

**CASE REPORT**

# Presumptive iatrogenic hypoadrenocorticism induced by high-dose ketoconazole administration in a dog

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**Abstract**

A 11-year-old male neutered Shih Tzu was referred to a tertiary facility with a history of weight loss, decreased appetite, polydipsia, and lethargy. The dog had a 10-year history of nonspecific allergic dermatitis and was being treated with 16 mg/kg of ketoconazole q12h for *Malassezia* dermatitis. Vague gastrointestinal signs, hypocholesterolemia, and lack of a stress leukogram increased suspicion for hypoadrenocorticism (HA). An adrenocorticotrophic hormone (ACTH) stimulation test identified hypocortisolemia on pre- and post-ACTH samples and ketoconazole was discontinued. After a short course of corticosteroid treatment, an ACTH stimulation test was repeated and pre-ACTH cortisol concentration was within the reference range, and the post-ACTH cortisol concentration was mildly increased. The temporal association between return of adequate adrenocortical cortisol production and discontinuation of ketoconazole led to the conclusion that the dog had developed iatrogenic HA secondary to ketoconazole treatment.

**KEYWORDS**

ACTH, Addison's disease, antifungal, *Malassezia spp*

**1 | INTRODUCTION**

Hypoadrenocorticism (HA) is characterized by a decreased production of glucocorticoids from the adrenal cortex with or without production of mineralocorticoids.<sup>1,2</sup> Hypoadrenocorticism is classified as primary, secondary, or iatrogenic. Primary HA is most commonly seen in dogs that have decreased production of cortisol because of adrenal atrophy with a normal hormonal stimulus from the pituitary gland. Although the specific cause is unknown, some cases are thought to be the result of immune-mediated adrenalitis. Predisposed dog breeds, such as Bearded Collies, have major histocompatibility complex class II genes that have been associated with autoimmune conditions such as HA.<sup>3</sup> In people, a rare immune-mediated cause has been reported in which

most patients develop antibodies against the steroidogenic enzyme, 21-hydroxylase, leading to the destruction of the adrenal cortices.<sup>4,5</sup> Secondary HA is caused by decreased adrenocorticotrophic hormone (ACTH) secretion from the cranial pituitary gland or decreased corticotropin-releasing hormone secretion from the hypothalamus. Possible causes include neoplasia, inflammation, trauma, or interfering drugs such as steroids.<sup>4</sup> Iatrogenic HA may result from the administration of adrenocorticolitic drugs.<sup>6</sup> Azole drugs have been reported to cause adrenal insufficiency in people without a history of hyperadrenocorticism.<sup>7-12</sup> Therefore, it has been advised to monitor for adrenal insufficiency in people receiving long-term azole treatment.<sup>11</sup>

Ketoconazole is a member of the azole antifungal class of drugs. It is primarily used for the treatment of mycotic infections caused by *Malassezia* sp., dermatophytes, and opportunistic fungal pathogens.<sup>13-15</sup> In people, it has been reported that ketoconazole can inhibit steroidogenesis.<sup>7</sup> Ketoconazole inhibits cytochrome P450 enzymes

**Abbreviations:** ACTH, adrenocorticotrophic hormone; CIRCI, critical illness-related corticosteroid insufficiency; eACTH, endogenous adrenocorticotrophic hormone; GI, gastrointestinal; HA, hypoadrenocorticism.

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and the cholesterol side-chain cleavage complex 17,20-lyase, 11 $\beta$ -hydroxylase, and 17 $\alpha$ -hydroxylase.<sup>11</sup> This inhibition is the reason ketoconazole can be used as a treatment for hyperadrenocorticism.<sup>16,17</sup> Recommended dosages for treating *Malassezia* dermatitis range between 5 and 10 mg/kg q24h and recommended dosages for hyperadrenocorticism range between 10 and 15 mg/kg q12h.<sup>13,15,16</sup> Reported adverse effects are hepatotoxicity and gastrointestinal (GI) upset.<sup>7-12</sup> Adrenal insufficiency has been reported in people, but this adverse effect has not been reported in dogs. The case presented here is an example of presumptive iatrogenic HA in a dog induced by a high PO dosage of ketoconazole used for the treatment of *Malassezia* dermatitis.

