Clinical usefulness of pentraxin 3 (PTX3) as a biomarker of acute pancreatitis and pancreatic cancer

Przydatność kliniczna pentraksyny 3 (PTX3) jako biomarkera ostrego zapalenia trzustki i raka trzustki

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Słowa kluczowe: ostre zapalenie trzustki, rak trzustki, pentraksyna 3.

Abstract

Introduction: Increased concentrations of pentraxin 3 (PTX 3) were diagnosed in acute pancreatitis (AP) and in pancreatic ductal adenocarcinoma (PDAC).

Aim of the research: To assess of the clinical usefulness of PTX3 in the early differentiation of AP from PDAC.

Material and methods: The test group consisted of 125 patients with AP and 24 people with PDAC, as well as 52 healthy subjects. The following concentrations were tested in plasma: PTX3, C-reactive protein (CRP), interleukin-6 (IL-6), and CA-19.9.

Results: The mean PTX3 concentration in the moderately-severe AP (MAP) or severe AP (SAP) equalled 16.53 ng/ml and was significantly higher in comparison with mild AP (9.60 ng/ml; \( p = 0.0007 \)) and the control group (2.31 ng/ml). In the case of patients with PDAC, the mean concentration of PTX3 was 9.20 ng/ml and was significantly higher than in the control group (2.31 ng/ml); \( p < 0.0001 \). A significantly higher average CRP value of 100.37 mg/l and IL-6 91.65 pg/ml was also found in patients with PDAC compared to the control group (\( p < 0.0001 \)). Tested pro-inflammatory cytokines were significantly higher in patients with MAP or SAP than in those with PDAC (\( p < 0.05 \)). The ROC curve confirms the clear connection of PTX3 level and PDAC in comparison with the control group (\( p = 0.0001 \)), relatively low sensitivity, and high specificity. However, the results were not significant enough to allow us to differentiate cancer from AP (\( p > 0.05 \)).

Conclusions: Pentraxin 3 can be a marker in the prediction of the severe course of AP, but its clinical usefulness for the differentiation of PDAC was not confirmed.

Streszczenie

Wprowadzenie: Wzrost stężenia pentraksyny 3 (PTX3) stwierdzono zarówno w ostrym zapaleniu trzustki (AP), jak i raku trzustki (PDAC).

Cel pracy: Ocena przydatności klinicznej PTX3 we wczesnym różnicowaniu AP i PDAC.

Materiał i metody: Zbadano 125 chorych na AP i 24 chorych z potwierdzonym histopatologicznie lub cytotologicznie PDAC oraz 52 osoby zdrowe jako grupę kontrolną. Próbki krwi pobierano w pierwszym dniu hospitalizacji. Oznaczono stężenia w osoczu PTX3, białka C-reaktywnego (CRP), interleukiny (IL-6) i aktywność CA-19.9.

Wyniki: Średnie stężenie PTX3 u chorych z AP i PDAC wynosiło 16,53 ±15,73 ng/ml i było istotnie wyższe niż średnie stężenia u pacjentów z łagodnym AP (9,60 ±9,65 ng/ml; \( p = 0.0007 \)) i grupy kontrolnej (2,31 ±0,58 ng/ml). Średnie stężenie PTX3 u chorych z PDAC wynosiło 9,20 ng/ml i było znacząco większe niż stężenie w grupie kontrolnej (2,31 ng/ml; \( p < 0.0001 \)). Stwierdzono również istotnie wyższą średnią wartość CRP 100,37 mg/l i IL-6 91,65 pg/ml u chorych z PDAC w porównaniu z grupą osób zdrowych (\( p < 0.0001 \)). Stężenia cytokin prozapalnych były znamnie wyższe u chorych z MAP i SAP niż z PDAC (\( p < 0.05 \)). Krzywa ROC potwierdza istotną zależność między stężeniem PTX3 a rozpoznaniem PDAC w porównaniu z grupą kontrolną, ze stosunkowo niską czułością i wysoką specyficznością. Nie wykazano istotnej zdolności do różnicowania PDAC z AP (\( p > 0.05 \)).

