Lethargy in a Boxer

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Prancer, a 9-year-old spayed boxer dog, was presented for lethargy and reluctance to move.

History

Approximately 2 weeks before presentation, Prancer had acute onset grade 2/4 left forelimb lameness after jumping off her owner's bed. Several hours after the incident, she had progressively severe lethargy and was found in lateral recumbency. The owner reported the dog refused to get up or lift her head.

During the 2 weeks before current presentation, Prancer was examined by several veterinarians for decreased appetite, panting, and possible fever. Diagnostic testing was not pursued. She was intermittently febrile despite treatment with enrofloxacin at 10 mg/kg PO once a day, amoxicillin at 33 mg/kg PO twice a day, and metronidazole at 17 mg/kg PO twice a day.

Prancer had previously been healthy with no known exposure to toxins or toxicants. Regular medications included monthly heartworm and flea and tick preventives. She was up-to-date on vaccines and had access to a 2-acre fenced-in backyard.

Examination Findings

On evaluation, Prancer was quiet, alert, and responsive. BCS was 4/9. Temperature was 103.7ºF; heart rate and respiratory rate were within normal limits. Mild enlargement of the popliteal lymph nodes was noted; the right was larger than the left.

Cardiac auscultation disclosed a grade I/VI left basilar systolic murmur. Pitting edema was present over the distal portions of the hindlimbs bilaterally. The left carpus was mildly effusive. Mild apparent pain was appreciated on palpation of the cranial abdomen. Probable melena was noted on rectal exam. No lameness was appreciated on walking, but Prancer was reluctant to ambulate.

Case Progress

During a 6-day observation, Prancer had intermittent fevers to 103.7ºF. Sloughing of the digital pad of the fifth digit on the left pes was noted (***Figure 1***, page 105).

Diagnostic Results

CBC disclosed an inflammatory leukogram characterized by a moderate neutrophilia (24.217×10^3/uL; range, 2.841-9.112) with a left shift (bands, 1.361×10^3/uL); mild anemia (PCV 38%); mild decrease in plasma protein (5.7 g/dL; range, 5.9-7.3); and 5 nucleated red blood cells (nRBCS) by 50× field in oil. Serum chemistry profile showed a low-normal glucose concentration

TABLE 1A

DIAGNOSTIC TEST AND RESULTS

Diagnostic	Results from Initial Presentation (Abbreviated with Notable Findings Stated)
CBC	Inflammatory leukogram with a mature neutrophlia and a left shift
Serum chemistry	Moderately low albumin, elevated ALP, ALT, mildly elevated CK, low BUN
Urinalysis	Isosthenuria, otherwise unremarkable USG (1.011)
ANA	Weakly positive (1:40)
Joint taps (left carpus, left hock, right hock, right carpus)	All marked suppurative inflammation with neutrophil counts ranging from 93%-98%. There were no bacteria; rare mononuclear cells were observed.
Bartonella spp culture and PCR with BAPGM media	Negative
Coagulation panel	Mildly elevated PTT, dimers, and fibrinogen values
Popliteal lymph node aspirates	Moderate-to-marked lymphoid reactivity
Urine culture and susceptibility	No growth
Bile acids	Normal value
Abdominal ultrasound	Mild left adrenomegaly, mild right medial iliac lymphadenopathy, cholecystic debris, urinary bladder debris
Thoracic radiographs	Unremarkable
Echocardiogram	All valves normal, no regurgitation noted, no evidence of endocarditis
Spinal radiographs	Multifocal disc narrowing, no evidence of discospondylitis
Appendicular joint survey radiographs	Normal joints
Left pes radiographs	Left third phalangeal swelling of the fifth digit with soft tissue defect, no evidence of osseous involvement
Liver aspirates and cytology	Moderate cholestasis
Bile cytology	Unremarkable
Blood culture and susceptibility	No growth
Comprehensive vector-borne panel (*Babesia canis, B gibsonii, Ehrlichia canis, Rickettsia rickettsii, Anaplasma* spp, *Bartonella vinsonii, B henselae, B koehlerae, Mycoplasma* spp, *Borrelia burgdorferi*, *Dirofilaria immitis*)	All negative
ACTH stimulation test	2.3, 17 µg/dL (Cortisol levels pre- and post-ACTH, respectively)
Venous blood gas	Unremarkable
Coombs' test	Negative
Biopsies of foot pad	Multifocal fibrinoid vascular necrosis with secondary fat necrosis; neutrophilic ulcerative dermatitis—concerning for systemic lupus erythematosus
Bile culture and susceptibility	No growth

and a low BUN concentration. Hypoalbuminemia, moderately elevated ALP, mild elevation of ALT, and a mildly elevated creatine kinase were also present (***Tables 1A***, previous page, and ***1B***).

