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The concentration and type of monoclonal protein and their impact on clinical severity in patients with symptomatic myeloma

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Abstract

Background and objectives: Multiple Myeloma is a clonal plasma cell proliferation in the bone marrow that produces abnormal monoclonal proteins in serum and /or urine that leads to end-organ damage. We aimed to evaluate concentration, type of monoclonal protein, and their impact on the severity of symptomatic multiple myeloma patients.

Methods: The study was conducted on 124 patients with symptomatic myeloma who were registered in the three centers in Kurdistan-Iraq from January–June 2019. Out of the 74 were males, and 50 were females. Demographic details, laboratory investigations, imaging study were reviewed, and informed consent was obtained for all patients; smoldering myeloma was excluded.

Results: The most prevalent subtypes were IgG followed by IgA (61.3%, 18.5% respectively), whereas free light chain and non-secretory myeloma forming the rest, 12.1% and 6.45% for each subtype. There is a statistically positive association found between the concentration of monoclonal protein and the level of hemoglobin, ß$_2$-microglobulin, and lactic acid dehydrogenase. There is no association for the concentration of monoclonal protein with each of calcium, albumin, creatinine, and erythrocyte sedimentation rate. **Conclusions:**

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We found a higher percentage of IgG/Kappa, high rates of non-secretory myeloma, low rates of light chain myeloma and younger age at presentation in comparison to western reports. The association between monoclonal protein concentration and some parameter of prognostic value in patients studied underscores its relevance to severity of disease in our locality.

Keywords: Multiple Myelomas; Immune-fixation; Light chain; Serum and Urine Protein electrophoresis.

Introduction

Multiple myelomas (MM) are a type of malignancy that arises from clonal plasma cells overgrowth in bone marrow with the production of an abnormal monoclonal (M)-protein in the serum and/or urine[1]. Myeloma may be asymptomatic, smoldering (no-end-organ-damage), and symptomatic myeloma when there is end-organ damage. The end-organ damage includes hypercalcemia, renal dysfunction, anemia, and bone lesion abbreviated as (CRAB)[2]. Symptomatic MM can be diagnosed by the presence of 10% or more clonal plasma cells in bone marrow trephine biopsy or biopsy-proven bony or extramedullary plasmacytoma plus any one or more of the CRAB features and myeloma-defining events. Depending on the revised International Myeloma Working Group (IMWG), the myeloma defining events includes either 60% or higher clonal plasma cells on marrow trephine biopsy, serum involved to uninvolved free light chain ratio of 100 and one or more lytic lesion greater than five mm on resonant magnetic imaging (MRI)[3.] Serum and urine protein electrophoresis (SPE, UPE) with immune fixation (IF) have been used for screening, staging, and monitoring of plasma cell disorders[4]. Despite less sensitivity, SPE and UPE are the most commonly used laboratory test for screening plasma cell disorder[5]. The free light chain assay (FLC) and the ratio will give additional sensitivity for diagnostic screening in patients with clinical features of MM, reaching 99%[6]. About 5% of symptomatic MM is non-secretory in case of using SPE and UPE for screening, but nearly about two-third of them could have free clonal immunoglobulin light chains in blood by doing FLC assay[7.] Malignant plasma cells most commonly produce an IgG (50%), IgA (20%), or light chain only (20%) monoclonal protein[8]. Prognosis depends on age, performance status, and serum albumin, stage

of the disease, beta 2-microglobulin (β2M), cytogenetic, lactic acid dehydrogenase (LDH), C - reactive protein (CRP), plasma cell labeling index, IL6, and bone marrow microenvironment. The international prognostic index used as a prognostic tool for symptomatic myeloma patients[9]. The study aimed to detect the concentration and types of abnormal M-protein in blood and urine. The second aim is to correlate the amount and kind of M-protein versus disease severity at presentation.

Patients and methods

The study was conducted on 124 patients with symptomatic myeloma who were registered in the three centers in Kurdistan-Iraq {Hiwa (sulaimani), Nanakali (Erbil), and Azadi (Duhok)} from January–June 2019, of them: 74 were males, and 50 were females.

