Peliosis hepatis and hemoperitoneum in a dog with diphacinone intoxication

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Abstract

Objective: To describe the clinical course of a dog presented with peliosis hepatis and hemoperitoneum in concert with anticoagulant rodenticide intoxication.

Case summary: A 7.75-year-old spayed female Shetland Sheepdog presented with clinical signs consistent with hypovolemia, hemoperitoneum, and a history of bright green stool 3 days before the onset of clinical signs. Initial packed cell volume/total solids were consistent with acute hemorrhage. A coagulation profile showed prolongation in activated clotting time and prolongation of both prothrombin and activated partial thromboplastin time, suggesting abnormal coagulation. Abdominal hemorrhage persisted in the face of normalization of the hemodynamic status and coagulation profile, and treatment with Vitamin K_1. Abdominal ultrasound revealed multiple patchy hypoechoic areas throughout the caudate liver lobe. An exploratory laparotomy was performed 24 hours after presentation and revealed the caudate liver lobe as the source of the hemorrhage. Histopathologic examination of a specimen of the liver was consistent with peliosis hepatis. Toxicologic testing identified diphacinone levels in the blood consistent with anticoagulant rodenticide intoxication. Postoperative recovery was uneventful, and within 48 hours the dog was discharged. The dog returned to full function and a hepatic ultrasound performed 15 months postoperatively showed no significant abnormalities.

New or unique information provided: Exposure to anticoagulant rodenticides may be associated with the development of peliosis hepatis in dogs.

(J Vet Emerg Crit Care 2008; 18(4) 388–392) doi: 10.1111/j.1476-4431.2008.00322.x

Keywords: anticoagulant rodenticide, *Bartonella henselae*, canine, liver, stoat

Introduction

Peliosis hepatis is a vasculoproliferative disorder characterized by the presence of multiple cystic, blood-filled spaces in the liver. In humans, peliosis hepatis has been associated with anabolic androgens, human immunodeficiency virus infection, tuberculosis, spherocytic hemolytic anemia, contraceptive steroids, tamoxifen therapy, chronic wasting disease, chemotherapeutic usage, hypervitaminosis A, and azathioprine therapy.[1–4] Human peliotic cysts are often of no clinical concern; however, in some instances they may lead to hepatomegaly, liver failure, or intraperitoneal hemorrhage.[4] An association between anticoagulant rodenticide exposure with the development of peliosis hepatis has been proposed in wild stoats, but has not been reported previously in the dog.[5]

Case Summary

A 7.75-year-old spayed female Shetland Sheepdog weighing 8 kg was presented to the primary care veterinarian with the chief complaint of acute collapse 1 hour before the time of presentation. Initial major body systems assessment revealed pale, gray, tacky mucous membranes, tachycardia, increased respiratory rate and effort, and a depressed level of consciousness. Physical examination revealed abdominal pain and severe hypothermia, with a rectal temperature too low to register at the time of presentation. No abnormalities were noted during thoracic auscultation. No other major physical examination abnormalities were noted. No external evidence of trauma was identified. Further historical questioning revealed that the dog was last normal 8 hours prior. The dog was current on all vaccines and received year-round heartworm preventative.

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No previous medical problems were noted with the exception of seasonal atopic dermatitis. At the time of presentation, the dog was not being treated with any medications. The dog was not closely supervised when outside and was allowed to roam free in the neighborhood. Bright green stool was noted 3 days before presentation.

A 20-G over-the-needle catheter was placed in the right cephalic vein and blood for a complete blood count (CBC) and serum biochemical profile (SBP) was collected. A 200 mL bolus (25 mL/kg) of 0.9% sodium chloride was delivered over 15–30 minutes. In response to the fluid bolus, the dog's heart rate decreased and mucous membrane color improved.

