Case Report

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Suspected relative adrenal insufficiency in a critically ill cat

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Abstract

Objective: To describe a case of likely relative adrenal insufficiency (RAI) in a cat with critical illness.
Case summary: A cat recovering from polytrauma developed hypotension unresponsive to intravenous fluid support and vasopressor therapy. An adrenocorticotropin hormone stimulation test documented insufficient adrenal function. Treatment with exogenous low-dose glucocorticoids in addition to standard therapies resulted in rapid hemodynamic and clinical improvement. The cat ultimately recovered and was weaned from supplemental glucocorticoids.
New or unique information provided: This is the first report of changes consistent with acquired RAI in a cat with critical illness.

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Introduction

Relative adrenal insufficiency (RAI) has been recognized with increasing frequency in critically ill humans, particularly in association with sepsis. The specific mechanism for the development of RAI is unclear, and is likely multifactorial, but may include elevated cytokine levels and other inflammatory mediators.[1] Sepsis and systemic inflammatory response syndrome (SIRS) are the most common underlying causes of RAI,[2] with reports of RAI occurring in 24–77% of humans with sepsis.[1,3,4] In critically ill humans, treatment for RAI consists of exogenous low-dose glucocorticoid therapy, which results in improvement in hemodynamic stability as well as reduced morbidity and mortality.[3] Early treatment with low doses of glucocorticoids is also routinely used in humans considered at high risk for RAI. RAI has been described in a foal with severe enteritis and an initial suspicion of septicemia; however, 2 small studies in dogs and cats have failed to document the presence of RAI in critically ill small animals.[5,6,a]

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The purposes of this report are to document the presence of likely RAI in a critically ill cat and to report on the clinical findings, management, and outcome.

Case Summary

An 8-year-old castrated male domestic short-hair cat weighing 5 kg was evaluated by the referring veterinarian after being struck by a car. During the initial examination, the cat was laterally recumbent with blood dripping from the nose and mouth. A severe degloving wound of the right forelimb and abrasions to the legs and abdomen were also identified. The initial evaluation revealed a respiratory rate of 60 breaths/min, a heart rate of 200 beats/min, and a temperature of 36.4 °C (97.6 °F). The initial packed cell volume and total solids were 24% and 6.0 g/dL. The initial treatment consisted of intravenous fluids, cefazolin[b] (22 mg/kg IV, q 8 h), butorphanol[c] (0.2 mg/kg IV, q 4 h), supplemental oxygen administration, and active warming with a circulating water blanket. The temperature increased to 37.3 °C (99.2 °F), and an improvement in mentation was noted. The wound was managed with a soft padded bandage, and the cefazolin, butorphanol, and intravenous fluids were continued. Two days later, the cat was referred for management of anemia and surgical correction of the limb wound.

Significant abnormalities at the time of referral included a degloving wound of the proximal right antebrachium with evidence of tissue necrosis, abdominal bruising, and multiple abrasions. The cat was quiet but responsive. The rectal temperature was 39.1 °C (102.3 °F), the heart rate was 220 beats/min, and the respiratory rate was 36 breaths/min. The indirect systolic blood pressure measured by Doppler was 76 mmHg. No prior blood pressure was available for comparison.

Initial point-of-care testing at the referral center documented an anemia (17%, reference 31–46%), hyperglycemia (190 mg/dL, reference 70–120 mg/dL), hyperlactatemia (5.9 mmol/L, reference 0.3–1.0 mmol/L), hyponatremia (143 mEq/L, reference 149–164 mEq/L), and hypochloremia (104 mmol/L, reference 119–134 mmol/L). Leukocytosis (23,529/μL, reference 4500–15,700/μL), with a differential cell count composed of 90% neutrophils, 7% lymphocytes, 2% monocytes, 1% band neutrophils (with evidence of toxic change), was noted on the complete blood count. Hyperbilirubinemia (4.5 mg/dL, reference 0.1–0.3 mg/dL) was present, along with elevation of several liver enzymes (ALT 175 U/L and aspartate aminotransferase [AST] 487 U/L, reference 29–145 and 12–42 U/L, respectively). Urinalysis documented concentrated urine (specific gravity 1.040) with 3+ bilirubinuria. The prothrombin time (PT) was normal (20 seconds; normal 15–23 seconds), the activated partial thromboplastin time (aPTT) was prolonged by 20% over the upper limit (144 seconds; normal 70–120 seconds), and the platelet count was estimated to be normal at 200,000–500,000/μL. There was no traumatic injury visible on thoracic radiographs, although the cardiac silhouette was assessed as small, possibly consistent with hypovolemia. Abdominal ultrasonography was unremarkable, except for severe body wall thickening. The adrenal glands were not visualized during the ultrasound examination.