## 2 | CASE HISTORY AND CLINICAL FINDINGS

An 11-year-old, male neutered, Shih Tzu was evaluated for a 1-week history of weight loss, decreased appetite, polydipsia, and lethargy. There was no history of vomiting and feces had been of normal consistency. The dog had a 10-year history of nonspecific allergic dermatitis managed by the primary veterinarian and was being treated for chronic otitis externa and *Malassezia* dermatitis with twice weekly medicated baths (SilVet MC Antiseptic Shampoo Chlorhexidine 2% and Miconazole 2%, Henry Schein, Melville, New York), 20 mg of lokivetmab (Cytopoint, Zoetis, Parsippany, New Jersey) SC every 4 weeks, and ketoconazole (Ketoconazole Quad Table 100 mg/tab, Wedgewood Pharmacy, Swedesboro, New Jersey) at a dosage of 16 mg/kg PO q12h for the previous 28 days. Hematology results were within normal limits showing a hematocrit of 50% (reference range, 37%-55%), white blood cell count of 10.54 K/ $\mu$ L (reference range, 5.50-16.90 K/ $\mu$ L), neutrophil count of 7.94 K/ $\mu$ L (reference range, 2.00-12.00 K/ $\mu$ L), lymphocyte count of 1.18 K/ $\mu$ L (reference range 0.50-4.90 K/ $\mu$ L), and eosinophil count of 0.27 K/ $\mu$ L (reference range, 0.10-1.49 K/ $\mu$ L). A serum biochemistry profile disclosed sodium and potassium concentrations within the reference interval (148 and 5.1 mmol/L, respectively), glucose concentration of 127 mg/dL, albumin concentration of 3.2 g/dL, and hypocholesterolemia (94 mg/dL). The remainder of the serum biochemistry profile was within reference range. A urinalysis identified adequately concentrated urine (>1.040 specific gravity; voided sample) indicative of normal renal function. An in-house rapid enzyme-linked immunosorbent assay for pancreatitis (SNAP cPL, IDEXX Laboratories, Inc, Westbrook, Maine) was normal, and no ova or parasites were observed with a negative fecal antigen test (Fecal Dx antigen testing, IDEXX Laboratories, Inc). Abdominal radiographs disclosed multiple small mineral opacities in the cranial abdomen suggestive of cholecystoliths and a nonobstructive gas pattern in the GI tract.

The dog was referred to the Florida Veterinary Referral Center & 24-Hour Emergency Hospital that same day for abdominal ultrasonography and further diagnostic testing for the nonspecific clinical signs. On physical examination, the dog had dull mentation and a heart rate of 70 beats per minute. Multifocal skin lesions characterized by lichenification, alopecia, crusts, and erythema were noted in the inguinal

and axillary regions, consistent with a history of *Malassezia* dermatitis secondary to chronic allergic dermatitis. No additional abnormalities were noted on physical examination. Abdominal ultrasonography confirmed cholecystolithiasis, but the gallbladder was of normal size and the common bile duct showed no evidence of obstruction. The adrenal glands were normal in size and echogenicity. The maximum dorsoventral measurements of the right and left adrenal glands were 0.51 and 0.48 cm, respectively. All other ultrasonographic findings were normal. Based on the history, physical examination findings, and laboratory results, the differential diagnoses included HA, either primary or iatrogenic (ie, ketoconazole administration), ketoconazole-mediated GI toxicity, mild pancreatitis, or primary GI disease.

