Thrombin activatable fibrinolysis inhibitor (TAFI), tissue factor pathway inhibitor (TFPI), and prothrombin fragment 1+2 levels in patients with advanced colorectal cancer

İleri evre kolorektal kanser hastalarında trombinle aktive fibrinolizis inhibitörü (TAFI), doku faktör yolak inhibitörü (TFPI) ve protrombin fragment 1+2.

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ÖZET

Giriş ve Amaç: Tromboembolizm kanser hastalarında yaygın olarak görülmektedir. Kolorektal kanser gelişimi ve progresyonu sırasında koagülasyon ve fibrinolitik sistemdeki pek çok molekül aktive olmaktadır.Trombinle aktive fibrinolizis inhibitörü (TAFI), doku faktör yolak inhibitörü (TFPI) ve protrombin fragmant 1+2 koagülasyon ve fibrinoliziste yeni tanımlanan moleküllerdir.Bu çalışmanın amacı ileri evre kolorektal kanser hastalarında klinikopatolojik özelliklerle TAFI, TFPI ve protrombin fragment 1+2 düzeyleri arasındaki ilişkinin araştırılmasıdır.

Yöntem ve Gereçler: Seksen iki ileri evre kolorektal kanser hastası (32 metastatik,50 lokal ileri hasta) çalışmaya alındı.Serum TAFI, TFPI, and prothrombin F1+2 düzeyleri enzim bağlı immünosorbent yöntemi (ELISA) ile saptandı. Hastaların klinikopatolojik özellikleri tıbbi kayıtlardan retrospektif olarak değerlendirildi.

Bulgular: 28 (%34) kadın ve 54 erkek (%66) olgu çalışmaya alındı. Olguların ortalama yaşı 56 idi. Hastalarda plasma TAFI, TFPI ve protrombin F1+2 düzeyleri sırasıyla %70, %71 ve %96 oranında yüksek olarak saptandı. Protrombin F1+2 düzeyleri düşük performans skoru olan hastalarda yüksek bulundu. TFPI düzeyleri tümör grade 2 ve 3 olan hastalarda yüksek bulunurken TAFI düzeyleri rektal kanser hastalarında daha yüksek bulundu.Yaş, cins, beden kitle endeksi, metastatik ve lokal ileri hastalık, tümör çapı, vasküler invazyon, perinoral invazyon karsinoembriyonik antijen, hemoglobin ve trombosit sayısı ile TAFI, TFPI ve prothrombin F 1+2 düzeyleri arasında anlamlı ilişki bulunmadı.

Tartışma ve Sonuç:. Yüksek grade'li tümörlerde TFPI düzeylerinin yüksek bulunması tümör grade'i ile koagülasyon sistemi arasındaki ilişkinin bir belirtisi olarak düşünülmüştür. Düşük performanslı hastalarda protrombin fragmant 1+2 düzey yüksekliği bu hastalarda daha aktif bir koagülasyon kaskadını göstermektedir. Rektal kanser hastalarındaki TAFI yüksekliği bu hastaların daha kötü giden seyri ile ilişkili olabilir

Anahtar Kelimeler: Kolon kanseri, TAFI, TFPI, protrombin fragment 1+2

ABSTRACT

Introductıon: Thromboembolism is common in cancer patients. During colorectal cancer development and progression, many molecules located in coagulation and fibrinolytic systems are activated. Thrombin activatable fibrinolysis inhibitor (TAFI), tissue factor pathway inhibitor (TFPI) and prothrombin fragment 1+2 (F1+2) are newly identified molecules involved in coagulation and fibrinolysis. The aim of this study was to investigate the relationship between clinicopathologic characteristics and TAFI, TFPI and F1+2 levels in patients with advanced colorectal.

Methods: Eighty-two patients (32 metastatic, 50 locally advanced disease) diagnosed with colorectal cancer in the medical oncology clinic. Serum TAFI, TFPI, and prothrombin F1+2 levels were evaluated via enzyme-linked immunosorbent assay. Clinicopathologic characteristics of the patients were investigated retrospectively from the medical records of the patients.

