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Diagnosis and management of disseminated intravascular coagulation and primary hyperfibrinolysis

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Introduction

Disseminated intravascular coagulation (DIC) is the systemic activation of coagulation that leads to a widespread intravascular fibrin formation in small- to medium-sized vessels with concomitant hyperactivation of the fibrinolytic system.[1,2] This severe imbalance of the hemostatic system can cause bleeding and organ dysfunction.[1,2] Poor prognosis of DIC has prompted some authors to read the acronym DIC as 'death is coming'.

DIC is always the final stage of a coagulopathy caused by an underlying condition: unprovoked DIC has never been described till now.[1-4] Severe infections, neoplasia, and obstetric complications are the major underlying cause of DIC. DIC affects almost 30% of patients with severe sepsis and 50% of patients with obstetric complications, such as abruptio placentae and amniotic embolism. Moreover, nearly 90% of patients with acute promyelocytic leukemia have DIC.

In patients with sepsis, systemic inflammatory response liberates intracellular proteases and produces cytokines that activate the coagulation system by increasing generation of tissue factor (TF), inhibiting natural mechanisms of anticoagulation and reducing the expression of thrombomodulin on the endothelium.[5] Increased levels of NETs induce apoptosis of vascular endothelial cells and degrade tissue factor pathway inhibitor, which promote platelet aggregation and increase hypercoagulability, respectively. Finally, increased plasminogen activator inhibitor 1 (PAI-1) levels inhibit fibrinolytic response.

Solid tumors may both activate the coagulation system by procoagulant molecules, such as TF, and inhibit the fibrinolytic system[6]. Some cancer cells, such as in prostatic adenocarcinoma, may express plasminogen activators molecules that can directly activate fibrinolysis and cause a primary hyperfibrinolysis syndrome. Extensive tissue damage, such as in burns, increase TF levels that lead to an uncontrolled generation of thrombin. A localized DIC is typical of some vascular abnormalities, such as giant hemangioma (the so called 'Kasabach-Merritt syndrome') and large aortic aneurysms, in which deposition of fibrin is limited to abnormal vessels and not disseminated.[4]

Current state of the art

Patients with DIC may present with bleeding, organ dysfunction, thrombosis of large vessels, or can be totally asymptomatic despite laboratory test abnormalities.[4,7] There are four main clinical phenotypes of patients with DIC: 'bleeding patient', 'patient with severe bleeding', 'patient with organ dysfunction' and 'asymptomatic patient'.[4] Clinical phenotypes are the results of the relative imbalance of the coagulation and fibrinolytic system.[4] When secondary hyperfibrinolysis is prevalent, such as in some patients with acute promyelocytic leukemia and obstetric complications, the first clinical manifestation is bleeding. When hypercoagulability overcomes hyperfibrinolysis, such as in patients with sepsis, organ dysfunction is the main clinical manifestation. When both coagulation and fibrinolytic system are only minimally altered, such as in some cancer patients, mild bleeding or asymptomatic coagulation test abnormalities are the typical clinical presentation. DIC may be also defined as acute or chronic: patients with acute DIC have major bleeding and/or organ dysfunction as main clinical presentation; patients with chronic DIC have usually mild bleeding or are completely asymptomatic. Different underlying pathophysiological processes and clinical phenotype suggest that the acronym DIC may be also read as 'disease-induced coagulopathy' and, therefore, new acronyms can be proposed for each underlying DIC causes (Table 1).

Diagnosis of DIC and identification of the underlying cause should be the most rapid as possible: if left untreated, patients have an unavoidable poor prognosis.[8-11] Unfortunately, no gold standard for the diagnosis of DIC exists, not a single laboratory test has shown sufficiently high diagnostic accuracy to establish or rule out the diagnosis of DIC, and it is not possible to diagnose DIC in the early phases.[7,12,13] A combination of the following altered laboratory tests suggests DIC: reduced

platelet count, prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), reduced fibrinogen and increased D-dimer.[2] None of these tests is specific, as each abnormal value may be explained by other conditions and by the underlying disease itself. A reduction of natural anticoagulants such as antithrombin and protein C is common, and may be useful to support DIC diagnosis when rapidly available.

