Clinical Value of Serum Neopterin, Tissue Polypeptide-Specific Antigen and CA19-9 Levels in Differential Diagnosis between Pancreatic Cancer and Chronic Pancreatitis

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Key Words
Pancreatic adenocarcinoma · Chronic pancreatitis · CA19-9 · Neopterin · Tissue polypeptide-specific antigen

Abstract
Background: Neopterin and tissue polypeptide-specific antigen (TPS) have been suggested to be useful in differential diagnosis between pancreatic adenocarcinoma (PA) and chronic pancreatitis (CP). The aim of our study was to compare the clinical usefulness of CA19-9, neopterin and TPS serum levels in patients with PA and CP. Methods: The study included 85 patients with PA, 72 with CP and 50 healthy controls. The serum concentrations of neopterin, TPS and CA19-9 were measured (DRG International, USA). The associations of the analyzed markers and clinical data at diagnosis have been evaluated. Results: Serum levels of neopterin, TPS and CA19-9 were higher in PA patients compared to CP (p < 0.001). TPS and CA19-9 levels were also elevated in patients with CP compared to the control group (p < 0.001). In contrast, there was no difference between neopterin serum levels in CP patients and the control group (p > 0.05). Neopterin showed the best sensitivity and specificity (91.8 and 87.5%) in PA diagnosis compared to CA19-9 (respectively 83.5 and 75%) and TPS (75.3 and 65.3%). Conclusion: Our results indicate that neopterin may be potentially useful in differential diagnosis between PA and CP. Assessment of TPS probably adds no significant information to that obtained with CA19-9 and neopterin.

Differential diagnosis between pancreatic adenocarcinoma (PA) and chronic pancreatitis (CP) represents a significant challenge, particularly in case of detected pancreatic masses. CA19-9, carbohydrate cell-surface antigen, is the most popular serum-based marker for PA diagnosis, useful for detecting recurrent disease and surveillance of patients after surgery [1–3]. However, CA19-9 levels may be normal in patients with localized disease, therefore its use as a screening marker for early pancreatic cancer is limited. Furthermore, high CA19-9 levels may also be found in benign pathologies such as CP as well as non-malignant jaundice [1, 2, 4].

To improve the effectiveness of PA diagnosis, other tumor markers have been investigated, among them neopterin and tissue polypeptide-specific antigen (TPS). Neopterin is a low-molecular mass substance synthesized from guanosine triphosphate in monocytes and macrophages in response to IFN-γ stimulation. It is an indica-
tor of systemic immune activation, elevated in viral infections, autoimmune disorders and neoplastic diseases, such as colorectal, gastric and breast cancers [5–8]. It may also be elevated in patients with PA, therefore its use in differential diagnosis of pancreatic masses has been suggested [9, 10].

TPS is the cytokeratin belonging to the intermediate filament protein group, which forms a part of the cytoskeleton. It has been suggested that TPS reflects the activity of tumor growth, however its clinical utility in cancer diagnosis is controversial [11–14]. In some studies, TPS has been found to be superior to CA19-9 [15, 16], but inferior in others [14, 17]. The aim of our study was to compare the clinical usefulness of CA19-9, neopterin and TPS serum levels in differential diagnosis of PA and CP as well as to assess their possible prognostic value.

**Patients and Methods**

The study included 207 patients: 85 with PA (41 men and 44 women aged 47–84), 72 with CP (44 men and 28 women, aged 21–76) and 50 gender- and age-matched healthy volunteers. Analyzed patients were hospitalized in the Department of Digestive Tract Diseases of Lodz Medical University or in the Department of Digestive Surgery of Silesian Medical University between 2003 and 2007.

Only patients with confirmed pathologic diagnosis of PA were included in the study. 29 patients (34.1%) with PA underwent Whipple resection or distal pancreatectomy, 33 patients (38.8%) underwent palliative surgery and 23 patients (27.1%) underwent palliative chemotherapy and/or palliative endoscopic treatment. 19 patients (26.4%) with CP had surgical therapy. Indications for surgical intervention in CP were intractable pain, suspicion of pancreatic cancer and pancreatic pseudocyst. In the remaining cases (73.6%), CP diagnosis was established based on a typical clinical history and characteristic findings on pancreatic imaging.

The associations of the CA19-9, neopterin and TPS and clinical data at diagnosis have been evaluated. The following clinical variables were analyzed: age and sex of patients, tumor size and histological grade, lymph node involvement, distant metastases and liver function (bilirubin as well as alanine and aspartate aminotransferases levels).

Peripheral venous blood samples were obtained from all analyzed patients at the time of hospital admission. Patients with fever and acute viral infections were excluded from the study. Sera were separated by centrifugation at 3,000 rpm and were stored at −80°C until the levels of analyzed markers were assessed. The serum concentrations of neopterin, TPS and CA19-9 were measured by an enzyme-linked immunosassay (DRG International, USA), according to the manufacturer’s recommendations.

