RESEARCH ARTICLE

Clinicopathology Profile and Bone Involvement of *Multiple Myeloma* Patients in Dharmais National Cancer Hospital, Indonesia

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Abstract

Background: Even though rarely found in Indonesia, the incidence of multiple myeloma (MM) is increasing every year. Bone involvement of MM is the most often a clinical disorder which leads to worsening clinical conditions and low quality of life of patients. Purpose: To determine the clinicopathology profile of bone involvement of MM patients in Indonesia. Materials and Methods: The cross-sectional study of MM conducted at Dharmais National Cancer Hospital (DNCH) by collecting data from medical records of MM patients who came to DNCH in period 2008-2012. Results: There were 39 MM patients all with age above 60 years. There were 56.4% male and 43.6% female patients. Most were diagnosed at stage III (32.4%), and 41% had obesity. The comorbid conditions were anemia (82.9%), hypoalbuminemia (60%), increased creatinine level (38.5%), increased β2 microglobulin level (94.1%), increased LDH level (23.1%) and plasmocytes above 30% (65%), but only 4.2% patients presented with hypercalcemia. Meanwhile, bone involvement occurred in 76.9% of MM patients with 4 lesions on average and a maximum of 16 lesions. The locations of bone lesions were spine (70%), skull (70%), pelvis (33.3%), humerus (30%), and femur (30%). Conclusions: The incidence of MM in Indonesia is increasing annually with bone involvement in more than three-fourths, but interestingly without hypercalcemia.

Keywords: Multiple myeloma - clinicopathology profile - bone involvement - Indonesia.

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Introduction

Multiple Myeloma (MM) is a plasma cells malignancy produces monoclonal protein causing bone destruction, bone marrow failure, renal failure, hypercalcemia, and immunocompromised (Saraf et al., 2012; NCCN, 2015). The incidence of MM was predicted 1% of all cancers and 13% of blood malignancies (Palumbo and Anderson, 2011). Globocan Data 2008 reported there were about 102,000 new cases of MM every year in the world. It was 0.8% of all cancers with 72,000 mortality every year or about 1% of all deaths caused by cancer (Ferlay et al., 2008). American Cancer Society (ACS) predicted there were 22,350 new cases and 10,750 deaths caused by MM in 2013 (Siegel et al., 2013). The incidence and deaths of MM are more common in developed countries like US, Australia, or Europe than in Asian countries for unexplained reason (Alexander et al., 2007; Saraf et al., 2012). Caucasians incident was 3-5 per 100,000 people compared with 0.5-3 per 100,000 people for Asians (Lee et al., 2010). Based on population-based Cancer Registration of Dharmais National Cancer Hospital (DNCH), the incidence of MM in Indonesia during 2005-2007, was 0.23 per 100,000 people (Sinuraya, in press).

MM occurs more to males, and to elder people with the median age 70 and only 37% whose age less than 60. Diagnosis of MM is based on clonal plasma cells found in bone marrow at least 10% and monoclonal protein in serum or urine (NCCN, 2015; Palumbo and Anderson, 2011). MM is classified into symptomatic and asymptomatic depends on the organ/tissue dysfunctions related to myeloma such as hypercalcemia, kidney insufficiency, anemia and bone involvement. Anemia appeared to 73% of the patients during the diagnosis and usually related to the infiltration of myeloma cell to bone marrow or because of renal failure. Bone lesions occurred to almost 80% of the patients with new diagnosis, so it usually caused complaints of bone pain. Kidney disorders appeared to 20-40% of the patients especially due to the damage of direct tubular from excessive protein, dehydration, hypercalcemia, and the usage of nephrotoxic drugs (Palumbo and Anderson, 2011).

Until now epidemiology study about the characteristics of MM is relatively rare to conduct in Indonesia. The

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purpose of this research is to know the clinical and laboratory description also bone involvement of MM patients in Indonesia. This basic data hopefully could become some additional information to clinicians in giving therapies and could be used as a reference for further study of the disease.

