Case Report Rapport de cas

Hypoadrenocorticism mimicking protein-losing enteropathy in 4 dogs

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Abstract — Four dogs referred for suspected protein-losing enteropathy based on clinical signs, severe hypoalbuminemia, and hypocholesterolemia, and in 2 dogs, abdominal effusion or peripheral edema, were diagnosed with hypoadrenocorticism. Dogs with hypoadrenocorticism may have features of protein-losing enteropathy, including ascites or peripheral edema, which have not been described in dogs with hypoadrenocorticism.

Résumé — Hypoadrénocorticisme imitant l'entéropathie avec perte de protéines chez 4 chiens. Quatre chiens recommandés pour une entéropathie suspectée avec perte de protéines fondée sur les signes cliniques, accompagnée d'une hypoalbuméniémie grave et de l'hypocholestérolémie et, chez 2 chiens, d'une effusion abdominale ou d'un œdème périphérique, ont reçu un diagnostic d'hypoadrénocorticisme. Les chiens atteints d'hypoadrénocorticisme peuvent présenter des signes d'entéropathie avec perte de protéines, y compris de l'ascite ou de l'œdème périphérique, qui n'ont pas été décrits chez les chiens atteints d'hypoadrénocorticisme.

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Some clinicopathologic abnormalities of hypoadrenocorticism, such as hypoalbuminemia, hypoglycemia, and hypocholesterolemia (1) could be misinterpreted as liver disease or gastrointestinal disease from protein-losing enteropathy (PLE), potentially leading to inappropriate diagnostic and treatment interventions. To the authors' knowledge, there are no published reports in the veterinary literature of hypoadrenocorticism resulting in hypoalbuminemia severe enough to cause abdominal effusion or edema. The purpose of this report is to describe 4 dogs with PLE-like features, including abdominal effusion and peripheral edema, that were attributed to hypoadrenocorticism.

Case descriptions

Case 1

A 5-year-old spayed female Labrador retriever (dog 1) weighing 35.1 kg was referred with a 6- to 8-week history of worsening lethargy, decreased appetite, chronic anemia, ascites, and panhypoproteinemia. There was no history of vomiting or diarrhea, but there were 3 episodes of regurgitation. The dog had developed melena at the time of presentation. The dog was up-to-date on vaccinations had not travelled outside the Pacific Northwest, and was not on any medications prior to referral.

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On hematologic evaluation performed 4 d before referral, there was a mild hypochromic anemia. Mean corpuscular volume (MCV), reticulocyte count, and blood smear examination were not performed. There was no evidence of a stress leukogram. Serum biochemical abnormalities included hypoproteinemia, hypoalbuminemia, and hypoglobulinemia (Table 1). A post-prandial bile acid concentration was normal. No abnormalities were noted on urinalysis.

On examination at the referral hospital 4 days later, the dog was quiet, alert, and responsive. The dog was underweight with a body condition score (BCS) of 2/5. The rectal temperature was 38.7°C. There was mild to moderate generalized muscle atrophy. Abdominal effusion made abdominal palpation challenging. Heart and lung sounds were normal. Peripheral lymph nodes appeared normal. There was no information regarding rectal examination noted in the medical record. The remainder of the physical examination was normal.

Abdominal ultrasound showed marked ascites and mild enlargement of medial iliac (1.5 cm) and mesenteric lymph nodes (1.4 cm). No abnormalities were noted in the stomach, or small or large intestine. The adrenal glands were not visualized. Results of peritoneal fluid analysis were consistent with a pure transudate (protein: 15 g/L, nucleated cell count/μL: 1430 with 46% non-degenerate neutrophils, 38% small lymphocytes, 12% macrophages, and 4% eosinophils) attributed to hypoalbuminemia.

Serum biochemical abnormalities included hypocholesterolemia, hypoalbuminemia, hypoglobulinemia, and hypocalcemia (Table 1); ionized calcium was not determined. The diagnosis of hypoadrenocorticism was confirmed on adrenocorticotropic hormone (ACTH) stimulation test (Table 1).

