Etiopathophysiology of Disseminated Intravascular Coagulation

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Abstract
Disseminated intravascular coagulation (DIC) involves activation of clotting as well as fibrinolytic pathways. Thrombosis from thrombin release results in end-organ damage, whereas consumption of coagulation factors results in bleeding. Sepsis is the commonest cause of DIC. The consumption of antithrombin in sepsis abrogates its anti-inflammatory role and so its low level is a poor prognostic marker in sepsis. The increased release of plasminogen activator inhibitor-1 (PAI-1) as seen in sepsis decreases fibrinolysis and promotes increased microvascular thrombosis. Here, we discuss the role of inhibitors of coagulation, cytokines, kinins, complement and vasoactive peptides in DIC.

Etiology/Triggering Factors (Table 1)
Sepsis is the most common cause of acute DIC. Septic patients who develop DIC have a higher mortality rate than those who exhibit no signs of DIC and they have more organ dysfunction. In a large prospective study, the incidence of DIC in sepsis was 16%, in severe sepsis 18% and in septic shock 38%. In Gram-negative septicemia, coagulation occurs by activation of the tissue factor dependent extrinsic pathway that is initiated through sepsis-induced tissue factor expression by monocytes and endothelial cells (Fig. 1). There is also inadequate fibrinolysis due to increased levels of plasminogen activator inhibitor-1 in sepsis.

Table 1: Etiology of DIC

1. Infections
   • Bacterial sepsis
   • Viral hemorrhagic fevers
2. Obstetrical accidents
   • Placental abruption
   • Retained fetus syndrome
   • Amniotic fluid embolism
3. Malignancies
   • Acute promyelocytic leukemia
   • Solid tumours
4. Trauma
   • Head injuries
   • Burns
5. Intravascular hemolysis
6. Hemangiomas and vasculitis
   • Kassabach Merritt syndrome
   • Hereditary hemorrhagic telangiectasia
7. Miscellaneous
   • Prosthetic shunts
   • Acidity
   • Heat stroke
   • Snake bites
plasminogen activator inhibitor type 1 (PAI-1). Many viral infections such as HIV, varicella, CMV, EBV, rubella, rubeola and influenza have been associated with DIC possibly to endothelial injury. There is some suggestion that viral hemorrhagic fevers may lead to biosynthesis of selenoprotein which could impose an unprecedented selenium demand on the host, potentially leading to severe lipid peroxidation and cell membrane destruction contributing to hemorrhagic symptoms.

Obstetrical accidents such as placental abruption, amniotic fluid embolism and the retained fetus syndrome can all trigger DIC related to the release of placental tissue factor and a direct activator of the prothrombinase complex into the maternal circulation. Often the retained fetus syndrome triggers chronic DIC. Sepsis by gram-negative bacteria and clostridium perfringens are among the more common causes of sepsis encountered during pregnancy and they are frequently associated with DIC.

Acute promelocytic leukemia (APL) is the most frequent leukemia associated with life threatening hemorrhage that may be due to primary fibrinolysis related to abnormally high levels of expression of annexin II on these leukemic cells that increase plasmin production. In solid tumours, there are many tumor procoagulants that have been identified and are compiled in the International Society for Thrombosis and Hemostasis registry. The two principal tumour cell procoagulants are tissue factor and cancer procoagulant. All major traumas, head injuries and burns induce DIC due to a massive exposure of tissue factor to blood. No matter what the cause of trauma, there appears to be a direct relationship of the coagulopathy to the severity of injury. Intravascular immune hemolysis especially transfusion reactions triggers DIC probably due to the antigen antibody reactions and decreased mononuclear phagocytic activity with increase in monocyte procoagulant activity. Hereditary vascular disorders such as Kassabach-Merritt syndrome and hereditary hemorrhagic telangiectasia, and those with systemic vasculitic syndromes and chronic inflammatory disorders are also predisposed to compensated DIC.

Prosthetic devices such as intra-aortic balloon pumps, Leveen or Denver valve shunts can trigger DIC. Even prolonged conditions of acidosis have lead to sufficient endothelial damage to initiate and promote intravascular coagulation. Heat stroke can also cause endothelial damage with release of tissue factor leading to DIC. Various snakes, especially Crotalidae (pit vipers) affect different aspects of the coagulation cascade, and death may occur typically due to hemorrhage, shock or renal failure.

**Pathophysiology**

The pathogenesis of DIC requires an understanding of the entire coagulation, fibrinolytic and their inhibitor pathways. Recent literature has suggested the role of various cytokines in the pathophysiology of DIC and their role appears to be interlinked in a highly complex manner.

**Coagulation (Fig. 1)**

The process of DIC is initiated when there is a triggering stimulus for thrombin generation that occurs usually via the extrinsic pathway due to release or increased expression of tissue factor as in sepsis and obstetrical accidents, and occasionally via the intrinsic pathway due to endothelial damage as in vascular disorders. Activated factor X generates thrombin from prothrombin by cleaving its N-terminal end and forms prothrombin fragments 1 and 2 (F1+2). Thrombin cleaves fibrinogen into fibrinoepeptides A and B (FPA and FPB), and generates fibrin monomers. Thrombin also releases interleukin-1 (IL-1) and tumour necrosis factor (TNF) from the monocytes and macrophages, and this process is enhanced in the presence of gram-negative lipopolysaccharide endotoxemia. In addition, thrombin induces vascular endothelium to release endothelin and selection, the role of which will be discussed later. If there is no fibrinolytic activity, then the fibrin monomers that are formed as a result of procoagulant activation would polymerize to form complex fibrin polymers in the presence of factor XIII resulting in diffuse thrombosis.

