Risk Factors and Prognosis of Extramedullary Disease in Newly-Diagnosed Multiple Myeloma Patients

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ABSTRACT

Extramedullary Disease (EMD) in Multiple Myeloma (MM) is detected in 4-7% of patients at the time of diagnosis and increases to 6-20% in relapsed/refractory patients. In our study, we aimed to determine the risk factors for EMD, and the effects of bone marrow (BM) fibrosis on survival in newly diagnosed MM patients presenting with EMD at the time of diagnosis. A total of 189 MM patients who were newly diagnosed between November 2016 and September 2023 were included in the present study. EMD is defined as soft tissue plasmacytomas that occur due to hematogenous spread and have no contact with bone structures. EMD was detected in 21 (11.1%) of the 189 patients who were included in the present study. In multivariate analysis, the presence of fibrosis in the BM (OR: 3.45, 95% CI: 1.09-10.89; p= 0.032) were found to be independent risk factors for EMD. After a median follow-up period of 36 months, the median overall survival (OS) in patients with EMD was 13 months, and the median OS in those without extramedullary involvement was 77 months (HR: 3.09; 95% CI: 1.52-6.26, p= 0.002). No difference in OS was observed between patients with BM fibrosis (Grade 1-3) and patients without fibrosis (HR:1.04, 95% CI: 0.60-1.79; p= 0.885). As a result of the present study, it was found that BM fibrosis might be a predictive factor for the presence of EMD. A detailed examination for EMD might be required in newly diagnosed MM

Keywords: Extramedullary Disease, Multiple Myeloma

INTRODUCTION

Multiple Myeloma (MM) is defined as the presence of more than 10% of Clonal Plasma Cells (BMPCs) in the bone marrow (BM) (or biopsy-proven plasmacytoma) with end-organ damage defined as hypercalcemia, renal failure, anemia, or the presence of lytic bone lesions or myeloma-defining events such as the presence of ≥ 60% BMPCs, involved to uninvolved FLC ratio ≥ 100, or the presence of ≥ 2 focal marrow lesions on Magnetic Resonance Imaging (MRI).[1] MM accounts for 1% of all cancers and 10% of all hematologic malignancies in the United States and is the second most common hematologic malignancy.[2] Although patients' survival has improved with autologous stem cell transplantation and new treatment approaches, it is still an incurable disease.[3] Therefore, the limited success that can be achieved with conventional chemotherapies targeting only myeloma cells led to the requirement for a better understanding of the BM microenvironment.[4]

EMD has different definitions in the literature. As well as studies that exclude bone-related plasmacytomas and accept completely extramedullary plasmacytomas as EMD[5], some publications consider bone-derived (or para-skeletal) plasmacytomas as EMD.[6,7] In recent publications, EMDs' are soft tissue plasmocytomas arising from hematogenous spread and not in contact with bony structures.[8,9] In our study, EMD was defined based on this definition.

EMD is detected in 4-7% of MM patients at the time of diagnosis, which is stated to be 6-20% in relapsed myeloma patients.[10] The diagnosis of EMD is usually made by imaging such as Positron Emission Tomography/Computed Tomography (PET/CT) and MRI. The incidence of EMD increased with the widespread use of PET/CT at the time of diagnosis and its incidence has been reported to be 6-10% in newly diagnosed patients.[9,11]

Many genetic risk factors have been suggested in the etiopathogenesis of EMD, such as 17p deletion[12], P53 nuclear expression[13], or t(4;14).[14] Kishimoto et al. reported that genetic abnormalities were detected in approximately 30-50% of MM patients.[15]

The BM microenvironment has a very complex structure. The MM microenvironment consists of clonal plasma cells, extracellular matrix proteins, BM stromal cells, inflammatory cells, and vascular structures.[4] Recent studies report that the interaction between these components plays crucial roles in myeloma cell survival, proliferation, clonal evolution, development of drug resistance, and disease progression.[4,16] BM fibrosis is characterized by an increase of reticulin fibers or reticulin and collagen fibers in the BM stroma. Case reports and small case series reporting the association of BM fibrosis in myeloma were conducted in the literature.[17,18] The underlying etiology and clinical significance of the increase in BM stromal fibers have not been fully elucidated.[8] Data were published showing that the frequency of EMD is increased in patients who had BM fibrosis.[19]

In this retrospective study, our purpose was to examine the clinical characteristics of newly diagnosed MM patients presenting with EMD at the time of diagnosis, to determine the risk factors for EMD, to investigate the relationship between BM fibrosis and EMD at the time of diagnosis and the effects of EMD and BM fibrosis on the OS.

