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TF and TFPI in myeloproliferative neoplasms — a preliminary study

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ABSTRACT

Introduction. Haemostatic disturbances such as thrombosis or diathesis are frequent complications in patients with myeloproliferative neoplasms (MPNs). The purpose of this study was to evaluate the concentration of tissue factor (TF), tissue factor pathway inhibitor (TFPI), and thrombin–antithrombin (TAT) complexes in patients with MPNs.

Patients and methods. The study involved 43 patients with MPNs (mean age 60.5 years), including 16 patients with essential thrombocythaemia, eight with polycythaemia vera, ten with chronic myeloid leukaemia, and nine with primary myelofibrosis. The control group consisted of 30 healthy volunteers who were age- and sex-matched. TF, TFPI and TAT complexes concentration were measured using the immunoenzyme method.

Results. TF and TAT complex concentrations were significantly higher, but the TFPI concentration was lower, in the total study group compared to the control group. TF concentration in each of the subgroups was significantly higher than in the control group. TFPI concentration was significantly lower in essential thrombocythaemia and polycythaemia vera than in controls. In addition, the concentration of TAT complex in patients with chronic myeloid leukaemia was significantly higher than in the control group.

Conclusions. Elevated TF levels and decreased TFPI levels in patients with essential thrombocythaemia and polycythaemia vera indicate the activation of blood coagulation process depending on the TF (an extrinsic pathway). These patients represent a group at high risk of thrombotic complications.

Key words: myeloproliferative neoplasms, thrombin–antithrombin complexes, tissue factor, tissue factor pathway inhibitor, thrombotic complications

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Introduction

Myeloproliferative neoplasms (MPNs) are the result of clonal proliferation of stem cells of bone marrow, characterised by the proliferation of one or more myeloid lines (granulocyte, erythrocyte, and megakaryocyte) of the bone marrow [1]. The diverse clinical manifestations of various myeloproliferative neoplasms appear to be the result of the clonal cells acquiring additional molecular abnormalities that lead to disturbances in the signal transduction pathways of cell proliferation signals and the signals initiating and sustaining the cell maturation. The first cancer to have been associated with the development of specific cytogenetic changes, the translocation of the fragments of the long arms between chromosomes 9 and 22, resulting in the emergence of fusion gene BCR-ABL on the Ph chromosome, was chronic myeloid leukaemia.

In 2008, the World Health Organisation (WHO) changed the previously applicable classification of chronic myeloproliferative diseases (CMPDs). The reason for the changes in this classification was to investigate the molecular causes of myeloproliferative neoplasms, the beginning of which was the 2005 discovery of the relationship between gene mutation V617F Janus tyrosine kinase 2 (JAK-2) and polycythaemia vera and the 2006 discovery of two other somatic mutations: W515L and W515K within the gene sequence for thrombopoietin (MPL) [2]. It was the discovery of fusion genes with the participation of PDGFRA and PDGFRB genes located on chromosome 4q12 and 5q33, respectively, which was of great importance in

developing the understanding of the pathogenesis of myeloproliferative neoplasms. The creation of these genes, e.g. FIP1L1-PDGFRA or PDGFRB, leads to the activation of oncogenic tyrosine kinases and the occurrence of myeloproliferative neoplasms with eosinophilia [3].

In the new classification, the term 'chronic myeloproliferative syndromes' has been replaced by 'myeloproliferative neoplasms', which better reflects the clinical pattern and course of the diseases. The new WHO classification covers the following myeloproliferative neoplasms: chronic myeloid leukaemia (CML), polycythaemia vera (PV), essential thrombocythaemia (ET), primary myelofibrosis (PMF), mastocytosis (SM), chronic eosinophilic leukaemia (CEL), unclassified differently chronic neutrophilic leukaemia (CNL), and unclassified MPNs [4, 5].

The changes proposed by the WHO are due to the discovery of gene mutations that result in the overproduction of proteins with the properties of tyrosine kinases that are responsible for the proliferation of various cell lines. The presence of the fusion gene BCR / ABL, KIT gene mutations, fusion gene FIP1L1/PDGFRA and JAK2 gene mutations indicates the oncogenic origin of myeloproliferative neoplasms [6]. The JAK2 mutation has been confirmed in more than 90% of patients with polycythaemia vera and in 50% of patients with primary myelofibrosis and essential thrombocythaemia [7]. The detection of mutations in JAK2 gene or MPL excludes a diagnosis of reactive erythrocytosis, thrombocytosis, or bone marrow fibrosis. However, it does not determine the differential diagnosis between the types of myeloproliferative neoplasms [8].

