

CASE REPORT #3

SIGNALMENT

Sophie, 4 yr old, female spayed, Standard Poodle.

HISTORY

Sophie presented to the Internal Medicine service at the Veterinary Emergency Clinic and Referral Centre on Oct 2, 2013 with a 2 day history of lethargy. She was seen by her referring veterinarian (RDVM) earlier the same day and was found to be weak and tachycardic (HR of 160bpm), with very pale/icteric mucous membranes (MM). They performed a CBC and serum biochemical profile. The CBC revealed a marked macrocytic anemia and a moderate leukocytosis with a neutrophilia^(see table). RBC morphology showed mild anisocytosis, mild hypochromasia, polychromatic cells, and spherocytes were noted. The biochemical profile showed elevated total bilirubin, conjugated bilirubin, and mild hypokalemia^(see table). A urinalysis had not been performed, however the owner reported that her urine was red in color. Her vaccinations were current and she had no travel history.

INITIAL PHYSICAL EXAM

Upon arrival, Sophie was dull. Her physical exam revealed: wt of 19.5kg, a body condition score (BCS) of 3/5 (lean/ideal), temperature (T) of 39.2C, HR of 160bpm with weak pulses, and a respiratory rate (RR) of 48bpm. She had pale, moist, slightly icteric MM. Lung sounds were normal on auscultation and a grade II/VI mid thoracic heart murmur was noted. No abnormalities were found on abdominal palpation.

PROBLEM LIST

Problem list included lethargy, anemia, and hyperbilirubinemia. Prognosis was guarded.

INITIAL DIAGNOSTICS AND RESULTS

Sophie was admitted for a workup that consisted of an abdominal ultrasound, thoracic radiographs, urine culture/sensitivity, and additional bloodwork including a slide agglutination test, blood typing and PCV/TP. An 18Gx2inch IV catheter was placed and Plasmalyte™ was started at a maintenance rate of 40ml/hr (50ml/kg/day). PCV was 12% (N=36-60), TP 7.0g/L (N=5.0-7.4), and a slide agglutination test was performed by placing one drop of EDTA whole blood on a microscope slide with one drop of 0.9% saline and was positive, showing marked agglutination grossly. An aFAST ultrasound was performed and no free fluid or obvious abnormalities were noted. A full abdominal ultrasound and thoracic radiographs were postponed due to the urgent need to stabilize Sophie.

A presumptive diagnosis of immune mediated hemolytic anemia (IMHA) was made and immunosuppressive therapy was initiated: dexamethasone 0.25mg/kg (4.9mg) IV q24h and azathioprine 2mg/kg (39mg calculated, however 50mg was prescribed) PO q24h. Dogs with IMHA have been shown to have a risk of developing DIC or thrombosis¹, so low dose aspirin therapy was also started at 0.5mg/kg (10mg) PO q 24h.

Blood typing was performed utilizing a RapidVet™ testing kit – result: DEA 1.1 negative. A full unit of DEA 1.1 negative packed red blood cells (pRBCs) was obtained and mixed well. The bag was aseptically punctured with a blood filter drip set and a small sample was collected for a PCV. The volume required to double the PCV was calculated using the formula $85 \times \text{wt (kg)} \times (\text{desired change in PCV}/\text{donor PCV})$. The desired PCV was 24% (double original PCV) and donor PCV was 78%, therefore the volume to be delivered was 255ml. Since

most pRBC units contain a volume of approximately 200ml, the decision was made to administer the entire bag and then reassess the patient to determine whether more was required. In addition to the TPR at admission, a baseline BP was taken and was 120/76 MAP 97. A test dose of pRBCs at a rate of 0.25ml/kg/hr (4.9ml/hr) was administered for 15 minutes. Sophie's vitals were unchanged at that point so the transfusion rate was increased to 50ml/hr to allow the total volume to be administered over 4 hours. Vitals were checked at 15min, 30min, 1hr, 2hr, 3hr, and upon completion of transfusion. Vitals were monitored closely due to the risk of acute transfusion reaction - clinical signs of which include: pyrexia, vomiting, urticaria, tachycardia, hypertension, and collapse². Sophie did not exhibit any of these clinical signs. Her HR, RR, and T had all improved by the completion of the transfusion (120bpm, 24bpm, and 38.7C respectively). A PCV was then performed and was 25% so another unit was not administered.

An abdominal ultrasound was performed and revealed a slightly enlarged, hyperechoic spleen with no other abnormalities. Thoracic radiographs were normal. Urine was collected and sent for a culture and sensitivity.

