Acute Hepatopathy Associated With Mitotane Administration in a Dog

An adult dog with a persistent elevation in alkaline phosphatase enzyme activity was started on mitotane for suspected hyperadrenocorticism. One month later, the dog was presented for intermittent anorexia and acute icterus. The dog's liver enzyme activities and total bilirubin were markedly elevated, prothrombin time was prolonged, and blood urea nitrogen and glucose were low. Histopathology revealed marked, centrilobular, hepatocellular loss. After discontinuation of the mitotane, the dog recovered with supportive care and was normal 3 months later, which was consistent with mitotane-associated hepatic failure. **J Am Anim Hosp Assoc 2006;42:298-301.**

Craig B. Webb, PhD, DVM, Diplomate ACVIM

David C. Twedt, DVM, Diplomate ACVIM

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From the Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Colorado State University, Fort Collins, Colorado 80523.

Introduction

Making a definitive diagnosis of hyperadrenocorticism and determining the underlying etiology (i.e., pituitary-dependent, adrenal tumor) are potentially challenging. The diagnosis of hyperadrenocorticism is based on clinical signs, laboratory abnormalities, and specialized testing.[1] Approximately 90% of dogs with hyperadrenocorticism have an elevated alkaline phosphatase (ALP) from the production of a steroid-inducible isoenzyme, although this ALP elevation is not specific for this condition.[2] Currently available screening tests for hyperadrenocorticism (i.e., adrenocorticotropic hormone [ACTH] stimulation test, low-dose dexamethasone suppression test, and urine-cortisol:creatinine ratio) have variable sensitivities and specificities.[3] Discriminating between pituitary-dependent hyperadrenocorticism and an adrenal tumor etiology relies on diagnostic tests that may be subjective (e.g., abdominal ultrasonography), require special sample processing (e.g., endogenous ACTH level), or lack the desired specificity (e.g., high-dose dexamethasone suppression test).[4]

The most common medical treatment for pituitary-dependent hyperadrenocorticism in North America is mitotane.[a,5] Mitotane is adrenocorticolytic and works primarily on hyperplastic adrenal cortical cells. Adrenal tumors are less responsive to the drug.[6] The reported side effects of mitotane include anorexia, lethargy, vomiting, diarrhea, and hypoadrenocorticism.[7] The purpose of this case report is to describe the acute onset of hepatic failure in a dog that was receiving mitotane after a diagnosis of hyperadrenocorticism based on an elevation in ALP and an abnormal ACTH stimulation test result.

Case Report

A 34-kg, 8-year-old, spayed female mixed-breed dog was referred to the Veterinary Teaching Hospital at Colorado State University (VTH-CSU) for liver failure. One month prior to presentation, the dog was seen by the referring veterinarian for recheck of an elevated ALP that was first noted on routine laboratory testing 5 months earlier. No abnormal clinical signs or physical examination findings were noted. A biochemical panel

revealed a persistent elevation in ALP (922 IU/L; reference range 5 to 60 IU/L) with normal alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyltransferase (GGT) activities. An ACTH stimulation test was performed for suspected hyperadrenocorticism. The pre-ACTH cortisol concentration was 5.7 µg/dL (reference range 2 to 6 µg/dL), and the post-ACTH cortisol value was 23.5 µg/dL (reference range 6 to 18 µg/dL), which was consistent with hyperadrenocorticism (>22 µg/dL). A diagnosis of hyperadrenocorticism was made, and the dog was placed on 1000 mg of mitotane[a] (29 mg/kg per os [PO] *q* 24 hours) for 5 days of induction, followed by 250 mg (7.2 mg/kg PO) four times per week as maintenance therapy.

Approximately 2 weeks later, the dog developed anorexia. The mitotane was discontinued, and the dog was started on a tapering dose of 10 mg of prednisone[b] (0.3 mg/kg PO *q* 24 hours). The dog continued to be intermittently anorectic and lethargic and had occasional vomiting for an additional 2 weeks. It then became acutely icteric and was referred. Upon presentation at VTH-CSU, the dog was lethargic and had icteric sclera and mucous membranes. Large ecchymoses were seen on the ventral abdomen.

