Lymphocytic Hypophysitis in a Dog with Diabetes Insipidus

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Summary

An 8-year-old male German longhaired pointer was referred for diabetes insipidus responsive to treatment with desmopressin. The dog had polyuria and polydipsia, exercise intolerance and a dull hair coat. Plasma concentrations of thyroid-stimulating hormone, thyroxine, growth hormone (GH) and insulin-like growth factor-1 were decreased; plasma adrenocorticotropic hormone (ACTH) was slightly elevated and plasma α-melanocyte-stimulating hormone (MSH) was within the reference range. Computed tomography revealed a heterogeneously contrast-enhancing pituitary mass compressing the hypothalamus. Transsphenoidal hypophysectomy was performed and microscopical examination of the surgical biopsy samples revealed hypophysitis without evidence of pituitary adenoma. The hypophysitis was characterized by marked lymphocytic infiltration of the adenohypophysis that contained a mixed population of neuroendocrine cells expressing GH, ACTH or α-MSH. The lymphocytes were identified as T cells, resulting in a final diagnosis of lymphocytic hypophysitis strongly resembling human primary lymphocytic hypophysitis.

Keywords: diabetes insipidus; dog; hypophysitis; pituitary

Pituitary masses occur frequently in dogs and are almost always pituitary adenomas (De Bruin et al., 2009; Meij et al., 2010). The most commonly encountered adenoma is the pituitary corticotroph adenoma that causes excess secretion of adrenocorticotropic hormone (ACTH) and results in pituitary-dependent hypercortisolism (Cushing’s-like disease) (Hanson et al., 2005). The pituitary somatotroph adenoma causes hypersecretion of growth hormone (GH) and results in acromegaly, but is rare in dogs (Fracassi et al., 2007). Clinically non-functional pituitary adenomas do not cause an endocrine syndrome, but may result in neurological signs or diabetes insipidus due to expansion and compression of surrounding brain structures (Théon and Feldman, 1998). Treatment of pituitary masses in dogs involves containment of hormone excess by medical management or by hypophysectomy or irradiation aimed at completely removing or reducing the pituitary mass.

An 8-year-old male German longhaired pointer was referred with a history of acute onset polydipsia and polyuria. Over a period of 1 week the dog had started drinking five times the normal amount. In the second week the dog became depressed and developed exercise intolerance. Urine examination revealed a specific gravity of 1.006. Kidney, liver, pancreas and muscle serum biochemistry panels were normal. Ultrasonography of the abdomen showed normal left and right adrenal glands. The dog was treated with the vasopressin analogue desmopressin (Minrin 0.01%; Ferring B.V., Hoofddorp, The Netherlands; 8 μg q12h administered into the conjunctival sac). The dog responded immediately with normalization of drinking and urination. Central diabetes insipidus was suspected and computed tomography (CT) of the skull was performed.
Contrast-enhanced CT (Van der Vlugt-Meijer et al., 2002) revealed a heterogeneously enhancing pituitary mass measuring 12.3 mm in height, 17.5 mm in width and 15.0 mm in length, consistent with a pituitary tumour. The pituitary height/brain area ratio (P/B) was 0.75, indicating pituitary enlargement (reference P/B <0.31; Kooistra et al., 1997). Abdominal CT scans showed normal adrenal glands.

Plasma levels of pituitary hormones and their target hormones were assessed. Plasma concentrations of thyroid-stimulating hormone (TSH) and thyroxine (Kooistra et al., 2000), and GH and insulin-like growth factor-1 (IGF-1) (Fracassi et al., 2007) were decreased (Table 1), indicating hypopituitarism, secondary hypothyroidism and hyposomatotropism. The pituitary–adrenocortical system was further investigated by measuring plasma concentrations of ACTH and α-melanocyte-stimulating hormone (MSH) by methods described previously (Hanson et al., 2006). The basal plasma concentration of ACTH was elevated and that of α-MSH was within the reference range (Table 1).

The dog continued to become more depressed and lethargic and the owner elected debulking pituitary surgery. The dog underwent transsphenoidal hypophysectomy (Meij et al., 1997). The ventral surface of the pituitary mass was visualized through the sphenoid slot and was dark red in colour. The dura mater was incised and the pituitary mass was extracted in four fragments (3/3 × 5 mm each; specimen 1). There was more than average diffuse haemorrhage from the pituitary tissue itself in comparison with pituitary adenoma surgery. Haemostasis was accomplished with thrombin gel foam. After debulking, the dorsum sellae was located caudally in the sphenoid slot and the pituitary fossa was inspected for remnant pituitary tissue, but it was difficult to assess complete removal of the pituitary mass since diffuse haemorrhage prevented an unobstructed view of the ventral hypothalamic surface. At the end of the procedure, a small white unalfecked tissue fragment (8 × 5 mm) was collected separately from the caudal part of the pituitary fossa (specimen 2). Both specimens were fixed in 10% neutral buffered formalin.

