CASE REPORT

Lymphocytic hypophysitis in a patient with Graves’ disease

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ABSTRACT. A case of lymphocytic hypophysitis is described in a patient with Graves’ disease and diabetes mellitus. The 62-year-old man was admitted to hospital with the complaints compatible with hyperthyroidism in April 1993. His medical history, physical examination, thyroid function tests, thyroid scintigraphy and thyroid ultrasonography revealed Graves’ disease. The patient had also suffered from diabetes mellitus for three years. After this, the patient’s progress was not monitored for two years. The patient presented himself again in September 1995 with complaints of hypothyroidism, hypogonadism and hypoadrenalism. Hormonal investigation showed panhypopituitarism. A magnetic resonance imaging of the pituitary gland disclosed an enlarged pituitary and a thickened infundibulum. The high intensity signal of the neurohypophysis was absent. Transsphenoidal hypophysectomy was performed which revealed a grey-white, relatively avascular pituitary mass. Histology showed diffuse infiltration of the anterior pituitary by numerous lymphocytes. The neurohypophysis also showed evidence of lymphocytic infiltration. On the basis of these findings we suggest that lymphocytic hypophysitis may be associated with Graves’ disease.
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INTRODUCTION

Lymphocytic hypophysitis, which is a rare disorder, has recently been recognized as a distinct clinicopathologic entity resulting in hypopituitarism (1, 2). Nearly 100 cases have been reported since the first description of the entity in 1962 (3, 4). Most cases occur in women, usually in relation to pregnancy; this, together with the frequent occurrence of circulating autoantibodies, has suggested an autoimmune etiology (5). Commonly, lymphocytic hypophysitis presents with features of a mass lesion, with variable loss of anterior pituitary function. Posterior pituitary involvement is rare. It may also appear with suprasellar extension that may result in compression of the optic chiasm. Spontaneous resolution has been reported and some authors recommend conservative treatment with or without a trial of steroids (6-8). Corticosteroid therapy has been advocated to reduce inflammation and has been reported to cause full endocrinological recovery (8, 9). In the present report we describe a male patient with diabetes mellitus and Graves’ disease who developed panhypopituitarism due to lymphocytic hypophysitis.

CASE REPORT

A 62-year-old man was admitted to the University of Erciyes, Medical School Hospital in April 1993 with complaints of weight loss, finger tremors, palpitations, increased sweating, and goitre. The patient had also been suffering from diabetes mellitus for three years and this was being controlled with a sulphonylurea drug. His medical history, physical examination, thyroid function tests, thyroid scintigraphy, and thyroid ultrasonography revealed Graves’ hyperthyroidism. Thyroid ultrasonography showed that the gland was enlarged in size and the echogenicity was inhomogeneous and low in intensity. The thyroid gland was diffusely enlarged. The serum T4 (normal, 61.9-165.1 nmol/l) free T4 (normal, 10.3-24.5 pmol/l), T3 (normal, 0.8-2.6 nmol/l) and free T3 (normal, 3.4-7.2 pmol/l) concentrations were markedly elevated (205.1 nmol/l, 47.7 pmol/l, 4.4 nmol/l and 10.5 pmol/l, respectively) and the serum TSH (normal, 0.3-4.1 mU/l) level was undetectable. The erythrocyte sedimentation rate (ESR) was 70mm/h. Propylthiouracil therapy (300 mg/day) was initiated. The patient was seen at monthly intervals for two months and at the

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end of this period thyroid function tests were as follows: T4, 150.9 nmol/l; free T4, 24.5 pmol/l; T3, 2.6 nmol/l; free T3, 6.2 pmol/l and TSH, 0.6 mU/l, respectively. The dosage of propylthiouracil was reduced to 150 mg/day. After this the patient’s progress was not monitored for some two years. The patient again presented himself in September 1995 with complaints of hypothyroidism, nausea, vomiting, weakness and dizziness. Physical examination on admission revealed a chronically ill-appearing man with a blood pressure of 90/60 mmHg and a pulse rate of 50 per minute. Ophthalmological examination showed normal visual fields. The results of a complete blood count revealed the following: Hemoglobin, 140 g/l; white cell count, 8 x 10^9/l; ESR was 110 and 115 mm/h. Electrolytes, kidney and liver function tests were normal. He stated that he had used propylthiouracil for approximately one year but he had not taken this drug for at least the last six months. The serum, T4, free T4, T3, free T3 and TSH levels were, 11.6 nmol/l, 9.0 pmol/l, 0.6 nmol/l, 2.8 pmol/l and 0.1 mU/l, respectively. These results were compatible with secondary hypothyroidism. For the findings suggesting hypopituitarism, further investigations related to pituitary function were carried out. The basal hormone levels were as follows: FSH, 1.9 U/l (normal, 1-9); LH, 3.8 U/l (normal, 1-15.6); Cortisol, 77.3 nmol/l (normal, 100-700); testosterone, 3.4 nmol/l (2-5.5); PRL, 138.0 mU/l (5-350). Then dynamic pituitary function tests were performed. TSH and PRL responses to TRH (200 µg), LH and FSH responses to GnRH (100 µg), cortisol responses to ACTH (250 µg) and GH responses to L-Dopa (250 mg) stimulation tests were evaluated. The results are shown in Table 1. Investigation revealed the patient to be suffering from panhypopituitarism. Thyroid autoantibodies were negative. Magnetic resonance imaging (MRI) demonstrated an enlarged pituitary mass measuring 18 mm of height and a thickened infundibulum. A homogeneous enhancement of this mass was observed after a gadolinium injection (Fig. 1). The high intensity signal of the neurohypophysis was absent on T1-weighted images. Transsphenoidal hypophysectomy was performed which revealed a greywhite, relatively avascular pituitary mass. Histology showed diffuse infiltration of the anterior pituitary by numerous lymphocytes which were confirmed by leucocyte common antigen stain (Fig. 2). No lymphoid follicles were present. Although a few multinucleate macrophages were seen, no granulomas were present. Immunohistochemical staining for prolactin, GH, ACTH, gonadotropins, and TSH confirmed the presence of pituitary glandular tissue. The neurohypophysis also showed evidence of lymphocytic infiltration (Fig. 3). Postoperatively, he remains well on thyroxine and prednisolone replacement. During the postoperative period, the patient developed moderate diabetes insipidus and this was controlled with DDAVP nasal spray. The ESR was 15 mm/h two months after surgery.