Neutropenia (1780 cells/μL; reference interval, 3000–11,800/μL) lymphocytosis (9680/μL; reference interval, 1000–4800 cells/μL) and mild anemia (hematocrit 36.8%; reference interval, 37–55%) were abnormalities noted on the CBC. A manual differential count was not performed. Serum biochemistry abnormalities included hypoalbuminemia (19.8 g/L [1.98 g/dL]; reference interval, 27–38 g/L [2.70–3.80 g/dL]), increased alanine aminotransferase (127 U/L; reference interval, 10–100 U/L), hyperglycemia (20.5 mmol/L [369.0 mg/dL]; reference interval, 4.3–6.9 mmol/L [77.0–125.0 mg/dL]), hyperphosphatemia (3.9 mmol/L [11.95 mg/dL]; reference interval, 0.8–2.2 mmol/L [2.50–6.8 mg/dL]) and decreased total protein (48 g/L [4.80 g/dL]; reference interval, 52–82 g/L [5.20–8.20 g/dL]). Abdominal radiographs showed a moderate loss of serosal detail, and suggested free peritoneal fluid. No abnormalities were present on thoracic radiographs. Fluid therapy with 0.9% sodium chloride was continued (5.5 mL/kg/hr) and the dog was referred to the Michigan State University Veterinary Teaching Hospital for definitive diagnosis and treatment.

At the time of presentation from the referring veterinarian (approximately 4 hours after the onset of collapse), assessment of major body systems revealed pale mucous membranes, prolonged capillary refill time, tachycardia (209/minute), and weak femoral pulses. Dorsal metatarsal arterial pulses were not palpable. The respiratory rate was 28/minute and the dog was depressed but responsive to its environment. No abnormalities were present during auscultation of the heart and lungs, and the abdomen was tense and slightly distended on palpation. Body temperature was 37.7 °C (99.9 °F). No other abnormalities were detected on physical examination. A second 20-G over-the-needle catheter was placed in the left cephalic vein and blood was collected from the catheter hub for determination of packed cell volume (PCV), total solids (TS), activated clotting time (ACT) and venous blood gas+electrolytes, BUN, lactate, and glucose.[a] A 300 mL IV bolus (37 mL/kg) of warmed lactated Ringer's solution[b] (LRS) was started immediately and administered over 20 minutes. Oxygen was delivered by mask (2 L/min).

Initial mean arterial pressure (MAP) measured by oscillometric methods[c] was 56 mmHg and initial oxygen saturation measured by pulse-oximeter[d] (SpO$_2$) was 98% while receiving oxygen support by mask. Initial PCV/TS were 35% and 47 g/L (4.7 g/dL) and suggested acute hemorrhage. ACT was 140 seconds (reference interval, 60–90 seconds) and suggested abnormal coagulation. Initial bloodwork abnormalities included hyperlactatemia (3.6 mmol/L; reference interval, 0.3–3.2 mmol/L) and an acid–base abnormality, a component of which was metabolic acidosis (pH 7.255; reference interval, 7.35–7.45; base excess − 6.5 mmol/L; reference interval, − 3 to +3 mmol/L). Full interpretation of the acid–base abnormality was not possible because of the venous nature of the sample.

Following delivery of the fluid bolus, MAP increased to consistent readings within the range of 70–79 mmHg, but sinus tachycardia persisted at a rate of >200/minute. A second intravenous fluid bolus of 300 mL (37 mL/kg) LRS was started immediately and administered over 20 minutes. Abdominocentesis performed at this time yielded non-clotting hemorrhagic fluid (PCV = 30%) consistent with hemoperitoneum. Samples of the abdominal fluid were submitted for cytological examination. CBC, SBP, coagulation profile (prothrombin [PT], activated partial thromboplastin time [aPTT], fibrinogen, fibrin degradation products, and D-dimer), anticoagulant rodenticide screen and blood type were submitted for analysis.

