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Systemic bleeding disorders responsible for spontaneous or inappropriate haemorrhage are common in dogs and cats. Most are acquired but some are inherited. Because bleeding disorders can be potentially life-threatening, it is imperative that a logical diagnostic approach be used to quickly establish the diagnosis and implement appropriate therapy. Such an approach requires a sound understanding of haemostasis and the pathophysiology of the disorders themselves.

**History and Physical Examination**

In haemostatic emergencies, the first priority is to control haemorrhage and combat shock. The clinician must then confirm that bleeding is a systemic phenomenon rather than referable to local factors. Whether the defect involves primary and/or secondary haemostasis and is likely to be inherited or acquired must then be determined. Important clues are usually provided by obtaining a detailed history and conducting a meticulous physical examination.

Most animals with haemostatic disorders are presented because of haemorrhage but some may have a history of shifting lameness, impaired vision or signs of systemic illness. Owners may not recognise petechiae, ecchymoses, melaena or haematemesis as being indicative of haemorrhage.

The signalment of the patient can be highly informative. Severe inherited haemostatic disorders (e.g. haemophilia A and B) usually manifest within the first six months of life. Milder inherited disorders (e.g. Type 1 von Willebrand’s disease (vWD)) may manifest later. It is important to discover if the patient has had prior episodes of inappropriate haemorrhage (e.g. at desexing, after venipuncture or other minor trauma, or during oestrus) and if related animals have had bleeding problems or reproductive failure (abortions, stillbirths or neonatal mortalities). The breed affected may arouse suspicion of specific inherited disorders (e.g. dobermans and Scottish terriers - vWD; German shepherd dogs - haemophilia A; beagles, miniature schnauzers and Alaskan malamutes - factor VII deficiency).

Other important historical information includes any prior or current illnesses, recent or current medication, and potential exposure to trauma or toxins (especially anticoagulant rodenticides). Drugs that may induce thrombocytopenia or platelet dysfunction include antibiotics, NSAIDs, thiazide, digoxin, quinidine, propanolol, hydralazine, halothane and heparin. Modified live virus vaccines, especially against canine distemper virus, can also cause a transient thrombocytopenia and/or platelet dysfunction.

A thorough physical examination is necessary to determine if bleeding is a local or systemic phenomenon and to detect any evidence of potential underlying processes such as infection, hepatic disease, renal failure or neoplasia. The examination should include an ophthalmoscopic assessment, palpation of joints and detailed inspection of the skin, mucous membranes and, when feasible, urine and faeces. The distribution and severity of the haemorrhage usually indicate whether bleeding is referable to a defect in primary or secondary haemostasis or both.
Disorders of primary haemostasis are characterised by a failure to produce an adequate plug of platelets at sites of vascular injury. Failure may be due to thrombocytopenia, thrombocytopathy (inherited or acquired platelet dysfunction), vWD (deficiency of von Willebrand factor (vWF)) or a vasculopathy (e.g. vasculitis). Animals that cannot form primary haemostatic plugs have multiple brief episodes of haemorrhage from small superficial vessels. As primary haemostasis is the major mechanism that controls bleeding from such vessels and minor capillary injury is a daily phenomenon, the defect usually manifests spontaneously shortly after onset. Typical are multiple petechiae and ecchymoses in mucous membranes and skin (especially over pressure points and on the ventrum). There may be epistaxis, gingival bleeding, haematuria, haematemesis, melaena or haematochezia. Ocular haemorrhage (conjunctival, scleral, iridal and/or retinal petechiae or hyphaema) is common. If larger blood vessels are injured, bleeding will cease once fibrin is generated; prolonged but finite bleeding is therefore observed after venipuncture. Haemorrhage in most animals with vWD conforms to this pattern (although it is often not spontaneous) but severe vWf deficiency (Types 2 and 3 vWD) may provoke more severe bleeding suggestive of a secondary haemostatic defect.

Disorders of secondary haemostasis involve a quantitative or qualitative deficiency of one or more coagulation factors. This is most often referable to vitamin K antagonism by anticoagulant rodenticides. Other important causes include chronic or severe acute hepatic disease (with decreased synthesis of coagulation factors) and inherited factor deficiencies. An inherited deficiency of vitamin K-dependent coagulation factors occurs in Devon Rex cats. Infrequently, vitamin K deficiency may develop in animals with complete extra-hepatic bile duct obstruction, chronic lipid maldigestion/malabsorption (e.g. exocrine pancreatic insufficiency), prolonged oral antibiotic use, or in neonates born to dams malnourished through pregnancy or treated with antibiotics.

