A REVIEW OF THE CLINICAL MANIFESTATIONS AND LABORATORY FEATURES OF PATIENTS WITH PLASMA CELL MYELOMA: A SINGLE CENTRE EXPERIENCE.

RESEARCH PROJECT REPORT IN PARTIAL FULFILLMENT OF THE DEGREE OF MASTER OF PATHOLOGY.

Dr. Salwana Binti Mohd Ali

MGA110015

Supervisor: Dr. Hemalatha Shanmugam

Co-supervisor: Associate Professor Dr. Bee Ping Chong.

Department of Pathology, Faculty of Medicine,

University of Malaya.

2016

CANDIDATE'S DECLARATION

I hereby declare that this research report is prepared by me, based on research work led by my supervisors, Dr. Hemalatha Shanmugam, Senior Lecturer, Department of Pathology, Faculty of Medicine, University Malaya and Associate Professor Dr. Bee Ping Chong, Consultant Hematologist, Department of Medicine, Faculty of Medicine, University Malaya.

Name of Candidate : Salwana Binti Mohd Ali

Candidate's ID Number : MGA 110015

Programme : Master of Pathology (Haematology)

Faculty : Medicine.

Manuscript Title : A review of the clinical manifestations and laboratory features of patients with plasma cell myeloma: A single centre experience.

Signature of Candidate : 

Date : 25/3/16

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Authors:
Mohd Ali S, MD (USM)
Shanmugam H, MPATH (UM)
Bee PC, MMED (UM)

Department and institution:
Department of Pathology, University Malaya, Kuala Lumpur, Malaysia.

Correspondence to:
Dr. Hemalatha Shanmugam, Department of Pathology, University Malaya, 50603 Kuala Lumpur, Malaysia.
Phone number: +603-79493121 Fax number:+603-79556845
E-mail address: hema@ummc.edu.my

Conflict of Interest:
None

ABSTRACT

Multiple Myeloma is a clonal plasma cell disorder that varies widely in its clinical course, ranging from relatively indolent forms to frankly aggressive neoplasm. The purpose of this study was to review in detail cases of multiple myeloma diagnosed in University Malaya Medical Centre. We retrospectively reviewed 49 cases of Multiple Myeloma diagnosed within a 7 year period using patient-information system and laboratory information system. Data obtained were patient's demographic, clinical history and diagnosis, laboratory data included complete blood counts, erythrocyte sedimentation rate (ESR), serum calcium, serum albumin, serum creatinine, serum alkaline phosphatase, Bence Jones Protein, serum monoclonal protein, bone marrow findings, cytogenetics and radiological results. Of the 49 patients, 8.2% were younger than 50 years, and 24.5% were 70 years or older. The median age was 66 years. Lumbar back pain was the most common presenting complaint (38.8%) and 12.2% of patients had extramedullary plasmacytoma at diagnosis. Anaemia was present in all patients, hypercalcaemia (calcium level ≥2.6mmol/L) in 14%, and all 7 patients with positive Bence Jones proteinuria had a creatinine level more than 200µmol/L. Ig G kappa was the most common M protein subtype seen in 57.1%. Majority of patient with available FISH results showed normal study. Renal failure and infection were the most common specific cause of death.

