Thrombosis Research 179 (2019) 11–14

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Letter to the Editors-in-Chief

The progression from coagulopathy to disseminated intravascular coagulation in representative underlying diseases

ARTICLE INFO

Keywords:
Sepsis
Disseminated intravascular coagulation
Coagulopathy
Fibrinolysis
Anticoagulants

1. Introduction

The International Society on Thrombosis and Haemostasis (ISTH) scientific standardization subcommittee on disseminated intravascular coagulation (DIC-SSC) defined DIC as "an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes that can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction" [1]. This definition has gained worldwide acceptance and has not changed since the original report in 2001. The concept of DIC is that regardless of the underlying pathophysiologic condition, the coagulation disorder is categorized by a single set of diagnostic criteria proposed by the DIC-SSC [1]. However, the characteristics of DIC from various underlying causes are not uniform, and there are subtypes of DIC with different pathophysiologies and phenotypic expression.

DIC is characterized by hemostatic activation but may vary in its clinical manifestation. For example, one presentation is with fibrinolytic shutdown that causes fibrin deposition in the vasculature and often complicated by organ dysfunction (thrombotic phenotype). Another presentation is characterized by fibrinolysis together with hemostatic activation (fibrinolytic phenotype), and presents more commonly with major hemorrhage. As with any biologic response, DIC can also have features common to both thrombotic and fibrinolytic manifestations.

Coagulopathy can also precede the laboratory diagnosis of DIC and is commonly initiated by sepsis, trauma, hematologic malignancies, cancer, and complications of pregnancy. In the following part, we introduce above representative underlying diseases, but many other causes induce coagulopathy such as aortic aneurysm, pancreatitis, and rhabdomyolysis. Coagulopathy associated with these different clinical scenarios can lead to DIC diagnosed based on laboratory findings (Table 1, Fig. 1). The need for early DIC recognition is important to facilitate treatment of the underlying diseases and initiating causes, but also for potential therapy using anticoagulants or antifibrinolytic agents that may be indicated only if given at an appropriate time in the course of progression of the disease. Hereby, ISTH/DIC-SSC will review the pathophysiologies of coagulopathies arising from different underlying diseases as follows.

2. Sepsis-induced coagulopathy (SIC)

Sepsis is a common underlying cause of DIC that produces a thrombotic coagulopathy that can follow a fulminant course. The pathogenesis of sepsis-induced coagulopathy (SIC) is complex since coagulation is an important host defense mechanism closely linked to inflammatory responses [2]. A novel concept of "immunothrombosis," has been proposed linking interactions between coagulation and innate immunity, an important event in sepsis that can lead to DIC. Microorganisms and their components such as lipopolysaccharides, described as pathogen-associated molecular patterns (PAMPs), induce the expression of tissue factor on monocytes and macrophages by binding to pattern-recognizing receptors. Tissue factor, a major initiator of coagulation, and the tissue factor-initiated pathway induces both prothrombotic and proinflammatory responses in part via protease-activated receptors (PARs). Phosphatidylserine on the cellular membrane can also active PARs. Tissue factor and phosphatidylserine on the extracellular vesicles also play important roles in the activation of coagulation [2]. In addition to PAMPs, proinflammatory and procoagulant substances such as free-DNA, histones, and high-mobility group box 1 protein (HMGB1) from damaged cells that are called damage-associated molecular patterns (DAMPs) will all participate in thrombus formation [2].

Similarly, neutrophil extracellular traps (NETs) are mesh-like DNA fibers comprised of histones and antimicrobial peptides. NETs are important host defense mechanisms that prevent bacterial dissemination [2], however, they can also produce endothelial, and glycocalyx injury that increases the extravasation of anticoagulants, such as antithrombin and protein C. In SIC, plasminogen activator inhibitor-1 (PAI-1) release suppresses fibrinolysis tissue-plasminogen activator (t-PA) release. As a result, the fibrinolytic system is suppressed by PAI-1, producing microcirculatory thrombosis, the hallmark of sepsis-induced coagulopathy.

