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Associations between M-protein and bone marrow fibrosis in newly diagnosed multiple myeloma

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ABSTRACT

Objectives: Myelofibrosis may occur as a primary condition or secondary to several malignant or non-malignant conditions. Multiple myeloma (MM) is a malignant condition in which collagen fibrosis and reticulin fibrosis may coexist. This study aimed to investigate the prevalence of bone marrow fibrosis in newly diagnosed MM and potential associations between serum M-protein concentrations and bone marrow fibrosis.

Material and Methods: Ninety patients with newly diagnosed MM were retrospectively assessed in this study. Demographic characteristics, blood counts, blood biochemistry, bone marrow plasma cell percentage, and bone marrow fibrosis grades were recorded.

Results: The bone marrow plasma cell percentage was ≥50% in 34.4% of patients and <50% in 65.6% of patients. The bone marrow plasma cell percentage was found to be 55% in the high fibrosis group and 42% in the low fibrosis group ($P = 0.04$). Bone marrow fibrosis was detected at a high level in 23.3% of the patients. No statically significant differences were found between the high fibrosis group and the low fibrosis group in the parameters, including age, sex, the type of myeloma, hemoglobin concentrations and platelet counts at diagnosis, β2 microglobulin, lactate dehydrogenase, disease stage, and erythrocyte sedimentation rate that were assessed in the study ($P > 0.05$). A statically significant association was found between lower fibrosis levels and higher Ig M and serum kappa levels and serum kappa/lambda ratio ($P = 0.02$, $P = 0.03$, and $P = 0.03$, respectively).

Conclusion: In this study, significant correlations were found between low-grade bone marrow fibrosis to high IgM and the kappa/lambda ratio. In conclusion, in this study, it was shown that bone marrow fibrosis in MM differs according to subtypes.

Keywords: M-protein, Bone marrow fibrosis, Multiple myeloma

INTRODUCTION

Myelofibrosis may be a primary condition or may occur as a pathological condition secondary to malignant or nonmalignant diseases. Collagen, reticulin, laminin, and fibronectin are the most commonly found structural fibers in the bone marrow.[1] The bone marrow collagen primarily includes Type I and Type III. The development of bone marrow fibrosis requires several cytokines released by megakaryocytes and platelets. Platelet-derived transforming growth factor β, epidermal growth factor, and the endothelial cell growth factor is potent stimulants of fibroblast proliferation, in particular.[2]

Multiple myeloma (MM) is a malignant condition characterized by uncontrolled clonal expansion of plasma cells in the bone marrow and is among the conditions that may be accompanied by bone marrow fibrosis. A generalized myelofibrosis consisting of collagen fibrosis along with reticulin

fibrosis may be seen in MM.[1,3] The presence of M-protein is the most typical feature of MM. Monoclonal protein can be detected in 97% of sera from patients with MM.[4,5]

The goal of this study was to investigate the prevalence of bone marrow fibrosis in newly diagnosed MM and the potential associations between serum M-protein concentrations and bone marrow fibrosis.

MATERIAL AND METHODS

This study included 90 patients who attended our Hematology Outpatient Clinics and were diagnosed with MM based on International Myeloma Working Group (IMWG) criteria, between January 2015 and March 2018. Demographic characteristics, blood counts, blood biochemistry, bone marrow plasma cell rates, and bone marrow fibrosis grades were recorded retrospectively. Bone marrow fibrosis was graded based on European Consensus on grading bone marrow fibrosis.[6]

Using the European Consensus on the grading of bone marrow fibrosis, 90 cases were classified as miyelofibrosis 0–3. Myelofibrosis in the bone marrow was defined as 0–1 low fibrosis and 2–3 high fibrosis groups. Patients were divided into two groups according to their bone marrow fibrosis at diagnosis with European Consensus on grading bone marrow fibrosis criteria. There were 69 patients in the low myelofibrosis group and 21 patients in the high myelofibrosis group.

All of the ethical considerations had been strictly followed in accordance with the principles of the Helsinki Declaration.

Statistical analysis

A Statistical Package for the Social Sciences (version 20) for Windows software was used for statistical analyses. Percentage change ratios were used for correlation analysis. $P < 0.05$ was considered statistically significant, with a confidence interval of 95%. Pearson correlation analysis was performed and the Student's *t*-test and Mann–Whitney U test were used for intergroup comparisons.

