Association of Thrombosis-Inducing Activity (TIA) With Fatal Hypercoagulable Complications in Patients With Lung Cancer

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We previously reported that thrombosis-inducing activity (TIA) is present in plasma from patients with advanced lung cancer. Of 73 patients with non-small cell lung cancer, stages IIIb and IV, 41 (56 percent) had such activity in plasma. The median survival time was significantly shorter in the TIA-positive vs the TIA-negative group. When 34 of those 73 patients who had died at Kyushu University Hospital were evaluated for the incidence of disseminated intravascular coagulation (DIC) and adult respiratory distress syndrome (ARDS), they were significantly higher in the TIA positive group (p<0.05). The DIC occurred in 7 of 20 patients positive for TIA and 5 of ARDS. In contrast, in the 14 TIA-negative subjects, only 1 patient experienced DIC and none died of ARDS. Peripheral platelet counts, which had been rather elevated on the day of hospital admission, were below normal within 1 week of death in 40 percent of the 20 patients who were positive for TIA. These observations suggest that TIA may be responsible at least in part for the increased activity of the coagulation system and the high incidence of DIC and ARDS in patients with advanced lung cancer.

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Hypocoagulopathy is a frequent complication of malignant disease that is associated with a shortened survival.1,2 A procoagulant activity such as tissue factor3 and cancer procoagulant4 is produced by tumor cells and may contribute to the pathogenesis of the hypocoagulopathy. However, the true culprit remains a matter of controversy. Recently, we found a factor with thrombosis-inducing activity (TIA) in the plasma of patients with advanced lung cancer.5 Further study revealed that it also appears in the plasma of patients with acute pulmonary infections as well as those who recently had undergone surgery.6,7 The appearance of TIA in plasma has been associated with an increase in plasma fibrinogen levels and peripheral platelet counts. This finding suggested a participation of TIA in the induction of the hypercoagulopathy seen in patients with lung cancer.5 The present study was undertaken to elucidate whether the appearance of TIA coincides with clinical status of hypercoagulopathy.

METHODS

Population

Seventy-three patients with non-small cell lung cancer at stages IIIb and IV, who were admitted to Kyushu University Hospital during June 1986 and September 1992, were included in this study. There were 53 men and 20 women aged 33 to 85 years (mean, 61.9 years). The diagnosis and clinical stage of disease were determined by lung biopsy specimen appearance, the findings of computed tomography, and bone scintigraphy. Of those patients, 34 died at Kyushu University Hospital and were further studied for the causes of their death. Thirteen subjects underwent autopsy. The primary cause of death in the remaining 21 was estimated from clinical and laboratory findings. A diagnosis of adult respiratory distress syndrome (ARDS) was made following the criteria of Pontoppidan et al.8 The diagnosis of acute disseminated intravascular coagulation (DIC) was based on the criteria of Al-Mondhiry.9

Animals

Male Balb/c mice weighing 14 to 16 g were used in measuring plasma TIA.

Preparation of Plasma

Blood samples were collected into plastic syringes. Nine parts of whole blood were added to one part of 3.13 percent sodium citrate and the specimen was immediately centrifuged at 3,000 rpm for 20 min. Plasma was stored at ~80°C until assayed.

Measurement of Plasma TIA

The TIA in plasma was measured as described previously.5 In brief, 0.5 ml of plasma was administered to mice via the central tail vein. Plasma was judged to possess TIA if it met all criteria: (1) the mice became almost motionless within 2 min and died within 3 to 30 min after the injection; (2) pathologic studies re-

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DIC = disseminated intravascular coagulation; TIA = thrombosis-inducing activity.

For editorial comment see page 1639.
Table 1—Clinical Features of 73 Subjects

<table>
<thead>
<tr>
<th>TIA Status</th>
<th>No</th>
<th>Stage, IIIb/IV</th>
<th>Sex, M/F</th>
<th>Age, yr, Mean ± SEM</th>
<th>Karnofsky Index 100–80</th>
<th>70–50</th>
<th>40–</th>
<th>Response Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>41</td>
<td>11/30</td>
<td>28/13</td>
<td>59.9 ± 11.2</td>
<td>15</td>
<td>22</td>
<td>4</td>
<td>9.8</td>
</tr>
<tr>
<td>Negative</td>
<td>32</td>
<td>9/23</td>
<td>25/7</td>
<td>64.4 ± 11.8</td>
<td>12</td>
<td>18</td>
<td>2</td>
<td>14.4</td>
</tr>
</tbody>
</table>

*All responses were partial.

vealed the formation of numerous thrombi in the lungs; and (3) thrombosis was inhibited completely by the administration of 50 U of heparin prior to the injection of plasma, and these mice survived.

Laboratory Data

Peripheral platelet counts were measured at the Laboratory Center of the Kyushu University Hospital.

Statistics

Life-table analyses were presented as Kaplan-Meier plots. Generalized Wilcoxon's test was used to determine if a significant difference existed between these curves. Other data are presented as mean ± standard error of the mean (SEM). The x² test was used to test the differences among sex, disease stage, and performance status. Peripheral platelet counts at the time of death were compared with those at the time of hospital admission by the paired t test. A level of p<0.05 was accepted as statistically significant.

