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Disseminated intravascular coagulation (DIC) is a complex acquired disorder of haemostasis. It is a dynamic and potentially life-threatening syndrome characterised by inappropriate and widespread activation of blood coagulation. Paradoxically, what commences as a thrombotic disorder may progress to sustained fibrinolysis and haemorrhage.

Although DIC is associated with high morbidity and mortality, early DIC is manageable if the underlying disorder can be identified and is amenable to treatment. If haemostatic screening tests are performed routinely in dogs and cats with diseases known to trigger DIC, the chances of detecting the early subclinical phase can be maximised. Awareness of the diseases that can initiate DIC is therefore paramount in improving patient outcomes.

Aetiology

DIC is a relatively common complication of various primary disorders of dogs and cats. Potential triggers include sepsis (especially Gram-negative infections), dirofilariasis, babesiosis, systemic viral and rickettsial infections (e.g. infectious canine hepatitis, feline infectious peritonitis (FIP), Rocky Mountain spotted fever), heat stroke, hypothermia, snake envenomation, electrocution, extensive tissue necrosis (e.g. trauma, burns, gangrene, severe pneumonia or hepatic injury), gastric dilation-volvulus (GDV), pancreatic necrosis, malignant neoplasia, immune-mediated haemolytic anaemia (IMHA), incompatible blood transfusion, vasculitides, systemic lupus erythematosus, erythema multiforme, hyperviscosity syndromes and anaphylaxis.

In dogs, the most common primary disorders are malignancy (especially haemangiosarcoma), severe hepatic injury, sepsis, GDV, and immune-mediated cytopenias. In cats, DIC is most commonly triggered by malignancy (especially lymphoma), pancreatitis, sepsis, hepatic disease (especially hepatic lipidosis, probably as a consequence of lipid embolism), and systemic infections such as FIP and toxoplasmosis.

What links these disparate disorders is the exposure of blood to procoagulant factors and/or widespread injury to vascular endothelium.

Pathogenesis

The initial (non-overt or compensated) phase of DIC is one of hypercoagulability during which extrinsic coagulation is activated but thrombin activity is counterbalanced by inhibitors. With sustained thrombin generation, however, coagulation inhibitors (e.g. antithrombin (AT), protein C) may be consumed. This may be compounded by inhibition of fibrinolysis. Widespread microthrombosis develops and DIC becomes clinically overt or decompensated. With continued consumption of procoagulants (platelets and coagulation factors), enhanced fibrinolysis and anticoagulant effects of fibrin degradation products (FDP), a hypocoagulable (haemorrhagic) phase may emerge.

Most cases of DIC are initiated by exposure of blood to tissue factor (TF), a membrane-anchored glycoprotein that activates factor VII of the extrinsic coagulation pathway. In health,
only a small concentration of TF is present in blood as microparticles derived from haematopoietic cells or as a soluble form in plasma. Vascular injury, however, exposes perivascular cells such as fibroblasts that express TF. Microparticle TF may adhere to the surface of activated endothelium. Induction of TF activity in cultured endothelium in response to bacteria, rickettsia and viruses has been demonstrated in vitro. Vascular injury also exposes subendothelial collagen to promote platelet adhesion, activation and aggregation and trigger contact activation of factor XII to initiate intrinsic coagulation. These events contribute to microthrombosis in DIC.

Monocytes and macrophages activated by endotoxin, immune complexes, cytokines and anaphylatoxins can also express TF and other procoagulant molecules. Activated monocytes/macrophages release interleukin-1 (IL-1) and tumour necrosis factor, both of which promote adhesion of microparticle TF to endothelium. Endotoxin can also directly activate factor XII, inhibit fibrinolysis, promote leukocyte and platelet aggregation, and directly injure endothelium to promote DIC.

Severe tissue necrosis may permit entry of TF from damaged cells into circulation. Some neoplastic cells may constitutively express or release TF; others may instead trigger coagulation by releasing proteolytic enzymes, mucin, fatty acids or other procoagulants. Some snake venoms contain proteolytic enzymes that can directly activate factor X or prothrombin. Circulating trypsin in pancreatic necrosis can also activate factor X.

Once coagulation is initiated in DIC, thrombin generation is sustained and amplified by intrinsic coagulation (triggered by feedback loops from the extrinsic pathway and by contact activation) and by consumption of anticoagulants. Endothelium becomes activated to a procoagulant phenotype that augments local coagulation; simultaneously, thrombin promotes platelet adhesion, activation and aggregation. Activated endothelium down-regulates expression of anticoagulant molecules (e.g. thrombomodulin) and tissue-type plasminogen activator (t-PA), and releases platelet activating factor and vasodilators (e.g. nitric oxide, prostacyclin). Down-regulation of endothelial thrombomodulin expression is a major contributor to decreased protein C activation in DIC. Anionic phospholipid microparticles shed by activated, damaged or apoptotic cells (including endothelium, platelets and granulocytes) are also procoagulant.

