

DIAGNOSIS OF MYELOMA BASED ON THE 2014 INTERNATIONAL MYELOMA WORKING GROUP

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ABSTRACT

Myeloma is a cytogenetically heterogeneous clonal plasma cells proliferative disorder and is almost always preceded by an asymptomatic premalignant stage termed monoclonal Gammopathy of Undetermined Significance (MGUS). Diagnosis of myeloma is based on International Myeloma Working Group (IMWG) 2003 which requires one or more CRAB features including hypercalcemia, renal insufficiency, anemia and lytic bone lesions. The IMWG 2014 updated criteria for the diagnosis of myeloma allows the use of early indicators for therapy before CRAB features happen. This is a case of a 53-year-old male, based on complete blood count and peripheral blood smear having normochromic normocytic anemia, NRBC 7/100 leucocytes, thrombocytopenia, 1% plasmoblasts, 11% plasmocytes and Erythrocyte Sedimentation Rate (ESR) 40 mm. The bone marrow evaluation showed plasmocytes 22.5% ANC with abnormal morphology. The diagnosis myeloma was made based on IMWG 2014 by the presence of plasmocytes 22.5% ANC the bone marrow and having one of Myeloma Defining Events (MDEs) in the form of anemia with hemoglobin level 8.5 g/dL. In addition, patient did examinations of protein electrophoresis, immunofixation and ratio involved/uninvolved Free Light Chain (FLC) serum. The results of those examination confirmed the diagnosis that has been made based on IMWG 2014. Prognosis of the patient is poor by the presence of 11% plasmocytes on blood peripheral and ratio FLC kappa/lambda 0.0010.

Key words: Myeloma, update diagnosis myeloma, free light chain serum, myeloma defining events

INTRODUCTION

Myeloma is a proliferative disorder of clonal plasma cells with heterogeneous cytogenetic abnormalities and always preceded by asymptomatic premalignant states of monoclonal Gammopathy of Undetermined Significance (MGUS).¹ The incidence of myeloma increases with age, less than 2% are diagnosed under the age of 40 years with a median age of 70 years.² Myeloma is also known to be more common in males than females with a ratio of 1.25:1 and more common in the African American race compared to Caucasians.³

Moreover, the diagnostic criteria of myeloma used are usually based on IMWG in 2003. The first and second criteria, as well as one of the third criteria as shown in Table 1 must be fulfilled to diagnose myeloma. The World Health Organization (WHO) in 2008 adopted the IMWG diagnostic criteria, but excluded the criteria for normocytic and normochromic anemia, and severe osteopenia.

⁴ Furthermore, the diagnosis of myeloma has enforced and initiated therapy in the presence of one or more

CRAB features for several decades. Unfortunately, in the past the choice of treatment was limited to drugs that showed no clear clinical benefit and had many toxic effects. Intervention in asymptomatic patients with high risk can prolong survival.¹

The choice of drug type has recently undergone many changes and the data suggest that early The International Myeloma Working Group (IMWG) in 2014 has issued the updated criteria for the diagnosis of myeloma, as shown in Table 2. The new diagnostic criteria are considered as a paradigm shift in the myeloma diagnosis approach with a major impact on disease management. The IMWG Revision Criteria of 2014 use three additional markers of the classic features of CRAB as myeloma defining events. First, bone marrow examination is conducted with a clonal plasma cell percentage of $\geq 60\%$. Second, a serum involved/uninvolved FLC ratio is ≥ 100 . Involved FLC is FLC that is above the normal value with a ratio exceeding 100, while uninvolved FLC is FLC within or below the normal value. Another way to assess serum

Table 1. The IMWG diagnostic criteria of 20034

Diagnosis of myeloma is established when fulfilling the following three criteria:

1. Clonal plasma cell percentage of $\geq 10\%$
2. Monoclonal protein found in serum and / or urine
3. There is evidence of organ damage (hypercalcaemia, renal insufficiency, anemia and lytic bone lesion = CRAB) caused by plasma cell proliferation:
 - a. Hypercalcaemia: a serum calcium level of ≥ 11.5 mg/dL, or
 - b. Renal insufficiency: a serum creatinine level of > 1.73 mmol/L (or > 2 mg/dL) or a creatinine clearance value of <40 mL/min
 - c. Anemia: normocytic with a hemoglobin level of > 2 g/dL below the lower limit of the reference level, or a hemoglobin level of <10 g/dL
 - d. Bone lesions: lytic lesions, severe osteopenia, or pathologic fractures