Sophie had an uneventful night and in the morning she was quiet, alert and responsive (QAR). Her wt was 19.8kg. She had passed red-tinged urine twice overnight, no bowel movements (BM), and had not vomited. Her vitals were: BP 150/69 MAP 117, T=38.3°C, HR=114bpm, RR=panting, heart and lung sounds were normal, good pulse quality, and MM were icteric/pink and moist. She had eaten a small amount of canned dog food and had consumed a normal volume of water. A blood sample was taken for PCV/TP (19%/7.0g/dL), and electrolytes^(see table) which revealed hypokalemia, so 30mEq/L (15ml of 2mEq/ml in 1L) of

potassium chloride was added to her IV fluids. Her vitals were monitored closely throughout the day and remained stable. A PCV was performed in the evening and was 18%.

The following morning, she was QAR. Her wt was 19.9kg. She had passed amber urine three times overnight, no BM, and had not vomited. Her vitals were: BP 154/81 MAP 103, T=38.9°C, HR=132bpm, RR=40, heart and lung sounds normal, good pulse quality, and MM were icteric/pale pink and moist. She had eaten well. A blood sample was taken for CBC^(see table), PCV/TP (14%/6.2g/dL), and electrolytes^(see table). Due to the progression of her anemia, a second pRBC transfusion was performed utilizing the same procedure listed above. A crossmatch was not required as it had only been 48 hours since the initial transfusion. Dogs do not have naturally acquired antibodies against blood group antigens³; they acquire them 72hrs+ post transfusion, or after pregnancy, and Sophie had never had a litter. The pRBC transfusion was uneventful and her PCV was 26% at completion. The final urine culture results were reported with no growth.

The following morning, she was bright, alert and responsive (BAR). Her wt was 19.4kg. She had passed dark yellow urine twice overnight, one normal BM, and had not vomited. Her vitals were: BP 142/75 MAP 95, T=38.6°C, HR=102bpm, RR=28, heart and lung sounds normal, good pulse quality, and MM were slightly icteric/pink and moist. She had eaten well. A blood sample was taken for PCV/TP (29%/7.2g/dL), and electrolytes^(see table). Her vitals were monitored closely throughout the day and remained stable. A PCV was performed in the evening and was 28%.

The following morning, she was BAR. Her wt was 19.6kg. She had passed normal colored urine four times overnight, one normal BM, and had not vomited. She was drinking

water well and had eaten two meals. Her vitals were: BP 140/80 MAP 91, T=38.2°C, HR=100bpm, RR=24, heart and lung sounds normal, good pulse quality, and MM were pink and moist. A blood sample was taken for PCV/TP (32%/7.0g/dL), and electrolytes^(see table). Her IV fluids were discontinued and she was discharged to the owner later that day with prednisone 37.5mg PO q24h, azathioprine 40mg PO q24h for 5 days, then 20mg PO q24h thereafter, and aspirin 10mg PO q24h . The owner was educated on how to monitor MM color and HR/pulse quality.

FOLLOWUP EXAMINATIONS

Sophie returned for a recheck 4 days later. On physical exam, she was BAR. Her physical exam revealed: a wt of 19.2kg, a BCS of 3/5, normal T of 38.2C, HR of 100bpm, RR of 20bpm, MM pink and moist, and heart and lung sounds normal on auscultation. Her icterus had resolved completely. The owner reported that her energy level had greatly improved, she was eating well, and she was polyuric and polydipsic due to the prednisone. Blood was collected and sent for CBC and total bilirubin. The CBC revealed a persistent macrocytic regenerative anemia, with spherocytes still noted on RBC morphology^(see table). PCV was 31%, TP 7.0g/dL. Tbili was improved but still elevated. Medication instructions were unchanged and a recheck was recommended in two weeks. The owner decided to continue follow-up care with their RDVM , and two weeks later we received an update stating that she was doing very well. Her PCV was 42% and bilirubin was normal. The RDVM was to prescribe a gradually decreasing dose of the immunosuppressive medications.

DISCUSSION OF CASE

IMHA is a hematologic disease characterized by destruction of RBCs. It can occur at any age, but is most commonly seen in young adults to middle aged dogs. Females appear to be slightly more predisposed than males, and a genetic predisposition is evident in some dogs by familial occurrence and breed predilection. American Cocker Spaniels represent approximately one third of all dogs with IMHA. Other commonly affected breeds include the English Springer Spaniel, Old English Sheepdog, Irish Setter, Poodle, and Daschund⁴. Clinical signs often include and acute onset of lethargy, weakness, exercise intolerance, pale MM, and icterus. Physical exam findings usually include pallor (with or without icterus), tachycardia, splenomegaly, and a heart murmur.⁵ The disease can be either primary or secondary, and either extravascular or intravascular. When no underlying cause is identified, the condition was historically classified as primary or idiopathic; in more intense clinical investigations, however, an underlying trigger or disease process could be identified, including recent vaccination, drug exposures, neoplasia, bee stings, infections, or other immune disorders⁶, thereby classifying the condition as possibly secondary to these events. In IMHA, the RBCs become coated with immunoglobulin G (IgG) and IgM antibodies, which causes their extravascular removal in the mononuclear phagocytic system primarily in the spleen. RBCs may be completely destroyed, or phagocytes may only remove a portion of their membrane, resulting in a cell with a reduced surface area/volume ratio. This deformed cell is known as a spherocyte. Intravascular hemolysis occurs when RBCs that are heavily coated with IgG activate the complement system, causing lysis and release of free hemoglobin into the bloodstream. The released hemoglobin will cross the glomerulus and cause hemoglobinuria.

