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Original Article

Fibrinolytic Activity in Patients with Newly Diagnosed Multiple Myeloma

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ABSTRACT

Aim: Coagulation and fibrinolysis are in balance in the normal hemostatic system, and disruption of this balance can result in bleeding disorders or thrombotic events. Studies on the fibrinolytic system in patients with multiple myeloma (MM) are few in number and have yielded conflicting results. Impaired fibrinolysis may contribute to the development of thrombotic complications in these patients.To measure levels of the fibrinolysis activator, tissue plasminogen activator (tPA) and the major fibrinolysis inhibitors, plasminogen activator inhibitor-1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI) in MM patients and compare with a control group.

Methods: The study group included 48 newly diagnosed, previously untreated MM patients who presented to the Hematology Outpatient Clinic of Zonguldak Bülent Ecevit University Faculty of Medicine for 20 months. The control group consisted of 20 individuals with no systemic disease who presented to the general internal medicine outpatient clinic for routine check-ups.

Results: Mean plasma tPA level was 9 (6.58-15.36) ng/mL in the patient group and 12.35 (8.4-19.7) ng/mL in the control group (p=0.221). Plasma PAI-1 level was 9.36 (1.28) ng/mL in the patient group and 9.56 (0.26) ng/mL in the control group (p=0.057). Plasma TAFI level was significantly lower in the patient group [7.6 (6.2-9.19) µg/mL] compared to the control group [9.46 (8.83-13.02) µg/mL] (p<0.001) but was not correlated with disease stage. There was no statistically significant difference in plasma D-dimer levels between the MM patients and the control group (p=0.406).

Conclusion: While impaired fibrinolytic activity is expected in MM patients, our results demonstrated that MM patients had low TAFI levels without significant changes in tPA and PAI-1 levels. Decreased TAFI levels may play a role in other mechanisms that can cause bleeding in MM patients.

Keywords: Multiple myeloma, fibrinolytic system, tPA, TAFI, PAI-1

Introduction

Multiple myeloma (MM) is one of the most common hematological malignancies, accounting for approximately 1% of all human cancers. It is characterized by strong and abnormal proliferation of malignant plasma cells that secrete monoclonal immunoglobulins or light chains and is associated with bone destruction, suppressed bone marrow function, and renal dysfunction [1,2]. As with other lymphoproliferative diseases, MM is associated with hemostasis disorders that cause both thrombosis and hemorrhage [3,4].

The reported risk of thromboembolism in patients with MM, especially those receiving multi-agent chemotherapy, is as high as 30% [5]. Hemorrhage is observed in less than 10% of patients with MM. The interaction between plasma paraprotein and platelets and coagulation factors is the most common pathophysiological mechanism [6]. Other risk factors for bleeding include thrombocytopenia caused by plasma cell replacement of bone marrow, renal failure, invasive procedures, and treatment-related toxicities [7].

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Clot dissolution is mediated by the fibrinolytic system (plasminogen-plasmin). Tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) are the main activators of the fibrinolytic system, whereas plasminogen activator inhibitor-1 (PAI-1), α2-antiplasmin (α2-AP), and thrombin activatable fibrinolysis inhibitor (TAFI) are the main inhibitors. Disruptions in the fibrinolytic system may cause thrombosis or hemorrhage. Patients with impaired fibrinolytic activity are more susceptible to thrombosis. Increased fibrinolysis with bleeding has been reported in several cases, including patients with MM and amyloidosis. Impaired fibrinolytic activity may occur due to decreased synthesis and/or release of plasminogen activators or increased concentrations of PAIs [3,8,9].

In the literature, different results have been reported on the fibrinolytic system in patients with MM. Several studies have suggested that disruption of the fibrinolytic system contributes to the development of thrombosis [3,4,6,7,9]. Carr et al. [10] reported that myeloma protein concentration was associated with the formation of abnormally thin fibrin fibers, resulting in impaired fibrinolysis. However, fibrinolysis activator and inhibitor levels were not analyzed in this study. Very few studies have investigated fibrinolytic system activators and inhibitors in this disease. Therefore, in this study, we aimed to evaluate fibrinolytic system activity by measuring tPA, TAFI, and PAI-1 levels in patients with MM and comparing them with healthy controls.

