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SPONTANEOUSLY ARISING DISEASE

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.

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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 × 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 unaffected 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 gasses 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 μm) were stained with haematoxylin and eosin (HE). Microscopical 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

Table 1
Plasma hormone concentrations

Hormones	*Values*	*Reference values*
TSH (μg/l)	<0.03	<0.6[*]
T4 (total T4) (nmol/l)	<9	13–61[*]
GH (μg/l)	1.7	2–5[†]
IGF-1 (μg/l)	71	137–425[†]
ACTH (pmol/l)	40.6	2.2–19.8[‡]
α-MSH (pmol/l)	7.8	1.5–15[‡]

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).

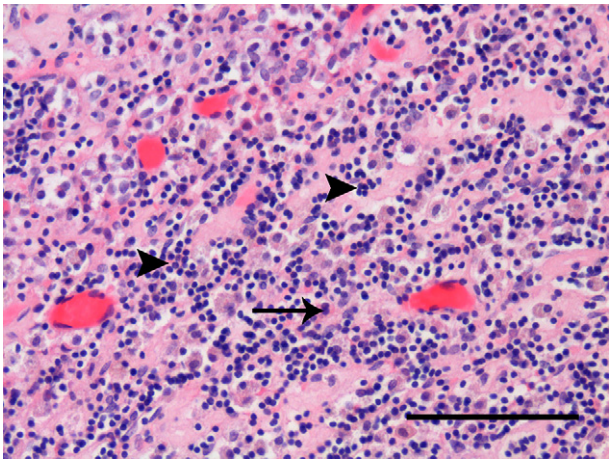

Fig. 1. Surgical biopsy sample removed during transsphenoidal hypophysectomy. The vascularized tissue is infiltrated by small cells (arrowheads) with scant cytoplasm and a dark nucleus, consistent with lymphocytes. There is local infiltration with plasma cells and there are few pre-existing acidophilic neuroendocrine cells (arrow). HE. Bar, 100 μm.