The cat was admitted to the intensive care unit (ICU) and treatment for hypovolemia consisting of 100 mL of 0.9% NaCl[d] was administered as a bolus, and then followed by a continuous rate infusion of 20 mL/hr (4 mL/kg/hr). One unit of type-specific packed red blood cells was given for the treatment of anemia, and buprenorphine[e] (0.01 mg/kg IV, q 6 hr) was administered for pain control. The indirect systolic blood pressure improved to 120 mmHg, the heart rate decreased to 180 beats/minutes, the respiratory rate decreased to 26 breaths/min, and the temperature normalized to 37.5 °C (99.5 °F). Following volume resuscitation, the antebrachial wound was cleaned and debrided under propofol sedation (4 mg/kg IV) and a wet to dry bandage was placed. A urinary catheter and closed urine collection system were placed for convenience. Cefazolin (22 mg/kg, q 8 h) and enrofloxacin[f] (5 mg/kg, q 24 hr) were administered intravenously for empiric broad-spectrum antimicrobial coverage.

Over the next 2 days, the demeanor of the cat improved and he began to eat small amounts of food. The systolic blood pressure ranged from 110 to 125 mmHg, the heart rate varied from 180 to 220 beats/min, and the temperature was within normal limits. The packed cell volume remained stable at 20%, although the serum was noted to be icteric on the second day post-transfusion.

On the morning of the third day of hospitalization, pain was noted during palpation of the caudal abdomen. Abdominal ultrasonography was repeated and documented the presence of a body wall hernia, containing segments of bowel and urinary bladder. Owing to the concern for bladder entrapment and the possibility of compromised bowel, the cat was urgently taken to surgery for hernia repair. Pre-anesthetic blood work consisted of a packed cell volume ([PCV] 22%), total solids ([TS] 5.0 g/dL), blood glucose (152 mg/dL), lactate (1.8 mmol/L), and PT/aPTT (both normal). Anesthesia was induced with hydromorphone[g] (0.05 mg/kg IV), midazolam[h] (0.12 mg/kg IV), and ketamine[i] (5 mg/kg IV), and was maintained with isoflurane[j] in oxygen. Systolic blood pressure at the time of induction was 80 mmHg. Surgical findings included a prepubic tendon rupture and no evidence of vascular compromise to the herniated gastrointestinal tract or bladder. The hernia was repaired by securing the abdominal muscles to the pubic bone. Before closure of the abdomen, a liver biopsy was taken. Postoperatively, a multilumen catheter[k] was placed in the jugular vein and an esophagostomy tube[l] was placed for nutritional support.

Intraoperatively, despite aggressive fluid therapy consisting of 225 mL of lactated Ringer's solution[m] (42 mL/kg), the cat was persistently hypotensive with a Doppler blood pressure measurement of less than 70 mmHg. Dopamine[n] was administered as a continuous infusion (6–12 μg/kg/min) that was titrated to maintain a systolic blood pressure greater than 70 mmHg. Postoperatively, the cat remained dependent on dopamine at 10 μg/kg/min to maintain a systolic blood pressure of greater than 80 mmHg, despite intravenous crystalloids titrated to maintain a central venous pressure of 8–10 cmH_2O. The postoperative PCV and TS were 18% and 4.5 g/dL. A type-specific fresh-frozen plasma transfusion (6 mL/kg IV) was administered both for oncotic support, through the addition of albumin, and to provide coagulation factors in the event that a dilutional coagulopathy had been created. Twenty-four hours after surgery, the cat remained dependent on dopamine. Owing to the suspicion of RAI, an adrenocorticotropin hormone (ACTH) stimulation

test was performed to evaluate adrenal function. The ACTH stimulation test was performed by administering cosyntropin[o] (125 μg IM), followed by sample collection at 0, 30, and 60 minutes after injection. Pending test results, dexamethasone[p] (0.08 mg/kg, IV) was administered daily at a dose equivalent to 0.5 mg/kg of prednisone.

The following morning, the PCV and TS were 19% and 4.2g/dL, respectively. A complete blood count demonstrated a leukocyte count of 14,400/μL (reference 4500–15,700/μL), and a differential cell count consisting of 73% neutrophils, 13% lymphocytes, 11% eosinophils, 2% bands, and 1% monocytes. Toxic changes were observed in the white blood cell morphology. The plasma was icteric and a biochemistry profile demonstrated elevations in total bilirubin (1.40 mg/dL, reference 0.10–0.30 mg/dL), and (AST, 118 U/L, reference 12–42 U/L). Glucose was within the normal reference interval (120 mg/dL, reference 70–120 mg/dL). Histological examination of the liver biopsy showed moderate to severe canalicular cholestasis, mild multifocal hepatocellular necrosis, and mild diffuse hepatocellular vacuolar change.

