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CASE REPORT

Companion or pet animals

Autoimmune polyendocrine syndrome in a standard poodle with concurrent non-endocrine immune-mediated diseases

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Abstract

A 6-year-old female neutered standard poodle was referred with a 4-week history of rapidly progressive weight loss, muscle atrophy, hyporexia, hind limb weakness and lethargy. In the preceding 3-month period, the dog had been diagnosed with both keratoconjunctivitis sicca (KCS) and hypoadrenocorticism. Clinical deterioration had occurred despite treatment for hypoadrenocorticism. Following referral, the dog was diagnosed with concurrent hypothyroidism, exocrine pancreatic insufficiency (EPI) and suspected generalised myositis. Treatment with hormone replacement therapy, pancreatic enzyme supplementation and immunosuppressive doses of prednisolone and mycophenolate resulted in marked clinical improvement. This case describes a rapidly progressive, presumed autoimmune, polyglandular endocrinopathy in a dog with concurrent non-endocrine autoimmune diseases.

KEYWORDS

autoimmune disease, endocrinology, hypoadrenocorticism, hypothyroidism, polyendocrine syndrome

BACKGROUND

Autoimmune polyendocrine syndrome (APS) is a rare but well described entity in human medicine, characterised by the development of autoimmunity against two or more endocrine organs.[1] APSs are divided into juvenile type 1 APS (also known as autoimmune poly-endocrinopathy candidiasis-ectodermal dystrophy) and an adult-onset types II-IV. Type II APS, also known as Schmidt's syndrome, is characterised by the presence of autoimmune-induced hypoadrenocorticism with at least one other autoimmune endocrine disorder affecting either the thyroid gland or pancreatic beta cells (type I diabetes mellitus). Type III APS refers to the presence of auto immune thyroid disease and type 1 diabetes mellitus; hypoadrenocorticism is not present. Type IV APS refers to the presence of two or more autoimmune endocrinopathies that cannot be assigned to either of the previous two classes. In addition to endocrine dysfunction, a number of non-endocrine immune-mediated disorders can be seen concurrently, including coeliac disease, pemphigus, myasthenia gravis (MG), alopecia, autoimmune hepatitis and rheumatoid arthritis.[2]

Polyglandular endocrine disease is also reported in veterinary medicine.[3–8] Up to 2.3% of dogs diagnosed with endocrine disease are diagnosed with multiple endocrinopathies.[9] While in some dogs it is clear that their concurrent endocrine disorders do not share an immune-mediated aetiology (e.g., diabetes mellitus and hyperadrenocorticism), in others a common immune-mediated aetiology similar to human APS has been proposed.[5–9] However, the occurrence of concurrent non-endocrine autoimmune diseases has, to the authors' knowledge, not been reported.

CASE PRESENTATION

A 6-year-old female neutered standard poodle was referred to a veterinary teaching hospital in December 2018, for investigation of rapidly progressing weight loss (25% loss in body weight over a 4-week period) and muscle atrophy, hyporexia, hind limb weakness and lethargy.

The dog had been diagnosed with keratoconjunctivitis sicca (KCS) 3 months prior to presentation (with a Schirmer tear test measurement of 5 mm in the left eye and 7 mm in the right eye). This had been picked up at a routine check-up for annual vaccination. She was started on ciclosporin eye ointment (Optimmune; MSD animal health) and lubricating eye gel (Lubrithal; Dechra). At that point there were no overt signs of systemic illness, and she weighed 31.2 kg. She re-presented a few weeks later with signs compatible with a urinary tract infection (UTI), and her owners also reported that she seemed to be weak on her pelvic limbs. Although the UTI resolved with amoxicillin (Amoxycare; Animalcare) at 15 mg/kg PO, q12 for 10 days, her pelvic limb weakness persisted despite empirical treatment with meloxicam (Metacam; Boehringer Ingelheim) dosed for a 30 kg dog, PO, q24. Three weeks later she collapsed while posturing to urinate, prompting further evaluation, at this point her owners also reported a reduction in appetite and mild weight loss (weight 29.8 kg).