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Results: There were 28 (34%) females and 54 males (66%) included in the study. The mean age of the participants was 56 years. The plasma TAFI, TFPI, and prothrombin F1+2 levels were high in 70, 71, and 96% of the patients, respectively. Prothrombin F1+2 levels were higher among patients with lower performance scores. TFPI levels were higher among patients with tumor grades of 2 and 3. TAFI levels were higher among rectal cancer cases. Age, gender, BMI, metastatic or locally advanced disease, size of tumor, vascular invasion, perineural invasion, carcinoembryonic antigen, hemoglobin and thrombocyte levels were not associated with TAFI, TFPI, and prothrombin F 1+2 levels

Discussion and Conclusıon: Higher TFPI levels in case of tumors at higher stages can indicate that there is an association between tumor grade and coagulation cascade. The higher prothrombin F1+2 levels, an indicator of active coagulation cascade, among patients with low performance scores may indicate that the coagulation cascade of these patients is more active. Higher TAFI levels among rectal cancer patients may be related to the natural course of the disease.

Key words: Colon cancer, thrombosis, TAFI, TFPI, prothrombin fragment 1+2.

Introduction

Detection of the association between thrombosis and cancer dates back to mid-18th century. Armand Trosseau was first in 1862 to describe the clinical condition appearing as aching edema in the upper and lower extremities of cancer patients (1). The relationship between malignancy and thrombosis has been demonstrated in numerous studies. While its pathogenesis is still not thoroughly understood, hypercoagulopathy-prothrombotic state, impacted by many factors and specially cancer cells, endothelial cells, procoagulants, thrombocytes, hereditary factors, chemotherapy, radiation therapy and invasive procedures, is considered responsible for the development of thrombosis in patients with malignant disease process. This activation in hemostasis contributes to the tumor development via affecting intracellular signal transduction systems in malignant diseases (2-4). Anti-tumor effects of anticoagulants have been determined (5).

Colorectal cancer (CRC), as the 3rd most common cancer in both genders, is the 2nd leading cancer type in the United States of America (USA) in terms of cancer-related mortalities (6). The tendency to have thrombosis increases during CRC development and progression due to the activation of many molecules in coagulation and fibrinolytic systems (7).

TAFI is an important, newly defined molecule, which connects the coagulation and fibrinolysis ensuring the balance between the coagulation, fibrinolysis, and inflammation pathways in the hemostatic response (8,9). TAFI is a zymogen, which can be activated by thrombin, thrombin-thrombomodulin complex, and plasmin. Activated TAFI slows down the fibrinolytic system by influencing the carboxyl-terminal lysine in fibrin leading to degradation. Pharmacologic inhibition of TAFI pathway is evaluated as a new strategy due to its ability to block thrombosis or its contribution to thrombolytic treatment (10).In contrast, TAFI also provides bleeding control in hemophilia via pathway stimulation (11).

TFPI is a serine protease inhibitor released primarily by microvascular endothelium and about 10% by thrombocytes. It is a molecule composed of 276 amino acids synthesized by the long arm of chromosome 2, weighing 32 kDa. A vast amount of TFPI is released from the endothelium when in contact with heparin (12,13). TFPI inhibits FXa by complete binding, but tissue factor (TF) / FVIIa / FXa / TFPI should all come together for DF/FVIIa inhibition. Hypothetically, increased thrombosis is expected in TFPI deficiency, however, TFPI deficiency has not been detected in patients with abetalipoproteinemia except for occurring due to deficiency of lipoproteins that are its carriers. Kataoka et al. have demonstrated increased TFPI gene expression in colon cancer cell line (14), breast cancer (15) and small cell lung cancer (16). Factor Xa-TFPI complex is higher among CRC cases, compared to hematologic malignancies and healthy population, and this complex is believed to be important in micro-thrombosis and cancer cell's spread across organs (17).