Recovery from surgery in the intensive care unit was complicated. The dog remained stuporous and did not respond to external stimuli except for deep pain stimuli. The dog’s respiration was normal and plasma sodium and potassium, central venous pressure and arterial blood gases were within reference ranges. It was suspected that there was brain oedema due to the removal of the pituitary mass and subsequent brain shift and/or surgically inflicted hypothalamic damage. Repeated intravenous mannitol infusions (0.5 g/kg) did not lead to clinical improvement. After 3 days of intensive care treatment the owner elected for humane destruction. Necropsy examination was not permitted.

Specimens 1 and 2 were processed routinely and embedded in paraffin wax. Sections (3 mm) were stained with haematoxylin and eosin (HE). Microscopic examination of specimen 1 revealed several groups of chromophobic, acidophilic and basophilic neuroendocrine cells in a well-vascularized oedematous stroma with multifocal haemorrhage and a moderate multifocal lymphocytic infiltrate (Fig. 1). Additionally, some plasma cells and scattered individual macrophages were present. In specimen 1 no neoplastic tissue was detected and specimen 2 consisted of cerebral white matter.

Immunohistochemistry (IHC) was performed on serial sections of specimen 1 with antibodies specific for

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**Table 1**

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Values</th>
<th>Reference values</th>
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<tbody>
<tr>
<td>TSH (μg/l)</td>
<td>&lt;0.03</td>
<td>&lt;0.6*</td>
</tr>
<tr>
<td>T4 (total T4) (nmol/l)</td>
<td>&lt;9</td>
<td>13–61†</td>
</tr>
<tr>
<td>GH (μg/l)</td>
<td>1.7</td>
<td>2–5‡</td>
</tr>
<tr>
<td>IGF-1 (μg/l)</td>
<td>71</td>
<td>137–425§</td>
</tr>
<tr>
<td>ACTH (pmol/l)</td>
<td>40.6</td>
<td>2.2–19.8§</td>
</tr>
<tr>
<td>α-MSH (pmol/l)</td>
<td>7.8</td>
<td>1.5–15§</td>
</tr>
</tbody>
</table>

Basal plasma concentrations of ACTH, α-MSH, GH and IGF-1 are means calculated from two values and the values are in SI units. Reference values:
* Kooistra et al. (2000).
† Fracassi et al. (2007).
‡ Mol and Meij (2008).

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Fig. 1. Surgical biopsy sample removed during transphenoidal hypophysectomy. The vascularized tissue is infiltrated by small cells (arrowheads) with scant cytoplasm and a dark nucleus, consistent with lymphocytes. There is local infiltration with plasma cells and there are few pre-existing acidophilic neuroendocrine cells (arrow). HE. Bar, 100 μm.
ACTH$_{1-24}$, α-MSH, GH, the T-cell marker CD3 and the B-cell marker CD79 (Table 2). Normal canine pituitary tissue served as control tissue for ACTH, α-MSH and GH, while for CD3 and CD79 sections of a normal canine lymph node were used. For all antibodies, the negative control consisted of omission of the primary antibody. α-MSH labelling was negative, while individual cells expressed GH (Fig. 2) and ACTH (Fig. 3) with a GH:ACTH ratio of 5:1. The population of lymphocytes in specimen 1 expressed CD3 (Fig. 4), but not CD79. Based on these findings, specimen 1 was identified as pre-existent adenohypophyseal tissue with a moderate to severe infiltration of T lymphocytes. The microscopical lesions were consistent with lymphocytic hypophysitis. No neoplastic changes were encountered in either specimen.

Lymphocytic hypophysitis in man is a neuroendocrine disorder characterized by autoimmune inflammation of the pituitary gland with various degrees of pituitary dysfunction (Rivera, 2006). It occurs mainly in women during pregnancy or the postpartum period, although there are also reported cases in men (Couldwell and Weiss, 1999). The disorder is an important differential diagnosis when space-occupying lesions of the sellar region are encountered. Lymphocytic hypophysitis may present as endocrine dysfunction and a diffuse mass, which can mimic a non-functional pituitary tumour. The adenohypophysitis is heavily infiltrated by T lymphocytes and plasma cells (Saeger, 2001). During the acute inflammatory phase, the pituitary gland may be markedly enlarged with suprasellar extension. During the chronic phase, the pituitary becomes atrophic due to replacement of adenohypophyseal tissue with connective tissue (Thapar and Kovacs, 1998; Stefaneanu et al., 2000). Microscopically, three main morphological subtypes of primary hypophysitis can be discerned, lymphocytic, granulomatous and xanthomatous, but it is unclear whether these are truly distinct entities or represent different stages of the same disease.