Following the administration of the glucocorticoids, the cat's blood pressure rapidly improved, and the dopamine was discontinued. Within 24 hours of administering glucocorticoids, a systolic blood pressure of 150 mmHg was obtained without vasopressor support. ACTH stimulation test results were interpreted as an inadequate response with a baseline cortisol level of 1.1 μg/dL (reference baseline cortisol 0.5–5 μg/dL) and 4.3 and 4.2 μg/dL (reference poststimulation cortisol 5–15 μg/dL) at 30 and 60 minutes, respectively. The delta cortisol (change from baseline) was 3.2 μg/dL.

The cat made an uneventful recovery and was discharged 7 days postoperatively. The supplemental glucocorticoids (prednisone,[q] 1 mg orally q 12 h) were tapered over 2 weeks. The icterus resolved before discharge. Four weeks after discharge, the owners were contacted, and the cat was reported to be eating without tube feedings and was making a full recovery. Several months following the trauma, the owners and referring veterinarian reported that the cat was clinically normal.

Discussion

To the authors' knowledge, RAI associated with critical illness has not been previously reported in a cat. In the case reported here, a cat with polytrauma had a subnormal poststimulation cortisol concentration and a positive response to low-dose glucocorticoid therapy. The administration of low-dose glucocorticoids was associated with successful weaning from vasopressor therapy. These findings lend support to a diagnosis of RAI. Intravenous rather than oral glucocorticoids were selected due to inappetance and reduced mentation, and daily dosing was chosen due to concern for possible RAI and the lack of an ability to generate a stress response. The dose of dexamethasone selected in this case was based on an equivalent dose of prednisone of 0.5 mg/kg/day.

The diagnosis of likely RAI in this cat was based on a positive response to glucocorticoid administration as well as subnormal poststimulation cortisol concentration. Cortisol levels in critically ill humans are highly variable. Several human studies have supported the concept that patients with basal cortisol levels of ≤ 15 μg/dL appear to benefit from cortisol replacement, while patients with basal cortisol levels >34 μg/dL are unlikely to have RAI.[7] An ACTH stimulation test may also be used to differentiate critically ill humans with RAI, with a change of <9 μg/dL from baseline (delta cortisol) supporting a diagnosis of acquired RAI.[3] Guidelines published as part of the Surviving Sepsis Campaign currently recommend the administration of hydrocortisone (200–300 mg/day) for 7 consecutive days in three or four divided doses or by continuous infusion for humans with septic shock, who, despite adequate fluid replacement, require vasopressor therapy to maintain adequate blood pressure.[8] Nonresponders in these guidelines were identified using an ACTH stimulation test and a poststimulation cortisol change (delta cortisol) of <9 μg/dL.[8]

The appropriate criteria for critically ill cats and dogs have not yet been proposed or validated, and caution must be exercised with direct extrapolation across species. A normal response to ACTH stimulation several weeks following cessation of prednisone therapy would have confirmed the transient nature of the adrenal dysfunction in this case but was declined by the owners. Owing to the inability to document return of normal adrenal function following recovery, a definitive diagnosis of RAI cannot be made. However, the diagnosis of RAI was strongly supported by an inappropriately low basal cortisol level, failure to respond into a normal range, and the positive response to low-dose glucocorticoid therapy.

Prior investigation of the potential for RAI in dogs and cats has been limited to small studies. In one study of 20 dogs with a variety of naturally occurring illnesses, basal cortisol levels, endogenous ACTH levels, and ACTH-stimulated cortisol levels were evaluated at admission and then daily until death, euthanasia, or discharge from the ICU. Although a loss of correlation between the measured ACTH levels and the measured cortisol concentrations was observed in a segment of

the study population, the study did not identify changes consistent with RAI.[6] The same investigators evaluated 20 cats hospitalized in an intensive care unit.[a] Basal levels of plasma cortisol, ACTH-stimulated cortisol, and delta cortisol were measured and compared with 10 healthy control cats. Basal cortisol levels were obtained within 24 hours of admission and the ACTH-stimulated cortisol was obtained every other day until death, euthanasia, or discharge from the hospital. The results of this study included increased basal cortisol levels as compared with the control group, but the ACTH-stimulated cortisol levels did not differ between the 2 groups. No significant differences in measured variables were found between survivors and non-survivors, or between septic and non-septic cats. However, cats with neoplasia were found to have a lower delta cortisol, and were more likely to die than other cats in the study.

The relative adrenal insufficiency was investigated in 10 cats with cytologic or histopathologic evidence of lymphoma.[r] As adrenal involvement has been described in cats with lymphoma (which may directly cause adrenal dysfunction), ultrasonographic examination of the adrenal glands was performed in this study and none of the cats appeared to have involvement of the adrenal glands.[9] Basal cortisol, ACTH-stimulated cortisol, and plasma ACTH concentrations were analyzed. Nine of the cats had subnormal cortisol response to ACTH, 5 had high plasma ACTH concentrations, and 1 cat had an abnormal sodium:potassium ratio. The authors concluded that many of the cats in this study had RAI.

