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ABSTRACT

***Background*: very little is known about musculoskeletal features of multiple myeloma (MM) in Africa.**
***Objectives*: To describe the musculoskeletal features of multiple myeloma at presentation in a tertiary health care centre in sub-Saharan Africa.**
***Design*: A Cross sectional observational study.**
***Setting*: The Douala General Hospital, Cameroon from 2007 to 2013.**
***Subjects*: A patient was said to have MM according the current international consensus criteria for diagnosis and staging of MM. Patients with monoclonal gammopathy of undetermined significance, solitary plamocytoma and other haematologic malignancies were excluded.**
***Results*: A total of 62 patients were diagnosed with multiple myeloma, 63% were female. Mean age was 57± 12,1 (19-81) years. Musculoskeletal presentation included spine bone pains (75.6%); vertebral fracture with spinal cord compression in 46.8 %. Other clinical features at presentation included anaemia (70.93%), and nephropathy (17.74%). The average percentage of bone marrow plasmacytosis at diagnosis was 33% and Immunoglobulin G was found in 86% of patients. Sixty three per cent of patients were diagnosed at stage III of the disease.**
***Conclusion*: Presence of bone pain and anaemia should alert the clinician to investigate along the lines of multiple myeloma. Majority of the patients have osteolytic lesions and pathologic fractures at the time of diagnosis.**

INTRODUCTION

Multiple myeloma also known as plasma cell myeloma, myelomatosis, Kahler's disease, is a neoplastic disorder which is characterised by proliferation of a single clone of plasma cells derived from B cells in the bone marrow, accompanied by production of monoclonal (M) protein. Frequently, thereis invasionof the adjacent bone, which destroys skeletal structures and results in bone pain and fractures. Occasionally, plasma cellsinfiltrate multiple organs and produce a variety of symptoms. The M protein can lead to renal failure (light chains called Bence Jones protein) or hyperviscosityfrom its excessive amounts in the blood. The diagnosisdepends on the identification of abnormal monoclonal plasma cells in the bone marrow, M protein in the serum or urine, evidence of end-organ damage and aclinicalpicture consistent with MM (1,2). Multiple myeloma represents about 2% of all cancers and 10-12% of haematologic malignancies (3). Studies in Nigeria show that Multiple myeloma constitutes 8.2% of haematologic malignancies (4). In contrast with the predominance of white compared to blacks described in most haematopoietic neoplasms, age-adjusted incidence of MM is twofold higher in African Americans (9.5 per 100 000 per year) than in whites (4.1 per 100 000 per year); thus MM is thought to be more common in blacks but the race-related difference is not clearly understood (5) and reports show a consistently higher incidence and mortality among blacks(6-8). The principal manifestation of MM is musculoskeletal (bone pain and fractures),

followed by haematologic disturbances (anaemia), as a result of the accumulation of malignant plasma cells in the bone marrow, with frequent invasion of adjacent bone producing skeletal destruction(9). Few African studies demonstrated that bone pain and radiological lesions were the most important signs encountered, and patients were seen at late stage of the disease, often with complications(8, 10, 11). Fractures in MM are known to be associated with increased morbidity and poorer prognosis (12). Preventing this complication may help improve the outcome of MM in a resource poor setting (13). Even though Magnetic Resonance Imaging (MRI), and Computed Tomography / Positron Emission Tomography are considered gold standard diagnostic imaging tool for MM (3), simple plain radiographs easily accessible in a healthcare centre of a developing country may be useful in improving early diagnosis in the presence of MKL suggestive symptoms. In Cameroon few data is available on multiple myeloma: In 2005, MM though not found to fall among the ten most common cancers in Cameroon according to the Yaounde cancer registry (14), however accounted for 7.0% of haematologic malignancies diagnosed in HIV-1 patients (15) and 3.6% of haematologic malignancies (16). Very little is known about musculoskeletal features of MM at diagnosis in our setting, as it has been stated as the most common presenting feature.

The aim of this study was to describe the clinical features of MM, particularly the musculoskeletal characteristics at presentation, in view to promote early diagnosis and appropriate care to patients with MM in Cameroon.

