Presumptive nontraumatic adrenal hemorrhage preceding hypoadrenocorticism in a dog

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Abstract
Nontraumatic adrenal hemorrhage (NTAH) has been associated with stress-induced catecholamines release in underlying conditions such as sepsis and recent surgery in humans. It can lead to primary hypoadrenocorticism (HOAC) when both adrenal glands are involved, with nonspecific clinical signs and laboratory findings that can lead to a missed diagnosis. Bilateral thickening of the adrenal glands with periadrenal fat stranding was identified in a 10-year-old male Maltese dog after abdominal surgery. The dog showed clinical signs and biochemical changes consistent with HOAC, but treatment for presumed critical illness-related corticosteroid insufficiency was initiated. Clinical signs relapsed with a 3-week dose reduction of hydrocortisone, and a reduction in adrenal size was observed on follow-up ultrasound examination. Hormonal testing confirmed HOAC in the dog. To the best of our knowledge, HOAC caused by spontaneous NTAH has not been reported in the veterinary literature. This report describes a dog that developed HOAC with presumed adrenal atrophy after suspected spontaneous bilateral NTAH.

KEYWORDS
adrenal atrophy, diagnostic imaging, periadrenal fat stranding, thickened adrenal glands

INTRODUCTION
Hypoadrenocorticism (HOAC) is a life-threatening disease characterized by hypovolemia, hypotension, hyperkalemia and associated arrhythmias, hypoglycemia, and acidosis in the acute crisis phase if appropriate treatment is delayed.1 Hypoadrenocorticism is classified as primary, secondary, or iatrogenic. The typical etiology of primary HOAC is immune-mediated destruction of the adrenal glands and is most commonly seen in dogs.2 Spontaneous nontraumatic adrenal hemorrhage (NTAH) is reported rarely in human patients who are critically ill.3 Although the exact pathogenesis is unclear, it could be caused by a stress-induced physiological increase in vascularization, edema, venous stasis, and subsequent adrenal gland hemorrhage.3-5 Various predisposing factors, including sepsis, hypotension, recent surgery, and coagulopathy have been associated with the onset of NTAH.5 It can lead to primary HOAC when both adrenal glands are involved, with nonspecific clinical signs and laboratory findings that often overlap with those of other concurrent severe illnesses, leading to a missed diagnosis.4,5 Therefore, hormonal testing and treatment for HOAC may be delayed, leading to a worse prognosis.5 Imaging Abbreviations: CT, computed tomography; CIRCI, critical illness-related corticosteroid insufficiency; HU, Hounsfield units; HOAC, hypoadrenocorticism; NTAH, nontraumatic adrenal hemorrhage; US, ultrasound; RI, reference interval.
potentially can identify early adrenal changes caused by adrenal hemorrhage, and lead to an improved prognosis through early diagnosis and prompt treatment. To our knowledge, HOAC caused by spontaneous NTAH has not been reported in the veterinary literature.

We describe a dog that developed HOAC associated with presumed adrenal atrophy after suspected acute spontaneous bilateral NTAH including diagnostic imaging features of adrenal hemorrhage and atrophy.

FIGURE 1 Multiphase computed tomography (CT) images of the adrenal glands. Dorsal images of bilateral adrenal glands (right one; black arrows, left one; white arrows) on precontrast (A) and delayed phases (B). Transverse precontrast image (C), aortic phase image (D), portal phase image (E), and delayed phase image (F) of the adrenal glands. The adrenal glands are thickened (dorsoventral diameter of right one: 1.0 cm of the cranial pole, 0.7 cm of the caudal pole; left one: 0.8 cm of the cranial pole, 1.0 cm of the caudal pole) and have a focal hyperattenuated lesion (open black arrowhead). The adrenal glands show heterogeneous parenchyma with strongly marginal and focal enhancement (black arrowheads) on contrast phases. There are fat strandings in the retroperitoneal space (white arrowheads)

2 | CASE HISTORY

A 10-year-old male Maltese dog was presented for evaluation of abdominal distention and vomiting. On physical examination, the dog was alert and responsive, with a body condition score of 5/9, no history of endocrine disease, and severe abdominal distention and pain. Abnormal laboratory findings included mild leukocytosis (23.79 × 10⁹/L; reference interval [RI], 5.05-16.762), hyperglobulinemia (5.3 g/L; RI, 2.0-3.5 g/L).

