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MULTIPLE MYELOMA IN YOUNG POPULATION

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ABSTRACT

Multiple myeloma (MM) is overall the 14th most common malignancy and is generally diagnosed in patients over the age of 60 years. Interestingly, MM is rarely observed in younger patients, less than 40 years of age. Only a few cases of MM afflicting young patients have been reported thus far with 2% on average. In this study, we discussed on the distribution, demographic, laboratory data and clinical presentation of the young population (≤40 years old) affected by MM. A retrospective institutional record review of patients ≤40 years from January 2019–December 2021 was reviewed. Total of 106 samples was screened for MM using Serum and Urine Protein Electrophoresis (SUPE) and immunofixation (IFX). SUPE and IFX were carried out on Sebia Hydrasys 2 Scan and HYDRAGEL 2 IF by following the manufacturer's protocol. Heavy and light chain of M protein, demographic data on age, ethnicity, gender and clinical presentation features were collected. Out of 106 young patients, 23 (21.6%) showed the presence of M protein. IgG kappa was predominant followed by light chain lambda, IgM lambda and dimeric G lambda. Clinical presentation shows the majority presented with bone pain (11/23), followed by bone fracture (6/23) and anaemia (6/23). The median age is 37 years old at diagnosis with a ratio of 1:1.2 male to female. The disease is predominant in Malay, followed by Indian and Chinese ethnic. The distribution of MM in the young population is high in this study and thus may draw attention to the physicians on the MM among the young population in Malaysia.

KEYWORDS: M protein; Multiple myeloma; Immunofixation; Protein electrophoresis, Younger age

INTRODUCTION

Multiple Myeloma (MM) is a cancer of plasma cells characterized by the excessive production of monoclonal immunoglobulin (Ig) heavy and/or light chain (M protein) (1). Surveillance, Epidemiology and End Result programme (SEER) Cancer Statistics Review 2021 reported that Myeloma is the 14th most common malignancy accounting for 1.8% of all malignancies and 10% of hematologic malignancies (2). Diagnosis of the disease and monitoring of MM patients were by invasive or non-invasive techniques including peripheral blood-based of serum protein electrophoresis (SPE) with immunofixation (IFX) and free light chain (FLC) ratios, urine-based protein electrophoresis (UPE) with IFX, and bone marrow (BM)-based techniques (flow cytometry, immunohistochemical analysis, cytogenetics, and molecular genetics) (3). Moreover, MM can be described based on the typical clinical features shortened by the acronym CRAB which represents hypercalcaemia, renal failure, anaemia and bone pain.

MM is a disease of older people with a median age of 69 years old at diagnosis and it is rare in people younger than 40 years old (4). Nevertheless, a study has shown that there is a steady increase in MM incidence and mortality of younger patients with MM over time in the United State, Europe, Denmark and Sweden (5). Age has been recognized as an important prognostic factor in MM. It is reported that the young age has improved survival, showed favourable to treatment and better outcome compared to general population (6). A study on the trends in MM incidence shows that the highest increase in incidence is among the age groups in 40-49 years (1.9-2.7; 2.1).

In Malaysia, total incidence of MM ranges from 0.4 to 0.7 per 100,000 people. In young population (15 -49 years old), the incidence was 0.5, meanwhile 2.6-3.3 per 100,000 people for those within 50-60 year of age. The incidence is highest in those over 70 year of age where it is 1.8-5 per 100,000 people (7). There is still lack of published information and data related to the MM in young population amongst Malaysian. The current published data was a case report on 47-year-old lady diagnosed with kidney myeloma (7). Other than that, the data on young population is limited to western and developed countries (8). New cases are increasing among young population of age 30s and 40s where approximately 1,500 to 2,000 cases were reported (9). As the MM patient population becoming younger, more aggressive treatment may be warranted to improve survival in patients (4). In Malaysia, medical literature on this population is still lacking, thus, this study is important to report and provide information on the distribution, demographic, laboratory and clinical presentation of young population (≤40 years old) affected with MM in Malaysia.

MATERIALS AND METHODS

Study design, participant and setting

We performed a retrospective institutional record review of patients ≤40 years from January 2019–December 2021. Patients were identified from Institute for Medical Research, Special Protein Unit (UPK) database. UPK is a referral centre serving three states (Melaka, Johor, Perak) and two regions (Putrajaya, Labuan) in Malaysia with a referral population average of one thousand samples yearly. A total of 106 samples were received for MM screening using Serum and Urine Protein Electrophoresis (SUPE) and IFX along with collection of demographic, laboratory data and clinical features.

Ethics

This study was approved by the Medical Research of Ethic Committee (MREC), Ministry of Health Malaysia (NMRR ID-22-01523-9E8).