MATERIALS AND METHODS

Research setting: The study was conducted in the Douala General Hospital a 320 beds referral tertiary health centre serving approximately four million inhabitants in Douala, the economic capital of Cameroon. This centre was chosen as it offers Hematology, Rheumatology and orthopedic units. All patients with haematologic malignancies seen in other units of GHD are referred to the care of oncologists and haematologists. MM patients were all referred to the haematologists.

Study design: After prior ethical clearance from the Institutional Review Board, we performed an observational cross sectional descriptive study over a six year-period, from January 2007 to December 2013. Patients medical records were reviewed (One patient=one file) and data reported on a pre-designed, pre-tested data collection sheet. Clinical, laboratory, and radiographic profiles of these patients was extracted from their medical files.

Case ascertainment: Patients included for the study were all black Africans of Cameroonian origin with an established diagnosis of MM followed up in the Haematology unit of DGH during the study period. A patient was said to have MM accordingthe current international consensus criteria for diagnosis and stagingof MM (1). Patients with monoclonalgammopathy of undetermined significance, solitaryplamocytoma and other haematologic malignancies were excluded.

Assessment: Data collected from each patient included: demographic (age, sex, residence, occupation, toxic exposure); clinical (past and recent medical history, presenting complains, MKL manifestations at diagnosis, complications); relevant laboratory and radiographic findings. The normal values for Calcium, creatinine, Gamma globulin, beta-2- macroglobulin, protein immunofixation in patients were done according to GHD normal values. Renal impairment implied raised serum creatinine greater than 15mg / l. Anaemia was defined as haemoglobin level less than 12 g / dl, and severe anaemia was described in patients with haemoglobin ≤ 8g / dl; Percentage of plasma cells was estimated on bone marrow aspirate: greater than or equal to 10% of plasma cells in the bone marrow aspirate of patients was considered significant. Measurable disease is defined as serummonoclonal (M) protein≥1 g / 100 ml or urine M protein ≥200 mg per 24 h. The Durie-Salmon Staging system was used to grade MM: Patients were classified under stage one if they had one or more of the following: haemoglobin greater than 10g / dl, a normal skeletal survey, normal calcium levels and serummonoclonal (M) protein. Patients were classified under stage two if they had one or more of the following; haemoglobin between 8 and 10g / dl, less than 3 lytic bone lesions, serum calcium less than 15mg / dl, and a low M protein. Those who were classified under stage three were expected to have one or more of the following; haemoglobin less than 8g / dl, serum calcium greater than 15mg / dl, ≥3 lytic bone lesions and a high M protein (17).

Radiographs features were recorded according to the attending radiologist description.

Statistical analysis: Categorical variables were presented as frequencies and continuous variables as mean and standard deviation. Statistical significance was considered at p-values < 0.05. Data were analysed using the Stata® software (College Station, Texas, USA).

RESULTS

A total of 1,206 patientswere seen in the Haematology unit during the study period, 470 were haematological malignancies, out of which 62 were diagnosed MM. MM thus constituted 5.1% of pathologies in the unit, and 13.2% of haematologic malignancies.

Sixty-two patients fulfilled our inclusion criteria,39 (63%) were female. The mean age was 57 ± 12.1 (19-81) years; 35.48% of patients were within the age group of 45 and 54 years. The most common presenting complaints were bone pain (75.6%), fatigue (64.5%) and inability to walk (24.2%). The complications at the time of diagnosis were anaemia (70.93%), spinal cord compression (35.5%), renal impairment (17.7%) and pathologic fracture (9.7%).

Mean values of laboratory findings included: haemoglobin (Hb) concentration was 9.37±2.79 (4.04 – 16.3), total white cell count was 9.62 ± 15.01 (2.0 – 8.1) x103, platelets was 238.98 ± 151.14 (41 – 941), serum albumin was 34.09 ± 9.63 (11.27 – 60.5), and serum β-2 microglobulin was 15.85 ± 19.03 (0.14 – 78.20).

