VERY HIGH CONCENTRATION OF D-DIMERS IN PORTAL BLOOD IN PATIENTS WITH PANCREATIC CANCER

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Nowadays, increasing attention has been focused on relation between increased D-dimer levels and cancer among patients without detectable thrombosis. The aim of the study was to measure plasma D-dimer levels in portal and peripheral blood in pancreatic cancer patients with absence of venous thromboembolism.

Material and methods. Fifteen consecutive patients hospitalized in the Department of General and Transplant Surgery of Medical University in Łódź, from January to March 2012 who underwent surgery due to a pancreatic cancer were enrolled. At laparotomy, portal and peripheral blood were sampled concurrently. D-dimer and fibrinogen levels were measured. Moreover, to investigate overall coagulation function prothrombin time (PT), prothrombin index (PI), international normalized ratio (INR), thrombin time (TT), activated partial thromboplastin time (APTT), TT and APTT index were evaluated.

Results. Peripheral plasma D-dimer levels above normal range were found in 10/15 patients (66.67%), whereas D-dimer above normal values were confirmed in all portal blood samples. Mean D-dimer values were higher in portal than in peripheral blood (3279.37 vs 824.64, by 297%, p=0.025). These discrepancies were accompanied by normal limits of portal and peripheral levels of fibrinogen and comparable coagulation function indexes.

Conclusion. Our preliminary study showed the close relation between activation of hemostasis, reflected by elevated D-dimers in portal blood and presence of pancreatic cancer. These data suggest that measurement of portal blood D-dimer levels may be a potentially useful technique for screening the pancreatic cancer.

Key words: D-dimers, pancreatic cancer, portal blood, peripheral blood

Pancreatic cancer is the fourth leading cause of death from malignancy in the United States, sixth in Europe and has the lowest survival rate for any solid cancers worldwide (1). The main reason for this extremely poor prognosis is that only less than 15% of patients are diagnosed with resectable tumor (2). Since surgery remains the only curative modality, the detection of early pancreatic cancer is crucial. Existing diagnostic methods are not sufficiently sensitive or specific for early diagnosis. Thus, to improve detection rate new serum markers of pancreatic cancer are urgently needed.

Nowadays, increasing attention has been focused on plasma D-dimer level that is elevated in patients with a variety of solid tumors and may be associated with tumor size, histological type and lymph node status in carcinoma of the stomach, cervix, breast, esophagus and urinary bladder (3-8). D-dimers are degradation product of cross-linked fibrin. Previous studies proved the fibrin coating on the cancer cells may be essential for tumor growth (9). Furthermore, fibrin formation was proved to play a role in tumor spread and distant metastasis (10). The measurement of D-dimer...
level would be therefore useful for screening of malignancy. However, there is lack of data about the relation of pancreatic cancer and D-dimer levels.

The aim of the present study was to evaluate circulating D-dimers in portal and peripheral blood in pancreatic cancer patients with absence of venous thromboembolism.

MATERIAL AND METHODS

This preliminary study enrolled patients hospitalized in the Department of General and Transplant Surgery of Medical University in Łódź, from January to March 2012 who underwent surgery due to a pancreatic cancer. Radical surgical management included Whipple procedure, whereas explorative laparotomy, Roux-en-Y gastrojejunal or triple by-pass anastomoses were performed in irresectable cases (tab. 1). Final diagnosis of pancreatic cancer was confirmed by histopathological examination of postoperative specimens. All patients provided written informed consent for the study.

At laparotomy, following the dissection of hepatoduodenal ligament, samples of portal vein were taken. Concurrently, peripheral blood was sampled via central line. Blood was collected into tubes containing EDTA solution. After centrifugation at 3000 rpm for 10 minutes plasma D-dimer and fibrinogen levels were measured by using commercial kits. Moreover, to investigate overall coagulation function prothrombin time (PT), prothrombin index (PI), international normalized ratio (INR), thrombin time (TT), activated partial thromboplastin time (APTT), TT and APTT index were evaluated.