**DISCUSSION**

Lymphocytic hypophysitis is a rarely occurring inflammatory lesion of the pituitary gland. A firm diagnosis of lymphocytic hypophysitis can be made only histologically and, it may coexist with normal pituitary tissue and with functioning pituitary adenomas, left untreated, it can progress to severe panhypopituitarism (5). It has been reported that complete removal of a pituitary mass is needed to make an accurate tissue diagnosis and to decide on the correct definitive treatment (5). But, spontaneous pituitary function recovery has been described in some patients with lymphocytic hypophysitis (6, 7). On the other hand, the pituitary function may ultimately return to normal in any case after corticosteroid treatment (8, 9). For this reason, we think that surgical intervention should be avoid-

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<th>Table 1 - Serum levels of TSH, PRL, FSH, LH, cortisol and GH after administration of TRH, GnRH, ACTH, and L-Dopa.</th>
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ed whenever possible. To perform a limited surgical biopsy to obtain a histologic diagnosis and to follow the evolution of the mass with MRI or CT scan may be another reasonable approach (10). Since our patient had panhypopituitarism and all the findings suggested lymphocytic hypophysitis, we preferred the complete removal of the mass. While the pathogenesis of lymphocytic hypophysitis is unclear, an autoimmune cause has been suggested. In 1962, Goudie and Pinkerton reported the case of a young woman with histologically confirmed Hashimoto’s disease and lymphocytic infiltration of the adenohypophysis (3). Many subsequent cases with lymphocytic hypophysitis associated with thyroiditis or hypothyroidism were also described in the literature (11-13). Lymphocytic hypophysitis may be associated with other autoimmune disorders: adrenalitis, atrophic gastritis, pernicious anemia, lymphocytic parathyroiditis and isolated ACTH deficiency (4, 14, 15). During the patient’s treatment, accelerated ESR titers were observed repeatedly, and he finally fell into overt secondary hypothyroidism while the patient developed panhypopituitarism. Graves’ disease, thyroiditis and hypothyroidism are now considered autoimmune in origin, representing the spectrum of the same pathogenetic mechanisms (16). Hypothyroidism in patients with Graves’ hyperthyroidism who had been treated with antithyroid drugs may spontaneously occur as a result of different mechanisms including a mechanism due to blocking antibodies to the TSH receptor and autoimmune thyroid destruction resulting in abruptly or slowly progressive irreversible hypothyroidism (17). The occurrence of hypothyroidism characterized by a low TSH level coincided with the development of panhypopituitarism due to lymphocytic hypophysitis in our patient. Since the TSH receptor stimulating or blocking antibodies was not detected in our patient, it is not possible to say whether or not the mechanisms limited to the thyroid gland played a role in the development of hypothyroidism. But negative thyroid autoantibodies are against Hashimoto’s disease. At least to our knowledge this is the first case of Graves’ disease who developed lymphocytic hypophysitis.
patients cannot develop clinically manifest diabetes insipidus as shown in our patient and also neurohypophysis cannot be examined histologically.

Our patient developed panhypopituitarism due to lymphocytic hypophysitis demonstrated by radiological and histological investigation, neurohypophyisis revealed after histological examination and the involvement of the stalk which was enlarged and thickened demonstrated by MRI. Ahmed et al. reported two men with diabetes insipidus, hypopituitarism, and involvement of the adenohypophysis, neurohypophysis, and hypothalamus, with a characteristic MRI appearance of the pituitary stalk (20). They suggested that these two cases represent a unique clinical syndrome in which inflammatory pathology is different in its anatomical extent and histological characteristics from that classically seen in lymphocytic hypophysitis (20). The characteristics of our patient show that lymphocytic hypophysitis may involve the anterior and posterior hypophysis and probably also the infundibulum.

In conclusion, the report based on a man with diabetes mellitus and Graves' disease who developed lymphocytic hypophysitis involving the anterior and posterior pituitary gland and pituitary stalk. We think that lymphocytic hypophysitis should be born in mind in the patients with Graves’ disease who develop hypothyroidism characterized by a low TSH level.

REFERENCES