It is well known that in patients with MPNs a frequent complication and clinical problem at the same time are haemostatic disturbances: thrombosis or diathesis. The mechanisms of bleeding and thrombotic complications in those patients are complex and can be the result of: morphological or functional platelets abnormalities, blood hyperviscosity state, the interactions between blood morphology components (an increase in the adhesion of platelet-leukocyte complexes, monocytes-platelets), the disorders of coagulation factors and some inhibitors, fibrinolytic system disorders as well as endothelial dysfunction disorders [9–11].

Currently, it is believed that the activation of the extrinsic coagulation process dependent on the tissue factor (TF) plays a key role in the initiation of blood coagulation. The activation of this pathway starts from the generation of tissue factor (TF), which is a cell membrane glycoprotein with the molecular weight of 47kDa acting as cofactor for factor VII. Having activated factor VII, TF forms a complex with factor VIIa, and then activates factors IX and X, which, in turn, leads to the formation of fibrin fibres [12]. Recent studies have indicated that the tissue factor can be a link between haemostasis, angiogenesis and inflammation [13, 14].

The main tissue factor-dependent coagulation regulator is the tissue factor pathway inhibitor (TFPI). TFPI is a protein consisting of 276 aminoacids. TFPI inactivates the complex of TF/FVIIa and active factor X (FXa). TFPI is mainly synthesised by endothelial cells and so is responsible for maintaining the endothelium anticoagulant potential [15, 16].

Information regarding coagulation disorders in the course of myeloproliferative neoplasms is scarce. Thus the purpose of this study was to evaluate the concentration of TF, TFPI and TAT complexes in patients with MPNs.

Materials and methods

The study involved 43 patients with myeloproliferative neoplasms aged 21–86 years (mean age 60.53), hospitalised and diagnosed at the Clinical Ward of Haematology of the Dr. J. Biziel University Hospital No. 2 in Bydgoszcz. These patients were enrolled in the study at the time of the diagnosis of MPNs and prior to the implementation of appropriate treatment. Patients without clinically overt thrombosis were included in the study. The study group *consisted of* 16 patients with ET, eight with PV, ten with CML, and nine with PMF. The diagnosis of essential thrombocythaemia was based on the diagnostic criteria of essential thrombocythaemia according to the WHO (2008) and the exclusion of other malignant and non-malignant diseases in the course of which there can be observed essential thrombocythaemia. The diagnosis of polycythaemia vera was based on the diagnostic criteria for polycythaemia vera according to the WHO (2008), including a genetic test for the JAK2 V617F gene mutation. In all patients with polycythaemia vera, there were initially excluded secondary causes of polycythaemia vera: hypoxia induced in the course of pulmonary and heart diseases or other causes due to increased production of EPO independent of tissue hypoxia, and there were excluded the causes of alleged polycythaemia. In these patients the erythropoietin level in serum was not determined. The diagnosis of chronic myeloid leukaemia was based on: the clinical picture, the study results, including additional cytogenetic and molecular studies, which demonstrated the presence of the translocation t(9;22) (q34;q11) and the presence of gene BCR/ABL in RQ-PCR testing. Myelofibrosis diagnosis was based on the diagnostic criteria for spontaneous bone marrow fibrosis, according to the WHO (2008), including the study on the presence of cytogenetic V617F mutation in JAK2 gene.

Table 1. Concentration of TF, TFPI and TAT complexes in the study group compared to the control group

Parameter	Study group n = 43			Control group n = 30			Significance level (p)
	Me	Min–Max	Q1; Q3	Me	Min–Max	Q1; Q3	
TF [pg/mL]	334.43	123.82–6,315.64	250.52; 836.44	164.28	90.44–355.13	117.39; 183.85	**< 0.00001**
TFPI [ng/mL]	54.48	26.24–375.80	41.64; 82.64	83.533	52.22–137.92	68.96; 94.78	**0.000263**
TAT [ng/mL]	6.09	0.02–176.96	1.72; 14.20	2.49	0.73–10.60	1.44; 3.92	**0.038394**

TF — tissue factor; TFPI — tissue factor pathway inhibitor; TAT — thrombin–antithrombin complexes

The control group consisted of 30 healthy volunteers, age- and gender-matched.