TABLE 1 Haematology and serum biochemistry prior to referral

Analyte (units)	27/11/2018	27/12/2018	Reference range
Haematology			
Red cell count (x10^12/L)	*4	*4.45	5.50–8.50
Haematocrit (L/L)	*0.284	*0.326	0.37–0.55
Haemoglobin (g/L)	126	*110	120–180
Mean corpuscular volume (fL)	71	73.4	60.0–77.0
Mean cell haemoglobin (pg)	*31.7	24.8	18.5–30.0
Mean cell haemoglobin concentration (g/L)		338	300–375
Reticulocytes (K/μl)	29.7	47.6	10–110
White blood cells (x10^9/L)	*17.01	*16.95	5.50–16.90
Neutrophils (x10^9/L)	7.54	*12.2	2.00–12.00
Lymphocytes (x10^9/L)	*6.51	1.11	0.50–4.90
Monocytes (x10^9/L)	*2.64	*3.46	0.30–2.00
Eosinophils (x10^9/L)	0.28	0.15	0.10–1.49
Basophils (x10^9/L)	0.04	0.03	0.00–0.10
Platelets (x 10^9/L)	248	*656	175–500
Serum Biochemistry			
Glucose (mmol/L)	4.55	6.87	4.11–7.95
Creatinine (μmol/L)	63	*41	44–159
Urea (mmol/L)	5.7	*1.7	2.5–9.6
Phosphorus (mmol/L)	1.26	1.34	0.81–2.20
Calcium (mmol/L)	2.29	2.19	1.98–3.00
Sodium (mmol/L)	151	150	144–160
Potassium (mmol/L)	5.1	4.1	3.5–5.8
Sodium:Potassium ratio	29	37	
Chloride (mmol/L)	114	114	109–122
Total protein (g/L)	59	62	52–82
Albumin (g/L)	*21	25	23–40
Globulin (g/L)	38	37	25–45
Alanine aminotransferase (U/L)	*181	Invalid	10–125
Alkaline phosphatase (U/L)	*18	*397	23–212
γ - Glutamyl transpeptidase (U/L)	0	5	0–11
Total bilirubin (μmol/L)	2	2	0–15
Cholesterol (mmol/L)	*1.38	*2.67	2.84–8.26
Amylase (U/L)	1125	526	500–1500
Lipase (U/L)	436	296	200–1800

*Outside of the reference range

Laboratory analysis revealed a mild normocytic, normochromic anaemia (HCT 0.284 g/dl) and a moderate lymphocytosis with normal serum biochemistry and T4 (Tables 1 and 2, 27/11/2018). Radiographs of her hips, stifles, hocks and lumbosacral region revealed mild lumbosacral spondylosis of unknown clinical significance. Given the breed and vague clinical signs, an adrenocorticotropic hormone (ACTH) stimulation test was subsequently performed. The result was compatible with a diagnosis of hypoadrenocorticism (Table 2, 10/12/2018). She weighed 26.4 kg at the time of diagnosis.

Treatment with desoxycorticosterone pivalate (DOCP) (Zycortal; Dechra) at 2.2 mg/kg S/C every 28 days and prednisolone (Prednidale; Dechra) at 0.33 mg/kg PO, q24 resulted in some improvement in the dog's mobility, appetite and demeanour. However, at her 10-day post-zycortal electrolyte check, a week prior to referral, further and more marked weight loss was noted (weight 24.1 kg) along with generalised muscle atrophy. The dose of prednisolone was increased to 0.63 mg/kg PO, q24 but over the following week the dog became anorectic and lost a further 1.7 kg in weight (Figure 1). Repeat haematology showed a persistent non-regenerative anaemia with a stress leukogram now present, likely reflecting steroid therapy. On this occasion mild reductions in urea and creatinine were observed, thought to be due to poor nutritional status and loss of muscle mass respectively; alanine aminotransferase (ALT) was unmeasurable, presumed high, raising concerns for liver disease (Table 1, 27/12/2018). Thoracic radiography and abdominal ultrasonography was performed to screen for neoplastic disease; aside from marked gastric dilation, no abnormalities were found. The patient was referred for further assessment.

On presentation at the referral hospital, the most striking abnormalities on physical examination were poor body condition score (BCS 2/9, weight 22.3 kg), severe generalised muscle atrophy, bilateral enophthalmos (likely associated with a loss of both retro-orbital fat and extraocular muscle mass) and mild dehydration. A grade 2 of 6 systolic heart murmur was auscultated with a regular heart rate of 80 beats per minute and strong synchronous pulses. Transient periods of tachypnoea were noted. Mucopurulent vaginal discharge was also present.

LEARNING POINTS/TAKE-HOME MESSAGES

- Dog suffering from one endocrinopathy can go on to develop one or more additional endocrinopathies.
- Dogs affected by one or more endocrinopathy may develop immune-mediated diseases associated with non-endocrine organs.
- Multiple endocrinopathies or autoimmune diseases of non-endocrine organs can develop in rapid succession of one another.
- Hypothyroidism can be associated with a spectrum of neuromuscular abnormalities including gastrointestinal dysmotility and pharyngeal weakness.
- Nutritional support is an integral part of case management and oesophageal feeding tubes can be used for medium to long-term nutritional and fluid support.

