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Plasma level of osteopontin in multiple myeloma: Its correlation with international staging system and clinical and laboratory findings

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Abstract:

BACKGROUND: Multiple myeloma (MM) is a hematological malignancy that affects the bone marrow (BM) and results from the multiplication and infiltration of malignant plasma cells into the BM. Osteopontin (OPN) regulates the processes of osteoclast differentiation, translocation, and activation. Furthermore, it has an important role in angiogenesis in MM.

OBJECTIVES: The objective of this study was to assess the association between plasma OPN level in MM patients with both the disease stage and bone involvement and to find the correlation of OPN level with laboratory parameters and glomerular filtration rate (GFR).

PATIENTS, MATERIALS, AND METHODS: Eighty individuals were enrolled in the study; 40 of them were patients diagnosed with *de novo* MM before starting any treatment and 40 were healthy individuals as a control group. Enzyme-linked immunosorbent assay technique was utilized for measurement of the levels of OPN and β2-microglobulin (β2M) in plasma.

RESULTS: The median plasma OPN level was significantly higher in MM patients compared to the control group ($P < 0.001$). Plasma OPN level was significantly correlated with serum uric acid ($P = 0.029$), GFR ($P = 0.001$), and β2M ($P < 0.001$). Patients in Stage III had higher OPN level than those in Stages I and II ($P < 0.001$). Patients with lytic bone lesions and/or pathological fractures had significantly higher OPN than patients with osteoporosis alone or no bone lesion ($P = 0.029$).

CONCLUSIONS: Plasma OPN can be considered a prognostic parameter in evaluating patients with MM, given its significant elevation in Stage III, and a predictor of the severity of bone disease and renal insufficiency.

Keywords:

Glomerular filtration rate, multiple myeloma, osteopontin, β2-microglobulin

Introduction

Multiple myeloma (MM) is defined as a complex and heterogeneous hematologic neoplasm, which is identified by the growth and buildup of clonal plasma cells into the bone marrow (BM), with production of a monoclonal immunoglobulin protein (M-protein) detectable in the serum and/or the urine.[1]

Myeloma cells infiltrate the BM microenvironment, where their interaction with the extracellular matrix and marrow accessory cells (such as osteoblasts, osteoclasts, and stromal cells) promotes cell growth and survival signals and plays a role in developing resistance to treatment. The patients will have signs of anemia, renal failure, bone pain, pathological fractures, amyloidosis-related problems, and infections.[2]

Bone disease is a major complication of MM, significantly impacting quality of

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life.[3] The physiological process of bone remodeling is mainly regulated by complex interactions between the bone matrix, osteocytes, osteoclasts, osteoblasts, and immune cells.[4]

Myeloma bone disease involves profound dysregulation in bone remodeling processes, which result in excessive osteoclast activity and impaired osteoblast function, ultimately resulting in bone loss. Osteocytes are crucial in these pathways by producing receptor activator of NF-κB ligand (RANKL), sclerostin, osteopontin (OPN), and other factors. Myeloma cells induce apoptosis of osteocytes, which modifies the BM microenvironment to create a niche for their growth. In patients with MM, the decline in viable osteocytes is associated with a higher extent of bone disease.[5-8]

Renal impairment is a frequent complication of MM that can manifest at the time of diagnosis.[9] Glomerular filtration rate (GFR) is a reliable indicator of renal function and can be estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[10]

An International Staging System (ISS) for MM is defined as an easy, reliable risk stratification algorithm based on the level of β2-microglobulin (β2M) and albumin.[11]

OPN is a multifunctional protein that belongs to the small integrin-binding glycoprotein.[12] It is implicated in various physiological and pathological mechanisms, such as inflammation, adhesion, invasion, migration, apoptosis, bone resorption, and tumor progression.[13,14]

It regulates osteoclast differentiation, migration, and activation, and it aids in the attachment of osteoclasts to the bone and the formation of ruffled border zones crucial for bone resorption.[15,16] OPN binds to CD44 on the osteoclast surface, which results in osteoclast motility and bone resorption.[17] The overexpression of OPN in myeloma patients could result from OPN secretion from both tumor cells and tumor-induced nontumor cells.[18]

OPN plays a critical role in promoting angiogenesis in MM, as it is closely linked to BM microvascular density. Conditioned media from myeloma cells, depleted of OPN, fail to trigger a pro-angiogenic response, and anti-OPN antibody can inhibit myeloma-induced angiogenesis.[19,20]

The study aims to assess the association of plasma OPN with the stage of the disease and with bone involvement and to elaborate on the correlation of OPN level with laboratory parameters and GFR in MM patients.