PATIENTS and METHODS

The diagnosis of MM was made based on the revised criteria by the International Myeloma Working Group (IMWG) in 2014.[1] All of the newly diagnosed MM patients, in the Department of Hematology Gulhane Training and Research Hospital between November 2016 and September 2023 were included in the present study.

Patients

A total of 197 newly diagnosed MM patients Between November 2016 and September 2023 were screened in the Ankara Gülhane Training and Research Hospital Hematology Clinic, and 189 MM patients who had complete follow-up and treatment data were included in the present study. Eight patients whose diagnosis, treatment, or follow-up data could not be accessed, were excluded from the study. Also, Smoldering Myeloma patients who did not require treatment were not included in the study.

All patients underwent BM aspiration and biopsy at the time of diagnosis. BM aspiration and biopsy samples were examined and BM plasma cell ratio, presence, and grading of fibrosis were recorded. At the time of diagnosis, PET/CT or MRI or CT imaging was performed in all patients to diagnose myeloma bone disease and to investigate the presence of extramedullary involvement.

The BM aspiration samples of the patients were analyzed by using both conventional cytogenetics and fluorescence in situ hybridization (FISH). The diagnosis of MM was made according to the revised criteria by the International Myeloma Working Group (IMWG) in 2014.[1] The ISS and R-ISS stages of the cases were calculated and the high cytogenetic abnormalities were defined as 1q alterations, del(17p), t(4;14), and t(14;16).[20-22]

The extramedullary disease (EMD) was defined as the presence of soft tissue plasmacytomas resulting from hematogenous spread or soft tissue plasmacytomas without contact with bony structures.[9,23]

Overall Survival (OS) was defined as the duration from the date of diagnosis of MM to the death or the date of the last follow-up.

Pathology

It was found in the immunohistochemical evaluation of the cases that the plasma cells were positively stained with CD79a, CD38, CD138, and for

the determination of clonality, kappa, and lambda were applied with the Chromogenic In Situ Hybridization (CISH) method and clonality was shown. Reticulin staining was performed to evaluate BM fibrosis, and the fibrosis level was graded between 0-3, according to the European consensus.[24] The presence of fibrosis in the BM has been defined as the presence of grade 1-3 reticulin fibrosis based on scoring. Other possible accompanying hematological and non-hematological causes were excluded in patients who had Grade 2-3 fibrosis in the BM.

Written informed consent was obtained from all the patients. The Declaration of Helsinki and good clinical practice protocols were adhered to in the study design, data collection, and analysis. Ethics committee approval was obtained from the Gulhane Faculty of Medicine, University of Health Sciences, dated 31.10.2023, numbered 46418926 and decision numbered 2023-366.

Statistical Analysis

Statistical assessment was performed using SPSS 23 for Windows (IBM SPSS Inc., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to assess whether the data fit normal distribution. Numerical variables with normal distribution were denoted as mean ± standard deviation, and those that did not fit a normal distribution were denoted as median min–max) values. Categorical variables are demonstrated as numbers and percentages. The distribution of numerical variables in two groups was evaluated with Mann–Whitney U-test (numerical variables that did not fit a normal distribution). Comparison of categorical variables in groups was tested with Chi-square or Fisher exact chi-square tests. Survival plots were generated with Kaplan–Meier analysis and the log-rank test was used for testing the equality of survival curves. Analysis of predictors of survival was performed using the Cox regression test. Parameters with p values ≤0.15 in univariate tests were included in the multivariate analysis. Multivariate logistic regression analysis with a forward-like-hood ratio method was performed to understand the parameters that are related to EMD. Values of $p < 0.05$ were recognized to be significant in statistical analyses.