Animals with secondary haemostatic defects can form short-lived primary platelet plugs at sites of vascular injury but cannot generate fibrin. Bleeding after venipuncture is usually delayed for several minutes by primary haemostasis but is then prolonged and severe. The defect may manifest as single or multiple subcutaneous bruises, deep haematomas, major bleeds into body cavities, haemarthrosis, epistaxis, haematuria, haematemesis and/or melaena. Severely affected animals will have physical evidence of hypovolaemia and anaemia. It is important to appreciate that blood extravasated into a body cavity undergoes fibrinolysis over time; aspiration of unclotted blood from the thorax or abdomen therefore does not confirm that a secondary haemostatic defect is present.

Some secondary haemostatic defects can be clinically silent until haemorrhage into a critical location (e.g. central nervous system or pericardial sac) or a major bleed takes place or haemostatic capacity is challenged by trauma. This is particularly true of sedentary cats (e.g. with rodenticide poisoning) and of dogs with certain inherited factor deficiencies. Inherited factor VII deficiency is usually subclinical or responsible for only minor bleeding. Inherited factor XI deficiency (haemophilia C) usually only causes mild haemorrhage but major trauma may provoke massive bleeding.

Haemorrhage consistent with concurrent primary and secondary haemostatic defects is indicative of disseminated intravascular coagulation (DIC) and reflects deficiency of platelets and coagulation factors compounded by enhanced fibrinolysis.
Laboratory Tests

Multiple diagnostic tests are usually required to thoroughly investigate bleeding disorders. If only one or two test results are evaluated, the extent of the defect may be underestimated, potentially endangering life or causing erroneous diagnosis. A single assay may, however, be sufficient in some circumstances (e.g. a prothrombin time (PT) in an animal known to have ingested an anticoagulant rodenticide).

Assessing Primary Haemostasis

As thrombocytopenia is the most common acquired haemostatic disorder in small animals, the investigation should begin with a platelet count. An EDTA blood sample should be collected with minimal trauma and the first blood drops discarded to prevent any sample contamination by tissue factor (which stimulates platelet agglutination). Analysis should be within a few hours of collection. As there is a significant size overlap between platelets and erythrocytes in cats, platelet number is usually estimated in this species from a blood smear (there should be at least 10 platelets per x100 (oil immersion) field) or determined manually using a haemocytometer. In dogs, automated counts are the most accurate but electronic impedance analysers (Coulter counters) will underestimate the count if platelet clumping occurs in vitro or if a significant number of large shift platelets is present. Analysers that measure the platelet distribution width and mean platelet volume provide a better estimate of the platelet functional mass than does the platelet count alone. Before a low automated platelet count is accepted as a genuine finding, a blood smear must be examined to check for platelet clumps (found especially in the feathered edge) and/or shift platelets.

Patients with Thrombocytopenia

If thrombocytopenia is confirmed, its clinical relevance needs to be determined. Spontaneous haemorrhage is unlikely until the count drops below 25 x 10^9/L (and often below 10-20 x 10^9/L). However, animals with significant numbers of shift platelets may not bleed despite counts below 10 x 10^9/L and haemorrhage may occur at counts of 40-50 x 10^9/L if platelet function is also reduced or the haemostatic challenge is severe. If an animal has clinical signs suggestive of a primary haemostatic defect but the platelet count is above 50 x 10^9/L, a cause other than thrombocytopenia should be sought.

Because thrombocytopenia can be referable to DIC or to bleeding in animals with secondary haemostatic disorders, secondary haemostatic function and fibrinolytic activity should be assessed in all thrombocytopenic patients.

Thrombocytopenia unaccompanied by secondary haemostatic defects may be due to decreased marrow production, increased destruction, haemorrhage or sequestration (in an enlarged liver or spleen or within the lung in acute interstitial injury). Sequestration and haemorrhage are usually responsible for only mild thrombocytopenia.

Decreased platelet production is the most common cause in cats and is most often referable to retroviral infection (especially FeLV), myelodysplasia or myeloproliferative disease. Megakaryocytic hypoplasia can also develop in animals with myelophthisis, marrow aplasia, immune-mediated thrombocytopenia, late stages of *Ehrlichia platys* infection, and as an adverse effect of drugs (e.g. oestrogen and phenylbutazone in dogs, griseofulvin and
methimazole in cats). Affected animals may have concurrent leukopenia and non-regenerative anaemia.