Methods

A total of 48 newly diagnosed patients with MM aged 51-80 years who were admitted to the Hematology Outpatient Clinic of Zonguldak Bülent Ecevit University between July 2009 and February 2011 were included in this study. Patients previously treated for MM, those diagnosed with thyroid and/or coagulation disorders, and those with chronic liver disease and those or controls using anticoagulant drugs were excluded from the study. The control group included 20 individuals aged 53-80 years who presented to the general internal medicine outpatient clinic for routine checkups, had no known systemic disease, and were not diagnosed with any disease as a result of examinations. Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Zonguldak Karaelmas University Local Ethics Committee (date: 29.06.2009, decision no: 2009/09).

Blood was collected from all patients and healthy controls at 8:00 in the morning into 5 mL biochemistry tubes for analysis of urea, creatinine, total protein, albumin, calcium, and β2 microglobulin levels. At the same time, blood was collected in 5 mL 3.8% citrate tubes for the measurement of plasma fibrinogen, D-dimer, tPA, PAI-1, and TAFI. After centrifugation, plasma samples were stored at -80 °C until analysis.

Determination of plasma tPA, TAFI, PAI-1, and D-dimer levels:

- Quantitative measurement of tPA was performed by enzyme-linked immunosorbent assay (ELISA) using the Asserachrom® tPA kit (Diagnostica Stago, France) according to the manufacturer's instructions (normal range, 2-12 ng/mL).

- Quantitative measurement of plasma PAI-1 was performed by sandwich ELISA using the Asserachrom® PAI-1 kit (Diagnostica Stago, France) according to the manufacturer's instructions (normal range: 4-43 ng/mL).

- TAFI was measured using the Asserachrom® TAFI ELISA kit (Diagnostica Stago, France). A normal range of 0.1-25 µg/mL was used, as stated in the commercial kit.

- D-dimer was analyzed using an Amax D-dimer kit (Trinity Biotech, USA) in an AMAX 200 device. Values <147 ng/mL were accepted as normal.

Statistical Analysis

The Statistical Package for Social Science 26 package program was used for the statistical evaluation of the data obtained in the study. The Shapiro-Wilk test was used to evaluate whether the measured variables were suitable for normal distribution. Student's t-test was used for normally distributed data, and Mann-Whitney U and Kruskal-Wallis tests were used when the assumption was not met. In order to summarize group comparisons and demographic characteristics, mean and standard deviation values for parametric data, median and interquartile range for non-parametric data, and measures of dispersion were used as descriptive statistics. Spearman's correlation analysis was used to explain the relationship between the parameters. $P<0.05$ was accepted as the statistical significance level.

Results

The study included 48 newly diagnosed patients with MM in the study group and 20 healthy subjects in the control group. There were 27 male (56.2%) and 21 female (43.8%) in the patient group and 9 male (45.0%) and 11 female (55.0%) in the control group. 18.15% (n=9) of the patient group were diabetic and 41.66% (n=20) were hypertensive. The mean ages in the patient and control groups was 68±9.9 years (51-80 years) and 63.9±7.5 years (53-80 years), respectively. There were no significant differences in age or sex between the control and patient groups. Myeloma protein type was IgG in 64.6% of the patients (n=31), IgA in 29.2% (n=14), lambda light chain in 4.2% (n=2), and IgM in 2.1% (n=1) (Table 1). MM disease stage determined at the time of diagnosis according to the international staging system was stage 3 in 27 patients (56.3%), stage 2 in 14 patients (29.2%), and stage 1 in 7 patients (14.6%). The demographic and clinical characteristics of both groups are presented in Table 1.