A complete blood count (CBC) revealed icteric plasma, a normal packed cell volume (49%; reference range 40% to 55%), a mild lymphopenia ($0.8 \times 10^3/\mu L$; reference range 1.0 to $4.8 \times 10^3/\mu L$), and thrombocytopenia ($149 \times 10^3/\mu L$; reference range 200 to $500 \times 10^3/\mu L$). Urinalysis of a voided sample revealed a urine specific gravity of 1.008 and 3+ bilirubinuria. Abnormalities on a biochemical profile included hypoglycemia (46 mg/dL; reference range 75 to 130 mg/dL), a low blood urea nitrogen (4 mg/dL; reference range 7 to 32 mg/dL), hyperbilirubinemia (9.1 mg/dL; reference range 0 to 0.3 mg/dL), and elevations in ALP (2371 IU/L; reference range 20 to 142 IU/L), ALT (1091 IU/L; reference range 10 to 110 IU/L), AST (214 IU/L; reference range 16 to 50 IU/L), and GGT (37 IU/L; reference range 0 to 9 IU/L). Albumin and cholesterol were within normal limits. An ACTH stimulation test[c] revealed a pre-ACTH cortisol level of 2.0 µg/dL and a post-ACTH cortisol level of 4.4 µg/dL.[1] An activated prothrombin time was normal, but the prothrombin time was prolonged (13.1 seconds; reference range 7.5 to 10.5 seconds). Serology for leptospirosis was consistent with previous vaccination. Abdominal ultrasonography revealed a small liver. The left adrenal gland appeared normal in size and shape, but the right adrenal gland was not observed.

The dog was given two units of plasma and was started on intravenous (IV) isotonic crystalloid[d] fluids supplemented with potassium chloride (20 mEq/L) and 2.5% dextrose, famotidine[e] (1 mg/kg IV *q* 24 hours), metoclopramide[f] (1 µg/kg per day IV, continuous-rate infusion), and vitamin K_1[g] (1 mg/kg subcutaneously *q* 12 hours). Laparoscopy was performed 24 hours after admission to obtain a liver biopsy. The liver appeared diffusely abnormal; all lobes were swollen, and the surfaces had a "nutmeg" appearance. Multiple, depressed areas suggestive of hepatic parenchymal collapse [Figure 1] were seen. Four liver biopsies were taken from multiple lobes, and histopathology revealed diffuse, hydropic, and fatty changes with marked, centrilobular (i.e., cells surrounding the central vein, periacinar), hepatocellular loss [Figure 2]. Hepatic copper levels were normal, and aerobic bacterial culture of liver tissue produced no growth.

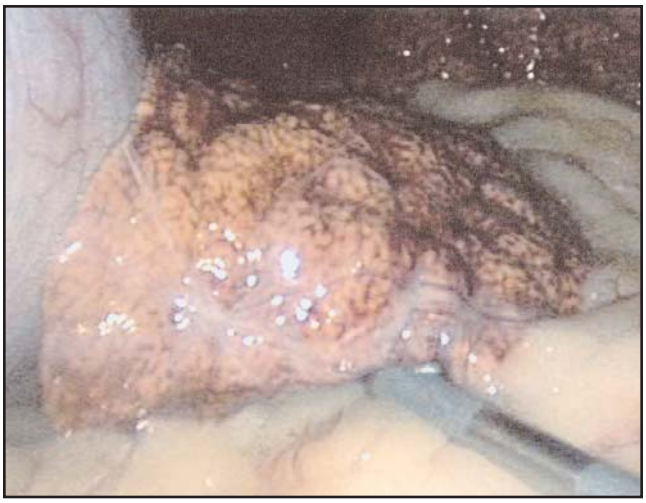

Figure 1—Laparoscopic view of a portion of the caudate liver lobe abutting the right kidney. All other liver lobes (not pictured) had a similar appearance. The liver surface has a diffuse, nutmeg coloration with irregular surface depressions that create a nodular appearance. The textured length of the probe at its termination is 1 cm.

