DIAGNOSIS AND TREATMENT OF IMMUNE-MEDIATED THROMBOCYTOPENIA

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Thrombocytopenia is a common disorder in small animals. There are several causes, which can be grouped into four categories. These are accelerated platelet destruction, decreased production, increased consumption, and sequestration. Specific disorders in each category are listed in Table 1. Of the causes of thrombocytopenia in which the platelet counts are less than 30,000/ul, immune-mediated thrombocytopenia (IMT),disseminated intravascular coagulopathy, and bone marrow disorders are most common.

Immune-mediated thrombocytopenia can be a life-threatening immunohematologic disease. The pathophysiologic basis for IMT is a type II hypersensitivity reaction, also called a "cytotoxic reaction". The mediators of a type II reaction are lymphocytes, phagocytic cells, complement, and IgG/IgM. Complement mediated lysis occurs when the surface of the target cell (the platelet) is covered with sufficient types and amounts of antibody and complement to result in activation of complement and finally cellular lysis. Antibody/complement coated platelets can also be removed by phagocytosis by the mononuclear phagocytic system. This mechanism is probably most important in IMT.

As with other primary immune-mediated diseases, genetic and environmental factors probably play a role in the development of the disease in individual animals. The fact that certain breeds and, indeed, families of dogs within a breed, acquire the disorder suggests that a genetic component is important. In humans with IMT, identification of shared major histocompatibility antigens and chromosomal defects supports a genetic basis for the disease. Environmental factors such as physical or emotional stress, exposure to drugs or chemicals, and exposure to infectious agents can act as triggers to set off a reaction against self-antigens.

Immune-mediated thrombocytopenia can occur alone or with other disorders such as immune-mediated hemolytic anemia, systemic lupus erythematosus, neoplasia, and infectious diseases. When it occurs alone or with IMHA or SLE, it is called primary IMT as the mechanism is true autoimmunity. Neoplasia and infectious diseases can cause secondary IMT, in which platelets are destroyed as innocent bystanders in an immune response against foreign antigens.

Immune-mediated thrombocytopenia results in dangerously low platelet numbers and consequently a coagulopathy. The disease presentation is typically acute in nature but chronic, almost sub-clinical forms are also seen. The typical signalment of affected animals is the young to middle aged female dog. The median age of affected dogs is 6 years. Females outnumber males almost 2:1. Cocker Spaniels, Poodles and Old English Sheepdogs have been reported to be represented more frequently than other breeds.

The most common historical findings include an acute onset of lethargy, weakness, decreased appetite, and various signs of coagulopathy such as epistaxis,

melena, or hematuria; GI hemorrhage can be severe! Episodes of IMT may be preceded by a stress such as surgery, boarding, or estrus.

Physical examination can reveal active bleeding or mucosal and/or cutaneous petechiation. Epistaxis, hematemesis, melena, hyphema, or retinal hemorrhages may also be noted. If bleeding has been severe, pale mucous membranes are seen. Fever, lymphadenopathy, hepatosplenomegaly are also identified in some patients.

The diagnosis of IMT is one of ruling out all other possible causes initially (see Table 1). The complete blood count confirms thrombocytopenia (usually < 50,000 and oftentimes < 5000). Platelets can also be estimated off of a blood smear, if clumping is absent. One platelet per oil power field equals approximately 15,000 platelets/ul. Platelet morphology is often abnormal in that megathrombocytes (young platelets) and platelet fragments or microthrombocytes are often present. Anemia may be present secondary to blood loss or IMHA. About 20% of dogs with IMT also have IMHA, in which case spherocytes may also be identified. Usually the anemia is regenerative unless it is very acute. An inflammatory leukogram, i.e., neutrophilia with a left shift, may also be noted.

There are no pathognomonic changes on the serum chemistry panel. Hyperglobulinemia may be seen with IMT or with thrombocytopenia secondary to infectious or neoplastic causes. Hypoxia due to severe anemia may lead to non-specific elevations in liver enzymes. If anorexia has been a significant part of the history, then pre-renal azotemia may also be noted.

The urinalysis may not be helpful in the diagnosis of IMT, however, it is important in ruling out other diseases. Hematuria may be the only abnormal finding on the urinalysis from the dog with uncomplicated IMT. Significant proteinuria in the absence of an active urine sediment may be indicative of other diseases such as SLE. Bacturia and pyuria may be seen with urinary tract infections or bacterial endocarditis. Because bacteremia can cause throbocytopenia, a urinalysis is extremely important in the diagnostic work-up. A urine culture and antibiotic sensitivity should be done and appropriate antibiotic treatment started.

Specific tests for IMT are not readily available. An enzyme-linked immunosorbent assay (ELISA) has been developed for the detection of antiplatelet antibodies. It is quite sensitive (90%) for the presence of antibodies, however, is not necessarily specific for IMT. An alternative test is the megakaryocyte immunofluorescence assay, which detects the presence of antibodies on the megakaryocyte surface. Again, the specificity of this test in cases of IMT is unknown.