Venous blood was collected from the elbow vein into tubes containing 3.2% sodium citrate (anticoagulant/blood ratio 1:9). The basic parameters of coagulation, such as activated partial thromboplastin time (APTT), prothrombin time (PT), concentrations of fibrinogen and D-dimer, were assayed using a BCS XP coagulation analyser (Siemens). In plasma the following tests were performed using the ELISA method: the concentration of TF (Imubind Tissue Factor ELISA kit, American Diagnostica Inc.), the concentration of TFPI (Imubind Total TFPI ELISA kit, American Diagnostica Inc.), and TAT complexes concentration (Imubind TAT ELISA kit, American Diagnostica Inc.).

Statistical analysis was performed using Statistica 9.1 software (StatStoft®). The Shapiro-Wilk test was used to assess the normality of the distribution. For the parameters with a normal distribution, arithmetic mean (X) and standard deviations (SD) were determined, and the parameters with abnormal distribution were presented as medians (Me) and quartiles: lower (Q1) and upper (Q3). The Mann Whitney U test was used to compare the differences between groups. Spearman correlation coefficients were calculated to determine if there were any correlations between the parameters. The p-values < 0.05 were considered significant.

The study was approved by the Bioethics Committee of Collegium Medicum in Bydgoszcz, the Nicolaus Copernicus University in Torun (no. KB/396/2010).

Results

The tissue factor and the TAT complex concentration were significantly higher in patients with myeloproliferative neoplasms compared to the control group. However, the concentration of tissue factor pathway inhibitor was significantly lower in the total study group compared to the control group (Tab. 1).

Tables 2 and 3 show a detailed analysis of the results recorded in respective subgroups of patients with myeloproliferative neoplasms compared to the control group.

The results of the basic parameters of haemostasis (APTT, PT) in all subgroups were different from the values reported in the control group, although these results fell within the reference ranges. The concentration of fibrinogen in the subgroups with essential thrombocythaemia, chronic myeloid leukaemia and myelofibrosis were significantly higher than in the control group. These results also fell within the normal range. The D-dimer concentration was significantly higher in the subgroups with CML and PMF compared to the control group.

Moreover, it was observed that the TF concentration in each of the subgroups: essential thrombocythaemia, polycythaemia vera, myelofibrosis and chronic myeloid leukaemia was significantly higher than in the control group. The TFPI concentration was lower in each of the subgroups analysed compared to the control group, although the difference was significant only for essential thrombocythaemia and polycythaemia vera. In addition, analysing the concentration of TAT complex in patients with MPNs, it was observed that only for patients with chronic myeloid leukaemia was the concentration of this parameter significantly higher than in the control group.

The genetic studies analysis showed that out of eight patients with PV, seven revealed the presence of V617F JAK-2 mutation, while the other one did not show such a mutation. Among the ET respondents, JAK-2 mutation occurred in 11 and did not occur in five.

In view of the hypothesis by Rak et al., assuming that TF is a molecular link between genetic determinant of tumour progression and cancer coagulopathy, we performed a statistical analysis to evaluate the concentrations of the parameters tested in ET patients to identify the presence of the JAK-2 gene mutations [13]. We found no significant differences in the subgroups of patients with essential thrombocythaemia, although the median TF levels differed, and it was clearly higher in the patients with JAK-2 mutation (Tab. 4). The study needs to be continued on a greater number of patients.

Discussion

Haemostatic disorders in the form of thromboembolic complications, bleeding complications, and disseminated intravascular coagulation syndrome are among frequent abnormalities in cancer patients. These complications are the second cause of death in patients diagnosed with cancer [17, 18].