In dogs, thrombocytopenia is usually due to platelet destruction, especially by immune-mediated attack but potentially directly by drugs or infectious agents (e.g. *E. platys*, *Rickettsia rickettsii* and various bacteria and viruses). Immune-mediated thrombocytopenia (IMTP) can be drug-induced (e.g. sulphonamides) or develop secondary to infection, systemic lupus erythematosus (SLE) or neoplasia (especially lymphoma). Infrequently, it may be accompanied by immune-mediated haemolytic anaemia (Evans' syndrome).

A thorough physical examination may provide clues to the mechanism responsible for thrombocytopenia. Additional clues may be provided by performing a complete haematology and biochemistry screen. Review of a blood smear is mandatory, not only to confirm that thrombocytopenia is present but to check for infectious agents, spherocytes, schistocytes, dysplastic or neoplastic cells, or toxic change in neutrophils. The presence of significant numbers of shift platelets in a genuinely thrombocytopenic patient is an important observation as it indicates a marrow thrombopoietic response. All thrombocytopenic cats require FeLV and FIV serology. Bone marrow examination is required if bi- or pancytopenia is present or there is morphological atypia of circulating cells.

The history in all thrombocytopenic patients should be reviewed carefully for exposure to drugs. A diagnosis of drug-induced thrombocytopenia is usually a presumptive one, based on an increase in the platelet count within 2-6 days of drug withdrawal. Confirmation of IMTP can be attempted by demonstrating circulating antibodies or platelet-bound IgG by flow cytometry or ELISA assay but diagnostic specificity is poor. In practice, IMTP is usually diagnosed by exclusion of other causes of thrombocytopenia and by obtaining resolution with immunosuppressive therapy. A therapeutic response is usually seen within 48-96 hours of commencing therapy. Failure of response within this timeframe warrants bone marrow examination to evaluate megakaryocytes. Ancillary tests to check for underlying disease processes capable of triggering IMTP may include serology tests (for infectious agents, occult dirofilariasis or anti-nuclear antibodies), urinalysis, a direct Coombs’ test, and diagnostic imaging.

Patients Without Thrombocytopenia

If the platelet count is adequate, the buccal mucosal bleeding time (BMBT) should be determined in-house to assess primary haemostatic function. If the BMBT is normal in a bleeding animal, secondary haemostatic function should be evaluated next.

If the BMBT is prolonged and there is a high index of suspicion of vWD, it may be logical to perform a vWf assay next. However, vWD is unlikely if the patient has tolerated traumatic stimuli in the past without inappropriate bleeding. All patients with a protracted BMBT and adequate platelet number should have their history re-evaluated to exclude a drug-induced thrombocytopenia. Disorders such as chronic liver disease, renal failure, SLE, dysproteinenaemias, myeloproliferative disease, and FeLV/FIV infection can also cause platelet dysfunction; it is therefore prudent to perform a complete haematology and biochemistry screen. Depending on the results, ancillary diagnostic tests might include urinalysis, retroviral or FIP serology, diagnostic imaging, bone marrow examination or serum/urine protein electrophoresis.
If acquired thrombocytopathy and vWD are excluded, the remaining diagnostic options are inherited thrombocytopathies or primary vasculopathies. Confirmation of platelet dysfunction requires sophisticated platelet function tests that are available only in specialised referral laboratories. Primary vasculopathies infrequently cause bleeding in small animals and are usually associated with additional clinical signs. Integrity of blood vessels is difficult to evaluate without tissue biopsy and biopsy is usually only contemplated in bleeding patients when all other diagnostic avenues have been exhausted.

Assessing Secondary Haemostasis

To assess the intrinsic and common coagulation pathways, the activated coagulation time (ACT) can be determined in-house but it is less sensitive than the activated partial thromboplastin time (APTT). The ACT will only be prolonged if an intrinsic or common pathway factor activity is less than 5% of the reference. A prolonged ACT should always be confirmed by performing an APTT because the ACT may be slightly prolonged by severe thrombocytopenia (< 10 x 10⁹/L) or if the tube is not pre-warmed to 37° C and maintained at that temperature until clot development.

