

Pan-immune-inflammation value in FMF patients

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ABSTRACT

Objective: Familial Mediterranean fever (FMF) is the most common disease that leads to secondary amyloidosis related to persistent subclinical inflammation in Turkish patients. Pan-immune-inflammation value (PIIV), a recently-developed index validated to predict prognoses of several malignancies. We investigated PIIV in FMF patients.

Material and Methods: We included 100 FMF patients with regular follow-ups, defined as at least two visits yearly. Demographic characteristics, prominent attack features, and treatment choices of the patients were noted. We also calculated PIIV and other inflammation-related laboratory results at attack-free periods. In the comparative analysis of quantitative data, Student's t-test (for normal distribution) and the Mann-Whitney U test (for non-normally distribution) were used. P <0.05 was accepted as a statistically significant value.

Results: A total of 100 patients were included in the study. Forty-two patients were male, whereas fifty-eight patients were female. The patients were between 18 and 69 years old, and the mean age of the study group was 39.65 ± 13.83 years. MEFV mutation analyses of eighty-six patients were present in the medical record system. Exon 10 mutations were detected in 67 (77.9%) patients, whereas non-exon 10 mutations (exon 2 and 3) were in 8 (9.3%) patients. Homozygous Exon 10 mutations were detected in 19 patients (22.1%). Although acute phase reactants, including erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), and serum amyloid A (SAA), were significantly higher in patients with homozygous exon 10 mutations, there was no statistical difference in PIIV between groups.

Conclusion: The results were also similar to the recent literature in the northern part of the country. The need for biological agents and male gender was significantly higher in patients with homozygous exon 10 mutations compared to other groups.

Keywords: familial Mediterranean fever, Pan-immune-inflammation value, subclinical inflammation

INTRODUCTION

Familial Mediterranean fever (FMF) is an autoinflammatory disease symbolised by periodic serositis and fever attacks (1). FMF is frequently seen in individuals of Turkish, Armenian, Jewish, and Arab descents (2). Although regional prevalences have been differently reported in our country, a higher incidence rate (0.82%) was obtained in Tokat and the surrounding region in the North part of Turkey (3).

Amyloidosis is the most severe complication of FMF, especially in patients with persistent subclinical inflammation. It is well known that patients with amyloidosis have a worse prognosis and increased mortality risk due to chronic kidney disease (4). Although the certain pathophysiological mechanisms are unknown, persistent subclinical inflammation in attack-free periods has been emphasized as a main culprit factor for the development of amyloidosis (5).

Pan-immune-inflammation value (PIIV) is a recently-developed index calculated from the complete blood count. PIIV is derived from four blood cell counts, including neutrophils, platelets, monocytes, and lymphocytes, and shows the severity of inflammation. Higher values were related to increased death and progression rates. It has an expanding interest in predictive scores of variable malignancies (6). The PIIV is validated as a strong predictor of survival in patients with metastatic diseases (7).

Recently, PIIV has also been investigated in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV) (8). The authors showed a lower survival rate in AAV patients with the highest baseline PIIV values. We investigated PIIV as a simple and cheap tool derived from commonly performed blood cell counts as a possible prognostic index in these patients at attack-free periods.

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MATERIAL and METHODS

This study was conducted following the Declaration of Helsinki and local Ethical Committee approval (Ethical Review Board date/number, 2023/08).

A total of 100 patients followed by us in a tertiary center, were included in the study. All patients were diagnosed with Familial Mediterranean Fever following the Tel Hashomer criteria (9). Demographic features of patients, including age, gender, detailed prominent attack characteristics (serositis, arthritis/arthralgia, and fever), treatment choices, and Mediterranean fever (MEFV) mutations (if available) were obtained.

We investigated inflammation biomarkers including erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), serum albumin, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and PIIV in these patients. We noted all these results and indexes in the attack-free periods.

Inclusion criteria: having at least two clinical evaluations per year and patients aged with above 18 years

Exclusion criteria: having other autoimmune and autoinflammatory diseases, chronic infectious diseases.

