

Cutaneous & Renal Glomerular Vasculopathy in a Springer Spaniel

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▲ **FIGURE 1** Digits IV and V of the right pelvic limb with interdigital ulceration

Molly, a 2-year-old, 40-lb (18-kg) spayed springer spaniel living in the United Kingdom, was presented for a 4-day history of progressive, multifocal, ulcerative skin lesions and a 24-hour history of lethargy, anorexia, and vomiting. The skin lesions initially affected only the right pelvic limb; however, the day before presentation, additional ulcers developed over both inguinal areas, the lips, and the nasal planum. Molly was up-to-date on vaccinations and received monthly imidacloprid and moxidectin topical parasite prevention.

Physical Examination

Mucous membranes were slightly dry, and clinical dehydration was assessed at approximately 6%. Examination

showed interdigital ulceration and soft tissue swelling of digits IV and V on the right pelvic limb (**Figure 1**), superficial erosion of the skin in the inguinal area, and multiple erosions and ulcers over the rostral aspect of the upper and lower lips and nasal planum (**Figure 2**, next page). No other abnormalities were noted.

Diagnostics

Systolic blood pressure measured by Doppler ultrasonography was persistently increased (195 mm Hg; range, 100-150 mm Hg). CBC showed thrombocytopenia (platelet count, $50 \times 10^3/\mu\text{L}$; range, $150\text{-}500 \times 10^3/\mu\text{L}$), and serum chemistry profile revealed hypoalbuminemia, hyperbilirubinemia, and azotemia. International Renal Interest Society (IRIS) grade III acute kidney injury (AKI) was suspected (**Table**, next page).¹ Basal cortisol concentration ($4.4 \mu\text{g/dL}$; normal, $>2 \mu\text{g/dL}$) was within normal limits, making glucocorticoid-



▲ **FIGURE 2** Multiple erosions and ulcers are present over the rostral aspect of the patient’s upper and lower lips and nasal planum.

TABLE

SERUM CHEMISTRY PROFILE RESULTS

Analyte	Result	Reference Range
Albumin	2.0 g/dL	2.5-4.0 g/dL
Bilirubin	0.88 mg/dL	<0.58 mg/dL
Blood urea nitrogen	112 mg/dL	8.4-25.2 mg/dL
Creatinine	4.0 mg/dL	0.7-1.4 mg/dL

deficient hypoadrenocorticism unlikely. PCR for *Leptospira* spp in a single blood sample was negative. Antinuclear antibody test results were not suggestive of systemic lupus erythematosus.

Urine specific gravity was 1.025; urinalysis was otherwise unremarkable. Urine protein: creatinine ratio was elevated at 2.5 (normal, <0.4). Urine culture was negative. A urinary catheter was placed to monitor urinary output and adjust fluid therapy accordingly as part of standard management of AKI.

No significant findings were identified on abdominal ultrasonography or radiography of the thorax, abdomen, and limbs. Skin biopsy samples were not obtained because of concerns regarding the effects of sedation on renal perfusion.

Presumptive Diagnosis

Skin lesions and clinical abnormalities were suggestive of cutaneous and renal glomerular vasculopathy (CRGV). Differential diagnoses included leptospirosis, pyelonephritis, intoxication (eg, grape, ethylene glycol), immune-complex glomerulonephritis, and previous or current renal hypoperfusion (eg, prerenal azotemia), although these conditions are not typically associated with ulcerative skin lesions. A concurrent or associated dermatologic condition (eg, immune-mediated vasculitis, chemical burn) could not be excluded but was considered less likely.

Treatment

Standard AKI and supportive treatments were initiated (see *Treatment at a Glance*), including amlodipine (0.1 mg/kg PO q24h initially, then increased to 0.1 mg/kg PO q12h in the absence of clinical response), maropitant (1 mg/kg SC q24h), omeprazole (1 mg/kg PO q12h), and methadone (0.2 mg/kg IV q4h). Antibiotic therapy (ampicillin [15 mg/kg IV q8h]) was initiated to manage secondary infection of skin lesions, pending PCR for *Leptospira* spp and urinalysis results.

