Case Report Rapport de cas

Hemodialysis in a dog with acute renal failure from currant toxicity

Skye W. Stanley, Cathy E. Langston

Abstract — A 3 1/2-year-old Labrador retriever being presented for acute onset vomiting and lethargy was diagnosed with acute renal failure (ARF). The dog had ingested dried currants, a type of raisin. Hemodialysis was successfully performed to treat the ARF. Raisin toxicity can cause ARF and warrants early recognition and aggressive treatment.

Résumé — Hémodialyse sur un chien présentant une insuffisance rénale aiguë à la suite d'une intoxication aux raisins. Une insuffisance rénale aiguë (IRA) a été diagnostiquée chez un Labrador retriever âgé de 3 ans et demi présentant une poussée de vomissement et de léthargie. Le chien avait ingéré des raisins de Corinthe. L'IRA a été traitée avec suivi par hémodialyse. La toxicité des raisins de Corinthe peut se traduire par une IRA et justifier une identification rapide et un traitement agressif.

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A 3 1/2-year-old 39.6 kg, castrated, male Labrador retriever was referred to the Animal Medical Center for acute onset vomiting and lethargy. The patient had ingested 308 g of dried currants, potato chips, a plastic wrapper, and a small amount of garlic 4 d prior to presentation. The vomiting had started 12 h after the ingestion of these products. Three weeks previously, the dog had been examined by the referring veterinarian because of lower urinary tract signs (stranguria, dysuria, and pollakiuria); a tentative diagnosis of a lower urinary tract infection was made and cephalexin, 25 mg/kg body weight (BW), PO, q12h was prescribed for 10 d. Results from a complete blood (cell) count (CBC), serum chemical profile, and urinalysis submitted at that time were normal, with a urine specific gravity of 1.008. A urine culture and fecal flotation were negative. The hematuria resolved and the patient was clinically normal prior to the ingestion of currants. He was an indoor dog with no prior medical history. There was no other toxin exposure and the dog was up-to-date on vaccinations.

Case description

On initial presentation, results of the physical examination were unremarkable. The rectal temperature was 37.5°C, the heart rate was 95 beats/min, and the respiratory rate was 16 breaths/min. The dog was in good body condition (body condition score 6/9), well-hydrated, and quiet and alert. Auscultation of the thorax revealed normal lung sounds in all fields. Results of abdominal palpation were normal.

Samples for a complete blood (cell) count (CBC), serum biochemical analysis, and urinalysis were submitted. Abnormalities detected were lymphocytopenia (0.296×10^9 cells/L; reference range, 1.0 to 4.8×10^9 cells/L), mild anemia (0.37 L/L; reference range, 0.37 to 0.55 L/L), elevated blood urea nitrogen (BUN) (36.4 mmol/L; reference range, 2.5 to 9.6 mmol/L), elevated creatinine (999 μmol/L; reference range, 35 to 159 μmol/L), and hyperphosphatemia (3.36 mmol/L; reference range 0.68 to 2.03 mmol/L). The mean arterial blood pressure was 100 mmHg. An analysis of urine, obtained by cystocentesis, revealed isothenuria (specific gravity 1.011). Proteinuria, pyuria, and bacteruria were not evident. Antibody titers to *Leptospira* were negative. Results from a urine culture were negative. Abdominal radiographs revealed no abnormalities. Abdominal ultrasonographs showed no abnormalities. Both kidneys had normal renal architecture and the cortices had normal echogenicity.

A diagnosis of acute renal failure (ARF) was suspected, based on the short duration of signs, the significant azotemia, and the isosthenuric specific gravity of 1.011. Acute renal failure can be caused by a prerenal cause, such as severe dehydration or decreased perfusion due to cardiac disease; renal causes, such as toxic insult, infectious agent, ischemic event, or a sequela to a systemic disease; or a postrenal cause, such as a ureteral or urethral obstruction (1). Because of the recent ingestion of black currants, raisin toxicity was highly suspected. There had been no recent anesthetic events; no exposure to ethylene glycol, drugs, or toxins; and no evidence of a systemic disease such as pancreatitis. The abdominal ultrasonographs showed no evidence of pre-existing renal disease, which would further help support acute renal failure. The dog was also in good body condition

The Animal Medical Center, 510 East 62nd Street, New York, New York 10021, USA.

Dr. Stanley's current address is Department of Internal Medicine, Fifth Avenue Veterinary Specialists, 1 West 15th Street, New York, New York 10011, USA.