TABLE 2 Endocrinology testing prior to referral

Analyte (units)	27/11/2018	10/12/2018	Reference Range
Total T4 (nmol/L)	17		13–51
Cortisol (mmol/L) - Baseline		* < 10	25–125
Cortisol (mmol/L) - post ACTH		* < 10	125–520

*Outside of the reference range

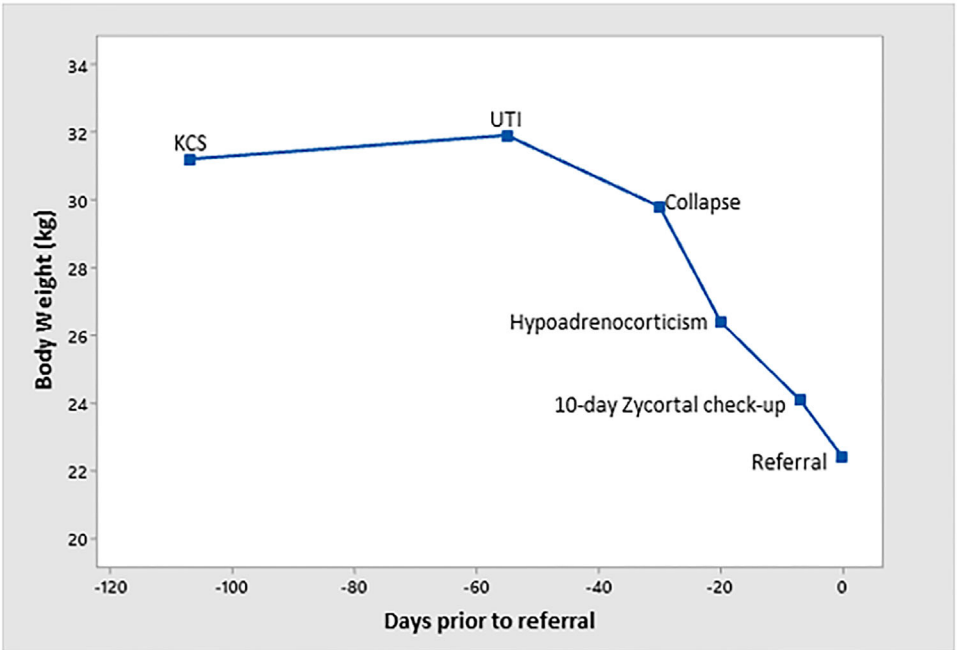

FIGURE 1 Graphical representation of the dog's weight loss in the 3-month period prior to referral

A neurological examination showed equivocal reduced proprioception and spinal reflexes on the pelvic limbs thought to be due to generalised weakness.

INVESTIGATIONS

Further laboratory evaluation confirmed the persistence of a mild non-regenerative anaemia and mild leucocytosis and revealed a marked increase in ALT at 1844 U/L, with more modest increases in aspartate transaminase (AST) and alkaline phosphatase. Creatine kinase (CK) was also moderately increased at 1035 U/L. Borderline hypokalaemia was also noted despite supplementation, which was attributed to DOCP overdose or unnecessary mineralocorticoid supplementation (Table 3, 31/12/2018).

Abdominal ultrasound revealed a diffusely hyperechoic liver with otherwise sharp margins and no appreciable hepatomegaly. The stomach was distended, and gas filled, and there was diffuse gas present within the small intestinal loops limiting visualisation; changes were suggestive of a functional ileus. The adrenal glands measured at the lower end of the normal reference range, with the left and right adrenal gland measuring 3.6 mm and 3.5 mm, respectively, further supporting the diagnosis of hypoadrenocorticism.[10] Echocardiography showed mild mitral valve and tricuspid valve regurgitation presumed to be due to degenerative atrioventricular valve disease. The left atrium to aortic ratio was reduced, consistent with hypovolaemia.

Samples were submitted for *Toxoplasma* and *Neospora* serology to further evaluate the muscle atrophy and high CK, and given the dramatic weight loss, she was also screened for exocrine pancreatic insufficiency (EPI) and malabsorptive disease.

The dog was managed supportively pending laboratory results, with intravenous fluid therapy (IVFT) with Hartmann's solution (Vetivex 11; Dechra) supplemented with potassium chloride (Potassium chloride; Mercury Pharma) at 20 mmol/l, maropitant (Cerenia; Zoetis) at 1 mg/kg q24, a metoclopramide (Emeprid; Ceva) continuous rate infusion (CRI) at 2 mg/kg/q24h, SAMe (Samylin; Vet Plus Global) PO, SID and intravenous (IV) cefuroxime (Zinacef; Glaxo Smith Kline) 20 mg/kg q8 for the mucopurulent vaginal discharge. The dose of prednisolone was reduced from 15 mg to 10 mg (0.45 mg/kg) PO, q24. A naso-oesophageal tube was placed to facilitate nutritional support with Royal Canin gastrointestinal liquid diet.

Within 12 hours of starting treatment the dog's appetite had markedly improved, and for the next 48 hours she ate 100% of her resting energy requirement. However, following reduction in IVFT and discontinuation of the metoclopramide CRI she became inappetent again, and repeat radiographs showed severe gastric dilation raising the possibility of a gastrointestinal functional disorder and/or gastric instability[11] (Figure 2).

