Immune-Mediated Thrombocytopenia

M.J. Day

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of decreased vWF:Ag in plasma by immuno-electrophoresis or ELISA (6,14,13). Carriers can be detected in the same way but there is considerable overlap with normals. DNA tests have been developed now for carrier detection in Dutch kooiker dogs and German wire haired pointers in the Netherlands.

Treatment of vWD is the same as treatment of hemophilia A. In addition, subcutaneous administration of desmopressin may temporarily increase the vWF:Ag concentration in the plasma and decrease the bleeding tendency (6,14).

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**IMMUNE-MEDIATED THROMBOCYTOPENIA**

M. J. Day1

INTRODUCTION

Immune-mediated thrombocytopenia involves destruction of platelets by type II hypersensitivity (antibody-dependent cytotoxicity) via mechanisms analogous to those described previously for immune-mediated hemolytic anemia. Where a true autoantibody binds to a structural component of the platelet membrane, in the absence of underlying disease, the thrombocytopenia is autoimmune in nature and the disease is primary immune-mediated thrombocytopenia (IMTP) or autoimmune thrombocytopenia (AITP). AIHA or AITP may occur together (Evans’ syndrome) or as part of the multisystemic autoimmune disease, systemic lupus erythematosus (SLE). Alternatively, antibody can bind to the surface of a platelet secondary to infection or drug administration, as described for IMHA. In these cases, the thrombocytopenia is considered secondary and the disease referred to as secondary IMTP.

CANINE IMTP

Thrombocytopenia is not uncommon in the dog and in many cases, elimination of other causes leads to a presumptive diagnosis of IMTP. The prevalence of IMTP is probably underestimated due to the lack of readily available diagnostic tests. In a recent survey, AITP was diagnosed in 5% of dogs with thrombocytopenia, but 59% had thrombocytopenia of unknown cause. Canine secondary IMTP has been induced by drugs or may be associated with vaccination. Platelet-specific antibodies have been documented in thrombocytopenic dogs experimentally infected with *Erlichia canis*. There is an association between secondary IMTP and neoplasia (particularly lymphoma and hemangiosarcoma) in the dog. In the absence of such underlying causes the disease is likely to be autoimmune in nature (AITP). Breed predispositions are reported for the poodle, old English sheepdog and cocker spaniel, and familial AITP is documented. AITP may occur more frequently in females, and disease may be triggered by kennelling, estrus, parturition or surgery.

The pathogenesis of AITP involves removal of antibody-coated platelets in excess of replacement by bone marrow thrombopoiesis. The spleen is the primary site of platelet removal and is likely the major site of autoantibody synthesis. Some autoantibody may also inhibit platelet function but this effect is poorly characterized. IgG antibodies are most frequently documented and these are specific for the platelet membrane glycoproteins (GP) IIb and/or IIIa.

Dogs with AITP generally present with acute onset disease. The thrombocytopenia predisposes to spontaneous hemorrhages, presenting as:

- petechiae to ecchymoses of oral, nasal, conjunctival, preputial or vaginal mucous membranes
- melena, hematemesis, hematuria or epistaxis
- subcutaneous bruising at pressure points
- intraocular hemorrhage
- gastrointestinal hemorrhage with chronic blood loss anemia.
- protracted clotting after trauma or venipuncture.

Other clinical signs include: weakness and lethargy, anorexia, pyrexia, mucous membrane pallor, lymphadenopathy and/or splenomegaly.

The number of circulating platelets is reduced and counts of 10,000/µl are not uncommon. Examination of a blood smear will confirm thrombocytopenia and may reveal the presence of 'shift platelets' indicative of bone marrow regeneration. Examination of bone marrow is indicated in the absence of such evidence of thrombopoiesis. Megakaryocytes may be reduced in number, or have cytoplasmic degeneration suggestive of antibody-mediated damage. Concurrent regenerative anemia (due to hemorrhage or AIHA) and neutrophilia may be present. Hemostasis may be assessed by determining bleeding time (e.g., from a standard buccal incision this should be < 5 minutes). Assessment of coagulation pathways (prothrombin time, activated partial thromboplastin time) will generally reveal no abnormality if the platelet count is > 10,000/µl.

Confirming the presence of AITP remains difficult, as there is no standard immunodiagnostic test. The majority of antibody will be platelet-bound rather than circulating, but in severe thrombocytopenia it may be difficult to isolate sufficient platelets from a blood sample for diagnostic purposes. Tests for platelet autoantibody include:

I. the platelet factor 3 test. The usefulness of this test is questionable and many laboratories no longer offer this assay.