Following the second fluid bolus MAP increased to 80 mmHg, but the dog remained tachycardic (200/minute). The PCV/TS had dropped to 22% and 28 g/L (2.8 g/dL), lactate had increased to 5.3 mmol/L (reference interval, 0.3–3.2 mmol/L), and the blood glucose was 13.0 mmol/L (235 mg/dL) (reference interval, 2.9–6.3 mmol/L [53–117 mg/dL]). The latter 2 findings suggested progressively decreasing oxygen delivery to the tissues due to hypovolemic shock and the stress response secondary to activation of the sympathetic nervous system, respectively. At this time, small volumes of hemorrhagic diarrhea were noted.

Dog Erythrocyte Antigen 1.1 (DEA 1.1) status was immediately determined using a commercial card test[e] and the result confirmed the presence of DEA 1.1. Warmed, diluted (0.9% sodium chloride[f]), type-specific (DEA 1.1 positive) packed red blood cells (PRBC) (125 mL; 15 mL/kg) was administered over 10 minutes and fresh frozen plasma (FFP) (250 mL; 31 mL/kg) was administered over 1 hour to provide oxygen carrying capacity and to combat coagulopathy and hypovolemia. Vitamin K$_1$[g] (5 mg/kg, SQ) was administered

at this time due to the possibility of anticoagulant rodenticide intoxication. Broad-spectrum antibiotic therapy (ampicillin,[h] 20 mg/kg, IV, q 8 h and cefoxitin,[i] 20 mg/kg, IV, q 6 h) was initiated due to the concern for poor gastrointestinal perfusion and gastrointestinal mucosal integrity and the possibility of subsequent bacterial translocation. In response to volume expansion efforts, the patient continued to show signs of hypovolemic shock as evidenced by persistent tachycardia, pale mucous membranes, poor pulses, and depressed level of consciousness. The PCV continued to decrease to 17%. Over the ensuing 3 hours, the dog received an additional 180 mL of PRBC, 250 mL of FFP, and a total of 800 mL of LRS.

The leukogram abnormalities seen on the CBC from the referring veterinarian were not repeatable. Normocytic, normochromic anemia was the only abnormality noted on the CBC. Panhypoproteinemia (total protein 30 g/L [3.0 g/dL]; reference interval, 56–76 g/L [5.6–7.6 g/dL]; albumin 15 g/L [1.5 g/dL]; reference interval, 32–47 g/L [3.2–4.7 g/dL]; globulin 15 g/L [1.5 g/dL]; reference interval, 21–29 g/L [2.1–2.9 g/dL]) consistent with hemorrhage was found on SBP. The coagulation profile revealed prolongations in the PT (40.1 seconds; reference interval, 6.3–8.6 seconds) and aPTT (83 seconds; reference interval, 13.9–22.1 seconds), hypofibrinogenemia (<0.5 g/L [50 mg/dL]; reference interval, 1.08–2.87 g/L [108–287 mg/dL]), normal FDP (<5 µg/mL), and D-dimer in the intermediate range (250–500 ng/mL). The coagulation profile was consistent with a coagulopathy that, when considered in light of the historical information and clinical signs, was consistent with anticoagulant rodenticide intoxication; however, the contribution of dilutional coagulopathy secondary to aggressive fluid therapy could not be discounted at the time. Cytological examination of the abdominal fluid was consistent with acute blood loss and neither etiologic agents nor cells with cytologic characteristics of malignancy were identified.

