CASE REPORT

Clinical Case Reports Open Access WILEY

Long-term survival in a dog with probable thyroid storm

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Key Clinical Message: Thyroid storm is a rare, life-threatening endocrine emergency that may occur in dogs. With rapid identification and early aggressive therapy, long-term survival is possible.

Abstract: The aim of this paper was to describe the successful emergency management and long-term survival of a dog with probable thyroid storm. We present proposed guidelines for the characterization of thyroid storm in dogs, and treatment considerations as utilized for this patient. A 6-year-old female spayed German Shepherd Dog was presented to a multispecialty center for radiation planning and treatment of a previously diagnosed nonresectable functional thyroid carcinoma. Recovering from anesthesia, the patient developed clinical features that would qualify as thyroid storm using human metrics. The patient improved with aggressive treatment of thyroid storm, extrapolating from human and feline recommendations. This is the first known report of long-term survival in a canine with suspected thyroid storm. The crisis was effectively identified and emergently treated.

KEYWORDS
canid < veterinary, emergency medicine, endocrinology and metabolic disorders, oncology

JEL CLASSIFICATION
Veterinary, Critical care medicine, Emergency medicine

1 | INTRODUCTION

Thyroid storm is a clinical syndrome that represents the extreme manifestation of thyrotoxicosis.[1,2] In humans, thyroid storm is a well-described clinical diagnosis based on the presence of thyrotoxicosis complicated by thermoregulatory, cardiovascular, central nervous system, and gastrointestinal or hepatic system decompensation.[1] The mortality rate in humans treated aggressively is 8%–25% and approaches 80%–100% in untreated patients[3–5] There are only two cases in the veterinary literature of probable thyroid storm: one cat who survived and one dog who did not.[4,6] This report describes the successful emergency management and long-term survival of a dog with probable thyroid storm.

2 | CASE DESCRIPTION

A 6-year-old, spayed female German Shepherd dog presented to the radiation oncology service of a multispecialty private practice hospital for computed tomography (CT) scan and radiation planning for treatment of a previously diagnosed, nonresectable functional thyroid carcinoma.

The data in the manuscript have not been previously presented or published.

Total T4 was 12.4 μg/dL (158 nmol/L) when methimazole (10 mg/day) was started approximately 1 month prior to referral. The family reported several weeks of progressive anxiety, polydipsia and polyuria, constant panting, and intermittent vomiting prior to diagnosis. On presentation to the radiation oncology service, the dog was panting and anxious, with a heart rate of 156 beats/min, pink mucous membranes, capillary refill time 1–2 s, and body weight of 31.7 kg. Intake temperature was not acquired due to lack of patient cooperation. An approximately 4×5 cm firm, fixed ventral cervical mass was palpated. The remainder of the physical examination was normal.

A cephalic IV catheter was placed, and the dog was premedicated with maropitant 0.94 mg/kg IV and butorphanol 0.3 mg/kg IV. Anesthesia was induced with midazolam 0.19 mg/kg IV and propofol 4.4 mg IV. The patient was intubated and maintained on isoflurane in oxygen and mechanically ventilated. Plasmalyte A was administered IV at 5 mL/kg/h for the duration of anesthesia. An individualized patient positioning device was constructed, and pre- and postcontrast CT images were obtained. The patient was administered 50 mL (1.6 mL/kg) of iohexol (240 mg/mL) solution for the postcontrast series. Throughout anesthesia and imaging, the patient was monitored using ETCO2, ECG, NIBP, and pulse oximetry with a total anesthetic duration of 33 min. All monitored parameters remained within normal limits.

During recovery, approximately 18 min after cessation of inhalant anesthesia, the patient became markedly agitated and dysphoric requiring abrupt extubation. The patient then developed generalized muscle tremors, extensor rigidity of the forelimbs, regurgitation, and profuse mucoid hematochezia. Acepromazine 10 mcg/kg IV was administered with no effect. Butorphanol 0.2 mg/kg IV followed a few minutes later by midazolam 0.2 mg/kg IV was also administered without effect. The patient was reinstrumented with ECG and found to have atrial fibrillation with a ventricular rate of 180–220 beats/min, intermittent ventricular premature contractions NIBP revealed hypertension with systolic blood pressures >200 and MAP 90–110 mm Hg. Rectal temperature was 104.1°F (40.1°C). Pulse oximetry could not be obtained due to the patient′s degree of agitation, and flow-by oxygen was initiated and continued empirically throughout the event. Venous blood gas identified mild hyperlactatemia 2.8 mmol/L and mild hyperglycemia 191 mg/dL (10.6 mmol/L).

