

Study of The Role of Soluble Mannose Receptor (sMR/sCD206) in Multiple Myeloma

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Abstract

Background: Multiple Myeloma is an incurable B cell tumor characterized by the accumulation of malignant plasma cells in the bone marrow (BM). **Objective:** to assess serum level of soluble mannose receptor (sMR/CD206) in multiple myeloma patients and to predict its role in pathogenesis of multiple myeloma. **Methods:** A case- control study was conducted on thirty Egyptian patients (15 males and 15 females; their age ranged between 40-73 years) diagnosed with multiple myeloma and twenty race and sex matched healthy controls. Patients attending the clinical oncology and nuclear medicine department ,Faculty of medicine , Menoufia University. Informed consent was obtained from the patients, and this study was approved by local ethical committee of Faculty of medicine, Menoufia University and Benha University Hospital. **Results:** All studied MM cases were evaluated, 26.6% had ISS I, 40% had ISS II and 33.3% had ISS III. Hemoglobin level was significantly lower in MM cases when compared to control group ($P < 0.001$). Whereas, WBCs and platelets did not differ significantly between both groups ($P > 0.05$ for each). MM patients had significantly higher sMR level

when compared to control group at diagnosis (P value < 0.001). Initial sMR level showed significant positive correlations with age of onset. Otherwise, no significant correlations were found regarding sMR levels with other studied parameters in MM group. **Conclusion:** This study indicates that sMR is a potentially interesting biomarker in MM, and should be explored in further studies.

Keywords: Multiple Myeloma; sMR; CD206.

Introduction

Multiple Myeloma is an incurable B cell tumor characterized by the accumulation of malignant plasma cells in the bone marrow (BM). The interaction of malignant plasma cells with the bone marrow microenvironment contributes to their growth, proliferation, invasion, metastasis, and chemo-resistance. The multiple myeloma bone marrow micro-environment is composed of cells, extracellular matrix, and soluble factors, among which macrophages (MQs) are an abundant and important component. Several studies have shown that the degree of macrophages infiltration can serve as prognostic marker in newly diagnosed patients with multiple myeloma⁽¹⁾.

The role of macrophages (MQs) in the pathophysiology of human malignancies has received increasing interest. A subset of macrophages called tumor-associated macrophages (TAMs) is now known to be important for development of malignant diseases, due to suppression of anti-tumor immunity, promotion of angiogenesis and facilitation of metastasis⁽²⁾. It is now established that tumor associated macrophages (TAMs) are

hijacked by cancer cells to perform several pro-tumor functions which are inherent to M2-macrophages including: suppression of anti-tumor immunity, matrix remodeling and promotion of angiogenesis⁽³⁾. The macrophage mannose receptor (MR/CD206/MRC1) is a recognized marker of alternatively activated macrophages, mannose receptor (MR) is commonly expressed in selected populations of macrophages and dendritic cells (DCs) and mediates the phagocytosis of pathogens. It was shown that serum levels of soluble mannose receptor is remarkably elevated in patients with multiple myeloma and may be demonstrated as an independent marker for overall survival⁽⁴⁾.

Thus, we aimed to assess serum level of soluble mannose receptor (sMR/sCD206) in multiple myeloma patients and to predict its role in pathogenesis of multiple myeloma.

Patients and Methods

This case- control study was conducted at clinical pathology department, Benha University hospitals in collaboration with clinical oncology and nuclear medicine department, Faculty of Medicine, Menofia University. Thirty Egyptian patients (15

males and 15 females; their age ranged between 40-73 years) newly diagnosed with multiple myeloma and twenty age and sex-matched healthy controls were included in the study during the period from January 2021 to December 2021.

Informed consent was obtained from the patients after explanation of the study procedure and this study was approved by local ethical committee of faculty of medicine, Menofia University and Benha University.

Subjects were divided into the following groups:

Group I: 30 newly diagnosed MM patients who met the diagnostic criteria of myeloma. Blood samples were obtained from all patients at the time of diagnosis prior to start of treatment.

Group II: 20 age and sex matched healthy volunteers as control group.

Inclusion Criteria:

- Newly diagnosed multiple myeloma patients that not received treatment.

Exclusion Criteria:

- Patients with other types of any malignancy.

- Multiple myeloma patients already on treatment.
- Alcoholic liver disease.
- Patients refuse to sign the consent of sample collection.

Methods

Sampling

Three milliliters of peripheral venous blood were withdrawn from all enrolled subjects under complete aseptic conditions in empty vacutainer tubes. The samples were allowed to clot at room temperature for 30 min and then centrifuged at 3000xg for 5 min. Serum was separated and stored at -80° C for measurement of serum sMR level by enzyme immunoassay technique using enzyme immunoassay kit (cat no SEA733hu for sMR, Cloud-Clone Corp.).

Statistical methods

The collected data is revised, coded and tabulated using Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data are presented and suitable analysis is done according to the type of data obtained for each parameter.

Kolmogorov Smirnov test was used to test the normality of data distribution. The parametric numerical data were expressed in the form of Mean, Standard deviation (\pm SD), while the non-parametric numerical data were expressed by Median and range. Frequency and percentage were reported for non-numerical data .

Differences between groups were tested using Student T Test between two study group means, while for a non-parametric variables; Mann Whitney Test (U test) was used between two study groups.

The correlation coefficient was used to define the strength and direction of the linear relationship between two variables.

A P value was considered significant if <0.05 at confidence interval 95%.

