Anorexia & Lethargy in a Dog with Presumed Giardiasis

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Rylie, a 7-year-old, 48.4-lb (22-kg), spayed German shorthaired pointer, was initially presented to her primary veterinarian for anorexia and lethargy. She had experienced a self-limiting episode of vomiting and diarrhea 2 weeks before presentation. Rylie was up to date on vaccines and flea and tick preventives and had no pertinent travel history.

Three months prior to presentation, Rylie's housemate, Henderson, a 2-year-old, 42.8-lb (19.4-kg), neutered male Labrador retriever crossbreed, was diagnosed with *Giardia* spp infection. Although fecal testing had not been performed for Rylie on Henderson's diagnosis, both dogs were prescribed fenbendazole, a broad-spectrum benzimidazole anthelmintic, at 60 mg/kg every 24 hours for 3 days.

Subsequently, when the owner observed diarrhea in either Rylie or Henderson, deworming was repeated in both dogs with fenbendazole obtained from an online pharmacy. Accordingly, Rylie received a second course of fenbendazole 2 months later at 60 mg/kg every 12 hours for 5 days and a third course a month after the second course at 60 mg/kg every 12 hours for 7 days. The final course of fenbendazole was completed 2 days before Rylie was initially presented to her primary veterinarian.

Initial Diagnostics & Treatment

Physical examination demonstrated a BCS of 3/9 and 5% dehydration. Rylie's temperature was normal (101.6ºF [38.7ºC]). CBC and serum chemistry results revealed 1518 neutrophils/µL (reference range, 2060-10,600/µL) and 572 lymphocytes/µL (reference range, 690-4500/µL). Results of point-of-care testing for heartworm disease, Lyme disease, anaplasmosis, and ehrlichiosis were negative. Rylie received lactated Ringer's solution (500 mL SC) as an outpatient for supportive care of dehydration. Lethargy improved, and her temperature remained normal for 2 days before she became anorexic and markedly lethargic with a temperature of 105.2ºF (40.7ºC), at which point her owner presented her to an emergency clinic.

Emergency Presentation

Rylie was hospitalized, and blood and urine samples were obtained for CBC, serum chemistry profile, urinalysis, urine culture and susceptibility testing, blood gas analysis, and PCR testing for infectious and tick-borne diseases.* Abdominal radiographs revealed heterogeneous material, presumed to be food, in the gastric lumen and increased small intestinal gas consistent with diffuse gastroenteritis. Abdominal sonograms revealed a moderate decrease in corticomedullary distinction in both kidneys; no other abnormalities were noted.

CBC and serum chemistry profile revealed 100 leukocytes/µL (reference range, 5050-16,760/µL), 10 neutrophils/µL (reference range, 2950-11,640/µL), 70 lymphocytes/µL (reference range, 1050-5100/µL), 20 monocytes/µL (reference range, 160-1120/µL), 67,000 platelets/µL (reference range, 148,000-484,000/µL), and mildly increased ALP activity (294 U/L; reference range, 23-212 U/L). Hematocrit was normal (41.8%; reference range, 37.3%-61.7%). Urinalysis showed trace proteinuria with inactive sediment.

Treatment with ampicillin/sulbactam (30 mg/kg IV every 8 hours) and enrofloxacin (5 mg/kg IV every 24 hours) was initiated, pending results of urine culture and susceptibility and PCR testing. Supportive care included IV fluids and antiemetics. Rylie's temperature remained above 104ºF (40ºC), and she was emergently referred to a specialty service for further diagnostic investigation and treatment.

Emergency Referral

On admission to the referral service, Rylie's temperature was 103.4ºF (39.7ºC). Heart and respiratory rates were within normal limits. No other significant findings were noted on physical examination.

Packed cell volume, total solids, and blood glucose and lactate concentrations were within normal limits. CBC with pathologist review showed 570 leukocytes/µL (reference range, 4400-15,100/µL), 6 neutrophils/µL (reference range, 2800-11,500/µL), 560 lymphocytes/µL (reference range, 1000-4800/µL), 10 monocytes/µL (reference range, 100-1500/µL), and 17,000 platelets/µL (reference range, 173,000-486,000/µL). Hematocrit was in the low-normal range (39%; reference range, 39%-55%), and rare eccentrocytes, 1+ acanthocytes, 1+ to 2+ crenation, occasional keratocytes, and 2+ poikilocytes were seen. No abnormalities were noted on 3-view thoracic radiographs with radiologist review. Bone marrow and core biopsies both revealed a cell population composed almost entirely of adipocytes, with only rare hematopoietic precursor cells; these findings were consistent with generalized bone marrow hypoplasia/aplasia, although aspiration of an area of inactive marrow could have had a similar appearance. However, if the bone marrow sample was representative, Rylie would likely exhibit a decreased hematocrit/nonregenerative anemia in the near future, as erythrocytes are typically the last cell line to decrease following decreased hematopoiesis.

*PCR testing for infectious and tick-borne disease for both Rylie and Henderson included *Anaplasma* spp, *Babesia* spp, *Bartonella* spp, *Blastomyces dermatitidis*, *Brucella canis*, *Coccidioides* spp, *Cryptococcus* spp, *Ehrlichia* spp, *Hepatozoon* spp, *Histoplasma capsulatum*, *Leishmania* spp, *Leptospira* spp, *Mycoplasma hemocanis/hematoparvum*, *Neorickettsia risticii*, *Neospora caninum*, *Rickettsia rickettsii*, *Toxoplasma gondii*, and *Trypanosoma cruzi*.