Thoracic point-of-care ultrasound (POCUS) evaluation identified a subjectively thickened left ventricular wall, subjectively adequate intravascular volume status, and a scant amount of pleural effusion that could not be sampled. Given the clinical history of a functional thyroid tumor and resulting clinical signs, thyrotoxicosis resulting in thyroid storm was suspected. The patient developed

TABLE 1 Medications at initial discharge.

Methimazole 20 mg (0.3 mg/kg) PO q12h
Propranolol (0.16 mg/kg) PO q8h
Prednisone 15 mg (0.48 mg/kg) PO q12h
Cholestyramine 32 g (1 g/kg) PO q8h
Omeprazole 40 mg (1.3 mg/kg) PO q24h

progressive agitation and regurgitation; therefore, the patient was induced with propofol and re-intubated for patient and staff safety. The muscle tremors and arrhythmia persisted despite induction. Propranolol was administered in 0.02 mg/kg IV aliquots up to a total dose of 3.1 mg (0.1 mg/kg) over approximately 30 min. Simultaneously, methimazole 40 mg (1.26 mg/kg) was crushed and administered as a retention enema. Additional propofol was administered as needed to maintain a level of sedation adequate for extended intubation. The heart rate, blood pressure, and tremors gradually decreased over 20–30 min, and the patient was successfully extubated approximately 30 min following propranolol and methimazole administration. Within an hour of administering propranolol and methimazole, the patient had a normal sinus rhythm, heart rate 100–110 beats/min, mean arterial pressures of 80–90 mm Hg, complete resolution of tremors, and was sleeping quietly. The gastrointestinal signs resolved over the next several hours and a repeat venous blood gas was normal.

Treatment was continued with IV crystalloid fluids at 60 mL/h (1.9 mL/kg/h), dexamethasone SP 4 mg (0.13 mg/kg) IV q24h, pantoprazole 32 mg (1 mg/kg) IV q24h, cisapride 15 mg (0.47 mg/kg) PO q8h, methimazole 20 mg (0.63 mg/kg) PO q 12h, and cholestyramine 32 g (1 g/kg) PO q 8h. She remained hospitalized for observation and rested quietly overnight with no additional emergent intervention required. The patient was notably calm and relaxed compared with previous hospital visits and was discharged the following morning with instructions to continue medications as described in Table 1. A thyroid panel on blood collected at the same time as the first venous blood gas sample was submitted to an outside laboratory for analysis and returned 3 days later. Total T4 was 12.6 μg/dL (162 nmol/L) [reference range 1.0–4.0 μg/dL; 12.9–51.5 nmol/L] and T3 was 204 ng/dL (3.1 nmol/L) [reference range 55–150 ng/dL; 0.8–2.3 ng/dL].

The patient was represented 1 week later for radiation treatment. The owners reported the patient was "almost back to her normal self" with a marked reduction in anxiety-related behaviors at home. Despite instructions to the contrary, the owners had withheld all medications starting at 22:00 the evening before treatment. She was treated with stereotactic body radiation in a single fraction due to concerns about multiple anesthetic events. She had

a similar but much milder event during and in recovery from anesthesia, developing marked sinus tachycardia, muscle tremors, hyperthermia, and mild agitation. Due to mechanical issues concurrent with developing the thyroid storm-like signs, treatment was terminated at a total dose of 16.218 Gy (prescribed dose was 20 Gy). Anesthesia drugs and doses were the same as those used for the CT scan. She was managed with IV propranolol, IV dexamethasone SP, and methimazole retention enema in the same doses as the previous event and signs resolved within an hour. Oral medications were continued in hospital as noted for the discharge instructions above. No additional thyroid storm-like events occurred. She was discharged on the day following radiation treatment, with instructions to continue all medications as before.

