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Assessment of Mean Platelet Volume in Patients with AA Amyloidosis and AA Amyloidosis Secondary to Familial Mediterranean Fever: A Retrospective Chart – Review Study

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Background: Amyloidosis is a protein-misfolding disease characterized by the deposition of aggregated proteins in the form of abnormal fibrils that disrupt tissue structure, ultimately causing disease. Amyloidosis is very frequent in untreated familial Mediterranean fever (FMF) patients and it is the most important feature that determines the prognosis of FMF disease. The mean platelet volume (MPV) in FMF has been previously studied. However, whether MPV level in FMF patients is lower or higher compared to healthy controls remains a topic of ongoing debate. In this study, we aimed to investigate MPV values and to assess the correlation between MPV and proteinuria in patients with AA amyloidosis and AA amyloidosis secondary to familial Mediterranean fever (AA-FMF) through a retrospective chart-review.

Material/Methods: This study was carried out on 27 patients with AA amyloidosis, 36 patients with AA amyloidosis secondary to FMF (a total of 63 patients with AA), and 29 healthy controls. There was no statistically significant difference between the AA patients and the control group (p=0.06) or between the AA-FMF group and the control group in terms of MPV values (p=0.12).

Results: We found a statistically significant negative correlation between MPV and thrombocyte count in all groups (p<0.05 for all groups), but there was no correlation between MPV and proteinuria levels in AA patients (p=0.091).

Conclusions: While similar results also exist, these findings are contrary to the majority of previous studies. Therefore, further controlled clinical prospective trials are necessary to address this inconsistency.

MeSH Keywords: Amyloidosis • Familial Mediterranean Fever • Mean Platelet Volume • Proteinuria

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Background

Amyloidosis is a clinical disorder in which abnormal insoluble amyloid fibrils disrupt tissue structure and function. To date, at least 30 distinct types of proteins in humans have been determined as causative agents of amyloid diseases [1].

The continuing acute phase response with excessive production of serum amyloid A (SAA) protein in chronic inflammatory and infective diseases leads to AA amyloidosis as a complication [2]. The overall incidence of amyloidosis has declined over the last 10 years due to advanced treatment of underlying diseases as well as increased use of disease-modifying therapy and generalized use of biologic therapies. However, AA amyloidosis is still a common disorder in developing countries [3]. The prevalence of AA amyloidosis is reported to be 5–78% in patients with rheumatoid arthritis (RA) and 10–13% in patients with FMF [4]. However, the actual prevalence of AA amyloidosis is expected to be much lower than these values because most these studies were performed before widespread use of advanced therapies in these patients [4]. Familial Mediterranean fever (FMF) is a genetic autoinflammatory disorder characterized by recurrent febrile episodes and serosal inflammation which last for 2–3 days and resolve spontaneously. It is common in Mediterranean populations. Amyloidosis is very frequent in untreated FMF patients and it is the most important feature that determines the prognosis of FMF disease [5].

Previous studies have determined a correlation between platelet size and platelet function [6]. Hence, mean platelet volume (MPV) is accepted as a platelet activation marker. Also, MPV has been used as a marker of inflammation in both cardiac and noncardiac disorders [7,8]. It is reported that MPV is increased in cerebrovascular disorders and myocardial infarction, while it is decreased in active rheumatoid arthritis [9–13]. Also, MPV is suggested to be an indicator of the probability of atherosclerosis [14]. Due to these relationships between inflammatory activity and MPV value, MPV has been suggested by many to be a marker of inflammatory activity in various diseases [9,15,16]. The MPV levels in FMF have been previously studied [17]. However, whether MPV levels in FMF patients are lower or higher compared to healthy subjects remains as a topic of ongoing debate.

Our aim in the present study was to explore whether MPV values differ in AA amyloidosis patients compared to a control group, and to evaluate the correlation between MPV and proteinuria levels in patients with AA amyloidosis.

