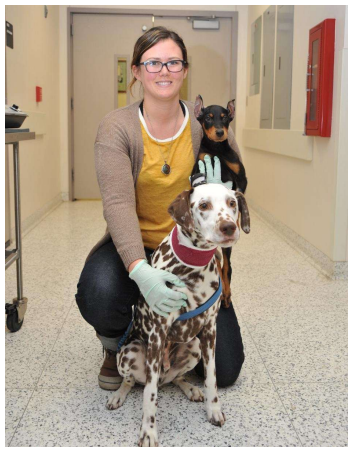
Von Willebrand's Disease (vWD)

vWD is characterized by a deficiency of von Willebrand factor (vWF) in the blood. wWF is a glycoprotein involved in primary hemostasis due to its role in "gluing" platelets, fibrin and endothelial cells together. vWF glycoproteins polymerize into multimers of different lengths -- the longer the multimer, the more effective it is in hemostasis. The three types of vWD are differentiated by the multimers that are diminished or absent.

- **Type I**: a deficiency in all sizes of vWF multimers, most common in dogs, rare in cats, clinical signs vary depending on the breed
- **Type II**: due to a relative decrease in high molecular weight (large) multimers, more severe than type I, reported in dogs and horses
- **Type III**: due to a near complete absence of vWF, reported in dogs, cats, pigs and monkeys, inherited as an autosomal recessive trait; most severe

OUR CASE - RIGBY

Rigby, a 16-week old intact male Doberman Pinscher presented with unresolved gingival bleeding for a duration of ~3 weeks. On intake, Rigby was BAR and physical examination revealed mild gingival bleeding from small lacerations and erupting premolars, pale mucus membranes, submandibular lymphadenopathy, a distended abdomen, and melena. A CBC and Chemistry panel was performed, revealing an anemia, increased ALT and ALP, hypoalbuminemia, hyperglobulinemia and mild thrombocytopenia while the BMBT showed a prolonged clotting time of 6 minutes. Overnight, the patient's PCV dropped from 17% to 15% and he became lethargic, although he was still alert and responsive. The next morning his lymphadenopathy had progressed to multicentric. A 4DX SNAP test was positive for *E. Cani* / *E. ewingii* and the vWF:Ag test was positive for vWD and a transfusion was performed. Due to the signs, symptoms and test results, we diagnosed Rigby with Ehrlichiosis with concurrent underlying von Willebrand's Disease. Rigby was discharged the day after his transfusion though he will continue to be monitored closely.



CLINICAL SIGNS

Physical exam findings include hemorrhage from mucosal surfaces, prolonged bleeding after surgery or trauma, and blood loss anemia from abnormal hemorrhage.

DIAGNOSIS

vWF:Ag assay -- tests amount of vWF compared to antibody in the blood

Genetic test -- screens for genetic markers associated with vWD (not all dogs with clinical signs have a positive genetic test, as other genes may be involved for some animals).

TREATMENT

Treatment is as needed and includes desmopressin acetate and plasma transfusion. Desmopressin acetate (DDAVP) can be administered to increase vWF levels in the blood; however, it is not effective in type III vWD because those animals lack intracellular stores. Plasma transfusions (fresh, fresh frozen, or cryoprecipitate) can also be used as they contain vWF. Cryoprecipitate is more beneficial than plasma in times of hemorrhage because plasma does not contain sufficient vWF to stop hemorrhage. In general, either DDAVP or a plasma product is used preoperatively to reduce bleeding during surgery.

PATHOGENESIS

Von Willebrand's disease (vWD) is a blood disease caused by a deficiency of von Willebrand Factor (vWF), an adhesive glycoprotein in the blood required for normal platelet binding (i.e., clotting) at the sites of small blood vessel injuries. In addition, vWF is a carrier protein for coagulation Factor VIII (necessary for blood to clot). A lack of vWF impairs platelet stickiness and clumping. Similar to hemophilia in humans, this condition can lead to excessive bleeding following an injury, due to the lack of clotting.

PATHOPHYSIOLOGY

vWF is a glycoprotein which exists in chains of varying lengths; the longer multimers are more effective in hemostasis, and therefore deficiencies of the longer multimers produces more severe bleeding. vWF is produced in endothelial cells and megakaryocytes. vWF serves to "glue" the platelets, endothelium and fibrin together to form to initial plug before secondary hemostasis forms a clot. There are multiple breed predilections associated with vWD, including the Doberman Pinscher. There are three types of classifications found in dogs. Type 1 demonstrates mild to moderate signs and has a quantitative protein deficiency. In type 2, there are severe signs where there is a quantitative and functional protein defect, and typically see a low vWF:Ag. Lastly, in type 3 there are severe signs and a complete lack of plasma vWF.

