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A Ten Year Review of the Biochemical Profile of Patients Diagnosed with Multiple Myeloma in Port Harcourt, Nigeria

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Abstract
Background: *Multiple Myeloma is the commonest haematological malignancy in people of African descent. Diagnosis depends on the presence of plasma cells which produce monoclonal proteins or abnormal free light chains.*
Aims & Methods: *The aim was to assess certain biochemical parameters in patients diagnosed with multiple myeloma. This was a ten year retrospective hospital based study.*
Results: *There was a total of 29 patients with a male to female ratio of 1.9:1. Median age at diagnosis was 60 years. There were 75.9% with anaemia and 51.7% had renal impairment (chronic kidney stages 2 – 4). Only 6.7% had hypercalcaemia, while hypocalcaemia was more common (20%). Four cases did not show a monoclonal protein on serum protein electrophoresis while 3 (11.1%) had a biclonalgammopathy. All cases with monoclonal proteins had an M-spike located in the gamma region. Of those that had free light chains assay done, 76.9% had kappa chain involvement while in 23.1% cases the lambda chains were involved.*
Conclusion: *Our study revealed a lower median age of 60 years. There were uncharacteristically more cases with hypocalcaemia than expected hypercalcaemia. More than half had anaemia with renal impairment.*
Keywords: *Multiple myeloma, MM, Biochemical parameters, Nigeria*

I. Introduction

Multiple Myeloma (MM) is a neoplasm of the bone marrow that involves clonal proliferation of malignant plasma cells which produce monoclonal proteins (M-proteins or paraproteins)detected in the blood and urine, as well as a complex array of clinical manifestations including hypercalcaemia, renal impairment, anaemia, lytic bone lesions (CRAB), and hypogammaglobulinaemia.

Multiple myeloma accounts for 1% of human cancers, 2% of cancer deaths, 10-15% of hematological malignancies and 20% of deaths related to haematological malignancies.' The median age at diagnosis is 70 years and the incidence increases with age. MMisthe most common haematological malignancy in people of African descent and is twice as common in blacks than other races. The exact cause of MM is unknown, however there is a potential genetic susceptibility and there are several reports of MM occurring in families. Patients with MM evolve from preclinical stages of monoclonal gammopathy of undetermined significance (MGUS), or smoldering multiple myeloma (SMM) which do not require therapy. Development of end organ damage or clinical symptoms heralds the onset of MM. The diagnosis of this disorder depends on the presence of characteristic clinical findings (includinganaemia,bone pains andfeatures of renal insufficiency) with identification of abnormal monoclonal plasma cells in the bone marrow, M-proteins in the urine or serum, evidence of end organ damage, lytic bone lesions, hypercalcaemia and immunodeficiency. A number of factors such as renal function, haemoglobin concentration, serum calcium, extent of bone lesion, serum albumin, lactate dehydrogenase, beta 2 microglobulin and performance status at the time of diagnosis are known to be important in relation to survival in patients with MM.

II. Aim And Methods

The aim of this study was to assesscertain biochemical parameters at first presentation in patients newly diagnosed with MM, with specific reference to renal and hepatic function, paraprotein concentration and presence of light chian disease.

This was a hospital-based retrospective study conducted at the University of Port Harcourt Teaching Hospital which is a tertiary institution in the South-South regionof Nigeria. Data was obtained from the case notes retreived from both the department of haematology and blood transfusion, as well as the medical records department. All confirmed cases of MM between August 2006 and July 2016 were included in the study. Diagnosis of MM was made using bone marrow aspiration, presence of monoclonal protein on serum protein electrophoresis and/ or serum free light chains analysis.

Biodata extracted included age, sex and ethnicity. Other data included laboratory investigations done at first presentation: full blood count (FBC), erythrocyte sedimentation rate (ESR), bone marrow aspiration

(BMA), serum electrolytes, urea and creatinine (EUCR), liver functions test (LFT), fasting plasma glucose (FPG), serum protein electrophoresis (SPE) and serum free light chains (FLC).Data was analyzed using statistical software package Microsoft Xcel® 2013.