Material and Methods

This single-center, retrospective study was conducted between July 2015 and April 2017 on 63 AA amyloidosis patients of which 36 had FMF disease at the Istanbul Medeniyet University Goztepe Training and Research Hospital, Nephrology Clinic. A total of 29 subjects without any chronic disease were chosen as a healthy control group, based on exclusion criteria, from patients admitted to the nephrology and internal medicine clinics for routine evaluations. All subjects in the control group were non-smokers. All necessary information about the patients included in the study were obtained from their medical records. The diagnosis of FMF was based on Tel-Hashomer criteria [18]. MEFV gene analysis was performed in some patients suspected to have FMF but in whom the AA etiology was not determined. While all patients with AA amyloidosis (AA, n=63) were evaluated, a subgroup of these patients (AA-FMF, n = 36) were also evaluated and compared with controls. Non-FMF inflammatory conditions associated with AA amyloidosis were as follows: rheumatoid arthritis, ankylosing spondylitis, chronic bronchitis, bronchiectasis, tuberculosis, sarcoidosis, and Crohn's disease. In this study, we compared the AA group and AA-FMF group with the control group in terms of various demographic characteristics and clinical measurements. All FMF patients were in the attack-free period and they were using colchicine 0.5–1.5 mg/day. The diagnosis of AA was made mainly on the basis of biopsies from different tissues such as the kidney, gingiva, rectum, duodenum, or bone marrow. Patients with acute and chronic infections, primary amyloidosis, diabetes mellitus, hypertension, liver diseases, hyperthyroidism, hypothyroidism, hematological disorders, and malignancy were not enrolled into the study. Additionally, patients using drugs that could have an influence on the count and activity of platelets and/or the coagulation system, such as aspirin, oral anticoagulants, non-steroidal anti-inflammatory drugs, heparin, and chemotherapeutic agents, were also excluded from the study.

All complete blood count (CBC) studies were conducted in the hematology laboratory of Istanbul Medeniyet University, Goztepe Training and Research Hospital. MPV values were analyzed with a Cell-Dyn Sapphire (Abbott) device based on Coulter's electrical impedance principle. Demographic data, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell (WBC) count, hemoglobin (Hgb), platelet count (PLT), MPV, creatinine, urea, total protein, albumin, Na, K, Ca, P, PTH levels, and BMI were evaluated. The study was approved by Istanbul Medeniyet University, Goztepe Training and Research Hospital Clinical Research Ethics Committee on April 10, 2018 (protocol number: 2013-KAEK-64), and informed consent was obtained from all participants.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software (version 21.0, IBM, Armonk, NY)

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for Windows. The normality of distribution of continuous variables was evaluated by the Shapiro-Wilk test. We analyzed descriptive statistics and compared dual groups using the Mann-Whitney U test. Data are given as medians (minimum-maximum). The correlations between 2 variables were determined by calculation of Spearman's rho. Statistical significance was determined when p value was found to be less than 0.05.

Results

There were 63 participants (68.4%) in the AA group and 29 participants (31.6%) in the control group. The number of the AA-FMF patients was 36 (67.9% of AA patients). The female/male distribution in the groups was 29 (46%)/34 (54%) in the AA group, 19 (52.7%)/17 (47.3%) in the AA-FMF group, and 21 (72.4%)/8 (27.6%) in the control group. Sex distribution was different between the AA patients and the control group, but there was no statistically significant difference between the AA-FMF group and the control group. The mean age of each group was as follows: 49.6±14.8 years in the AA group, 45.7±16.4 years in the AA-FMF group, and 48.3±9.0 years in the control group. There was no statistically significant difference between groups in terms of age.

