Original Article

The Clinical and Laboratory Features of Plasma Cell NeoplasiaIn the University of Port Harcourt Teaching Hospital

Omunakwe HE, Korubo KI, Onodingene N, Nwauche CA
Haematology Department, University of Port Harcourt Teaching Hospital. Rivers State Nigeria.

ABSTRACT
OBJECTIVE: To analyze the clinical and laboratory features of Multiple Myeloma at presentation in a tertiary centre in Port Harcourt, Southern Nigeria.
METHODS: The medical records of all patients diagnosed for plasma cell neoplasia within a 10 year period at the University of Port Harcourt Teaching Hospital were reviewed retrospectively. Clinical presentation, investigation results, support and specific therapy used were documented.
RESULTS: A total of 20 patients were diagnosed with multiple myeloma, 70% were males, the mean age was 61.30 ± 8.8 years, 50% of them had pathological fractures. The mean duration before presentation was 11.89 ± 11.7 months (Median = 7 months) and associated with poor outcome. The most common method of treatment was chemotherapy with Melphalan and Prednisolone.
CONCLUSION: MM is a disease of the elderly that can negatively impact on the quality of life due to the complications associated with it. A long duration of symptoms before presentation is a common problem and it has been associated with substantial morbidity and mortality in this study.

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INTRODUCTION

Multiple Myeloma (MM) is a common haematological malignancy and it is characterized by the clonal proliferation of plasma cells in the bone marrow with accompanying increased levels of monoclonal proteins (M-proteins) in urine and/or blood. It is usually preceded by premalignant conditions Monoclonal Gammopathy of Undertermined Significance (MGUC) or Smoldering Myeloma (SM) which also have proliferation of plasma cells and M-proteins however they are asymptomatic and lack end organ involvement., The underlying pathophysiologic mechanism involves both numerical and structural genetic alteration, resulting from hyperdiploidy or translocation. Hyperdiploidy in Myeloma usually involves non-random trisomies of odd numbered chromosomes 3,5,7,9,11,15,19 and 21. Translocation involves the IgH gene during immunoglobulin class switching, somatic hypermutation or rearrangement of the variable, diversity and joining genes (VDJ rearrangement), which are required for the production of highly specialized antibodies. There are 5 recurrent translocations involving the IgH gene accounting for about half of the genetic abnormalities in Myeloma. This aberrant recombinations juxtapose oncogenes involved in cell proliferation or survival to close proximity of the powerful transcriptionally active IgH gene, giving rise to a neoplastic terminally differentiated B-cell that homes to the bone marrow.[7] The myeloma cell actively interacts with the bone marrow microenvironment and is dependent on it for its survival and drug resistance. When the myeloma cell adheres to the bone marrow stroma, it induces secretion of various cytokines and growth factors, including interleukin 6 (IL-6) and Osteoclast activating factor (OAF). The secreted OAF induces the stroma and osteoblasts to produce receptor activator of Nuclear Factor-κB ligand (RANKL), which stimulates osteoclast activity for bone destruction. This in turn causes increased release of cytokines from the bone matrix and these cytokines continue to stimulate growth of the myeloma cell. RANKL is inhibited by Osteoprotegerin (OPG), however CD138 (Syndecan-1) on the myeloma cell traps OPG and internalizes it. The myeloma cell also adheres to the extracellular matrix proteins to cause upregulation of cytokines involved in angiogenesis e.g. IL-6. Imbalance of osteoclast bone resorption and osteoblast bone formation results in bone disease.[7] The clinical features of multiple myeloma are variable and include anemia, low back pain, pathological fractures, neuropathy, hyperviscosity, recurrent infections and amyloidosis. The diagnostic criteria of multiple myeloma requires bone marrow plasmacytosis, presence of M-protein and related organ tissue impairment which manifests as hypercalcaemia (C), renal insufficiency (R), anaemia (A) or bone disease (B) which constitute the CRAB syndrome.[8] Overwhelming predictors of prognosis include albumin, 2-microglobulin, and chromosomal karyotype.