Address all correspondence to Dr. Skye Stanley; e-mail: skye.stanley@vcamail.com

and had no history of polydypsia or polyuria; although the dog was mildly anemic, a blood analysis 3 wk earlier had shown a normal hematocrit (0.4 L/L), so the anemia was unlikely due to chronic renal failure. The mild anemia was attributed to gastrointestinal bleeding or the decreased erythrocyte life span that occurs in acute renal failure due to a malfunctioning of the membrane Na^+-K^+-ATPase pump and impaired regeneration of reduced glutathione needed to prevent hemoglobin oxidation (2). Although the dog had also ingested garlic, it was unlikely that the garlic had caused the anemia, as there were no Heinz bodies or eccentrocytes seen on the CBC (3). Initial treatment consisted the administration of a crystalloid solution (Plasma-Lyte 148; Baxter HealthCare, Deerfield, Illinois, USA), 3.8 mL/kg BW/h, IV ranitidine (Zantac; GlazoSmithKline, Research Triangle Park, North Carolina, USA), 2.2 mg/kg BW, IV, q24h; sucralfate (Aventis Pharmaceuticals, Kansas City, Missouri, USA), 1 g, PO, q8h; ampicillin (Sandoz, Broomfield, Colorado, USA), 22 mg/kg BW, IV, q6h; and nothing, PO, for the first 12 h. Metoclopramide (Reglan, Baxter Healthcare), 2.2 mg/kg BW, IV, q24h, was initiated because of the continued vomiting in the hospital.

After being administered fluids, IV, for 12 h, the dog had gained 0.6 kg BW, and clinically, appeared overhydrated; the plasma potassium concentration had increased from 4.99 to 5.57 mmol/L. A urinary catheter was placed to monitor urine production. Urine production was 0.25 mL/kg BW/h for the first 2 h after placement, and increased to 1.3 mL/kg BW/h after administration of mannitol (25% mannitol; Hospira, Lake Forest, Illinois, USA), 0.25 gm/kg BW, IV, and furosemide (Furoject; Butler, Dublin, Ohio, USA), 2 mg/kg BW, IV. The rate of IV fluid administration was decreased to match urine output, plus 1 mL/kg BW/h to account for insensible fluid loss. Within 24 h of admission, the azotemia had worsened (BUN, 35.8 mmol/L; creatinine, 1134.2 μmol/L, respectively). The lack of rise in the BUN may have been due to the fact the dog was not eating. Because of the progressive azotemia and oliguria relative to the volume of administered fluid despite diuretic therapy, hemodialysis was started on day 2. The dog was premedicated with a combination of butorphanol tartrate (Torbugesic; Fort Dodge Animal Health, Fort Dodge, Iowa, USA), 0.02 mg/kg BW, SC, and atropine sulfate (Phoenix Scientific, St. Joseph, Missouri, USA), 0.02 mg/kg BW, SC. Anesthesia was induced with diazepam (Hospira), 3 mg/kg BW, IV, and propofol (Propoflo; Abbott Laboratories, Chicago, Illinios, USA), 3 mg/kg BW, IV, and then maintained with isoflurane. A 40-cm dual lumen dialysis catheter (Quinton PermCath; Tyco Healthcare/Kendall, Mansfield, Massachusetts, USA) was placed in the right jugular vein. During the same anesthesia, a percutaneous gastrotomy tube [PEG (Ponsky Pull PEG Kit; Bard Access systems, Salt Lake City, Utah, USA)] was placed. Mean arterial blood pressure was maintained between 100 and 140 mmHg throughout the anesthesia and placement of the PEG tube. A 2-hour dialysis treatment was performed; the postdialysis BUN and creatinine values improved to 19.6 mmol/L and 698 μmol/L, respectively. Four hours following the dialysis treatment, the dog experienced head tremors and seizure-like activity. Dialysis disequilibrium syndrome, a central nervous system (CNS) disturbance, thought to be caused by a rapid decrease in serum osmolality induced by effective dialysis, was considered, although the urea reduction ratio, a measure of dialysis efficacy, was within the target range for a 1st dialysis treatment at 45.5% (4). Mannitol (25% mannitol; Hospira); 0.25 g/kg BW, IV, was given for treatment of possible dialysis disequilibrium syndrome. Intermittent tremors persisted for approximately 6 h, and the dog remained dull. On day 3, the predialysis BUN and creatinine values were 30.4 mmol/L and 1016.6 μmol/L, respectively. Hemodialysis was again performed and the postdialysis BUN and creatinine values were 12.8 mmol/L and 541.9 μmol/L, respectively. Urine production remained adequate (1–2 mL/kg BW/h) throughout day 2 and day 3. The intermittent focal facial seizures continued during day 3, so diazepam (Hospira), 0.25 mg/kg BW/h, IV, as a constant rate infusion was started to help in controlling the seizure-like activity. Magnetic resonance imaging was considered to evaluate for intracranial disease but was not done. Aspirin (St. Joseph Chewable Aspirin; McNeil-PPC, Fort Washington, Pennsylvania, USA), 1 mg/kg BW, PO, q24h, was started on day 3 to inhibit thrombus formation around the dialysis catheter. Nutrition requirements were addressed by feeding a renal diet (Canine K/D diet; Hill's Pet Nutrition, Topeka, Kansas, USA) at 1/3 of the maintenance resting energy requirement (RER) (BW kg × 30 kcal + 70 kcal) through the PEG tube, and giving aluminum hydroxide (Pharmaceutical Associates, Greenville, South Carolina, USA), 320 mg (5 mL), PO, q6h, with the meals to help to control the hyperphosphatemia. The feedings were increased to 2/3 of the maintenance RER on day 5 and full RER was given on day 6.

