

Clinico-Laboratory Features of Multiple Myeloma in Selected Patients at University of Ilorin Teaching Hospital, North Central Nigeria

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Abstract

Multiple myeloma is an haematological disorder characterized by clonal proliferation of bone marrow plasma cells with production of increased amounts of monoclonal immunoglobulins which are detectable in blood and/or urine. The aim of the study was to describe the clinical and laboratory characteristics as well as treatment outcome in multiple myeloma patients diagnosed and managed at the Haematology Department of the **University of Ilorin Teaching Hospital (U.I.T.H)**, Ilorin, North Central Nigeria, between 1st January 2008 and 31st December 2018. The study materials included bone marrow registers from the department and case folders of all multiple myeloma patients diagnosed within the study period. Relevant data including socio-demographic characteristics of patients, clinical features at presentation and laboratory tests results were extracted, documented and analyzed. Diagnosis was made in all patients based on the presence of major and/or minor criteria as described by the International Myeloma Working Group guidelines. Fifty eight (58) patients were diagnosed with multiple myeloma comprising of 31 males and 27 females (M:F ratio = 1.15:1). The median age of patients was 62.6 years (range = 39 – 85 years), and the most common presenting features included back pains (86.2%), bone pains (69%), inability to walk (67.2%) and anaemia (67.2%). High erythrocyte sedimentation rate > 30mm/Hr was seen in all patients (100%), Immunoglobulin G (Ig G) was the commonest monoclonal immunoglobulin demonstrated on serum protein electrophoresis (82.8%), and “punched out” osteolytic bone lesion on X-rays was demonstrated in 79.3% of cases. In resource-limited settings such as ours, the diagnosis and monitoring of patients with multiple myeloma still rely on the clinical and laboratory features of the disease to a large

extent, hence the need for haemato-oncologists and physicians to be conversant with these features.

Keywords: Multiple myeloma, clinico-laboratory, features, UITH

Introduction

Multiple myeloma (MM) is an haematologic malignancy which belongs to a group of B-lymphoproliferative disorders generally referred to as myelomatosis or plasma cell dyscrasias. The disease is characterized by excessive proliferation and accumulation of clonal plasma cells in the bone marrow, and secretion of monoclonal proteins (M proteins/paraproteins) which are detectable in blood and/or urine (O'Donnell *et al.*, 2016; Acquah *et al.*, 2019)

Multiple myeloma was first documented in a 39 year-old woman, Sarah Newbury, by Samuel Solly in 1844 (Kyle, 2000). The disease represents a spectrum of disorders which range from the benign asymptomatic monoclonal gammopathy of undetermined significance (MGUS) to plasma cell leukemia. MGUS is present in about 3% of the population above 50 years of age and may progress to multiple myeloma or any of the related malignancy at a rate of 1% per year (Acquah *et al.*, 2019).

Multiple myeloma has an annual worldwide incidence of 1.0 per million population, and constitutes about 2% of all malignancies, and 5-10% of haematologic malignancies (Rajkumar *et al.*, 2005; Babatunde *et al.*, 2009; Jemal *et al.*, 2009; Ullah *et al.*, 2010; Dosunmu *et al.*, 2019). The incidence of MM is reported to be higher in blacks compared to Caucasians but much lower in Asians (Landgreen *et al.*, 2009).

It affects males more than females, with a male to female (M: F) ratio of 2.0-3:1 (Omoti *et al.*, 2007; Madu *et al.*, 2014; Collins *et al.*, 2015). The median age at diagnosis has been estimated to be 70 years, with about 37% of patients diagnosed below 65years while about 26% of patients are found between 65-75years (Becker *et al.*, 2011; Olaniyi *et al.*, 2015).

The clinical and laboratory features found in multiple myeloma can be attributed to the effects of the proliferating malignant plasma cells and the paraproteins they secrete (Babatunde *et al.*, 2009). These clinical features include bone pains usually involving the bones of the axial skeleton, anaemia, body weakness, hypercalcaemia, renal impairment, bleeding disorders, pathological fractures and neurological complications (Acquah *et al.*, 2019). The accumulation of malignant plasma cells in the bone marrow suppresses haemopoiesis thereby resulting in progressive bone marrow failure which manifests as anaemia, leucopenia and thrombocytopenia (Omoti *et al.*, 2007). Bone resorption as a result of raised osteoclast activity stimulated by cytokines secreted by the malignant plasma cells (Omunakwe *et al.*,

2013). This also causes osteolytic lesions which give rise to pathological fractures and hypercalcaemia in patients with MM (Olaniyi *et al.*, 2014; Salawu *et al.*, 2005).