F1+2 is formed by leaving the amino-terminal ends, following FXa activation of prothrombin to form thrombin. Initially, it was shown to have high plasma levels in disseminated intravascular coagulation (DIC) and in cases using oral contraceptives (18,19). Among CRC patients, significantly high levels

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of prothrombin F1+2 and TAT were detected (20). Higher levels of F1+2, TAT, and soluble fibrinogen were detected among metastatic cases compared to cases that were non-metastatic and had benign intestinal diseases (21).

Development of thrombosis is an important cause of morbidity and mortality among CRC patients. The aim of this study was to evaluate the association of TAFI, TFPI, and F1+2 molecules (shown in prior studies to be significant in cancer-related hypercoagulapathy and thrombogenesis) with the clinicopathological features, and prognosis of metastatic CRC patients (22).

Materials And Methods:

Eighty-two CRC patients (32 metastatic, 50 locally advance) were included in the study. Patients with history or suspicion of thromboembolism, those receiving anticoagulant therapy or coagulation disrupt drugs, with history of intravenous port catheter or similar interventions and those were diagnosed diabetes mellitus, chronic renal failure excluded from the study.

Verbal informed consent was obtained before the study and the procedures were in accordance with the guidelines of the Helsinki Declaration.

Samples were taken before chemotherapy. After 12-14 h fasting, the specimen were drawn using standart venipuncture technique and collected in a serum separator tube (Vacuette, Greiner Bio-One, Austria) allowed to clot for 30 minutes. The samples were centrifuged at 1,500 x *g* for 15 minutes and then serum samples were stored at -20˚C until the study day.The procedures (Human TAFI ELISA kit-America Diagnostica Co Human TFPI Kit Duoset R&D System Co, protrombin fragment 1+2 ELISA kit USCN Life Science inc.) employ the sandwich enzyme immunoassay technique for serum TAFI, TFPI, and F1+2 measurements. This is a noncompetitive assay technique which analytes to be measured between two antibodies. Serum samples were added to microwells precoated with a murine monoclonal antibody specific for human TAFI, TFPI or F1+2. The antibody captures the antigen present in the solutions during in a incubation period. After a washing period, a goat anti-human TAFI, TFPI or F1+2 polyclonal antibody coupled to horseradish peroxidase is added to the microwells and binds to the captured TAFI, TFPI or F1+2 antigen.Following another wash step Tetramethylbenzidine is added to the microwells and the color varies blue. After addition of sulfuric acid the reaction is stopped and the color turns to yellow. (It stops the reaction by the addition of sulfuric acid and the color turns yellow.) The absorbances of the solution were measured at 450 nm and were directly proportional to the amount of TAFI, TFPI or F1+2 present in the sample.

The data obtained were analyzed using the NCSS 2007 and PASS 2008 Statistical Software (Utah, USA) programs. Data evaluation involved use of descriptive statistics (mean, standard deviation) along with one-way analysis of variance test in comparison of three or more groups of parameters from quantitative data that had normal distribution; and t-test in comparison of two groups. Evaluation of the associations between the parameters was done using Pearson correlation analysis. The results were evaluated within a 95% confidence interval with significance level set at $p<0.05$.

RESULTS:

Demographic and clinicopathological characteristics of the patients are summarized in Tables 1 and 2.

Table 1. Demographic characteristics of the patients

		Min – Max	Mean±SD
Age (years)		24 – 76	56, 47±13, 60
		N	%
Gender	Female	28	34, 1%
	Male	54	65, 9%
BMI (kg/m^2)		17, 20 – 38	25, 98±4, 55

BMI: Body Mass Index

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Table 2. Clinicopathological characteristics of the patients

		Min –Max	Mean±SD
Tumor size		2.50 – 10 cm	4.92±1.68
		Number	%
Performance score	1	40	48.8
	2	42	51.2
Localization	Colon	55	67.1
	Rectum	27	32.9
Grade	1	10	12.1
	2	54	65.8
	3	18	21.9
Vascular invasion	positive	62	75.6
	negative	20	24.4
Perineural invasion	positive	53	64.6
	negative	29	35.4

