Summary. Disseminated intravascular coagulation (DIC) is an acquired syndrome that induces extensive intravascular coagulation due to various causes. Microthrombus formation and endothelial cell injuries are generated mainly in the small veins and arteries, and organ failure can even occur in patients demonstrating severe DIC. DIC is characterized by an elevated generation of fibrin-related products and the presence of hemostatic abnormalities due to either inflammation (with vascular endothelial cell injury) or noninflammatory causes (without vascular endothelial cell injury). This disease is divided into two types: overt DIC and nonovert DIC. The frequency of DIC was reported to be about 1% among hospitalized patients in a 1992 investigation. The outcome of DIC might also be poorer in patients with infectious diseases than in those with noninfectious diseases. Although three diagnostic criteria for DIC have been established, more sensitive and specific criteria for DIC are required for patients with infectious diseases. The treatment of underlying diseases is essential for DIC. Anticoagulant therapy is also essential, but heparin/heparinoids should be carefully administered in patients with marked bleeding. As a result, antifibrinolytic therapy needs to be carefully monitored using hemostatic molecular markers. The use of physiological protease inhibitor might be an effective treatment for DIC. Early diagnosis and treatment are therefore required to improve the outcome of patients with DIC.

Key words. DIC • Infectious diseases • Poor outcome • Hemostatic molecular marker • Protease inhibitor

Introduction

Although many definitions of disseminated intravascular coagulation (DIC) have been advocated up to now, the definition and concept of DIC have not yet been formally established [1]. DIC is generally considered to result from disseminated fibrin formation, which mainly occurs in the small veins and arteries owing to various causes, and most of the fibrin in such cases tends to be simultaneously dissolved by secondary fibrinolysis [2]. The definition and concept of DIC were proposed by the International Society of Thrombosis and Haemostasis (ISTH)/Scientific Standardization Committee (SSC) of 2001 [3] (Table 1). Two mechanisms have been proposed to play a role in the onset of DIC: noninflammatory pathogenesis (without vascular...
TABLE 1. Definition and concept of DIC

Definition—DIC is an acquired syndrome that causes extensive intravascular coagulation due to various causes. Microthrombus formation and endothelial cell injuries are mainly generated in small veins and arteries. Organ failure can occur in severe cases of DIC.

Concept—DIC is characterized by increased generation of fibrin-related products and hemostatic abnormalities due to inflammation (with vascular endothelial cell injury) or noninflammatory causes (without vascular endothelial cell injury).

Stage of disease—DIC is classified into two types: overt DIC (noncompensatory DIC) and nonovert DIC (compensatory DIC).

The definition and concept are cited from Taylor et al. [3]

DIC, disseminated intravascular coagulation

endothelial cell injury) and inflammatory pathogenesis (with vascular endothelial cell injuries). Noninflammatory DIC tends to occur in patients with acute leukemia and aortic aneurysms, among other conditions, whereas inflammatory DIC tends to occur in patients with, for example, severe sepsis, trauma, or burns. The importance of elevated fibrin-related products [4] has also been previously proposed to play a role in the pathological state of DIC. ISTH proposed that DIC should be divided into overt DIC (noncompensation stage) and nonovert DIC (compensation stage) similar to pre-DIC [5] owing to the fact that greater efficacy was achieved in the treatment of pre-DIC than in the treatment of DIC (overt DIC) in a retrospective study [6]. In addition, in overt DIC, comparatively controllable DIC (e.g., obstetrics DIC) should also be distinguished from uncontrollable DIC (e.g., severe sepsis).

Pathogenesis

The pathogenesis for DIC differs greatly between noninflammatory DIC and inflammatory DIC. Noninflammatory DIC is caused by a markedly elevated expression or release of tissue factor (TF) [7], plasminogen activator (PA) [8], or anexin II on tumor cells in patients with acute leukemia or a solid cancer and due to a blood flow abnormality in aneurysms (Fig. 1). TF can trigger the extrinsic pathway of coagulation. High TF activity results in the activation of prothrombin to thrombin to form a fibrin thrombus. Increased TF production is considered to be the most important factor regarding the onset of DIC. TF is significantly high in both leukemic cells [7] and the plasma of patients with DIC, suggesting that DIC in leukemia is caused by elevated TF from leukemic cells. In hemostatic abnormalities, hyperfibrinolysis and hypercoagulability are marked, but the plasma levels of antithrombin (AT) and thrombomodulin (TM), which are vascular endothelial cell injury markers, are often normal. The degree of vascular endothelial cell injury tends to be slight, and few clinical manifestations occur except for the hemorrhaging. In contrast, the leukocytes are markedly activated, and the expression of TF mRNA [9] in leukocytes is reported to be significantly high. High plasma levels of inflammatory cytokines and PA inhibitor I (PAI-1) have been observed in inflammatory DIC, which is frequently accompanied by vascular endothelial cell injury. Therefore, fluid, albumins, and AT, among others, leak out of blood vessels; thereafter, edema and clinical manifestations such as shock are observed (capillary leak syndrome). In addition, AT in the blood and TM in injured vascular endothelial