Secondary haemostatic capacity is more accurately assessed by determining the PT and APTT in citrated blood. The APTT assesses factors in the intrinsic and common coagulation pathways whereas the PT assesses those in the extrinsic and common pathways. Blood samples for ACT, APTT and PT assays should be collected quickly and as atraumatically as possible. Difficult venipuncture or prolonged iatrogenic venous stasis may cause tissue factor release and activation of extrinsic coagulation (to falsely shorten the ACT and APTT). Splenic contraction may occur in stressed patients (especially cats) at venipuncture and boost platelet numbers and activity of factors I, V and VIII and vWF. For PT and APTT assays, the preferred anticoagulant is 3.8% sodium citrate, with a ratio of anticoagulant to blood of 1:9. Underfilling citrate tubes with blood causes a relative excess of citrate which lowers the calcium level, delays fibrin formation and falsely prolongs the coagulation times. Once collected, samples should be thoroughly mixed to prevent clotting.

If the APTT is prolonged but the PT is normal, there may be a deficiency of factor VIII (haemophilia A) (the most likely cause in a young male dog), factor IX (haemophilia B), factors VIII and IX (haemophilia AB), factor XI (haemophilia C), factor XII, prekallikrein (PK) or high molecular weight kininogen (HMWK). Definitive diagnosis of inherited factor deficiencies requires specific factor analysis in reference coagulation laboratories. However, deficiency of PK, HMWK or factor XII does not cause clinical haemorrhage because of redundancies in the coagulation cascade. APTT prolongation with a normal PT may also be seen in heparinised animals and in those with chronic hepatic disease or DIC. Presence of antibodies directed against specific haemostatic components such as platelet phospholipid can also cause APTT prolongation; in vivo, these so-called lupus antibodies promote hypercoagulability rather than haemorrhage.

If the PT is prolonged and the APTT is normal, factor VII deficiency is present. This may be inherited but is more commonly acquired due to vitamin K antagonism or deficiency. The vitamin K-dependent factors are II, VII, IX and X. As factor VII (in the extrinsic pathway) has the shortest half-life (4-6 hours) of all the coagulation factors, the PT is prolonged before the APTT in vitamin K antagonism or deficiency but ultimately both will be prolonged. A similar pattern can be seen in animals in early hepatic failure with decreased synthesis of coagulation factors. In vitamin K antagonism or deficiency, the liver produces inactive non-carboxylated protein.
precursors of factors II, VII, IX and X (so-called PIVKA or proteins induced by vitamin K absence or antagonism); a PIVKA assay can be used to confirm the diagnosis. PIVKA are detectable in circulation prior to prolongation of the PT and are rapidly converted to their functional forms once vitamin K is administered. PIVKA are also detectable in hepatobiliary diseases in cats (prior to any prolongation of the PT), due to impaired enterohepatic recycling of bile acids and decreased intestinal absorption of vitamin K.

Prolongation of both the PT and APTT suggests deficiency of a factor in the common pathway or of multiple factors in the intrinsic, extrinsic and common pathways. This pattern can be seen in inherited deficiencies of factors I, II, V or X, in Devon Rex cats with inherited deficiencies of the vitamin K-dependent factors, in acquired vitamin K antagonism or deficiency, in inherited or acquired dysfibrinogenaemia, in hepatic failure (especially severe acute disease), in DIC and in animals receiving heparin. Anticoagulant rodenticide poisoning is the most common cause. To determine if there is hypo- or dysfibrinogenaemia, a thrombin time can be performed but this may be prolonged in some dysproteinaemias and in the presence of inhibitors such as heparin and fibrin degradation products (FDP).

In DIC, the PT and APTT are expected to be prolonged due to consumption of coagulation factors. However, it is not uncommon to find only a prolonged APTT. In peracute DIC, both can be normal or even shortened. The D-dimer assay is the most sensitive assay for DIC in dogs but the plasma latex agglutination assay for FDP has relatively high sensitivity and specificity. A decrease in AT activity to less than 80% is also a sensitive indicator of DIC in dogs. In animals with disorders known to predispose to DIC, a peripheral blood smear should be examined for schistocytes.

Few dogs and cats with hepatic disease are presented for haemorrhage. In those that are, it can be difficult to distinguish severe hepatic disease from DIC on the basis of laboratory tests of haemostasis. Both thrombocytopenia and platelet dysfunction may be present. The PT and APTT may both be prolonged or only the APTT. Decreased hepatic synthesis can cause a decrease in AT activity (and also fibrinogen concentration). Excessive fibrinolysis may occur due to reduced hepatic clearance of plasminogen activators and reduced synthesis of inhibitors of fibrinolysis so that FDP and D-dimer concentrations may increase. Confirmation of hepatic disease may depend on clinical findings, serial analysis of serum liver enzymes, serum bile acids assays, diagnostic imaging and eventually hepatic biopsy.

REFERENCES