**Statistical Analysis**

Statistical analysis comprised arithmetical mean, median and standard deviation. The Mann-Whitney t test was used to determine differences between groups. Association between continuous variables was analyzed with Pearson’s correlation test. p values <0.05 were considered to be significant. Receiver operating characteristic (ROC) curves depicting the ability to discriminate between PA and CP were plotted for each of the markers. The cutoff point of neopterin was set at 9.5 nmol/l, of TPS at 73.5 U/l, and of CA19-9 at 37 U/ml.

**Results**

Serum levels of CA19-9, neopterin and TPS were higher in patients with PA compared to the CP and control groups (p < 0.001; fig. 1–3). In PA patients the median neopterin levels were 17.3 nmol/l (range 3.9–36.7), TPS levels were 136.9 U/l (17.5–881.4) and CA19-9 levels were 101.2 U/ml (1.1–1,383.5). The median TPS and CA19-9 levels were also elevated in patients with CP compared to the control group (p < 0.05; fig. 2, 3). In contrast, there was no statistically significant difference between neopterin serum levels in CP patients and the control group (fig. 1).

ROC curves for the abilities of neopterin, CA19-9 and TPS to distinguish between PA and CP are plotted in figure 4. Neopterin showed the best sensitivity and specificity (91.8 and 87.5%) in pancreatic cancer diagnosis compared to CA19-9 (83.5 and 75% respectively) and TPS (75.3 and 65.3%). Area under the curve (AUC) was 0.957 (95% CI 0.926–0.988) for neopterin, 0.859 (95% CI 0.8–
0.917) for CA19-9, and 0.777 (95% CI 0.706–0.849) for TPS (fig. 4).

In patients with PA the tumor size ranged from 2 to 7 cm (mean 3.9 \pm 1.3). Lymph node metastases were observed in 39 patients with PA (45.9%) and liver metastases in 16 patients (18.8%). A relationship was found between higher neopterin, TPS and CA19-9 serum levels and larger tumor size as well as presence of lymph nodes and distant metastases (p < 0.001). In contrast, analyzed markers were neither correlated with patients’ age and sex nor with laboratory findings or tumor grades (data not shown).

**Discussion**

The wide availability of CA19-9 assay for conventional clinical use together with a good ratio between sensitivity and specificity make this tumor marker the best known and the most recommended for diagnosis and recurrence of pancreatic cancer. Similarly to previous data in our study, CA19-9 levels were significantly elevated in patients with PA compared to the CP and control groups. Higher CA19-9 levels were also associated with larger tumor size, as well as the presence of lymph nodes and liver metastases. Our results are in agreement with other studies which reported that higher serum levels of CA19-9 were associated with the presence of distal metastases and worse prognosis of patients with pancreatic cancer [17, 18]. In contrast, other authors have not found the relationship between CA19-9 value and the clinical advancement of pancreatic cancer [16, 19].

**Fig. 2.** Comparison of serum CA19-9 levels in patients with PA, CP and the control group.

**Fig. 3.** Comparison of serum TPS levels in patients with PA, CP and the control group.

**Fig. 4.** ROC curves analyses of neopterin, TPS and CA19-9 for the diagnosis of PA. AUC is 0.957 for neopterin, 0.859 for CA19-9, and 0.777 for TPS.
However, it is also known that individuals Lewis A negative with PA do not express CA19-9 in serum. Moreover, high CA19-9 serum levels may be found in benign pathologies, particularly in CP [1, 2, 18]. In our study, CA19-9 serum levels were also elevated in 11 (15.3%) patients with CP and were significantly higher in CP patients compared to the control group. CA19-9 sensitivity of 83.5% and specificity of 75%, demonstrated in our study, were not different from those reported by previous studies. According to published data, the median sensitivity of CA19-9 is 79% (70–90%) and median specificity – 82% (68–91%) [1, 4, 20].

We hypothesized that the combination with other markers may improve CA19-9 accuracy in differential diagnosis of pancreatic tumors. We assessed the diagnostic utility of neopterin, which elevated serum and urinary levels were reported in breast, gastric and colon cancer [5, 6, 8]. We – as well as Birk et al. [10] – observed elevated neopterin serum levels in patients with PA compared to CP and healthy groups. Furthermore, in our study, neopterin showed the best sensitivity and specificity (91.8 and 87.5%) in pancreatic cancer diagnosis compared to CA19-9 and TPS. Higher specificity of neopterin results from the less frequent and only slight elevation in the serum in patients with CP.

In contrast, in the study of Manes et al. [21], neopterin showed lower sensitivity and specificity compared to CA19-9, at the recommended cut-off 37 U/ml. However, they analyzed a smaller group of patients with different disease stages, so the data may be difficult to compare. This issue needs further evaluation, based on long-term prospective studies in patients with PA and CP.

Recently, Sahin et al. [22] have published promising data about usefulness of neopterin in thyroid malignancy detection. They observed a significant difference in neopterin levels between malignant and benign thyroid disorders, suggesting that monitoring of urinary neopterin profile may be used in early diagnosis of papillary thyroid cancer.

