

Case Log #20

4587B Kirby

Kirby, a canine 5 year old male neutered Maltese, presented to the neurology service on 12/7/09 for difficulty walking. In October 2009, Kirby began to list to the right with a right head tilt. He was thought to have idiopathic vestibular signs by the RDVM. The signs did not resolve spontaneously, so an antibiotic (cefprozime proxtil 50mg SID) was started in case of otitis media. The clinical signs did not improve with this therapy. A course of steroids (prednisone 5mg PO BID) was then started to reduce inflammation in case the vestibular signs were caused an inflammatory process. His clinical signs improved but returned when the prednisone dose was tapered. At that point he became ataxic, inappetent and lethargic.

Thoracic and abdominal radiographs were performed by the RDVM and were within normal limits with the exception of decreased hepatic size. Bloodwork performed on 6/29/09, 10/19/09 and 11/25/09 showed increasing values of the liver enzymes alanine transaminase (ALT), alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT) but was otherwise unremarkable. The increases in the liver enzymes were thought to be due to prednisone hepatopathy, a commonly seen reaction to prednisone in which the liver begins to accumulate more fat, glycogen or water than is appropriate. These changes can usually be reversed by decreasing or stopping prednisone therapy and/or with the use of adjunctive liver supportive agents such as ursodiol or s-adenosyl methionine. Antibiotics, lactulose and/or a low-protein diet may also be used to reduce ingested and bacteria produced protein-metabolites in the gastro-intestinal tract and thusly decrease the toxin load on the liver. Kirby's prednisone therapy was discontinued

and he was started on ursodiol (300mg PO BID) and amoxicillin (50mg PO BID) on 12/1/09.

On 12/7/09, Kirby returned to the RDVM for worsening ataxia, lethargy and poor appetite. An IV catheter was placed and he was started on lactated ringers solution IV in preparation for transfer to the neurology service.

On presentation Kirby weighed 4.2 kg. His temperature (101.8F), pulse (80 bpm) and respiratory rate (24 breaths per minute, normal effort) were within normal limits. He was dull and depressed. Neurologic examination revealed a decreased menace in the left eye (OS) as well as a decreased palpebral blink response OS. He had decreased left facial sensation as compared to the right. A positional ventrolateral strabismus was noted in the right eye (OD) and a mild right head tilt was also noted. Kirby was tetraparetic and unwilling to walk. His conscious proprioception (CP) was absent in both front limbs and the right rear limb, and decreased in the left rear limb. Spinal reflexes were normal. The physical exam was otherwise normal.

Due to the left sided cranial nerve signs and right-sided CP deficits, the neuro-anatomical localization was deemed multifocal with right forebrain, right caudal fossa and C₁-C₅ myelopathy as areas of interest. Given the age, breed and multifocal nature of the symptoms, an inflammatory or infectious disease process such as granulomatous meningoencephalitis (GME) was considered most likely. Due to the decreased mentation and increased ALT, hepatopathy like microvascular dysplasia (MVD) or porto-systemic shunt (PSS) causing hepatic encephalopathy was also considered.

Initial diagnostics included bloodwork (an electrolyte/chemistry panel), an MRI study of the brain and CSF analysis. The electrolyte panel revealed a mildly increased

sodium (157.6mEq/L, normal 138-146) likely due to dehydration but was otherwise unremarkable. MRI of the brain and cervical spine was recommended to rule out intracranial causes of the multifocal neurologic signs.

Kirby was anesthetized with IV diazepam (0.85mg, 0.17mL) and propofol (17mg, 1.7mL) and a 5.5 mm endotracheal tube was placed. Anesthesia was maintained on 1.5-2% isoflurane. Anesthetic monitoring included pulse-oximetry, ET_{CO}₂ and non-invasive blood pressure. IV Normosol-R was given at rate of 21mL/h during the procedure. Kirby was placed in prone position in the MRI on a quadrature knee coil for a brain series. T2-weighted transverse images, T2 FLAIR transverse images, T1-weighted pre- and post-contrast (IV gadolinium, 0.22mL/kg, 0.92mL) transverse images, T2-weighted sagittal images of the brain and T2-weighted sagittal images of the cervical spine were obtained.

