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Application of serum C-reactive protein in comparison with βeta-2-microglobulin in patient with multiple myeloma

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Abstract:

BACKGROUND: Multiple myeloma (MM) is a clonal proliferation of malignant plasma cells in the bone marrow that produced monoclonal protein, and associated with different organ dysfunction. β 2 Microglubulin is a known prognostic marker while CRP is proposed to be of equivalent significance.

OBJECTIVE: To assess the usefulness of C-reactive protein (CRP) as an alternative to β 2 Microglobulin in term of MM staging and related organ tissue injury in case of limited resources circumstances.

PATIENTS AND METHODS: A hospital based cross sectional study was conducted from the 1st of Mar 2015 till the 1st of Jan 2016 at the hematology department in Al-Imamain Al-Kadhimain Medical City and Baghdad Medical City. It included 25 patients who were newly diagnosed with Multiple myeloma from both genders. CRP and β 2 Microglubulin were estimated using ELISA in relation to diseases stage and manifestation.

RESULTS: The mean age was 56.5 ± 12.6 years. Fatigue and bone pain were the predominant presenting features. Mean CRP was 20.87 ± 11.20 µg/ml with a very significant positive correlation with staging (r = 0.779, P = 0.0001) as well as with bone marrow (BM) Plasma Cells % (r = 0.665, P = 0.0001) and β 2 Microglubulin (r = 0.816, P = 0.0001).

CONCLUSIONS: C-reactive protein can be considered as an independent prognostic parameter to replace $\beta 2$ microglobulin in evaluating patients with MM staging and related tissue organ injury in case of limited resources, with equivalent clinical applications.

Keywords:

C-reactive protein, multiple myeloma, plasma cell disorders, prognosis, βeta-2-microglobulin

Introduction

Multiple myeloma is a neoplastic disorder characterized by clonal proliferation of malignant plasma cells in the bone marrow with the production of monoclonal protein (M-protein) with its consequences.^[1]

It results in extensive bone destruction with or without hypercalcemia and anemia.^[2] While the excessive production of M-protein can result in renal failure, in addition the effect of recurrent bacterial infections due to associated immunoparesis.^[2]

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The median age at diagnosis is approximately 70 years; 37% of patients are younger than 65 years.^[3,4]

A retrospective analysis of 1027 MM patients at a single institution demonstrate the common manifestations at diagnosis such as normocytic, normochromic anemia (73%) while bone pain, particularly in the back, chest, or less often in the extremities, in 60% of patients. Renal impairment in almost half of patients may be a presenting feature as well as hypercalcemia or radiculopathy. In addition to increased risk for infection due to a combination of immune dysfunction and physical factors.^[5]

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Serum protein electrophoresis (SPE) revealed a localized band in 82% of patients; however, immunoelectrophoresis or immunofixation can show a monoclonal protein in 93%.^[6]

The serum β eta-2-microglobulin (S β 2M) level is increased in 75% of cases and used as indicator for prognosis. Levels <3.5 mg/L imply a relatively good prognosis unlike levels above 5.5 mg/L.^[7,8]

It can determine tumor burden, and therefore it is used for staging in the international staging system (ISS) instead of the old Durie-Salmon staging system.^[9,10]

β2M is expressed on the surface of virtually all normal nucleated cells as well as by many tumor cell lines.^[11]

A low concentration of free β 2M (0.9–2.5 mg/L) is found in the serum of healthy subjects due to its "shedding" from the cell membrane^[12] but its function remains obscure, and it is eliminated through the kidneys.^[13] Elevated serum concentrations in the presence of normal glomerular filtration rate suggest increased production or release.^[13,14]

It is elevated in several conditions such as chronic inflammation, liver disease, and renal dysfunction in addition to multiple myeloma.^[15,16]

C-reactive protein (CRP) is the prototypical acute phase serum protein that rises rapidly in response to inflammation as a component of the innate immune response.^[17] It has both pro- and anti-inflammatory actions. As a result, the CRP response to tissue injury may worsen tissue damage in some settings.^[18,19]

Plasma levels of CRP may rise rapidly and markedly after an acute inflammatory stimulus, largely reflecting increased synthesis by hepatocytes.^[20]

High-sensitivity CRP (hsCRP) means an assay designed to measure very low levels of CRP.^[21-23]

The objective of this study is to assess the usefulness of measuring CRP as an alternative to β 2-microglubulin in term of MM staging and related organ tissue injury under limited resources circumstances.

Patients and Methods

A hospital based cross-sectional study was conducted from March 1, 2015, to January 1, 2016 in the hematology unit in Al-Imamain Al-Kadhimain Medical City and in Baghdad Medical City.