- Diagnosis of multiple myeloma is often made based on the presence of certain clinical and laboratory features which include: Presence of a serum or urinary monoclonal protein (M-protein/paraproteins), presence of clonal plasma cells in the bone marrow or a plasmacytoma, presence of end organ damage due to effects of malignant plasma cells such as osteolytic bone lesions, anaemia, bleeding, hypercalcaemia and renal insufficiency (Kiraka *et al.*, 2014; International Myeloma Working Group, 2003).

Multiple myeloma is a progressive disease with a median survival of 6 months without treatment and about 3 years with therapy (Madu *et al.*, 2014). Disease staging at diagnosis is necessary and aimed at identifying the adverse prognostic factors which affects the overall disease survival and outcome (Fasola *et al.*, 2008). The patients who present with adverse prognostic factors would benefit from aggressive and more toxic chemotherapy than those with favourable prognostic factors (Salawu *et al.*, 2005). A major dilemma among surgeons and physicians is the late presentation of most patients with MM and this has been reported to contribute to the poor prognosis of the disease in Nigeria and other sub saharan African countries (Anderson *et al.*, 1998; Nwabuko *et al.*, 2017). Therefore, an increasing understanding of the clinical and laboratory characteristics of multiple myeloma by haematologists and physicians in our environment will help to increase clinical suspicion and ensure early referral and diagnosis as well as recognition of those complications that are associated with disease progression and poor prognosis. While there have been studies on MM from other parts of Nigeria, there is paucity of data from the northern part of the country. The aim of this study, therefore, was to characterize the clinical and laboratory features as well as treatment outcome of MM patients at the University of Ilorin Teaching Hospital, Ilorin, North Central Nigeria, and compare our findings with previous studies from other centers in Nigeria and elsewhere.

Materials and methods

This study was a retrospective review of all cases of MM which were seen and diagnosed at the Department of Haematology and Blood Transfusion, University of Ilorin Teaching Hospital (U.I.T.H), Ilorin between 1st January 2008 and 31st December 2018 inclusive. The U.I.T.H is a 650 bedded Tertiary Health Institution located in Ilorin, north central geo-political zone of Nigeria. It serves as a referral center for neighboring states of Oyo, Osun, Ekiti, Kogi and Niger states of Nigeria. The Haematology department is involved in the investigations, clinical evaluation and management of blood and blood related disorders. It also carries out laboratory services, interpretation of laboratory test results and receives consultations from other clinical departments of the hospital.

The materials used were data obtained from patient's case folders and bone marrow aspiration registers. The case folders of all the patients that were included in our study were retrieved from the Health Information Management Department of the Hospital and relevant information's extracted from the case notes included patients' biodata, clinical features of patients at presentation, laboratory and radiological investigations results, and treatment records. Results of other investigations done to guide in diagnosis such as serum protein electrophoresis, serum total protein and albumin, urinalysis and Bence-Jones protein detection and measurement of serum immunoglobulins (IgA, IgG and IgM) were also documented where available.

The diagnosis of MM in the patients was made based on the International Myeloma Working Group Criteria guidelines of presence of two (2) major and one (1) minor criteria or three (3) minor criteria (Table 1). The data generated from the above sources were analyzed using the Statistical Package for the Social Sciences (SPSS) version 21 (IBM Corporation, Armonk, NY, USA) and results were presented in the form of frequency tables.

Table 1: International Myeloma Working Group criteria for the diagnosis of Multiple myeloma.

Major Criteria	i. Plasmacytoma on tissue biopsy
	ii. $\geq 30\%$ plasma cells on Bone marrow examination
	iii. Monoclonal Immunoglobulin spike on serum protein electrophoresis(IgG $> 35\text{g/L}$, IgA $> 20\text{g/L}$)
	iv. Urinary Bence Jones proteinuria
Minor Criteria	a. 10 – 30% plasma cells on Bone marrow examination
	b. Paraproteins levels below values mentioned above
	c. Osteolytic bone lesions on x-rays
	d. Normal IgM $< 0.5\text{g/L}$, IgA $< 1\text{g/L}$ or IgG $< 6\text{g/L}$

IgG = Immunoglobulin G, IgA = Immunoglobulin A, Ig M =

Immunoglobulin M

Results

A total of fifty eight (58) multiple myeloma patients were diagnosed and managed by the haematologists at the Department of Haematology, University of Ilorin Teaching Hospital, Ilorin, within the study period.