The dog underwent a coeliotomy for prophylactic gastropexy and for gastric, intestinal and hepatic biopsies to further investigate the weight loss, gastrointestinal motility disorder and hepatopathy, respectively. During surgery the stomach was noted to be malpositioned but not torsed, both adrenal glands were small, and the pancreas was atrophied along its entire length. The liver, biliary and intestinal tract were grossly normal. A prophylactic incisional gastropexy was performed, and a gastric-through-oesophagostomy tube (G-through-O tube: Figure 3) placed to facilitate gastric decompression and nutritional support.

Histopathology revealed non-specific low-grade oedema and lympho-plasmacytic inflammation in the gastric, duodenal, jejunal and ileal mucosa with mild lymphatic dilation also noted in the ileum. The appearance and distribution of the autonomous nervous system in the gastrointestinal sections was normal. Liver histopathology showed diffuse, moderate hepatocellular hydropic degeneration, mild centrilobular hepatitis (lymphocytic, histiocytic and

TABLE 3 Haematology and serum biochemistry following referral

Analyte (units)	31/12/2018	03/01/2019	11/01/2019	23/01/2019	15/03/2019	Reference range
Haematology						
Red cell count (x10^12/L)	4.72*	4.68*	4.2*	4.07*		5.5–8.5
Haemoglobin (g/dL)	11.6*	11.4*	10.6*	10.5*		12–18.0
Haematocrit (%)	34.3*	34.6*	33.4*	33.2*		37–55
Mean corpuscular volume (fl)	72.7	74	79.4	81.7*		60–77
Mean cell haemoglobin (pg)	24.5	24.4	25.1*	25.7*		19.5-24.5
Mean cell haemoglobin concentration (g/dl)	33.7	32.9	31.6*	31.5*		32–36
White blood cells (x10^9/L)	16.19*	11.62	19.1*	18.5*		6–12.0
Band neutrophils (x10^9/L)	0.324*	0	0.192*	0		0–0
Neutrophils (x10^9/L)	10.524	8.831	14*	*15.5		3–11.8
Lymphocytes (x10^9/L)	3.562	1.394	0.38	1.486		1–4.8
Monocytes (x10^9/L)	1.457*	1.162	4.6*	1.3		0.15–1.35
Eosinophils (x10^9/L)	0.324	0.232	0	0.186		0.1–1.25
Basophils (x10^9/L)	0	0	0	0		0-0
Platelets (x 10^9/L)	578*	627*	832*	633*		200–500
Partial thromboplastin time	10.3					8–12.0
Kaolin cephalin clotting time	25.7*					17–24.0
Fibrinogen	190*					200–400
Serum biochemistry						
Creatinine Kinase (U/L)	1035*	1335*	140	147	*223	0–150
Sodium (mmol/L)	151.1	152	153.9	147.9	145.8	136–159
Potassium (mmol/L)	3.6	3.9	3.4	4.1	4.8	3.4–5.8
Sodium:Potassium ratio	41.97	38.97	45.26	36.07	30.38	
Chloride (mmol/L)	114.7	113.5	111.5	99.8	104.4	95–115
Calcium (mmol/L)	2.23*	2.24*	2.18*	2.31*		2.34–3
Phosphate (mmol/L)	1.22*	1.18*	1.15*	1.53		1.29–2.9
Urea (mmol/L)	1.6	2.3	5.2	1.7		2.5–8.5
Creatinine (umol/L)	54	42*	43*	28		45–155
Glucose (mmol/L)	6.1*	4.1		5.1		3–5.5
Cholesterol (mmol/L)	3.57	3.75	4.9	6.75		2.0–7
Triglyceride (mmol/L)	0.71*	0.57	0.38	1.02*		0–0.6
Total bilirubin (umol/L)	4	3	8	4		0–10
Alkaline phosphatase (U/L)	345*	217	258*	249*		0–230
Aspertate transaminase (U/L)	93*	95*	52*	8		0-40
Alanine aminotransferase (U/L)	1844*	870*	*591	*600		0–90
γ - Glutamyl transpeptidase (U/L)	14	13	17	22		0–20
Total protein (g/L)	54	49*	57	64		50–78
Albumin (g/L)	25*	23*	*27	33		29–36
Globulin (g/L)	29	26*	30	31		28–42

*Outside of the reference range

neutrophilic) and capsular fibrosis, suggestive of chronic cardiovascular disturbances/congestion, rather than a primary hepatitis.

Due to recurrent gastric dilation and ileus, the dog was again screened for hypothyroidism and on this occasion a low T4 (<3.2 nmol/L: RI 15–45) and high cTSH (0.83 ng/ml: RI 0.1–0.69) were found confirming hypothyroidism (Table 4). TLI was subsequently reported as 1.6 ng/ml (RI > 5) consistent with a diagnosis of EPI. *Toxoplasma* and *Neospora* titres were negative.