Patients, Materials, and Methods

This cross-sectional study enrolled 40 newly diagnosed *de novo* MM patients. It was conducted from January 2019 to July 2019 at Hematology Center of Medical City Complex. Initial laboratory results: complete blood counts, blood urea, serum creatinine, calcium, uric acid, albumin, protein electrophoresis and immunofixation, skeletal surveys, and BM aspirate results were all taken from patients' records.

Following the ISS, patients were categorized into two groups for statistical purposes:
- Non-Stage III (Stages I and II): with β2M < 5.5 mg/L
- Stage III: with β2M ≥ 5.5 mg/L.

Regarding bone lesions, patients were further categorized into two groups:
- Group I: Presence of lytic bone lesions (LBLs), LBL plus osteoporosis (OP), or OP with bone fracture
- Group II: Presence of OP alone or no bone lesion.

The study included a control group of 40 healthy individuals who were matched with the patients' group for age and sex.

Pretreatment EDTA-blood samples underwent centrifugation at 1000 g for 15 min. Plasma was obtained and kept in a deep freezer (−40°C).

Plasma samples were tested via enzyme-linked immunosorbent assay technique (ELISA) for the levels of OPN using the human OPN immunoassay, Quantikine ELISA kit (R & D Systems, USA), and β2M using the human β2M ELISA kit (R & D Systems, USA).

Ethical approval

This study had granted approval from the Ethical Committee of the Scientific Council of Pathology at the Iraqi Board for Medical Specializations (Issue No. Path. 3 on January 3, 2019) and informed consent was obtained from all participants before the study.

Statistical analysis

The Statistical Package for the Social Sciences version 24 (IBM Corp., Armonk, NY, USA) was employed for data interpretation. The hematological and biochemical parameters were expressed as mean ± standard deviation (SD) and range. The other data were displayed as median, interquartile range (IQR), and range, and the comparison of the study groups was carried out using the Mann–Whitney *U* test. Spearman's rank correlation was calculated to reveal the relation between OPN level and hematological and biochemical parameters. A *P* value under 0.05 was considered statistically significant.

Results

Of the 40 patients with *de novo* MM, 19 were males (47.5%) and 21 were females (52.5%) with a male-to-female ratio

of 1:1.1. The mean age for patients was 61.48 ± 14.27 years with an age range of 38–90 years. The mean age for the control group was 59.73 ± 12.39 years within an age range of 38–85 years.

The essential clinical features in patients at diagnosis were bone pain (87.5%), pallor (82.5%), neurological manifestation (25%), pathological fracture (15%), and fever (7.5%).

Hemoglobin (Hb) <10 g/dL was found in 72.5%, neutropenia with absolute neutrophil count (ANC) less than 2×10^9/L was found in 10%, neutrophilia with ANC > 7×10^9/L was found in 7.5%, and thrombocytopenia (platelet count < 150×10^9/L) was found in 17.5%. GFR < 60 mL/min/1.73 m^2 was encountered in 67.5%. Table 1 shows the laboratory findings at presentation.

A statistically significant difference in OPN and β2M median levels was identified when comparing the patients and control groups ($P < 0.001$ for both) [Table 2].

Table 3 shows significant positive statistical correlations of OPN with uric acid ($P = 0.029$) and β2M ($P < 0.001$) and a negative correlation with GFR ($P = 0.001$). The correlations of OPN with Hb, ANC, platelet count, ESR, BM plasma cells %, and serum calcium were statistically insignificant.

