Mean platelet volume in familial Mediterranean fever related AA amyloidosis and comparison with common primary glomerular diseases

Abstract

Background/Aim:

Compared to healthy controls, mean platelet volume (MPV) is frequently higher in patients with Familial Mediterranean fever (FMF) but lower in AA amyloidosis patients. The reason for the difference in MPV levels in FMF patients with and without AA amyloidosis is unclear. The aim of the study was to determine whether low MPV is unique to AA amyloidosis or MPV is similarly low in all glomerular diseases as a result of proteinuria and/or renal dysfunction.

Materials and Methods:

We compared pre-biopsy MPV levels of patients with AA amyloidosis secondary to FMF, to MPV levels of patients with membranous glomerulonephritis, focal segmental glomerulosclerosis (FSGS) and IgA nephropathy that all present with proteinuria and renal dysfunction.

Results:

703 patients (411 male, 292 female) were included in the study. Mean age was 42.6±14.3 years. There were 124 patients with AA amyloidosis, 224 patients with IgA nephropathy, 188 patients with membranous glomerulonephritis and 167 patients with FSGS. Patients with AA amyloidosis had lower MPV levels compared to patients without AA amyloidosis (7.9±1.2 fL vs. 8.2±0.9 fL respectively, p=0.008). Patients with AA amyloidosis had significantly lower MPV compared to patients with each of the other diagnoses. Independent predictors of MPV were platelet count ($\beta = -0.321$, $p < 0.001$) and CRP ($\beta = -0.134$, $p < 0.03$).

Conclusion:

This study is the largest study of MPV in patients with biopsy proven AA amyloidosis and confirms previous studies reporting low MPV in AA amyloidosis. This study indicates that low MPV in AA amyloidosis cannot be explained with proteinuria and renal dysfunction.

Keywords: AA Amyloidosis, familial Mediterranean fever, glomerulonephritis, mean platelet volume

1. Introduction

Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by self-limiting recurrent attacks of fever, serositis and arthritis [1,2]. It is prevalent in Turks, Jews, Armenians and Arabs [3]. Colchicine and anti-interleukin 1 drugs are the main treatment options and prevent both the symptomatic attacks and also the development of AA amyloidosis [4,5]. Once amyloidosis develops in untreated or drug-resistant patients, the course is characterized by severe nephrotic syndrome and progressive renal dysfunction leading to end stage renal disease.

Mean platelet volume (MPV) is routinely reported during complete blood count examinations and regarded as a marker of platelet function and activity [6]. Since inflammation has a direct effect on platelet reactivity and platelet volume, MPV had been widely evaluated in patients with FMF. However, there are discrepancies among the results of the studies. Although most of the studies revealed higher MPV levels in FMF patients compared to the control group [7-12], some other studies reported similar [13,14] or even lower MPV levels in FMF patients [15, 16].

On the other hand, previous studies consistently revealed lower MPV levels in patients with FMF related AA amyloidosis compared to FMF patients without AA amyloidosis or healthy controls [10,17]. The cause of differing MPV levels in FMF patients with and without AA amyloidosis and also mechanism of low MPV in AA amyloidosis is not clear.

Since the most striking clinical differences in FMF patients with and without AA amyloidosis are renal dysfunction and severe proteinuria that is commonly in the nephrotic range, we hypothesized that these parameters could be responsible from low MPV in patients with FMF related AA amyloidosis in contrast to FMF patients without AA amyloidosis. Therefore, we aimed to determine whether low MPV is unique to AA amyloidosis or MPV is similarly low in commonly seen glomerular diseases including membranous glomerulonephritis, focal segmental glomerulosclerosis (FSGS) and IgA nephropathy that all present with proteinuria and renal dysfunction.

2. Materials and methods

In this retrospective study we evaluated the reports of all kidney biopsies performed in Hacettepe University Medical Faculty Nephrology Department between 1 January 2001 and 1 January 2018. The patients who were > 18 years old at the time of biopsy and diagnosed with membranous glomerulonephritis, FSGS, IgA nephropathy or AA amyloidosis secondary to FMF as a result of these biopsies were included in the study. Patients with more than one diagnoses in renal biopsy examinations were excluded. Patients under any immunosuppressive

treatment including patients with a previous diagnosis of glomerulonephritis that underwent control biopsy were also excluded. Diagnosis of FMF was made according to the Tel-Hashomer criteria [2].