In conclusion, in addition to KCS and hypoadrenocorticism, the dog was diagnosed with hypothyroidism and EPI, with the suspicion of concurrent myositis.

DIFFERENTIAL DIAGNOSIS

In the absence of recent steroid administration, an ACTH stimulation test with both basal- and post-ACTH cortisol levels of less than 10 nmol/L reliably confirmed a diagnosis

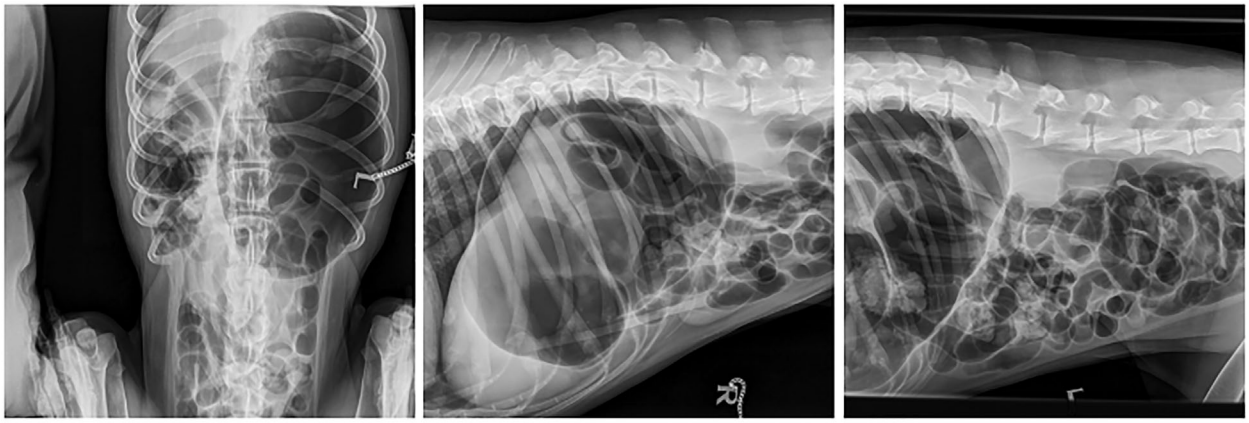

FIGURE 2 Orthogonal radiographs of the abdomen prior to coeliotomy showing marked gas distension of the stomach, which extends slightly beyond the costal arch, but remains normal in shape and position. The entire small and large intestines are moderately distended and gas filled. Findings are consistent with a functional ileus

TABLE 4 Endocrinology and vitamin levels following referral

Analyte (units)	07/01/2019	08/01/2019	11/01/2019	23/01/2019	07/02/2019	15/03/2019	Reference range
Total T4 (nmol/L)	* < 3.2		*13.4	*6.34	*9.9	*14.9	15–45
TSH (ng/ml)	*0.83						0.01–0.69
Folate (ng/ml)		7					3.0–13.0
TLI canine (ng/ml)		*1.6					>5.0
Cobalamin (pg/ml)		652					>200

*Outside of the reference range

of hypoadrenocorticism.[12] As the dog had normal sodium and potassium levels at the time, this diagnosis was made, it was unclear initially if the patient was deficient in both glucocorticoids and mineralocorticoids (typical hypoadrenocorticism) or only glucocorticoid deficient (atypical hypoadrenocorticism). Despite normal electrolyte measurements, dogs are often deficient in both, and aldosterone measurements pre- and post- ACTH stimulation would have enabled this distinction to be made.[13]

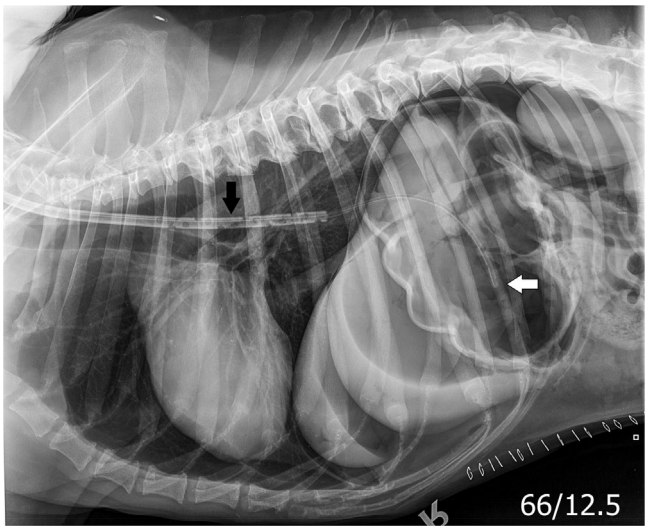

FIGURE 3 Right lateral radiograph illustrating the G-through-O tube positioning: a 55 cm long 20 Fr fenestrated oesophagostomy feeding tube (Mila International) extends to the level of the 7th intercostal space (black arrow), and a 75-cm long 8 Fr feeding tube (Portex) has been inserted through the oesophagostomy tube, terminating in the lumen of the gastric fundus (white arrow)