Crystalloid fluid therapy (ie, lactated Ringer’s solu-

tion) was initiated at 12.75 mL/kg/hr to provide maintenance fluid therapy and correct 6% dehydration. Urine output measurement after 6 hours of fluid therapy demonstrated urine production of 0.4 mL/kg/hr (normal, >1 mL/kg/hr). Fluid therapy rate was adjusted to match the dog's urine output and avoid volume overload. A furosemide bolus (1 mg/kg IV) was administered, and furosemide (0.5 mg/kg/hr CRI) was started; urine output remained <0.5 mL/kg/hr over the next 6 hours.

Outcome

Eighteen hours after admission, serum chemistry profile showed worsening azotemia with a creatinine concentration of 7.7 mg/dL (IRIS Grade IV oliganuric AKI). The patient was obtunded. Several options were discussed with the owner, including use of mannitol and/or fenoldopam to promote diuresis, referral for therapeutic plasma exchange and/or continuous renal replacement therapy, and euthanasia. Therapeutic plasma exchange has been used in humans with conditions similar to CRGV.^{2,3} After consideration, Molly was euthanized. Postmortem examination disclosed renal and cutaneous lesions consistent with thrombotic microangiopathy, including fibrinoid necrosis of the glomerular arterioles with frequent vessels occluded by thrombi and concurrent evidence of tubular necrosis and cutaneous coagulative necrosis with rare intravascular thrombi. The presence of these lesions with Molly's clinical signs and progression confirmed CRGV.⁴

The Take-Home

CRGV is an uncommon disease of unknown cause and is also referred to as *Alabama rot* in reference to a North American disease of unknown origin that is characterized by similar histopathologic lesions.⁵ CRGV has been reported in greyhounds in North America⁵ and a Great Dane in Germany.⁶

Until 2012, few (<5) cases had been reported in Europe. Since then, more than 150 cases in the United Kingdom, including one in Northern Ireland, have been confirmed by postmortem examination in nongreyhound breeds; 30 of these cases were

reported in 2018, making CRGV a rare condition. Although a definitive cause has not yet been identified, research investigating environmental and genetic causes (mainly complement system dysfunction) is ongoing.

Ulcerated, vasculitis-like skin lesions of the extremities, ventrum, face, and tongue are typically reported first.⁴ Some dogs develop skin lesions and azotemia; others develop skin lesions only and do not become azotemic, although the percentage of dogs that develop skin lesions only is

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TREATMENT AT A GLANCE

- ▶ Fluid therapy (typically over 4-6 hours to allow accurate assessment of urine output) should aim first to correct suspected hypovolemia (rare) and/or dehydration. Once the fluid deficit has been corrected, urine output should be monitored, and the fluid rate should be adjusted to match urine production and avoid volume overload.⁷
- ▶ Systemic hypertension should be managed with amlodipine (or hydralazine if immediate control is necessary). ACE inhibitors may reduce glomerular filtration rate and are contraindicated in these cases.⁷
- ▶ CRGV skin lesions tend to heal spontaneously over days to weeks with appropriate management, including broad-spectrum antibiotic therapy, if indicated, and appropriate wound management.⁷

AKI = acute kidney injury

CRGV = cutaneous and renal glomerular vasculopathy

IRIS = International Renal Interest Society

unknown due to the lack of gold standard testing antemortem and the lack of specificity of the skin lesions. The average time from onset of skin lesions to development of azotemia is 3 days (range, 1-10 days).⁴ Once AKI is present, prognosis is poor, with a mortality rate of 85%.⁵ Dogs that do not develop azotemia have an excellent prognosis, provided that wounds are adequately managed with standard local care and systemic antibiotic therapy. Thus far, there have been no reports of CRGV recurrence in a dog that survived the disease or of CRGV transmission between dogs. CRGV does not appear to be zoonotic, although standard precautions should be followed (eg, wearing gloves and a protective apron) until more is known about the disease etiology. ■