Table 2. The IM4G revision criteria of 2014 for diagnosis of myeloma

If clonal plasma cells on bone marrow or biopsy specimens are $\geq 10\%$, there will be an indication of plasmacytoma * defined as solitary plasmacytoma of the bone (SBP) and extramedullary plasmacytoma with one or more myeloma defining events:

Myeloma defining events

- There is evidence of organ damage (hypercalcemia, renal insufficiency, anemia and lytic bone lesion = CRAB) caused by plasma cell proliferation:
 1. Hypercalcaemia: a serum calcium level of > 0.25 mmol/L (> 1 mg/dL), above the reference value or a serum calcium level of ≥ 11 mg/dL,
 2. Renal insufficiency: a serum creatinine level of > 1.77 mmol/L (> 2 mg/dL) or a creatinine clearance value of <40 mL/min
 3. Anemia: a hemoglobin level > 2 g/dL below the reference level, or a hemoglobin level of <10 g/dL
 4. Bone lesions: one or more lytic lesions on radiological examinations, such as CT scan or PET-CT **
- One or more markers below:
 1. Clonal plasma cell percentage of $\geq 60\%$ *
 2. Serum involved/uninvolved FLC ratio of > 100 ***
 3. More than one focal lesion on MRI ****

PET-CT: F-fluorodeoxyglucose PET with CT

* Clonalities should be established by a light chain restriction of κ / λ using flow cytometry, immunohistochemistry, or immunofluorescence method. The percentage of bone marrow plasma cells should be calculated from biopsy specimens. If there is a discrepancy between aspiration and biopsy results, the highest plasmacyte presentation value is used.

** If a clonal plasma cell percentage in bone marrow is $<10\%$, it will take more than one bone lesion to differentiate it from solitary plasmacytoma with minimum bone marrow involvement

*** Serum FLC value is determined using Freelite Assay (The Binding Site Group, Birmingham, UK). Involved FLC should be ≥ 100 mg/L

**** Each focal lesion has a size of ≥ 5 mm

FLC is to calculate kLCa/lambda FLC ratio. Under normal circumstances, the kappa/lambda FLC ratio is 0.26-1.65. The deviating result of the ratio indicates the presence of monoclonality. The third is the presence of more than one focal lesion in Magnetic Resonance Imaging (MRI) sized at least 5 mm or more. The presence of at least one of the three markers is considered adequate for the diagnosis of myeloma, regardless of whether or not CRAB symptoms are present.⁵

Table 3. Staging system and prognosis markers in patients with myeloma⁵

International Staging System (ISS)	Stage	Survival
$\beta 2$ -microglobulin level of < 3.5 mg/L; Albumin level of ≥ 3.5 g/dL	I	62 months
$\beta 2$ -microglobulin level of < 3.5 mg/dL; Albumin level of < 3.5 or $\beta 2$ -microglobulin level of $3.5 - 5.5$ mg/dL	II	44 months
$\beta 2$ -microglobulin level of > 5.5 mg/L	III	29 months

Other prognosis markers:

Cytogenetics:

Good: hyperploid, t (11; 14)

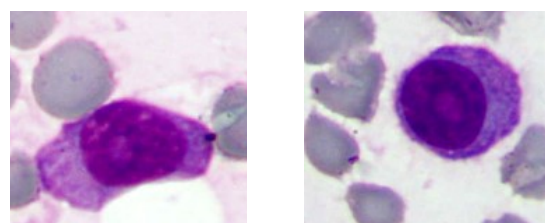
Poor: hypoploid, del 13q, t (4; 14), t (14; 16), chromosomal abnormality 1, del 17p

Another marker:

Poor: Old age, poor general condition, high CRP, high LDH, type M protein (IgD tends to lead to kidney failure and amyloidosis), plasmacyte peripheral blood, bone marrow plasmacyte level of $> 50\%$, kLCa/lambda FLC ratio (< 0.03 or > 32)

Next, staging is performed to determine prognosis and predict survival. The staging system used today is the International Staging System (ISS) based on serum $\beta 2$ -microglobulin and serum albumin levels, as shown in Table 3.⁷

CASE

**Figure 1.** Morphology of plasmoblasts on peripheral blood smear preparations

Bone marrow features

Preparations stained with: Wright Stain
 Particles: yes
 Cell density: hypocellular
 Fat cells: many
 Thrombopoiesis: megakaryocytes hard to find, distressed thrombopoiesis