FIGURE 2 Serial ultrasonographic (US) images showing normal (A), enlarged (B), and reduced (C) sizes of left adrenal gland. There are no specific findings for the adrenal gland at the first screening examination (A). The adrenal gland is larger than that in the first US obtained 7 days earlier. However, the size is smaller than that of the computed tomography (CT) obtained 3 days earlier (B). Focal retroperitonitis around the adrenal gland is visible as in CT observations (white arrow). The image of adrenal gland is consistent with atrophy, 4 weeks after the first US (C)
In our case, because the dog did not have any other known cause for HOAC. Therefore, failure to diagnose this condition early may lead to a worse prognosis because of untreated HOAC, with mortality rates of 15% reported in human patients with HOAC secondary to NTAH. In our case, although biochemical changes and both pre- and ACTH-stimulated serum cortisol concentrations were consistent with HOAC, we first suspected CIRCI because the dog did not have any other known cause for HOAC. Although still controversial in veterinary medicine, CIRCI is a transient condition secondary to critical illness, wherein adrenal function normalizes after recovery. However, our dog did not have normal adrenal function after discharge from the hospital. Eventually, HOAC was diagnosed when findings consistent with bilateral adrenal atrophy were identified during follow-up US examination. Similar to our case, in a retrospective study of HOAC secondary to NTAH, irreversible bilateral adrenal atrophy was identified in 9 of 14 human patients who underwent CT examination.14

Secondary NTAH occurs in severely ill patients. The clinical features are nonspecific, including abdominal pain, vomiting, fever, weakness, and hypotension, making it difficult to diagnose, particularly in the postoperative period. In addition, because biochemical changes such as hyperkalemia and hyponatremia vary in patients with HOAC and may be attributed to other diseases, the diagnosis is confirmed by post-ACTH serum cortisol concentration. Therefore, failure to diagnose the condition early may lead to a worse prognosis because of untreated HOAC, with mortality rates of 15% reported in human patients with HOAC secondary to NTAH. In our case, although biochemical changes and both pre- and ACTH-stimulated serum cortisol concentrations were consistent with HOAC, we first suspected CIRCI because the dog did not have any other known cause for HOAC. Although still controversial in veterinary medicine, CIRCI is a transient condition secondary to critical illness, wherein adrenal function normalizes after recovery. However, our dog did not have normal adrenal function after discharge from the hospital. Eventually, HOAC was diagnosed when findings consistent with bilateral adrenal atrophy were identified during follow-up US examination. Similar to our case, in a retrospective study of HOAC secondary to NTAH, irreversible bilateral adrenal atrophy was identified in 9 of 14 human patients who underwent CT examination.14

In our case, although biochemical changes consistent with HOAC, but treatment for presumed critical illness-related corticosteroid insufficiency (CIRCI) was initiated with hydrocortisone 2 mg/kg IV q12h, and recurrent hyperkalemia and hyponatremia relapsed after a 3-week dose reduction of hydrocortisone. Four weeks after the first US, a reduction in adrenal thickness was identified on US examination, and the change in peritoneal fat around the adrenal glands disappeared (Figure 2C). The low pre- and post-ACTH serum cortisol concentrations (<0.5 μg/dL) on the ACTH stimulation test confirmed HAOC in the dog. The dog remains clinically healthy and does not show clinical signs of HOAC on prednisone (0.25 mg/kg PO q24h) and a monthly injection of deoxycorticosterone pivalate (1.8 mg/kg) after 8 months.