The MRI revealed bilateral intraaxial hyperintense (on T2 and FLAIR images) lesions in the dorsal frontal, parietal and occipital lobes. These areas predominately affected the white matter and were more pronounced on the left side. The changes were isointense on T1-weighted pre-contrast images and revealed a mild heterogeneous enhancement following contrast administration. There were also hyperintense lesions in the bilateral ventral thalamus, midbrain (right more pronounced than left), and medulla (left more pronounced than right) on T2-weighted and FLAIR images. These lesions were isointense on T1-weighted images but did not enhance with contrast.

The lesions noted on the MRI were suspicious of GME, but an analysis of CSF would be needed to help diagnose GME as a neoplastic process could have a similar appearance on MRI. Kirby was clipped over the dorsal region of L₄-S₁ and the skin

aseptically prepared for a lumbar CSF tap. He was positioned in right lateral recumbency, and a 22-gauge 1.5-inch spinal needle was carefully inserted into the spinal canal.

Approximately 1.2 mL of clear CSF was obtained and submitted in lavender top and red top tubes for analysis. The CSF analysis revealed increased protein (94 mg/dL, normal 15-35 mg/dL) and increased WBC (165 per μ L, normal <5 per μ L). A lymphocytic pleocytosis was found on a differential cell count and the cells did not appear neoplastic.

The multifocal lesions seen on the MRI in conjunction with the inflammatory spinal tap combined to support a presumptive diagnosis of GME. GME is an immune-mediated disease of the central nervous system in which leukocytes invade the meninges and white matter of the brain and occasionally spinal cord causing inflammation of these tissues. The origin of the disease is not well understood, but is thought to be a combination of environmental and genetic factors. It is most commonly found in younger, female, small breed dogs.

Confirmation of GME is based on histopathologic evaluation of brain tissue, either via biopsy or necropsy. Since these diagnostics require potential brain damage or death, a presumptive diagnosis is often based on a combination of brain imaging findings and CSF analysis. Brain imaging of patients suspected of having GME usually reveals patchy areas of inflammation that may enhance with contrast administration. CSF analysis usually reveals an increased protein level and WBC count, most commonly with a lymphocytic pleocytosis.

Prognosis of GME is fair to poor depending on the severity of clinical signs and response to therapy. Treatment is aimed at reducing inflammation and may be as simple as prednisone (a steroidal anti-inflammatory drug), however many cases also need other

immunosuppressants such as cyclosporine or chemotherapeutic agents such as cytarabine to control the clinical signs. Anti-epileptic medications may be indicated if the inflammation causes seizures.

Kirby recovered well from anesthesia and was kept overnight for observation. A pre- and post-prandial bile acids was obtained. The results were elevated at 102.1 and 82.3 $\mu\text{mol/L}$ respectively (normal less than 30 $\mu\text{mol/L}$). MVD or PSS of the liver was considered more likely than prednisone hepatopathy at this time since discontinuation of the prednisone did not help the liver values. An abdominal ultrasound to further evaluate possible hepatopathy was offered but declined by the owners.

Kirby remained on IV fluids (Normosol-R at 10mL/h). A dose of dexamethasone sodium phosphate (0.84mg, 0.21mL) was given IV and he was started on prednisolone 4.5mg PO BID to reduce intracranial edema and decrease the immune response in the brain. Given the elevated bile acids he was continued on amoxicillin 50mg PO BID and lactulose was started at 666mg (1mL) PO TID. Since it did not seem to be effective in Kirby's case, the ursodiol was discontinued. He was offered a low-protein diet but did not eat.

On 12/8/09, Kirby was more alert and ambulatory but compulsively circling to the left. Over the course of the day he became dull, tachypnic and developed bilateral miosis. He was given two doses of mannitol 20% (2g, 10mL), an osmotic diuretic, to help reduce intracranial inflammation. Kirby's mentation improved after the second dose but that evening he had a tonic-clonic seizure and was given 1.25mL (6.25mg) diazepam IV. He was started on the anti-epileptic levetiracetam (80mg, 0.8mL) PO BID due to its rapid onset and because it is not metabolized by the liver (as is phenobarbital). His blood

pressure was monitored every six hours overnight and was 200 and 220 millimeters of mercury (mmHg) systolic.