The demographic characteristics of patients and all laboratory results are presented and compared in Table 1. MPV values of the AA group were lower than the AA-FMF and control groups, but the differences were not statistically significant. Comparison of PLT values showed that there was no statistically significant difference between the AA group and the control group (p=0.06) and between the AA-FMF group and the control group (p=0.12). CRP and ESR levels were significantly higher in the AA and AA-FMF groups compared to the control group (p<0.001). Also, BMI and albumin values were lower in the AA and AA-FMF groups compared to the control group (p<0.001). Regarding WBC levels, the AA and AA-FMF groups had higher WBC levels compared to controls; however, this difference was only statistically significant when the AA group was compared with controls (p=0.010).

When the remaining parameters were evaluated, we found statistically significant differences between the AA and the control group in terms of Hgb, Na, Ca, P, and PTH (p<0.05, for each comparison), while K levels were similar. Also, there were statistically significant differences between the AA-FMF and the control group in terms of Hgb, Ca, P, and PTH (p<0.05, for each comparison), while the levels of Na and K were similar.

Correlation analyses revealed that a statistically significant negative correlation between MPV and thrombocyte count was present in all groups (AA: r=–0.364, p=0,003; AA-FMF: r=–0.381, p=0.022; and controls: r=–0.476, p=0.009). However, there was no correlation between MPV and proteinuria levels in the AA and AA-FMF groups (p=0,091 and p=0.956, respectively) (Table 2).

Discussion

In this study, we found that MPV values were similar to controls in patients who had amyloidosis with or without FMF, which is contrary to the findings of previous studies [19,20]. Although a few studies determined similar and even lower MPV levels in patients with FMF [21], most of the studies reported high MPV levels in FMF patients compared to controls [19,22].

In a recent study, Basaran et al. showed that there was no significant difference between MPV values of FMF patients with attack (8.35±4.91 fL) and attack-free FMF patients (8.43±1.15 fL). However, MPV values of all FMF patients were significantly higher than in healthy controls (7.99±0.81). Therefore, they proposed that MPV may be used as subclinical inflammation marker in patients with FMF [23]. In 2015, Uluca et al. found that the MPV values of children with FMF were significantly higher compared to healthy controls (7.8±1.1 *vs.* 7.3±1.4 fL) [24]. Similarly, Ozkayar et al. reported that FMF patients without AA had significantly higher MPV level compared to the control group [19]. In 2015, Marzouk and colleagues found that 84% of the patients with FMF had high MPV levels and they proposed that MPV values may be used as useful markers of subclinical activity in Egyptian children with FMF [17].

In 2012, Sakallı et al. studied MPV levels in adult and pediatric patients with FMF, finding that FMF patients had significantly higher MPV levels compared to controls. Also, they observed that patients with proteinuria had higher MPV levels in both adult and pediatric FMF patients. Therefore, they concluded that constantly having higher MPV levels during the course of the disease, particularly in patients with proteinuria, may be a marker of ongoing increase in subclinical inflammation, which in turn leads to emergence of amyloidosis and increased proteinuria [20].

Contrary to previous studies, Yildirim Cetin et al. found that FMF patients had significantly lower MPV values compared to healthy controls. They concluded that low MPV levels can provide further information about subclinical inflammation in FMF patients, but they also stressed that other strong predisposing factors affecting subclinical inflammation in FMF should be considered [25].

Uluca et al. conducted another study on 75 FMF patients in attack, 157 attack-free patients, and 77 healthy controls, in which they determined that mean MPV and platelet distribution width (PDW) value were not significantly different between

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Table 1. Demographic and biochemical characteristics in AA, AA-FMF, and control groups.

