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MULTIPLE MYELOMA – A HOSPITAL BASED CROSS SECTIONAL STUDY IN BANGLADESH.

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Abstract

Bone marrow morphological examination was performed on 835 patients either admitted in the inpatient departments of BIRDEM General Hospital or examined on outpatient basis. 760 of them were adults and 75 of them were children. 74 of the patients were diagnosed as suffering from a blood cancer known as Multiple Myeloma (MM). The age range of MM in our study was 40 to 85 years with a mean age of 63.25 years. Male to female ratio was 5:2 with a slight male preponderance. The median age of presentation was lower in females (60 years) than in males (65 years). MM was the second most frequent haematological disorder among all the patients examined, the most frequent one being leukemia. The frequency of MM was slightly higher among patients admitted in BIRDEM Hospital (10.4%) than those examined on outpatient basis (8.3%) although the difference was not statistically significant (P = 0.379 by Pearson's Chi square test). The highest frequency of MM was found in patients admitted in the department of Orthopaedic Surgery (20.8%) followed by the Department of Nephrology (16.7%). This data represents a cross sectional picture of the prevalence of MM in elderly population.

Keywords: Myeloma, Elderly, Bangladesh, Bone marrow, Morphology

Introduction

Multiple myeloma (MM) is a debilitating cancer that originates from plasma cells. Plasma cells are a distinct set of blood cells typically found in the bone marrow but usually not in the peripheral blood. First described in 1848 (Bence Jones, 1848 and Clamp 1967), MM is characterized by a clonal proliferation of malignant plasma cells and a subsequent over abundance of monoclonal paraprotein or M protein. An intriguing feature of MM is that the plasma cells which in normal condition, produce antibody and protect the body from infections, become cancerous and thus produce unusual manifestations like an immunodeficient state of the body. The aberrant antibodies whatever are produced lead to impaired humoral immunity, and patients have a high prevalence of infection, especially with encapsulated organisms such as *Pneumococcus*. The over production of these antibodies may lead to hyperviscosity, amyloidosis, and renal failure.

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The proliferation of plasma cells in MM may interfere with the normal production of blood cells resulting in leucopenia, anemia, and thrombocytopenia. The cells may cause soft-tissue masses (plasmacytomas) or lytic lesions in the skeleton. Feared complications of MM are osteolytic lesions, hypercalcemia, renal failure, and spinal cord compression due to tumour mass or pathological fracture of bone.

The presentation of MM can range from asymptomatic to severely symptomatic with complications requiring urgent treatment. Systemic ailments include bleeding, infection and renal failure. Although patients benefit from treatment (i.e., longer life, less pain, fewer complications), currently no cure exists. Recent advances in therapy have helped to lessen the occurrence and severity of adverse effects of MM.

The precise etiology of MM has not yet been established. Roles have been suggested for a variety of factors including genetic, environmental and occupational. Monoclonal Gammopathy of Undetermined Significance (MGUS), radiation, chronic inflammation, and infection have also been implicated as associated factors.

Case-controlled studies (Alexander *et al*. 2007 and Lope *et al*. 2008) have suggested a significant risk of developing MM in individuals with significant exposures to chemicals in the agriculture, food, and petrochemical industries. An increased risk has been reported in farmers, especially in those who use herbicides and insecticides, and in people exposed to benzene and other organic solvents. Long-term (>20 y) exposure to hair dyes has been linked to an excessive risk of developing MM.

MM accounts for 10% of all haematologic cancers (Caers *et al.* 2008 and Kyle and Rajkumar 2009). The median age of patients with MM is 68 years for men and 70 years for women. Only 18% of patients are younger than 50 years, and 3% of patients are younger than 40 years. The male-to-female ratio of multiple myeloma is approximately 3:2. The 5-year relative survival rate for MM is around 35%. Survival is higher in younger people and lower in the elderly (Bergsagel *et al.* 1979 and Rodon 2002 and Ludwig *et al.* 2008). Relevant demographic studies of MM pertaining to our country are not available except for few sporadic cross sectional studies (Kibria *et al.* 2010). According to the US based reports, myeloma is rare among people of Asian descent, with an annual incidence of only 1-2 cases per 100,000 people.

Diabetics with multiple myeloma constitute a challenging specific population to physicians. BIRDEM is a general hospital accommodating patients referred from all over the country. This study presents the experience with morphological examination of bone marrow aspirates from 834 patients in BIRDEM and the incidence of MM among these cases along with its correlation with other factors commonly associated with old age especially diabetes. Since the patients of our study group had not been referred for haematological disorders per se, our data represents a general picture of the incidence of blood cancers in elderly population.