Wnioski: Pentraksyna 3 może być markerem w przewidywaniu ciężkiego przebiegu AP, ale nie potwierdzono jej przydatności klinicznej w różnicowaniu z PDAC.
Introduction

Pentraxins (PTX) belong to the group of acute phase proteins. They can be divided into short pentraxins, such as C-reactive protein (CRP), and long pentraxins. One of the long pentraxins is pentraxin 3. Similarly to CRP, PTX3 is a marker of inflammation, secreted locally in the inflamed area.

Production of protein PTX3 is dependent on cytokines, mainly interleukin-1β (IL-1β) and tumour necrosis factor α (TNF-α), and is secreted by macrophages, dendritic cells, vascular endothelial cells, smooth muscle cells, fibroblasts, and adipocytes. Normal serum concentration of PTX3 equals less than 2 ng/ml. The concentration of PTX3 rises and reaches its highest values within 6–8 h of the inflammatory response [1].

The clinical relevance of PTX3 has been confirmed as a biomarker of inflammation, i.e. in the course of atherosclerosis and cardiovascular diseases [2], chronic obstructive pulmonary disease (COPD) [3], rheumatoid arthritis (RA) [4], kidney failure [5], and sepsis. PTX3 and CRP are the main indicators of inflammation taking place in the body [6]. Pentraxin plays an important role in angiogenesis by modulating the secretion of vascular epidermal growth factor-2 (VEGF-2) and fibroblast growth factor (FGF) [6]. The prognostic importance of PTX was confirmed in the prediction of deaths from various causes among patients with sepsis [7, 8]. It is also suggested that the increase of PTX3 level in blood may be connected with smoking [3]. Acute pancreatitis is an illness during the course of which the increased concentration of PTX3 was confirmed. The highest levels were observed in the first 24 h of the illness, and the concentration of PTX3 was higher in those with a severe condition of acute pancreatitis (AP) than in the case of mild AP [9, 10].

PTX3 is taken into account as a potential biomarker of cancer, although its clinical significance in cancer has not been discovered. Molecular tests show the autocrine and paracrine effect of PTX3 on tumour cells, in which the effect may be the progression of the disease. PTX3 was tested as a marker in patients suffering from lung cancer [11]. The concentration of PTX3 decreased after surgical resection of lung cancer and increased during a recurrence of the cancerous process.

The assumed cut-off value of concentration was 8.03 ng/ml. The reasons for a PTX3 concentration increase in blood serum in the case of patients suffering from lung cancer are unknown [11, 12]. It is suspected that it is connected with local inflammation around the tumour and the role the protein plays in apoptosis. The increase of PTX3 is connected with the increase of concentration of CRP and interleukin-6 (IL-6) in blood. Increased concentration of PTX3 in blood was also observed in patients with other types of cancer, such as prostate cancer, liposarcoma, and pancreatic cancer. The concentration of PTX3 is connected with the advancement of the cancer invasion and can be used as a prognostic marker [12].

Pancreatic cancer has one of the poorest prognoses among cancers of the digestive system. It is usually diagnosed in a very advanced stage of the disease, and less than 5% of patients reach 5 years of survival with the disease. It was found that the cells of pancreatic cancer in in vitro conditions secrete PTX3 directly. The observed increase of PTX3 concentration in patients with advanced stages of pancreatic cancer allows for the formulation of a hypothesis that it can be a good prognostic marker. The level of PTX3 was positively correlated with the level of CRP and IL-6 [13]. Patients with pancreatic adenocarcinoma had significantly higher concentrations of PTX3 in blood serum than the group with non-cancerous diseases of the pancreas or the group of healthy volunteers. The assumption was made that PTX3 can be a useful biomarker in differentiation of those pathologies [7].

However, the mechanism of the functioning of pentraxin in the environment of the tumour remains unknown. Pancreatic stellate cells (PSCs) are cells similar to myofibroblasts and the main producers of fibre in pancreatic parenchyma. It is assumed that they are responsible for the fibrosis of pancreatic parenchyma occurring during the development of pancreatic cancer. Stellate cells obtained in cell cultures of pancreatic cancer secrete significant amounts of PTX3. Results of tests show that the mediator of inflammatory response PTX3 was almost eight times higher in stellate cells from a cancerous tumour than in those from healthy tissue. Moreover, this result suggests that PTX3 can be connected with the advancement of pancreatic cancer [14].