Parameter	AA (Group 1) (n=63)	AA-FMF (Group 2) (n=36)	Control (Group 3) (n=29)	Group comparisons (p value)
Age (years)	51 (21–76)	47 (21–76)	48 (24–66)	G 1–3: 0.366 G 2–3: 0.444
Gender F/M (n)	29/34	19/17	21/8	G 1–3: 0.019 G 2–3: 0.108
MPV (fL)	9.3 (6.3–12.4)	9.4 (6.3–12.4)	9.5 (8–14.4)	G 1–3: 0.062 G 2–3: 0.122
PLT (×10³/mm³)	256 (99–657)	226.5 (99–527)	264 (130–389)	G 1–3: 0.782 G 2–3: 0.335
CRP (mg/dl)	1.32 (0.11–13.8)	1.61 (0.11–13.8)	0.33 (0.33–1.71)	G 1–3 < 0.0001 G 2–3 < 0.0001
ESR (mm/h)	63 (9–144)	60 (9–144)	5 (1–23)	G 1–3 < 0.0001 G 2–3 < 0.0001
BMI (kg/m²)	24.8 (15.4–30.4)	24.05 (15.4–30.4)	28.15 (22.8–36.7)	G 1–3 < 0.0001 G 2–3 < 0.0001
Creatinine (mg/dL)	1.5 (0.2–10.7)	1.38 (0.2–10.7)	0.68 (0.56–1.26)	G 1–3 < 0.0001 G 2–3 < 0.0001
Urea (mg/dL)	51 (19–208)	60.5 (19–208)	25 (14–62)	G 1–3 < 0.0001 G 2–3 < 0.0001
Total Protein (g/dL)	5.9 (3.47–8.2)	6.17 (4.16–8.2)	7.2 (6.3–8)	G 1–3 < 0.0001 G 2–3 < 0.0001
Albumin (g/dL)	3.2 (1.3–4.7)	3.5 (1.7–4.7)	4.6 (4.3–5)	G 1–3 < 0.0001 G 2–3 < 0.0001
WBC (×10³/mm³)	8.9 (3.4–21.4)	7.75 (3.4–21.4)	7 (3.9–11.6)	G 1–3 < 0.0001 G 2–3 < 0.0001
Hgb (g/dL)	11.7 (11.3–16.7)	11.1 (8.7–16.2)	13.8 (11.3–15.8)	G 1–3 < 0.0001 G 2–3 < 0.0001
Na (mg/dl)	139 (134–144)	139 (132–144)	138 (134–141)	G 1–3: 0.025 G 2–3: 0.060
K (mg/dl)	4.6 (3.8–6.1)	4.65 (3–6.1)	4.4 (3.8–5.2)	G 1–3: 0.078 G 2–3: 0.114
Ca (mg/dl)	8.7 (8.5–9.9)	9 (7.3–9.6)	9.5 (8.5–10.6)	G 1–3 < 0.0001 G 2–3 < 0.0001
P (ng/ml)	3.8 (2.2–8.9)	4 (2.6–8.9)	3.4 (2.2–4.2)	G 1–3: 0.001 G 2–3: 0.003
PTH (pg/ml)	71.3 (8.7–1109)	85 (11.6–1109)	46.95 (8.7–156.3)	G 1–3: 0.044 G 2–3: 0.024

MPV – mean platelet volume; PLT – platelet count; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; BMI – body mass index,; WBC – white blood cell count, Hgb – hemoglobin; Na – sodium; K – potassium; Ca – calcium; P – phosphorus; PTH – parathyroid hormone; G – group.

the groups [26]. Similar to the present study, we found that there was no statistically significant difference in MPV levels between AA-FMF patients and the control group.

Many studies have suggested the existence of a correlation between MPV levels and higher inflammatory disease activity. However, there are only a few studies in which the MPV levels were evaluated in FMF patients with AA amyloidosis. Erdem et al. studied MPV levels in AA patients, demonstrating that red cell distribution width (RDW), ESR, and PLT levels in AA patients were significantly higher than in healthy controls, and they also determined that MPV levels in AA patients

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Table 2. Correlations between various parameters and MPV in regard to groups.

