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Study of Multiple Myeloma Occurrence in Patients With 5%-10% Bone Marrow Plasma Cells: A Case Series Regarding Revised IMWG Diagnostic Criteria

Hasan Jalaeikhoo[1], Mohammad Zokaasadi[1], Mohsen Rajaeinejad[1], Manoutchehr Keyhani[2], Morteza Sharifzadeh[1,*]

[1] AJA Cancer Epidemiology Research and Treatment Center (AJA- CERTC), AJA University of Medical Sciences, Tehran, Iran

[2] Hematology and Oncology Research Center, Vali-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran

**Corresponding authors:Morteza Sharifzadeh, West Fatemi Avenue, Shahid Etemadzadeh Street, 501 army hospital, Tehran, Iran. Tel.: +982143823545; Fax: +982143823545; E-mail: morteza.sharifzade@gmail.com*

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Abstract

Introduction: Utilizing lower limit of bone marrow plasma cells (BMPCs) is the main existing criterion to diagnose multiple myeloma (MM). According to the revised international myeloma working group (IMWG) diagnostic criteria, the value of 10% is agreed among experts as the cut off level for diagnosis. Symptomatic patients with BMPC above this value are identified as definite cases of MM. However, there are MM patients who have BMPC of less than 10%. Therefore, the above-mentioned cut off point could delay the diagnosis, which in turn results in adverse effects in patients' clinical course.

Case Presentation: The current study represented data from consecutive patients with 5%-10% BMPC at our center from 2004 to 2013. MM existed among patients, as expected. This series provides a quantitative approximation of MM prevalence in the studied cases.

Conclusion: The reported patients' status demonstrated the limitations of the abovementioned cutoff criterion to diagnose myeloma, and emphasizes the importance of employing further diagnostic procedures in patients with marginal amounts of BMPC and high clinical suspicion. It is shown that supplementary examination is especially required for two subgroups of patients with certain clinical and laboratory characteristics.

INTRODUCTION

Multiple myeloma (MM) is the second most common hematologic malignancy [1, 2]. Its diagnosis is challenging in some cases [3]. In order to enhance the accuracy of myeloma diagnosis, different criteria are proposed. According to the newest versions of myeloma guidelines[4-6], the most acceptable diagnostic method is the revised international myeloma working group (IMWG) criteria [7]. Based on the revised IMWG [7], at least 10% of bone marrow plasma cell (BMPC) is required to confirm the diagnosis of MM. Defining a certain cut off point for BMPC rate is a major difference between the latest (2014) and the previous IMWG criteria [8].

It is known that MM could infrequently present with BMPC 5%-10% [8]. Nonetheless, it is unknown whether MM frequency in the aforementioned range of BMPC is rare, relatively common, or quite common. This study aimed to report 35 consecutive patients with 5%-10% BMPCs, in order to elucidate their features and roughly estimate MM occurrence in

this range of plasma cells. Furthermore, the accuracy of revised IMWG criteria to distinguish between myeloma and non-myeloma patients was investigated. Finally, the differences between MM and non-MM cases in primary assessments were studied and the characteristics that made patients potential candidates for further evaluations were introduced.

CASE PRESENTATION

In order to collect data "Plasma Cell" keyword was searched in the database of Pathology Center of Arad Hospital. From 2004 to 2013, all cases with 5%-10% plasma cells in their bone marrow biopsies were selected. Other biopsies and clinical documents of cases were studied and the ones with the prior history of multiple myeloma, plasmacytoma (either prior or concurrent), or monoclonal gammopathy of undetermined significance (MGUS) were excluded. Clinical records of cases were reviewed. In addition, in cases where it deemed necessary to follow further, they were called by phone to update their status. Final diagnoses were made based on evaluations in the first admission in our center and later assessments in our center or elsewhere. The study protocol was approved by the Ethical Committee of AJA University of Medical Sciences, Tehran, Iran.

Final Diagnoses and Baseline Characteristics of Cases

Thirty-five cases presented with 5%-10% BMPC. Eight cases were diagnosed with MM. The main characteristics of cases with MM are summarized in Table 1. MM was definitely ruled out in the remaining 27 cases.