The role of PTX3 in cancerous diseases is still being analysed. So far, there have been no differences found in marking the concentration of PTX3 in various cancer locations in other organs of the body. The research aims at the assessment of the values of the PTX3 concentration in patients with pancreatic cancer and with pancreatitis. Tests conducted by Bonavita confirm that those two processes are strictly related to one another [15, 16].

Aim of the research

Taking into account the potential importance of PTX3 in carcinogenesis connected with inflammation, the aim of the research was to determine the clinical usefulness of PTX3 as a biomarker of acute pancreatitis and pancreatic cancer.

Material and methods

The test group consisted of 125 subjects diagnosed with AP (83 with a mild form of AP and 42 with moderately-severe AP (MAP) or severe AP (SAP)), 24 people diagnosed with pancreatic ductal adenocarcinoma.
(PDAC) confirmed by histopathological tests or in cytological smear tests, and 52 healthy people (without declared acute or chronic diseases in prior history) as the control group (Table 1). All patients consented to take part in the research. Tests were conducted prospectively from October 2014 to February 2018. The criterion that excluded subjects from tests was the diagnosis of chronic pancreatitis. AP was diagnosed on the basis of criteria from Atlanta [17]. Potential subjects were deemed fit for recruitment into the study when two out of the three following criteria were met: 1) abdominal pain with an acute onset, 2) a three-fold increase in the levels of amylase or lipase in blood serum, and 3) the results of abdominal ultrasonography (USG) imaging characteristic of AP. The patients were subsequently divided into three groups corresponding to the three grades of disease severity, based on the Revised Atlanta Classification for Acute Pancreatitis. Mild AP was diagnosed when there were no organ dysfunctions or local or systemic complications, moderately severe course was diagnosed when there was transient (< 48 h) organ dysfunction and/or the presence of local or systemic complications, and severe course was diagnosed when there was persistent dysfunction of one or more organs for > 48 h [17, 18]. Pancreatic cancer was diagnosed on the basis of imaging studies (computed tomography of the abdomen with contrast, magnetic resonance imaging of the abdomen), endoscopic (gastroscopy) and cytological smear test and/or histopathological test. Every patient diagnosed with pancreatic cancer in the clinical stage of the disease was determined in accordance with TNM. In patients with cancer the assessment of resectability of tumour was conducted on the basis of results of imaging test results and/or diagnostic laparoscopy results. Blood for laboratory testing was collected during the first day of hospitalisation after receiving permission from the patient. The material for tests was veresinate plasma. In order to obtain the plasma, venous blood was collected for EDTA. The sample was then centrifuged for 15 min with an acceleration of 1000 g.

The study was approved by the Committee on Bioethics at Jan Kochanowski University in Kielce, Poland, No. 16/2017.

**Measurement of PTX3 concentration in serum**

The PTX3 concentration test was conducted in the obtained plasma with the use of the immunoenzymatic method ELISA. Determination of PTX3 concentration was done with the use of a set of reagents manufactured by R&D, catalogue number: DPTX30. The range of values determined by the producers in the group of healthy volunteers was from 0.0 to 1.18 ng/ml. CRP was determined with the use of immunoturbidimetric measurement. The range of reference values was from 0.05 to 5.0 mg/l. AU680 apparatus from Beckman Coulter company were used.

IL-6 was determined with the use of immunoenzymatic method (‘sandwich’ type) using DXI800 apparatus from Beckman Coulter.

The range of reference values was as follows: adults < 50 years of age < 2.9 pg/ml; adults > 50 years of age < 4.5 pg/ml

Carbohydrate antigen 19-9 (CA 19-9) was determined with the use of immunoenzymatic method (‘sandwich’ type) using DXI800 apparatus from Beckman Coulter. The range of reference values was: adults 0.0-35.0 U/ml.

