Pancreatic Polypeptide is Increased in Patients with Advanced Malignant Disease

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Abstract. Background: Augmented secretion of pancreatic polypeptide (PP) has been demonstrated in patients with severe systemic diseases or endocrine tumors. The aim of this study was to evaluate PP and autonomic neuropathy in patients with advanced malignant disease. Materials and Methods: Basal PP assessments and five cardiovascular tests for autonomic function were used. Twenty patients, including 11 patients with lung cancer (69 yrs±11, mean±SD) and 10 healthy age-matched controls, were studied. Results: PP levels were significantly higher in the patients than in the controls (pmol/L 107.0±111.4 versus 28.2±13.4, p<0.05). In the parasympathetical tests, the patients showed significantly decreased heart rate response to the Valsalva manoeuvre (ratio 1.20±0.19 versus 1.46±0.23, p<0.005). Also, in the sympathetical tests, the blood pressure response to standing up was significantly decreased (mmHg –3.84±17.53 versus 10.80±8.89, p<0.05). The heart rate response to standing up and deep breathing, as well as the blood pressure response to sustained handgrip, did not differ significantly between the groups. In spite of the apparent autonomic dysfunction among cancer patients with advanced malignant disease, PP levels were significantly higher in these patients when compared with healthy controls. Conclusion: PP levels were significantly higher in patients with advanced cancer than controls, regardless of autonomic dysfunction in the cancer patients. This finding supports the hypothesis that PP may, in some cancer patients, be a marker of advanced malignant disease.

Previous studies have shown that pancreatic polypeptide (PP) is reduced in diabetic patients with autonomic neuropathy (1,2). PP consequently has been considered a useful marker of vagal efferent integrity (1,2). However, other studies have shown augmented PP secretion regardless of autonomic dysfunction in patients with severe chronic obstructive pulmonary disease as well as in patients with systemic lupus erythematosus (3,4). PP secretion has been localized to a specific population of human islet cells and has also been shown to be produced and released by pancreatic endocrine tumors (5). PP-producing tumors are mostly located in the pancreas and may present as three pathological lesions: pure PP-omas, mixed tumors with minor PP cell population and PP-cell hyperplasia. Numerous types of extrapancreatic endocrine tumors are able to synthesize and secrete PP (5,6).

The aim of this study was to assess serum PP concentrations in patients with advanced malignant disease including lung cancer. We also assessed autonomic neuropathy as an indirect measure of vagal stimulation (7-10). Since all these test results may be age-dependent, an age-matched control group was included (6,11).

Materials and Methods

Patients. Twenty patients with advanced malignant disease including 11 patients with lung cancer, were enrolled in the study. The mean age was 69 years (range 38-82) and 65% of the patients were male. The cancer diagnosis was based on histological examination and disease extension was confirmed by CT-scan and/or whole body scintigraphy. The tests were performed before the start of chemo- or radiotherapy. Ten age-matched healthy subjects served as controls. Informed consent was obtained from all the subjects. The study was approved by the regional Ethics Committee.

Methods. The Performance Status was assessed according to a 5-point scale by WHO (12).

Basal pancreatic polypeptide. Prior to cytotoxic treatment, fasting blood samples for basal serum PP were collected, stored and analyzed as previously described (13).

Tumor markers. Fasting blood samples for carcinoembryonal antigen (CEA), neuron-specific enolase (NSE) and prostate-specific antigen (PSA) were analyzed prior to treatment start.

Cardiovascular tests. Five cardiovascular tests of autonomic function were employed as previously described (7,8,14,15) in the following order: heart rate response to Valsalva manoeuvre; heart rate...
Variation during deep breathing; immediate heart rate response to standing up; blood pressure response to standing up; and blood pressure response to sustained handgrip. The tests were performed in the same order in all subjects.

**Statistical analysis.** Results are given as means±SD. At first the Student’s t-test for unpaired data was used to compare results between the groups. Then, for selected tests we used analysis of variance (ANOVA) and the Mann-Whitney test when comparing test results between the groups. p<0.05 was considered statistically significant.