Once the concentration of factor Xa increases, extrinsic coagulation is normally inhibited by tissue factor pathway inhibitor (TFPI) expressed by endothelium and smooth myocytes. Thereafter, components of the intrinsic coagulation pathway (particularly factors VIIIa and IXa) become the dominant regulators of thrombin generation. The role of TFPI in the pathogenesis of DIC has yet to be determined. Factor XIIa of the intrinsic pathway can activate the kallikrein-kinin, complement and fibrinolytic systems. Kinins (e.g. bradykinin) contribute to vasodilation, increased vascular permeability, systemic hypotension and shock in DIC. Factor XIIa also activates plasminogen to plasmin, although its role is subordinate to that of t-PA derived from endothelium. Plasmin cleaves fibrinogen and fibrin to FDP and also hydrolyses factors V and VIII.

That DIC also involves stimulation of systemic inflammatory responses and cytokine cascades has been best characterised in sepsis. Activated coagulation factors are pro-inflammatory and their inhibitors (e.g. protein C) anti-inflammatory. Factor XIIa activates the complement system to promote chemotaxis of leukocytes, and factor Xa, thrombin and fibrin activate endothelial cells which then synthesise pro-inflammatory cytokines and growth factors. Thrombin, for
example, promotes endothelial expression of leukocyte adhesion molecules and synthesis of IL-6, IL-8 and platelet derived growth factor.

Thrombosis in decompensated DIC results from sustained thrombin generation and consumption of anticoagulants. Suppression of fibrinolysis may contribute. Both thrombin and inflammatory cytokines can suppress fibrinolysis by promoting release of plasminogen activator inhibitors by endothelial cells. Endotoxaemia and consumption of protein C, plasminogen and t-PA may also contribute. Multiple fibrin thrombi form simultaneously, especially within arterioles and capillaries. Thrombosis can be generalised or restricted to a single organ. At necropsy, thrombi are most often identified in capillaries of the brain, renal glomeruli, adrenal glands, pulmonary alveolar septa and myocardium. Thrombosis may induce congestion, oedema, haemorrhage and, in more severely affected or vulnerable organs, ischaemic necrosis. Fibrin strands within vessels may damage passing erythrocytes, provoking intravascular lysis (microangiopathic haemolytic anaemia) and formation of schistocytes.

Impaired tissue perfusion due to microthrombosis results in development of secondary enhancers of DIC. These include blood stasis, tissue hypoxia, acidosis, hepatic, renal and pulmonary dysfunction, release of myocardial depressant factor, and shock. Blood stagnation, tissue hypoxia and acidosis promote platelet aggregation and blood hypercoagulability. Splanchnic hypoperfusion in shock impairs removal of procoagulants and FDP from blood by hepatocytes and splenic and hepatic macrophages and may impair hepatic synthesis of coagulation factors. Macrophage clearance of bacteria entering circulation from the gastrointestinal tract may also be compromised.

The haemorrhagic phase of DIC is a consequence of consumption of platelets and coagulation factors and the anticoagulant effects of FDP. Consumption of α2-antiplasmin may contribute to bleeding by enhancing fibrinolysis. At high concentrations, FDP inhibit platelet adhesion, activation and aggregation, cleavage of fibrinogen by thrombin, and fibrin polymerisation. They may also cause increased vascular permeability and chemotaxis of leukocytes. The nature of the bleeding reflects the loss of both primary and secondary haemostatic capacity, with appearance of mucosal and/or cutaneous petechiae and ecchymoses, epistaxis, deep haematoma formation and/or bleeding into body cavities and joints.

The prognosis in DIC is highly variable and depends to a large extent on the underlying disorder. Mortality in dogs with DIC ranges from 50 to 77%. In a recent study of DIC in 46 cats, 93% died or were euthanised. In most patients, high morbidity and mortality are referable to microvascular thrombosis rather than to haemorrhage.

Clinical Signs

The clinical signs of DIC are highly variable and are influenced by the underlying disease process, the duration of DIC, the extent and location of microthrombosis, and the severity of bleeding. There may be rapid, unpredictable and often marked changes in the clinical status of an affected animal over the disease course.

