Eosinophil count is related with coronary thrombus in non ST-elevated acute coronary syndrome

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Background. White blood cells are reported as important not only in plaque vulnerability but also in thrombus formation and thrombus growth in acute coronary syndromes. Eosinophils contain granules that promote thrombus formation and thrombus growth in some heart diseases. In this study we aimed to investigate the relation of eosinophil count with coronary thrombus formation in patients with non ST-elevated acute coronary syndrome (NST-ACS).

Method. A total of 251 consecutive patients were hospitalized in our hospital with a diagnosis of NST-ACS. Venous blood is collected for measurement of hematologic indices in all patients undergoing the coronary angiography. Coronary angiographies were performed in our clinic using the standard Judkins technique and angiographic assessment of the presence of thrombus was made.

Results. During coronary angiography, coronary thrombus was not detected in 82 patients (Group 1). In the coronary angiography of 169 patients, coronary thrombus was detected at various grades (Group 2). While the neutrophil count (6.84 ± 1.94 vs. 5.53 ± 1.37 ; $P < 0.001$) and eosinophil count (0.257 ± 0.125 vs. 0.163 ± 0.114 ; $P < 0.005$) was significantly increased in the group with coronary thrombus, the lymphocyte count (1.87 ± 0.66 vs. 2.00 ± 0.70 ; $P < 0.001$) was significantly decreased in the group with coronary thrombus as compared to the patient group without coronary thrombus. In the correlation analyzes; presence of coronary thrombus is correlated with total cholesterol, LDL-C, total CK, CK-MB, troponin, total number of diseased coronary, platelet count, neutrophil count, lymphocyte count and eosinophil count. On multivariate linear regression analysis, total leukocyte count, neutrophil count, lymphocyte count, eosinophil count, troponin and total cholesterol was found to be independent predictor of coronary thrombus in patients with NST-ACS.

Conclusion. Beside the increased neutrophil count, increased eosinophil count in CBC should alert the clinician about coronary thrombus development in patients with NST-ACS in order to make early medical interventions at acute phase of the disease.

Key words: white blood cell, eosinophil, coronary thrombus, coronary artery disease, non ST-elevated acute coronary syndromes

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INTRODUCTION

Atherosclerotic plaque disruption is the crucial point of arterial thrombogenesis^{1,2}. White blood cells are reported as important not only in plaque vulnerability but also in thrombus formation and thrombus growth in acute coronary syndromes³. Monocyte and neutrophils were reported to play significant roles in vulnerability of atherosclerotic plaques⁴. Additionally, increased neutrophil count was reported to predict coronary thrombus formation in patients with acute myocardial infarction⁵.

Eosinophils are associated with multiple diseases including allergic diseases, infections, autoimmune diseases and myelodysplastic syndromes. Eosinophils contain granules that promote thrombus formation and thrombus growth in various heart diseases⁶⁻⁸.

In this study we aimed to investigate the relation of eosinophil count with coronary thrombus formation in patients with NST-ACS. The powerful vasoactive and pro-

coagulant effects of eosinophils made us hypothesize that there might be a correlation between eosinophil concentration and coronary thrombus development.

METHODS

A total of 251 consecutive patients were hospitalized in our hospital with a diagnosis of NST-ACS. ACS were defined as presentation with symptoms of ischemia in association with electrocardiographic changes, positive cardiac enzymes, new documentation of coronary artery disease, or the previous coronary artery disease diagnosis as defined by similar previous studies⁹. Symptomatic patients were assessed by a standard diagnostic flowchart that included clinical and electrocardiographic monitoring as well as biochemical measurements of myocardial necrosis markers. Patients diagnosed with acute myocardial infarction (AMI) with non ST-elevation (NSTEMI),