The total number of haematological malignancies diagnosed during the period under study was 375, thus giving the incidence rate of MM as 15.5% of all haematologic cancers.

The mean age of the patients at diagnosis was 62.6 years (range 39-85 years), and the highest incidence was found in the 60 – 69 years age group (n = 23, 39.6%). Table 2 shows the age and sex distribution of multiple myeloma cases.

The commonest presenting features in our patients were back pains (n = 50, 86.2%), bone pains (n = 40, 69%), inability to walk (n = 39, 67.2%) and anaemia (n = 39, 67.2%). Other features which were also observed in the patients included body weakness (41.4%), paraplegia (19%), pathological bone fractures (17.2%) and bleeding diathesis (10.3%). (Table 3). The mean values of haematological parameters of the patients at presentation were: packed cell volume (26.0%), haemoglobin concentration (8.8 g/dL), white blood cell count ($7.8 \times 10^9/L$), platelet count ($173.3 \times 10^9/L$), erythrocyte sedimentation rate (85.5 mm/hr Westergreen) and bone marrow plasma cells (40.7% of all marrow nucleated cells). The mean values of biochemical parameters of patients were: total proteins (104.0 g/L), albumin (35.0 g/L), globulin (56.8 g/L), serum calcium (2.46 mmol/L) and serum creatinine (108.0 mmol/L). Table 4 shows the haematological and biochemical parameters of multiple myeloma patients.

Immunoglobulin (Ig) subtype was IgG in 82.8% of cases and IgA in 17.2% of cases. IgM was not recorded in any of the patients. Thick monoclonal band on serum protein electrophoresis (SPE) was demonstrated in 48 patients (82.8%), and radiological investigation (X- rays of flat and long bones) showed “punched out” osteolytic bone lesions in 46 patients (79.3%) while Bence Jones protein was detected in the urine of 16 patients (27.6%). Table 3.

In the treatment of these patients following diagnosis, MPT (Melphalan, Prednisolone, Thalidomide) was the commonest regimen given (n = 23, 39.7%), followed by MP (Melphalan, Prednisolone) in 20.7% and VAD (Vincristine, Adriamycin, Dexamethasone) in 17.2% of patients.. Other drugs which were used for treatment included C-VAD (cyclophosphamide + VAD) 12.7%, Melphalan only (8.6%), while Bortezomib (newer agent) was used in only one patient (1.7%). Table 5.

The mean duration of follow-up in the patients was 10 months (ranged from 1 month to 3.5 years). As at 31st December 2018, 27 patients (46.5%) were dead, 15 patients

(25.9%) were lost to follow-up while 16 patients (27.6%) are alive and being followed up in the Haematology Outpatient Clinic.

Table 2: Age and sex distribution of selected multiple myeloma patients at UIH, Ilorin

Age (Years)	Sex		Total (%)
	Male (%)	Female (%)	
< 40	1 (1.7)	0 (0)	1 (1.7)
40 – 49	5 (8.6)	2(3.5)	7 (12.1)
50 – 59	7 (12.1)	6 (10.3)	13 (22.4)
60 – 69	10 (17.2)	13 (22.4)	23 (39.6)
70 - 79	8 (13.8)	3 (5.2)	11 (19.0)
> 80	0 (0)	3 (5.2)	3 (5.2)
Total	31 (53.4)	27 (46.6)	58 (100)

Table 3: The frequency of occurrence of some clinico-laboratory features in selected multiple myeloma patients at UITH, Ilorin

Clinical Features	Frequency	Percentage (%)
Anaemia (Hb < 10g/dL)	39	67.2
Bone pain	40	69.0
Back pain	50	86.2
Inability to walk	39	67.2
Paraplegia	11	19.0
Pathological fractures	10	17.2
Bleeding diathesis	6	10.3
Bence Jones proteinuria		
Serum Albumin > 35g/L at diagnosis	16	27.6
Immunoglobulin G subtype at diagnosis		
Immunoglobulin A subtype at diagnosis	20	34.5
Gamma band on electrophoresis(SPE)		
Osteolytic bone lesions on X rays	48	82.8
	10	17.2
	48	82.8
	46	79.3

