimmune disease. Such a process may follow a regional tissue distribution including pituitary, thyroid, lachrymal and salivary glands.

Acknowledgements

We are grateful to Jéréme Bertharet and Vincent Calvez for their helpful discussions.

References