Urinalysis showed isosthenuria; no other abnormalities were noted. Results of pre- and postprandial bile acid testing were within the reference ranges. Bile acid testing was performed to rule out hepatic dysfunction as the cause of hypoalbuminemia.

Abdominal ultrasonography revealed mild left adrenomegaly, mild right medial iliac lymphadenopathy, cholecystic debris, and urinary bladder debris. Thoracic radiography, echocardiography, and joint survey radiography were unremarkable. Spinal radiography showed multifocal disk narrowing with no evidence of discospondylitis.

Radiography of the left pes showed swelling of the left third phalanx of the fifth digit with a soft tissue defect; no evidence of osseous involvement was noted. The left carpus was mildly effusive; no other joints were effusive on palpa-

TABLE 1B

CBC

Test Code	Results	Expected	Units
White blood cells (WBC)	27.21	4.39 – 11.61	$\times 10^3/\mu L$
Red blood cells	5.69	5.7 – 8.01	$\times 10^6/\mu L$
Hemoglobin	13.1	13.8 – 20.3	g/dL
Hematocrit	39.2	39.2 – 55.9	%
Mean corpuscular volume	68.8	61.8 – 75.1	fL
Mean corpuscular hemoglobin	23.0	20.2 – 25.3	pg
Mean corpuscular hemoglobin concentration	33.4	30.8 – 35.4	g/dL
Red blood cell distribution width	13.7	11.3 – 13.5	%
Platelet	226	190 – 468	$\times 10^3/\mu L$
Mean platelet volume	13.9	7.9 – 13.8	fL
Plateletcrit (PCT)*	0.32	0.2 – 0.58	%
Packed cell volume	38	39 – 58	%
Plasma protein	5.7	5.9 - 7.3	g/dL
Segmented neutrophils	24.217	2.841 – 9.112	$10^3/\mu L$
Band neutrophils	1.361		$10^3/\mu L$
Lymphocytes	0.272	0.594 – 3.305	$10^3/\mu L$
Eosinophil	0.272	0.03 – 1.264	$10^3/\mu L$
Basophil		0 – 0.192	$10^3/\mu L$
Abnormal lymphocytes	0.816		$10^3/\mu L$
Nucleated red blood cells	5 nucleated red blood cells per 100 WBCs		/100 WBC
Platelet number	Normal		
Large platelets	Moderate		
Toxic neutrophils	Slight		
Acanthocyte	Rare		/100× field
Echinocyte	Rare		/100× field
Target cells	Occasional		/100× field

*PCT represents the volume of blood on a percentage or L/L basis that comprises platelets and is a better indicator of the circulating mass of platelets, an important physiologic variable.

SLE = systemic lupus erythematosus

CHEMISTRY

Test Code	Results	Expected	Units
Glucose	73	70 – 131	mg/dL
BUN	5	6 - 26	mg/dL
Creatinine	0.6	0.7 – 1.5	mg/dL
Phosphorus	3.7	2.5 – 5.6	mg/dL
Calcium	8.7	9.4 – 11.4	mg/dL
Magnesium	1.7	1.8 – 2.5	mg/dL
Total protein	4.5	5.2 – 7.3	g/dL
Albumin	2.0	3 – 3.9	g/dL
Globulins	2.6	1.7 – 3.8	g/dL
Albumin/globulin ratio	0.77	0.9 – 1.8	
Cholesterol	193	124 – 344	mg/dL
Total bilirubin	0.2	0 – 0.2	mg/dL
ALP	836	16 – 140	U/L
ALT	76	12 – 54	U/L
Gamma-glutamyltransferase	<3	0 – 6	U/L
CK	760	43 – 234	U/L
Sodium	151	140 – 156	mmol/L
Potassium	3.6	4 – 5.3	mmol/L
CL	124	108 – 122	mmol/L
Bicarbonate	17	18 – 25.8	mmol/L
Anion gap	14.0	11.2 – 19.9	
NA/K	41.8	27.7 – 35.9	
Calculated osmolality	294.4	278.7 – 311.6	mosm/kg
Amylase	819	236 – 1337	U/L
Lipase	53	12 – 147	U/L

tion. Arthrocentesis of the carpi and tarsi was performed, and cytology was suspicious for immune-mediated polyarthritis (***Figure 2***, page 105).

