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Review

DISSEMINATED INTRAVASCULAR COAGULATION IN CANINES: OLD DISEASE WITH NEW HOPE

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SUMMARY

Disseminated intravascular coagulation (DIC), also known as 'Dysfibrinogen syndrome', is a complex syndrome of disorders and deregulation of the coagulation. It is a continuum in clinico-pathological severity, which is characterised by diffuse intra vascular thrombosis causing haemostatic defect due to a reduction in clotting factor and platelets as a result of their utilisation in the thrombotic process. Although the first clinical observation on DIC was reported in the 19th century, the condition of widespread and disordered coagulation has probably affected animals for as long as trauma and infections have beset them.

Keywords: Disseminated intravascular coagulation (DIC), 'Dysfibrinogen syndrome', dogs

INTRODUCTION

Today Disseminated intravascular coagulation (DIC), has emerged as a problem in many breeds of dogs. This condition can occur in dogs of any age, breed or sex. Its importance is supported by two key observations. Firstly, the presence of DIC increases the risk of mortality beyond that associated with primary disease. Secondly, removal of the underlying cause does not necessarily alleviate the process in most cases. As this disorder develops slowly, the affected animal dies with not much signs or symptoms. This is an overview of DIC and how its onset may indicate the turning point from which an adaptive response becomes maladaptive and a potential threat to the host.

AETIOLOGICAL FACTORS

DIC is not a primary disease *per se*, but a serious and often life-threatening complication of a variety of diseases. The various diseases and conditions associated with DIC in dogs are as follows:

1. Neoplasia: Includes hemangioma, hemangiosarma, metastatic thyroid carcinoma, metastatic mammary carcinoma, prostatic adenocarcinoma, lymphoma and cholangiocarcinoma.
2. Infectious disorders: Include sepsis, bacterial endocarditis, leptospirosis, canine infectious hepatitis, babesiosis and dirofilariasis,
3. Inflammatory conditions: Include suppurative dermatitis, suppurative bronchopneumonia, acute hepatic necrosis, chronic active hepatitis, pancreatitis and hemorrhagic gastroenteritis.
4. Miscellaneous: Shock, heatstroke, venomous snakebite, cirrhosis, aflatoxicosis, immune-mediated hemolytic anemia, cold agglutinin disease, gastric dilatation-volvulus, congestive heart failure, valvular fibrosis, diaphragmatic hernia, perioperative complications, embryonic mycetoma, renal amyloidosis, pulmonary thromoembolism and hepatic lipidosis.

PATHOPHYSIOLOGY

The main event in DIC is systematic activation of coagulation to an extent, which cannot be contained by the body's anticoagulant mechanisms. It includes the following mechanisms.

- Activation of the coagulation cascade leads to fibrin formation from fibrinogen by the action of thrombin deposition in the microvasculature (thrombosis). Thrombus formation results in ischemia and end organ damage.
- This activation of coagulation results in consumption and depletion of coagulation factors, including procoagulant factors (especially those that are non-enzymatic factors fibrinogen, factor V, and factor VIII) and anticoagulant factors such as AT-III.
- Platelets activated by the thrombin, generated from coagulation, are trapped by fibrin deposited in the microvasulature and participate in formation of intravascular thrombi. This leads to thromocytopenia. Red cells are also damaged by fibrin in the microvasculature leading to formation of schistocytes.

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- Plasmin, the active enzyme of fibrinolysis, is generated by tissue plasminogen activator and it degrades fibrin clots as well as circulating fibrinogen thereby elevating the concentration of FDPs.
- Although clinical signs of bleeding predominate, it is seen that organ damage due to thrombosis and ischemia occurs simultaneously.
- Hypotension and shock in DIC affected animals are promoted by plasmin and various kinins, which lead to increased vascular permeability and vasodilatation.
- There has been a recent challenge, however, to the basic assumptions and interpretations of the pathophysiology of DIC. A study of sepsis and DIC in animal models has shown that a highly-expressed receptor on the surface of hepatocytes, termed the Ashwell-Morell receptor, is responsible for thrombocytopenia in bacteremia and sepsis due to *Streptococcus pneumoniae* and possibly other pathogens. The thrombocytopenia observed in SPN sepsis was not due to increased consumption of coagulation factors such as platelets, but instead was the result of this receptor's activity enabling hepatocytes to ingest and rapidly clear platelets from circulation. By removing pro-thrombotic components before they participate in the coagulopathy of DIC, the Ashwell-Morell receptor lessens the severity of DIC, reducing thrombosis and tissue necrosis, and promoting survival. The hemorrhage observed in DIC and among some tissues lacking this receptor may thereby be secondary to increased thrombosis with loss of the mechanical vascular barrier.

