Fortnightly Review

Disseminated intravascular coagulation: diagnosis and treatment

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The normal response to tissue damage is a contained explosion of thrombin generation at the site of injury. This localised thrombin explosion on the surface of damaged microvessels results in coagulation of blood and stops blood loss. In disseminated intravascular coagulation an unregulated thrombin explosion causes release of free thrombin into the circulation. Widespread microvascular thrombosis produces tissue ischaemia and organ damage. In an attempt to maintain vascular patency, excess plasmin is generated so that systemic fibrinogenolysis as well as local fibrinolysis occurs. It is the generation of free thrombin and plasmin within the circulation that leads to the clinical features of disseminated intravascular coagulation, with thrombin and plasmin responsible for the thrombotic and haemorrhagic manifestations respectively. The diagnosis and treatment of this syndrome require an understanding of the thrombin explosion, awareness of the disorders that can trigger disseminated intravascular coagulation, and recognition of the syndrome.

Summary points

- Disseminated intravascular coagulation is primarily a clinical diagnosis, and laboratory tests are used to confirm the diagnosis and monitor replacement of blood components
- Tests required are platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, and a measure of fibrinogen degradation products
- Treatment of disseminated intravascular coagulation is primarily that of the underlying condition
- Maintenance of blood volume and tissue perfusion is essential in all cases of disseminated intravascular coagulation
- Replacement of blood components is indicated if the patient is bleeding or an invasive procedure is required and must be monitored

The thrombin explosion

Tissue factor is released locally at sites of tissue damage (see fig 1). This tissue factor complexes with factor VII and directly generates the enzymatic components of the tenase and prothrombinase complexes that are required for thrombin generation. Analogous to lighting a fire, the spark of tissue factor-factor VII

Fig 1—The thrombin explosion. Tissue damage releases tissue factor (TF), which activates enzymatic components of tenase (factor IX) and prothrombinase (factor X) complexes, leading to thrombin generation. Thrombin generation amplifies itself through series of positive feedback loops—for example, exposure of internal platelet membrane leaflet and activation of non-enzymatic cofactors VIII and V, which bind coagulation enzymes to platelet surface

complex is rapidly extinguished by tissue factor inhibitor, and the spark is insufficient to maintain a flame (thrombin generation). However, the spark ignites the tenase complex, which acts as a firelighter, and this continues to fire the wood (the prothrombinase complex) after the spark has been extinguished. This produces a flame of thrombin generation sufficient to burn the coal (convert fibrinogen to fibrin).

Obviously, the firelighter, wood, and coal must be in the right place. In the case of the haemostatic system the platelets build the fire. The external membrane of the platelet is normally inert, but in the presence of minute amounts of thrombin (20 nmol/l) the internal anionic phospholipid leaflet is flipped onto the exterior. This recognises, binds, concentrates, and orientates all the components of the haemostatic system so that ordered sequential activation results in an explosion of thrombin generation.¹

CONTAINING THE THROMBIN EXPLOSION

The endothelium acts like a fire extinguisher. Functional healthy endothelium concentrates anti-thrombin molecules on its surface and expresses thrombomodulin molecules. If thrombin is generated next to healthy intact endothelium it is either captured and neutralised by antithrombin or binds to thrombomodulin, which alters its substrate specificity so radically that it is no longer capable of converting fibrinogen to fibrin. Instead, thrombomodulin bound thrombin activates the natural anticoagulant protein C system, which rapidly dismantles the fire. Thus, the

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When thrombin is generated at a site of tissue damage there is no intact endothelium and thus no extinguisher, and explosive thrombin generation causes blood to clot. As the thrombin explosion spreads, it eventually meets intact healthy endothelium outside the area of tissue damage. The explosion is then rapidly ended by the extinguishing properties of the antithrombin and protein C system associated with intact endothelium. Hence, the thrombin explosion is contained at the site of tissue damage.

ulopathy eventually occurs unless the uterus is evacuated.

Liver disease may be a cause of disseminated intravascular coagulation, but it is still not clear whether the intravascular coagulation is a major component of the coagulopathy of liver disease. The prolonged survival of radiolabelled fibrinogen in the circulation after administration of heparin is the strongest evidence for consumptive coagulopathy in patients with liver failure, but it does not seem to be a major contribution to the coagulopathy.¹⁰

Localised chronic intravascular coagulation occurs in patients with aortic aneurysms, haemangiomas (Kasabach-Meritt syndrome), or empyema. The local generation of thrombin and plasmin may be so great that coagulation factors and platelets are depleted, leading to a systemic hypocoagulable state and haemorrhagic complications indistinguishable from true disseminated intravascular coagulation.

