Plasma Levels of Plasminogen Activator Inhibitor-1 (PAI-1) and Thrombin Activatable Fibrinolysis Inhibitor (TAFI) in Patients with Disseminated Intravascular Coagulation (DIC)

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ABSTRACT

Plasma levels of thrombin activatable fibrinolysis inhibitor (TAFI) and total plasminogen activator inhibitor-1 (PAI-1) and tissue type plasminogen activator (tPA)/PAI-1 complex in patients with disseminated intravascular coagulation (DIC) to examine the relationship between hypofibrinolysis and the pathogenesis with DIC.

We examined 39 patients with DIC, 23 with pre-DIC, 181 without DIC and 17 healthy volunteers. Both plasma levels of total PAI-1 and tPA/PAI-1 complex were significantly high in patients with DIC. Those levels were also high in patients with organ failure, especially sepsis. Both TAFI activity and antigen levels in the plasma were significantly low in patients with DIC. TAFI activity in plasma was correlated with TAFI antigen. TAFI activity and antigen levels were negatively correlated with TAT and D-dimer. The TAFI activity in plasma was significantly low in patients with infection and in those with organ failure, suggesting that TAFI may play an important role in the mechanism of organ failure in DIC-associated sepsis. Regulation of fibrinolysis by TAFI and PAI-1 may play an important role in the pathogenesis of DIC and organ failure.

Key Words: PAI-1, TAFI, DIC.

Turk J Haematol 2002;19(2):235-237

INTRODUCTION

Disseminated intravascular coagulation (DIC) is often associated with severe bleeding tendency and multiple organ failure (MOF), its clinical course being in some cases, very rapid and severe[1]. Sepsis is a common cause of acute DIC. It is believed that hypofibrinolysis associated with MOF is due to elevated plasma levels of plasminogen activator inhibitor-1 (PAI-1). Thrombin activatable fibrinolysis inhibitor (TAFI), a carboxypeptidase B-like pro-enzyme, is a recently described inhibitor of fibrinolysis that can be converted to its active form (TAFIa) by the thrombin-thrombomodulin (TM) complex. The mechanism by which TAFI down regulates fibrinolysis has been suggested to involve the removal of carboxy-terminal lysines (and arginines) from fibrin. Although the role of TAFI in diseases is not clear, may be involved in hemorrhagic or thrombotic diseases. We measured the plasma levels of total PAI-1 and tissue type plasminogen activator/PAI-1 (tPA/PAI-1) complex and TAFI in patients with DIC to examine the relationship between hypofibrinolysis and the pathogenesis of DIC[2,3].

MATERIALS and METHODS

We examined 39 patients with DIC, 23 with pre-DIC, 181 without DIC and 17 healthy volunteers. The underlying diseases of the patients were leukemia (30 patients), malignant lymphoma (70 patients), infection (18 patients), solid cancer (44 patients), and other diseases (81 patients). The diagnosis of DIC was based on a modified version of the criteria established by the Japanese Ministry of Health and Welfare. Patients with high levels thrombin-antithrombin complex (TAT), plasmin-$a_2$plasmin inhibitor complex (PPIC), D-dimer and fibrin monomer (FM) although their DIC score did not satisfy the DIC criteria, were defined as being in pre-DIC state. Plasma levels of fibrinogen, TAT, PPIC, D-dimer, TM, total PAI-1 and t-PA/PAI-1 complex were measured using Multifibren U (Dade Behring, Marburg, Germany), TAT-test (Kokusai-Shiyaku, Kobe, Japan), PIC-test (Kokusai-Shiyaku), D-dimer-test (Kokusai-Shiyaku), TM-test (Kokusai-Shiyaku), LPIA tPAI test (Dia-Iatron, Tokyo, Japan) and tPAIc-test (Kokusai-Shiyaku). TAFI activity was determined by actichrome plasma TAFI activity kit (American diagnostica inc., CT, USA). This is a chromogenic assay that measures the carboxypeptidase activity of TAFI in plasma and biological samples using a novel, high affinity substrate and color development system. The plasma level of TAFI antigen was measured using a sandwich ELISA kit (Kordia, Leiden, Netherlands).

RESULTS and DISCUSSION

The plasma levels of TAT, PPIC and D-dimer were significantly higher ($p< 0.01$) in patients with DIC than in those with non-DIC, suggesting the occurrence of hypercoagulability and hyperfibrinolysis in DIC patients. These findings suggest that the fibrinolysis system plays an important role in pathogenesis of DIC. On the other hand, the plasma levels of TM were significantly increased in our patients with DIC. The plasma level of TM is a marker of vascular endothelial cell injury. In our patients with DIC, one of the causes for vascular endothelial cell injuries were probably the underlying disease such as sepsis. Both plasma levels of total PAI-1 and tPA/PAI-1 complex were significantly high in patients with DIC (238.7 ± 61.5 ng/mL and 62.6 ± 30.0 ng/mL), particularly in those with acute leukemia (158.4 ± 65.5 ng/mL and 86.0 ± 54.3 ng/mL). The plasma levels of total PAI-1, but not those of tPA/PAI-1 complex, were significantly increased in patients with sepsis or solid cancer. Therefore, the tPA/PAI-1 complex/total PAI-1 ratio is high in acute leukemia, suggesting that this disease is associated with hyperfibrinolysis. Conversely, the tPA/PAI-1 complex/total PAI-1 ratio is low in sepsis, suggesting that patients with sepsis are in a state of hypofibrinolysis. These findings suggest that patients with leukemia may have a bleeding tendency and that patients with sepsis tend to have organ failure. In all cases, total PAI-1 and tPA/PAI-1 complex was not significantly correlated with any hemostatic marker. The plasma levels of total PAI-1 and tPA/PAI-1 complex were both significantly higher in patients with organ failure than in those without organ failure. Measurement of total PAI-1 and tPA/PAI-1 complex may be useful in the diagnosis of DIC.

Both activity and antigen levels of TAFI in the plasma were significantly lower ($p< 0.01$) in patients with DIC (1.97 ± 1.41 μg/mL and 106.9 ± 16.1%) than in those with non-DIC (3.37 ± 1.21 μg/mL and 127.8 ± 15.1%) and healthy controls (3.52 ± 0.33 μg/mL and 122.8 ± 10.2%), respectively. TAFI activity in plasma was correlated with TAFI antigen, indicating that activity and antigen correspond well. The decrease of TAFI activity in DIC may be due to enhanced consumpti-

on. Since the plasma TAT level was found to be elevated in DIC, increase of TM-thrombin complex generation is suggested in this state. TAFI activity and antigen levels were negatively correlated with TAT and D-dimer, suggesting that the plasma levels of TAFI were reduced by thrombin generation. Since TAFI was not correlated with fibrinogen, PPIC and tPA/PAI-1 complex, TAFI might be a secondary modulator of fibrinolysis. The TAFI activity in plasma was significantly low in patients with infection and in those with organ failure, suggesting that TAFI may play an important role in the mechanism of organ failure in DIC-associated sepsis.

Disturbance of the balance between coagulation and fibrinolysis may result in a bleeding disorder or in a thrombotic tendency. The finding of a markedly reduced TAFI activity in DIC suggests that reduction in TAFI may be one of the most important risk factor for DIC and potential predictor of the low-grade fibrinolysis seen in DIC. Regulation of fibrinolysis by TAFI and PAI-1 may play an important role in the pathogenesis of DIC and organ failure.

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