Table 2. Comparison of the concentration of haemostatic parameters in various subgroups of patients with MPNs, and in relation to the control group

Parameter	ET n = 16 (I)	PV n = 8 (II)	CML n = 10 (III)	PMF n = 9 (IV)	Control group n = 30 (C)	Significance level (p)
	M/Me ± SD/ /(Q1; Q3)	M/Me ± SD/ /(Q1; Q3)	M/Me ± SD/ /(Q1; Q3)	M/Me ± SD/ /(Q1; Q3)	M/Me ± SD/ /(Q1; Q3)	
APTT [s]	36.10 (33.80; 39.60)	39.50 (33.40; 46.30)	34.05 (29.05; 38.10)	33.70 (29.80; 36.60)	30.00 (27.90; 32.80)	I vs. C **p = 0.000031** II vs. C **p = 0.000987** III vs. C **p = 0.080267** IV vs. C p = 0.098944
PT [s]	12.70 ± 0.90	13.20 ± 0.70	13.25 ± 0.50	12.80 ± 0.80	12.30 ± 0.90	I vs. C p = 0.119526 II vs. C p = 0.067837 III vs. C **p = 0.050884** IV vs. C p = 0.170166
Fibrinogen [g/dL]	3.10 (2.60; 3.70)	2.50 (2.00; 2.90)	3.3 (2.90; 3.60)	4.60 (3.65; 5.45)	2.60 (2.00; 3.00)	I vs. C **p = 0.028844** II vs. C p = 0.969067 III vs. C **p = 0.001456** IV vs. C **p = 0.000170**
D-dimer [ng/mL]	340.00 (245.00; 414.00)	293.50 (225.00; 1,243.00)	616,00 (457.00; 1,167.00)	881,00 (417.00; 1,814.00)	242.00 (188.00; 312.00)	I vs. C p = 0.050842 II vs. C p = 0.274801 III vs. C **p = 0.000030** IV vs. C **p = 0.000437**

ET — essential thrombocythaemia; PV— polycythaemia vera; CML — chronic myelogenous leukaemia; PMF — primary myelofibrosis; APTT — activated partial thromboplastin time; INR — international normalised ratio; PT — prothrombin time

In our study, patients diagnosed with myeloproliferative neoplasms demonstrated significantly higher TF levels in the total study group compared to the control group. A detailed analysis of the results reported in different subgroups of patients with MPNs, compared to the control group, showed that the TF concentration in each of the subgroups: essential thrombocythaemia, polycythaemia vera, myelofibrosis, and chronic myeloid leukaemia was significantly higher than in the control group.

The coagulation activation is initiated by the extrinsic pathway, the key element of which is the tissue factor (TF). The TF is found on the surface of many cells (e.g. subendothelial layer and adventitia vessels); it is a cellular receptor of plasma factor VII. In the place of the vessel wall damage, the tissue factor comes into contact with factor VII and complex TF/VIIa is formed, which gives rise to the processes leading to the production of thrombin and, consequently, the fibrin clot [19].

The findings of other studies show that the presence of the tissue factor in tumour cells is of highly predictive and prognostic value [20, 21]. A positive correlation has been found between the TF expression in tumour cells and the frequency of the incidence of metastasis and progression of the disease, e.g. in patients diagnosed with colorectal cancer, breast cancer, and non-small cell lung cancer [21–23]. A correlation was also observed between the increase in the occurrence of thrombotic events in cancer patients and significantly higher levels of tissue factor expression [21]. Uno et al. observed an increased TF expression in patients with ovarian cancer, which was positively correlated with the development of venous thromboembolism in those patients [23].

An analysis of the available literature showed that there are few reports on the role of the tissue factor in patients with myeloproliferative neoplasms. Increased TF levels in patients with acute myeloid leukaemia have been reported, which, according to the

Table 3. Comparison of the concentration of TF and TFPI and TAT complexes in various subgroups of patients with MPNs, and in relation to the control group

Parameter	ET n = 16 (I)	PV n = 8 (II)	CML n = 10 (III)	PMF n = 9 (IV)	Control group n = 30 (C)	Significance level (p)
	Me Q1; Q3	Me Q1; Q3	Me Q1; Q3	Me Q1; Q3	Me Q1; Q3	
TF [pg/ml]	378.36 257.32; 964.67	319.70 211.14; 705.04	463.78 306.32; 666.56	334.43 195.94; 530.32	130.13 106.83; 170.19	I vs. C **p = 0.000001** II vs. C **p = 0.00024** III vs. C **p = 0.000046** IV vs. C **p = 0.004372**
TFPI [ng/ml]	47.98 42.30; 71.18	41.98 37.22; 60.70	74.26 47.44; 105.20	63.84 55.04; 102.64	72.50 53.76; 98.72	I vs. C **p = 0.01082** II vs. C **p = 0.03029** III vs. C p = 0,254259 IV vs. C p = 0.166564
TAT [ng/ml]	2.74 1.66; 11.26	6.09 0.51; 9.50	19.14 5.24; 19.76	2.84 0.28; 27.50	2.24 1.67; 3.40	I vs. C p = 0.11758 II vs. C p = 0.40015 III vs. C **p = 0.013329** IV vs. C p = 0.925162