Serum total protein, urea, and creatinine levels were significantly higher in the patient group than in the control group ($p<0.001$, $p<0.001$, $p=0.001$, respectively), and albumin levels were significantly lower in the patient group than in the control group ($p<0.001$). However, there was no statistically significant difference in serum calcium levels between the groups ($p=0.319$) (Tables 2, 3).

In the comparisons of fibrinolytic system factors between patients with MM and the control group, no significant differences were detected in the mean plasma tPA, PAI-I, or D-dimer levels (p>0.05 for all). The mean plasma TAFI level was significantly lower in the patient group [7.6 (6.2-9.19) µg/mL] than in the control group [9.46 (8.83-13.02) µg/mL] (p<0.001). The relationship between diabetes, hypertension, and TAFI was evaluated using the Spearman correlation test, but no significant correlation was found. Levels of plasma tPA, TAFI, PAI-I, and D-dimer measured in the patient and control groups are presented in Tables 2 and 4. In the post-hoc analysis, the G*Power value was found to be 0.584.

Discussion

MM is a malignant plasma cell disease that accounts for 1% of all cancers and approximately 10% of all hematological malignancies. Thrombotic and hemorrhagic events are common complications of MM [11]. Numerous independent mechanisms are believed to be responsible for hypercoagulability in patients with myeloma. The main causes of hypercoagulability include the effects of abnormal and increased immunoglobulins on fibrin polymerization; the production of procoagulant antibodies; activation of the coagulation system by inflammatory cytokines; disorders

Table 1. The demographic and clinical characteristics of the patient and control groups

	Patients (n=48)	Controls (n=20)	p
Age (years), mean±SD	68±9.9	63.9±7.5	0.099
Sex, n (%) Female Male	 21 (43.7) 27 (56.2)	 11 (55) 9 (45)	0.562
Comorbidity DM, n (%) HT, n (%)	 16 (33) 23 (47.9)	- - -	
Paraprotein type, n (%) IgG IgA IgM Lambda	 31 (64.6) 14 (29.2) 1 (2.1) 2 (4.2)	 - - - -	
ISS stage, n (%) Stage 1 Stage 2 Stage 3	 7 (14.6) 14 (29.2) 27 (56.3)	 - - -	

SD: Standard deviation, DM: Diabetes mellitus, HT: Hypertension, ISS: International scoring system, Ig: Immunoglobulin

Table 2. Comparison of biochemical test results between the patient and control groups

Biochemical markers	Patients	Control	p
	Mean (SD)	Mean (SD)	
Albumin (g/dL)	3.56 (0.7)	4.25 (0.18)	<0.001
Total protein (g/dL)	9.36 (2.04)	7.02 (0.4)	<0.001
Calcium (mg/dL)	9.36 (1.28)	9.56 (0.26)	0.319
D-dimer (ng/mL)	110.39 (16.12)	106.8 (16.27)	0.406

Mean values of biochemical parameters between patient and control groups, measured by Student's t-test.
SD: Standard deviation

Table 3. Comparison of biochemical test results between the patient and control groups

Biochemical markers	Patients	Control	p
	Median (IQR)	Median (IQR)	
Urea (mg/dL)	23 (17.25-31.75)	14.5 (12.25-19.5)	<0.001
Creatinine (mg/dL)	1.2 (0.9-1.6)	0.9 (0.8-1)	<0.001
β2-microglobulin	58.41 (3890-9141)		

Median values of biochemical parameters between patient and control groups, measured by Mann-Whitney U test.
IQR: Interquartile range

Table 4. Comparison of tPA, PAI-1 and TAFI levels between the patient and control groups

Biochemical markers	Patients	Control	p
	Median (IQR)	Median (IQR)	
tPA (ng/mL)	9 (6.58-15.36)	12.35 (8.4-19.7)	0.221
TAFI (µg/mL)	7.6 (6.2-9.19)	9.46 (8.83-13.02)	<0.001
PAI-I (ng/mL)	9.36 (1.28)	9.56 (0.26)	0.057

