RESEARCH ARTICLE

Clinical and Biochemical Profile of Monoclonal Gammopathies in Caribbean Patients in a Resource-limited Setting

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Abstract

Background: Multiple myeloma is the most common malignant plasma cell dyscrasia and ranks second among primary haematological malignancies. This study describes the epidemiologic, clinical and pathologic profile of monoclonal gammopathies seen in the University Hospital of the West Indies (UHWI), a tertiary care referral centre. Materials and Method: A retrospective analysis of 85 cases diagnosed at UHWI over the 5-year period 2003-2007 was conducted. The cases were identified from the bone marrow records as well as the computerized database of the Medical Records Department. Clinical presentation, family and personal history and demographic data were retrieved. Haematological and biochemical results were also analyzed. Results: There were 85 patients diagnosed with monoclonal gammopathies. The M:F ratio was 1.2:1 and the mean age was 65.7±1.3 years. Eighty percent of the patients had skeletal pain and 40% experienced weight loss. Of the patients experiencing bone pain 56.7% had multiple lytic lesions, 26.7% had pathological fractures and 26.7% had compression fractures. Seventy-four patients (87.1%) had a haemoglobin level <12.0 g/dL with 52.9% having values <8.0 g/dL. Renal impairment was evident at diagnosis in 36.5% . Hypercalcemia was seen in 26.5% and hyperuricemia in 45.9%. Of the 79 patients who had serum protein electrophoresis performed, 77.2% had at least one monoclonal band and of these 24.6% had a monoclonal protein also present on urine protein electrophoresis. Conclusions: The demographic profile in this group of patients is largely similar to other studies in predominantly Caucasian populations; however there was a notable increase in prevalence of severe disease at presentation, with the majority of patients presenting at the most advanced stage. It is probable that these differences reflect socioeconomic factors and not merely inherent ethnic variation in disease biology.

Keywords: Monoclonal gammopathy - multiple myeloma - clinical and biochemical abnormalities

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Introduction

The plasma cell dyscrasias are a group of clinical conditions that have in common, the presence of a paraprotein in blood and/or urine. This paraprotein is the result of expansion of a single clone of plasma cells. The group of disorders characterized by this monoclonal protein includes Monoclonal Gammopathy of Uncertain Significance (MGUS), Waldenstrom's Macroglobulinaemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes), Solitary Plasmacytoma and Multiple Myeloma (International Myeloma Working Group, 2003).

Multiple myeloma (Myelomatosis) accounts for 1% of malignant disorders, but is the most common malignant plasma cell dyscrasia and ranks second among primary haematological malignancies, with a peak incidence in the 7th decade. It is rarely diagnosed in patients younger than thirty years (Kyle and Rajkuma, 2004). The classical clinical picture is the combination of anaemia, pathological fractures, and the presence of monoclonal protein in serum and/or urine (Rajkumar and Kyle, 2007). However the presentation of multiple myeloma is variable, and a high index of suspicion should be maintained particularly in orthopaedic and renal patients. Multiple myeloma is reported to be twice as common in African Americans as in Caucasians and more common in men than in women. The contribution of genetic and socioeconomic factors to this profile remains unclear (Verma et al., 2008).

Cytokines play an important role in the disease process and Interleukin (IL)-6 is a potent growth factor for myeloma, possibly via an autocrine mechanism. Osteolytic lesions seen in the disease are due to increase activity of osteoclasts, probably the result of osteoclast-activating factor (OAF) mainly tumour necrosis factor (TNF) and IL-1, secreted by myeloma cells (Oyajobi and Mundy, 2004).

Monoclonal proteins (paraproteins) present in the serum and/or urine are secreted by malignant plasma cells which have clonally rearranged immunoglobulin genes (Weiss et al., 2011). Genetic deletions, additions and structural alterations of different chromosomes

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are frequent with clonal evolution. A number of clonal chromosomal alterations have been identified but the most frequent monosomy is of chromosome 13 which confers a poor prognosis (Zhou et al., 2009).

Most myelomas produce complete immunoglobulin molecules of a single type; IgG, IgA and IgD accounting for 55%, 22% and 1.5% of cases respectively. The quantity of paraprotein produced is often proportional to tumour mass. Excessive amounts of Ig fragments (light chains or parts of heavy chains) are also produced in approximately 85% of cases (Nowrousian et al., 2005).