Diagnosis of disseminated intravascular coagulation

The diagnosis of this syndrome is essentially clinical, with laboratory tests providing confirmatory evidence. A pathological degree of bleeding in a sick patient should alert doctors to the possibility of disseminated intravascular coagulation. Depending on the relative rates of formation and breakdown of fibrin, the syndrome may be asymptomatic or cause severe bleeding or thrombosis, or both.

Haemorrhage is the commonest presentation and is caused by generation of free plasmin and depletion of coagulation factors and platelets. Hyperfibrinolysis due to the excess generation of plasmin seems to be the major cause, as bleeding is most severe in patients with low antiplasmin activity.¹¹ Furthermore, pharmacological induction of hyperfibrinolysis by alteplase (rt-PA) or streptokinase causes more bleeding than induction of hypofibrinogenaemia by ancrod, a derivative of snake venom.¹² Nevertheless, microvascular thrombosis is the primary mechanism in most cases of disseminated intravascular coagulation, and end organ failure is a major cause of death.

Spontaneous bruising, petechiae, mucosal oozing, prolonged bleeding at venepuncture sites, and secondary haemorrhage into surgical wounds are common. Bleeding from multiple sites should immediately suggest the syndrome, which can be confirmed with laboratory tests. In acute disseminated intravascular coagulation the haemorrhagic features are also associated with hypovolaemia, hypotension, and shock. This is probably the result of activation of contact factor, which leads to production of bradykinin¹³ and interaction between cytokines such as tumour necrosis factor and interleukin 1.² Hypotensive shock does not seem to be due to the release of tissue factor from damaged tissues: in an experimental model of the syndrome, administration of antibody to tissue factor reduced formation of fibrin but had no effect on hypotension.¹⁴

Acute renal failure is typical and probably results from a combination of microvascular thrombosis in the kidney and reduced renal blood flow due to hypotension. Acute tubular necrosis is common. Disseminated microvascular thrombosis in the brain leads to generalised cortical and brain stem dysfunction with impaired consciousness and coma. A sudden deterioration in association with localising signs suggests intracranial bleeding. Thrombosis and haemorrhage in the lungs causes hypoxia and progressive respiratory failure identical to that seen in patients with the adult respiratory distress syndrome. The syndromes of disseminated intravascular coagulation and adult respiratory distress syndrome overlap, with 20% of patients sharing the features of both.⁸

Submucosal necrosis in the gastrointestinal tract causes secondary haemorrhage, and in the most fulminant cases, usually due to infection, adrenal haemorrhagic necrosis is typically seen at necropsy (Waterhouse-Friedrichsen syndrome).

Purpura fulminans is a particularly severe form of disseminated intravascular coagulation, with haemorrhagic skin necrosis and gangrene that is typically associated with infection. It may occur during infection with Gram negative bacteria or seven to 10 days after chickenpox or scarlet fever in children.

CONFIRMATION OF DIAGNOSIS BY LABORATORY TESTS

While many laboratory methods are available to detect excess generation of thrombin and plasmin, only a few simple, readily available tests are required to confirm the diagnosis of disseminated intravascular coagulation.

Thrombin generation

Thrombocytopenia due to thrombin generation is an almost universal finding in acute disseminated intravascular coagulation.¹⁵⁻¹⁷ Production of platelets by the bone marrow is increased,¹⁸ but platelet survival is so short that severe thrombocytopenia is common.

Global tests of the capacity of the coagulation system to generate thrombin may show prolonged prothrombin times and activated partial thromboplastin times because of consumptive deficiency of the components of the tenase and prothrombinase complexes and the precursor of thrombin itself, prothrombin. However, prothrombin time and activated partial thromboplastin time are abnormal in only 70% and 50% of patients respectively.¹⁷ Similarly, fibrinogen concentrations are low in less than half of patients.^{16,17} The thrombin clotting time is usually prolonged but does not give any indication of the severity of the syndrome in addition to that provided by the concentrations of fibrinogen and fibrin degradation products.

The concentrations of individual coagulation factors and of the natural anticoagulants antithrombin and protein C are often low because of consumption, and high concentrations of prothrombin and fibrinogen activation peptides reflect generation of thrombin. However, it is not necessary to perform these tests for diagnostic or routine therapeutic purposes, and it is sufficient to measure platelet count, prothrombin time, activated partial thromboplastin time, and fibrinogen concentration.