Key words: multiple myeloma, monoclonal protein, bence jones

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INTRODUCTION

Multiple myeloma is a malignant disorder characterized by the proliferation of a single clone of plasma cells derived from B cells in the bone marrow. Myeloma accounts for 1% of all cancers and 10% of all haematological malignancies [1, 2]. It is slightly more common in men than in women [3]. The median age of patients at the time of diagnosis is about 65 years [4]. Almost all cases of myeloma evolve from monoclonal gammopathy of undetermined significance [5, 6].The clinical manifestations of myeloma are varied. Multiple myeloma usually presents with bone destruction, hypercalcaemia, anaemia, renal impairment and increased susceptibility to infection. Bone disease is the main cause of morbidity. Osteolytic bone lesions in myeloma exhibit no new bone formation, unlike other malignancies that metastasize to bone [7].Renal failure is due to tubular damage resulting from monoclonal light chain proteinuria; recurrent infection may be partly a consequence of depressed immunoglobulin production; and anaemia results from bone marrow replacement and renal damage with resultant loss of erythropoietin [8]. A proportion of patient are diagnosed following the incidental finding of a raised erythrocyte sedimentation rate (ESR), hyperviscosity syndrome or the presence of a monoclonal paraprotein in serum or urine [9].

The latest guidelines for diagnosis and management of myeloma [9], recommend diagnostic criteria of myeloma should be as proposed in 2003 by the International Myeloma Working group (IMWG).This guideline principally distinguishes between myeloma and monoclonal gammopathy of undetermined significant (MGUS) on the basis of monoclonal protein concentration, percentage of bone marrow plasma cells and presence or absence of myeloma related organ or tissue impairment [1, 9].

There are many investigations which are useful in diagnosing patient with suspected myeloma. Screening tests such as Full Blood Count, ESR (erythrocyte sedimentation rate) or plasma viscosity, urea, creatinine, calcium, albumin, serum and urine electrophoresis and skeletal survey. These are followed by confirmatory tests such as bone marrow aspiration with trephine biopsy,

serum protein and urine electrophoresis followed by immunofixation. Molecular cytogenetics with serum albumin and β2-microglobulin levels are important for prognostic evaluation and for further management [1, 9]. Quantification of serum free light chain (SFLC) levels and κ/λ ratio is an additional tool for the assessment of light chain production. These tests are particularly useful for the diagnosis and monitoring of light chain only myeloma. Quantification of urinary total protein and light chain excretion can be performed on a 24 hour urine sample [9].

Bone marrow studies at the time of initial diagnosis should include Fluorescence In situ hybridization (FISH) designed to detect t(11;14), t(4:14), t(14;16), t(6;14), t(14;20), hyperdiploidy and deletion 17p [11]. Chromosomal aberrations associated with multiple myeloma were first described in the late 1970s and early 1980s. Due to very low mitotic activity of myeloma tumour cells compared to other haematological disease, conventional cytogenetic is informative in less than 30% of patients. Karyotypes are typically complex and exhibit more than 10 abnormalities in almost half of the patients [4]. There is now a consensus that conventional karyotyping has little or no added value in the routine setting [16].

One of the aims of cytogenetic risk stratification is to define high risk groups who should be managed differently from standard risk patients. Three genetic risk groups have been defined. The term 'high risk' should include those patients with at least one of the following features; deletion of 17p, t(14;16) or t(14;20), intermediate risk with t(4;14) and standard risk with at least one of these features; trisomies, t(11;14) and t(6;14). [2]. Recent data suggest that chromosome 13 deletion is not an independent prognostic marker and the adverse effect relates to its close association with high risk abnormalities, particularly the t(4;14) [9]. A risk stratification model that relies on a number of independent molecular cytogenetic markers to assess disease aggressiveness is useful for both counselling and therapeutic decision making [16]. Patients with standard risk myeloma have a median overall survival (OS) of 6-7 years while those with high risk

disease have a medium OS of less than 2-3 years despite tandem autologous stem cell transplantation (ASCT) [1].

For the past 10 years, the overall survival of multiple myeloma has improved considerably. 5 year survival rates of more than 70% with modern therapy in patients who are transplant eligible and about 50% survival rate for elderly transplant ineligible patients have been reported [2]. However, the improvement has not been uniform and varies considerably based on a variety of prognostic factors. Prognosis in myeloma also depends on a host factors (age, ECOG performance status and comorbidities), stage, disease aggressiveness, response to therapy and cytogenetic abnormalities [12]. ECOG (Eastern Cooperative Oncology Group) performance status describes a patient's level of functioning in terms of their ability to care for themselves, daily activity and physical ability (walking, working, etc). Disease staging in Myeloma is done using the Durie-Salmon staging [8, 13] or the International Staging System [8, 14, 15].

