Disseminated Intravascular Coagulopathy in Infection Compared with That in Malignant Neoplasia

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Abstract
The organic symptoms and results of coagulation tests of disseminated intravascular coagulopathy (DIC) in 17 patients with infection were compared with those in 12 patients with malignancy. The infectious diseases were mainly sepsis and pneumonia, and the malignancy was mainly lung cancer. The mean antithrombin III (AT III) before treatment was 54% in infection and 68% in malignancy, and the AT III values improved after administration of 1500 U of AT III concentrates per day. The mean thrombin-antithrombin complex level decreased from 22 ng/ml to 9 ng/ml after the treatment in infection, but it increased in malignancy. There were no differences in DIC scores between infection and malignancy before treatment; however, the scores were significantly more improved in infection than in malignancy after treatment (p<0.05). The fibrin/fibrinogen degradation product level, platelet count, and fibronectin level were also significantly more improved in infection than in malignancy. This better response to treatment in infection than in malignancy is probably due to eradication of the causative organisms by antibiotics in infection. These data suggest that therapy against both DIC and the underlying disease is crucial for successful treatment.

Introduction
Infection is one of the major cause of disseminated intravascular coagulopathy (DIC), which results in activated coagulation and/or fibrinolysis. Administration of antithrombin III (AT III) concentrates has been reported to be effective in the treatment of DIC. Heparin, which used to be the only treatment for DIC, results in more cures of DIC resulting from severe infection than from malignancy. We studied the difference in DIC scores and coagulation parameters between infection and malignancy to find the optimal treatment.

Materials and Methods

Patients
Twenty-nine patients whose DIC scores were more than 4 were enrolled in this prospective study during the period from July 1988 through December 1991. Seventeen patients (11 men and 6...
women, 51–84 years old with a mean age of 69) had infectious diseases: 7 sepsis by Candida spp. (3), Escherichia coli (1), Klebsiella pneumoniae (1), Proteus mirabilis (1), and meticillin-resistant Staphylococcus aureus (MRSA) (1); 4 pneumonia; 2 bile duct infection; 1 lung abscess; 1 empyema; 1 MRSA enteritis; 1 peritonitis. Twelve patients (9 men and 3 women, 53–79 years old with a mean age of 67) had malignancies: 3 adenocarcinoma, 2 small cell carcinoma, 1 squamous cell carcinoma, 1 large cell carcinoma, and 1 adenosquamous carcinoma of the lung; 1 gastric cancer; 1 ovarian carcinoma; 1 ureteral carcinoma; 1 malignant meningioma. Malignancy complicated by infection was excluded. Multiple organ failure was defined according to Fry's criteria6).

### Treatment
AT III, 1,500 U/day, was administered with heparin, 5,000–10,000 U/day, for 3–5 days as a rule. However, heparin was not administered to 7 of the 17 patients with infection or to 1 of the 12 patients with malignancy. Antibiotics were also administered to 14 of the patients with infection, and antineoplastic agents to 3 of the patients with malignancy.

### Coagulation assays
Blood was drawn into 0.13 M trisodium citrate solution. Platelets were counted electronically with NE-8000 (Toa Medical Electronics, Tokyo Japan). All assays were performed as specified by the manufacturer. Prothrombin time was measured with thromboplastin C (Baxter, Miami, FL, U.S.A.), fibrinogen using LA-fibrinogen (Eiken, Tokyo), fibrin/fibrinogen degradation products (FDP) using Cobas (Baxter), AT III using Berychrom antithrombin III (Behring, Vienna Italy), thrombin-antithrombin complex (TAT) using Enzygnost (Behring), D-D dimer using LPIA-100 (Iatron, Tokyo), and fibronectin by LC Paltigen (Behring). Endotoxin was measured by Endospecy (Seikagaku Kogyo, Tokyo) according to the manufacturer's instructions.

### Statistical analysis
Differences in coagulation test results were analyzed by the Dunnett type multiple comparison test at 3 different points (before, just after cessation, and 1 week after cessation of AT III). The difference between infection and malignancy was statistically analyzed by Fisher's exact probability method or student t test.

### Results
#### Hemorrhagic diathesis and organ failure
Hemorrhagic diathesis was observed more frequently in malignancy (9/12, 75%) than infection (8/17, 47%) (p <0.25), and the rates of improvement of hemorrhagic diathesis after treatment were 50% (4/8) and 56% (5/9), respectively. The mean DIC scores in infection improved markedly with a statistically significant difference (p <0.001) after treatment (Table 1). The scores in malignancy improved just after cessation of AT-III, but they were worse 1 week after cessation.

<table>
<thead>
<tr>
<th>DIC score</th>
<th>Infection</th>
<th>Malignancy</th>
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<tbody>
<tr>
<td>Before AT-III administration</td>
<td>7.18±2.10 (n=17)</td>
<td>6.67±1.56 (n=12)</td>
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<tr>
<td>Just after cessation</td>
<td>5.15±2.88 (n=13) ***</td>
<td>5.00±1.94 (n=10)</td>
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<tr>
<td>1 week after cessation</td>
<td>4.00±1.63 (n=7) ***</td>
<td>7.00±2.00 (n=8)</td>
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***=p<0.001

Table 1 DIS Score before and after Treatment
Organ failure was observed in 14 (82%) of the patients with infection and in 8 (67%) of the patients with malignancy. Organ failure in infection included 7 respiratory failures, 8 hepatic failures, 10 renal failures, and 2 heart failures, and the organ failure in malignancy included 4 respiratory failures, 6 hepatic failures, 4 renal failures, and 2 heart failures. Organ failure was reversed in 67% (10/14) in infection and 38% (3/8) in malignancy following treatment (p<0.18).