BMPC, bone marrow plasma cell; Ca, calcium; Cr, creatinine; CT, computed tomography; CXR, chest X-ray; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; IgM, immunoglobulin M; MM, multiple myeloma; M-spike, monoclonal spike; MTX, methotrexate; N/A, not available in medical records; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis

In two cases (No. 1 and 2) repeating the bone marrow biopsy led to myeloma diagnosis. Two other cases (No. 3 and 4) were diagnosed as their overall evaluations were consistent with MM; moreover their BMPCs after relapse were considerably higher than 10%. In one case (No. 5) flow cytometry was suggestive of myeloma [9] and further cytogenetic evaluation confirmed the diagnosis. Case No. 6 was diagnosed with MM based on further evaluations in another center. In two cases (No. 7 and 8) computed tomography (CT)-guided biopsy confirmed the diagnosis.

In 27 cases MM was excluded. Six cases had gammopathy with unrelated signs. Three cases had lymphoma, two cases were RA and anemia of chronic disease, two cases had renal failure due to other causes and two cases had CVA. AML, discopathy, gastric ulcer, Deep vein thrombosis (DVT), and septic arthritis were the final diagnoses of five other cases. In the seven remaining cases, MM was ruled out and they were referred to other clinics or services for further evaluations.

Distribution of BMPC% in Myeloma and Non-myeloma Patients

Only two (No. 1, and 5) out of eight myeloma patients had less than 8% BMPC. This finding demonstrated the importance of a relatively higher BMPC%, even in the cases with less than 10%. The frequency of BMPC% in all patients is shown in Figure 1.

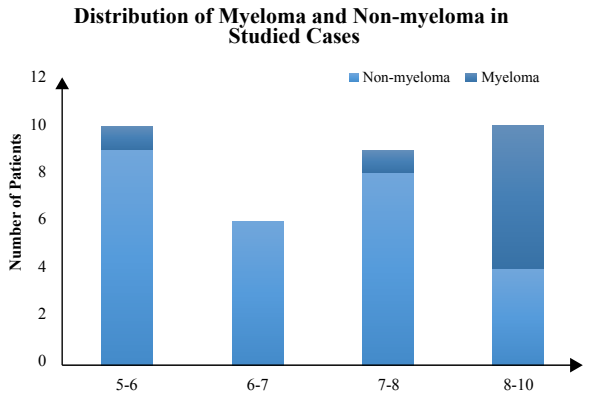

Figure 1: Distribution of Myeloma and Non-Myeloma Diagnoses Based on the Percentage of BMPC in Cases

The authors would like to highlight two groups of cases based on the evaluations of patients. These groups emphasized the importance of "protein electrophoresis" and "number of CRAB features (hyperCalcemia, Renal impairment, Anemia, and myeloma defining Bone lesions)" to diagnose MM in such perplexing situations.

Differences Between Myeloma and Non-myeloma Groups

One of the CRAB features + intense and obvious M-spike in protein electrophoresis, No. 1, 3, 5-8:

This group comprised of six cases (No. 1, 3, 5-8) who had 3 characteristics including: 1. at least one of CRAB features, 2. abundant monoclonal gammopathy with obvious M-spike in SPEP, and 3. BMPC range 5%-10% and no proven plasmacytoma. This group was