	r	*p*
MPV and thrombocyte count		
AA patients	–0.364	0.003
AA-FMF patients	–0.381	0.022
Control	–0.476	0.009
MPV and proteinuria levels		
AA patients	–0.215	0.091
AA-FMF patients	–0.010	0.956
Control	NA	NA
MPV and CRP levels		
AA patients	–0.390	0.002
AA-FMF patients	–0.256	0.132
Control	–0.117	0.546
MPV and serum albumin levels		
AA patients	0.431	<0.001
AA-FMF patients	0.363	0.029
Control	–0.232	0.225
MPV and eGFR levels		
AA patients	0.055	0.671
AA-FMF patients	–0.074	0.668
Control	–0.197	0.306

MPV – mean platelet volume; CRP – C-reactive protein; NA – not applicable; eGFR – estimated glomerular filtration rate.

were lower than in controls. They concluded that low MPV and high RDW can be present in inflammatory disorders such as AA amyloidosis [27]. Also, Ozkayar et al. showed that AA patients had significantly lower MPV levels than in FMF patients and healthy controls [19]. Similar to these studies, we found that patients with AA had lower MPV levels compared to the AA-FMF and control groups. However, these differences were not statistically significant in our study. However, as MPV is considered as a marker of inflammation, the changes in its level may be associated with acute and chronic inflammatory activation due to other causes[28]. In the present study, CRP levels were significantly higher in the AA and AA-FMF groups compared to controls. However, we strictly excluded patients with acute or chronic infections and other diseases that can influenced inflammatory activity. Therefore, we believe the difference in CRP values are solely associated with the studied disease, and our results are not hampered by additional effects from other causes. The lower Hgb levels observed in AA and AA-FMF patients were also interesting, as the difference between these groups and controls were significant. However, AA amyloidosis is a known cause of anemia of chronic disease through effects of interleukins [29], while FMF patients suffer from anemia associated with iron status as well as treatment success with colchicine [30]. As such, considering that the anemia observed in the AA and AA-FMF groups is related to different mechanisms, we believe the similar decrease in Hgb values is not necessarily associated with MPV values. Nevertheless, these may be considered as limitations of the study, as we cannot provide conclusive evidence of the origin of the changes in CRP and Hgb levels.

To conclude, when taken as a whole, our findings do not support the suggestion of increased platelet activation in FMF, as we showed that MPV levels in AA-FMF patients were similar to those in healthy controls. The most remarkable finding of the present study was that the MPV levels in AA patients and AA-FMF patients were not significantly different from healthy controls.

Ozkayar et al. suggested that platelet count is negatively correlated with MPV values in AA patients, but there was no correlation between FMF and control groups [19]. In the present study, we determined a statistically significant negative correlation between thrombocyte count and MPV in all groups. These results support the view that there may be a negative correlation between MPV and thrombocyte count in patients with AA.

There were some limitations to this study. Firstly, the sample size of AA patients in our study was small. Secondly, this was a retrospective cross-sectional evaluation of patients from a single center, and therefore carries all the limitations inherent in such studies, which may limit the generalization of our findings. Thirdly, there are various other inflammatory parameters that may have been evaluated and compared to MPV values and this is an important limitation; however, our focus was to question the relevance of prior findings in terms of MPV levels and correlations that were reported in previous studies. We believe our findings address these questions, but future studies would benefit from inclusion of these parameters. Finally, although we enforced rigid inclusion and exclusion criteria, many other factors may have had an influence on platelet indices (and other parameters) and we cannot reliably exclude this possibility.

Conclusions

AA amyloidosis is a chronic inflammatory process. There are different views regarding the usefulness of MPV and PLT as indicators of inflammation in this patient group. The present study showed that there was no difference in terms of MPV

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values between healthy controls and patients who had AA amyloidosis with or without FMF. Our findings also demonstrated that there was no correlation between the MPV and proteinuria levels in patients with AA. These results are contrary to the majority of previous studies; however, the views regarding this topic also show stark contrasts from study to study. Therefore, further controlled clinical prospective trials are necessary to resolve this inconsistency.

Conflict of interest

Noe.

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