Some studies have been carried out to analyze the clinical presentation and the laboratory findings of MM in Nigeria. The aim of this study is to determine the pattern of clinical and laboratory features of MM patients seen in the Haematology department of UPTH between 2003 -2013.

MATERIALS AND METHODS

Correspondence: Dr. H.E. Omunakwe; Email: hannahomunakwe@yahoo.com

Study design: All cases of Multiple Myeloma seen in UPTH from January 2003 January 2013 were reviewed. The clinicopathological and demographic features of these patients extracted included the name, age, sex, occupation, history of exposure to chemicals at work, presenting features, Eastern Cooperative Oncology Group (ECOG) performance status, staging according to Durie and Salmon criteria. A diagnosis of MM was made using standard criteria of qualitative and/or quantitative abnormalities in the bone marrow plasma cells, presence of malignant forms (multinucleated, flame cells, mott cells and plasmablasts), characteristic osteolytic lesions on plain radiograph and monoclonal gammopathy in serum or urine. Results of Full Blood Count (FBC), Erythrocyte Sedimentation Rate (ESR), Electrolytes, Urea and Creatinine (EUC), Total Protein (TP) and Albumin were extracted; results of Bone Marrow Aspiration (BMA) and x-ray done for the patients were also retrieved. These data was analyzed using SPSS Version 17.0, released in August 2008.

RESULTS

A total of 20 patients were seen in the haematology department of UPTH in the 10 year period January 2003 January 2013. Seventy percent of them were males. The mean age at presentation was 61.30 yrs, and the median was 61.50yrs and a range of 45-78yrs. The mean duration of presentation after onset of symptoms was 11.89 months and a range of 1-48 months[2]. Twenty percent of them had history of exposure to chemicals Agrochemical, spray paint, rubber industry. The odds of those exposed to chemicals having poorer outcome was 0.013 (P value = 0.0123). This may associated with the fact that we have a small sample size.

Ninety percent of them had Multiple Myeloma, 5% each were plasma Cell Leukemia and Extramedullary Plasmacytoma respectively. Average duration before Presentation was 11.9 months, a range of 1- 48 months. As at the time of this review 40% of the cases were dead, 25% were lost to follow-up. The patients that had longer duration of symptoms before presentation had poorer outcome, there was a positive statistical correlation between this two variables (r = 0.557, P = 0.013).

The clinical presentations of the patients are shown in figure 1. some of these symptoms include bone pain, low back pain, weakness, fever, weight loss, inability to work and bleeding. The most common presentation was bone pain in 16 (80%) of the cases, weakness was associated with anaemia which was found in 14 (70%) of the patients, 7 (35%) of the patients presented with inability to walk which was as a result of pathological fractures. Ten (50%) of the cases presented with fractures affecting either the vertebrae, upper or lower limbs, ribs. Seven (35%) had evidence of infections commonly chest and joint infections. Bleeding (15%), abdominal complications (10%) and severe renal affectation requiring dialysis were quite infrequent in our case. There was one case of frontal lobe CNS involvement and urinary bladder plasmacytoma as extra medullary manifestation. Generally, the performance status as evaluated by ECOG scale showed that 70% of the cases were at a low level of activity (2-4) at presentation.

