Disseminated Intravascular Coagulation

Subjects: Hematology
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Disseminated intravascular coagulation (DIC) is a serious condition involving widespread, persistent activation of coagulation in the presence of underlying disease, resulting in diffuse microthrombi in small blood vessels. Although significant activation of coagulation is always observed in DIC, the degree of fibrinolytic activation depends on the underlying disease or condition. Depending on the degree of fibrinolytic activation, DIC can be classified into three disease types.

DIC | Enhanced-Fibrinolytic-Type DIC | Suppressed-Fibrinolytic-Type DIC | Balanced-Fibrinolytic-Type DIC | aortic aneurysms | hemangioma | blue rubber bleb nevus syndrome | plasmin-α2 plasmin inhibitor complex | COVID-19

1. Enhanced-Fibrinolytic-Type DIC

The first of the three types is “enhanced-fibrinolytic-type DIC”, as represented by the DIC associated with aortic aneurysms. Underlying diseases causing enhanced-fibrinolytic-type DIC include hemangiomas and vascular malformations (e.g., Kasabach-Merritt syndrome [1][2], Klippel-Trenaunay-Weber syndrome [3], blue rubber bleb nevus syndrome [4][5][6]), acute promyelocytic leukemia [7][8][9][10], prostate cancer [11][12], and severe coronavirus disease 2019 (COVID-19) (**Table 1**) [13][14][15][16][17][18][19]. In enhanced-fibrinolytic-type DIC, multiple fibrin clots produced by marked coagulation activation dissolve one after another due to the marked activation of fibrinolysis. As a result, ischemic organ damage due to multiple microthrombi is rarely seen as a clinical manifestation [20]. In contrast, severe bleeding symptoms are more likely to occur with the dissolution of hemostatic thrombi. Characteristic laboratory findings include a low platelet count, a normal-to-prolonged prothrombin time (PT), and a shortened-to-prolonged activated partial thromboplastin time (APTT). In other words, diagnosing or excluding DIC based on PT and APTT alone is not possible. Both thrombin-antithrombin complex (TAT) (or prothrombin fragment 1 + 2 [F_{1+2}]), a marker of coagulation activation, and PIC, a marker of fibrinolysis activation, are significantly increased. Due to the enhanced fibrinolysis, the FDP/D-dimer ratio is increased. In other words, FDP levels increase markedly while D-dimer levels show only a mild to moderate increase (**Table 2**). In addition, levels of PAI-1, a fibrinolytic inhibitor, are normal or only mildly elevated [21]. Concentrations of α_2PI are markedly decreased, and especially when it is less than 50%, caution should be taken against major bleeding. Fibrinogen levels are also markedly decreased in typical cases, not only because of the consumption associated with the dissolution of multiple microthrombi, but also because of the degradation of fibrinogen by plasmin.

Table 1. Diseases underlying enhanced-fibrinolytic-type DIC.

1. Anomalies of the Great Vessels
Aortic aneurysm
Aortic dissection
2. Vascular malformation
Kasabach-Merritt syndrome
Klippel-Trenaunay-Weber syndrome
Blue rubber bleb nevus syndrome, etc.
3. Hematological malignancies
Acute promyelocytic leukemia (APL)
Acute myelocytic leukemia other than APL
Acute lymphoblastic leukemia
Part of non-Hodgkin lymphoma, etc.
4. Non-hematological malignancies
Prostate cancer
Part of gastric adenocarcinoma
Part of colon cancer
Solid tumors with bone metastases
Malignant melanoma
Vascular-related sarcoma, etc.
5. Early phase of heat stroke
6. Early phase of severe trauma
7. Part of severe COVID-19

Abbreviations: COVID-19, coronavirus disease 2019.

Table 2. DIC classification and laboratory findings.

Clinical Exams	Suppressed-Fibrinolytic-Type DIC	Balanced-Fibrinolytic-Type DIC	Enhanced-Fibrinolytic-Type DIC
Typical diseases	sepsis	solid tumor	acute promyelocytic leukemia
			aortic aneurysm
			severe COVID-19
Platelets	decreased	decreased	decreased
PT	prolonged	prolonged	normal to prolonged
APTT	prolonged	prolonged	mildly shortened to prolonged
Fibrinogen	normal to increased	decreased	markedly decreased
FDP	mildly increased	increased	markedly increased
D-dimer	mildly increased	increased	increased
FDP/D-dimer ratio	approximately 1	approximately 1–2	approximately 2–5
Antithrombin	decreased	decreased to normal	normal
TAT or F_{1+2}	markedly increased	markedly increased	markedly increased
PIC	mildly increased	increased	markedly increased
α_2 PI	normal	mildly decreased	markedly decreased
Plasminogen	decreased	mildly decreased	decreased
PAI-1	markedly increased	mildly increased	normal to mildly increased

Important findings for differentiating between disease types are highlighted in yellow. Abbreviations: DIC, disseminated intravascular coagulation; COVID-19, coronavirus disease 2019; PT, prothrombin time; APTT, activated partial thromboplastin time; FDP, fibrin/fibrinogen degradation products; TAT, thrombin-antithrombin complex; F_{1+2}, prothrombin fragment 1 + 2; Fbg, fibrinogen; PIC, [22][23][24][25]; α2PI, α2plasmin inhibitor; PAI-1, plasminogen activator inhibitor-1.

2. Suppressed-Fibrinolytic-Type DIC

The second type is “suppressed-fibrinolytic-type DIC”. This type is represented by sepsis-associated DIC, in which TAT (or F_{1+2}) is markedly increased, and the plasminogen activator inhibitor-1 (PAI-I), fibrinolysis inhibitor, is also markedly increased, resulting in only mildly elevated PIC [10][26][27]. Fibrinolysis is therefore suppressed and

multiple thrombi become difficult to dissolve, resulting in significant ischemic organ damage due to failure of the microcirculation. However, suppressed-fibrinolytic-type DIC is not so associated with bleeding symptoms. Fibrinogen levels are often increased, reflecting inflammation, and FDP and D-dimer levels are somewhat elevated to reflect thrombus formation, but the increase is milder than in enhanced-fibrinolytic-type DIC. Antithrombin (AT) levels are decreased, and AT supplementation should be considered, especially for levels below 70%. While levels of α_2PI often appear normal, values are sometimes decreased (not consumptive) in the presence of hepatic insufficiency, reflecting decreased production. PT and APTT are prolonged in many cases, with more prominent prolongation of PT. The reason for this is that factor VII, which is involved in PT, has the shortest half-life among the coagulation factors. As a result, PT is likely to reflect consumption or decreased production of factor VII, and APTT is unlikely to be prolonged because of the increased production of factor VIII due to inflammation.

3. Balanced-Fibrinolytic-Type DIC

The third type is “balanced-fibrinolytic-type DIC”. This type of DIC is intermediate between the enhanced- and suppressed-fibrinolytic types. Solid tumors are a typical underlying disease for balanced-fibrinolytic-type DIC. When the balance between coagulation activation and fibrinolysis activation is suitable, hemorrhagic symptoms and organ damage are unlikely to be observed, but once the balance is broken, organ damage due to microcirculation failure or hemorrhagic symptoms become prominent. However, among the malignant tumors, prostate cancer and some other solid tumors are more often associated with enhanced-fibrinolytic-type DIC (**Table 1**).

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