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NexGard®
(afoxolaner) Chewables

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description:

NexGard® (afoxolaner) is available in four sizes of beef-flavored, soft chewables for oral administration to dogs and puppies according to their weight. Each chewable is formulated to provide a minimum afoxolaner dosage of 1.14 mg/lb (2.5 mg/kg). Afoxolaner has the chemical composition 1-Naphthalenecarboxamide, 4-[5-[3-chloro-5-(trifluoromethyl)-phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl].

Indications:

NexGard kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*), and the treatment and control of Black-legged tick (*Ixodes scapularis*), American Dog tick (*Dermacentor variabilis*), Lone Star tick (*Amblyomma americanum*), and Brown dog tick (*Rhipicephalus sanguineus*) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month.

Dosage and Administration:

NexGard is given orally once a month, at the minimum dosage of 1.14 mg/lb (2.5 mg/kg).

Dosing Schedule:

Body Weight	Afoxolaner Per Chewable (mg)	Chewables Administered
4.0 to 10.0 lbs.	11.3	One
10.1 to 24.0 lbs.	28.3	One
24.1 to 60.0 lbs.	68	One
60.1 to 121.0 lbs.	136	One
Over 121.0 lbs.	Administer the appropriate combination of chewables	

NexGard can be administered with or without food. Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes to ensure that part of the dose is not lost or refused. If it is suspected that any of the dose has been lost or if vomiting occurs within two hours of administration, redose with another full dose. If a dose is missed, administer NexGard and resume a monthly dosing schedule.

Flea Treatment and Prevention:

Treatment with NexGard may begin at any time of the year. In areas where fleas are common year-round, monthly treatment with NexGard should continue the entire year without interruption.

To minimize the likelihood of flea reinfestation, it is important to treat all animals within a household with an approved flea control product.

Tick Treatment and Control:

Treatment with NexGard may begin at any time of the year (see **Effectiveness**).

Contraindications:

There are no known contraindications for the use of NexGard.

Warnings:

Not for use in humans. Keep this and all drugs out of the reach of children. In case of accidental ingestion, contact a physician immediately.

Precautions:

The safe use of NexGard in breeding, pregnant or lactating dogs has not been evaluated. Use with caution in dogs with a history of seizures (see **Adverse Reactions**).

Adverse Reactions:

In a well-controlled US field study, which included a total of 333 households and 615 treated dogs (415 administered afoxolaner; 200 administered active control), no serious adverse reactions were observed with NexGard.

Over the 90-day study period, all observations of potential adverse reactions were recorded. The most frequent reactions reported at an incidence of > 1% within any of the three months of observations are presented in the following table. The most frequently reported adverse reaction was vomiting. The occurrence of vomiting was generally self-limiting and of short duration and tended to decrease with subsequent doses in both groups. Five treated dogs experienced anorexia during the study, and two of those dogs experienced anorexia with the first dose but not subsequent doses.

Table 1: Dogs With Adverse Reactions.

	Treatment Group			
	Afoxolaner		Oral active control	
	N ¹	% (n=415)	N ²	% (n=200)
Vomiting (with and without blood)	17	4.1	25	12.5
Dry/Flaky Skin	13	3.1	2	1.0
Diarrhea (with and without blood)	13	3.1	7	3.5
Lethargy	7	1.7	4	2.0
Anorexia	5	1.2	9	4.5

¹Number of dogs in the afoxolaner treatment group with the identified abnormality.

²Number of dogs in the control group with the identified abnormality.

In the US field study, one dog with a history of seizures experienced a seizure on the same day after receiving the first dose and on the same day after receiving the second dose of NexGard. This dog experienced a third seizure one week after receiving the third dose. The dog remained enrolled and completed the study. Another dog with a history of seizures had a seizure 19 days after the third dose of NexGard. The dog remained enrolled and completed the study. A third dog with a history of seizures received NexGard and experienced no seizures throughout the study.