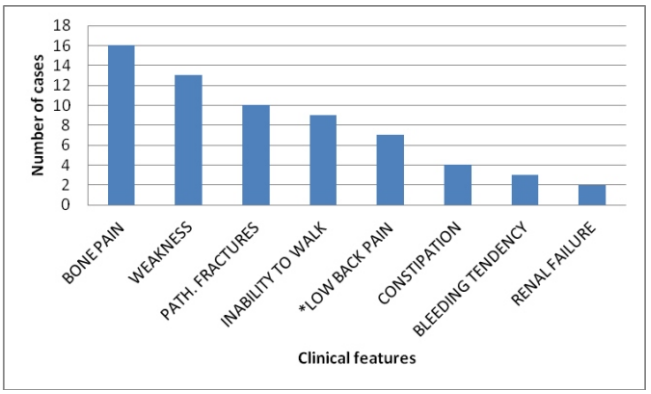

FIGURE1 Clinical Features

Haematologic findings

All the patients had Bone Marrow Aspiration (BMA) for diagnosis, save 1 that had BMB because the BMA produced a 'dry tap'. The mean marrow plasmacytosis was 38.5% a range of 5-70%. However in all the cases, there were malignant forms such as multinucleated forms, plasmablasts or flame cells. The patient that had Bone Marrow Biopsy (BMB) showed sheets of plasma cells in the core of bone with depressed erythropoiesis.

On evaluating the FBC at presentation, mean haemoglobin was 7.8g/dl. Anaemia was seen in 88% of the cases at presentation and it was mostly moderate to severe anaemia. There was a negative Pearson correlation (r = - 0.176), between the duration of symptoms before presentation and severity of anaemia which was not statistically significant. However, lower Hb was associated with poorer outcome which was statistically significant (P= 0.035). ESR was elevated in all cases; other haematologic indices are in Table 1 .

Sex	Mean	Median	Range
Heamoglobin(g/dl)	7.8	7.5	2.7-15.3
Total WBC(x10^9/L)	7.9	5.6	1.70 24.80
Platelet count(x10^9/L)	188.55	168	27 367
ESR (mm/Hr)	126.9	150	59 170

TABLE 1 Haematology findings

Biochemical Values The Serum Protein Electrophoresis showed monoclonal gammopathy in 10

(83.3%) of the 12 patients that had their results documented. Of the 9 cases that assayed for Bence Jones Proteins (BJP) in urine, 8 of them were positive. The findings of the blood chemistry are as follows.

Index	Mean	Range
Ca^{2+}	2.06	1 - 3
K+	4.01	3 - 5
Urea	27.26	2 -293
Creatinine	181.14	70 -910
Total protein	83	61 - 118
Albumin	30.85	18 - 47
Globulin	51.51	20 - 100

TABLE 2 Biochemical findings

Conventional radiography
Among the 15 patients with radiographic data, 9 (60%) had osteopenic bones, 5 (33.3%) had osteolytic lesions, 10(66.7%) had evidence of pathologic fracture. 6(60%) of these were in the vertebrae. Others affected the long bones, ribs and clavicle. One case however had a cranial involvement which was diagnosed by CT scan and was treated with radiotherapy

Chemotherapeutics and surgical intervention
The chemotherapeutic combinations used in our centre include Melphalan + Predicosolone(MP), Cyclophosphamide + Predinisolone(CP), Vincristine + Adryiamycin +Dexamthasone(VAD), Cyclophosphamide +Vincristine +Adryiamycin +Predisolone(CVAP), Bortezomib + Melphalan +Prednisolone(VMP) at the recommended doses. Nine(45%) of the cases were on MP, 4(20%) were given BMP, 2(10%) were on CP, 1(5%) on VAD and 1(5%) on CVAP. Two of the patients with relapse after MP, had thalidomide added to their therapy with good response. Another case of relapse after MP was treated with weekly Bortezomib with good control of the disease. 40% of these patients were not eligible for transplantation due to either age[3], Serum Creatinine > 221umol/L[3] and ECOG status >3 or 4, not due to bone pain[2].

Three of the patients did not commence chemotherapy either due to early demise while being optimized to commence chemotherapy on admission or the fact that they were unable to afford the drugs, so they left the hospital and never returned for follow-up.

One patient received radiotherapy for frontal lobe plasmacytoma with a good outcome (follow-up brain CT after 1 year showed no progression of the tumor). Other medications used were bisphosphonates in 8 of the patients.

Surgical intervention given included conservative management of intestinal obstruction/ileus in 2 cases by the general surgeons, a partial cystetomy was done for 1 patient who had urinary bladder plasmacytoma by the urologist. The orthopedic surgeons provided throraco-lumbar jackets for 3 patients at risk of vertebral collapse. More invasive interventions were in the form of craniotomy and curettage for 1 case, 3 cases had insertion of plates to immobilize pathological fractures of the femur. Synovectomy was done for 1 patient with severe septic arthritis of the knee.