Response to therapy is assessed using the International Myeloma Working Group uniform response criteria [17] and further modifications were subsequently proposed [18]. There are 5 response categories, stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR) and stable disease (SD). However, the response category sCR is recommended only for use in the clinical trial setting. Response criteria basically measuring SFLC ratio, percentage of serum and urine M-protein reduction, presence or absence phenotypically aberrant plasma cells by flow cytometry, disappearance of any soft tissue plasmacytomas and reduced numbers of bone marrow plasma cells. This study aims to analyze the clinical features, biochemical, histological and genetic abnormalities of multiple myeloma in newly diagnosed patients in University Malaya Medical Centre.

MATERIALS AND METHODS

PATIENTS

This is a retrospective study analyzing the clinical features and laboratory findings of newly diagnosed multiple myeloma patients in University Malaya Medical Centre within the period of January 2009 to October 2015. Patient data was obtained from the clinical case notes and Laboratory Information System (LIS). The clinical, demographic and laboratory information consisted of 36 data points, including age, gender, race, initial symptoms, haemoglobin level, white blood cell count, platelet count, bone destruction and type of bone involved, bone marrow cellularity and plasma cell numbers at diagnosis, conventional cytogenetic and FISH results. Other parameters including quantitative and subtype analysis of M protein in the serum, Bence Jones protein, ESR level, creatinine, alkaline phosphatase, β2-microglobulin, calcium and albumin. This study has been approved by the University Malaya Medical Centre Medical Ethics Committee (ref no 20161-2017).

Statistical analysis.

Data was analysed using SPSS software version 20 (IBM Corp., IBM SPSS Statistics for Windows, Armonk, NY, USA). Quantitative variables were summarized in the forms of mean and standard deviation (SD). Categorical variables were summarized in number of events observed and percentage within each category. Frequency tables were constructed and a test of significance was applied. The chosen level of significance was $p<0.05$. Mann-Whitney U test was used to compare two independent groups when the dependent variable was continuous but not normally distributed. All data retrieved were summarized with descriptive statistics.

RESULTS

Patient characteristics and laboratory findings.

There was a total of 54 patients who were newly diagnosed with multiple myeloma between January 2009 till October 2015 in our centre. 49 patients were included in this study as the remaining 6 patients had incomplete clinical and laboratory information. The median age was 66 years (60.5-71). There were 31 male (63.3%) and 18 (36.7%) female patients with a male to female ratio of 1.72:1, the mean age of males being 66.1 years and that of females being 65.5 years. There was no significant age differences between the two genders (P= 0.817). Chinese patients accounted for 42.9%, followed by Malays (34.7%) and Indian (22.4%) of all cases of multiple myeloma in our centre. The patients' characteristics are summarized in Table 1.

(19/49) 38.8% of patients presented with lumbar pain as a presenting complaint, pain severity varied from mild, intermittent pain to severe and continuous pain in some cases. This was followed by anaemia symptoms (13/49) 26.5%. Pathological fractures, mainly involved the spine and head of femur and accounted for (10/49) 20.4% of the presenting symptoms. (6/49) 12.2% of patients had extramedullary plasmacytoma at initial diagnosis; 2 cases in the spine (both in lumbar region), the rest were in the anterior neck, sternum, 5th rib and knee. Non-specific bone pain (6%) and renal failure (7%), hypercalcaemic symptoms (4.1%) and the remaining 4% of patient presented with pancytopenia, fever with loss of appetite and weight.