Although the dog was convincingly diagnosed with hypoadrenocorticism, the ongoing extreme weight-loss, severe muscle wasting, and anorexia warranted further investigation. Considering the investigations and results discussed above, the main differential diagnoses for the dog's significant weight loss were the combination of her decreased food intake and concurrent EPI (maldigestive disorder). In retrospect the owner commented that, latterly, the dog had continued to produce large volumes of faeces despite a declining appetite. The dog's severe muscle wasting may also have contributed to the perceived weight loss. Severe generalised muscle wasting with a significant elevation in CK and AST despite a low muscle condition score was most suggestive of myositis which in the absence of a positive titre for *Neospora* or *Toxoplasma* was considered most likely immune mediated in origin. The dog's anorexia was likely to be due to an absolute disinterest in food due to the underlying systemic disease processes and intermittent gastric dilation.

In the post-operative period, the dog had recurrent episodes of gastric dilation occurring after exercise-associated aerophagia. The aerophagia was thought to be secondary to pharyngeal weakness (on reassessment her gag reflex was absent and, in hindsight, her owners reported dysphonia) caused by the speculated myositis. Both hypothyroidism and hypoadrenocorticism can also cause neuromuscular dysfunction in dogs and therefore these pathologies may have contributed to the development of pharyngeal weakness and

gastrointestinal motility disturbances.[14,15] Furthermore, MG should also be considered as a differential diagnosis for pharyngeal weakness and dysphonia. Evaluation of the myenteric plexus excluded dysautonomia as a cause of gastrointestinal ileus.

TREATMENT

In the immediate post-operative period (25–29 days post-Zycortal injection), the dog's hypoadrenocorticism was managed with intravenous hydrocortisone (Solu-Cortef; Pfizer) as a CRI at 3.3 mg/h, but in the face of persistently borderline potassium despite incremental supplementation, this was changed to dexamethasone at 0.1 mg/kg IV q24 until transitioning to oral prednisolone. Further hormone replacement was started with L-Thyroxine (Thyroforon; Dechra) at 0.02 mg/kg q12 and pancreatic enzyme supplementation (Lypex; VetPlus). Fluid therapy was continued as previously mentioned, and the dog received post-operative opioid analgesia.

A metoclopramide (Emeprid; Ceva) CRI at 1–2 mg/kg was continued, and cisapride introduced as an additional prokinetic (Cisapride; Wedgewood pharmacy) at 0.2 mg/kg PO, q8. The G-through-O tube was used for frequent gastric decompression and nutritional support (Royal Canin GI Low fat liquid diet). Mirtazapine (Mirtazapine; Actavis) at 1.3 mg/kg PO, q24 was administered as an appetite stimulant.

Due to the rapid evolution of her endocrine and non-endocrine organ dysfunction and the clinical suspicion of concurrent polymyositis, she was started on immunosuppressive therapy 1 week after the coeliotomy. Prednisolone was reintroduced at an initial daily dose of 1 mg/kg PO, q24 (increasing to 2 mg/kg PO q24 after 5 days) in conjunction with mycophenolate PO at 10 mg/kg, q24 (increasing to 10 mg/kg PO q12 after 5 days). At this stage omeprazole (Omeprazole; Sandoz) at 1 mg/kg PO was also introduced. Two weeks into treatment, the G-tube was removed as it was no longer needed for gastric decompression, and ongoing nutritional support, medication and fluid requirements provided through the O-tube. Prior to discharge, fludrocortisone (fludrocortisone acetate; global) was introduced at 0.1 mg/kg PO, q24.

OUTCOME AND FOLLOW-UP

The patient was discharged 3 weeks after initial presentation, with the O-tube in place as she was still not eating or drinking voluntarily; she weighed 19.8 kg. At this point she was receiving L-thyroxine (0.02 mg/kg PO q12), prednisolone (2 mg/kg PO q24), mycophenolate (10 mg/kg PO q12), fludrocortisone (0.1 mg/kg PO q24), Lypex capsules, omeprazole (1 mg/kg PO q12), metoclopramide (0.25 mg/kg PO q8), maropitant (1.5 mg/kg PO q24), and lubrithal eye ointment (one drop in both eyes q6).

Gradual clinical improvement was seen over the next 4 weeks; the dog became brighter, more energetic, began first to take water and then food per os, and no episodes of abdominal distention or aerophagia were reported. Follow-up laboratory evaluation showed normalisation of CK and electrolytes; a mild non-regenerative anaemia persisted (Table 3, 23/1/19). T4 levels (Table 4, 23/1/19 and 7/2/19) remained subtherapeutic; therefore the dose of L-thyroxine was increased to 0.03 mg/kg q12. As she was maintaining her discharge weight, was eating, and had an acceptable hydration status, the O-tube was removed 6 weeks following surgery, and the dose of prednisolone reduced to 1.5 mg/kg q24 and mycophenolate to 10 mg/kg q24. Other medications remained unchanged.

