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Invited critical review

Disseminated intravascular coagulation: Testing and diagnosis

Hideo Wada [a,*], Takeshi Matsumoto [b], Yoshiki Yamashita [c], Tsuyoshi Hatada [d]

[a] Department of Molecular and Laboratory Medicine, Mie University Graduate School of Medicine, Tsu, Japan
[b] Blood Transfusion and Emergency Critical Care Center, Mie University Hospital, Tsu, Japan
[c] Department of Hematology and Oncology, Mie University School of Medicine, Mie, Japan
[d] Emergency Critical Care Center, Mie University Hospital, Tsu, Japan

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ABSTRACT

Abnormalities of the hemostatic system in patients with DIC result from the sum of vectors for hypercoagulation and hyperfibrinolysis. DIC is classified into hyperfibrinolysis, hypercoagulation, massive bleeding or nonsymptomatic types according to the balance of the two vectors. Both the antithrombin (AT) and protein C (PC) levels are significantly low in patients with septic DIC, and reduced amounts of AT and PC result in the lack of inhibition of thrombin and activated FVIII, respectively. Thrombin activates FVIII, while activated FVIII accelerates the coagulation pathway to generate thrombin; thus activation of the coagulation system persists. Three sets of diagnostic criteria have been established by the Japanese Ministry of Health, Labour and Welfare, International Society of Thrombosis and Haemostasis and Japanese Association for Acute Medicine, respectively. Although these three diagnostic criteria score hemostatic abnormalities using similar global coagulation tests, the sensitivity and/or specificity for death differ. Treatment with AT or activated PC may not improve the outcomes of patients with sepsis at the early stage, although they may improve the outcomes in those with DIC. Therefore, new diagnostic criteria for determining the appropriate time to initiate anticoagulant treatment are required.

Contents

1. Introduction

Disseminated intravascular coagulation (DIC) was first reported in patients with gynecological disease, leukemia and solid cancer [1,2], and the concept of DIC was established from these reports. Severe bleeding and/or consumptive coagulopathy are observed in most cases, and it is necessary to detect microthrombi in DIC patients with bleeding prior to administering heparin before the establishment of the concept of DIC. Although several groups have proposed various diagnostic criteria for DIC [3–6], the treatment of a pathological state as DIC does not require antithrombotic or antifibrinolytic therapy in cases in which the patient is considered to have coagulopathy due to an underlying disease. Additionally, although previous criteria have been applied in research, they are difficult to implement in clinical practice. In 1979, the Japanese Ministry of Health, Labour and Welfare (JMHLW) established diagnostic criteria for DIC involving the evaluation of global coagulation tests, underlying diseases and clinical symptoms [7]. Therefore, most Japanese physicians have been able to easily diagnose DIC since 1979. In contrast, most physicians in North America and Europe experienced difficulty in diagnosing DIC before 2001. In 2001, the International Society on Thrombosis and

* Corresponding author at: Department of Molecular and Laboratory Medicine, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu-city, Mie-ken 514-8507, Japan. Tel.: +81 59 232 1111; fax: +81 59 231 5204.
E-mail address: wadahide@clin.medic.mie-u.ac.jp (H. Wada).

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Haemostasis (ISTH) published a definition of DIC and overt-DIC diagnostic criteria involving the use of global coagulation tests based on the JMHLW criteria [8]. Subsequently, diagnosing DIC in North America and Europe has become easier, and these diagnostic criteria have since been used and analyzed in many clinical studies. Importantly, the ISTH guidance recommends that the diagnosis of DIC is made based on the above scoring system not with a single test [9].

Many clinical trials have been conducted using antithrombin (AT) [10], recombinant human activated protein C (rhAPC) [10,11] and rh tissue factor pathway inhibitor (rhTFPI) [12] in cases of severe sepsis, as well as plasma-derived APC [14] and rh-thrombomodulin (rhTM) [13] in subjects with DIC. Although treatment with AT, rhTFPI and rhAPC has not been shown to improve mortality, these drugs reduce the hemostatic abnormalities. Many patients with severe sepsis were treated with rhAPC before 2012, primarily in North America and Europe, while those with septic DIC are treated with AT or rhTM in Japan. Therefore, the ISTH guidance proposes that the administration of AT, rhTM or ahAPC might be considered in DIC patients [9].