In the hypercoagulable phase of DIC, clinical signs may be absent despite accelerated coagulation and consumption of anticoagulants. The decompensated (consumptive) phase of DIC may manifest as shock, organ failure, dyspnoea, cyanosis or extreme respiratory distress, oliguria, seizures, coma, haemorrhage or haemolytic anaemia. Haemorrhage may be spontaneous or triggered by venipuncture.
In dogs, DIC may be acute in clinical onset and fulminant (manifesting as severe spontaneous haemorrhage, shock or microthrombosis-induced organ failure) or chronic and either subclinical or associated with signs referable to microthrombosis. The acute form may be triggered suddenly by such conditions as heat stroke, electrocution or pancreatic necrosis but more often represents abrupt decompensation of a chronic smouldering disorder (such as haemangiosarcoma or dirofilariasis). In many animals, the chronic form is detectable only by performing haemostatic function tests.

Most cats with DIC do not bleed spontaneously and the clinical signs may be non-specific or reflect the primary disease process. The most common signs are depression, lethargy and anorexia; others include weakness, vomiting, dyspnoea, hypo- or hyperthermia, a weak femoral pulse, tachycardia or bradycardia, a cardiac murmur and diarrhoea.

**Diagnosis**

Comparable diagnostic DIC scoring systems to those proposed for humans by the International Society of Thrombosis and Haemostasis have yet to be devised in small animals. In the past, confirmation of DIC in dogs and cats with a predisposing disorder was most often based upon detection of at least three of the following:

- thrombocytopenia
- prolongation of the activated partial thromboplastin time (APTT) or PT
- erythrocyte fragmentation
- hypofibrinogenaemia
- increased FDP.

The advent of assays for AT and D-dimers has improved diagnostic sensitivity and specificity in dogs.

Thrombocytopenia is usually present in animals with DIC. The platelet count is usually the last parameter to normalise after successful treatment of DIC because of the time required for thrombopoiesis. However, platelet numbers may be within the reference range in peracute DIC and a declining trend may only be detected by performing serial counts over several hours. Obtaining an accurate estimate of platelet numbers is difficult in cats.

Schistocytes and other poikilocytes are inconsistent findings in animals with DIC and can also be identified in animals with other disorders characterised by altered microvasculature or blood turbulence. In a retrospective study of 252 dogs with DIC, erythrocyte fragmentation was noted in only 10%.

The fibrinogen assay is insensitive as a test for DIC, especially if performed by the heat precipitation method. The fibrinogen concentration may be normal or even increased in some animals with DIC, especially in chronic phases or if there is increased hepatic synthesis in response to active inflammation or tissue injury.

The APTT has greater sensitivity than the PT in the diagnosis of DIC in dogs and cats but an optimised PT is superior to both in dogs. The APTT and PT may be normal or even shortened in peracute DIC because of circulating activated coagulation factors or because of increased
hepatic synthesis of factors that are also acute phase reactants (fibrinogen and factors V and VIII).

FDP result from digestion of fibrinogen or soluble fibrin by plasmin. An increased plasma FDP concentration may reflect fibrinogenolysis, fibrinolysis or decreased removal of circulating FDP by macrophages (e.g. in hepatic disease). The sensitivity and specificity of the plasma latex agglutination assay in the diagnosis of DIC in dogs approach those of the D-dimer assay but results of these tests are not always concordant and ideally both tests should be performed concurrently. Increased FDP can occur in animals with severe internal haemorrhage, anticoagulant rodenticide poisoning and in conditions promoting fibrinogenolysis (e.g. parvoviral enteritis).

D-dimers are a type of FDP produced when plasmin digests insoluble cross-linked fibrin. An increased D-dimer concentration is therefore a specific marker of fibrinolysis (but not necessarily of thrombosis or DIC). Increases have also been observed in dogs with malignancy, internal haemorrhage, IMHA, cardiac or renal failure, and hepatic disease. An in-house, semiquantitative, rapid latex agglutination assay is available for use with EDTA or heparinised plasma but is less sensitive than the ELISA assay. The negative predictive value of the D-dimer assay in the diagnosis of DIC in dogs is reported to be as high as 99.5% but false negatives can occur in endotoxaemia. The D-dimer assay appears to have high sensitivity in detecting DIC in cats. However, cats with inflammatory or neoplastic disease may have a high concentration.

A decrease in AT activity to less than 80% of reference values is a sensitive indicator of DIC in dogs but can also be a feature of nephrotic syndrome and hepatic failure. Dogs with less than 60% activity require heparin and AT replacement. In cats, AT behaves as an acute phase reactant and its activity may be normal to increased in DIC.

REFERENCES