To report suspected adverse events, for technical assistance or to obtain a copy of the MSDS, contact Merial at 1-888-637-4251 or www.merial.com/NexGard. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

Mode of Action:

Afoxolaner is a member of the isoxazoline family, shown to bind at a binding site to inhibit insect and acarine ligand-gated chloride channels, in particular those gated by the neurotransmitter gamma-aminobutyric acid (GABA), thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes. Prolonged afoxolaner-induced hyperexcitability results in uncontrolled activity of the central nervous system and death of insects and acarines. The selective toxicity of afoxolaner between insects and acarines and mammals may be inferred by the differential sensitivity of the insects and acarines' GABA receptors versus mammalian GABA receptors.

Effectiveness:

In a well-controlled laboratory study, NexGard began to kill fleas four hours after initial administration and demonstrated >99% effectiveness at eight hours. In a separate well-controlled laboratory study, NexGard demonstrated 100% effectiveness against adult fleas 24 hours post-infestation for 35 days, and was ≥ 93% effective at 12 hours post-infestation through Day 21, and on Day 35. On Day 28, NexGard was 81.1% effective 12 hours post-infestation. Dogs in both the treated and control groups that were infested with fleas on Day -1 generated flea eggs at 12- and 24-hours post-treatment (0-11 eggs and 1-17 eggs in the NexGard treated dogs, and 4-90 eggs and 0-118 eggs in the control dogs, at 12- and 24-hours, respectively). At subsequent evaluations post-infestation, fleas from dogs in the treated group were essentially unable to produce any eggs (0-1 eggs) while fleas from dogs in the control group continued to produce eggs (1-141 eggs).

In a 90-day US field study conducted in households with existing flea infestations of varying severity, the effectiveness of NexGard against fleas on the Day 30, 60 and 90 visits compared with baseline was 98.0%, 99.7%, and 99.9%, respectively. Collectively, the data from the three studies (two laboratory and one field) demonstrate that NexGard kills fleas before they can lay eggs, thus preventing subsequent flea infestations after the start of treatment of existing flea infestations.

In well-controlled laboratory studies, NexGard demonstrated >97% effectiveness against *Dermacentor variabilis*, >94% effectiveness against *Ixodes scapularis*, and >93% effectiveness against *Rhipicephalus sanguineus*, 48 hours post-infestation for 30 days. At 72 hours post-infestation, NexGard demonstrated >97% effectiveness against *Amblyomma americanum* for 30 days.

Animal Safety:

In a margin of safety study, NexGard was administered orally to 8 to 9-week-old Beagle puppies at 1, 3, and 5 times the maximum exposure dose (6.3 mg/kg) for three treatments every 28 days, followed by three treatments every 14 days, for a total of six treatments. Dogs in the control group were sham-dosed. There were no clinically-relevant effects related to treatment on physical examination, body weight, food consumption, clinical pathology (hematology, clinical chemistry, or coagulation tests), gross pathology, histopathology or organ weights. Vomiting occurred throughout the study, with a similar incidence in the treated and control groups, including one dog in the 5x group that vomited four hours after treatment.

In a well-controlled field study, NexGard was used concomitantly with other medications, such as vaccines, antihelmintics, antibiotics (including topicals), steroids, NSAIDs, anesthetics, and antihistamines. No adverse reactions were observed from the concomitant use of NexGard with other medications.

Storage Information:

Store at or below 30°C (86°F) with excursions permitted up to 40°C (104°F).

How Supplied:

NexGard is available in four sizes of beef-flavored soft chewables: 11.3, 28.3, 68 or 136 mg afoxolaner. Each chewable size is available in color-coded packages of 1, 3 or 6 beef-flavored chewables.

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Marketed by: Frontline Vet Labs™, a Division of Merial, Inc. Duluth, GA 30096-4640 USA

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