Lymphocytic Hypophysitis Occurring Simultaneously with a Functioning Pituitary Adenoma

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Abstract. Lymphocytic Hypophysitis (LH) is a rare and previously under-recognised disorder, most commonly affecting young females in the post-partum period. It presents clinically with symptoms and signs related to either a pituitary mass or hypopituitarism, frequently mimicking a pituitary adenoma; the diagnosis of LH can only be made histologically with the presence of a dense lymphocytic infiltration usually confined to the anterior pituitary. We present two case histories of patients who presented with symptoms suggestive of a functioning pituitary adenoma who also had concomitant LH confirmed histologically. The first case was a 39 year old lady, with a history of primary hypothyroidism, who presented with weight gain and hirsutism and clinical and biochemical features of Cushing’s syndrome. The second case was a 61 year old male, also with a history of primary hypothyroidism, who presented with visual field loss and biochemically with hyperprolactinaemia. In both patients, magnetic resonance (MR) imaging of the pituitary demonstrated an enlarged partially cystic pituitary mass with slight suprasellar extension. Both patients were treated surgically with transphenoidal drainage and excision and histological examination of the surgical specimens demonstrated a mixture of pathologies with fragments of adenohypophyseal tissue (staining positive for ACTH and prolactin respectively) with a dense chronic inflammatory cell infiltrate suggestive of LH in nearby normal anterior pituitary. In both cases a joint diagnosis of a functioning pituitary adenoma with LH was made. There have been only several reported cases of this combination of pathologies but LH even in isolation is becoming increasingly recognised.

Key words: Lymphocytic hypophysitis, Pituitary adenoma, Prolactinoma, Cushing’s disease

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Case 1

A 39 year old lady presented with a two year history of general lethargy, weight gain and hirsutism of the face and breasts. She had a history of hypothyroidism, assumed to be auto-immune although the general pra-
Preliminary laboratory investigations were normal including full blood count, renal function and glucose. Thyroid function was consistent with thyroxine replacement with normal T4 and suppressed TSH. Gonadotrophins were low (LH 1.7 u/l, FSH 3.0 u/l) as was oestradiol (95 pmol/l). Other biochemistry included testosterone 1.6 nmol/l (normal <3.5 nmol/l), prolactin 253 nmol/l (normal <500) and androstenedione 10.9 nmol/l (normal range 3.0–10.0 nmol/l).

A diagnosis of Cushing’s syndrome was confirmed by failure of suppression of cortisol after an overnight dexamethasone (2 mg) suppression test to 299 nmol/l (normal <50 nmol/l), loss of diurnal rhythm (806 nmol/l, 0800; 678 nmol/l, 2300) and elevated urinary free cortisol at 1518 nmol/l (normal <350 nmol/l). Cortisol suppressed to 168 nmol/l from 448 nmol/l with high dose dexamethasone (normal <50 nmol/l). ACTH was elevated at 21.9 pmol/l (normal range 2–11.3) at 08.00 with cortisol 805 nmol/l. A normal response to GnRH was observed, peak LH 33.8, FSH 11.9 with a pre test oestradiol of 202 pmol/l. During an insulin tolerance test (0.2 units insulin/kg) achieving adequate hypoglycaemia (blood glucose 2.0 mmol/l), cortisol rose from 608 nmol/l to 738 nmol/l with no growth hormone response 1.1 to 5.7 mU/l. The response of ACTH to hypoglycaemia was not measured and a corticotrophin releasing hormone (CRH) test was not performed.

Magnetic resonance (MR) imaging of the pituitary revealed an enlarged, complex, partially cystic pituitary mass (12 × 10 × 10 mm) containing a small enhancing central component that extended into the infundibulum (indicating suprasellar involvement) and a larger non-enhancing peripheral component (in keeping with a cystic component) (Fig. 1).

The patient was treated with metyrapone prior to a transphenoidal excision. The surgical specimen removed consisted of multiple portions of tissue measuring up to 7 mm in maximum diameter. Anterior pituitary tissue was noticeable beside two separate portions of adenoma tissue. On histological examination, the anterior pituitary tissue exhibited normal architecture, which in several areas was overshadowed by dense lymphocytic CD3+ cells that surrounded adenoma clusters (Fig. 2a). Although the infiltrate was located predominantly in the intervening connective tissue (Fig. 2b), many areas showed partial or complete replacement of anterior pituitary cells by lymphocytes. The adenoma tissue featured cuboidal cells with round ovoid regular nuclei and ACTH-positive cytoplasm arranged in sheets and broad trabecular fashion (Fig. 2c).