III. Results

A total of 29 patients were diagnosed with MMbetween August 2006 and July 2016. All patients were Nigerians. Males were twice as affected as females (19 males and 10 females with a M:F ratio of 1.9:1). The mean age at presentation was 54.2 ± 15.9years, with a median age of 60 (range 24 – 83 years), *see Figure 1*.The average weight was 75.9 ± 15.6kg. There were 25 (86.2%) caseswith anaemia; mean haemoglobin (Hb) concentration was 8.4 ± 1.8g/dL. *Table 1* shows the full blood count (FBC) parameters and erythrocyte sedimentation rate of the subjects.

The values of the biochemical parameters are presented in *Table 2*. Although the serum creatinine value was elevated in 9 (31%) patients; 15 (51.7%) had renal impairment with estimated glomerular filtration rate (eGFR) values <90 fitting intochronic kidney disease stages 2-4 (Fig. 2). The creatinine was significantly higher in patients with renal impairment compared to those without (162mmol/L vs. 69.4mmol/L; p-value 0.004); while the eGFR was significantly lower in those with renal impairment compared to those without (56 vs. 146.2; p-value 0.0001). Although the Hb concentration was lower in those with renal impairment, this was not statistically significant (Hb 7.7g/dL vs. 9g/dL; p-value 0.06). There was a weak positive correlation between the eGFR and Hb concentration (+0.22); while a weak negative correlation existed between creatinine and Hb concentration (-0.23). A majority of the cases presented with acidosis (15, 60%), renal impairment (15, 57.7%), hyperuricaemia (12, 57.1%), hypoalbuminaemia (12, 66.7%) and hyperproteinaemia (9, 50%). Using the corrected calcium, only one patient (6.7%) had hypercalcaemia while 3 (20%) had hypocalcaemia.

For the diagnosis of myeloma, all patients (100%) had a bone marrow aspiration (mean plasmacytosis was 39.7 ± 24.2%), 18 (62.1%) had SPE while 13 (44.8%) had serum FLC done. Urinary Bence Jones proteins (BJP) was assayed in 11 (37.9%) patients and was positive in all cases. Of the 18 (62.1%) patients who had serum protein electrophoresis done, 4 (22.2%) had non-secretory myeloma (no monoclonal protein detected), while 14 (77.8%) had monoclonal protein detected in serum with a mean of 39.1 ± 37.1g/L. Three patients (11.1%) had 2 monoclonal peaks present. All cases (100%) including those with 2 monoclonal peaks had the M-proteins located in the gamma region on SPE, except 1 (5.6%) case who had two monoclonal peaks of which one peak was located in the beta region (58g/L) while the other peak was in the gamma region (4g/L).

Of the 29 patients, 13 (44.8%) had serum free light chains done. Patients with kappa chain involvement were significantly more (10, 76.9%) than those with lambda chain involvement (3, 23.1%). Amongst the cases with increased kappa chains, 6 (60%) had diagnostic values >100mg/L (range 310 – 5850mg/L); while 4 (40%) had elevated kappa values but <100mg/L (range 28.8 – 73.5mg/L). The four cases of non-secretory myeloma who did not have an M-protein on SPE all had light chain disease involving the kappa chains(mean 1969.6mg/L; range 73.5 – 5,850mg/L).

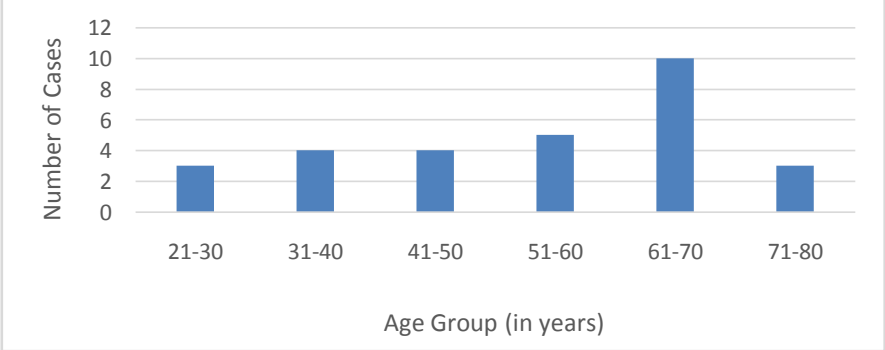

Figure 1: Distribution of age groups among cases

Table 1:

Haematological Parameter	Mean (±Sd)	Range	No. (%) With Values Lower Than Reference Range	No. (%) With Values Higher Than Reference Range
Hb. Conc (G/Dl)	8.4 (±1.8)	5.1 – 11.5	22 (75.9)	0 (0)
Pcv (%)	25.7 (±5.7)	16 – 35	21 (72.4)	0 (0)
Wbc (X 10^9/L)	5.8 (±3)	1.7 – 13.5	3 (10.3)	2 (6.9)

Platelets (X 10^9/L)	207 (±148.6)	18 – 582	8 (27.5)	3 (10.3)
Esr	107.5 (±45)	24 – 150	0 (0)	23 (79.3)
Bm Plasmacytosis	36.9 (±24.2)	5 – 85	0 (0)	29 (100)

Table 2

Biochemical Parameter	Mean	(±Sd)	Range	No. (%) With Values Lower Than Reference Range	No. (%) With Values Higher Than Reference Range
Sodium	137.4	(±6.4)	122 – 146	2 (8)	5 (20)
Potassium	4.0	(±0.8)	2.8 – 6.7	5 (20)	4 (16)
Bicarbonate	24.9	(±14.7)	13 – 92	15 (60)	1 (4)
Urea	4.6	(±2.6)	1.3 – 10	8 (30.8)	9 (34.6)
Creatinine (60-120)	122.8	(±92.4)	43 – 500	2 (7.7)	9 (34.6)
Egfr (Ml/Min/1.73m2)	94.2	(±58.2)	15 – 222	15 (57.7)	11 (42.3)
Fbg	5.2	(±2.1)	0.15 – 9.6	1 (3.4)	10 (34.5)
Uric Acid	476.7	(±237.6)	151 – 1,100	0 (0)	12 (57.1)
Ca2+	2.1	(±0.3)	1.5 – 2.6	5 (33.3)	0 (0)
Corr. Ca2+	2.3	(±0.3)	1.79 – 2.8	3 (20)	1 (6.7)
Total Bilirubin	9.7	(±3.9)	5 – 19	0 (0)	1 (7.8)
Conj.Bilirubin	1.4	(±0.8)	0 – 2	1 (14.2)	0 (0)
Alt	24.1	(±12.5)	2 – 48	2 (14.3)	2 (14.3)
Ast	31.7	(±17.7)	3 – 60	1 (3.4)	5 (17.2)
Alk Phos	171.9	(±193.3)	5.3 – 620	3 (25)	4 (33.3)
Kappa	791	(±1,593. 6)	0.87 – 5,850	1 (7.7)	10 (77)
Lambda	1,278	(±3,467. 4)	6.9 – 12,352	0 (0)	4 (30.8)
Total Protein	93	(±35.3)	53 – 160	1 (5.6)	9 (50)
Albumin	31.9	(±9.6)	18 – 48	12 (66.7)	0 (0)
Alpha-1-Glob	3.5	(±1.2)	2 – 6.6	1 (5.6)	6 (33.3)
Alpha_2-Glob	8.1	(±2.7)	2.8 – 13.8	2 (11.1)	5 (27.8)
Beta-Glob-	15.4	(±21.1)	3.7 – 75.1	5 (27.8)	4 (22.2)
Gamma Glob	31.5	(±36.9)	2.3 – 109.6	5 (27.8)	10 (55.6)
Paraprotein	37.9	(±36.8)	0 – 107.5	4 (16.7)	15 (83.3)