Kirby had another seizure on the morning of 12/9/09 and was given 1.25mL (6.25mg) diazepam IV. The levetiracetam dose was increased to 80mg TID. At this point, due to the progressively worsening neurologic status, his prognosis was considered guarded to poor. His owners elected to continue supportive care despite his clinical deterioration.

Blood was drawn and submitted for Toxoplasma and Neospora titers to rule out infectious causes of brain inflammation that mimic or could lead to GME. A CSF titer for Cryptococcus was also preformed. Kirby was started on clindamycin (50mg, 2mL PO BID) for potential protozoal infection.

His mentation remained dull and he was laterally recumbent throughout the day. Kirby's head was kept elevated by approximately 30 degrees to encourage venous drainage from the brain and regulate ICP. He was not offered food, as due to his decreased mentation Kirby may not have been able to swallow properly and risked choking or aspiration pneumonia. He started twitching sporadically throughout the day. His systolic blood pressure lowered to 160mmHg. Kirby remained tachypnic, with a respiratory rate of 60 to 100 breaths per minute and mildly to moderately increased respiratory effort. Radiographs of the thorax revealed a significantly narrowed and possibly collapsing trachea.

That evening Kirby was started on cytarabine 12.5mg (0.625mL) SC every twelve hours. Cytarabine is a chemotherapeutic agent that acts as a DNA polymerase inhibitor. Unlike many chemotherapeutic agents, cytarabine is able to traverse the blood-brain

barrier in a limited capacity. For this reason it is used for CNS lymphoma and other myeloproliferative diseases. As GME is an immune-mediated disease of the CNS, cytarabine can be a useful adjunctive therapy to reduce CNS inflammation.

When used as a treatment for GME, cytarabine is given as a dose of 50mg/m² SC twice daily for two days. This treatment is repeated every three to four weeks for four to six treatments. Cytarabine can induce myelosuppression, so CBCs should be evaluated before each treatment and one-week post treatment. A CBC performed before Kirby's first treatment on 12/9/10 was essentially normal, but did show an increased amount of toxic-appearing neutrophils, which were likely consistent with an inflammatory reaction.

Over the course of the evening his twitching episodes subsided and by the morning of 12/10/09 he seemed more alert and was no longer twitching. His respiration normalized to an average of 30 breaths per minute with little to no increased effort. His other vital signs remained within normal limits. He began eating and was able to stand briefly on his own.

Kirby remained hospitalized for four more days. A total of four doses of cytarabine were administered. Fluids were discontinued 12/10/09. Kirby's mentation and neurologic status steadily improved until he was ambulatory with normal conscious proprioception in all four limbs. No further seizures were seen. Kirby continued to have a slight head tilt to the left, but he had normal facial sensation, PLR and menace responses in both eyes.

Kirby was discharged to his owners on 12/14/09 on prednisolone 4mg (1.3mL) PO BID, levetiracetam 80mg (0.8mL) PO TID, lactulose 1mL PO TID, amoxicillin 50mg (1mL) PO BID, clindamycin 50mg (2mL) PO BID and samples of a low-protein diet. The

owners were instructed to return to their RDVM in one week for a follow-up CBC, and to return to our hospital in one month for the next dose of cytarabine.

A CBC at the RDVM 12/18/09 showed marked inflammation with a mature neutrophilia. Kirby returned to our hospital for a recheck examination on 1/5/10. At this time he had a slightly decreased CP in the right front limb but otherwise had a normal neurologic exam. His vital parameters including temperature were normal. He was doing well at home and was not febrile. An in-house CBC at that time was normal. Another treatment regimen of cytarabine (12.5mg, 0.625mL SC every 12h for four doses) was started. A repeat CBC and bile acids test was scheduled with the RDVM for the following week. The bile acids were improved and amoxicillin was discontinued. All titers also returned negative and the clindamycin was also discontinued. Lactulose, prednisolone and levetiracetam were continued.