Repeat PT/aPTT after FFP therapy were within the reference interval. A multi-lumen central venous catheter was placed in the right jugular vein for monitoring central venous pressure, administering multiple infusions, and serial blood sampling. A 22-G over-the-needle catheter was placed in the right dorsal metatarsal artery for the continuous monitoring of arterial blood pressure and assessment of arterial blood gases. An 8-Fr red rubber nasal oxygen catheter was placed in the right nostril for the administration of 1–2 L of oxygen/min, and a 5-Fr foley catheter was placed into the urinary bladder to monitor urine output and collect urine for urinalysis. An abdominal ultrasound was performed during this period due to concern that the hemoabdomen may not have been the result of antico-
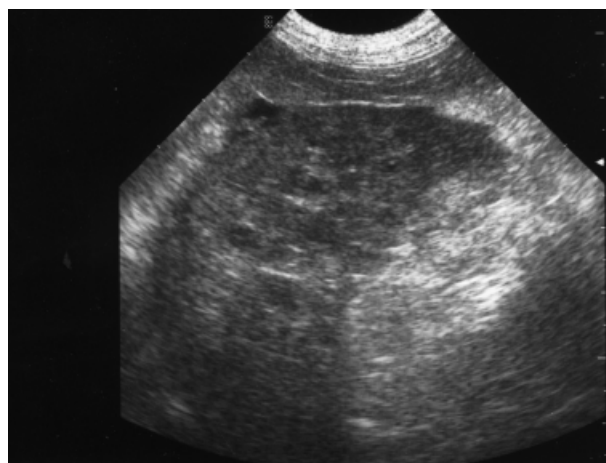

Figure 1: Abdominal ultrasound image illustrating multiple patchy hypoechoic areas throughout the caudate liver lobe.

agulant rodenticide intoxication. The refractory nature of the ongoing hemorrhage in the face of vigorous plasma supplementation and normalization of the coagulation profile were atypical of anticoagulant rodenticide intoxication.

An abdominal ultrasound examination revealed multiple patchy hypoechoic areas throughout the caudate liver lobe (Figure 1) and large amounts of echogenic effusion consistent with the known hemorrhage. Differential diagnoses included multiple hepatic hematomas, hepatocellular carcinoma, trauma, and hemangiosarcoma.

Between 6 and 10 hours after initial collapse, hemodynamic status stabilized as was evidenced by normalization of heart rate, arterial blood pressure, CVP, urine output, blood glucose, and lactate. Because of slow, ongoing hemorrhage over the ensuing 12 hours (10–22 hours after initial collapse) in the face of normalization of the coagulation profile, the requirement for additional PRBC transfusions and the ultrasonographic liver abnormalities, exploratory abdominal surgery was performed.

An opioid–benzodiazepine anesthetic induction (midazolam,[j] 0.2 mg/kg, IV and oxymorphone,[k] 0.2 mg/kg, IV) was chosen due to the perceived increased anesthetic risk to the dog. Additional intravenous induction agents were not required for successful intubation. Following endotracheal intubation, anesthesia was maintained using isofluorane in oxygen inhalant anesthesia. A routine exploratory laparotomy was performed, and approximately 400 mL of hemorrhagic fluid was removed. All of the abdominal organs were grossly within normal limits except for the papillary process of the caudate liver lobe. A large blood clot was found at this site along with evidence of active bleeding. The liver lobe was packed off with

laparotomy sponges and its supporting ligamentous structures were dissected free. The affected liver lobe was routinely removed with a TA 55[l] stapling device and a circumferential ligature using 3-0 PDS[m] was placed to control ongoing hemorrhage from the surgical site. Hydromorhone[n] (0.05 mg/kg, IV and 0.05 mg/kg, IM) was administered for immediate postoperative pain relief. The transected liver lobe was placed in 10% formalin and submitted for histopathologic analysis. *Ex vivo* sectioning of the caudate lobe revealed multiple blood-filled cavities.

The dog recovered from surgery without complication. Postoperative monitoring included vital signs (temperature, pulse, respiratory rate, and effort), direct arterial blood pressure, central venous pressure, urine output, electrocardiogram, arterial blood gas, and serial monitoring of PCV/TS every 4 hours. Analgesia was provided using hydromorphone (0.1 mg/kg, IV, q 6 h). The patient was encouraged to stand every 4 hours and was turned every 4 hours as necessary to combat dependent atelectasis. Oxygen therapy was continued to maintain the SpO_2 above 94%. Vitamin K_1 therapy was continued (2.5 mg/kg, SQ, q 12 h) pending the toxicologic profile results. Injectable antibiotic therapy (cefoxitin, 20 mg/kg, IV, q 6 h) was continued for 24 hours postoperatively. Within 18 hours of surgery, the dog was eating and drinking. Over the ensuing 48 hours, the dog was weaned from IV fluids, deinstrumented, and discharged from the hospital. The dog went on to make a full recovery and returned to her normal activity level over the following 7 days. Hepatic ultrasound was repeated 15 months after discharge and revealed no significant abnormalities.