Median values of biochemical parameters between patient and control groups, measured by Mann-Whitney U test.
tPA: Tissue plasminogen activator, PAI-1: Plasminogen activator inhibitor-1, TAFI: Thrombin-activatable fibrinolysis inhibitor, IQR: Interquartile range

of the natural anticoagulation mechanisms; and an increase in adhesion molecules caused by both tumor cells and chemotherapy [6,8]. The causes of bleeding in patients with MM are also multifactorial. Hemorrhage can occur for various reasons, including decreased factor X and α2-AP levels; amyloid accumulation in vessel walls; and inhibition of fibrin polymerization, factor VIII, and Von Willebrand factor, and disruption of platelet function by paraprotein [6].

The fibrinolytic system plays a role in many physiological and pathological events. The major activators of the fibrinolytic system are tPA and uPA, whereas PAI-1 and PAI-2 are its inhibitors [12]. TAFI is another recently identified fibrinolysis inhibitor that acts by separating carboxy terminal lysine residues from fibrin after activation by thrombin [13].

In the present study, we compared tPA, PAI-1, TAFI, and D-dimer levels between 48 patients newly diagnosed with MM and a healthy control group. Our patients had comparable tPA levels to healthy controls. In contrast, although the difference did not quite reach statistical significance, the PAI-1 level was lower in the patients with MM than in controls. Interesting finding was that the patients with MM had significantly lower TAFI levels than the controls.

In a study by Spicka et al. [3] involving 49 patients with monoclonal gammopathy (44 patients with MM, 3 patients with Waldenstrom macroglobulinemia, and 2 patients with monoclonal gammopathy of undetermined significance), increased tPA activity was the most common abnormality, although increased PAI-1 levels were also reported. Anticoagulant system defects were detected in 26.5% of the same patient group. The risk of venous thromboembolism was higher in the group with anticoagulant and/or fibrinolytic system abnormalities, but not significantly. Yağci et al. [9] published one of the most comprehensive studies investigating fibrinolytic system activator and inhibitor levels and their relationship with cytokines in patients with MM. In their study, tPA, PAI-1, interleukin (IL)-6, IL-1β, and IL-11 levels and global fibrinolytic capacity were compared between 66 patients with MM and a healthy control group. Levels of tPA were similar between the two groups. However, patients with MM were found to have significantly higher PAI-1 levels and resulting lower fibrinolytic activity, and a positive correlation was observed between PAI-1 and IL-6 levels. TAFI levels were not analyzed. Shortened clot lysis time, increased fibrinolysis characterized by increased levels of fibrin degradation products, and consequent bleeding have also been reported in patients with MM and amyloidosis [6].

TAFI levels have been studied in patients with solid tumors and hematological malignancies. Higher TAFI levels were observed in patients with non-small-cell lung cancer compared with the control group, suggesting that this antigen may be secreted by cancer cells themselves [14]. In the same study, increased TAFI was proposed to play a role in the pathogenesis of venothrombotic events in patients with lung cancer. In another study comparing levels of TAFI and TAFIa (active enzyme) between patients with antiphospholipid syndrome (APS) and a control group, APS patients had higher TAFI and TAFIa levels than controls, and patients with arterial thrombosis had higher TAFIa levels than those with other APS phenotypes. The authors concluded that TAFIa could be a new biomarker of arterial thrombosis in APS patients [15]. In contrast, the Hypercoagulability and Impaired Fibrinolytic Function Mechanisms Predisposing to Myocardial Infarction study suggested that increased TAFI antigen levels could protect against myocardial infarction [16].