URINALYSIS

Test Code	Results	Expected	Units
Color	Yellow		
Turbidity	Slightly Cloudy		
pH	9	4.5 – 8.5	
Protein	Negative		
Glucose	Normal		
Ketones	Negative		
Bilirubin	Negative		
Blood	Trace		
Protein	Negative		
USG	1.011	1.015 – 1.045	
White blood cells	Rare		/HPF
Red blood cells	Rare		/HPF
Epithelial cells	0-5		/HPF
Fat Drops	Few		/HPF

Results of infectious disease testing for vector-borne diseases prevalent in the region were negative. Blood culture, *Bartonella* spp enrichment culture, and PCR and culture and susceptibility testing of the urine were negative. An aspirated specimen of the right popliteal lymph node was interpreted as reactive. ANA was present with a 1:40 titer; no reference range was provided.

Biopsy specimens of the area of the paw pad that sloughed and associated tissue were obtained. Histopathologic examination disclosed multifocal fibrinoid vascular necrosis with secondary fat necrosis and neutrophilic ulcerative dermatitis.

ASK YOURSELF

- How do you determine if a dog has systemic lupus erythematosus (SLE)?
- Which treatments are recommended for SLE in dogs?

Diagnosis

Systemic Lupus Erythematosus (SLE)

Prancer was diagnosed with SLE based on the presence of 3 criteria: positive ANA titer, characteristic cutaneous lesions on histopathology, and polyarthritis.[1]

Although glomerular disease is common, it does not have to be present for a diagnosis of SLE. Prancer's urine was negative for protein both with a dipstick and on measurement of albumin, so no urine protein:creatinine ratio was performed. A possible cause of Prancer's hypoalbuminemia was vasculitis, particularly with evidence noted on her cutaneous biopsy specimen.

Another possible source of loss was through the GI tract. Prancer's melena may have been multifactorial. Human patients with SLE are known to have mesenteric vasculitis and acute pancreatitis as sequelae to their disease.[2] It is possible that vasculitis may have manifested in Prancer's GI tract or that pancreatitis was present.

It is interesting that Prancer's BUN was low in the face of overt GI bleeding, clinically evidenced by melena. BUN is an insensitive biomarker for GI bleeding, and in the author's experience it can be low despite profuse melena. This could be because of poor absorption through the GI tract or decreased production by the liver.

In Prancer's case, pre- and postprandial bile acid levels were normal, making hepatic dysfunction less likely. However, the patient did have evidence of a hepatopathy prior to the administration of steroids. This was likely secondary to SLE, but pancreatitis or cholangiohepatitis could not be ruled out.

The cause of Prancer's isosthenuria was thought to be secondary to nephrogenic presumptive diabetes insipidus; however, it was notable that she became polyuric after initiation of steroid therapy.

Treatment

Prancer was hospitalized and supportively treated for her GI bleed with omeprazole, sucralfate, maropitant, and ondansetron.

Pain management included IV fentanyl at varying rates depending on the perceived pain level. Broad-spectrum antibiotic treatment included doxycycline at 5 mg/kg PO twice a day, cefpodoxime at 10 mg/kg PO once a day, enrofloxacin at 10 mg/kg IV that was switched to PO once a day, and metronidazole at 10 mg/kg PO twice a day.

Initially, Prancer was treated for bacterial infection and possible bacteremia, and metronidazole was chosen for GI translocation and anaerobes. Her SLE could have been secondary to a drug reaction, particularly with the cephalosporins.

Prancer received immunosuppressive treatment after all cultures were returned. Initially, leflunomide (2 mg/kg PO twice per day) was chosen because polyarthritis was confirmed. A review of the veterinary literature supports the use of leflunomide with immune-mediated polyarthritis.[3-4] Results of examination of the digital pad biopsy specimens[1] and the presence of ANA lead to a presumptive diagnosis of SLE, and she was switched to mycophe-

ANA = antinuclear antibody
BUN = blood urea nitrogen
SLE = systemic lupus erythematosus

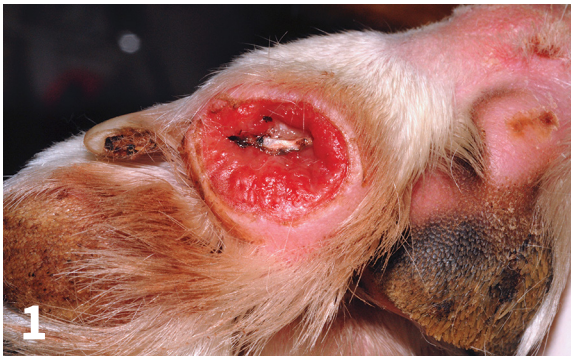
nolate because of the plethora of available human literature supporting the use of mycophenolate in patients with SLE.[1-5]

An anti-inflammatory dose of prednisone (1 mg/kg PO once a day) was initiated on hospital day 3, because of concerns over the GI bleed and the potential for the digital pad lesion to act as a source for infection. While larger, immunosuppressive doses of steroids are necessary for achieving remission of SLE in dogs, use of lower doses of steroids may help improve clinical signs and result in fewer side effects.