Materials and Methods

This research used cross-sectional design, with the data source from the patients' medical records. The inclusion criteria of this research are MM patients who came to DNCH during 2008-2012 and the MM patients whose BMP/ radiology/ immunofixation/ electrophoresis result kept in the medical records. The patients' data acquired from the medical records contains demographic data (age, sex, marital status, address, job, and type of payment), clinical data (body mass index, complaints, and stage), laboratory data (hemoglobin, thrombocytes, leucocytes, protein, albumin, globulin, creatinine, calcium, LDH, β2-microglobulin, serum immunofixation, and protein electrophoresis), and bone involvement data. Body Mass Index (BMI) is classified into underweight (<18.5 kg/m^2), normal weight (18.5-25 kg/m^2), overweight (>25 kg/m^2). Normal laboratory values in our institution are hemoglobin (male 13-18 g/dL, female 12-16 g/dL), thrombocytes (150-440x10^3/μL), leucocytes (5-10x10^3/μL), protein (6.6-8.7 g/dL), albumin (>3.5 g/dL), globulin (1.5-3 g/dL), creatinine (male<0.95 mg/dL, female<1.1 mg/dL), calcium (8.1-10.4 mg/dL), β2-microglobulin (670-1310 μg/mL), LDH (240-480 U/L). The data result from laboratory would be classified into normal, decreased, and increased. Serum immunofixation consists of IgG Lambda, IgA Lambda, IgG Kappa, and IgA Kappa. Protein electrophoresis consists of positive and negative.

Table 1. Demographic Profile of MM Patients (n=39)

Characteristic		Frequency (%)/ Mean+SD
Sex	Male	22 (56.4%)
	Female	17 (43.6%)
	Age (years old)	60.36+9.37
Age classification	>40 y.o	2 (5.1%)
	40-60 y.o.	17 (43.6%)
	>60 y.o.	20 (51.3%)
Marital Status	Single	1 (2.6%)
	Married	36 (92.3%)
	Widow/Widower	2 (5.1%)
Address	Jakarta	14 (35.9)
	Outside Jakarta	25 (64.1)
Job	Jobless	22 (56.4%)
	Has Job	17 (43.6%)
Type of Payment	Private	30 (76.9%)
	Government	9 (23.1%)

Table 2. Clinical Profile of MM Patients

Variable	N	Frequency (%)/ Mean+SD
Body weight (kg)	31	62.56+11.17
Body height (m)	22	1.6+0.08
BMI (kg/m^2)	22	24.26+3.37
Underweight		1 (4.5%)
Normal		12 (54.5%)
Overweight		9 (41%)
Complaints	39	
Yes		24 (61.54%)
No		15 (38.46%)
Type of Complaints	24	
Bone pain		11 (45.83%)
Anemia symptoms		9 (37.5%)
Other pain symptoms		5 (20.83%)
Gastrointestinal symptoms		3 (12.5%)
Neurological symptoms		3 (12.5%)
Others		3 (12.5%)
Stage	37	
I		12 (32.4%)
2		13 (35.1%)
3		12 (32.4%)

Table 3. Laboratory Profile of MM Patients

Variable	N	Frequency (%)/Mean+SD/ Median (Min-Max)
Hemoglobin (g/dL)	35	9.73+2.59
Decreased		29 (82.9%)
Normal		5 (14.3%)
Increased		1 (2.9%)
Thrombocytes (10^3/μL)	34	193 (156-411)
Decreased		8 (23.5%)
Normal		26 (76.5%)
Leucocytes (10^3/μL)	34	7.6 (3.59-64)
Decreased		12 (35.3%)
Normal		16 (47.1%)
Increased		6 (17.6%)
Protein (g/dL)	28	9.37+1.75
Decreased		1 (3.6%)
Normal		8 (28.6%)
Increased		19 (67.9%)
Albumin (g/dL)	30	3.25+0.66
Decreased		18 (60%)
Normal		12 (40%)
Globulin (g/dL)	30	8.52+14.03
Decreased		1 (3.3%)
Normal		3 (10%)
Increased		26 (86.7%)
Creatinine (mg/dL)	26	1.51+1.33
Normal		16 (61.5%0
Increased		10 (38.5%)
Calsium (mg/dL)	24	8.86+1.66
Decreased		7 (29.2%)
Normal		16 (66.7%)
Increased		1 (4.2%)
B2 Microglobulin (μg/mL)	17	4627.57+6257.62
Decreased		1 (5.9%)
Increased		16 (94.1%)
LDH (U/L)	13	318.44+170.84
Decreased		3 (23.1%)
Normal		7 (53.8%)
Increased		3 (23.1%)
Serum Immunofixation	21	
IgG Lambda		2 (9.52%)
IgA Lambda		4 (19.1%)
IgA Kappa		7 (33.3%)
IgG Kappa		8 (38.1%)
Protein Electrophoresis	27	
Positive		26 (96.3%)
Negative		1 (3.7%)
Percentage of Plasmocyte	20	
10-30%		7 (35%)
>30%		13 (65%)

Table 4. Bone Lesions Profile of MM Patients

Variable		Frequency (%)
Bone Involvement (n=39)	Yes	30 (76.9%)
	No	9 (23.1)
Bone Lesions (n=30)	1	4 (13.33%)
	2	5 (16.67%)
	3	2 (6.67%)
	> 3	19 (63.33%)
Bone Lesions Location (n=30)	Spine	21 (70%)
	Skull	21 (70%)
	Pelvis	10 (33.3%)
	Humerus	9 (30%)
	Femur	9 (30%)
	Others	13 (43.3%)

Plasmocyte percentage from BMP is classified into 10-30% and >30%. The decision of MM stage is based on Durie Salmon criteria.