Table 3. Carcinoembryogenic antigen (CEA), hemoglobin, thrombocyte count, thrombin activatable fibrinolysis inhibitor (TAFI), tissue factor pathway inhibitor (TFPI) and prothrombin fragment 1+2 (F 1+2) results

	CEA		**Hemoglobin**		**Trombosit**	
	r	*p*	r	*p*	r	*p*
TAFI	0,033	*0,768*	-0,020	*0,681*	-0,200	*0,072*
TFPI	0,115	*0,303*	0,180	*0,105*	-0,126	*0,261*
F1+2	-0,070	*0,530*	0,084	*0,455*	-0,017	*0,882*

r: Pearson corelation analysis

As factors of thrombosis, TAFI was found to be high in 69.5% of the cases (normal range: 40-150 ng/dl), TFPI was high in 71% of the cases (normal range: 50-100 ng/dl), and F1+2 was high in 96.3% of the cases (normal range: 60-230 pl/L).
No statistically significant difference in terms of TAFI, F1+2, and TFPI results in terms of age, gender, BMI, tumor size, metastatic or locally advanced disease, vascular invasion, perineural invasion, carcinoembryonic antigen, hemoglobin and thrombocyte levels was detected. Patients grouped by histopathologic grade did not differ based on TAFI and F1+2. TFPI was higher in tumors of greater grade. However, the difference did not reach the level of statistical significance (Table 4).

Table 4. Evaluation of thrombosis factors by histologic grades

	Grade			*p
	Grade 1	Grade 2	Grade 3	
	Mean ±SD	Mean ±SD	Mean ±SD	
TAFI	177.60 ±72.96	204.01 ±73.43	189.61 ±48.94	*0.822*
TFPI	29.57 ±5.69	46.64± 25.89	45.20 ±18.69	*0.143*
F1+2	528.34 ±273.04	431.54 ±147.70	460.04 ±176.15	*0.520*

**: One-way analysis of variance test*

Cases with rectal localization had significantly higher TAFI levels compared to cases with colon localization (p=0.016). There was no difference between the TFPI and F1+2 levels. Carcinoembryogenic antigen (CEA), hemoglobin levels and thrombocyte count were found to be not significantly associated with TAFI, TFPI, and F1+2 levels (Table 5)

Table 5. Evaluation of thrombosis factors by localization

	Localization		*p
	Colon	Rectum	
	Mean±SD	Mean±SD	
TAFI	185.45±65.73	224.66±72.28	*0.016 **
TFPI	46.64±28.05	43.84±15.60	*0.632*
F1+2	450.21±136.80	452.058±192.56	*0.964*

**: Student's t test*

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The patients with performance scores of 1 and 2 were not different in terms of TAFI and TFPI. F1+2 was higher among the group with performance score of 2 (487.7 ±174.2 vs. 410.2±123.3; *p*=0.02) (table 6).

Table 6: Evaluation of thrombosis factors by performance status

	ECOG performance status		
	1 mean±SD	2 mean±SD	*p
TAFI	206, 52±70, 72	190, 96±69, 35	*0, 318*
TFPI	48, 95±27, 90	42, 78±21, 04	*0, 259*
F1+2	410, 20±123, 28	487, 67±174, 19	*0, 024**

**: Student's t test*

DISCUSSION:

The TAFI, TFPI, and F 1+2 levels were found to be above normal range in the patient group in this study. Additionally, evaluation of groups by factors that may affect TAFI, TFPI, and F1+2 levels such as age, gender, BMI, metastatic or locally advanced disease, vascular and perineural invasion, carcinoembryonic antigen, hemoglobin and thrombocyte levels did not yield a significant difference across the subgroups.

TAFI, an important molecule in the balance between fibrinolysis and coagulation in hemostasis, was found to be high in 69% of the patients. Moreover, cases with rectal localization had significantly higher TAFI levels compared to cases with colon localization. TAFI and TFPI levels were not different across the patient groups formed based on the ECOG performance score. F1+2, on the other hand, was higher in the group with lower performance scores. There is increased activity in the coagulation system in case of advanced stage CRC patients and in other malign diseases. Increased levels of activator and inhibitor molecules of coagulation may be observed in this case. Above normal TAFI, TPFI, and F1+2 levels in the majority of the patients may be associated with this situation.