A total of 703 patients were included in the analysis. In addition to demographic parameters and pathological diagnosis; hemoglobin, leukocyte, thrombocyte values and MPV levels measured in complete blood counts taken before the procedure on the morning of biopsy, and the most recent serum creatinine, albumin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and 24-hour urine protein values before biopsy were recorded from the database system of the hospital. Complete blood count examinations had been performed on samples anticoagulated with ethylenediamine tetraacetic acid (EDTA). Samples had been studied within 2 hours after sampling to prevent time-dependent swelling of platelets that may be caused by EDTA. The duration and dose of colchicine and anti-IL-1 treatments for patients with FMF were recorded.

MPV and other laboratory parameters were compared between patients with AA amyloidosis and patients with membranous glomerulonephritis, FSGS and IgA nephropathy. Factors affecting MPV were also determined.

Statistical Package of Social Sciences (SPSS) version 20 was used for statistical analyses. Distribution characteristics of the variables were analyzed with Kolmogorov-Smirnov test. Data were expressed as mean±standard deviation, standard deviation, median and 25th–75th interquartile range or numbers and percentages. Comparisons were performed with Chi-square test for categoric variables. For comparison of continuous variables between two groups, independent-samples t-test and Mann-Whitney U tests were used. Pearson and Spearmen tests were used for correlation analyses. A linear regression analysis was introduced to determine the independent predictors of MPV. The capacity of MPV values in predicting presence of AA amyloidosis was analyzed using ROC (Receiver Operating Characteristics) curve analysis. P values < 0.05 were considered statistically significant.

3. Results

The mean age of the 703 patients that was included in the study was 42.6±14.3 years. There were 411 male and 292 female patients. The distribution of number of the patients with regard to the biopsy diagnoses were as follows: FMF related AA amyloidosis 124 patients, IgA nephropathy 224 patients, membranous glomerulonephritis 188 patients and FSGS 167 patients. Demographic characteristics and laboratory values of the patients according to the biopsy diagnoses are presented in Table 1.

Mean age of the patients with AA amyloidosis was similar to patients with membranous glomerulonephritis but significantly higher compared to patients with FSGS and IgA nephropathy. Female patients were more prevalent in FSGS group but the majority of the patients were male in other groups. In AA amyloid group compared to other groups, mean hemoglobin level was significantly lower and mean leucocyte and platelet counts were significantly higher. Mean creatinine level of patients with AA amyloidosis was significantly higher compared to patients with FSGS and membranous glomerulonephritis but similar to patients with IgA nephropathy. Mean proteinuria level of patients with AA amyloidosis was similar to patients with FSGS and membranous glomerulonephritis but higher than patients with IgA nephropathy. Serum albumin level of patients with AA amyloidosis was similar to patients with membranous glomerulonephritis but significantly lower compared to patients with FSGS and IgA nephropathy. ESR and CRP values were significantly higher in patients with AA amyloidosis compared to other groups.

Patients with AA amyloidosis (n= 124) had significantly lower MPV compared to patients without AA amyloidosis (n= 579) (7.9±1.2 fL vs. 8.2±0.9 fL respectively, p=0.008). Patients with AA amyloidosis had also significantly lower MPV compared to patients with each of the other diagnoses (Table 1). Among the AA amyloid group, 29 patients had previous diagnosis of FMF and all of them were under colchicine treatment at the time of biopsy while remaining 95 patients had no previous diagnosis of FMF and hence was not using colchicine. Although patients that were using colchicine at the time of biopsy had higher MPV levels compared to patients not using colchicine, the difference was not statistically significant (8.0±1.0 fL vs. 7.8±1.3 fL respectively, p=0.506). No patient was using anti IL-1 treatment at the time of biopsy in the AA amyloidosis group.

Female patients had higher MPV compared to male patients (8.2±1.0 fL vs. 8.1±1.0 fL respectively, p=0.04). In the whole study population MPV was negatively correlated with platelet count ($r = - 0.351$, $p < 0.001$). This correlation was still present when patients with different diagnoses were evaluated separately and was the most prominent in AA amyloidosis group (Table 2). MPV levels were also negatively correlated with ESR ($r = - 0.162$, $p = 0.001$) and CRP ($r = - 0.160$, $p = 0.007$). There was no significant correlation of MPV with other laboratory parameters including hemoglobin, leucocyte, creatinine, serum albumin and proteinuria levels. A linear regression analysis revealed that independent predictors of MPV were platelet count ($\beta = - 0.321$, $p < 0.001$) and CRP ($\beta = - 0.134$, $p < 0.03$).