and unstable angina (UA) were included in this study. Patients with a history of trauma, surgery, neoplasm, or infectious disease in the last 30 days prior to hospitalization as well as current use of immunosuppressants (including corticosteroids) were excluded from the study. We also excluded any patients with history of postadmission complications such as cardiogenic shock, serious arrhythmias with hemodynamic instability, or heart failure. The study protocol was approved by the institutional review board in our center, and informed consent was obtained from all patients. Demographic characteristics, medical histories, laboratory studies including leukocyte counts and peripheral differential counts, and a variety of hospital outcomes data were collected. Clinical information included data on systemic hypertension (HT), diabetes mellitus (DM), dyslipidemia, smoking, previous history of CAD, including coronary angioplasty or myocardial revascularization and early family history of CAD. Diabetes was determined by physician report and was based on a fasting blood sugar level ≥ 126 mg/dL or use of an antidiabetes medication. Hypertension was physician-reported for systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of anti-hypertensive agents. Hyperlipidemia was physician reported for total cholesterol ≥ 200 mg/dL, low-density lipoprotein cholesterol (LDL-C) level ≥ 130 mg/dL, or use of cholesterol-lowering medication. Family history was self-reported when a first order relative had suffered cardiovascular death, MI, or coronary revascularization before age 65. Smoking included active or previous (>10 pack-years) tobacco use. The blood sample for complete blood count (CBC) assessment was collected 1 hour after admission to the hospital. In our hospital, blood samples are collected from the ante-cubital vein by an atraumatic puncture and are sent to the laboratory for analysis within 1 h after collection. Venous blood is collected in a tube containing K3 EDTA for measure-

ment of hematologic indices in all patients undergoing the coronary angiography. Hematologic indices are evaluated from CBC analysis performed by a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc. Mervue, Galway, Ireland). Coronary angiographies were performed in our clinic using the standard Judkins technique and angiographic assessment of the presence of thrombus was made¹⁰.

Statistical analysis

Patient demographic characteristics are presented as means and standard deviations for continuous variables and as proportions (percentages) for categorical variables. Simple two-group comparisons used chi-square for categorical and *t*-test statistics for continuous variables. In order to investigate the distribution of data, the Shapiro-Wilk test was used. Comparison of the two groups for normally distributed data was performed with *t*-tests. Mann-Whitney U test was used for skewed data. Relationships between variables were examined by Pearson's correlation coefficient. Threshold values of the ROC analysis were statistically significant. The level of significance set at $\alpha = 0.05$. Statistical analyses were performed with SPSS 20.0.

RESULTS

Of 251 consecutive patients admitted with NST-ACS to our institution during the study period. During coronary angiography, coronary thrombus was not detected in 82 patients (Group 1). In the coronary angiography of 169 patients, coronary thrombus was detected at various grades (Group 2). Differential leukocyte counts were obtained. The baseline characteristics across the population are listed in Table 1.

Table 1. The baseline characteristics of the study groups.

	Group 1 (n=82)	Group 2 (n=169)	<i>P</i>
Age (years)	60.68 $\pm$ 11.73	61.37 $\pm$ 12.34	NS
Male/Female	65/17	126/43	NS
Smoking (n,%)	38(46%)	62(36%)	NS
Hypertension (n,%)	46(56%)	82(48%)	NS
Diabetes mellitus (n,%)	19(23%)	49(28%)	NS
Heart rate (beats/min)	78.95 $\pm$ 14.38	79.62 $\pm$ 13.41	NS
Total cholesterol (mg/dL)	184.90 $\pm$ 42.15	202.67 $\pm$ 52.84	<0.05
LDL-cholesterol (mg/dL)	114 $\pm$ 37.44	129.37 $\pm$ 45.32	<0.05
Triglycerid (mg/dL)	144.13 $\pm$ 15.17	157.66 $\pm$ 13.38	NS
Unstable angina pectoris (n)	44(53%)	48(28%)	<0.001
Non ST-elevated MI (n)	38(46%)	121(71%)	<0.001
Total CK (ng/mL)	280.65 $\pm$ 38.75	433.41 $\pm$ 41.57	<0.05
CK-MB (ng/mL)	26.14 $\pm$ 3.10	44.82 $\pm$ 3.52	<0.01
Troponin (μ g/mL)	3.45 $\pm$ 0.82	9.02 $\pm$ 1.10	0.001
History of PCI	13(15%)	23(13%)	NS
History of CABG	1(1.2%)	1(0.59%)	NS
T. leukocyte count ($\times 10^9$ /L)	9.06 $\pm$ 2.47	9.93 $\pm$ 2.71	<0.05
Lymphocyte count ($\times 10^9$ /L)	2.00 $\pm$ 0.70	1.87 $\pm$ 0.66	<0.001
Neutrophil count ($\times 10^9$ /L)	5.53 $\pm$ 1.37	6.84 $\pm$ 1.94	<0.001
Eosinophil count ($\times 10^9$ /L)	0.163 $\pm$ 0.114	0.257 $\pm$ 0.125	<0.005
Platelet count ($\times 10^9$ /L)	227.53 $\pm$ 63.46	242.04 $\pm$ 69.83	<0.01

