Lymphocytic hypophysitis simulating a pituitary adenoma in a nonpregnant woman

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Abstract. Lymphocytic adenohypophysitis can cause pituitary expansion and hypopituitarism closely mimicking the features of a pituitary adenoma. In contrast to pituitary adenoma, lymphocytic adenohypophysitis occurs almost exclusively in young women in relation to pregnancy. We report a case of a 43-year-old nonpregnant nullipara who exhibited an intrasellar mass with diffuse homogeneous contrast enhancement on magnetic resonance imaging scanning. Serum hormone analyses revealed secondary hypoadrenalism, hypothyroidism, and hypogonadism. The patient underwent surgery for a presumed nonsecreting pituitary adenoma. Histopathological examination showed extensive infiltration of the anterior pituitary gland by chronic inflammatory cells. The immunohistochemical pattern of the inflammatory cells indicated the chronic and putatively autoimmune nature of the disease.

Key words: lymphocytic adenohypophysitis – pituitary gland – hypopituitarism – magnetic resonance imaging

Introduction


We report a case of hypophysitis in a 43-year-old nonpregnant nullipara who underwent surgery under the suspicion of a pituitary adenoma.

Case report

A 43-year-old woman presented with a 5-month history of increasing attacks of left-sided frontal headaches. Further complaints were myalgias, arthralgias as well as weakness and tiredness. She had gained 7 kilograms in weight within the last year. Oral contraceptives had been used for 23 years. Physical examination revealed no pathological findings except a symmetrical diffuse swelling of both hands with no preference to certain joints. Ophthalmological examination including Goldmann perimetry showed no visual disturbances. The erythrocyte sedimentation rate was elevated (51/83 mm) while all other laboratory parameters studied were within the normal range including protein electrophoresis and the rheumatoid factor. Skull X-ray revealed a moderately enlarged sella turcica. The computed tomographic scan demonstrated an intra- and suprasellar contrast-enhancing mass with compression of the optic chiasm. Magnetic resonance imaging with gadolinium confirmed the marked homogenous uptake of the contrast medium (Figure 1a,b). The various hormone analyses revealed secondary hypoadrenalism, hypothyroidism, and hypogonadism. Normal hormone secretion was found for growth hormone (GH) as well as for insulin-like growth factor (IGF-I) and prolactin (PRL) (Table 1).
Fig. 1 a: preoperative magnetic resonance imaging with gadolinium contrast medium demonstrating a contrast-enhancing mass compressing the optic chiasm (coronal view); b: preoperative magnetic resonance imaging (sagittal view, gadolinium-enhanced) with a contrast-enhancing intra- and suprasellar mass.

After substitution with hydrocortisone (25 mg daily given orally) and thyroxine (75 μg daily given orally) almost all clinical symptoms disappeared except headaches. Based on the assumption of a nonsecreting pituitary adenoma the pituitary was surgically exposed via the transnasal-transphenoidal route. After incision of the capsule a firm mass was found and a biopsy was taken. Histopathological sections showed extensive infiltration of the anterior pituitary gland by chronic inflammatory cells (Figure 2a,b). A small number of plasma cells and some lymphoid follicles with germinal centers were also identified (Figure 3a,b). These features represent chronic lymphocytic hypophysitis.

Material and methods

Paraffin sections were investigated with routine and immunohistochemical methods using monoclonal antibodies against FSH, LH, and TSH (Biobonex MA 026-5C), α-HCG (Immunotech 375, Marseille, France), PRL (BioGenex Laboratories LS031079, San Ramon, California), and polyclonal antibodies against ACTH (Dako, A 571, Glostrup, Denmark), GH (Sigma, G 2894, Deisenhofen, Germany), and GFAP (Dako Z 334). The infiltrating blood cells were characterized by monoclonal antibodies (Table 2). For electron microscopy the specimen was fixed in 2.5% glutaraldehyde. Ultrathin sections of the araldite-embedded material were investigated with Zeiss EM 10.

Table 2 Characterization of infiltrating blood cells by immunohistochemistry

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Dilution</th>
<th>Catalogue number</th>
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<tr>
<td>LCA anti-human leucocyte</td>
<td>1:100</td>
<td>Dako M 701</td>
</tr>
<tr>
<td>MT1 anti-human T cell</td>
<td>1:100</td>
<td>Dako M 786</td>
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<td>CD3 anti-human T cell</td>
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<td>Dako A 452</td>
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<tr>
<td>βF1 T cell receptor antigen</td>
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<td>Diagnostics,</td>
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<td>TA 1151</td>
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<td>Massachusetts,</td>
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<tr>
<td>CD20 anti-human B cell</td>
<td>1:1</td>
<td>Dako M 755</td>
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<td>1:10</td>
<td>Dako M 784</td>
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<tr>
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<td>Immunotech</td>
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<td>1228</td>
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<td>CD68 anti-human macrophage</td>
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<td>Dako 814</td>
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<tr>
<td>KPi</td>
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<tr>
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<td>Dianova 404</td>
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<td></td>
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<tr>
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<td>Dako M728</td>
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<td>1:6,000</td>
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<td>Lambda anti-human lambda light chain</td>
<td>1:3,000</td>
<td>Dako A 194</td>
</tr>
<tr>
<td>C3br anti-human C3b receptor</td>
<td>1:20</td>
<td>Dako M 710</td>
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</table>