**Fibrinolysis (Fig. 2)**

In DIC, the fibrinolytic system also gets activated and plasmin is generated. Plasmin cleaves the carboxy terminal end of fibrinogen and forms X, Y, D and E fragments. These fragments form the fibrin (ogen) degradation products (FDPs). The X and Y fragments combine with the fibrin monomer and

![Fig. 1: Coagulation cascade showing thrombin generation through intrinsic and extrinsic pathway. Inhibitors of coagulation are shown with a dotted line](image-url)
form soluble fibrin monomer, so-called since it cannot get polymerized and hence this would aggravate bleeding. The soluble fibrin monomer forms the basis of the paracoagulation reactions such as ethanol gelation and protamine sulfate tests. When either protamine sulfate or ethanol is added to plasma, they remove the X and Y fragments and the fibrin monomers polymerize seen as fibrin strands that is interpreted as a positive test. The D and E fragments bind to the platelet membrane resulting in platelet dysfunction that would further aggravate bleeding.

Plasmin cleaves the complex fibrin polymer formine D-dimer, which is a more specific fibrin degradation product. The complement system also gets activated by plasmin, which results in aggravation of many of the clinical manifestations of DIC as discussed later. Plasmin activation would lead to enhanced bleeding, however, the FDPs and D-dimer releases PAI-1 from the monocytes and macrophages that would decrease fibrinolysis and enhance fibrin polymer precipitation. The increased levels of PAI-1 are especially seen in sepsis that explains why in sepsis-induced DIC, thrombosis is predominant and further contributes to the end organ damage.

**Cytokines (Fig. 3)**

Recently the role of various cytokines and vasoactive peptides has been elucidated which may be contributing to the end organ damage seen with disseminated intravascular coagulation and also in potentiation of the entire process. Thrombin induced release of TNF from the monocytes activates the complement. The FDPs and D-dimer releases PAI-1 from the monocytes and macrophages that would decrease fibrinolysis and enhance fibrin polymer precipitation. The increased levels of PAI-1 are especially seen in sepsis that explains why in sepsis-induced DIC, thrombosis is predominant and further contributes to the end organ damage.

**Complement (Fig. 3)**

In DIC, the complement is activated by plasmin and TNF. This results in hemolysis and thrombocytopenia. Complement induced platelet lysis provides more procoagulant material further accentuating the coagulation process. The complement increases vascular permeability leading to hypotension and shock.

**Kinins (Fig. 3)**

The activation of factor XII converts prekallikrein to kallikrein that in turn converts high molecular weight kininogen to kinins. The kinins also increase vascular permeability and so induce hypotension and shock.

**Inhibitors of coagulation (Fig. 1)**

During the process of DIC, the inhibitors such as protein C, protein S and antithrombin also get consumed along with other coagulation factors. Protein C and cofactor Protein S mainly regulates the amounts of thrombin and factor Xa that are formed from their respective precursors. Antithrombin in contrast directly inhibits the enzymes generated during activation of the clotting cascade, especially thrombin, Xa and IXa. The role of antithrombin in DIC has been extensively studied in sepsis and trauma patients. Antithrombin needs to bind to a specific pentasaccharide unit in the heparin molecule to get activated. Glycosaminoglycan (GAG) heparan sulfate on the endothelial cell surfaces also contains the pentasaccharide unit and can thus activate antithrombin. Most of the enzyme activation by antithrombin occurs on the endothelium. The binding of antithrombin to the GAGs also releases prostacyclin that possesses strong anti-inflammatory properties. Tissue factor pathway inhibitor (TFPI), which is produced constitutively in the endothelial cells, seems to play a role in inhibiting thrombosis and DIC.
However, the plasma levels of TFPI do not decrease in sepsis but may even increase due to release from the endothelial cells.\(^{10}\)

**SUMMARY**

Summarizing, in DIC both clotting and fibrinolytic systems are activated. If the clotting system is more activated, it leads to microvascular thrombosis with resultant end organ damage. However, ultimately consumption of coagulation factors and platelets would result in consumption coagulopathy. If fibrinolytic system is more activated as in acute promyelocytic leukemia, then there is increased bleeding due to formation of sFM, disruption of the complex fibrin clot and platelet dysfunction. Activation of coagulation system activates anticoagulant inhibitors that get consumed during the process thereby resulting in enhanced coagulation. The consumption of antithrombin in sepsis abrogates its anti-inflammatory role and so its low level is a poor prognostic marker in sepsis. The increased release of PAI-1 as seen in sepsis decreases fibrinolysis and promotes increased microvascular thrombosis. Finally the role of kinins, complement, cytokines and vasoactive peptides in DIC is noteworthy.

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