Coagulation and Fibrinolysis Activation Markers in Prostatic Carcinoma Patients

Remy W. F. Geenen¹, Karl P. J. Delaere¹ and Jan W. J. van Wersch²

¹ Department of Urology,
² Department of Haematology,
De Wever Hospital, Heerlen, The Netherlands

Summary: In 49 patients with benign prostatic hyperplasia, 24 metastatic prostatic carcinoma patients all under palliative hormonal treatment, 17 untreated prostatic carcinoma patients without metastases and 14 untreated prostatic carcinoma patients with metastases, plasma levels of thrombin-antithrombin III complex, D-dimer and plasmin-α₂-antiplasmin were determined.

The coagulation activation marker thrombin-antithrombin III complex did not show any significant difference between the different patient groups. Of the fibrinolysis markers, D-dimer levels were elevated in both metastatic groups compared to the non-metastatic group and the benign prostatic hyperplasia group. Surprisingly, the levels of the other fibrinolysis marker, plasmin-α₂-antiplasmin, showed no significant difference. The nature of these findings is discussed and related to other relevant literature. The general conclusion is that fibrinolysis may not play such a prominent role in prostatic carcinoma as described and expected.

Introduction

Prostatic carcinoma can affect the coagulation and fibrinolytic system (1, 2). The first report on coagulation abnormalities in a patient with a prostatic carcinoma was published more than 60 years ago (3). In the last decades, attention was drawn to coagulation and fibrinolysis abnormalities in patients with prostatic carcinoma treated with estrogens. Estrogen treatment in patients with prostatic carcinoma is associated with a significant decrease in antithrombin III (4). Coagulation and fibrinolysis abnormalities in non-treated patients or non-estrogen treated patients with prostatic carcinoma, have not been addressed frequently. In the present study, coagulation and fibrinolysis activation (fig. 1) was determined in patients with prostatic carcinoma, non-estrogen treated patients with prostatic carcinoma, and in patients with benign prostate hypertrophy. Coagulation activation was assessed by the thrombin-antithrombin III complex, a sensitive marker which indicates generation of thrombin in vivo (5). The fibrinolytic system activity was evaluated by measuring the D-dimer and the plasmin-α₂-antiplasmin. D-dimer is produced as a result of cleavage of cross-linked fibrin by plasmin. D-dimer reflects in vivo plasmin-induced fibrinolysis (6). Plasmin-α₂-antiplasmin is a relatively new assay and a sensitive marker for plasmin generation in vivo (5). In the last few years some studies were published in which plasmin-α₂-antiplasmin was determined in patients with different kinds of solid tumours, arterial thromboembolism and dissem-
Extrinsic system

Thrombin

Antithrombin III

Fibrinogen

Fibrin monomer + Fibrinopeptides A + B

Fibrin polymer

Plasmin-antiplasmin complex

+ α2-Antiplasmin

Tissue plasminogen activator

Urokinase-type plasminogen activator

Plasminogen

D-dimer

Intrinsic system

Thrombin-antithrombin-III complex

Fig. 1 Relevant part of the coagulation and fibrinolysis cascade.

phatic and/or haematologic metastases who had not received any kind of treatment at the time of blood sample taking formed group 4 (14 patients). In all patients, the haematological metastases were bone metastases.

Samples and methods

Blood samples were drawn from a cubital vein in sitting position before any prostatic manipulation took place. The various constituents were determined in citrated plasma. This was prepared by centrifugation of a mixture of nine volumes freshly drawn blood with one volume trisodium citrate (0.11 mol/l) during 30 minutes (1600 g) at 25 °C. The plasma was stored at -70 °C in plastic tubes and thawed at 37 °C for 5 minutes before batch analysis.

For the thrombin-antithrombin III complex determination, an Elisa test kit was used (Behring Corporation, Marburg, Germany) (intra-assay CV = 7.1%). The fibrin degradation products were measured by means of the D-dimer test of the Behring Corporation (Marburg, Germany) (intra-assay CV = 4.9%).

For the plasmin-α2-antiplasmin measurements, the Elisa test kit Enzygnost® plasmin-α2-antiplasmin of the Behring Corporation (Marburg, Germany) was employed (intra-assay CV = 5.4%). As a reference point, additionally, prostate-specific antigen was determined in serum by the method of Pharmacia Delfia PSA (Rubi Pharmacia, Woerden, The Netherlands).

Statistics

The Mann-Whitney-Wilcoxon test for paired samples and the χ²-test, where appropriate, were used. A p-value less than 0.05 was considered to be statistically significant.

Results

The median values and p-values are listed in table 1 and the proportions of decreased or increased values and p-values are listed in table 2.

No significant difference in thrombin-antithrombin II complex values was found between the different groups. A trend toward significance though, was found between the untreated group with metastases and the benign prostate hypertrophy group. Thrombin-antithrombin III complex was higher in the untreated cancer group with metastases compared to the benign prostate hypertrophy group and the p-value was nearly significant (0.08). A significantly larger proportion of both metastatic groups had increased thrombin-antithrombin III complex and D-dimer values compared to the benign prostate hypertrophy group and the non-metastatic group.