Results

No significant difference was detected regarding age and sex between 2 groups (Table 1). All studied MM cases were evaluated, 26.6% had ISS I, 40% had ISS II and 33.3% had ISS III (Table 2).

Hemoglobin level was significantly lower in MM cases when compared to control group ($P <0.001$). Whereas, WBCs and platelets did not differ significantly between both groups ($P >0.05$ for each) (Table 3). MM patients had significantly higher sMR level when compared to control group at diagnosis ($P <0.001$) (Table 4).

Initial sMR level showed significant positive correlations with age of onset. Otherwise, no significant correlations were found regarding sMR levels with other studied parameters in MM group (Table 5).

Table (1): Comparison of demographic data between studied groups.

		Control N=20		MM N=30		P
Age (years)	Mean \pm SD	59.3	7.3	58.9	8.3	0.646
Males	N, %	11	55%	15	50%	0.44
Females	N, %	9	45%	15	50%	

SD: standard deviation.

Table (2): ISS stages in all studied MM cases.

			MM N=30	
ISS	I	N, %	8	26.6%
	II	N, %	12	40%
	III	N, %	10	33.3%

ISS: International Staging System

Table (3): Comparison of CBC between studied groups.

		Control N=20		MM N=30		<i>P</i>
WBCs (X10 ⁹ /L)	Median (range)	5.2	(4.5-11.6)	4.8	(1.5-17.5)	0.145
HB (g/dL)	Median (range)	12.7	(11.2-15.7)	9.85	(6.1-12.5)	<0.001
Platelets (X10 ⁹ /L)	Median (range)	218	(154-312)	200	(74-349)	0.567

Table (4): Comparison of initial level sMR between studied groups.

		Control		MM		<i>P</i>
sMR (ng/ml)	Median (range)	223.1	(126.7-482.1)	414.5	(154.5-690)	<0.001

Table (5): Correlations of sMR level with other studied parameters in MM group.

	sMR	
	<i>Rs</i>	<i>P</i>
Age of onset	0.556	<0.001
Creatinine	0.121	0.088
β2M	0.30	0.053
BM Biopsy	0.150	0.266

Rs: Spearman's correlation coefficient

Discussion

Multiple myeloma (MM) is an incurable hematological malignancy in which clonal

plasma cells proliferate and expand within the bone marrow, leading to osteolytic bone

destruction, hyper-calcemia, renal failure, and anemia ⁽⁵⁾. Unlike other malignancies that metastasize to bone, the osteolytic bone lesions in multiple myeloma exhibit no new bone formation ⁽⁶⁾. Approximately 1% to 2% of patients have extramedullary disease (EMD) at the time of initial diagnosis, while 8% develop EMD later on in the disease course ⁽⁷⁾.

The relatively macrophage-specific receptor CD206 is commonly used marker of macrophages both in vivo and in vitro. CD206 is mainly expressed by macrophages, but may be found on dendritic cells and endothelial cells. CD206 can be cleaved from the cell surface, resulting in soluble protein (soluble CD206 [sCD206/sMR]) that can be detected in blood samples ⁽⁸⁾.

This study aimed to assess serum level of soluble mannose receptor (sMR/CD206) in multiple myeloma patients and to predict its role in pathogenesis of multiple myeloma.

This study was conducted in collaboration between clinical pathology department of Benha University hospital and clinical oncology and nuclear medicine department of faculty of medicine, Menoufia University.

The study included 2 groups: group **I** including 30 multiple myeloma patients and group **II** including 20 apparently healthy age and sex matched individuals as a control group.

Regarding hemoglobin level, the present study showed that it was significantly lower in MM cases when compared to control group ($P < 0.001$). While WBCs and platelets did not differ significantly among both groups .

In the same line it was found that ⁽⁹⁾, hemoglobin was significantly lower in patients with MM. Also, partially agreed with our results, a highly significant decrease in the mean value of hemoglobin in patients with MM was found ⁽¹⁰⁾. Meanwhile, platelet and WBC count decreased significantly ($P < 0.01$) when they were compared with control group. The most frequent underlying pathophysiological mechanism of decreased hemoglobin level is anemia of chronic disease (ACD), relative erythropoietin (EPO) deficiency due to partially renal impairment ⁽¹¹⁾.

The present study results revealed that the newly diagnosed MM patients had significantly higher levels of serum sMR level compared to control group ($P < 0.001$).

In a study performed ⁽³⁾ on newly diagnosed MM patient, the study revealed that 27% of patients had elevated sMR levels, while other studies ⁽¹²⁾ found no difference in sCD206 among MM patients.

Previous studies explained the pathophysiology of increased sMR/sCD206 in MM. It was reported that ⁽¹³⁾ macrophages are a major cellular component of the tumor microenvironment in the pathogenesis of myeloma. Furthermore, other studies suggest that these tumor-associated macrophages (TAMs) actively promote tumor initiation, growth and progression and in human CD206 were considered an important marker of macrophage lineage. Also, it was revealed that soluble mannose receptor (sMR) is a macrophage activation marker which has been demonstrated to be increased in patients with inflammation, auto-immune diseases and malignancies ⁽⁴⁾.

The results of the present study revealed highly significant positive correlations between the level of sMR at diagnosis and age of onset with P value <0.001 while no significant correlations with creatinine, B2M and BM biopsy. Partially agreed with our findings, those presented by Andersen et al. ⁽³⁾ who found no significant association between sMR and creatinine nor

plasma cell (PC) infiltration of BM but found positive association to B2M.

Conclusion

Our results indicate that sMR is a potentially interesting biomarker in MM, and should be explored in further studies.

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