We have also demonstrated the relationship between elevated neopterin value and larger tumor size as well as the presence of lymph nodes and distant metastases. Similarly, Yildirim et al. [5] found that the serum levels of neopterin were higher in patients with metastatic breast cancer compared to patients without distal metastases. Unal et al. [8] also observed that serum neopterin concen-

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**Table 1. Clinical profiles of the patients with PA and the relationship to the CA19-9, neopterin and TPS serum levels**

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>n = 85</th>
<th>CA19-9 U/ml</th>
<th>p</th>
<th>Neopterin nmol/l</th>
<th>p</th>
<th>TPS U/l</th>
<th>p</th>
</tr>
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<tbody>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>47</td>
<td>117.3</td>
<td>NS</td>
<td>17.5</td>
<td>NS</td>
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<td>NS</td>
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<td>95.2</td>
<td>NS</td>
<td>16.8</td>
<td>NS</td>
<td>131.8</td>
<td>NS</td>
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<tr>
<td>Age</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;65</td>
<td>41</td>
<td>101.7</td>
<td>NS</td>
<td>16.2</td>
<td>NS</td>
<td>157.8</td>
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<tr>
<td>≥65</td>
<td>44</td>
<td>121.3</td>
<td>NS</td>
<td>17.9</td>
<td>NS</td>
<td>122.9</td>
<td>NS</td>
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<td>Tumor size</td>
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<tr>
<td>≤3.5 cm</td>
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<td>90.1</td>
<td>p &lt; 0.01</td>
<td>15.2</td>
<td>p &lt; 0.05</td>
<td>79.8</td>
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<td>Head of the pancreas</td>
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<td>88.6</td>
<td>NS</td>
<td>16.6</td>
<td>NS</td>
<td>123.8</td>
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<tr>
<td>Body or tail</td>
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<td>134.2</td>
<td>NS</td>
<td>18.1</td>
<td>NS</td>
<td>154.2</td>
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<tr>
<td>Histological grade</td>
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<td></td>
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<tr>
<td>G1 + G2</td>
<td>50</td>
<td>101.2</td>
<td>NS</td>
<td>18.0</td>
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<td>p &lt; 0.01</td>
<td>22.4</td>
<td>p &lt; 0.01</td>
<td>253.6</td>
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<td>14.1</td>
<td></td>
<td>96.5</td>
<td></td>
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<tr>
<td>Distant metastases</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
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<td>p &lt; 0.01</td>
<td>21.5</td>
<td>p &lt; 0.01</td>
<td>268.5</td>
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<tr>
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<td>69</td>
<td>56.4</td>
<td></td>
<td>14.7</td>
<td></td>
<td>99.1</td>
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</table>
trations were significantly higher in patients with gastric carcinoma than in the control group and were correlated with tumor stage, gastric wall involvement and the number of metastatic lymph nodes. In study of Birk et al. [10], higher neopterin serum levels were also an independent prognostic factor in resectable PA patients.

The proposed neopterin estimation can be measured easily in clinical practice, not only in hospitals specialized for pancreatic diseases. The availability of technical instruments (ELISA system), a low cost as well as high sensitivity and specificity, make neopterin a useful biological marker for everyday management of PA differential diagnosis.

The last analyzed marker – TPS – in our and other studies was also significantly elevated in patients with PA [11, 16]. It is known from the literature that TPS serum levels increased in other neoplastic diseases. Hwa et al. [15] found that the TPS serum level was elevated in patients with breast cancer and showed the best predictive value among analyzed tumor markers, with a sensitivity of 80%. Assessment of TPS serum levels also appeared effective in improvement early diagnosis of recurrent ovarian cancer [14]. Treska et al. [23] reported that TPS represented an important predictive marker for the disease-free interval and patient survival after surgery for colorectal liver metastases.

However in our study the sensitivity of TPS was only 75.3% and specificity was 65.3%, which was lower than neopterin and CA19-9. Data from the literature about its clinical usefulness in differential diagnosis of pancreatic diseases are not uniform. Plebani et al. [17] reported that TPS lacked both sensitivity and specificity in PA detection compared to CA19-9. Pasanen et al. [16] also found that the TPS diagnostic value in PA was less accurate than other analyzed tumor markers, however when TPS was combined with other markers, the specificities clearly improved, being highest in the combination of TPS and CA-242 (92.5%). In contrast, in the study of Slezak et al. [13], TPS, at the cut-off level 200 U/l, was almost completely discriminated between PA and CP. The same authors have shown that TPS serum levels were useful in a long-term follow-up of PA and CP patients reflecting their clinical status more accurately than CA19-9 [11]. The role of TPS has to be further studied in order to explain the different results and to establish its usefulness in PA differential diagnosis.

In conclusion, we suggest that neopterin may be useful in differential diagnosis between pancreatic cancer and CP, and its serum levels are worth determining in patients in whom the character of pancreatic tumor is difficult to establish. According to our results, assessment of TPS probably adds no significant information to that obtained using neopterin and CA19-9.

References