	Total (%)	Reference values (%)
Neutrophil granulopoiesis	24.5 %	63.2(46.8-74.8)
Blast	0.0	0.6(0.1 – 1.1)
Promyelocyte	0.0	2.0(0.5 – 3.7)
Myelocyte	1.0	8.9(2.6 – 13.5)
Metamyelocyte	3.5	14.0(5.8 – 20.8)
Band	2.0	16.4(10.8 – 20.4)
Segmented	13.5	19.3(7.8 – 37.8)
Eosinophil	2.5	0(0 – 0.6)
Basophil	0.0	1.5(0.4 – 4.4)
Monocyte	2.0	2.1(0.6 – 3.6)
Others	-	
Erythropoiesis	8.5 %	23.8(11.9 – 48.4)
Rubriblaste	0.0	0.2(0 – 1.0)
Prorubricyte	0.0	1.1(0.1 – 3.2)
Rubricyte	2.5	7.4(4.2– 12.8)
Metarubricyt	6.0	14.7(6.6 – 33.4)
Lymphoid system	67.0%	8.3(3.6-17.2)
Lymphocyte	44.5	7.4(3.4 – 17.0)
Plasmocyte	22.5	0.5(0.1 – 1.6)
M : E Ratio	3:1	2.7(0.9 – 6.6)

Impression: Hypocellular bone marrow. Distressed thrombopoiesis, erythropoiesis and granulopoiesis activities with 44.5% ANC lymphocytes, 22.5% ANC plasmocytes, as well as abnormal morphology. M to E Ratio of 3: 1

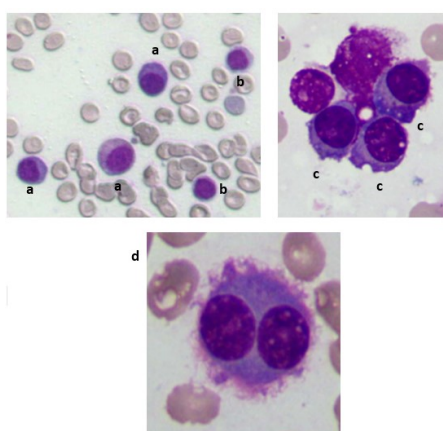


Figure 2. Morphology of lymphocytes and plasmocytes in bone marrow evaluation: a. Plasmocytes, b. Lymphocytes, c. Plasmocytes with abnormal morphology, d. Binuclear plasmocytes

Table 4. Laboratory test results

Types of examination	Results	Unit	Reference values
Complete hematology			
Hemoglobin	8.5	g/dl	13.0 – 16.0
Hematocrit	25.4	%	40.0 – 48.0
Erythrocytes	2.70	10 ⁶ /μL	4.50 – 5.50
Platelets	109	10 ³ /μL	150 – 400
Leukocytes	7.90	10 ³ /μL	5.00 – 10.00
Types of leukocytes			
Basophil	0	%	0-1
Eosinophil	0	%	1-3
Band	3	%	2-6
Segmented	37	%	50-70
Lymphocyte	42	%	20-40
Monocyte	6	%	2-8
Others		%	
Plasmocyte	11%		
Plasmablast	1%		
Nuclear erythrocyte	7/100 leukocytes		
Erythrocyte sedimentation rate	40	mm	<10
Preparation of peripheral blood smear			
Erythrocytes	normocytic and normochromic, nuclear erythrocyte to leukocyte count ratio of 7/100		
Leukocytes	normal leukocyte count, normal morphology, differential count 0/3/37/42/6; 1% plasmoblasts; 11% plasmocytes		
Platelets	less platelet count, normal morphology		
Impression	bicytopenia, nuclear erythrocyte to leukocyte count ratio of 7/100, 1% plasmoblasts; 11% plasmocytes		

Table 5. Laboratory test results

Type of examination	Results	Unit	Reference values
Free Light Chain (FLC) serum			
FLC Kappa	14.62	mg/L	3.30 – 19.40
FLC Lambda	15.090	mg/L	5.71 – 26.30
Kappa/Lambda FLC ratio	0.001		0.26 – 1.65
Involved/uninvolved FLC ratio	1.032		-

Impression: an increase in FLC lambda with an increase in lambda/kappa FLC ratio corresponding to monoclonal gammopathy of undetermined significance (MGUS).