Rectal cancer is evaluated separately from and treated with different modalities than colon cancer due to its genetic, biologic, and behavioral differences. In our study, TAFI levels of rectal cancer patients were higher than those of colon cancer patients. There is no study in medical literature that shows whether or not there is a difference between the rectal and colon cancers in terms of thrombotic processes. Prospective studies can be conducted to investigate the existence of an association of the rectal cancer's different prognosis than colon cancer and TAFI levels.

The histopathological degree of the tumor has a prognostic significance for CRC patients (22). Tumors with high histopathological degree have a more invasive character locally and systematically. This invasive feature may lead to over-stimulation of especially the coagulation cascade and severe increases in hypercoagulability. In our study, though the difference between them was not statistically significant, TFPI values were high among CRC patients with histologic degrees of 2 and 3. TFPI may increase as a response to the over stimulated coagulation cascade in patients who have tumors of high histopathological degrees. The impact of this condition on prognosis can be investigated. The failure to demonstrate a difference between the TFPI levels of different histopathological degrees may be associated with the small sample size. The increased TFPI in course of malignancy has been associated with its synthesis by neoplastic cells,

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endothelium damage, and increased response to hypercoagulability (23,24).

F1+2 have been found to be more reliable than the most commonly used diagnostic parameters, D-dimer and FDP (25). It is found at higher rates in colorectal cancer patients group operated due to malignancy related causes compared to patients operated for benign diseases. Metastatic CRC patients have higher levels of F1+2 than non-metastatic patients (26). In this study, F1+2 levels were high in 96% of the patients. This finding, considering the patients were advanced stage CRC patients, is in accordance with the medical literature. F1+2 ranges need to evolution according to new trials in cancer patients.The stage of the disease and the patient performance are in leading positions as prognostic factors for cancer patients (27). F1+2 levels of patients with poor performance were higher than those of the patients performing well. With worsening in performance conditions, immobility increases and this constitutes another risk factor for thromboembolism other than the effects of malignancy. An increased F1+2 level in nearly all (96%) of the patients has been interpreted as a possible indicator of increased thrombotic processes.

The increase in the studies conducted in hemostasis over the recent years, lead to an investigation of coagulation and fibrinolysis cancer cases including colorectal cancers (28). Clinical studies defined the molecules activated in coagulation and fibrinolysis during development and progression of colorectal cancer (29).

Though the cause of the increased hypercoagulability of CRC cases is not clear, there are changes in the tissue factor (primary activator of coagulation system) and its inhibitor tissue factor plasminogen especially during progression (30). Other risk factors can accompany this condition.

Conclusion

Thromboembolism is a serious and fatal condition, which is common among cancer patients and has negative effects on prognosis and quality of life. While its pathophysiology is not clearly defined, hypercoagulability that develops in relation with the malignancy and many other factors is the underlying factor. In this study, the higher TFPI levels in case of tumors at higher stages can indicate that there is an association between tumor grade and coagulation cascade. The higher F1+2 levels, an indicator of active coagulation cascade, among patients with low performance scores may indicate that the coagulation cascade of these patients is more active. Higher TAFI levels among rectal cancer patients may be related to the natural course of the disease. Bevacizumab, a monoclonal antibody used widely in cancer treatment, is known to increase thromboembolism risk.These molecules may use during bevacizumab treatment to predict thrombosis. It is important to identify the symptoms that carry predictive significance in terms of thrombosis in this patient group prior to bevacizumab use. This is a field in need of further research. Studies investigating prognostic symptoms in colon cancer patients, other indicators, and TAFI, TFPI, F1+2 levels in colon cancer patients, with larger samples and more homogeneous patients groups in terms of treatment and clinicopathological features will provide clearer results.

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