In about 10-20% of cases myeloma dimers of light chains (Mr 44 kDa), either of the κ or λ type (Bence Jones proteins), can be demonstrated by immonoelectrophoresis of urine. In 75% of cases, paraproteins are present in both urine and serum. Electrophoresis of the serum sample taken from the affected patient followed by protein staining usually reveals the presence of an abnormal/monoclonal band of inter β-γ mobility, with a reduction in staining intensity for the remainder of the γ and albumin regions (Drayson et al., 2001).

We describe the epidemiologic, clinical and pathologic profile of monoclonal gammopathies seen in the University Hospital of the West Indies (UHWI), a tertiary care referral centre over a five-year period.

Materials and Methods

A retrospective analysis of 85 cases with Monoclonal Gammopathies diagnosed at UHWI over the 5-year period 2003-2007 was conducted. The cases were identified from the Bone marrow records in the Department of Haematology as well as the computerized database of the Medical Records Department.

The diagnosis of multiple myeloma was based on (1) increased number of bone marrow plasma cells greater than 10% or the histopathologic evidence of plasmacytoma, (2) presence of monoclonal protein (M-protein) in the serum or urine or both, and (3) presence of end-organ damage. The diagnosis of MGUS was made when there was less than 10% marrow plasmacytosis, serum M-protein (<3 g/dL), no monoclonal protein in urine and absence of end-organ damage. Smoldering myeloma is characterized by marrow plasmacytosis >10%, serum M-protein (>3g/dL) and no end-organ damage. Solitary plasmacytoma of bone or soft tissue required the histopathologic diagnosis of monoclonal plasma cells in the bone or soft tissue, in the absence of marrow plasmacytosis (<10%) as well as a negative skeletal survey and absence of end-organ damage. Plasma cell leukemia required the presence of at least 2 x 10^9/L plasma cells in the peripheral blood. A diagnosis of Extramedullary plasmacytoma is based on the detection of the plasma cell tumour in an extramedullary site, in the absence of bone marrow plasma cell infiltration, bone lytic lesions and end-organ damage. Patients who could not be unequivocally assigned to one of the above categories were placed in the category labeled "Unclassified".

Clinical presentation, family and personal history and demographic data were retrieved from the medical records. Laboratory investigations collected were haematological (hemoglobin, white blood cell count, and platelets) and biochemical (urea, creatinine, serum protein levels, uric acid, total and direct bilirubin, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), aspartate transaminase (AST), lactate dehydrogenase (LDH), calcium, phosphate, β_2 microglobulin, immunoglobulin levels, serum and urine protein electrophoresis).

Data was captured from the records of the Department of Pathology and analyzed using SPSS 11.5 (SPSS Inc., Chicago, Illinois, United States). The statistical analysis includes absolute (n) and relative frequency (%) distribution of the qualitative parameters. Values for continuous variables are expressed as mean±SEM. Data was also analyzed by the Student's t-test for independent samples and the Fisher test for independent variables with the level of significance set at 5%.

Results

There were 85 patients diagnosed with Monoclonal Gammopathies, the subtypes of which are outlined in Table 1. The distribution according to gender were 47 males and 38 females resulting in a M:F ratio of 1.2:1. The prevalence of multiple myeloma increased with age but sharply declined in the ninth decade. The mean age was 65.7±1.3 years (range 38-96) with males being predominant for each decade of life except for the eighth decade where there was a gender reversal.

Table 1. Subtype of Monoclonal Gammopathy

Subtype of Monoclonal Gammopathy	Number (%)
Multiple myeloma	75 (88.2)
Smoldering myeloma	3 (3.5)
Extramedullary Plasmacytoma	2 (2.4)
MGUS	2 (2.4)
Solitary plasmacytoma of bone	1 (1.2)
Plasma cell leukaemia	1 (1.2)
Unclassified	1 (1.2)