3. Trauma-induced coagulopathy (TIC)

Coagulopathy is common following trauma and occurs in over 25% of patients with major trauma [3]. Trauma-induced coagulopathy (TIC) is amajor cause of bleeding and death after massive injury.

https://doi.org/10.1016/j.thromres.2019.04.030
Received 21 January 2019; Received in revised form 10 April 2019; Accepted 26 April 2019
Available online 29 April 2019
0049-3848/

Table 1
SIC and ISTH overt-DIC scoring systems.

	Sepsis-induced coagulopathy (SIC)	Trauma-induced coagulopathy (TIC)	Hematologic malignancy-induced coagulopathy (HIC)	Cancer-induced coagulopathy	Pregnancy-related coagulopathy
Types of coagulopathy	Thrombotic type	Fibrinolytic→ thrombotic type		Thrombotic~fibrinolytic depending on the underlying conditions	Fibrinolytic~thrombotic depending on the underlying conditions
Platelet count	↓□	↓□	↓□	↓□	↓□
FDP and D-dimer	↑□	Early phase↑ Late phase ↑	↑	↑	↑~↑ depending on the underlying conditions
Prothrombin time	↑□	↑	↑	↑	↑~↑ depending on the underlying conditions
Fibrinogen	↑~→□	Early phase ↓ Late phase↑~→□	↓□	↓□	↓□
PAI-1	↑	Early phase→ Late phase ↑	→	→	↑~→
Antithrombin activity	↓□	↓□	→	→	↓~→

FDP fibrin/fibrinogen degradation products, *PAI-1* plasminogen activator inhibitor 1.

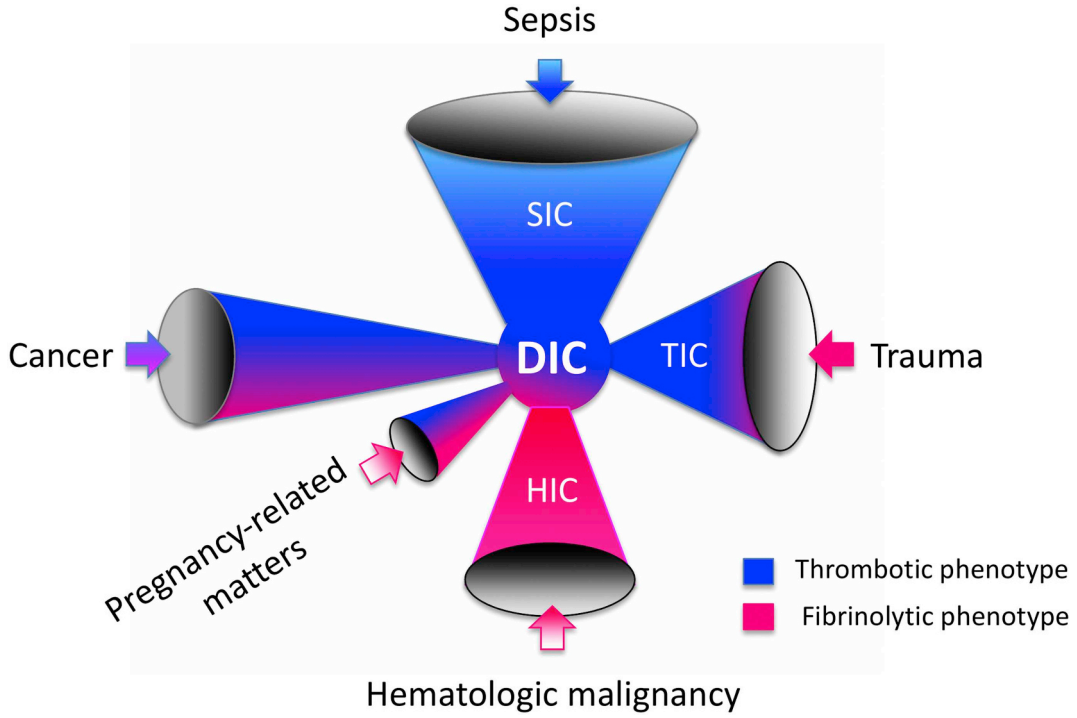

Fig. 1. Coagulopathy arises from various backgrounds. Sepsis, trauma, hematologic malignancy, cancer and pregnancy-related problems are the major causes of coagulopathy. The characteristics and time-courses differ depending on the basal conditions. However, each coagulopathy ultimately progresses to disseminated intravascular coagulation (DIC) if inadequately treated.