*cycle and age related, **no normal range can be given, ***age-dependent
Fig. 2  a: Preserved pituitary tissue invaded by mononuclear cells (HE 380); b: dense infiltration of pituitary tissue by lymphocytes (leucocyte common antigen, APAAP method × 380).

Fig. 3a  Aggregation of B cells within a lymphoid follicle (CD21, APAAP method × 380); b: electron micrograph (× 7,200) showing lymphocytes (right margin), hormone producing cell (top), and plasma cells (arrows). Destruction of the pituitary tissue is apparent by dispersed hormone-containing granules.
Results

Histological results

Paraffin sections revealed anterior pituitary gland parenchyma with dense infiltrates of lymphocytes and plasma cells, and to a lesser extent macrophages. The inflammatory process involved the entire resected tissue. The infiltrating lymphocytes were polyclonal. Hormone expression of the autochthonous pituitary tissue was altered in the following manner: numerous cells stained positively for HGH and a large number of cells expressed α-HCG. Expression of PRL, FSH, and LH was limited to a few cells only. No reaction was found with anti-ACTH and anti-TSH. The majority of cells within the dense infiltrates were T cells. Germinal centers contained CD21- and L26-positive B cells (Figure 3a). Among the immunoglobulines the expression of IgM was strongest, focussing on the external nuclear membrane. IgG-positive cells were scattered diffusely. IgA-positive cells were rare. IgG-positive cells were found predominantly within the germinal centers. Peripherally situated T lymphocytes were positive for CD3 and MT1. CD68- and KP1-positive macrophages were scattered at random throughout the specimen. Electronmicroscopy confirmed the finding of chronic inflammation and its adverse effect to the pituitary gland. Cytoplasmatic fragments of hormone-producing cells were distributed among the infiltrating inflammatory cells (Figure 3b).

Postoperative course

Following the operation the headaches disappeared whereas the hormonal insufficiencies persisted. Clinical symptoms of hypothyroidism such as pasty swelling of face and ankles, weight gain, and lethargy disappeared after substitution with hydrocortisone and thyroxine. Three months postoperatively our patient developed a GH deficiency syndrome (Table 3) which was treated with human growth hormone supplementation.

The patient is now – at 3 years of follow up – still under substitution with hydrocortisone, thyroxine, and estrogen/progesteron. Furthermore, she is treated with recombinant human growth hormone (Genotropin) injections. Until now the patient is well. A control MRI study 1 year after operation revealed no signs of recurrence.

Discussion


Clinically lymphocytic hypophysitis may often mimick a pituitary adenoma. Headaches and impaired vision are the most frequent symptoms reported. Further misleading symptoms include amenorrhea [Miura et al. 1989, Prasad et al. 1991, Wild and Kepley 1986], galactorrhea [McCUTCHEON and Oldfield 1991, Wild and Kepley 1986], polydipsia, and polyuria [Lee et al. 1994] as well as rheumatoid complaints such as myalgias [Castle et al. 1988, Cosman et al. 1989, Jensen et al. 1986, Richtsmeier et al. 1980, Vanneste and KAMPHORST 1987] and arthralgias [Lee et al. 1994, Vanneste and KAMPHORST 1987]. Myalgias and a painful swelling of various joints were among the leading symptoms of our patient.

Secondary hypothyroidism as in our case was reported in a single case of a 24-year-old woman [Miura et al. 1989]. Lowered T3 and T4 levels were reported by Prasad et al. [1991]. However, the case presented by Vanneste and KAMPHORST [1987] suggests a low T3/T4 syndrome with normal TSH secretion. The symptoms of one patient were suggestive of hyperthyroidism which was documented by high basal serum concentrations of T3 and T4 as well as lowered TSH levels [Ozawa and Shishiba 1993]. Hypocortisolism as in our patient was a common