Materials and Methods

The present study was carried out over a period of 9 years and 2 months from November 2002 to December 2011. During this period, a total of 834 bone marrow smears was examined. As multiple myeloma is a cancer of adults and the onset before 40 years of age is very uncommon (Hwell and Alexanian 1976), statistical analysis was performed among adult patients only. Adults were defined as age of above 18 years. Elderly patients were defined as those having the age of 50 years or above. Multiple Myeloma was diagnosed according to the criteria of the International Myeloma Working Group (International Myeloma Working Group 2003). Chronic Kidney Disease was defined as having a serum creatinine of 1.5 to 6.0 mg/dL (females) or 2.0 to 6.0 mg/dL (males) according to the National Kidney Foundation Practice Guidelines (National Kidney Foundation 2002). Anemia was defined as a haemoglobin level of less than 10.0 g/dl according World Health Organization (WHO) guidelines. Unexplained anemia (UA) was defined as normocytic normochromic anemia that could not be explained by nutritional deficiency or any other existing co morbidities of the patients. Bone marrow aspiration was performed using modified Salah needles either from posterior superior iliac spine or sternum or anterior iliac crest in rare occasions. Various clinico-haematological parameters were noted. Statistical analysis was performed with the help of SPSS 17.

Results and Discussion

A total of 834 bone marrow smears was examined. Among them, 760 were adults and 74 were children. Among the adults, 358 cases (47.10%) were diagnosed as suffering from any haematological disorder (Table 1). Among them, 300 (83.79%) were malignant and the rest were non-malignant like nutritional anemia or other causes. There were 13 cases of secondary metastatic carcinoma, which comprised of 1.71% of all adult cases. We came across 74 cases of MM. This specific entity comprised of 9.73% of all diagnoses.

Table 1. Marrow morphological diagnoses of all adult patients examined.

Diagnosis	Number of cases	Percentage of total cases (%)
Normoblastic active marrow	75	9.87
Multiple myeloma	74	9.74
Leukemia	103	13.55
Aplastic or hypoplastic anemia	63	8.3
Myelodysplastic Syndrome	41	5.4
Secondary Reactive Marrow	272	35.79
Visceral Leishmaniasis	9	1.18
Metastatic cancer	13	1.71
Megaloblastic anemia	24	1.71
Idiopathic thrombocytopenic purpura (ITP)	13	3.16
Congenital Dyserythropoietic Anemia (CDA)	1	0.13
Lymphoma	4	0.53

The distribution of various hematological malignancies is shown in Fig. 1. Multiple Myeloma turned out to be the second most commonly encountered hematological malignancy, second only to leukemias altogether.

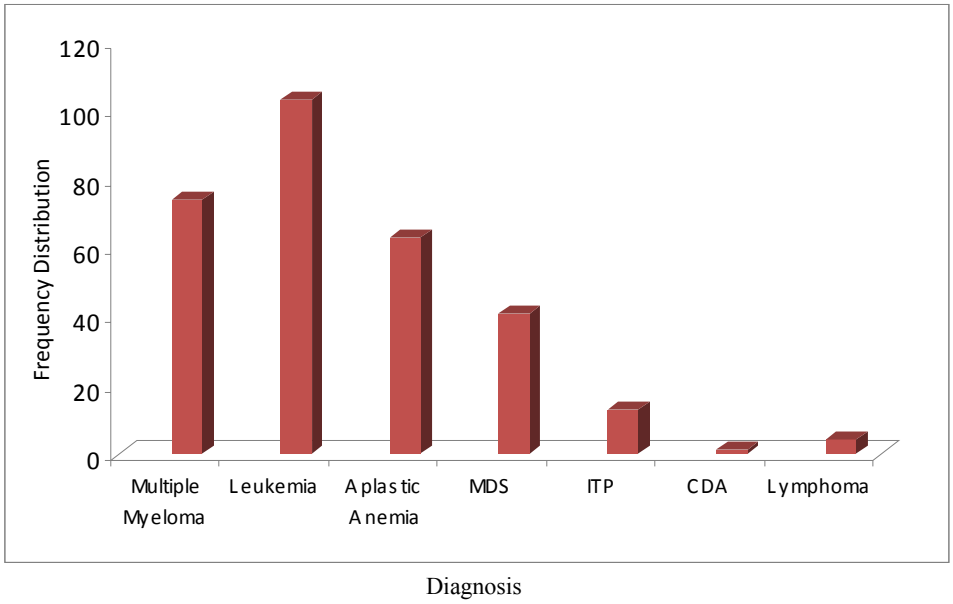

Fig. 1. Total number of haematological malignancies and their distribution among patients undergoing bone marrow examination in BIRDEM during November 2002 to December 2011.