Long-term follow-up care was managed through the primary care veterinarian. Medications were tapered over the next several weeks, and the patient had successfully discontinued all medications by 3 months postradiation treatment. One-year post-treatment, the dog is reported to be euthyroid (values not available), asymptomatic, and off all medications.

3 | DISCUSSION

Thyrotoxicosis is the clinical manifestation of excess thyroid hormone activity at the tissue level due to inappropriately high thyroid hormone concentration.[7] It can occur secondary to excess thyroid hormone production in the thyroid follicles, release of preformed hormone, or ingested thyroid hormone.[8] Clinical signs of thyrotoxicosis are similar in dogs, cats, and humans and include agitation, diarrhea, hyperthermia, tachycardia, tachypnea, tremors, and weight loss.[4,6,9,12]

Thyroid storm is the most severe clinical manifestation of thyrotoxicosis.[1] However, this syndrome is poorly defined and only recently reported in veterinary medicine.[4,6] In humans, it is well-described and associated with significant mortality in human emergency and intensive care units.[10] There is thought to be a precipitating event that causes a rapid and catastrophic rise in circulating thyroid hormone. Reported inciting causes are numerous in human medicine and include primary insult to the thyroid gland such as thyroid surgery, vigorous manipulation of the gland or nearby tissue, administration of radioactive iodine, iodinated contrast, and trauma; additionally, systemic insults such as diabetic ketoacidosis, nonthyroid surgery, emotional stress, parturition, and infection have also been implicated.[2,10] In veterinary medicine, it is a rare phenomenon most commonly discussed in the context of cats with diagnosed or undiagnosed hyperthyroidism.[11,12] Textbooks and review articles propose possible

precipitating events similar to those reported in human medicine and include radioactive iodine therapy, thyroid and parathyroid surgery, iodinated contrast dyes, stress, and vigorous manipulation of the thyroid gland.[11,12] However, the frequently cited review article by Ward, which lists these clinical signs of feline thyroid storm, was not peer-reviewed, and the strength of the claims was questioned by Peterson. *[11]

There are only two published case reports of probable thyroid storm in veterinary patients. The cat described by Potter et al developed unexpected severe tachycardia, hypertension, hypercapnia, severe respiratory and metabolic acidosis, and ventricular arrhythmias while under anesthesia for thyroidectomy, all of which resolved upon removal of the thyroid gland.[6] The patient developed congestive heart failure and hypertension in recovery, which was also attributed to thyrotoxicosis and thyroid storm. The authors proposed that manipulation of the thyroid gland in surgery was the most likely cause of the storm event. No inciting cause for a storm event was proposed for the dog reported by Merkle et al.[4] The inciting cause for the dog in the current report is not known. Iodinated contrast was only administered during the CT scan. The same drugs were used to premedicate, induce, and maintain anesthesia for the two anesthetic events, and it is possible one of these drugs, or the stress of anesthesia (or emerging from anesthesia), was the inciting cause.

Thyroid storm is a clinical diagnosis. There is no diagnostic test available for identification or confirmation to distinguish it from thyrotoxicosis. Multiple scoring systems exist for humans and, acknowledging the limitations of applying a human scoring system to a veterinary patient without validation, have been used when reporting suspected thyroid storm events in the previously mentioned case reports in one dog and one cat.[4,6] These studies used the Burch–Wartofsky Point Scale for Thyrotoxicosis.[13] This rubric is a numeric severity score graded from 10 to 140 with scores >45 being consistent with thyroid storm while <25 suggests the patient is not having a thyroid storm. The categories recognized in human medicine include fever, central nervous system effects, gastrointestinal and hepatobiliary clinical signs, probable inciting cause, and various cardiovascular abnormalities. A summary of the diagnostic criteria is included in Table 2. Using the same scoring system, the score for this patient was minimally 115, well above the established threshold for thyroid storm in humans.

Treatment of thyroid storm in human patients includes antithyroid therapy, reducing peripheral effects of thyroid hormone, supportive care for the systemic effects of thyrotoxicosis, and resolving or removing the inciting cause of the storm when possible.[2,4,6,11] Antithyroid therapy is multimodal and includes inhibiting thyroid hormone

TABLE 2 Burch–Wartofsky point scale for thyrotoxicosis.