Moreover, peritoneal fat stranding also was found (Figure 2A). The overall attenuation values of the adrenal glands were approximately 30 Hounsfield units (HU), and a focal hyperattenuated lesion of approximately 45 HU was identified in the caudal pole of the left adrenal gland on the precontrast CT examination. The adrenal glands had heterogeneous parenchyma on contrast-enhanced CT, with strong marginal and focal enhancement (Figure 1). Initially, the possibility that the adrenal glands were underestimated on the US examination owing to the mass and that intra-abdominal inflammation may have affected the retroperitoneal cavity were considered.

Three days after surgical resection of the mass, the dog showed lethargy, hypotension (80 mm Hg), hyperkalemia (6.8 mmol/L; RI, 3.5-5.8) and hyponatremia (141 mmol/L; RI, 144-160). The sodium/potassium (Na/K) ratio was 21, and both resting serum cortisol concentration (RI, 1.0-5.0 μg/dL) and ACTH-stimulated serum cortisol concentration (RI, 8.0-17.0 μg/dL) were <0.5 μg/dL). Furthermore, the thickness of the adrenal glands (Figure 2B) on US re-examination was smaller than observed on CT, which was performed 3 days earlier. Increased echogenicity of peritoneal fat around the adrenal glands was identified during the US examination. The dog showed clinical signs and biochemical changes consistent with HOAC, and the change in peritoneal fat around the adrenal glands disappeared (Figure 2C). The low pre- and post-ACTH serum cortisol concentrations (<0.5 μg/dL) on the ACTH stimulation test confirmed HAOC in the dog. The dog remains clinically healthy and does not show clinical signs of HOAC on prednisone (0.25 mg/kg PO q24h) and a monthly injection of deoxycorticosterone pivalate (1.8 mg/kg) after 8 months.

DISCUSSION

Nontraumatic adrenal hemorrhage has been reported to be induced by stress and a sudden increase in circulating catecholamines, leading to increased arterial blood flow into the adrenal glands and vasoconstriction of the draining venules in underlying conditions such as sepsis, pregnancy, adrenal tumors, and recent surgery in humans. High concentrations of catecholamines may promote platelet aggregation and adrenal venous thrombosis, leading to adrenal vein rupture because of increased adrenal venous congestion and pressure. Furthermore, antiphospholipid syndrome, anticoagulant use, and hematological disorders have been associated with this condition.9 Because adrenal hemorrhage can cause compression and destruction of all 3 layers of the adrenal glands, resulting in the deficiency of adrenal hormones, it can cause acute HOAC. Approximately 50% of human patients with bilateral adrenal hemorrhage eventually develop HOAC.11 In our case, because the dog did not have any other known cause of HOAC (e.g. primary or secondary hypoadrenocorticism, prolonged corticosteroid use), stress-induced catecholamine release after systemic inflammation and surgery of the abdominal mass were suspected to have caused HOAC secondary to NTAH. In retrospective studies on NTAH in humans, sepsis and postoperative complications have been reported as major predisposing factors. Moreover, sepsis was reported to increase the risk of bilateral adrenal hemorrhage 6-fold in humans. Such changes in the adrenal glands in our case potentially could be explained by fulminant immune-mediated inflammation of the adrenal glands leading to atrophy or necrosis of adrenal tissue, and also would lead to initial enlargement followed by rapid reduction in size. However, in studies on experimentally-induced autoimmune adrenalitis in animals, no such changes in adrenal glands were found.14