RESULTS

A total of 189 MM patients who were diagnosed between November 2016 and September 2023 were included in the study. The median follow-up time was 36 months. 182 (96.3%) of the patients were examined with PET/CT, 5 (2.6%) with CT, and 2 (1.1%) with MR imaging modalities for both bone involvement and extramedullary disease (EMD) at the time of diagnosis. EMD was detected in 21 (11.1%) patients at the time of diagnosis.

The median age of the patients was 65 (37-86) years, 115 (60.8%) were male and 74 (39.2%) were female. The median White Blood Cell Count (WBC) of the patients at the time of diagnosis was 6.2 $x10^9$/L (1.6-26), the median hemoglobin (Hgb) value was 10.3 g/dl (5-13.4) and the median platelet value was 222 $x10^9$/L (60-447). The median lactate dehydrogenase (LDH) was 193 U/L (85-1210). The median albumin level of the patients was 3.5 g/dl (1.8-5.2), and the median β2Microglobulin level was 5.6 mg/dl (1.1-55). IgG type M protein was detected in 61.3% of the patients, IgA type in 16.9%, and IgM type M protein in 1.1% of the patients, 10.3% of the patients had kappa light chain disease and 8.4% had lambda light chain disease. Non-secretory myeloma was diagnosed in 2% of the patients. The kappa-type light chain was found in 55% of patients, and the lambda-type light chain was found in 43% of patients. 21.7% of the patients were found to be ISS Stage I, 36.5% were ISS Stage II, and 41.8% were ISS Stage III. According to the R-ISS staging system, 17.9% of the patients were Stage I, 67.2% were Stage II, and 14.9% were Stage III. High cytogenetic risks were detected in 20 (10.5%) of the patients. The median BM plasma cell ratio of the patients was 50% (10-90%), and the BM plasma cell ratio was 10-50% in 64% of the patients, while the bone marrow plasma cell ratio was above 50% in 36% of patients. While no fibrosis was detected in the BM in 42.9% of the patients, Grade 1 fibrosis was detected in 42.3%, Grade 2 fibrosis was detected in 9.5%, and Grade 3 fibrosis was detected in 5.3%. The distribution, demographic data, and clinical characteristics of the patients included in the study according to the presence or absence of EMD are summarized in Table 1.