Understanding the pathophysiology of TIC is important for determining therapeutic strategies. The thrombomodulin-activated protein C system is reported to play a role in TIC based on observations of increased activated protein C levels, reduced protein C levels, and elevated soluble thrombomodulin levels. Activation of protein C can be a possible mechanism of TIC, however, following tissue injury, thrombin generation occurs, that is consistent with other types of coagulopathy and DIC. Thus, the initial phase of TIC is a fibrinolytic type of coagulopathy that changes over time. The initial manifestation of TIC is a fibrinolytic phenotype for several hours produced by t-PA released from the endothelium by tissue injury, thrombin, hypoxia, epinephrine, and vasopressin that contribute to hyperfibrinolysis. After this initial fibrinolytic state, the coagulopathy transforms into a thrombotic phenotype in response to elevated PAI-1 production (fibrinolytic shutdown). Viscoelastic studies are expected to offer the potential for timely identification of fibrinolytic dysregulation [4]. The management of TIC initially is tranexamic acid that should be administered within 3 h after injury, as reported in randomized controlled trials [5]. However, there is also controversy regarding antifibrinolytic use due to concerns about fibrinolytic shutdown, but this may also reflect the coagulation changes that occur over time.

4. Hematologic malignancy-induced coagulopathy (HIC)

Fibrinolytic-phenotype coagulopathy is often seen in acute promyelocytic leukemia (APL), but hematologic malignancy-induced

coagulopathy also complicates acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia and chronic myeloid leukemia [6]. This coagulopathy is characterized by a combination of thrombocytopenia, hypercoagulation, hyperfibrinolysis, and a reduction in protein C and antithrombin. The main feature of this condition is the enhanced generation of thrombin, together with excessive fibrinolysis. The pathogenesis is based on a tissue factor-mediated initiation of systemic coagulation that is insufficiently contained by the physiological anticoagulant pathways and is amplified by impaired endogenous fibrinolysis. Increased levels of annexin II are expressed on APL cells [7], a co-receptor for plasminogen and t-PA, that increases plasmin activation. Promyelocyte-derived extracellular vesicles have also been implicated as well. Treatment of the underlying disease must be the cornerstone of therapy, and the introduction of all-trans retinoic acid (ATRA) into chemotherapy regimens has dramatically improved overall survival. However, since bleeding-related causes of death are still common in APL, additional supportive anticoagulant and antifibrinolytic approaches may be necessary.

5. Cancer-induced coagulopathy

Cancer can be complicated by hypercoagulability resulting in intravascular fibrin deposition and depletion of clotting factors and platelets. Cancer-related coagulopathies may present with an insidious and sustained manifestation, whereby consumption of platelets or coagulation factors (and bleeding as a consequence) may be the dominant feature. At the same time patients with systemic cancer-related coagulopathies have a several-fold increased risk of thromboembolic complications. Tissue factor on cancer cells and other cancer procoagulant factors such as cancer procoagulant, proinflammatory cytokine-mediated dysfunction of anticoagulant systems, and deranged fibrinolysis play roles in pathogenesis, and endothelial injury caused by cancer therapies may further propagate the prothrombotic environment [8]. The clinical features of cancer-induced coagulopathy are a latent progression and sustainability. The initial characteristics are usually a mixture of thrombotic type and fibrinolytic type. Ultimately, cancer-induced coagulopathy often results in thrombocytopenia and the severe depletion of coagulation factors, followed by hemorrhagic features becoming dominant. This type of coagulopathy can have a sudden onset, especially after radiation or chemotherapy. Clinically, bleeding at the tumor site, venous puncture points or surgical sites are the first symptoms. The thrombotic type typically shows recurrent superficial thrombophlebitis known as Trousseau syndrome, while other types are known to show thrombotic microangiopathy [9]. Again, tumor-derived tissue factor-positive extracellular vesicles are an important cause of thrombosis. The therapeutic foundation of cancer-induced coagulopathy is the management of the underlying condition, but in some cases, supportive interventions specifically targeting the hemostatic system may be needed. To avoid adverse events, risk assessments by monitoring the hemostatic status are important for cancer patients.