ROC analysis for MPV showed that the area under the curve was 0.60, 95% confidence interval: 0.54-0.66, p = 0.001, and the cut-off value of ≤8.1 fL had a sensitivity of 62.1% and a specificity of 54.2% to predict AA amyloidosis.

4. Discussion

This study confirmed the previous results of the studies that reported low MPV in patients with AA amyloidosis secondary to FMF in a much larger sample size. Furthermore, low MPV could not be explained with severe proteinuria or low glomerular filtration rate (GFR) in AA amyloidosis, as patients with AA amyloidosis had significantly lower MPV levels when compared to patients with different types of glomerulonephritis with similar proteinuria or GFR.

Few studies have previously investigated MPV levels in AA amyloidosis and all concluded that MPV is low in AA amyloidosis [10,17]. Erdem et al. included 33 AA amyloidosis patients with different etiologies and compared MPV levels in AA amyloidosis patients with control group. Mean MPV was 7.4 fL in AA amyloidosis group and 8.4 fL in the control group ($p < 0.0001$) [17]. Ozkayar et al. compared MPV levels of 29 patients with AA amyloidosis secondary to FMF with MPV levels in amyloid negative FMF patients and control subjects. Mean MPV of AA amyloid group was significantly lower (6.9 fL) compared to amyloid negative FMF patients (10.2 fL) and control group (9.2 fL) ($p<0.001$ for both comparisons) [10]. Neither of these studies had investigated the association between MPV levels and amount of 24-h proteinuria. In another study Sakalli et al reported higher MPV in patients with proteinuria compared to patients without proteinuria however authors did not specifically disclose MPV levels in patients with and without AA amyloidosis [7]. In a small sample size study investigating the effect of renal function on MPV in AA amyloidosis, no significant relationship was found between MPV and GFR [13]. In our study with the largest sample size that included 124 AA amyloidosis patients and a total of 703 patients with glomerulonephritis, we did not observe a correlation between MPV and proteinuria or renal function in AA amyloidosis group and in whole study population.

The results of this study indicate that there should be other mechanisms responsible from low MPV in AA amyloidosis rather than proteinuria or renal functions. Previously some authors argued that severe inflammation might be directly responsible from low MPV. IL-6, one of the main inflammatory mediators in FMF [18-20] is the most widely studied inflammatory marker for MPV and have a clear effect on stimulating thrombocytosis and decreasing MPV considering the inverse relation between platelet count and MPV yielding a constant mass of platelet [21,22]. Clarke et al, revealed that when recombinant IL-6 is administered

subcutaneously to patients with advanced malignancy to stimulate thrombopoiesis, platelet numbers reached to a peak level at the end of second week with accompanying decrease in MPV about 10% [21]. Similarly van Gameren et al, observed increased platelet counts and a decrease in mean MPV value from 8.3 fL to 7.1 fL in patients with breast and lung cancer with IL-6 treatment [22]. IL-1 and TNF-alpha are the other inflammatory markers that affect platelet size and number [23,24]. Anti-TNF-alpha treatments result in significant increase in MPV levels in inflammatory conditions [25]. MPV was found to be negatively correlated with ESR and CRP in patients with rheumatoid arthritis and inflammatory bowel disease [26,27]. However, the largest study about the relation between MPV and CRP come from a population study of National Health and Nutrition Examination Survey (NHANES) data in 16.329 subjects revealing a significant negative correlation between MPV and CRP [28].

In this study we also observed that patients with AA amyloidosis had significantly higher CRP levels compared to patients with other glomerular diseases and in multivariate analysis CRP was one of the few parameters that predict the MPV levels. We observed that patients with AA amyloidosis had significantly lower hemoglobin levels and higher leucocyte and platelet counts compared to other groups. The high platelet count in AA amyloidosis patients together with the negative correlation between platelet count and MPV in this current study strengthens the hypothesis that inflammatory markers stimulate thrombopoiesis and result in low MPV. Another probable explanation of low MPV in inflammation may be related to consumption of large active platelets in the inflammation sites like vessel walls and serosal membranes leading to decreased MPV levels of circulating platelets in inflammatory diseases like FMF [16,23,29]. However, these hypotheses do not explain why most of the studies report high MPV in FMF patients without AA amyloidosis. In this regard the effect of colchicine on MPV should be considered. It is known that colchicine has the potential to increase MPV [30]. It is possible that low MPV in patients with AA amyloidosis, which is a result of ongoing inflammation, can be explained by severe inflammation. However, the MPV increasing effect of colchicine may be more pronounced compared to the MPV lowering effect of inflammation in patients with FMF without severe inflammation and no accompanying AA amyloidosis. In our study AA amyloidosis group included 29 patients that already had a diagnosis of FMF and using colchicine at the time of biopsy, in addition to 95 subjects that underwent renal biopsy for nephrotic syndrome and had no previous diagnosis of FMF and usage of colchicine. Although we observed higher MPV levels in patients under colchicine treatment, this difference did not reach statistical significance probably as a result of low number of these subjects. In this regard

it will be interesting to determine the changes in MPV values after the introduction of colchicine and anti Il-1 treatments in future studies.