Table 6. Laboratory test results

Type of examination	Results	Unit	Reference values
Chemistry Creatinine	2.37	mg/dL	0.8 - 1.3
calcium	10.9	mg/dL	8.5 - 10.1

Chemical Examination

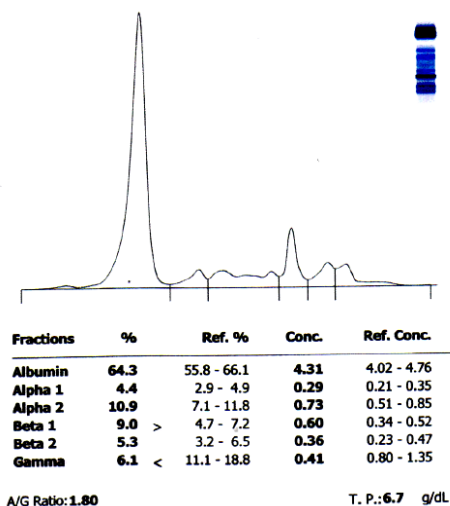


Figure 3. Serum protein electrophoresis: monoclonal patterns in beta 1 globulin and gamma globulin fractions

Immunological Examination

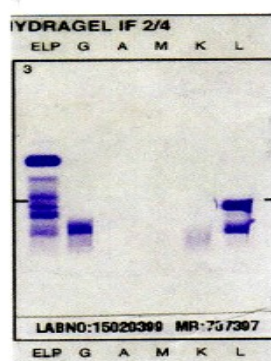


Figure 4. Immunofixation: monoclonal IgD lambda and free light chain lambda

On May 13, 2015, a male patient aged 53 years old came without clinical information. Complete hematological examination, peripheral blood smear preparation screening and bone marrow evaluation then were performed. In addition, the patient also obtained protein electrophoresis, immunofixation, serum free light chain (FLC), creatinine and blood calcium screenings.

DISCUSSION

A male patient aged 53 years-old came without clinical information. Next complete hematological examinations, peripheral blood smear preparation screening and bone marrow evaluation were performed. Based on the results of the complete hematological examination and peripheral blood smear preparation screening, normocytic and normochromic anemia, NRBC 7/100 leukocytes, 1% plasmoblasts, 11% plasmocytes, thrombocytopenia and high LED were found. Meanwhile, based on the results of the bone marrow evaluation, hypocellular bone marrow was obtained with distressed thrombopoiesis, erythropoiesis and granulopoiesis activities, 44.5% ANC lymphocytes, 22.5% ANC plasmocytes, abnormal morphology, as well as the M to E ratio of 3: 1. These findings led to impression of plasmacytosis, possibly myeloma.

Next, the definitive diagnosis of myeloma in this patient was establish based on the IM4G revision criteria of 2014, i.e. the presence of a 22.5% ANC plasmocyte in the bone marrow, as well as myeloma defining events, i.e. anemia with a hemoglobin level of 8.5 g/dL. Examinations of protein electrophoresis, immunofixation and serum involved/uninvolved FLC ratio then were conducted for myeloma diagnosis in this research based on the IM4G Revision Criteria of 2014. The results of the serum protein electrophoresis examination indicated that there were monoclonal patterns in beta 1 globulin fraction corresponding to lambda FLC, as well as in gamma globulin fraction corresponding to IgG lambda.

In addition, the migration of proteins in protein electrophoresis is also known to be influenced by Molecular Weight (MW). IgG has a molecular weight of 150 kDa, while lambda FLC has a molecular weight of 45 kDa. Consequently, in protein electrophoresis, IgG was found in the gamma globulin fraction, while FLC was in the beta-1 globulin fraction. Besides this, the results of this research also revealed that the serum involved/uninvolved FLC ratio was 1,032, while the kappa/lambda FLC ratio was 0.001. Both ratio values were in accordance with monoclonal Gammopathy of Undetermined Significance (MGUS).

In other words, the results of protein electrophoresis, immunofixation and serum FLC ratio examinations confirmed myeloma diagnosis based on the IM4G revision criteria of 2014.

in the peripheral blood indicated that plasmocytic leukemia was excluded and associated with a poor prognosis. In plasmocytic leukemia, the amount of plasmocytes the peripheral blood is more than 20% or more than 2000/mL

Thus, to assess the prognosis of myeloma according to the International Staging System (ISS), levels of beta-2 microglobulin and albumin then were examined in this research. Besides this, FLC kappa, FLC lambda and kappa/lambda FLC ratio were also calculated. The results indicated that the prognosis of this patient was poor because of the kappa/lambda FLC ratio of 0.0010 and the plasmocytes of 11% in the peripheral blood.⁵

CONCLUSION

Mr. UD aged 53 years-old had complete hematological examination, peripheral blood smear preparation screening and bone marrow evaluation. The diagnosis of myeloma then was confirmed by the presence of a 22.5% ANC plasmocyte with abnormal morphology, as well as one of myeloma defining events, namely anemia with a hemoglobin level of > 8.5 g/dL. The prognosis of this patient was also known to be poor with plasmocytes of 11% in the peripheral blood as well as the kappa/lambda FLC ratio of <0.03 i.e 0.0010.

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