Table 2. Presenting Clinical Features of Patients with Monoclonal Gammopathy

Clinical features at Presentation	Number of patients (%)
Bone pain	68 (80.0)
Weight loss	34 (40.0)
Fatigue	25 (29.4)
Other symptoms of Anaemia	14 (16.5)
Symptoms of Hypercalcemia	15 (17.6)
Fever	11 (12.9)
Symptoms of Spinal cord compression	12 (14.1)
Bleeding	5 (5.9)

Table 3. Haemoglobin Distribution in Patients with Monoclonal Gammopathies

Haemoglobin (G/Dl)	Gender		
	Male	Female	Total (%)
< 4.0	1	0	1 (1.2)
4.1-6.0	8	8	16 (18.8)
6.1-8.0	17	11	28 (32.9)
8.1-10.0	9	10	19 (22.4)
10.1-12.0	6	4	10 (11.8)
12.1-14.0	5	4	9 (10.6)
14.1-16.0	1	1	2 (2.4)

Table 4. Biochemical Distribution in Patients with Monoclonal Gammopathies

Biochemical Parameters	Patients (Mean±S.E.)	%Abnormal
Urea (mmol/L)	10.67±0.93	55.1
Creatinine (μmol/L)	255.61±31.41	59.5
Total Protein (g/L)	94.44±2.57	61.9
Albumin (g/L)	33.32±0.88	72.6
Globulin (g/L)	61.04±2.97	77.4
Uric acid (mmol/L)	0.47±0.02	47.6
Total Bilirubin (μmol/L)	10.67±0.90	11.9
ALP (U/L)	72.64±4.12	10.7
GGT (U/L)	45.04±8.45	14.1
AST (U/L)	36.39±2.51	51.4
LDH (U/L)	229.33±14.52	49.0
Phosphorous (mmol/L)	1.20±0.01	20.4

Table 5. Distribution of Monoclonal Bands

Immunoglobulin (Ig) Type	Reduced	Normal	Elevated	Result not available
	No.	No.	No.	No.
IgG	8	7	35	11
IgA	34	8	2	17
IgM	39	9	1	12

Table 2 outlines the presenting clinical features. Eighty percent of the patients had skeletal pain and 40% experienced weight loss while 29.4% complained of fatigue with 16.5% having other symptoms of anaemia. Of the patients experiencing bone pain 34 (56.7%) had multiple lytic lesions, 16 (26.7%) had pathological fractures, 22 (26.7%) had compression fractures and 21 (35.0%) had diffuse osteopenia.

The most important haematological and biochemical data are presented in Tables 3 and 4. Seventy-four patients (87.1%) had haemoglobin level <12.0 g/dL with 45 patients (52.9%) having values <8.0 g/dL. The leucocyte count was normal in most patients with 8.2% having leucopenia (WBC $<4x10^9$/L) and 2.4% with leucocytosis (WBC $>11x10^9$/L). Only one case of plasma cell leukaemia was identified. Thrombocytopenia (platelet count $<150x10^9$/L) was evident in 17 patients (20.0%) with two patients having counts $<30x10^9$/L and associated haemorrhage. Renal impairment (creatinine value >177 μmol/L) was evident at diagnosis in 36.5% of the patients. Hypercalcemia was seen in 22 (26.5%) patients of which eight (36.4%) were mild (2.76-3.00 mmol/L) type, eleven (50%) moderate (3.01-3.50 mmol/L) and three (13.6%) had severe (>3.50 mmol/L). Hyperuricemia (uric acid >0.47 mmol/L) was seen in 39 patients (45.9%). Twenty (23.5%) patients had β2 microglobulin performed with 50% having elevated values.

Of the 79 patients who had serum protein electrophoresis (SPE) performed 61 (77.2%) had at least one monoclonal band and of these 15 (24.6%) had a monoclonal protein also present on urine protein electrophoresis (UPE). M proteins were limited to the urine in 11 (12.9%) patients. The γ-region was the most frequent (51.8%) location of the monoclonal band on SPE. IgG was the most common class. Table 5 outlines the distribution according to M-protein type.

Most patients with multiple myeloma (73.3%) had stage III disease classified according to the Durie-Salmon classification. The absence (subtype A) or presence (subtype B) of renal impairment was equally distributed within the group.