Table 1: Laboratory parameters and glomerular filtration rate in multiple myeloma patients at diagnosis

Parameters	Mean±SD	Range
Hb (g/dL)	8.66±1.86	4.84–13
ANC (×10^9/L)	4.04±2.04	1.1–11
Platelet count (×10^9/L)	230.83±112.89	44–574
ESR (mm/1st h)	111.52±33.53	25–150
BM plasma cells (%)	42.5±21.6	11–90
Serum calcium (mg/dL)	10.2±2.2	7.1–16
Serum uric acid (mg/dL)	6.7±3.72	2.4–21.2
GFR (mL/min/1.73 m^2)	50.04±34.78	2.88–124.89

The normal range for serum calcium was 8.4–10.4 mg/dL and serum uric acid was 2.5–7.2 mg/dL. GFR=Glomerular filtration rate, ANC=Absolute neutrophil count, BM=Bone marrow, SD=Standard deviation, ESR=Erythrocyte sedimentation rate, Hb=Hemoglobin

Table 2: Comparison between osteopontin and β2-microglobulin levels in multiple myeloma patients with the control group

Parameter	MM patients (*n*=40)	Healthy controls (*n*=40)	*P**
OPN (ng/mL)			
Median (IQR)	236.14 (398.32)	65.98 (24.59)	<0.001
Range	7.3–935.48	7.3–169.88	
β2M (μg/mL)			
Median (IQR)	10.17 (9.48)	2.66 (0.81)	<0.001
Range	2.32–19.33	1.87–3.82	

*Mann–Whitney *U*-test. OPN=Osteopontin, IQR=Interquartile range, MM: Multiple myeloma, β2M=β2-microglobulin

Regarding patient distribution according to ISS, stage I included 2 patients (5%), Stage II included 8 patients (20%), and Stage III included 30 patients (75%). Table 4 shows a statistically significant difference in OPN levels between patients in Stages I and II with those in Stage III ($P < 0.001$).

The radiological survey showed that 27 patients (67.5%) had LBL, 10 patients (25%) had OP, and 5 patients (12.5%) had no bone lesions. Interestingly, two patients had both LBL and OP. Pathological fractures were reported in six patients (15%): two patients with LBL, two patients with OP, and two patients with both LBL and OP.

OPN levels exhibit a statistically significant difference when comparing patients with LBL and/or pathological fracture and those having OP alone or no bone lesion ($P = 0.029$) [Table 5].

Table 3: Spearman's rank correlation of osteopontin level with hematological and biochemical parameters and glomerular filtration rate in multiple myeloma patients

Parameters	OPN	
	r	*P*
Hb (g/dL)	−0.186	0.251
ANC (×10^9/L)	<0.001	1
Platelet count (×10^9/L)	−0.268	0.094
ESR (mm/1st h)	−0.07	0.669
BM plasma cells (%)	0.053	0.746
Serum calcium (mg/dL)	−0.079	0.629
Serum uric acid (mg/dL)	0.345	0.029
β2M (mg/L)	0.705	<0.001
GFR (mL/min/1.73 m^2)	−0.519	0.001

OPN=Osteopontin, GFR=Glomerular filtration rate, ANC=Absolute neutrophil count, BM=Bone marrow, ESR=Erythrocyte sedimentation rate, β2M=β2-microglobulin, Hb=Hemoglobin

Table 4: Comparison between the osteopontin level in Stage I and II patients and those with Stage III multiple myeloma

Parameter	Stage I and II (*n*=10)	Stage III (*n*=30)	*P**
OPN ng/mL			
Median (IQR)	88.55 (49.44)	285.2 (412.29)	<0.001
Range	7.3–235.45	74.26–935.48	

*Mann–Whitney U-test. OPN=Osteopontin, IQR=Interquartile range

Table 5: Comparison of osteopontin values among multiple myeloma patients regarding bone lesions

Parameter	LBL alone (25), LBL+OP (2), OP+pathological fracture (2) (*n*=29)	OP alone (6) or no bone lesion (5) (*n*=11)	*P**
OPN ng/mL			
Median (IQR)	280.03 (414.11)	125.2 (169.5)	0.029
Range	57.2–935.48	7.3–285.95	