As for the Multiple Myeloma subtype, Ig G type was the most common in 63.3% of patients, Ig A type was found in 34.7% of patients and Light Chain only disease (Kappa light chain) was found in 2% of cases. Among the 32 cases of Ig G-type Multiple Myeloma, 5 cases (15.2%) were Ig G lambda and 28 cases (84.8%) were Ig G Kappa. For Ig A-type Multiple Myeloma, Ig A kappa was found in 11 patients (73.3%) and Ig A lambda found in 4 patients (26.7%).

In our hospital, plain x-ray is the main screening method for bone lesions. Radiological evidence of bone involvement was found mainly to affect the skull bone. There were 11 (22.4%) patients who did not have bone involvement radiologically at the time of diagnosis. The prevalence of other skeletal disease is shown in Figure 1. Bone marrow examination showed (24/48) 50% patients had a hypercellular marrow at initial presentation, (19/48) 39.6% with normocellular and only (2/48) 4.2% with hypocellular marrow (Figure 2). Plasma cells percentage was measured by differential count in the marrow aspirate. (36/49) 75% of patients with plasma cells count 20% or more in the marrow with mean value of 38.

Complete blood counts at initial presentation showed that all 49 patients had anaemia at presentation; ranging from mild to severe anaemia. The white cell count was normal in 47 patients with a mean value of 6.33. Only 2 patients presented with low white cell count; below $3x10^9$/L. There were 3 patients with platelet count less than $150x10^9$/L and 4 patients with count below $100x10^9$/L. (24/49) 48.9% patients had hypercalcaemia and only 18 (36.7%) cases had albumin levels more than 3.5g/dl. Bence Jones protein was tested in 15 patients of which 7 patients (14.3%) were positive. (Figure 3). All cases with positive Bence Jones proteinuria had a creatinine level of more than 200µmol/L. 14% of patients had a corrected calcium level of more than 2.6mmol/L. There were only 9 patients with β2-microglobulin results and 3 patients with serum free light chain (SFLC) results, probably because these tests were only recently offered by laboratory in UMMC in 2014 and 2015 respectively. There were only 14 patients with results for conventional cytogenetics. (The results are summarized in Table 3). A total of 27 from 49 patients (55.1%) had FISH result: 28.5% (14/27) with normal FISH, 12.2% (6/27) with t (11;14) and only 1 case with high risk cytogenetic t(14;16). The results are shown in Table 4.

DISCUSSION

Multiple Myeloma is a plasma cell malignant disease with a high degree of heterogeneity. The reason for this heterogeneity is the variability in its biological characteristics among patients. In this retrospective study, we analyzed all newly diagnosed patients with Multiple Myeloma for a period of 7 years in University Malaya Medical Centre. Seventy three percent of patients were diagnosed at age 60 and older with median age at diagnosis being 66 years. The overall prevalence is expected to increase as the population ages. Therefore, patients who are most likely to have Multiple Myeloma are also likely to have one or more chronic illness that can cause the biochemical and physical abnormalities found in Multiple Myeloma. It is important and challenging to determine whether observed "CRAB" (hyper**C**alcemia, **R**enal insufficiency, **A**naemia, **B**one disease) abnormalities are due to multiple myeloma or the patient's comorbidities. A significant proportion of patients (69%) in this study had at least one underlying medical illness. Two patients had an underlying non hematological malignancy; pre-pyloric ring tumour and malignant melanoma, respectively.

In this analysis, the most common presenting complaint was lumbar back pain. It is often initially misdiagnosed as 'sciatica' or neoplastic secondary. Bone metastasis can cause severe pain, pathological fracture, hypercalcaemia and anaemia. The low level of suspicion by health care providers in primary and secondary health care facilities may lead to missed or delayed diagnosis in this group of patients. Early diagnosis would have given patients the benefit of commencing definitive therapy before the emergence of myeloma related complications.