The D-dimer levels showed significant differences between the benign prostate hypertrophy group and the treated group with metastases (p < 0.05), between the treated group with metastases and the untreated group without metastases (p < 0.01) and between both untreated groups (p < 0.05). In all cases, D-dimer levels were significantly higher in the metastatic cancer
groups. A borderline significant difference was found between the benign prostate hypertrophy group and the untreated group with metastases \((p = 0.05)\).

No significant difference was found between the median plasmin-\(\alpha_2\)-antiplasmin levels of the different groups. Plasmin-\(\alpha_2\)-antiplasmin was higher in both metastatic groups compared to the benign prostate hypertrophy group and the \(p\)-value was nearly significant, 0.09 for benign prostate hypertrophy versus treated metastatic group and 0.08 for benign prostate hypertrophy versus untreated metastatic group. The metastatic cancer group without treatment had significantly more patients with increased plasmin-\(\alpha_2\)-antiplasmin levels compared to all three other groups.

**Discussion**

It has been reported that fibrinolysis seems to play a prominent role in (metastatic) prostatic carcinoma, as indicated by increased D-dimer levels and increased urokinase-type plasminogen activator levels in the blood of patients with (metastatic) prostatic carcinoma \((1, 2, 9, 10)\). In our patient groups, increased D-dimer levels were found in the treated cancer group with metastases. Between the two untreated cancer groups, the D-dimer levels were higher in the group with metastases compared to those in the group without metastases.

Surprisingly, the plasmin-\(\alpha_2\)-antiplasmin levels did not show an increase. This might be a methodological problem as a result of the action of neutrophil elastase, which is enhanced in carcinoma patients. Elastase can degrade fibrin so that similar, but not identical, fibrin split products are formed and the trigger for reactive plasmin-\(\alpha_2\)-antiplasmin formation is not really strong. On the other hand it has been reported that D-dimer test kits detect both plasmin- and neutrophil elastase-derived split products \((11)\). So, there are two pathways, which supply substances reacting in the D-dimer test and only one pathway in which plasmin-\(\alpha_2\)-antiplasmin formation is provoked. This might explain why significantly increased median D-dimer values have been found and were found in the present study in patients with prostatic carcinoma and no significant increase in median plasmin-\(\alpha_2\)-antiplasmin values was found in prostatic carcinoma patients in the present study.

To our knowledge, there has been only one study published in which thrombin-antithrombin III complex was measured in patients with prostatic carcinoma \((1)\). Thrombin-antithrombin III complex was higher in the prostatic cancer group compared to two control groups, but no \(p\)-value was mentioned. The cancer group consisted of 51 patients with different stages of prostatic carcinoma. One control group consisted of 40 blood donors and the other of 20 patients with benign prostate cancer.
Tab. 2 Proportions of decreased (D) or increased (I) values (%) in the various patients groups.

<table>
<thead>
<tr>
<th>Analytes</th>
<th>(Reference values)</th>
<th>Patients with benign prostate hypertrophy</th>
<th>Patients with metastases, treated</th>
<th>Patients without metastases, untreated</th>
<th>Patients with metastases, untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
<td>Group 4</td>
</tr>
<tr>
<td>Thrombin-antithrombin III complex</td>
<td>(1.04–4.1 μg/l)</td>
<td>D 0</td>
<td>D I</td>
<td>D 0</td>
<td>D I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasmin-α2-antiplasmin</td>
<td>(50–500 μg/l)</td>
<td>D 0</td>
<td>D I</td>
<td>D 0</td>
<td>D I</td>
</tr>
<tr>
<td>D-dimer</td>
<td>(&lt;80 μg/l)</td>
<td>D 0</td>
<td>D I</td>
<td>D 0</td>
<td>D I</td>
</tr>
</tbody>
</table>

hypertrophy. The present study was not able to confirm the results found by others. First, no coagulation pathway activation and fibrin formation has ever been described in prostatic carcinoma (12). Therefore, the coagulation activation in prostatic carcinoma patients found by others, may have a cause other than the prostatic carcinoma. Second, the fibrinolysis marker D-dimer showed significance in the present study and other studies. However, the most direct fibrinolysis marker, plasmin-α2-antiplasmin, did not. This may be due to the, with other fibrin split products, cross-reacting D-dimer test kits. Thus, fibrinolysis may not play such a prominent role in prostatic carcinoma as described and expected. Before a definite answer can be given to this matter, we think that new studies with larger patient groups are necessary.

References


Received August 7/November 4, 1996

Corresponding author: Dr. J. W. J. van Wersch, De Wever Hospital, Department of Haematology, P.O. Box 4446, NL-6401 CX Heerlen, The Netherlands