<table>
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<th>Time</th>
<th>Arginine test (0.5 mg/kg i.v.)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120 (min)</th>
<th>GHRH test (50 μg i.v.)</th>
<th>0.5b</th>
<th>3.7</th>
<th>4.9</th>
<th>–</th>
<th>–</th>
<th>GHRH (ng/ml)</th>
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<tr>
<td></td>
<td></td>
<td>0.5a</td>
<td>0.5</td>
<td>0.6</td>
<td>0.5</td>
<td>0.5</td>
<td>GH (ng/ml)</td>
<td>0.5b</td>
<td>3.7</td>
<td>4.9</td>
<td>–</td>
<td>–</td>
<td>GH (ng/ml)</td>
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a = IGF-1 concentration 14 ng/ml, b = IGF-1 concentration 30 ng/ml (normal age related range: 97 – 295 ng/ml)
finding in all cases except one [McCutcheon and Oldfield 1991]. Normal serum prolactin secretion was found in our case as well as in 2 of the previously reported cases [Miura et al. 1989, Vanneste and Kamphorst 1987]. Hyperprolactinemia was reported as the only hormonal disturbance by McCutcheon and Oldfield [1991]. Subnormal prolactin levels were described by Prasad et al. [1991] and Ozawa and Shishiba [1993]. GH deficiency syndrome was observed in 2 of the reported cases [Miura et al. 1989, Ozawa and Shishiba 1993]. Hypogonadotropic hypogonadism as in our patient was described by Miura et al. [1989]. Normal serum concentrations of FSH and LH were reported by Vanneste and Kamphorst [1987], whereas McCutcheon and Oldfield [1991] describe a slightly decreased LH secretion. Diabetes insipidus was reported by Vanneste and Kamphorst [1987] and Miura et al. [1989] in 2 women.

In search for a clinical indicator of lymphocytic hypophysitis the following parameters were investigated:

General signs of inflammation were documented by Ozawa and Shishiba [1993] with an increased sedimentation rate of 32 mm/h. This finding corresponds to the patient presented here. Lymphocytosis and eosinophilia were seen in 1 male patient [Guay et al. 1987]. In a single case immunoelectrophoresis showed an increased quantity of IgG and slightly increased IgM [Sobrinho-Simoes et al. 1985]. In the majority of the cases published parameters of inflammation were not documented.

By lumbar puncture, Vanneste and Kamphorst [1987] detected lymphocytes in the CSF of their patient. Among 2 male patients lumbar puncture revealed an increased leucocyte count in CSF [Lee et al. 1994]. Mc Grail et al. [1987] demonstrated clear CSF with a normal cell count while lumbar puncture was not described or not done in other cases, ours included. Thus, it is questionable whether an elevated cell count in the CSF is an indicator of lymphocytic hypophysitis.


The radiological findings in our case were in accordance with the most common features: moderately enlarged sella turcica in skull X-ray, circumscribed intra- and suprasellar contrast enhancing mass in CT scan, strikingly diffuse homogenous gadoliumine enhancement in MRI. An angiogram was not performed.


So far, only 2 reports refer to the immunohistochemical differentiation of the infiltrating inflammatory cells [Jensen et al. 1986, McCutcheon and Oldfield 1991]. In our specimen the dominant expression of CD3 and MT1 represents the predominance of T cells over B cells and macrophages. This is in agreement with the characteristics of infiltrates in other autoimmune diseases [McCutcheon and Oldfield 1991]. The inflammatory nature of the disease was confirmed by the successful conservative treatment with hydrocortisone in 2 patients [Bevan et al. 1992, Ozawa and Shishiba 1993]. The absence of ACTH-producing cells and TSH staining cells probably as a result of the inflammatory disease is in accordance with the endocrinological diagnosis of secondary hypocortisolism and hypothyroidism.

Conclusions

Lymphocytic hypophysitis is most frequently misdiagnosed as a pituitary adenoma. Findings on skull X-ray and CT scan as well as in cerebral angiograms in patients with lymphocytic adenohypophysitis are similar to those obtained in patients suffering from pituitary adenomas. However, it is striking that in patients with proven lymphocytic hypophysitis a homogenous contrast enhancement has been found in MRI scans. Thus, it may be suggested that the homogenous contrast enhancement in MRI studies may indicate a diffuse inflammatory disease of the pituitary and justify a conservative therapeutic approach.
Abbreviations

ACTH: adrenocorticotropic hormone
α-HCG: human chorionic gonadotropin
CSF: cerebrospinal fluid
CT: computed tomography
FSH: follicle-stimulating hormone
GFAP: glial fibrillary acidic protein
GHRH: growth hormone-releasing hormone
GHG: human growth hormone
IGF-I: insulin-like growth factor
LH: luteinizing hormone
MAB: anti-microsomal antibodies
MRE: magnetic resonance imaging
PRL: prolactin
T3: triiodothyronine
T4: thyroxine
TAK: anti-thyroglobulin antibodies
TRAK: TSH-receptor antibodies
TRH: thyrotropin releasing hormone
TSH: thyroid-stimulating hormone

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