Demographic details, laboratory investigation concentrating on SPE, UPE, IF, biochemistry, calcium, serum albumin, and bone marrow aspirate/trephine biopsy, flow cytometry, and skeletal bone imaging. Written informed consent was obtained from all patients; smoldering myeloma was excluded.

The revised International myeloma working group (IMWG) criteria were applied for the diagnosis of all patients[3].Evidence of end-organ damage was defined as hypercalcemia: serum calcium ≥1mg/dL higher than the upper limit of normal or (≥11mg/dL), renal insufficiency: creatinine clearance ≤ 40 mL /minute or serum creatinine ≥ 2mg/dL), anemia: hemoglobin of ≤10g/dl[3]. We used Graft Pad Prism version 5.0 for statistical analysis. The age of the patients measured as a mean age ±SD. The relationship between two continuous data was measured by coefficient correlation (Pearson test) and ANOVA with the post-Tukey test used for detecting statistical significance among means of different categories. Mann Whitney U test was used for testing the significant difference of median among different groups (p-value below 0.05 considered statistically significant).

Results:

Out of 124 patients with newly diagnosed symptomatic MM, 74 (59.7%) males, and 50 (40.3%) females, males to female's ratio of 1.48:1. The median age was 61 years with a range between 35-89 years, about 2.4% of

them were below 40 years. Table1 shows the age and sex distribution of the enrollees.

Table (1): The Demographic characteristics, including age and sex distribution of 124 patients with symptomatic myeloma at the presentation of the disease.

Factor			**No. (%)**
Age	<40		3(2.4)
	40-49		18(24.5)
	50-59		34(27.4)
	60-69		39(31.5)
	70-79		21(16.9)
	≥ 80		9 (7.25)
	Median		61
	Range		35-89
Sex	Male		74(59.7)
	Female		50(40.3)

The IF and SPE pattern showed a localized band or spike in nearly 80.6 % of cases, with hypo-gammaglobulinemia in the rest. In those patients with positive M-band in serum, the most frequent M-protein subtype was IgG, which accounts for about 66 (61.3%), followed by IgA in 18.5% of patients and the free light chain myeloma (LC M) accounts for only 15(12.1%); Non-Secretory Myeloma (NSM) was documented in 6.45%, and lastly bi-clonal (IgG and IgA) 1 (0.8%) and IgD 1(0.8%). Among those with the positive band in the serum, the kappa was 70%, while lambda 30% of patients (Table 2).

Table (2): The distribution of types and percentage of monoclonal protein among the patients with symptomatic myeloma.

Types	**No. (%)**
IgG κ	57(45.9)
IgG λ	19(15.3)
IgA κ	10(8)
IgA λ	13(10.5)

Biclonal	1(0.8)
IgD κ	1(0.8)
IgD λ	0(00)
Free κ only	9(7.25)
Free λ only	6(4.8)
No band	8(6.45)
Total	124(100)

A monoclonal light chain protein in the urine (BJP) found in 77 (62%) of patients. In patients who had M-protein in serum, urine BJP was detected in nearly 93.55% of patients. The median concentration of serum M-protein in our study was 3 gm/dl ranging from (0.3-6) and median urine BJP concentration of 42 mg/dl ranging from 2-970 mg/dl. (Table 3). The Calcium level was elevated above the >11 mg/dl in17 (13.3 %) of patients at diagnosis. Renal involvement with serum creatinine above 2 mg/dl, found in 31 (25.6%) and bone pain, was found in 98 (79 %) of patients while bone lesions detected in nearly 75 (59.7%).

Table (3): Laboratory blood test results among the 124 patients with symptomatic myeloma at presentation.