Table 4: Haematological and biochemical profiles of selected multiple myeloma patients at UITH, Ilorin

Parameter	Mean $\pm$ S.D	Range	Normal Range
Packed cell volume (%)	26.0 $\pm$ 6.4	<u>12</u> – 41	42 – 54 (M) 38 – 48 (F)
Haemoglobin concentration (g/dL)	8.8 $\pm$ 2.1	4.1 – 13.5	13.5 – 17.5 (M) 11.5 – 15.5 (F)
White blood cell count ($\times 10^9/L$)	7.8 $\pm$ 4.3	2.8 – 29.9	4 – 11
Platelet count ($\times 10^9/L$)	173.3 $\pm$ 98.0	19 – 533	100 – 400
Erythrocyte sedimentation rate (mm/Hr)	85.5 $\pm$ 23.3	34 – 148	0 – 15
Bone marrow plasma cells (%)	40.7 $\pm$ 8.2	31 – 60	2 – 3
Total Protein (g/L)	104.1 $\pm$ 12.8	54 – 138	60 – 80
Albumin (g/L)	35.3 $\pm$ 7.4	26 – 62	35 – 50
Globulin (g/L)	56.8 $\pm$ 8.6	42.2 – 92.6	20 – 35
Calcium (mmol/L)	2.6 $\pm$ 1.1	0.9 – 4.2	2.3 – 2.7
Creatinine (mmol/L)	108.5 $\pm$ 24.3	78 – 785	53 – 106

M = Male F = Female

Table 5: Chemotherapeutic drug regimens used in treatment of selected multiple myeloma patients at UITH, Ilorin

Chemotherapeutic drugs	Frequency	Percentage
Melphalan only	5	8.6
Melphalan + Prednisolone (MP)	12	20.7
Melphalan + Prednisolone + Thalidomide (MPT)	23	39.7
Vincristine + Adriamycin + Dexamethasone (VAD)	10	17.2
	7	12.1
Cyclophosphamide + Vincristine + Adriamycin + Dexamethasone (C-VAD)	1	1.7
Bortezomib based therapy		
Total	58	100

Discussion

Multiple myeloma is a haematologic malignancy with a worldwide distribution and considerable differences in incidence and survival among the Caucasians and black populations (Fasola *et al.* 2008; Dosunmu *et al.*, 2018). The incidence of MM in this study was 15.5% of all haematologic malignancies diagnosed within the study period. This observation was higher than what was previously reported (Salawu *et al.*, 2005; Babatunde *et al.*, 2009; Ullah *et al.*, 2010). This may be due to improved health education and increased awareness in seeking medical help. The median age at presentation in the patients was 62.6 years (age ranged from 39 – 85 years). Similar median age at diagnosis was reported in previous studies (Madu *et al.*, 2014; Salawu *et al.*, 2005; Omoti *et al.*, 2007; Kiraka *et al.*, 2014; Kim *et al.*, 2014) but at variance with higher median age above 70 years reported among Caucasians (Rajkumar *et al.*, 2005).

Multiple myeloma has been reported to be diagnosed more in males than females, and several authors have reported a male to female (M:F) ratio ranging from 1.1-4.4:1 (Omunakwe *et al.*, 2013; Olaniyi *et al.*, 2015). In the present study, we recorded a slight preponderance of MM in males compared to females (M:F ratio = 1.15:1). This finding was in agreement with the previous studies (Collins *et al.*, 2015; Acquah *et al.*, 2019) but in contrast with the findings of Ngouadjeu-Dongho

et al. (2018) and Hussein *et al.* (2011) where higher incidences among females were reported.

The most frequent clinical features at presentation in the MM patients in this study were back pains (n = 50, 86.2%), bone pains (n = 40, 69%), anaemia (n = 39, 67.2%), inability to walk (n = 39, 67.2%), body weakness (n = 24, 41.4%), paraplegia (n = 11, 19%) and pathological fractures (n = 10, 17.2%). The pattern of clinical features which were recorded in the index study was in agreement with those reported previously (Omoti *et al.*, 2007; Fasola *et al.*, 2008; Madu *et al.*, 2014). The high prevalence of anaemia and the skeletal abnormalities (bone pains, paraplegia and pathological fractures) observed in this study was an indication of advanced disease and late presentation in majority of our patients. Nwabuko *et al.* (2017) and Nghouadjeu *et al.* (2018) also reported similar complications associated with poor prognosis due to late presentation of patients in their studies.