Table 1. Baseline patient characteristics

		Total patients	Non-Extramedullary Disease	Extramedullary Disease
Patients		189	168 (88.9%)	21 (11.1%)
Age (Median)	Years	65 (37-86)	64.5 (40-86)	67 (37-78)
Age Groups	≤65 years	101 (53.4%)	91 (54.2%)	10 (47.6%)
	>65 years	88 (46.6%)	77 (45.8%)	11 (52.4%)
Gender	Male	115 (60.8%)	103 (61.3%)	12 (57.1%)
	Female	74 (39.2%)	65 (38.7%)	9 (42.9%)
WBC	Median- x10^9/L	6.2 (1.6-26)	6.1 (1.6-26)	6.5 (3-20)
Hemoglobin	Median - g/dl	10.3 (5-13.4)	10.3 (5-13.4)	11.8 (6.5-13.1)
Platelet	Median x10^9/L	222 (85-447)	221 (85-447)	222 (59-347)
LDH	Median U/L	193 (60-1210)	189 (60-1210)	208 (160-540)
Albumin	Median – g/dl	3.5 (1.8-5.2)	3.5 (1.8-5.2)	3.5 (2.4-4.4)
β2Microglobulin	Median – mg/L	5.6 (1.1 – 55)	5.6 (1.1-55)	5.7 (2.2-30)
Type of M Protein	IgG	116 (61.3%)	102 (60.7%)	14 (66.7%)
	IgA	32 (16.9%)	28 (16.7%)	4 (19%)
	IgM	2 (1.1%)	2 (1.2%)	–
	Non-secretory	4 (2.1%)	4 (2.4%)	–
	Kappa Light Chain	19 (10.1%)	17 (10.1%)	2 (9.5%)
	Lambda Light Chain	16 (8.4%)	15 (8.9%)	1 (4.8%)
Type of M protein	IgG	116 (61.3%)	102 (60.7%)	14 (66.7%)
	Non-IgG	73 (38.7%)	66 (39.3%)	7 (33.3%)
Type of Light Chain	Kappa	104 (55%)	92 (54.8%)	9 (42.9%)
	Lambda	81 (42.9%)	72 (45.2%)	12 (57.1%)
International Staging System (ISS)	I	41 (21.7%)	36 (21.4%)	5 (23.8%)
	II	69 (36.5%)	62 (36.9%)	7 (33.3%)
	III	79 (41.8%)	70 (41.7%)	9 (42.9%)
Revised-International Staging System (R-ISS)	I	34 (17.9%)	29 (17.3%)	5 (23.8%)
	II	127 (67.2%)	116 (69 %)	11 (52.4%)
	III	28 (14.9%)	23 (13.7%)	5 (23.8%)
Cytogenetics	Normal	111 (58.7%)	97 (57.7%)	14 (66.7%)
	1q abnormalities	7 (3.7%)	6 (3.6%)	1 (4.8%)
	t(4;14)	4 (2.1%)	3 (1.8%)	1 (4.8%)
	t(14;16)	2 (1.1%)	2 (1.2%)	–
	t(11;14)	10 (5.3%)	9 (5.4%)	1 (4.8%)
	del(17p)	7 (3.7%)	7 (4.2%)	–
	del(13q)	9 (4.8%)	7 (4.2%)	2 (9.5%)
	Hypodiploidi	7 (3.7%)	7 (4.2%)	–
	Hyperdyploidi	2 (2.1%)	2 (1.2%)	–
	Missing	30 (15.9%)	28 (16.7%)	2 (9.5%)
High Risk Cytogenetics*	Yes	20 (10.5%)	18 (10.7%)	2 (9.5%)
Bone Marrow Plasma Cell Percentage	Median (%)	50% (10-90)	50% (10-90)	45% (10-80)
Bone Marrow Plasma Cell Percentage	10-50%	121 (64%)	107 (63.7%)	14 (66.7%)
	>50%	68 (36%)	61 (36.3%)	7 (33.3%)
Bone Marrow Fibrosis	No fibrosis	81 (42.9%)	77 (45.8%)	4 (19%)
	Grade I	80 (41.8%)	70 (41.7%)	10 (47.6%)
	Grade II	18 (9.5%)	12 (7.1%)	6 (28.6%)
	Grade III	10 (5.3%)	9 (5.4%)	1 (4.8%)
Bone Marrow Fibrosis (Grade I-III)	No	81 (42.9%)	77 (45.8%)	4 (19%)
	Yes	108 (57.1%)	91 (54.2%)	17 (%81%)