Results

Thrombosis-inducing activity in plasma, studied in 73 patients with inoperable lung cancer, was present in 41 patients (56 percent) (Table 1). There was no difference in clinical stage, sex, age, performance status, and response to chemotherapy between the TIA-positive and TIA-negative groups. Response to chemotherapy was evaluated after two cycles of an administration of cisplatin, 100 mg/m², plus vin-desine, 3 mg/m²×3 on days 1, 8, and 15. All responses were partial. The median survival time was 8.2 months in the TIA-positive group, significantly shorter than the 11.7 months in the TIA-negative group (p<0.05) (Fig 1).

The cause of death was investigated in 34 of the 73 patients who died at Kyushu University Hospital. Of that group, 20 were TIA positive and 14 were TIA negative. Autopsy was performed in 13 of those subjects. The cause of death in the other 21 was estimated from the results of clinical and laboratory examinations. In the TIA-positive group, five patients died of ARDS, one of portal venous thrombosis, while seven patients had acute DIC (Table 2). Disseminated intravascular coagulation occurred in only 1 of the 14 patients in the TIA-negative group, and none experienced ARDS. Peripheral platelet counts, measured on the day of hospital admission and again within 1 week of death, were compared in each patient (Fig 2). There was no significant difference between the values in the TIA-negative group (p>0.05), whereas in the TIA-positive group, the values measured within 1 week of death were significantly lower vs
Table 2—Primary Cause of Death in 34 Patients With Lung Cancer*

<table>
<thead>
<tr>
<th>Cause</th>
<th>TIA Positive</th>
<th>TIA Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor invasion to major organs</td>
<td>11 (2)</td>
<td>81 (0)</td>
</tr>
<tr>
<td>ARDS</td>
<td>5 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Infection</td>
<td>28 (2)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>1 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ileus</td>
<td>0 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>20 (7)</td>
<td>14 (1)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses indicate numbers of patients with acute DIC.
Includes six patients with diffuse lung invasion, three patients with pericarditis carcinomatosa, one patient with bilateral pleuritis carcinomatosa, and one patient with brain metastasis.
Includes four patients with diffuse lung invasion and four patients with brain metastasis.
Includes two patients with bronchopneumonia.
Includes three patients with bronchopneumonia and two patients with acute bronchitis.

those obtained on the day of hospital admission (p<0.01). A fall in peripheral platelet count to below 100,000/μl was seen in 8 of the 20 patients positive for TIA.

**DISCUSSION**

Hypercoagulability is commonly associated with malignant disease and may lead to such fatal com-

plications as thromboembolism and DIC. Several studies have been conducted to evaluate the presence of such hypercoagulability in relation to the presence of the malignancy. Tissue factor, the most potent initiator of the extrinsic coagulation cascade, has been identified on various tumor cells. A cysteine protease capable of directly activating factor X has been eluted from human cancer cell lines. Although the pathogenesis of hypercoagulability may be explained by the production of those factors by tumor, the responsible factor is unknown.

We recently found that the plasma from some patients with advanced lung cancer contains TIA that can induce a DIC-like status in mice. A short-term fall in the peripheral platelet count and the formation of numerous pulmonary thrombi was induced in mice by the intravenous injection of plasma containing TIA. It shares some characteristics with tissue factor in that the activity is lost after treatment with phospholipase C, binds to concanavalin A, is precipitated by 50 percent saturated ammonium sulfate, and is heat labile. However, TIA and tissue factor are supposed to be different molecules as monoclonal antibodies specific to human tissue factor failed to neutralize TIA activity (unpublished data). Although the origin of plasma TIA has not been determined, it is assumed to be a tumor cell product that is released into the circulation. In support of this concept, we

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21695/ on 06/26/2017)
observed a patient with lung cancer in whom plasma TIA appeared following successful treatment with chemotherapy. Thrombosis-inducing activity has been detected in almost 50 percent of patients with advanced lung cancer and may be a prognostic factor. The survival time of patients with non-small cell lung cancer stages IIIb and IV was significantly shorter in the TIA-positive group vs the TIA-negative group. Hypercoagulation induced by TIA may be responsible for their shorter survival. Several studies have investigated the favorable effects of anticoagulants on survival of cancer patients, but the precise mechanism is not known. In the present study, we selected 34 patients with advanced lung cancer who died at the Kyushu University Hospital and investigated the primary cause of death in detail. Of the 20 TIA-positive patients, 7 developed DIC and 5 died of ARDS. In contrast, only 1 of the 14 TIA-negative patients experienced DIC, and none died of ARDS.

Our findings indicate that the shortened survival of TIA-positive patients with advanced lung cancer is due to the high incidence of ARDS and DIC, and that TIA may be responsible, at least in part, for the development of ARDS and DIC. At present, the biologic and clinical significance of TIA is not well clarified. Further effort and study should lead to the hope of finding a new therapeutic approach in lung cancer patients.

REFERENCES

9 Al-Mondhiry H. Disseminated intravascular coagulation: experience in a major cancer center. Thoram Diath Haemorrh 1975; 34:181-93