CLINICAL FINDINGS

Signs associated with DIC depend on the individual dog, the length of time the dog has been ill and the underlying conditions. Initial signs typically reflect the underlying disease or disorder. Advanced signs may include lethargy, weakness, pale mucous membranes or icterus (yellow), bruising (ecchymosis), pinpoint hemorrhages (petechiae), bleeding from any orifice – urinary tract, blood in stool, blood in vomit, rapid breathing (tachypnea) and fast heart rate (tachycardia).

Clinically the disorder is divided into two forms:

a) Acute form: It is a hemorrhagic disorder characterised by multiple petechiae, ecchymoses on skin, mucosal bleeding, visceral hemorrhages, bleeding from surgical, traumatic and venipuncture sites, deep tissue hematomas, acral cyanosis and gangrene. It is usually seen after acute trauma or manifests as secondary to the primary disease.

b) Chronic form: It is more subtle, usually does not have spontaneous bleeding and is characterised by superficial venous thrombosis, signs of deep venous or arterial thrombosis, and serial thrombotic episodes. This form is more commonly seen in dogs with concomitant malignancy or chronic disorders.

DIAGNOSIS

Disseminated intravascular coagulation is usually difficult to diagnose as it can be triggered by many unrelated diseases and the clinical manifestation is variable. There is quasi-consensus about the definitive diagnosis. Veterinary care should include diagnostic tests to determine the underlying disorder as well as the blood clotting parameters. There is not a single test that can diagnose DIC. Disseminated intravascular coagulation is generally diagnosed based on the presence of an underlying disease that causes DIC combined with laboratory changes that suggest problems in the coagulation (clotting) system. Diagnosis is based on the following criteria:

- Complete medical history and thorough physical examination to find out clinical findings and the presence of underlying diseases known to be associated with DIC. Special attention need to be paid to any bruising or bleeding.
- Complete blood count (CBC) can discover anemia, abnormal platelet numbers and abnormal white blood cell counts. Infections are a common contributing factor in the development of DIC. The red blood cells may be fragmented (schistocytes) or damaged by fibrin strands that are present within the blood vessels.
- Blood smear may be performed to evaluate the red blood cell morphology and presence of platelets.
- Clotting tests such as an activated clotting time (ACT), prothrombin time (PT) and activated partial thromboplastin time (APTT) are used to determine if anemia and/or bleeding are due to the inability of the animal to clot its blood. These values are greatly prolonged in the hemorrhagic phase of DIC. The values can be short in the early phases.
- Serum fibrinogen concentration and fibrin degradation products (FDPs) are tests used to identify the presence of breakdown products of fibrin which are elevated in DIC.
- Packed cell volume (PCV) may be routinely monitored to evaluate the anemia.

Overall, haemogram and serum chemistry in dogs with DIC will reveal hypofibrinogenemia, increased FDPs (more than 1:10) and D-dimers concentrations, prolonged APTT, decreased antithrombin III concentration (50-80%), hemolytic anemia, thromocytopenia (20-80,000/ml), increased schistocytes, left shift neutrophilia, rarely neutropenia, hyperbilirubinemia, hyperphosphatemia, increased liver enzymes, decreased total CO_2 (metabolic acidosis) and panhypoprotenemia (severe bleeding).

Additional tests may be recommended on an individual basis. They may be recommended to help evaluate or determine the underlying cause for DIC. These tests include:

- Serum biochemical profile to determine potential underlying causes of DIC.
- Analysis of the urine to check abnormalities like hemoglobinurea, bilirubinurea, occasional proteinurea and cylindruria (urine sample should not be obtained via cystocentesis).
- If anemia is present, a reticulocyte count determines whether the animal's body is trying to regenerate red blood cells that have been lost.
- Abdominal radiography (xray) and/or ultrsonography (ultrasound) may be done to rule out changes in size of organs like the liver or kidneys or to look for evidence of abdominal tumors.