PIIV was calculated as follows: neutrophil count ($\times 1000/\text{m}^3$) $\times$ monocyte count ($\times 1000/\text{m}^3$) $\times$ platelet count ($\times 1000/\text{mm}^3$) / lymphocyte count ($\times 1000/\text{m}^3$) (7).

Statistical analysis: Statistical Package for the Social Sciences (SPSS) 23.0 statistical program was used for the analysis. Demographic data such as age and gender and the laboratory analysis of the patients were evaluated with descriptive statistical methods. The Mean, standard deviation, median, minimum-maximum, frequency, and ratio (%) values were used. Normal distribution of Quantitative variables; if $n > 50$ was evaluated with the Kolmogorov-Smirnov test, if $n < 50$ with the Shapiro-Wilk test. In the comparative analysis of quantitative data, Student's t-test (for normally distribution) and the Mann-Whitney U test (for non-normally distribution) were used. The chi-square test was used in the analysis of qualitative data. $P < 0.05$ was accepted as statistically significant value.

RESULTS

A total of 100 patients were included in the study. Forty-two patients were male, whereas fifty-eight patients were female. The patients were between 18 and 69 years old, and the mean age of the study group was 39.65 ± 13.83 years. MEFV mutation analyses of eighty-six patients were present in the medical record system. Exon 10 mutations were detected in 67 (77.9%) patients, whereas non-exon 10 mutations (exon 2 and 3) were in 8 (9.3%) patients. Homozygous exon 10 mutations were present in 19 patients (22.1%). The distribution of the genetic analyses was grouped in **Table 1**.

Serositis (abdominal pain and rarely chest pain) was present in all patients ($n=100$) following by fever in 39 patients. Arthritis has been detected in 15 patients, and skin findings (erysipeloid skin rash) were present in seven patients. Only six patients have received biological agents in addition to colchicine. Two were on canakinumab treatments, whereas the other four were on anakinra treatment due to insufficient response to colchicine treatment. Amyloidosis was not present in any patient. Acute phase reactants, including erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), and serum amyloid A (SAA), and total daily colchicine dose were significantly higher in patients with homozygous exon 10 mutations compared with other patients.

The necessity for biological agents and male gender were significantly higher in patients with homozygous exon 10 mutations compared with other groups.

Table 1. Distribution of the genetic analyses of the whole study group.

MEFV Mutations	n (%)
M694V Heterozygous	28 (32,6)
M694V Homozygous	17 (19,8)
M680I Heterozygous	4 (4,7)
M680I Homozygous	2 (2,3)
V726A Heterozygous	3 (3,5)
E148Q Heterozygous	3 (3,5)
R202Q Homozygous	1 (1,2)
P369S Heterozygous	3 (3,5)
M694V + V726A Heterozygous	6 (7)
M694V + M680I Heterozygous	5 (5,8)
M680I + V726A Heterozygous	1 (1,2)
M694V + P369S Heterozygous	1 (1,2)
Absence of MEFV mutation	12 (14)

Table 2. Comparison of the patients in different terms whether having homozygous exon 10 mutations or not.

VARIABLES	Homozygous Exon 10 Mutations				p
	n	Present Median (Min - Max) or Mean $\pm$ SD	n	Absent Median (Min - Max) or Mean $\pm$ SD	
Age (years)	19	48 (18 - 69)	67	36 (18 - 65)	0.059
Colchicine dose (mg/day)	19	1 (0 - 2)	67	1 (0 - 2)	0.026
ESR (mm/h)	18	29 (3 - 95)	66	18 (2 - 58)	0.016
CRP (mg/L)	18	10.8 (0.6 - 137.1)	66	2.6 (0.1 - 39.5)	0.001
SAA (mg/L)	11	63.8 (6.2 - 550)	27	9.4 (2.5 - 418)	0.014
WBC ($\times 10^9/\text{L}$)	18	7 (4.7 - 11.4)	61	7.1 (3.8 - 12.6)	0.462
Neutrophil ($\times 10^9/\text{L}$)	18	4.3 (2.6 - 7.3)	61	4.5 (2.2 - 9.1)	0.925
Lymphocyte ($\times 10^9/\text{L}$)	18	1.92 $\pm$ 0.68	61	2.09 $\pm$ 0.59	0.303
Monocyte ($\times 10^9/\text{L}$)	18	0.415 (0.14 - 0.89)	61	0.39 (0.16 - 1.16)	0.447
Thrombocyte ($\times 10^9/\text{L}$)	18	250.3 $\pm$ 64	61	273.4 $\pm$ 65	0.189
PIIV	18	249.4 (59.3 - 715.9)	61	203.1 (70 - 2225.7)	0.640
NLR	18	2.34 (1.26 - 6.16)	61	2.13 (0.84 - 9.11)	0.362
PLR	18	129 (69 - 320)	61	130 (70 - 293)	0.944

ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein, SAA: Serum Amyloid A, WBC: White Blood Cell, PIIV: panimmune inflammation value, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio.

Table 3. Comparison of variables according to the presence of homozygous exon 10 mutations.

VARIABLES		Homozygous Exon 10 Mutation		P
		Present n (%)	Absent n (%)	
Gender	Male	13 (34.2)	25 (65.8)	0.032
	Female	6 (12.5)	42 (87.5)	
Biologic agents	(+)	4 (21.1)	2 (3)	0.020
	(-)	15 (78.9)	65 (97)	
Arthritis	(+)	4 (21.1)	11 (16.4)	0.733
	(-)	15 (78.9)	56 (83.6)	
Fever	(+)	8 (42.1)	24 (35.8)	0.817
	(-)	11 (57.9)	43 (64.2)	
Erysipeloid skin rash	(+)	2 (10.5)	4 (6)	0.610
	(-)	17 (89.5)	63 (94)	

DISCUSSION

Regarding rheumatic diseases, authors recently found an association between high PIIV values and worse prognosis in patients with AAV (10). Lee LE et al. reported a cut-off value for PIIV in their study. The patients with having PIIV $\geq$ 1011.3 at diagnosis, had a lower survival rate. In our study PIIV was similar in the patient subgroups according to MEFV gene mutations. However, we calculated the index at the attack-free periods in addition to NLR, PLR, ESR, CRP, and serum amyloid A. In another study, NLR and PLR were compared in patients with in attack period and in attack-free periods. There was no difference between different mutations concerning NLR or PLR levels in the attack-free periods (11).

The stunning result of the study was that the patients with homozygous exon-10 mutations had higher inflammatory values despite of attack-free periods. In support of this finding, a recent observational study revealed that the presence of homozygous exon 10 mutation was associated with high SAA in attack-free period (12). However, it's also known that homozygous exon 10 mutations is not the only factor. Corsia A et al. showed that low adherence to colchicine is one of the reasons for subclinical inflammation in severe MEFV genotypes (13). However, in our study, daily colchicine doses were significantly higher in patients with homozygous exon-10 mutations in addition to proinflammatory mediators. In a large cohort in which the MEFV mutations were explored in Turkish patients, M694V homozygosity was present in 24% of all patients, and next to half of the patients were detected to have at least one M694V mutation (14). Our analysis also has similar results related to recent literature in terms of genotype distribution (M694V homozygous n=17 (19.8%), M694V heterozygous n=40 (46.6%)).

Colchicine is still the mainstay of treatment. No more effective alternative treatment modality than colchicine was present among resistant cases. Successful daily treatment of FMF patients with colchicine may prevent the development of renal amyloidosis and stabilise or improve renal function for those with amyloidosis (15). There are a few limitations of the study. Firstly, this is a single-center experience. Although Giresun is one of the most disease-seen cities, a relatively small study size is present. The PIIV was calculated in attack-free periods. The mentioned index was not compared with patients who are in attack periods or control study population. The reason was the presence of few patients in the attack periods..

CONCLUSION

Inflammatory markers, including ESR, CRP, and serum amyloid A, were higher in patients with homozygous exon 10 mutations. These markers may help us prioritize patients needing more intensive drug maintenance and closer monitoring for amyloidosis.

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Ethical approval: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions.

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