The dog was treated with prednisone (PredniSONE Tablets USP; Boehringer Ingelheim Roxane Laboratories, Columbus,

Table 1. Hematologic and biochemical abnormalities in 4 dogs with hypoadrenocorticism and signs of gastrointestinal disease

	Dog 1[a]	Dog 2[b]	Dog 3[c]	Dog 4[c]
Neutrophils/μL (2000 to 12 000)	4256	7300	1014	11 070
Lymphocytes/μL (1500 to 6000)	2508	1500	2496	2160
Monocytes/μL (0 to 800)	304	300	156	135
Eosinophils/μL (0 to 1200)	532	0	0	135
Total protein g/L (54 to 82)	33	50	32	22
Albumin g/L (29 to 38)	13	9	12	11
Cholesterol mmol/L (3.5 to 9.2)	2.8	0	1.5	0.9
Glucose mmol/L (3.6 to 6.9)	3.9	3.8	2.4	6.2
Sodium mmol/L (149 to 158)	149	145	154	153
Potassium mmol/L (3.7 to 5.3)	4.1	4.2	4.4	4.2
Total calcium mmol/L (2.3 to 2.8)	2.1	2.4	2.1	1.9
Resting cortisol nmol/L	< 27.6	< 27.6	< 27.6	< 27.6
Post ACTH cortisol nmol/L (> 2)[d]	< 27.6	< 27.6	< 27.6	< 27.6

Reference ranges are in parentheses.
[a] Results from the CBC were obtained 4 d before presentation to the VTH; the biochemistry results are from the day of presentation.
[b] Results obtained 1 d before referral.
[c] Results obtained on day of presentation to the VTH.
[d] ACTH stimulation tests were performed after presentation to the VTH.

Ohio, USA), 0.28 mg/kg body weight (BW), PO, q24h and discharged to follow-up with the regular veterinarian. Two weeks after discharge there was improvement in the laboratory abnormalities and all had resolved 2 mo after discharge. The ascites, regurgitation, and melena had reportedly resolved and the dog had a good appetite and energy level. The patient was continued on the same dose of predisone.

Case 2

A 5-year-old castrated male great Dane (dog 2) weighing 52.4 kg was referred for endoscopic examination and biopsy of the gastrointestinal tract for hypoproteinemia presumed secondary to gastrointestinal disease. Three days prior to presentation to the referral hospital the dog was seen for acute gastric dilation at an emergency clinic, at which time laboratory abnormalities included hypoalbuminemia, hypoglycemia, hypocholesterolemia, and anemia. Clinical signs resolved after orogastric tube decompression. The dog had been losing weight over the last 6 mo, despite a good appetite. There was no history of vomiting or diarrhea. The dog was up to date on vaccinations and had not travelled outside the Pacific Northwest.

Two days before referral the dog had mild to moderate anemia; a reticulocyte count was not performed. There was no evidence of a stress leukogram. Abnormalities on a limited serum chemistry panel included hypoproteinemia, severe hypoalbuminemia, hypoglycemia, and no measureable cholesterol on repeated tests (Table 1). The only abnormality on urinalysis was mild hyperbilirubinuria. On abdominal ultrasound the liver, gastrointestinal tract, spleen, kidneys, bladder, and pancreas were unremarkable. The adrenal glands were small with the right and left measuring 5 mm and 4.1 mm, respectively.

At the referral hospital the dog was quiet, alert, responsive, and underweight with a BCS of 1.5/5. There was severe generalized muscle atrophy. Mucous membranes were pale pink with a capillary refill time of 2 s. Heart and lung sounds were apparently normal. No abnormalities were noted on abdominal palpation. Peripheral lymph nodes were normal. No abnormalities were noted on rectal examination.

Abnormal results of a complete blood (cell) count (CBC) included a microcytic, non-regenerative anemia [reticulocyte count $0.025 \times 10^6/\mu L$, reference interval (RI): $> 0.1 \times 10^6/\mu L$ for regeneration]. There was still no evidence of a stress leukogram and abnormalities of the biochemical profile persisted. The diagnosis of hypoadrenocorticism was confirmed on ACTH stimulation test (Table 1).

The dog was treated with prednisone, 0.29 mg/kg BW, PO, q24h, and discharged to follow-up with the regular veterinarian. All laboratory abnormalities had resolved at examination 4 wk after discharge, and the dog had gained weight. At this time the prednisone dose was decreased to 0.19 mg/kg, BW PO, q24h, and the dog was reported to do well on this dose.

Case 3

A 10-year-old spayed female husky (dog 3) weighing 37.6 kg was referred for an 8- to 12-week history of colitis. Initially, colitis was treated with an unspecified dose of metronidazole resulting in weakness that resolved after discontinuation of metronidazole. One week before presentation to the referral hospital the dog developed hematochezia. At the time of presentation the dog also had hematemesis. The dog was up-to-date on vaccinations. Travel history was not noted in the medical record.

On examination the dog was quiet, alert, and responsive. Heart and lung sounds were normal. There were no abnormalities noted during abdominal palpation. Mucous membranes were pale pink with a capillary refill time of 3 s. Peripheral lymph nodes appeared normal. The dog had pitting edema of the peripheral limbs, ventral abdomen, and thorax. There was no information regarding rectal examination recorded in the medical record.