2. Definition

The definition of DIC differs depending on whether the term is used by clinicians, laboratory technologists, research scientists, administrators or businessmen in the private sector and can also vary depending on social infrastructure, geographical location, economic conditions, the level of health care, the history of research on DIC, etc [14]. DIC may eventually be considered a condition that can be effectively treated with anticoagulant therapy, rather than a disease with a poor prognosis. The expression "death is coming (DIC)" is used to reflect the severity of DIC as a disease with a poor outcome. The earliest definition and concept of DIC required evidence of the presence of microthrombi and emphasized the tendency for prominent hemorrhage caused by consumptive coagulopathy resulting from the formation of multiple microthrombi [1]. It is difficult to directly prove the presence of microthrombi in most patients with DIC; therefore, the results of clinical laboratory tests of fibrin-related markers are used instead. In addition, symptoms of organ failure due to microthrombosis are now considered to be more important than those deriving from hemorrhagic conditions. The concept of disseminated intravascular fibrin formation was previously proposed, and researchers have attempted to diagnose DIC based on increases in the level of soluble fibrin (SF) [17,18]. The ISTH confirmed the importance of fibrin-related products in patients with DIC and proposed a definition of DIC as follows; "DIC is an acquired syndrome characterized by the intravascular activation of coagulation with the loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction [8]."

2.1. Pathophysiology of DIC

Abnormalities of the hemostatic system in patients with DIC result from the sum of vectors for hypercoagulation and hyperfibrinolysis (Fig. 1). When the vector for hyperfibrinolysis is remarkable and dominant, bleeding is the primary symptom; this type is called the bleeding type or hyperfibrinolysis type of DIC. This form of DIC is often observed in patients with leukemia, such as acute promyelocytic leukemia (APL), obstetric diseases or aortic aneurysms [1,2]. On the other hand, when the vector for hypercoagulation is remarkable and dominant, organ failure due to microthrombi is the main symptom; this type of DIC is called the organ failure type, hypercoagulation type or hypofibrinolysis type of DIC. This form of DIC is often observed in patients with infection, paticularly sepsis [16]. An increase in the level of plasminogen activator inhibitor I (PAI-I) induced by marked increased levels of cytokines [17,18] and lipopolysaccharide (LPS) [1,2] in the blood has been reported to be a cause of hypofibrinolysis. Moreover, neutrophil extracellular traps (NETs) [19], which release DNA with histone, neutrophil elastase and cathepsin G in order to trap and kill pathogens, are present in patients with sepsis. Histones promote the apoptosis of vascular endothelial cells and platelet aggregation [20], while neutrophil elastase and cathepsin G decompose tissue factor pathway inhibitor (TFPI) to promote thrombus formation [21]. Moreover, high mobility group box 1 (HMGB-1) [22] is emitted from injured and dead cells in order to enhance the inflammatory reaction. When both vectors for hypercoagulation and

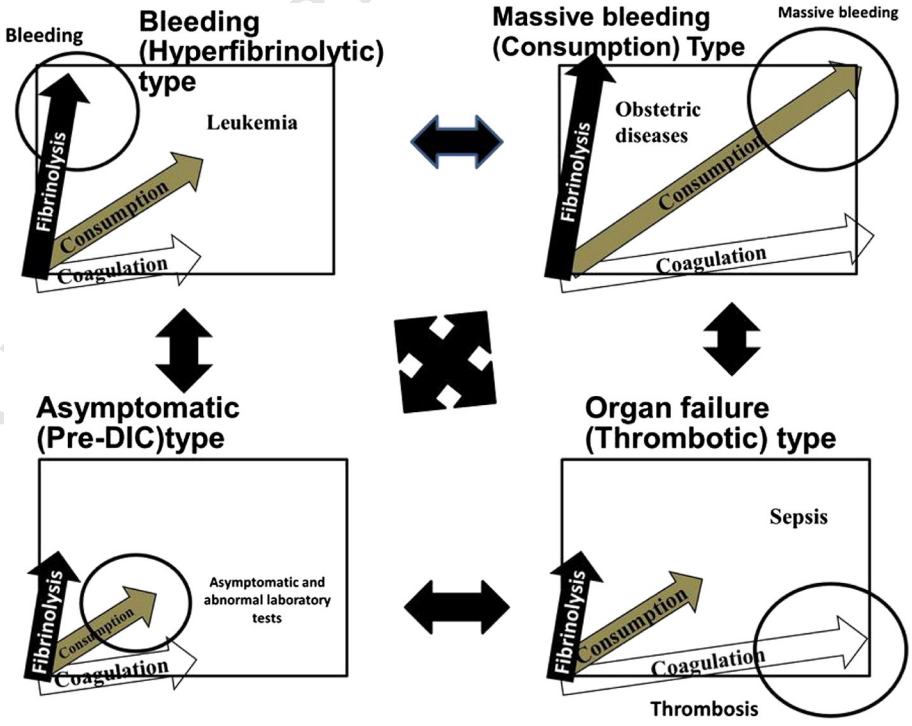

Fig. 1. Four types of DIC.

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