The type, phase and degree of lymphocytic infiltration determine the clinical symptoms in human patients. Marked lymphocytic infiltration disrupts the architecture of the adenohypophysitis leading to pituitary insufficiency. Most frequently, diabetes insipidus, hypopituitarism, headache and visual defects are reported (Rivera, 2006). In the case of inflammation of the anterior part of the pituitary only, the lesion is termed lymphocytic adenohypophysitis, when the posterior lobe and the infundibulum are affected it is called lymphocytic infundibuloneurohypophysitis, and if there is a global infiltration of the pituitary gland it is called lymphocytic panhypophysitis. Lymphocytic infundibuloneurohypophysitis typically presents as acute onset diabetes insipidus with intracranial mass-effect symptoms (Abe, 2008) and resembles the course of the disease in the present case. Radiological differentiation from neoplasia is impossible (Schubiger, 1996). Pituitary magnetic resonance imaging in people with lymphocytic hypophysitis presenting with diabetes insipidus shows loss of the "bright spot" of the posterior lobe, thickening of the pituitary stalk and pituitary gland enlargement with suprasellar extension (Shimono et al., 1999; Akahori and Sugimoto, 2010).
After treatment with glucocorticoids, the pituitary reduces in size (Akahori and Sugimoto, 2010). Pituitary insufficiency may affect all pituitary hormones, but normal and elevated plasma levels have also been reported, probably representing different stages of the disease (Shimono et al., 1999). Indeed, in the present case there was reduced TSH and GH, but normal to elevated a-MSH and ACTH concentrations. The importance of recognizing lymphocytic hypophysitis is that it may be self-limiting and respond to medical anti-inflammatory treatment with glucocorticoids.

In the present case, lymphocytic hypophysitis was diagnosed by histopathological examination of surgical biopsies. The uniform cellular appearance of the lymphocytes and the simultaneous presence of few other inflammatory cells (plasma cells and macrophages) were consistent with an inflammatory reaction rather than lymphoma. No other evidence of lymphoma was found in this dog and primary pituitary lymphoma has not been reported in the literature. The suprasellar expansion of pituitary adenomas in dogs primarily affects the hypothalamus, which contains the supraoptic and paraventricular nuclei where vasopressin is synthesized. In pituitary masses with suprasellar expansion, these nuclei may become compromised, possibly leading to diabetes insipidus. This may also occur after hypophysectomy (Hanson et al., 2005, 2007). Plasma ACTH concentration was moderately elevated in the present case, which may be a reflection of the acute systemic inflammatory phase of the disease before destruction of the adenohypophysis leads to complete pituitary insufficiency. In a recent case report in a 4.5-year-old great Pyrenees dog with hypothyroidism and hypoadrenocorticism, lymphocytic adenohypophysitis and adrenalitis were found. B lymphocytes and plasma cells dominated the adenohypophysitis, but T cells dominated the adrenalitis (Adissu et al., 2010). In that dog the pituitary gland was slightly enlarged and the adrenal and thyroid glands were bilaterally atrophic. This combination of primary hypothyroidism and hypoadrenocorticism resembled type II autoimmune polyendocrine syndrome or Schmidt syndrome in man (Adissu et al., 2010). In the present case the adrenal glands were of normal size on ultrasonography, the pituitary gland was markedly enlarged and the thyroid gland, although less active, still showed some hormonal activity. Moreover, the dominant T-cell infiltration of the pituitary gland of the present case represents a distinct difference compared with the infiltration of the pituitary gland of the great Pyrenees dog and suggests that inflammation in the present case had an underlying disease mechanism more comparable with human lymphocytic hypophysitis. Lymphocytic adenohypophysitis in the dog may therefore reveal different histopathological patterns and lead to variants in clinical presentation.

In dogs with pituitary masses that are not associated with an endocrine syndrome (Cushing’s-like disease or acromegaly), a histological biopsy of the pituitary mass is necessary to differentiate between non-functional pituitary adenoma and lymphocytic hypophysitis. In non-functional adenoma, treatment is aimed at cytoreduction with pituitary surgery or radiotherapy, while in lymphocytic hypophysitis the treatment of choice is medical intervention with glucocorticoids.

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