Post-operative assessment of pituitary function demonstrated no cortisol response (27 nmol/l) and a blunt growth hormone response (10.2 mU/l) to hypoglycaemia (blood glucose 1.7 mmol/l). Gonadotrophin responses to GnRH were normal (peak LH 30.7 u/l and FSH 4.0 u/l). The patient is maintained on oral hydrocortisone, thyroxine, growth hormone injections and bisphophonates and having regular menses.
Case 2

A 61 year old male, under review for glaucoma, was referred from ophthalmology to the neurosurgical team with a right superior temporal quadrantopia observed with formal visual field testing. He was otherwise asymptomatic, and was treated only with thyroxine 75 mcg for hypothyroidism, assumed to be auto-immune (although no thyroid antibodies were checked). On clinical examination, the only abnormality was that of a small upper right quadrantic field defect on confrontation.

Preliminary laboratory investigations were normal including full blood count, renal function and glucose. Thyroid function was consistent with thyroxine under replacement with low T4 of 8.8 pmol/l (normal 9.9–22.0) and a normal TSH at 2.2 mU/l (normal 0.4–4.0). Testosterone and gonadotrophins were low: testosterone, 2.9 nmol/l (normal 10–35), LH 1.0 U/l and FSH 1.8 U/l (normal 1.0–33.0 and 1.0–23.0 respectively) consistent with secondary hypogonadism. Prolactin concentration was significantly elevated at 4091 mU/l (normal <350). A short synacthen test was normal, basal cortisol of 524 nmol/l rising to 872 nmol/l after 60 min (normal peak cortisol >550 nmol/l). MR imaging of the pituitary demonstrated a mixed solid/cystic mass (measuring approximately 1.7 × 1.7 × 1.3 cm) in the pituitary fossa with slight displacement but not compression of the optic chiasm (Fig. 3).

The patient underwent trans-sphenoidal drainage and excision of cystic lesion in the pituitary gland. He was discharged home on hydrocortisone and thyroxine.

Microscopy of the surgical specimens revealed a mixture of pathologies present- fragments of adenohypophyseal tissue with a dense chronic inflammatory infiltrate (suggesting lymphocytic hypophysitis) in normal nearby normal anterior pituitary while immunocytochemistry was consistent with a prolactinoma (with strong staining for prolactin but staining of all six anterior pituitary hormones). Staining for leucocyte common antigen confirmed the presence of a widespread infiltrate of macrophages and lymphocytes (Fig. 4).

Post-operative assessment demonstrated ongoing hypothyroidism (TSH 0.08 mU/l; total T3 2.1 nmol/l, free T4 14.3 pmol/l) and hypogonadism (testosterone 3.4 nmol/l) such that he continued on thyroxine and testosterone (Andropatch). There was no evidence of steroid deficiency with cortisol increasing from 446 to 674 nmol/l on insulin stress testing (0.2 u insulin/kg) achieving adequate hypoglycaemia (blood glucose 1.6 mmol/l); thus his hydrocortisone was discontinued.
Prolactin remained elevated at 2260 mU/l and so he was commenced on cabergoline which promptly corrected his hyperprolactinaemia.

Post-operative MR imaging of the pituitary showed replacement of the tumour by high signal material representing either secretions or haemorrhage. Follow up visual field testing demonstrated some improvement of his visual fields. He has been subsequently well with no further complications.

**Discussion**

Lymphocytic hypophysitis (LH) is a rare inflammatory disorder of the pituitary usually affecting young women, often in relation to pregnancy or the post-partum period [1, 2]. It has been described in non-pregnant women [3] and males [4]. It was previously considered to affect only anterior pituitary function (referred to as adenohypophysitis) although it is now considered it may also involve the posterior pituitary (infundibulohypophysitis), accounting for some cases of central diabetes insipidus [5].

Aetiology is thought to be auto-immune fulfilling a number of defining criteria for organ-specific autoimmunity [6] including an association with other auto-immune diseases [2, 7], the presence of pituitary auto-antibodies in up to 70% of biopsy-proven cases [8, 9], a relapsing and remitting course with a clinical response to steroids [10] or other immunosuppressive therapy [11] and a histopathological appearance of a dense polyclonal lymphocytic infiltration.