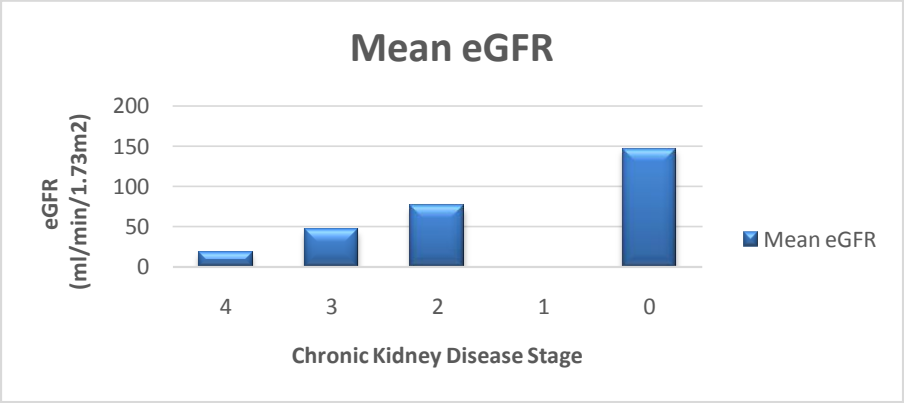

Figure 2: Mean estimated Glomerular Filtration Rate (eGFR) and chronic kidney disease stage of patients with renal failure

IV. Discussion

A total of 29 cases were studied within the ten year period.The mean age of incidence was 54.2 ±15.9 years with a lower median age of 60±15.9 years compared to other studies with median age of 66-73 years.[1, 6]However, MM has been found to occur at a lower age in blacks than other races,[6]as seen in our study where up to 14 (48.3%) cases were under the age of 60 years and 7 (24.1%) were under 40 years of age. As expected in MM [6], there was a male preponderance.

The serum sodium and potassium analysis was insignificant. Majority of the patients[60%] presented with metabolic acidosis with a low mean bicarbonate level. Our study showed 57.1% cases with hyperuricaemia.The mean total uncorrected calcium was 2.1±0.3mmol/L giving a 33% hypocalcaemia whereas no patient had hypercalcaemia. However, on correcting the calcium value with the serum albumin concentration, the meancorrected (adjusted) calcium value was 2.3±0.3mmol/L. This highlights the importance of using

corrected or adjusted calcium in interpretation of calcium assays. Withthe adjusted calcium, there was hypercalcaemiain only 6.7% of cases. This is unexpected as in MM there is typically hypercalcaemia in up to 45% of cases. This also constitutes part of the diagnostic criteria of CRAB, where C denotes hypercalcaemia.[6]Despite using the adjusted calcium, up to 20% still had hypocalcaemia which is not characteristic of MM at diagnosis. Hypocalcaemia may occur in MM as a side effect following the use of bisphosphonates or monoclonal antibodies against receptor activator of nuclear factor ƙB ligand (RANKL) such as Denosumab as therapy for hypercalcaemia.

Production of paraproteins by the malignant plasma cells in MM causes hyperproteinaemia associated with hypoalbuminaemia and this was the case in our study with a high mean total protein of 93 (±35) g/dL and low albumin levels of 31.9 (±9.5) g/dL respectively. Total protein to albumin ratio was increased in all the patients.Detection of an M-spike on SPE is one of the hallmarks in diagnosis of MM. Out of the 18 cases of multiple myeloma that had SPE done, 14(77.8%) were found to have monoclonal gammopathy as expected in MM.Although non-secretory myeloma (where there is an absence of monoclonal proteins) occurs in <5% cases of MM, this number was much higher in our study where 4 of the 18 cases (22.2%) with SPE did not reveal a monoclonal protein. However this number may be due to the small sample size of this study and the fact that of the 29 cases, SPE was done in only 18 of them as the facility to perform SPE was available only recently in our institution.