**Statistical analysis**

The continuous variables were represented as medians with interquartile range, and in some cases the average with the standard deviation was presented.

| Parameter | AP (n = 125) | PDAC (n = 24) | Controls (n = 52) |
|-----------|-------------|--------------|------------------|
| Sex (female/male) | 56/69 (44.8%/55.2%) | 10/14 (41.7%/58.3%) | 40/12 (76.9%/23.1%) |
| Age [years] | 60.8 ±18.7 | 66.0 ±13.2 | 56.0 ±11.2 |
| Stage PDAC: | | | |
| II | – | 6 (25%) | – |
| III | 9 (37.5%) | – | – |
| IV | 9 (37.5%) | – | – |
| Clinical course of AP: | | | |
| Mild | 83 (66.4%) | – | – |
| Moderately severe or severe | 42 (33.6%) | – | – |

PDAC – pancreatic ductal adenocarcinoma, AP – acute pancreatitis.
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The normality of continuous variables was tested using the Shapiro-Wilk test. Due to the failure to meet the normality assumption, in the case of continuous variables, the significance of differences between the studied groups was assessed by the Mann-Whitney U test.

Continuous variables were presented as medians with interquartile range and by mean value with standard deviation, and were compared using the Mann-Whitney U-test due to non-normality, which was assessed by the Shapiro-Wilk test. Categorical data were expressed as number and percentage distributions. The relationships between continuous variables were assessed by Spearman rho correlation coefficient. The receiver operating characteristic (ROC) curve was built to test the ability of PTX-3 to discriminate between outcomes of interest (PDAC vs. controls or PDAC vs. AP). The areas under the ROC curves (AUC) with 95% confidence intervals were estimated, and the optimal cut-off values were determined by maximizing the Youden index. A two-tailed p-value < 0.05 was considered as statistically significant. All statistical analyses were performed using R (version 3.1.2; R Foundation for Statistical Computing, Vienna, Austria) and Statistica (TIBCO Software Inc. [2017]. Statistica data analysis software system, version 13. http://statistica.io).

Results

Demographic and clinical characteristics of the tested groups are presented in Table 1. In the group of patients with AP (125 people), most people were diagnosed with a mild form of the disease – 83 patients (38 men and 45 women). A moderately-severe or severe condition was diagnosed in 42 cases (31 men and 11 women). The most common causes of disease were cholelithiasis (69 patients) and alcohol (18 patients). Hypercholesterolaemia was the cause of AP in the case of 3 patients, and in the remaining 35 patients the cause of disease was not diagnosed during their stay in hospital.

The medians of tested inflammatory cytokine concentrations: PTX3, CRP, IL-6, and CA-19.9 were significantly higher in the group of patients with AP, in comparison with the control group (p < 0.0001) and the group with cancer and the control group (p < 0.0001).

Clinical value of PTX3 as a biomarker of more severe course of AP

Only 4 patients with mild AP and one patient with SAP had a concentration of PTX3 in the range of reference values (0.0–1.18 ng/ml) during the first day of hospitalisation. Among the remaining patients the concentrations of PTX3 exceeded from a few- to nine-times the reference values. The median PTX3 concentration in patients with MAP or SAP was 11.15 (8.21–24.12) ng/ml; average 16.53 ±15.73 ng/ml and was significantly higher than in patients with mild AP (5.98 (3.00–12.17) ng/ml; average 9.60 ±9.65 ng/ml; p = 0.0007); and in all patients with AP in comparison with the control group: 1.99 (1.91–2.62) ng/ml; average 2.31 ±0.58 ng/ml; p < 0.0001.

Similar dependencies were observed in reference to the remaining tested inflammatory cytokines. The median CRP concentration reached significantly higher values in patients with MAP or SAP: 224.79 (128.81–325.02) mg/l in comparison with group with mild AP: 64.48 (18.16–190.93) mg/l and all patients with AP 134.56 (25.46–260.39) mg/l and the test group: 0.91 (0.49–1.65) mg/l; p < 0.0001.