RESULTS

This study included 90 patients who attended the hematology department and were diagnosed with MM based on IMWG criteria and continued follow-up assessments between January 2015 and March 2018. Forty-one of the patients were female (45.6%) and 49 were male (54.4%) with an average age of 67 years (age range: 37–86 years).

A serum protein electrophoresis was performed in every study patient and the highest M protein concentration measured in study patients was 18 g/dL.

Regarding the type of myeloma; 28 patients (31.1%) had IgG kappa, 22 patients (24.4%) had IgG lambda, 20 patients (22.2%) had IgA kappa, 6 patients (6.6%) had IgA lambda, 4 patients (4.4%) had IgM kappa, 3 patients (3.3%) had IgM lambda, 6 patients (6.7%) had lambda light chain, and 1 patient (1.1%) had kappa light chain paraproteinemia. None of the patients had non-secretory myeloma.

An immunofixation electrophoresis test was performed at diagnosis on samples of 24-h urine from every study patient. Twenty-seven patients (30%) tested positive for kappa and 27 patients (30%) tested positive for lambda whereas 36 patients (40%) tested negative in 24-h urine immunofixation electrophoresis.

The mean β2 microglobulin level was 5.3 mg/L with the lowest β2 microglobulin level of 2.1 mg/L and the highest β2 microglobulin level of 29.7 mg/L. Twenty-four patients (26.7%) were Stage I, 33 (36.7%) were Stage II, and 33 (36.7%) were Stage III based on the R-ISS staging system.

The study patients were divided into two groups: The low fibrosis group which included patients with Grade 0–1 fibrosis and the high fibrosis group which included patients with grade 2–3. The low fibrosis group included 69 patients (76.7%) and the high fibrosis group included 21 patients (23.3%). Fibrosis was not detected in 23 patients in the low fibrosis group who was considered as having Grade 0 fibrosis whereas 9 (10%) patients had Grade 3 fibrosis.

The lowest hemoglobin concentration was 5.8 g/dL and the highest hemoglobin concentration was 14.6 g/dL at diagnosis. Hemoglobin concentrations were <10 g/dL in 49 (54.4%) patients.

The lowest platelet count was 48,000/mm^3 and the highest platelet count was 420,000/mm^3. Platelet counts were <100,000/mm^3 in 8 (8.8%) patients.

The bone marrow plasma cell percentage was ≥50% in 31 (34.4%) patients and <50% in 59 (65.6%) patients.

No statically significant differences were found between the high fibrosis group and low fibrosis group in study parameters including age, sex, the type of myeloma, hemoglobin concentrations and platelet counts, β2 microglobulin, lactate dehydrogenase (LDH), and erythrocyte sedimentation rate at diagnosis ($P > 0.05$, for all). Statically significant associations were found between lower levels of fibrosis and higher IgM and serum kappa levels and serum kappa/lambda ratio ($P = 0.02$, $P = 0.03$, and $P = 0.03$, respectively). The bone marrow plasma cell percentage was 55% in the high fibrosis group and 42% in the low fibrosis group and the intergroup difference was found to be statistically significant ($P = 0.04$). No statistically significant was found between the disease stage and the level of myelofibrosis ($P > 0.05$) [Table1].

Table 1: Associations between the grade of bone marrow fibrosis and other parameters.