The presence of monoclonal proteins in the serum or urine causes a spike or peak in the SPE pattern.This spike is usually located in the gamma region, less frequently in the beta region and rarely in the alpha regions, as seen in our cases.Of the 14 cases with monoclonal proteins, all (100%) had the spike or M-protein located in the gamma region on SPE, but one case (5.6%) had a spike in the beta region (although this case actuallyhad a biclonalgammopathy where there were 2 M-spikes on SPE,one peak was in the beta region and the other in the gamma region). Our findings are similar to that by Dash et al whoreported that the M-spike was localized in the gamma region in 89% cases, beta region in 8% cases and alpha region in 1% cases. In about 2 – 9% of cases, monoclonal proteins may be located in more than one region on SPE (biclonalgammopathy), this was present in 11.1% of our cases. Chopra et al reported 84.8% of myeloma cases had an M-spike in the gamma region with 15.2% in the beta globin region while Tripathyet al reported M-spike of the gamma region in 87.5% cases and 12.5% in the beta region. [16,] Of the 13 patients who had free light chains assay done, majority had kappa chain involvement (76.9%)than lambda chain involvement which was seen in 23.1% cases. In 2015, the international myeloma working group updated the diagnostic criteria for MM to include serum involved/uninvolved free light chain ratio ≥100, provided the involved FLC is ≥100mg/L. Among the cases with increased kappa chains, 60% had diagnostic values (involved chain >100mg/L; involved/ uninvolved ratio >100)while in 40%, although there was elevated kappa values, these wereless than the diagnostic criteria (involved kappa chains were <100mg/l; *range* 28.37 – 73.gmg/L).

MM is a cause of renal impairment. Although the creatinine value was elevated in 31% patients, 51.7% had renal impairment with the estimated glomerular filtration rate (eGFR)values < 90 ml/min/1.73m^2 which spans along stages 2-4 of chronic kidney disease.Renal dysfunction in MM is one of the complications that requires careful attention as it is one of the factors that predicts survival.Renal impairment may occur via various mechanisms. These include the deposition of free light chains in the glomeruli, hypercalcaemia, dehydration, the use of contrast media, nephrotoxic medication and recurrent urinary tract infections. Free light chains are mainly deposited in glomeruli with massive fibrillary structure associated with insidious progression of renal failure.Light chain myeloma accounts for 40 – 60% of severe myeloma associated kidney injury reflecting the nephrotoxicity of the filtered light chains. Although more than half (51.7%) of our cases had renal impairment, this study did not investigate the causes of renal impairment in these patients. However, of the 15 cases with renal impairment, 6 had FLC done of which 4 (66.7%) had light chain disease (2 cases with kappa involvement and 2 cases with lambda involvement). Therefore, light chain cast nephropathy may have accounted for the renal impairment in the majority of our cases.It is also documented that hypercalcaemia associated with osteolysis by myeloma cells and hyperviscosity syndromes causes renal dysfunction. Unlike other reports,[(6)] hypocalcaemia was more common than hypercalcaemia in our study; hypercalcaemia was seen in only one case, but this singular case had renal impairment. Renal dysfunction may be irreversible if not managed on time and this is associated with worse prognosis, thereforeprompt diagnosis and treatment is required as this improves outcome.

Erythropoietin is essential for red cell production and >90% of this hormone is synthesized by the kidneys. Therefore it is not surprising that patients with renal impairment have anaemia. Our study showed only a weak negative correlation between serum creatinine levels and haemoglobin concentration; with a weak positivecorrelation between the eGFR and haemoglobin concentration. This may be due to the fact that anaemia in MM is multifactorialThe proliferation of the malignant plasma cells in the marrow causes anaemia and the plasma cells also secrete interleukin 6 which stimulates hepcidin, causing anaemia of chronic inflammation due

to inhibition of absorption of iron in the gut and inhibition of uptake of macrophage iron by developing erythroblasts in the marrow.

V. Conclusion

Our study revealed a lower median age for onset of myeloma which may be due to racial predisposition of blacks in developing MM. We also found that 20% uncharacteristically had hypocalcaemia at diagnosis, while only 6.7% had hypercalcaemia. More than half had renal impairment which may have been attributed to free light chains or hypercalcaemia.

Recommendation

This study was done using a small number of MM cases, therefore larger multi-centre studies in our environment are encouraged.

Limitations Of The Study

Due to lack of facility to assess both beta-2-microglobulin and lactate dehydrogenase in our centre, these investigations were not done for any patient, therefore staging of the MM using the revised International Staging System was not done.

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