II. megakaryocyte immunofluorescence. A bone marrow smear from the patient may be immunostained to demonstrate the presence of megakaryocyte-bound immunoglobulin. This test is reported to be positive in 30-80% of dogs with AITP.

III. direct platelet agglutination or immunofluorescence. Platelets isolated from the affected dog are incubated with antoglobulin reagent (equivalent to the Coombs' reagent) and examined for microscopic agglutination. Alternatively, such platelets are incubated with FITC conjugated

1 Department of Pathology and Microbiology, University of Bristol, Langford, United Kingdom.
anti-dog IgG and examined by UV microscopy. IV. An indirect ELISA for serum platelet-specific antibody (34% of AITP cases positive) or direct immunoassay for platelet-bound immunoglobulin (up to 94% of AITP cases positive) has been reported.

Dogs with AITP may have serum ANA, and if concurrent hemolytic anemia is suspected a Coombs’ test should be performed. AITP is a severe condition and approximately 30% of dogs die during the initial episode, largely from extensive gastrointestinal hemorrhage. Intensive therapy can induce recovery but recurrence is common.

FELINE IMTP IMTP is poorly characterized in the cat and most cases are likely to be secondary (FeLV associated) rather than autoimmune in nature. Thrombocytopenia in the cat has a less severe clinical presentation, and may be recognized on hematological examination of an animal with anemia, lethargy, anorexia and pyrexia. Mucous membrane or cutaneous hemorrhage may not be present, but hemorrhage can be precipitated by trauma, venipuncture or parturition. Bone marrow megakaryocyte hyperplasia may occur, and the platelet factor 3 test and megakaryocyte immunofluorescence test have been adapted for the cat. Immune-mediated amegakaryocytic thrombocytopenia and hemolytic anemia has been documented in a cat.

DIAGNOSIS OF LIVER DISEASE IN COMPANION ANIMALS

D.C. Twedt

INTRODUCTION
The veterinarian is often presented with patients that have abnormal liver enzymes identified on the routine biochemical profile. Correct interpretation of laboratory data is important when dealing with liver disease or deciding if a liver biopsy is indicated. The hepatic tests will be grouped as either serum enzymes or as function tests. Only those commonly found on the biochemical profile will be discussed.

SERUM ENZYME TESTS
The serum hepatic enzyme tests are grouped into those that: 1. indicate hepatocellular injury/repair or 2. reflect increased production stimulated in cholestasis.

HEPATOCELLULAR INJURY/REPAIR
Canine and feline hepatocyte cytoplasm is rich in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Altered permeability of the hepatocellular membrane caused by injury or a metabolic disturbance results in a release of these soluble enzymes. Subsequent to an acute, diffuse injury, the magnitude of increase crudely reflects the number of affected hepatocytes. Clinical experience in veterinary medicine indicates that there is value in the interpretation of the serum activities of ALT and AST for liver disease. Following an acute injury resulting in a moderate to marked increase in the serum ALT and AST activities, the serum AST activity will return to normal (days) due to their difference in plasma half-lives and cellular location (2). Persistent mild to moderate increases of the serum ALT and AST activities (documented abnormal multiple times for several months) suggest a ‘smoldering’ inflammatory process with chronic degeneration or necrosis as occurs in chronic hepatitis. Microscopic evaluation of hepatic tissue will confirm or deny the diagnosis. A recent study found that the measurement of serum AST value had high specificity for liver disease in the dog. Another important finding from recent studies is that there is an increased production and release of ALT and AST by the regenerating hepatocytes (4).

MARKERS OF CHOLESTASIS AND DRUG-INDUCTION
Alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) show minimal activity in normal hepatic tissue but can become markedly increased in the serum subsequent to increased enzyme production stimulated by either impaired bile flow or drug-induction. These enzymes have a membrane location; ALP associated with the canalicular membrane and GGT associated with epithelial cells comprising the bile ductular system. The plasma half-life for hepatic ALP in the dog is 66 hours in contrast to 6 hours for the cat and the magnitude of enzyme increase (presumably a reflection of the synthetic capacity) is greater for the dog than the cat (3). Alkaline phosphatase is present in a number of tissues but only two are diagnostically important; bone and liver. Mildly increased serum ALP activity is present during growth and may develop subsequent to bone pathology. In the adult without bone disease, an increased serum ALP activity is

1 Department of Clinical Sciences, Colorado State University, Fort Collins, Colorado, USA.