Materials and methods

SUPE and IFX were carried out on a semi-automated instrument of Sebia Hydrasys 2 Scan (Sebia, France) and HYDRAGEL 2 IF (Sebia, France) by following the manufacturer's protocol. 4 ml of urine were collected in urine container meanwhile 3 mL of serum were collected in plain tube. Upon receiving samples for SUPE and IFX, urine was concentrated using Amicon Ultra-4 filter (Eppendorf, Germany). 4 mL of urine was centrifuged at 4000 rpm until the volume is approximately 40-50 µL for about 30 minutes. Then, the concentrated urine and serum were applied on HYDRAGEL 2 IF agarose gel and subjected to electric current for 50 minutes. Migration program of 'No. 3 (15/30) Protein E' was chosen in the Sebia Hydrasys 2 Scan. Migration pattern of SUPE was compared to the normal control. Following migration, the gel was stained using No. 1 Protein E B1-B2 staining programme for another 20 minutes. In case of increased, decreased or additional bands observed, the IFX was required. IFX separated the protein according to its size in two stages of procedure, which are high resolution electrophoresis and immune-precipitation stage. For IFX, ready-to-use kit (Hydragel 4 IF) was used.

Concentrated urine and serum samples were subjected to migration and staining using acid violet stain (4BJ/4IF) (Sebia, France). Migration programme of 2/4 IF SM/DM* from the Sebia Hydrasys 2 Scan were chosen.

Data collection

Heavy and light chain of M protein were recorded. The presence of monoclonal protein (gammopathy) is characterized by a detection of monoclonal band with one of the anti-heavy chain antisera (gamma, alpha or mu) and either with anti-kappa or anti-lambda light chain antiserum. Biclonal gammopathy is characterized by the presence of two bands of heavy chain (identical or different) and two bands of light chain (identical or different). CRAB factors are assessed using the criteria from European Blood and Bone Marrow Transplantation (EBMT). Anemia is defined as haemoglobin ≤12 g/dL; hypercalcaemia is defined as a corrected calcium ≤2.75 mmol/L; and renal failure as a creatinine ≥177 µmol/L. Demographic data on age, ethnicity and gender as well as clinical presentation features were collected (4).

RESULTS AND DISCUSSION

Out of 106 young patients with suspected MM, 23 showed presence of M protein in the serum and urine, which are positive indicator for MM. UPK had received increasing number of samples for screening using SUPE and IFX. In year 2019, 2020 and 2021, UPK had screened 9, 44 and 53 young patients' samples; whereby 100%, 13.6% and 15% of the them were positive for M protein in the respective year. The distribution of young population with MM within three years study (2019-2021) was 21.6%. Our findings showed high distribution as compared to a previous study with frequency of 0.02% to 0.3% in patients less than 30 years of age (10). Meanwhile, reported that 3.26% of MM occurs in patient ≤40 years old of age. Small sample size in this study contributed to high distribution whereas other study had up to 10,549 samples in their institutions (10). On the other hand, the distribution of MM in young population is still low as compared to older population (11).

Table 1 shows the demographic data of these patients. The median age in this study was found in parallel to a study conducted by French Myeloma Intergroup where the median age of 37 at diagnosis were identified in 214 patients (12). Moreover, the female to male ratio in our study is in parallel to the ratio reported by Nayak et al. (13) (1:1.2) and Tripathy (14) (1:1.7) where there is a slight male predominance found. The disease manifested in the later ages more predominantly in females (61-70 years), than in the male patients (51-60 years) (10).

Table 1. Demographic data of patients ≤40 years of age with MM

Characteristics	
Age-years old	
Median	37
Range	12-40
Mean	34
Gender-No of pts (%)	
Female	11 (47.8%)
Male	12 (52.2%)
Ethnic-No of pts (%)	
Malay	16 (69.6%)
Indian	3 (13.0%)
Chinese	1 (4.3%)
Others	3 (13.0%)

In our study, IgG kappa was found in more than half of the patients (Table 2) and this is consistent with the older MM population. Figure 1 shows the IFX result for a patient who was positive for IgG kappa. We also discovered LC MM occurred at a higher rate than IgM and this finding is similar to Cheema et al. (4). We did not find any IgD in our patients, which agrees with most of the studies that this immunoglobulin is always associated with the older population (15). The patients with IgD are commonly associated with renal failure where majority of them were seen to have Bence Jones proteinuria (16). In addition to the presence of M protein, all of our patients can be diagnosed as MM although we were not able to provide the bone marrow examination results. This is because, according to the revised International Myeloma Working Group (IMWG) criteria for the CRAB factors (Table 2), the presence of at least one of these markers is considered sufficient for a diagnosis of MM (17).