The data analysis was done by SPSS program for Windows version 19. The numerical data with normal data spread was presented in the form of mean and standard deviations, and with abnormal data spread was presented with median (minimum-maximum).

Results

Within five years it has been found 101 patients diagnosed with MM at DNCH. However, there were only 39 patients who met the criteria and became the research subjects. There were 4 patients each in 2008 and 2009, 12 patients in 2010, 9 patients in 2011, and 10 patients in 2012.

In Table 1 we could see the demographic characteristics of the research subjects. Most subjects are males. The median age is 60 years old; the youngest is 39 and the oldest is 80. Mostly the patients come from outside Jakarta, do not work, and the type of the payment is private (not covered by insurance).

Clinical profile of the patients could be seen in Table 2: most patients have normal BMI. Complaints that were mostly made by the patients are bone pain (45.83%) and followed by complaints related to anemia, such as dizziness and easy to get tired. Almost a third of the patients are in Durie Salmon stage III.

Table 3 summarized the laboratory data of MM patients. There are 82.9% of the patients having anemia, 60% hypoalbuminemia, and 38.5% creatinine level above normal, 94.1% β2-microglobulin above normal, and 23.1% LDH above normal, and 23.1% LDH above normal, yet there's one patient having an increase of calcium level (4.2%). Serum immunofixation is found in 21 patients and positive protein electrophoresis in 26 patients. Twenty patients had Bone Marrow Puncture (BMP) examination and there were 13 patients (65%) having plasmocytes above 30%.

Bone involvement was involved in more than three fourth patients with MM with the average number of lesions is 4 and maximum is 16. The location where bone lesions found the most was in the spine (cervical, thoracolumbar) and the skull. The other locations of bone lesions were ribs, clavicle, scapula, tibia, and fibula.

Discussion

Multiple myeloma is a type of blood malignancies rarely found, including in Indonesia. However, the incidence of MM in developing countries such as Indonesia is having an increase annually. This research also found that there is an increase of the case every year. Based on the data from DNCH which is the center of national cancer reference, it had been reported that 43 cases of MM occurred during 2003-2007. The number had an increase by 37.2% from the period 1993-1997 (Sinuraya, 2012a; 2012b).

The risk factors to the occurrence of MM that have been known are males, aging, life style (food and obesity), and chemical exposure in the workplace (Khan et al., 2006; Saraf et al., 2012). The incidence of MM occurs more in males than females. This is in accordance with the world data, Globocan 2008 that reported the male incidents in developing countries were more than females, respectively 0.9 and 0.7 per 100,000 people (Ferlay et al., 2010). A research conducted by Khan et al. (2006) in Japan also found that MM was more common to males. The age difference of MM, especially dominated by males, is probably related to the gene involving in this disease in the sex chromosome. *Monoclonal gammopathy*, one of the risk factors to blood malignancies, is also found more often on males than females.

Besides that, the incidence of MM also raises along with the age increase. This research showed that MM patients mainly are above 60 years old. This thing is in accordance with the research by Rajabli et al. (2013) in Iran that found the average of MM patients' age were 62.4 years old. Meanwhile, in Korea and Japan the median of MM patients' age was older-66 years old (Lee et al., 2010; Chou, 2012). The similar result was also reported by Kyle et al. (2003): the median patients were 66 years old out of 1027 MM patients. In this research there were only two subjects aged below 40 years old (5%). This number is higher than what had been reported by Kyle et al. (2003)-about 2% of the MM patients aged below 40.

In this research, it is found that almost more than 40% of the subjects had overweight/obese. Obesity is known as one of the factors that could increase the risk of MM incident. A population-based case-control study in Canada also found there's a significant increase of risk along with the increase of BMI, which was BMI 25-30 had odds ratio (OR) 1.49 and BMI 30 had OR 2.06 (Pan et al., 2004). Other cohort study conducted by Friedman and Herrinton (1994) for 24 years found the relative risk (RR) 1.07 per unit BMI increase on white men, but not on white women or black men and women. Brown et al. (2001) found that obese had 1.9 times higher risk than people with normal BMI to get MM. However, the cohort study in Korea did not find the relationship between BMI and MM incidence (Oh et al., 2005).