Toxicologic testing by high-performance liquid chromatography[o] identified the presence of diphacinone in the blood at a concentration of 0.74 p.p.m., confirming a diagnosis of anticoagulant rodenticide intoxication. Vitamin K_1 therapy (2.5 mg/kg, PO, q 12 h) was continued for a total of 4 weeks. Histopathologic examination of the caudate liver lobe revealed large, irregular blood-filled spaces throughout the liver parenchyma. In some instances, endothelial cells did not line the blood-filled spaces. The intervening hepatic parenchyma appeared to be essentially normal. Some of the blood-filled spaces also contained fibrin and numerous neutrophils. The biopsy specimen was consistent with peliosis hepatis. A liver specimen was submitted for diagnosis of *Bartonella henselae* DNA using a polymerase chain reaction (PCR) assay[p] and a serum sample was submitted for serologic testing by indirect fluorescent antibody (IFA).[p] Results of the PCR assay were negative, as was serologic testing by IFA for antibodies to *B. henselae* and *B. vinsonii* ssp. *berkhoffii*.

Discussion

Three differential diagnoses were initially considered for the cause of this patient's hemoabdomen. A diagnosis of anticoagulant rodenticide intoxication was considered given the history of bright green stool noted 3 days before presentation. This may have reflected rodenticide ingestion 4–5 days before presentation and was supported as a differential by the presence of bleeding into a body cavity and abnormalities in coagulation parameters (prolonged ACT, PT, and aPTT). A second differential diagnosis was hemorrhage secondary to left lateral hepatic lobar disease with secondary consumptive coagulopathy and dilutional coagulopathy. This diagnosis was supported by the ultrasonographic findings, as well as persistent hemorrhage in the face of normalization of the coagulation profile. The third and most plausible differential diagnosis proposed a combination of the above-mentioned processes with anticoagulant rodenticide intoxication exacerbating or causing primary left lateral liver lobe pathology (peliosis hepatis) resulting in hemorrhage.

Two types of peliotic cysts, parenchymal and phlebectatic, have been identified and they range in size from microscopic to several centimeters in diameter.[4] Irregular parenchymal cysts lack lining cells and are diffusely distributed, while phlebectatic cysts are characterized by their round shape, presence of lining cells, and location within the centrilobular region of the liver.[4] Parenchymal cysts are associated with focal hepatic necrosis, while phlebectatic cysts do not routinely demonstrate necrosis.[4] Rupture of these spaces with subsequent hemoperitoneum can occur when cystic formation occurs at the level of the liver capsule.[1,4] Histopathologic examination of liver biopsy specimens of this dog noted the absence of endothelial cells lining the blood-filled spaced, suggesting the presence of peliotic parenchymal cysts.

Peliosis hepatis has been documented in a variety of species including man, cattle, dogs,[6,7] mice, cats, and wild stoats (*Mustela erminea*, short-tailed weasel).[5,8,9] Clinical manifestations of peliosis hepatis in humans are rare and include asymptomatic hepatomegaly, liver failure, or in rare cases intraperitoneal hemorrhage.[1] In humans, the condition has been associated with anabolic androgen therapy, estrogenic steroid therapy, human immunodeficiency virus infection, contraceptive steroid therapy, tamoxifen therapy, chronic wasting disease, chemotherapy, hypervitaminosis A, and azathioprine therapy.[2–4] Duration of drug therapy before recognition of peliotic lesions has varied from a few months to several years.[4] A prospective study showed an association between peliosis hepatis and circulating tumor-derived endothelial growth factor, in which