A total of 25 patients with a newly diagnosis of multiple myeloma (based on the Diagnostic criteria of the

International Myeloma Working Group from both genders were included in this study. A full clinical evaluation was done for each of them recording their presenting features and complication. Those with evidence of active infection or fever were excluded from the study.

Data were collected from each patient using a preformed questionnaire which included age, gender, presenting complaints, and comorbid conditions (diabetes, hypertension, coexisting renal diseases, ischemic heart diseases, heart failure).

Initial laboratory results were recorded from tests performed already for the patients. A complete blood count, erythrocyte sedimentation rate, blood urea, serum creatinine, serum calcium, serum albumin, SPE, Bence Jones protein in urine, skeletal surveys, bone marrow aspirate, and bone marrow biopsy results were registered for each patient.

The measurement of hsCRP and β 2M was done using ELISA. "Enzyme Immunoassays for the quantitative high sensitive determination of CRP" and "Enzyme Immunoassays for the quantitative determination of β 2M" kits were used (demeditec-Germany).

This work is approved by institute review board at Al Nahrain University College of medicine.

The collected data were organized, tabulated, and statistically analyzed using the Statistical Package for Social Science (SPSS) version 23.

Several statistical equations were used to determine the correlations between different parameters of the study sample.

For the parametric variables, Pearson correlation coefficient was used, and for the nonparametric variables the spearman correlation coefficient was used, and to correlate hsCRP with the β 2M the linear regression was used.

Results

Those 25 multiple myeloma patients were categorized according to the (ISS) into two categories which are early (Stage I) and advanced (for both Stage II and III). The majority of 17 patients (68%) were in the advanced stage as demonstrated in [Table 1]. Fifteen were females (60%). Patients' age ranged from 36 to 80 years with a mean of 56.5 ± 12.6 years.

Fourteen patients had comorbid conditions such as any of these or any combination (Diabetes, hypertension, coexisting renal diseases, ischemic heart diseases, and heart failure), there was no statistical significance

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correlation (P = 0.149) with staging, nor with results such as hsCRP (P = 0.176) and β 2M (P = 0.128).

As shown in Figure 1, fatigue was the most common manifestation (76%), which is significantly correlated to anemia (r = 0.634, P = 0.001).

While bone pain presented in 68% that is correlated with the serum calcium (r = 0.600, P = 0.002), as shown in Figure 1.

Anemia is significantly associated with the stage of the disease (P = 0.004) [Table 2].

Renal impairment is reported in 64% with statistically significant correlation with the stage of the disease (r = 0.665, P = 0.0001) [Table 3].

The mean concentration of M-band as reported by SPE was 23.4 g/dL which was detected in 17 patients only (68%). Its detection is statistically associated with advanced stage disease (ISS II and III) (P = 0.0001). Unlike detection of a positive Bence-Jones protein in urine that was documented in 4 patients but of no statistical association with disease stage (P = 0.315) [Table 2].

 β 2-microglubulin mean was 5.25 ± 2.12 µg/ml with a very significant association with disease stage (*P* = 0.0001) [Table 3].

It was found to be elevated in patients with renal impairment higher than those with normal renal function (6.501 µg/ml and 4.100 µg/ml, respectively) with significant positive correlation between the level of β 2M and the degree of renal impairment (r = 0.588, P = 0.002) [Table 4].

β2-microglubulin was also significantly associated with other manifestations such as anemia (P = 0.001), fatigue (P = 0.002), serum creatinine, bone pain and the presence of M-band, but not with hypercalcemia (P = 0.396), lytic bone lesion (P = 0.874), or Bence-Jones protein (P = 0.309) [Table 4].

Total hsCRP mean was $20.87 \pm 11.20 \,\mu\text{g/ml}$ with a very significant positive correlation with staging (r = 0.779, P = 0.0001) [Table 3].

It was elevated in patients with renal impairment in contrast to patients with normal renal figures (27.205 µg/ml and 15.035 µg/ml, respectively) which has significant positive correlation between the 2 parameters (r = 0.588, P = 0.002) [Table 4], as with other manifestations such as anemia (P = 0.001), fatigue (P = 0.002), serum creatinine, bone pain and the presence of M-band, but not with hypercalcemia (P = 0.338), lytic bone lesion (P = 0.632), or Bence-Jones protein (P = 0.275) [Table 4].