Table 1: Important Characteristics of Patients with Confirmed MM

	Admission Date, Last Contact (Survival Status)	Case Information	BMPC Rate	Final Diagnosis
Case 1	January 2008- November 2009 (dead)	78-year-old male with history of CABG and RA using MTX+ prednisone, Hb=8.5 g/dL, ESR=106 mm/h, Cr=1.4 mg/dL, Ca=10 mg/dL, lumbar MRI: multiple collapsed vertebrae - osteoporosis, SPEP: M-spike; gamma=3.1 g/dL (43%)	7%-8%	MM
		Five months after admission BMB showed 10%-12% plasma cells and he was treated with thalidomide-dexamethasone.		
Case 2	November 2004- February 2005 (dead)	55-year-old male with Hb=7 g/dL, ESR=125 mm/h, Cr=1.3 mg/dL, Ca=8.5 mg/dL, radiography: no osteolytic lesion, total Pr=12.1 g/dL, albumin=2.2 g/dL, SPEP= N/A, urine B.J lambda chain: +, ↑IgG (more than 2050 mg/dL)	8%-10%	MM
		He was re-evaluated after 27 days and his BMPC rate was 30%-35% in the second biopsy. He was treated with VAD chemotherapy.		
Case 3	February 2012- February 2013 (dead)	70-year-old male with history of myelofibrosis and CABG, Hb=7.4 g/dL, ESR=125 mm/h, Cr=1.5 mg/dL, Ca=9.2 mg/dL, skull and vertebrae X-ray: numerous hypo dense lesions, SPEP: M-spike; gamma=4.2 g/dL (49%), IgA=443 mg/dL (↑), flow cytometry: CD38= 79%, CD138= 83%	8%-10%	MM
		He was treated with Velcade®.		
Case 4	May 2010- April 2016 (dead)	49-year-old male with bone pain, Hb=12.9 g/dL, ESR=19 mm/h, Cr=N/A, Ca=9 mg/dL, radiography: N/A, SPEP: N/A, IgG= 2469 mg/dL (↑), flow cytometry: highly suggestive for MM	8%-10%	MM
		He was treated with VAD upfront, and after the first relapse (BMPC=40%) treated with cyclophosphamide-etoposide in the second line and then Velcade® in the third line.		
Case 5	October 2011- March 2015 (alive)	78-year-old male with Hb=7.6 g/dL, ESR=110 mm/h, Cr=2 mg/dL, Ca=10.5 mg/dL, radiography: N/A, SPEP: M-spike; gamma=4.9 g/dL (48%), IgM=7000 mg/dL, flow cytometry: CD38=80.1%, CD138=71.2%, CD20=9.0%, cytogenetic: t(11;14)	5%-6%	IgM MM
		He was treated with cyclophosphamide-Velcade®.		

Case 6	December 2012-February 2016 (alive)	68-year-old male with Hb=10.4 g/dL, ESR=125 mm/h, Cr=1 mg/dL, Ca=9.2 mg/dL, skull-X ray: no osteolytic or osteoblastic lesions, SPEP: M-spike; gamma=4.3 g/dL (46%)	9%-10%	MM
Case 7	August 2005-August 2005 (unknown)	68-year-old male with bone pain, Hb=10.4 g/dL, ESR=111 mm/h, Cr=0.8 mg/dL, Ca=7.8 mg/dL, skull-X-ray: punch-out lesions, CXR: severe osteopenia, CT-scan: extensive vertebral lesions, SPEP: M-spike; gamma=3.7g/dL (42%)	8%-10%	MM
		CT-guided biopsy from L1 lesion was performed and it showed clusters of plasma cells. Treatment was started with VAD therapy.		
Case 8	May 2007-July 2007 (dead)	81-year-old male with Hb= 8.5g/dL, ESR=125 mm/h, Cr=1.5 mg/dL, Ca=8.1 mg/dL, CT-scan: lytic lobulated mass lesion of the left iliac bone with soft tissue component, CXR: normal, SPEP: M-spike; gamma=2.3 g/dL (32%)	8%-10%	MM
		Biopsy of ischium lesion showed clusters of plasma cells, and he was treated with VAD therapy.		

BMPC, bone marrow plasma cell; Ca, calcium; Cr, creatinine; CT, computed tomography; CXR, chest X-ray; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; IgM, immunoglobulin M; MM, multiple myeloma; M-spike, monoclonal spike; MTX, methotrexate; N/A, not available in medical records; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis

not MGUS, since immunoglobulin monoclonal level was very high [7]. This group was also not smoldering MM due to patients' symptoms and it was not also symptomatic MM as the level of BMPC was less than 10% [7]. Only one patient from non-MM group met the criteria. It is noteworthy that in the remaining MM cases that were not in this group (No. 2, 4), SPEP was not available. According to immunoglobulin level, which presents in gamma region of SPEP, and also the difference between the amounts of total protein with albumin in No. 2, it can be predicted that M-spike would be presented in these cases if SPEP was available.