*Mann–Whitney *U*-test. OPN=Osteopontin, IQR=Interquartile range, LBL=Lytic bone lesions, OP=Osteoporosis

Discussion

The mean age for patients is comparable to what has been mentioned by other Iraqi studies,[21,22] a Saudi Arabian study,[23] a Jordanian study,[24] and an international report in 2015.[25]

MM cases were observed slightly more frequently in females, consistent with findings from other Iraqi studies,[22,26] a Saudi Arabian study in 2019,[27] and an Italian study.[28] However, this finding contradicts those of other Iraqi reports[29] and an Indian report.[30]

Most patients presented with bone pain and pallor, and to a lesser extent neurological manifestation, this is comparable to what was reported by Alwan[31] and followed by pathological fracture in 15% of patients which is comparable to Mortada *et al*.'s finding.[32]

Anemia is frequently observed (Hb < 10 g/L) which is in consisting to what is noted by Joshi *et al*.,[30] and the mean Hb level is comparable to other studies.[33-35] Anemia is an important feature in MM, arising from marrow infiltration by myeloma cells, cytokines, like TNF-α IL-1 which may suppress erythropoiesis, and inadequate erythropoietin production due to myeloma-related renal insufficiency.

The mean of GFR and the high frequency of patients having GFR < 60 ml/min/1.73 m^2 are comparable to what was found by Omosule.[36] Renal impairment is a well-recognized complication of MM.

Most cases are presented at Stage III of the ISS, in agreement with an Egyptian study by Al-Feky *et al*.[37] and an Emirati study by Abu Haleeqa *et al*.[38] This points to a high risk of progression and complications.

LBL and pathological fractures occurred in more than two-thirds of cases and to a lesser extent OP. These observations are comparable to studies in Croatia,[39,40] Pakistan,[41] and India.[42] Bone disease is one of the main complications of MM that significantly impacts the quality of life.

The β2M level in MM patients is much higher than reported by previous Iraqi studies.[43] This difference may be due to a high frequency of Stage III in our patients.

The comparison of the median OPN value in MM patients with the control group reveals a statistically significant difference. This finding is in agreement with other international studies.[39,44,45] This result may reveal the implication of OPN in MM biology.

Plasma OPN is significantly correlated with β2M, and this positive correlation may indicate that OPN is associated with tumor burden.

The correlations between OPN and both serum uric acid and GFR were statistically significant. There are no previous studies correlating OPN plasma levels with uric acid and GFR; however, Standal *et al*.[44] had demonstrated an association between OPN and serum creatinine, the latter is used in estimating GFR.

A comparison between the OPN level in patients with Stage I and II patients versus those in Stage III shows a significant difference in the median values, demonstrating that elevated plasma OPN level is associated with disease progression in MM patients. This finding aligns with a previous report by Valković *et al*.[39] which found significantly higher OPN levels among Stage III patients compared to those with Stages I and II but based on the Durie-Salmon staging system.

Mechanisms underlying this association may be due to the contribution of OPN in the activation of angiogenesis by vascular endothelial cells and the enhancement of proliferation and apoptosis prevention of tumor cells.[46,47]

An important complication that affects patients with MM is bone disease, which affects their quality of life. Patients with LBL and/or pathological fracture had a significantly higher median plasma OPN level than those with OP alone or no bone lesion, and this finding is similar to what was reported by other international studies.[39,45,48] This mechanism appears to result from the stimulation of CD44 on the osteoclast surface by OPN, which is crucial to osteoclast motility and bone resorption. Hence, this observation supports the concept that OPN is pivotal to bone disease pathology in MM.[17]

Conclusions

plasma OPN is a valuable biomarker in anticipating prognosis in patients with MM and associated with advanced disease. Plasma OPN reflects the extent of bone disease, correlates with renal insufficiency severity, and is associated with increased serum uric acid and a decline in GFR.

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Conflicts of interest
There are no conflicts of interest.

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