There was also a significant difference found in the median values of antigen CA 19-9, which in the whole group of patients with AP and the control group 1.38 (0.97–2.23); p < 0.0001. However, there was no significant difference in values found between moderately-severe MAP, severe AP- SAP, and a mild course of AP (p > 0.05), Figure 1.

PTX3 positively co-related with CRP (R = 0.51; p < 0.0001) and IL-6 (R = 0.66; p < 0.0001) but only in the mild AP (Table 2).

Clinical value of PTX3 as a biomarker of pancreatic cancer

The median PTX3 concentration in patients with pancreatic cancer equalled 5.12 (2.70–11.95) ng/ml, average 9.20 ±9.82 ng/ml vs. 1.99 (1.91–2.62) ng/ml, average 2.31 ±0.58 ng/ml in the group of healthy patients p < 0.0001. Similar dependencies were observed in reference to CRP (Figure 1).

The median CA 19-9 concentration in the group of patients with cancer was 151.50 (18.80–148.75) U/ml and in the control group 3.75 (1.98–6.43) U/ml; p < 0.0001. There was no significant difference in values found between moderately-severe MAP, severe AP- SAP, and a mild course of AP (p > 0.05), Figure 1.

A positive correlation was shown in concentrations of PTX3 and IL-6 (R = 0.75; p = 0.001) in patients with pancreatic cancer (Table 2).

Clinical significance of PTX3 in the differentiation of pancreatitis and pancreatic cancer

Tested inflammatory cytokines were significantly higher in patients with MAP or SAP than in those with pancreatic cancer (p < 0.05); Figure 1.
The ROC curve confirms the important connection between PTX3 concentration and diagnosing pancreatic cancer, in comparison with the control group: AUC = 0.785 (95% CI: 0.642–0.927); p = 0.0001, with cut-off value 3.87 ng/ml, relatively low sensitivity and high specificity (sensitivity 64.0%; specificity 96.2%). However, the results were not significant enough to allow us to differentiate cancer from acute pancreatitis (AUC = 0.586; 95% CI: 0.457–0.714; p = 0.19); Figure 2.

**Discussion**

By the 1990s the relationship between pancreatitis and the risk of pancreatic cancer was already confirmed [19]. Although the results are divergent in this topic, a new cohort study in Germany highlighted a 20-times higher risk of pancreatic cancer in the first two years after an event of severe acute pancreatitis (adjusted HR = 19.28; 95% CI: 14.62–25.41). The risk of developing cancer remained on a high level also in
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Further years of observation, after 5 and 10 years (adjusted HR = 2.43; 95% CI: 1.73–3.41) [20]. That is why it is important to seek simple indicators that can be used in the identification of patients at risk of pancreatic cancer.

Pentraxin 3 is a molecule that takes part in the immunological response in the course of inflammation and the development of cancer. PTX3, contrary to CRP, can serve as a rapid marker of primary local innate immunity activation and inflammatory condition [1]. The correlation between the concentration of PTX3 and the intensity of the processes is unknown. It is suspected that the increased concentration of PTX3 is connected with a poorer prognosis in cancerous diseases, including pancreatic cancer. In our study, we assessed the concentration of PTX3 and other inflammatory cytokines in patients with pancreatitis and pancreatic cancer. Patients with AP and pancreatic cancer had significantly higher average values of tested inflammatory cytokines: PTX3, CRP, and IL-6 in comparison with the control group (p < 0.0001).

The significantly more rapid increase of PTX3 and CRP concentrations was confirmed in the course of MAP or SAP disease in comparison with the mild form of the disease (p < 0.005). An increase of concentrations of PTX3 and CRP in severe, acute pancreatitis was confirmed in the study conducted by Simsek et al. [21]. It was found that the positive predictive value of PTX3 is far better than CRP. It was concluded that PTX3 is a better biomarker than CRP to monitor the inflammatory reactions in AP [21]. In the study conducted by Watt et al. [22], people with pancreatic adenocarcinoma had a significantly higher concentration of PTX3 in serum in comparison with patients with other pancreatic diseases, as well as healthy volunteers.