Table 1. Blood urea nitrogen (BUN) and creatinine concentrations before and after each hemodialysis treatment

	Pretreatment values		Posttreatment values		Duration of hemodialysis treatment (hours)
	BUN (mmol/L)	Creatinine (μmol/L)	BUN (mmol/L)	Creatinine (μmol/L)	
Day 2	35.8	1134.2	19.6	698.4	2
Day 3	30.4	1016.6	12.8	541.9	2.5
Day 4	26.5	795.6	11.6	413.7	2.75
Day 6	22.7	470.3	3.2	157.4	5

On day 4, the BUN and creatinine values were 26.5 mmol/L and 795.6 μmol/L, respectively. Dialysis was again performed and the posttreatment BUN and creatinine values were 11.6 mmol/L and 413.7 μmol/L, respectively. On day 5, the diazepam infusion was discontinued and the dog appeared alert and tremor-free. On day 6, a 4th hemodialysis treatment was performed. The pretreatment BUN and creatinine values were 22.7 mmo/L and 470.3 μmol/L, respectively. Following the 5-hour dialysis treatment, the azotemia normalized to a BUN value of 3.2 mmol/L and creatinine value of 157.4 μmol/L, respectively. Over the following 3 d, the azotemia resolved spontaneously, and no further dialysis was needed.

On day 8, the BUN and creatinine values had increased slightly to 11.8 mmol/L and 265.2 μmol/L, respectively, and the body temperature was 41.1°C. There was swelling and a small amount of discharge around the PEG tube site. Material from the PEG tube site was submitted for aerobic and anaerobic

culture. Enrofloxacin (Baytril; Bayer HealthCare, Shawnee Mission, Kansas, USA), 10 mg/kg BW, IV, q24h, was added to the treatment regimen, and warm compresses were applied to the PEG tube site q6h. On day 9, the dog was normothermic for 12 h, then the fever returned to 39.8°C.

On day 10, there was a fever of 40.7°C. Urine was submitted for culture, as were samples from both ports of the dialysis catheter. A diagnostic peritoneal lavage was performed and the fluid submitted for cytologic examination and culture. The culture of the diagnostic peritoneal lavage was positive for *Escherischia coli* and the cytologic results were consistent with a modified transudate. The culture from the PEG tube site also grew an *E. coli* organism as well as a *Proteus* organism. The cultures from the access ports of the dialysis catheter were also positive for *E. coli.* Results of the urine culture were negative. All organisms were sensitive to enrofloxacin. The dialysis catheter was removed on day 11. On day 14, the BUN and creatinine values were 5.7 mmol/L and 176.8 μmol/L, respectively, and the dog was afebrile. The dog was discharged on day 16. The azotemia was completely resolved by 21 d after discharge, and 2 y later, the serum chemical values are still normal.

Discussion

Toxin ingestion is a common cause of ARF in dogs (5). Several different toxins have been reported to cause ARF (1). Raisins and grapes have been reported recently as an underlying etiology for ARF in dogs, although the underlying mechanism of nephrotoxicity remains unknown (6–9). Hemodialysis can be an effective treatment for ARF.

Raisin toxicity has been well described as an underlying cause for ARF in recent publications (8,9). In this dog, ARF was caused by dried currant ingestion. Dried currants are very small raisins made from Black Corinth grapes. The presenting clinical signs of vomiting, lethargy, and anorexia, as well as the time of onset of clinical signs, were similar to those in a recent publication of 43 cases (9). Acute pyelonephritis was also considered as a differential diagnosis in this case, since there had been a recent history of lower urinary tract signs that potentially could have been caused by a bacterial urinary tract infection 3 wk prior to presentation. However, based on the lack of a positive urine culture on presentation, lack of pelvic dilation on abdominal sonographs, and the known toxin exposure, acute pyelonephritis seemed unlikely. The most common clinical signs in raisin toxicity are vomiting, lethargy, anorexia, and diarrhea. Vomiting is the earliest and most consistent sign seen in raisin toxicity. A majority of dogs will show signs of vomiting within 24 h. Anorexia, diarrhea, and lethargy will follow the signs of vomiting. Abdominal pain, ataxia, and weakness can also be seen as abnormal signs in dogs with raisin toxicity. The toxic principle and mechanism of damage that cause ARF in dogs are still unknown. Possible toxic mechanisms include mycotoxins (such as ochratoxin A and citrinin); presence of pesticides, fungicides, herbicides, and insecticides; or the inability to process flavinoids, tannins, and excess quantities of monosaccharides. Ochratoxin has been measured in dogs with raisin toxicity and all results were negative (9). No specific testing was performed in this case, because the dog had eaten all of the contents of the container and no additional currants were available for testing.