Blood tests	**No. of patients**	**Median**	**Range**	**Distribution of results**	**% of patients**
Hb (gm/dl)	121	10.1	6-16	≤10	16.12
				8.1-10	33.87
				10.1-12	31.45

				>12	18.54
Serum M-Protein Concentration (gm/dl)	100	3	0.3-6	≤ 0.9	7
				1.0-1.9	5
				2.0-2.9	35
				3.0-3.9	18
				4.0-4.9	26
				>5	9
Urine M-protein Concentration (mg/dl)	72	42	2-970	<15	23.6
				16-100	50
				≥ 100	26.4
Serum creatinine mg/dl	124	1.1	0.1--10.6	≤1.2	58.3
				1.3-1.9	19.1
				≥2	25.6
Serum Calcium mg/dl	124	9.2	7.8-15	≤10	74
				10.1-10.9	12.67
				≥11	13.33
B2M (mg/L)	80	4.1	0.4-17	<3.5	40
				3.5-5.5	25
				>5.5	33.75
LDH (U/L) Reference(140-280)	113	310	18-812	<280	44.24
				>280	53.76

The number of osteolytic bone lesions per site was 144/101 (sites/patients) in those with positive serum M-band (1.4 bone lesion /patient). In the case of LCM and NSM, we found a statistically non-significant (p-value 0.28) higher number of the osteolytic bone lesion in comparison to those with only positive serum M-protein, 2.13/1, and 2/1; respectively. The most frequent sites were spine, skull, pelvis, humerus, and femurs (Table 4)

Table 4. Number and site of osteolytic bone lesions in those patients with positive serum M-protein, LCM, and NSM.

		Type of myeloma	
Site of osteolytic bone lesions	**Myeloma with a serum M- band**	**LCM**	**NSM**
lumber sacral	62	9	6
skull	34	2	4
pelvis and sacrum	12	4	3
dorsal spine	10	5	2
Humerus	9	1	0
femur,	7	3	0
plasma cytoma	2	2	0
ribs	6	1	1
radius	1	4	0
cervical Spine	1	1	0
total bone lesions	144	32	16
Number of patients	101	15	8

When patients were categorized into groups according to their hemoglobin, it was found that those with higher M-band concentration were associated with lower hemoglobin categories. (P=0.0309). (Fig.1A). We detected serum β2M > 5.5 mg/L in 33.75% of patients, which indicates stage three of the disease according to the international staging system (Table 3). Furthermore, we found a positive relationship between the concentration of serum M–protein and serum β2M. The higher the amount of M-protein in the serum, the higher the β2M. (Fig 1B). The LDH (>280 U/L, reference range (140-280 unit/L) was raised in more than 53 % of our patients at presentation. We found a positive association between serum M-protein and LDH but it was statistically non-significance (p-value 0.796). (Fig.1C).