An average of 5.56 units of blood was transfused to 9 of the cases, (a total 50 units, and range of 2-10 units). Erythropoietin was found to improve quality of life and reduce transfusion dependence in 6(30%) of the patients.

Stage and Course of disease
Mortality was common in patients that presented late (10-24 months after the onset of symptoms) or with multiple fractures affecting the vertebrae, ribs and long bone and anaemia (Hb $\leq$6g/dl). The patients that are stiil alive had a short duration of symptoms before presentation (mean 7 months), Hb 9.7g/dl and fewer Skeletal Related Events.

DISCUSSION
MM is a haematologic malignancy characterized by clonal proliferation of immunoglobulin secreting plasma cells in the bone marrow. It is mainly a disease of the elderly and has steep increase in the incidence with advancing age after 50 years. However, younger ages of incidence have been reported.

In our experience, the male to female ratio of incidence was 2.3:1. MM occurred mostly in the elderly in the 6th to 7th decade of life. The median age at representation (61yrs) in our analysis was similar to that reported in Ile-ife, (60yrs)[3], but higher than reports from Benin (54yr)[2]; India (55yrs). Some reports are higher than ours, such as reports from Ibadan (65yrs) and Europe (70yrs)[7].

Many of the patients presented late (6-12 months after onset of symptoms) and this was associated with poorer Performance status (ECOG 2-4 in 70% of cases), there was a positive correlation between these two variables (r = 0.422) although it was not statistically significant. The mean time of follow up was 8.86 months (median 2.6, range 1-44 months). Skeletal-related events (SREs) are common in patients with osteolytic lesions from MM and result in substantial morbidity. Pathological fractures (PF) occur in 40% of patients with MM, however in our case, 50% of the patients had pathological fractures. PF results from direct deposition

of myeloma cells within the bone, also there is release of cytokines from the tumor and the bone marrow microenvironment leading to osteoclastic activity and bone resorption. In our patients, vertebral fractures were found to be more common (60%) than non-vertebral fractures, this is comparable with a report by Sonmez et al . PFs are associated with reduced survival and increased mortality in MM patients in some studies[10], however in our study, there was only a weak positive relationship (r = 0.212) which was not statistically significant.

Considering the fact that many patients present late with advanced disease, supportive care should be a major component of the treatment. Red cell transfusion to correct anaemia and then rHuEPO to reduce transfusion dependence; plasmapheresis to reduce circulating paraprotein; bisphosphonates to inhibit bone resorption and surgical treatment of PF has been found to be useful in improving survival.

The mainstay of the treatment of MM today is chemotherapeutics and Stem cell transplantation. The availability of novel agents such as thalidomide, bortezomib and lenalidomide has expanded the treatment options and has improved the outcome of patients with MM. The oral combination of melphalan and prednisolone has been the standard treatment for patients with MM in most centres in Nigeria[2,3].

MP is also the most commonly used combination in our centre and with good control of the disease. However a few patients default from regular chemotherapy due to the financial burden and some relapse. The clinical outcome of our patients has improved with the addition bortezomib to MP in our treatment plan for those with a relapse after MP-only treatment or as part of the first line of treatment. We have noticed an improved quality of life and faster relief of symptoms such as bone pain and anaemia. They are also now able to support themselves in some activities at home such feeding, bathing and doing light laundry within a short duration of treatment. However, the cost of this drug has been a huge burden on those that have accepted the option of adding it to their therapy because of its advantage.

In conclusion, MM is a disease of the elderly that can negatively impact on the quality of life due to the complications associated with it. Early investigation of patients with bone pains and low back pain may be helpful to detect, monitor, follow-up and treat early disease to achieve a better outcome. Active supportive care in a multidisciplinary approach will also impact positively on survival of these cases.

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