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Diagnostic imaging potentially can identify adrenal hemorrhage early. Computed tomography is considered the most reliable and widely available method for the early diagnosis of adrenal hemorrhage, allowing prompt initiation of corticosteroid treatment in humans.\textsuperscript{5,12} The CT findings of adrenal hemorrhage vary depending on the time that has elapsed between the onset of bleeding and CT examination.\textsuperscript{8,16} Computed tomography shows diffuse thickening of the adrenal glands bilaterally with periadrenal fat stranding within adrenal hemorrhage.\textsuperscript{3,16} Increased hydrostatic pressure within the adrenal capillary sinusoids causes diffuse adrenal gland enlargement, and fluid or bleeding extravasation leads to periadrenal stranding.\textsuperscript{3,11,16} Another possible explanation for the adrenal gland thickening is congestion followed by hemorrhage.\textsuperscript{3} Adrenal hematoma appears as a round or oval lesion with duration-dependent variable attenuation values.\textsuperscript{4,16} Typically, acute to subacute hematomas contain a high attenuation area with decreased size and attenuation over time.\textsuperscript{4} However, because both benign and malignant adrenal conditions can have hemorrhagic lesions, with periadrenal fat stranding, careful follow-up should demonstrate a typical decrease in idiopathic hemorrhagic lesions compared with what is observed in malignant lesions.\textsuperscript{4,5} In our case, thickening of the adrenal glands bilaterally could have been caused by adrenal congestion or hemorrhage. The focal hyperattenuated lesions in the adrenal glands were suspected to be acute hematomas because the adrenal glands were normal on the US examination 4 days before the CT scan and were consistent with atrophy on follow-up US scans. Periadrenal fat stranding indicated fluid extravasation or bleeding from the adrenal glands. In such situation, continuous monitoring of follow-up imaging examinations is pivotal to diagnose adrenal hemorrhage as soon as possible and allow prompt steroid treatment for HOAC.\textsuperscript{5} Ultrasound examination is the most widely available method for follow-up evaluation, as performed in our dog.\textsuperscript{5}

Most HOAC patients with NTAH are treated conservatively with steroid replacement.\textsuperscript{5,6} If hemorrhage persists, open or laparoscopic surgical resection is performed.\textsuperscript{5} A retrospective study of affected humans describing long-term morbidity and mortality suggests a relatively favorable prognosis for survivors of the acute phase of HOAC-induced bilateral adrenal hemorrhage.\textsuperscript{7} Therefore, early identification of adrenal gland changes caused by adrenal hemorrhage can lead to a better prognosis. As observed in human medicine, adrenal dysfunction can result from adrenal congestion or hemorrhage without cellular dysfunction-mediated atrophy.\textsuperscript{3,16} In some such cases, HOAC was suspected based on the results of hormonal testing, even when adrenal atrophy was not clearly identified.\textsuperscript{3} In our case, although HOAC was not diagnosed initially in the dog, we believe that early steroid treatment, with suspicion of CIRCI, resulted in a good outcome. Recovery of partial adrenal function in affected humans has been reported, but its prevalence low and none of the cases showed complete atrophy of the adrenal glands.\textsuperscript{7} Therefore, follow-up imaging may help establish the prognosis of NTAH. Considering the bilateral adrenal atrophy in our case, the possibility of restoration of adrenal function is low. However, we intend to conduct follow-up examinations on the dog.

The main limitation of our case report is that histological verification of adrenal hemorrhage was not performed for ethical reasons. However, continuous monitoring of hormone concentrations and follow-up imaging are justified for the early diagnosis of adrenal hemorrhage and prompt steroid replacement,\textsuperscript{5} as done in our case.

In conclusion, NTAH should be considered if thickening of the adrenal glands with periadrenal fat stranding is identified during CT examination in dogs with underlying conditions such as sepsis or recent surgery. Nontraumatic adrenal hemorrhage can cause HOAC, and careful monitoring of the patient, hormonal testing, and prompt glucocorticoid replacement can lead to a good prognosis. Subsequent reduction in adrenal size indicates a low possibility of recovery of adrenal function.

ACKNOWLEDGMENT
No funding was received for this study.

CONFLICT OF INTEREST DECLARATION
Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION
Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION
Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION
Authors declare human ethics approval was not needed for this study.

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**How to cite this article:** Lee N, Choi J, Yoon J. Presumptive nontraumatic adrenal hemorrhage preceding hypoadrenocorticism in a dog. J Vet Intern Med. 2022;36(6):2160-2164. doi:10.1111/jvim.16531