The patient was re-assessed 2 months after discharge and continued to make good progress. She weighed 22.2 kg with a clear improvement in muscle mass. No concerning abnormalities were noted on a repeat CK, electrolytes and T4 (Tables 3 and 4, 15/3/2019). A further dose reduction in both prednisolone (0.68 mg/kg q24) and mycophenolate (10 mg/kg q48) was made. The doses of L-thyroxine, lypex, fludrocortisone and lubrithal remained unaltered; all other medications were withdrawn.

Over the 6-month period following discharge, the dog was monitored regularly (CK, electrolytes, PCV and T4). The dose of prednisolone was reduced over a 3-month period to a maintenance dose of 0.33 mg/kg Q24. Furthermore, her mycophenolate dose was gradually tapered and discontinued after 6 months, as was the fludrocortisone. An ACTH stimulation test performed 2 weeks after discontinuation of fludrocortisone, showed normal pre- and post-stimulation aldosterone levels at 89 pmol/L and 177 pmol/L, respectively; therefore mineralocorticoid supplementation was not restarted. At this point her weight was 30 kg, BCS 5/9.

The dog has been continued on hormone replacement therapy (prednisolone and thyroxine) and pancreatic enzyme supplementation and was alive at the time of writing, 18 months after diagnosis.

DISCUSSION

Here, we present an unusual case of a rapidly progressive polyglandular endocrine disorder in an adult standard poodle, with concurrent presumed non-endocrine autoimmune disease. Although polyglandular endocrine dysfunction has been reported in the dog,[9] to the authors' knowledge concurrent non-endocrine autoimmune disorders have not been reported. This case has similarities with human type-II APS because of the concomitant presence of hypothyroidism and hypoadrenocorticism. The presence of concurrent KCS and EPI in this case however overlaps more with the non-endocrine disease manifestations reported in conjunction with type-I APS.[16] While rare, polymyositis has also been reported in association with human APSs.[17]

The aetiology of APSs in both humans and canines is thought to be multifactorial with genetic factors and environmental factors being involved in the development of the disease.[18,19] More specifically certain haplotypes of the major histocompatibility complex (which plays a critical response in the immune response) in both humans and dogs have been implicated in the concurrent presentation of multiple autoimmune disorders.[2,19] Due to selective breeding, the standard poodle is predisposed to a substantial number of autoimmune diseases with hypoadrenocorticism and sebaceous adenitis being most commonly reported. An increased incidence of, among others, Evans syndrome, chronic

thyroiditis and temporal-mandibular myositis has also been documented in the breed.[20]

APSs in humans are characterized by defects in the cellular and humoral immune responses with the presence of circulating autoantibodies and lymphocytic infiltration of the affected tissues or organs.[16,17] Testing for autoantibodies against target tissues is therefore routinely incorporated in the diagnostics of human APS. While in veterinary medicine autoantibodies against target tissues are less uniformly observed,[21–24] there is good evidence for an immune-mediated aetiopathogenesis in multiple canine endocrinopathies including hypoadrenocorticism and hypothyroidism, with lymphocytic infiltration and destruction of affected glands.[21,25] Similarly, when looking at the individual non-endocrine conditions affecting this case, there is also ample evidence for an immune mediated mechanism for canine KCS, EPI and myositis.[26–28]

While autoantibodies are not part of the routine screening mechanism for canine endocrinopathies, Cartwright et al documented increased serum concentration of both thyroglobulin autoantibodies and 21-hydroxylase autoantibodies in a Dobermann presenting with both hypothyroidism and hypoadrenocorticism. In a study by Rick et al, all 21-hydroxylase autoantibodies were identified in 30% of dogs diagnosed with hypoadrenocorticism, but this test is not currently commercially available.[24] Furthermore, thyroglobulin autoantibodies (TgAA) are reported to be found in only 50% of dogs diagnosed with hypothyroidism despite an autoimmune pathophysiology (with lymphocytic thyroiditis seen on histopathology) being the most common reason for primary hypothyroidism to occur.[21] In this instance while a positive TgAA may have strengthened our argument for an autoimmune pathophysiology, it would not have changed patient management.

In human type-II APS, there are usually many years separating the onset of the endocrine and non-endocrine comorbidities; however simultaneous development of multiple endocrinopathies has also been reported.[29] It should be noted that the various comorbidities can develop in any order.[30] A wide variation in time of onset is also seen in canine polyglandular autoimmune syndromes with the time of onset between the first and second endocrinopathy being reported to range from 0 to 53 months with a median of 4 months.[9] In this case we observed rapid development of both endocrine and non-endocrine disorders, illustrated in part by the fact that T4 levels were normal just prior to the diagnosis of hypoadrenocorticism, but undetectable a month later, and by the exponential weight loss that was observed in the 3 weeks prior to referral.