The results presented in Table 2 showed that 76.97% (585/760) of all the adult patients in our study had been admitted cases of BIRDEM general Hospital. Among them, 55 inpatients and 19 outpatients had been diagnosed as MM. While comparing the incidence of MM between hospitalized patients and outpatients referred to BIRDEM for bone marrow examination only, the incidence was found to be higher among inpatients (55/535) than outpatients (19/225), 10.28% versus 8.44% respectively. The highest frequency of MM was found among patients suffering from chronic kidney disease and admitted to Nephrology Department (22.22%). Higher frequency was also observed among patients admitted to orthopedic surgery (20.83%) and cardiology departments (17.64%) indicating bony and cardiac complications respectively.

Table 2. Distribution of MM among various departments of BIRDEM hospital and outpatients.

Sl. No.	Name of the department	Number of cases of MM	Total cases examined	Percentage(%) within cases examined
1	All inpatients	55	535	10.28
2	Internal Medicine	12	131	9.16
3	Gastroenterology	6	69	8.69
4	Endocrinology	6	63	9.52
5	Nephrology	14	63	22.22
6	Neurology	2	17	11.74
7	Critical Care Medicine	4	46	8.69
8	Orthopaedic Surgery	5	24	20.83
9	Cardiology	6	34	17.64
10	Gynaecology and Obstetrics	0	2	0
11	Paediatrics	0	26	0
12	Outpatients	19	225	8.44

Among all the patients examined in BIRDEM, 760 cases were adults and 489 cases were of the age of 50 years or above. They comprised of 64.34% (489/760) of the adult group (Table 3). Among the elderly patients MM was found in 67 cases (13.70%). Seven MM patients were below the age of 50 years and comprised of 9.45% of the total diagnosed cases (Table 4).

Table 3. Age distribution of patients undergoing bone marrow examination.

Age range	Number of cases	Percentage (%)
0-12 Years	36	4.32
13-17 Years	39	4.64
18-49 Years	270	32.37
50 Years and Above	489	58.63

There was no patient diagnosed below the age of 40 years. Maximum number of cases was found in the age group of 60-69yrs (Table 4). 35.14% of all MM cases were in the age group of more than 60 years. Among the MM patients, 53.40% (43/74) were elderly. There was a strong correlation between MM and age more than 50 years ($P<0.0001$, CI 95%).

Table 4. Age adjusted frequency distribution of MM.

Age Range	Frequency	Percentage (%)
Below 40 Years	0	0
41-49 Years	7	9.45
50-59 Years	18	24.32
60-69 Years	26	35.14
70-79 Years	17	22.97
80-89 Years	6	8.1

The age range of the patients suffering from MM was 40-85 years (Table 5) with a male to female ratio of 5:2(53/21). Mean age was 63.25±10.69 SD (Table 5). Median age for males was 65 years and for females was 60 years. The results showed good correlation to international values, although the median age of presentation especially for females was somewhat lower. This could be due to a larger young population in our country as compared to developed countries but it merits further studies to exclude other possibilities.

Table 5. Comparison of statistical findings of MM in BIRDEM study and international figures.

Criteria	Study in BIRDEM	International study [3,5]
Percentage of all haematological cancers	16.66 %	10 %
Age range	40 -85 Years	40 years onwards
Mean age	63.25±10.69SD	65
Median age (Male)	65	68
Median age (Female)	60	70
Male female ratio	5:2	3:2
Prevalence below 40 years	0 %	3 %
Prevalence below 50 years	9.45 %	18 %

Multiple myeloma is a malignant plasma cell disorder that accounts for approximately 10 % of all haematologic cancers. It is characterized by accumulation of clonal plasma cells, predominantly in the bone marrow. The prevalence of type 2 diabetes is increasing; therefore, it is expected that there will be an increase in the diagnosis of multiple myeloma with concomitant diabetes mellitus. The treatment of multiple myeloma and diabetes mellitus is multifaceted. The coexistence of the two conditions in a patient forms a major challenge for the physicians.

Multiple Myeloma is essentially a disease of the elderly. In elderly persons, the triad of anemia, renal insufficiency and bone lesions in the presence of hypercalcemia provides a clue to the diagnosis of this not so uncommon blood cancer. Patients with multiple myeloma frequently present with vague symptoms such as back pain, bony pain, fatigue,

and anemia commonly found in elderly persons. The diagnosis is often made incidentally following an episode of pathological fracture. Since anemia is a common feature among patients suffering from renal diseases, the low haemoglobin is often assumed to be due to low erythropoietin production by the kidneys. This leads to delay in diagnosis of other causes of anemia like haematological malignancies especially Multiple Myeloma. Given that elderly patients with diabetes are often anemic, and that renal insufficiency in these patients can result from diabetes, careful evaluation before erythropoietin administration should exclude haematological causes of these coexistent conditions, particularly multiple myeloma. Measurement of the erythrocyte sedimentation rate (ESR) may be helpful in spotting the disease, for a rapid rate in patients with bone pain and anemia suggests multiple myeloma (Newton 1977). Without early recognition of multiple myeloma and referrals to oncology specialists, patients are left with a delayed diagnosis and poor symptom control. Our study shows that Multiple Myeloma is not at all an uncommon diagnosis among diabetic patients with anaemia and nephropathy. Despite the increased prevalence of malignancy among patients with ESRD (Maisonneuve *et al.* 1999), routine cancer screening has not been considered cost effective relative to survival time gained for this population as a whole (Chertow *et al.* 1996). A strong clinical suspicion is, therefore, important in establishing early diagnosis of myeloma and thus preventing untoward neurological complications from fractures involving the spinal cord.