After an additional 48 hours of intensive care (previously described), the dog began to eat voluntarily. The dog was discharged on S-adenosylmethionine[h] (6.8 mg/kg PO *q* 12 hours), ursodiol[i] (9 mg/kg PO *q* 24 hours), vitamin E[j] (12 mg/kg PO *q* 24 hours), and prednisone[b] (0.3 mg/kg PO *q* 24 hours). S-adenosylmethionine and vitamin E were used for their antioxidant properties; ursodiol was given for its

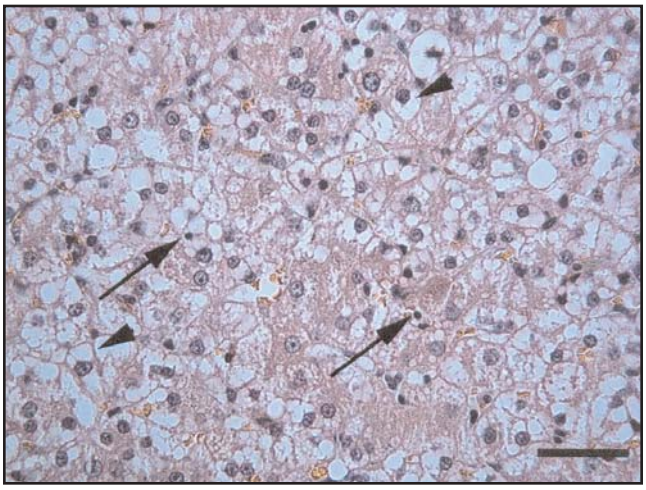

Figure 2—Histopathology of the liver depicted in Figure 1. A complete loss of normal hepatic architecture has occurred. Severe hepatocellular degeneration with multiple pyknotic nuclei (arrows) and vacuolated hepatocytes (arrowheads) can be seen (Hematoxylin and eosin stain, 40×; bar=85 µm).

antioxidant and choleretic effects; and prednisone was administered because there was minimal response to the ACTH stimulation test. Over the course of the next 3 months, the owners added to the dog's treatment regimen three nutraceutical products containing various herbs.[k]

Three months after discharge, the owners reported the dog was normal. Laboratory tests done by the referring veterinarian revealed a persistent elevation of ALP (1931 IU/L), a mildly elevated ALT (154 IU/L; reference range 5 to 55 IU/L), and a normal total bilirubin (0.1 mg/dL). An ACTH stimulation test yielded a pre-ACTH cortisol concentration of 3.5 µg/dL and a post-ACTH cortisol level of 3.9 µg/dL.

Discussion

This report describes a suspected case of mitotane-associated liver failure. Supporting evidence included a lack of clinical signs until shortly after mitotane administration, as well as acute elevations in ALT and AST after mitotane administration (which previously were normal). Along with the hepatic enzyme elevations, the dog's total bilirubin was elevated, prothrombin time was prolonged, and serum glucose was low—all of which were consistent with decreased hepatic function.[8] The collapse of hepatic parenchyma observed grossly on laparoscopy and the hepatocellular loss seen on histopathology were also supportive of an acute hepatotoxic event.[9] The eventual recovery and improvement in biochemical test results following discontinuation of the mitotane were also supportive of a drug-induced hepatopathy.

