A Clinical Approach to Disorders of Primary Hemostasis

Linda Kidd, DVM, PhD, DACVIM
Western University College of Veterinary Medicine
Pomona, CA

Primary hemostasis refers to the formation of the platelet plug, while secondary hemostasis refers to activation of the coagulation cascade and the formation of a fibrin network. This separation of primary and secondary hemostasis is a bit artificial as recent in vivo studies using animal models suggest that during normal hemostasis, activation of coagulation and platelets occurs simultaneously, and cells, including platelets, are intimately involved in initiating and sustaining the process of secondary hemostasis. However, it is clinically useful to separate hemostasis into these two stages because disorders of primary and secondary hemostasis have distinct clinical presentations. Considering the clinical presentation and results of diagnostic testing helps the clinician limit differential diagnoses when this division is kept in mind.

Primary hemostasis is initiated when endothelial damage results in exposure of subendothelial collagen. Platelet adhesion and aggregation is facilitated by von Willebrands factor. From a clinical standpoint, the three key players in primary hemostasis are platelets, vonWillebrands factor, and endothelium. Most disorders of primary hemostasis can be attributed to deficiency or dysfunction of one or a combination of these components of primary hemostasis. These may include thrombocytopenia, thrombocytopathia, von Willebrands disease (vWd) and/or vasculitis.

Generally speaking, clinical signs of disorders of primary hemostasis include evidence of "superficial bleeding". Bleeding from mucosal surfaces such as the nasal mucosa (epistaxis), petechiation and ecchymosis of the skin and mucosal surfaces such as the gums and vulva are evidence of a disorder of primary hemostasis. This is in contrast to disorders of secondary hemostasis or coagulation that usually present with evidence of "deep bleeding". Hemarthrosis, bleeding into the peritoneal cavity, lungs, and mediastinum may be observed in patients with disorders of secondary hemostasis. Clinical presentation doesn't always provide a clue as to whether a bleeding disorder is due to a defect in primary or secondary hemostasis however. For example, bleeding in to the gastrointestinal tract or the urinary bladder and bruising or ecchymosis can be associated with disorders of primary or secondary hemostasis and dogs with coagulopathies can present with epistaxis.

Platelet disorders can attributed to thrombocytopenia or thrombocytopathia. Thrombocytopenia is commonly categorized as being due to decreased production, destruction, use, or sequestration. Examples of thrombocytopenia secondary to decreased production include primary bone marrow disorders such as infiltrative neoplasia, chronic ehrlichiosis, immune mediated disease or estrogen toxicity. Destruction of mature platelets can be caused by immune mediated thrombocytopenia (ITP). ITP is a common cause of thrombocytopenia in dogs. Immune mediated thrombocytopenia may be primary (idiopathic), or secondary to an underlying infection, neoplasia, drug administration or other inciting events. Thrombocytopenia due to platelet use can be attributed to hemorrhage or DIC. Platelets can be sequestered in the spleen or during vasculitis.

The magnitude of thrombocytopenia can provide clues as to which of these categorizations are responsible for the decrease in platelet count and also whether inadequate hemostasis in a patient can be attributed to thrombocytopenia. For example, most patients with ITP or bone marrow disease have markedly decreased platelet counts, whereas thrombocytopenia due to hemorrhage is usually milder. Platelet counts have to be moderately to markedly decreased to cause signs of inadequate hemostasis, usually less than 50,000/uL. This fact can be useful from a diagnostic standpoint. For example, in a dog presenting for evaluation of epistaxis, if the platelet count is 120,000/uL then thrombocytopenia alone is not responsible for the epistaxis but rather the thrombocytopenia is more likely a result of epistaxis. That said, some diseases can affect multiple components of primary hemostasis. For example, *Ehrlichia canis* infection is associated with antiplatelet antibody production, platelet dysfunction and vasculitis. Therefore, the clinician should keep in mind that vasculitis and thrombocytopathia could contribute to the clinical manifestation of petechiation or epistaxis in a patient with mild thrombocytopenia.

Thrombocytopathia can be due to metabolic disease such as uremia and hyperglobulinemia or liver dysfunction. Drug administration or inherited disorders of platelet function can also cause platelet dysfunction. Inherited disorders of platelet dysfunction are rare in dogs, but several have been described.

von Willebrands disease is an inherited disorder of primary hemostasis that is relatively common in dogs. Often there is no history of bleeding in dogs with vWd, but rather bleeding develops after trauma or a surgical procedure. In a recent study of dogs with vWd, the most frequent hemorrhagic sign observed was bleeding from the oral cavity, including bleeding during tooth eruption, spontaneous bleeding of the gingiva, bleeding of the gingiva after brushing the teeth or chewing a toy or bone, excessive bleeding after tooth extraction, or after bites to the lip or tongue. The second most frequent hemorrhagic sign, was bleeding from minor wounds, followed by excessive surgical bleeding, cutaneous hematomas or bruising and epistaxis. Excessive estral bleeding and urinary bleeding were not common. Interestingly, petechiation is not a feature of vWd in dogs like other disorders of primary hemostasis.

There are three types of vWd disease in dogs, types 1, 2 and 3. Type 1 is the most common. Variably decreased amounts of VWF Ag levels with a normal distribution of multimers characterizes this type of vWd. Doberman pinschers and other breeds have Type 1 vWd. Type 2 is characterized by decreased amounts of large, more hemostatically active monomers, and variably decreased amounts

of total von Wilebrands factor antigen. German shorthaired pointers and German wirehaired pointers have an inherited form of this type of vWd. Type 3 is characterized by an absence of von Willebrands factor. Type 3 vWd has been described in Shetland sheepdogs Dutch Kooikers and other breeds.

Vasculitis is associated with many infectious, neoplastic, inflammatory and immune mediated diseases. Dramatic manifestations of vasculitis can be seen in dogs infected with *Rickettsia rickettsii.* This organism infects endothelial cells and therefore most of the clinicial signs of infection are characterized by vasculitis. Other rickettsial diseases such as ehrlichiosis and leishmaniasis have been also associated with vasculitis. Systemic infection or inflammation such as endocarditis, SIRS, sepsis or DIC may also be associated with vasculitis and result in petechiation and disordered primary and secondary hemostasis.

Initial diagnostic testing in the assessment of a dog presenting with evidence of a bleeding disorder includes a platelet count, PT and aPTT. In patients with a disorder of primary hemostasis, PT and PTT will be normal. The automated platelet count should always be verified with a manual count as platelet clumping interferes with automated analyzers.

In a patient with a platelet count that is normal further testing of primary hemostasis is accomplished by performing the buccal mucosal bleeding time (BMBT). Prolongation of the BMBT in a dog with a normal platelet count suggests that vWd, vasculitis, or thrombocytopathia may be the cause of abnormal bleeding. Other clinical signs usually signal when vasculitis is a likely differential. Von willebrands factor antigen assays can help determine if a patient is bleeding due to Type 1 or Type 3 vWd. Because the antigen assay is quantitative, Type 2 vWD cannot be diagnosed using this test alone, but rather it can be combined with collagen binding activity assays that measure von Willebrands factor binding. Some laboratories can also determine the distribution of multimers. Genetic testing is also available for vWd. Advanced platelet function testing for platelet function defects is available at specialized laboratories.

References

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