Table 1: Distribution of gender according toInternational Staging System

Gender	Mean (years)		Total		
		Stage I, n (%)	Stage II, n (%)	Stage III, n (%)	
Male	55	3 (12)	3 (12)	4 (16)	10 (40)
Female	58	5 (20)	4 (16)	6 (26)	15 (60)
Total	56.5	8 (32)	7 (28)	10 (40)	25 (100)

ISS = International Staging System

Table 2: Distribution of manifestations according to International Staging System

	ISS		Total, <i>n</i> (%)	Р
	Stage I, <i>n</i> (%)	Stage II and III, n (%)		
Fatigue	4 (16)	15 (24)	19 (76)	0.061
Bone pain	4 (16)	13 (20)	17 (68)	0.199
Anemia*	1 (4)	13 (20)	14 (56)	0.004**
Renal Impairment**	0	12 (16)	12 (48)	0.0001**
Hypercalcemia***	3 (12)	9 (12)	12 (48)	0.350
Lytic bone lesions	4 (16)	7 (12)	11 (44)	0.692
M-band	2 (8)	15 (20)	17 (68)	$0.0001^{\dagger\dagger}$
Bence-Jones protein	0	2 (8)	4 (16)	0.315

*Reference range for hemoglobin for males=13.0, females=11.5 (g/dL), **Reference range for serum creatinine (0.68-1.36 mg/dL), ***Reference range for serum calcium (8.5-10.5 mg/dL). ISS = International Staging System

Table 3: Laboratory parameters according to International Staging System

	ISS (means)		Total	Р
	Stage I	Stage II and III	Mean±SD	
Serum calcium (mg/dL)	10.43	11.46	11.14±2.47	0.366
Serum creatinine (mg/dL)*	0.79	2.57	1.57±1.13	0.0001**
Hemoglobin (g/dL)	10.0	9.8	9.85±2.10	0.555
ESR (mm/h)	115	123	120.44±29.29	0.515
BM plasma cells (%)	22	46	38.16±15.37	0.0001**
Serum albumin (g/dL)	3.57	3.01	3.18±0.54	0.035^{\dagger}
β2-microglubulin (µg/ml)	3.206	6.971	5.25±2.12	0.0001**
hsCRP (µg/ml)	10.713	26.733	20.87±11.20	0.0001**

*An odd figure was excluded from the calculations for statistical interpretations, *Significant correlation, ^{††}Highly significant correlation. SD = Standard deviation, ESR = Erythrocyte sedimentation rate, hsCRP = High sensitivity C-reactive protein, BM = Bone marrow, ISS = International Staging System

The hsCRP was strongly correlated with bone marrow plasma cells % (r = 0.665, P = 0.0001) [Figure 2].

The hsCRP correlated with the β 2M using Pearson's correlation coefficient (r = 0.816, P = 0.0001), and using the linear regression model there was a very significant correlation ($R^2 = 0.666$, t = 6.767, P = 0.0001) [Figure 3].

Discussion

Any prognostic markers must be reproducible and accurate to allow better classification of the disease.

Table 4: Correlations between C-reactive protein,

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β2-microglubulin and different clinical manifestations					
	Mean CRP (µg/ml)	Р	Mean β2-microglubulin (μg/ml)	Р	
Sex					
Male	15.928	0.123	5.046	0.701	
Female	24.176		5.390		
Fatigue					
+ve	23.925	0.002**	5.744	0.012 [†]	
-ve	11.222		3.694		
Anemia*					
+ve	26.141	0.001**	6.135	0.006 ^{††}	
-ve	14.177		4.128		
Renal impairment**					
+ve	27.205	0.002 ^{††}	6.501	0.001**	
-ve	15.035		4.100		
Hypercalcemia***					
+ve	22.232	0.338	5.384	0.396	
-ve	19.625		5.130		
Lytic bone lesions					
+ve	21.678	0.632	4.946	0.874	
-ve	20.247		5.492		
Bone pain					
+ve	23.289	0.050^{\dagger}	5.641	0.133	
-ve	15.750		4.427		
M-band					
+ve	23.751	0.041 [†]	6.095	0.0001 ^{††}	
-ve	14.769		3.461		
Bence-Jones protein					
+ve	26.177	0.275	6.085	0.309	
-ve	19.867		5.094		

*Reference range for hemoglobin for males=13.0, females=11.5 (g/dL), **Reference range for serum creatinine (0.68-1.36 mg/dL), ***Reference range for serum calcium (8.5-10.5 mg/dL), *Significant correlation, **Highly significant correlation. CRP = C-reactive protein

In addition, it should be less complex and less time-consuming.^[24,25]