* Any of t(4;14), t(14;16), del(17p), 1q abnormalities

Table 2. Factors affecting extra-medullary disease

		Non-Extramedullary Disease	Extramedullary Disease	P value
Patients		168 (88.9%)	21 (11.1%)	
Age (Median)	Years	64.5 (40-86)	67 (37-78)	0.849
Age Groups	≤ 65 years	91 (54.2%)	10 (47.6%)	0.646
	> 65 years	77 (45.8%)	11 (52.4%)	
Gender	Male	103 (61.3%)	12 (57.1%)	0.712
	Female	65 (38.7%)	9 (42.9%)	
WBC	Median- $x10^9$/L	6.1 (1.6-26)	6.5 (3-20)	0.589
Hemoglobin	Median - g/dl	10.3 (5-13.4)	11.8 (6.5-13.1)	0.504
Platelet	Median $x10^9$/L	221 (85-447)	222 (59-347)	0.323
LDH	Median U/L	189 (60-1210)	208 (160-540)	0.123
Albumin	Median – g/dl	3.5 (1.8-5.2)	3.5 (2.4-4.4)	0.829
β2Microglobulin	Median – mg/L	5.6 (1.1-55)	5.7 (2.2-30)	0.538
Type of M Protein	IgG	102 (60.7%)	14 (66.7%)	
	IgA	28 (16.7%)	4 (19%)	
	IgM	2 (1.2%)	–	–
	Non-secretory	4 (2.4%)		
	Kappa Light Chain	17 (10.1%)	2 (9.5%)	
	Lambda Light Chain	15 (8.9%)	1 (4.8%)	-
Type of M protein	IgG	102 (60.7%)	14 (66.7%)	0.475
	Non-IgG	66 (39.3%)	7 (33.3%)	
Type of Light Chain	Kappa	92 (54.8%)	12 (57.1%)	1.000
	Lambda	72 (45.2%)	9 (42.9%)	
International Staging System (ISS)	I	36 (21.4%)	5 (23.8%)	
	II	62 (36.9%)	7 (33.3%)	0.942
	III	70 (41.7%)	9 (42.9%)	
Revised-International Staging System (R-ISS)	I	29 (17.3%)	5 (23.8%)	
	II	116 (69 %)	11 (52.4%)	0.839
	III	23 (13.7%)	5 (23.8%)	
Cytogenetics	Normal	97 (57.7%)	14 (66.7%)	
	1q abnormalities	6 (3.6%)	1 (4.8%)	
	t(4;14)	3 (1.8%)	1 (4.8%)	
	t(14;16)	2 (1.2%)	–	
	t(11;14)	9 (5.4%)	1 (4.8%)	
	del(17p)	7 (4.2%)	–	
	del(13q)	7 (4.2%)	2 (9.5%)	
	Hypodiploidi	7 (4.2%)	–	
	Hyperdyploidi	2 (1.2%)	–	
	Missing	28 (16.7%)	2 (9.5%)	
High Risk Cytogenetics*	Yes	18 (10.7%)	2 (9.5%)	0.801
Bone Marrow Plasma Cell Percentage	Median (%)	50 % (10-90)	45 %(10-80)	0.805
Bone Marrow Plasma Cell Percentage	10-50%	107 (63.7%)	14 (66.7%)	1.000
	> 50%	61 (36.3%)	7 (33.3%)	
Bone Marrow Fibrosis (Grade I-III)	No	77 (45.8%)	4 (19%)	0.019
	Yes	91 (54.2%)	17(%81%)	
Bone Marrow Fibrosis	No	147 (87.5%)	14 (66.7%)	0.011
	Yes	21 (12.5%)	7 (33.3%)	

* Any of t(4;14), t(14;16), del(17p), 1q abnormalities

Demographic data and clinical characteristics of 21 patients (11.1%) who had EMD were compared with 168 patients (88.9%) without EMD. Grade 1-3 fibrosis was detected in the BM in 81% of patients who had extramedullary involvement, and Grade 1-3 fibrosis was detected in 54% of patients without extramedullary involvement. A significant correlation was found between the presence of Grade 1-3 fibrosis and EMD (p= 0.019). No significant differences were detected in clinical and demographic data with the presence of EMD other than the presence of BM fibrosis and these data are summarized in Table 2.

In univariate analysis, factors that might affect the presence of EMD were analyzed; a significant association was found between the presence of fibrosis in the BM (OR: 3.61; 95% CI: 1.16-11.14, p= 0.027). In multivariate analysis, the presence of fibrosis in the BM (OR: 3.45; 95% CI: 1.09-10.89, p= 0.032) was found to be an independent risk factor for EMD.

When the factors that affect the presence of BM fibrosis were evaluated, no significant relationship was detected between age, age group, gender, M protein type, light chain type, ISS stage, R-ISS stage, cytogenetic risk, WBC count at the time of diagnosis, Hgb level, platelet level, LDH level, albumin level, and B2 microglobulin level, whereas a significant correlation was detected between BM plasma cell ratio and BM fibrosis. While the median plasma cell ratio in the BM of patients without Grade 1-3 fibrosis was 40% (10-90%), the median plasma cell ratio in the BM of patients who had Grade 1-3 fibrosis was 50% (10-90%) (p= 0.035).