6. Pregnancy-related coagulopathy

Pregnancy-related coagulopathy includes a variety of conditions including amniotic fluid embolism, placental abruption, HELLP syndrome, preeclampsia/eclampsia and acute fatty liver of pregnancy [10]. Clinically, pregnancy-related coagulopathy leads to a wide range of manifestations from life-threatening thrombosis to uncontrollable bleeding. Among them, massive postpartum hemorrhage is the most common severe complication showing a sudden onset and rapid change along with the clinical course. In the case of placental abruption, the released procoagulant substances from the placenta and fetal waste enter the maternal circulation and trigger coagulopathy [10]. Subsequently, hypovolemia and hypoxia caused by thrombus formation lead to endothelial damage and microcirculatory abnormalities. Soon after, massive bleeding arising from consumptive coagulopathy and hemodilution secondary to fluid therapy occur. While, in case of uterus atony, severe coagulopathy is induced primarily by loss of platelets and coagulation factors due to massive hemorrhage. In both cases, once the causes has been removed.

7. Summary

DIC represents the end-stage of different coagulation disorders. The characteristics of the multiple coagulopathies described may differ considerably depending on the pathophysiology, time in the disease course. For adequate treatment, a clear diagnosis is needed, including parameters for coagulation activation and fibrinolytic activation/capacity. Currently, the diagnostic criteria primarily focus on the hemostatic potential and contain no parameters for the fibrinolytic system. Fibrinogen depletion is a central pathomechanism for bleeding in DIC and treatment with fibrinogen concentrate is important for management, however, we have very little data concerning treatments influencing fibrinolysis, or anticoagulant drugs in DIC.

Conflicts of interest statement

All the authors state that they have no conflicts of interest.

Authors' contributions

Iba T, Levy JH and Levi M wrote the draft. J. Thachil, and Wada H reviewed and revised the manuscript.

Acknowledgements

A part of this study was presented at the 63rd Annual Scientific and Standardization Committee meeting of International Society on Thrombosis and Haemostasis. We did not receive any fund.

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Toshiaki Iba[a,*], Jerrold H. Levy[b], Jecko Thachil[c], Hideo Wada[d], Marcel Levi[e], the Scientific and Standardization Committee on DIC of the International Society on Thrombosis and Haemostasis,
[a] *Department of Emergency and Disaster Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan*
[b] *Department of Anesthesiology, Critical Care, and Surgery, Duke University School of Medicine, Durham, NC, USA*
[c] *Department of Haematology, Manchester Royal Infirmary, Manchester, UK*
[d] *Department of Molecular and Laboratory Medicine, Mie University School of Medicine, Tsu, Mie, Japan*
[e] *Department of Medicine, University College London Hospitals NHS Foundation Trust, London, UK*
E-mail addresses: toshiiba@cf6.so-net.ne.jp (T. Iba), jerrold.levy@duke.edu (J.H. Levy), Jecko.Thachil@cmft.nhs.uk (J. Thachil), wadahide@clin.medic.mie-u.ac.jp (H. Wada), marcel.levi@nhs.net (M. Levi).

* Corresponding author at: Juntendo University Graduate School of Medicine, 2-1-1 Hongo Bunkyo-ku, Tokyo 113-8421, Japan.