Serum level of β 2M can predict tumor burden (in term of cell size and proliferative activity) and the outcome as well as the survival independently as myeloma cells known to produce it.^[26,27]

During this study, MM patients age tend to be lower than expected (56.5 years) in comparison to worldwide reports (70 years),^[28] and other previous Iraqi records (63.4 years).^[22] Interestingly, 16% of patients in this study were under the age of 40 years while in other studies it was 2% only.^[5,23]

Gender distribution shows that female incidence is higher than male (54% for females), which is the similar to that reported by Alwan study.^[22]

The most common manifestations in our study were similar to what is reported by Kyle *et al.* as both



Figure 1: Distribution of manifestations according to international staging system. *Reference range for S. Creatinine (0.68–1.36 mg/dL). **Reference range for S. Calcium (8.5-10.5 mg/dL). ***Reference range for hemoglobin for males = 13.0, females = 11.5 (g/dL)



Figure 2: Correlation between high-sensitivity C-reactive protein and bone marrow plasma cell percent



Figure 3: Relation between high-sensitivity C-reactive protein and β 2-microglobulin

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fatigue and bone pain are the predominant presenting features.^[5,15]

It is shown that fatigue is correlated with the presence of anemia (P = 0.001) but it is unrelated to the severity of anemia (P = 0.140), and similarly the bone pain is positively correlated with hypercalcemia.

The primary cause of the hypercalcemia is widespread tumor-induced bone destruction as a result of increased osteoclastic bone resorption by cytokines secreted locally from myeloma cells.^[12]

The incidence of anemia is reported in 56% of patients with positive correlation with tumor burden expressed by plasma cell percentage in bone marrow (P = 0.004), as well as with renal impairment (P = 0.001)

Both impaired erythropoiesis and decreased erythropoietin production leading to further worsening of anemia,^[13,14] however, the severity of anemia has no positive correlation with neither the tumor burden nor with renal impairment. This discordant result can be explained by the common use of symptomatic treatment or even liberal use of blood transfusion as common practice by general physicians in cases of delayed diagnosis.

It is well documented that renal impairment is a common consequence of Multiple Myeloma,^[15,16] which is reported in 48% of patients similar to Kyle *et al.* 2003 report.^[5] The two major reasons for renal impairment are light chain nephropathy and hypercalcemia.^[29-32] The latter cause could not be proved in this study as there is no correlation between hypercalcemia and renal impairment (P = 0.078).

Hypercalcemia is demonstrated in (48%) of patients which is more than Kyle *et al.*(28%) results. It may be due to advanced disease stage as well as the common use of calcium supplements as an over counter medication.^[5]

BM Plasma cells percentage median is 40% which is much higher than Rajkumar *et al.* findings. The difference can indicate late diagnosis and aggressiveness of the disease.^[33]

The mean serum β 2M level is higher than what had been reported by Greipp *et al.* level (5.25 µg/ml compared 3.8 µg/ml) which indicates more advanced stage at diagnosis or even the effect of significant renal impairment in the studied patients.^[10] It is shown to have a positive correlation with disease activity parameters such as anemia (*P* = 0.006), fatigue (*P* = 0.012), and renal impairment (*P* = 0.001).

However, its use may be limited to our country by its availability, high expense, and reliability between different laboratories, in addition to its chance to be excreted by renal system. The hsCRP as an acute phase reactant protein is already established in the majority of hospitals laboratories with good experiences and easy reproducibility in estimation.

Thus, hsCRP can be considered as another useful marker in Multiple Myeloma patients.^[10,24,26] as it is established by many authors like Tienhaara *et al.* to have the same application of β 2M or even as more powerful prognostic marker as it is synthesized by hepatocyte.^[24,34]

In this study, CRP is found to have the same significance of β 2M in term of staging and disease activity parameters especially anemia (*P* = 0.001), fatigue (*P* = 0.002), renal impairment (*P* = 0.002) with no relation to other comorbid diseases (*P* = 0.176).

Therefore, it can substitute the use of β 2M with very good reliability, also it has a good correlation with tumor burden expressed by BM plasma cells percentage (*P* = 0.0001). While some other researchers like Brown *et al.* 1993 discouraged the use of CRP to monitor disease activity which may not necessarily reflect changes in disease activity and therefore may not be useful to monitor and follow the disease.^[35]

There is a positive linear correlation between the level of serum β 2M and hsCRP that encourage its use as an alternative parameter in staging and assessing multiple myeloma patients in our country with good reliability and noninferiority in its interpretation in term of advanced disease or related tissue injury in circumstances of limited resources.

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Conflicts of interest

There are no conflicts of interest.

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