An antinuclear antibody test is useful in the diagnosis of IMT if it is a component of SLE. A positive test may offer a poor prognostic sign for future control of the thrombocytopenia. A Coomb's test may be positive if IMHA is present concurrently. Bone marrow examination is not contraindicated and may be helpful in the diagnosis of IMT. Twenty to 33% of dogs with IMT may have reduced numbers of megakaryocytes in the bone marrow. Although one study suggested this is a poor prognostic indicator, larger studies need to be completed to support this. Increased

numbers of plasma cells can be seen in the bone marrow of dogs with certain disorders associated with thrombocytopenia, such as ehrlichiosis and neoplasia. Depending on the location and time of year, Ehrlichia and Rocky Mountain Spotted Fever titers are an important part of the diagnostic work-up of IMT. It is crucial to rule out these infectious diseases as the treatment is different than IMT. Although a clotting profile is not usually necessary to make the diagnosis of IMT, it can provide additional information that may support the diagnosis of another disease such as disseminated intravascular coagulopathy as a cause of the thrombocytopenia.

The therapy of IMT is primarily immunosuppressive dosages of glucocorticoids. A dose of 2mg prednisone or prednisolone/kg PO BID is recommended initially. The majority of dogs with IMT in the author's experience are very steroid responsive so other immunosuppressive agents are not often necessary. Usually, within 3 to 4 days of initiating therapy with prednisone, the platelet count will begin to rise. The platelet count should be checked daily to every other day until it is above 50,000-100,000/ul. Dogs with platelet counts less than 50,000/ul are hospitalized to reduce the risk of trauma-induced hemorrhage. Once the platelet count is over 50,000/ul, the chance of spontaneous hemorrhage is low, but the dogs should still be kept quiet until the platelet count is normal. The platelet count can be checked weekly when it is above 100,000/ul, then every 3 weeks after it has normalized and the dose of prednisone is being reduced. Recommendations for reduction of the dose of prednisone are as follows. If the dog has experienced 5 to 7 days of a rising platelet count, the dose of prednisone can be reduced by 25-50%. If the platelet count normalizes, the dose can be reduced by 50% every 3 to 4 weeks. The platelet count should be checked prior to any dosage reduction. If the dog is still in remission on a dose of 0.5 mg/kg daily, then an alternate day regime is instituted at that dose. If, in 4 to 6 weeks, the platelet count is still normal, then the prednisone can be discontinued.

Vincristine can be used in the therapy of IMT in dogs non-responsive to prednisone alone. The dose is 1 mg/M^2 IV weekly for 1 to 3 treatments. Vincristine causes release of platelets from megakaryocytes in the bone marrow. There is still a debate as to whether these platelets are actually functional, however. In addition to vincristine, azathioprine at a dose of 0.5 mg/kg PO daily for 4 to 7 days, then every other day, is beneficial in those dogs that do not respond to other immunosuppressive therapies.

Usually, transfusion therapy is not necessary in dogs with IMT. Occasionally, bleeding is so severe that anemia results. In these cases, a fresh whole blood transfusion is indicated to restore erythrocyte numbers and provide some platelets. The platelets will be utilized immediately and will not cause a significant rise in the patient's platelet count, however, this will hopefully support the patient until the immunosuppressive therapy has taken effect. Platelet-rich plasma is an unrealistic therapeutic option in most cases. True platelet-rich plasma is a platelet concentrate from at least 5 units of fresh whole blood from canine donors. Special centrifugation equipment is required to spin the blood at the proper speed and temperature so that the maximum number of platelets may be harvested. It is not economically feasible in

most cases to do this time-intensive procedure.

In certain cases of IMT that are chronic, splenectomy may be indicated. The spleen houses the majority of the mononuclear/phagocytic system, which is responsible for platelet destruction in this disease. In small studies of dogs with IMTP, splenectomy has allowed dogs with IMT to be controlled with lower dosages of immunosuppressive drugs or no drugs at all. It should not be performed on patients with platelet counts that are so low that hemorrhage is likely to occur during surgery. If this is unavoidable, fresh plasma can be prepared and administered during surgery.

The prognosis for dogs with IMTP is fair to good. The majority of dogs will go into remission easily and, if the drugs are reduced slowly, relapses should not occur. Some dogs do require lifelong therapy.

TABLE 1 :

Causes of Thrombocytopenia

Accelerated platelet destruction

Immune-mediated Destruction

Primary Immune-mediated Thrombocytopenia
Immune-mediated Thrombocytopenia secondary to:
- neoplasia
- infectious diseases (Ehrlichia, Rocky Mountain Spotted Fever, Histoplasma. etc)
- drugs (methimazole, quinidine, etc)

Microangiopathy

Increased Platelet Consumption

Severe hemorrhage
Disseminated Intravascular Coagulopathy
Vasculitis
Hemolytic -uremic Syndrome

Sequestration

Splenomegaly
Sepsis
Splenic Torsion

Decreased Bone Marrow Production
Myeloproliferative Disorder
Neoplasia in the Bone Marrow
Drug Reaction (estrogen, chloramphenicol, etc)
Chronic Ehrlichiosis
Idiopathic Aplasia