In the first study to investigate TAFI in patients with MM, TAFI levels measured in 27 patients with newly diagnosed myeloma were significantly higher than those in the control group [17]. The authors reported that TAFI level was associated with disease activity and suggested a link between the higher TAFI level in myeloma and thrombotic complications in these patients. Similar results were obtained in another subsequent study [18]. Misiewicz et al. [19] compared the relationship between certain rotational thromboelastometry parameters and tPA and PAI-1 levels in newly diagnosed patients with MM and a healthy control group and detected high PAI-1 levels indicative of hypofibrinolysis in patients with MM. In a study investigating the effect of induction therapy on fibrin clot properties in patients with MM, Undas et al. [20] observed ischemic stroke in 2 patients and venous thromboembolism in 10 patients despite thromboprophylaxis and determined that these patients had high TAFI and PAI-1 levels before treatment. In contrast to these data, the TAFI levels in the present study were significantly lower in patients with MM than in the control group.

Increased TAFI levels have also been reported as the cause of hypofibrinolysis in various endocrine disorders, such as obesity and diabetes [21,22]. There are also many studies in the literature that investigated plasma TAFI Ag or TAFIa levels in patients with overt hypothyroidism. Erem et al. [23] reported no significant correlation between TAFI Ag and thyroid hormone levels, and another study determined higher plasma TAFI Ag levels in hypothyroid patients [24].

Ermantas et al. [25] found that TAFI and TAFIa levels were higher in hypothyroid patients than in the control group, and they suggested that thyroid insufficiency may have affected circulating TAFI Ag levels. However, we detected no correlation between TAFI levels and disease stage, diabetes, and hypertension. One of the limitations of the study was that we could not access the patients' body mass index and lipid panel. Since obvious thyroid dysfunctions were excluded from our patient population, fibrinolytic system-thyroid disorders are outside the scope of this study.

In our study, clinical bleeding was observed in 4 of the MM patients. There were no significant differences between patients with MM and controls in terms of the levels of D-dimer, an *in vivo* coagulation marker. Therefore, we do not believe coagulation activation or subsequent secondary fibrinolysis. However, less than 10% of patients with MM, Waldenstrom macroglobulinemia, and primary amyloidosis present with bleeding complications. We believe that the decreased TAFI levels detected in our study may also contribute to increased fibrinolysis, especially in patients with myeloma who have bleeding. In patients with acute leukemia, it was reported that TAFI activity was lower than that of the control group but inversely proportional to the severity of bleeding [26]. In various studies, low TAFI was associated with hyperfibrinolysis. Van Thiel et al. [27] reported that plasma TAFI levels were quite low in patients with advanced hepatocellular liver disease. Colucci et al. [28] showed that clots obtained from patients with cirrhosis were more sensitive to exogenous tPA at physiological concentrations. They stated that TAFI deficiency is the main cause of hyperfibrinolysis. Denorme et al. [29] examined the inhibition of TAFI and PAI-1 in a mouse model of transient middle cerebral artery occlusion. Inhibition of TAFI or PAI-1 significantly reduced cerebral infarct size by 50% at 24 hours after stroke. On the contrary, an experimental agent (DS-1040) has recently been shown to inhibit the activated form of TAFI but to have no effect on bleeding time [30]. Although it was difficult to determine the cause of the low plasma TAFI levels, it may be related to the different laboratory methods used in the studies.

Study Limitations

The main limitation of our study was that plasmin-AP complex level, which is a direct indicator of *in vivo* fibrinolysis and TAFI gene polymorphisms, could not be examined due to technical reasons.

Conclusion

In conclusion, although impaired fibrinolytic activity is generally expected in patients with MM, the present study demonstrated that these patients had low TAFI levels without significant changes in tPA and PAI-1 levels. Decreased TAFI levels may play a role in other mechanisms that can cause bleeding in patients with MM. However, further clinical studies with a large number of patients measuring plasmin-AP levels are needed.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Zonguldak Karaelmas University Local Ethics Committee (date: 29.06.2009, decision no: 2009/09).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.Ö.T., F.C.S., Concept: M.K., Design: H.Ş., M.K., Data Collection or Processing: M.K., H.Ş., Analysis or Interpretation: İ.Ö.T., F.C.S., Literature Search: M.K., H.Ş., Writing: M.K., H.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

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