NS - Non-significant

Table 2. Subgroup analyzes of the patients according to the final diagnosis.

	UA (n=92)	NSTEMI (n=159)	<i>P</i>
Age (years)	60.57±11.69	61.48±12.39	NS
BMI (kg/m ²)	27.36±3.96	27.49±3.71	NS
Hypertension (n,%)	50(54%)	78(49%)	NS
Diabetes (n,%)	25(27%)	43(27%)	NS
Heart rate (beats/min)	77.61±13.15	80.43±13.96	NS
Smoking status (n,%)	33(35%)	67(42%)	NS
CABG history (n,%)	2(0.02%)	0(0%)	NS
PCI history (n,%)	17/92	19/159	NS
Total Cholesterol (mg/dL)	186±51.6	203±48.4	<0.05
LDL-cholesterol (mg/dL)	111.8±41.5	131.5±43	<0.001
Total CK (ng/mL)	117.4±27.1	537.4±46.6	<0.001
CK-MB (ng/mL)	17.9±7.8	53.3±16.9	<0.001
Troponin (µg/mL)	0.06±0.003	14.57±4.38	<0.001
T. leukocyte count (×10 ⁹ /L)	8.7±2.6	10.2±2.5	<0.001
Neutrophil count (×10 ⁹ /L)	4.9±1.82	6.8±1.87	0.001
Lymphocyte count (×10 ⁹ /L)	1.93±0.69	1.87±0.65	NS
Platelet count (×10 ⁹ /L)	235.25±68.72	238.49±67.82	NS
Eosinophil count (×10 ⁹ /L)	0.191±0.112	0.232±0.129	<0.05
LVEF(%)	55.22±9.01	47.87±9.97	<0.001

NS - Non-significant

In the analyzes of the study groups, total cholesterol and LDL-C was significantly increased in the patient group with coronary thrombus as compared to the patient group without coronary thrombus. CK, CK-MB and troponin were significantly increased in the group with coronary thrombus. LVEF was significantly decreased in the patient group with coronary thrombus. The platelet count was significantly increased in the group with coronary thrombus as compared to the group without coronary thrombus. While the platelet count was significantly different between the study groups, MPV was not different between the groups with and without coronary thrombus. The neutrophil count and eosinophil count was significantly increased in the group with coronary thrombus, the lymphocyte count was significantly decreased in the group with coronary thrombus as compared to the patient group without coronary thrombus. Between the study groups with and without coronary thrombus, there was no significant difference for patients' age, smoking status, hypertension prevalence, diabetes prevalence, average heart rate, aspirin use, hemoglobin and hematocrit levels (Table 1).