Hematologic findings usually reveal a regenerative macrocytic anemia with the presence of spherocytes, polychromasia, and nucleated RBCs. There is also commonly a leukocytosis with a neutrophilia due to the activation of bone marrow production. RBC autoagglutination is a common finding, and when coupled with polychromasia and spherocytosis, is considered pathognomonic for IMHA. In dogs that do not present with these classic findings, a direct Coombs' test can be performed to detect Ig on the RBC membrane. This test, however, is negative in 10-30% of dogs with IMHA, so a false negative result is a possibility.⁷ Hemoglobinemia and hemoglobinuria are observed in patients with intravascular hemolysis, but not extravascular hemolysis. Hyperbilirubinemia and bilirubinuria can be present in both intra and extravascular IMHA due to the by-products generated from RBC degradation.

The goal in the treatment of IMHA is to suppress the immune response by reducing antierythrocyte antibody production, complement activation, and phagocytosis. Glucocorticosteroids are the initial treatment of choice as they immediately impair the destruction of the IgG and IgM coated RBCs by interfering with the receptors on the macrophages. Glucocorticosteroids may also minimize the degree of complement activation and antibody binding on the RBCs and also eventually decrease the production of autoantibodies.⁸ A response should be seen within a week, however, the full therapeutic benefit may not be seen until 2-4 weeks after treatment is begun. Once the dog's condition is stable, treatment is slowly tapered over a 3-6 month period. Slow tapering is mandatory as rapid drug withdrawal often leads to a relapse, which is much harder to control. Glucocorticosteroid therapy can be totally stopped only if a dog has remained stable (with no relapses) for 6 months. Dogs that relapse will need cortisone therapy for life. Azathioprine is another immunosuppressive drug that is

often used in combination with glucocorticosteroids in the treatment of IMHA. The use of azathioprine is a controversial subject. Some specialists advocate starting it when treatment is begun because the drug can take weeks to reach therapeutic levels, while others choose to wait and see if glucocorticosteroids alone will work. Azathioprine is not a benign drug and can cause severe bone marrow suppression and liver damage. Therefore, the decision to add azathioprine depends on the judgment of the individual veterinarian. The dose is tapered gradually, as with the glucocorticosteroids, once the dog is stable. Aggressive supportive care is also indicated while immunosuppressive therapies are being initiated. Severely anemic patients require blood transfusions to prevent organ damage or even death due to hypoxia, and dogs with secondary IMHA will require additional therapies to deal with the associated underlying cause. All affected dogs are at risk for developing DIC or thrombosis because of immune mediated interference with normal clotting function, therefore, anticoagulants are often prescribed, such as ultra low dose aspirin. In extreme cases, dogs with extravascular hemolysis who either don't respond to therapy, or cannot tolerate it, may require a splenectomy.⁹

The prognosis for dogs with IMHA is variable and even with aggressive supportive and immunosuppressive therapy, the mortality rate is high, ranging from 20-75%. Negative prognostic indicators include elevated serum bilirubin, non-regenerative anemia, thromboemboli, intravascular hemolysis, persistent autoagglutination, and a rapid decrease in PCV.¹⁰ Dogs fortunate enough to survive may be at risk of developing other immune mediated disease later in life. Vaccination should probably be avoided in recovering dogs, even though a definitive association has not been proven. Instead, vaccine titers should be used to monitor immunity.

CASE LOG #3
, RVT
Internal Medicine (SAIM)
PATIENT: Sophie Giancola154788
SEEN: Oct 2-6, 10/2013