Elevated erythrocyte sedimentation rate (ESR) greater than 30 mm/Hr fall in the first hour was observed in 100% of patients in this study. This finding was in agreement with other previous studies which reported high ESR greater than 20 mm/Hr (Salawu *et al.*, 2005, Fasola *et al.*, 2008). The malignant plasma cells in the bone marrow secrete increased amounts of monoclonal proteins which are detectable in blood and/or urine. Accumulation of the M- proteins in blood results in increased sedimentation of erythrocytes when whole blood is allowed to stand in a column. The ESR > 30 mm/Hr (range 34 – 148 mm/Hr) recorded in majority of patients in this study further demonstrated presence of advanced disease and late presentation in the patients. Haematological investigations such as Full blood count (FBC), erythrocyte sedimentation rate (ESR), and bone marrow aspiration (BMA) cytology for malignant plasma cells constituted important tools for establishing diagnosis and monitoring of therapy in multiple myeloma especially in our society where access to molecular methods of diagnosis and monitoring are not readily available.

Serum protein electrophoretic analysis showed that Ig G was the commonest form of M proteins found in the patients (n = 48, 82.8%). This finding was similar to what was reported by Nwabuko *et al.* (2017), Olaniyi *et al.* (2014) and Doualla-Bija *et al.* (2014) but in contrast with the study of Madu *et al.* (2014) which found Ig A as the commonest immunoglobulin subtype encountered in their study. IgG had been reported to be associated with poor prognosis in MM patients when compared with other immunoglobulin subtypes (Salawu *et al.*, 2005).

Radiological investigations in the form of skeletal survey of flat and long bones of the axial skeleton showed the presence of “punched out” osteolytic bone lesions in 79.3% of patients in this study. Similar observations were reported by many authors (Salawu *et al.*, 2005; Madu *et al.*, 2014; Acquah *et al.*, 2019). Osteolytic lesions result from increased bone resorption due to stimulation of osteoclasts and increased activity that occurs in close proximity to myeloma cells (clonal plasma cells) thereby

resulting in bone demineralization and weakness. This could explain the findings of pathological fractures commonly found in multiple myeloma (Roodman *et al.*, 2004; Oyajobi *et al.*, 2004; Hussein *et al.*, 2011).

The use of chemotherapeutic agents still remain the mainstay of treatment for MM patients in many centres in Nigeria and other low income countries where the use of novel agents or stem cell transplantation is unavailable. The oral administration of melphalan alone or in combination with prednisolone was the standard treatment until the advent of novel agents like bortezomib and lenalidomide and the re-introduction of thalidomide. In the present study, melphalan-based regimens consisting of MPT, MP and melphalan alone were used for treatment in majority of our patients (n = 40, 69%). Bortezomib was used in only one. This finding was in agreement with previous studies by Madu *et al.* (2014) and Acquah *et al.* (2019) which reported that melphalan-based combinations were used mainly for treatment of their patients. This finding was at variance with studies from Western countries where most of their patients received the newer drugs, bortezomib or lenalidomide based regimens with or without stem cell transplantation (Richardson *et al.*, 2007; Kumar *et al.*, 2007; Jacob *et al.*, 2017). The median duration of follow-up in this study was 10 months (ranged from 1 month – 3.5 years). This finding corroborated the report of Madu *et al.* (2014) which recorded median follow-up duration of 6 months in their study.

As at 31st December 2018, 16 (27.6%) patients are still alive and being followed up. This was attributed to the introduction of thalidomide as part of the treatment regimen in the latter part of the study.

Stem cell transplantation is the ultimate treatment for MM but is presently not available in Nigeria while the novel drugs which are associated with good prognosis and better survival outcome are quite expensive and therefore not affordable to the majority of our patients.

Conclusion and Recommendation

Multiple myeloma is an haematologic disorder with diverse clinico-laboratory features, and represents a significant proportion of haematologic malignancies in our community. Special tests such as immunophenotyping, immunofixation or genetic studies which could have been used for prognostic classification of our patients were not done and may not be practicable in many other centres in Nigeria due to non-availability or high costs. Hence, there is need for haemato-oncologists and physicians in resource-limited centres like ours to be familiar with the clinical and laboratory characteristics of MM which are relevant and quite useful in the diagnosis and management of multiple myeloma patients in our society, and this will go a long way to improve the prognosis and survival outcome of these patients.

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