Discussion

In this group of hospital patients of predominantly African origin, multiple myeloma accounted for the majority (88.2%) of monoclonal gammopathies thus influencing the pattern of clinical and biochemical abnormalities that were identified. The median age of 65.5 years and the male: female ratio is consistent with published reports. Kyle et al reported a median age of 66 years in 1,027 newly diagnosed patients with multiple myeloma (Kyle et al., 2003).

Bone pain was the most consistent presenting complaint, with a prevalence of 80% which is higher than in most previous reports (Umeda et al., 2002). This reflects the advanced stage of presentation of these subjects. Myeloma bone disease is a result of uncompensated osteoclast function and increased bone resorption due to the induction of several cytokines which possess Osteoclast Activiating Factor (OAF) activity including IL-1, RANK ligand and tumor necrosis factor–β. Additionally, the action of tumor necrosis factor–related cytokines leads to differentiation and maturation of osteoclasts (Roodman, 2001). Durie and Salmon initially reported that the absence of skeletal lesions on plain X-rays implied improved survival (Durie and Salmon, 1975). This claim was challenged with the appearance of alternate variables such as serum albumin and β2 microglobulin as valid and reliable prognostic factors. In this group of patients, there was no correlation between the presence of lytic lesions and experiencing bone pain.

Constitutional symptoms of weight loss and fatigue were reported by 40.0% and 29.4% of patients respectively. Severe anaemia defined as haemoglobin levels of less than 8 g/dL was present in 52.9% of subjects with 45.9% of patients reporting symptoms of anaemia. The severity of disease at presentation is reflected by the finding of haemoglobin concentration below 6 g/dL in 20.0% of subjects. The factors leading to anaemia in multiple myeloma are multiple and varied, including bone marrow infiltration, and renal disease (Nau and Lewis, 2008), which are both related to the level of disease burden. In these patients the degree of bone marrow failure was severe enough to cause symptomatic thrombocytopaenia in 20.0% of patients. In addition to thrombocytopaenia, bleeding complications in multiple myeloma are also aggravated by M protein interference with both coagulation factor and platelet function (Podczaski and Cain, 2002).

The biochemical parameters also reflected the level of severity of disease with renal failure, and hypercalcaemia seen in 36.5% and 26.5% respectively. The pathogenesis of renal failure in multiple myeloma is complex, and related to tubular damage by excreted light chains (myeloma kidney) as well as secondary features of the disease such as renal vein thrombosis, hypercalaemia or pyelonephritis.

Sixty-one (77.2%) patients demonstrated a monoclonal

band in serum, of which 15 (24.6%) also demonstrated a urine monoclonal band. M proteins were limited to the urine in 11 (12.9%) patients. The class of immunoglobulin involved conformed to published reports with IgG being the predominant monoclonal protein. The presence of a urine M band has been linked to more aggressive disease; however some reports have failed to show any difference of survival attributable to presence of urine light chains (van Rhee et al., 2007; Dispenzieri et al., 2008).

The International Staging system (ISS) has replaced the Durie-Salmon staging for multiple myeloma because the prognostic groups identified by the latter lacked homogeneity. Survival can be more accurately predicted by use of the serum albumin and serum β_2 microglobulin, which reflect disease burden and the level of renal impairment (Anderson et al., 2011). Serum β_2 microglobulin levels were available for 20 patients and showed elevated values in 10 (50%). This ranged from 1,893.9 ng/mL to 98,420.0 ng/mL. Due to resource limitations the test was not consistently available and could not be used as the standard for assigning patient stage. Nevertheless, the likely extent of disease is reflected by the percent of patients (67%) with serum albumin less than 35 g/L thus indicating stage II disease at best. Currently cytogenetic and molecular markers such as deletions of Chromosome 13, 17p deletions and t(4:14) are also emerging as potential markers of adverse prognosis (Sawyer, 2011).

Concluding, in this group of patients the demographic profile was largely similar to other studies in predominantly Caucasian populations; however there was a notable increase prevalence of severe disease at presentation, with the majority of patients presenting at the most advanced stage. It is probable that these differences reflect socioeconomic factors and not merely inherent ethnic variation in disease biology. Resource limitations precluded the more accurate ISS staging and the use of cytogenetics for prognostic assessment, though the serum albumin levels were consistent with severe disease in the majority of patients.

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