An ACTH stimulation test was performed to assess for HA. The test was performed according to previously reported methods<sup>18-21</sup> and samples were stored at 4°C for <12 hours before being transported to the reference laboratory. The samples then were submitted for a chemiluminescence assay (ACTH Response Test, Antech Diagnostics, Fountain Valley, California) and were available within 24 hours. Results identified pre- and post-ACTH hypocortisolemia (pre-ACTH sample, <0.2 mg/dL; range, 1.0-5.0 mg/dL; post-ACTH sample, 0.8 mg/dL; range, 8.0-17.0 mg/dL). Because of these findings and the drug history, iatrogenic HA was suspected and ketoconazole treatment therefore was discontinued. The dog was treated for HA with prednisone (PrednisONE Tablets USP, West-ward Pharmaceuticals Corp, Eatontown, New Jersey) at an initial dosage of 0.5 mg/kg PO daily for 3 days and then decreased to the recommended maintenance dosage for chronic HA of 0.25 mg/kg PO daily.<sup>2,22</sup> The dog experienced moderate adverse effects (restlessness, polyuria, polydipsia) from corticosteroid treatment, and was tapered off completely after 1 week of treatment. Five days later, the ACTH stimulation test was repeated and adequate adrenocortical cortisol production capacity was observed (pre-ACTH sample, 2.5 mg/dL; range, 1.0-5.0 mg/dL; and post-ACTH sample, 19.1 mg/dL; range, 8.0-17.0 mg/dL). It was suspected the post-sample showed mild hypercortisolemia because of stress from blood sampling as previously reported.<sup>18</sup> These findings indicated complete resolution of the iatrogenic HA and return to adequate adrenal gland function. It was recommended to discontinue treatment with ketoconazole and consider other treatment options for *Malassezia* dermatitis.

## 3 | DISCUSSION

We describe a dog presenting with lethargy and decreased appetite in the setting of recent treatment with high doses of ketoconazole. The dog was found to have hypocortisolemia on an ACTH stimulation test suggestive of iatrogenic HA which resolved after discontinuation of the ketoconazole. Additional testing such as an endogenous ACTH (eACTH) concentration would have strengthened our suspicion. This test would differentiate primary from secondary HA.<sup>21</sup> However, it would not differentiate between primary and iatrogenic HA because some people with intact hypothalamic-pituitary-adrenal axis have a marked increase in eACTH concentrations when receiving high doses of ketoconazole PO.<sup>7</sup>

Adrenal insufficiency secondary to ketoconazole in people has been reported to be dose-dependent, idiosyncratic, or cumulative in nature. Dose-dependent adrenal insufficiency is the predominant mechanism by which iatrogenic HA develops in people treated with ketoconazole.<sup>7,9,12</sup> Dose-dependent adrenal insufficiency caused by repeated high doses of ketoconazole was suspected to be the cause of HA in this dog, but idiosyncratic, dose-independent adrenal suppression cannot be completely ruled out without ketoconazole drug challenge.

Ketoconazole is a PO active, broad-spectrum antimycotic drug of the azole class.<sup>7</sup> It disturbs fungal membrane growth by inhibiting the conversion of lanosterol to ergosterol.<sup>16,23,24</sup> At higher concentrations, ketoconazole affects steroid biosynthesis by interacting with the imidazole ring and the cytochrome P450 component of various mammalian steroidogenic enzyme systems.<sup>7,16</sup> In normal dogs, ketoconazole administration decreases serum cortisol and testosterone concentrations, but does not affect mineralocorticoid concentrations.<sup>16,23,24</sup> Similarly, its marked effects on the cytochrome P450 pathway also contribute to its GI and hepatic toxicity as well as many drug interactions.<sup>23</sup> In this case, the dog had decreased cortisol concentrations and serum sodium and potassium concentrations within the reference range. Although primary atypical HA was a possibility, it was ruled out because of the transient nature of the hypocortisolemia.

Chronic treatment with ketoconazole requires monitoring for GI toxicity, including vomiting and diarrhea, and hepatotoxicity by evaluating changes in liver enzyme activity.<sup>15,23,24</sup> If these adverse effects are noted, dose reduction or discontinuation of ketoconazole is warranted.<sup>15,23,24</sup> Although vomiting and diarrhea are reported adverse effects of treatment with ketoconazole,<sup>17,24</sup> it is not known if these signs are caused by direct irritation of the GI tract or because of hypocortisolemia. In addition, a large retrospective study indicated that adverse effects were relatively uncommon (14.6%) in dogs treated with ketoconazole for skin disorders, and the most common adverse effect was GI disturbance.<sup>25</sup> Increased liver enzyme activities were reported rarely and the adverse effects were considered idiosyncratic and not dose-dependent.<sup>25</sup> In this case, the dog did not have abnormal liver enzyme activities despite receiving a high dose of ketoconazole, which supports that alterations in liver enzyme activity after receiving this drug may be idiosyncratic in nature.