After a median follow-up of 36 months, the median OS in patients who had EMD was found to be 13 months while the median OS in patients without extramedullary involvement was 77 months (HR: 3.09, 95% CI: 1.52-6.26, p= 0.002). Extramedullary involvement had a significant negative effect on OS and was shown to increase the mortality risk 3.09-fold. No difference in OS was observed between patients with BM fibrosis (Grade 1-3) and those without BM fibrosis (HR: 1.04; 95% CI: 0.60-1.79, p= 0.885). The survival plots of the patients are shown in Figure 1 and Figure 2.

DISCUSSION

Although the prognosis of MM varies depending on the patient, the disease, and the treatment options applied, it is a hematological malignancy still no cure has been achieved. EMD is a clinical condition that worsens the disease prognosis and is associated with shorter survival rates. In a study that included 3744 patients, it was reported that paraskeletal involvement was 14.5% and extramedullary involvement was 3.7%.[10] The incidence of EMD has increased over the years with the use of imaging methods such as PET/CT and MRI.[11] EMD was detected in 11.1% of patients at the time of diagnosis in our study. It is considered that the reason why the incidence of EMD varies between publications is due to the differences in the definition of EMD and different imaging methods used in EMD detection. EMD was detected by PET/CT in 95% of the patients in the present study.

The risk factors of EMD have not been elucidated fully because of the insufficient number of studies. Mangiacavalli et al. concluded that patients who had extramedullary involvement were younger and more likely to have IgA and non-secretory type myeloma.[25] Stork et al. found in their retrospective study that young age (<65 years), high LDH levels, Ig A, and non-secretory myeloma types were risk factors for extramedullary involvement.[26] In our study, no significant relationship was detected between EMD and patient age, myeloma type, light chain type, BM plasma cell ratio, LDH level, B2 microglobulin level, ISS, and R-ISS stage.

It is considered that cytogenetic abnormalities might be responsible for EMD in MM.[27] High-risk cytogenetics was detected in 41% of the patients in the study of Gagelmann et al., in which they analyzed the clinical and genetic risk factors of 488 myeloma patients who had EMD. 22% of patients with EMD had more than one high-risk cytogenetic abnormality.[28] In the study conducted by Usmani et al., it was stated that EMD was more common in MM patients who had t(14;16) and t(14;20) at the time of admission and was associated with worse poorer OS.[29] In our study, high cytogenetic risk was observed in 9.5% of patients with EMD. However, the cytogenetic characteristics of EMD are still not clearly defined in the literature.[23]