Temperature (F)		Cardiovascular dysfunction	
99–99.9	5 pts	Tachycardia (beats/min)	
100–100.9	10 pts	99–109	5
101–101.9	15 pts	110–119	10
102–102.9	20 pts	120–129	15
103–103.9	25 pts	130–139	20
		≥140	25
		Atrial fibrillation	10
Central nervous system effects		Heart failure	
Absent	0	Mild (pedal edema)	5
Mild (agitation)	10	Moderate (bibasilar edema)	10
Moderate (delirium, psychosis, extreme lethargy)	20	Severe (pulmonary edema)	15
Severe (seizure, coma)	30	Precipitant history	
Gastrointestinal-hepatic dysfunction		Positive	0
Moderate (diarrhea, nausea/vomiting, abdominal pain)	10	Negative	10
Severe (unexplained jaundice)	20		
Total: <25, storm unlikely; 25–45, impending storm; >45, thyroid storm			

synthesis, reducing functional thyroid hormone release, suppressing recirculation, and extracorporeal elimination.[2] Thyroid hormone is synthesized in follicular cells of the thyroid gland. Dietary iodine is reduced to iodide in the gastrointestinal (GI) tract and absorbed into plasma. Plasma iodide enters the thyroid follicular cell via sodium iodide symporters and is transported to the apical surface, where it crosses into the follicular lumen and is joined with thyroglobulin by the enzyme thyroid peroxidase. This complex subsequently re-enters the thyroid follicular cell and is converted to thyroxine (T4) and the active form of the hormone, triiodothyronine (T3). Both methimazole and propylthiouracil (PTU) inhibit thyroid hormone production by inhibiting thyroid peroxidase. -Propylthiouracil is the most commonly used antithyroid medication in humans; however, adverse effects and limited studies prevent use in dogs.[2,4,14] Methimazole is routinely used to manage hyperthyroidism in cats and occasionally used in dogs.[15] In humans with thyroid storm, the recommended dosing for methimazole (and PTU) is markedly higher than maintenance dosing, with wide variation in recommended dose and frequency.[2,11] Both medications have been shown to be effective with rectal administration, either as suppositories or as retention enemas, although bioavailability is reduced in both.[2]

Other antithyroid therapies include the administration of iodine and treatments intended to remove circulating thyroid hormone. Thyroid hormone production is reduced in the presence of increased circulating iodide (the Wolff–Chaikoff Effect), and therapy with large amounts of iodide can reduce both thyroid hormone production and release into circulation.[16] In humans with thyroid storm, either saturated solution of potassium iodine (SSKI) or Lugol's solution is administered PO or by retention enema.[2] Potassium iodate and iopanoic acid have been used in cats to reduce signs of thyrotoxicosis.[11] When used in thyrotoxic patients, these agents should be administered at least 1 h after methimazole. Otherwise, the initial influx of iodide will increase thyroid hormone production before autoregulatory mechanisms inhibit hormone synthesis and release. Thyroid hormone is metabolized in the liver, conjugated to bile acids, and undergoes enterohepatic circulation. Oral cholestyramine can be administered to bind the products of conjugation and facilitate excretion from the body.[2,17] Although there is limited published information, cholestyramine is considered safe and thought to be effective in veterinary patients for the clearance of toxins that undergo enterohepatic recirculation.[18] Human studies have shown effective clearance of T3 and T4, as well as other molecules such as inflammatory mediators.[2,19] There is no uniform prescription for TPE sessions for human thyroid storm; however, authors generally advocate for the efficacy of this procedure in extreme settings, and effective protocols have been reported in human patients.[1,2,19] Although TPE to reduce thyrotoxic signs is not reported in veterinary medicine, TPE has become generally accepted as an effective and safe means of toxin clearance in companion animals, and it is reasonable to presume it would be an effective therapy for thyroid storm.[20]