All statistical calculations were performed using SigmaPlot version 12.0 (Systat Software Inc., San Jose, CA, USA) with the level of statistical significance \( p < 0.05 \). To compare the differences in D-dimer levels and PT, PI, INR, APTT and TT between portal and peripheral blood, we applied the parametric t-test and non-parametric Mann-Whitney test. The t-test, equal variance test were performed in order to demonstrate differences in fibrinogen levels, APTT and TT indexes between aforementioned groups. All data are given in text and tables in means, medians and standard deviations (± SD).

RESULTS

The study group included 15 patients (mean age 66.73±5.21 years, 5 females and 10 males). In majority of cases tumor was localized in the head of the pancreas (tab. 1). Peripheral plasma D-dimer levels above normal range were found in 10/15 patients (66.67%), whereas D-dimer above normal values were confirmed in all portal blood samples. Mean D-dimer values were higher in portal than in peripheral blood (by 297%, \( p=0.025 \)). As shown in tab. 2, these discrepancies were accompanied by normal limits of portal and peripheral levels of fibrinogen and comparable coagulation function indexes.

DISCUSSION

The D-dimer is generated as a result of fibrin formation and fibrinolysis that take place during hemostasis, thrombosis and tissues repair (12). As D-dimers are specific final degradation
Very high concentration of D-dimers in portal blood in patients with pancreatic cancer

Product of cross-linked fibrin that are stable and resist further lysis, it can be useful marker in numerous clinical scenarios. It is widely used to exclude deep vein thrombosis (13); elevated levels indicate a risk of myocardial infarction and may be a marker of pathological coagulation underlying cardiovascular diseases (14). Increased D-dimer levels may be observed following trauma and surgery or in pregnancy, contagious diseases and also cancer.

Previous studies pointed towards a relation between activation of coagulation and enhanced cancer growth, angiogenesis, metastases, and eventually worse prognosis (15, 16). Patients with malignancy are characterized by well known tendency to hypercoagulability with a high prevalence of venous thromboembolism as a paraneoplastic phenomenon, which was firstly described by Trousseau in 1865. Pancreatic cancer is among the most common malignancies associated with thrombosis as it occurs in 50% of patients (17). Clinical manifestations of thromboembolic disease in pancreatic cancer include deep vein thrombosis, pulmonary embolism, disseminated intravascular coagulation, portal vein thrombosis and arterial tromboembolism. Occurrence of thromboembolic events is often associated with advanced stage of pancreatic tumor and decrease in survival. Recurrence of thromboembolism predicts shorter life expectancy (18). Still the causative factors for these homeostatic disorders are not very clear, but impact of tumor localization, increased prothrombotic factors and platelet aggregation and decrease of inhibitors of anticoagulation have been proposed.

The main research interest is in relation between increased D-dimer levels and cancer among patients without detectable thrombosis. Previous studies proved that inexplicable elevated D-dimer levels may be markers of occult malignancy (19). Higher D-dimer values are associated with advanced tumors, positive metastatic lymph nodes, and short postoperative survival in colorectal cancer patients without thrombosis (20). Moreover it should be considered as a predictor of overt or occult cancer (21).

Recent studies proved that cancer of the pancreas tend to be characterized by the highest levels of D-dimer among all cancer sites (22), and it was considered as an independent predictor of the venous thrombosis occurrence in future. Together with previous observations, in our group of pancreatic cancer and absence of venous thrombosis we noticed moderately elevated peripheral blood D-dimer values in majority of patients. Furthermore, as a first worldwide, we evaluated plasma D-dimers in portal blood of patients with pancreatic cancer and we observed enormous high levels in all investigated individuals (tab. 2). It may be explained by previously established association between disorders in hemostasis and the pathogenesis of malignancy. The initiation of coagulation was proved to be mainly the result of increased expression of tissue factor (TF),

Table 2. Distribution of plasma D-dimer, fibrinogen and coagulation indexes in portal and peripheral blood in pancreatic cancer patients with absence of venous thromboembolism. Mean D-dimer values were statistically significantly higher in portal than in peripheral blood