There are two ways to decide the stage of MM: Durie-Salmon and The International Staging System (ISS) (Palumbo and Anderson, 2011; NCCN, 2015). The ISS is only based on β2-microglobulin level, and that is a new, simpler way to decide the stage of MM which has been widely used (Palumbo and Anderson, 2011). However,

this research used the Durie-Salmon way to decide the staging since there's only 17 patients (43.59%) who had done β2-microglobulin level examination. The staging decision criteria of Durie-Salmon is based on hemoglobin level, serum calcium level, creatinine level, bone imaging test, and rate of M protein production. Durie-Salmon divides the stage into three, and usually more than 70% patients come at stage III-which is the worst prognosis (Palumbo and Anderson, 2011). In this research the result is better; only third of the patients who came to DNCH at stage III. Stage III according to Durie-Salmon describes the condition of the patient has already been bad like having a severe anemia, an increase of calcium level, an advanced lytic bone lesions, and an increase of M protein production. Meanwhile, according to ISS stage III is marked by the increase of β2-microglobulin level (NCCN, 2015). The staging decision according to Durie-Salmon describes the deterioration of the patient's condition and also has an impact on the patient's survival rate. Pasqualetti et al. (1996) reported that patients with stage I have a median survival of 68 months, stage II 36 months, and stage III only 13 months.

Laboratory description and radiology test do not only act as supporting factors in deciding the stage, but also become prognostic factors in the success of the therapy and the patient's survival. The laboratory result that having the prognostic interest are hemoglobin level, serum creatinine level, serum albumin level, β2-microglobulin level, the percentage of plasma cell in the bone marrow, and also the degree of bone lytic lesion. In this research it is found that most patients had an anemia in which the hemoglobin level below 12 g/dL and 31.43% had a severe anemia (Hemoglobin level<8.5). Moreover, the majority of the patients had hypoalbuminemia. These are alike with Shaheen's study (1999) that most MM patients came in the stage III, 39% having severe anemia and 63% hypoalbuminemia. However, the subjects of this research still had better creatinine level which is only 11.54% had an increase of creatinine above 2 mg/dL. These are different with what had been found by Shaheen et al. (1999)-57% subjects had creatinine level above 2.2 mg/dL. In this research it is also found the β2-microglobulin level is above normal (94.1%). That number is higher than what had been found by Kyle et al. (2003) that found the increase of β2-microglobulin by 75%.

Myeloma is a unique disease that can cause osteolytic lesion, in which 80% of the patients will suffer from progressive bone destruction (Blade et al., 1996). This bone involvement certainly could deteriorate the patient's condition because it could inhibit activities and worsen the quality life of the patient. This is marked by the most complaints reported by the patients: bone pain about 45.83%, followed by fatigue due to anemia. Similar things also found by Blade et al. (1996), in which 66% of the patients complained about the bone pain and 26% about the fatigue. Even Shaheen et al. (1999) discovered that the bone pain complaints found in 82% of the patients, followed by fatigue in 78% of the patients. Bone involvement detected from the radiology test occurred to 76.9% of the patients and most patients had lesions more than three with the most common location was in the spine and skull. Scutellari et al. (1992) also found that the most common bone lesions were at the spine (49%), skull (35%), pelvis (34%), ribs (33%), humerus (22%), femur (13%), and mandible (10%). One of the complications of bone destruction is hypercalcemia. Hypercalcemia that could manifest into mild or severe and threaten lives is a metabolic complication of MM, often occurred to third of the patients (Oyajobi, 2007). However in this research hypercalcemia only occurred to one patient (4.2%). This may be caused by several things: there were about 38% of the patients whose calcium level was unknown, and the probability of the patient had already had a treatment before coming to DNCH.

The weakness of this research is the way of collecting the data done retrospectively from the medical records and there are some unrecorded data such as the laboratory data which probably had been done outside DNCH. Furthermore, the number of collected samples was relatively little. Nevertheless, this is the first research showing the data of clinicopathology and bone involvement in Indonesia so that it could be a precious additional data for clinicians and researchers inside and outside Indonesia.

In conclusion, *Multiple Myeloma* is a type of blood cancer that is still rarely found in Indonesia, but this cancer needs to be paid attention since the incidents keep increasing every year-in the world and in Indonesia. MM incidents in this research showed the distribution to the elders, more to males, and the high proportion of obesity. Most patients had anemia and hypoalbuminemia and the microglobulin is above normal, but the kidney still functions well. A third of the patients came to DNCH in the advanced stage, yet more than three-fourth of the MM patients had already had bone involvement with the number of lesions more than 3, especially in the spine and skull. These high incidents of bone involvement could affect the MM patients' condition and quality of life. Therefore, caution and further treatment are required to prevent more serious complications of bone lesions.

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