A concentration of PTX3 higher than 8 ng/ml was the basis for diagnosis of pancreatic cancer. In our tests the concentration of PTX3 was significantly higher in patients with pancreatic cancer than in the control group, at 9.20 ng/ml vs. 2.31 ng/ml. Analysis of ROC curve has shown that a concentration of PTX3 higher than 3.87 ng/ml suggests the necessity of broadening the diagnostics towards pancreatic cancer. Such a dependency was not confirmed in differ-

Table 2. Dependencies between PTX3 and IL-6 and CA-19.9 in mild AP, MAP, or SAP and in pancreatic cancer

| PTX3 [ng/m] | CRP | IL-6 | CA-19.9 |
|-------------|-----|------|---------|
| Mild AP:    |     |      |         |
| 9.60 ±9.65  | R* = 0.51 | R = 0.66 | R = 0.05 |
| 5.98 (3.00–12.17) | p < 0.0001 | p < 0.0001 | p > 0.05 |
| MAP and SAP:|     |      |         |
| 16.53 ±15.73 | R = 0.16 | R = 0.27 | R = –0.19 |
| 11.15 (8.21–24.12) | p > 0.05 | p > 0.05 | p > 0.05 |
| Pancreatic cancer: |     |      |         |
| 9.20 ±9.82  | R = 0.45 | R = 0.75 | R = 0.28 |
| 5.12 (2.70–11.95) | p > 0.05 | p = 0.001 | p > 0.05 |

*R – Spearman rho correlation coefficient. AP – acute pancreatitis, MAP – moderately severe acute pancreatitis, SAP – severe acute pancreatitis, CRP – C-reactive protein, IL-6 – interleukin-6, CA 19.9 – carbohydrate antigen 19.9.

Figure 2. ROC analysis for PTX3 in patients with pancreatic cancer in comparison with healthy controls (A) and pancreatic cancer and patients with MAP or SAP (B)
entation between patients with MAP or SAP and cancer. A more severe course of AP was connected with higher concentrations of PTX3. A suggested cut-off point for pancreatitis is 8.74 ng/ml (p > 0.05).

An increased concentration of PTX3 is considered as a biomarker in lung cancer and prostate carcinoma. A study by Ying et al. confirmed that a higher activity of PTX3 was connected with a greater advancement and worse differentiation of cervical cancer cells. Blocking the activity of PTX3 observed in cells of cervical cancer caused the inhibition of cell division and at the same time, in clinical practice, could decrease the invasiveness and aggressiveness of the cancer cells [23]. The study by Deng et al. states that the levels of 13 of 29 cytokines were significantly different among the mild, moderately severe, and severe AP patients. The concentration of PTX3 was significantly higher only in patients with severe acute pancreatitis, and it was considered an independent prognostic factor in the course of the disease. The concentration of PTX3 reached a maximum concentration earlier than CRP and reached similar values in the early stage of the disease to the concentration of IL-6 [24]. In our tested group of patients with AP, the concentration of PTX 3 in the first 24 h of the disease was four times higher in mild AP and seven times higher in SAP, in comparison with the control group. Kusnierz-Cabala et al. marked the PTX3 and CRP in severe acute pancreatitis and confirmed a higher concentration in patients with MAP or SAP in comparison with patients with a mild form of AP. The highest concentrations of PTX3 were recorded in the first 24 h of the disease [9]. In a recent study published in Turkey, in patients with mild AP, there was no difference in PTX3 concentration in comparison with the control group, both in the first as well as the second 24 h of hospitalisation [25].

Shiraki et al. [6] suggest that PTX3 regulates the inflammatory hyperactivity in macrophages and can be a new method of treating acute inflammation, i.e. in systemic inflammation.

A limitation for our tests was the small number of people with disease in the test group analysed, particularly those with diagnosed pancreatic cancer. It would also be interesting to analyse the concentrations of inflammatory cytokines over the following days of testing.

Conclusions

The observed results suggest that PTX3 can be used as a prognostic marker of a more severe course of AP and an indicator of the necessity to conduct further medical tests of pancreatic cancer. However, there was no effectiveness shown of the pentraxin concentration use in the differentiation between PAP or SAP and pancreatic cancer.

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Conflict of interest

The authors declare no conflict of interest.

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