One alternative explanation for this dog's illness would be exposure to some unknown hepatotoxic substance in the time between discontinuation of mitotane and the onset of icterus (approximately 2 to 3 weeks). Although the time delay between mitotane administration and acute fulminate hepatic failure (i.e., onset of icterus) did not support a direct cause, the dog first became ill while on the mitotane and continued to have intermittent bouts of lethargy, anorexia, and vomiting after its discontinuation. Another possible explanation for this dog's illness was that it had some degree of hepatic disease prior to mitotane administration that was not clinically evident but predisposed the dog to a mitotane reaction. In addition to steroid induction, differential considerations for elevations of ALP include exposure to other drugs, hepatic nodular hyperplasia, cholestasis, hepatic neoplasia, cholangiohepatitis, or a reaction secondary to a systemic disease not directly involving the liver.[10,11]

Alkaline phosphatase activity is elevated in 90% of dogs with hyperadrenocorticism, making it a very sensitive marker of hyperadrenocorticism; but the specificity of this biochemical abnormality is low.[2] The sensitivities of the ACTH stimulation test are approximately 87% for pituitary-dependent hyperadrenocorticism and 61% for an adrenal tumor.[12-15] The specificity of the ACTH stimulation test is between 82% and 91%.[16-18] Although results of the initial ACTH response test were suggestive of hyperadrenocorticism, other factors may have accounted for the results. Repeating the test at a later date, measuring an endogenous ACTH level, evaluating other adrenal steroid hormone levels, and performing abdominal ultrasonography may have provided valuable additional information in confirming the presence of hyperadrenocorticism.

The adrenocorticolytic activity of mitotane is the basis for its effectiveness as a therapeutic agent in pituitary-dependent hyperadrenocorticism.[19] Side effects of mitotane in dogs include anorexia, lethargy, weakness, and diarrhea.[20,21] In normal animals, mitotane has caused fatty degeneration and centrolobular atrophy of the liver.[22] These latter adverse effects were more pronounced in mitotane-treated dogs with preexisting liver disease, although the changes were not often clinically significant.[23] The histopathology from the dog in this case report included evidence of severe fatty degeneration and marked lobular atrophy. The dose of mitotane (29 mg/kg daily) given to the dog in this case was not excessive. Dogs have been given 50 to 75 mg/kg daily for 25 days to induce nonselective adrenocorticolysis without adverse consequences.[24] The time lag between mitotane administration and the onset of clinical signs was similar to the time of onset of signs in dogs experiencing carprofen toxicity, suggesting that mitotane-associated hepatotoxicity may be an idiosyncratic reaction or may arise secondary to an adverse immune-mediated response to administration of a drug.[25]

Conclusion

Mitotane treatment was initiated in a dog after diagnosis of hyperadrenocorticism that was based on a persistently elevated ALP and an abnormal ACTH stimulation test result, although the dog did not exhibit any of the classic clinical signs of hyperadrenocorticism. While on mitotane, the dog became anorectic and eventually developed signs of acute hepatic failure that was confirmed by histopathology. Following withdrawal of the mitotane and intensive supportive care, the dog became clinically normal and liver enzyme values improved. Further studies are necessary to determine whether the diagnosis of hyperadrenocorticism should be made only after extensive testing in animals showing no clinical signs, especially considering the potential adverse side effects of treatment with mitotane.

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[a] Lysodren; Bristol-Myers Squibb, New York, NY 10154
[b] Prednisone; Cardinal Health Care Pharmacy, New Castle, IN 47362
[c] Cortrosyn; Amphaster Pharmaceuticals, Rancho Cucamonga, CA 91730
[d] Normosol-R; Hospira, Inc., Lake Forest, IL 60045
[e] Famotidine; Merck, Whitehouse Station, NJ 08889
[f] Metoclopramide; Faulding Pharmaceutical, Aguadilla, Puerto Rico 00604
[g] Vitamin K_1; Vedco, St. Joseph, MO 64507
[h] Denosyl; Nutramax Laboratories, Inc., Edgewood, MD 21040
[i] Actigall; Ciba Specialty Chemicals, Basel, Switzerland
[j] dl-Alpha tocopheryl; Major Pharmaceuticals, Livonia, MI 48150
[k] Lidan, Refresh, and ACT; E. Excel International, Inc., Springville, UT 84663

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