Recognition of disseminated intravascular coagulation

Plasmin generation (haemorrhage)

- Spontaneous bruising
- Petechiae
- Gastrointestinal bleeding
- Respiratory tract bleeding
- Persistent bleeding at venepuncture sites
- Bleeding at surgical wounds
- Intracranial bleeding

Thrombin generation (thrombosis)

- Renal failure
- Coma
- Liver failure
- Respiratory failure
- Skin necrosis
- Gangrene
- Venous thromboembolism

Cytokine and kinin generation (shock)

- Tachycardia
- Hypotension
- Oedema

Plasmin generation

Elevated plasma concentrations of fibrin and fibrinogen degradation products reflect generation of plasmin, and abnormal concentrations are found in 85% of patients.^{16 17 19} While monoclonal antibodies to specific epitopes of fibrin and fibrinogen now permit distinction between fibrinolysis and fibrinogenolysis, the main advantage of a fibrin specific monoclonal antibody test is that it can be performed on routine plasma samples rather than specially prepared serum samples.¹⁹ High plasma concentrations of fibrinogen degradation products are not specific for disseminated intravascular coagulation and occur after surgery, in patients with haematomas, and in patients with liver or renal failure.

Generation of free plasmin can also be identified by a short clot lysis time and low plasma concentrations of its precursor plasminogen and its inhibitor α_2 -antiplasmin. However, these tests are not routinely required, and a simple measure of fibrin degradation products, such as the D-dimer latex agglutination test, is sufficient.

Other tests

Examination of a blood film may reveal red cell fragmentation, but this is variable and is not always present. The mechanism is unknown, and its presence does not help to elucidate the cause of disseminated intravascular coagulation. Considerable fragmentation with moderate to severe thrombocytopenia but only mildly abnormal coagulation tests raises the possibility of thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome rather than disseminated intravascular coagulation. In such cases the clinical features will indicate which of the conditions is most likely.

Other laboratory tests should be used to determine the degree of renal and liver impairment. Blood should be taken for bacterial culture and testing of antibiotic sensitivity before antibiotics are given, though the clinical situation may dictate the use of antibiotics before the results are available. Arterial blood gases may be complicated by severe haemorrhage, and respiratory function is more safely assessed by pulse oximetry.

Treatment of disseminated intravascular coagulation

Treatment of the underlying cause is essential for treating disseminated intravascular coagulation. The condition will not resolve until the trigger mechanism is removed, and deaths of patients with disseminated intravascular coagulation are often the result of the underlying disease. Patients may be treated with blood components to replace depleted coagulation factors, platelets, and natural inhibitors of thrombin and plasmin in an attempt to reduce bleeding while the underlying problem is corrected. Only rarely is pharmacological manipulation of the haemostatic system attempted. Unfortunately, the optimal regimen for treatment with blood components and the absolute indications for anticoagulant and antifibrinolytic treatments are unknown.

Critically ill patients may develop a coagulopathy because of vitamin K deficiency, and 10 mg of vitamin K should be given on two consecutive days before coagulopathy is attributed exclusively to disseminated intravascular coagulation.²⁰ Patients with disseminated intravascular coagulation can also become vitamin K deficient because of its increased use, and administration of vitamin K to all patients with suspected disseminated intravascular coagulation will replenish stores. Some doctors also give folic acid in order to prevent acute folate deficiency and impaired platelet

production. Tissue perfusion and respiratory function must be maintained by replacing intravenous fluid and providing oxygen to correct hypoxia.

Parenteral antibiotics should be administered without delay when bacterial infection is suspected. In obstetric cases removal of the fetus and placenta will usually result in rapid resolution of the condition. Surgical removal of an aortic aneurysm or ablation of the vascular bed of a haemangioma will also halt localised generation of thrombin causing a consumptive coagulopathy.

TREATMENT WITH BLOOD COMPONENTS

Measuring the concentration of platelets and fibrinogen and assessing the prothrombin times and activated partial thromboplastin times are essential for guiding management. However, the decision to start replacing blood components is determined by whether the patient is bleeding and whether an invasive procedure is required. If there is no bleeding and such a procedure is not required then replacement is not indicated. If the patient is bleeding or a procedure is required then an attempt to restore haemostatic capacity by replacing platelets and coagulation factors is indicated. Replacement should be monitored by assessing the immediate effect after transfusion of blood components and a few hours later to determine the severity of disseminated intravascular coagulation and whether further treatment is required.