<table>
<thead>
<tr>
<th>Coagulation factors and indexes</th>
<th>Portal blood</th>
<th>Peripheral blood</th>
<th>Differences in the portal and peripheral blood values (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer (µg/l)</td>
<td>3279,37 ± 3293,68</td>
<td>2918</td>
<td>824,64 ± 764,46</td>
</tr>
<tr>
<td>Fibrynogen (mg/dl)</td>
<td>338,39 ± 127,26</td>
<td>308,4</td>
<td>374,28 ± 91,61</td>
</tr>
<tr>
<td>Prothrombin time (PT) (seconds)</td>
<td>15,83 ± 22,49</td>
<td>14,7</td>
<td>14,49 ± 1,29</td>
</tr>
<tr>
<td>Prothrombin index (PI) (%)</td>
<td>86,67 ± 12,08</td>
<td>91,05</td>
<td>80,73 ± 33,03</td>
</tr>
<tr>
<td>INR</td>
<td>1,21 ± 0,24</td>
<td>1,1</td>
<td>1,08 ± 0,13</td>
</tr>
<tr>
<td>Thrombin time (TT) (seconds)</td>
<td>15,97 ± 3,13</td>
<td>15,35</td>
<td>15,63 ± 4,02</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (APTT) (seconds)</td>
<td>28,5 ± 7,3</td>
<td>26,65</td>
<td>28,16 ± 9,24</td>
</tr>
<tr>
<td>TT index</td>
<td>1,15 ± 0,23</td>
<td>1,14</td>
<td>1,14 ± 0,11</td>
</tr>
<tr>
<td>APTT index</td>
<td>0,87 ± 0,22</td>
<td>0,8</td>
<td>0,91 ± 0,16</td>
</tr>
</tbody>
</table>
that contributes to tumor growth, angiogenesis and metastatic spread. Its expression was proved to occur very early in pancreatic neoplastic cells (23), triggering clotting cascade with subsequent fibrin deposition. This fibrin biofilm evades host immune system and prevents the cancer cells from being killed by natural-killers cells (24). Fibrin deposits are scaffold for progressing tumor, make it unfavorable for immune cells interventions and adopt tumor to immune surveillance. The result of this process is subsequent D-dimer production that is a biomarker indicating the activation of hemostasis and fibrinolysis. That may explain enormous high level of D-dimer in portal blood in our group of patients.

Portal vein collect blood directly from the pancreas and its sampling avoid the possible effect of D-dimer inactivation in the liver. A sample of portal blood can be obtained intraoperatively or during ultrasound guided percutaneous cannulation that is well known procedure during islet cells transplantation (25). Intraoperative sampling of portal vein seems to be a safe method (26).

Chronic pancreatitis shares clinical similarities with pancreatic cancer and differentiating the two conditions poses a diagnostic challenge. Increase in circulating D-dimer levels may be also associated with inflammation and endothelial activation that are characteristic for chronic pancreatitis. Thus further differential studies are needed to elucidate sensitivity and specificity of portal blood D-dimer levels as a biomarker of pancreatic cancer.

D-dimer and other large fragments degradation products of crosslinked fibrin are excreted by kidneys (27). However, high D-dimer levels were observed in decompensated liver cirrhosis with ascites (28). We hypothesize that liver may play important role in D-dimer metabolism, although we are not able to clearly demonstrate correlation between portal and peripheral blood D-dimer levels and liver function. On the basis of this finding, liver contribution in D-dimer metabolism should be clarified in future studies.

The levels of fibrinogen in portal and peripheral blood of our patients were within normal range that is in opposite to previous reports. The elevated fibrinogen level was considered to be associated with pancreatic cancer invasiveness and lymphatic metastasis (29). However it was proved that level of fibrinogen is higher in patients with pancreatic cancer and jaundice. Most of our patients were non-jaundiced that may be the reason of this difference.

In conclusion, our preliminary study evaluated plasma D-dimer levels in portal blood of patients with pancreatic cancer as a first worldwide. We showed the close relation between activation of hemostasis, reflected by elevated D-dimer levels in portal blood and presence of pancreatic cancer that is malignancy with extremely aggressive tumor biology. Our data suggest that measurement of portal blood D-dimer levels may be a potentially useful technique for screening the pancreatic cancer.

REFERENCES


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