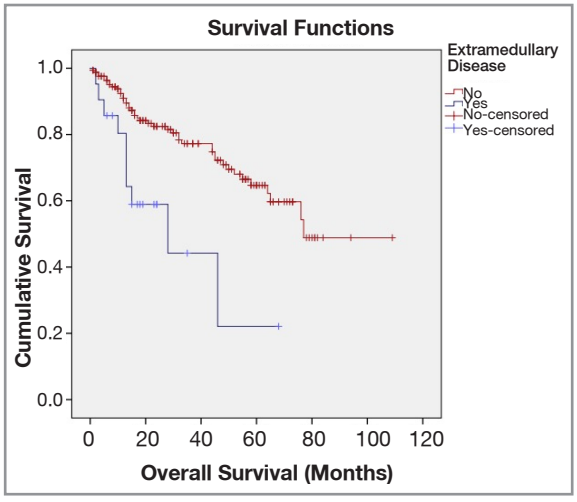

Figure 1. Survival plots of patients according to extramedullary disease

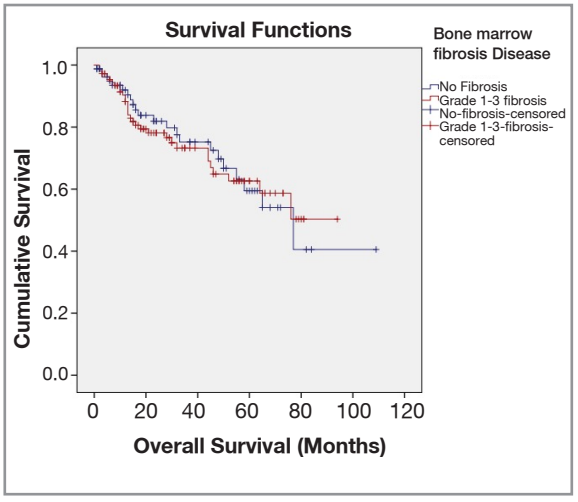

Figure 2. Survival plots of patients according to bone marrow fibrosis

The frequency of BM fibrosis in myeloma is reported to be between 8-57% at the time of diagnosis.[30,31] In our study, Grade I-III fibrosis was detected in the BM in 57.1% of patients. Fibrosis in the BM was detected in 48.2% of 393 newly diagnosed MM patients in a previous study conducted by Paul et al. It was reported that BM fibrosis increases in direct proportion to the plasma-cell percentage.[17] Abildgaard et al. reported increased fibrosis in 9 (36%) of 25 myeloma patients in BM biopsy and again found a positive correlation between the degree of fibrosis and the BM plasma cell percentages.[32] A significant relationship was established in our study between the plasma cell percentage in BM and BM fibrosis. This can be explained by the development of fibrosis secondary to increased pro-inflammatory cytokine release from increased plasma cells.

In a recent study that was conducted by Koshiishi et al.,[19] newly diagnosed myeloma patients were investigated. They reported Grade I-III fibrosis in the BM in 37.1% of the patients. Although they did not detect a significant relationship between clinical characteristics and laboratory findings between patients with and without fibrosis, they also reported that the incidence of extramedullary disease was significantly higher in patients who had fibrosis in BM.[19] In our study, it was shown in univariate and multivariate analysis that the frequency of EMD increased significantly in patients who had BM fibrosis. Koshiishi et al. hypothesized that downregulation in the expression of adhesion molecules on plasma cells might have a role in the extramedullary localization of plasma cells in the BM. It was emphasized that fibrosis in the BM might also reduce the expression of adhesion molecules and increase the frequency of EMD. It was also shown in solid tumors that fibrotic progression of the tumor microenvironment is an important step in cancer cell metastasis.[33]

In the literature, publications are reporting that BM fibrosis has prognostic importance in MM.[34,35] Sailer et al. reported that survival decreased to 18 months in myeloma patients with increased BM fibrosis[35] while Krzyzaniak et al. found no association between fibrosis and survival.[36] However, the majority of patients were treated with conventional chemotherapies in both of these studies. Following the use of proteasome inhibitors and Immunomodulatory Drug-based therapies in clinical practice, Paul et al.'s study reported that BM fibrosis was associated with shorter OS and PFS. However, when adjusted for age, ISS, and cytogenetic risk, there was no statistically significant association between bone marrow fibrosis and OS and PFS.[17] In the present study, no significant effect of BM fibrosis on OS was observed.

The association of EMD with poor prognosis has also been established in previous studies. It was shown in the study by Moreau et al. that in patients who had EMD at the time of diagnosis, OS was re-

duced significantly and the risk of death increased by 3.8-fold.[37] In the study of 51 MM patients conducted by Badar et al., it was reported that the presence of EMD was associated with shorter OS and increased the risk of death by 3.05 fold.[38] It was found in our study that the OS of patients presenting with EMD was significantly shorter and the risk of death increased by 3.09-fold.

Conclusion

EMD is a clinical presentation with unmet needs in clinical practice because there is no standardization on its definition, risk factors are not fully revealed and pathophysiology is not fully elucidated. EMD is an exclusion criterion in many clinical trials, and its prognosis is still poor despite the development of novel targeted therapies.[26,39] As a result of our study, it was found that fibrosis in the BM might predict the presence of EMD. It might be necessary to determine the presence of BM fibrosis, to perform accurate grading and a detailed examination for EMD in the presence of fibrosis in newly diagnosed MM patients. We believe that it will contribute to the improvement of prognosis, especially if the definition and treatment of EMD is standardized and if the risk factors are fully determined through prospective studies with a larger number of patients.

Study Limitations: The limitations of the present study were the fact that it had a retrospective design, the number of patients was relatively limited, cytogenetic data were missing in some of the patients, and the induction treatments of the patients were not standardized because of their age groups, eligibility of the autologous transplant, performance status and comorbidities.

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