LH frequently mimics a pituitary adenoma [12, 13] with clinical features attributable to either an expanding mass with headaches, diplopia, reduced visual acuity and visual field defects or symptoms attributable to hypopituitarism. For this reason, it has been referred to as pseudotumoural LH [14]. A subtle difference between an adenoma and LH is the hierarchy of endocrine loss: in LH there is a predilection for destruction of ACTH and TSH secreting cells unlike that in an adenoma where ACTH secretion is last to be lost.

This preferential destruction of ACTH secreting cells with consequent secondary adrenocortical insufficiency may have been responsible for up to 9 deaths in patients with LH [15]. Early detection of such cases is therefore of vital importance. This hierarchy was not evident in these cases because of over production of other hormones by the co-existing pituitary adenoma.

On MR imaging, LH typically presents with an enlarged lobulated pituitary mass that typically displays intermediate signal intensity on T1-weighting, high signal on T2-weighting and shows marked intraslesional and adjacent dural enhancement. It often extends along the infundibulum but does not usually enlarge the sella [16]. A normal sized or minimally enlarged sella has also been recorded in intra-sellar meningioma, metastasis, craniopharyngioma and germ cell tumours.
cell tumours. In view of the cystic nature of the lesion various cystic lesions including Rathke’s cleft cyst, arachnoid cyst, dermoid/epidermoid cysts have to be considered. In contrast, almost all macroadenomas enlarge the sella. Preservation of the hyperintense bright spot of the posterior pituitary on T1-weighting depends on whether there is involvement of the posterior lobe. In the present cases, while many of the typical features were present, a large cystic component was also found, an unusual feature that has only been described in several other cases [17–19]. The true diagnosis may only be made histologically.

Histologically, although up to 3% of pituitary adenomas may contain lymphocytic infiltration [20], normal anterior pituitary tissue is not infiltrated thus we can be sure that the histology observed truly represents LH.

Optimal treatment of LH is controversial with some advocating conservative management or steroid therapy [21, 22]. Others suggest surgical treatment of LH as the diagnosis can only be definitively made with tissue with frequently normal intervening pituitary tissue with the clinical course being so unpredictable [23]. It is interesting to note that the LH was still apparent even in the presence of Cushing’s disease where the high circulating cortisol might be expected to reduce or even completely resolve the LH. However, it is unclear what dose of corticosteroid would be required to cause complete resolution or indeed whether the endogenous steroid had had a partial effect and reduced the area of inflammation.

Although LH has been described in conjunction with ruptured Rathke cleft cysts [24], germinomas [25] and craniopharyngiomas [26], there have been only several reports of LH occurring in conjunction with a pituitary adenoma, which they frequently mimic. Two reports of LH in combination with a non-functioning pituitary adenoma (where histological evidence was provided) have been presented [27, 28], one of them very recently. However, although LH has been reported in conjunction with a GH secreting adenoma [29], we present two cases of LH co-existing with a functional adenoma, in the first case a corticotroph (or ACTH-secreting) adenoma and in the second a lactotroph (or prolactin-secreting) adenoma. In each case the biochemical and immunohistochemical evidence for a functional adenoma rather than a Rathke’s cleft cyst was convincing. In the first case there was documented hypercortisolaemia, loss of dexamethasone suppression and ACTH positivity on the pathological specimen while in the second case, significant hyperprolactinaemia and prolactin positivity on the histological specimen. These findings would not be present with a Rathke’s cyst.
The co-existence of LH and other pituitary pathologies including Rathke cleft cysts, germinomas, craniopharyngiomas and pituitary adenomas suggest a possible relationship. Although the mechanism by which these dual pathologies may co-exist within the pituitary gland has not been fully elucidated various theories have been proposed. These include the elaboration by the tumour or cyst of pro-inflammatory cytokines, hormones or other non-hormonal proteins inducing local inflammation within neighbouring anterior pituitary tissue. It was not possible to test for the expression of these cytokines or other proteins within the pituitary. However, it is also possible that there is no specific causal relationship between pituitary adenomas and lymphocytic hypophysitis but that in both cases, the two pathologies appeared simultaneously by co-incidence. If the latter is correct, these cases highlight the likelihood underdiagnosis of LH in patients with idiopathic hypopituitarism.

Thus in summary we present two cases of LH which is a rare diagnosis in itself but in both cases there was a co-existing functional pituitary adenoma.

References