The most common monoclonal protein was IgG kappa and the prevalence of renal insufficiency was 28%, which is in accordance with two similar studies. [4, 19] .Of 49 patients included in this study, 16 (37.7%) patients had died by the end of this study period. Two of these patients relapsed and progressed within a few months post autologous transplantation. There were 2 patients with high percentage of plasma cells and high level of M protein whom succumbed to

the disease within a few days of diagnosis. Other causes of death included upper gastrointestinal bleeding (12.5%), renal failure and hypercalcemia (31.3%), pneumonia (18.7%) and 12.5% of patients refused further treatment and died at home.

There were a number of cases in this study with incomplete data. For example β2-microglobulin level results were only available for 9 cases from 49 studied cases. With regards to cytogenetics, only 14 cases had conventional cytogenetic analysis and 27 cases out of 49 cases with FISH results. Conventional cytogenetic analysis in myeloma is difficult because of the low proliferation rate of malignant plasma cells, together with a variable degree of bone marrow infiltration. Three common cytogenetic abnormalities, t(4;14), t(14;16), and del(17p), were detected by FISH in 6 (22.2%) patients, which is in accordance with similar study [19].

There were some limitation in this study. First, this was retrospective study; some initial symptoms may have been under evaluated. Second, because of the small number of patients, no definite final conclusion could be reached with respect to prognosis and the true figure may be higher than reported. Third, some data especially old cases cannot be obtained due to inadequate documentation inside the patients' folder and some of the investigations were not performed.

As a conclusion, we found out that mean age, clinical presentation and laboratory findings in this study were similar to other cohorts of multiple myeloma in western population. Clinician should also be advised on the need to request for newer available tests such as β2-microglobulin and SFLC assay as these are important markers in prognostication and disease monitoring.

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Table1: Baseline Characteristics of Multiple Myeloma patient.

Characteristics (n= 49)		n	(%)
Age (years)			
Median		65.9	
Range		60.5-71.0	
Gender			
Male		31	(63.3)
Female		18	(36.7)
Race			
Malay		17	(34.7)
Chinese		21	(42.9)
Indian		11	(22.4)
Symptom & sign	LUMBAR BACK PAIN	19	(38.8)
	ANAEMIA	13	(26.5)
	PATHOLOGICAL FRACTURE	10	(20.4)
	BONE PAIN	6	(12.2)
	PLASMACYTOMA	6	(12.2)
	RENAL FAILURE	7	(14.2)
	WEIGHT LOSS	3	(6.1)
	HYPERCALCAEMIA	2	(4.1)
	PARAVERTEBRAL MASS	1	(2.0)
	PANCYTOPENIA	1	(2.0)
	FEVER, LOA AND LOW	1	(2.0)
Type			
Ig G		31	(63.3)
Ig A		17	(34.7)
Light Chain		1	(2.00)
Number of bone with lytic lesion			
0-1		23	(46.9)
2		14	(28.7)
≥ 3		6	(12.2)

Table 2: Descriptive analysis

	N	Mean	SD	Minimum	Maximum	Median	Range
Age	49	65.94	8.26	47.00	86.00	65.00	60.50-71.00
HB	49	9.61	1.72	5.30	13.10	9.50	8.50-10.70
WBC	49	6.33	2.75	2.70	15.50	5.50	4.45-8.15
PLT	49	208.14	85.66	37.00	409.00	195.00	151.00-270.00
Plasma cell	48	37.67	22.97	10.00	94.00	31.00	20.00-52.50
M-protein	48	43.50	21.77	4.00	99.00	42.00	24.50-62.75
ESR	30	118.53	32.18	13.00	145.00	131.00	111.50-140.00
Calcium	49	2.54	0.36	1.96	3.59	2.50	2.27-2.69
Albumin	48	29.63	8.33	11.00	49.00	28.50	24.25-36.00
ALP	49	104.31	114.35	30.00	818.00	80.00	58.00-107.00
Creatinine	49	171.86	182.11	21.00	877.00	105.00	75.00-194.00
B2-microglobulin	9	9.19	6.72	1.98	21.70	7.29	3.08-14.65

* Incomplete data in some cases; to calculate statistical value, denominator = number for which information was available.