Hemodialysis was chosen as the preferred treatment in this case, because the medical therapy was not resolving the azotemia. Dialysis should be initiated when the clinical consequences of the azotemia and the fluid, electrolyte, and acid-base disturbances cannot be managed effectively with medical therapy alone; in this case, the azotemia worsened despite fluid therapy, and to conduct more aggressive diuresis was considered imprudent, given the apparent limitation of fluid excretion by the kidneys. Animals with oliguria or anuria in which an effective diuresis cannot be induced with replacement fluids, osmotic or chemical diuretics, and renal vasodilators should be treated with dialysis. Other indications for dialysis are volume overload, acute exacerbation of chronic renal failure, pre-operative management of renal transplant recipients, and postoperative delayed graft rejection (10). Hemodialysis is an efficient method of controlling azotemia, but if hemodialysis is not available, peritoneal dialysis is an alternative therapy that can be used to manage ARF. Hemodialysis can also be used for the treatment of acute intoxications. Since the toxin in raisin toxicity is unknown at this time, it is also unknown whether the toxic principle is dialyzable. Hemodialysis is uniquely suited for the management of acute poisoning for certain toxins. Toxins have ideal characteristics for removal by hemodialysis if the toxin has a small molecular weight, a small volume of distribution in the blood stream, and is not extensively bound to plasma proteins (11).

Hemodialysis is a technically sophisticated therapy that is used to remove uremic toxins and correct the electrolyte, hydrogen ion, and fluid imbalances associated with renal failure (1). Hemodialysis is principally used for the management of acute and chronic renal failure that is refractory to conventional medical therapy. The basic principal for hemodialysis is that it treats renal failure by removing uremic toxins by using the extracorporeal circulation of a patient's blood to exchange solute through an artificial kidney (hemodialyzer or dialyzer). The toxins are removed by diffusion down a concentration gradient across a semipermeable membrane that is housed in the dialyzer.

The neurological signs that were seen in this dog after the 1st hemodialysis consisted of seizure-like activity and tremoring. Possibilities for this activity were dialysis disequilibrium syndrome (DDS), uremic encephalopathy, a vascular accident, inflammation, infection, CNS hemorrhage, neurotoxicity from some component of grapes/raisins, or pre-existing CNS disease. Dialysis disequilibrium syndrome is caused by a rapid, dialysis-induced change in the composition of the blood. Hemodialysis can remove osmotically active substances, such as sodium and urea, from the blood more rapidly than they can diffuse from the intracellular compartment. The resultant osmotic gradient causes intracellular swelling, and the clinical signs are related to cerebral edema. An alternate theory incriminates rapid correction of metabolic acidosis by the bicarbonate in the dialysate, leading to paradoxical CNS acidosis (12). Treatment for DDS includes administration of an osmotic agent, namely, mannitol. The timing and character of the CNS signs were atypical for DDS, especially in a large dog with a low BUN to start and only a 17.9 mmol/L decrease in BUN. Because of the risk of

DDS, initial dialysis treatments are generally short and remove a limited amount of urea. With each successive treatment over the first several days, the predialysis BUN generally decreases, and progressively longer treatments that remove a greater amount of urea are prescribed.

The source of the fever and bacteremia was most likely due to the PEG tube, dialysis catheter, or both, or secondary to the indwelling urinary catheter. The PEG tube exit site was painful, had discharge, inflammation, and was slightly swollen. Positive cultures were obtained from both heparin ports in the dialysis catheter, the PEG tube site, and peritoneal lavage fluid. The dog was hemodynamically stable and his appetite was returning to normal during the febrile period. Because the PEG tube exit site infection was noted several days prior to development of fever and detection of infection of the dialysis catheter, we surmise that the local infection induced bacteremia, which lead to colonization of the dialysis catheter, and the dialysis catheter then served as a nidus of infection. The dialysis catheter was maintained until clinical recovery was apparent, based on almost normal kidney values. However, on day 11, since there was an on-going fever, we chose to remove the catheter. Because the fever resolved within 12 h of removing the dialysis catheter, more aggressive therapy for the PEG tube exit site was not deemed necessary, and the exit site infection resolved with medical management. Bacteria can produce a biofilm composed of glycocalyx and the bacterial community, which adheres to the catheter and protects the bacteria from eradication. Removal of the catheter is generally required for control of the bacteremia (13). CVJ

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