ET — essential thrombocythaemia; PV — polycythaemia vera; CML — chronic myelogenous leukaemia; PMF — primary myelofibrosis; TF — tissue factor; TFPI — tissue factor pathway inhibitor; TAT – thrombin–antithrombin complexes

Table 4. TF, TFPI and TAT complexes in the subgroups of patients with essential thrombocythemia JAK-2(+) V617F and JAK-2 V617F(–)

Parameter	JAK-2 V617F (+) N=11			JAK-2 V617F (–) N=5			p
	Me	Min.–Max.	Q1; Q3	Me	Min.–Max.	Q1; Q3	
TF [pg/mL]	378.36	209.76–1417.24	269.52; 957.88	258.68	217.92–971.46	223.36; 823.04	NS
TFPI [ng/mL]	48.76	28.45–115.36	41.64; 77.56	43.52	33.48–87.80	42.96; 64.80	NS
TAT [ng/mL]	2.74	0.62–176.96	1.66; 11.26	7.40	1.60–14.36	1.78; 14.04	NS

JAK-2 — Janus tyrosine kinase 2; TAT — thrombin–antithrombin complexes; TF — tissue factor; TFPI — tissue factor pathway inhibitor; V617F — gene mutation V617F

authors, could suggest an increased procoagulant activity [24]. Recent studies have indicated a relationship between elevated tissue factor levels and the presence of JAK2 mutation in cancer patients with myeloproliferative neoplasms and an increased tendency to thrombosis in these patients [25, 26]. In the present study, the analysis of the TF, TFPI and TAT concentration, due to JAK-2 mutation or its lack, was carried out in ET patients. We found no significant difference in the concentrations of the analysed parameters in the group of patients with JAK-2 mutation and without any such mutation, even though the median TF in the patients with JAK-2 gene mutations was higher than in the control group. It is possible that an assessment of concentrations in a larger group of patients would identify the significance of the differences.

The thrombin generation process is controlled at different stages of the coagulation cascade. In this process, natural blood coagulation inhibitors are involved, including the tissue factor pathway inhibitor (TFPI) [27].

Based on the results reported in this study, we have shown significantly lower TFPI concentration in the total study group compared to the control group. The TFPI levels were lower in each of the subgroups analysed compared to the control group. However, only for essential thrombocythaemia and polycythaemia vera was the

difference significant. The lack of significant differences in patients with chronic myeloid leukaemia and myelofibrosis could be due to the small group of patients involved.

A low concentration and a decreased TFPI activity has been observed in patients with acute myeloid leukaemia complicated by disseminated intravascular coagulation (DIC). According to the authors, a low TFPI concentration could be responsible for the occurrence of thrombotic events in these patients [28]. Different results were reported by Radziwon et al. who found significantly elevated TFPI levels, although the TFPI activity was decreased in the course of chronic myeloid leukaemia [29].

Our results, and the literature data, suggest that low TFPI levels accompanied by high TF concentrations can be a predisposing factor to the occurrence of thrombotic events in patients with cancer.

Additionally, in this study it was observed that the TAT complex concentration was significantly higher in the total study group compared to the controls. A detailed analysis showed that only in patients with CML was the TAT complex concentration significantly higher compared to the control group. A high TAT complex concentration can indicate an excessive thrombin generation process. Our findings are consistent with the previous report by Rość et al. who also observed a significantly higher TAT complex concentration in chronic myeloid leukaemia [11]. An elevated TAT has also been reported in patients with stomach, colon, kidney, and prostate cancer [11, 30].

In conclusion, in myeloproliferative neoplasms, despite the lack of clinical symptoms of haemostatic disorders, the so called 'thrombophlebitis emergency' occurs, expressed by increased TF and TAT complex levels. Low TFPI levels are an additional factor that enhances the prothrombotic threat.

Conclusions

The elevated TF levels and decreased TFPI levels in patients with essential thrombocythaemia and polycythaemia vera indicate the activation of blood coagulation depending on the TF (an extrinsic pathway). These patients represent a high-risk group of thrombotic complications.

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