Several diagnostic score have been proposed to increase diagnostic accuracy.[7,12,14] The International Society of Thrombosis and Hemostasis (ISTH) score was extensively investigated in cohort studies and was recommended by national and international guidelines. Recently, DIC subcommittee of the Japanese Society on Thrombosis and Hemostasis proposed new diagnostic criteria for DIC and an extensive list of alternative diagnoses.[14] Indeed, differential diagnosis includes other conditions that can cause blood test abnormalities such as liver disease, thrombotic microangiopathy and primary hyperfibrinolysis.[2,1]. Clinical suspicion of primary hyperfibrinolysis should be high in cases in which bleeding continues despite hemostatic replacement therapy, platelet levels are relatively conserved but fibrinogen levels are disproportionately low, and D-dimer levels are disproportionately high for DIC. [2] Inherited primary hyperfibrinolysis is a rare condition associated with congenital deficiency of α_2 plasmin inhibitor (α_2-PI) and PAI-1.[15] In cancer-associated primary hyperfibrinolysis, there are often reduced levels of α_2-PI and thrombin activatable fibrinolysis inhibitor, and an impaired hepatic clearance of tissue plasminogen activator. In acute promyelocytic leukemia-associated primary hyperfibrinolysis, PML-RAR-α fusion protein enhances the expression of a S100 protein, which forms a heterotetrameric complex with annexin-A2 that promotes plasminogen activation and protect plasmin against inhibitors.[16]

DIC invariably worsens prognosis of the underlying disorder and can anticipate the fatal outcome if patients are left untreated.[17] In patients with severe sepsis and DIC, mortality is about twice that in patients with sepsis without DIC.

Future perspectives

There are three possible theoretical therapeutic strategies: treatment of the underlying disorder, interruption of fibrin deposition with anticoagulant drugs and prevention/treatment of clinical manifestations (the so called 'supportive therapy').[8-11,18-19] Only treatment of the underlying disorders has been proved to improve survival. Available evidence does not support a routine use of anticoagulant agents (such as antithrombin, protein C and therapeutic dose of unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH]). Recombinant thrombomodulin is under investigation with promising results.

Platelet transfusion should be given to maintain platelet count

Table 1. Underlying causes of disseminated intravascular coagulation (DIC).

Main subgroups and example of specific causes	Proposed new acronyms
Severe infection	
- Severe sepsis	
- Malaria	SIC: Sepsis-induced coagulopathy
Obstetrical complication	
- Abruptio placentae	
- Amniotic fluid embolism	PIC: Pregnancy-induced coagulopathy
Hematological neoplasia	
- Acute promyelocitic leukemia	LIC: Leukemia-induced coagulopathy
Solid tumor	
- Prostate adenocarcinoma	
- Gastric adenocarcinoma	CIC: Cancer-induced coagulopathy
Toxic or immunological reactions	
- Snake bites	
- Transfusion reactions	TIC: Toxic-induced coagulopathy
Other causes	
- Acute pancreatitis	
- Burns	
- Hypoxia	OIC: Other-induced coagulopathy
Vascular abnormalities (localized DIC)	
- Large aortic aneurysm	
- Hemangioendothelioma (Kasabach-Merrit syndrome)	VIC: Vascular-induced coagulopathy

>50×10^9/l in case of bleeding while a lower threshold of 20 to 30×10^9/l may be used in DIC without bleeding.[19] Fresh frozen plasma should be considered when PT ratio is more than 1.5 and/or aPTT ratio is more than 1.5 and/or fibrinogen level is less than 1 g/l. Thromboprophylaxis with UFH or LMWH is advised until bleeding ensues or platelet count drops below 30×10^9/l. When a venous thromboembolic event occurs is indicated to place a vena cava filter in bleeding patient just waiting to introduce unfractionated heparin or low molecular weight heparin as soon as the bleeding stops.[19]

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