Table 3: Results of Conventional cytogenetic in Newly diagnosed Multiple Myeloma.

		Frequency	Percent
Cytogenetic	COMPLEX CHROMOSOMAL REARRANGEMENT, LOSS CHR X	1	2.0
	HYPERDIPLOIDY	1	2.0
	MULTIPLE NUMERICAL CHROMOSOMAL ABNORMALITY	1	2.0
	NO METAPHASE	3	6.1
	NORMAL	7	14.3
	NOT DONE	35	71.4

Table 4: Results of Fluorescence in situ hybridization in Newly diagnosed Multiple Myeloma

	Frequency	Percent
IGH/MAF	1	2.0
TRISOMY 11, 13, LOSS OF ONE COPY OF TP53	1	2.0
FGFR3/IGH	4	8.2
CCND1/IGH	6	12.2
NORMAL	14	28.5
NOT DONE	23	46.9

APPENDICES

UNIVERSITY OF MALAYA MEDICAL CENTRE

MEDICAL ETHICS COMMITTEE
UNIVERSITY MALAYA MEDICAL CENTER
ADDRESS : LEMBAH PANTAI, 59100 KUALA LUMPUR, MALAYSIA
TELEPHONE : 03-79493209/2251 FAXIMILE : 03-79492030

NAME OF ETHICS COMMITTEE/IRB Medical Ethics Committee, University Malaya Medical Center	**MECID.NO**: 20161-2017
ADDRESS : LEMBAH PANTAI, 59100 KUALA LUMPUR	
PROTOCOL.NO(if applicable) :	
TITLE: A REVIEW OF THE CLINICAL MANIFESTATIONS AND LABORATORY FEATURES OF PATIENTS WITH PLASMA CELL MYELOMA: A SINGLE CENTRE EXPERIENCE	
PRINCIPAL INVESTIGATOR : Doctor Salwana Mohd Ali	**SPONSOR** -

The following item [✓] have been received and reviewed in connection with the above study to conducted by the above investigator.

[✓]	Application to Conduct Research Project(form)	Ver.No :	Ver.Date : 06-01-2016
[✓]	Study Protocol	Ver.No :	Ver.Date :
[ ]		Ver.No :	Ver.Date :
[ ]		Ver.No :	Ver.Date :
[ ]	Questionnaire	Ver.No :	Ver.Date :
[✓]	Investigator's CV / GCP (Doctor Salwana Mohd Ali,HEMALATHA A/P SHANMUGAM,)	Ver.No :	Ver.Date :
[ ]	Insurance certificate	Ver.No :	Ver.Date :
[✓]	Other Attachments		
	1) PURSUE FORM	Ver.No : R2016/3	Ver.Date : 15-01-2016

and the decision is [✓]

[✓] Approved

[ ] Rejected(reasons specified below or in accompanying letter)

Comments:

Retrospective study

Investigator are required to:

1) *follow instructions, guidelines and requirements of the Medical Ethics Committee.*
2) *report any protocol deviations/violations to Medical Ethics Committee.*
3) *provide annual and closure report to the Medical Ethics Committee.*
4) *comply with International Conference on Harmonization – Guidelines for Good Clinical Practice (ICH-GCP) and Declaration of Helsinki.*
5) *obtain a permission from the Director of UMMC to start research that involves recruitment of UMMC patient.*
6) *ensure that if the research is sponsored, the usage of consumable items and laboratory tests from UMMC services are not charged in the patient's hospital bills but are borne by research grant.*
7) *note that he/she can appeal to the Chairman of MEC for studies that are rejected.*
8) *note that Medical Ethics Committee may audit the approved study.*
9) *ensure that the study does not take precedence over the safety of subjects.*

Date of approval : 25-03-2016

This is a computer generated letter. No signature required.