The baseline demographic and clinical patients' characteristics are summarised in Table 1.

Table 1
Baseline characteristics of the population

Characteristics	Items	Frequency
Mean age (years)		57± 12,1 (19-81)
sex	F/M	39/24
Age range	<44	4 (6.4)
	45-54	22 (35.5)
	55-64	18 (29.0)
	65-74	14 (22.6)
	>74	4 (6.4)
Exposure to ionising radiation n(%)		2 (3,2)
Family history of cancers n,(%)		3 (4,8)
HIV positive n,(%)	2 (3)	
Presenting symptoms n,(%)	Bone pain	45 (75.6)
	Fatigue	40 (64.5)
	Inability to walk	15 (24,9)
Complications at diagnosis n(%)	Anaemia	44 (70,9)
	Spinal cord compression	22 (46,8)
	Renal impairment	11 (17,7)
	Hypercalcemia (n=51)	13 (25,5)
	Pathologic fracture	7 (14,9)
	Hyperviscosity (ESR>20mm)	40
Laboratory findings at diagnosis	Mean haemoglobin	9,4 +/- 2,8 (4 - 16,3)
	Mean gamma globulin	36,9 +/- 21,2(3,17- 59.6)
	Types of Immunogb(n=15)	
	Ig G	13(86.7%)
	Ig A	2(13.3%)
	Bence Jones proteinuria (n=10)	2(%)
	Medullar plasmocytosis(n=42)	
	<10	3(7.1%)
	>10	39(92.8%)
	Raised Serum β-2 microglobulin (n=30)	22(73.3%)

Musculoskeletal findings at the time of diagnosis included bone pain: vertebral (75.6%);paraparesia from spinal cord compression (35.5%), diffuse bone pain (9.7%); hip and shoulder joint pain (6.4%). Radiographic lesions included: lytic lesions (57.4%), vertebral fracture (44.8), increased bone transparence considered as bone demineralisation in (44.7%). Table 2.

Table 2
Musculoskeletal features of MM

Characteristics	Items	Frequency	Percentage (%)
Symptoms and signs	Nerve root limb pain	1	1.61
	Bone swelling	4	6.45
	Joint pain	4	6.45
	Rib pain	4	6.45
	Diffuse bone pains	6	9.68
	Vertebral bone pain	45	72.58
	Spinal cord compression	22	44.8
Plain radiographs	Lytic lesions	27	57.45
	Vertebral fracture	22	44.80
	Bone demineralisation	21	44.68
	Pathologic fracture	7	14.89
	No lesion found	6	12.7
Site of radiographic lesions	Lumbar region	37	59.57
	Long bones	14	23.40
	Skull	9	14.89

On staging, 39 (62.9%) were at stage III of Durie-Salmon at the time of diagnosis. Female were more often involved at severe stage. Twenty-two (35.5%) patients were within 45-54 years, when diagnosed at stage III.

Table 3

Stage	Total	Gender	Frequency	Percentage
1	15	Female	11	17.74
		Male	4	6.45
2	8	Female	6	9.68
		Male	2	3.23
3	39	Female	22	35.48
		Male	17	27.45
Total	62		62	100

DISCUSSION

Our study confirmed that bone pain is the most frequent clinical symptom, mainly localised in the spine, lytic lesion on plain radiographs and Durie Salmon stage III are the main presenting features of MM in our setting; MM is more common in female around their fifth decade, and patients are seen late in the course disease. As in retrospective data collections, there was lack of standardisation of tests at diagnosis as plain radiographs which were done mainly on the painful areas, may be leaving out asymptomatic radiographic lesions and systematic laboratory tests as regard to Bence Jones proteinuria, serum calcium level and protein immune electrophoresis were not systematically performed; this may render some results difficult to generalise in the population.