On a CBC there was no evidence of a stress leukogram, but there was moderate neutropenia. Abnormal serum chemistry panel results (Table 1) included hypocholesterolemia,

hypoproteinemia, hypoalbuminemia, hypoglycemia, and hypocalcemia attributed to hypoalbuminemia; ionized calcium was not determined. The diagnosis of hypoadrenocorticism was confirmed on ACTH stimulation test (Table 1). The CBC was repeated the following day and the neutrophil count had normalized.

An abdominal ultrasound showed fluid-filled and hypomotile small and large bowels and a scant amount of free peritoneal fluid. The remaining abdomen was normal; however, there was no specific mention of the adrenal glands in the ultrasound report. The thoracic radiographs were unremarkable except for evidence of hypovolemia.

The patient was administered prednisolone sodium succinate (Zoetis, Kalamazoo, Michigan, USA), 0.5 mg/kg BW, IV, q12h, for 1 d until she regained her appetite. With resumption of food consumption the dog was discharged to follow-up with the regular veterinarian with prednisone, at 0.53 mg/kg BW, PO, q24h for 1 wk and then decreased to 0.13 mg/kg BW, PO, q24h. Four weeks after discharge all previously documented clinical and biochemical abnormalities had normalized.

Case 4

A 5-year-old neutered male Labrador retriever (dog 4) weighing 28 kg was evaluated for a 2-day history of lethargy, vomiting, diarrhea, and hematochezia. Previous history included an avulsion of the right front dew claw 2 wk earlier, and an episode of vomiting and diarrhea 8 mo prior.

On examination, the dog was quiet, alert, and responsive, but shortly became obtunded and laterally recumbent. The dog had a BCS of 3/5. Mucous membranes were pink and capillary refill time was < 1 s. The rectal temperature was 36.8°C. Heart rate was 156 beats/min and respiratory rate was 16 breaths/min. Femoral pulses were hypokinetic but synchronous. There were normal breath sounds and no arrhythmia, but there was a left-sided grade I/VI systolic murmur loudest over the left apex. The dog seemed uncomfortable with abdominal palpation, but there were no other abnormalities. Peripheral lymph nodes apeared normal. Hematochezia was noted on rectal examination. The remainder of the physical examination was normal.

Abdominal radiographs were taken at the time of presentation to the referral hospital. There was good serosal detail, but the small and large bowels were fluid-filled with no evidence of obstruction. There was no stress leukogram on a CBC. Abnormal results of a serum chemistry panel (Table 1) included hypocholesterolemia, hypoproteinemia with both hypoalbuminemia and hypoglobulinemia, and hypocalcemia attributed to hypoalbuminemia. An ionized calcium test performed the following day (day 2) was normal (1.32 mmol/L, RI: 1.12 to 1.40 mmol/L). The diagnosis of hypoadrenocorticism was confirmed on ACTH stimulation test (Table 1).

After establishing a diagnosis of hypoadrenocorticism, prednisone, 0.27 mg/kg BW, PO, q12h, was given for 1 wk and then decreased to 0.27 mg/kg BW, PO, q24h. The dog was clinically normal at the time of discharge on day 3, with no lethargy, vomiting, or diarrhea. At a 4-week follow-up the dog was clinically normal except for mild polyuria/polydipsia. All biochemical abnormalities had resolved.

Discussion

All 4 dogs in this report were referred for evaluation of what was believed to be primary gastrointestinal (GI) disease; all were diagnosed with hypoadrenocorticism. Although the presence of a primary enteropathy was not definitively excluded in any of these dogs, resolution of both clinical signs and laboratory abnormalities of hypoproteinemia, hypoalbuminemia, and hypocholesterolemia following therapy with physiologic replacement doses of prednisone supports the likelihood that all of the clinical features of these dogs were a consequence of untreated hypoadrenocorticism and not a concurrent enteropathy.

The dogs in this report were suspected of having PLE, a spectrum of GI diseases characterized by loss of serum proteins into the GI tract. Dogs with PLE are often seen for chronic or relapsing diarrhea and/or vomiting, and commonly exhibit weight loss. They may have ascites, pleural effusion, or peripheral edema, usually as a consequence of hypoalbuminemia and low oncotic pressure (2). Common laboratory findings include hypoalbuminemia, hypocholesterolemia, and potentially hypoglobulinemia, lymphopenia, hypocalcemia, hypomagnesemia, and hypocobalaminemia (1–2). The diagnostic approach to a dog suspected of having PLE commonly involves exclusion of other causes of hypoalbuminemia including protein-losing nephropathy, liver failure, and third space losses, but hypoadrenocorticism is not routinely mentioned as a differential diagnosis (2–3). The 4 cases described here highlight the importance of considering hypoadrenocorticism as a differential diagnosis for a PLE-like presentation in dogs with hypoalbuminemia and/or hypocholesterolemia, even when such dogs exhibit clinical consequences of enteric protein loss, such as peripheral edema or ascites.