<u>TEST</u>	<u>RDVM Initial Presentation Oct 2/12</u>	<u>OCT 2/12 Admission</u>	<u>Oct 3/12</u>	<u>Oct 4/12</u>	<u>Oct 5/12</u>	<u>Oct 6/12</u>	<u>Oct 10/12</u>	<u>Oct 24/12 RDVM</u>
WBC (4.0-15.5x10 ⁹ /L)	23.0			20.1				
RBC (4.8-9.310 ⁹ /L)	2.1			1.6				
Hemoglobin (121-203g/L)	53			40				
Hematocrit (36-60%)	17			14				
MCV (58-77fL)	80			88				
MCH (19-28pg)	25			25				
MCHC (320-380g/L)	313			286				
Platelet Count (170-400x10 ⁹ /L)	171			180				
Neutrophils (2.06-10.6x10 ⁹ /L)	20.7			17.09				
Bands (0-0.3x10 ⁹ /L)	0			0.2				
Lymphs (0.69-4.5x10 ⁹ /L)	0.7			2.01				
Monocytes (0-0.84x10 ⁹ /L)	0.8			0.8				
Eosinophils (0-1.2x10 ⁹ /L)	0.2			0				
Basophils (0-0.15x10 ⁹ /L)	0			0				
Hypochromasia	Mild			Moderate				
Anisocytosis	Mild			Moderate				
Spherocytes	Noted			Noted				
Polychromasia	2-5/hpf							
NRBC (0-1/100WBC)	3			4				
Reticulocytes (0-1%)				14.7				
Absolute Retics (<60x10 ⁹ /L)				235				
Total Bilirubin (0-5.1umol/L)	58.4						25	5.0
Conj Bilirubin (0-2.0umol/L)	12.3							
PCV%/TPg/dL (36-60/5.0-7.4)	17/5.7	12/7.0	19/7.0	14/6.2	29/7.2			42/unknown
Potassium (3.7-5.7mmol/L)	3.5		3.3	3.9	4.6	4.5		
Weight (kg)		19.5	19.8	19.9	19.4	19.6	19.2	

¹Giger,Urs., Section XIX, Chapter 270, Hematology and Immunology, Regenerative Anemias Caused by Blood Loss or Hemolysis, in **Textbook of Veterinary Internal Medicine; Diseases of the Dog and Cat, Sixth Edition; Volume II**, Ettinger, Stephen J and Feldman, Edward C., Elsevier Saunders, St. Louis, Missouri, 2005 Pg. 1898

² Cuoto, C. Guillermo, Part XII Chapter 85, Hematology and Immunology - Anemia, in **Small Animal Internal Medicine, Third Edition**, Mosby, St. Louis, Missouri, 2003 Pg. 1169

³ Cuoto, C. Guillermo, Part XII Chapter 85, Hematology and Immunology - Anemia, in **Small Animal Internal Medicine, Third Edition**, Mosby, St. Louis, Missouri, 2003 Pg. 1168

⁴Giger,Urs., Section XIX, Chapter 270, Hematology and Immunology, Regenerative Anemias Caused by Blood Loss or Hemolysis, in **Textbook of Veterinary Internal Medicine; Diseases of the Dog and Cat, Sixth Edition; Volume II**, Ettinger, Stephen J and Feldman, Edward C., Elsevier Saunders, St. Louis, Missouri, 2005 Pg. 1897

⁵ Cuoto, C. Guillermo, Part XII Chapter 85, Hematology and Immunology - Anemia, in **Small Animal Internal Medicine, Third Edition**, Mosby, St. Louis, Missouri, 2003 Pg. 1162

⁶ Giger,Urs., Section XIX, Chapter 270, Hematology and Immunology, Regenerative Anemias Caused by Blood Loss or Hemolysis, in **Textbook of Veterinary Internal Medicine; Diseases of the Dog and Cat, Sixth Edition; Volume II**, Ettinger, Stephen J and Feldman, Edward C., Elsevier Saunders, St. Louis, Missouri, 2005 Pg. 1896

⁷ Cuoto, C. Guillermo, Part XII Chapter 85, Hematology and Immunology - Anemia, in **Small Animal Internal Medicine, Third Edition**, Mosby, St. Louis, Missouri, 2003 Pg. 1162

⁸ Giger,Urs., Section XIX, Chapter 270, Hematology and Immunology, Regenerative Anemias Caused by Blood Loss or Hemolysis, in **Textbook of Veterinary Internal Medicine; Diseases of the Dog and Cat, Sixth Edition; Volume II**, Ettinger, Stephen J and Feldman, Edward C., Elsevier Saunders, St. Louis, Missouri, 2005 Pg. 1900

⁹ Giger,Urs., Section XIX, Chapter 270, Hematology and Immunology, Regenerative Anemias Caused by Blood Loss or Hemolysis, in **Textbook of Veterinary Internal Medicine; Diseases of the Dog and Cat, Sixth Edition; Volume II**, Ettinger, Stephen J and Feldman, Edward C., Elsevier Saunders, St. Louis, Missouri, 2005 Pg. 1901

¹⁰Giger,Urs., Section XIX, Chapter 270, Hematology and Immunology, Regenerative Anemias Caused by Blood Loss or Hemolysis, in **Textbook of Veterinary Internal Medicine; Diseases of the Dog and Cat, Sixth Edition; Volume II**, Ettinger, Stephen J and Feldman, Edward C., Elsevier Saunders, St. Louis, Missouri, 2005 Pg. 1901