Concurrent occurrence of at least two CRAB features (except elevated creatinine and anemia), No. 1, 3, 5, 7, 8: Five cases (No. 1, 3, 5, 7, 8) in myeloma group concurrently had two CRAB features. In non-MM group, four patients had two CRAB features, which were anemia and elevated creatinine. Regardless of anemia and renal impairment, which may be presented together, the coincidence of two CRAB features and borderline amounts of BMPCs in non-MM cases was not common and none of non-MM patients in the current study were classified in this subgroup.

DISCUSSION

Accurate diagnosis of MM is critical in suspicious cases. Failure to diagnose MM early could lead to missing the standard treatment, which would prevent organ damage and mortality [10] On the other hand, overdiagnosis of MM leads to costly interventions and adverse effects for the patients.

Former studies on MM diagnostic criteria were intended to optimize diagnosis in patients. One of challenging and controversial issues in MM diagnosis is the required percent of plasma cells to confirm the diagnosis. In previous IMWG criteria in 2003, there was no minimum level set for clonal BMPCs, as 5% of patients with symptomatic myeloma show less than 10% plasma cells [11]. But in the revised IMWG criteria in 2014, 10% was defined as the cut off point to diagnose MM [7]. According to the revised criteria, if BMPC is below 10% and there is no plasmacytoma, CRAB features cannot be related to MM. This cutoff level was proposed in order to avoid misclassification of patients with MGUS as MM by merely showing the features of anemia, hypercalcemia, or renal dysfunction.

In the current study, eight out of 35 cases (22.8%), whose BMPC at presentation was 5% to 10% and did not have concurrent plasmacytoma, were diagnosed as MM. Based on our cases probability of MM in cases

with marginal amounts of BMPCs was about 20%, neither high nor negligible. Therefore, in cases with borderline amounts of BMPCs, if other evaluations are strongly suggestive, an expert can rule out or rule in MM; otherwise, image guided biopsy [12] or repeating bone marrow biopsy should be considered. These evaluations were recommended for eliminating diagnostic errors caused by patchy or uneven distribution of plasma cells in the bone marrow of MM patients.

Currently, the most applied method for myeloma diagnosis is the revised IMWG criteria. In MM cases (No. 1-8), it was difficult to make a diagnosis based on revised IMWG criteria. Although the revised IMWG criteria mentioned that in suspicious cases more evaluations including repeating bone marrow examination or imaging guided biopsy should be performed, the specifications of patients that needed further assessments are still unclear.

Protein electrophoresis is a primary diagnostic approach performed on suspicious cases in almost all centers. Therefore, the authors proposed that symptomatic cases with obvious M-spike and extensive amount of protein in gamma region should be evaluated further for MM, even though their first BMPC evaluation was less than 10%.

This series had two limitations. First, the number of studied patients (35) was not large. It is worth mentioning that borderline amount (5%-10%) of BMPC in myeloma patients at the time of diagnosis is uncommon. This percentage is also unusual in cases that symptoms occur due to other causes. Therefore, 5%-10% BMPC is not generally common in bone marrow biopsies. Second, as it was a retrospective study, some of the work-ups that were also evaluated at the time of admission such as urine protein electrophoresis (UPEP), were not available in medical records of some cases. However, most of the valuable examinations were documented in patients' medical records and reported in this series. It should be stated that oncological diagnoses were made based on essential examinations available at the time of diagnosis. Furthermore, as cited earlier herein, several cases also were followed up via phone call. According to the mentioned limitations, the authors believe more studies should be conducted on this important and challenging issue.

In conclusion, as expected, 10% plasma cells was not a certain cut off point in order to exclude MM. In a rough estimation, 20% of cases with 5%-10% plasma cells in bone marrow biopsy could be MM. This rate of BMPC in a symptomatic patient, especially when primary assessments showed obvious M-spike in electrophoresis or presence of two CRAB features simultaneously, should not be considered as a normal finding and should be evaluated further.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

ETHICS APPROVAL

This study was approved by the Ethics Committee of AJA University of Medical Sciences.

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