According to the Prevalence of Anemia in Early Renal Insufficiency (PAERI) study, multiple myeloma/dysproteinemia could be attributed to 0.4% of all causes of CKD (McCellan and Tran 2002). Studies pertaining to incidence of multiple myeloma in our country or neighboring countries are infrequent. In a single study conducted in India, multiple myeloma was found to be one of the rarer causes of patients presenting with pancytopenia (Khodke *et al.* 2001). According to the UK CKD management guidelines, patients with CKD should not be subjected to routine “myeloma screening” prior to referral (Burden *et al.* 2005).

Association between diabetes and multiple myeloma per se could not be established. Although results in the literature are contradictory, in a recent study conducted by Khan *et al* (2008) there was no association between self reported diabetes and multiple myeloma whereas the highest level of postload glucose was associated with risk of mortality from multiple myeloma (HR, 3.06; 95% CI, 1.05–8.93) in another study by Chiu *et al.* (2006). This is in contrast with observations of other studies based in Asia (Vineis *et al.* 2000). In one study, insulin use has been found to be associated with an increased risk of non-Hodgkin's lymphoma (Tseng 2012) but similar findings are not available regarding multiple myeloma. Larger, multicentre-based studies may be conducted in our region to identify any association between myeloma and insulin use.

Another important issue is that most chemotherapy protocols used for treating multiple myeloma include glucocorticoids at a very high dose, which in itself is diabetogenic. Dexamethasone and prednisone-based regimens are part of the conventional and new

methods to treat newly diagnosed or recurrent/multiple Myeloma. These medications raise blood glucose through increased insulin resistance, gluconeogenesis, glycogenolysis, and decreased insulin production and secretion. Awareness among oncologists managing these patients regarding control of glucose level and managing complications of diabetes is important. In this regards, a specialized hospital for diabetes can be an efficient centre for managing multiple myeloma and other oncology patients receiving glucocorticoids and having the propensity to develop diabetes.

There were 2 cases of multiple myeloma that did not have a monoclonal paraprotein. Non-secretory myeloma is a specific entity of myeloma that projects a greater challenge to the clinician during diagnosis. Although the nephrotoxic effects of immunoglobulin light chain over production are absent in these patients, the clinical course can be equally disturbing by other cause of acute renal failure like massive renal infiltration by plasma cells (Adamidis *et al.* 2010). On the other hand all patients with a monoclonal band on serum protein electrophoresis do not essentially develop MM. These latter patients are referred as monoclonal gammopathy of undetermined significance. In a study conducted by Doyle *et al.* (2009), among 40 subjects with renal insufficiency who had abnormal serum electrophoresis, none subsequently developed MM and the renal abnormalities were found to be unrelated. Serum protein electrophoresis is, therefore, not considered to be a useful screening test to identify MM.

Early diagnosis of elderly diabetic patients with blood cancers like Multiple Myeloma can offer them a longer progression free survival. Multiple myeloma by itself and its related treatments can complicate the microvascular and macrovascular complications of diabetes. The treating physician has to recognize the treatment-related complications and closely follow up diabetic patients for the emergence or the worsening of hyperglycemia, neuropathy, nephropathy, or retinopathy in addition to cardiovascular diseases. In addition, adequate control of blood glucose levels reduces the risk of infection in patients with multiple myeloma and decreases the risk and severity of diabetic microvascular complications, thus, minimizing the increased morbidity of multiple myeloma (Bloomgarden 2001). As diabetes is a disease of the elderly with complications which are also common to multiple myeloma that is anemia, immunoincompetency and nephropathy, a strong clinical suspicion of Multiple Myeloma is essential to screen out prospective patients clinically and direct those patients for bone marrow examination. All elderly patients who satisfy the CRAB (Hypercalcemia, Renal insufficiency, Anemia and Bone Lesions) criteria for symptomatic MM should be completely investigated to exclude MM. Cancer incidences are increasing worldwide and awareness about cancers including blood cancers is essential nowadays. It is imperative for clinicians especially those handling geriatric age groups like elderly diabetics to develop awareness about this not so uncommon blood cancer of the elderly.

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