peliosis hepatis lesions developed in mice 23 days post subcutaneous injection with melanoma cells.[10] The exact pathogenesis of the formation of peliotic cysts has not been identified. Suggested pathways include parenchymal necrosis with subsequent vascular dilation, hepatocyte hyperplasia, angiitis, congenital weakness of vessel walls, venous obstruction with subsequent dilation, and direct toxic insult to endothelial cells resulting in the formation of blood-filled lacunae.[1] Medical records provided by the primary care veterinarian ruled out a history of ongoing neoplastic processes, chronic wasting, administration of chemotherapeutic agents, and supplementation with Vitamin A, tamoxifen, or steroid therapy as possible contributors to the development of this dog's peliosis hepatis. The owners of this dog noted no history of oral contraceptive exposure or known ingestion before the onset of clinical signs. However, given that this dog was often unsupervised outdoors, these known predisposing factors could not be completely discounted.

Peliosis hepatis with concurrent *B. henselae* infections has been reported in dogs.[7,11] Results of the PCR assay were negative as was serologic testing by IFA for antibodies to *B. henselae* and *B. vinsonii* ssp. *berkhoffii*, making bartonellosis-induced peliosis hepatis an unlikely contributor to the hemorrhage seen in this dog.

Peliosis hepatis occurs with some frequency in wild stoats, and prompted a closer examination of documented cases in this species. A prospective study examining the demise of native stoats in England identified 2 out of 44 (4.5%) trapped stoats to be positive for lesions consistent with peliosis hepatis.[5] A high incidence of *Bartonella* spp. in wild stoats has been documented[5] and was consequently considered a possible contributor to the development of the peliotic lesions in the affected stoats. A second differential considered, however, was sublethal exposure to anticoagulant rodenticides following ingestion of smaller rodents with anticoagulant rodenticide toxin within their system (secondary intoxication).[5]

The clinical course of this patient is suggestive of either a direct association between anticoagulant rodenticide intoxication and the development of peliosis hepatis or preexisting lobar peliosis hepatis exacerbated by anticoagulant rodenticide intoxication. Peliosis hepatis should be included in the list of differential diagnoses for canine patients presenting with spontaneous hemoabdomen. Additional consideration should be given to the presence of peliosis hepatis in canine patients with hemoabdomen and the presence of refractory hemorrhage coupled with historical or laboratory evidence of anticoagulant rodenticide exposure.

Footnotes

a STAT Profile M, Nova Biomedical, Waltham, MA.
b Lactated Ringer's solution, Hospira Inc., Lake Forest, IL.
c Neonatal V24CT, Agilent, 71034 Boeblingen, Germany.
d Datex-Ohmeda 3900, Louisville, CO.
e Rapid Vet-H, dms laboratories Inc., Flemington, NJ.
f 0.9% sodium chloride solution, Abbott Laboratories, North Chicago, IL.
g Vitamin K_1, The Butler Company, Dublin, OH.
h Ampicillin, American Pharmaceutical Partners Inc., Schaumburg, IL.
i Cefoxitin, Watson Laboratories Inc., Corona, CA.
j Midazolam, Baxter Healthcare Corporation, Deerfield, IL.
k Oxymorphone, Endo, Chadds Ford, PA.
l TA 55, United States Surgical, Norwalk, CT.
m PDS II, Ethicon Inc., Somerville, NJ.
n Hydromorphone, Baxter Healthcare Corporation. Deerfield, IL.
o HPLC, Diagnostic Center for Population and Animal Health, Lansing, MI. Waters 2695/Waters 600 Fluorescence Detectors, Waters Corporation, Milford, MA.
p Tick Borne Diagnostic Laboratory, NCSU College of Veterinary Medicine, Raleigh, NC.

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