Several drugs can reduce peripheral conversion of T4 to the active hormone T3 and may have additional beneficial effects during thyrotoxicosis and thyroid storm. Propranolol, a nonselective beta-adrenergic antagonist, is commonly used in humans to manage the cardiac effects of thyrotoxicosis. Propranolol inhibits the enzyme responsible for converting T4 to the active hormone T3 in peripheral tissue and provides systemic beta-blockade reducing peripheral effects of thyroid storm, including cardiac arrhythmias and hypertension. Esmolol can also be considered and might be preferred in patients with thyrotoxic cardiac changes.[2,11,21]

Additional supportive care in humans generally includes managing hyperthermia, correcting fluid losses secondary to GI upset and fever, and addressing possible

disruption to the adrenal axis. Passive cooling and fluid therapy are the recommended mechanisms for cooling.[2,11] Salicylates have been shown to increase free thyroid hormone in human medicine, potentiating the effect of thyroid storm, and should not be used.[2] Excessive thyroid hormone increases glucocorticoid metabolism. Adrenal insufficiency has been documented in humans and animals with hyperthyroidism and can be a complicating comorbidity in thyroid storm.[2,3,11,22] Some references suggest treating patients in thyroid storm with stress dose steroids until adrenal insufficiency is ruled out.[3] In addition to supporting patients with adrenal insufficiency, glucocorticoids also reduce peripheral conversion of T4 to T3.[1–3,22]

For the patient in this report, the treatment plan and drug doses were extrapolated from a combination of the human and veterinary literature and clinical experience of the local veterinary medical oncologist, internist, and criticalist managing patients with less-severe thyrotoxicosis. A dosing strategy of 5 mg methimazole per cat was extrapolated to be roughly 1 mg/kg; however, significantly lower doses were reported to be used in dogs with milder signs of thyrotoxicosis. Because the human literature suggests much higher doses of methimazole are needed during thyroid storm, a therapeutic dose used by one of the local veterinarians in a similar-sized hyperthyroid dog was tripled and administered to this patient. This dose of methimazole is high and was well-tolerated by this patient but might be associated with adverse effects in other dogs.[14,15] Iodine could not be sourced from local pharmacies, hospitals, or the practice's distributors on the day of the crisis or in time to be used preventively during radiation therapy, so it was not included in the treatment plan. Propranolol was used to control the tachyarrhythmia, reduce the peripheral effects of thyrotoxicosis, and reduce T4 to T3 conversion. Steroids were chosen because of their effect on peripheral T4 to T3 conversion. The patient did not have signs of adrenal insufficiency, and baseline cortisol was not measured. Cholestyramine was administered to help speed hormone elimination by reducing the amount available for enterohepatic recirculation. Therapeutic plasma exchange was briefly considered; however, the patient was not stable enough to transfer to a facility with this capability, and she stabilized quickly with the treatments provided.

In conclusion, thyroid storm appears to occur in veterinary patients with limited data on survival and outcomes. To the authors' knowledge, this is the first report of a dog with probable thyroid storm with successful treatment and long-term survival. It should be differentiated from milder forms of thyrotoxicosis and is likely less common than some review articles and texts may suggest. Definitive diagnosis is difficult to make because there are no diagnostic tests or validated veterinary clinical scoring rubrics. Patients with signs of severe thyrotoxicosis and acute cardiovascular decompensation may have thyroid storm. They should be treated aggressively with a multimodal approach to reduce thyroid hormone production, reduce the conversion of pre-formed thyroid hormone to the active form, manage the systemic effects, and, when possible, remove or treat the inciting cause.

AUTHOR CONTRIBUTIONS

Jeffrey Beverly: Conceptualization; writing – original draft; writing – review and editing. **Armi Pigott:** Conceptualization; supervision; writing – original draft; writing – review and editing. **Claire Elizabeth Puzio:** Conceptualization; writing – review and editing. **Meghan Rivera:** Conceptualization; data curation; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no financial or other conflicts of interests.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENT

Not applicable. This manuscript is a clinical case report. No experimental data were generated.

PATIENT CONSENT

Written informed consent was obtained from the pet owner to publish this report in accordance with the journal's patient consent policy.

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ENDNOTE

* https://endocrinevet.blogspot.com/2015/04/methimazole-treatment-of-canine.html.

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