Low-dose corticosteroid replacement in human cases of RAI has been found to reduce vasopressor requirements and is associated with a more rapid reversal of shock.[3,7,10,11] In a trial of 300 human patients with septic shock, an inadequate response to the ACTH stimulation test (defined as a delta cortisol $<9\,\mu g/dL$) was obtained in 76% of patients, and reduced mortality was documented in non-responders receiving low-dose corticosteroid (50 mg hydrocortisone IV q 6 h) replacement compared with those receiving placebo.[3] This study failed to document a reduction in mortality in the group of responders receiving corticosteroids when compared with placebo. In another prospective, randomized, double-blind, placebo-controlled trial of 41 patients with septic shock in which 22 patients received low-dose corticosteroid (100 mg hydrocortisone IV q 8 h) replacement and 19 received placebo, 15 (68%) patients receiving low-dose corticosteroids and 4 (21%) patients receiving placebo achieved shock reversal based on a stabilization of blood pressure (>90 mmHg) without vasopressors.[11] The 28-day mortality was also lower in the group receiving corticosteroids (32% vs 63%). Reversal of shock within 7 days of therapy was a strong predictor of survival in this study of humans with sepsis.

The decision to perform an ACTH stimulation test in this cat was based upon persistent hypotension despite fluid therapy, and vasopressor dependence. Hypoadrenocorticism is a very rare disease in cats.[12] In humans, classic signs of hypoadrenocorticism such as decreased sodium–potassium ratios are rare with acquired RAI of critical illness, likely due to concurrent fluid therapy.[7] Eosinophilia is uncommon in critically ill patients, but if present should raise the index of suspicion for RAI. In a population of high-risk human surgical patients, the relative and absolute number of eosinophils were found to be significantly higher in the adrenal insufficiency group compared with the normal ACTH responders.[13] Eosinophilia was evident in the white blood cell differential on the second complete blood count in this cat. The most important diagnostic clues in humans are hemodynamic instability and vasopressor dependence, despite aggressive fluid resuscitation.

The ACTH stimulation test performed in this cat was accomplished using an intramuscular injection of cosyntropin. It could be argued that IV administration of cosyntropin would be superior in ensuring adequate cortisol response. However, the results of a study evaluating the administration of cosyntropin IM or IV to 10 healthy cats suggested that both IM and IV administration of cosyntropin will reliably induce an adrenocortical response in cats.[14] The study results indicated that IV administration did achieve a higher mean peak plasma cortisol concentration than IM administration in cats.[14] The maximal cortisol response did require longer response times with IV administration than with IM administration.[14]

In order to diagnose RAI, other factors that could alter the pituitary–adrenal axis should be excluded. The anesthetic etomidate and the antifungal agent ketoconazole have been documented to inhibit the enzymes involved in cortisol synthesis.[15] Etomidate was not used for anesthesia in this cat, and no other cause for altered adrenal function, such as previous administration of glucocorticoids, could be identified. Other causes for adrenal insufficiency in this cat could include traumatic brain injury affecting the pituitary, neoplasia (lymphoma) of the adrenal glands, and adrenal hemorrhage secondary to septicemia or coagulopathy.[7,9,16] Other causes of acute adrenal insufficiency documented in humans include immunosuppression from human immunodeficiency virus, tuberculosis, fungal disease, as well as rifampin therapy.[17]

In this cat, RAI may have occurred secondary to either sepsis or systemic inflammation from poly-

trauma. Ideally, blood and wound cultures would have been performed to confirm or exclude a diagnosis of septic shock. The presence of a necrotic wound led to a strong suspicion of sepsis in this cat. Changes suggestive of sepsis included a leukocytosis with a left shift, coagulation abnormalities (elevated aPTT), and hyperbilirubinemia. Previous studies of cats have shown that sepsis can be a clinically challenging diagnosis.[18,19] Criteria for the diagnosis of SIRS in cats have been proposed but have not been clinically validated.[19]

This case strongly suggests the existence of acquired RAI in a critically ill cat. Extrapolation from this case and from studies in humans support ACTH stimulation testing and the administration of low-dose replacement glucocorticoids in cats with persistent hypotension that is unresponsive to fluid resuscitation and who are dependent on vasopressors.

Footnotes

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[e] Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA.
[f] Bayer Healthcare LLC., Shawnee Mission, KS.
[g] Baxter Healthcare Corporation.
[h] Hospira Inc., Lake Forest, IL.
[i] Fort Dodge Animal Health, Fort Dodge, IA.
[j] Abbott Laboratories, North Chicago, IL.
[k] Mila International, Florence, KY.
[l] Cook Australia, Queensland, Australia.
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[q] Roxane Laboratories, Columbus, OH.
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