**Coagulation tests results (Table 2)**

The decreased platelet counts before treatment increased markedly after treatment, with a statistically significant difference (p<0.001) in DIC resulting from infections. However, they did not change after treatment of DIC complicating malignancy (Fig. 1). The prothrombin time and fibrinogen did not change significantly after treatment in patients with either infection or malignancy. The FDP level, high before treatment, decreased after treatment in patients with infection, but it continued high in spite of treatment in patients with malignancy. There was a statistically significant
Fig. 1  Platelet and FDP levels before and after treatment.

Fig. 2  D-dimer and fibronectin levels before and after treatment.
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Fig. 3 AT III and TAT before and after treatment.

difference in FDP 1 week after cessation between the group with infection and the group with malignancy (p<0.05) (Fig. 1). D-D dimer, a marker of fibrinolysis, decreased from 2629.6 ± 3720.7 ng/ml to 632.0 ± 421.8 ng/ml in patients with infection after treatment, but it did not change in patients with malignancy (Fig. 2). AT III was 54.2 ± 21.0% in infection and 68.6 ± 23.1% in malignancy, and it returned to normal levels after AT III administration in both infection (101.0 ± 28.5, p<0.001) and malignancy (104.6 ± 22.1, p<0.05) (Fig. 3). The TAT level decreased from 22.4 ± 14.3 ng/ml to 10.3 ± 8.0 ng/ml after treatment in infection (p<0.05), but in malignancy the level increased in spite of treatment, suggesting continuous hypercoagulability (Fig. 3). The fibrinectin level was lower in infection than in malignancy before treatment (p<0.05), and it increased markedly in infection after treatment (p<0.01) (Fig. 2). The endotoxin level was 1.94 ± 1.40 pg/ml in 16 patients with infection, and 1.89 ± 1.53 pg/ml in the 12 patients with malignancy. No increase in endotoxin was observed in any patients. The efficacy of AT III and other drugs against DIC was evaluated in this study. The clinical efficacy was 57% (8/14) in infection and 18% (2/11) in malignancy, and the hematological efficacy was 50% (7/14) in infection and 60% (6/10) in malignancy.

Discussion

DIC is induced by severe infection or metastatic malignancy. In infection, gram-negative bacteremia is the most frequent cause of DIC which occurs in 10% of these patients7). This is probably due to the role of endotoxin in activating both intrinsic and extrinsic coagulation factors to produce thrombin8). Malignant tissue produces a factor X-activating cysteine protease to activate coagulation factors9). Procoagulant activity detected in monocytes of patients with malignant tumors is mainly dependent on the tissue factor of monocytes10). It is correlated with the level of TAT, and plays an

平成 7年 3月20日
important role in intravascular coagulation in malignant diseases\(^1\).

Our data suggest that the higher incidence of hemorrhagic diathesis observed in malignancy (75\%) than in infection (47\%) is probably due to activated fibrinolysis in DIC. Organ failure was a complication in 82\% of the infections and 62\% of the malignancies. Renal failure was the most common complication, and was probably due to microthrombi in DIC. Plasminogen activator inhibitor 1, which inhibits fibrinolysis, is produced in infection and often induces organ failure\(^2\).

Heparin and/or AT III are administered for the treatment of DIC. AT III inactivates most of the serine protease of coagulation by binding to thrombin and factors Xa, IXa and XIa. When AT III is added to heparin there is a dramatic increase in the speed of inactivation of clotting enzyme\(^3\). Heparin is ineffective clinically unless the AT III activity is more than 50\%\(^4\). Addition of AT III is also necessary for the treatment of DIC in infection because granulocytes activated by complement may aggregate in the microvessels and can release several proteases among which elastase rapidly inactivates AT III\(^5\,^6\). The low levels of AT III and high levels in TAT in infection of the present study also suggest that AT III substitution is necessary for the treatment of DIC in infection. High DIC scores in both infection and malignancy, were more significantly improved in infection than in malignancy after treatment. Takahashi reported that AT III was more efficient in infection than in malignancy\(^7\).

Coagulation tests revealed several differences in DIC between malignancy and infection. After treatment, platelet counts and FDP, D-D dimer, TAT and fibronectin levels improved more markedly in infection than in malignancy. Increased TAT and D-D dimer levels in malignancy after treatment suggests that hypercoagulability was not improved by this treatment and activated fibrinolysis, slightly depressed by AT III, was aggravated after cessation of the treatment. These changes were probably due to the continuous influence of malignant tissues on the coagulation cascade.

Kobayashi reported that AT III was especially effective against pre-DIC, the DIC scores of which were between 4 and 6\(^8\). The present study also revealed good clinical efficacy (60\%) and a good response to coagulation tests (62\%). Treatment failures were mainly due to severe underlying diseases. DIC resulting from infection is more curable than that resulting from malignancy by treatment for DIC, with elimination of the causative organisms by antibiotics.

References

DIC in Infection


感染症に伴う DIC の臨床的検討
——悪性腫瘍との比較において——

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要 旨

感染症に合併した DIC の患者17名における臨床症状や凝固学的検査、治療効果などについて、悪性腫瘍に合併した DIC 患者12名と比較検討した。感染症は主に肺炎や敗血症であり、悪性腫瘍は主に肺癌であった。DIC の治療後、DIC スコアは感染症群で有意に改善がみられたのに対し、悪性腫瘍群では改善がみられなかった。凝固学的検査では、治療前に両群間には差はみられなかった。