It is unknown if the high dose of ketoconazole used in this dog was intentional or a miscalculation. As stated previously, the recommended dosage to treat *Malassezia* dermatitis is 5-10 mg/kg q24h.<sup>13-15</sup> *Malassezia* is a surface commensal, and overgrowth in most cases is treated primarily by topical medication alone.<sup>13-15</sup> Systemic treatment is reserved for severe infections that are not responsive to topical treatment alone, dogs that are immunocompromised, or dogs with moderate to severe onychomycosis.<sup>13-15</sup> In dogs presented for chronic recurrent secondary bacterial and fungal infections, as in the dog reported here, the primary disease (eg, atopic dermatitis, food allergies, endocrinopathy) should be treated to successfully manage the secondary infection. The secondary fungal infection present in our dog was not thought to be the cause of the hypocortisolemia because the cortisol concentrations returned

to normal upon discontinuation of the antifungal treatment despite ongoing fungal dermatitis.

Potential explanations for low cortisol concentrations can include collection or laboratory error. In this case, the testing and sample collection were performed using standard procedures for an ACTH stimulation test.<sup>2,18-21</sup> Although laboratory error cannot be ruled out, it is not typical for ACTH stimulation tests to be repeated to confirm accuracy in a clinical setting when the dog's history and clinical signs fit the diagnosis.

An additional differential diagnosis for the adrenocortical insufficiency identified in this dog could be critical illness-related corticosteroid insufficiency (CIRCI), which is a syndrome characterized by inadequate production of cortisol in relation to increased demand during periods of severe stress.<sup>26</sup> Although it can be considered a possibility, most reported cases of CIRCI have been in patients with a critical illness, such as sepsis or septic shock.<sup>26</sup> In this case, it is unlikely that the adrenocortical insufficiency was related to CIRCI because the dog did not show signs of critical illness such as a severe leukocytosis or leukopenia, a rectal temperature >103°F or <99°F, or a heart rate >120 beats per minute.<sup>26</sup>

Another explanation for cortisol insufficiency is autoimmune adrenalitis and insufficiency secondary to lokivetmab administration. Although no cases of monoclonal antibody-induced autoimmune adrenalitis have been reported in veterinary medicine, there are reports in people in whom transient autoimmune adrenalitis secondary to monoclonal antibody treatment develops.<sup>27-29</sup> It is possible that dogs may be at a similar risk to develop autoimmune disease secondary to monoclonal antibody treatment. The dog in this report continued to receive monthly lokivetmab injections for management of allergic dermatitis after the adrenal insufficiency resolved with no relapses of hypocortisolemia. Therefore, autoimmune adrenalitis secondary to lokivetmab administration is unlikely in this case.

To our knowledge, this case is the first report of presumptive iatrogenic hypocortisolemia in a dog receiving high doses of ketoconazole which resolved after discontinuation of the medication. Although we suspect this dog experienced iatrogenic HA because of inhibition of steroidogenesis from dose-dependent ketoconazole treatment, some limitations must be considered such as lack of additional testing to further confirm our suspicion. In addition, ketoconazole could have been used at a recommended dosage for *Malassezia* spp. infections (5-10 mg/kg daily) to determine if HA would recur in this dog. Future studies on both the pathomechanisms of adrenal insufficiency related to ketoconazole and monoclonal antibody treatment are warranted. Although the preliminary clinicopathologic testing showed only hypocholesterolemia and all other results were within normal limits, this case demonstrates the importance of considering iatrogenic adrenocortical insufficiency in dogs with GI clinical signs treated with ketoconazole.

#### 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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