In the subgroup analyzes of the study patients according to the final diagnosis as NSTEMI and UA, there was no significant differences between the patients with NSTEMI and UA for age, body mass index, hypertension incidence, diabetes incidence, heart rate, smoking status, CABG and PCI history, platelet counts, MPV and lymphocyte count. On the other hand, LDL-C, Total CK, CK-MB, troponin value, aspirin use, LVEF, total leukocyte count, eosinophil count, neutrophil count was significantly different between the groups with NSTEMI and UA (Table 2).

In the correlation analyzes; presence of coronary thrombus was correlated with total cholesterol, LDL-C, total CK, CK-MB, troponin, total number of diseased coronary, platelet count, neutrophil count, lymphocyte count and eosinophil count (Table 3).

On multivariate linear regression analysis, total leukocyte count, neutrophil count, lymphocyte count, eosinophil count, troponin and total cholesterol was found to be independent predictor of coronary thrombus in patients with NST-ACS (Table 4).

Since patients who had coronary thrombus had significantly higher eosinophil counts, we performed a receiver-operating characteristic curve analysis to determine the best cut-off value of eosinophil count predict thrombus formation in coronaries. For eosinophil count; the area under the curve was 0.66 (95% confidence interval [CI]

Table 3. Correlations between the coronary thrombus formation and the patient variables.

	Coronary thrombus	
	<i>r</i>	<i>P</i>
Total cholesterol	0.134	<0.05
LDL-C	0.179	<0.005
Total CK	0.197	<0.005
CK-MB	0.213	<0.005
Troponin	0.264	<0.001
Total number of diseased coronary	0.130	<0.05
Platelet count	0.180	<0.005
Neutrophil count	0.382	<0.001
Lymphocyte count	-0.440	<0.001
Eosinophil count	0.276	<0.01

Table 4. Predictors of coronary thrombus formation in multivariate linear regression analysis.

Model		Coefficients ^a						
		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	1.295	0.158		8.183	0.000	0.984	1.607
	T.Cholest.	0.001	0.001	0.088	1.019	0.309	-0.001	0.002
	LDL-C	0.000	0.001	0.032	0.367	0.714	-0.002	0.002
	Troponin	0.003	0.002	0.088	1.670	0.096	-0.001	0.007
	WBC	-0.012	0.011	-0.068	-1.120	0.264	-0.033	0.009
	Platelet	0.001	0.000	0.117	2.206	0.028	0.000	0.002
	Neutrophil	0.088	0.014	0.350	6.058	0.000	0.059	0.116
	Lymphocyte	-0.310	0.035	-0.449	-8.785	0.000	-0.379	-0.240
	Eosinophil	0.001	0.000	0.138	2.658	0.008	0.000	0.001

^aDependent Variable - THROMBUS+/-

0.56 to 0.70, $P < 0.001$), and the best cut-off value was 182.2 with sensitivity and specificity 70%, and 55%, respectively. For neutrophil count; the area under the curve was 0.73 (95% confidence interval [CI] 0.61 to 0.78, $P < 0.001$), and the best cut-off value was 4.50, with sensitivity and specificity 87%, and 70%, respectively. For platelet count; the area under the curve was 0.61 (95% confidence interval [CI] 0.56 to 0.70, $P < 0.005$), and the best cut-off value was 220000, with sensitivity and specificity 60%, and 47%, respectively (Fig. 1).

DISCUSSION

The principal finding of our study is that increased eosinophil count, increased neutrophil count and decreased

lymphocyte count are independent predictors of coronary thrombus formation in patients with NST-ACS. Patients with higher eosinophil and neutrophil counts and lower lymphocyte counts showed increased coronary thrombus incidence thus providing an additional level of risk stratification in patients with NST-ACS.