The pathophysiologic mechanism driving hypoalbuminemia in hypoadrenocorticism is unknown. Loss of albumin into the GI tract or decreased intake/assimilation of proteins, is the main suspected cause (4). The human literature suggests that glucocorticoids enhance barrier function of epithelial cells due to suspect epithelial-specific properties, but more research is needed in this area (5).

Two of the 4 dogs had fluid accumulation (abdominal effusion, dog 2; peripheral edema, dog 3) attributed to hypoalbuminemia. It is well-known that hypoadrenocorticism can mimic gastrointestinal disease; however, to our knowledge there is no literature describing ascites or peripheral edema secondary to hypoadrenocorticism-induced hypoalbuminemia (4,6). Effusions and edema are, however, relatively common in dogs with PLE, potentially increasing the likelihood that a clinician erroneously suspects PLE as the cause of the clinical features in dogs affected by hypoadrenocorticism.

Hypocholesterolemia is common in dogs with what has been historically referred to as atypical, or glucocorticoid-deficient, hypoadrenocorticism. A recent paper (7) found that dogs with "atypical" hypoadrenocorticism had mineralocorticoid deficiencies despite having normal electrolyte concentrations, but for the sake of this discussion, we will retain the atypical hypoadrenocorticism designation. In one study, 13/17 (76.5%) dogs with atypical hypoadrenocorticism had hypocholesterolemia

(6). In a study by Thompson et al (8), dogs with glucocorticoid-deficient hypoadrenocorticism had significantly lower albumin and cholesterol concentrations than dogs with typical hypoadrenocorticism. The diagnostic challenge posed by atypical hypoadrenocorticism, and often the more prolonged course of disease before diagnosis, could contribute to the increased frequency of hypocholesterolemia in affected dogs (8,9). All the dogs of our report had hypocholesterolemia, and in dog 2, the hypocholesterolemia was severe. The mechanism for hypocholesterolemia in hypoadrenocorticism is not known. It has been suggested that glucocorticoids play a role in fat absorption from the GI tract; decreased mobilization or increased utilization of fatty acids secondary to high ACTH concentrations has also been proposed (1,6,9).

Dogs with hypoadrenocorticism often have no stress leukogram because of cortisol deficiency. In the study by Thompson et al (8), all dogs had normal lymphocyte, monocyte, and eosinophil counts, and Scott-Moncrief (9) reported that 97% of dogs with hypoadrenocorticism lacked a stress leukogram. Since hyperkalemia and/or hyponatremia often prompt suspicion of hypoadrenocorticism and subsequent testing for the disease, recognition that a patient lacks a stress leukogram becomes critical to generating suspicion of atypical hypoadrenocorticism even when none of the classic electrolyte abnormalities are present (8–9). None of the dogs in this report had a stress leukogram.

In a retrospective study, pre- and post-ACTH serum cortisol concentrations were below 27.6 nmol/L in 37/42 of dogs with hypoadrenocorticism, whereas the remaining 5/42 had pre- and post-ACTH serum cortisol levels between 27.6 and 55.2 nmol/L (8). Thus, a resting cortisol can be a useful and relatively inexpensive tool in ruling out hypoadrenocorticism. It could be argued that an ill patient without a stress leukogram should have a basal cortisol concentration measured before more invasive and expensive diagnostics are performed. If the basal cortisol is less than 55.2 nmol/L the sensitivity and specificity for detecting hypoadrenocorticism are 100% and 63% to 78%, respectively, and obtaining post-ACTH cortisol concentration is recommended to confirm the diagnosis (10–11).

Three dogs in this report had small or non-detectable adrenal glands during abdominal ultrasonography. It has previously been described that dogs with hypoadrenocorticism had significantly thinner adrenal glands than those of healthy dogs, but dogs with atypical hypoadrenocorticism were not well-represented in these reports (12,13). All patients in the paper by Wenger et al (13) had unspecified electrolyte abnormalities, and Hoerauf and Reusch (12) did not describe laboratory results/abnormalities for their patients. Adrenal ultrasonography may be of value in dogs with clinical signs otherwise suggestive of PLE as small adrenal glands could enhance the suspicion of hypoadrenocorticism.

In conclusion, the challenge of diagnosing atypical hypoadrenocorticism resides in generating clinical suspicion. The absence of a stress leukogram in dogs with hypoalbuminemia and/or hypocholesterolemia, even with ascites or peripheral edema, should warrant a resting cortisol, and ACTH stimulation testing if indicated, before pursuing causes of primary GI disease. CVJ

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