TREATMENT

Despite the bad prognosis, animals with DIC can survive, if the underlying cause is a treatable illness and the coagulation abnormalities are treated appropriately and promptly. Patients with DIC will require initial in-hospital stabilisation. Treatment is primarily directed at the underlying disease. In-hospital therapy includes intensive care and frequent evaluation of bleeding and blood clotting parameters. The aim is to treat the underlying condition while trying to control hemorrhage that results from DIC.

While treatment of DIC needs individual attention, the following principles are helpful:

1. Diagnose and remove or treat the underlying cause of the DIC.
2. Supportive care: Aggressive fluid therapy with crystalloids or plasma extenders (dextran) is an essential component of case management to maintain good tissue perfusion, to dilute activated clotting and fibrinolytic factors, to flush out microthrombi, to maintain precapillary and arteriole patency to increase blood flow to hypoxic areas. Corticosteroids can be used to establish perfusion.
3. Prevent secondary complications by maintaining oxygen mask, cage oxygen, or nasopharyngeal catheter, by checking secondary bacterial infections and by correcting acidosis and cardiac arrhythmias.
4. Prevent intravascular coagulation by administration of heparin, aspirin, blood or blood products. Low-molecular weight heparin may be the more appropriate choice as high molecular fractions of standard heparin have a platelet pro-aggregating effect.
5. Therapy: Heparin dose ranges from mini-dose heparin: 5-10U/kg SC TID to high-dose heparin:750-1000 U/kg SC or IV TID. Add the initial mini-dose heparin to the blood/plasma prior to transfusion and allow to sit at room temperature for 30 min. Use the intermediate or high dose heparin if marked azotemia, isosthenic urine, increased liver enzymes, dyspnea or hypoxemia supervene. If overheparinisation occurs, use protamine sulfate to slow IV infusion (1 mg / 100 U of the last dose of heparin given) as 50% of the calculated dose 1 h after heparin, and 25% given 2 h after heparin. Once clinical and clinico-pathological features have improved, taper the heparin dose gradually over 3 to 4 days.
6. Plasma that has been frozen soon after collection (fresh frozen plasma) may be administered to provide clotting factors in cases of DIC where the dog has been treated with heparin to prevent ongoing coagulation. Sometimes heparin is mixed with the fresh frozen plasma.
7. Blood transfusions may be recommended for dogs with anemia or heavy blood loss.
8. Frequent monitoring of PCVs, platelet counts, blood clotting times and other tests that can evaluate the primary cause may be preformed to help evaluate the effectiveness of a guide for additional therapy.
9. Aspirin is not an effective treatment in most of the dogs with acute DIC, but can be used to manage chronic cases or to prevent recurrence @ 5 –10 mg / kg PO BID.

PROGNOSIS

Prognosis varies depending on the underlying disorder, the extent of the intravascular thrombosis (clotting) and the response of the dog to the therapy. The prognosis for dogs with DIC, regardless of cause, is often grim: between 10% and 50% mortality. DIC with sepsis has a significantly higher rate of death than DIC associated with trauma.

CONCLUSION

Disseminated intravascular coagulation (DIC), judging by the lack of clinical reports, is probably less common in dogs when compared to humans. To some extent, this may be due to shortage in documentation attributable to limited application of suitable diagnostic tests in emergency patients. Moreover, there is no agreement concerning guidelines to establish diagnosis in dogs. Many cases may have been overlooked. Certainly, there are various reports of pathologic abnormalities in coagulation profiles in dogs. New information about the pathophysiology and treatment of DIC promises new hope of an improved prognosis for this disorder. It has long been associated with unacceptably high mortality. Important breakthroughs will

need a conceptual shift that emphasises relations between the various mediators and factors that propagate generation of thrombin, especially with regard to the links between inflammation and coagulation. Additional studies promise to provide new insights into DIC, not as an isolated mechanism but rather as a coordinator of events that substantially affects outcome in sepsis and critical illness.

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