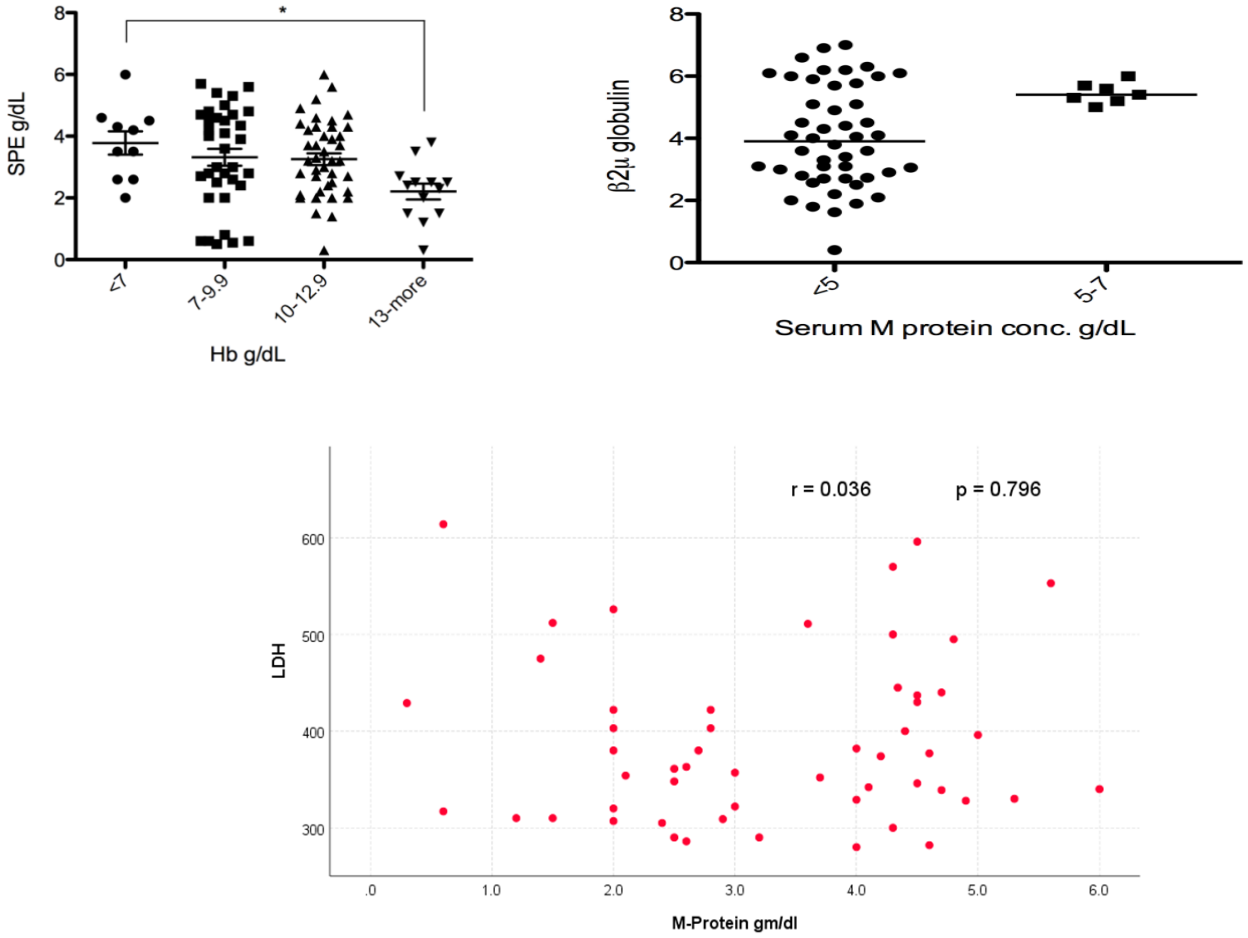

Figure 1: Comparing the amount of serum M-protein concentration with each of Hb (A), and B2M (B) and LDH (C).

We could not find a statistically significant association between the concentration of serum protein in gm/dl with each of the performance status (ECOG) (Fig.2), calcium, albumin, creatinine, and erythrocyte sedimentation rate ESR (p-values were 0.51, 0.1154, 0.287, 0.78 respectively). There was no relation between the median of each of albumin, calcium, creatinine, Hb, and ESR with the type of symptomatic MM (positive M-band, LCM and NSM). The median percentage of plasma cells in marrow aspirate was 40%, not related to the amount of serum M-protein and no difference found in the proportion in those with positive serum M-protein, LCM, or NSM patients using Mann Whitney U test.