Table 2. Laboratory data of patients ≤40 years of age with MM

	No of pts (%)	**Light chain**	
Monoclonal protein		Kappa	Lambda
IgG	18 (78.2%)	14 (77.8%)	4 (22.2%)
Light chain	3 (13.0%)	1 (33.3%)	2 (66.7%)
IgM	1 (4.34%)		1 (100%)
Dimeric G	1 (4.34%)		1 (100%)
Factor		Range	Limit
Hemoglobin (g/L)	15 (65.2%)	7-21.8	<12
Calcium (mmol/L)	14 (60.8%)	1.96-3.36	≥2.75
Creatinine(μmol/L)	3 (13.0%)	51-1269	≥177

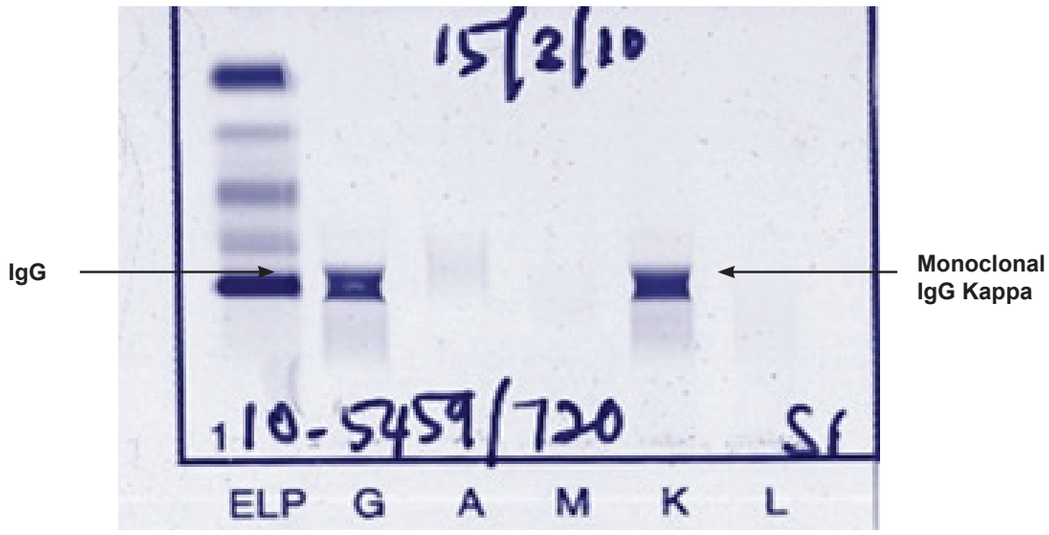

Figure 1. Presence of monoclonal band IgG Kappa using IFX or SUPE on HYRDAGEL IF 2

Table 3 shows clinical features of the patients. Majority of them presented with bone pain (11/23), followed by bone fracture (6/23) and anaemia (6/23). Other symptoms recorded include muscle weakness, lymphadenopathy, hepato/splenomegaly, nephrotic syndrome, peripheral neuropathy, as well as respiratory and vision problems. Consistent with other study, the first three symptoms were the most common related to MM (16). The atypical neurological symptoms which usually seen in CNS disease have been reported to occur in young female with this disease.

Table 3. Clinical features of MM patient in young population

Patient No	Clinical presentation
1	Anaemic, bone pain.
2	Anaemic, bone fracture, constitutional symptoms, muscle weakness, peripheral neuropathy.
3	Bone pain, muscle weakness.
4	Constitutional symptoms.
5	Anaemic, bone fracture, bone pain, nephrotic syndrome.
6	Anaemic, bone fracture, bone pain, hepato/splenomegaly, muscle weakness.
7	Constitutional symptoms, lymphadenopathy.
8	Anaemic, lymphadenopathy.
9	Bone fracture, bone pain, lymphadenopathy.
10	Peripheral neuropathy.
11	No symptoms related to MM.
12	Bone pain.
13	No symptoms related to MM.
14	Anaemic.
15	Bone pain.
16	Bone pain.
17	Anaemic, bone fracture, bone pain, muscle weakness, nephrotic syndrome.
18	Respiratory symptoms.
19	Vision problem.
20	Bone fracture, bone pain.
21	Bone pain.
22	Muscle weakness.
23	Bone pain, constitutional symptoms and lymphadenopathy.

CONCLUSION

Age has been recognized as an important prognostic factor in MM and whenever the disease affects the young patients, it is found to be more aggressive. However, a good response to therapy has been observed with an improved survival rate (median of 54 months) as compared to the older population.

The distribution of MM in young population is high in this study thus may draw attention to the physicians on the MM among young population in Malaysia. Medical literature on young population remains lacking in Malaysia and this is the first report reporting on ≤40 years old of age population with MM. It is important, as a timely diagnosis will aid in disease management and overall treatment for the patients in this population.

FUTURE RESEARCH

There were some unavoidable limitations in this study. At first more on laboratory data can be added including bone marrow aspirate, immunophenotyping and radiological findings. The laboratory data then can be used to correlate with patient treatment and outcome. All these limitations will be improved in the near future research with other findings in hope for a better understanding on MM.

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