A majority of our patients had bone pain mainly at the spine pain as presenting symptom. This was a finding similar to that in a report by other studies

and case reports (12,18, 19). Sudden intense back pain is often a sign of pathologic vertebral fracture that may be accompanied by neurologic symptoms, usually a consequence of nerve root or spinal cord compression. More than 50% of our study patients had lytic lesion and 33.87% of our study population had bone demineralisation on skeletal plain radiographs. The radiographic appearance of myelomas is variable depending on the clinical type; which may vary from myeloma induced osteoporosis, osteolyses or compression fracture; the most common picture is a one or numerous round or oval osteolytic lesion with a characteristic punch-out aspect found on plain radiographs of affected areas. This goes further to make plain radiographs a simple diagnostic tool to ease the choice of prompt and appropriate referral, and consequently better management. The mechanism of bone disease in MM is the fact that tumoral cells produce osteoclast-activating factors (OAFs) and inhibit osteoblasts activities through the action of local cytokines like Interleukine (IL) I beta, IL-6 and Tumor necrosis factor alpha.

With pathologic fracture, bony involvement is typically lytic in nature, thus destruction of bone and its replacement by tumour may lead to pain, spinal cord compression. The mechanism of spinal cord compression symptoms may be the development of an epidural mass with compression, a compression fracture of a vertebral body destroyed by tumoural cells, or, rarely, an extradural mass. Thirty five point five percent of our patients presented spinal cord compression at diagnosis, 9.7% had pathologic fracture. Fractures in MM are known to be associated with increased morbidity and poorer prognosis (12,19), spinal cord compression carries a heavy comorbidity making the prognosis even poorer. Preventing this complication may help improve the outcome of MM in a resource poor setting (13). Most of our patients were diagnosed with myeloma at stage three of Durie Salmon classification, with certainly more than three osteolytic lesions found at presentation. The late presentation of the patients in a tertiary health care unit raises the question of delayed referral by primary healthcare providers or lack of financial accessibility to specialised haematology care in our setting, as there is not medicare or health insurance to cover health expenditures. Early identification of clinical presentation of MM and early referral to adequate hospital units may reduce the number of patients seen at late stage of the disease. Plasma-cell proliferation causes extensive skeletal destruction with osteolytic lesions, as well as anaemia, and hypercalcaemia. Fatigue was one of the most frequent symptom in our study which may correspond to anaemia, hypercalcaemia and hyperviscosity. Anaemia, hypercalcaemia,hyperviscosity were found in similar proportion than in other studies (10,20).Raised calcium, renalimpairment, anaemia, and bonelesions (CRAB) symptoms are the currentlyaccepted diagnostic criteria for diagnosis of symptomaticmyeloma(12,21). About 25% of tested patients in our study had hypercalcaemia at the time of diagnosis even though it wasn't systematically tested. Serum calcium is an independent predictor of quality of life in MM and hypercalcemiais a lifethreatening condition requiring emergency action (22).

Anaemia was the second most frequent clinical sign in our study as frequently published (23,24,). Bone marrow infiltration by plasma cells results in neutropenia, anaemia, and thrombocytopenia. Gammopathy on serum protein electrophoresisis is more likely to turn out positive than Bence Jones proteinuria, and immunoglobulin G is the most frequent type of paraprotein found(10,11,24). Therefore, in a resource poor setting investigations should be targeted at those parameters with a high frequency of positivity and greater diagnostic power in order to avert debilitating complications (10).

The incidence of multiple myeloma is thought to increase with age, thus occuring more frequently in the elderly men with a mean age at diagnosis of 69 years (22-24).The mean age of our patients was 57 years closer to some reports (7, 8, 25) and we also found that 6.45% of patients in our study were age less than 40 and this finding as in a few studies (19, 26, 27). Not only that MM is more common in black population, but at a younger age.

CONCLUSION

Spinal bone pain, when associated to anaemia in young adults should be an index of suspicion to investigate multiple myeloma. Plain radiographs represent simple and affordable diagnostic tools in a resource poor setting. MM is diagnosed at late stage in our patients, due to delayed referral, and also because the most common symptom which is bone pain is frequently found in other pathologies. Larger prospective studies may be necessary to better characterise the common presenting musculoskeletal features, especially in a resource poor and predominantly black population to serve as a guide and necessary aid to early diagnosis.

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