Correlations between the tests and pulmonary function characteristics were performed using the Spearman’s rank correlation coefficient.

**Results**

**Patient characteristics.** Characteristics for patients and controls are given in Table I. The patients’ performance status was significantly reduced when compared to age-matched controls. According to the WHO performance status (grades 0-4), the majority of patients were ambulatory and capable of self-care but unable to carry out any work; up and about more than 50% of waking hours; grade 3 = capable of only limited self-care; confined to bed or chair more than 50% of waking hours; grade 4 = completely disabled; cannot carry out any self-care; totally confined to bed or chair.

**Biochemical markers.** The patients’ PP levels were significantly higher than in the controls (p<0.05) (Table II).

**Autonomic tests.** The data are given in Table III. In individual autonomic tests, the patients had significantly decreased heart rate response to the Valsalva manoeuvre and blood pressure response to standing up compared to controls. The heart rate response to deep breathing and standing up, as well as the blood pressure response to sustained handgrip, did not differ significantly between the groups.

**Correlations.** There were no significant correlations between patient characteristics, PP values, tumor markers and autonomic tests in the patient group, and no significant difference in PP levels between lung cancer patients compared to patients with other malignant diseases.

**Discussion**

In the present study, patients with advanced malignant disease had a higher basal serum PP value than healthy controls. To our knowledge, this finding has not been reported before.
Table III. Autonomic function in patients and controls.

<table>
<thead>
<tr>
<th>Cardiovascular tests</th>
<th>Patients, n=20</th>
<th>Controls, n=10</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate response to Valsalva manoeuvre (ratio)</td>
<td>1.20±0.19</td>
<td>1.46±0.23</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Heart rate response to deep breathing (ratio)</td>
<td>6.89±4.56</td>
<td>6.50±3.50</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate response to standing up (ratio)</td>
<td>0.97±0.24</td>
<td>1.09±0.13</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure response to standing up (mmHg)</td>
<td>-3.84±17.53</td>
<td>10.80±8.89</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Blood pressure response to sustained handgrip (mmHg)</td>
<td>10.32±11.80</td>
<td>16.90±14.22</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Higher score = better performance

When evaluated with tests for cardiovascular reflexes, patients with advanced malignant disease demonstrated dysautonomia when compared with controls. This is in agreement with results reported previously. Paraneoplastic dysautonomia is associated with cancer of the lungs (16). Previous studies have shown that the PP levels decrease in diabetic patients with autonomic neuropathy (2). The PP level, therefore, has been considered as a marker for vagal tone. Consequently, the increased PP levels in the advanced cancer patients were unexpected. However, a similar finding of augmented PP secretion inspite of autonomic dysfunction has also been seen in patients with severe chronic obstructive pulmonary disease, as well as in patients with systemic lupus erythematosus (3,4).

PP has been reported to be produced and released by pancreatic endocrine tumors, but in most cases PP cells represent a subpopulation in tumors with heterogeneous multihormonal cell composition. Pure PP cell tumors have also been identified (5,6). PP-producing cells may also occur as a minor population in non-functional tumors with predominance of the non-hormone-producing cells (5,6). This previous finding is supported by our study.

The PP concentrations observed in our study are remarkably elevated. It would be interesting to know whether some of the malignant tumors actually express PP or whether it is the pancreatic secretion of the peptide that is increased. It cannot be excluded that PP should enter the panel of tumor markers. With regards to its relation to autonomic neuropathy, it is probably irrelevant to look at fasting concentrations; instead the first phase response to a meal should have been examined. In addition, it might have been informative to examine the fasting concentrations after the administration of atropine.

In conclusion, the PP levels were significantly higher in patients with advanced cancer than controls, regardless of autonomic dysfunction in the cancer patients. This finding supports the hypothesis that PP may, in some cancer patients, be a marker of advanced malignant disease.

Acknowledgements

We wish to thank Tordis Arild and the Department of Clinical Research, University Hospital of Northern Norway, Tromsø, Norway, for skillful technical assistance.

References


Received March 15, 2004
Accepted June 2, 2004