Kirby returned to the hospital 2/8/10, 3/8/10, and 4/13/10 for subsequent cytarabine treatments. His CBC remained within acceptable limits with occasional increases in WBC, but never developed a significant decrease below normal parameters. Kirby's neurologic exam returned to normal. The prednisolone dose was slowly tapered with each visit.

On 5/11/10, Kirby returned to the hospital for a repeat MRI. A pre-anesthetic chemistry panel revealed increased ALT and ALP while the kidney and total bilirubin values were within normal limits. The MRI showed a normal brain appearance; with all previously visualized lesions were gone. Kirby was restarted on amoxicillin at 50mg PO BID (1mL) for the liver disease and the prednisolone was reduced to 1.2mg (0.4mL) in

the morning and 0.6mg (0.2mL) in the evening. Lactulose and levetiracetam were continued.

Kirby returned one week later for his sixth and final cytarabine treatment. His neurologic examination remained normal. Due to the increase in liver values a slightly lower dose of cytarabine was administered (8mg, 0.4mL) SC every twelve hours for four injections.

Another CBC, liver chemistry and bile acids was done at the RDVM on 8/3/10, these revealed still increasing values. Kirby has not shown any clinical signs of liver disease. The treatment plan for Kirby is to slowly reduce the prednisolone dose, though he will likely stay on a low dose of that medication long-term. The levetiracetam and lactulose will also be continued long-term, with amoxicillin as needed for periodic increases in liver values.

HEMATOLOGY LAB CHART Kirby PAGE 1

Test	Date 11/25/09	Date 12-9-10	Date 12/18/09	Date 1/5/10	Reference
WBC	13.7	15.3	27.1	15.7	4.0-15.5
RBC	6.4	5.58	5.54	6.46	4.8-9.3
HGB	15.3	12.8	13.4	14.9	12.1-20.3
PCV	44	38.6	37.3	46.1	38-51
MCV	68	69	67.4	71	58-79
MCHC	35	33.2	35.8	32.3	30-38
PLAPROT					
PLATELET	569	332	270	650	170-400
SEGS	80	77	89	85.9	0-100
ABSONEUT	10960	11800	24119	13600	3000-11500
LYMPHS	7	5	4	8.6	0-100
ABLYMPH	959	800	1084	1300	1000-4800
MONOS	7	16	7	5.5	0-100
ABSMONO	959	2400	1897	800	150-1250
EOS	6	0	0		
ABSEOS	822	0	0		100-12500
NRBC		0	0		<5
BANDS		2	0		
ABSBANDS		300	0		0-300

URINALYSIS

Test	Date 11/25/09	Date 12/15/09	Date	Date	Reference
COLOR	Clear Yellow	Cloudy Yellow			
SPGR	1.037	1.027			
PH	6.0	6.0			5.5-7.0
PRO	Trace	Trace			Negative
GLUC	Negative	Negative			Negative
KETO	Negative	Negative			Negative
BILI	1+	Negative			Negative to 1+
BLOOD	Negative	2+			Negative

UROB					
VOLSUB					
VOLCENT					
WBC/lpf	0	0			0
UR/LIP					

CHEMISTRY

Test	Date 6/29/09	Date 10/19/09	Date 11/25/09	Date 12/7/09	Reference
GLU	122	110	90	107	64-118
CHOL		144	202		65-225
BUN	9	17	14	18	14-36
CREA	1.0	0.8	0.7	0.7	0.8-2.4
Mg		1.8	1.9		1.7-2.3
Ca		10.0	10.2		8.1-11.6
PHOS		3.1	4.6		3.1-7.5
TP	6.9	6.0	6.8		5.4-7.9
ALB		3.9	3.9		2.6-3.9
GLOB		2.1	2.9		2.4-4.4
ALT	29	129	95	43	0-65
ALKP	123	26	318	170	0-193
GGT		10	57		0-8
TBIL		0.1	0.1		0-0.5
Na+		146	148		138-146
K+		4.4	4.9		3.5-4.9
Cl-		112	113		98-109
ECO2					19-24
AGPK					10-20