Differential diagnoses for generalized bone marrow hypoplasia/aplasia are numerous and can include infectious disease (eg, anaplasmosis, ehrlichiosis, canine parvovirus), bone marrow necrosis (eg, from endotoxins or toxins), and myelophthisic disease (eg, myelofibrosis, neoplasia). Other causes can include hemophagocytic syndrome, malignant histiocytosis, hypersplenism, radiation damage, cobalamin deficiency, immune-mediated disease, and pancytopenia from drugs such as estrogen, chemotherapeutic agents, phenylbutazone, meclofenamic acid, trimethoprim/sulfadiazine, quinidine, thiacetarsamide, captopril, albendazole, and cephalosporins.[1-3]

Diagnostic imaging and bone marrow evaluation showed no evidence of neoplasia, urine culture results were negative, and results of prior infectious and tick-borne disease testing were negative; therefore, fenbendazole-associated bone marrow suppression was strongly suspected.

DIAGNOSIS:
PRESUMPTIVE BONE MARROW HYPOPLASIA/APLASIA SECONDARY TO FENBENDAZOLE ADMINISTRATION

Treatment
Due to Rylie's marked neutropenia, ampicillin/sulbactam (30 mg/kg IV every 8 hours) and enrofloxacin (5 mg/kg IV every 24 hours) were continued (see ***Treatment at a Glance***). Doxycycline (5 mg/kg PO every 12 hours) was initiated but discontinued, as results of infectious and tick-borne disease testing were negative.

Rylie tolerated treatment well. She began eating readily, her temperature returned to normal limits, and her vital signs remained within normal limits. She was discharged 24 hours after presentation to reduce the risk for hospital-acquired infection. Enrofloxacin (5 mg/kg PO every 24 hours) was continued at home, and ampicillin/sulbactam was substituted with amoxicillin/clavulanic acid (16.7 mg/kg PO every 12 hours for 14 days). Because bone marrow disease may be immune mediated, prednisone (1.8 mg/kg PO every 24 hours) was also initiated.

Outcome
Rylie's clinical signs resolved quickly. CBC performed 3 days postdischarge showed normal neutrophil and platelet counts and 700 lymphocytes/µL (reference range, 1000-4800/µL).

At the recheck examination 12 days after initial emergency referral, Rylie's owner noted that Henderson was undergoing treatment for recurrent fever. Henderson had become febrile (104.5ºF [40.3ºC]) a month earlier after his second course of fenbendazole. He was presented to an emergency service and received fluids (500 mL SC) and amoxicillin (250 mg PO every 12 hours), which the owner discontinued after 5 days.

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TREATMENT AT A GLANCE

- When bone marrow suppression is present, drug toxicity should be considered and myelosuppressive medications discontinued.
- Animals with bone marrow suppression are at risk for acquiring severe, life-threatening infection, and appropriate broad-spectrum antibiotic therapy is recommended when severe neutropenia of <500 neutrophils/µL is identified.[4]
- Serial CBCs should be obtained postdischarge to monitor response to therapy and ensure complete recovery of all cell lines.

When bone marrow suppression is present, drug toxicity should be considered and myelosuppressive medications discontinued.

Henderson became febrile again (103.5ºF [39.7ºC]) following his third course of fenbendazole. CBC results showed 0 neutrophils/µL (reference range, 2000-12,000/µL) and 138,000 platelets/µL (reference range, 175,000-500,000/µL). Seven days later, a recheck CBC, serum chemistry profile, and PCR testing for infectious and tick-borne diseases revealed 1200 WBCs (reference range, 5500-16,900/µL), 140,000 platelets/µL (reference range, 175,000-500,000/µL), 60 neutrophils/µL (reference range, 2000-12,000/µL), and a sodium concentration of 136 mEq/L (reference range, 139-154 mEq/L). Henderson received lactated Ringer's solution (500 mL SC) and was prescribed at-home medications, including enrofloxacin (10 mg/kg PO every 24 hours) and doxycycline (5 mg/kg PO every 12 hours). Results from a CBC performed 5 days later showed normal neutrophil and platelet counts; thus, antibiotics were discontinued.

Based on Henderson's clinical course and response to antibiotic therapy alone, Rylie's prednisone dose was tapered then discontinued, as fenbendazole toxicity was considered the likely cause of clinical illness in both dogs (see ***Take-Home Messages***). One week after completing antibiotic treatment, Rylie's CBC with pathologist review showed 12,580 neutrophils/µL (reference range, 2000-12,000/µL) and 447,000 platelets/µL (reference range, 175,000-500,000/µL).

Hematocrit was 44% (reference range, 39%-55%) with occasional toxic changes, occasional acanthocytes, and 1+ poikilocytes.

TAKE-HOME MESSAGES

- Bone marrow cells are susceptible to drug toxicity, as they divide rapidly and are metabolically active.[5] Drug toxicity should always be considered a differential diagnosis for patients with generalized bone marrow hypoplasia/aplasia.[5]
- Benzimidazoles bind to tubulin, a structural protein of microtubules, and can adversely affect rapidly dividing cells.[6]
- Bone marrow toxicity has been reported with albendazole use in cats and dogs[7]; however, few case reports of bone marrow toxicity after fenbendazole administration exist.[8,9]
- The labeled fenbendazole dose for dogs is 50 mg/kg PO every 24 hours with food for 3 consecutive days.[10] Extended courses of up to 14 days are generally used to treat certain parasites (eg, lungworms).
- Rylie's presumptive generalized bone marrow hypoplasia/aplasia could have been an idiosyncratic reaction unrelated to the pharmacologic action of fenbendazole. However, because another dog in the household experienced the same clinical course following similar dosing, both dogs' signs were likely dose dependent.

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