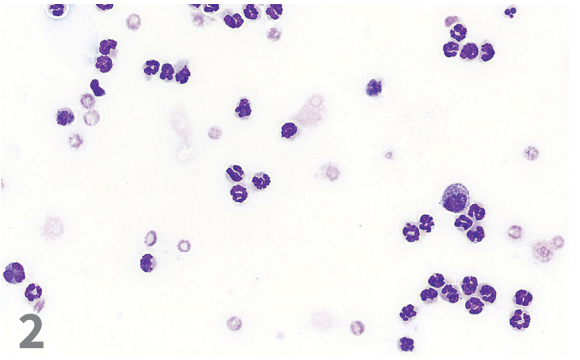
Outcome

Within 24 hours of starting prednisone, Prancer had improved dramatically. She was willing to eat, she walked outside comfortably, and the inflammatory leukogram had improved. The day before steroid administration, WBC count was 39000 cells/mm^3 with 2700 bands. One day after steroid initiation, total WBC count decreased to 31000 cells/mm^3 with 900 bands. She also appeared brighter and more energetic. After the biopsy specimen showed vasculitis consistent with SLE, leflunomide was switched to mycophenolate, and pentoxifylline was added for vasculitis.

Lesions and ulcers developed over several paw pads within 1 week of discharge; the lesions showed marked healing within several weeks. A slow prednisone taper was initiated after the paw pads had fully healed; results of serum studies improved and the dog continued to do well at home.



▲ Left pes with ulcerative lesion of the digital pad. The third phalanx can be seen in the deep portions of the ulcer. *Image courtesy of Chie Tamamoto-Mochizuki, DVM.*



▲ Suppurative joint fluid. *Image courtesy of Jennifer Neel, DVM, DACVP.*

TABLE 2

TREATMENT AT A GLANCE

Secondary Agent	Dose
Azathioprine	2.2 mg/kg PO once a day until remission achieved, then given every 2 days
Cyclosporine	5 mg/kg PO once to twice a day
Mycophenolate mofetil	10-20 mg/kg PO or IV twice a day
Immunoglobulin G	0.5-1 g/kg once a day for 1-4 days, for refractory cases or cases that present on emergency
Levamisole	2-5 mg/kg (150 mg max dose) every 2 days for 4 months

DID YOU ANSWER?

- SLE is a complex multisystemic immune-mediated disease that is reported infrequently in dogs. Diagnosis requires documentation of multisystemic involvement, elimination of underlying infectious disease, and positive serologic tests (ANA or lupus erythematosus cell preparation). Criteria have been established for diagnosis in humans, and they have been modified for veterinary patients[6] (***Table 1***, page 101). SLE is characterized by pathogenic autoantibody production as a consequence of uncontrolled T- and B-lymphocyte activity and immune-complex deposition in various organs. In canine patients, the most common manifestations are polyarthritis, dermatologic disease, glomerulonephritis, hemolytic anemia, or thrombocytopenia.[3,6,8]

- The mainstay of treatment is corticosteroids. Dogs are generally treated with prednisone from 1.0 to 2.2 mg/kg/day. This is tapered to the lowest effective dose over time after remission is achieved. Relapses are common, and many animals will require increased amounts of steroids during these times. It is important to recognize that the clinical manifestations can vary between patients and over time, so animals should be monitored carefully. For animals with cutaneous involvement, avoidance of sunlight may be necessary, as photosensitization can occur. For animals with more severe disease or when steroid side effects need to be minimized, a secondary agent should be used (***Table 2***, page 105). Many new drugs are being developed based on the immune dysregulation that occurs in SLE.[9,10] Phosphoinositol-3 kinase δ (PI3Kδ) is a promising target in this respect; it is essential in mediating B- and T-cell function in mice and humans. Recently, oxacyclododecindione (Oxa), a macrocyclic lactone isolated from the imperfect fungus *Exserohilum rostratum*, has been described as a potent transcription inhibitor of inducible proinflammatory and profibrotic genes in cell culture models. This drug is also being studied, particularly in cases with renal involvement and glomerular sclerosis. Currently, there are no data on the use of these new medications in veterinary medicine, but it is likely that these medications or others with similar mechanisms of action will be of clinical use in the future. Their use in clinical patients is not recommended at this time.

ANA = antinuclear antibody

SLE = systemic lupus erythematosus

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