HEMATOLOGY LAB CHART Kirby PAGE 2

Test	Date 1/12/10	Date 2/4/10	Date 2/17/10	Date 3/4/10	Reference
WBC	20.7	12.7	15.1	20.0	4.0-15.5
RBC	6.02	6.33	5.61	5.76	4.8-9.3
HGB	15.1	15.4	14.6	15.2	12.1-20.3
PCV	43.3	46.5	40.3	43.5	38-51
MCV	71.9	73.4	71.8	75.6	58-79
MCHC	34.8	33.1	36.1	34.8	30-38
PLAPROT					
PLATELET	526	613	433	751	170-400
SEGS	85	83	79	85	0-100
ABSONEUT	17590	10540	11929	17000	3000-11500
LYMPHS	6	2	4	3	0-100
ABLYMPH	1240	250	604	600	1000-4800
MONOS	8	15	15	12	0-100
ABSMONO	1660	1910	2265	2400	150-1250
EOS	1	0	1	0	
ABSEOS	210	0	151	0	100-12500
NRBC			1		<5
BANDS					
ABSBANDS					0-300

CHEMISTRY

Test	Date 12/8/09	Date 12/9/10	Date 5/17/10	Date 5/25/10	Reference
GLU	102	81		121	64-118
CHOL				280	65-225
BUN	12	8	7	9	14-36
CREA	0.6	0.6	0.4	0.6	0.8-2.4
Mg	1.24	1.46			1.7-2.3
Ca	4.29 (ionized)	5.01 (ionized)		9.6 (total)	8.1-11.6 (t) 3.8-5.6(i)
PHOS				3.9	3.1-7.5
TP				6.1	5.4-7.9
ALB				3.1	2.6-3.9
GLOB				3.0	2.4-4.4
ALT			696	507	0-65
ALKP			Too high to read	2653	0-193

GGT				427	0-8
TBIL				0.0	0-0.5
Na+	157.6	153.2		146	138-146
K+	3.57	4.25		4.6	3.5-4.9
Cl-	130.9	125.9		111	98-109
ECO2	10.0	16.0		22	19-24
AGPK	17.1	12.2		18	10-20

HEMATOLOGY LAB CHART Kirby PAGE 3

Test	Date 3/15/10	Date 4/8/10	Date 4/21/10	Date 5/7/10	Reference
WBC	17.4	20.5	16.9	23.9	4.0-15.5
RBC	5.51	5.83	5.78	5.81	4.8-9.3
HGB	14.2	15.1	15.0	15.5	12.1-20.3
PCV	40.7	43.7	44.0	44.9	38-51
MCV	73.8	74.9	76.2	77.3	58-79
MCHC	34.9	34.6	34.0	34.5	30-38
PLAPROT					
PLATELET	700	602	534	691	170-400
SEGS	79	82	84	81	0-100
ABSONEUT	13746	16810	14190	19350	3000-11500
LYMPHS	2	1	3	2	0-100
ABLYMPH	348	205	510	480	1000-4800
MONOS	12	16	10	13	0-100
ABSMONO	2088	3280	1690	3110	150-1250
EOS	1	1	2	1	
ABSEOS	174	205	340	240	100-12500
NRBC	1	1			<5
BANDS	6			3	
ABSBANDS	1044			720	0-300

HEMATOLOGY LAB CHART Kirby PAGE 4

Test	Date 5/11/10	Date 5/25/10	Date	Date	Reference
WBC	16.1	16.4			4.0-15.5
RBC	5.72	5.76			4.8-9.3
HGB	14.9	15.2			12.1-20.3
PCV	43.5	43.6			38-51
MCV	76	75.7			58-79
MCHC	34.2	34.9			30-38
PLAPROT					
PLATELET	605	360			170-400
SEGS	80.2	78.1			0-100
ABSONEUT	13000	12830			3000-11500
LYMPHS	10.7	8.1			0-100
ABLYMPH	1700	1330			1000-4800
MONOS	9.1	11.4			0-100
ABSMONO	1400	1880			150-1250
EOS		2.2			
ABSEOS		370			100-12500
NRBC					<5
BANDS					
ABSBANDS					0-300

Additional laboratory work that was submitted by applicant is not included in this example case report (CSF analysis, serology *Toxoplasma gondii* and *Neospora caninum*, cryptococcal antigen).