The main limitation of this study is related with retrospective design which leads to lack of reliable data about several parameters which have the potential to affect MPV. These parameters are co-morbid conditions like type 2 diabetes mellitus, acute coronary syndromes, moderate-to-severe valvular heart disease, smoking status, hypertension, hypercholesterolemia, liver diseases, obesity, the metabolic syndrome, hematological diseases, malignancy, acute and chronic infections, stroke and usage of statins and antihypertensive drugs. However, since the study was conducted in large patient population with similar demographic characteristics and laboratory values in each group, we believe that these factors are evenly distributed among the groups.

In conclusion despite the limitation stated above, this study is the largest study of MPV in patients with biopsy proven FMF related AA amyloidosis and confirms previous studies reporting low MPV in AA amyloidosis. This study clearly indicates that low MPV cannot be explained with severe proteinuria and impaired renal function. Considering the low hemoglobin, high platelet counts and high levels of inflammatory markers in AA amyloidosis, the low MPV is probably related with the direct effect of inflammation on bone marrow.

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Table 1. Demographic characteristics and laboratory values of the patients at the time of biopsy according to the biopsy diagnoses

	FMF Related AA Amyloidosis (n= 124)	Focal Segmental Glomerulosclerosis (n=167)	Membranous Nephropathy (n= 188)	IgA Nephropathy (n= 224)
Age (years)	46.3±15.4	40.1±14.1 (p < 0.001)	47.8±14.4 (p = 0.393)	38.1±11.8 (p < 0.001)
Males (n,%)	80 (64.5)	77 (46.1) (p=0.002)	104 (55.3) (p=0.126)	150 (67.0) (p=0.723)
Hemoglobin (g/dL)	11.9±2.3	12.9±2.1 (p = 0.001)	13.3±2.0 (p < 0.001)	13.0±2.0 (p < 0.001)
Leucocyte (x10^9/L)	9.3±3.1	8.3±2.5 (p = 0.001)	7.9±2.6 (p < 0.001)	8.0±2.2 (p < 0.001)
Platelet (x10^9/L)	357.3±125.5	277.6±83.0 (p < 0.001)	278.6±79.7 (p < 0.001)	246.6±70.0 (p < 0.001)
Creatinine (mg/dL)	2.03±2.41	1.48±1.35 (p= 0.02)	1.05+0.94 (p < 0.001)	1.86±1.49 (p = 0.458)
Albumin (g/dL)	2.47±0.89	3.31±0.98 (p < 0.0001)	2.66+0.72 (p= 0.04)	3.81±0.60 (p < 0.001)
Proteinuria (mg/day)	6161±5426	4678±7569 (p = 0.07)	7054±11377 (p = 0.435)	2488±2083 (p < 0.001)
ESR (mm/hour)	62.1±34.6	38.3±32.8 (p < 0.001)	38.7±27.0 (p < 0.001	28.0±25.9 (p < 0.001)
CRP (mg/dL)	1.91[0.88-6.34]	0.47[0.28-0.90] (p < 0.001)	0.31[0.22-0.63] (p < 0.001)	0.54[0.28-1.52] (p < 0.001)
MPV (fL)	7.9±1.2	8.2±0.9 (p = 0.01)	8.1±1.0 (p = 0.04)	8.3±0.9 (p = 0.001)

P values demonstrate the difference between AA amyloid group and other groups.

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, FMF: Familial Mediterranean fever, MPV: Mean platelet volume

Table 2. Correlation between platelet count and mean platelet volume at the time of biopsy according to the biopsy diagnoses

	r value	p value
Whole group	- 0.351	<0.001
AA Amyloid group	- 0.408	< 0.001
FSGS group	- 0.314	< 0.001
Membranous nephropathy group	- 0.336	< 0.001
IgA nephropathy group	- 0.237	< 0.001

FSGS: Focal segmental glomerulosclerosis