DIFFERENTIAL DIAGNOSES

- von Willebrand's disease
- Thrombocytopenia
- Acquired coagulation factor deficiency
- Hereditary coagulation factor deficiencies
- Hereditary platelet function defects

CANINE BLOOD TYPING

The clinically relevant dog blood types in Doberman Pinschers involve DEA (dog erythrocyte antigens) 1.1, 1.2, and 4, and Dal. DEA 1.1 and 1.2 are the antigens of clinical importance in all dogs -- as they are the only source of acute hemolytic reaction. However, more specific to Doberman Pinschers, approximately 98% of dogs are positive for DEA 4, while 25% of Dobermans are negative, creating a transfusion dilemma. Similarly, most dogs have the Dal antigen, while 39% of Dobermans lack it. In Rigby's case, it is likely that he was lacking either DEA 4, Dal or both, and due to his previous transfusion, was sensitized creating incompatibilities with the original dogs tested.

Ehrlichiosis

Ehrlichiosis canis is a gram negative bacterium transmitted to hosts by the brown dog tick which is a biological vector for the pathogen. *E. canis* is an obligate intracellular parasitic pathogen that can remain in the tick's gut and saliva and then be transmitted during a blood meal. Animals infected with this can have an acute, subclinical, or chronic infection with no sign of infection or variable clinical signs.

CLINICAL SIGNS

ACUTE

- Anemia
- Thrombocytopenia
- Leukopenia
- Morulae in monocytes or granulocytes
- Increases in ALT, ALP, BUN, creatinine, and rarely bilirubin
- Hypoalbuminemia (usually lost in the urine)
- Progressive hyperglobulinemia
- Proteinuria

CHRONIC

- Pancytopenia with monocytosis/lymphocytosis
- Progressive hyperglobulinemia
- Hypoalbuminemia
- Azotemia from primary renal disease

DIAGNOSIS

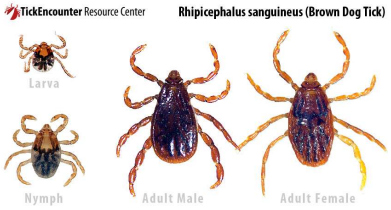
Indirect tests include 4DX SNAP test and serology. Direct tests include PCR using blood or tissue aspirates (spleen, lymph nodes, or bone marrow), FAT, and cytology.

TREATMENT

A Tetracycline antibiotic treatment for a minimum of 28 days is used to clear the infection. Fluid therapy and blood transfusions are indicated in more severe infections. In cases with a severe thrombocytopenia, glucocorticoids can be administered to prevent immune mediated destruction of thrombocytes. In chronic infections where hypoplastic marrow is seen, androgenic steroids can be given to stimulate bone marrow production.

PATHOGENESIS/PATHOPHYSIOLOGY

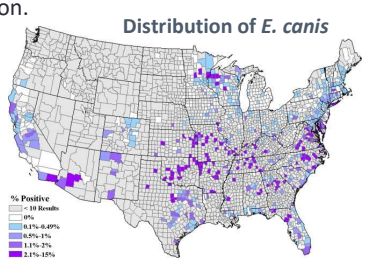
The tick contracts *Ehrlichia canis* when biting an infected host. The tick acts as a biological vector where the pathogen can persist for 155 days, transmitting it to new hosts in the tick's saliva during a blood meal. As a new host is infected *E. canis* enters the host's monocytes and macrophages via receptor mediated endocytosis. Phago-lysosome fusion is prevented allowing the bacteria to persist within host cells. *E. canis* continues to replicate intracellularly before lysing cells and infecting new ones. An infection can produce lymphadenomegaly, splenomegaly, and hepatomegaly via chronic antigen stimulation and cellular infiltration. In addition to organ enlargement, chronic antigen stimulation and inflammation can cause hyperglobulinemia. Hypoalbuminemia can be caused by immune complex deposition in the glomerulus from chronic antigen stimulation allowing albumin to be lost in the urine, or by third space loss from vasculitis. Ehrlichia also causes anemia in hosts as it leads to bone marrow suppression while vasculitis can allow further blood loss to occur.



PREVENTION

The best way to prevent infection is implementation of a routine tick preventative such as a collar, topical, or oral treatment. Yard sprays that eliminate ticks can also aid in parasite control but they are not a substitute for a preventative medication.

If a tick is found on an animal it needs to be removed carefully using proper technique while wearing gloves.



PUBLIC HEALTH

While it is possible for humans to contract both Ehrlichia pathogens, there has been no evidence to prove direct transmission from dog to human. A person with Ehrlichiosis would have contracted it through a tick vector the same way a dog would be infected.

DIFFERENTIAL DIAGNOSES

- Rocky Mountain Spotted fever
- Immune-mediated thrombocytopenia
- Systemic lupus erythematosus
- Multiple myeloma
- Chronic lymphocytic leukemia
- Brucellosis

Bartsch, R. C. and Greene, R. T. (1996), Post-Therapy Antibody Titers in Dogs With Ehrlichiosis: Follow-Up Study on 68 Patients Treated Primarily With Tetracycline and/or Doxycycline. Journal of Veterinary Internal Medicine, 10: 271–274. doi:10.1111/j.1939-1676.1996.tb02061.

Thomas, J.S. 1996. Von Willebrand's Disease in the Dog and Cat. *Veterinary Clinics of North America: Small Animal Practice,* 26(5), pgs 1089-1110.

JACKS VETERINARY CLINIC

DR. JESSIE COSSEL
DR. ALLIE JOHNSTON
DR. CHARLOTTE DONNAN
DR. KIM MENKE
DR. STOREY DESHAZO