Polymorphonuclear and monocyte activation has been reported in patients with acute coronary syndrome (ACS) and ischemic heart disease. In the process of plaque vulnerability and disruption, inflammation was reported as a key pathophysiological element¹¹. In acute coronary syndrome, neutrophils induce atherosclerotic plaque rupture with releasing of proteolytic enzymes, superoxide radicals and arachidonic acid derivatives that make atherosclerotic plaque rupture easier¹². Increased neutrophils are associated with formation of platelet-leukocyte aggregates in the

Fig. 1. Receiver-operating characteristic (ROC) curve analysis to determine the best cut-off value of eosinophil count predict thrombus formation in coronaries.

vasculer lumen that causes to extend the infarct area^{13,14}. Lymphocyte concentrations were found to be lower in patients with ACS. The reduction in lymphocyte count might be related to physiological stress that leads to increased cortisol production and increased apoptosis of lymphocyte triggered by increased inflammation^{15,16}. In our study neutrophil count was increased and lymphocyte count was decreased significantly in the patients with coronary thrombus when compared to the patients without coronary thrombus. This finding was also reported in previous studies⁵.

Eosinophils induce coagulation system activation and platelet activation, also cause inflammation and aneurysm. Additionally eosinophils play significant role in vascular injuries¹⁷. Increased eosinophil count was found to be associated with occlusive coronary thrombus¹⁸ with intracardiac thrombus¹⁹, myocarditis²⁰ and vasculitis²¹. Eosinophils generate an increased tendency to thrombosis through leukocyte and platelet stimulation and release of tissue factor²². In an ACS, tissue factor, plasminogen activator inhibitor-I and fibrinogen are important factors for thrombus development²³⁻²⁶. Also, major basic protein or eosinophilic cationic protein-an eosinophilic granule protein, activates platelets and promotes thrombus formation by inhibiting the thrombomodulin in allergic diseases and hypereosinophilic syndromes. Activated eosinophils and secreted eosinophil granule proteins were evident within the necrotic and later stage thrombotic lesions and were found mainly within the areas of acute tissue damage in the endocardium and in the walls of small blood vessels. These findings suggest that eosinophil granule proteins are involved in vascular injury, also eosinophils may effect cardiovascular system through inflammatory cell infiltration^{8,27}. In our study, increased eosinophil count was significantly increased in patients with coronary thrombus. The presence of coronary thrombus was significantly correlated with increased platelet count, increased neutrophil count, increased eosinophil count and decreased lymphocyte count.

In subgroup analysis of our study, we found that, at admission to the intensive coronary unit, the eosinophil count and neutrophil count were significantly increased in the study group with increased cardiac biomarkers (NSTEMI) as compared to the patient group with UA whose cardiac biomarkers were not increased. Our finding was compatible with previous studies in which increased leukocyte count also might indicate maladaptive processes; circulating leukocyte-platelet aggregates facilitate vascular plugging and consequently infarct extension²⁸.

Our study is important for the fact that in previous studies the eosinophil count which was related with cardiac diseases was reported as hypereosinophilic ($>1,5 \times 10^9/L$) but in our study, the eosinophil count was not increased so much in the patients with coronary thrombus as compared to the patients with hypereosinophilic syndromes. With this result, it may be emphasized that eosinophils may be involved in formation of coronary thrombus without reaching higher counts in CBC as well. Also, our study is the first to report the relation of eosinophil

count with coronary thrombus development in patients with NST-ACS. Previously, increased eosinophil count was found to be associated with stent thrombosis²⁹, intracardiac thrombus¹⁹ and coronary thrombus in patients with acute ST-elevated myocardial infarction¹⁸.

CONCLUSION

The thrombus formation in coronaries is essentially important not only for the extension of the infarct area but also for making the management decisions prior to or during the coronary interventional procedures. In addition to the increased neutrophil count, increased eosinophil count in CBC should alert the clinician for coronary thrombus development in patients with NST-ACS in order to make early medical interventions in the acute phase of the disease. At this point, increased eosinophil count may facilitate the early medical interventions for preventing catastrophic results of coronary thrombus formation and growth. This relatively inexpensive, and universally available blood parameter can give insight into thrombus formation in coronary beds in patients with NST-ACS.

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