	Low myelofibrosis group (*n*=69)	High myelofibrosis group (*n*=21)	*P*-value
Age	64±9	68±10	0.12
Sex			
Female	35 (50.7%)	6 (28.5%)	0.07
Male	34 (49.3%)	15 (71.5%)	
Myeloma type			
IgG/kappa	21 (30.4%)	7 (33.3%)	0.25
IgG/lambda	15 (21.7%)	7 (33.3%)	
IgA/kappa	16 (23.2%)	4 (19%)	
IgA/lambda	4 (5.8%)	2 (9.5%)	
IgM/kappa	4 (5.8%)	0	
IgM/lambda	3 (4.3%)	0	
Kappa	1 (1.4%)	0	
Lambda	5 (7.4%)	1 (4.9%)	
Average paraprotein (g/dL)			
IgG	2206	2992	0.2
IgA	1134	1173	0.94
IgM	186	49	0.02
Serum Kappa	809	86	0.03
Serum Lambda	14	156	0.09
Serum Kappa/lambda	1351	15	0.03
Urine Kappa	383	247	0.42
Urine Lambda	271	458	0.29
Urine Kappa/lambda	91	55	0.37
At diagnosis			
Hemoglobin (g/dL)	9.9±1.7	9.2±1.7	0.14
Average platelet count (mm^3)	233,000	205,000	0.25
Average β2 microglobulin (mg/L)	5.3	4.9	0.62
Average lactate dehydrogenase (U/L)	179	205	0.21
Average erythrocyte sedimentation rate	107	107	0.90
Bone marrow plasma cell persentage	42%	55%	0.04
Stage (R-ISS)			
I	17 (24.6%)	7 (33.3%)	0.97
II	28 (40.5%)	5 (23.8%)	
III	24 (34.9%)	9 (42.9%)	

DISCUSSION

The increased amount of connective tissue in the bone marrow and its prognostic significance in patients with MM was first demonstrated by Vandermolen *et al.*[7] The development of fibrosis resulting from cytokine release is of paramount importance considering its prognostic significance. Myelofibrosis has been linked to poor prognosis in previous studies.[8,9]

Myelofibrosis has been reported at a rate of 10–30% in patients with untreated MM in previous studies.[9] In line with the previous studies, the rate of myelofibrosis was found to be 23.3% in our study.

IgG lambda type[10] and IgD lambda[11] type myelomas have been associated with myelofibrosis in several case reports. In our study, an association was found between the MM subtype and grade of myelofibrosis whereas higher levels of IgM and serum kappa have been associated with lower fibrosis levels in our study. The rate of IgM kappa type myeloma was found to be 5.8% while all cases of IgM kappa myeloma were in the low fibrosis group. Similarly, serum IgG and serum lambda levels were higher in the high fibrosis group but the intergroup difference was not statistically significant.

Positive correlations were reported between myelofibrosis and increased LDH levels and increased plasma cell rates in a study[12] in 175 patients with MM whereas no significant correlation was found between LDH levels and myelofibrosis. In our study, a positive correlation was found between myelofibrosis and plasma cell percentage: Myelofibrosis became more severe with a higher plasma cell percentage. This finding may be particularly explained by diffuse bone marrow involvement with increased bone marrow plasma cell percentage and increased pro-inflammatory cytokine release.

In the medical literature, myelofibrosis was more severe in patients with MM compared to patients with monoclonal gammopathy of unknown significance (MGUS) whereas the grade of myelofibrosis increased as the MM stage increased in a study in 561 patients with MGUS or MM.[13] A case with a prefibrotic phase of primary myelofibrosis in combination with MGUS was seen in the literature.[14] In our study, all patients were at the MM stage and no statistically significant correlations were found between the disease stage and myelofibrosis.

In a previous study Hasselbalch *et al*.[15] reported that immune complexes might increase PDGF release by binding to platelet Fc receptors and the high serum IgG and IgM levels measured in a group of patients might cause this finding. In our study, no associations were found between myelofibrosis and IgG, while higher IgM levels were associated with lower grades of myelofibrosis.

In our study, no statistically significant associations were found between myelofibrosis and β2 microglobulin levels and erythrocyte sedimentation rates, whereas a positive correlation was found between plasma cell percentage and myelofibrosis. These findings may be explained by the small sample size as higher erythrocyte sedimentation rates and β2 microglobulin levels might be expected with increased plasma cell percentage.

CONCLUSION

Associations were found between lower grades of bone marrow fibrosis and higher IgM, serum kappa levels, and kappa/lambda ratio in this study, which was conducted to assess potential associations between M-protein levels and myelofibrosis that might be present at diagnosis and has been known to have prognostic significance. In conclusion, in this study, it was shown that bone marrow fibrosis in MM difference according to subtypes. Further randomized and prospective studies with larger sample sizes and clinical, laboratory, and histopathological data from such studies are required to support the results of this study.

Compliance with ethical standards

All of the ethical considerations had been strictly followed in accordance with the Helsinki declaration.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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