If the decision to give blood components has been made platelet concentrates should be given at a dose of 1 donor unit/10 kg body weight when the platelet count is below $50 \times 10^9/l$. Fresh frozen plasma contains more fibrinogen than cryoprecipitate as well as all the coagulation factors and natural anticoagulants such as antithrombin and protein C. It should be given at a dose of 15 ml/kg body weight. If fresh frozen plasma cannot maintain the fibrinogen concentration above 0.5 g/l then cryoprecipitate can be given as well.

THROMBIN AND PLASMIN INHIBITORS

Heparin

The indications for treatment with heparin and the dose required are not established.²¹ There is no conclusive evidence that heparin treatment reduces morbidity or mortality in acute disseminated intravascular coagulation. Because of the heterogeneity of the disease there are no controlled prospective trials comparing different treatments. For the same reason, tentative conclusions from retrospective analyses must be regarded cautiously. All that can be concluded about the role of heparin in treating disseminated intravascular coagulation is that, while some patients seem to benefit, it should be used with extreme caution and at a low dose.⁸ Its use in patients with purpura fulminans is debatable.^{8 9}

Heparin can restore fibrinogen concentrations in the retained dead fetus syndrome, but simple replacement of blood components will achieve the same effect without increasing the risk of haemorrhage. Heparin treatment in patients with acute promyelocytic leukaemia has been supported by one retrospective study²² but not by another.²³ There are no adequate studies of heparin treatment in patients with septic shock and disseminated intravascular coagulation. When heparin is used a dose of 1000 units/hour or 15 units/kg/hour by continuous infusion has been recommended as there are no data on dose responses and the coagulopathy makes it extremely difficult to monitor the treatment.

Patients with cancer and large vessel thrombosis should receive conventional doses of heparin to maintain the activated partial thromboplastin time at twice normal as this can be extremely beneficial.⁷

Natural inhibitors

Infusion of concentrates of natural thrombin inhibitors such as antithrombin or protein C, with or without heparin, has been attempted. In an animal model of sepsis, infusion of antithrombin before endotoxin prevented disseminated intravascular coagulation and improved survival. However, survival was not improved when the antithrombin was given after the endotoxin. This may explain the relatively disappointing results in the limited clinical studies that have been performed.²⁴ Nevertheless, an apparent reduction in mortality associated with resolution of disseminated intravascular coagulation in patients given antithrombin infusions indicates that a large multicentre trial is justified to determine if and when antithrombin treatment is indicated.²⁵ Antithrombin has some inhibitory effect on the tissue factor-factor VII complex, but use of a specific inhibitor such as tissue factor inhibitor requires evaluation. As the complex has a pivotal role in many patients with disseminated intravascular coagulation, the effect of specific inhibition should be examined.

Infusion of protein C also prevented disseminated intravascular coagulation in an animal model of sepsis,²⁶ but a beneficial effect in humans has not yet been established.

Synthetic inhibitors

Heparin treatment may be ineffective because it requires antithrombin for anticoagulant activity, and this is usually reduced in disseminated intravascular coagulation. Direct thrombin inhibitors may be more effective as they do not require antithrombin. Recombinant hirudin reduces thrombin activity in disseminated intravascular coagulation, but clinical benefit has not yet been evaluated.²⁷

Plasmin inhibitors such as tranexamic acid or aprotinin are generally considered to be contraindicated because of the risk of increased end organ damage from microvascular thrombosis.⁸ However, they are occasionally given when patients continue to bleed despite treatment with blood components.

The combination of a thrombin inhibitor such as heparin and a plasmin inhibitor may be most beneficial, but this combination has not been evaluated in a clinical trial. Gabexate mesylate is a synthetic inhibitor of serine proteases, including thrombin and plasmin. It would therefore seem to be a potentially useful agent for treating disseminated intravascular coagulation. In a non-randomised study in which all patients were treated, the severity of disseminated intravascular coagulation seemed to improve as judged retrospectively by changes in a score for disseminated intravascular coagulation.²⁸ Unfortunately, this drug has not been examined in controlled trials.

Conclusion

Disseminated intravascular coagulation is a clinical syndrome, and laboratory tests provide confirmation. Treatment is that of the underlying condition. Replacement of blood components is indicated if bleeding is present or an invasive procedure is required. Indications for treatment with heparin are not established. Provisional studies suggest that

infusion of natural anticoagulants such as antithrombin are beneficial, but further studies are needed for clarification. Theoretically, the combined inhibition of thrombin and plasmin might be beneficial, but this has not yet been tested in clinical trials. Better understanding of the influence of cytokines on coagulation may lead to new treatments for disseminated intravascular coagulation associated with infection or carcinoma.

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