The initial assessment of thyroid status in this case was made based on a total T4 measurement using the IDEXX catalyst in-house analyser, without the concurrent measurement of canine thyroid stimulating hormone (TSH). While this analyser is found to be accurate for serum total T4 (TT4) concentrations within the reference range.[31] it is conceivable that thyroid hormone autoantibodies, which have reported to be detected in 6.3% of cases diagnosed with hypothyroidism, could have resulted in a falsely normal TT4 result via assay interference.[32] A normal TSH would have increased confidence in the diagnosis of euthyroidism at that timepoint, while an elevated TSH may have suggested the patient was in the early stages of the disease, prompting further assessment, for instance measurement of free-T4. It should however be noted that TSH can also be increased in up to 36% of dogs with untreated hypoadrenocorticism (thought to be due to a lack of inhibitory effect of cortisol).[39] As TSH normalises following steroid treatment, where concurrent hypoadrenocorticism and hypothyroidism are suspected, thyroid function is better assessed after glucocorticoid treatment has been started.[33]

Lifelong hormone replacement therapy forms the basis of treatment for endocrine disorders associated with APSs in both human and veterinary medicine. Although immunosuppressive therapy is not part of the standard management of acquired human APSs, it has occasionally been reported to be used with good effect in some of the conditions associated with APS type I, including autoimmune hepatitis and EPI, with regression of other manifestations and disappearance of circulating autoantibodies.[34] In this case, prompted by what was perceived to be a very rapid development of multiple autoimmune disorders and a strong suspicion for immune mediated polymyositis we elected to immunosuppress the dog in addition to continuing her on hormone replacement therapy. In the absence of a specific marker of autoimmunity, other than CK, it is unclear whether the decision to institute immunosuppressive therapy contributed to the positive outcome in this case. Cautious withdrawal of therapy over a 6-month period was not associated with clinical relapse.

Nutritional support played a key role in the management of this case. Current WSAVA guidelines are to initiate assisted nutrition in hospitalised patients with a history of anorexia/hyporexia of 5 days duration, particularly where the need for ongoing nutritional support is anticipated and where there is evidence of pre-existing malnutrition.[35] The decision to place a G-through-O tube was based on the anticipated need for intermittent gastric decompression and for medium to long-term nutritional support. The technique was based on a modification of the oesophagojejunostomy (J-though-O) tube feeding technique previously reported.[36] An alternative would have been to place a surgical gastrostomy tube. Despite the benefits of oesophagostomy feeding tubes, complications are not uncommon following oesophagostomy tube placement with 43.1% of dogs experiencing a complication related to tube placement according to a recent review.[37] Although in the study by Nathanson et al no direct association was found between immunosuppression and an increased risk of O-tube complications, the increased risk of O-tube complications, specifically O-tube site infection, when receiving immunosuppressive agents has been reported in cats.[38]

This case report has several limitations. Most importantly, the diagnosis of polymyositis is purely speculative based on marked elevation in dog's CK and AST in the face of poor muscle condition, and absence of an alternative explanation. While electromyography may have been supportive, muscle biopsies are required for definitive diagnosis of immune mediated polymyositis.[27] In retrospect, MG should also have been considered as a cause of the dog's neuromuscular weakness, particularly the pharyngeal weakness and dysphonia. Concurrent myositis and MG has been reported in both people and dogs, and positive AChR antibodies may have altered patient management with the inclusion of acetylcholinesterase inhibitors alongside immunosuppressive therapy.[39–42]

Despite the diagnosis of APS with concurrent non-endocrine immune mediated manifestations, the cause of the patient's mucopurulent vaginal discharge was not accounted

for but thought to be due to bacterial vaginitis. Adult-onset vaginitis is recognised in spayed female dogs, and it is often a secondary problem, with UTIs being the most frequently reported primary problem.[43] Although this patient historically had a UTI, starting the patient on antibiotics without urine analysis, vaginal cytology and culture of both urine and vaginal swab, did not demonstrate good antibiotic stewardship.

Lastly, although in this case report we discuss KCS and hypothyroidism as two separate conditions, reduced tear production and KCS are found more commonly in hypothyroid dogs. The reason for this association is not yet clearly understood but an immune mediated aetiology has been suggested.[44]

The current literature suggests that the presence of one endocrinopathy should alert a veterinary professional to the possibility of a patient developing a poly-endocrinopathy. Moreover, based on what is known in humans with APSs and our experience with this case, practitioners should be aware of the possibility of additional autoimmune non-endocrine organ involvement resulting in highly variable disease manifestations and clinical presentation.

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