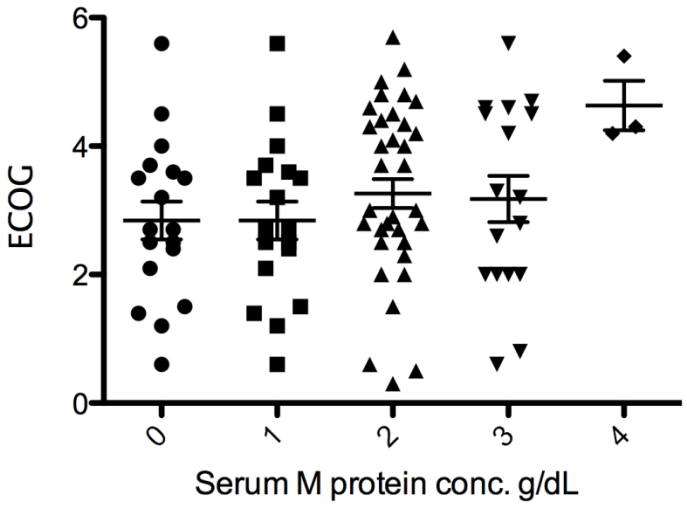

Figure2. The serum M-protein concentration versus ECOG performance status

Discussion

The median age at diagnosis in our study was 61 years, while in a study done by Kyle et al., it was 66 years[13]. The earlier age presentation is valid for all types of cancer in our region, as reported previously[10-12]. We used SPE and UPE with IF but not using the FLC assay; for that reason, we found a higher percentage of NSM (6.45%) in our study, while other studies report only 3%[13] and 5%[10]. nearly about two-third of those who have NSM have a positive light chain by using FLC assay according to previously reported studies [5-7, 14,15]. We found M-protein in almost 80.6%, which is near to that found by Kyle et al., who reported it in 82% of his cases[13]. The most prevalent M-protein subtype was IgG, which accounts for about 61.3% and IgA in 18.5%, while the lower percentage recorded (IgG in 50% and IgA in 20%) by RajKumar[8] & Kyle[8]. The free LCM accounts for only 12.1% (kappa 7.25% and lambda 4.85%), which is lower than that reported by earlier studies, which was 20% [4, 13].

It has been reported among those with the positive M-band in the serum the kappa was found in 63%, while lambda is 37%[13], which is similar to our study 70% kappa (κ) and 30 % lambda (λ). A monoclonal light chain found in 62% of cases, which related to more renal impairment at the time of diagnosis, as we saw in nearly 25% of our patients[16]. Anemia (Hb less or equal to 12 gm/dl) found in 81.4% of patients, which similar to that report by Rajkumar & Kyle[8].

Renal impairment with creatinine > 2mg/dl found in about 18.5 % of cases in our study at diagnosis, while a higher figure (40%) was reported in an earlier study[16]. Hypercalcemia in our research found in 13.33%, which similar to that reported by Kyle et al. 13%[13]. Bone pain was found in 98(79 %) of patients, while bone lesions detected in nearly 75 (59.7%) while less bone pain and less bone lytic lesion found in a study published by Palumbo et al. and Yassin[10,17].

We found higher osteolytic lesion sites per each person in both LCM (2.13/1) and NSM (2/1) in comparison to those with positive serum M-band MM 1.4/1 cases, but have no statistical significance, as shown in (Table4).

We found a positive relationship between the amount of serum M–protein and serum β2M (Fig.1B) but in other studies, showed no prognostic significance, although β2M is an essential value in the staging of the symptomatic myeloma in international staging system[16, 18].

In our study, more than 53% of patients recorded to have a high level of LDH. The LDH concomitantly elevated with the serum M-protein as shown in (Fig.1C). As we know, LDH associated with defining prognosis as put in a newly revised international staging system (ISS-R)[19-21].

Besides the use of concentration and type of M-protein in urine and serum for the diagnosis of plasma cell disorders (MGUS, smoldering myeloma, and symptomatic myeloma), it may be used to detect clinical severity of myeloma at presentation as we found some positive relation with Hb level and β2M(Fig.1A,B) . On the other hand, we could not find a positive association with some other values, as explained in results.

Despite the limitation in using serum-free light chain assay and cytogenetic tests in our study, but still, the SPE, UPE, and IF give us a definite clue in assessing the severity of the disease at diagnosis.

Conclusions

In our study, we found a higher percentage of IgG/Kappa in serum, high rates of NSM, low rates of LCM, and younger age at presentation of symptomatic myeloma in comparison to other studies reported in the literature.

The SPE, UPE and IF still can be in use in assessing severity of disease in our locality because they have been found to be associated with some well documented prognostic factors.

Conflict of interests

The authors recorded no conflict of interests.

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